UNIVERSITY OF BIRMINGHAM

CHIRAL LITHIUM AMIDES: REACTIVITY STUDIES AND APPLICATIONS TO TARGET SYNTHESIS

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Abstract

Chiral lithium amide bases allow the desymmetrisation of prochiral substrates and the production of enantiomerically enriched products, which are vital for the pharmaceutical industry and the total synthesis of natural products. Chapter 1 gives a brief review of this area and the progress that has been achieved over the last three decades.

In Chapter 2 deprotonation of a ketone and an imide substrate using both chiral and achiral bases is described. Within the development of catalytic chiral lithium amide base methodology, competition reactions (Chapter 3) and lithium exchange experiments (Chapter 4) were carried out between two amine species. It was found that there were appreciable differences in the rate of deprotonation of the substrate between the lithium amides studied.

Chapter 5 describes the design and synthesis of new fluorinated chiral diamines which we hoped could be used as effective chiral lithium amide bases in sub-stoichiometric amounts.

Initial work was also carried out on the total synthesis of the diterpenoid alkaloid concavine. A chiral lithium amide base was used to introduce asymmetry into the synthetic route and the synthesis of the fused oxazepane ring moiety was completed (Chapter 6).

Declaration

I declare that this thesis is the result of my own work and has not, whether in the same or a different form, been presented to this or any other university in support of an application for any degree other than that for which I am now a candidate.

_____

Mark Robert Prestly, MSci

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Lastly, I would like to thank my wife, Amanda, for her patience, understanding and love during the time I have carried out this work.

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Appendices

Abbreviations

Å	Angstrom
ACCN	1, 1′-Azo*bis*(cyclohexanecarbonitrile)
ATPH	Aluminium tris (2,6-diphenylphenoxide)
Bn	Benzyl
Brine	Saturated aqueous sodium chloride solution
Bz	Benzoyl
°C	Degrees centigrade
CSA	Camphorsulfonic acid
^{c}Hex	Cyclohexyl
COSY	Correlation spectroscopy
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	Di*iso*butylaluminium hydride
DIPA	Di*iso*propylamine
DKP	Diketopiperazine
4-DMAP	4-dimethylaminopyridine
DMDO	Dimethyldioxirane
DMEDA	*N*,*N*'-dimethylethylenediamine
dppe	1,2-bis(diphenylphosphino)ethane
ee	Enantiomeric excess
EI	Electron impact ionisation
EQ	External quench
ES	Electrospray ionisation

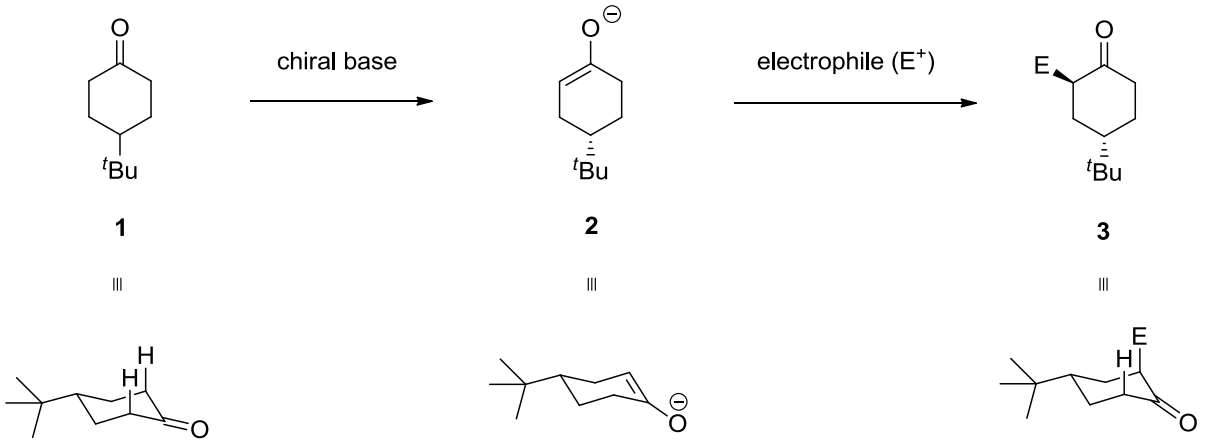
GC	Gas chromatography
GP	General Procedure
h	Hour
HMBC	Heteronuclear multiple bond correlation
HMDS	Bis(trimethylsilyl)amine
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
IR	Infrared
ISQ	*In situ* quench
J	Coupling constant
K	Kelvin
kPa	Kilopascal
LDA	Lithium di*iso*propylamide
LHMDS	Lithium hexamethyldisilazane
LTMP	Lithium tetramethylpiperidide
M	Molar
*m*CPBA	*meta*-Chloroperoxybenzoic acid
MEM	β-Methoxyethoxymethyl
Mes	Mesityl/ 2, 4, 6-trimethylbenzyl
MHz	Megahertz
min	Minute
mp	Melting point
Ms	Mesyl

MS	Mass spectrometry
MTPA	α-Methoxy-α-trifluoromethylphenylacetic acid/Mosher's acid
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
PENDANT	Polarization enhancement nurtured during attached nucleus testing
PMB	*para*-Methoxybenzyl
R_f	Retention factor
ROESY	Rotating frame nuclear Overhauser effect spectroscopy
rt	Room temperature
TBAF	Tetra *n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TEMPO	(2, 2, 6, 6-Tetramethylpiperidin-1-yl)oxyl
TBS	*tert*-butyldimethylsilyl
TFA	Trifluoroacetic acid
TfOH	Trifluoromethanesulfonic acid/Triflic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMCDA	Tetramethyl-1,2-diaminocyclohexane
TMEDA	Tetramethylethylenediamine
TMP	2, 2, 6, 6-Tetramethylpiperidine
TMS	Trimethylsilyl
UV	Ultraviolet

Chapter 1: Introduction to Chiral Lithium Amide Deprotonations

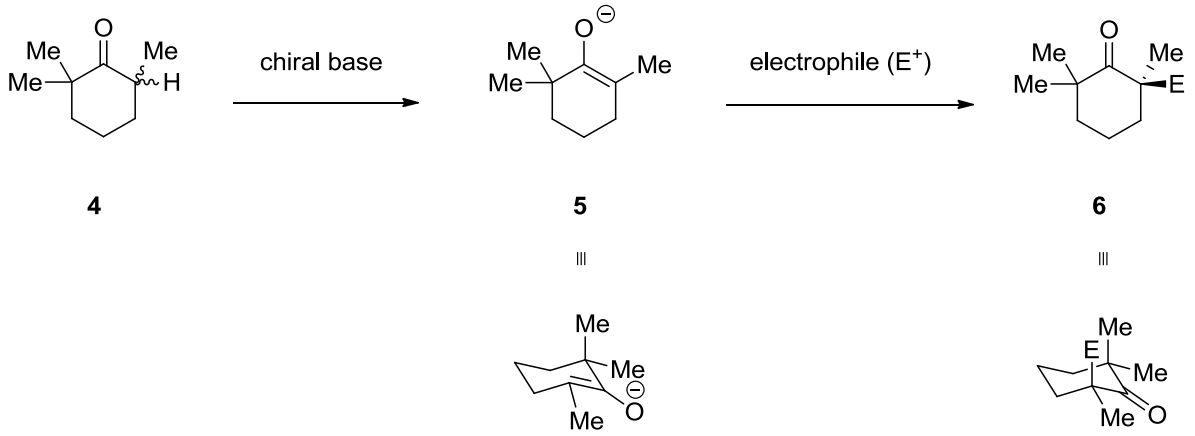
1.1 Overview

The use of chiral lithium amide bases to deprotonate prochiral substrates has become well explored over the last few decades.[1] These deprotonations can be categorised as either of two processes; firstly when a chiral lithium amide base is able to differentiate between enantiotopic protons within a prochiral substrate and secondly when the base acts initially as only a strong base to form a prochiral carbanion which then reacts in the presence of the chiral base to form an optically active product. The most common instance of the first case is the removal of an acidic proton from a prochiral ketone to form an enantiomerically enriched enolate which can react with the electrophile of choice. An example of this is shown in Scheme 1.1. With a bulky *tert*-butyl group in the 4 position the ketone (**1**) is conformationally biased toward the chair conformation shown and has two axial enantiotopic protons available to be removed. The chiral base is able to selectively remove one of these protons to give enantiomerically enriched enolate **2** which reacts with an electrophile to give a product of type shown (**3**).



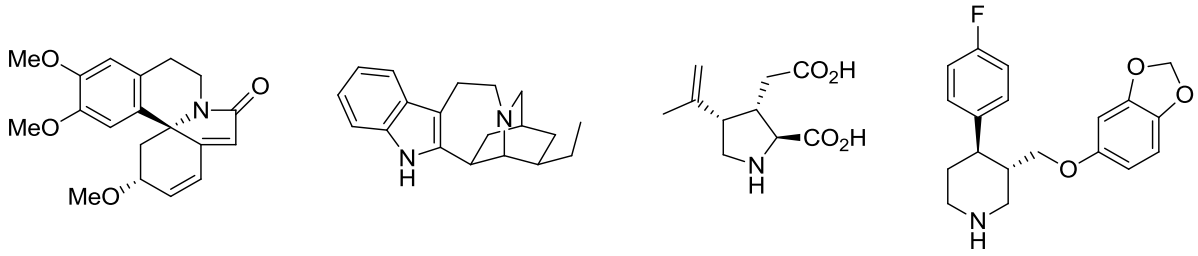
Scheme 1.1

In the second case the stereochemistry of the product is determined after the deprotonation step with the complexed chiral base acting as a non-covalently bonded chiral auxiliary directing the electrophile which is attacked by the prochiral carbanion. An example of this is shown in Scheme 1.2. As there is only one acidic proton available in ketone **4** the chiral lithium amide behaves simply as a strong base forming prochiral enolate **5**. In this illustrative example the presence of the chiral lithium amide within the mixture leads to the enolate attacking the electrophile on the top face of the molecule preferentially, forming enantiomerically enriched ketone **6**.



Scheme 1.2

The use of chiral lithium amide bases allows asymmetry to be introduced into molecules and the production of chiral building blocks for the synthesis of natural products and pharmaceutically active compounds. In order to complete an enantioselective total synthesis of a natural product there may be a key step within the synthesis in which a chiral base could be used to produce a non-racemic building block which could allow access to an enantiopure target molecule. It is also vitally important that chiral pharmaceuticals can be produced enantioselectively as within the chiral environment of the human body enantiomers can produce very different responses. Selected examples of molecules to which chiral base methodology has been applied are shown in Figure 1.1.



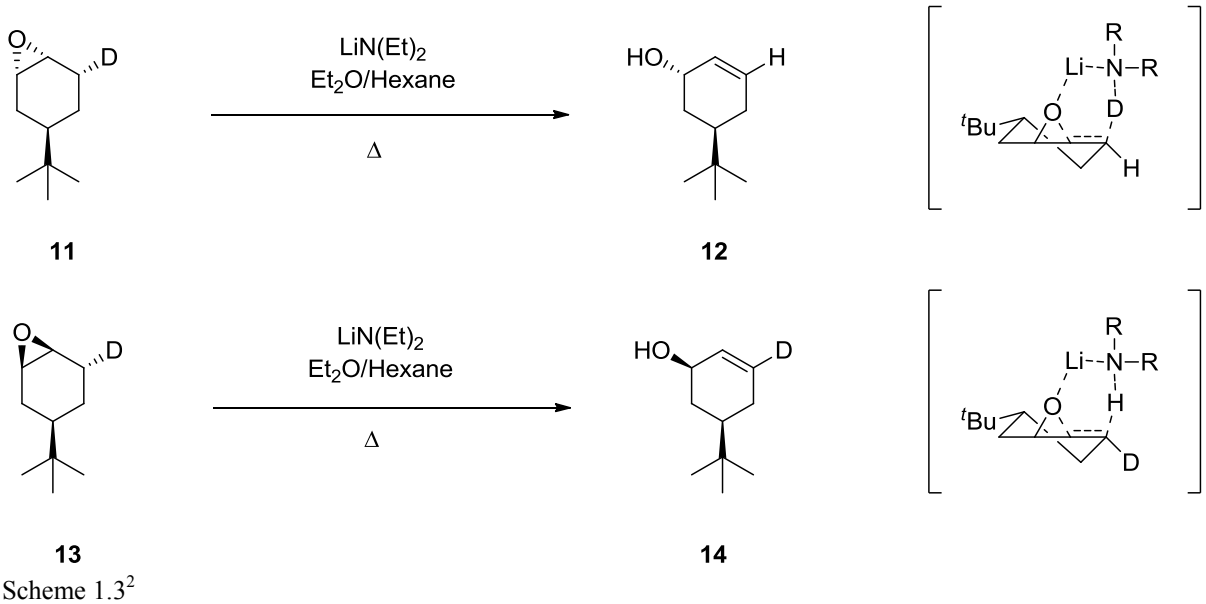
(+)-erysotramidine, **7** (+)-ibogamine, **8** (–)-kainic acid, **9** (–)-paroxetine, **10**

Figure 1.1: Target molecules synthesised using chiral lithium amide methodology.

1.2 Asymmetric Deprotonations

1.2.1 Asymmetric Deprotonation of Epoxides

The rearrangement of epoxides to allylic alcohols has been shown to proceed by *syn* elimination of a proton from the β-carbon upon treatment with a lithium amide base. In 1970, deuterium labelling experiments were reported by Thummel and Rickborn which showed that within a substituted cyclohexene oxide a proton (or deuterium atom) would be removed from the same face of the molecule as the epoxide using lithium diethylamide.[2] As shown in Scheme 1.3 when epoxide **11** was treated with lithium diethylamide the deuterium atom was removed giving allylic alcohol **12** which was free of deuterium. The equivalent reaction using epoxide **13** gave deuterated allylic alcohol **14**. These experiments show that the proton which is removed in this rearrangement is *syn* to the epoxide.

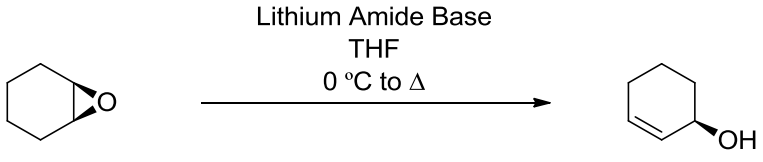


11 **12**

13 **14**

Scheme 1.3[2]

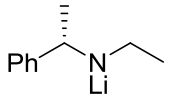
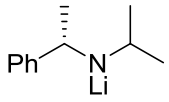
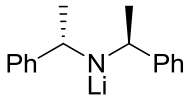
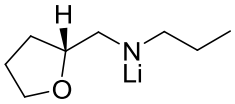
In 1980, Whitesell reasoned that this process could be adapted to induce asymmetry within the product by using a chiral lithium amide.[3] Cyclohexene oxide (**15**) was treated with various chiral lithium amide bases at 0 °C and the mixture was heated to reflux for 2 hours (Scheme 1.4). A selection of the chiral bases used are shown in Table 1.1. Chiral lithium amide base (*S*, *S*)-**19** was found to give the best enantioselectivity, allylic alcohol (*R*)-**16** was produced in 65 % yield with 31 % ee.



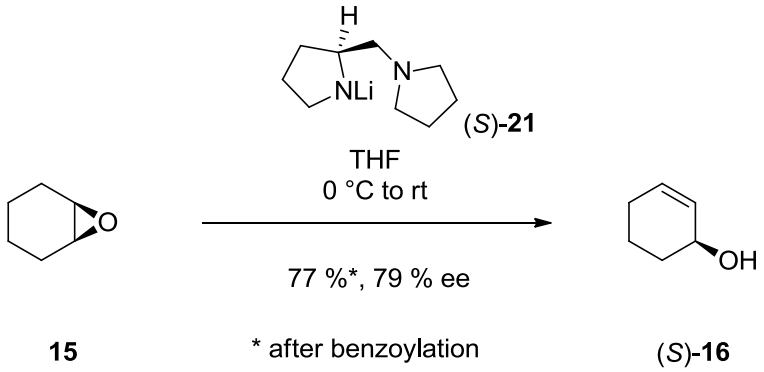
15 (*R*)-**16**

Scheme 1.4[3]

Table 1.1: Synthesis of (*S*)-**16** from epoxide **15**.[3]

Entry	Base		Yield (%)	% ee (config.)
1		(*S*)-**17**	69	11 (*R*)
2		(*S*)-**18**	95	9 (*R*)
3		(*S*, *S*)-**19**	65	31 (*R*)
4		(*R*)-**20**	76	18 (*S*)

In 1984, Asami reported the use of proline derived chiral base (*S*)-**21** to give enantiomerically enriched allylic alcohol (*S*)-**16** (Scheme 1.5).[4] The enantiomeric excess of (*S*)-**16** from this reaction was originally stated to be 92 % ee based on the previously reported optical rotation of enantiomerically pure (*S*)-**16** ($[\alpha]_D$ –112 (*c* 0.6, $CHCl_3$)).[5] This value was later revised to 79 % ee after a larger maximum optical rotation ($[\alpha]_D$ +130.6 (*c* 1.21, $CHCl_3$)) for allylic alcohol (*R*)-**16** was reported in the literature.[6]



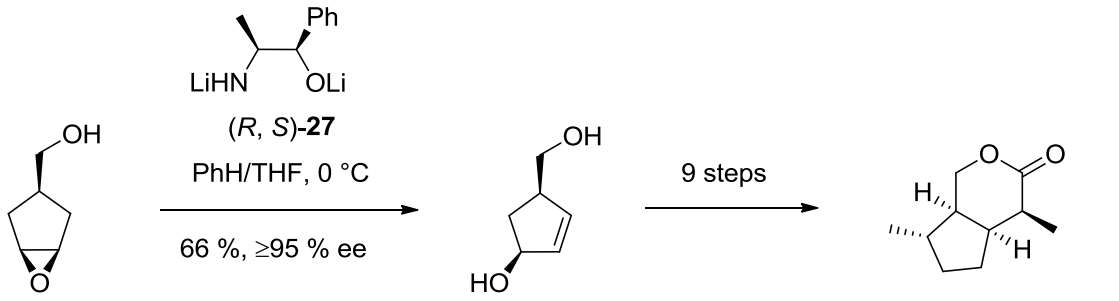
Scheme 1.5[4]

This methodology has also been used for the enantioselective synthesis of natural products. For example, in 1995 Asami reported the synthesis of (–)-untenone A (**25**).[7] Starting from 3-cyclopentenone (**22**), epoxide **23** was synthesised in 3 steps and then deprotonated with chiral base (*S*)-**21** to give alcohol (*S*)-**24** with 89 % ee in 75 % yield (Scheme 1.6). The target, (–)-untenone A (**22**), was then synthesised in 3 steps from alcohol (*S*)-**24**.

22 **23** **24** (–)-untenone A (**25**)

Scheme 1.6[7]

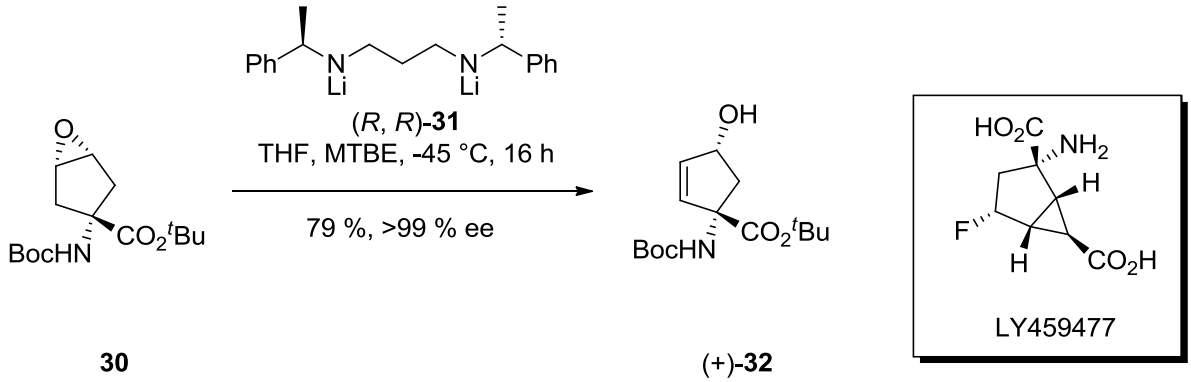
The synthesis of the insecticidal iridoid (+)-iridomyrmecin (**29**) was reported by Hodgson in 1997.[8] Based on previous work by Murphy,[9] norephedrine derived *bis*-lithiated chiral base (*R*, *S*)-**27** was used for the deprotonation of unprotected *meso*-epoxide **26** (Scheme 1.7). Diol (+)-**28** was obtained in 66 % yield with ≥95 % ee. The synthesis of (+)-iridomyrmecin (**29**) was completed in 9 steps, including a Claisen rearrangement, from diol (+)-**28**.



26 (+)-**28** (+)-iridomyrmecin (**29**)

Scheme 1.7[8]

The asymmetric synthesis of allylic alcohols from epoxides using chiral lithium amides has also been used as the key step in numerous other syntheses. The synthesis of prostaglandin intermediates,[10] leukotriene intermediates,[11] norleukotriene D_4 intermediates,[12] carbovir,[13] faranal[14] and lasiol[15] have all been carried out using this methodology. More recently chemists at Eli Lilly and Co. have used chiral base (*R*, *R*)-**31**, previously used by Alexakis,[16] in the synthesis of metabatropic glutamate receptor agonist LY459477.[17] After optimisation studies it was found that epoxide **30** could be opened at -40 °C over 16 hours to give allylic alcohol (+)-**32** with >99 % ee after recrystallisation.

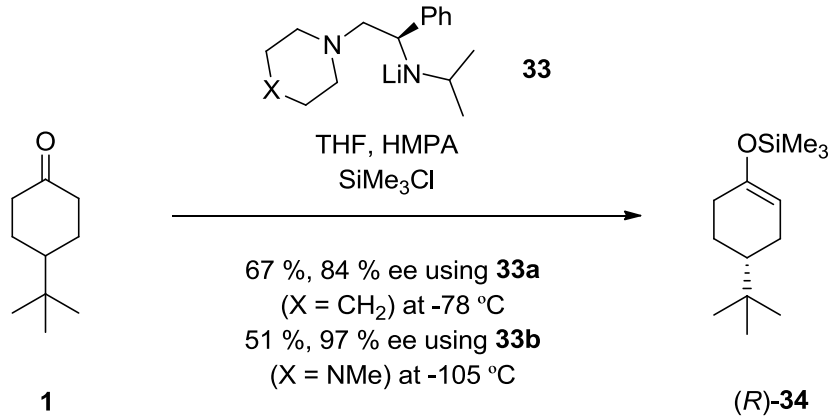


30 (+)-**32**

Scheme 1.8[17]

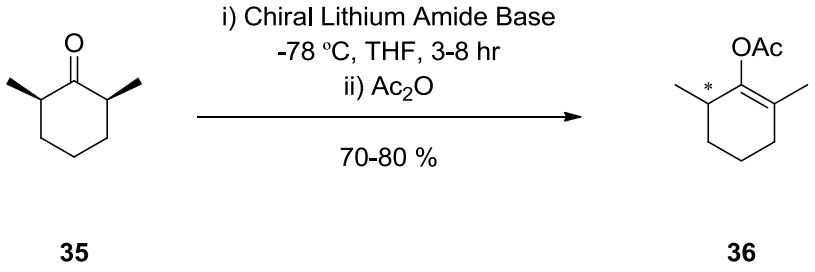
1.2.2 Asymmetric Deprotonation of Ketones

In 1986, both our group and the research group of Koga reported the use of chiral lithium amide bases for the asymmetric deprotonation of prochiral ketones. Koga's group showed that deprotonation of 4-*tert*-butylcyclohexanone (**1**) at -78 °C using diamine chiral base **33a** in the presence of trimethylsilyl chloride (5 eq.) and hexamethylphosphoramide (HMPA) (2 eq.), allowed enol silane (*R*)-**34** to be obtained in 67 % yield with 84 % ee (Scheme 1.9).[18] Using triamine chiral base **33b** and HMPA (1 eq.) at -105 °C, enol silane (*R*)-**34** was isolated in 51 % yield and reported to have 97 % ee.



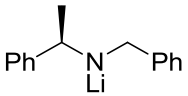
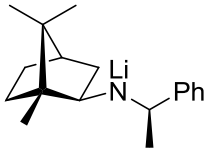
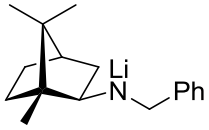
Scheme 1.9[18]

Our group reported the asymmetric deprotonation of *cis*-2, 6-dimethylcyclohexanone (**35**) using various chiral lithium amide bases derived from α-methylbenzylamine and camphor (Scheme 1.10).[19] Chiral base (*R*)-**37** was shown to produce enol acetate **36** (after addition of acetic anhydride) with 29 % ee (Entry 1). (+)-Camphor derived chiral bases (*R*, *R*)-**38** and (*R*)-**39** were found to give enol acetate **36** with 65 and 74 % ee respectively (Entries 2 & 3).

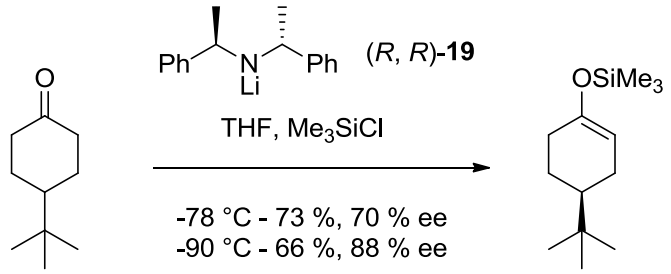


Scheme 1.10[19]

Table 1.2: Synthesis of enol acetate **36** from ketone **35**.[19]

Entry	Base		% ee (Config.)
1		(*R*)-**37**	29 (*R*)
2		(*R*, *R*)-**38**	65 (*S*)
3		(*R*)-**39**	74 (*R*)

In 1990, our group showed that chiral base (*R*, *R*)-**19** could be used for the asymmetric deprotonation of 4-*tert*-butylcyclohexanone (**1**).[20] Using Corey's *in situ* quench method (ISQ),[21] enol silane (S)-**34** was obtained with 70 % ee when the reaction was carried out at -78 °C and 88 % ee when the reaction was carried out at -90 °C (Scheme 1.11). The enantiomeric excess was determined by conversion of (*S*)-**34** to the equivalent α-hydroxyketone using *m*CPBA followed by formation of a MTPA ester by addition of MTPACl. Examination of the ^{1}H NMR spectrum allowed the enantiomeric excess to be determined.



1 (*S*)-**34**

Scheme 1.11[20]

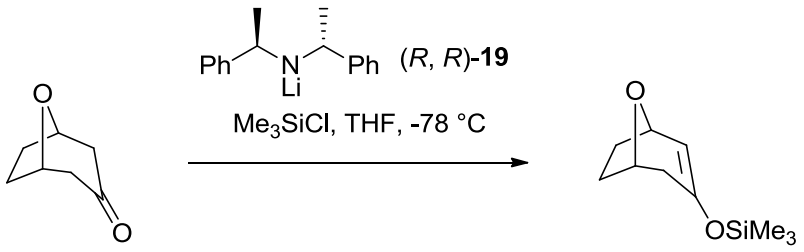
Deprotonations of ketone substrates have also been used to probe the effect of additives and different reaction procedures. It has been consistently shown that reactions carried out using the ISQ procedure gave products with higher enantiomeric excess than when the external quench (EQ) procedure was used. This enhancement in enantioselectivity was thought to be derived from the presence of *in situ* generated lithium chloride, produced either by reaction of the lithium amide with trimethylsilyl chloride[22] or when the lithium enolate was quenched with trimethylsilyl chloride. In 1993, our group reported investigations into the role of lithium chloride in the asymmetric deprotonation of several ketone substrates.[23] For the conversion of ketone **1** to enol silane (*S*)-**34** using chiral bases (*R*)-**18** and (*R*, *R*)-**19**, vastly different enantiomeric excesses were obtained when the ISQ and EQ procedures were used (Table 1.3

Entries 1 & 2, 4 & 5). When the EQ procedure was used with added lithium chloride (0.5 eq.) the enantiomeric excess of the product was found to be higher than when the ISQ procedure was used (Entries 3 & 6).

Table 1.3: Synthesis of enol silane (*S*)-**34** from ketone **1** using chiral bases (*R*)-**18** and (*R*, *R*)-**19**.[23b]

Entry	Base	Procedure	(*S*)-**34** % ee
1	(*R*)-**18**	ISQ	46
2	(*R*)-**18**	EQ	23
3	(*R*)-**18**	EQ + LiCl (0.5 eq.)	86
4	(*R*, *R*)-**19**	ISQ	69
5	(*R*, *R*)-**19**	EQ	23
6	(*R*, *R*)-**19**	EQ + LiCl (0.5 eq.)	83

Similar results were found for the conversion of bicyclic ketone **40** to enol silane (–)-**41** using chiral base (*R*, *R*)-**19** (Scheme 1.12). In the absence of lithium chloride, enol silane (–)-**41** was obtained with 82 % ee using the ISQ procedure and 33 % ee using the EQ procedure (Table 1.4, Entries 1 & 2). Using the EQ procedure and between 0.1 and 1.5 equivalents of lithium chloride, enol silane (–)-**41** was obtained with 84 % ee (Entries 3-5).



40 (–)-**41**

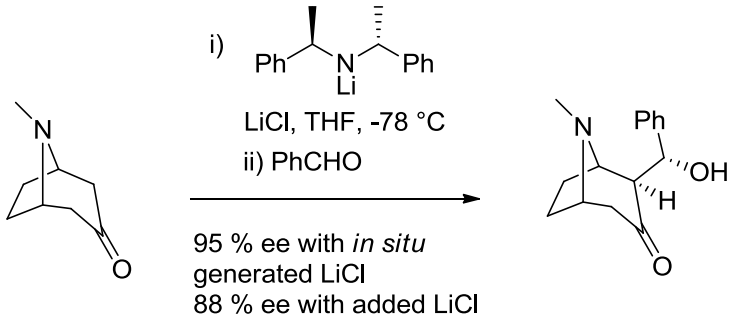
Scheme 1.12[23b]

Table 1.4: Synthesis of enol silane (–)-**41** from ketone **40** using (*R*, *R*)-**19**.[23b]

Entry	Procedure	Eq. LiCl	% ee
1	ISQ	-	82
2	EQ	-	33
3	EQ	0.1	84
4	EQ	0.7	83
5	EQ	1.5	84

The asymmetric deprotonation of tropinone (**42**) has also been explored by both our group[23] and the research group of Majewski[24] and similar results have been found. Majewski

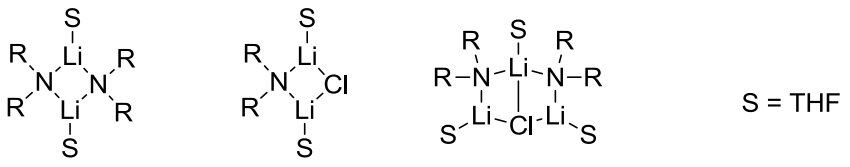
introduced the *in situ* generation of a 1:1 mixture of chiral base (*R*, *R*)-**19** and lithium chloride by addition of 2 equivalents of *n*-butyllithium to the hydrochloride salt of the amine precursor. This allowed the synthesis of aldol product (–)-**43** with 95 % ee, whereas "classical" introduction of solid lithium chloride into the reaction mixture gave (–)-**43** with 88 % ee (Scheme 1.13). It was thought that the reduced enantiomeric excess when the chiral amine was added as an oil and lithium chloride was added as a solid was due to absorption of carbon dioxide into the amine and moisture into lithium chloride. The purification and use of the amine hydrochloride salt is without these problems.



42 (–)-**43**

Scheme 1.13[24a]

It was suggested that the introduction of lithium chloride into the previous reactions leads to greater enantioselectivity because the active reagent has changed.[23b, 24a] It is thought that in the absence of lithium chloride the chiral base could be present as homodimer **44** (Figure 1.2). In the presence of lithium chloride the chiral base may exist as a mixed aggregate such as **45** or **46**.



44 **45** **46**

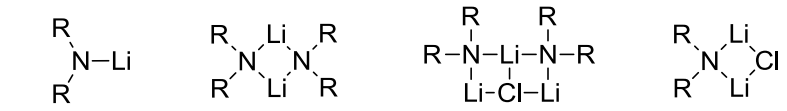
Figure 1.2

These effects were then investigated further by Koga in 1996.[25] Enol silane (*S*)-**34** was first synthesised from ketone **1** using chiral base (*R*, *R*)-**19** and either TMSI, TMSBr or TMSCl as electrophile under ISQ conditions. Enol silane (*S*)-**34** was found to have 31, 65 and 90 % ee respectively (Table 1.5, Entries 1-3). Under EQ conditions in the absence of lithium chloride, enol silane (*S*)-**34** was found to have 44 % ee (Entry 4) and in the presence of 0.6-3.6 equivalents of lithium chloride the enantiomeric excess of (*S*)-**34** was found be 87-88% (Entries 5-7).

Table 1.5: Synthesis of enol silane (*S*)-**34** from ketone **1** using chiral base (*R*, *R*)-**19**.[25]

Entry	Electrophile	Procedure	Eq. LiCl	Yield (%) (*S*)-**34**	% ee
1	Me_3SiI	ISQ	-	97	31
2	Me_3SiBr	ISQ	-	86	65
3	Me_3SiCl	ISQ	-	71	90
4	Me_3SiCl	EQ	-	84	44
5	Me_3SiCl	EQ	0.6	86	87
6	Me_3SiCl	EQ	1.2	87	88
7	Me_3SiCl	EQ	3.6	73	88

In this report the results of ^{6}Li and ^{15}N NMR studies of the solution structure of (*S*, *S*)-**19** in the presence and absence of lithium chloride were disclosed. Based on the previous analysis of the NMR spectra of lithium dialkylamides by Collum,[26] four species were identified (**47**, **48**, **49** and **50**) (Figure 1.3). When no lithium chloride was present, homodimer **48** was the dominant species. A small amount of lithium amide **47** was also visible. On addition of lithium chloride two new species (**49** & **50**) could be identified. In the presence of 0.5 equivalents of lithium chloride, **48** was still the major species present. When 1.0 equivalents of lithium chloride were added the major species was **50** and in the presence of 3.0 equivalents of lithium chloride **50** was the only species present.

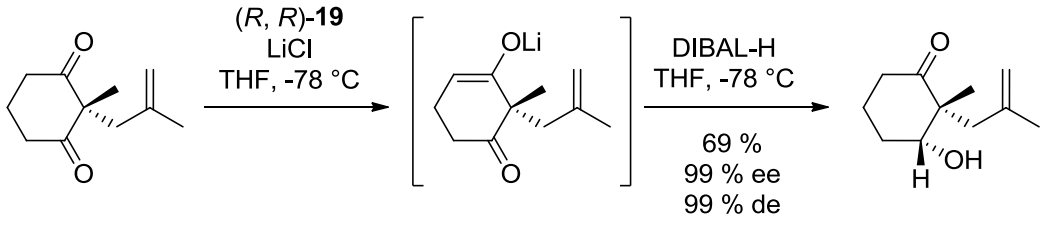


47 **48** **49** **50**

R = $CHCH_3Ph$

Figure 1.3: Lithium amide structures observed for [^{6}Li, ^{15}N]-(*S*, *S*)-**19**.[25]

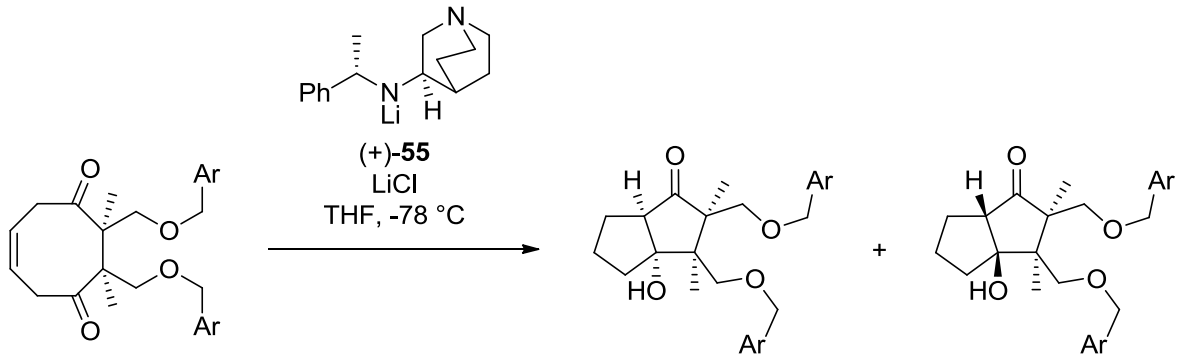
It has also been found to be possible to use chiral lithium amide bases for the desymmetrisation of prochiral diketones. In 2006, our group reported the asymmetric deprotonation of 1,3-diketones using chiral base (*R*, *R*)-**19** (Scheme 1.14).[27] The best reported result involved the deprotonation of diketone **51** using (*R*, *R*)-**19** followed by reduction of the intermediate lithium enolate (**52**) using DIBAL-H to give hydroxyketone **53** in 69 % yield. Hydroxyketone **53** was found to have 99 % ee and 99 % de.



51 **52** **53**

Scheme 1.14[27]

In 2007, Fukuyama used a chiral base desymmetrisation of a prochiral diketone in the synthesis of (+)-merrilactone A.[28] Diketone **54** was deprotonated using several chiral lithium amide bases and (+)-**55** was found to give the best enantioselectivity and good diastereoselectivity in a transannular aldol reaction, giving (–)-**56** and **57** in 78 and 12 % yield respectively (Scheme 1.15). Bicyclic hydroxyketone (–)-**56** was found to have 65 % ee. For the synthesis of (+)-merrilactone A, chiral base (–)-**55** was used to give bicyclic hydroxyketone (+)-**56** with 57 % ee; after recrystallisation this was improved to 99 % ee.



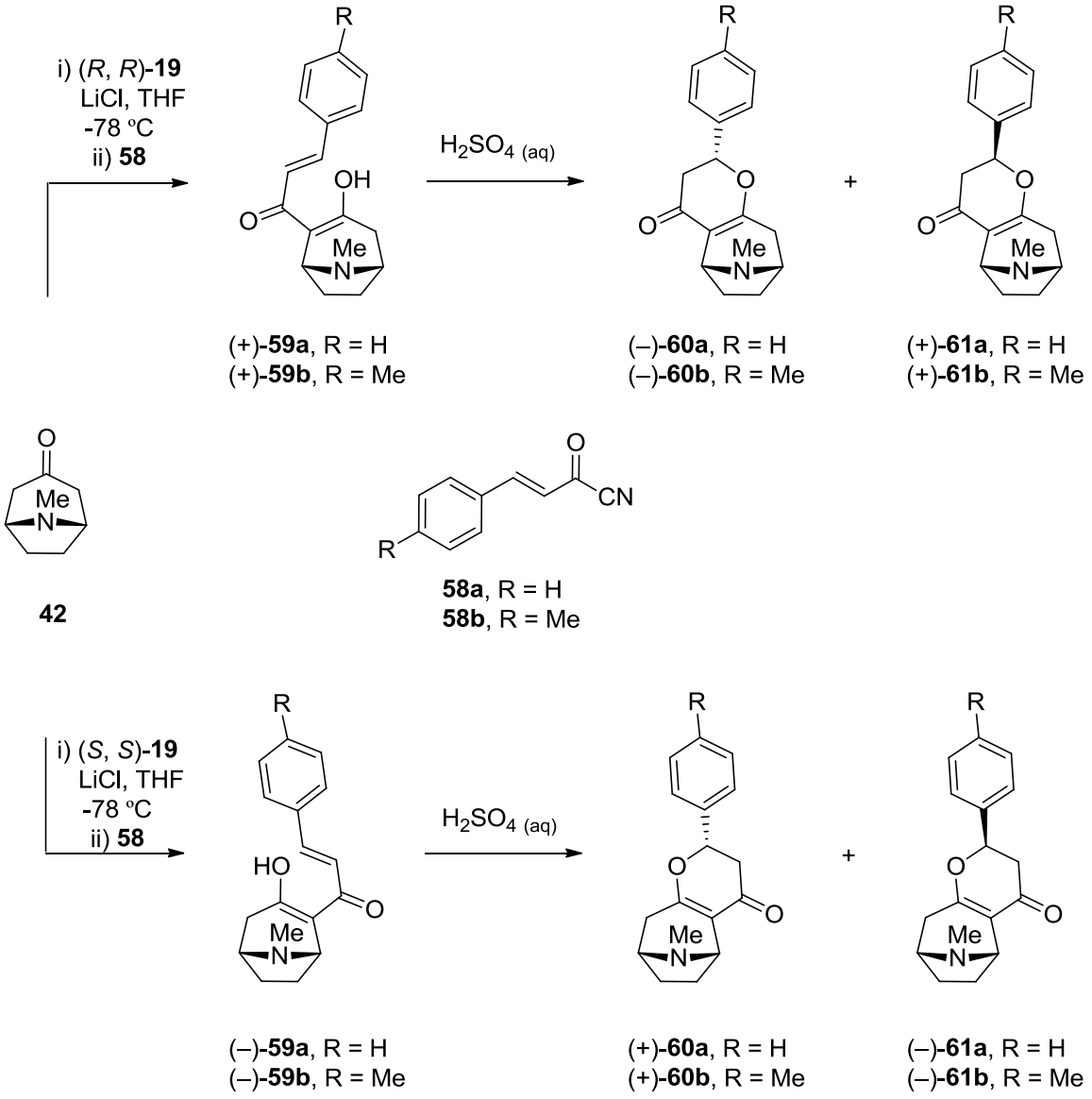
54
Ar = 2,6-dichlorophenyl

(–)-**56**
78 %, 65 % ee
99 % ee after recryst.

57
12 %

Scheme 1.15[28]

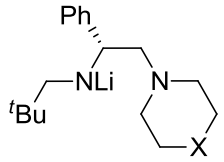
The following examples highlight recent use of chiral lithium amide bases to deprotonate ketones, which were not covered in the review by Simpkins and Weller.[1c] In 2010, Carroll utilised chiral base **19** for the enantioselective synthesis of both enantiomers of strobamine and strobamine's *para*-methyl analogue (Scheme 1.16).[29] Following the work of Majewski reported in 1995,[30] (*S*, *S*)-**19** or (*R*, *R*)-**19** were used to deprotonate tropinone (**42**) and the resultant enolate was quenched with cinnamoyl cyanide **58** to give (–)- or (+)-chalcostrobamine (**59**) respectively. The product, chalcostrobamine (**59**), could be isolated at this stage or, after work-up, be subjected to heating in aqueous sulfuric acid for 24 hours to give **60** and **61** (~1:1). No yields were reported in this article by Carroll.



Scheme 1.16[29]

The 8 isomeric products which were synthesised in this study were reported to be enantiomerically pure ("100 % ee") by HPLC. No explanation was given for the enantiopurity of these products; however based on the optical rotation data given for (–)-chalcostrobamine ((–)-**59a**) ($[\alpha]^{20}_D$ = –167 (*c* 1.7, $CHCl_3$)) and (+)-chalcostrobamine ((+)-**59a**) ($[\alpha]^{20}_D$ = +166 (*c* 1.75, $CHCl_3$)), an enantiomeric excess of 88-93 % ee may be realistic. In Majewski's studies of the tropane alkaloids, both (–)-chalcostrobamine with 95 % ee ($[\alpha]^{20}_D$ = –179 (*c* 1.04, $CHCl_3$)) and (+)-chalcostrobamine with 92 % ee ($[\alpha]^{20}_D$ = +165 (*c* 1.04, $CHCl_3$)) were

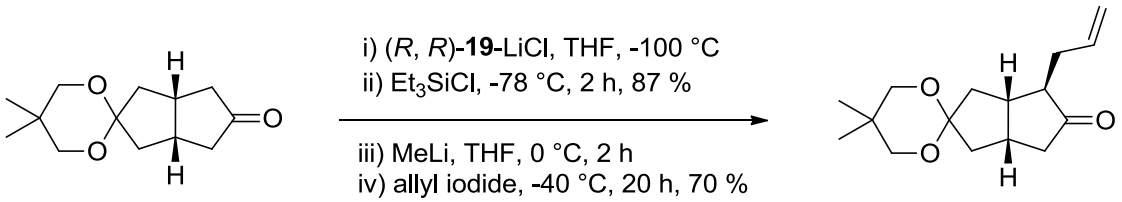
synthesised using (*R*, *R*)-**19** and (*R*)-**62** (Figure 1.4) respectively under the same conditions used by Carroll.[31]



(*R*)-**62**, X = CH_2
(*R*)-**63**, X = NMe

Figure 1.4

Prochiral substituted hydropentalenone derivatives have previously been used as substrates for asymmetric deprotonations using chiral lithium amide bases.[32] In 2010, Laschat reported the use of these substrates with alkyl and allyl halides, as these electrophiles had not previously been used with this type of substrate.[33] Chiral base (*R*, *R*)-**19** and lithium chloride were used to deprotonate ketone **64** and the resulting enolate was quenched with triethylsilyl chloride to give an intermediate enol silane in 87 % yield (Scheme 1.17). After purification of this enol silane, methyl lithium was added to regenerate the enolate and then allyl iodide was added to give ketone **65** in 70 % yield. Ketone **65** was found to have 84 % ee and a diastereomeric ratio of 95:5.

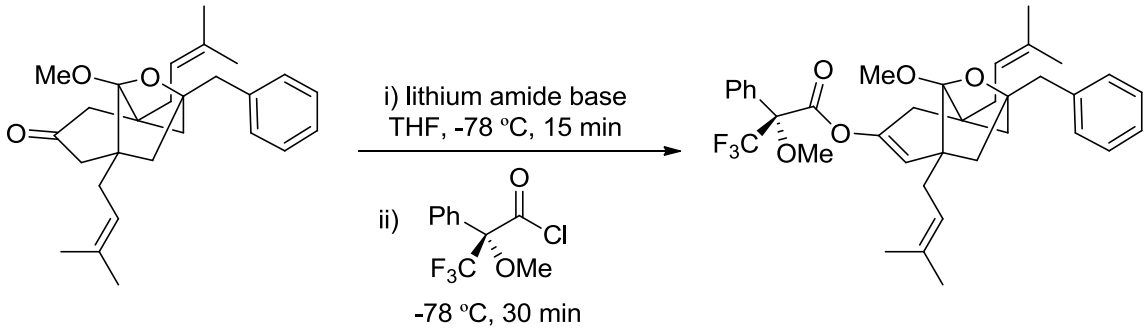


64 → **65**
84 % ee, 95:5 *dr*

Scheme 1.17[33]

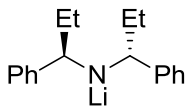
In 2011, Njardarson reported initial exploration of the desymmetrisation of ketone **66** using chiral bases (*R*, *R*)-**68** and (*S*, *S*)-**68** (Figure 1.5).[34] Ketone **66** was deprotonated and the resultant enolate quenched with (*S*)-Mosher's acid chloride to yield ester **67** (Scheme 1.18).

When lithium hexamethyldisilazide (LHMDS) was used for this deprotonation, ester **67** was found to have a diastereomeric ratio of 1.1:1 (Table 1.6, Entry 1). Chiral base (*R*, *R*)-**68** in the absence and presence of lithium chloride was found to give **67** with a diastereomeric ratio of 3:1 and 10:1 respectively (Entries 2 & 3). As would be expected chiral base (*S*, *S*)-**68**-LiCl gave the opposite diastereomer of **67**, interestingly however the diastereomeric ratio was only 6:1 (Entry 4). Normally the asymmetric induction of chiral bases improves as the temperature is reduced, however when (*R*, *R*)-**68**-LiCl was used at -100 °C a reduced dr of 3:1 was found. (Entry 5).



66 **67**

Scheme 1.18[34]



(*R*, *R*)-**68**

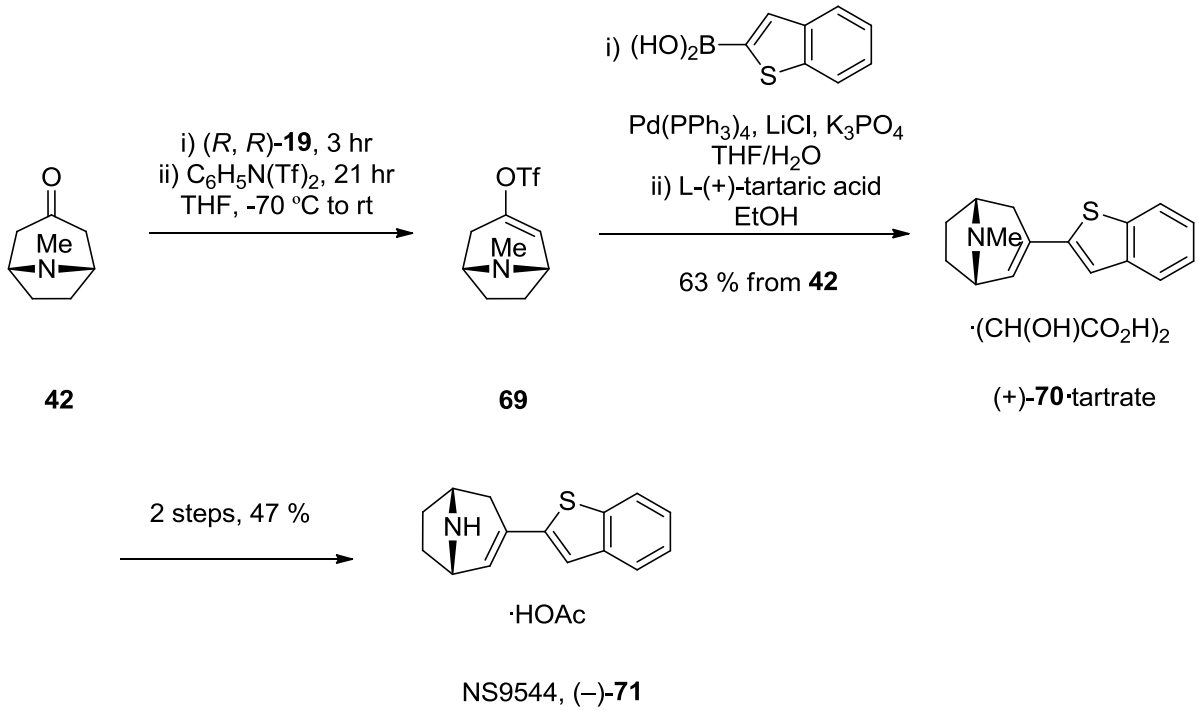
Figure 1.5

Table 1.6: Synthesis of ester **67** from **66** using chiral base **68**.[34]

Entry	Base	Additive	Temp (°C)	Yield (%)	dr
1	LHMDS	-	-78	85	1.1:1
2	(*R*, *R*)-**68**	-	-78	87	3:1
3	(*R*, *R*)-**68**	LiCl	-78	83	10:1
4	(*S*, *S*)-**68**	LiCl	-78	75	1:6
5	(*R*, *R*)-**68**	LiCl	-100	72	3:1

Chemists from DuPont Chemoswed reported the use of chiral base (*R*, *R*)-**19** within the synthesis of monoamine reuptake inhibitor NS9544.[35] On a 45 mole scale chiral base (*R*, *R*)-

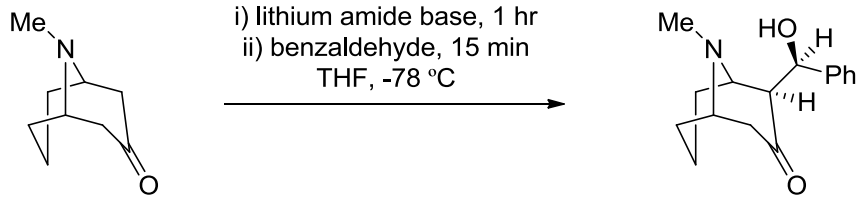
19 was used to deprotonate tropinone (**42**) and the intermediate enolate formed was treated with *N*-phenyl-bis(trifluoromethanesulfonimide) to generate enol triflate **69** which was not purified (Scheme 1.19). Crude enol triflate **69** was then coupled with benzo[*b*]thiophene-2-boronic acid by a Suzuki reaction and the product **70** was found to have 90 % ee, in accordance with previously reported deprotonations of tropinone (**42**) using **19**.[24a, 30, 36] In order to increase the enantiomeric excess, the L-(+)-tartrate salt (+)-**70** was formed and after recrystallisation from ethanol the enantiomeric excess was found to be 99 %. Previous attempts to resolve racemic (±)-**70** using chrial acids had failed. (+)-**70**·tartrate was synthesised in 2 synthetic steps from tropinone (**42**) in 63 % yield. Demethylation was achieved over 2 steps *via* an intermediate carbamate in 47 % yield, giving 9 kg of (–)-**71**·HOAc with 99 % ee.



Scheme 1.19[35]

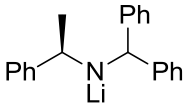
In 2011, the use of chiral lithium amide bases was reported by Lazny for the asymmetric deprotonation of granatanone (**72**).[37] Prochiral substrate granatanone (**72**) was deprotonated and the resultant enolate was reacted with benzaldehyde and various other aldehydes (Scheme

1.20). Using LDA for this deprotonation the reaction was found to proceed with excellent diastereoselectivity (98:2, *exo*, *anti*: *exo*, *syn*) and (±)-**73** was isolated in 97 % yield (Table 1.7, Entry 1). Upon purification by silica gel chromatography aldol product **73** was found to undergo decomposition and equilibration of diastereomers, therefore it was precipitated by addition of hexane to a concentrated solution of **73** in dichloromethane and then recrystallised. Using chiral base (*R*)-**62**, (–)-**73** was found to have 93 % ee and after recrystallisation the enantiomeric excess was increased to 99 % (Entry 2). Chiral base (*R*)-**63** was found to give (–)-**73** with 87 % ee (Entry 3). C_2-symmetric chiral base (*S*, *S*)-**19** gave (–)-**73** with a reduced enantiomeric excess of 77 % (Entry 4). In the presence of between 1.0 to 0.25 equivalents of lithium chloride, chiral base (*R*)-**74** (Figure 1.6) gave (+)-**73** with 80-83 % ee (Entry 5-7). The sample of (+)-**73** with 83 % ee was increased to 93 % ee after a single recrystallisation (Entry 6). In the absence of lithium chloride, (*R*)-**74** gave (+)-**73** with a greatly reduced enantiomeric excess of 65 %.



72 **73**

Scheme 1.20[37]



(*R*, *R*)-**74**

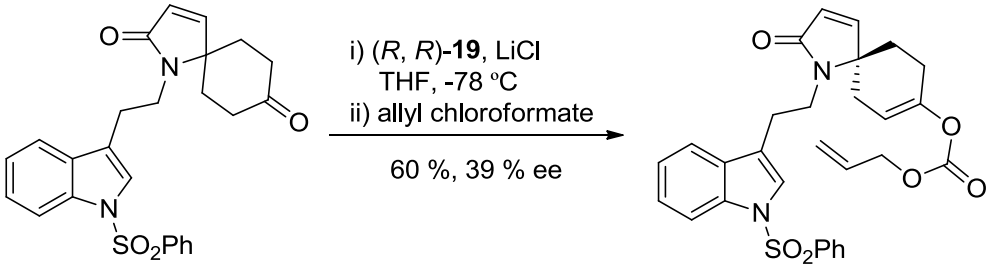
Figure 1.6

Table 1.7: Synthesis of **73** from granatanone (**72**).[37]

Entry	Base[a]	Eq. LiCl	Yield[b] (%)	Product	% ee[c]
1	LDA	1.0	97	(±)-**73**	-
2	(*R*)-**62**	1.0	67	(–)-**73**	93 (99)
3	(*R*)-**63**	0.5	72	(–)-**73**	87
4	(*S*, *S*)-**19**	1.0	81	(–)-**73**	77
5	(*R*)-**74**	1.0	60	(+)-**73**	82
6	(*R*)-**74**	0.5	78	(+)-**73**	83 (93[d,e])
7	(*R*)-**74**	0.25	96	(+)-**73**	80[e]
8	(*R*)-**74**	-	86	(+)-**73**	65

[a] 1.2 eq. [b] Yield of precipitated product. [c] Determined from the ^{1}H NMR spectrum of the crude product in the presence of (*R*)-(–)-2,2,2-trifluoro-1-(9-anthryl)ethanol. [d] The enantiomeric excess after a single recrystallisation. [e] The absolute structure of this product was determined by X-ray crystallographic analysis.

In 2012, Sarpong published preliminary deprotonations of ketone **75** using various chiral lithium amide bases.[38] Out of all the chiral bases used, (*R*, *R*)-**19** was found to give the highest enantiomeric excess. After deprotonation of ketone **75** using (*R*, *R*)-**19**, allyl chloroformate was added to form enol carbonate **76** in 60 % (Scheme 2.21). Analysis of this product by chiral HPLC showed that enol carbonate **76** had a modest enantiomeric excess of 39 %. The authors indicated that further work would be carried out to increase the enantiomeric excess of this deprotonation and apply it to the enantioselective synthesis of lapidilectine B and other *Kopsia* alkaloids.

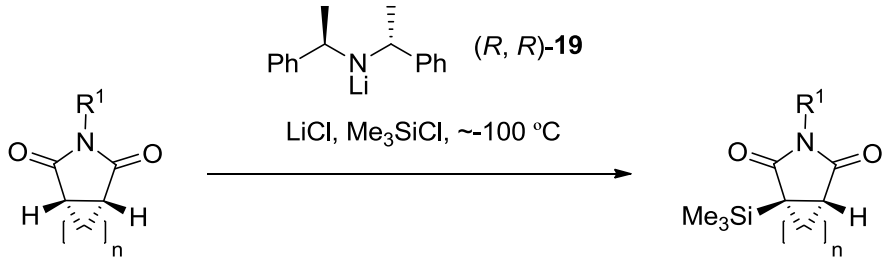


75 **76**

Scheme 1.21[38]

1.2.3 Asymmetric Deprotonation of Imides

In 1998, our group reported the use of chiral lithium amide base (*R*, *R*)-**19** for the asymmetric deprotonation of ring-fused imides (**77**).[39] Silylated cyclopropane fused imide **78a** with 95 % ee was isolated in 80 % yield when the deprotonation of **77a** was carried out at *ca*. -100 °C in the presence of trimethylsilyl chloride (Scheme 1.22, Table 1.8, Entry 1). Analogous deprotonations of cyclobutane and cyclopentane fused imides **77b** and **77c** gave silylated products **78b** and **78c** with 94 and 91 % ee respectively (Entry 2-3).



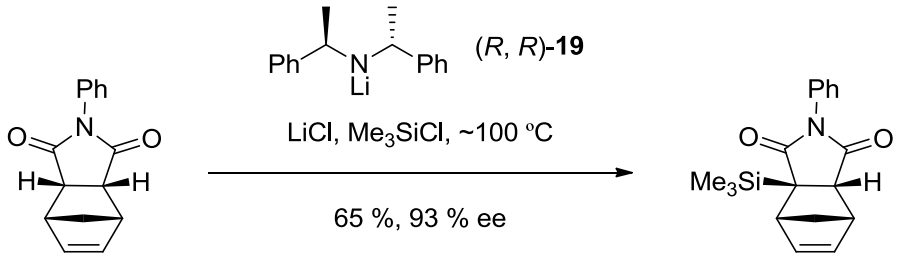
77a-c (n=1-3) **78a-c** (n=1-3)

Scheme 1.22[39]

Table 1.8: Synthesis of **78** from imide **77**. [39]

Entry	Substrate	n	R^1	Yield	% ee
1	**77a**	1	Ph	80	95
2	**77b**	2	Bn	37	94
3	**77c**	3	Bn	72	91

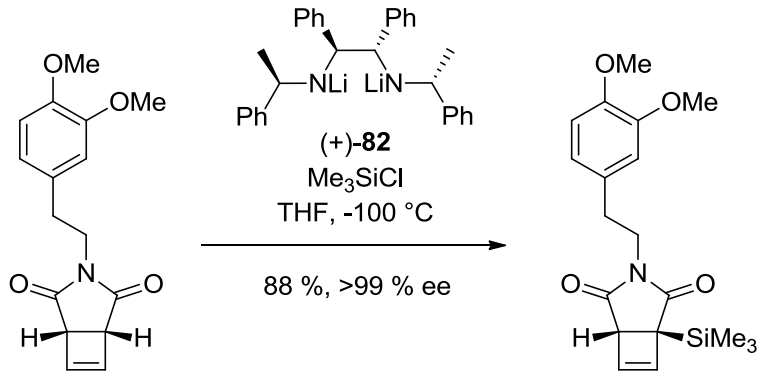
Deprotonation of bridged cyclohexene fused imide **79** using chiral base (*R*, *R*)-**19** was also reported to be highly enantioselective.[39] Silylated product **80** was isolated in 65 % yield with 93 % ee (Scheme 1.23).



79 **80**

Scheme 1.23[39]

In 2009, within studies towards the asymmetric synthesis of erysotramidine, our group reported the use of *bis*-lithiated chiral base (+)-**82** for the deprotonation of imide **81** (Scheme 1.24).[40] Chiral base (+)-**82** was added to a solution of imide **81** and trimethylsilyl chloride at -100 °C and after four hours silylated product (+)-**83** was isolated in 88 % yield with >99 % ee.

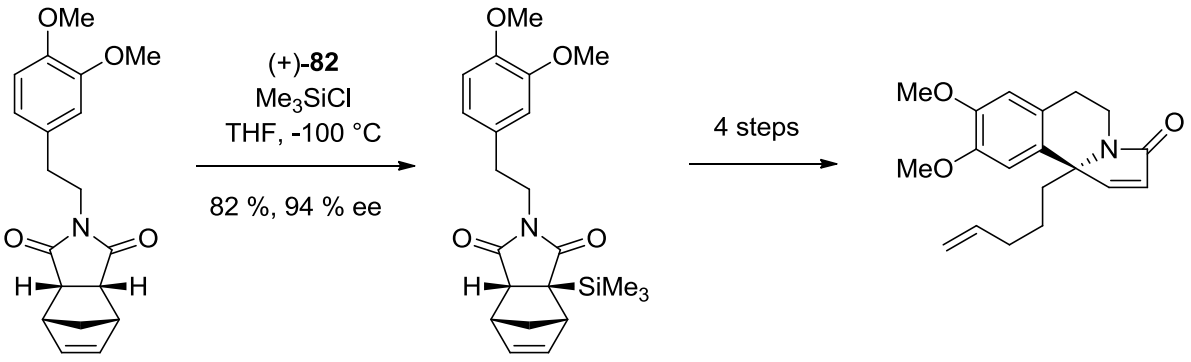


81 (+)-**83**

Scheme 1.24[40]

In the same study bridged cyclohexene imide **84** was also deprotonated by *bis*-lithiated chiral base (+)-**82**. In the presence of trimethylsilyl chloride, after 3 hours at -100 °C silylated product (+)-**85** with 94 % ee was isolated in 82 % yield (Scheme 1.25).[41] After 4 steps intermediate (–)-**86** was reached; the last of these steps involved a retro-Diels-Alder process

to remove the bridged cyclohexene moiety. The synthesis was continued from intermediate (–)-**86** and in 6 more steps the target, erysotramidine was reached.

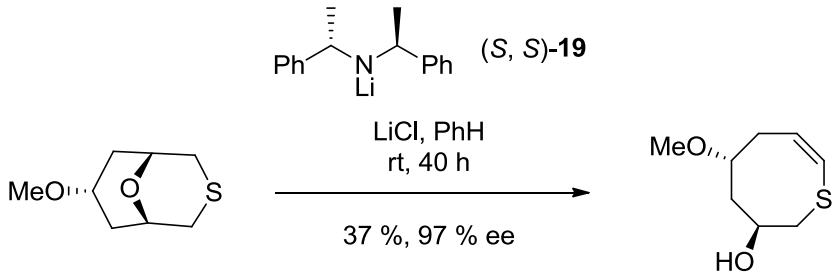


84 **85** (–)-**86**

Scheme 1.25[41]

1.2.4 Asymmetric Deprotonation Adjacent to Sulfur

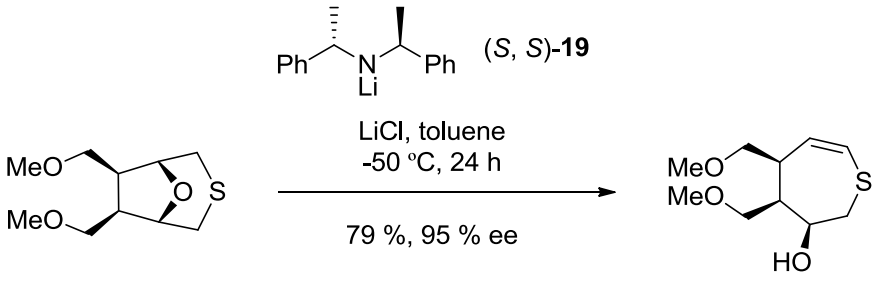
Chiral lithium amide bases have also been used for asymmetric deprotonation adjacent to sulfur at various oxidation states. In 1997, Lautens showed that chiral base (*S*, *S*)-**19** could be used for the conversion of thiaoxabicycle **87** to alcohol (–)-**88** with excellent enantioselectivity (Scheme 1.26).[42] Heterocycle (–)-**88** was obtained in 37 % yield with 97 % ee after 40 hours at room temperature.



87 (–)-**88**

Scheme 1.26[42]

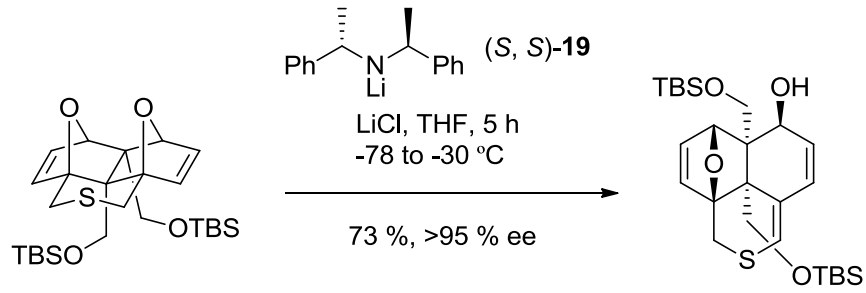
In the same article Lautens reported that *meso* thiaoxabicycle **89** could be converted to alcohol (–)-**90** with 95 % ee in 79 % isolated yield (Scheme 1.27).[42] This reaction was carried out over 24 hours at -50 °C.



89 (–)-**90**

Scheme 1.27[42]

In 1998, Lautens reported the use of chiral base (*S*, *S*)-**19** for the desymmetrisation of dioxapentacyclic compound **91** (Scheme 1.28).[43] In this reaction the chiral base differentiates between the two CH_2 groups adjacent to sulfur, resulting in the opening of one of the ether bridges preferentially. When this reaction was carried out using (*S*, *S*)-**19** at -78 to -30 °C over 5 hours, the product alcohol (+)-**92** was isolated in 73 % yield with >95 % ee.

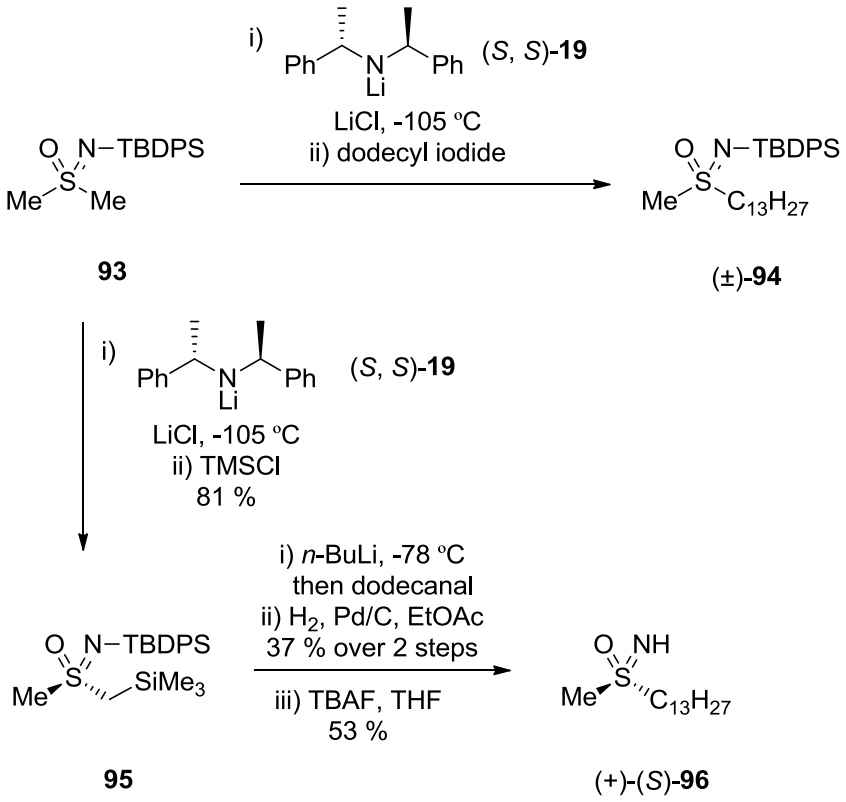


91 (+)-**92**

Scheme 1.28[43]

Recently, Bolm reported the use of chiral base (*S*, *S*)-**19** in the synthesis of enantiomerically enriched myristic acid analogues and 2-oxa-2-alkyl 3,4-dihydro 2,1-benzothiazines.[44] Initially

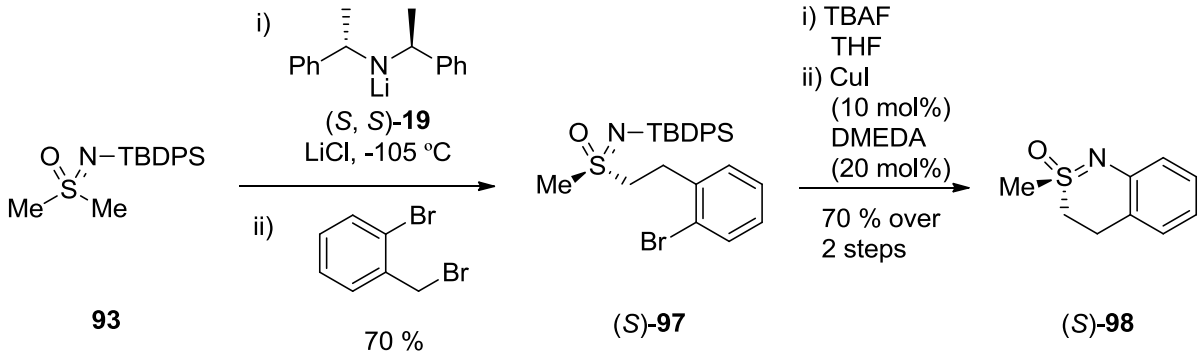
(*S*, *S*)-**19**-LiCl was used to deprotonate prochiral dimethyl sulfoximine **93** and the chiral carbanion which formed was alkylated with dodecyl iodide (Scheme 1.29). Unexpectedly the product (**94**) was found to be racemic. Dimethyl sulfoximine **93** was then deprotonated with (*S*, *S*)-**19**-LiCl as before and the chiral carbanion was silylated with trimethylsilyl chloride to give α-silylated sulfoximine (*S*)-**95** in 81 % yield. Treatment of (*S*)-**95** with *n*-butyllithium followed by dodecanal gave an intermediate alkene which was hydrogenated to give a saturated sulfoximine intermediate in 37 % yield over two steps. Desilylation was achieved in 53 % yield using tetrabutylammonium fluoride (TBAF) to give myristic acid analogue (+)-(*S*)-**96**. Analysis of both (*S*)-**95** and (*S*)-**96** by chiral HPLC indicated that the enantiomeric excess was 58 %.



Scheme 1.29[44]

The synthesis of enantiomerically enriched 2-oxa-2-alkyl 3,4-dihydro 2,1-benzothiazine **98** was also shown in the same report.[44] Prochiral dimethyl sulfoximine **93** was deprotonated

with (*S*, *S*)-**19**-LiCl and the chiral carbanion was treated with 1-bromo-2-(bromomethyl)benzene to give sulfoximine (*S*)-**97** with 54 % ee in 70 % yield (Scheme 1.30). Desilylation with TBAF followed by copper-catalysed cyclisation gave 2-oxa-2-alkyl 3,4-dihydro 2,1-benzothiazine (*S*)-**98** in 70 % yield over two steps.



Scheme 1.30[44]

1.2.5 Asymmetric Deprotonation of Chromium Arene Complexes

Tricarbonylchromium(0) complexes of aromatic compounds are useful synthetic tools for organic synthesis.[45] In these complexes both the aromatic protons and any benzylic protons have increased acidity and chiral lithium amide bases have been found to be able to differentiate between these enantiotopic protons (Figure 1.7).

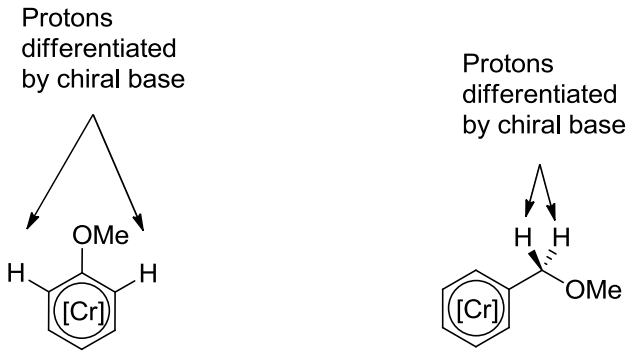
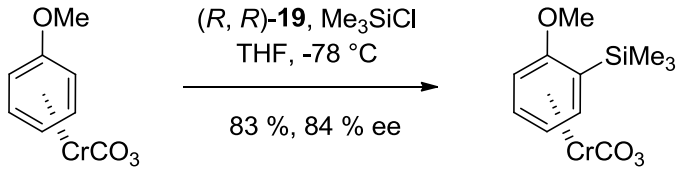


Figure 1.7

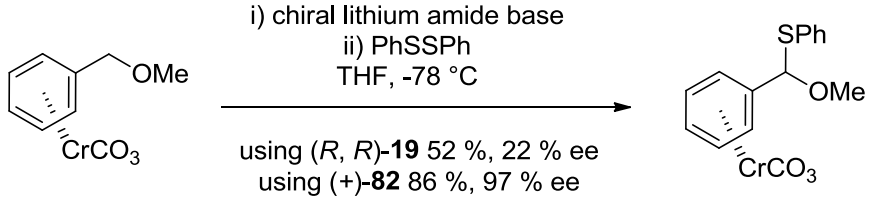
In 1994, several groups reported the asymmetric aromatic functionalization of various tricarbonylchromium(0) complexes using chiral lithium amide bases.[46] Our group found that chiral base (*R*, *R*)-**19** could be used in the presence of trimethylsilyl chloride to synthesise silyated complex (+)-**100** with 84 % ee in 83 % from the tricarbonylchromium(0) complex of anisole (**99**) (Scheme 1.31).



99 (+)-**100**

Scheme 1.31[46a]

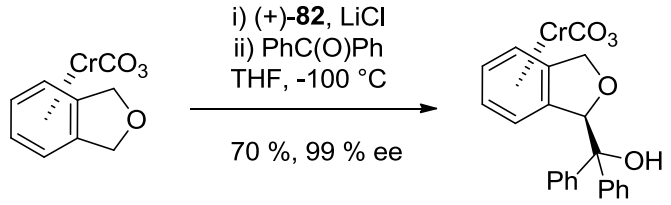
The benzylic functionalization of the tricarbonylchromium(0) complex of benzyl methyl ether (**101**) was explored by Gibson in 1996.[47] Complex **101** was deprotonated using chiral base (*R*, *R*)-**19** and then treated with diphenyl disulfide. This resulted in the formation of α-(phenylsulfenyl)benzyl methyl ether complex (+)-**102** with 22 % ee. This reaction was then carried out using *bis*-lithiated chiral base (+)-**82** and complex (–)-**102** was isolated in 86 % yield with 97 % ee. Further work using methyl iodide as the electrophile revealed that chiral base (+)-**82** produced a complex analogous to **102** with the absolute configuration *R* by comparison to literature data.



101 **102**

Scheme 1.32[47]

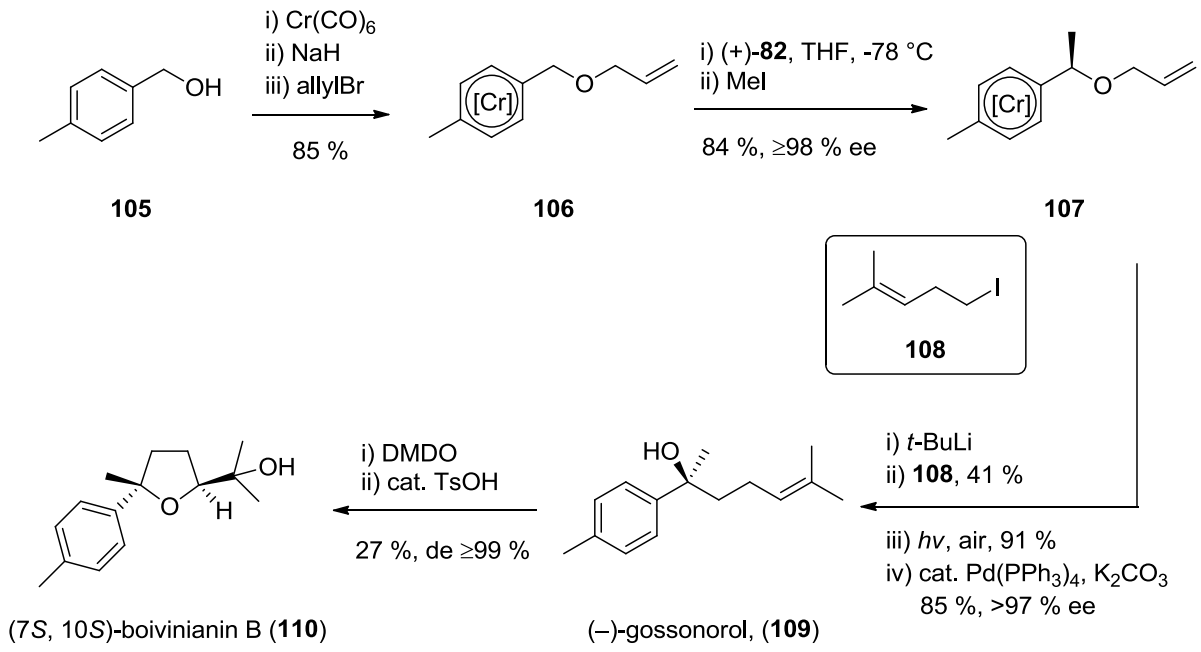
The deprotonation of cyclic ether complex **103** using chiral bases was also examined by our group.[48] It was found that deprotonation of complex **103** using *bis*-lithiated chiral base (+)-**82** followed by addition of benzophenone gave complex (–)-**104** with 99 % ee in 70 % yield. The opposite enantiomer ((+)-**104**) was obtained when (*R*, *R*)-**19** was used; however the enantiomeric excess of the product was found to be 75 % ee.



103 (–)-**104**

Scheme 1.33[48]

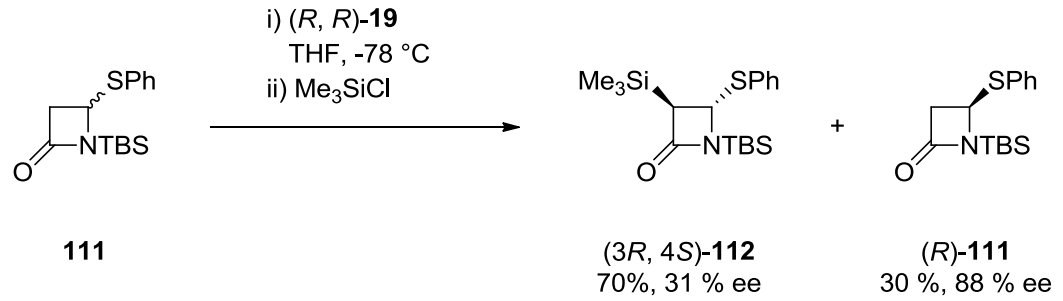
In 2010, Gibson reported the first enantioselective syntheses of gossonorol and boivinianin B, using a chiral base deprotonation of a chromium arene complex to introduce asymmetry.[49] Complex **106** was synthesised in 3 steps from 4-methylbenzyl alcohol (**105**) in 85 % yield and then deprotonated using *bis*-lithiated chiral base (+)-**82** (Scheme 1.34). After methylation with methyl iodide, complex **107** was isolated in 84 % yield with ≥98 % ee. In 3 steps from complex **107**, (–)-gossonorol was obtained in 32 % yield. Following this route using (–)-**82** allowed the synthesis of (+)-gossonorol with >99 % ee. Epoxidation followed by treatment with a catalytic amount of acid allowed the conversion of (–)-gossonorol to (7*S*, 10*S*)-boivinianin B (with ≥97 % ee & ≥99 % de) in 27 % yield.



Scheme 1.34[49]

1.3 Kinetic Resolutions and Other Transformations

It has also been found that chiral lithium amide bases can be used for purposes other than the asymmetric deprotonation of prochiral substrates, such as kinetic resolution of racemic substrates and regioselective deprotonation. It is possible to resolve a racemic substrate using <1.0 equivalent of a chiral base as it will react with one of the enantiomers of the substrate preferentially giving a new product and therefore increasing the enantiomeric excess of the slow reacting enantiomer of the substrate. For example, in 1992 our group reported the resolution of β-lactam (±)-**111** using chiral base (*R*, *R*)-**19**.[50] β-lactam **111** was deprotonated using (*R*, *R*)-**19** and the resulting enolate was quenched with trimethylsilyl chloride to give silylated product **112** (Scheme 1.35). Unreacted starting material was found to be optically active and by varying the amount of (*R*, *R*)-**19** present within the reaction it was found that (*R*)-**111** with 88 % ee was recovered when 70 % conversion to (3*R*, 4*S*)-**112** (with 31 % ee) was achieved.



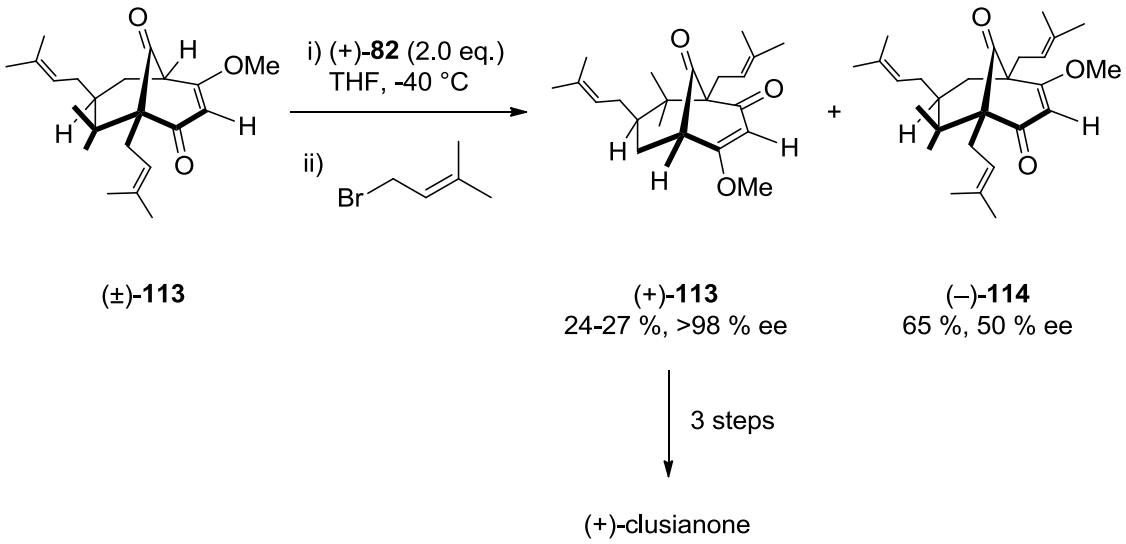
111

(3*R*, 4*S*)-**112**
70%, 31 % ee

(*R*)-**111**
30 %, 88 % ee

Scheme 1.35[50]

In 2007, our group also published the absolute structure determination of the natural product (+)-clusianone and within this report a highly enantiomerically enriched intermediate was obtained using a kinetic resolution.[51] Using 2 equivalents of *bis*-lithiated chiral base (+)-**82**, racemic intermediate **113** was deprotonated and alkylated using prenyl bromide to give intermediate (–)-**114** in 65 % yield with 50 % ee (Scheme 1.36). The unreacted starting material, (+)-**113**, was found to be essentially enantiomerically pure (>98 % ee) and its absolute configuration was determined by *p*-bromobenzylation followed by X-ray crystallography. Intermediate (+)-**113** was then prenylated to give (+)-**114** followed by two further steps to give (+)-clusianone.



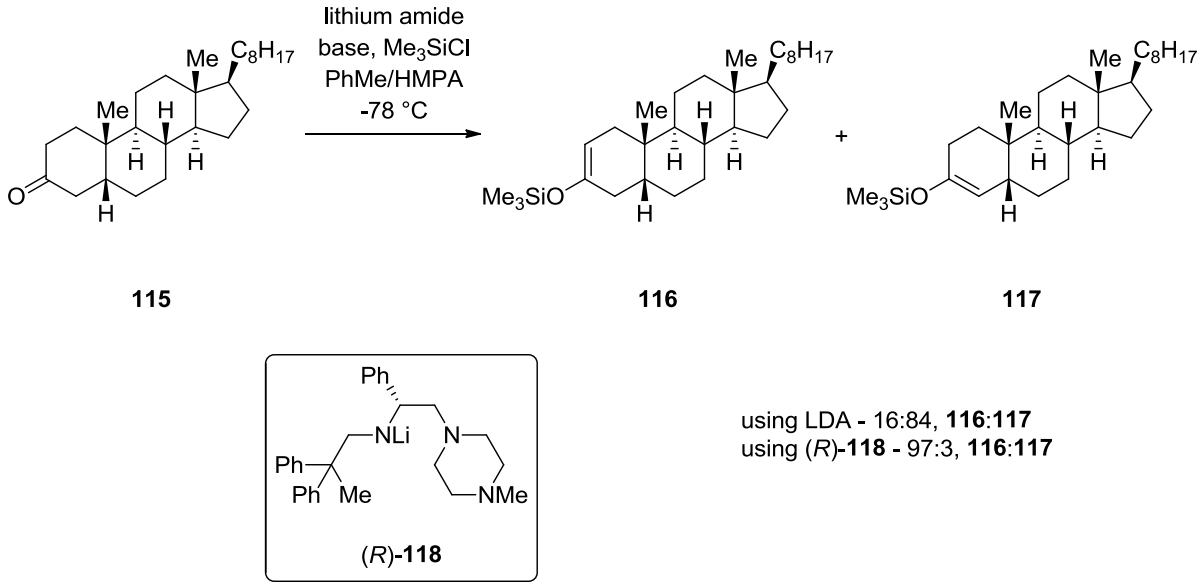
(±)-**113**

(+)-**113**
24-27 %, >98 % ee

(–)-**114**
65 %, 50 % ee

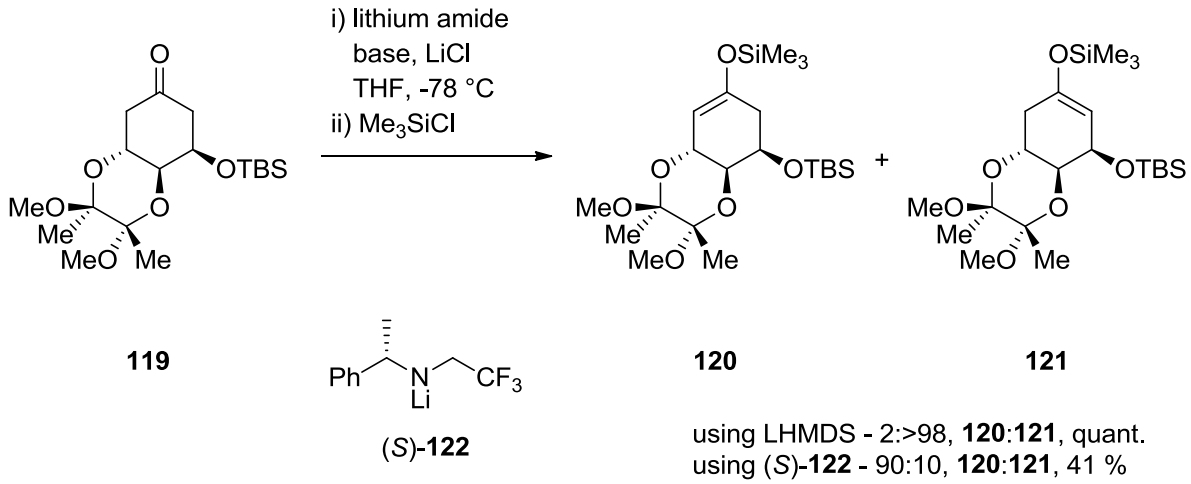
Scheme 1.36[51]

In 1990, Koga reported that chiral base (*R*)-**118** could be used for the regioselective enolisation of certain 3-keto steroids.[52] Deprotonation of ketone **115** using LDA in the presence of trimethylsilyl chloride gave enol silanes **116** and **117** in an 84:16 ratio (Scheme 1.37). It was found that chiral base (*R*)-**118** gave the opposite selectivity; enol silanes **116** and **117** were formed in a 97:3 ratio.



Scheme 1.37[52]

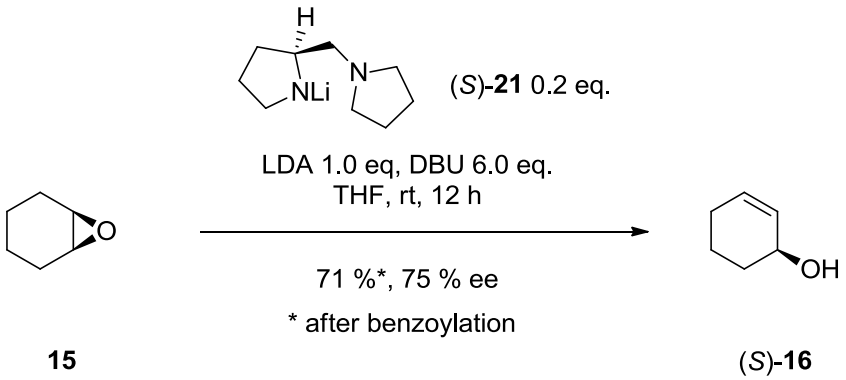
A similar example was reported by O'Brien in 2004.[53] Ketone **119** was deprotonated using LHMDS and following addition of trimethylsilyl chloride enol silane **121** was found to be formed selectively (>98:2, **121**:**120**) (Scheme 1.38). Use of trifluoroethyl substituted chiral base (*S*)-**122** was found to give the opposite regioselectivity; enol silane **120** was formed selectively (90:10, **120**:**121**).



Scheme 1.38[53]

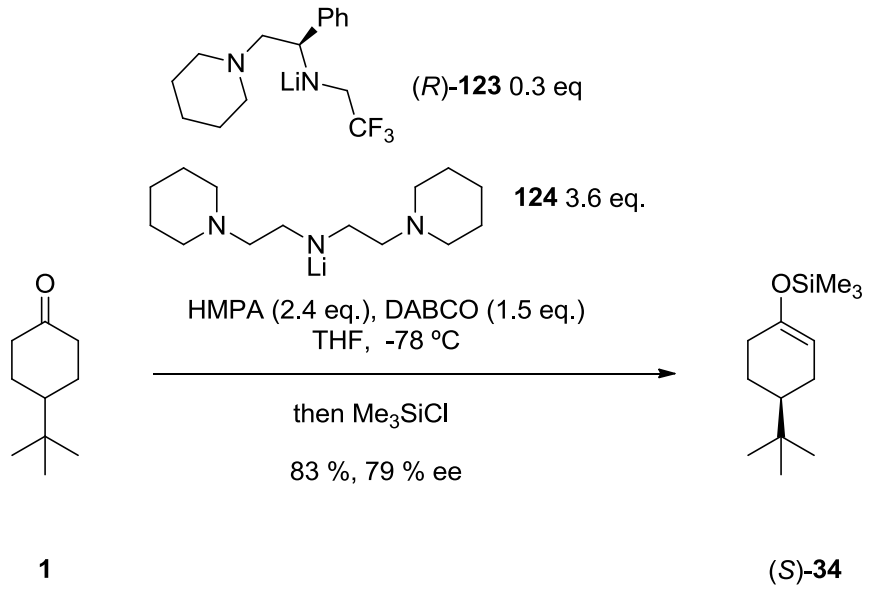
1.4 Sub-stoichiometric Chiral Base Use

The use of sub-stoichiometric amounts of chiral base which are recycled by a bulk achiral base is attractive. Several groups have reported research in this area and the majority of examples concern the asymmetric conversion of epoxides into allylic alcohols. In 1994, Asami reported the synthesis of (*S*)-**16** from cyclohexene oxide (**15**) using 0.2 equivalents of chiral base (*S*)-**21**, 1.0 equivalent of LDA and 6.0 equivalents of DBU (Scheme 1.39).[54] After 12 hours at room temperature, allylic alcohol (*S*)-**16** obtained with 75 % ee. In comparison, when 1.5 equivalents of chiral base (*S*)-**21** was used for this transformation (*S*)-**16** was found to have 79 % ee (Scheme 1.5).[4]



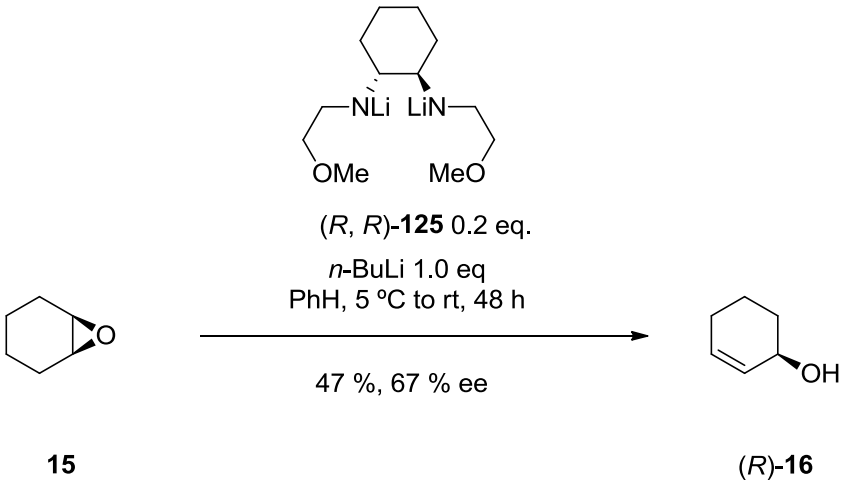
Scheme 1.39[54]

The only successful use of sub-stoichiometric amounts of chiral lithium amide bases for the asymmetric deprotonation of prochiral ketones was reported by Koga in 1996.[55] Enol silane (*R*)-**34** with 79 % ee was synthesised from ketone **1** in 83 % yield using 0.3 equivalents of chiral base (*R*)-**123**, 2.4 equivalents of achiral lithium amide **124**, HMPA and DABCO followed by addition of trimethylsilyl chloride (Scheme 1.40). For comparison, when 1.2 equivalents of chiral base (*R*)-**123** were used, enol silane (*R*)-**34** was obtained in 85 % yield with 81 % ee.



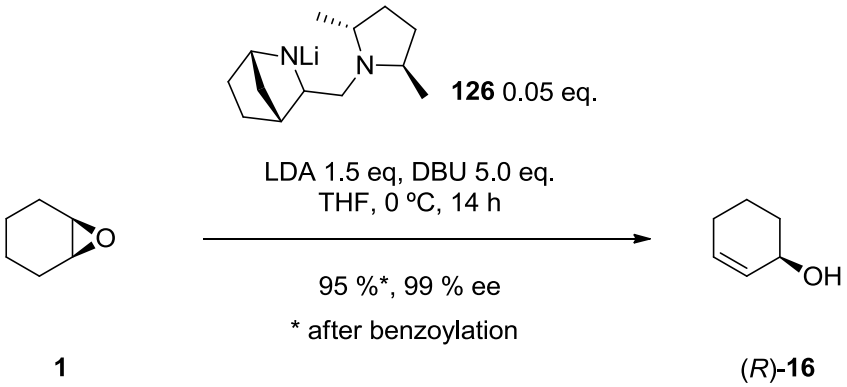
Scheme 1.40[55a]

In 1997, Alexakis reported the transformation of cyclohexene oxide (**1**) to allylic alcohol (*R*)-**16** with 67 % ee using 0.2 equivalents of *bis*-lithiated chiral base **125** and 1.0 equivalent of *n*-butyllithium (Scheme 1.41).[56] Using similar conditions (benzene, 5 °C, 44 h), 1.5 equivalents of *bis*-lithiated chiral base (*R*, *R*)-**125** gave (*R*)-**16** with 87 % ee in 49 % yield. Similar results were reported by Alexakis in 2004 using methyl lithium in place of *n*-butyllithium.[16]



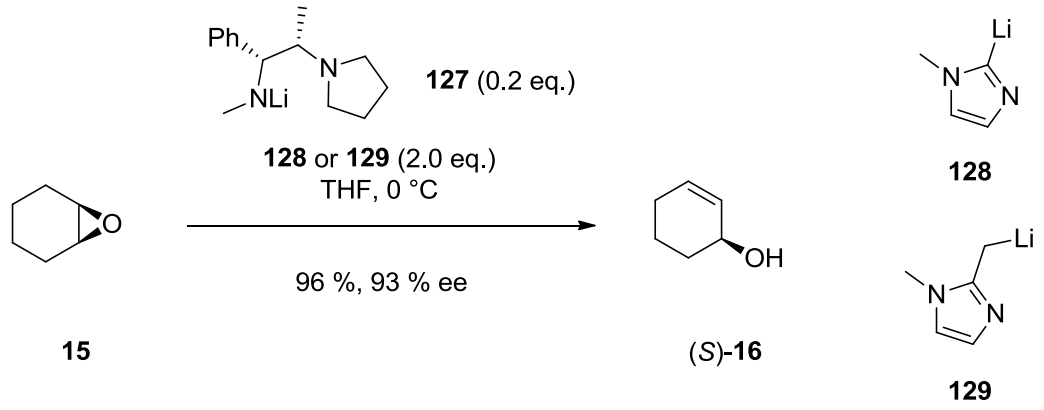
Scheme 1.41[56]

Andersson has also reported the highly enantioselective rearrangement of various epoxides using 5 mol % of chiral base **126**, 1.5 equivalents of LDA and 5.0 equivalents of DBU.[57] For example, allylic alcohol (*R*)-**16** with 99 % ee was synthesised in 95 % yield using this reagent mixture over 14 hours at 0 °C (Scheme 1.42).



Scheme 1.42[57a]

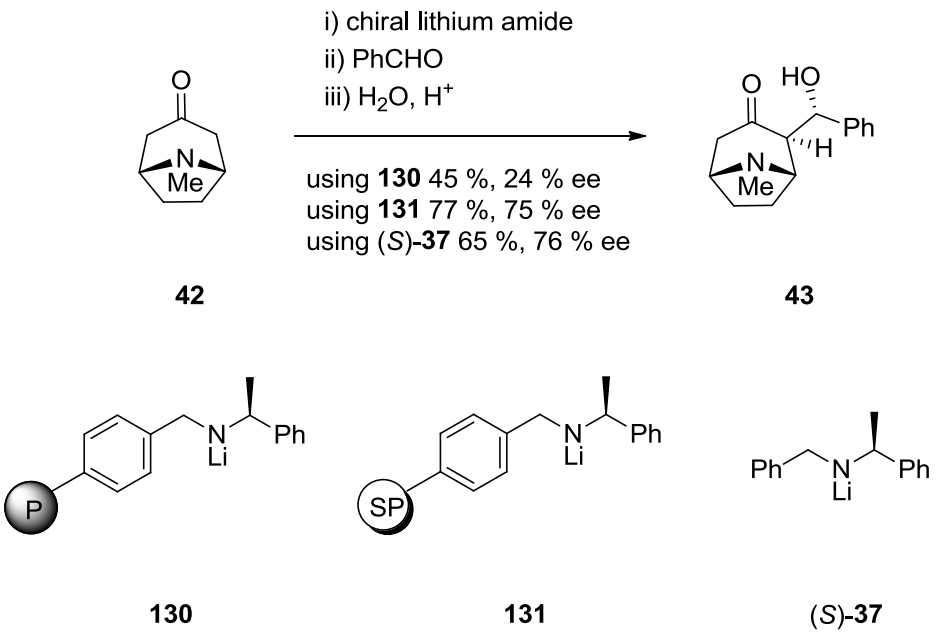
The use of lithiated azoles as bulk achial bases has also been reported by Ahlberg[58] and O'Brien.[59] For example, using 0.2 equivalents of chiral base **127** and 2.0 equivalents of either bulk base **128** or **129** in THF at 20 °C, allylic alcohol (*S*)-**16** was synthesised in 96 % yield with 93 % ee (Scheme 1.43).[58b]



Scheme 1.43[58b]

1.5 Recoverable Chiral Bases

There are several reports in the literature of work carried out to improve the recovery and subsequent purification of the amine precursors of chiral lithium amide bases. In 1999, Majewski reported the use of polymer supported chiral lithium amide bases.[60] Both Merrifield resin and soluble non-crosslinked polymers were used and as would be expected the chiral lithium amide supported on soluble polymers produced better results. The aldol reaction between tropinone (**42**) and benzaldyde was used to test these chiral bases and deprotonation of **42** with Merrifield resin supported chiral base **130** gave aldol product **43** with 24 % ee in 45 % yield (Scheme 1.44). However the equivalent soluble polymer supported chiral base **131** gave aldol product **43** with 75 % ee in 77 % yield, which was comparable to when non-polymeric chiral base (*S*)-**37** was used (65 %, 76 % ee).

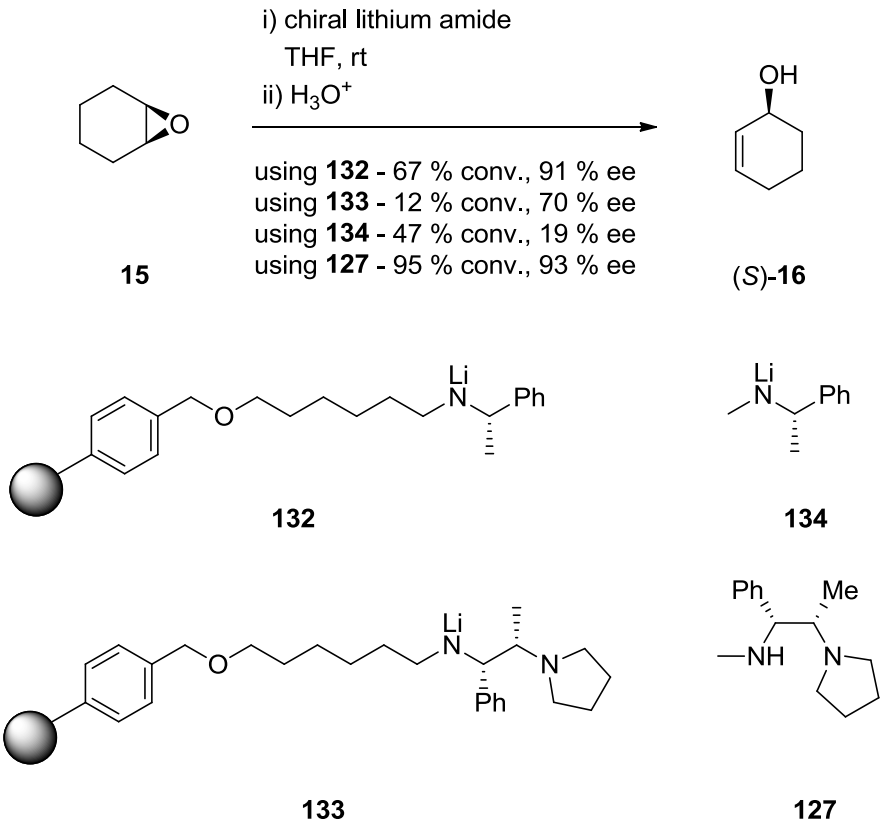


42 **43**

130 **131** (*S*)-**37**

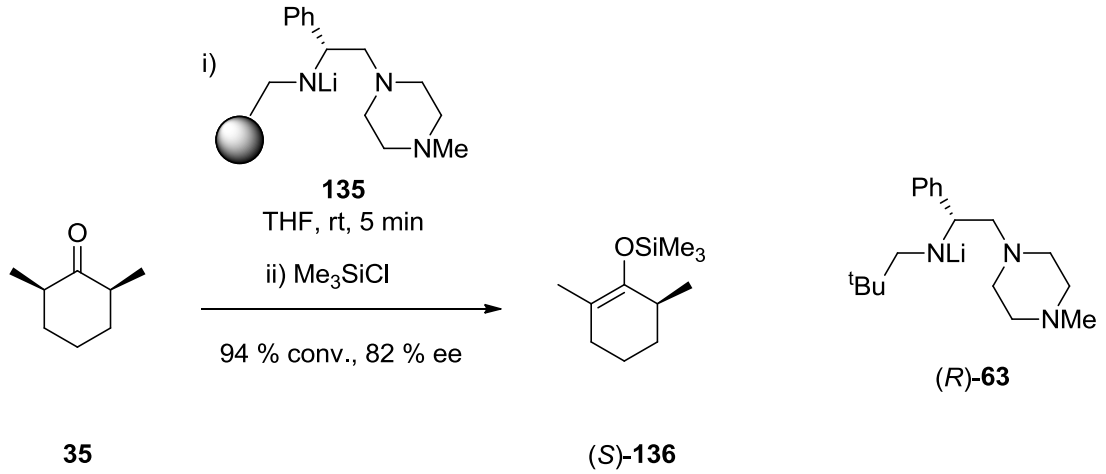
Scheme 1.44[60]

In 2003, Johansson reported the use of Merrifield resin supported chiral lithium amides for the asymmetric conversion of cyclohexene oxide to allylic alcohol **16**.[61] Solid supported lithium amide bases **132** and **133** were found to give allylic alcohol (*S*)-**16** with 91 and 70 % ee respectively (Scheme 1.45). The analogous non-polymeric lithium amide bases **134** and **127** were reported to give allylic alcohol (*S*)-**16** with 19 and 93 % ee respectively.



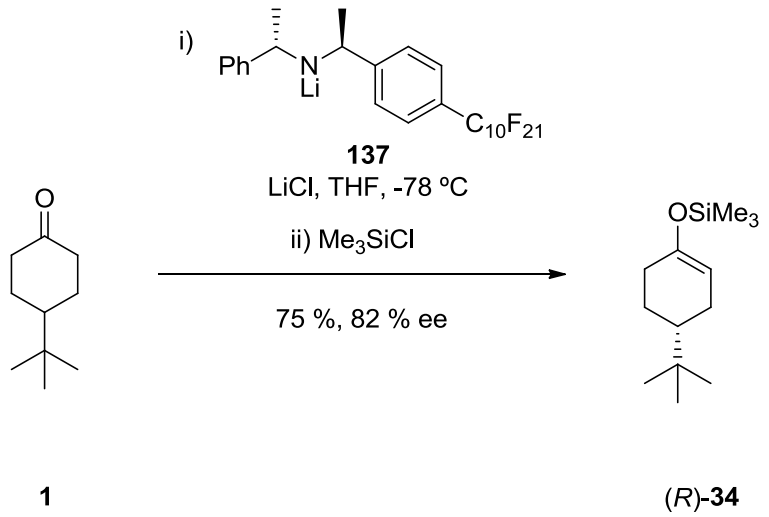
Scheme 1.45[61]

A reusable Merrifield resin supported chiral base was reported by Williard in 2006.[62] It was found that *cis*-2,6-Dimethylcyclohexanone (**35**) could be converted in 94 % to enol silane (*S*)-**136** with 82 % ee using chiral base **135** (Scheme 1.46). This transformation was carried out in 5 minutes at room temperature. The equivalent reaction using non-polymeric chiral base **63** needed to be carried out at -78 °C with 1.0 equivalent of HMPA present (73 %, 96 % ee). It was also reported that solid supported chiral base **135** was recovered and reused 5 times giving enol silane **136** in ≥85 % yield with ≥79 % ee.



Scheme 1.46[62]

The use of a fluorous-tagged chiral lithium amide base has also been reported by Ryu.[63] Fluorous-tagging of a compound should simplify the recovery of the valuable chiral amine by extraction using perfluorohexane and this methodology has been used by several research groups.[64] When fluorous-tagged chiral lithium amide base **137** was used for the deprotonation of ketone **1**, enol silane (*R*)-**34** was produced with 82 % ee in 75 % yield (Scheme 1.47). This result compares favourably to when untagged chiral base (*R*, *R*)-**19** was used for this transformation and enol silane (*S*)-**34** was found to have 83 % ee (Table 1.3, Entry 6). Ryu found that the extraction of the fluorous-tagged amine was tedious using perfluorohexane and it was easier to separate the enol silane product and the amine by flash chromatography using hexane followed by ethyl acetate. In either case the fluorous-tagged amine was recovered in 99 % and when reused in the above reaction was found to give enol silane (*R*)-**34** with 84 % ee in 76 % yield.



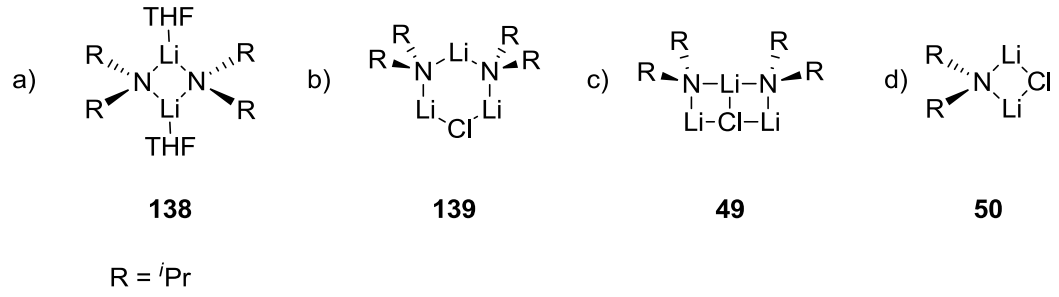
Scheme 1.47[63]

1.6 The Structure of Lithium Amide Bases

Determination of the structure of lithium amides, both in the solid state and in solution, has been carried out. Due to the high positive charge density of Li^+ the formation of organolithium aggregates is widespread. Electrostatic interactions are the main source of binding in these complexes however covalent bonding is also possible. The most stable electrostatic interaction involves lithium with a coordination number of 4, however, due to steric hindrance this arrangement can be prohibited.[65]

The structure of LDA in solution has also been investigated by Collum. In 1989, ^6Li and ^{15}N NMR spectroscopic studies were reported which showed that LDA exists in solution as a cyclic dimer (**138**) (Figure 1.8a).[66] In 1988, Seebach reported the X-ray crystal structure of LDA obtained by Williard from crystals grown in THF.[67] This dimeric structure, with the formula $[(^iPr_2NLi)_2(THF)_2]$, showed two molecules of LDA with coordination of lithium to both nitrogen atoms and a molecule of THF. Lithium chloride was thought to deaggregate LDA and therefore the ^6Li and ^{15}N NMR spectra of LDA in the presence of this salt were obtained. Upon addition of a low concentration of lithium chloride peaks corresponding to a

2:1 LDA/LiCl mixed trimer of the structure **139** or **49** (Figure 1.8b & c) were identified.[68] At higher concentrations of lithium chloride a 1:1 LDA/LiCl mixed dimer (**50**) became evident (Figure 1.8d).

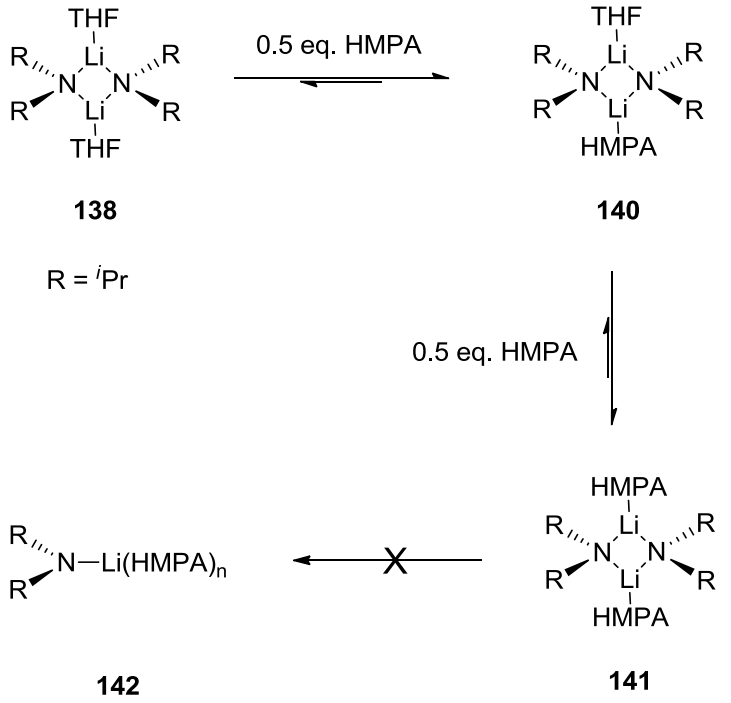


138 **139** **49** **50**

R = ^{i}Pr

Figure 1.8[66, 68]

Hexamethylphosphoramide (HMPA) is another additive which has been shown to increase organolithium reactivities and in the chiral lithium amide area was used especially by Koga to increase levels of enantioselectivity. It was thought that the role of HMPA was similar to lithium chloride; the deaggregation of lithium amide dimers. In 1991, Collum reported ^{6}Li and ^{15}N NMR spectroscopic studies involving the addition of HMPA to LDA (Scheme 1.48).[69] It was found that on addition of 0.5 equivalents of HMPA, mixed solvated LDA dimer **140** was formed. Upon addition of a further 0.5 equivalents of HMPA, cyclic dimer **141** was formed. It was found that the addition of further equivalents of HMPA did not deaggregate LDA as species **142** was not detected. Similar results have been found using both lithium tetramethylpiperidide (LTMP)[69] and lithium hexamethyldisilazide (LHMDS).[70]



Scheme 1.48[69]

As shown in Section 1.2.2, Koga has carried out ^{6}Li and ^{15}N NMR spectroscopic studies involving chiral lithium amide base (*S*, *S*)-**19** and lithium chloride.[25] The results obtained indicated behaviour analogous to that found by Collum.[66] In the absence lithium chloride (*S*, *S*)-**19** exists mainly as a dimer with the structure **138** (Figure 1.8a, R = $CHCH_3Ph$). In the presence of lithium chloride (*S*, *S*)-**19** was found to exist as 1:1 mixed dimer with the structure **50** (R = $CHCH_3Ph$). As with LDA, (*R*, *R*)-**19** has been crystallised as a cyclic dimer with the formula [((*R*, *R*)-**19**)$_2$(THF)$_2$].[71] Lithium amide (*S*, *S*)-**19** has also been crystallised from hexane and a trimeric crystal structure was found with the structure [((*R*, *R*)-**19**)$_3$].[72]

1.8 Project Aims and Plan

The aim of the project was to develop methodology which would allow sub-stoichiometric quantities of a chiral lithium amide base to be recycled *in situ* by an achiral bulk base (Figure 1.9). It was hoped that catalytic chiral lithium amide methodology could be developed which could be applied to ketone substrates and would not require the addition of additives such as HMPA. Initially lithium amide bases, both chiral and achiral, would be tested for the deprotonation of substrates to determine if there was a variation in reaction rate. We then planned to carry out competition reactions between two lithium amide bases in order to find a combination of a chiral and an achiral base which would be suitable for catalysis. If a suitable pair of bases were found then we planned to carry out reactions using sub-stoichiometric amounts of a chiral base and develop this methodology further.

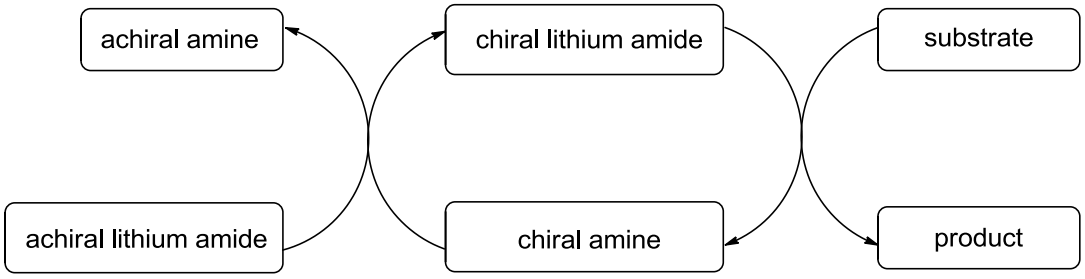
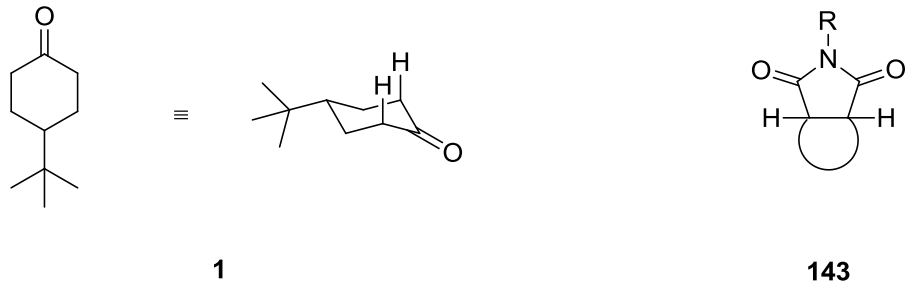


Figure 1.9

Chapter 2: Benchmark Enolisations of Ketone and Imide Systems

Before we set out to develop conditions in which sub-stoichiometric amounts of a chiral base could be used, we first needed to select substrates and test various chiral and achiral lithium amide bases under standard reaction conditions. As 4-*tert*-butylcyclohexanone (**1**) had been used extensively for the study of asymmetric deprotonations it was chosen as a substrate which was representative of conformationally biased cyclic ketones. The other group of substrates which was chosen for this study was bicyclic imides of the general structure **143**. This was because bicyclic imides had recently been shown to be deprotonated highly enantioselectively by chiral lithium amide bases and they are also important precursors for the total synthesis of natural products.

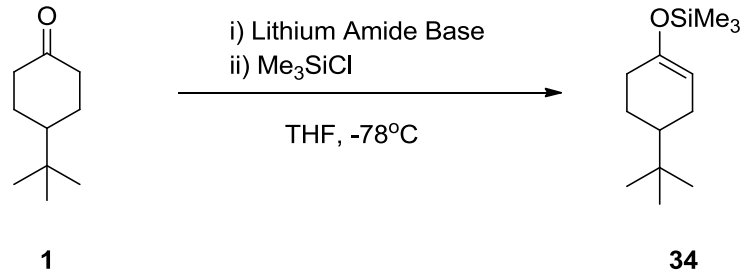


1 **143**

Figure 2.1: Ketone **1** and imide general structure **143** with removable protons highlighted.

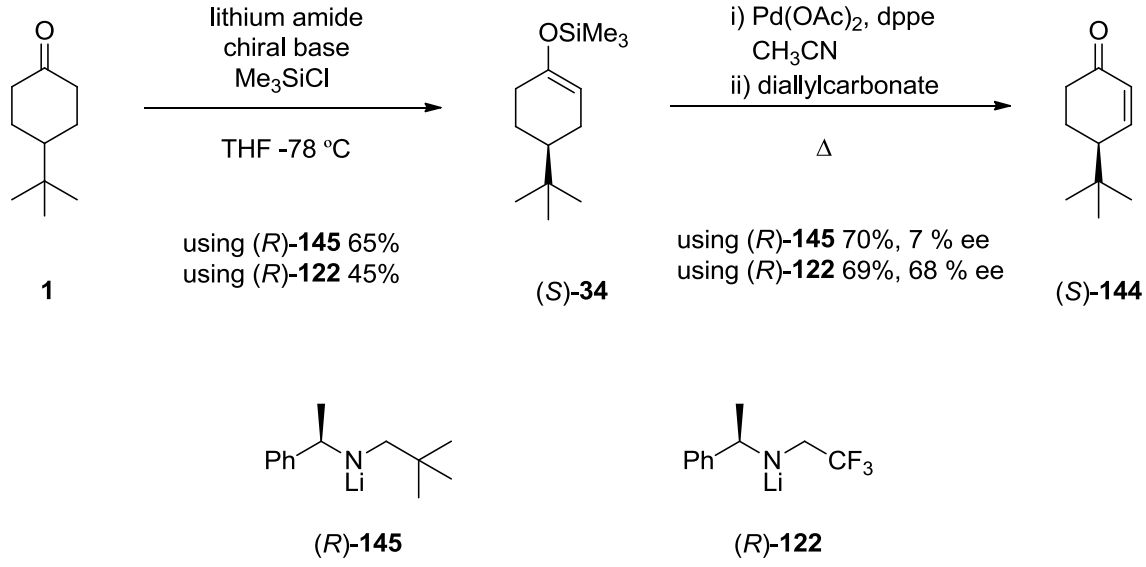
2.1 Enolisation of Ketone 1 with Chiral and Achiral Lithium Amide Bases

Chiral lithium amide bases have been shown to be able to selectively remove one of the two axial protons which are available for deprotonation leading to an enantiomerically enriched enolate. We chose to investigate the use of trimethylsilyl chloride as the electrophile which would lead to the formation of enol silane **34** (Scheme 2.1). This reaction had been used many times within our group and other research groups as a benchmark reaction for the use of chiral bases. The formation of enol silane (**34**) from the intermediate enolate would simplify the analysis of the product as no additional asymmetric centres would be formed.



Scheme 2.1

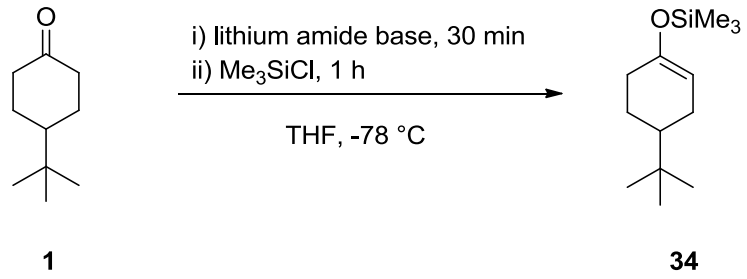
As we had access to a Chiralpak AD HPLC column at the start of this project, samples of enol silane **34** were converted into enone (*S*)-**144** by Saegusa–Ito oxidation as previously reported by our group and Tsuji.[20, 73] Enantiomerically enriched samples of enol silane (*S*)-**34** were synthesised from ketone **1** using chiral bases (*R*)-**145** and (*R*)-**122** in 65 % and 45 % yield respectively (Scheme 2.2). These samples of enol silane (*S*)-**34** were then oxidised to enone (*S*)-**144** in 70 % and 69 % yield. After analysis of the samples by chiral HPLC enone (*S*)-**144** was found to have 7 % ee and 68 % ee respectively. These chiral bases were previously reported to give enol silane (*S*)-**34** with 32 % ee and 89 % ee respectively.[74] It is possible that the optical purity of enone (*S*)-**144** was eroded by deprotonation at the 4-position by base present within the reaction.



Scheme 2.2

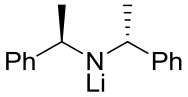
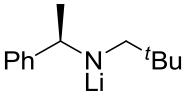
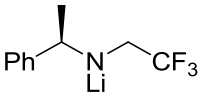
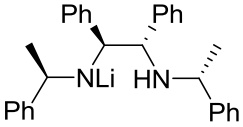
Since conversion of enol silane **34** to enone **144** was not a reliable method for determining the enantiomeric excess, we decided to determine the enantiomeric excess of **34** directly using chiral GC (Chirasil-Dex CB column).[75] In order to determine the effectiveness of our reactions efficiently we decided to submit crude reaction samples for analysis by GC to find the reaction conversion and enantiomeric excess. The reaction conversion was also confirmed by ^{1}H NMR analysis of the crude reaction mixture. We decided to not carry out flash column chromatography on all our samples as we had experienced conversion of enol silane **34** to ketone **1** on silica and alumina. Distillation of each sample using the Kugelrohr apparatus would also become time consuming.

Our standard conditions for the synthesis of silyl enol ether **34** involved the addition of a solution of ketone **1** to a solution of 1.2 equivalents of lithium amide base followed by addition of trimethylsilyl chloride after 30 minutes. After stirring the reaction mixture at -78 °C for 1 hour, the reaction was ended by addition of triethylamine and saturated aqueous sodium bicarbonate solution (Scheme 2.3). The conversion and enantiomeric excess data obtained is summarised in Table 2.1. These reactions were carried out in duplicate and good agreement between the samples was observed.



Scheme 2.3

Table 2.1: Synthesis of enol silane **34** from ketone **1**.[a]

Entry	Base		Eq. LiCl[b]	Conversion[c] (%)	% ee[c] (config.)
1	LDA		0	85	-
2			1.2	100	-
3		**146**	0	39	-
4			1.2	39	-
5	LTMP		0	50	-
6		(*R*, *R*)-**19**	0	99	42 (*S*)
7			1.2	99	81 (*S*)
8		(*R*)-**145**	1.2	73	11 (S)
9		(*R*)-**122**	0	93	44 (*S*)
10			1.2	99	79 (*S*)
11		(+)-**147**	0	98	49 (*R*)
12			1.2	99	58 (*R*)

a The reaction was carried out on a 0.65 mmol scale with 5.0 equivalents of chlorotrimethylsilane at -78°C. *b* Equivalents compared to substrate. *c* Determined by chiral GC using Chiralsil-DEX CB column.

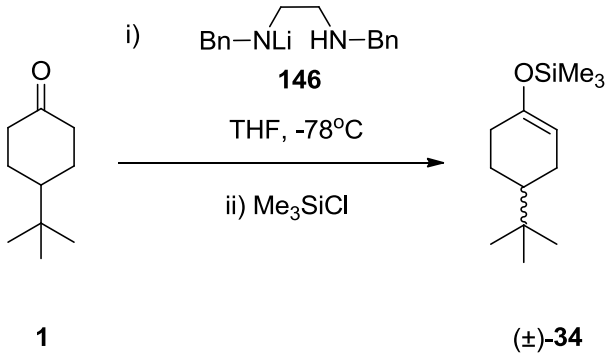
Deprotonation of ketone **1** using LDA gave a reaction conversion of 85 % under these conditions (Entry 1). In the presence of 1.2 equivalents of lithium chloride the conversion was found to be 100% (Entry 2). Mono-lithiated diamine base **146** was used to deprotonate ketone **1** under our standard conditions and conversion to silyl enol ether **34** was achieved in 39 % either in the absence or presence of lithium chloride (Entry 3 & 4). Lithium tetramethylpiperidide (LTMP) was also used in this reaction and conversion to enol silane **34** was found to be 50 % (Entry 5).

Lithium amide chiral base (*R*, *R*)-**19** was used to deprotonate ketone **1** under the above conditions. After analysis of the reaction by GC the conversion to (*S*)-**34** was found to be 99 % and the enantiomeric excess was found to be 42 % (Entry 6). In the presence of lithium

chloride the conversion was also 99 % and (*S*)-**34** was obtained with 81 % ee (Entry 7). Neopentyl substituted chiral base (*R*)-**145** and lithium chloride was found to give poor enantiomeric enrichment (Entry 8). Fluorinated chiral base (*R*)-**122** was also used to deprotonate ketone **1** and we found that conversion to (*S*)-**34** occurred in 93 %. The product was found to have 44 % enantiomeric excess (Entry 9). In the presence of lithium chloride, 99 % conversion to (*S*)-**34** was found to have occurred and the product had an improved enantiomeric excess of 79 % (Entry 10).

Mono-lithiated diamine chiral base (+)-**147** was used for the asymmetric deprotonation of ketone **1**. We found that the reaction proceeded with 98 % conversion to enol silane (*R*)-**34** and this product was found to have 49 % ee (Entry 11). An increased enantiomeric excess of 58 % was observed when lithium chloride was present in the reaction. In this case, ketone **1** was converted to enol ether (*R*)-**34** in 99 % (Entry 12).

The reduced conversion from ketone **1** to **34** using mono-lithiated diamine base **146** was investigated further (Scheme 2.4). A solution of ketone **1** was added to lithium amide **146** and after 30 minutes trimethylsilyl chloride was added. The reaction time between addition of trimethylsilyl chloride and the end of the reaction was varied between 15 and 180 minutes, in order to determine if the yield of **34** could be increased. As shown in Table 2.2, the conversion to enol silane **34** does not seem to follow a trend. After 15 and 45 minutes, conversion to **34** was found to be 50 and 51 % respectively (Entries 1 & 2). As shown above, using our standard reaction conditions conversion to **34** was found to be 39 % (Entry 3). An increased reaction time of 3 hours resulted in an increased conversion of 61 % (Entry 4). An increased quantity of **146** (4.0 equivalents) was also used in our standard reaction method and an increased conversion of 69 % was observed (Entry 5).



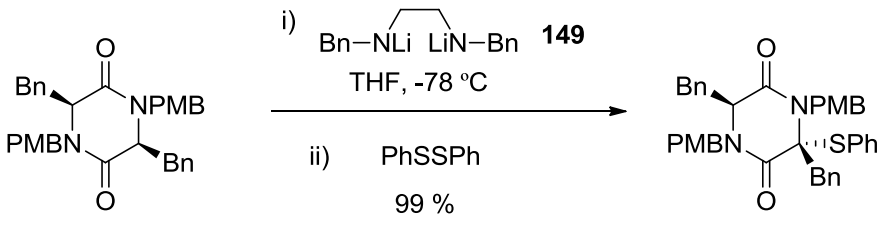
1 (±)-**34**

Scheme 2.4

Table 2.2: Synthesis of **34** using *mono*-lithiated base **146**.

Entry	Eq. **146**	Quench Time (min)	Conversion (%)
1	1.2	15	50
2	1.2	45	51
3	1.2	60	39
4	1.2	180	61
5	4.0	60	69

Bis-lithiated achiral diamine **149** has previously been used within our group for the deprotonation of diketopiperazines (DKP) when other more commonly used achiral lithium amide bases have not been effective.[76] For example, phenylalanine derived DKP (–)-**148** was deprotonated using *bis*-lithium amide **149** and after the addition of diphenyl disulfide, sulfur substituted DKP (+)-**150** was isolated in 99 % yield (Scheme 2.5). When we used *bis*-lithium amide **149** for the synthesis of enol silane **34** from ketone **1**, either a very low conversion was found or only starting material (**1**) was recovered.

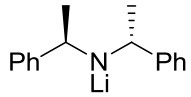
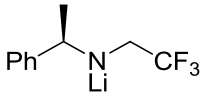
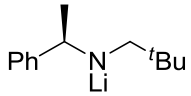
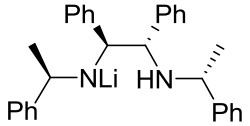


(–)-**148** (+)-**150**

Scheme 2.5[76]

Previously the enantiomeric excess of enol silane **34** has been determined by either measurement of the optical rotation or conversion to other derivatives including enone **144**. In this work the enantiomeric excess was determined by chiral GC. As stated above, the reactions in this work were carried out using an external quench (EQ) procedure. In Table 2.3 the enantiomeric excess data obtained is compared with previously reported values. Our group has previously reported the use of chiral base (*R*, *R*)-**19** in the absence of lithium chloride for the deprotonation of ketone **1**; enol silane **34** was reported to have 23 % ee (Entry 8).[23a] In 1996, Koga and co-workers reported that (*R*, *R*)-**19**-LiCl produced enol silane (*S*)-**34** with 88 % ee (EQ) (Entry 9).[25] Trifluoroethyl substituted chiral base (*R*)-**122** was reported to give enol silane (*S*)-**34** with 89 % ee using the ISQ method in the absence of lithium chloride (Entry 10).[74] No literature examples could be found using (*R*)-**122** and the EQ method which were equivalent to the reactions carried out in this work (Entries 3 & 4). In the same publication, neopentyl substituted chiral base (*R*)-**145** was reported to produce enol silane (*S*)-**34** with 32 % ee using the ISQ method (Entry 11).[74] Within our research group, chiral base (+)-**147** was found to give enol silane (*R*)-**34** with 54 % ee using the ISQ method (Entry 12).[77]

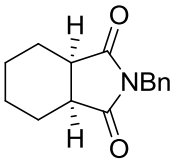
Table 2.3: Comparison of enantiomeric excesses with literature data.

Base		Entry	Eq. LiCl	% ee (config.)	Entry	Lit. % ee (config.)	Lit. Method
	(*R*, *R*)-**19**	1	0	42 (*S*)	8	23 (*S*)[23a]	EQ[23a]
		2[a]	1.2	81 (*S*)	9[b]	88 (*S*)[25]	EQ[25]
	(*R*)-**122**	3	0	44 (*S*)	10	89 (*S*)[74]	ISQ[74]
		4[a]	1.2	79 (*S*)	-	N/A	N/A
	(*R*)-**145**	5[b]	1.2	11 (*S*)	11[c]	32 (*S*)[74]	ISQ[74]
	(+)-**147**	6	0	49 (*R*)	12	54 (*R*)[77]	ISQ[77]
		7[b]	1.2	58 (*R*)	-	N/A	N/A

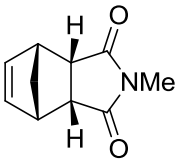
a LiCl present via addition of 2 eq. of *n*-BuLi to HCl salt of chiral amine. *b* LiCl solid added. *c* No LiCl present.

2.2 Enolisation of Imides 151 and 152 with Chiral and Achiral Lithium Amide Bases

The use of chiral lithium amide bases to deprotonate prochiral bicyclic imide substrates has been explored recently and chiral base **147** has been found to produce substituted imide products with extremely high enantioselectivity.[40, 78] We chose two easily prepared imide substrates, simple fused cyclohexane imide **151** and bridged cyclohexene imide **152** (Figure 2.2). Methods for the direct analysis of chiral products derived from such imides had previously been established by our group using chiral HPLC (Chiralcel OD column).[40, 78]



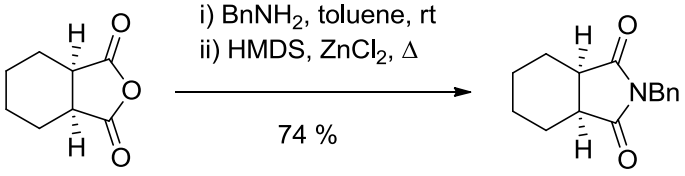
151



152

Figure 2.2: Imides **151** and **152**.

Bicyclic imide **151** was synthesised in one step from commercially available hexahydrophthalic anhydride (**153**) in 74 % yield (Scheme 2.6). Benzylamine was added to a solution of anhydride **153** to give an amic acid intermediate which, upon heating in the presence of hexamethyldisilazane (HMDS) and zinc(II) chloride yielded imide **151**.[79]

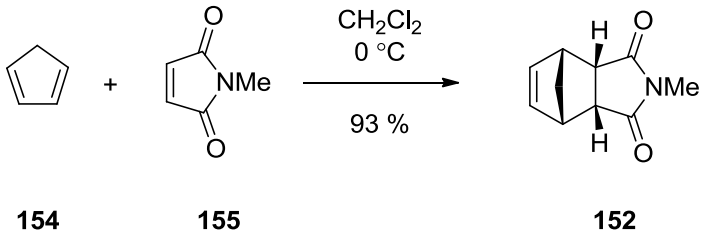


153 **151**

Scheme 2.6

Bridged imide **152** was synthesised in one step from commercially available *N*-methylmaleimide (**155**) and freshly prepared cyclopentadiene (**154**) (Scheme 2.7). Dropwise

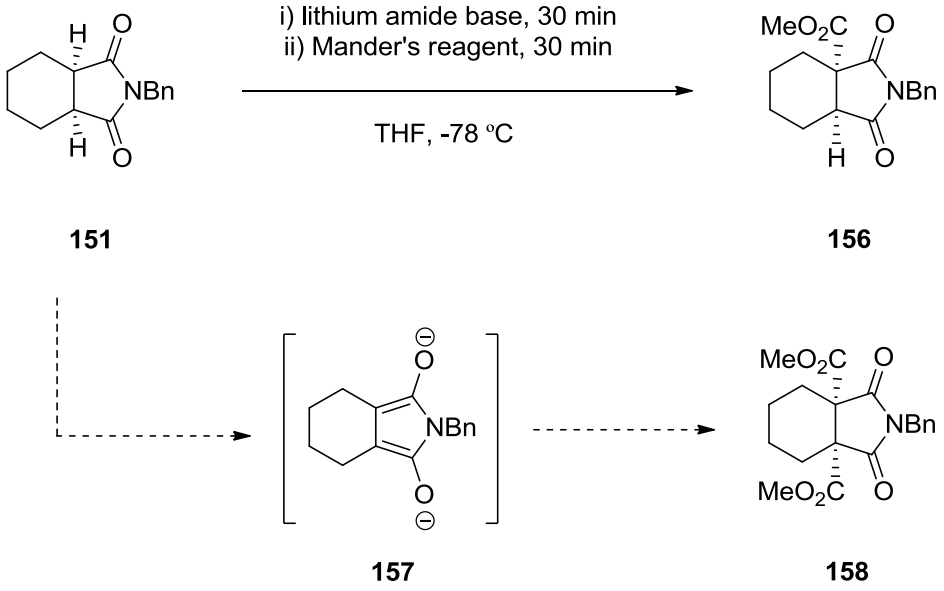
addition of cyclopentadiene (**154**) to a solution of *N*-methylmaleimide (**155**) rapidly produced Diels-Alder product **152** in 93 % yield.[80]



154 **155** **152**

Scheme 2.7

Our standard conditions for the synthesis of ester **156** from bicyclic imide **151** (Scheme 2.8) involved treatment of a solution of **151** with 1.3 equivalents of lithium amide base and after 30 minutes the resulting enolate was quenched with methyl cyanoformate (Mander's reagent). The base solution was added dropwise to the substrate in order to suppress formation of dianion **157** and subsequent formation of diacylated product **158**. After stirring for a further 30 minutes the reaction was ended with the addition of saturated aqueous ammonium chloride solution.



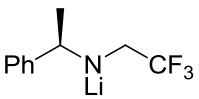
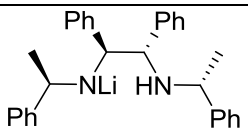
151 **156**

157 **158**

Scheme 2.8

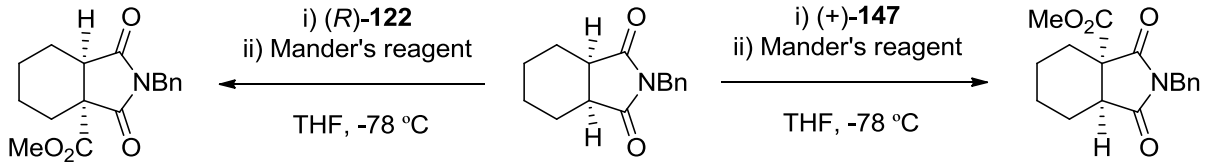
The isolated yield and enantiomeric excess data obtained from the synthesis of ester **156** from imide **151** is summarised in Table 2.4. These reactions were carried out in duplicate, good agreement between the samples was observed and only starting material and product was observed in the crude ^{1}H NMR spectra. Deprotonation of imide **151** with LDA using these conditions gave ester (±)-**156** in only 16 % yield (Entry 1). When 1.3 equivalents of lithium chloride were included within the reaction, ester (±)-**156** was isolated in 43 % yield (Entry 2). It was thought that LDA reacts relatively slowly with the substrate. Increasing the deprotonation time from 30 minutes would allow higher yields of ester **156** to be obtained using LDA. As we were interested in identifying lithium amide bases with contrasting reactivity, LDA may be a candidate for use as a bulk achiral base in a catalytic reaction. Use of *mono*-lithiated diamine base **146**, which we thought of as an achiral analogue of (+)-**147**, gave ester (±)-**156** in 55 % yield (Entry 3). In the presence of lithium chloride, ester (±)-**156** was obtained in 73 % yield (Entry 4).

Table 2.4: Deprotonation of imide **151** followed by acylation with Mander's reagent.[a]

Entry	Base		Eq. LiCl[b]	Yield (%)[c]	% ee[d] (sign of rot.)[e]
1	LDA		0	16	-
2			1.3	43	-
3		**146**	0	55	-
4			1.3	73	-
5		(*R*)-**122**	0	53	35 (+)
6			1.3	71	47 (+)
7		(+)-**147**	0	90	92 (–)
8			1.3	93	97 (–)

a The reaction was carried out on a 0.41mmol scale with 3.0 equivalents of methyl cyanoformate at -78ºC. *b* Equivalents compared to substrate. *c* Isolated yield. *d* Determined by chiral HPLC. *e* Sign of rotation of plane polarised light measured on an automatic polarimeter.

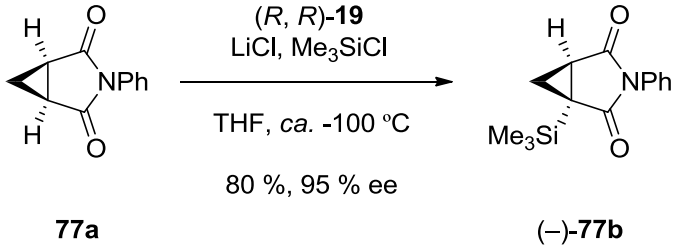
As noted above for the deprotonations of our ketone substrate (**1**), chiral bases (*R*)-**122** and (+)-**147** gave opposite enantiomers of ester **156**. Trifluoroethyl substituted chiral base (*R*)-**122** gave ester (+)-**156** in 35 % ee when used alone and (*R*)-**122**-LiCl was found to give ester (+)-**156** with 47 % ee (Entries 5 & 6). *Mono*-lithiated chiral base (+)-**147** gave ester (–)-**156** with 92 % ee and (+)-**147**-LiCl was found to produce ester (–)-**156** with 97 % ee (Entries 7 & 8). The absolute structures of (+)- and (–)-**156** are tentatively assigned, according to precedent from previous work within our group, as shown in Scheme 2.9.



(+)-**156** **151** (–)-**156**

Scheme 2.9

In 2002, our group reported the use of chiral base (*R*, *R*)-**19** for the deprotonation of prochiral imides.[81] Imide **77a** was deprotonated using (*R*, *R*)-**19** and after silyation with trimethylsilyl chloride (ISQ), (–)-**78b** was isolated in 80 % yield with 95 % ee (Scheme 2.10). The absolute structure was determined by single crystal X-ray analysis (Figure 2.3).



77a (–)-**77b**

Scheme 2.10[81]

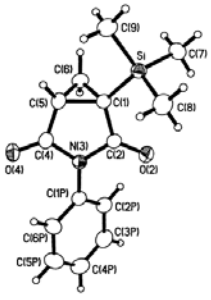
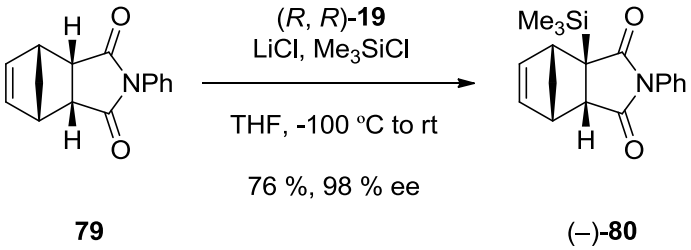


Figure 2.3: X-ray structure of (–)-**77b**.[81]

In the same report silylated product (–)-**80** was synthesised using chiral base (*R*, *R*)-**19** from bridged cyclohexene imide **79** (Scheme 2.11). (–)-**80** was isolated in 76 % yield with 98 % ee

and crystallisation allowed the absolute structure to be determined by single crystal X-ray analysis (Figure 2.4).



79 (–)-**80**

Scheme 2.11[81]

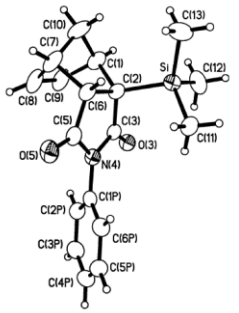
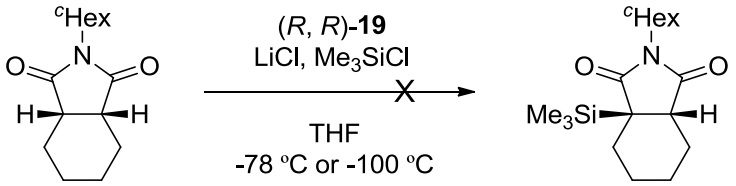


Figure 2.4: X-ray structure of (–)-**80**.[81]

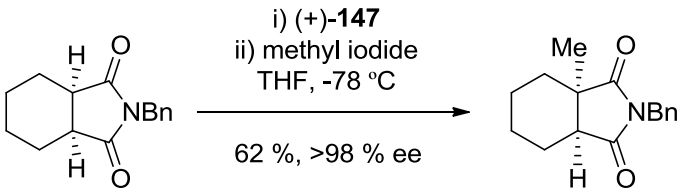
As we knew that chiral base (*R*)-**122** gave the same product enantiomer as (*R*, *R*)-**19** we tentatively assigned the structure of (+)-**156** as shown in Scheme 2.9 based on these imide deprotonations. Several attempts were made to effect the asymmetric deprotonation of imide **151** using (*R*, *R*)-**19**. However, whenever a yield of greater than ~20 % of ester **156** was achieved, the product was found to be racemic. In previous work within our group, deprotonations of the structurally similar imide **159** with LDA or (*R*, *R*)-**19** failed.[82] The silylated product, **160** was not isolated and only starting material was recovered (Scheme 2.12).



159 **160**

Scheme 2.12[82]

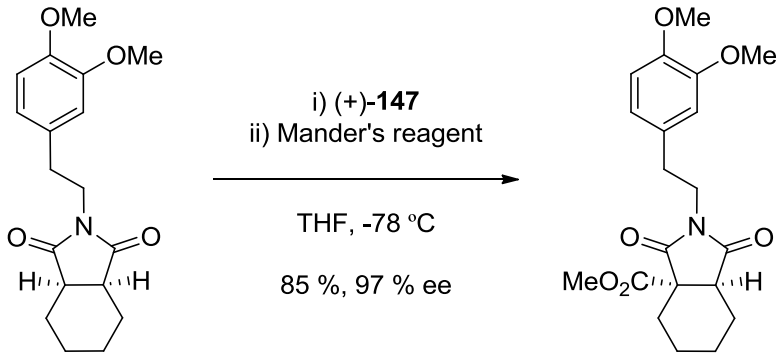
Previously imide **151** had been deprotonated using (+)-**147** and the resultant enolate was quenched using methyl iodide to give methylated imide (–)-**161** (Scheme 2.13).[78] This product was isolated in 62 % yield with >98 % ee.



151 **(–)-161**

Scheme 2.13

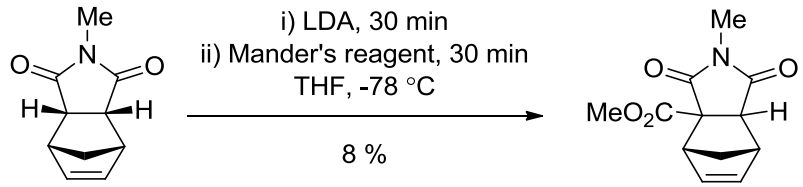
In the same report, structurally similar imide **162** was deprotonated using (+)-**147** and treated with Mander's reagent to give ester (–)-**163** in 85 % with 97 % ee (Scheme 2.14).[78] Ester (–)-**163** was then used in the asymmetric synthesis of the proposed structure of jamtine.



162 **(–)-163**

Scheme 2.14

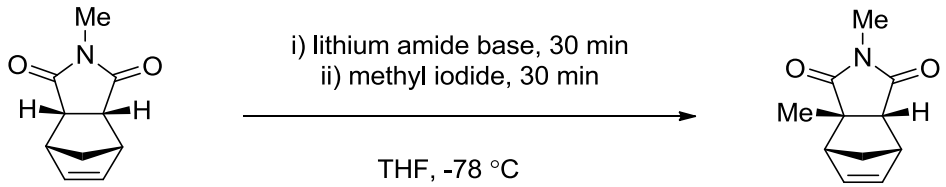
Within this project, ester **164** was synthesised in low yield from imide **152** by deprotonation with LDA and acylation with Mander's reagent (Scheme 2.15). We intended to repeat the above experiments using this transformation; however we found that it was not possible to separate the enantiomers of **164** using the chiral HPLC columns which were available to us. Therefore we did not pursue the synthesis of **164** further.



152 **(±)-164**

Scheme 2.15

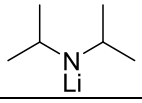
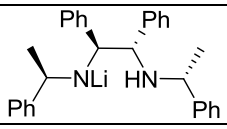
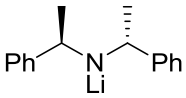
Imide **152** was deprotonated and methylated to give **165**, following a similar procedure to that outlined above. A solution of base was prepared by addition of *n*-butyllithium to a solution of amine in THF and this was added dropwise to a solution of imide **165** at -78 °C, as above, in order to minimise dianion formation. After stirring the reaction mixture at -78 °C for 30 minutes, 3 equivalents of methyl iodide was added in one portion. The reaction mixture was stirred at -78 °C for a further 30 minutes and then quenched by addition of saturated ammonium chloride (Scheme 2.16). The isolated yield and enantiomeric excess data obtained is summarised in Table 2.5.



152 **165**

Scheme 2.16

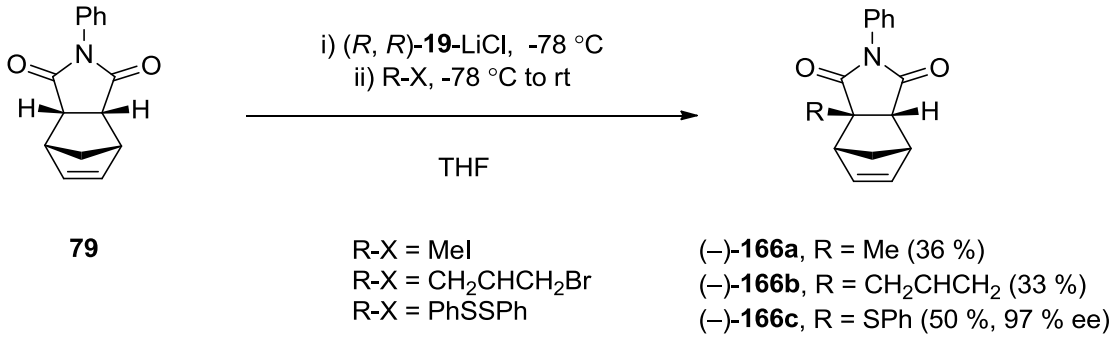
Table 2.5: Deprotonation of imide **152** followed by methylation with methyl iodide.[a]

Entry	Base		Eq. LiCl[b]	Yield (%)[c]	% ee[d] (sign of rot.)[e]
1		LDA	1.2	23	-
2		**146**	-	29	-
3		(+)-**147**	-	38	90 (+)
4		(*R*, *R*)-**19**	1.2	47	92 (–)

a The reaction was carried out on a 0.56 mmol scale with 3.0 equivalents of methyl iodide at -78°C. *b* Equivalents compared to substrate. *c* Isolated yield. *d* Determined by chiral HPLC. *e* Sign of rotation of plane polarised light measured on an automatic polarimeter.

Using a mixture of LDA and lithium chloride (1.2:1.2 eq.) to deprotonate imide **152**, methylated imide (±)-**165** was isolated in 23 % after addition of methyl iodide (Entry 1). A solution of monolithiated achiral diamine **146** (1.1 eq.) was used to deprotonate imide **152** and after methylation of the resultant enolate, the product ((±)-**165**) was isolated in 29 % (Entry 2). Chiral base (+)-**147** (1.3 eq.) was also used in this reaction and the methylated imide product ((+)-**165**) was isolated in 38 % yield with 90 % ee (Entry 3). Finally, a mixture of chiral base (*R*, *R*)-**19** and lithium chloride (1.2:1.2 eq.) was used for the deprotonation of **152** and (–)-**165** was isolated in 47 % yield with 92 % ee (Entry 4). Although we found that it was possible to form **165** in high enantiomeric excess using either chiral base (+)-**147** or chiral base (*R, R*)-**19** and lithium chloride, we decided not to investigate this reaction further because of the low yields of **165** we had obtained. After attempts to increase the yield of product by increasing the deprotonation time, increasing the time between introduction of the electrophile and quenching the reaction and also by increasing the amount of the electrophile we could not reproducibly obtain **165** in high yields. As shown above in Scheme 2.11,

bridged cyclohexene imide **79** has previously been silylated in good yield (76 %) and excellent enantiomeric excess (98 % ee). However the procedure which was used involved warming the reaction mixture from -100 °C to room temperature over 4 hours in order to achieve this result.[81] For the analogous reactions using methyl iodide, allyl bromide and diphenyl disulfide as electrophiles poor results were obtained (Scheme 2.17).[82]



Scheme 2.17[81-82]

As shown in Scheme 2.17, when methyl iodide was added, methylated product **166a** was isolated in 36 %. Introduction of allyl bromide allowed alkylated product **166b** to be isolated in 33 % and diphenyl disulfide gave product **166c** in 50 % yield. The enantiomeric excess of **166c** was determined to be 97 % ee. These three products (**166a-c**) were obtained in low yield despite the reaction mixture being warmed to room temperature and stirred overnight.[81-82]

2.3 Summary of Results

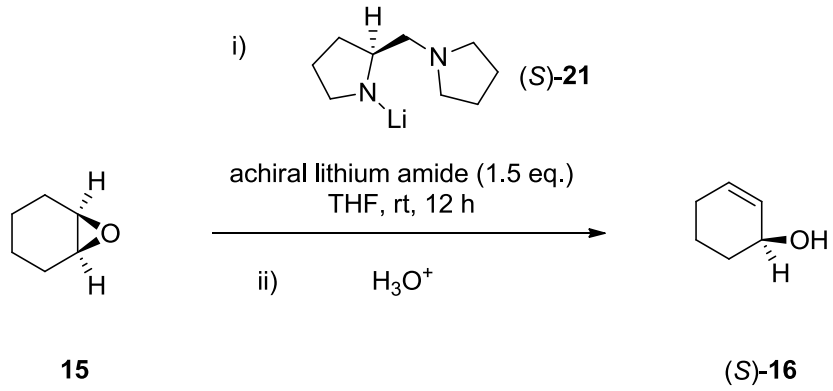
In the case of our ketone substrate, 4-*tert*-butylcyclohexanone (**1**), we found that chiral base (*R*, *R*)-**19** in the presence of lithium chloride gave the best enantioselectivity (81 % ee) for the synthesis of enol silane (*S*)-**34**. The highest enantiomeric excess of enol silane **34** reported for the use of this chiral base was 88 % (EQ, 1.2 eq. LiCl), however this value was derived from optical rotation measurements.[25] Using an *in situ* quench (ISQ) procedure with no added lithium chloride, an enantiomeric excess of 90 % has also been reported for this reaction.[25] From previous results within our own group we knew that chiral base (+)-**147** was not as effective for the asymmetric deprotonation of ketone **1**.[77] When chiral base (+)-**147** and lithium chloride were used, the product enol silane (*R*)-**34**, was found to have only 58 % ee. Trifluorinated chiral base (*R*)-**122** and lithium chloride were found to give enol silane (*S*)-**34** with 79 % ee, comparable to the use of chiral base (*R*, *R*)-**19** and lithium chloride. The previously described effect on the enantioselectivity of the reaction when lithium chloride was added was also observed.[23]

For our imide substrates, high enantioselectivities were found using chiral bases. Ester (–)-**156** was synthesised in high yield and excellent enantiomeric excess (93 %, 97 % ee) using chiral base (+)-**147**. Methylated bridged imide **165** was synthesised in high enantiomeric excess using either chiral base (+)-**147** (38 %, 90 % ee) or (*R*, *R*)-**19** (47 %, 92 % ee) however the isolated yields of this product were consistently low.

Chapter 3: Enolisation of Ketone and Imide Substrates Using Two Lithium Amide Bases

3.1 Literature Examples of Competition Reactions

In order to find reaction conditions where a sub-stoichiometric amount of a chiral lithium amide base could be used in the presence of an achiral regenerating base we needed to carry out competition reactions between two bases in order to gauge differences in the relative rate of deprotonation. Competition reactions have previously been used in the development of catalytic methodology for the deprotonation of *meso*-epoxides. In 1994, Asami reported the first exploration of this area.[54] In the process of identifying suitable achiral bulk bases, cyclohexene oxide (**15**) was deprotonated using various lithium amide bases (Scheme 3.1). When epoxide **15** was deprotonated with only chiral base (*S*)-**21** (1.5 eq.) with DBU additive, allylic alcohol (*S*)-**16** was isolated in 80 % yield with 81 % ee (Table 3.1, Entry 1). When competition reactions using a mixture of chiral base (*S*)-**21** (0.5 eq.) and various achiral lithium amides (1.5 eq.) were carried out, the enantiomeric excess of (*S*)-**16** was reduced (Entries 2-6). When lithium tetramethylpiperidide (LTMP) was used as the achiral base, (*S*)-**16** was essentially racemic (Entry 4). However when LDA and chiral base (*S*)-**21** were used the enantiomeric excess of (*S*)-**16** was found to be 48 % ee (Entry 3). Addition of 2 equivalents of DBU increased the enantioselectivity of the reaction and allylic alcohol (*S*)-**16** was found to have 61 % ee. Allylic alcohol (*S*)-**16** with 74 % ee was isolated when the amount of DBU was increased further to 10 equivalents. It has been shown that DBU was being deprotonated by LDA giving a lithiated species (Li-DBU).[83] It is possible that the chiral lithium amide and Li-DBU then form a heterodimer which is the active species for enantioselective deprotonation.



15 (*S*)-**16**

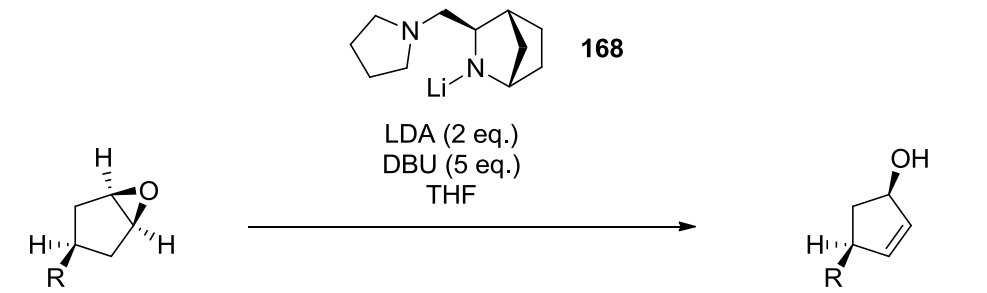
Scheme 3.1[54]

Table 3.1: Synthesis of alcohol (*S*)-**16** from epoxide **15**.[54]

Entry	Eq. (*S*)-**21**	Achiral Li Amide (1.5 eq)	Additive (eq.)	Yield[a] (%)	% ee[b]
1	1.5	-	DBU (1.65)	80	81
2	0.5	Et_2NLi	-	81	37
3	0.5	LDA	-	63	48
4	0.5	LiTMP	-	72	2
5	0.5	LDA	DBU (2)	71	61
6	0.5	LDA	DBU (10)	82	74

a Isolated yield after benzoylation. *b* Determined by the specific rotation value of 2-cyclohexen-1-ol.[6b]

In 2000, Andersson also reported competition reactions between LDA and chiral lithium amides which were performed during further development of catalytic epoxide deprotonation methodology (Scheme 3.2).[57b] A mixture of chiral lithium amide base **168** (1.2 eq.) and LDA (2 eq.) was used to deprotonate **167a** and **167b** (Table 3.2, Entries 1 & 3). Allylic alcohols **169a** and **169b** were found to have 95 % ee. These results show that the rate of deprotonation of the epoxides using chiral base **168** is much higher than the rate of deprotonation using LDA. When a mixture of 20 mol % of **168** and 2 equivalents of LDA was used in these reactions, allylic alcohols **169a** and **169b** were found to have 49 and 67 % ee respectively (Scheme 3.2).



167a R = H
167b R = OTBS

(*R*)-**169a** R = H
(*R*)-**169b** R = OTBS

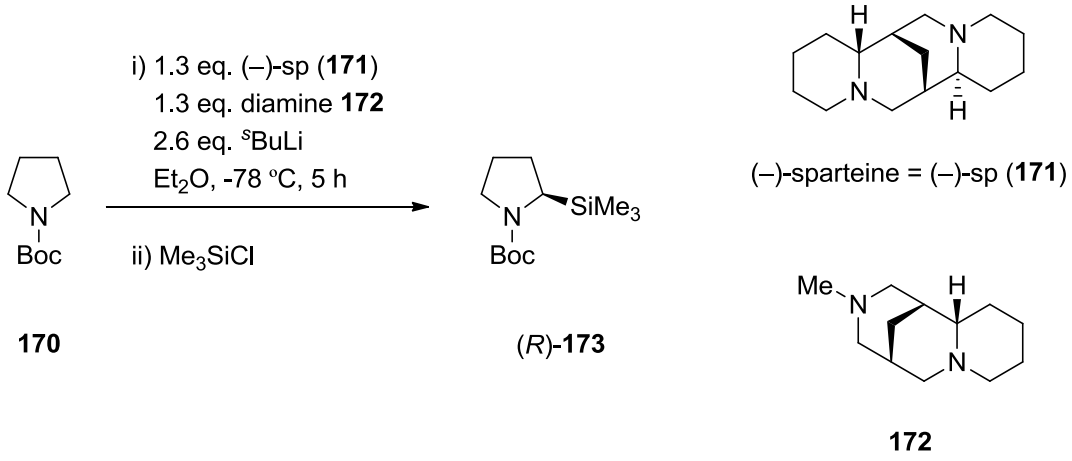
Scheme 3.2[57b]

Table 3.2: Synthesis of alcohol (*R*)-**169** from epoxide **167**.[57b]

Entry	Substrate	Eq. **168**	Yield[a] (%)	% ee[b]
1	**167a**	1.2	78[c]	95
2	**167a**	0.2	67[c]	49
3	**167b**	1.2	85	95
4	**167b**	0.2	60	67

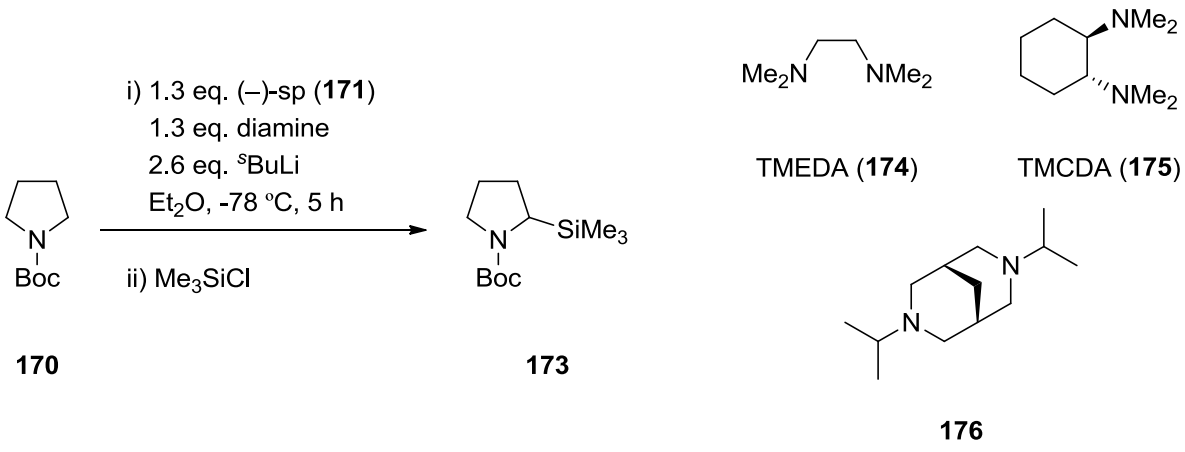
a Isolated yield. *b* Determined by GC (Chiralsil Dex-CB). *c* After benzoylation.

Although not using lithium amides, competition reactions have also been used by O'Brien in the development of catalytic methodology for the asymmetric deprotonaton of *N*-Boc pyrrolidine (**170**).[84] Various chiral and achiral ligands were included alongside (–)-sparteine (**171**) in a 1:1 ratio (1.3:1.3 eq.) with 2.6 equivalents of *sec*-butyllithium also present (Scheme 3.3). These mixtures were used to deprotonate **170** and after 5 hours trimethylsilyl chloride was added to give enantiomerically enriched product **173**. In a normal experiment using (–)-sparteine (**171**) (1.3 eq.) and *sec*-butyllithium (1.3 eq.), (*S*)-**173** was isolated in 87 % yield with 90 % ee (Table 3.3, Entry 1). In a competition reaction between (–)-sparteine (**171**) and diamine **172** ((+)-sparteine surrogate[85]) the product isolated was (*R*)-**173** (80 % ee) (Entry 2), indicating that the *s*-BuLi/diamine **172** complex reacts significantly faster with the substrate than the *s*-BuLi/(–)-sparteine (**171**) complex.



Scheme 3.3[84]

Other selected results from this report are shown in Table 3.3 (Scheme 3.4). The racemic diamines TMEDA (**174**) and *rac*-TMCDA (**175**) were used against (–)-sparteine (**171**) in competition reactions and the products obtained were essentially racemic (Entries 3 & 4). This indicates that these *s*-BuLi/diamine complexes react faster with the substrate than the *s*-BuLi/(–)-sparteine (**171**) complex. When diamine **176** and (–)-sparteine (**171**) were used in a competition reaction, product (*S*)-**173** was isolated with 90 % ee (Entry 5). This shows that the *s*-BuLi/diamine **176** complex reacts slowly with **170** compared to the *s*-BuLi/(–)-sparteine (**171**) complex and this fact is confirmed by the low yield of (±)-**173** obtained when **176** was used alone (5 %).



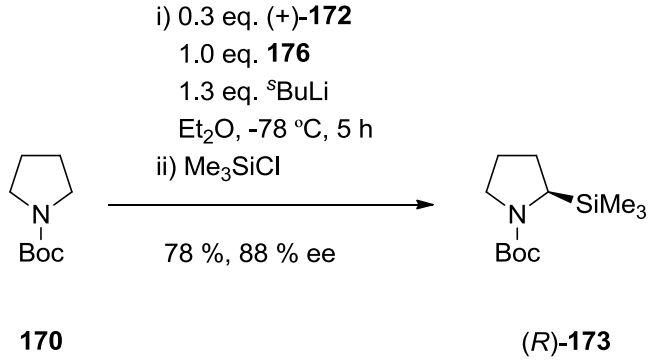
Scheme 3.4[84]

Table 3.3: Synthesis of **173** from N-Boc piperidine (**170**).[84]

Entry	Diamine	Competition Reaction[a]		Normal Reaction[b]	
		Yield[c] (%)	% ee[d] (config.)	Yield[c] (%)	% ee[d] (config.)
1	(–)-sp (**171**)	-	-	87[e]	90 (*S*)
2	**172**	62	80 (*R*)	84[e]	90 (*R*)
3	TMEDA (**174**)	63	4 (*S*)	86	*rac*
4	*rac*-TMCDA (**175**)	57	2 (*S*)	89[f]	*rac*
5	**176**	77	90 (*S*)	5	*rac*

a Competition reaction: (i) 2.6 eq. *s*-BuLi, 1.3 eq. (–)-sp (**171**), 1.3 eq diamine, -78 °C, 5 h; (ii) Me_3SiCl. *b* Normal experiment: (i) 1.3 eq *s*-BuLi, 1.3 eq diamine, -78 °C, 5 h; (ii) Me_3SiCl. *c* Isolated yield after chromatography. *d* % ee determined by chiral GC. *e* Determined previously by O'Brien.[86] *f* Determined previously by Beak.[87]

The results found in this investigation ultimately allowed O'Brien to access catalytic reaction systems, an example of this is shown in Scheme 3.5. Sparteine surrogate (+)-**172** (0.3 eq.), achiral diamine **176** (1.0 eq.) and *sec*-butyllithium (1.3 eq.) were used to produce silylated *N*-Boc pyrrolidine (*R*)-**173** with 88 % ee in 78 % yield.



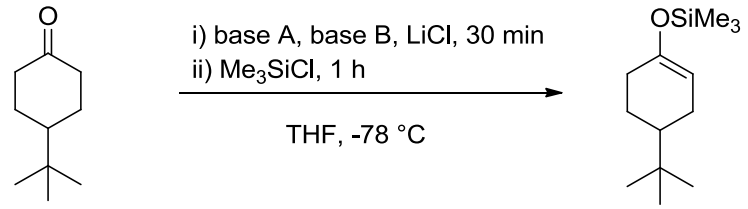
Scheme 3.5[84]

3.2 Deprotonation of Ketone 1 Using a Mixture of Two Lithium Amides

The standard conditions that we used for our competition reactions are as follows. A suspension of an amine and different amine hydrochloride in THF at -78 °C was prepared and 3 equivalents of *n*-butyllithium were added dropwise. The base solution was allowed to warm to 0 °C and then returned to -78 °C. A solution of ketone **1** was added dropwise to the base

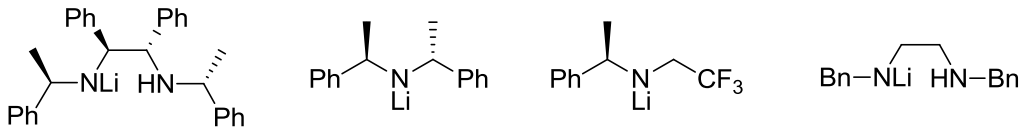
solution. The reaction mixture was stirred at -78 °C for 30 minutes and then trimethylsilyl chloride was added. After stirring the reaction mixture at -78 °C for a further 1 hour the reaction was ended by addition of triethylamine and saturated aqueous sodium bicarbonate solution. The crude product was then analysed by chiral GC in order to determine conversion of ketone **1** to enol silane **34** and the enantiomeric excess of **34**.

The data obtained for the conversion of ketone **1** to enol silane **34** (Scheme 3.6) is summarised in Table 3.4. These reactions were carried out in duplicate and good agreement between the samples was observed.



1 **34**

Scheme 3.6



(+)-**147** (*R*, *R*)-**19** (*R*)-**122** **146**

Figure 3.1

Table 3.4: Synthesis of enol silane **34** from ketone **1** using a mixture of two lithium amide bases.[a]

Entry	Base A (1 eq.)[b]	Base B (1 eq.)[b]	Conversion[c] (%)	% ee[c] (config.)	% ee (Normal Reaction using Base B-LiCl)[d]
1	LDA	(+)-**147**	98	57 (*R*)	58
2	LDA	(*R*, *R*)-**19**	99	36 (*S*)	81
3	LDA	(*R*)-**122**	99	50 (*S*)	79
4	**146**	(*R*, *R*)-**19**	56	11 (*S*)	81
5	**146**	(*R*)-**122**	93	65 (*S*)	79
6	(*R*, *R*)-**19**	(+)-**147**	99	35 (*R*)	58

a The reaction was carried out on a 0.65 mmol scale with 5.0 equivalents of chlorotrimethylsilane at -78°C. *b* Equivalents compared to substrate. *c* Determined by chiral GC using Chiralsil-DEX CB column. *d* From Table 2.1.

As shown in Table 3.4 when a 1:1:1 mixture of LDA, *mono*-lithiated chiral base (+)-**147** and lithium chloride was used, enol silane (*R*)-**34** was found to have 57 % ee (Entry 1). In comparison with when (+)-**147**-LiCl was used alone (58 % ee, Table 2.1, Entry 12), it appears that the presence of LDA does not affect the enantioselectivity of the reaction. It is possible that the chiral base (+)-**147** has a rate of deprotonation which is much greater than LDA, however other situations are possible and will be discussed further (*vide infra*). LDA was also used in competition with C_2-symmetric chiral base (*R*, *R*)-**19** and trifluoroethyl containing chiral base (*R*)-**122**; enol silane (*S*)-**34** was found to have 36 and 50 % ee respectively (Entries 2 & 3). By comparing these values to the equivalent values obtained when the chiral bases and lithium chloride were used alone (81 & 79 % ee, Table 2.1, Entries 7 & 10) we can see that the presence of LDA has lowered the enantioselectivity of the reaction.

Achiral *mono*-lithiated diamine base **146** was also reacted with ketone **1** in competition with chiral bases (*R*, *R*)-**19** and (*R*)-**122**; enol silane (*S*)-**34** was found to have 11 % and 65 % ee respectively (Entries 4 & 5). As above the enantioselectivity of the reactions are reduced

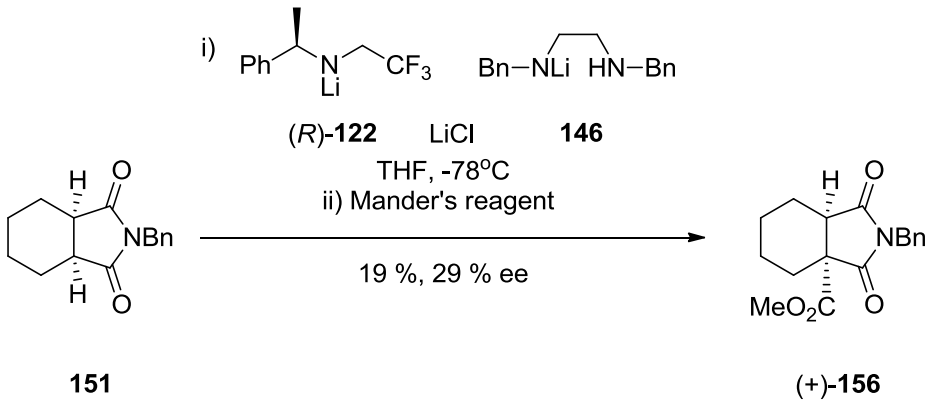
compared to when the respective chiral bases were used alone. A competition reaction was also performed between two chiral bases. As we knew that chiral bases (*R*, *R*)-**19** and (+)-**147** gave opposite enantiomers of enol silane **34**, this reaction would allow us to qualitatively measure the difference in the rates of deprotonation of these two bases. Enol silane (*R*)-**34** was obtained and found to have 35 % ee (Entry 6). Therefore chiral base (+)-**147** has a greater rate of deprotonation than chiral base (*R*, *R*)-**19**.

3.3 Deprotonation of Imide 151 Using a Mixture of Two Lithium Amides

The standard conditions that we used for our competition reactions involving imide **151** are as follows. A suspension of an amine and different amine hydrochloride in THF at -78 °C was prepared and 3 equivalents of *n*-butyllithium were added dropwise. The base solution was allowed to warm to 0 °C and then added dropwise to a solution of imide **151**. As stated in Chapter 2, the base solution was added slowly to the substrate in order to limit the formation of dianion **157** and the resulting undesired diacylated product **158**. The reaction mixture was stirred at -78 °C for 30 minutes and then methyl cyanoformate was added. After stirring the reaction mixture at -78 °C for a further 30 minutes the reaction was ended by addition of saturated aqueous ammonium chloride solution. The product (**156**) was isolated after flash column chromatography and a sample was analysed by chiral HPLC in order to determine the enantiomeric excess. These reactions were carried out in duplicate and good agreement between the samples was found.

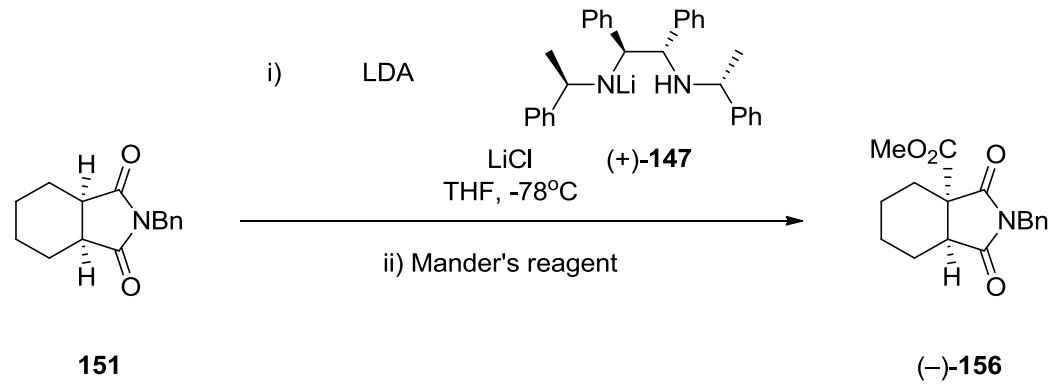
A solution of mono-lithiated base **146**, chiral base (*R*)-**122** and lithium chloride (1:1:1) was prepared and used to deprotonate imide **151**. After treatment with Mander's reagent, ester (+)-**156** was isolated in 19 % yield with 29 % ee (Scheme 3.7). As the use of chiral base (*R*)-**122** and lithium chloride alone gave a product with an enantiomeric excess of 47 % ee (Table 2.4,

Entry 6) we assume that the two bases within this reaction were deprotonating the substrate at a similar rate.



Scheme 3.7

Ester (–)-**156** was also synthesised using a mixture of LDA, mono-lithiated diamine chiral base (+)-**147** and lithium chloride (1:1:1) (Scheme 3.8). The product was isolated in 89 % yield with >99 % ee (Table 3.5, Entry 1). This reaction was also repeated without the addition of lithium chloride. A 1:1 mixture of LDA and chiral base (+)-**147** was prepared and used to deprotonate imide **151**. After addition of the electrophile, the ester product was isolated in 65 % yield with 87 % ee (Entry 2). We also used a mixture of LDA, mono-lithiated diamine chiral base (+)-**147** and lithium chloride in a 2:2:2 ratio to deprotonate imide **151** and after treatment with Mander's reagent the product ((–)-**156**) was isolated in 73 % yield with >99 % ee (Entry 3). The reaction was also carried out with 0.65 equivalents of both mono-lithiated diamine (+)-**147** and LDA present (no LiCl) and the product was isolated in 69 % with 75 % ee (Entry 4). The fact that these products were enantiomerically enriched shows that LDA must deprotonate the substrate at a much slower rate than chiral base (+)-**147**.



151 (–)-**156**

Scheme 3.8

As we had seen such high enantiomeric excesses when an achiral base was present and reasoned that (+)-**147** was deprotonating the substrate much faster than LDA, we performed some inital experiments to test if sub-stoichiometric amounts of chiral base could be regenerated *in situ* at -78 °C by LDA. As shown in Table 3.5 (Entries 5-7), the reactions were carried out using 0.75, 0.5 and 0.3 equivalents of chiral base (+)-**147** and 1 equivalent of LDA. It did not appear that the chiral base was being regenerated within these reactions because, as the amount of chiral base (+)-**147** present at the start of the reaction was decreased so did the isolated yield and enantiomeric excess of the product.

Table 3.5: Deprotonation of **151** with LDA/(+)-**147** mixture followed by acylation with Mander's reagent[a]

Entry	(+)-**147**:LDA:LiCl[b]	Yield (%)[c]	% ee[d] (α)[e]
1	1:1:1	89	99 (–)
2	1:1:0	65	87 (–)
3	2:2:2	73	99 (–)
4	0.65:0.65:0	69	75 (–)
5	0.75:1:0	48	72 (–)
6	0.5:1:0	42	53 (–)
7	0.3:1:0	33	32 (–)
8	0.75:1:1	50	97 (–)
9	0.5:1:1	46	58 (–)
10	0.3:1:1	35	83 (–)

a The reaction was carried out on a 0.41mmol scale with 3.0 equivalents of methyl cyanoformate at -78ºC. *b* Equivalents compared to substrate. *c* Isolated Yield. *d* Determined by Chiral HPLC. *e* Sign of rotation of plane polarised light measured on an automatic polarimeter.

We also carried out these reactions with 1 equivalent of lithium chloride present within the base mixture (Table 3.5, Entries 8-10). As the amount of chiral base (+)-**147** was reduced from 0.75 to 0.3 we observed that the isolated yield of the product decreased. When 0.75 and 0.3 equivalents of (+)-**147** were used the enantiomeric excess of the isolated product was relatively high, compared to the equivalent reactions without lithium chloride (Entries 5 & 7). In the reaction using 0.5 equivalents of (+)-**147**, the enantiomeric excess of the product was found to be 58 %, which was close to the value found for the equivalent reaction without lithium chloride (Entry 6).

From the results shown in Table 3.4 we can see that the rate of deprotonation of the substrate by chiral base (+)-**147** is faster than LDA (Entries 1-4). We hoped that by carrying out

reactions involving sub-stoichiometric amounts of chiral base (+)-**147** and stoichiometric amounts of LDA that the chiral base would be recycled and high enantioselectivity would be retained. However in the experiments we perfomed the yield of the product decreased as the amount of chiral base (+)-**147** was reduced.

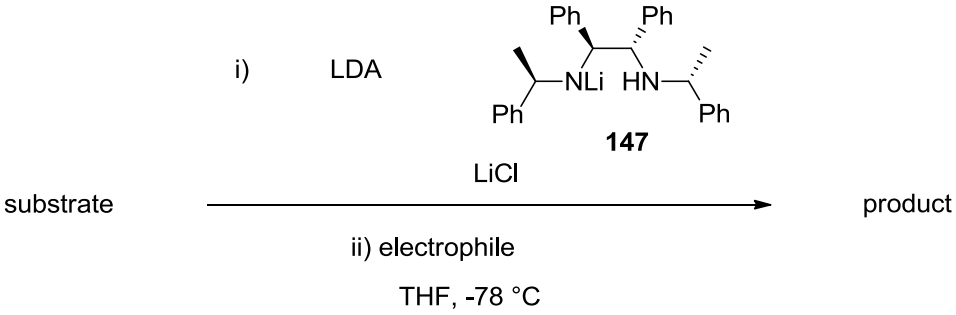
3.4 Summary and Conclusions

In summary, we have carried out competition reactions using various lithium amide bases which we have been studying. Chiral diamine base (+)-**147** has been found to have a much higher rate of deprotonation compared to LDA as enantiomerically enriched products were formed (with ees comparable to when (+)-**147** is used alone). This mixture of (+)-**147** and LDA (1:1) was found to be effective for the deprotonation of both ketone **1** and imide **151**. When enol silane (*R*)-**34** was formed from ketone **1** it was found to have an enantiomeric excess of 57 % ee (Table 3.4, Entry 1) and when imide **151** was deprotonated and acylated, the ester formed ((–)-**156**) was found to have 99 % ee (Table 3.5, Entry 1). The enantiomeric excesses when chiral base (+)-**147**-LiCl was used alone were 58 % ee and 97 % ee respectively.

A competition reaction between two chiral bases ((*R*, *R*)-**19** and (+)-**147**) was also performed in which (+)-**147** was found to have a greater relative rate of deprotonation (Table 3.4, Entry 6). Ketone **1** was deprotonated using this mixture and because the enol silane product which formed was (*R*)-**34** we knew that lithium amide (+)-**147** had a greater rate of deprotonation than lithium amide (*R*, *R*)-**19**. Monoamine chiral bases (*R*, *R*)-**19** and (*R*)-**122** were also found to compete well against achiral bases as the products isolated were enantiomerically enriched (Table 3.5, Entries 1-3). However the enantiomeric excess of the product was reduced compared to when the chiral base was used alone.

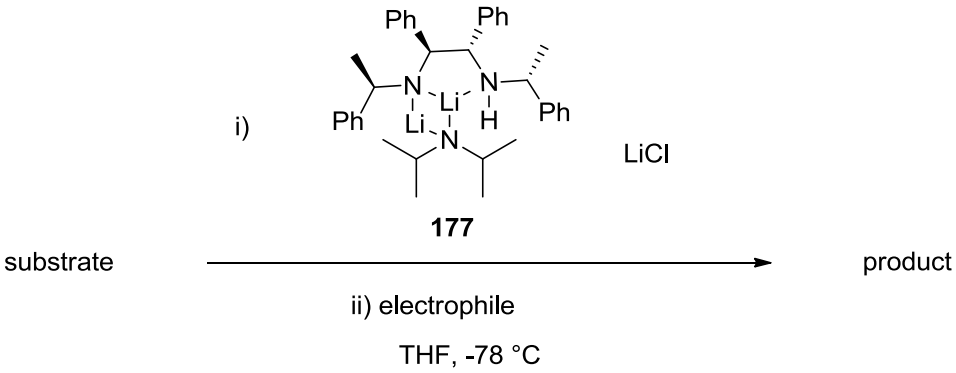
A key requirement for catalytic chiral base methodology is establishing a pair of lithium amide bases with vastly different reaction rates, one achiral and one chiral. In order to maintain enantioselectivity within the reaction the chiral base would need to have a much greater rate of deprotonation of the substrate compared to the achiral base. We have found that LDA and chiral base (+)-**147** satisfy these conditions. When a 1:1:1 mixture of LDA-(+)-**147**-LiCl was used in either of our test reactions, the enantioselectivity was found to be equal to, or slightly higher than, when (+)-**147** is used alone. Three rationalisations for this result are proposed:

1. LDA and (+)-**147** are reacting with the substrate independently.



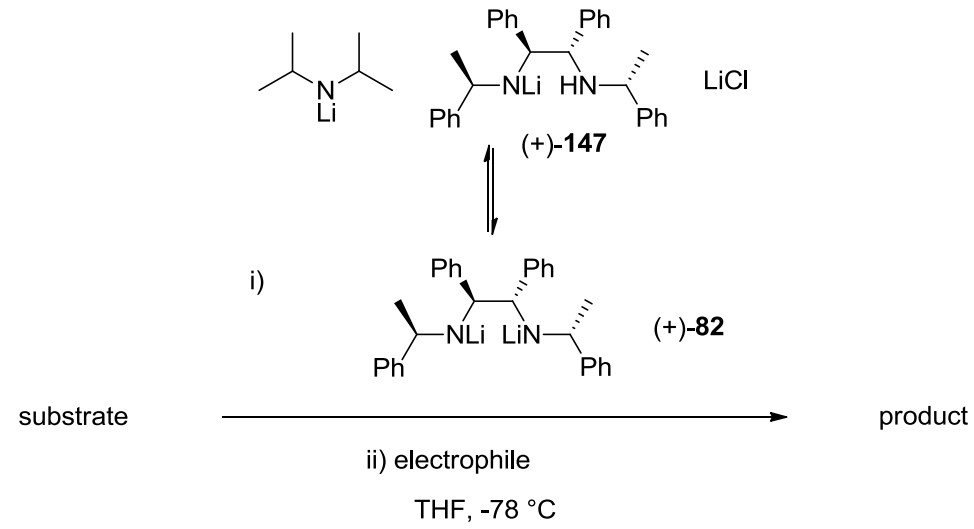
Scheme 3.9

2. LDA and (+)-**147** are forming a mixed dimer (**177**) which retains enantioselectivity.



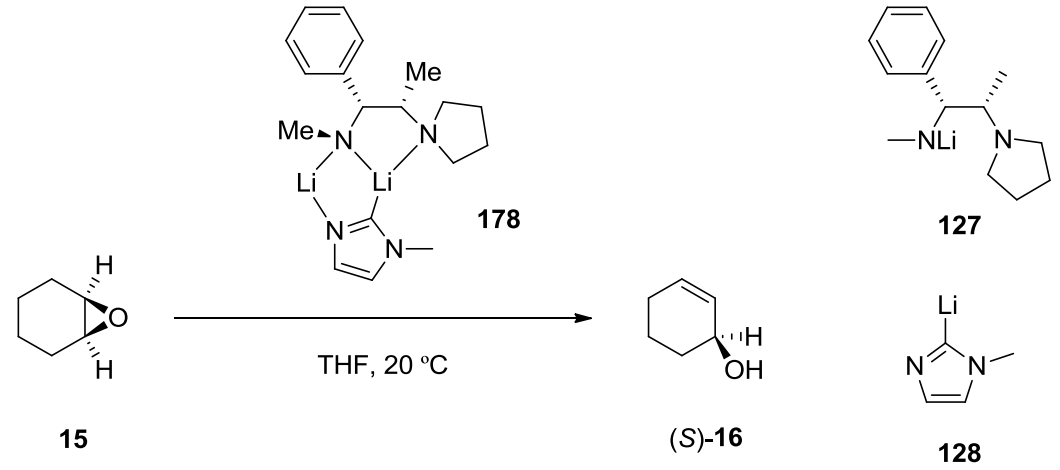
Scheme 3.10

3. LDA is donating lithium to (+)-**147** to allow *bis*-lithium amide base **82** to form.



Scheme 3.11

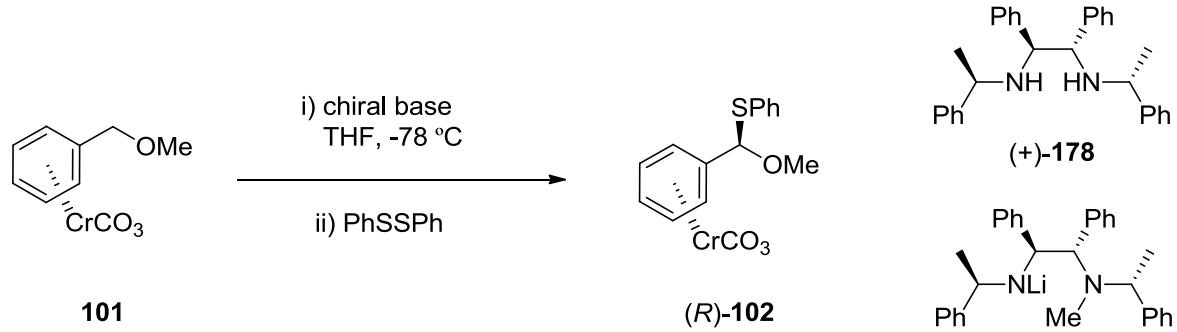
As we have seen in Chapter 2 for the deprotonation of our imide substrate (**151**), LDA-LiCl gave a lower yield of ester **156** (43 %) than (+)-**147**-LiCl (93 %) over the standard reaction time (30 min). This may be evidence to support situation 1 (Scheme 3.9), however the use of these two bases for the deprotonation of ketone **1** gave enol silane **34** in similar conversions (100 and 99 % conv.). It is also possible that situation 2 (Scheme 3.10) is taking place, mixed dimer **177** is the active species which is deprotonating the substrate. Ahlberg and co-workers reported that a mixture of chiral base **127** and 2-lithium-1-methylimidazole (**128**) (1:1) was used to deprotonate epoxide **15** and generate allylic alcohol (*S*)-**16** with 96 % ee (Scheme 3.12).[88] When 20 mol % of chiral base **127** was used with 2 equivalents of 2-lithium-1-methylimidazole (**128**), allylic alcohol (*S*)-**16** was isolated with 93 % ee. Use of LDA in place of **128** resulted in a reduced enantiomeric excess of 22 % which led them to believe that the combination of **127** and **128** was special. Investigation of this mixture by ^{1}H, ^{6}Li and ^{13}C NMR led Ahlberg to believe that heterodimer **178** was formed rather than the homodimer of **127**.



Scheme 3.12[88]

The third situation which may be possible (Scheme 3.11), is that LDA and (+)-**147** are in an equilibrium which favours the formation of *bis*-lithium chiral base (+)-**82**. In 1999, Gibson and O'Brien put forward the hypothesis that *mono*-lithiated chiral base (+)-**147** may not be effective as a chiral base and it is actually *bis*-lithiated chiral base (+)-**82** which is the highly selective reagent which is present.[89] Diamine (+)-**178** was deprotonated with *n*-butyllithium in varying ratios and the resulting chiral base mixture was used to deprotonate chromium arene **101** before addition of diphenyl disulfide to give adduct (*R*)-**102** (Scheme 3.13). As shown in Table 3.6 when 1.1 equivalents of diamine (+)-**178** was treated with between 2.2 and 0.275 equivalents of *n*-butyllithium, the enantioselectivity of the reaction is retained, although as expected, the yield of (*R*)-**102** diminished as the amount of *n*-butyllithium was reduced (Entries 1-4). When the quantity of *n*-butyllithium was kept constant at 1.1 equivalents and the amount of diamine (+)-**178** was reduced from 1.1 to 0.55 equivalents the result was essentially identical but when 0.275 equivalents of (+)-**178** was used a poor yield and enantiomeric excess was observed (Entries 2, 5 & 6). *N*-methylated chiral base **179** was also used to deprotonate **102** and the product ((*R*)-**102**) was found to have 40 % ee. This led Gibson and O'Brien to postulate that *mono*-lithiated chiral base (+)-**147** may not be effective as a chiral base and it is actually *bis*-lithiated chiral base (+)-**82** which is deprotoning **101**.

They assumed that (+)-**147** is not as selective as (+)-**82** and that "there is a ready exchange of lithium cations between all the nitrogen sites in the system" and stated that if these assumptions were not correct then the enantiomeric excesses of (*R*)-**102** would not have been as high as those observed (Entries 2-5). Entry 6 was explained as deprotonation of **101** by 0.275 equivalents of (+)-**82** occurring concurrently with competing non-enantioselective deprotonation of **101** by *n*-butyllithium.



101 (*R*)-**102**

Scheme 3.13[89]

Table 3.6: Synthesis of (*R*)-**102** from complex **101**.[89]

Entry	Eq. *n*-BuLi	Eq. Diamine (+)-**178**	Yield **102** (%)	ee (%)	Recovered **101** (%)
1	2.2	1.1	95	98	0
2	1.1	1.1	96	95	0
3	0.55	1.1	60	92	40
4	0.275	1.1	21	96	67
5	1.1	0.55	88	96	0
6	1.1	0.275	64	73	10

With regard to our competition reaction using LDA and chiral base (+)-**147**, we are currently unsure which of the three situations is taking place. ^{6}Li and ^{15}N NMR studies are currently planned to determine whether mono-lithiated chiral base **147**, mixed dimer **177** or *bis*-lithiated chiral base **82** is the predominant species.

Chapter 4: Lithium Exchange Reactions

4.1 Introduction

As stated in the previous chapter, two conditions need to be met in order to develop catalytic chiral lithium amide base methodology. Firstly, a chiral base and achiral base need to be found where the rate of deprotonation of the chiral base is much faster. Secondly the achiral base must deprotonate the conjugate chiral amine at the reaction temperature (-78 °C) in order to regenerate the chiral lithium amide *in situ*. We will describe the next type of reaction as a "Lithium Exchange Experiment" because when the reaction was analysed the result gave us a qualitative indication of the equilibrium position of lithium between the two secondary amine species present (Figure 4.1).

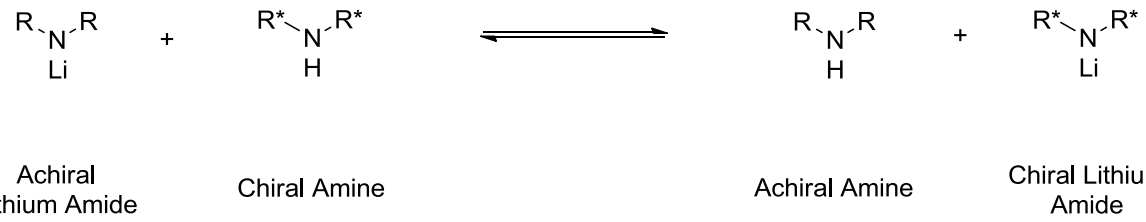
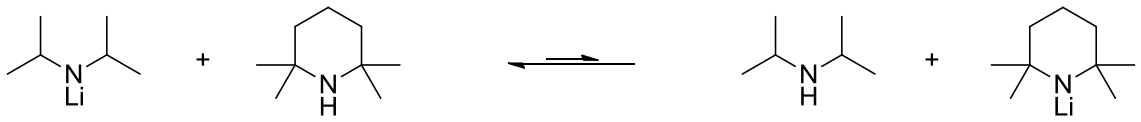


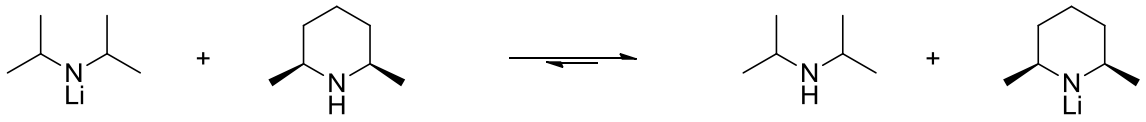
Figure 4.1

Previous work in this area started with a report by Fraser in 1982.[90] Lithium exchange experiments were used to determine the order of acidity of various bases. The ^{13}C resonances of neutral and lithiated amines were determined and used to identify the species present within the equilibrium mixtures. A mixture of LDA and tetramethylpiperidine (TMP) was prepared and after equilibrium was reached identifiable signals for each of the four species shown in Scheme 4.1 were observed. The intensities of these peaks allowed the equilibrium constant to be determined ($K = 0.026 \pm 0.003$) and thus $\Delta pK_A = 1.6 \pm 0.05$. This showed that LDA is 1.6 pK_A units less basic than lithium tetramethylpiperidide (LTMP).



Scheme 4.1[90]

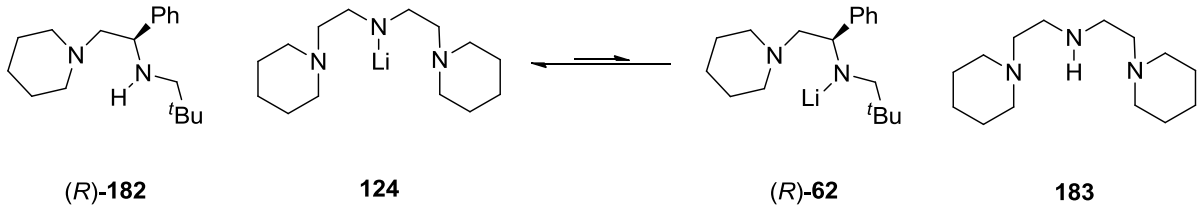
This experiment was also repeated using LDA and *cis*-2,6-dimethylpiperidine (**180**) (Scheme 4.2). The equilibrium constant was found to be K = 2.9 ± 0.5 which corresponds to ΔpK_A = 0.5 ± 0.05. This showed that LDA is 0.5 pK_A units more basic than lithium *cis*-2,6-dimethylpiperidide (**181**). Therefore the order of acidities of these three amines was found to be *cis*-2,6-dimethylpiperidine (**180**) > di*iso*propylamine (DIPA) > tetramethylpiperidine (TMP).



Scheme 4.2[90]

In 1996, Koga reported hydrogen-lithium equilibrium experiments using triamine base **124** and chiral bases (*R*)-**62** and (*R*)-**123**.[55a] The ^{6}Li- and ^{15}N-NMR spectra of [^{6}Li, $^{15}N_2$]-(*R*)-**62** and [^{6}Li, $^{15}N_2$]-(*R*)-**123** had previously been determined by Koga and showed that in THF-d_8 in the presence of HMPA-d_{18} (2 eq.) they exist in chelated monomer form.[91] The ^{1}H NMR spectrum of a solution containing a mixture of lithiated triamine base **124** (2 eq.) and (*R*)-**182** (1 eq.) at room temperature showed that only (*R*)-**182** was present and no (*R*)-**62** had formed. A mixture of (*R*)-**62** (2 eq.) and triamine **183** (1 eq.) was also prepared. The ^{1}H NMR spectrum of this mixture showed that (*R*)-**182** and (*R*)-**62** were present in a 1:1 ratio. This shows that lithium-hydrogen exchange is possible between these two bases, however the

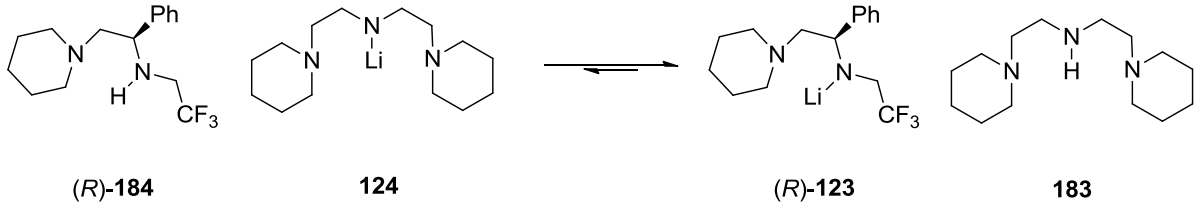
formation of (*R*)-**182** and **124** is favoured. The rationalisation given for the equilibrium in Scheme 4.3 being towards the left was that in (*R*)-**62** the lithium is di-coordinated and in **124** the lithium is tri-coordinated.



(*R*)-**182** **124** (*R*)-**62** **183**

Scheme 4.3[55a]

Koga then prepared a solution of (*R*)-**184** (1 eq.) and **124** (2 eq.) and the room temperature ^{1}H NMR spectrum was obtained. It showed that from the initial mixture (*R*)-**123** had formed and no (*R*)-**184** remained. A solution of (*R*)-**123** (2 eq.) and **183** (1 eq.) was also prepared and the ^{1}H NMR spectrum showed the presence of (*R*)-**123** and the absence of (*R*)-**184**. Therefore it was stated that the equilibrium shown in Scheme 4.4 is towards the right.



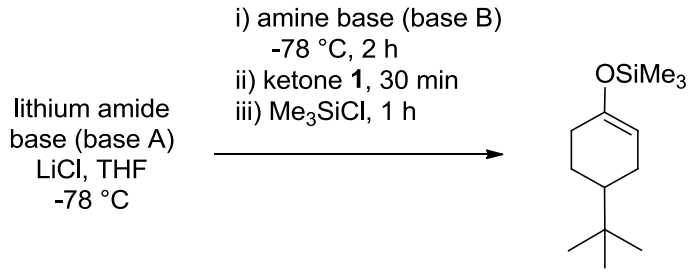
(*R*)-**184** **124** (*R*)-**123** **183**

Scheme 4.4[55a]

The rationalisation given for this was that the effect of the increased coordination of lithium in **124** was overcome by the increased acidity of the amine proton in (*R*)-**184** (compared to the acidity of the amine proton in (*R*)-**182**). The electron-withdrawing effect of the trifluoroethyl group within amine (*R*)-**184** causes the acidity of the amine proton to be greater. The pK_A of (*R*)-**182** has been calculated to be 35.0 and the pK_A of (*R*)-**184** has been found to be 27.0.[92] The above reactions were repeated by Koga at -78 °C, as this is the usual reaction temperature, and the same results were found.[55b]

4.2 Deprotonation of Ketone 1 Using a Mixture of a Lithium Amide and an Amine

The standard conditions that we used for our lithium exchange reactions are as follows. A suspension of an amine hydrochloride in THF at -78 °C was prepared and 2 equivalents of *n*-butyllithium were added dropwise. The base solution was allowed to warm to 0 °C and then cooled to -78 °C. A solution of a different amine in THF was then added to this base solution and the mixture was stirred at -78 °C for 2 hours. A solution of ketone **1** in THF was then added dropwise to the base mixture and after 30 minutes trimethylsilyl chloride was added. The reaction mixture was then stirred at -78 °C for a further 1 hour and the reaction was ended by addition of triethylamine and saturated aqueous sodium bicarbonate solution. The crude product was then analysed by chiral GC in order to determine conversion of ketone **1** to enol silane **34** and the enantiomeric excess of **34**. The data obtained using this method is summarised in Table 4.1.



34

Scheme 4.5

185 (*R*)-**186**

Figure 4.2

Table 4.1: Synthesis of enol silane **34** from ketone **1** using a mixture of a lithium amide and an amine.[a]

Entry	Base A[b] (N-Li)	Base B[b] (N-H)	Conversion[c] (%)	% ee[c] (config.)
1	(*R*, *R*)-**19**	**185**	54	0 (-)
2	LDA	(+)-**178**	77	6 (*R*)
3	**146**	(+)-**178**	25	0 (-)
4	(+)-**147**	**185**	46	0 (-)
5	(*R*)-**122**	DIPA	81	69 (*S*)
6	LDA	(*R*)-**186**	98	83 (*S*)
7	(*R*)-**122**	**185**	37	69 (*S*)
8	**146**	(*R*)-**186**	86	56 (*S*)

[a] The reaction was carried out on a 0.65 mmol scale with 5.0 equivalents of chlorotrimethylsilane at -78°C. [b] 1.2 equivalents compared to substrate. [c] Determined by chiral GC using Chiralsil-DEX CB column.

We first added a solution of dibenzylethylenediamine (**185**) to a solution of chiral base (*R*, *R*)-**19**-LiCl and after the two hour equilibrium period this mixture was used to deprotonate ketone **1**. After silylation we found that conversion to enol silane **34** was 54 % and the product was racemic (Table 4.1, Entry 1). This indicates that over the 2 hour equilibrium time period, lithium amide (*R*, *R*)-**19** has deprotonated the achiral diamine (**185**) and that it is achiral lithium amide **146** which deprotonates the substrate leading to a racemic product.

Our second reaction involved the creation of a solution of LDA and lithium chloride which was treated with a solution of chiral diamine (+)-**178**. When this solution was applied to ketone **1** followed by the addition of trimethylsilyl chloride the product ((*R*)-**34**) was formed in 77 % yield with an enantiomeric excess of 6 % (Entry 2). This shows that there was a small amount of deprotonation of diamine (+)-**178** and therefore formation of chiral base (+)-**147**. However as the enantiomeric excess of the product was very low the majority of the lithiated amine species was thought to be LDA.

An analogous reaction using *mono*-lithiated dibenzylethylendiamine (**146**) and chiral amine (+)-**178** was also carried out. A solution of **146** was prepared and then a solution of chiral amine (+)-**178** was added. After stirring at -78 °C for 2 hours this mixture was used to

deprotonate ketone **1**. Trimethylsilyl chloride was added and when the crude product was analysed the conversion to the product was found to be 25 % (Entry 3). The product was found to be racemic. This indicates that over the 2 hour equilibrium period base **146** was not deprotonating chiral amine (+)-**178** and therefore no chiral base (+)-**147** is being generated *in situ*.

A complementary process was also carried out using chiral base (+)-**147** and dibenzylethylenediamine (**185**). When the crude product was analysed the conversion to enol silane **34** was found to be 46 % (Entry 4). Again the product was determined to be racemic. This result seems to indicate that during the 2 hour equilibrium period chiral base (+)-**147** was deprotonating dibenzylethylenediamine (**185**) to give mainly achiral diamine base **146**.

A solution of chiral base (*R*)-**122** and lithium chloride was then prepared and a solution of di*iso*propylamine was added. When this mixture was used to deprotonate ketone **1** the enol silane product ((*S*)-**34**) was found to have been formed in 81 % conversion. Enol silane (*S*)-**34** was found to have 69 % ee (Entry 5). This shows that the majority of the lithiated amine species within the reaction was chiral base (*R*)-**122** and that there is little deprotonation of di*iso*propylamine by chiral base (*R*)-**122** taking place.

In order to carry out a complementary process, a solution of LDA and lithium chloride was formed and a solution of chiral amine (*R*)-**186** was added. Using this mixture to deprotonate ketone **1** gave enantiomerically enriched enol silane (*S*)-**34** in 98 % conversion with 83 % ee (Entry 6). As shown in Chapter 2 when a mixture of chiral base (*R*)-**122** and lithium chloride was used, enol silane (*S*)-**34** was found to have 78 % ee. Therefore this experiment showed us that within the equilibrium time period the lithium had fully transferred from LDA to chiral amine (*R*)-**186** to produce chiral lithium amide base (*R*)-**122** *in situ* at -78 °C.

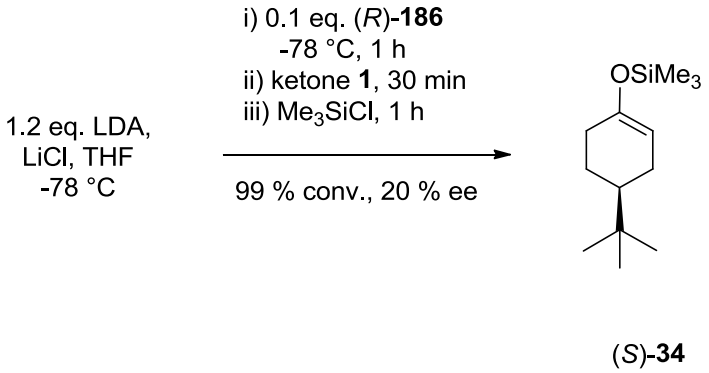
These two experiments were also repeated using dibenzylethylenediamine (**185**) in place of di*iso*propylamine. A solution of chiral base (*R*)-**122** and lithium chloride was prepared and a solution of dibenzylethylenediamine (**185**) was added. This mixture was used to deprotonate ketone **1** and the enol silane product (*S*)-**34** was found to have been formed in 37 % conversion with 69 % ee (Entry 7). This result again shows that chiral base (*R*)-**122** remains the major lithiated species after the equilibrium period.

A solution of achiral base **146** and lithium chloride was then formed and a solution of chiral amine (*R*)-**186** was added. When this mixture was applied to ketone **1**, followed by addition of the electrophile, enol silane product (*S*)-**34** was formed in 86 % conversion and found to have 56 % ee (Entry 8). Again this illustrates that the majority of the lithiated species in the base mixture after 2 hours at -78 °C is chiral base (*R*)-**122**.

4.3 Use of Sub-stoichiometric Chiral Base (*R*)-122

As we knew that it was possible to use LDA and diamine base **146** to deprotonate chiral amine (*R*)-**186** at the reaction temperature of -78 °C, we decided to test whether it was possible to use sub-stoichiometric amounts of chiral amine (*R*)-**186** within the reaction. It was hoped that chiral base (*R*)-**122** would be generated *in situ* by deprotonation by the achiral bulk base. After chiral base (*R*)-**122** had deprotonated the substrate, it was hoped that the conjugate chiral acid ((*R*)-**186**) would be deprotonated by the achiral bulk base and chiral base (*R*)-**122** would be regenerated. In the first example, a solution of 1.2 equivalents of LDA and lithium chloride was generated as usual and then a solution containing 10 mol % of chiral amine (*R*)-**186** was added (Scheme 4.6). This mixture was then stirred at -78 °C for 1 hour and a solution of ketone **1** was added. After 30 minutes, trimethylsilyl chloride was added and the reaction mixture was stirred at -78 °C for 1 hour before being quenched with triethylamine and

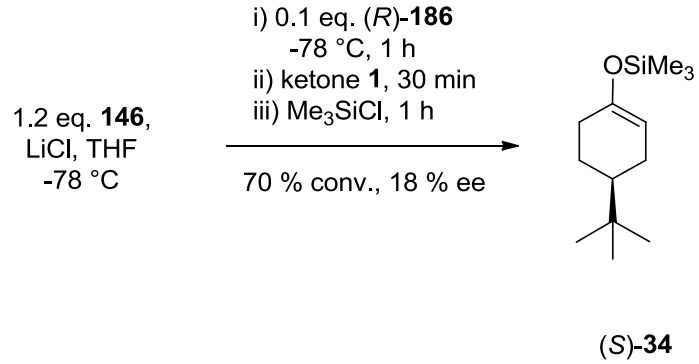
saturated sodium bicarbonate. When the crude product was analysed, the conversion to enol silane (*S*)-**34** was found to be 99 % with an enantiomeric excess of 20 % ee.



(*S*)-**34**

Scheme 4.6

This reaction was then repeated in the same way using achiral diamine base **146** in place of LDA (Scheme 4.7). The conversion of ketone **1** to enol silane (*S*)-**34** was found to be 70 % with an enantiomeric excess of 18 %.

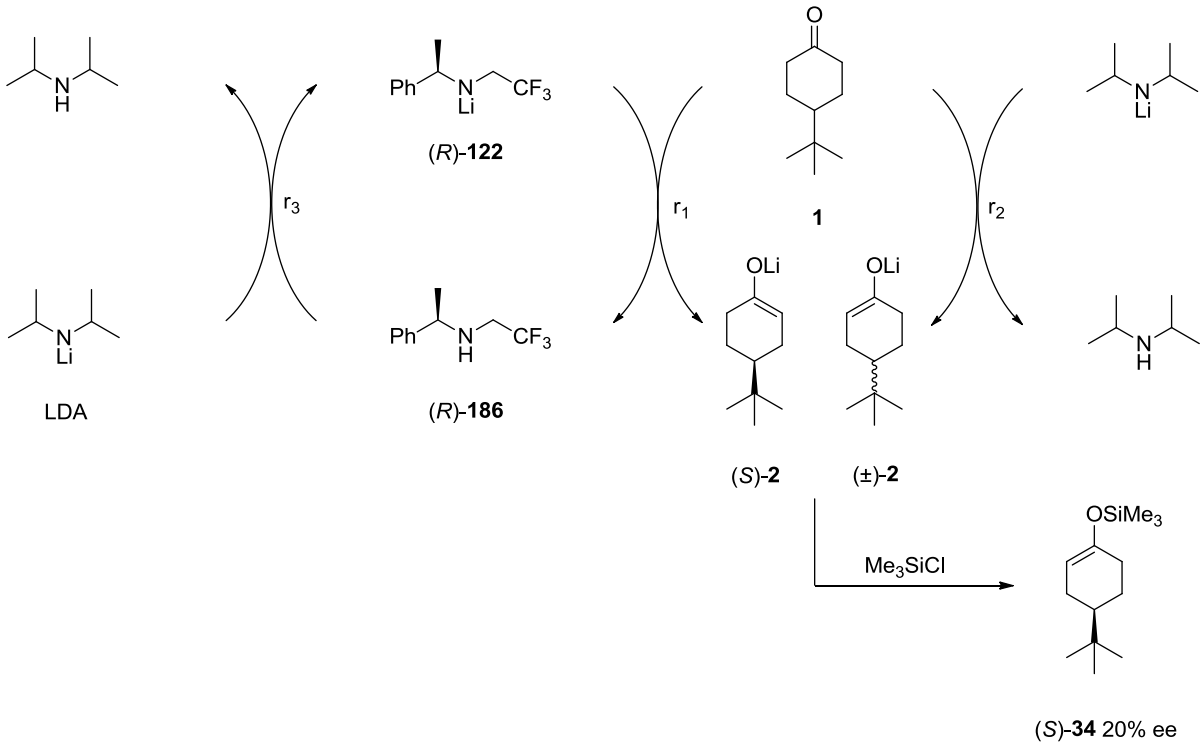


(*S*)-**34**

Scheme 4.7

These results show that although the chiral amine was deprotonated during the 1 hour equilibrium period, when the substrate was added the rate of recycling (deprotonation of chiral amine (*R*)-**186** by the achiral base) was lower than the rate of deprotonation of the substrate by the bulk achiral base. As summarised in Scheme 4.8, deprotonation of ketone **1** by chiral base (*R*)-**122** and LDA gives a mixture of (*S*)- and (±)- lithium enolate **2** which when

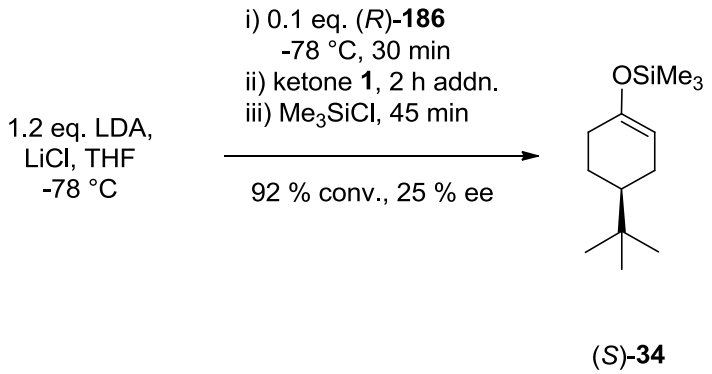
quenched with Me_3SiCl gives enol silane (*S*)-**34** with 20% ee. From our 1:1 competition reaction between LDA and (*R*)-**122** (35 % ee) we know that r_1 (rate of deprotonation by (*R*)-**122**) is greater than r_2 (rate of deprotonation by LDA). Therefore in the two reactions above, the rate of deprotonation of the chiral amine by the achiral base (r_3) must be lower than r_2. In order for a catalytic chiral base cycle to be developed r_3 and r_1 must be much greater than r_2 otherwise the product obtained can never be significantly enantiomerically enriched.



Scheme 4.8

We thought that slow addition of a solution of ketone **1** may increase the enantiomeric excess of enol silane (*S*)-**34**. As we knew from our competition reaction that chiral base (*R*)-**122** had a greater rate of deprotonation than LDA it was hoped that the low concentration of (*R*)-**122** present within the reaction would deprotonate the small amount of substrate (**1**) present within the reaction at any one time. It was envisioned that slow addition of the substrate would allow time for chiral base (*R*)-**122** to be regenerated via deprotonation by LDA. A solution of LDA

and lithium chloride was prepared and a solution of chiral amine (*R*)-**186** was added (Scheme 4.9). After 30 minutes a solution of ketone **1** was added over 2 hours at a rate of 0.017 mL min^{-1}. Trimethylsilyl chloride was added 30 minutes into this 2 hour period. The reaction was quenched with triethylamine and saturated sodium bicarbonate 45 minutes after the end of the addition of ketone **1**. When the crude product was analysed the conversion of ketone **1** to enol silane (*S*)-**34** was found to be 92 % with an enantiomeric excess of 25 %. In another experiment a solution of ketone **1** was added over 3 hours at a rate of 0.011 mL min^{-1}. Trimethylsilyl chloride was added 30 minutes after the end of the addition and the product ((*S*)-**34**) was found to have been formed in 97 % with 35 % ee.



Scheme 4.9

4.4 Summary and Conclusions

In summary, various lithium exchange experiments have been carried out. We have added solutions of amines to solutions of lithium amide bases and then stirred the mixtures at -78 °C for 2 hours. These mixtures were then used to deprotonate ketone **1** and the resultant enolate was quenched with trimethylsilyl chloride to form enol silane **34**. We carried out this reaction starting with either a chiral lithium amide and an achiral amine or an achiral lithium amide and a chiral amine. From these experiments we were able to determine the major lithiated

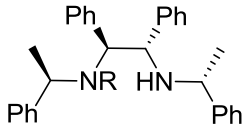
species within the reaction depending on the enantiomeric excess of the product which was obtained.

Although it is seemingly possible to deprotonate amine (*R*)-**186** using LDA at -78 °C, it does not seem that this happens at a rate which would allow us to use sub-stoichiometric amounts of this amine. In order to have an effective catalytic cycle, the rate of deprotonation of (*R*)-**186** by LDA (Scheme 4.8, r_3) must be greater than the rate of deprotonation of ketone **1** by LDA (r_2). The rate of deprotonation of ketone **1** by chiral base (*R*)-**122** (r_1) must also be much greater than the rate of deprotonation of ketone **1** by LDA (r_2). As we knew from our competition reactions, LDA and (*R*)-**122** have comparable rates of deprotonation of ketone **1** (Table 3.4, Entry 3). This resulted in a reduction in enantiomeric excess from 79 % ee (when (*R*)-**122-**LiCl was used) to 48 % ee (when a mixture of LDA-(*R*)-**122**-LiCl (1:1:1) was used). Therefore we concluded that in order to achieve an efficient catalytic chiral base system we needed to design new chiral bases.

Chapter 5: Design and Synthesis of Novel Fluorinated Chiral Bases

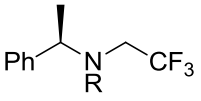
5.1 Introduction

The reactions described in the previous chapters led us to believe that the use of a fluorinated diamine chiral base is desirable. We thought that if the features of chiral base **147** and chiral base **122** could be combined then catalysis within a chiral base deprotonation reaction could be achieved. Diamine chiral base **147** had been found to react faster than bulk achiral bases (e.g. LDA) in competition reactions. This property would be desirable for catalysis as the chiral base could be regenerated *in situ* by the achiral lithium amide base without the enantiomeric induction of the reaction being compromised. Unfortunately when we attempted to deprotonate chiral amine **178** using achiral lithium amide bases at the normal reaction temperature (-78 °C), and use this mixture to deprotonate ketone **1**, the enol silane product (**34**) was essentially racemic. This suggests that the equilibrium of the lithiation was towards the achiral bases and there was no driving force to deprotonate chiral amine *in situ*. However mixtures of fluorinated chiral base **122** and achiral amines or fluorinated chiral amine **186** and achiral lithium amide bases gave enantiomerically enriched product (**34**). This indicated that the equilibrium position of these mixtures was towards lithiation of the fluorinated compound and that it is possible to deprotonate the chiral amine *in situ* using an achiral lithium amide base at the normal reaction temperature.



147 R = Li
178 R = H

Figure 5.1

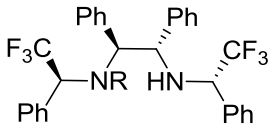


122 R = Li
186 R = H

Figure 5.2

5.2 Design of Fluorinated Diamine Base 187

Replacement of the two methyl groups present in chiral amine **178** with trifluoromethyl groups would allow the creation of new fluorinated chiral diamine **188** (Figure 5.3). It was hoped that chiral base **187** would have a high rate of deprotonation of the substrate (compared to the bulk achiral base) and that the conjugate acid (**188**) would be deprotonated at -78 °C by the bulk achiral base. If these two criteria were met then it may be possible to use sub-stoichiometric amounts of this chiral base within an asymmetric deprotonation reaction. By lowering the pK_A of the nitrogen atoms in the molecule, the chiral amine is more likely to be deprotonated *in situ* at -78 °C by another lithium amide. It was hoped that introduction of the trifluoromethyl group adjacent to the amine moieties would increase the acidity of the nitrogen to a level close to that of chiral amine (*R*)-**186** (calc. pK_A 27.4).[92] The calculated pK_A of diamine **178** was found to be 33.1 and replacement of the two methyl groups with trifluoromethyl groups (**188**) was found to lower the calculated pK_A to 25.9.



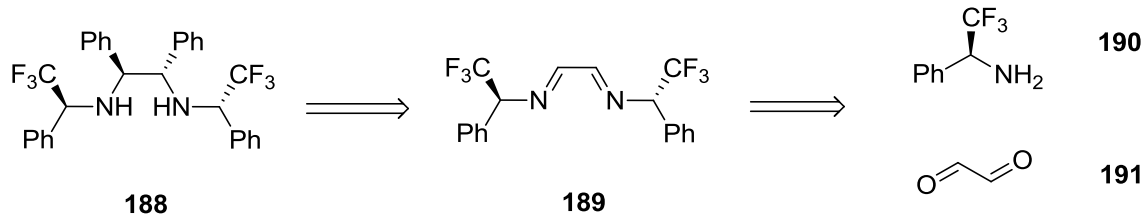
187, R = Li
188, R = H

Figure 5.3

5.3 Synthesis of Diamine 188

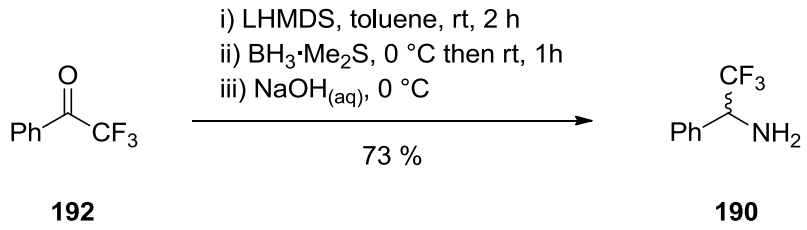
It was hoped that the required hexafluorinated diamine **188** could be synthesised by the same short reaction sequence used previously within our group for the synthesis of chiral diamine **178**.[93] A retrosynthetic analysis of this target begins with Grignard addition of two phenyl groups to a diimine (**189**), which would be synthesised from glyoxal (**191**) and two equivalents of chiral amine **190** (Scheme 5.1). This synthesis would hinge on the preparation

of highly enantiomerically enriched amine (*R*)-**190** or (*S*)-**190** which is not commercially available on a synthetically useful scale.[94]



Scheme 5.1

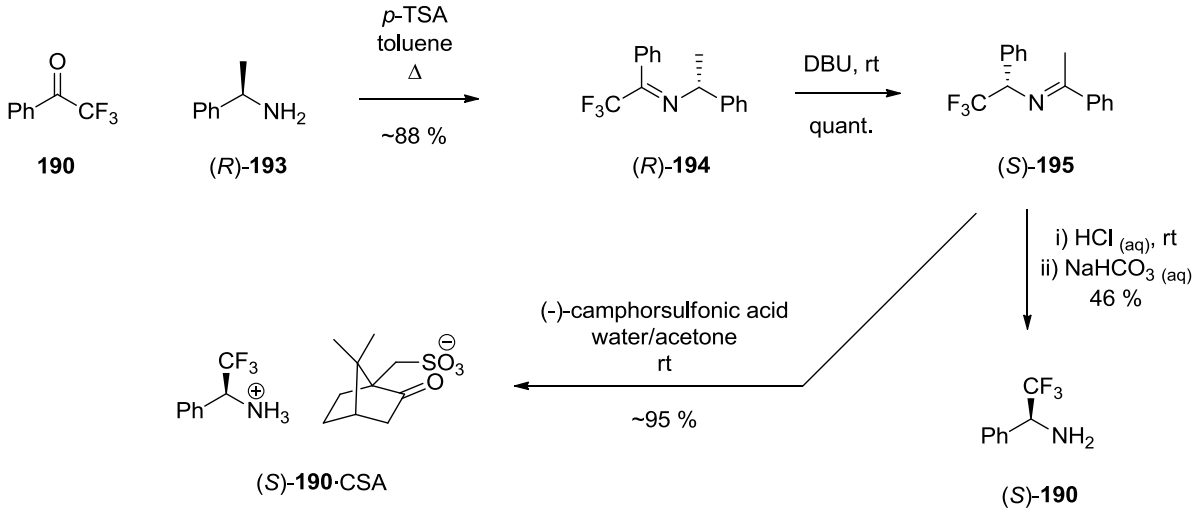
Initilly, our synthesis of enantiomerically enriched amine **190** involved the preparation of racemic **190** followed by resolution using tartaric acid. Commercially available trifluoroacetophenone (**192**) was treated with lithium bis(trimethylsilyl)amide to generate the intermediate imine which was directly reduced *in situ* using borane dimethylsulfide complex to give racemic amine (±)-**190** in 73 % yield (Scheme 5.2).[95] Subsequent attempts to resolve this amine using tartaric acid following a report from Mosher in 1991 were not successful.[96] By following this method exactly and also modifying the method, we were not able to observe the formation of crystals, as reported. The solid mass which formed was neutralised and when the fluorinated amine (**190**) was extracted and purified it showed no significant optical rotation.



Scheme 5.2

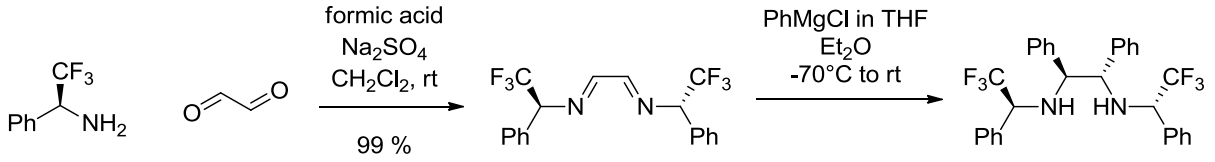
Since it was not possible to prepare enantiomerically enriched amine **190** by resolution of the racemic amine a longer route was needed. Imine (*R*)-**194** was prepared in 88 % yield by condensation of trifluoroacetophenone (**192**) and (*R*)-methylbenzylamine ((*R*)-**193**) involving

azetropic removal of water using a Dean-Stark apparatus (Scheme 5.3).[97] Treatment of this imine ((*R*)-**194**) with 2 equivalents of DBU resulted in a 1, 3 proton shift to give total conversion to imine (*S*)-**195**, as indicated by ^{1}H NMR.[98] Previously, Soloshonok reported that under these conditions enantiomerically pure imine (*S*)-**194** was converted to imine (*R*)-**195** with 87 % ee. The reason given for this transformation was as follows; the equilibrium between these two imines favours the formation of the species with the more acidic C-H bond, leading to proton transfer from a less to a more configurationally unstable stereogenic centre.[99] After conversion of (*R*)-**194** to (*S*)-**195** the majority of DBU was removed by filtration through a short silica column but some remained. This mixture was directly hydrolysed by addition of either aqueous hydrochloric acid or (–)-camphorsulfonic acid to give the required amine ((*S*)-**190**) as either the hydrochloride ((*S*)-**190**·HCl) or the camphorsulfonate salt ((*S*)-**190**·(–)-CSA). The amine camphorsulfonate salt was prepared as this would allow the diastereomeric ratio to be determined by ^{19}F NMR.[98a] The ^{19}F NMR spectrum of (±)-**190**·(–)-CSA showed two peaks with good baseline separation whereas our prepared (*S*)-**190**·(–)-CSA showed only one peak.



Scheme 5.3

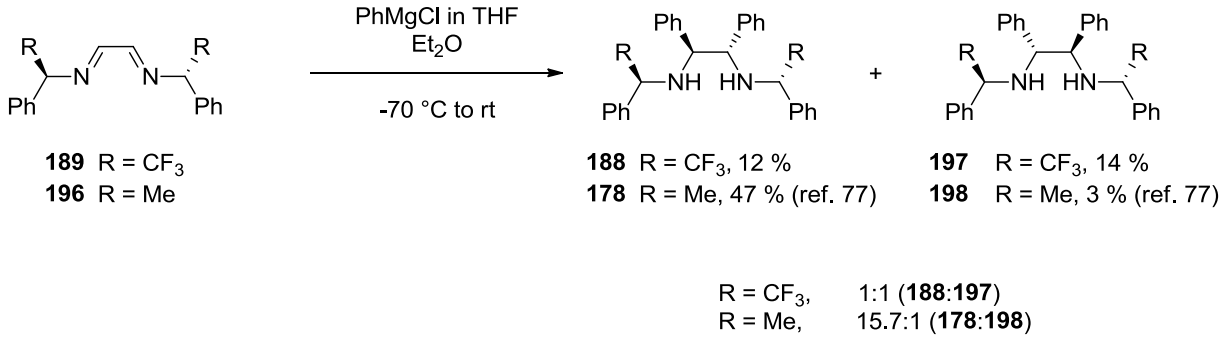
With highly enantiomerically enriched amine (*S*)-**190** in hand (~40 % yield over 3 steps from (*R*)-**193**), the synthesis of chiral diamine **188** was continued following the steps used previously for the synthesis of diamine **178** (Scheme 5.4). Treatment of a mixture of glyoxal (**191**) and formic acid with two equivalents of amine (*S*)-**190** followed by addition of sodium sulphate gave diimine **189** in 99 % yield. This diimine was then treated with phenyl magnesium chloride at -70 °C before the mixture was warmed to room temperature to give diamine **188** as a mixture of diastereomers.[93]



(*S*)-**190** **191** **189** **188**

Scheme 5.4

The mixture of diamine diastereomers was separated from the reaction impurities by silica column chromatography and the diastereomers were individually purified by reverse phase HPLC to give **188** and **197** in 12 % and 14 % respectively. Crystallisation of these two compounds followed by single crystal X-ray crystallography allowed the structures to be assigned (Figures 5.4 & 5.5). The ratio of the formation of these two diastereomers from diimine **189** was found to be 1:1 (**188**:**197**) from the crude ^{1}H NMR (Scheme 5.5). In the synthesis of chiral diamine **178** from imine **196**, the ratio between the diastereomers (**178** and **198**) was reported to be 15.7:1 in favour of **178**.[77]



Scheme 5.5

In comparison with the addition of phenyl magnesium chloride to diimine **196**, the addition to fluorinated diimine **189** was found to not be diastereoselective. Obviously, the substitution of trifluoro groups for methyl groups has affected the addition of the phenyl Grignard reagent to the imine moiety. This could be either because of the increased bulk of this group (CH_3 = 1.8 Å & CF_3 = 2.2 Å, for comparison ^{t}Bu = 3.6 Å)[100] or the altered electronics in the molecule due to the electron withdrawing nature of this group.

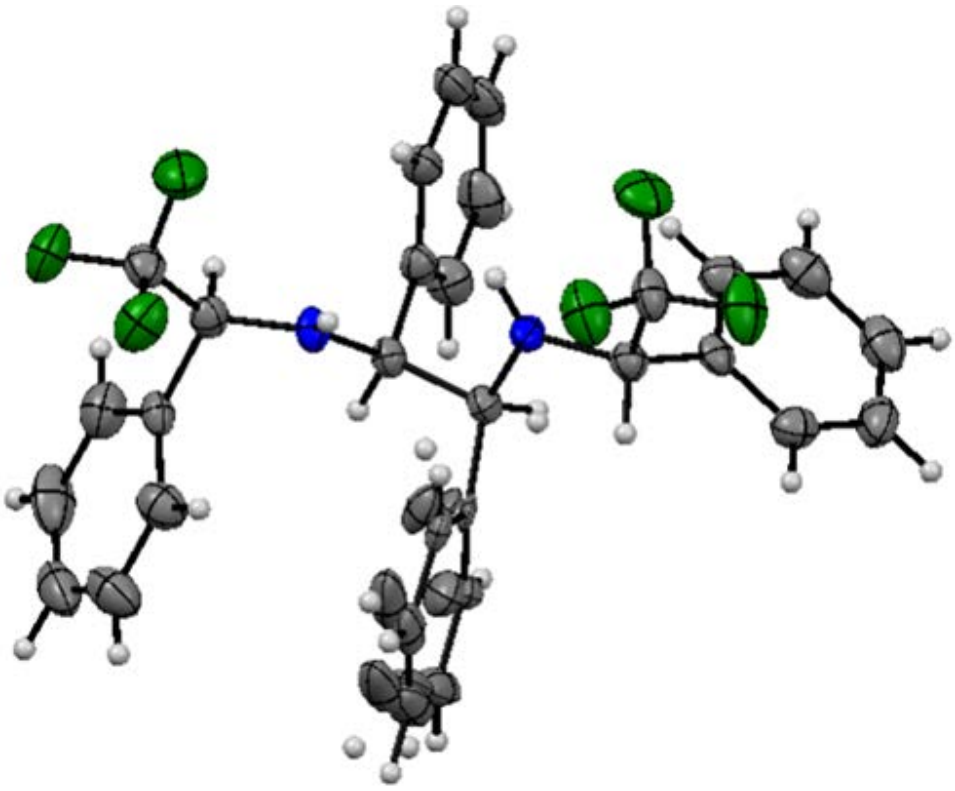


Figure 5.4: The structure of diamine **188** with ellipsoids drawn at the 50 % probability level. The phenyl group C17-C22/C17'C22' is disordered over two positions at an occupancy ratio of 50 (4):50 (4).

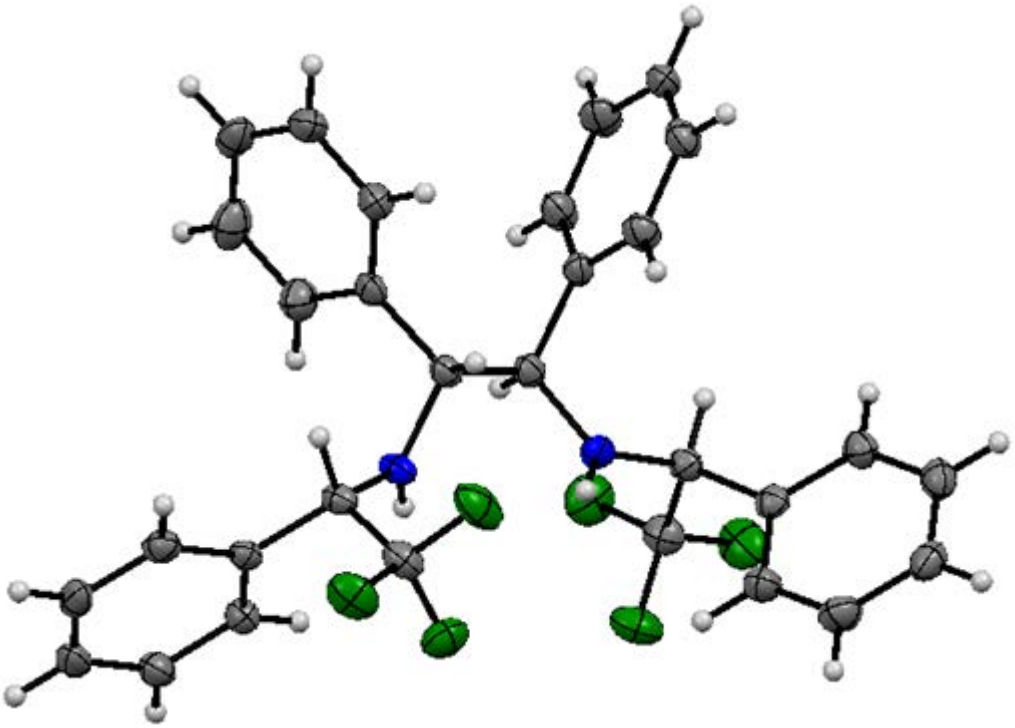
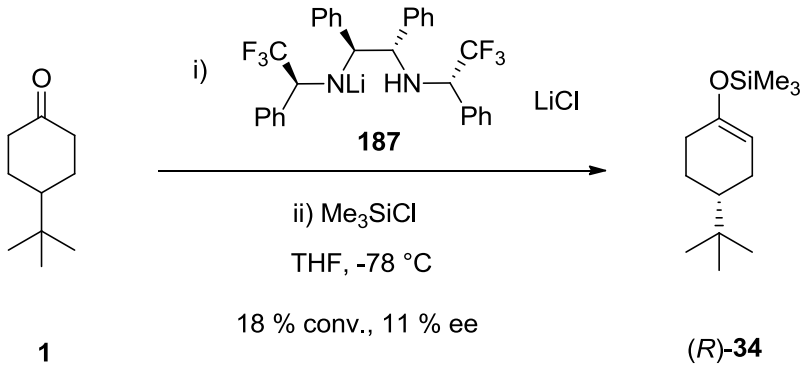


Figure 5.5: The structure of diamine **197** with ellipsoids drawn at the 50 % probability level.

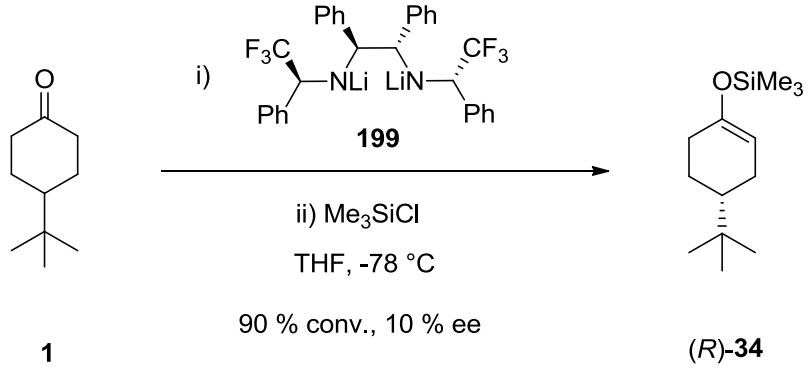
5.4 Use of Chiral Base 187

Chiral amine **188** was deprotonated using *n*-butyllithium (1 eq.) in the presence of lithium chloride and *mono*-lithiated chiral base **187** was used for the asymmetric deprotonation of ketone **1**. The conversion to enol silane (*R*)-**34**, with 11 % ee, was found to be 18 %.



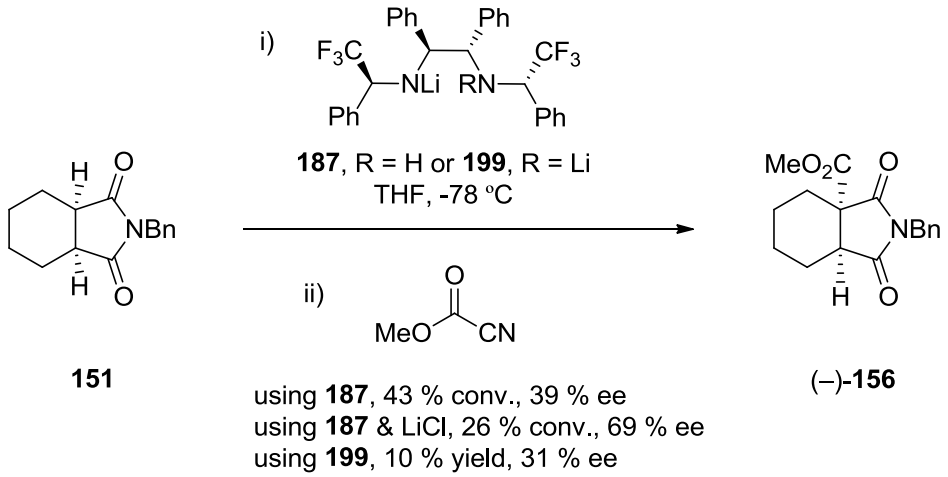
Scheme 5.6

New fluorinated chiral amine **188** was then deprotonated using 2 equivalents of *n*-butyllithium to generate *bis*-lithium chiral base **199**. Analysis of the crude product revealed that the reaction had preceded with 90 % conversion to (*R*)-**34** with 10 % ee.



Scheme 5.7

Imide **151** was then deprotonated using chiral bases derived from novel chiral amine **188** and acylated using Mander's reagent. Diamine **188** was treated with 1 equivalent of *n*-butyllithium to generate chiral base **187** which was then used in this reaction. Conversion to ester (–)-**156** from imide **151** was found to be 43 % and the product was determined to have an enantiomeric excess of 39 %.



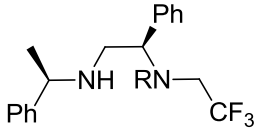
Scheme 5.8

A mixture of diamine **188** and lithium chloride was then treated with *n*-butyllithium (1 eq.) and chiral base **187**-LiCl was used in this reaction. Conversion from imide **151** to ester (–)-**156** was found to be 26 % and ester (–)-**156** had an enantiomeric excess of 69 %. We then added 2 equivalents of *n*-butyllithium to a solution of diamine **188** to generate *bis*-lithiated chiral base **199**, which was used to deprotonate imide **151**. The ester product ((–)-**156**), which was isolated in 10 % yield, was found to have 31 % ee.

5.5 Design of Chiral Base 200

As we had found that chiral bases **187** or **199** were not effective for the asymmetric deprotonation of ketone **1** or imide **151** we could not carry out experiments to determine if chiral bases **187** or **199** would be recycled *in situ* by an achiral bulk base. We reasoned that by addition of the trifluoromethyl groups into the structure of chiral base **187** we had either changed the structure of the base too much (compared to **147**) because of the additional bulk of the trifluoro group compared to the methyl group or that the desired electron withdrawing effect of the trifluoro group had a negative effect on enantioselectivity.

We decided to synthesise a new chiral amine which would again combine the structural features of both diamine chiral base **147** and fluorinated chiral base **122**. In order to incorporate the desired features without significantly increasing the steric bulk around the diamine moiety we decided that this base would not be symmetrical. The structure of this diamine ((*R*, *R*)-**201**) is shown in Figure 5.6.

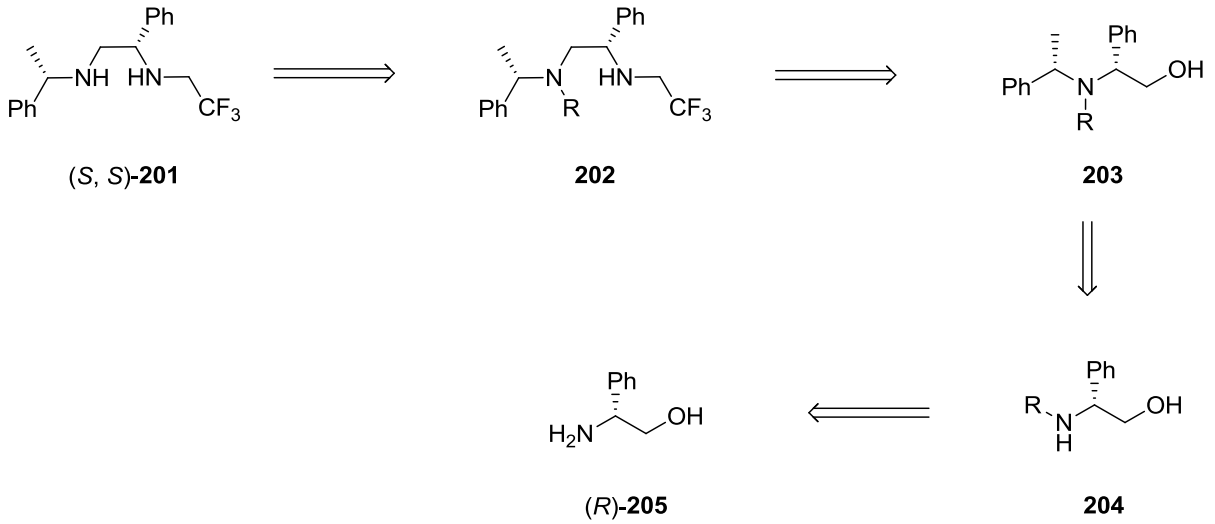


(*R*, *R*)-**200**, X = Li
(*R*, *R*)-**201**, X = H

Figure 5.6

5.6 Synthesis of Chiral Amine 201

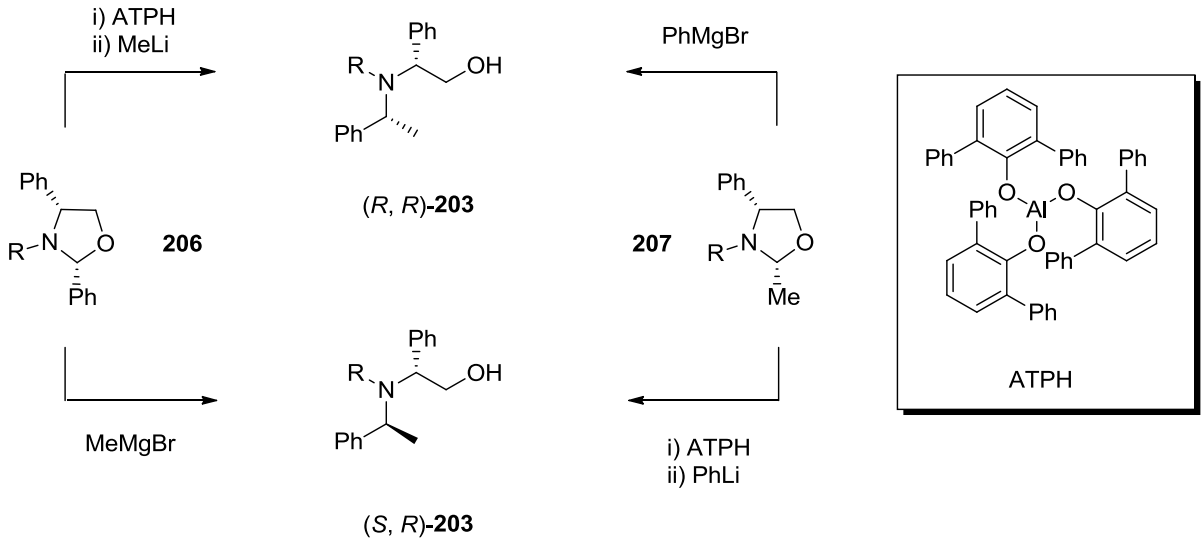
We decided to synthesise the opposite enantiomer of this compound as the chiral pool starting material needed was cheaper. Our retrosynthesis of (*S*, *S*)-**201** is shown in Scheme 5.9. The initial step in the retrosynthesis was the addition of a substituted benzylic protecting group to the nitrogen atom adjacent to the (*S*)-methylbenzyl group to give intermediate **202**. The next step was the replacement of the trifluoroethylamine moiety with a hydroxyl and the 1, 2-migration of the phenyl group to give compound **203**. Following this the (*S*)-methylbenzyl moiety was removed from the amine group to give intermediate **204** and then the protecting group was removed from nitrogen to give our chiral pool starting material (*R*)-phenylglycinol (**205**).[101]



Scheme 5.9

The first stage in the synthetic route started with the synthesis of intermediate **203**, specifically alcohol **203e** where the amine protecting group was 2, 4, 6-trimethylbenzyl. The synthesis of this compound had previously been described by Yamauchi *et al.* in 2005.[102] In this publication the diastereoselective addition of Grignard reagents to 1, 3-oxazolidines and organolithiums to 1, 3-oxazolidines complexed with aluminium tris (2, 6-diphenylphenoxide)

(ATPH) was reported. The chemistry described is summarised in Scheme 5.10. The synthesis of either (*R, R*)-**203** or (*S*, *R*)-**203** is possible from either oxazolidine **206** or **207**.



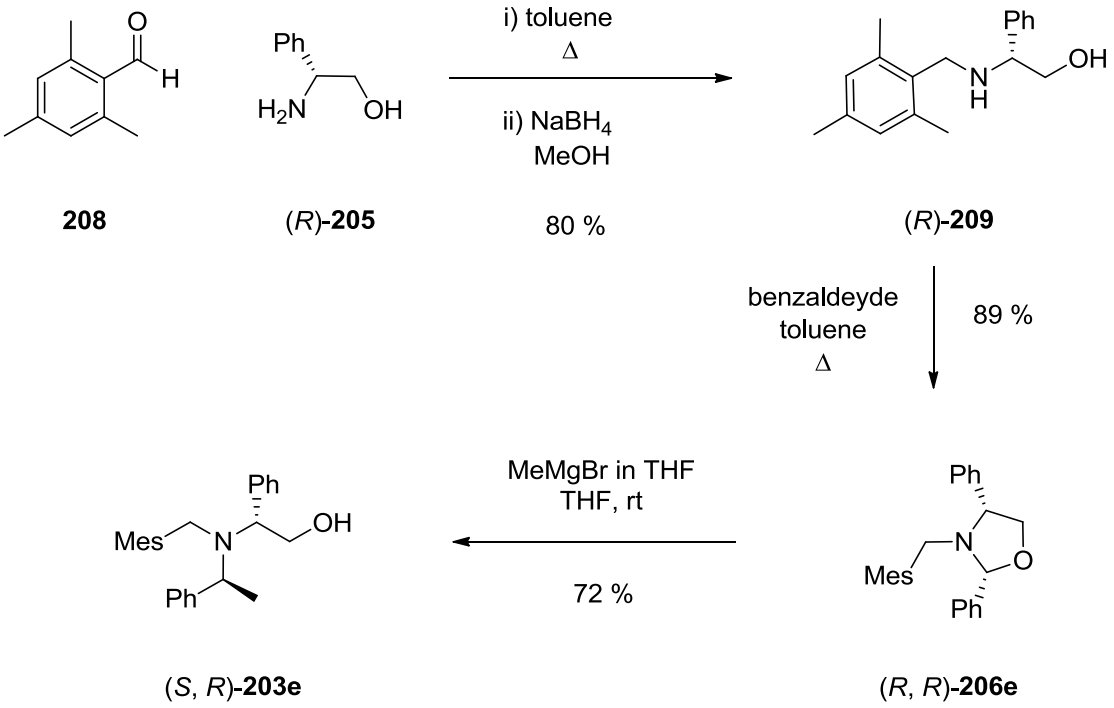
Scheme 5.10

Some important results that Yamauchi reported, as well as data from related publications, are shown in Table 5.1.[103] From these results we can see that it is possible to obtain good to excellent diastereoselectivity starting from either oxazolidine **206** or **207**. As we were planning the synthesis of highly diastereomerically enriched (*S*, *R*)-**203e** we were particularly interested in entries 3, 4, 5, 6 and 8. In entries 3-5 oxazolidines **206c-e** were treated with methyl magnesium bromide and (*S*, *R*)-**203c-e** was obtained in good yield with between 88 to 94 % de. In entries 6 and 8 oxazolidine **207a** and **207c** were treated with ATPH followed by phenyl lithium, (*S*, *R*)-**203a** and **203c** were obtained in good yields with 94 and 98 % de. Although the best diastereoselectivity for (*S*, *R*)-**203** was obtained when an *N-iso*-propyl group was present (Entries 3 & 8), we decided to carry out the synthesis of (*S*, *R*)-**203e** from **206e** using methyl magnesium bromide (Enty 5) because of the ease of removal of the 2, 4, 6-trimethylbenzyl group compared to the *iso*-propyl group.

Table 5.1: Synthesis of (*S*, *R*)-**203** & (*R*, *R*)-**203** from oxazolidines **206** & **207**.

Entry	Substrate	R	Grignard (R_1-MgBr)			ATPH/R_2-Li		
			R_1	Yield (%)	Ratio (*R*, *R*-**203**/*S*, *R*-**203**)	R_2	Yield (%)	Ratio (*R*, *R*-**203**/*S*, *R*-**203**)
1	**206a**	Bn	Me	94	16:84	Me	86	78:22
2	**206b**	Me	Me	86	34:66	Me	98	19:81
3	**206c**	*i*-Pr	Me	90	3:97	Me	86	97:3
4	**206d**	Diphenylmethyl	Me	85	6:94	Me	62	84:16
5	**206e**	2, 4, 6-Trimethylbenzyl	Me	85	6:94	Me	94	97:3
6	**207a**	Bn	Ph	92	77:23	Ph	90	3:97
7	**207b**	Me	Ph	90	78:22	Ph	83	27:73
8	**207c**	*i*-Pr	Ph	89	88:12	Ph	80	1:99

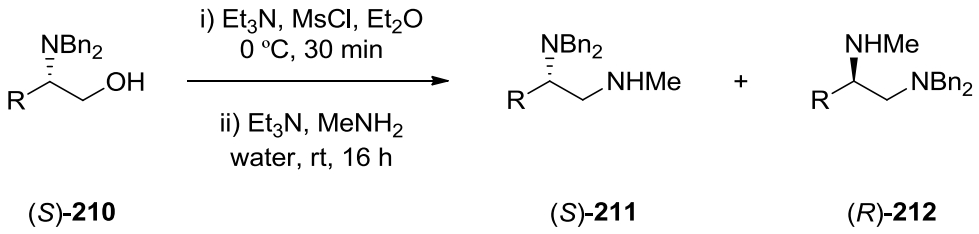
Amino alcohol (*R*)-**209** was synthesised in 80 % yield from mesitaldehyde (**208**) and (*R*)-phenylglycinol ((*R*)-**205**) by a two-step reductive amination procedure (Scheme 5.11). After introduction of benzaldehyde and heating at reflux in toluene, oxazolidine (*R*, *R*)-**206e** was isolated by distillation in 89 %. Oxazolidine (*R*, *R*)-**206e** was then treated with methyl magnesium bromide in THF at room temperature and after purification diastereomerically pure amino alcohol (*S*, *R*)-**203e** was isolated in 72 % yield.



Scheme 5.11

With Amino alcohol (*S*, *R*)-**203e** now in hand we had to complete the synthesis of diamine (*S*, *S*)-**201** by migration of the phenyl group, introduction of the amine functionality bearing a trifluoroethyl group and removal of the trimethylbenzyl group. In 2002, O'Brien reported the conversion of amino alcohols to diamines via aziridinium ions.[104] As shown in Scheme 5.12, amino alcohols of the type (*S*)-**210** were treated with triethylamine and methanesulfonyl chloride to form an intermediate aziridinium ion. The addition of a 40 % aqueous solution of methylamine gave two diamine products (*S*)-**211** and (*R*)-**212**. When the R group was aliphatic or benzylic ((*S*)-**210a-c**), (*S*)-**211a-c** was formed selectively indicating that the aziridinium ring was opened by the amine at the least sterically hindered position (Table 5.2, Entries 1-3). If however, the R group was phenyl ((*S*)-**210d**) then the major product was (*R*)-**212d** which indicates that methylamine attacks the aziridinium ring at the benzylic position resulting in the appearance of migration of the phenyl group. Diamine (*R*)-**212** was not

isolated but conversion to (*R*)-**212d** was good (78 %) and the regioselectivity of the aziridinium ring opening was excellent (98:2, **212**:**211**).



(*S*)-**210** (*S*)-**211** (*R*)-**212**

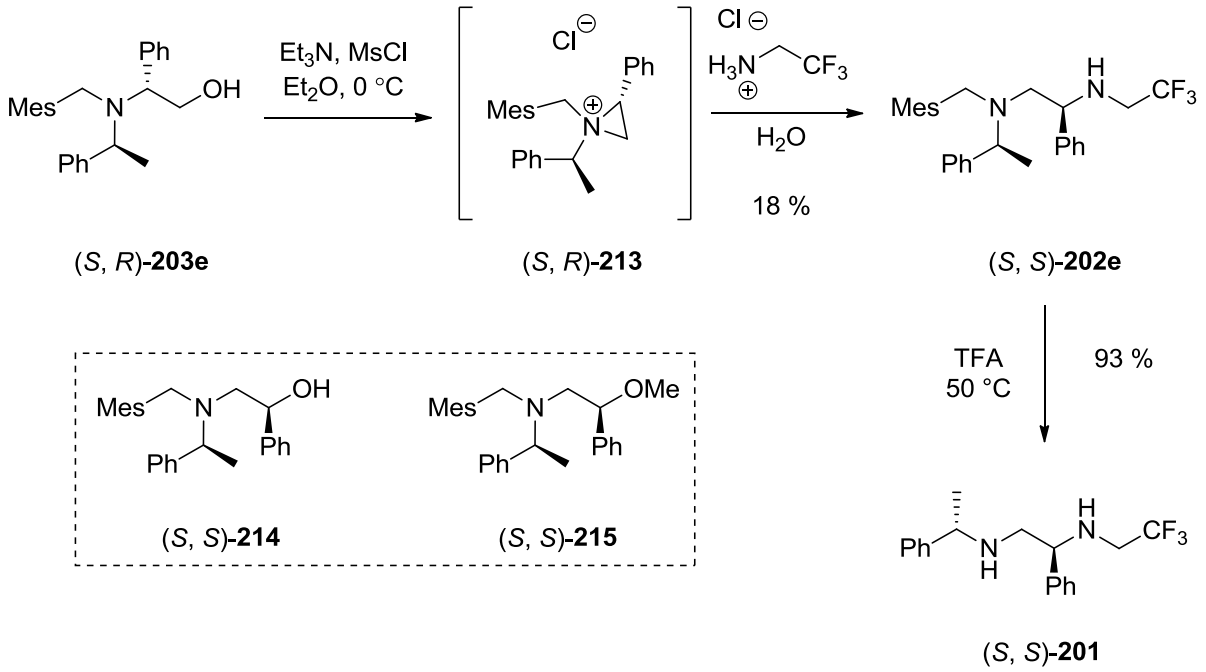
Scheme 5.12

Table 5.2

Entry	Substrate	R	Conv. (Yield) (%)	(*S*)-**211**/(*R*)-**212**
1	**210a**	Me	96 (78)	70:30
2	**210b**	Bn	94 (70)	94:6
3	**210c**	*i*-Pr	81 (62)	93:7
4	**210d**	Ph	78 (-)	2:98

We used this methodology to synthesise diamine (*S*, *S*)-**202e** from amino alcohol (*S*, *R*)-**203e** via intermediate aziridinium ion (*R*, *R*)-**213** (Scheme 5.13). In our work, trifluoroethylamine hydrochloride was used as the nucleophile and unfortunately (*S*, *S*)-**202e** was obtained in a low yield of 18 %. We found that as well as forming (*S*, *S*)-**202e** within the reaction, water was also opening the aziridinium ring to form amino alcohol (*S*, *S*)-**214**. In order to try to increase the yield of the desired product we carried out this reaction again and trifluoroethylamine hydrochloride was introduced into the reaction directly as a solid in order to remove the need for water in the reaction. We did not observe opening of the aziridinium ring therefore methanol was added followed by addition of a further equivalent of trifluoroethylamine hydrochloride in a minimum amount of water. From this reaction we isolated the desired product diamine (*S*, *S*)-**202e** in 28 % yield, amino alcohol (*S*, *S*)-**214** in 6 % and amino ether (*S*, *S*)-**215** in 12 %. With diamine (*S*, *S*)-**202e** in hand we then proceeded to

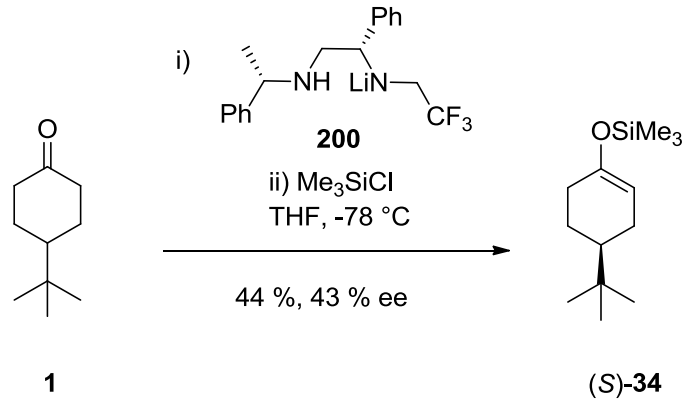
remove the trimethylbenzyl protecting group by heating in trifluoroacetic acid at 50 °C over several days.[102] The desired diamine (*S*, *S*)-**201** was obtained in 93 % yield.



Scheme 5.13

5.7 Use of Chiral Base 200

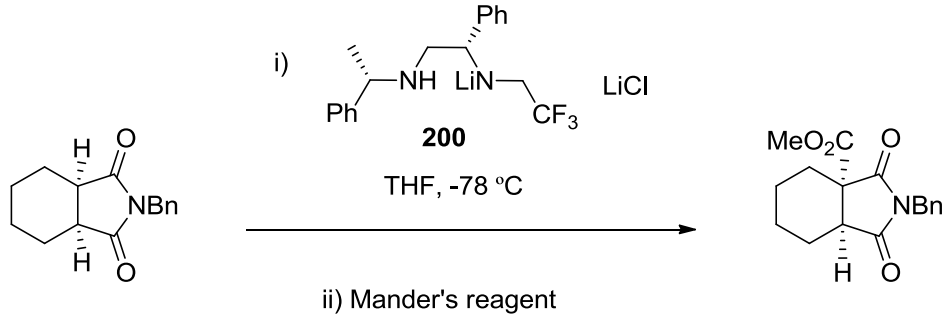
Novel chiral amine (*S*, *S*)-**201** was deprotonated using *n*-butyllithium and mono-lithiated chiral base **200** was used for the asymmetric deprotonation of ketone **1** (Scheme 5.14). After addition of trimethylsilyl chloride the crude product was analysed by chiral GC. The conversion to enol silane (*S*)-**34** was found to be 44 % and the enantimeric excess was determined to be 43 %.



1 (*S*)-**34**

Scheme 5.14

Chiral base **200** was also used to deprotonate bicyclic imide **151** and the enolate was quenched with Mander's reagent to give ester **156** (Scheme 5.15). After analysis by chiral HPLC the product was found to be racemic.



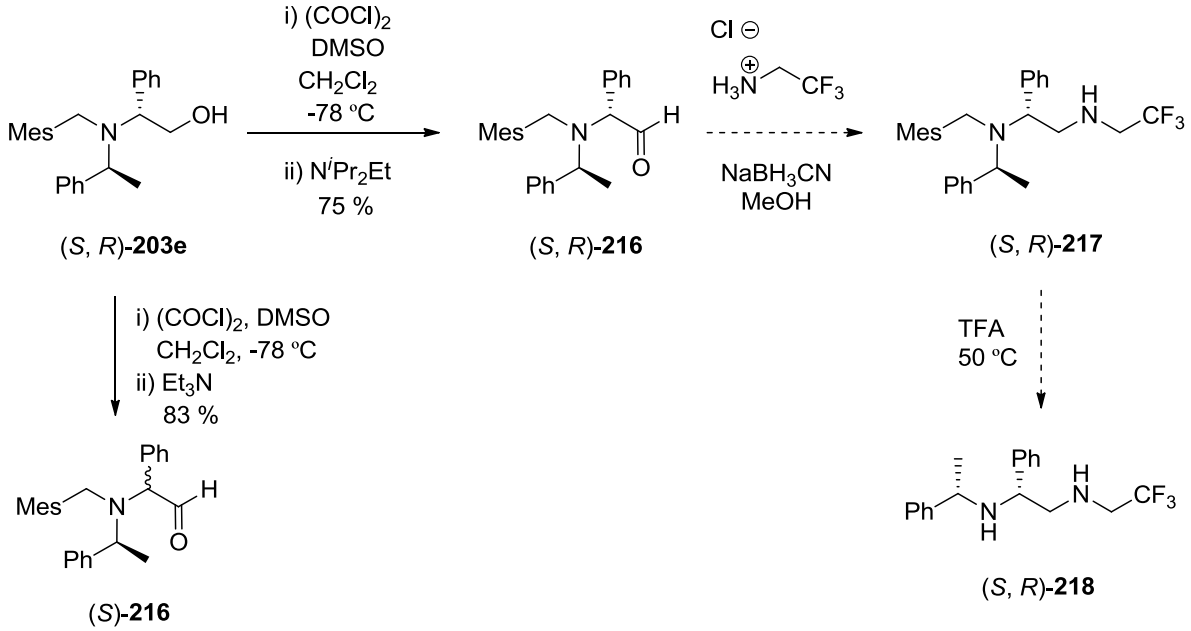
151 (±)-**156**

Scheme 5.15

5.8 Future Syntheses of Chiral Amines

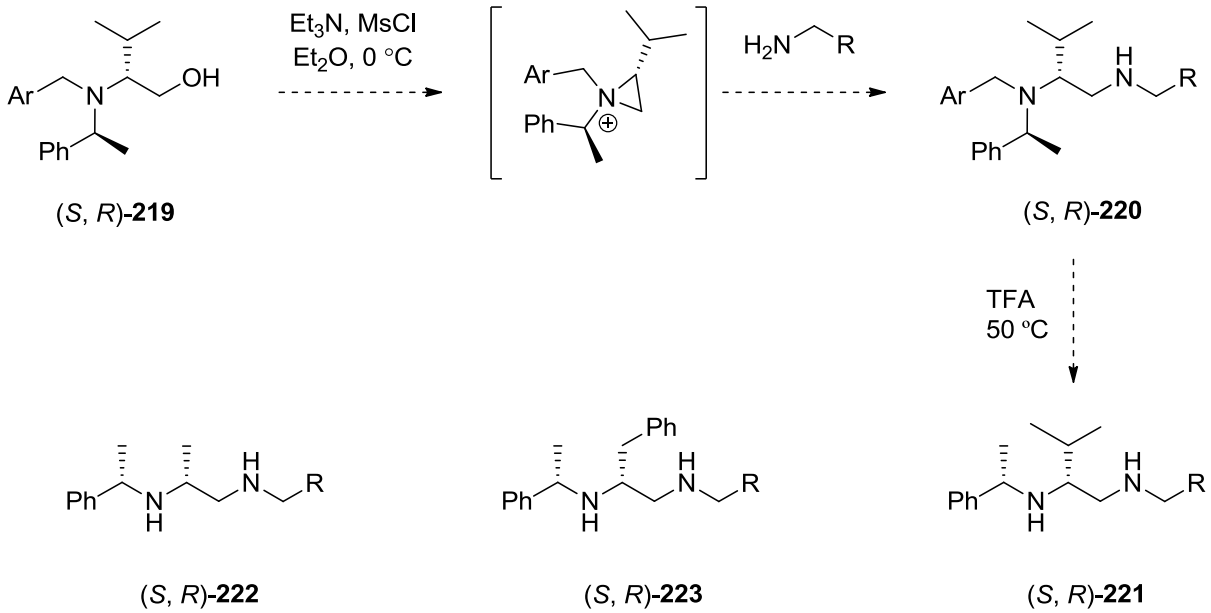
Using the synthetic route towards chiral amine **201** we could design several other chiral amines for the use as chiral lithium amide bases. From amino alcohol (*S*, *R*)-**203e** it may be possible to synthesise diamine (*S*, *R*)-**218** over 3 steps via aldehyde **216** (Scheme 5.16). A Swern oxidation was carried out on a sample of amino alcohol (*S*, *R*)-**203e** and epimerised aldehyde (*S*)-**216** was obtained in 83 % yield. In order to avoid this epimerisation and retain the diastereomeric purity, triethylamine was replaced with Hünig's base within the second

stage of the reaction. Diastereomerically pure aldehyde (*S*, *R*)-**216** was obtained in 75 %. We noted that a sample of aldehyde (*S*, *R*)-**216** in deuterated chloroform had partially epimerised (~70 % de) over 8 hours.



Scheme 5.16

Another route we could follow related to the synthesis of chiral amine **201** is the synthesis of a valine, alanine or phenylalanine derived chiral diamine ((*S*, *R*)-**221**, **-222** & **-223**) (Scheme 5.17). The results from O'Brien discussed above show that when the aziridinium ion ring substituent was aliphatic or benzylic then the ring would be opened at the least sterically hindered position. However, the synthesis of diastereomerically pure amino alcohol starting materials (e.g. (*S*, *R*)-**219**) would rely on the chemistry shown in Scheme 5.10 being effective when phenyl was replaced with *iso*-propyl, methyl or benzyl.



(*S*, *R*)-**219** (*S*, *R*)-**220**

(*S*, *R*)-**222** (*S*, *R*)-**223** (*S*, *R*)-**221**

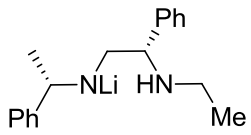
Scheme 5.17

5.9 Summary and Conclusions

In summary, two new fluorinated chiral amines, **188** and **201**, have been synthesised and the lithiated derivatives have been tested as chiral bases for the asymmetric deprotonation of ketone **1** and imide **151**. *Mono*-lithiated chiral base **187**-LiCl produced enol silane (*R*)-**34** with 11 % ee and ester (–)-**156** with 69 % ee. *Bis*-lithiated chiral base **199** gave enol silane (*R*)-**34** with 10 % ee and ester (–)-**156** with 31 % ee. *Mono*-lithiated chiral base **200** produced enol silane (*R*)-**34** with 43 % ee and ester **156** which was racemic.

As the enantiomeric excesses of the products obtained from deprotonation of ketone **1** and imide **151** (with either chiral base **187**, **199** or **200**) were low, we were not able to test our hypothesis that fluorinated chiral diamines would be suitable for catalysis. It was hoped that addition of trifluoromethyl groups into the structure of chrial bases would increase the acidity of the adjacent amine moiety and therefore allow efficient recycling of sub-stoichiometric quantities of the chiral base by an achiral bulk base such as LDA. The asymmetric induction of **187** and **199**, compared to **147**, was thought to have been negatively affected either by the

increased size of the trifluoromethyl groups compared to the methyl groups or the different electronic environment. With regard to new chiral base **200**, the equivalent non-fluorinated chiral base (**224**, Figure 5.7) has not previously been synthesised and used, therefore we are unsure whether it is the general structure of the chiral base which is leading to its ineffectiveness or the addition of the trifluoromethyl group. As this chiral base does not possess a C_2 symmetry axis, the expected enantioselectivity may be diminished by the increased number of transition states. In 1989, Whitesell proposed that in the majority of asymmetric reactions, chiral ligands with a C_2 symmetry axis will have an advantage, as the number of competing diastereomeric transition states will be greatly reduced.[105] It may be possible that other uses for novel chiral amines **188** and **201** are found in the future.



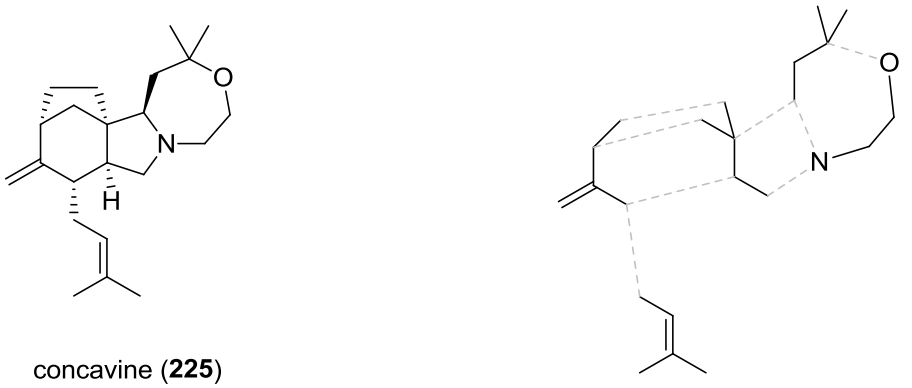
224

Figure 5.7

Chapter 6: Towards the Total Synthesis of Concavine

6.1 Introduction

In light of the observation that fused bicyclic imides could be deprotonated highly enantioselectively by diamine chiral base (+)-**147**, we were inspired to tackle the enantioselective total synthesis of the novel diterpenoid alkaloid concavine (**225**) (Figure 6.1). (+)-Concavine was isolated from the extracts of large scale cultures of the fungus *Clitocybe concava* (Basidiomycetae) by Arnone *et al.* in 2005.[106] The skeleton of this molecule is a new variant of the diterpenoid alkaloids containing four isoprene units connected in a previously unknown sequence and two extra carbons which link the oxygen and nitrogen to form the oxazepane ring. Concavine was tested for biological activity and did not show any antitumor (tyrosine-kinase test) or antifungal (*Cladosporium cladosporioides, Aspergillus niger)* activity. Weak antibacterial activities were detected against *Bacillius cereus* and *Bacillus subtilis*. Our main reason to attempt this synthesis was to confirm that the unprecedented structure proposed for this alkaloid was correct. There have been no reported total syntheses of convavine although interest has been expressed by the groups of Williams and Fukuyama.[107]



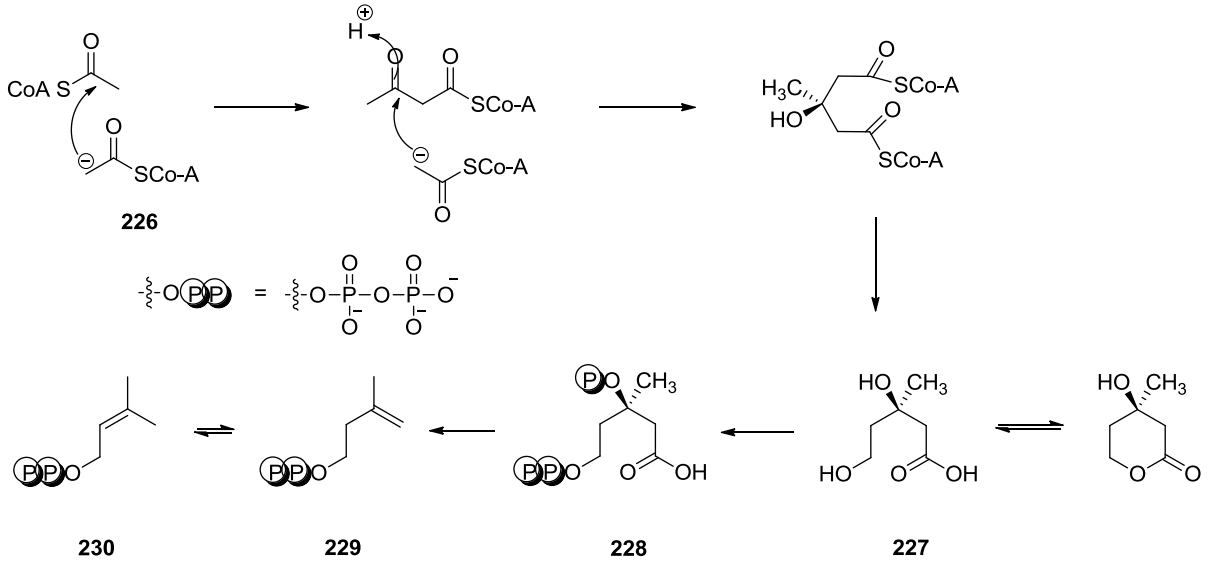
concavine (**225**)

Figure 6.1: Absolute structure of concavine (left) and depiction of the 4 isoprenoid residues (right).

6.2 Diterpenoids

Diterpenoids such as concavine (**225**) are naturally occurring molecules usually containing 20 carbon atoms derived from 4 isoprenoid residues. By examining the structure of concavine two of the isoprenoid residues are evident in the form of the prenyl chain and the geminal dimethyl moiety. The other two isoprenoid units form the bicyclo[3.2.1]octane ring system. Concavine (**225**) possesses two extra carbons which form the ethylene link between nitrogen and oxygen.

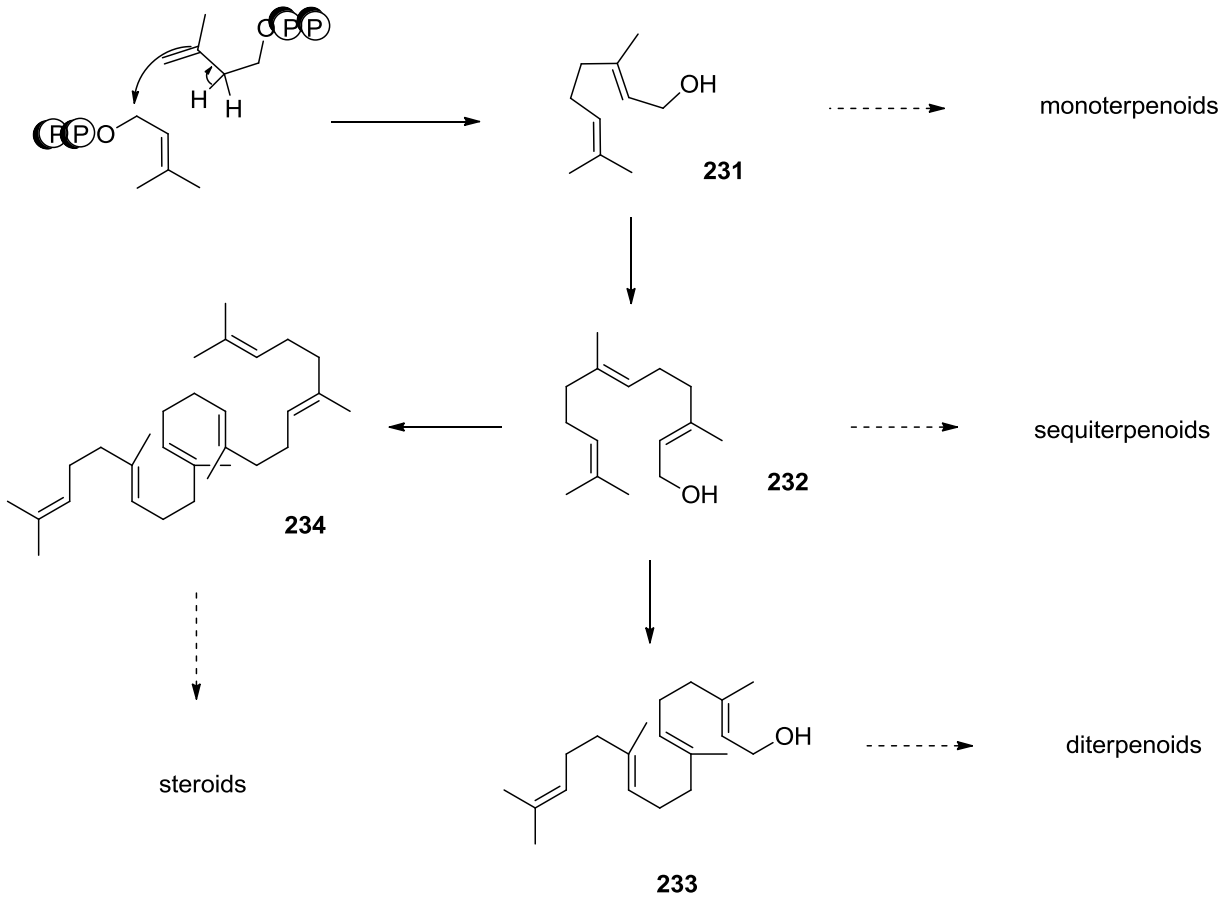
The biosynthesis of terpenoids and steroids begins with the combination of three units of acetyl coenzyme A (Co-A) (**226**) followed by reduction to give mevalonic acid (**227**) (Scheme 6.1). The corresponding pyrophosphate (**228**) can then be converted to isopentenyl pyrophosphate (**229**) which can isomerise to 3, 3-dimethylallyl pyrophosphate (**230**).



Scheme 6.1

The condensation of isopentenyl pyrophosphate (**229**) and 3,3-dimethylallyl pyrophosphate (**223**) gives the 10 carbon compound geranyl pyrophosphate and the corresponding free alcohol geraniol (**231**) (Scheme 6.2). Geranyl pyrophosphate or geraniol (**231**) are the precursors for the C_{10} monoterpenoids. Further addition of isopentenyl pyrophosphate (**229**)

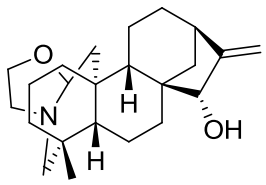
to geranyl pyrophosphate gives farnesol (**232**) and geranylgeraniol (**233**), which along with their pyrophosphate derivatives are the presumed precursors for the C_{15} sequiterpenoids and C_{20} diterpenoids respectively. The combination of two molecules of farnesyl pyrophosphate gives squalene (**234**), which is the precursor for the C_{30} steroids.



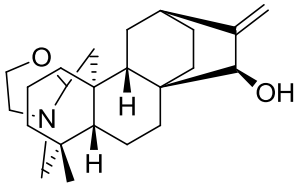
Scheme 6.2

Introduction of nitrogen into the structure can be achieved via incorporation of amino acids or their derivatives. For example, the *N*-(β-oxyethyl) moiety present in veatchine (**235**), atisine (**236**) and concavine (**225**) is most likely derived from the incorporation of ethanolamine into the diterpenoid structure. Ethanolamine is biosynthetically derived from the amine acid serine by decarboxylation *via* phosphatidylserine decarboxylase.[108] Varying degrees of oxidation of

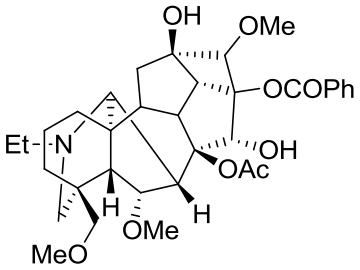
the diterpenoid framework can also be applied by hydroxylase enzymes and hydration;[109] for example, the heavily oxidised diterpene aconitine (**237**) (Figure 6.2).



veatchine (**235**)



atisine (**236**)



aconitine (**237**)

Figure 6.2

6.3 Structure Elucidation

As concavine (**225**) is not crystalline and therefore could not be subjected to X-ray crystallography, the proposed structure of this natural product was deduced by analysis of the mass spectrum, infrared spectrum and by nuclear magnetic resonance spectra. High resolution mass spectrometry indicated a *m*/*z* of 329.2720 which matches $C_{22}H_{35}NO$ (requires 329.2718). A peak in the mass spectrum at *m*/*z* 69/70 indicated the presence of an isoprenoid residue. Unsuccessful attempts were made to acetylate the compound and no significant peak was present in the carbonyl region of the IR spectrum which indicated the oxygen present in the molecule was part of an ether.

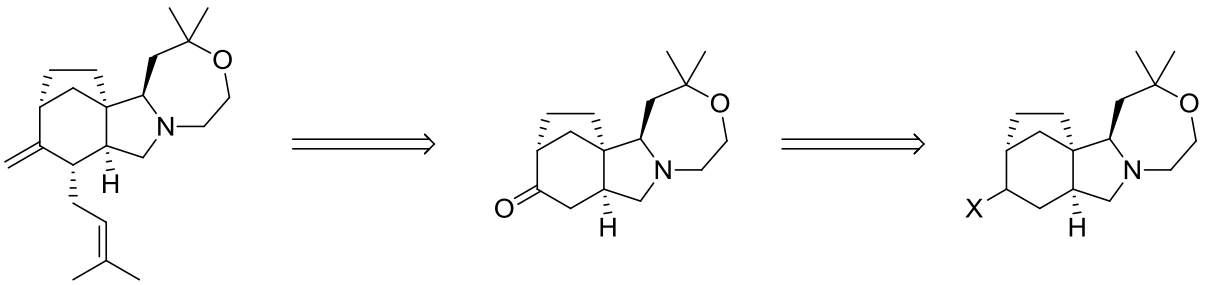
Further work to determine the overall structure and relative stereochemistry of this molecule relied on various NMR techniques. The ^{1}H NMR confirmed the presence of 35 hydrogen atoms and the ^{13}C NMR showed 22 resonances. Of the sp^3 hybridised carbon atoms within the molecule the following assignments were made: two quaternary carbons, four methine, eight methylene and four methyl. The ^{13}C NMR spectrum also showed the presence of one trisubstituted and one *gem*-disubstituted alkene. Two dimensional NMR spectra allowed the

framework to be constructed. Six separate fragments were identified using the proton-proton correlation technique (COSY) and then these fragments were connected using the long range proton-carbon correlation (HMBC).

The spatial arrangement within the molecule and therefore the relative stereochemistry was determined using NOESY and ROESY 2D NMR techniques which utilise the nuclear Overhauser effect (NOE).

6.4 Initial Retrosynthesis

Our initial retrosynthesis of concavine (**225**) started with the conversion of the exomethylene moiety to a ketone followed by removal of the prenyl chain to give tetracyclic ketone **238** (Scheme 6.3). This ketone (**238**) could conceivably be derived from an intermediate (**239**) containing a group (X) which would be introduced by the termination of a radical cyclisation cascade.

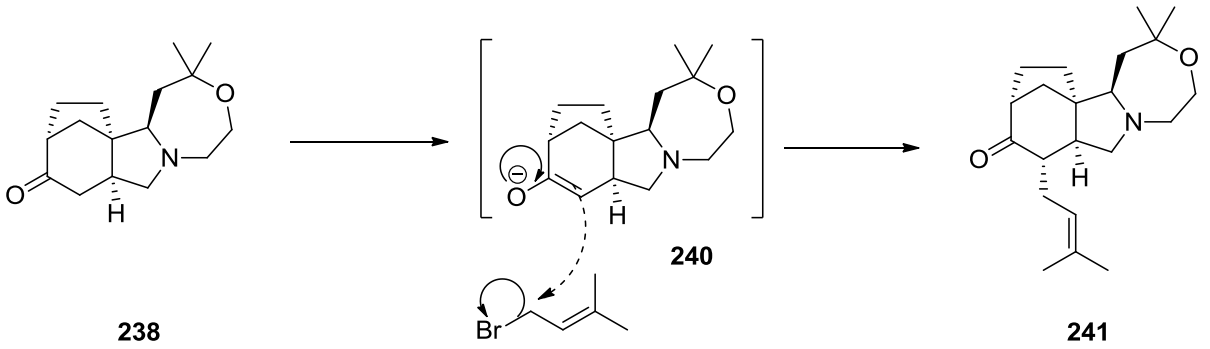


225 **238** **239**

Scheme 6.3

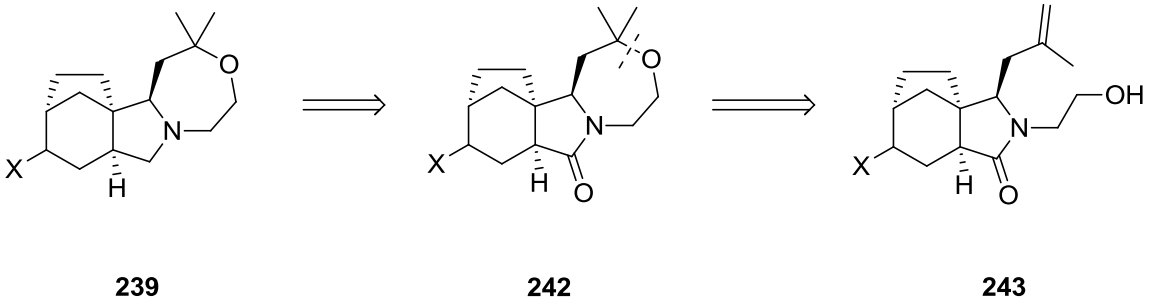
The synthesis of concavine (**225**) from ketone **238** would be achieved by deprotonation and alkylation followed by an olefination reaction such as the Julia-Kocienski olefination, the Wittig reaction or the use of the Tebbe reagent.[110] It was hoped that the prenyl chain could be introduced into the molecule by deprotonation of ketone **238** followed by addition of prenyl bromide to give alkylated product (**241**). The diastereoselectivity of this reaction was hoped to

arise from the shape of the molecule. The concave bicyclic core was predicted to direct the attack on the electrophile from the rear face of the molecule (**240**) (as drawn) anti to the pyrrolidine ring (Scheme 6.4).



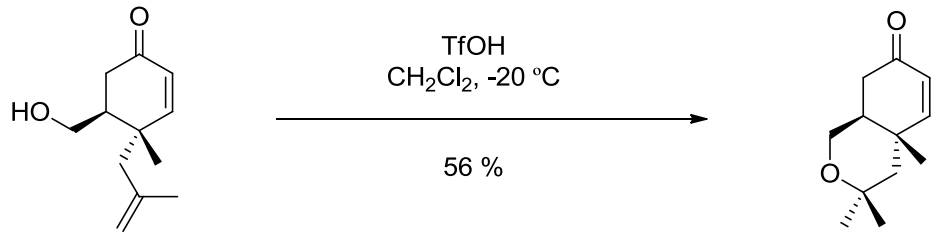
Scheme 6.4

If the X group in tertiary amine **239** was a xanthate then ketone **238** could be obtained by conversion to a sulphide followed by oxidation.[111] However, if the X group within intermediate **239** was *O*-tetramethylpyridyl (TEMPO) then conversion to a hydroxyl followed by oxidation would give ketone **238**.[112] The next step in our retrosynthesis was the introduction of a carbonyl to form a lactam (**242**) followed by the opening of the oxazepane ring to give compound **243** containing a hydroxyl and a methallyl group (Scheme 6.5). It was hoped that intermediate **239** could be synthesised from **242** by reduction of the γ-lactam using DIBAL-H or $LiAlH_4$.[113]



Scheme 6.5

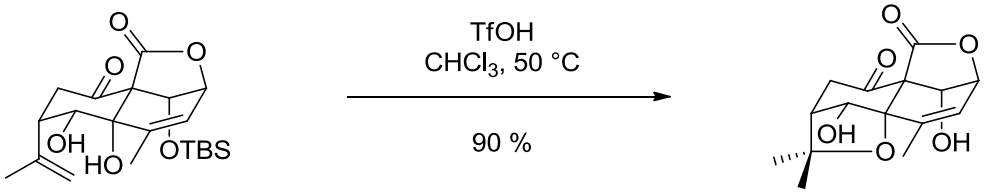
For the synthesis of the seven membered ether ring in concavine we found several examples in the literature which were relevant. In the process of preparing platensimycin analogues for biological evaluation, Nicolaou *et al*. reported the formation of a 6-membered ether ring.[114] Triflic acid was added to a solution of alcohol **244** in dichloromethane at -20 °C and ether **245** was isolated in 56 % (Scheme 6.6).



244 **245**

Scheme 6.6[114]

During the synthesis of (±)-3,4-Dideoxymaytol reported by White *et al.* in 1997 this methodology was also used.[115] A solution of diol **246** in chloroform was treated with triflic acid and the mixture was heated to 50 °C. The major compound which was isolated in 90 % was diol **247**, the product of cyclisation and desilylation (Scheme 6.7). The product of cyclisation with the silicon protecting group present was also obtained in 10 %.

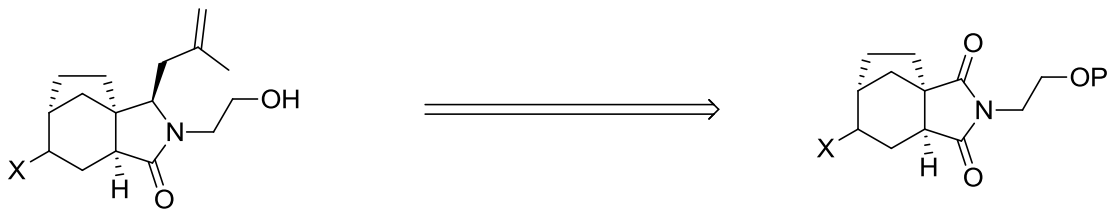


246 **247**

Scheme 6.7[115]

Our retrosynthesis continued with the replacement of the methallyl group with a carbonyl to form an imide and the protection of the hydroxyl to give compound **248** (Scheme 6.8). The

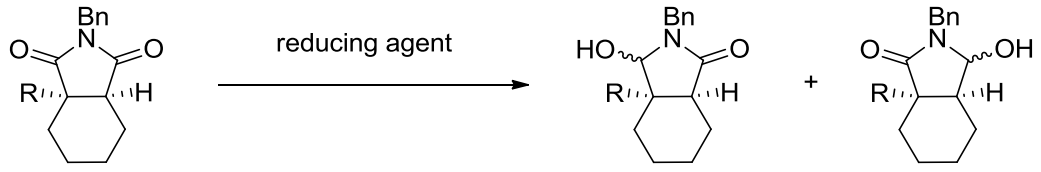
introduction of the methallyl group would be achieved by reduction of imide **248** to form a hydroxylactam followed by the use of *N*-acyl iminium ion methodology using a Lewis acid and an allyl silane.[116]



243 **248**

Scheme 6.8

In 2003, within the synthesis of the proposed structure of jamtine *N*-oxide our group reported the reductions of bicyclic imides **249a** and **249b**.[78] Using sodium borohydride in ethanol at -5 °C, benzyl substituted imide **249a** was reduced and a 2:1 mixture of hydroxylactams **250a** and **251a** was obtained in 68 % yield (Scheme 6.9). When **249a** was reduced with di*iso*butylaluminium hydride (DIBAL-H) in DCM at -78 °C the opposite outcome was found, a 2:1 mixture of **251a** and **250a** was isolated in 83 % yield. Methyl substituted imide **249b** was treated with both sodium borohydride and DIBAL-H, and **250b** was obtained exclusively in 99 and 82 % yield respectively. An array of similar results obtained using simpler cyclic imides have been collated by Speckamp.[117]



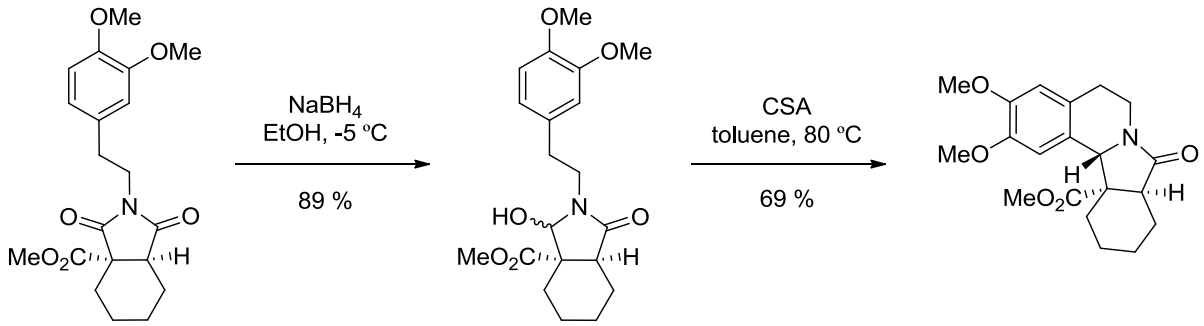
(+)-**249a** R = Bn
(–)-**249b** R = Me

250a R = Bn
250b R = Me

251a R = Bn
251b R = Me

Scheme 6.9[78]

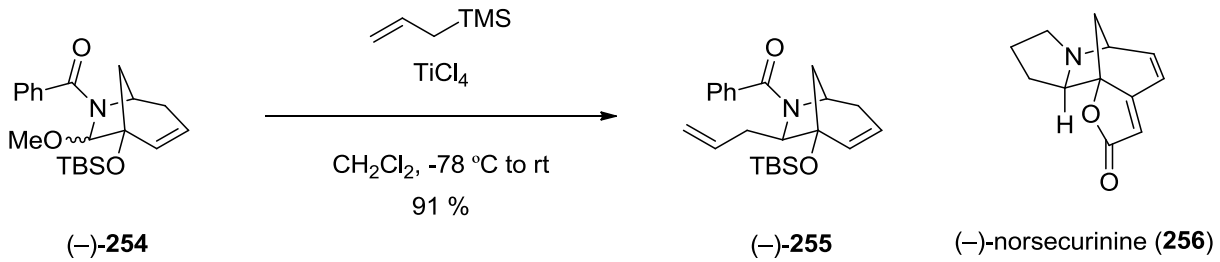
For the synthesis of jamtine *N*-oxide, acylated imide (–)-**163** was treated with sodium borohydride and exclusive proximal reduction of the imide moiety was observed, hydroxylactam **252** was isolated in 89 % (Scheme 6.10).[78] This hydroxylactam (**252**) was then heated in toluene in the presence of camphorsulfonic acid (CSA) to yield cyclised product (+)-**253** in 69 % via an *N*-acyliminium intermediate.



(–)-**163** **252** (+)-**253**

Scheme 6.10[78]

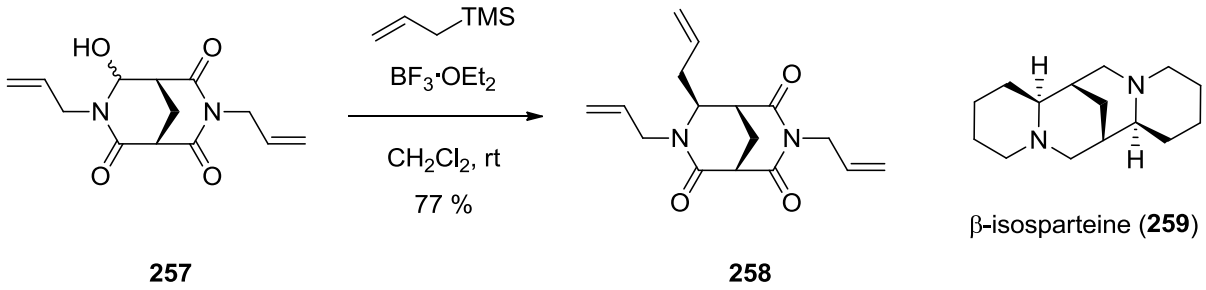
There are existing reports for the Lewis-acid mediated allylation of *N*-acyliminium ion intermediates derived from imides. For example, within investigations into the synthesis of (–)-norsecurinine (**256**), α-methoxybenzamide (–)-**254** was treated with allyltrimethylsilane and titanium tetrachloride leading to the isolation of allylation product (–)-**255** as a single diastereomer (Scheme 6.11).[118] This diastereoselectivity was rationalised as exclusive exo attack on the intermediate *N*-acyliminium ion by the allylsilane.



(–)-**254** (–)-**255** (–)-norsecurinine (**256**)

Scheme 6.11[118]

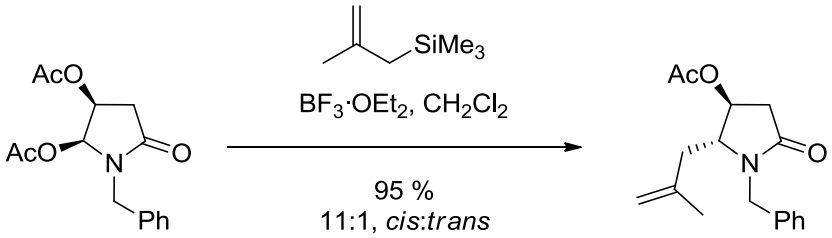
This methodology was also used in the total synthesis of (±)-β-isosparteine (**259**).[119] Allyltrimethylsilane and boron trifluoride diethyl etherate were added to hydroxylactam **257** and allylation product **258** was isolated in 77 % yield (Scheme 6.12).



257 **258**

Scheme 6.12[119]

The use of methallyltrimethylsilane in this type of reaction has also been previously reported by Speckamp.[120] Diacetate (–)-**260** was treated with methallyltrimethylsilane and boron trifluoride diethyl etherate and a 11:1 mixture (*cis:trans*) of allylation products was obtained. After recrystallisation *cis*-product (+)-**261** was isolated in 84 % yield (Scheme 6.13).



(–)-**260** (+)-**261**

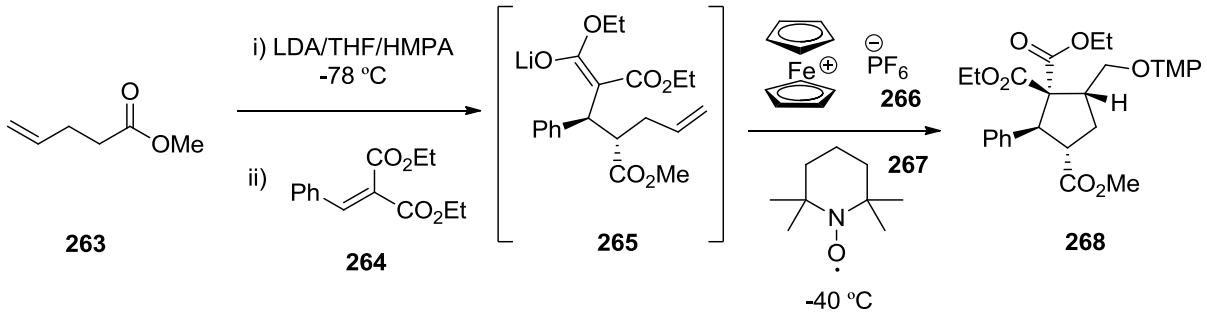
Scheme 6.13[120]

The conclusion of our retrosynthesis involved disconnection of the "X" group and the ethylene bridge to give unsaturated imide **262** (Scheme 6.14). We hoped that this could be achieved by a radical cyclisation terminating onto "X". As suggested above the "X" group could be either TEMPO or a xanthate moiety. Several publications gave us the inspiration to disconnect the molecule in this way.

248 **262**

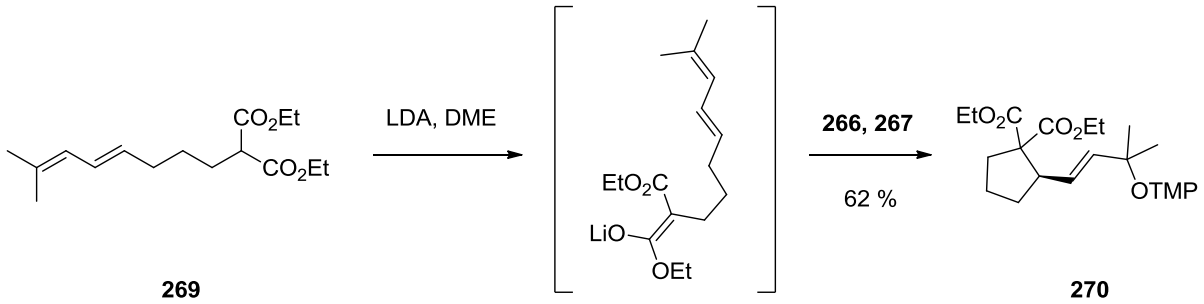
Scheme 6.14

In 2001, Jahn reported a tandem Michael addition/radical cyclisation for the synthesis of functionalised cyclopentanes.[121] Ester **263** was deprotonated using LDA/HMPA and the (*Z*)-enolate which formed attacked Michael acceptor **264** to give intermediate **265** (Scheme 6.15). This intermediate enolate was cooled to -40 °C and oxidised by addition of ferrocenium hexafluorophosphate (**266**). After radical cyclisation onto the terminal olefin the radical species which formed was quenched by the stable radical reagent TEMPO (**267**) to give compound **268**. This compound was then converted to the equivalent primary alcohol in 63 %.



Scheme 6.15[121]

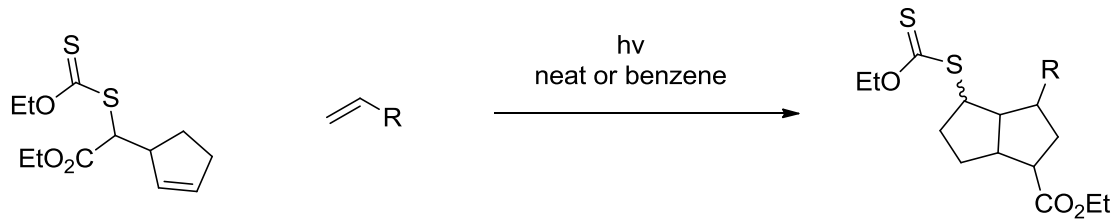
Another example of this type of radical cyclisation is shown in Scheme 6.16.[122] Dienylmalonate **269** was deprotonated by LDA and the resultant enolate was oxidised with ferrocenium hexafluorophosphate (**266**). After 5-*exo* radical cyclisation the radical species was trapped with TEMPO (**267**), giving adduct **270**.



269 **270**

Scheme 6.16[122]

As we were interested in carrying out an intermolecular radical cascade we were pleased to come across the following examples from the recent literature. In 1998, Saičić and co-workers showed that an intermolecular radical cyclisation cascade was possible using xanthate **271** and either alkene **272a** or **272b** (Scheme 6.17).[123] Neat alkene **272a** and xanthate **271** were irradiated with a 250 W high pressure mercury lamp and bicyclic product **273a** was isolated in 60 % yield. A solution of xanthate **271** and alkene **272b** in benzene were also irradiated in the same way and the product **273b** was isolated in 71 %.



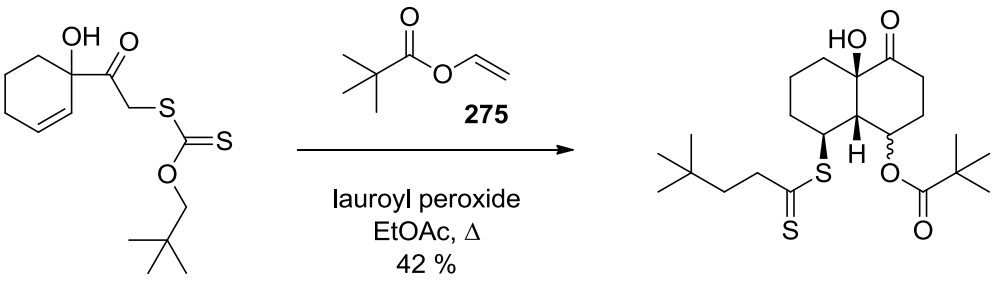
271

272a, R = OEt
272b, R= CH_2OAc

273a, R = OEt, 60 %
273b, R= CH_2OAc, 71 %

Scheme 6.17[123]

Another intermolecular radical cyclisation cascade is shown in Scheme 6.18. Treatment of xanthate **274** with alkene **275** and lauroyl peroxide in refluxing ethyl acetate gave rise to the formation of bicyclic product **276** in 42 % isolated yield.[124]

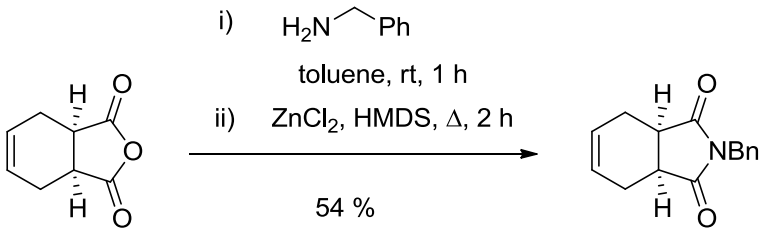


274 **276**

Scheme 6.18[124]

6.5 Radical Cyclisation Attempts

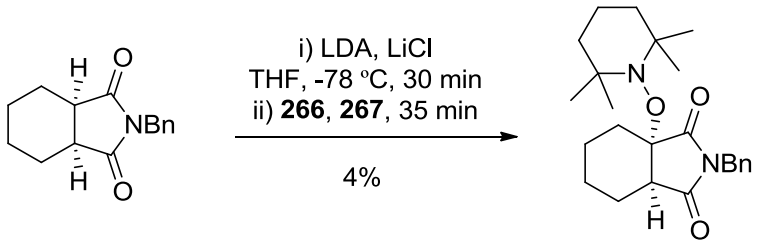
In order to test whether a cascade of radical cyclisations or a single radical cyclisation could be used to construct the ethylene bridge within the molecule a suitable model compound was constructed. Unsaturated bicyclic anhydride **277** was treated with benzylamine at room temperature followed by zinc(II) chloride and hexamethyldisilazane and the mixture was refluxed for 2 hours to give imide **278** in 57 % yield (Scheme 6.19).[79]



277 **278**

Scheme 6.19

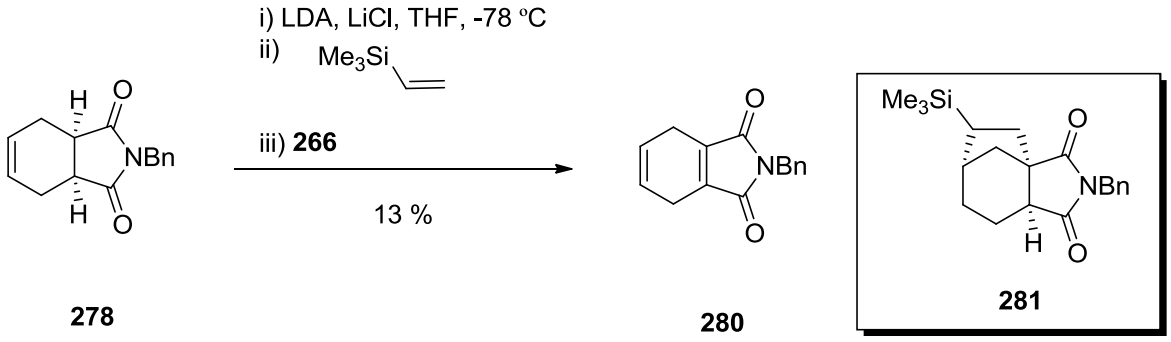
In order to test if the imide enolate could be oxidised directly to a radical species previously used imide substrate **151** was deprotonated with LDA and then a mixture of ferrocenium hexafluorophosphate (**266**) and the radical trap TEMPO (**267**) was added (Scheme 6.20). Adduct **279** was found to have been formed which proved that it was possible to oxidise the imide enolate to a radical however, **279** was only isolated in 4 % yield.



151 **279**

Scheme 6.20

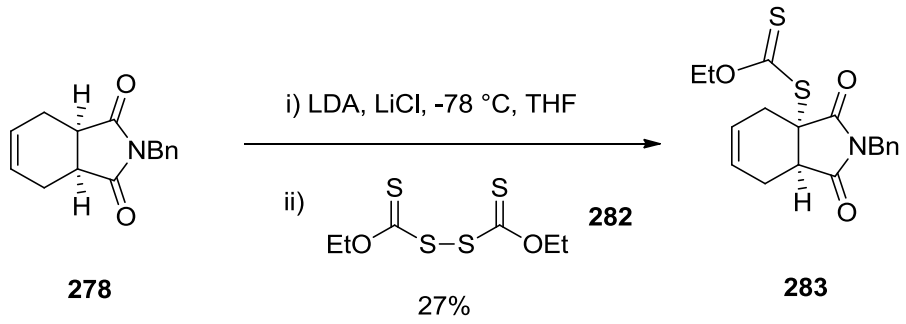
Unsaturated imide **278** was deprotonated using LDA-LiCl, vinyl trimethylsilane was added followed by addition of ferrocenium hexafluorophosphate (**266**) (Scheme 6.21). It was hoped that cyclised product **281** would be formed, however this product or a product analogous to **279** were not detected. Symmetrical unsaturated product **280** was isolated in 13 % yield.



278 **280** **281**

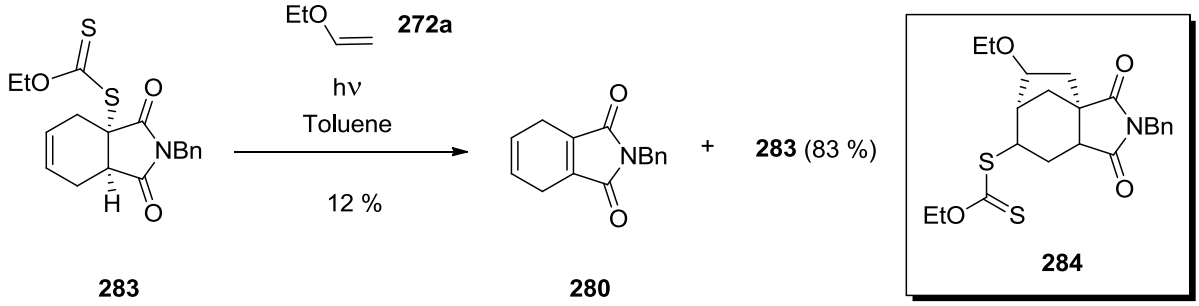
Scheme 6.21

Unsaturated imide **278** was then deprotonated using a mixture of lithium di*iso*propylamide and lithium chloride and treated with *O*, *O*-diethyl *bis*-xanthate (**282**), to yield xanthate **283** in 27 % yield (Scheme 6.22). *O*, *O*-diethyl *bis*-xanthate (**282**) was prepared, in accordance with a method previously reported by Beckman, in 52 % yield by exposure to an aqueous solution of potassium ethyl xanthate and a 10 % iodine/potassium iodide aqueous solution and vigorously stirring the mixture for one hour followed by standing for 48 hours.[125]



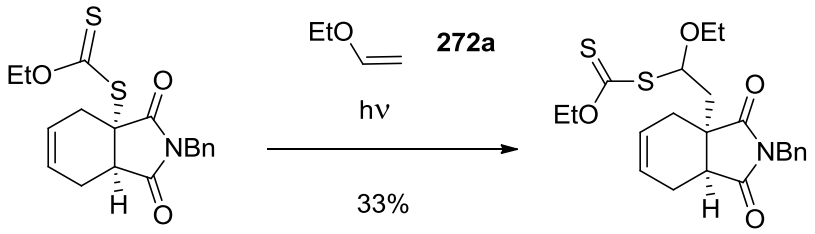
Scheme 6.22

An intermolecular radical cyclisation reaction was then attempted using substituted imide **283** following the methodology of Saičić (*vide supra*) (Scheme 6.17).[123] A solution of ethyl vinyl ether (**272a**) and xanthate **283** in toluene was irradiated with light for 100 minutes (Scheme 6.23). Our desired product (**284**) was not detected, however the dehydrogenated product (**280**) identified above was isolated in 12 % yield and unreacted xanthate **283** was recovered in 83 % yield.



Scheme 6.23

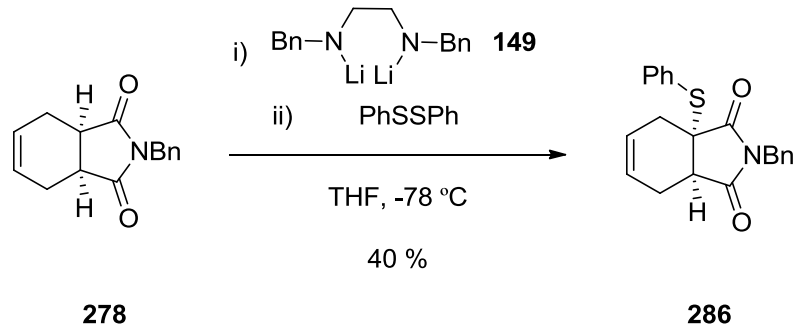
Imide **283** was then irradiated with light in neat ethyl vinyl ether (**272a**) for 90 minutes (Scheme 6.24). Once again none of the desired product (**284**) was detected, however intermediate xanthate **285** was isolated in 33 % yield as a single diastereomer. Further work to convert this product (**285**) to desired cyclised xanthate **284** was not successful.



283 **285**

Scheme 6.24

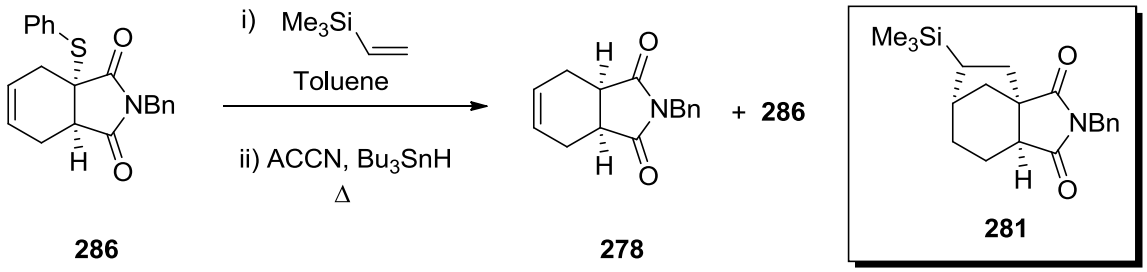
Substituted imide **286** was also synthesised (Scheme 6.25). Unsaturated imide **278** was treated with a solution of *bis*-lithiated base **149** followed by diphenyl disulfide and substituted imide **286** was isolated in 40 % yield.



278 **286**

Scheme 6.25

Using radical cyclisation methodology previously used within our group, for the synthesis of polycyclic indolines related to the stephacidin alkaloids, we attempted to synthesise tricyclic compound **281**.[126] A solution of substituted imide **286** and vinyl trimethylsilane in toluene at reflux was treated with 1, 1′-azo*bis*(cyclohexanecarbonitrile) (ACCN) and tributyltin hydride over 6 hours (Scheme 6.26). Tricyclic compound **281** was not detected, however symmetrical imide **278** and the substituted imide starting material (**286**) were found to be the two major species in the crude NMR. Analysis of samples taken over the course of the reaction time by ^{1}H NMR indicated that as imide **286** was consumed, the amount of imide **278** present increased.

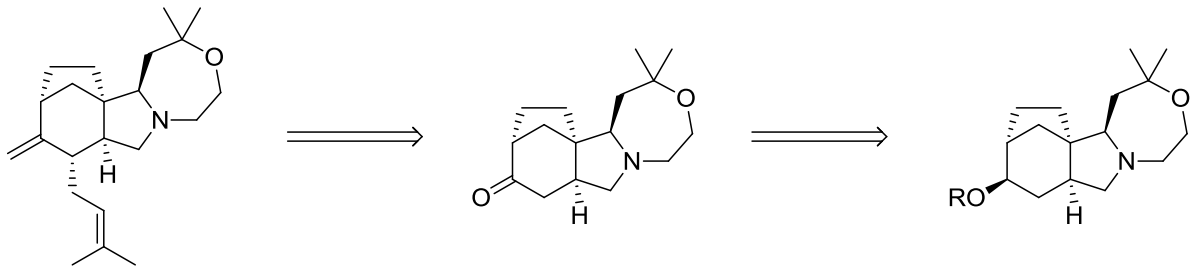


Scheme 6.26

As we had encountered problems forming the two carbon bridge moiety in the structure of concavine (**225**) we decided to explore other methods for forming this feature and investigate the synthesis of the oxazepane ring.

6.6 Revised Retrosynthesis

As we were not able to form the ethylene bridge by radical methodology a revised retrosynthesis was developed. This started as before with the conversion of the exo-methylene group to a ketone and the removal of the prenyl group to give **238** (Scheme 6.27). The ketone was then converted to an OR group, which could be acetate, methoxy or hydroxyl (**287a-c**).

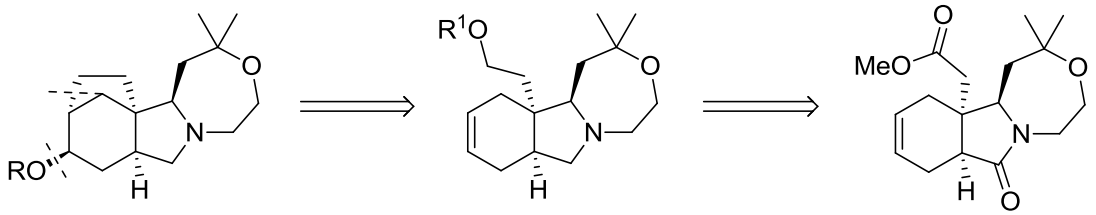


225 **238**

287a R = Ac
287b R = Me
287c R = H

Scheme 6.27

Removal of the hydroxyl (or protected hydroxyl) and disconnection of the adjacent bond (**287**) gives unsaturated sulfonic ester **288a-c** (X = Ts, Ms, Bs) (Scheme 6.28). Conversion of the sulfonic ester to a methyl ester and introduction of a carbonyl should give γ-lactam **289**.



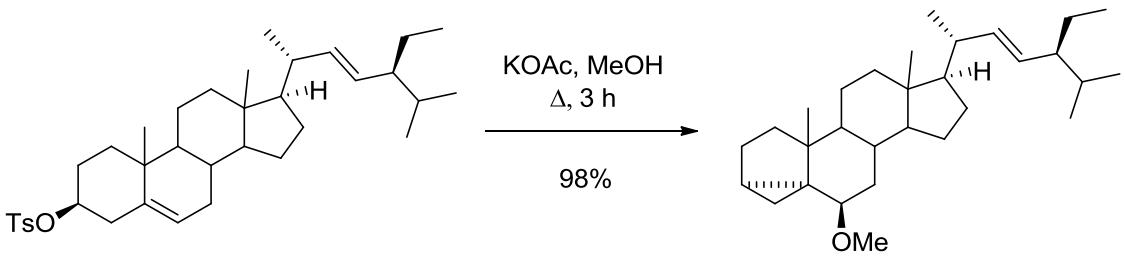
287

288a R^1 = Ts
288b R^1 = Ms
288c R^1 = Bs
288d R = H

289

Scheme 6.28

We hoped to be able to convert intermediate **288a-c** to **287** by a solvolysis reaction. There are several examples of this type of π-cyclisation reaction which have been reported in the literature. In 2011, Hoye and co-workers reported the tosylation of stigmasterol to give sulfonyl ester **290** in 75 % yield and then a solution of **290** in methanol was heated in the presence of potassium acetate to give cyclised product ester **291** in 98 % yield (Scheme 6.29).[127]

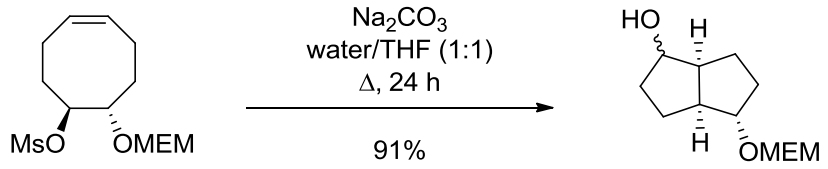


290

291

Scheme 6.29[127]

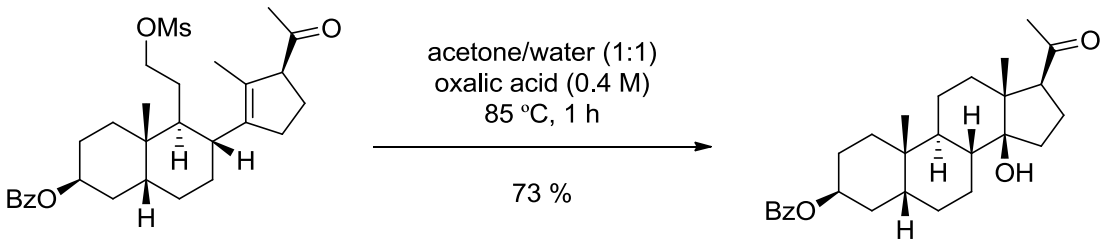
Another example of a solvolysis cyclisation was reported by Suemune and co-workers in 1998.[128] Sulfonyl ester **292** was heated in a mixture of water and THF (1:1) in the presence of sodium carbonate and alcohol **293** was isolated in 91 % as a 1:1 mixture of diastereomers (Scheme 6.30).



292 **293**

Scheme 6.30[128]

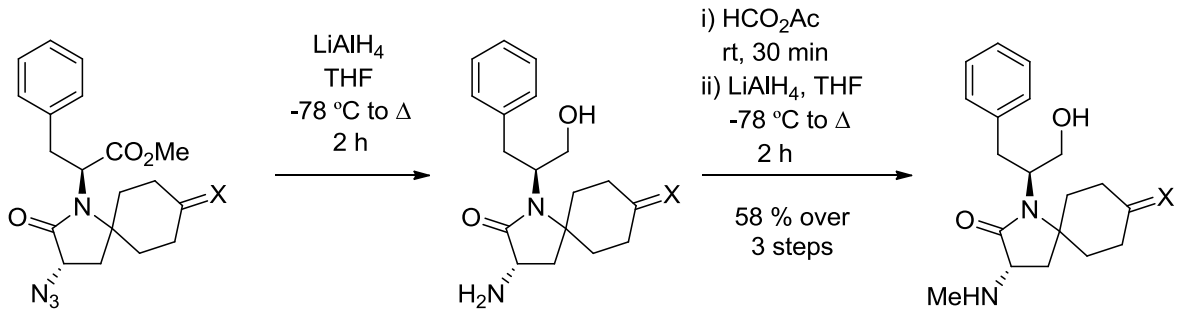
In 1989, Adeoti *et al.* reported the cyclisation of sulfonyl ester **294** using oxalic acid in acetone and water (1:1) (Scheme 6.31).[129] Tetracyclic alcohol **295** was isolated in 73 %.



294 **295**

Scheme 6.31[129]

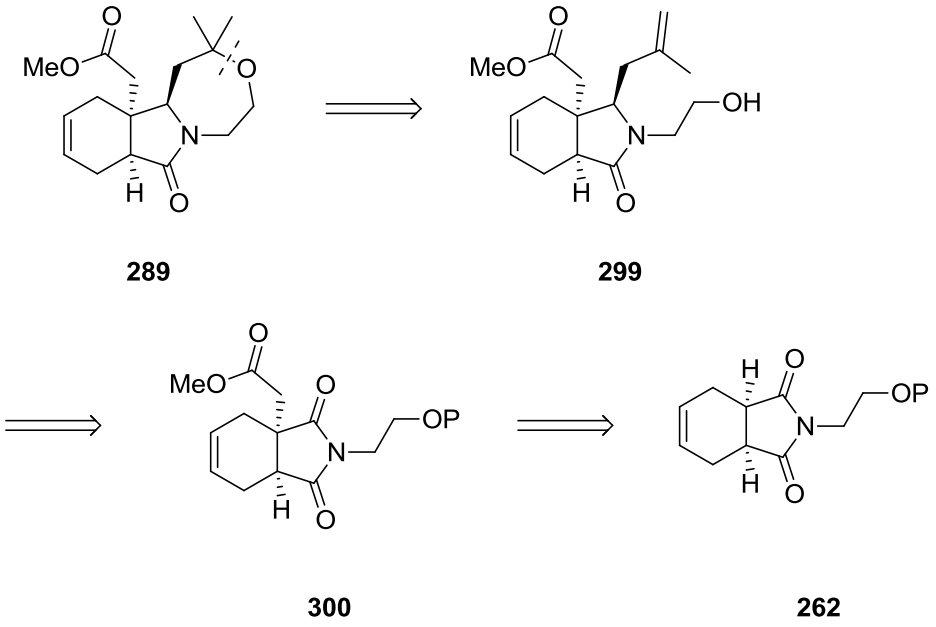
We planned to reduce the γ-lactam and the methyl ester present in intermediate **289** in one step using lithium aluminium hydride to give intermediate alcohol **288d** (X = H). Lithium aluminium hydride was used by Snider for the reduction of a methyl ester, a lactam and an azide in one step, within the synthesis of (+)-TAN1251C.[130] Azide (–)-**296** was treated with lithium aluminium hydride and crude amino alcohol **297** was obtained (Scheme 6.32). This amino alcohol was then formylated with acetic formic anhydride and then the resultant formamide was reduced with lithium aluminium hydride to give amino alcohol (–)-**298** in 58 % yield over 3 steps.



(–)-**296**, X = $O(CH_2)_4O$ **297**, X = $O(CH_2)_4O$ (–)-**298**, X = $O(CH_2)_4O$

Scheme 6.32[130]

The conclusion of the retrosynthesis involved the opening of the oxazepane ring to give **299** containing a hydroxyl and a methallyl group (Scheme 6.33). Replacement of the methallyl group with a carbonyl gave substituted imide **300** and the removal of the alkyl group containing the ester gave symmetrical imide **262**.



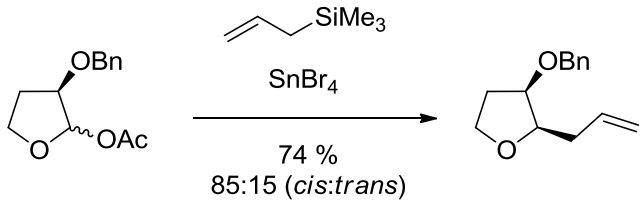
289 **299**

300 **262**

Scheme 6.33

It was hoped that the addition of the methallyl group to the *N*-acyliminium ion could be directed by the presence of the methyl ester on the opposite face of the molecule, to give compound **299** with the methallyl and ester groups *trans* with respect to each other. In the

comparable five-membered oxocarbenium ion system, the formation of a *cis* product is favoured. In 2005, Woerpel reported the allylation of dihydrofuran derivative **301** using tin(IV) bromide and allyltrimethylsilane (Scheme 6.34).[131] Allylated product **302** was formed in 75 % yield with a *cis*:*trans* ratio of 85:15.



301 **302**

Scheme 6.34[131]

This result is rationalised as follows. Intermediate conformation **303** is favoured over **304** in order for the alkoxy group (OBn) to be in pseudoequatorial orientation (Figure 6.3). Stereoelectronic effects dictate that the nucleophile will attack the oxocarbenium ion from the inside of the envelope conformation. For example, in conformer **303** the more electron-donating $\sigma_{C\text{-}H}$ orbital at C-3 (compared to $\sigma_{C\text{-}O}$) is efficiently overlapping and stabilising the developing σ^* orbital of the oxocarbenium ion at C-2 (Cieplak effect).[132] In conformer **304** it is the less electron-rich $\sigma_{C\text{-}O}$ bond at C-3 which overlaps the σ^* orbital at C-2. Therefore the addition of the nucleophile to conformer **303** from the inside face is favoured and this leads to selective formation of the 1,2-cis product **302**.

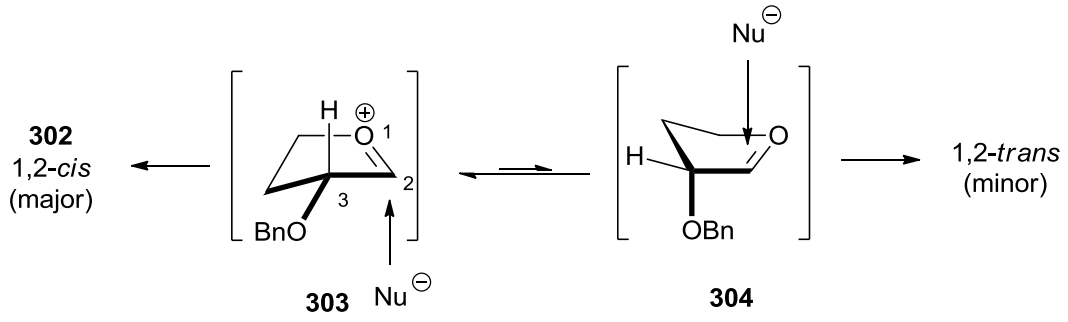


Figure 6.3

In the related five-membered-ring iminium ions (Figure 6.4), which we were interested in investigating, prediction of the stereochemical outcome is complicated by the presence of a carbonyl either within the ring or on the nitrogen substituent (R^1). Also the nature of the group attached to the oxygen atom (R^2) has been shown to affect the diastereoselectivity of the reaction and the following two examples demonstrate this effect.

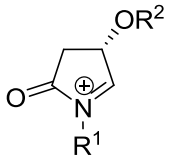
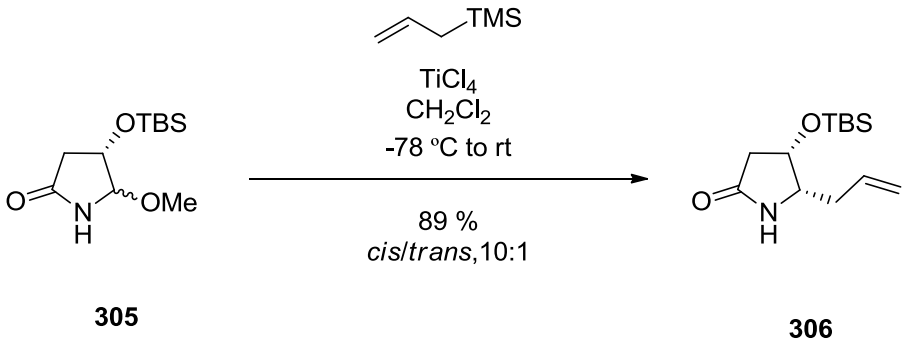


Figure 6.4

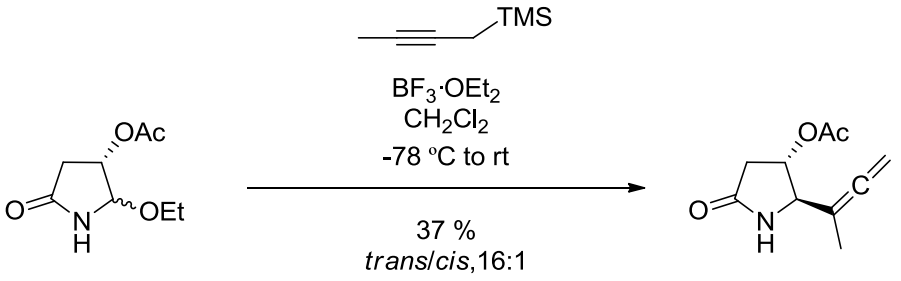
In 2000, Strekhan showed that the allylation of methoxylactam **305**, possessing a silyloxy group at C-4, was highly selective for the *cis* substituted lactam **306** (Scheme 6.35).[133] This lactam was formed in 89 % with a *cis*/*trans* ratio of 10:1.



305 **306**

Scheme 6.35[133]

In 2001, Hiemstra reported the formation of allene **308** from ethoxylactam **307**, with an acetoxy group at C-4, in 37 % yield (Scheme 6.36).[134] The reaction was found to be highly distereoselective with a *trans*/*cis* ratio of 16:1.



307 **308**

Scheme 6.36[134]

These two results can be explained in a similar way to the attack on oxocarbenium ions discussed above. For the conversion of methoxylactam **305** to lactam **306**, intermediate conformation **309** was proposed in order to maximise overlap between the $\sigma_{C\text{-}H}$ orbital at C-4 and the σ^* orbital at C-5 (Figure 6.5). Nucleophilic attack from the inside of the envelope conformation leads to *cis* product **306**. With regard to the conversion of acetoxy substituted ethoxylactam **307** to lactam **308**, the *trans* selectivity was explained by neighbouring-group participation of the acetoxy group. As shown in Figure 6.6, nucleophilic attack on bicyclic cationic intermediate **310** explains the selectivity for *trans* product **308**.

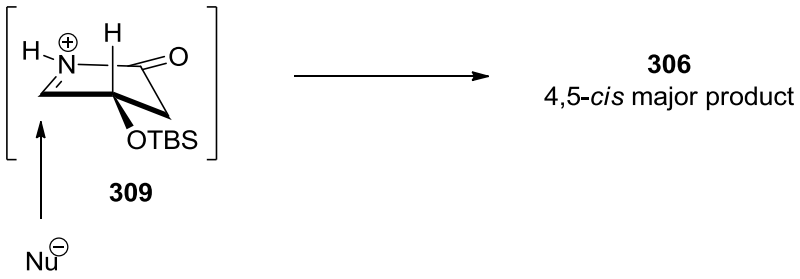
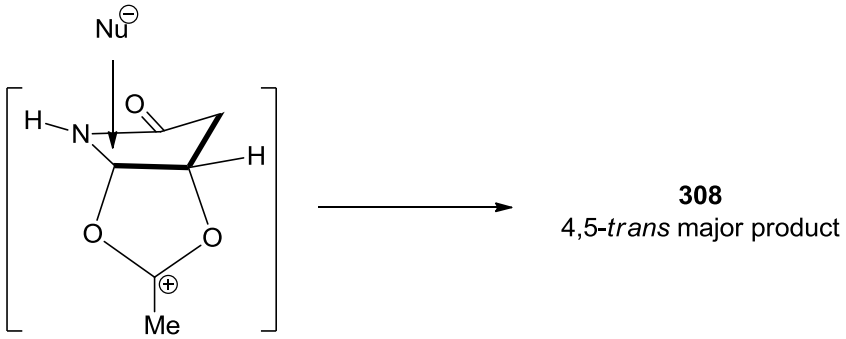


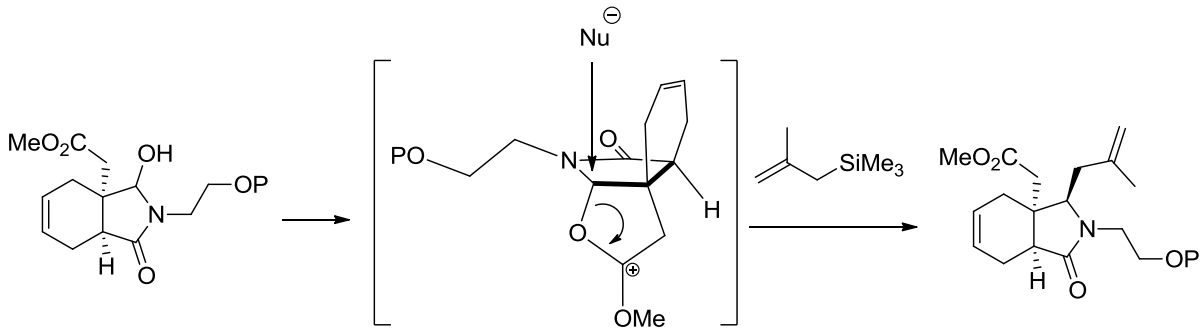
Figure 6.5



310

Figure 6.6

It was hoped that for our synthesis the methyl ester present in intermediate **311** would allow the formation of a similar cationic intermediate (**312**) (Scheme 6.37). Nucleophilic attack of this intermediate in a pseudo-S_N2 manner by a methallylsilane would allow selective synthesis of intermediate **313**.

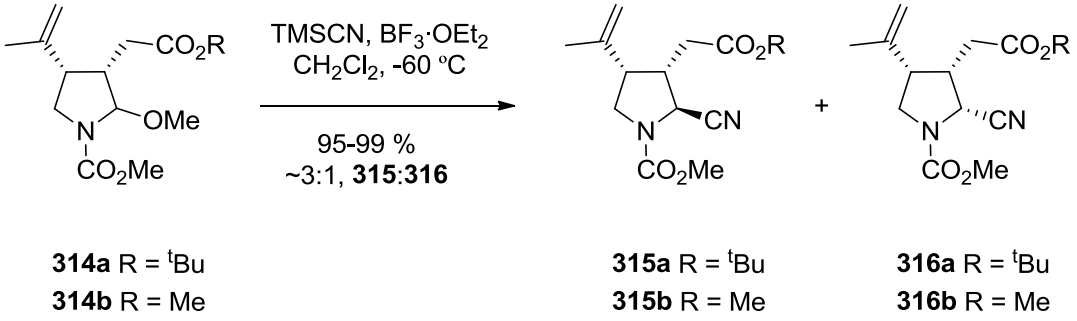


311 **312** **313**

Scheme 6.37

Obtaining a mixture of trans and cis products might be anticipated however. For example, in Fukuyama's synthesis of (–)-kainic acid from (+)-carvone, late stage intermediate **314** was cyanated using *N*-acyliminium methodology and *trans* product **315** was formed selectively in a ~3:1 ratio (*trans*:*cis*) (Scheme 6.38).[135] When a *tert*-butyl ester was present (**314a**), *trans* product **315a** and *cis* product **316a** were isolated in 73 % and 26 % yield respectively. Methyl

ester **314b** was found to produce 2,3-*trans* substituted pyrrolidine **315b** in 72 % yield and 2,3-*cis* substituted pyrrolidine **316b** in 23 %.



314a R = ^{t}Bu
314b R = Me

315a R = ^{t}Bu
315b R = Me

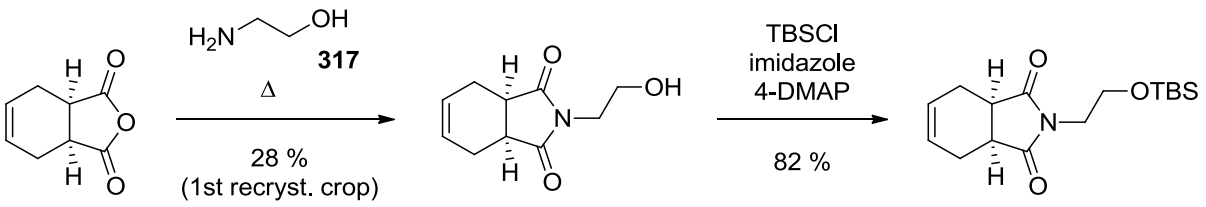
316a R = ^{t}Bu
316b R = Me

Scheme 6.38

Ultimately the diastereoselectively of this reaction did not matter in this case, as it was found that *cis* product **316a** could be epimerised to *trans* product **315a**. The formation of a cationic intermediate with participation of the C-3 ester group, similar to **312** (Scheme 6.37), was not discussed in this case however it is possible that formation of this species is leading to the modest *trans* selectivity.

6.7 Synthesis of the Fused Oxazepane Ring

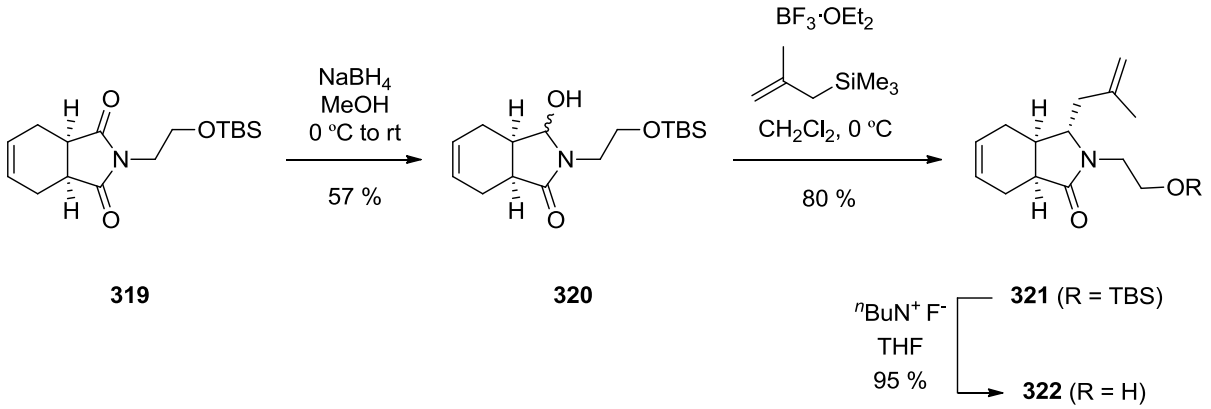
The required protected alcohol **319** was synthesised in two steps from commercially available anhydride **277** (Scheme 6.39). Heating anhydride **277** in the presence of ethanolamine (**317**) gave quantitative conversion to alcohol **318**, which was then silyl protected in 82 % yield to give *tert*-butyldimethylsilyl ether **319**.[136]



277 **318** **319**

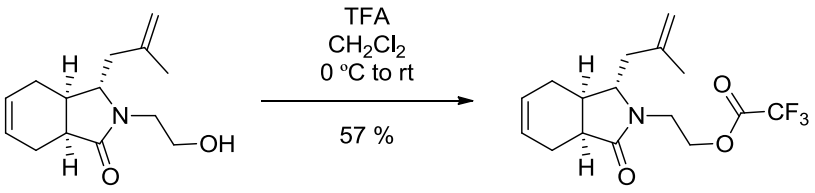
Scheme 6.39

A model compound was then constructed which would allow reaction conditions to be found for the acid catalysed ether formation (Scheme 6.40). Silyl ether **319** was reduced using sodium borohydride to give *N*-acyliminium ion precursor hydroxylactam **320** in 57 % yield as a 2:1 mixture of diastereomers. A mixture of hydroxylactam **320** and 2-methylallyltrimethylsilane in dichloromethane at 0 °C was treated with boron trifluoride diethyl etherate and after one hour allylated product **321** was isolated in 80 % yield. Treatment of this product (**321**) with tetrabutylammonium fluoride (TBAF) allowed alcohol **322** with the presumed stereochemistry shown to be isolated in 95 % yield.



Scheme 6.40

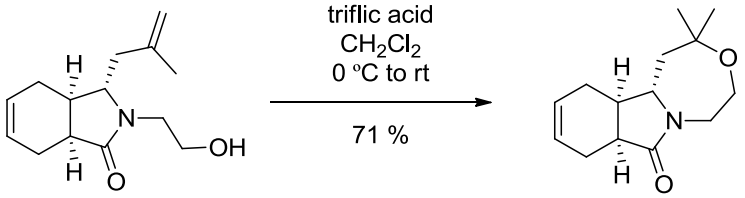
We then attempted to effect the formation of the oxazepane ring using various acidic reagents including Amberlyst-15, *para*-toluenesulfonic acid, trifluoroacetic acid and triflic acid. When Amberlyst-15 and *para*-toluenesulfonic acid were used no change was observed and the starting material was recovered. When trifluoroacetic acid (TFA) was used a new product was observed, however from the ^{1}H NMR it did not appear to have cyclised (Scheme 6.41). It was thought that ester **323** with the presumed stereochemistry shown had formed as a mass of 354.1297 was observed in the HRMS spectrum ($C_{16}H_{20}F_3NO_3Na$ requires 354.1293) and the methallyl chain was clearly visible in the ^{1}H NMR spectrum.



322 **323**

Scheme 6.41

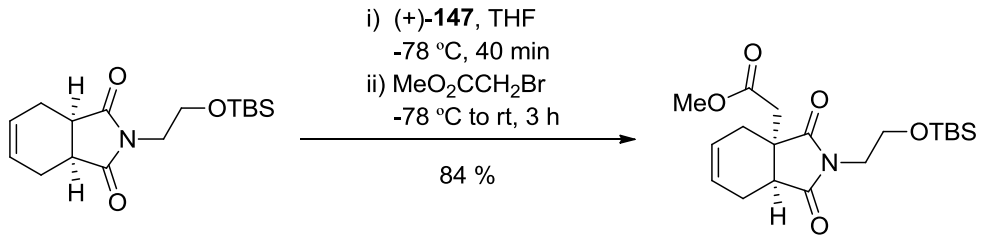
A solution of alcohol **322** was then treated with trifluoromethanesulfonic acid and analysis of the ^{1}H NMR spectrum indicated that a new product had formed, as two methyl singlets were present at 1.2-1.3 ppm. Ether **324** with the presumed stereochemistry shown was isolated in 71 % yield (Scheme 6.42).



322 **324**

Scheme 6.42

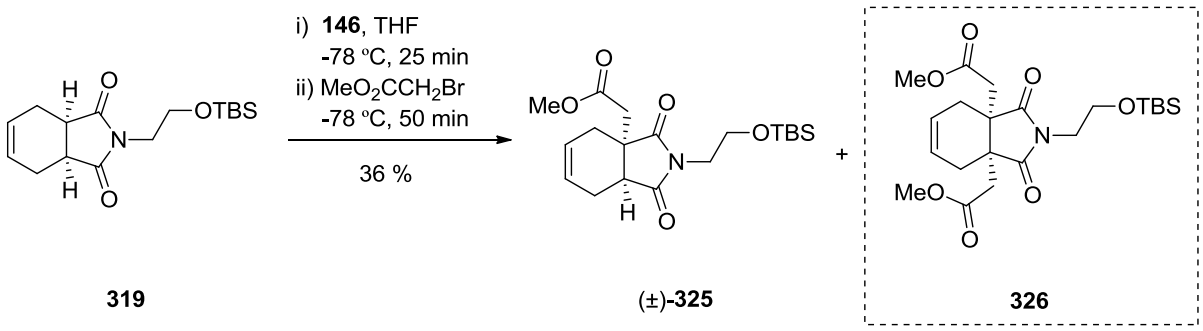
Enantioselective deprotonation of imide **319** with chiral lithium amide (+)-**147** allowed access to ester (–)-**325** by quenching the enolate with methyl bromoacetate (Scheme 6.43). Ester (–)-**325** was isolated in 84 % yield. The enantiomeric excess of this compound was not determined.



319 **(–)-325**

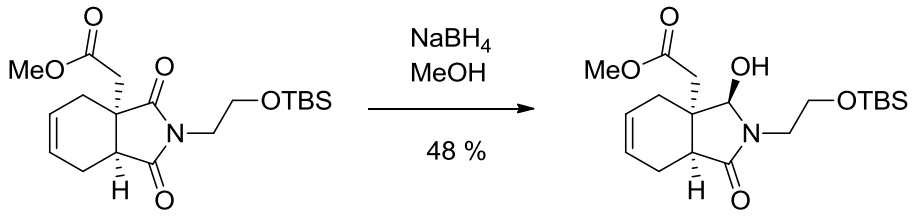
Scheme 6.43

Racemic ester (±)-**325** was also synthesised in 36 % yield using 2.0 equivalents of *mono*-lithiated achiral diamine base **146** (Scheme 6.44). When 1.1 to 1.3 equivalents of **146** were used for this transformation around 50 % conversion from **319** to (±)-**325** was found by ^{1}H NMR analysis of the crude product mixture. The separation of **319** and **325** by column chromatography was not found to be effective using various volumes of silica gel and solvent mixtures. Therefore in order to ensure full consumption of the starting material, 2.0 equivalents of *mono*-lithiated achiral base **146** were used. As expected the yield of the product ((±)-**325**) was reduced, as dialkylated product **326** was also formed. This situation was preferable though as it allowed access to pure (±)-**325**.



Scheme 6.44

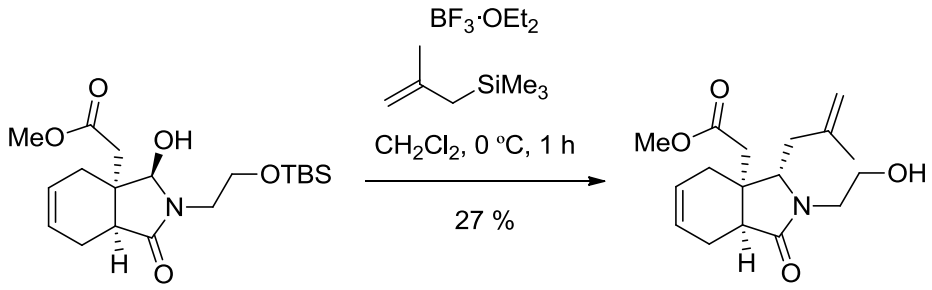
N-acyliminium ion precursor hydroxylactam **327** was then synthesised in 48 % from ester **325** using sodium borohydride (Scheme 6.45). As well as unreacted starting material, a single diastereomer was observed in the crude ^{1}H NMR (which is presumed to be the structure shown in Scheme 6.54) and after purification of this compound 2D NMR experiments allowed the regioselctivity to be determined. As shown previously by our group reduction with sodium borohydride occurred proximal to the substitution (*vide supra*).[78]



(±)-**325** **327**

Scheme 6.45

Hydroxylactam **327** was then treated with boron trifluoride diethyl etherate in the presence of 2-methylallyltrimethylsilane to form lactam **328** (Scheme 6.46). This compound arose via the formation of an *N*-acyliminium intermediate which was attacked by the allyl silane to form an intermediate TBS-protected alcohol, which was not isolated. The presence of fluoride within the reaction allowed free alcohol **328** to be isolated in 27 % yield. A similar example of this is present in Jamison's synthesis of amphidinolide T1.[137]



327 **328**

Scheme 6.46

As stated above, we hoped that the presence of the ester group on the convex outer face of the molecule would either block attack of the *N*-acyl iminium intermediate from this face or provide anchimeric assistance. Either of these effects would lead to desired product **299** with the methallyl and ester containing chain in an *anti* relationship. However when the isolated product alcohol **328** was submitted to ^{1}H NMR NOE techniques the relationship was found to

be *syn*. As shown in Figures 6.6 and 6.7, when proton H_4 was irradiated no interaction was found to H_8, however a NOE was observed to H_{9A}. This indicates that the allyl chain is on the same side of the molecule as the irradiated proton (H_4) and therefore the ester moiety. As would be expected a NOE was also observed to the CH_2 group adjacent to the ester (C_{15}) and the two protons *cis* to H_4 within the cyclohexene ring (H_{3A} and H_{6A}).

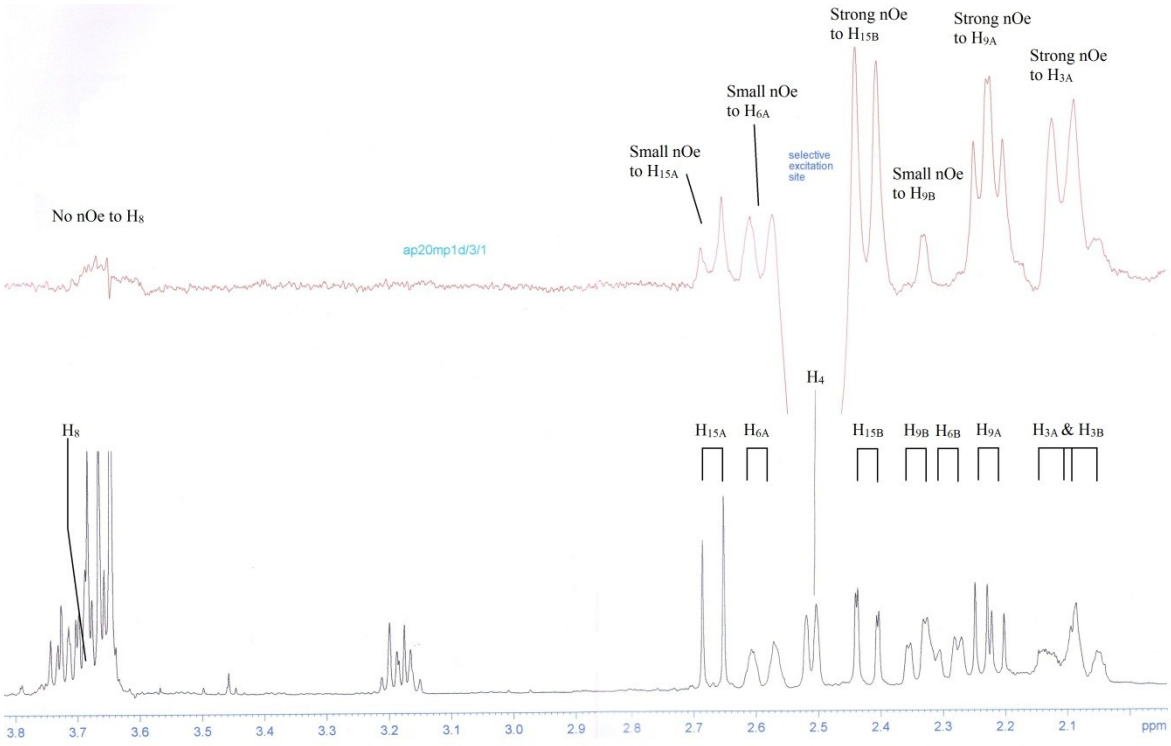


Figure 6.6: NOE Spectrum (500 MHz, $CDCl_3$) of alcohol **328** with irradiation at 2.46-2.54 ppm (H_4).

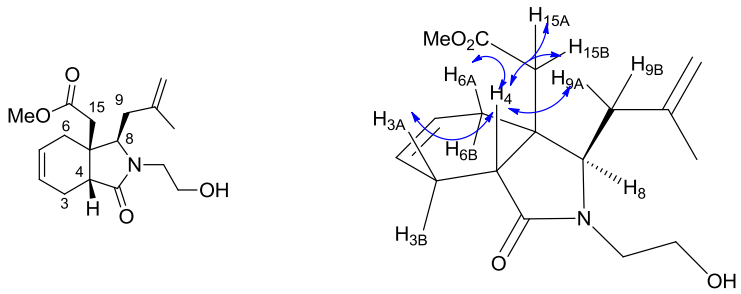
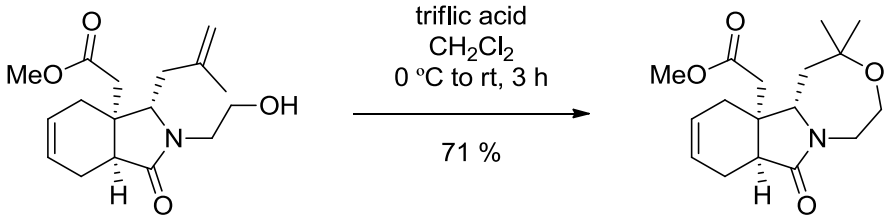


Figure 6.7: Alcohol **328** with NOE's highlighted.

Although we now knew that alcohol **328** did not have the desired stereochemistry we decided to attempt the cyclisation of this compound. Treatment of a solution of alcohol **328** with triflic

acid at 0 °C and subsequent warming to room temperature gave ether **329** in 71 % isolated yield (Scheme 6.47). We also found that cyclisation could be achieved using copper(II) triflate in refluxing dichloroethane, however the crude ^{1}H NMR spectrum indicated that the reaction did not proceed as smoothly and side products had formed. The crude ^{1}H NMR spectrum of the triflic acid mediated cyclisation reaction indicated the absence of **328** and the presence of only ether **329**.

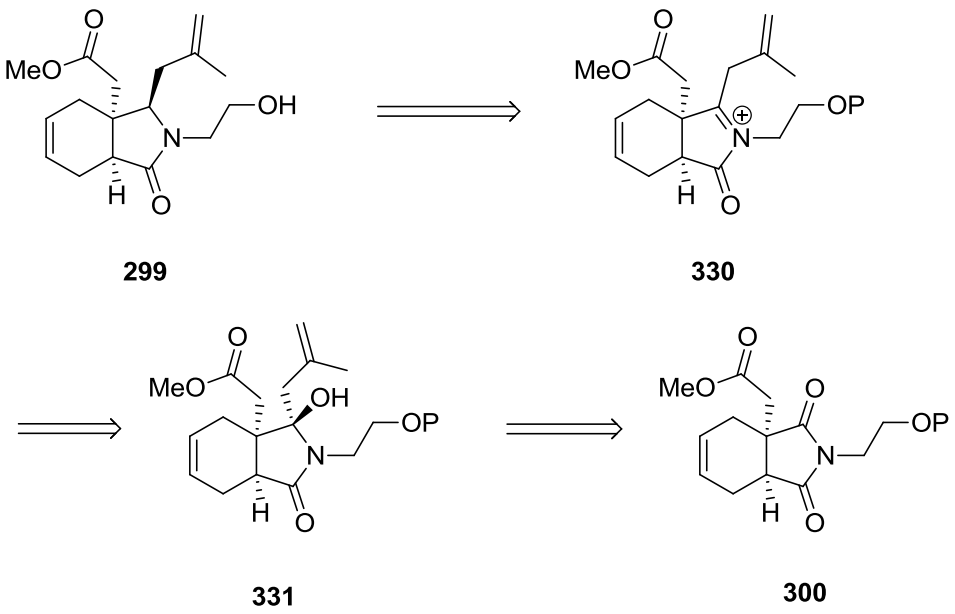


328 **329**

Scheme 6.47

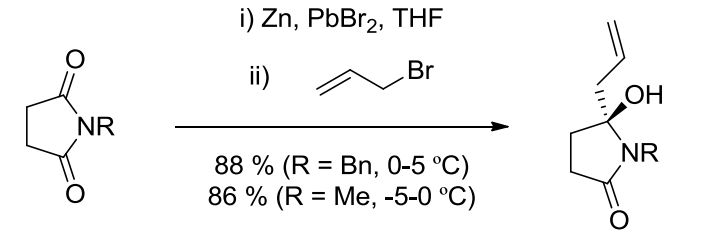
6.8 Revised Retrosynthesis II

As we had found that the addition of the allylsilane to the *N*-acyl iminium intermediate did not produce the stereochemistry required for the natural product we needed to change our planned synthesis. The key changes which are present in our most recent retrosynthesis are shown in Scheme 6.57. Protection of alcohol **299** followed by removal of a hydride gave *N*-acyl iminium cation **330**. This intermediate could be derived from the corresponding tertiary alcohol **331** and upon removal of the methallyl group from this compound we arrived at the previously synthesised imide (**300**) containing an ester group.



Scheme 6.48

It was hoped that hydride addition to *N*-acyliminum intermediate **330** would occur from the convex *exo* face of the molecule, in accordance with the previously observed addition of methallyl silane to the *N*-acyliminium ion derived from hydroxylactam **327**. This would allow us to access alcohol **299** with the correct relative stereochemistry. It was also hoped that addition of a methallyl organometallic reagent to imide **300** would occur at the imide carbonyl proximal to the ester moiety. In order to generate an intermediate analogous to hydroxylactam **331**, we decided to follow the method reported by Kim in 2004.[138] In this report, a solution of cyclic imide **332a** in THF was treated with zinc and lead(II) bromide and then allyl bromide was added dropwise. Hydroxylactam **333a** was isolated in 88 % (Scheme 6.49).



332a, R = Bn
332b, R = Me

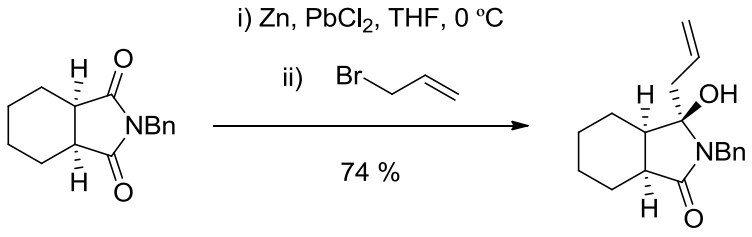
333a, R = Bn
333b, R = Me

Scheme 6.49

In addition, Kim reported that under similar reaction conditions *N*-methyl imide **332b** could be converted to hydroxylactam **333b** in 86 % isolated yield. *N*-benzylphthalimide was also reported to be allylated in 95 % yield.

6.9 Reversing the Stereochemistry Adjacent to Nitrogen

Owing to limitations of the remaining time, only initial additions of allyl groups to a symmetrical imide (**151**) were performed. Following Kim's procedure, substituting lead(II) chloride for lead(II) bromide, bicyclic imide **151** was allylated giving hydroxylactam **334a** in 74 % isolated yield (Scheme 6.50).

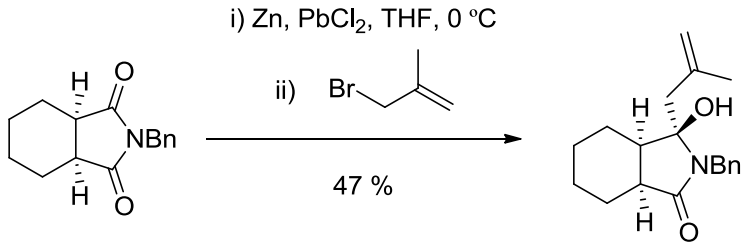


151

334a

Scheme 6.50

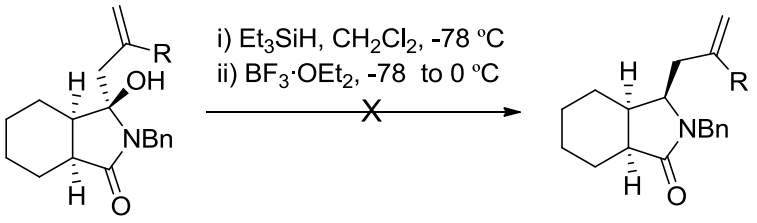
A suspension of bicyclic imide **151**, lead(II) chloride and zinc was also treated with 3-bromo-2-methylpropene and methallylated hydroxylactam **334b** was isolated in 47 % yield (Scheme 6.51).



151 **334b**

Scheme 6.51

We then attempted to convert these hydroxylactams (**334**) to lactam (**335**) *via* an *N*-acyliminium ion intermediate. A mixture of hydroxylactam **334** and triethylsilane in dichloromethane at -78 °C was treated with boron trifluoride diethyl etherate and allowed to warm gradually to 0 °C (Scheme 6.52). Unfortunately the desired products (**335a** & **335b**) were not isolated. In the case of the conversion of **334a** to **335a**, by TLC **334a** was consumed and two new products were formed.



334a, R = H
334b, R = Me

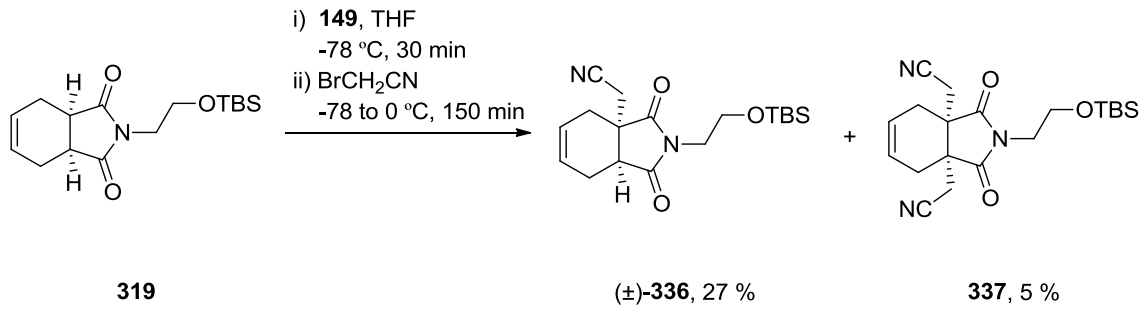
335a, R = H
335b, R = Me

Scheme 6.52

After isolation of these two products (presumed to arise from *exo* and *endo* addition of hydride to the *N*-acyliminium ion intermediate) by silica gel chromatography, we found by TLC and NMR that both products had degraded to approximately 3-4 compounds. Unfortunately this could not be reinvestigated with the time available.

6.10 Other Compounds Synthesised

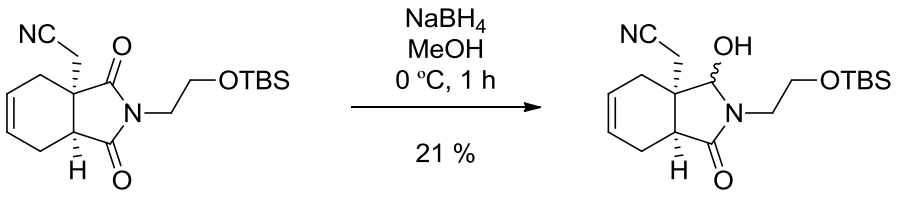
In the process of investigating the synthesis of concavine several other compounds were synthesised. Initially we simultaneously synthesised an analogue of **325** containing a nitrile group in place of the ester group (Scheme 6.53). *Bis*-lithiated diamine base **149** was used for the deprotonation of symmetrical imide **319** and the enolate formed was quenched with bromoacetonitile. Nitrile (±)-**336** was formed in 27 % isolated yield and dialkylated product **337** was found in 5 % yield.



319 (±)-**336**, 27 % **337**, 5 %

Scheme 6.53

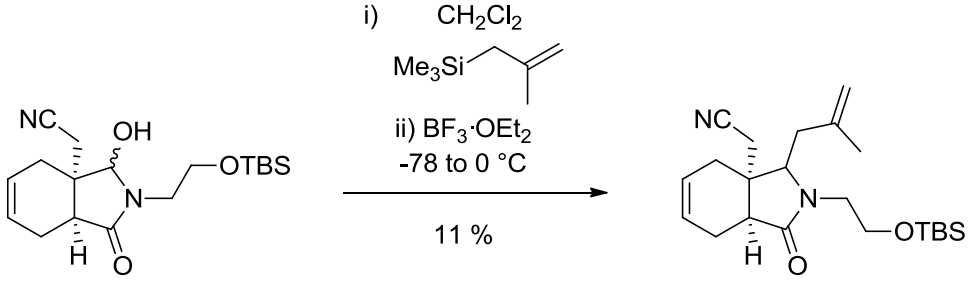
Imide **336** was then treated with sodium borohydride in methanol and hydroxylactam **338** was isolated in 21 % yield (Scheme 6.54). As the starting material appeared to be consumed it is possible that the rest of the material was a primary amine, where sodium borohydride had reduced the nitrile. However no primary amine product was isolated and in the literature reduction of nitriles with sodium borohydride requires elevated reaction temperatures and additives such as nickel,[139] iodine,[140] cobalt[141] or indium.[142]



(±)-336 **338**

Scheme 6.54

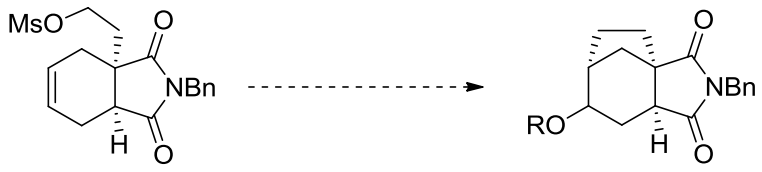
A mixture of hydroxylactam **338** and 2-methylallyltrimethylsilane at -78 °C was then treated with boron trifluoride diethyl etherate and the mixture was warmed to 0 °C (Scheme 6.55). TLC analysis indicated the consumption of hydroxylactam **338** and the presence of 4-5 products. After purification the desired product (**339**) was isolated in only 11 % yield. The relative stereochemistry of this compound was not investigated.



338 **339**

Scheme 6.55

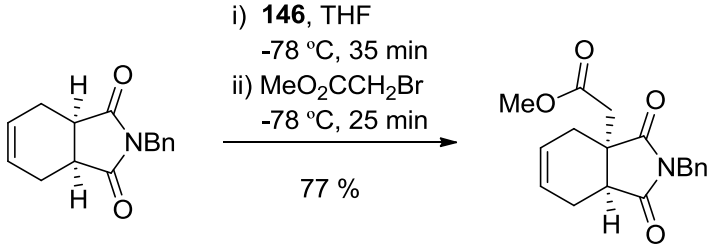
Towards the end of the project we attempted to synthesise a model compound (**340**) to test the application of a π-cyclisation for the introduction of the ethylene bridge and the synthesis of **341** (Scheme 6.56).



340 **341**

Scheme 6.56

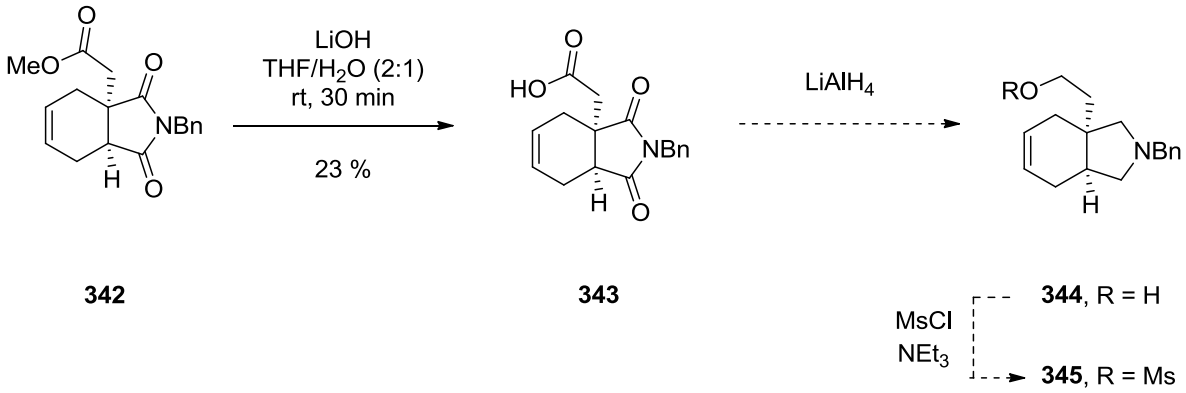
Previously prepared imide **278** was converted to ester **342** by deprotonation with *mono*-lithiated diamine base **146** and alkylation with methylbromoacetate (Scheme 6.57). Ester (±)-**342** was isolated in 77 %.



278 (±)-**342**

Scheme 6.57

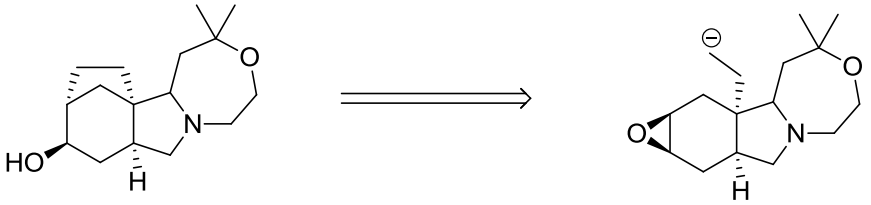
Saponification of ester **342** was then performed using lithium hydroxide in THF and water (2:1) at room temperature (Scheme 6.58). After 30 minutes the starting material was found to have been consumed, however after acidification and purification carboxylic acid **343** was isolated in only 23 % yield. Reduction of this compound with borane (BH_3·THF) at 0 °C resulted in hydroboration of the olefin whereas the use of DIBAL-H at -78 °C gave a mixture of between 4-5 products from which the desired product was not isolated. In the future, the use of lithium aluminium hydride to perform a global reduction and synthesise alcohol **344** may be preferable. Conversion of alcohol **344** to mesylate **345** would then allow a variety of π-cyclisation conditions to be tested.



342 **343**

Scheme 6.58

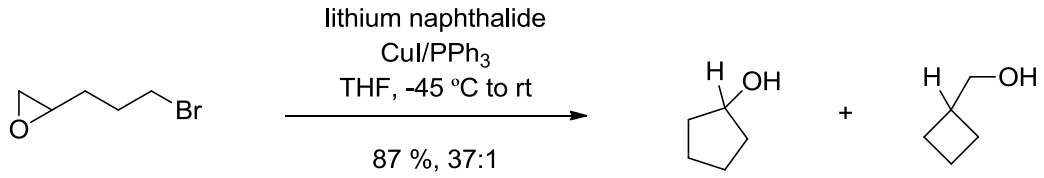
Earlier in the project we considered the construction of the ethylene bridge and installation of a hydroxyl group (as a precursor for the exo-methylene moiety) by the opening of an epoxide (Scheme 6.59).



287c **346**

Scheme 6.59

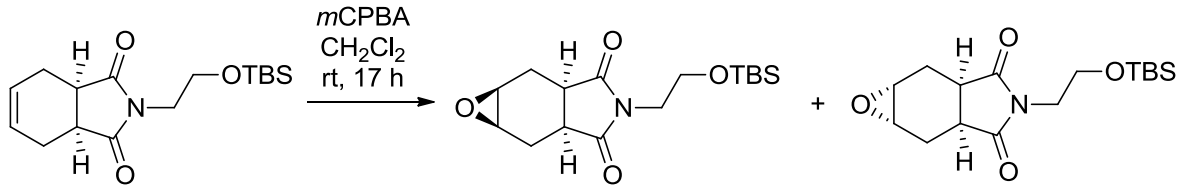
It was hoped that this could be achieved following a method reported by Rieke in 1989. The use of lithium naphthalide, copper iodide and triphenylphosphine to cyclise 5-bromo-1,2-epoxypentane (**347**) (Scheme 6.60) was reported. Conversion from **347** to alcohols **348** and **349** (37:1) was reported to be 87 %.



347 **348** **349**

Scheme 6.60[143]

Epoxidation of imide **319** using *meta*-chloroperoxybenzoic acid, following conditions reported by Kishali and Kara, was performed (Scheme 6.61).[144] In this report analogous *N*-ethyl and *N*-phenyl bicyclic imides were epoxidised and unexpectedly the *syn* isomer was found to be the major product (4:1, *syn*:*anti*). When we carried out the epoxidation of imide **319** under the same conditions, the crude ^{1}H NMR indicated that two products were present, also in a 4:1 ratio. After purification the major isomer (*syn*-**350**) was isolated in 57 % yield and the minor isomer (*anti*-**351**) was isolated in 17 % yield.



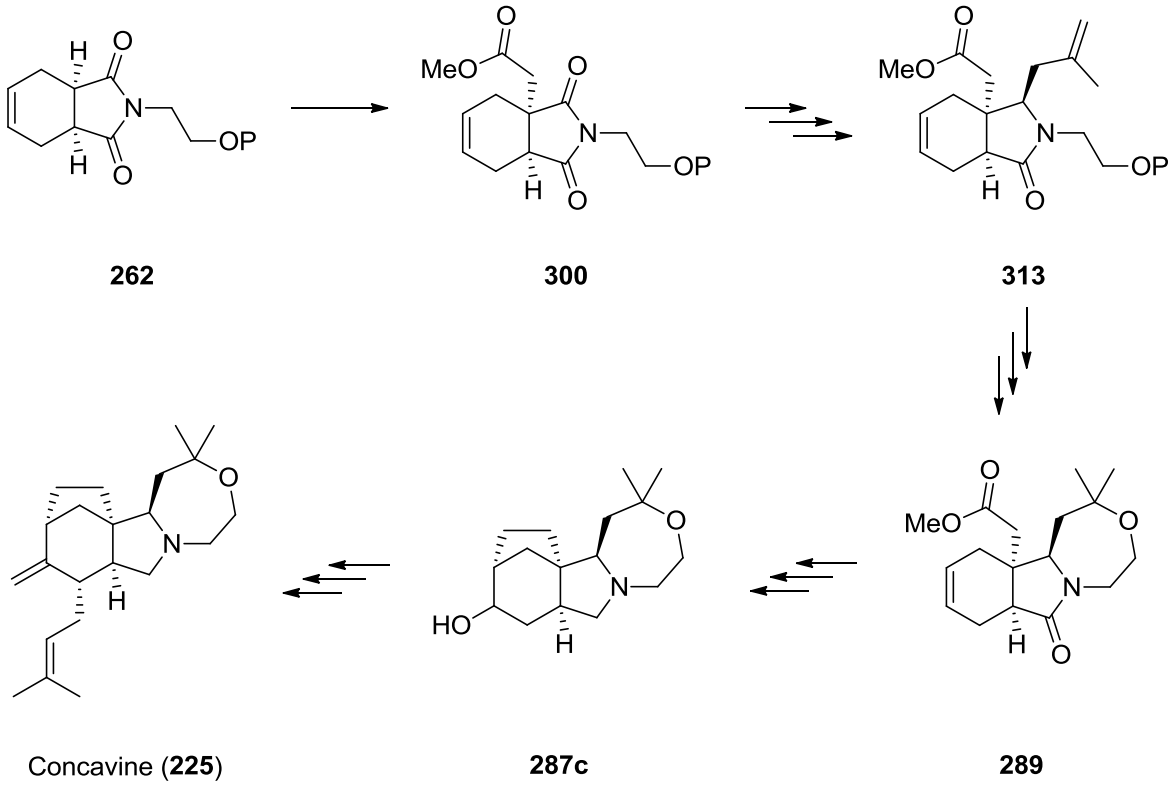
319 **350**, 57 % **351**, 17 %

Scheme 6.61

The unexpected *syn* epoxide formation, with respect to the imide moiety, was rationalised by invoking electronic interactions between the peroxy acid, the imide moiety and the alkene, which would not be possible during the formation of the *anti* isomer.[144] Previously the stereoselective oxidation of 5,6-dimethyl-2-phenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-diones were reported by Kishikawa and the selectivity for *syn* epoxide formation was explained using the same interactions.[145]

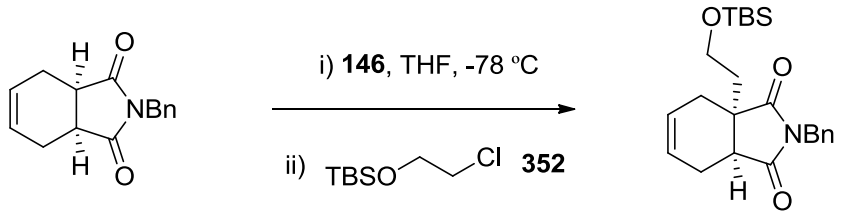
6.11 Future Work

In the future it is hoped that the synthesis of concavine (**225**) can be completed. The key steps in this enantioselective synthesis would be the use of chiral base **147** to introduce asymmetry, diastereoselective introduction of the methallyl chain and cyclisation to introduce the ethylene bridge (Scheme 6.62).



Scheme 6.62

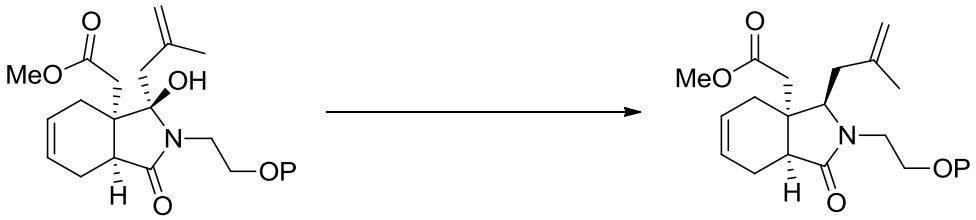
The synthesis of a model compound to test the introduction of the ethylene bridge *via* solvolysis/π-cyclisation should be investigated (Scheme 6.63). Rapid access to mesylate **340** may be achieved from symmetrical imide **278** *via* TBS-protected alcohol **353**. Deprotonation of imide **278** with base **146** and addition of commercially available alkyl halide **352**, would allow (±)-**353** to be synthesised. Deprotection of **353** and mesylation would give mesylate **340** which could then be subjected to the various π-cyclisation given above.



278 (±)-**353**

Scheme 6.63

More conditions also need to be attempted to synthesise compound **313** with the correct diastereoselectivity. With the material available we were only able to attempt the reduction of hydroxylactam **334** using triethylsilane and boron trifluoride diethyl etherate. If hydroxylactam **331** can be synthesised then hopefully reduction of the *N*-acyliminium ion intermediate will occur from the *exo* face of the molecule, in accordance with the previously observed addition of allyl silane in the formation of intermediates **321** and **328** (Scheme 6.64).



331 **313**

Scheme 6.64

If conditions for the synthesis of these two structural features can be found then the enantioselective total synthesis of concavine should be possible in 11-13 steps from hexahydrophthalic anhydride (**277**).

Chapter 7: Experimental

7.1 General Methods

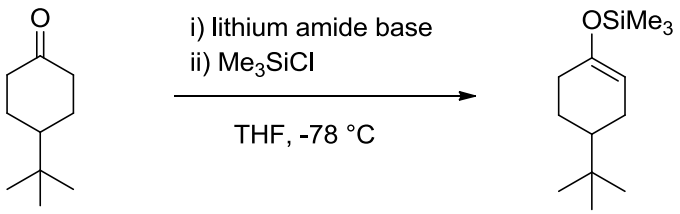
Reactions were carried out in oven dried flasks under nitrogen using dry solvents. Anhydrous tetrahydrofuran was distilled from sodium benzophenone ketyl and sodium metal under a nitrogen atmosphere. Trimethylsilyl chloride (Me_3SiCl) and di*iso*propylamine ($^{i}Pr_2NH$) were freshly distilled from calcium hydride under a nitrogen atmosphere. All reagents were used as received from commercial suppliers unless otherwise indicated.

NMR data were recorded on a Bruker AV300, AC300, AVIII300, AV400 or AVIII400 spectrometer in deuterated chloroform (unless otherwise indicated) and spectra were calibrated using residual solvent peaks (^{1}H = 7.26 ppm; ^{13}C = 77.16 ppm). The multiplicities of ^{1}H NMR signals are abbreviated as follows: br (broad), s (singlet), d (doublet), t (triplet), q (quartet), quin. (quintet), m (multiplet). Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FTIR spectrometer.

The progress of reactions was monitored by thin layer chromatography using Merck silica gel 60 F_{254} plates, which were visualized with UV light and *p*-anisaldehyde, potassium permanganate or ninhydrin. Flash column chromatography was carried out using Davisil 60Å silica gel and the indicated solvent systems. Melting points were measured using a Gallenkamp melting point apparatus. Optical rotations were measured using an Optical Activity PolAAr 2001 automatic polarimeter.

7.2 General Procedures

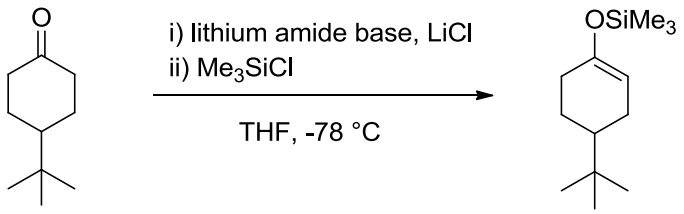
General Procedure A: Use of a single lithium amide base to synthesise enol silane **34**.



1 **34**

n-Butyllithium (488 μL, 0.78 mmol, 1.6 M solution in hexanes) was added dropwise to a solution of amine (0.78 mmol) in THF (2 mL) at -78 °C. The base mixture was stirred at -78 °C for 10 min and then at 0 °C for 20 min before being returned to -78 °C. A solution of 4-*tert*-butylcyclohexanone (**1**) (100 mg, 0.65 mmol) in dry THF (2 mL) at 0 °C under N_2 was added dropwise by syringe. After stirring at -78 °C for 30 min, freshly distilled chlorotrimethylsilane (412 μL, 3.25 mmol) was added. The reaction was stirred at -78 °C for 1 h and then triethylamine (0.2 mL) and sat. $NaHCO_{3\,(aq)}$ (5 mL) were added to quench and the mixture was returned to room temperature. The mixture was diluted with Et_2O (20 mL) and washed with sat. $NaHCO_{3\,(aq)}$ (2 × 20 mL). The aqueous phases were combined and extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield crude enol silane **34**: R_f = 0.75 (EtOAc:petroleum ether, 1:19); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.17 (s, 9H), 0.86 (s, 9H), 1.14-1.32 (m, 2H), 1.73-1.85 (m, 2H), 1.94-2.11 (m, 3H), 4.83 (dt, J = 5.7, 2.1 Hz, 1H). The reaction conversion and enantiomeric excess (when chiral bases were used) were determined by chiral GC using a Chiralsil DEX-CB capillary column: carrier gas H_2 (100 kPa); 127 °C (8 min)-129 °C; temperature gradient 0.2 °C/min; t_R = 11.5 [**1**], t_R = 12.7 [(*S*)-**34**], t_R = 13.0 [(R)-**34**].

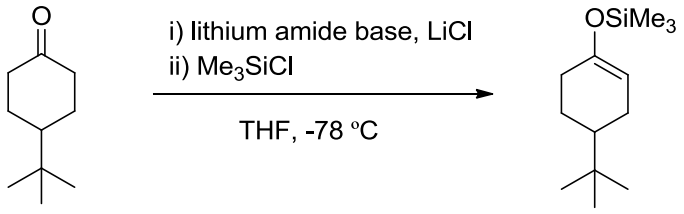
General Procedure B: Use of a single lithium amide base and *in situ*-generated lithium chloride (1:1) to synthesise enol silane **34**.



1 **34**

n-Butyllithium (975 μL, 1.56 mmol, 1.6 M solution in hexanes) was added dropwise to a suspension of amine hydrochloride salt (0.78 mmol) in THF (2 mL) at -78 °C. The base mixture was stirred at -78 °C for 10 min and then at 0 °C for 20 min before being returned to -78 °C. A solution of 4-*tert*-butylcyclohexanone (**1**) (100 mg, 0.65 mmol) in THF (2 mL) at 0 °C under N_2 was added dropwise by syringe. After stirring at -78 °C for 30 min, freshly distilled chlorotrimethylsilane (412 μL, 3.25 mmol) was added. The reaction was stirred at -78 °C for 1 h and then quenched and worked up exactly as in *General Procedure A* to yield crude enol silane **34** with the spectral and chromatographic characteristics stated above.

General Procedure C: Use of a single lithium amide base and added lithium chloride (as salt) (1:1) to synthesise enol silane **34**.

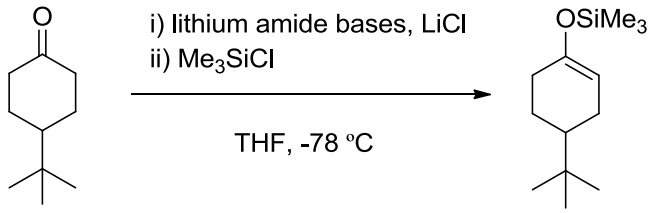


1 **34**

n-Butyllithium (488 μL, 0.78 mmol, 1.6 M solution in hexanes) was added dropwise to a suspension of lithium chloride (33 mg, 0.78 mmol), amine (0.78 mmol) in THF (2 mL). The

base mixture was stirred at -78 °C for 10 min and then at 0 °C for 20 min before being returned to -78 °C. A solution of 4-*tert*-butylcyclohexanone (**1**) (100 mg, 0.65 mmol) in THF (2 mL) at 0 °C under N_2 was added dropwise by syringe. After stirring at -78 °C for 30 min, freshly distilled chlorotrimethylsilane (412 μL, 3.25 mmol) was added. The reaction was stirred at -78 °C for 1 h and then quenched and worked up exactly as in *General Procedure A* to yield crude enol silane **34** with the spectral and chromatographic characteristics stated above.

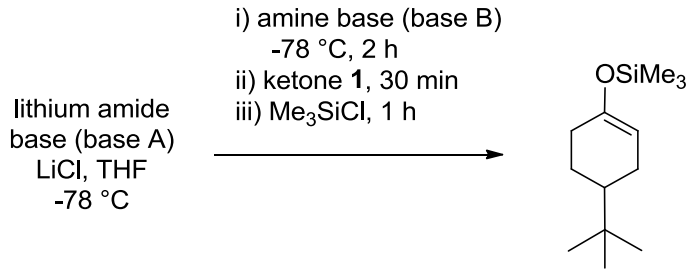
General Procedure D: Use of a mixture of two lithium amide bases and *in situ*-generated lithium chloride (1:1:1) to synthesise enol silane **34**.



1 **34**

n-Butyllithium (1.22 mL, 1.95 mmol, 1.6 M solution in hexanes) was added dropwise to a suspension of amine hydrochloride salt (0.65 mmol) and amine (0.65 mmol) in THF (2 mL) at -78 °C. The base mixture was stirred at -78 °C for 10 min and then at 0 °C for 20 min before being returned to -78 °C. A solution of 4-*tert*-butylcyclohexanone (**1**) (100 mg, 0.65 mmol) in THF (2 mL) at -78 °C under N_2 was added dropwise by syringe. After stirring at -78 °C for 30 min, freshly distilled chlorotrimethylsilane (412 μL, 3.25 mmol) was added. The reaction was stirred at -78 °C for 1 h and then quenched and worked up exactly as in *General Procedure A* to yield crude enol silane **34** with the spectral and chromatographic characteristics stated above.

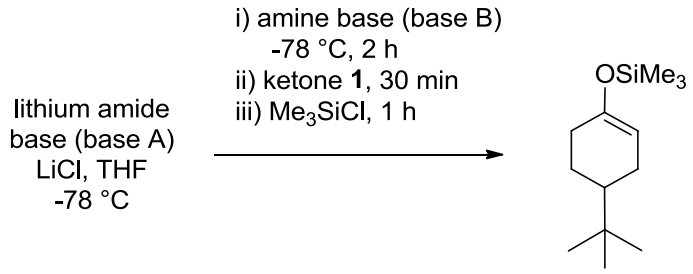
General Procedure E: Synthesis of enol silane **34** following lithium equilibration between two different amines, including *in situ* generated lithium chloride (1 eq.).



34

n-Butyllithium (975 μL, 1.56 mmol, 1.6 M solution in hexanes) was added dropwise to a suspension of amine hydrochloride salt (0.78 mmol) in THF (2 mL) at -78 °C. The base mixture was stirred at -78 °C for 10 min and then at 0 °C for 20 min before being returned to -78 °C. A solution of amine (**B**) (0.78 mmol) in THF (2 mL) was added dropwise to the base solution (**A**) and the mixture was stirred at -78 °C for 2 h. A solution of 4-*tert*-butylcyclohexanone (**1**) (100 mg, 0.65 mmol) in THF (2 mL) at -78 °C under N_2 was added dropwise by syringe. After stirring at -78 °C for 30 min, freshly distilled chlorotrimethylsilane (412 μL, 3.25 mmol) was added. The reaction was stirred at -78 °C for 1 h and then quenched and worked up exactly as in *General Procedure A* to yield crude enol silane **34** with the spectral and chromatographic characteristics stated above.

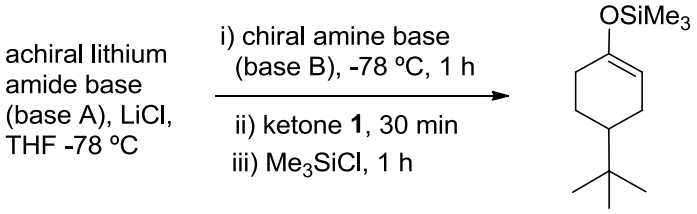
General Procedure F: Synthesis of enol silane **34** following lithium equilibration between two different amines, including lithium chloride (as salt) (1 eq).



34

n-Butyllithium (975 μL, 1.56 mmol, 1.6 M solution in hexanes) was added dropwise to a suspension of amine (0.78 mmol) and lithium chloride (0.78 mmol) in THF (2 mL) at -78 °C. The base mixture was stirred at -78 °C for 10 min and then at 0 °C for 20 min before being returned to -78 °C. A solution of amine (**B**) (0.78 mmol) in THF (2 mL) was added dropwise to the base solution (**A**) and the mixture was stirred at -78 °C for 2 h. A solution of 4-*tert*-butylcyclohexanone (**1**) (100 mg, 0.65 mmol) in THF (2 mL) at -78 °C under N_2 was added dropwise by syringe. After stirring at -78 °C for 30 min, freshly distilled chlorotrimethylsilane (412 μL, 3.25 mmol) was added. The reaction was stirred at -78 °C for 1 h and then quenched and worked up exactly as in *General Procedure A* to yield crude enol silane **34** with the spectral and chromatographic characteristics stated above.

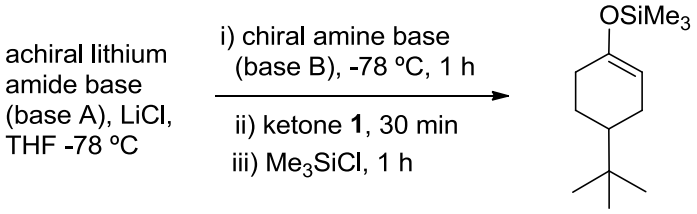
General Procedure G: Synthesis of enol silane **34** using a sub-stoichiometric amount of a chiral amine with a stoichiometric amount of an achiral lithium amide base, including *in situ* generated lithium chloride (1 eq.).



34

n-Butyllithium (975 µL, 1.56 mmol, 1.6 M solution in hexanes) was added dropwise to a suspension of amine hydrochloride salt (0.78 mmol) in THF (2 mL) at -78 °C. The base mixture was stirred at -78 °C for 10 min and then at 0 °C for 20 min before being returned to -78 °C. A solution of chiral amine (**A**) (0.07 mmol) in THF (2 mL) was added dropwise to the base solution (**A**) and the mixture was stirred at -78 °C for 1 h. A solution of 4-*tert*-butylcyclohexanone (**1**) (100 mg, 0.65 mmol) in THF (2 mL) at -78 °C under N_2 was added dropwise by syringe. After stirring at -78 °C for 30 min, freshly distilled chlorotrimethylsilane (412 µL, 3.25 mmol) was added. The reaction was stirred at -78 °C for 1 h and then quenched and worked up exactly as in *General Procedure A* to yield crude enol silane **34** with the spectral and chromatographic characteristics stated above.

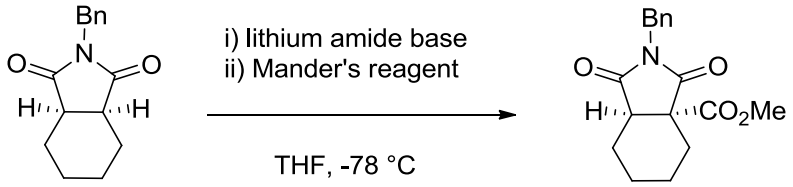
General Procedure H: Synthesis of enol silane **34** using a sub-stoichiometric amount of a chiral amine with a stoichiometric amount of an achiral lithium amide base, including lithium chloride (as salt) (1 eq.).



34

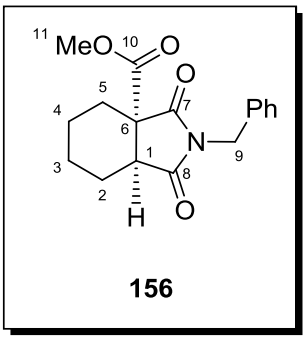
n-Butyllithium (975 μL, 1.56 mmol, 1.6 M solution in hexanes) was added dropwise to a suspension of amine (0.78 mmol) and lithium chloride (0.78 mmol) in THF (2 mL) at -78 °C. The base mixture was stirred at -78 °C for 10 min and then at 0 °C for 20 min before being returned to -78 °C. A solution of chiral amine (**A**) (0.07 mmol) in THF (2 mL) was added dropwise to the base solution (**A**) and the mixture was stirred at -78 °C for 1 h. A solution of 4-*tert*-butylcyclohexanone (**1**) (100 mg, 0.65 mmol) in dry THF (2 mL) at -78 °C under N_2 was added dropwise by syringe. After stirring at -78 °C for 30 min, freshly distilled chlorotrimethylsilane (412 μL, 3.25 mmol) was added. The reaction was stirred at -78 °C for 1 h and then quenched and worked up exactly as in *General Procedure A* to yield crude enol silane **34** with the spectral and chromatographic characteristics stated above.

General Procedure I: Use of a single lithium amide base to synthesise ester **156**.



151 **156**

n-Butyllithium (331 μL, 0.53 mmol, 1.6 M solution in hexanes) was added dropwise to a solution of amine (0.53 mmol) in THF (5 mL) at -78 °C. The base mixture was stirred at -78 °C for 10 min and then at 0 °C for 20 min. This base solution was then added dropwise over 5 min to a solution of imide **151** (100 mg, 0.41 mmol) in THF (2.5 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 30 min and then methyl cyanoformate (98 μL, 1.23 mmol) was added. The reaction mixture was stirred at -78 °C for a further 30 min before being quenched with sat. $NH_4Cl_{(aq)}$ (0.5 mL). The mixture was returned to room temperature, diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were washed with brine (15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10 % EtOAc/petroleum ether) to yield **156** as pale yellow oil: R_f = 0.58 (EtOAc:petroleum ether, 1:1); IR (neat) ν_{max} 2942, 1743, 1703, 1392, 1235, 1076, 914, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.12-1.26 (m, 1H, CH-3), 1.38-1.46 (m, 2H, CH_2-4), 1.49-1.60 (m, 2H, CH-3 & CH-5), 1.62-1.74 (m, 1H, CH-2), 2.06 (app. dq, *J* = 14.1, 4.5 Hz, 1H, CH-2), 2.35 (app. dt, *J* = 13.6, 5.3 Hz, 1H, CH-5), 3.31 (dd, *J* = 6.6, 3.9 Hz, 1H, CH-1), 3.76 (s, 3H, CH_3-11), 4.66 (collapsed AB system, *J* = 2.1 Hz, 2H, CH_2-9), 7.27-7.37 (m, 5H, Ar CH × 5); ^{13}C NMR ($CDCl_3$, 100MHz) δ 20.4 (CH_2, C-4), 20.7 (CH_2, C-3), 21.7 (CH_2, C-2), 28.4 (CH_2, C-5), 42.8 (CH_2, C-9), 44.1 (CH, C-1), 53.4 (CH_3, C-15), 54.5 (C, C-6), 128.1



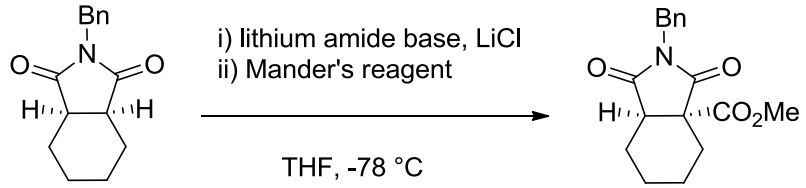
156

(CH, Ar CH), 128.7 (CH, Ar CH), 128.8 (CH, Ar CH), 135.6 (C, Ar C), 170.2 (C=O, C-14), 175.8 (C=O, C-8), 177.5 (C=O, C-7); MS (ES+) *m/z* 324.1 (M+Na, 100%); HRMS (ES+) found 324.1208, requires 324.1212 for $C_{17}H_{19}NO_4Na$.

The enantiomer ratios were determined by chiral HPLC (Chiralcel OD, 3% isopropylalcohol/hexane, 1 mL min^{-1}), the retention times were 18 min [(–)-**156**] and 20 min [(+)-**156**].

Example optical rotation values: 94 % ee: $[\alpha]_D^{20} = -68.3$ (*c* 1.03, $CHCl_3$); 87 % ee: $[\alpha]_D^{20} = -60.7$ (*c* 1.13, $CHCl_3$); 75 % ee: $[\alpha]_D^{20} = -55.0$ (*c* 1.09, $CHCl_3$).

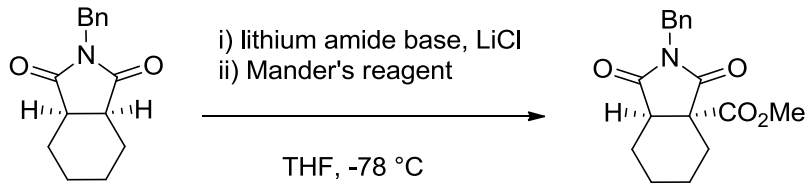
General Procedure J: Use of a single lithium amide base and *in situ*-generated lithium chloride (1:1) to synthesise ester **156**.



151 **156**

n-Butyllithium (331 μL, 0.53 mmol, 1.6 M solution in hexanes) was added dropwise to a suspension of amine hydrochloride salt (0.53 mmol) in THF (5 mL) at -78 °C. The base mixture was stirred at -78 °C for 10 min and then at 0 °C for 20 min. This base solution was then added dropwise over 5 min to a solution of imide **151** (100 mg, 0.41 mmol) in THF (2.5 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 30 min and then methyl cyanoformate (98 μL, 1.23 mmol) was added. After 30 min the reaction was then quenched, worked up, and purified as in *General Procedure D* to yield imide **156** as a pale yellow oil with the spectral and chromatographic characteristics stated above.

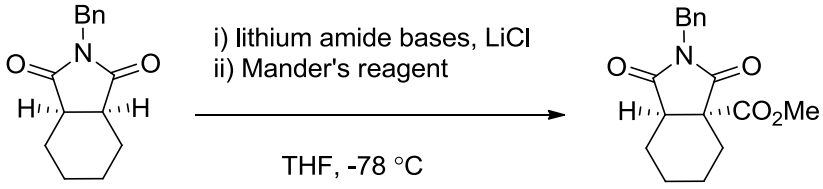
General Procedure K: Use of a single lithium amide base and lithium chloride (as salt) (1:1) to synthesise ester **156**.



151 **156**

n-Butyllithium (331 μL, 0.53 mmol, 1.6 M solution in hexanes) was added dropwise to a suspension of amine (0.53 mmol) and lithium chloride (22 mg, 0.53 mmol) in THF (5 mL) at -78 °C. The base mixture was stirred at -78 °C for 10 min and then at 0 °C for 20 min. This base solution was then added dropwise over 5 min to a solution of imide **151** (100 mg, 0.41 mmol) in THF (2.5 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 30 min and then methyl cyanoformate (98 μL, 1.23 mmol) was added. After 30 min the reaction was then quenched, worked up, and purified as in *General Procedure D* to yield imide **156** as a pale yellow oil with the spectral and chromatographic characteristics stated above.

General Procedure L: Use of a mixture of two lithium amide bases and *in situ*-generated lithium chloride (1:1:1) to synthesise ester **156**.

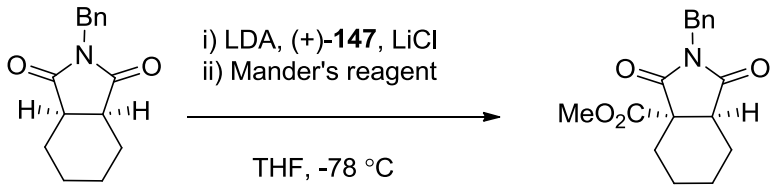


151 **156**

n-Butyllithium (769 μL, 1.23 mmol, 1.6 M solution in hexanes) was added dropwise to a suspension of amine hydrochloride salt (0.41 mmol) and amine (0.41 mmol) in THF (5 mL) at -78 °C. The base mixture was stirred at -78 °C for 10 min and then at 0 °C for 20 min. This

base solution was then added dropwise over 5 min to a solution of imide **151** (100 mg, 0.41 mmol) in THF (2.5 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 30 min and then methyl cyanoformate (98 μL, 1.23 mmol) was added. After 30 min the reaction was then quenched, worked up, and purified as in *General Procedure D* to yield imide **156** as a pale yellow oil with the spectral and chromatographic characteristics stated above.

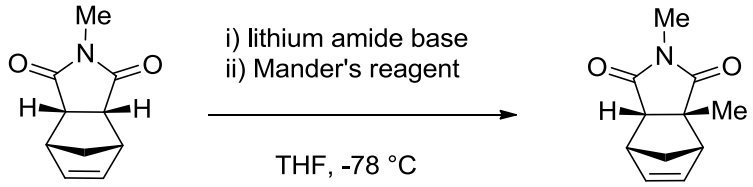
General Procedure M: Use of a mixture of two lithium amide bases to synthesise ester (–)-**156**.



151 (–)-**156**

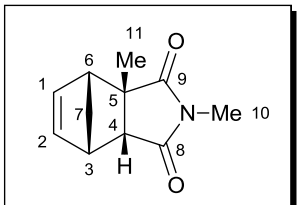
n-Butyllithium (for amount see Table 7.7) was added dropwise to a solution/suspension of DIPA or DIPA hydrochloride (for amount see Table 7.7) and (+)-**178** (for amount see Table 7.7) in THF (5 mL). The solution was cooled to -78 °C and. The base mixture was stirred at -78 °C for 10 min and then at 0 °C for 20 min. This base solution was then added dropwise over 5 min to a solution of imide **151** (100 mg, 0.41 mmol) in THF (2.5 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 30 min and then methyl cyanoformate (98 μL, 1.23 mmol) was added. After 30 min the reaction was then quenched, worked up, and purified as in *General Procedure D* to yield imide (–)-**156** as a pale yellow oil with the spectral and chromatographic characteristics stated above.

General Procedure N: Use of a single lithium amide base to synthesise imide **165**.



152 **165**

n-Butyllithium (0.62 or 0.73 mmol, 1.6 M solution in hexanes) was added dropwise to a solution of amine (0.62 or 0.73 mmol) in THF (5 mL) at -78 °C. The base mixture was stirred at -78 °C for 10 min and then at 0 °C for 20 min. This base solution was then added dropwise over 5 min to a solution of imide **152** (100 mg, 0.56 mmol) in THF (2.5 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 30 min and then methyl iodide (105 μL, 1.68 mmol) was added. The reaction mixture was stirred at -78 °C for a further 30 min before being quenched with sat. $NH_4Cl_{(aq)}$ (0.5 mL). The mixture was returned to room temperature, diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were washed with brine (15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (20 % EtOAc/petroleum ether) to yield **165** as a white solid (31 mg, 0.16 mmol, 29 %): mp 83-85 °C; R_f = 0.4 (1:1 EtOAc/petroleum ether); IR (neat) ν_{max} 2990, 1766, 1687, 1433, 1287, 1035, 714 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.48 (s, 3H, CH_3-11), 1.73-1.77 (m, 2H, CH_2-7), 2.79-2.81 (m, 1H, CH), 2.80 (s, 3H, CH_3-10), 2.87-2.91 (m, 1H, CH), 3.29-3.34 (m, 1H, CH), 6.01-6.05 (m, 1H, vinylic CH), 6.13-6.17 (m, 1H, vinylic CH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3 (CH_3, C-11), 24.2 (CH_3, C-10), 45.6 (CH), 50.2 (CH_2, C-7), 50.6 (CH), 51.7 (C, C-5), 53.1 (CH), 134.1 (vinylic CH), 136.5 (vinylic CH), 177.5 (C=O), 181.1 (C=O); MS (ES+) *m/z* 214.2 (M+Na, 100 %); HRMS (ES+) found 214.0836, requires 214.0844 for $C_{11}H_{13}NO_2Na$.

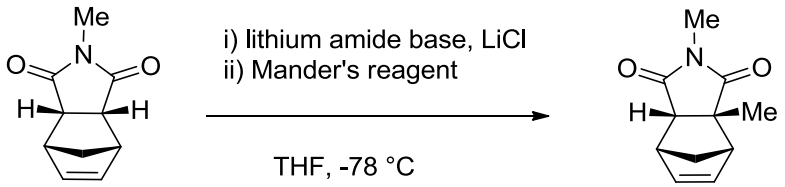


165

The enantiomer ratios were determined by chiral HPLC (Chiralcel OD, 10% isopropylalcohol/hexane, 1 mL min^{-1}), the retention times were 7 min [(–)-**165]** and 10 min [(+)-**165]**.

Example optical rotation values: 95 % ee: $[\alpha]_D^{20}$ = +58.1 (*c* 0.75, $CHCl_3$); 92 % ee: $[\alpha]_D^{20}$ = –35.1 (*c* 0.89, $CHCl_3$).

General Procedure O: Use of a single lithium amide base and *in situ*-generated lithium chloride (1:1) to synthesise imide **165**.

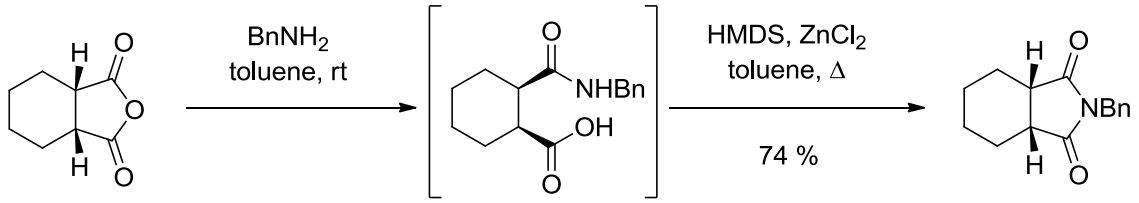


152 **165**

n-Butyllithium (419 μL, 0.67 mmol, 1.6 M solution in hexanes) was added dropwise to a solution of amine (0.67 mmol) in THF (5 mL) at -78 °C. The base mixture was stirred at -78 °C for 10 min and then at 0 °C for 20 min. This base solution was then added dropwise over 5 min to a solution of imide **152** (100 mg, 0.56 mmol) in THF (2.5 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 30 min and then methyl iodide (105 μL, 1.68 mmol) was added. The reaction mixture was stirred at -78 °C for a further 40 min before being quenched with sat. $NH_4Cl_{(aq)}$ (0.5 mL). The mixture was returned to room temperature, diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were washed with brine (15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (20 % EtOAc/petroleum ether) to yield **165** as a white solid with the spectral and chromatographic characteristics stated above.

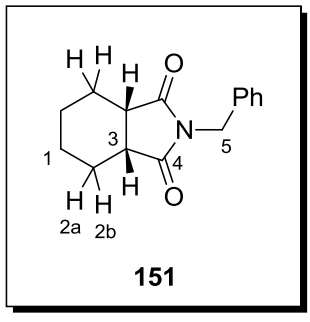
7.3 Synthesis of Substrates and Chiral Amines

*Synthesis of imide **151**.*



153 **151**

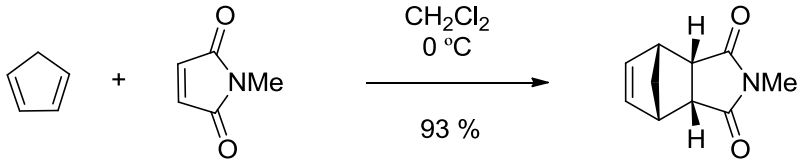
Following a literature procedure,[79] cyclohexane-1,2-dicarboxylic acid anhydride (**153**) (6.0 g, 0.039 mol) and dry toluene (100 mL) were added to a 500 mL flask followed by benzylamine (4.25 mL, 0.039 mol). The reaction mixture was stirred at room temperature for 1 h and then zinc (II) chloride (39 mL, 0.039 mol, 1 M soln. in Et_2O) was added. The flask was warmed to 80 °C and hexamethyldisilazane (12.2 mL, 0.056 mol) was added dropwise over 25 min. Following addition of HMDS the flask was fitted with a condenser and refluxed for 2 h, cooled and poured into $HCl_{(aq)}$ (45 mL, 1 M). The product was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were washed with saturated $NaHCO_{3\ (aq)}$ (3 x 20 mL) and brine (3 x 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by recrystallisation (petroleum ether/ EtOAc, major/minor) to give **151** (6.99 g, 0.029 mol, 74 %) as white crystals in three crops: mp 69-70 ^oC (lit. mp 71-72 °C)[79b]; R_f = 0.15 (petroleum ether:EtOAc, 9:1); IR (neat) ν_{max} 2936, 2851, 1693, 1394, 1344, 1170, 905, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23-1.43 (m, 4H, CH_2-1 × 2), 1.58-1.69 (m, 2H, CH-2a × 2), 1.71-1.83 (m, 2H, CH-2b × 2), 2.74-2.83 (m, 2H, CH-3 × 2), 4.57 (s, 2H, CH_2-5), 7.19-7.30 (m, 5H, Ar CH × 5); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5 (CH_2, C-1), 23.6 (CH_2, C-2), 39.8 (CH, C-3), 42.1 (CH_2, C-5), 127.8 (Ar CH), 128.5 (Ar CH), 128.6 (Ar CH), 136.1 (Ar C), 179.3 (C=O, C-4); MS (ES+)



151

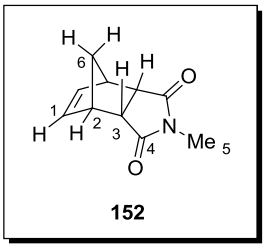
m/*z* 266.2 (M+Na, 100%), 244.2 (M+1, 11%); HRMS (ES+) found 266.1174, requires 266.1157 for $C_{15}H_{17}NO_2Na$.

*Synthesis of imide **152**.*



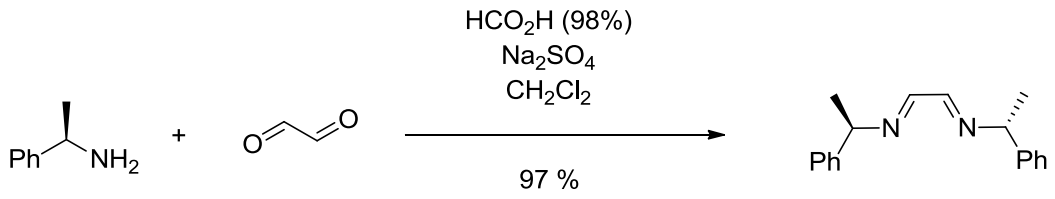
154 **155** **152**

Freshly cracked cyclopentadiene (**154**)[146] (10.2 mL, 121 mmol) was added dropwise to a solution of *N*-methylmaleimide (**155**) (13.4 g, 121 mmol) in CH_2Cl_2 (32 mL) at 0 °C. The reaction mixture was returned to room temperature and stirred for 30 min. The stirrer bar was then removed and the reaction mixture was concentrated *in vacuo* to yield an off-white solid (20 g, 93 %) which was purified by recrystallisation (petroleum ether/EtOAc, major/minor) to yield **152** as a white crystalline solid: R_f = 0.3 (petroleum ether:EtOAc, 1:1); mp 100-102 °C; IR (neat) ν_{max} 3436, 2981, 1684, 1275, 1127, 967, 844, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.49-1.52 (m, 1H, CH_2-6), 1.69 (dt, J = 8.8, 1.7 Hz, 1H, CH_2-6), 2.77 (s, 3H, CH_3-5), 3.22 (dd, *J* = 2.9, 1.5 Hz, 2H, CH-3 × 2), 3.34 (m, 2H, CH-2 × 2), 6.05 (app. t, J = 1.8 Hz, 2H, CH-1 × 2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.5 (CH_3, C-5), 45.1 (CH, C-2), 46.3 (CH, C-3), 52.5 (CH_2, C-6), 134.7 (CH, C-1), 178.1 (C=O, C-4); MS (ES+) *m*/*z* 200.1 (M+Na, 100%); HRMS (ES+) found 200.0687, requires 200.0687 for $C_{10}H_{11}NO_2Na$.



152

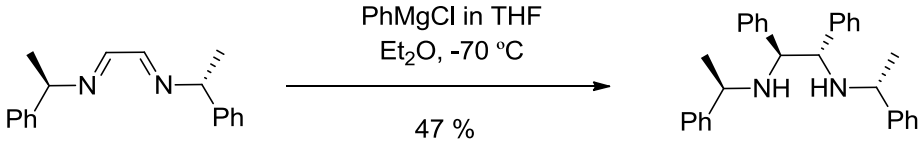
*Synthesis of diimine **196**.*



193 **191** **196**

Following a literature procedure,[93b, 147] aqueous glyoxal (**191**) (9.15 mL, 78 mmol, 40 %), dichloromethane (150 mL) and Na_2SO_4 (40 g) were added to a flask, the suspension was stirred vigorously for 20 min and then formic acid (98 %) (0.5 mL) and (*R*)-(+)-α-methylbenzylamine (**193**) (22 mL, 170 mmol) were added. After stirring at room temperature for 5 min, Na_2SO_4 (50 g) was added and the mixture was stirred at room temperature for 3 h. The reaction mixture was filtered and the residue washed with CH_2Cl_2 (3 × 50 ml). The organics were combined and concentrated *in vacuo*. The resulting concentrate was dissolved in petroleum ether (100 mL) and washed with water (5 × 50 mL) before being stored over 3 Å molecular sieves under N_2. Before use in the next reaction the solution was filtered and concentrated *in vacuo* to yield **193** (20 g, 75.7 mmol, 97 %) as an orange oil: R_f = 0.5 (MeOH:CH_2Cl_2, 2:98); IR (neat) ν_{max} 2971, 2865, 1626, 1493, 1450, 759, 697 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 1.50 (d, *J* = 6.6 Hz, 6H, CH_3 × 2), 4.43 (q, *J* = 6.6 Hz, 2H, CH × 2), 7.13-7.25 (m, 10H, Ar CH × 10), 7.98 (s, 2H, CH × 2).

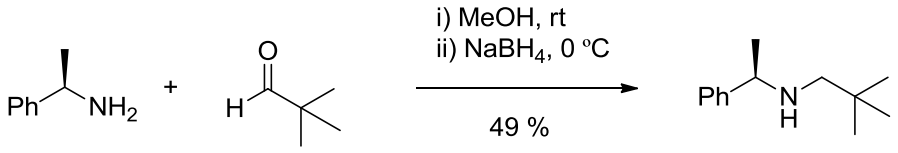
*Synthesis of diamine (+)-**178**.*



193 (+)-**178**

Following a literature procedure,[93] imine **193** (8.0 g, 0.03 mol) and Et_2O (100 mL) were added to a flask, the solution was stirred, cooled to -70 °C and PhMgCl in THF (60.6 mL, 0.12 mol, 2 M) was added dropwise over 1 h by syringe pump. The reaction mixture was then stirred at -70 °C for 3 h under N_2 before being gradually returned to room temperature over 2 h. After stirring at room temperature for 1 h the reaction mixture was cooled to 0 °C and quenched with the careful addition of sat. $NH_4Cl_{(aq)}$ (70 mL). The product was extracted with EtOAc (3 × 60 mL) and the combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether:EtOAc, 19:1) followed by recrystallisation from boiling petroleum ether to yield (+)-**178** (5.87 g, 14.0 mmol, 47 %) as off-white crystals in two crops: R_f = 0.25 (5% EtOAc: petroleum ether); mp 108-109 °C (lit. mp 113-115 °C)[93b]; IR (neat) ν_{max} 2961, 1454, 1205, 1107, 863, 771, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (d, *J* = 6.6 Hz, 6H, CH_3 × 2), 2.27 (br. s, 2H, NH × 2), 3.39 (s, 2H, CH × 2), 3.45 (q, *J* = 6.6 Hz, 2H, CH × 2), 6.93-6.98 (m, 4H, Ar CH × 4), 7.03-7.06 (m, 4H, Ar CH × 4), 7.12-7.16 (m, 6H, Ar CH × 6), 7.21-7.31 (m, 6H, Ar CH × 6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.4 (CH_3), 55.2 (CH), 65.9 (CH), 126.7 (Ar CH), 126.79 (Ar CH), 126.80 (Ar CH), 128.0 (Ar CH), 128.1 (Ar CH), 128.4 (Ar CH), 141.8 (Ar C), 145.8 (Ar C); MS (ES+) *m/z* 421.4 (M+1, 100%); HRMS (ES+) found 421.2651, requires 421.2644 for $C_{30}H_{33}N_2$.

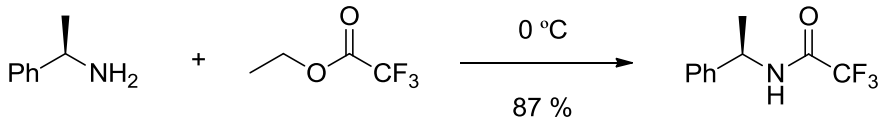
*Synthesis of secondary amine (R)-**21**.*



193 **354** (*R*)-**355**

Following a modified literature procedure,[148] pivaldehyde (**354**) (3.78 mL, 34.9 mmol) was added dropwise to a solution of (*R*)-(+)-α-methylbenzylamine (**193**) (5.32 mL, 41.8 mmol) in methanol (40 mL) and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was then cooled to 0 °C and sodium borohydride (2.11 g, 55.8 mmol) was added carefully in small portions. After 20 min, water (5 mL) was added to quench the reaction and the solvent was removed *in vacuo*. The resulting concentrate was partitioned between EtOAc (150 mL) and $NaHCO_{3\ (aq)}$ (50 mL), and the phases were separated. The organics were then washed with $NaHCO_3$ (2 x 50 mL) and brine (2 × 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (CH_2Cl_2) to give **355** (3.3 g, 17.2 mmol, 49 %) as a colourless oil: $[\alpha]_D^{23}$ = +66.0 (*c* 1.0, $CHCl_3$); R_f = 0.2 (MeOH:CH_2Cl_2, 1:49); ^{1}H NMR ($CDCl_3$, 300MHz) δ 0.81 (s, 9H, CH_3 × 3), 1.25 (d, *J* = 6.6 Hz, 3H, CH_3), 2.06 (d, *J* = 11.4 Hz, 1H, CH_2), 2.19 (d, *J* = 11.4 Hz, 1H, CH_2), 3.62 (q, *J* = 6.6 Hz, 1H, CH), 7.12-7.18 (m, 1H, Ar CH), 7.21-7.25 (m, 4H, Ar CH × 4), NH resonance was not observed; ^{13}C NMR ($CDCl_3$, 100MHz) δ 25.1 (CH_3), 27.9 (CH_3), 31.5 (C), 59.1 (CH), 60.3 (CH_2), 126.7 (Ar CH), 126.8 (Ar CH), 128.4 (Ar CH), 146.7 (Ar C); MS (ES+) *m/z* 192.3 (M+1, 100%); HRMS (ES+) found 192.1754, requires 192.1752 for $C_{13}H_{22}N$.

*Synthesis of amide (R)-**357**.*

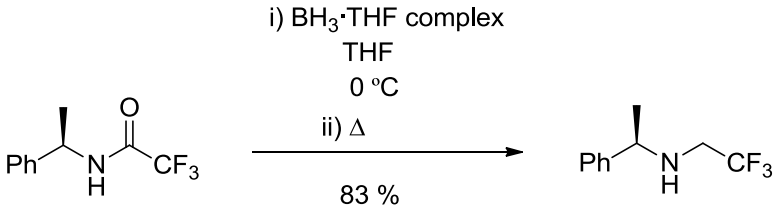


(*R*)-**193** **356** (*R*)-**357**

Following a literature procedure,[74] ethyl trifluoroacetate (**356**) (14.8 mL, 17.6 g, 123.9 mmol) was added dropwise to (*R*)-(+)-α-methylbenzylamine (**193**) (10.6 mL, 10 g, 82.5 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then returned to room temperature.

Toluene (20 mL) was added to the white crystalline solid which formed and the solution was concentrated *in vacuo*. This process was repeated twice (Toluene, 2 × 20 mL) to yield a white crystalline solid (18.1 g). The product was purified by recrystallisation from hexane (450 mL) to give the desired product (*R*)-**357** (15.6 g, 71.83 mmol, 87 %) as colourless white needles: mp 93-95 °C (lit. mp 93-93.5 °C)[74]; R_f = 0.13 (5% EtOAc:petroleum ether); IR (neat) ν_{max} 698, 760, 881, 1011, 1159, 1546, 1698, 3334 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.60 (d, *J* = 6.9 Hz, 3H, CH_3), 5.15 (quin., *J* = 7.1 Hz, 1H, CH), 6.45 (br. s, 1H, NH), 7.30-7.42 (m, 5H, Ar CH × 5); ^{19}F NMR ($CDCl_3$, 282 MHz) δ -75.9 (s, CF_3); ^{13}C NMR ($CDCl_3$, 100MHz) δ 21.0 (CH_3), 49.8 (CH), 115.2 (q, *J* = 286.5 Hz, CF_3), 126.2 (Ar CH), 128.2 (Ar CH), 129.0 (Ar CH), 129.4 (Ar C), 140.9 (s, no coupling to F observed, C=O); MS (ES+) *m*/*z* 240.0 (M+Na, 100%), 218.0 (M+1, 1%).

*Synthesis of amine (R)-**186**.*

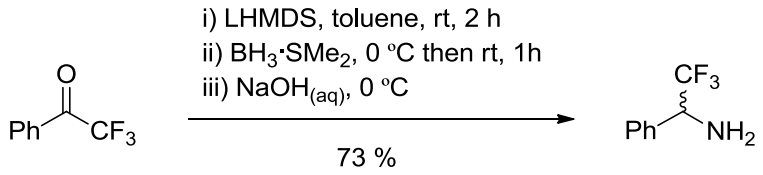


(*R*)-**357** (*R*)-**186**

Following a literature procedure,[74] BH_3·THF complex (270 mL, 267.0 mmol, 1 M) was added dropwise to a solution of amide (*R*)-**357** (14.5 g, 60.8 mmol) in THF (90 mL) at 0 °C. The reaction mixture was heated at reflux for 13 h and then cooled to 0 °C. Methanol (20 mL) was added dropwise to the reaction mixture to quench and the whole was concentrated *in vacuo*. To the crude residue, methanol (80 mL) was added followed by a solution of concentrated $HCl_{(aq)}$ in methanol (90 mL, 20 %) dropwise at 0 °C. The mixture was refluxed for 3 h, returned to room temperature and concentrated *in vacuo* to yield a white solid. The product

was then suspended in toluene and the whole was concentrated *in vacuo*. This process was repeated twice to give a white solid (15.5 g, 97 %). This crude hydrochloride salt was purified by recrystallisation from boiling *iso*-propanol to give the desired product (*R*)-**186**·HCl in three crops (13.3 g, 55.49 mmol, 91 %) as white needles: ^{1}H NMR ($CDCl_3$, 300MHz) δ 2.01 (d, *J* = 6.7 Hz, 3H, CH_3), 3.24-3.49 (m, 2H, CH_2), 4.49 (q, *J* = 6.7 Hz, 1H, CH), 7.40-7.51 (m, 3H, Ar CH × 3), 7.59-7.67 (m, 2H, Ar CH × 2), 11.04 (br. s, 2H, NH_2); ^{19}F NMR ($CDCl_3$, 282 MHz) δ -65.5 (s, CF_3); ^{13}C NMR ($CDCl_3$, 100MHz) δ 20.3 (CH_3), 45.0 (q, *J* = 35.7 Hz, CH_2), 60.0 (CH), 128.1 (Ar CH), 129.7 (Ar CH), 129.9 (Ar CH), 131.9 (q, *J* = 297.4 Hz, CF_3), 134.8 (Ar C); MS (ES+) *m*/*z* 204.1 (M+1, 100%). The salt was converted to the free amine by dissolving (*R*)-**186**·HCl (2.0 g, 8.34 mmol) in sat. $NaHCO_{3\,(aq)}$ (25 mL) and stirring vigorously with petroleum ether (50 mL) for 2 h. The phases were separated and any remaining amine was extracted from the aqueous phase with petroleum ether (2 × 50 mL). The organic phases were combined, washed with brine (30 mL), dried over $MgSO_4$, filtered and evaporated to yield the desired product (*R*)-**186** (1.41 g, 6.94 mmol, 83 %) as a colourless oil: $[\alpha]_D^{22}$ = +61.6 (*c* 1.0, MeOH) (lit. $[\alpha]_D^{25}$ = +54.9 (*c* 0.98, MeOH))[74]; ^{1}H NMR ($CDCl_3$, 300MHz) δ 1.38 (d, *J* = 6.5 Hz, 3H, CH_3), 1.58 (br. s, 1H, NH), 2.99 (q, *J* = 9.5 Hz, 1H, CH_2), 3.05 (q, *J* = 9.5 Hz, 1H, CH_2), 3.92 (q, *J* = 6.5 Hz, 1H, CH), 7.24-7.38 (m, 5H, Ar CH × 5); ^{13}C NMR ($CDCl_3$, 100MHz) δ 24.4 (CH_3), 48.3 (q, *J* = 30.9 Hz, CH_2), 57.3 (CH), 126.6 (Ar CH), 127.4 (Ar CH), 128.6 (Ar CH), 125.8 (q, J = 279.0 Hz, CF_3), 144.6 (Ar C); MS (EI) *m*/*z* 203.1 (M, 10%), 188.1 ($C_9H_9F_3N$, 100%); HRMS (EI) found 203.0928, requires 203.0922 for $C_{10}H_{12}NF_3$.

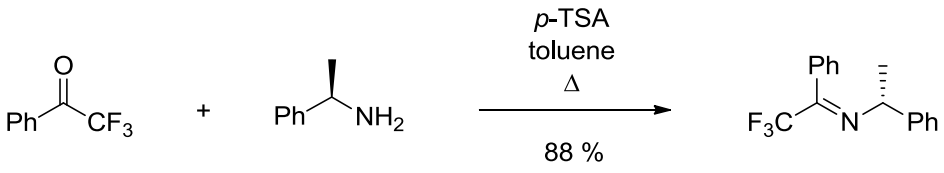
*Synthesis of amine (±)-**190**.*



192 (±)-**190**

Following a literature procedure,[95] a solution of lithium bis(trimethylsilyl)amide in THF (104 mL, 104.0 mmol, 1 M) was added dropwise over 30 min to a solution of 2,2,2-trifluoroacetophenone (**192**) (12.9 mL, 94.5 mmol) in toluene (335 mL). The reaction mixture was stirred at room temperature for a further 2 h before being cooled to 0 °C. A solution of borane dimethylsulfide complex in DCM (189 mL, 189 mmol, 1 M) was added dropwise over 45 min. The reaction mixture was warmed to room temperature and stirred for 1 h before being cooled to 0 °C. Cold $NaOH_{(aq)}$ (150 mL, 1 M) was added dropwise (***Caution: Evoultion of gas***). The phases were separated and the organics washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow solution. To this solution $HCl_{(dioxane)}$ (26 mL, 4 M) was added dropwise and the resultant amine hydrochloride was collected by filtration and washed with small portions of Et_2O. The amine hydrochloride was dissolved in water (300 mL) and the solution was basified by addition of $NaOH_{(aq)}$ (2 M). The product was extracted with Et_2O (4 x 50 mL), and the combined organics were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the desired free amine **190** as a light yellow oil (12.1 g, 69.08 mmol, 73 %): ^{1}H NMR (300 MHz) δ 1.79 (br. s, 2H, NH_2), 4.34-4.45 (m, 1H, CH), 7.37-7.46 (m, 5H, Ar CH × 5).

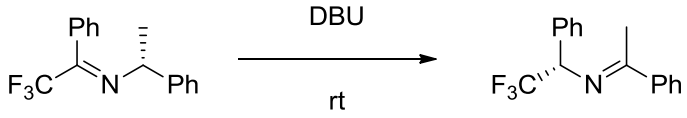
*Synthesis of imine (R)-**194**.*



192 (*R*)-**193** (*R*)-**194**

Following a literature procedure,[97b] (*R*)-(+)-methylbenzylamine (8.9 mL, 70.0 mmol) was added dropwise to a solution of 2,2,2-trifluoroacetophenone (11.4 mL, 84 mmol) and *para*-toluenesulfonic acid (437 mg, 2.1 mmol) in toluene (170 mL). The flask was fitted with a Dean-Stark trap and the reaction mixture was refluxed for 140 h before being returned to room temperature. The organics were washed with $NaOH_{(aq)}$ (3 × 30 mL, 1 M), sat. $NH_4Cl_{(aq)}$ (40 mL) and Brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a 4:1 mixture (**194**:**193**) as slightly yellow oil (19 g) (**194**: 17.1 g, 61.8 mmol, 88 %): ^{1}H NMR (300 MHz) δ 1.38 (d, *J* = 6.5 Hz, 3H, CH_3), 4.47 (q, *J* = 6.5 Hz, 1H, CH), 7.06-7.28 (m, 7H, Ar CH × 7), 7.36-7.43 (m, 3H, Ar CH × 3).

*Synthesis of imine (S)-**195**.*

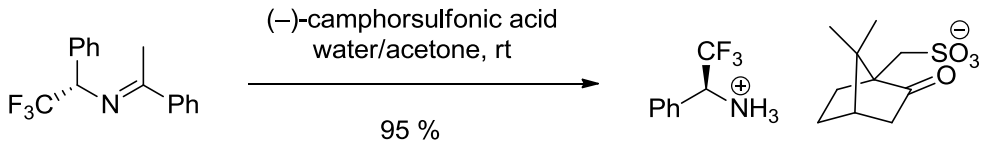


(*R*)-**194** (*S*)-**195**

Following a literature procedure,[98b] 1,8-diazabicyclo[5.4.0]undec-7-ene (16.7 mL, 112 mmol) was added dropwise to imine (*R*)-**194** (15.5 g, 56 mmol). The reaction mixture was stirred at room temperature for 65 h before being passed through a short silica plug which was washed with E_2O (500 mL). The organics were concentrated *in vacuo* to give an orange oil (27.2 g) containing DBU and the desired product (*S*)-**195** (15.5 g, 56 mmol, quant.): ^{1}H NMR ($CDCl_3$,

300 MHz) δ 2.19 (s, 3H, CH_3), 5.07 (q, *J* = 7.4 Hz, 1H, CH), 7.34-7.52 (m, 8H, Ar CH × 8), 7.90-7.93 (m, 2H, Ar CH × 2).

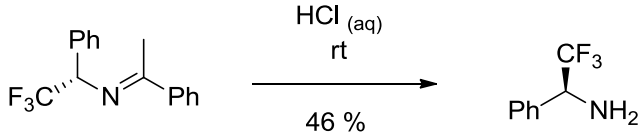
*Synthesis of (S)-**190**·(–)-10-camphorsulfonate salt.*



(*S*)-**195** (*S*)-**190**·CSA

Following a literature modified literature procedure,[98a] imine (*S*)-**195** (277 mg, 1.00 mmol) and (–)-10-camphorsulfonic acid (232 mg, 1.00 mmol) were dissolved in a mixture of water (1 mL) and acetone (1 mL). The reaction mixture was stirred for 18 h at room temperature before being concentrated to dryness under high vacuum to yield (*S*)-**190**·(–)-CSA as an off-white solid (388 mg, 0.95 mmol, 95 %) which was not purified further: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.71 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 1.19-1.43 (m, 2H, CH_2), 1.76-1.89 (m, 2H, CH_2), 1.95-1.98 (m, 1H, CH), 2.21-2.33 (m, 2H, CH_2), 2.41 (d, *J* = 14.9 Hz, 1H, C*H*$_2$SO$_3$), 2.98 (d, *J* = 14.9 Hz, 1H, C*H*$_2$SO$_3$), 5.09 (m, 1H, CH), 7.40-7.42 (m, 3H, Ar CH × 3), 7.56-7.58 (m, 2H, Ar CH × 2), 9.12 (br. s, 3H, NH_3); ^{19}F NMR ($CDCl_3$, 282MHz) δ 73.18 (s).

*Synthesis of amine (S)-**190**.*

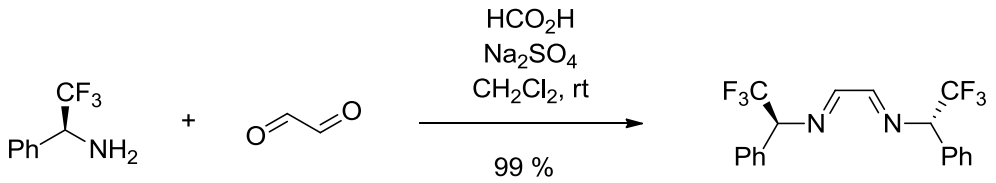


(*S*)-**195** (*S*)-**190**

Following a modified literature procedure,[98b] a solution of (*S*)-**195** (15.5 g, 56 mmol) in aqueous hydrochloric acid (250 mL, 2 M) was stirred at room temperature for 2 h before being neutralised with sat. $NaHCO_3$ (500 mL). The amine product was extracted with Et_2O (6

× 85 mL) and the organics were combined, washed with Brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a dark orange oil (13.3 g). The crude was purified by suspension in petroleum ether followed by acidification with conc. HCl. The precipitate which was formed was filtered and dried to give a light yellow solid (9.6 g). This amine hydrochloride salt was dissolved in water and sat. $NaHCO_3$ was added to neutralise. The amine was extracted with Et_2O (5 × 50 mL) and the organics washed with Brine (100 mL), dried over $MgSO_4$, filtered and concentrated to give a yellow oil (5.6 g) which was not sufficiently pure. The product was further purified by flash column chromatography (CH_2Cl_2:MeOH:NH_4OH, 98:2:0.2 → 96:4:0.4) to yield the desired product (*S*)-**190** as a yellow oil (4.63 g, 26 mmol, 46 %): R_f = 0.5 (5 % MeOH/CH_2Cl_2 + 1 drop NH_4Cl); $[\alpha]_D^{23}$ = +13.5 (*c* 1.2, EtOH) (lit. $[\alpha]_D^{20}$ = –21.6 (*c* 3.1, EtOH))[96]; ^{1}H NMR ($CDCl_3$, 300MHz) δ 1.79 (br. s, 2H, NH_2), 4.40 (m, 1H, CH), 7.38-7.41 (m, 5H, Ar CH × 5).

*Synthesis of diimine (S, S)-**189**.*

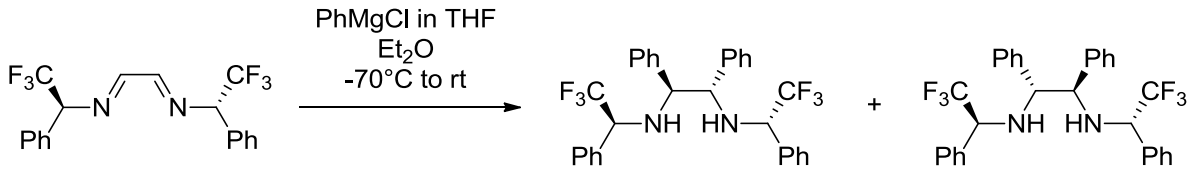


(*S*)-**190** **191** (*S*, *S*)-**189**

Following a modified literature procedure,[93b, 147] aqueous glyoxal (**191**) (1.49 mL, 40 %) was added to a solution of (*S*)-**190** (4.63 g, 0.026 mol) in CH_2Cl_2 (25 mL) containing Na_2SO_4 (14 g), followed by formic acid (0.08 mL). The reaction mixture was stirred for 45 min and then a further portion of Na_2SO_4 (17 g) was added before the mixture was stirred at room temperature for 22 h. The reaction mixture was filtered, the Na_2SO_4 washed with CH_2Cl_2 (100 mL) and the combined organics were concentrated *in vacuo* to give the desired product (*S*, *S*)-**189** as an orange oil (4.88 g, 99 %): R_f = 0.4 (10% EtOAc:petroleum ether); ^{1}H NMR ($CDCl_3$,

300MHz) δ 4.72 (q, *J* = 7.5 Hz, 2H, CH × 2), 7.29-7.36 (m, 10H, Ar CH × 10), 8.03 (s, 2H, CH × 2); ^{13}C NMR ($CDCl_3$, 100MHz) δ 75.0 (q, *J* = 29.0 Hz, CH), 124.3 (q, *J* = 279.0 Hz, CF_3), 128.9 (Ar CH), 129.0 (Ar CH), 129.5 (Ar CH), 133.6 (Ar C), 166.0 (CH, N=CH); MS (GCT TOF EI) *m*/*z* 372.1 (M, 8 %); HRMS (EI) found 372.1064, $C_{18}H_{14}N_2F_6$ requires 372.1061.

*Synthesis of diamine (+)-**188** and (+)-**197**.*

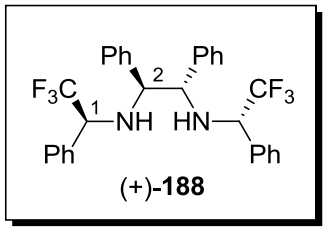


(*S*, *S*)-**189** (+)-**188**, 12 % (+)-**197**, 14 %

Following a modified literature procedure[93], a solution of phenyl magnesium chloride in THF (16 mL, 31.91 mmol, 2 M) was added dropwise over 50 min to a solution of diimine (*S*, *S*)-**189** (2.97 g, 7.98 mmol) in Et_2O (27 mL) at -70 °C. The mixture was stirred at -70 °C for 150 min and then warmed to room temperature over 1 h before being cooled to 0 °C. Sat. $NH_4Cl_{(aq)}$ (20 mL) was added dropwise and the reaction mixture was returned to room temperature. The product was extracted with Et_2O (3 × 80 mL) and the combined organics were washed with brine (80 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was initially purified by flash column chromatography (petroleum ether → 2% EtOAc/petroleum ether) followed by reverse phase preparative HPLC to yield diastereomeric diamines (+)-**188** (525 mg, 0.99 mmol, 12%) and (+)-**197** (608 mg, 1.15 mmol, 14%).

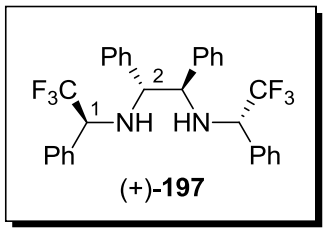
Diamine (+)-**188**: mp 102-103 °C; R_f = 0.43 (10% EtOAc/petroleum ether); $[\alpha]_D^{20}$ = +160.8 (*c* 6.0, Et_2O); ^{1}H NMR ($CDCl_3$, 300MHz) δ 2.84 (br. s, 2H, NH × 2), 3.47 (s, 2H, CH-2 × 2), 3.85 (quin., *J* = 7.4 Hz, 2H, CH-1 × 2), 6.93-6.99 (m, 4H, Ar CH × 4), 7.09-7.23 (m, 10H, Ar

CH × 10), 7.31-7.42 (m, 6H, Ar CH × 6); ^{13}C NMR ($CDCl_3$, 100MHz) δ 61.9 (q, *J* = 28.6 Hz, CH, C-1), 65.0 (CH, C-2), 125.4 (q, *J* = 278.8 Hz, C, CF_3), 127.8 (CH, Ar CH), 127.9 (CH, Ar CH), 128.5 (CH, Ar CH), 128.76 (CH, Ar CH), 128.82 (CH, Ar CH), 129.1 (CH, Ar CH), 133.6 (C, Ar C), 139.1 (C, Ar C) ; MS (ES+) *m/z* 551.3 (M+Na, 100 %), 529.3 (M+1, 10 %); HRMS (ES+) found 529.2079, requires 529.2078 for $C_{30}H_{27}N_2F_6$.



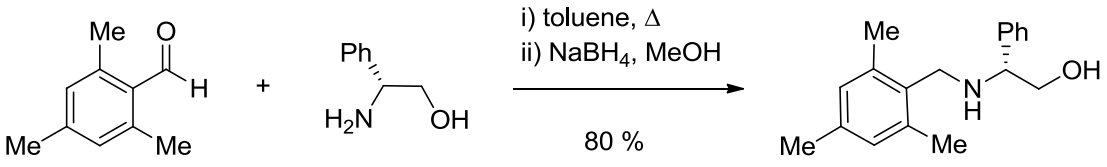
(+)-**188**

Diamine (+)-**197**: R_f = 0.40 (10% EtOAc/petroleum ether); $[\alpha]_D^{20}$ = +74.6 (*c* 3.7, Et_2O); ^{1}H NMR ($CDCl_3$, 300MHz) δ 2.98 (br. s, 2H, NH × 2), 3.94-4.09 (m, 4H, CH-1 × 2 & CH-2 × 2), 6.84-7.52 (m, 20H, Ar CH × 20); ^{13}C NMR ($CDCl_3$, 100MHz) δ 61.7 (q, *J* = 28.0 Hz, CH, C-1), 68.1 (CH, C-2), 126.4 (q, J = 282.3 Hz, C, CF_3), 127.6 (CH, Ar CH), 128.08 (CH, Ar CH), 128.14 (CH, Ar CH), 128.2 (CH, Ar CH), 128.7 (CH, Ar CH), 128.8 (CH, Ar CH), 135.7 (C, Ar C), 139.6 (C, Ar C); MS (ES+) *m/z* 551.3 (M+Na, 100 %), 529.3 (M+1, 7 %); HRMS (ES+) found 551.1901, requires 551.1898 for $C_{30}H_{26}N_2F_6Na$



(+)-**197**

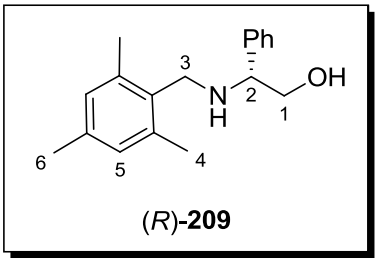
*Synthesis of amino alcohol (R)-**209**.*



208 (*R*)-**205** (*R*)-**209**

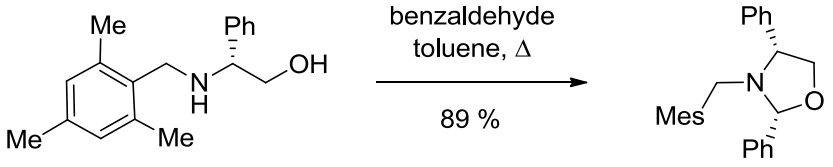
Following a literature procedure,[102] (*R*)-phenylglycinol (**205**) (4.89 g, 35.66 mmol), 2,4,6-trimethylbenzylaldehyde (**208**) (5.29 g, 5.26 mmol) and toluene (80 mL) were added to a flask fitted with a Dean–Stark trap and the solution was heated to reflux for 2 h before being cooled

to room temperature. The solution was concentrated *in vacuo* to remove toluene and the crude imine intermediate was dissolved in methanol (60 mL). The solution was stirred at room temperature and sodium borohydride (3.37 g, 89.15 mmol) was added carefully in small portions. The reaction mixture was stirred at room temperature for 30 min and then water (70 mL) was added carefully dropwise to quench residual sodium borohydride. The product was extracted with CH_2Cl_2 (200 mL then 2 × 50 mL) and the combined organics were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated to yield a white solid (9.85 g). The crude product was recrystallised from boiling hexane (250 mL) to yield (*R*)-**209** as colourless needles (7.71 g, 28.61 mmol, 80 %): mp 97-99 °C (lit. mp 98-99 °C)[102]; R_f = 0.15 (1:1 Et_2O/petroleum ether); $[\alpha]_D^{22}$ = –33.0 (*c* 1.2, $CHCl_3$) (lit. $[\alpha]_D^{22}$ = –72.5 (*c* 1.0, $CHCl_3$))[102]; IR (neat) ν_{max} 2845, 1453, 1203, 1041, 852, 758, 702, 627 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 1.49 (br. s, 1H, NH), 2.25 (s, 3H, CH_3-6), 2.26 (s, 6H, CH_3-4 × 2), 2.70 (br. s, 1H, OH), 3.51 (dd, *J* = 10.7, 9.1 Hz, 1H, CH_2-1), 3.57 (d, *J* = 11.5 Hz, 1H, CH_2-3), 3.67 (d, *J* = 11.5 Hz, 1H, CH_2-3), 3.71 (dd, *J* = 10.7, 4.4 Hz, 1H, CH_2-1), 3.83 (dd, *J* = 9.1, 4.4 Hz, 1H, CH-2), 6.84 (s, 2H, Ar CH-5), 7.30-7.41 (m, 5H, Ar CH × 2); ^{13}C NMR ($CDCl_3$, 100MHz) δ 19.5 (CH_3, C-4), 21.0 (CH_3, C-6), 45.5 (CH_2, C-3), 65.2 (CH, C-2), 66.7 (CH_2, C-1), 127.3 (CH, Ar CH), 127.9 (CH, Ar CH), 128.8 (CH, Ar CH), 129.1 (CH, Ar CH), 133.5 (C, Ar C), 136.8 (C, Ar C), 137.2 (C, Ar C), 141.0 (C, Ar C); MS (ES+) *m*/*z* 292.2 (M+Na, 100 %), 270.2 (M+1, 63 %); HRMS (ES+) found 292.1668, requires 292.1677 for $C_{18}H_{23}NONa$.



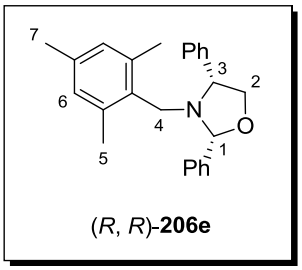
(*R*)-**209**

*Synthesis of oxazolidine (R, R)-**206e**.*



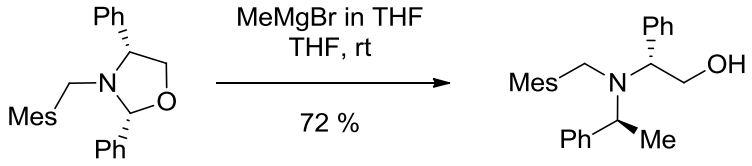
(*R*)-**209** (*R*, *R*)-**206e**

Following a literature procedure,[102] a solution of aminoalcohol (*R*)-**209** (7.65 g, 28.40 mmol) and benzaldehyde (8.66 mL, 85.20 mmol) in toluene (150 mL) was refluxed for 17 h in a flask fitted with a Dean–Stark trap. After being cooled, the mixture was concentrated under reduced pressure. The residue was distilled (230 °C, ~4 mm Hg) to afford the desired product (*R*, *R*)-**206e** (9.0 g, 25.18 mmol, 89 %) as a colorless oil: R_f = 0.75 (1:1 Et_2O/petroleum ether); $[\alpha]_D^{23}$ = –15.7 (c 1.5, $CHCl_3$) (lit. $[\alpha]_D^{20}$ = –7.4 (c 1.0, $CHCl_3$)[102]; ^{1}H NMR ($CDCl_3$, 300MHz) δ 2.03 (s, 3H, CH_3-7), 2.09 (s, 6H, CH_3-5 × 2), 3.64 (d, *J* = 12.5 Hz, 1H, CH_2-4), 3.71 (d, *J* = 12.5 Hz, 1H, CH_2-4), 3.93-4.01 (m, 1H, CH_2-2), 3.93-4.01' (m, 1H, CH_2-3), 4.28-4.36 (m, 1H, CH-2), 5.12 (s, 1H, CH-1), 6.41 (s, 2H, CH-6), 7.13-7.42 (m, 10H, Ar CH × 10); ^{13}C NMR ($CDCl_3$, 100MHz) δ 20.4 (CH_3, C-5 × 2), 20.7 (CH_3, C-7), 49.7 (CH_2, C-4), 69.2 (CH, C-3), 74.6 (CH_2, C-2), 98.7 (CH, C-1), 127.2 (CH, Ar CH), 127.5 (CH, Ar CH), 127.8 (CH, Ar CH), 127.9 (CH, Ar CH), 128.0 (CH, Ar CH), 128.4 (CH, Ar CH), 128.5 (CH, C-6), 130.8 (C, Ar C), 136.4 (C, Ar C), 137.3 (C, Ar C), 140.1 (C, Ar C), 140.2 (C, Ar C); MS (ES+) *m*/*z* 380.3 (M+Na, 100 %), 358.3 (M+1, 20 %); HRMS (ES+) found 380.2005, requires 380.1990 for $C_{25}H_{27}NONa$.



(*R*, *R*)-**206e**

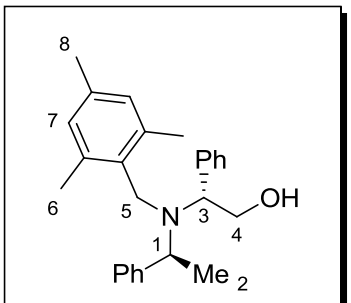
*Synthesis of amino alcohol (S, R)-**203e**.*



(*R*, *R*)-**206e** (*S*, *R*)-**203e**

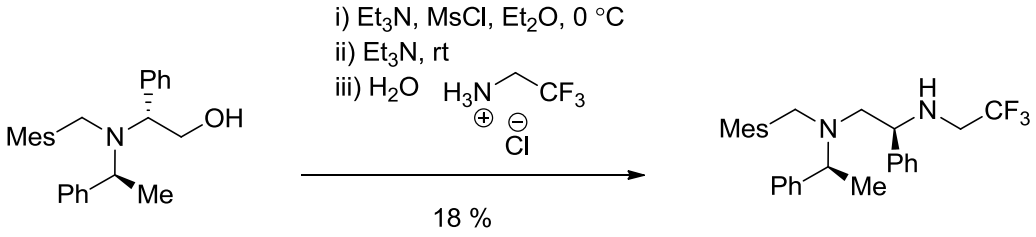
Following a literature procedure,[102] methylmagnesium bromide (44 mL, 132.0 mmol, 3 M in THF) was added dropwise to a stirred solution of oxazolidine (*R*, *R*)-**206e** (9.42 g, 26.4 mmol) in THF (200 mL) at room temperature over a 60 min period. After the reaction mixture was stirred for 20 h, a further portion of methylmagnesium bromide (56 mL, 168.0 mmol, 3M in THF) was added over 1 h. After stirring at room temperature for 70 h the reaction mixture was then quenched with a small amount of water and diluted with Et_2O (400 mL). The resulting white precipitate was filtered off and washed with Et_2O (400 mL). The combined organic phases were washed with NH_4Cl (200 mL) and brine (200 mL), dried over $MgSO_4$, and concentrated *in vacuo* to yield an oily residue. The crude product was purified by flash column chromatography (15 % → 50 %, Et_2O:petroleum ether) to yield an oily solid which upon further concentration under high vaccum gave the desired product (*S*, *R*)-**203e** as a white foam (7.10 g, 19.01 mmol, 72%): mp 49-51 °C; R_f = 0.3 (1:1 Et_2O/petroleum ether); $[\alpha]_D^{20}$ = –83.2 (*c* 1.0, Et_2O) (lit. $[\alpha]_D^{24}$ = –68.0 (*c* 1.4, $CHCl_3$))[102]; IR (neat) ν_{max} 3332, 2916, 1450, 1029, 851, 750, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.38-1.41 (m, 1H, OH), 1.51 (d, *J* = 7.0 Hz, 3H, CH_3-2), 2.05 (s, 6H, CH_3-6 × 2), 2.22 (s, 3H, CH_3-8), 3.66 (d, *J* = 12.7 Hz, 1H, CH_2-5), 3.86 (dd, *J* = 5.0, 9.3 Hz, 1H, CH-3); 4.00 (t, *J* = 7.0 Hz, 1H, CH-1), 4.02 (d, *J* = 12.7 Hz, 1H, CH_2-5), 4.12-4.18 (m, 1H, CH_2-4), 4.22-4.27 (m, 1H, CH_2-4), 6.77 (s, 2H, Ar CH-7 × 2), 6.93-7.00 (m, 4H, Ar CH × 4), 7.14-7.27 (m, 6H, Ar CH × 6); ^{13}C NMR ($CDCl_3$, 100MHz) δ 16.3 (CH_3, C-2), 19.9 (CH_3, C-6), 20.9 (CH_3, C-8), 44.1 (CH_2, C-5), 55.0 (CH, C-

1), 61.4 (CH_2, C-4), 61.9 (CH, C-3), 126.7 (CH, Ar CH), 127.2 (CH, Ar CH), 127.7 (CH, Ar CH), 128.3 (CH, Ar CH), 128.4 (CH, Ar CH), 128.9 (CH, Ar CH), 129.4 (CH, Ar CH), 132.6 (C, Ar C), 136.4 (C, Ar C), 138.4 (C, Ar C); MS (ES+) *m*/*z* 396.2 (M+Na, 100%), 374.2 (M+1, 5%); HRMS (ES+) found 396.2312, requires 396.2303 for $C_{26}H_{31}NONa$.



(*S*, *R*)-**203e**

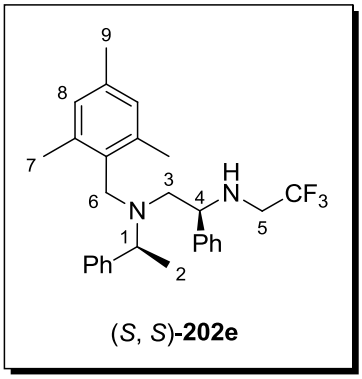
*Synthesis of diamine (S, S)-**202e**.*



(*S*, *R*)-**203e** (*S*, *S*)-**202e**

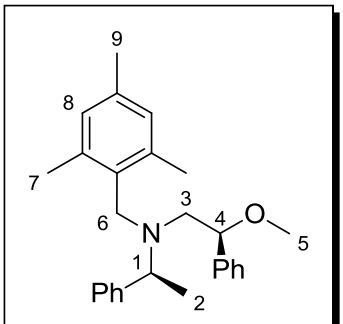
Following a modified literature procedure,[104] methanesulfonyl chloride (0.58 mL, 7.52 mmol) was added dropwise to a stirred solution of amino alcohol (*S*, *R*)-**203e** (2.4 g, 6.43 mmol) and Et_3N (1.4 mL, 10.04 mmol) in Et_2O (36 mL) at 0 °C. A white precipitate formed and the mixture was stirred at 0 °C for 30 min. A further portion of Et_3N (1.74 mL, 12.47 mmol) was added before the reaction was returned to room temperature. A solution of 2,2,2-trifluoroethylamine hydrochloride (2.6 g, 19.29 mmol) in water (7 mL) was added dropwise and the resultant biphasic mixture was stirred vigorously for 19 h. The mixture was diluted with Et_2O (125 mL) and the phases were separated. The aqueous was extracted with Et_2O (2 × 125 mL) and the organics were combined, washed with dilute $NaHCO_{3\ (aq)}$ (125 mL) and water (125 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (petroleum ether → 10% Et_2O/petroleum ether) to yield the desired product (*S*, *S*)-**202e** as a colourless oil (0.53 g, 1.17 mmol, 18 %): R_f =

0.85 (1:1 Et_2O/petroleum ether); $[\alpha]_D^{23}$ = +56.0 (*c* 1.9, $CHCl_3$); IR (neat) ν_{max} 2919, 1452, 1266, 1139, 757, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.45 (d, *J* = 6.8 Hz, 3H, CH-2), 1.98 (br. s, 1H, NH), 2.28 (s, 3H, CH_3-9), 2.38 (s, 6H, CH_3-7 × 2), 2.47-2.58 (m, 4H, CH_2-3 & CH_2-5), 3.16 (dd, *J* = 9.2, 4.4 Hz, 1H, CH-4), 3.76 (s, 2H, CH_2-6), 4.02 (q, *J* = 6.8 Hz, 1H, CH-1), 6.88 (s, 2H, Ar CH-8 × 2), 7.04-7.07 (m, 2H, Ar CH × 2), 7.17-7.38 (m, 8H, Ar CH × 8); ^{13}C NMR ($CDCl_3$, 100MHz) δ 12.1 (CH_3, C-2), 20.3 (CH_3, C-7), 21.0 (CH_3, C-9), 48.4 (q, *J* = 30.8 Hz, CH_2, C-5), 50.5 (CH_2, C-6), 58.1 (CH_2, C-3), 60.50 (CH, C-1), 60.54 (CH, C-4), 125.6 (q, *J* = 277.5 Hz, C, CF_3), 127.2 (CH, Ar CH), 127.41 (CH, Ar CH), 127.43 (CH, Ar CH), 128.2 (CH, Ar CH), 128.3 (CH, Ar CH), 128.5 (CH, Ar CH), 129.5 (CH, C-8), 132.7 (C, Ar C), 136.8 (C, Ar C), 137.9 (C, Ar C), 142.2 (C, Ar C), 143.1 (C, Ar C); MS (ES+) *m*/*z* 477.2 (M+Na, 72 %), 455.2 (M+1, 100 %); HRMS (ES+) found 477.2497, requires 477.2494 for $C_{28}H_{33}N_2F_3Na$.



(*S*, *S*)-**202e**

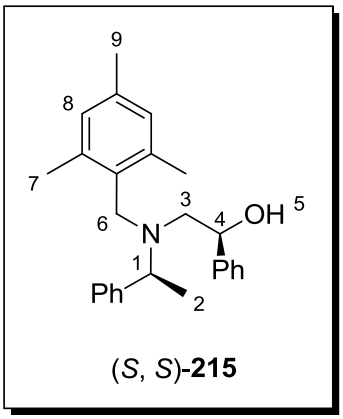
Ether (*S*, *S*)-**214**: R_f = 0.80 (1:1 Et_2O/petroleum ether); ^1H NMR ($CDCl_3$, 300MHz) δ 1.36 (d, *J* = 7.0 Hz, 3H, CH_3-2), 2.18 (s, 6H, CH_3-7 × 2), 2.25 (s, 3H, CH_3-9), 2.63 (dd, *J* = 13.7, 6.6 Hz, 1H, CH_2-3), 2.81 (dd, *J* = 13.7, 6.6 Hz, 1H, CH_2-3), 3.02 (s, 3H, CH_3-5), 3.48 (d, *J* = 12.5 Hz, 1H, CH_2-6), 3.69 (d, *J* = 12.5 Hz, 1H, CH_2-6), 3.72 (t, *J* = 6.6 Hz, 1H, CH-4), 3.87 (q, *J* = 7.0 Hz, 1H, CH-1), 6.76 (s, 2H, Ar CH-8 × 2), 6.92-6.98 (m, 2H, Ar CH × 2), 7.20-7.31 (m, 8H, Ar CH × 8); ^{13}C NMR ($CDCl_3$, 100MHz) δ 15.6 (CH_3, C-2), 20.3 (CH_3, C-7), 21.0 (CH_3, C-9), 49.6 (CH_2, C-6), 56.6 (CH_3, C-5), 57.0 (CH_2, C-3), 60.9 (CH, C-1), 83.5 (CH, C-4), 126.7 (CH, Ar CH), 127.3 (CH, Ar CH), 127.4 (CH, Ar CH), 127.9 (CH, Ar CH), 128.1 (CH, Ar



(*S*, *S*)-**214**

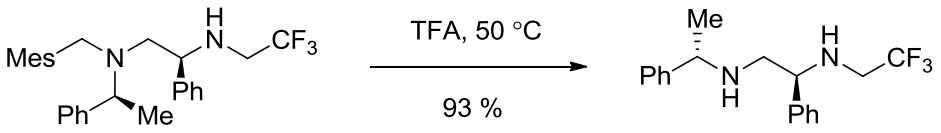
CH), 128.4 (CH, Ar CH), 129.1 (CH, C-8), 132.8 (C, Ar C), 136.2 (C, Ar C), 138.4 (C, Ar C), 141.6 (C, Ar C), 142.9 (C, Ar C); MS (ES+) *m*/*z* 388.2 (M+1, 100 %), 410.2 (M+Na, 40 %); HRMS (ES+) found 388.2641, requires 388.2640 for $C_{27}H_{34}NO$.

Alcohol (*S*, *S*)-**215**: R_f = 0.75 (1:1 Et_2O/petroleum ether); ^1H NMR ($CDCl_3$, 300MHz) δ 1.40 (d, *J* = 6.9 Hz, 3H, CH_3-2), 2.18 (s, 3H, CH_3-9), 2.22 (s, 6H, CH_3-7 × 2), 2.37 (dd, *J* = 13.3, 10.5 Hz, 1H, CH_2-3), 2.55 (dd, *J* = 13.3, 3.0 Hz, 1H, CH_2-3), 3.07 (br. s, 1H, OH-5), 3.71 (s, 2H, CH_2-6), 3.98 (q, *J* = 6.9 Hz, 1H, CH-1), 4.27 (dd, *J* = 10.5, 3.0 Hz, 1H, CH-4), 6.78 (s, 2H, Ar CH-8 × 2), 6.95-7.00 (m, 2H, Ar CH × 2), 7.09-7.31 (m, 8H, Ar CH × 8); ^{13}C NMR ($CDCl_3$, 100MHz) δ 11.3 (CH_3, C-2), 20.3 (CH_3, C-7 × 2), 21.0 (CH_3, C-9), 48.8 (CH_2, C-6), 57.7 (CH_2, C-3), 58.6 (CH, C-1), 70.2 (CH, C-4), 126.0 (CH, Ar), 127.4 (CH, Ar), 127.5 (CH, Ar), 128.2 (CH, Ar), 128.3 (CH, Ar), 128.4 (CH, Ar), 129.6 (CH, C-8 × 2), 131.8 (C, Ar), 136.9 (C, Ar), 137.9 (C, Ar), 142.6 (C, Ar), 143.0 (C, Ar).



(*S*, *S*)-**215**

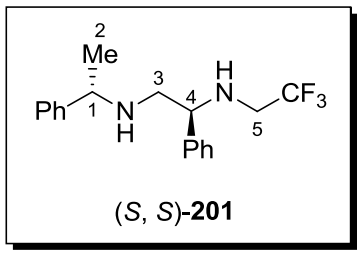
*Synthesis of diamine (S, S)-**201**.*



(*S*, *S*)-**202e** (*S*, *S*)-**201**

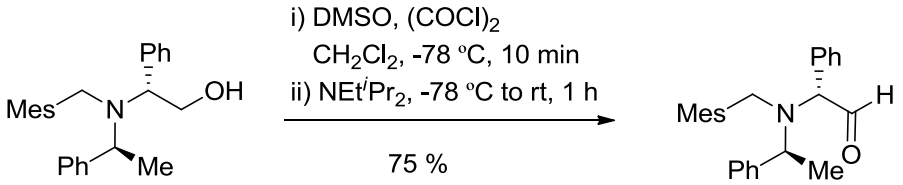
Following a modified literature procedure,[102] trifluoroacetic acid (32 mL) was added to diamine (*S*, *S*)-**202e** (0.95 g, 2.09 mmol) and the resultant mixture was heated to 50 °C for 59 h. After cooling to room temperature the mixture was basified with $NaOH_{(aq)}$ (2 M) and then extracted with CH_2Cl_2 (4 × 100 mL). The combined organics were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* yield a brown oil (~1 g). The

crude residue was purified by flash column chromatography (petroleum ether → Et_2O) to yield the desired product (*S*, *S*)-**201** as a yellow oil (0.62 g, 1.93 mmol, 93%): R_f = 0.15 (1:1 Et_2O/petroleum ether); $[\alpha]_D^{23}$ = +7.1 (*c* 0.9, $CHCl_3$); MS *m*/*z* (ES+) 323.2 (M+1, 100%); HRMS (ES+) found 323.1737, requires 323.1735 for $C_{18}H_{22}N_2F_3$; IR (neat) ν_{max} 3317, 2846, 1453, 1266, 1142, 759, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.35 (d, *J* = 6.6 Hz, 3H, CH_3-2), 1.99 (br. s, 2H, NH × 2), 2.59-2.72 (m, 2H, CH_2-3), 2.79-2.95 (m, 2H, CH_2-5), 3.54 (dd, *J* = 4.9, 8.7 Hz, 1H, CH-4), 3.73 (q, *J* = 6.6 Hz, 1H, CH-1), 7.21-7.35 (m, 10H, Ar CH × 10); ^{19}F ($CDCl_3$, 282MHz) δ -71.45 (CF_3); ^{13}C NMR ($CDCl_3$, 100MHz) δ 24.4 (CH_3, C-2), 48.2 (q, *J* = 30.9 Hz, CH_2, C-5), 55.2 (CH_2, C-3), 59.1 (CH, C-4), 62.0 (CH, C-1), 125.8 (q, *J* = 278.7 Hz, C, CF_3), 126.6 (CH, Ar CH), 127.2 (CH, Ar CH), 127.4 (CH, Ar CH), 127.8 (CH, Ar CH), 128.6 (CH, Ar CH), 128.7 (CH, Ar CH), 141.3 (C, Ar C), 145.9 (C, Ar C).



(*S*, *S*)-**201**

*Synthesis of aldehyde (S, R)-**216**.*

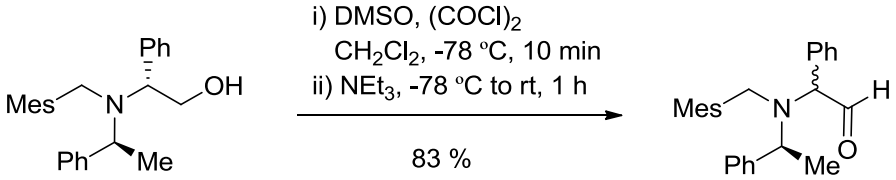


(*S*, *S*)-**202e** (*S*, *R*)-**216**

Following a modified literature procedure,[104] DMSO (0.08 mL, 1.2 mmol) was added dropwise to stirred solution of oxalyl chloride (0.06 mL, 0.72 mmol) in CH_2Cl_2 (2 mL) at -78 °C under N_2. After 5 min, a solution of amino alcohol (*S*, *S*)-**202e** (224 mg, 0.6 mmol) in CH_2Cl_2 (1 mL) was added dropwise. After an additional 10 min, *N*, *N*-di*iso*propylethylamine (0.42 mL, 2.4 mmol) was added dropwise and the reaction mixture was stirred at -78 °C for 1 h before $HCl_{(aq)}$ (2 mL, 1 M) was added. The layers were separated and the aqueous phase

were extracted with Et_2O (20 mL). The organic phase was washed with 5% $NaHCO_{3\ (aq)}$ (30 mL), water (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether → 10% Et_2O/petroleum ether) to yield the desired product (*S*, *R*)-**216** as a colourless oil (167 mg, 0.45 mmol, 75 %): R_f = 0.6 (Et_2O/petroleum ether, 1:1); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.61 (d, *J* = 7.1 Hz, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.26 (s, 6H, CH_3 × 2), 3.37 (d, *J* = 13.1 Hz, 1H, CH_2), 4.05-4.13 (m, 2H, CH × 2), 4.16 (d, *J* = 13.1 Hz, 1H, CH_2), 6.76 (s, 2H, Ar CH × 2), 7.06-7.10 (m, 2H, Ar CH × 2), 7.23-7.39 (m, 2H, Ar CH × 8), 8.82 (d, *J* = 4.0 Hz, 1H, CHO).

*Synthesis of aldehyde (R)-**216**.*



(*S*, *S*)-**202e** (*S*)-**216**

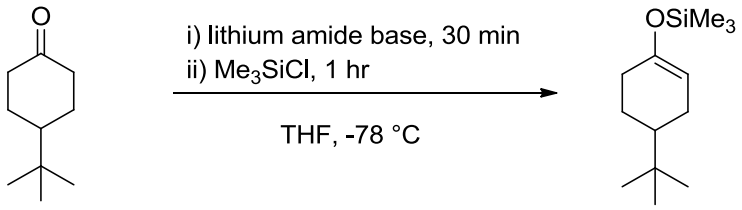
Following a modified literature procedure,[104] DMSO (0.16 mL, 2.4 mmol) was added dropwise to stirred solution of oxalyl chloride (0.12 mL, 1.4 mmol) in CH_2Cl_2 (4 mL) at -78 °C under N_2. After 5 min, a solution of amino alcohol (*S*, *S*)-**202e** (448 mg, 1.2 mmol) in CH_2Cl_2 (2 mL) was added dropwise. After an additional 10 min, Et_3N (0.72 mL, 4.8 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature over 1 h before water (15 mL) was added. The layers were separated and the aqueous phases were extracted with Et_2O (50 mL). The combined organic phases were washed with 5% $NaHCO_{3\ (aq)}$ (60 mL), water (25 mL) and Brine (25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether → 10% Et_2O/petroleum ether) to yield a 1:1 mixture of diastereomers as a colourless oil (0.37 g, 0.99

mmol, 83 %): ^{1}H NMR ($CDCl_3$, 300 MHz) (*S*, *R*)-**216** as above; (*S*, *S*)-**216** aldehyde signal δ 8.56 (d, *J* = 3.54 Hz, 1H, CHO).

7.4 Deprotonations Using Lithium Amide Bases

7.4.1 Syntheses of Enol Silane 34

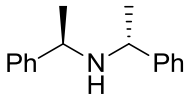
Table 7.1: Synthesis of enol silane **34** from ketone **1** using a single lithium amide base and LiCl (0 or 1.2 eq.)[a]



1 **34**

Entry	GP	Amine	Amount of Amine (0.78 mmol)	Conversion[b] (%)	% ee[b]
1	A	DIPA	109 μL	85 (79, 91)	-
2	B	DIPA·HCl	107 mg	100 (99[c], 100)	-
3	A	**185**	184 μL	39 (37, 41)	-
4	C	**185**	184 μL	39 (32, 46)	-
5	A	TMP	132 μL	50 (58, 42)	-
6	A	(*R*, *R*)-**358**	176 mg	99 (99, 99)	42 (*S*) (42, 42)
7	B	(*R*, *R*)-**358**·HCl	204 mg	99 (99, 99)	81 (*S*) (81, 80)
8	C	(*R*)-**355**	149 mg	73 (93, 52)	11 (*S*) (10, 12)
9	A	(*R*)-**186**	158 mg	93 (92, 93)	44 (*S*) (42, 46)
10	B	(*R*)-**186**·HCl	187 mg	98 (98, 99[d])	78 (*S*) (77, 79[d])
11	A	(+)-**178**	327 mg	98 (96[e], 99)	49 (*R*) (46[e], 52)
12	C	(+)-**178**	327 mg	99 (98, 99)	58 (*R*) (59, 57)

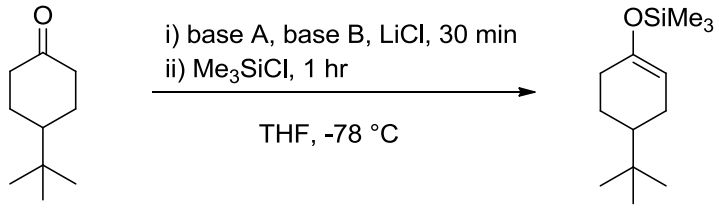
a The reaction was carried out on a 0.65 mmol scale with 5.0 equivalents of chlorotrimethylsilane at -78 °C. *b* Determined by chiral GC using Chiralsil-DEX CB column. *c* For chromatogram see Figure C1. *d* For chromatogram see Figure C2. *e* For chromatogram see Figure C3.



(*R*, *R*)-**358**

Figure 7.1

Table 7.2: Synthesis of enol silane **34** from ketone **1** using two lithium amide bases and LiCl (1 eq.).[a]

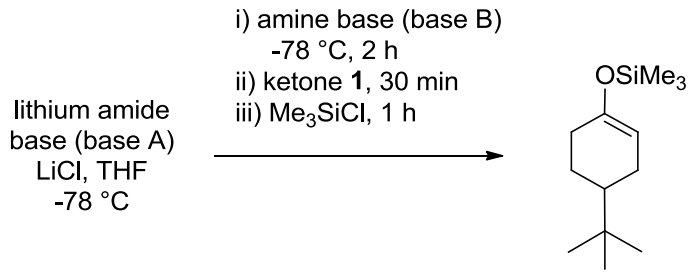


1 **34**

Entry	GP	Amine A[b]	Amount of amine A (0.65 mmol)	Amine B[b]	Amount of amine B (0.65 mmol)	Conv.[c] (%)	% ee[c]
1	D	DIPA·HCl	89 mg	(+)-**178**	273 mg	98 (98, 99)	57 (*R*) (60, 54)
2	D	DIPA	92 µL	(*R*, *R*)-**358**·HCl	170 mg	99 (99, 99)	36 (*S*) (37, 35)
3	D	DIPA	92 µL	(*R*)-**186**·HCl	156 mg	99 (98, 99)	50 (*S*) (58, 42)
4	D	**185**	153 µL	(*R*, *R*)-**358**·HCl	170 mg	56 (57, 55)	11 (*S*) (12, 10)
5	D	**185**	153 µL	(*R*)-**186**·HCl	156 mg	93 (93, 92)	65 (*S*) (66, 63)
6	D	(*R*, *R*)-**358**·HCl	170 mg	(+)-**178**	293 mg	99 (99, 99)	35 (*R*) (38, 32)

a The reaction was carried out on a 0.65 mmol scale with 5.0 equivalents of chlorotrimethylsilane at -78ºC. *b* 1.2 equivalents compared to substrate. *c* Determined by chiral GC using Chiralsil-DEX CB column.

Table 7.3: Synthesis of enol silane **34** from ketone **1** using a mixture of a lithium amide, LiCl (1.2 eq.) and an amine.[a]

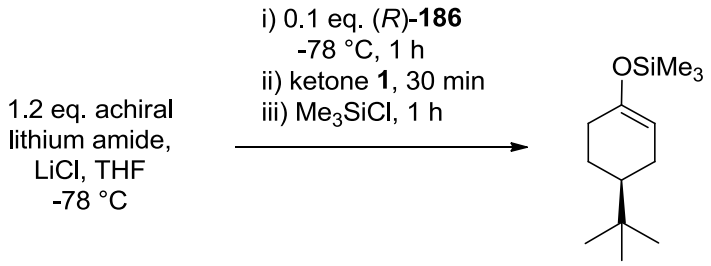


34

Entry	GP	Amine A[b]	Amount of Amine A (0.78 mmol)	Amine B[b]	Amount of Amine B (0.78 mmol)	Conv.[c] (%)	% ee[c]
1	E	(*R*, *R*)-**358**·HCl	203 mg	**185**	184 µL	54	-
2	E	DIPA·HCl	107 mg	(+)-**178**	328 mg	77	6 (*R*)
3	F	**185**	184 µL	(+)-**178**	328 mg	25 (26, 24)	-
4	F	(+)-**178**	328 mg	**185**	184 µL	46 (41, 51)	-
5	E	(*R*)-**186**·HCl	187 mg	DIPA	109 µL	81 (84, 78)	69 (*S*) (68, 69)
6	E	DIPA·HCl	107 mg	(*R*)-**186**	158 mg	98 (97, 99)	83 (*S*) (81, 84[d])
7	E	(*R*)-**186**·HCl	187 mg	**185**	184 µL	37	69 (*S*)
8	F	**185**	184 µL	(*R*)-**186**	158 mg	86	56 (*S*)

a The reaction was carried out on a 0.65 mmol scale with 5.0 equivalents of chlorotrimethylsilane at -78°C. *b* 1.2 equivalents compared to substrate. *c* Determined by chiral GC using Chiralsil-DEX CB column. *d* For chromatogram see Figure C4.

Table 7.4: Synthesis of enol silane **34** from ketone **1** using a mixture of an achiral lithium amide, LiCl (1.2 eq.) and 0.1 eq. of a chiral amine.[a]



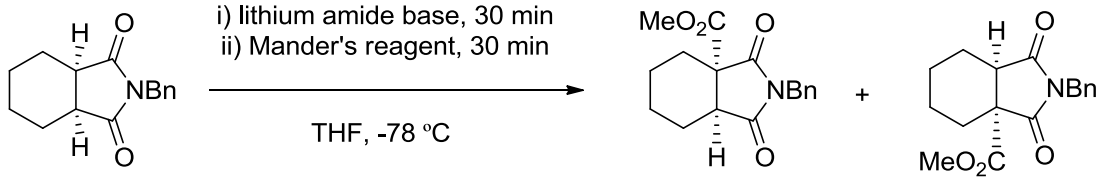
(*S*)-**34**

Entry	GP	Achiral Amine[b]	Amount of Achiral Amine (0.78 mmol)	Amount of (*R*)-**186** (0.07 mmol)	Conv.[c] (%)	% ee[c]
1	G	DIPA·HCl	107 mg	14 mg	99	20 (*S*)
2	H	**185**	184 µL	14 mg	70 (73, 67)	18 (*S*) (17, 19)

a The reaction was carried out on a 0.65 mmol scale with 5.0 equivalents of chlorotrimethylsilane at -78°C. *b* 1.2 equivalents compared to substrate. *c* Determined by chiral GC using Chiralsil-DEX CB column.

7.4.2 Syntheses of imide 156

Table 7.5: Synthesis of ester **156** from imide **151** using a single lithium amide base and LiCl (0 or 1.3 eq.).[a]

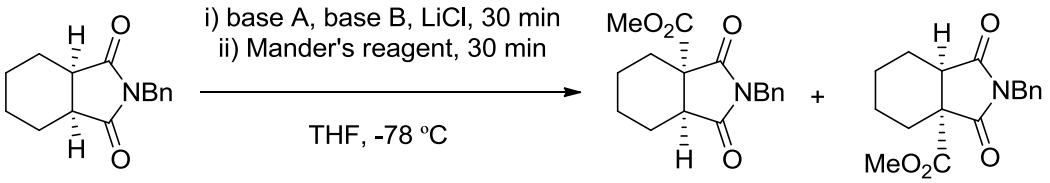


151 (–)-**156** (+)-**156**

Entry	GP	Amine[b]	Amount of Amine (0.53 mmol)	Yield (%)[c]	% ee[d] (sign of rot.)[e]
1	I	DIPA	74 µL	16 (9, 23)	-
2	J	DIPA·HCl	73 mg	43 (47[f], 39)	-
3	I	**185**	125 µL	55 (52, 57)	-
4	K	**185**	125 µL	73 (69, 77)	-
5	I	(*R*)-**186**	108 mg	53 (52, 54)	35 (32, 38) (+)
6	J	(*R*)-**186**·HCl	127 mg	71 (77, 64)	47 (45, 48[g]) (+)
7	I	(+)-**178**	223 mg	90 (90, 91)	92 (91, 93) (–)
8	K	(+)-**178**	223 mg	93 (92, 94)	97 (97[h], 97) (–)

a The reaction was carried out on a 0.41 mmol scale with 3.0 equivalents of methyl cyanoformate at -78ºC. *b* 1.3 equivalents compared to substrate. *c* Isolated yield. *d* Determined by chiral HPLC using a Chiralcel OD column. *e* Sign of rotation of plane polarized light measured on an automatic polarimeter. *f* For chromatogram see Figure D1. *g* For chromatogram see Figure D2. *h* For chromatogram see Figure D3.

Table 7.6: Synthesis of ester **156** from imide **151** using a mixture of two lithium amide bases and LiCl.[a]

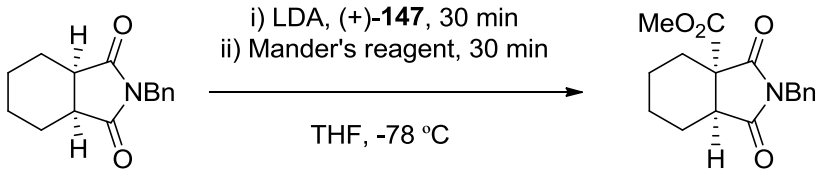


151 (–)-**156** (+)-**156**

Entry	GP	Amine A[b]	Amount of amine A	Amine B[b]	Amount of amine B	Yield[c] (%)	% ee[d] (sign of rot.)[e]
1	L	(*R*)-**186**·HCl	98 mg (0.41 mmol)	**185**	97 µL (0.41 mmol)	19 (19, 19)	29 (+) (28, 30)
2	L	DIPA·HCl	56 mg (0.41 mmol)	(+)-**178**	172 mg (0.41 mmol)	89 (85, 93)	99 (–) (99, 99[f])

a The reaction was carried out on a 0.41 mmol scale with 3.0 equivalents of methyl cyanoformate at -78°C. *b* 1.3 equivalents compared to substrate. *c* Isolated yield. *d* Determined by chiral HPLC using a Chiralcel OD column. *e* Sign of rotation of plane polarized light measured on an automatic polarimeter. *f* For chromatogram see Figure D4.

Table 7.7: Synthesis of ester **156** from imide **151** using a mixture of LDA, (+)-**147** & LiCl (0, 1 or 2 eq.).[a]

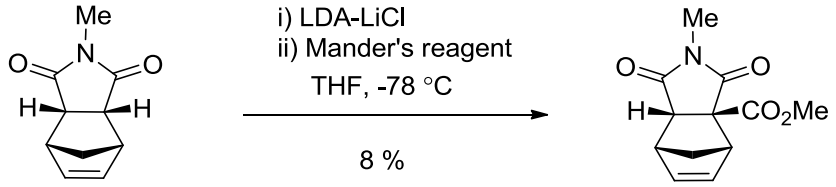


151 (–)-**156**

Entry	Amount of DIPA·HCl	Amount of DIPA	Amount of (+)-**178**	Amount of *n*-BuLi (1.6 M)	Yield[b] (%)	% ee[c] (sign of rot.)[d]
1	-	57 µL (0.41 mmol)	172 mg (0.41 mmol)	513 µL (0.82 mmol)	65	87 (–)
2	113 mg (0.82 mmol)	-	345 mg (0.82 mmol)	1.54 mL (2.46 mmol)	73 (65, 81)	99 (–) (99, 99)
3	-	38 µL (0.27 mmol)	112 mg (0.27 mmol)	331 µL (0.53 mmol)	69	75 (–)
4	-	57 µL (0.41 mmol)	130 mg (0.31 mmol)	450 µL (0.72 mmol)	48	72 (–)
5	-	57 µL (0.41 mmol)	86 mg (0.21 mmol)	384 µL (0.62 mmol)	42	53 (–)
6	-	57 µL (0.41 mmol)	52 mg (0.12 mmol)	333 µL (0.53 mmol)	33	32 (–)
7	56 mg (0.41 mmol)	-	130 mg (0.31 mmol)	705 µL (1.13 mmol)	50	97 (–)
8	56 mg (0.41 mmol)	-	88 mg (0.21 mmol)	641 µL (1.03 mmol)	46	58 (–)
9	56 mg (0.41 mmol)	-	50 mg (0.12 mmol)	589 µL (0.94 mmol)	35	83 (–)

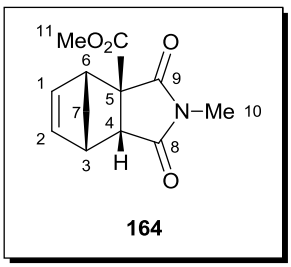
a The reaction was carried out on a 0.41 mmol scale with 3.0 equivalents of methyl cyanoformate at -78 °C following general procedure M. *b* Isolated yield. *c* Determined by chiral HPLC using a Chiralcel OD column. *d* Sign of rotation of plane polarized light measured on an automatic polarimeter.

7.4.3 Synthesis of ester 164



152 (±)-**164**

n-Butyllithium (538 μL, 1.34 mmol, 2.5 M solution in hexanes) was added dropwise to a suspension of di*iso*propylamine hydrochloride (93 mg, 0.65 mmol) in THF (5 mL) at -78 °C. The base mixture was stirred at -78 °C for 10 min and then at 0 °C for 20 min. This base solution was then added dropwise over 5 min to a solution of imide **152** (100 mg, 0.56 mmol) in THF (2.5 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 30 min and then Mander's reagent (133 μL, 1.68 mmol) was added. The reaction mixture was stirred at -78 °C for a further 40 min before being quenched with sat. $NH_4Cl_{(aq)}$ (0.5 mL). The mixture was returned to room temperature, diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were washed with brine (15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (40 % EtOAc/petroleum ether) to yield **164** as a yellow oil (10 mg, 0.04 mmol, 8 %): R_f = 0.5 (1:1 EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$, 300MHz) δ 1.73-1.78 (m, 1H, CH_2-7), 1.83 (dt, *J* = 9.3, 1.6 Hz, 1H, CH_2-7), 2.87 (s, 3H, CH_3-10), 3.37-3.41 (m, 1H, CH-3), 3.51 (d, *J* = 4.6 Hz, 1H, CH-4), 3.63-3.66 (m, 1H, CH-6), 3.79 (s, 3H, CH_3-11), 6.15-6.20 (m, 2H, CH-1 & CH-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.9 (CH_3, C-10), 45.1 (CH, C-3), 48.8 (CH, C-6), 51.9 (CH_2, C-7), 52.2 (CH, C-4), 53.4 (CH_3, C-11), 62.4 (C, C-5), 135.5 (CH, vinylic CH), 136.4 (CH, vinylic CH), 170.0 (C=O), 176.4 (C=O), 183.0



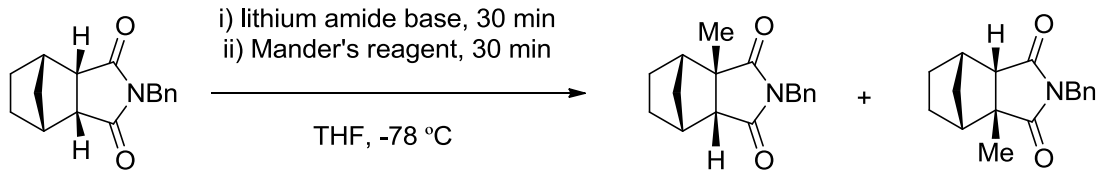
164

(C=O); MS (ES+) *m/z* 258.0 (M+Na, 100 %); HRMS (ES+) found 258.0739, requires 258.0742 for $C_{12}H_{13}NO_4Na$.

It was not found to be possible to separate the enantiomers using the available chiral HPLC columns (Chiralcel OD & Chiralpak AD).

7.4.4 Syntheses of Imide 165

Table 7.8: Synthesis of ester **165** from imide **152** using a single lithium amide base and LiCl (0 or 1.2 eq.).[a]



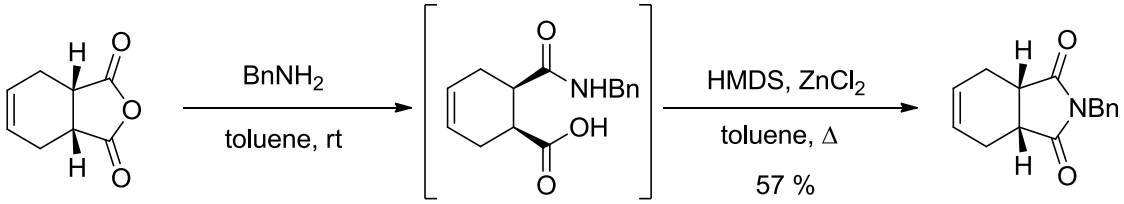
152 (–)-**165** (+)-**165**

Entry	GP	Amine[b]	Amount of Amine	Yield[c] (%)	% ee[d] (sign of rot.)[e]
1	O	DIPA·HCl	93 mg (0.67 mmol)	43[f]	-
2	N	**185**	146 µL (0.62 mmol)	73	-
3	O	(*R*)-**186**·HCl	176 mg (0.67 mmol)	47	92[g](–)
4	N	(+)-**178**	307 mg (0.73 mmol)	28	95[h] (+)

a The reaction was carried out on a 0.56 mmol scale with 3.0 equivalents of methyl iodide at -78°C. *b* 1.1-1.3 equivalents compared to substrate. *c* Isolated yield. *d* Determined by chiral HPLC using a Chiralcel OD column. *e* Sign of rotation of plane polarized light measured on an automatic polarimeter. *f* For chromatogram see Figure E1. *g* For chromatogram see Figure E2. *h* For chromatogram see Figure E3.

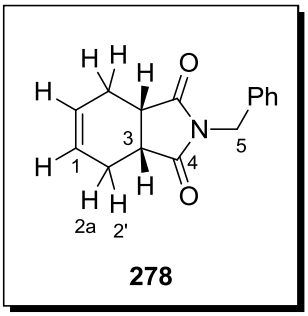
7.5 Synthesis of Compounds Towards the Total Synthesis of Concavine

*Synthesis of imide **278**.*



277 **278**

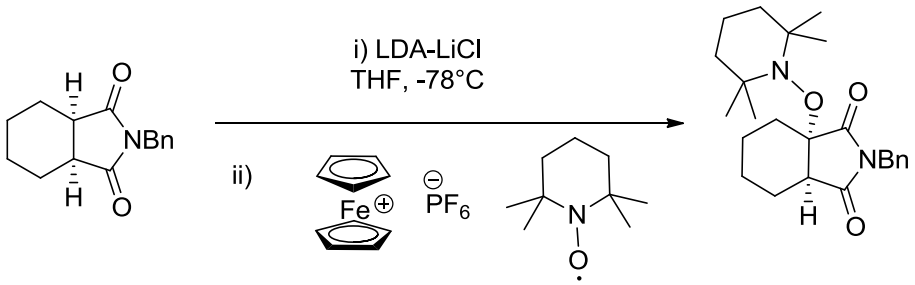
Following a modified literature procedure,[79] a solution of *cis*-1,2,3,6-tetrahydrophthalic anhydride (**277**) (7.61 g, 50.0 mmol) and benzylamine (5.5 mL, 50.0 mmol) in toluene (100 mL) was stirred at room temperature for 1 h. Zinc (II) chloride (50 mL, 50.0 mmol, 1M soln. in Et_2O) was added and the reaction mixture was heated to 80 °C. Hexamethyldisilazane (15.6 mL, 75.0 mmol) was then added and the reaction mixture was heated to reflux for 2 h before being returned to room temperature and then cooled to 0 °C. $HCl_{(aq)}$ (60 mL, 1 M) was added and the product was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with $NaHCO_{3(aq)}$ (3 × 50 mL), brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield a white solid (11.6 g). The crude product was purified by recrystallisation (EtOAc/petroleum ether, minor/major) to yield the desired product **278** as colourless needles (6.84 g, 28.3 mmol, 57% from 1st two crops): mp 82-83 °C; R_f = 0.15 (EtOAc:petroleum ether, 1:4); IR (neat) ν_{max} 2954, 1689, 1342, 1170, 928, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 2.14-2.45 (m, 2H, CH-2a × 2), 2.55-2.62 (m, 2H, CH-2b × 2), 3.05-3.07 (m, 2H, CH-3 × 2), 4.60 (s, 2H, CH_2-5), 5.84-5.86 (m, 2H, CH-1 × 2), 7.22-7.28 (m, 5H, Ar CH × 5); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 23.6 (CH_2, C-2), 39.3 (CH, C-3), 42.6 (CH_2, C-5), 127.9 (CH, C-1), 127.9 (CH, Ar CH), 128.4 (CH,



278

Ar CH), 128.7 (CH, Ar CH), 135.9 (C, Ar C), 179.9 (C=O, C-4); MS (ES+) *m/z* 264.2 (M+Na, 100%); HRMS (ES+) found 264.1005, requires 264.1000 for $C_{15}H_{15}NO_2Na$.

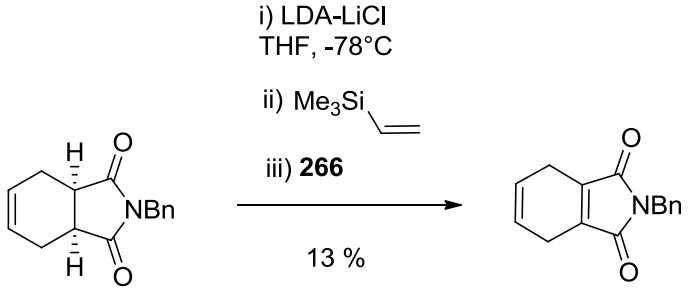
*Synthesis of imide **279**.*



n-Butyllithium (1.5 mL, 2.4 mmol, 1.6 M in hexanes) was added dropwise to a suspension of di*iso*propylamine hydrochloride (165 mg, 1.2 mmol) in THF (5 mL) at -78 °C. The base mixture was stirred at -78 °C for 10 min before being warmed to 0 °C and added dropwise to a solution of imide **171** (243 mg, 1.0 mmol) in THF (2.5 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 30 min and then a mixture of ferrocenium hexafluorophosphate (**266**) (662 mg, 2.0 mmol) and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (**267**) (313 mg, 2.0 mmol) was added in small portions under N_2 over 15 min and then the mixture was stirred at -78 °C for 35 min before addition of $NH_4Cl_{(aq)}$ (10 mL). The reaction was returned to room temperature and filtered through a silica plug which was washed with Et_2O. The organics were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether → 2% EtOAc/petroleum ether) to yield the desired product **279** (16 mg, 4 %) as an off-white solid: R_f= 0.5 (petroleum ether:EtOAc, 1:1); IR (neat) ν_{max} 2937, 1699, 1397, 1348, 1024, 926, 791, 698 cm^{-1} ^1H NMR ($CDCl_3$, 300MHz) δ 0.59 (s, 3H, CH_3), 0.81-0.91 (m, 1H), 1.04 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.10-1.17 (m, 1H), 1.24-1.44 (m, 4H), 1.45-1.64

(m, 4H), 1.71-1.86 (m, 2H), 1.98-2.07 (m, 2H), 4.02-4.04 (m, 1H, CH), 4.63 (s, 2H, benzylic CH_2), 7.24-7.30 (m, 3H, Ar CH × 3), 7.39-7.42 (m, 2H, Ar CH × 2); ^{13}C ($CDCl_3$, 100MHz) δ 16.1 (CH_2), 16.4 (CH_2), 16.7 (CH_2), 20.2 (CH_3), 20.29 (CH_2), 20.30 (CH_3), 27.9 (CH_2), 32.2 (CH_3), 33.6 (CH_3), 39.7 (CH), 40.2 (CH_2), 40.4 (CH_2), 42.1 (benzylic CH_2), 59.0 (C), 59.7 (C), 82.6 (C), 127.6 (Ar CH), 128.2 (Ar CH), 128.8 (Ar CH), 135.2 (Ar C), 178.7 (C=O), 179.4 (C=O); MS (ES+) *m/z* 421.3 (M+Na, 37%); HRMS (ES+) found 421.2472. $C_{24}H_{34}N_2O_3Na$ requires 421.2467.

*Synthesis of bicyclic compound **280**.*

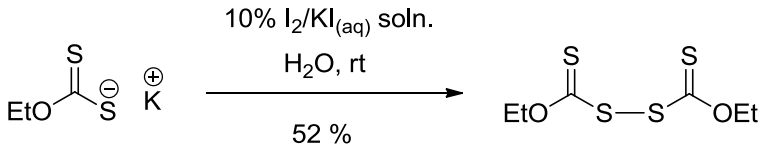


278 **280**

n-Butyllithium (0.7 mL, 1.1 mmol, 1.6 M in hexanes) was added dropwise to a suspension of di*iso*propylamine hydrochloride (76 mg, 0.6 mmol) in THF (2 mL) at -78 °C. The solution was stirred at -78 °C for 90 min before being warmed to 0 °C and added dropwise to a solution of imide **278** (121 mg, 0.5 mmol) in THF (2 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 20 min and then vinyltrimethylsilane (0.7 mL, 5.0 mmol) was added in 1 portion. The reaction mixture was stirred at -78 °C for 5 min and then ferrocenium hexafluorophosphate (**266**) (331 mg, 1.0 mmol) was added in small portions under N_2 over 15 min and then the mixture was stirred at -78 °C for 20 min before addition of $NH_4Cl_{(aq)}$ (10 mL). The reaction was returned to room temperature and filtered through a silica plug which was washed with Et_2O. The organics were washed with $NH_4Cl_{(aq)}$ (30 mL) and brine (100

mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether → 2% EtOAc/petroleum ether) to yield an undesired product **280** (15 mg, 13%) as an off-white solid: R_f = 0.35 (petroleum ether:EtOAc, 4:1); ^{1}H NMR ($CDCl_3$, 300MHz) δ 3.01 (d, *J* = 1.0 Hz, 4H, CH_2), 4.66 (s, 2H, benzylic CH_2), 5.83 (t, *J* = 1.0 Hz, 2H, vinylic CH_2), 7.23-7.37 (m, 5H, Ar CH); ^{13}C NMR ($CDCl_3$, 100MHz) δ 22.0 (CH_2), 41.4 (benzylic CH_2), 123.2 (vinylic CH), 127.8 (Ar CH), 128.6 (Ar CH), 128.8 (Ar CH), 136.8 (Ar C), 138.9 (α-carbonyl C), 170.6 (C=O); MS (ES+) *m*/*z* 262.1 (M+Na, 100%); HRMS (ES+) found 262.0835. $C_{15}H_{13}NO_2Na$ requires 262.0844.

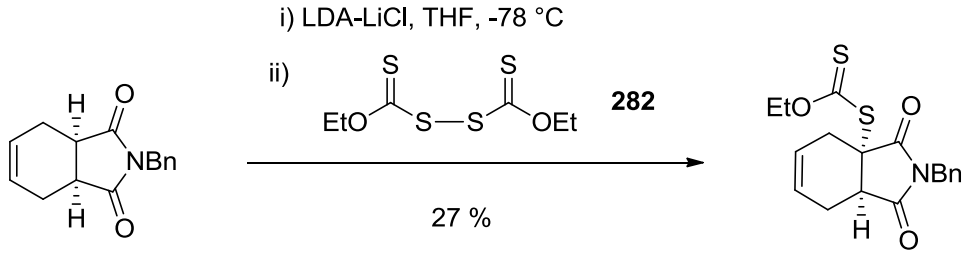
*Synthesis of ethylxanthate dimer **282**.*



282

Following a literature procedure[125] a solution of potassium ethyl xanthate (20.0 g, 125.0 mmol) in water (130 mL) was prepared in a 500 mL conical flask and stirred vigorously at room temperature. To this solution, a solution of I_2 (9.4 g) and potassium iodide (9.4 g) in water (94 mL) was added dropwise over 60 min before being left to stand for 60 h. To the reaction mixture, water (160 mL) was added and the product was extracted with Et_2O (3 × 120 mL). The combined organics were washed with water (2 × 200 mL) and brine (200 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield **282** as a yellow oil (7.9 g, 52 %): R_f = 0.7 (EtOAc:petroleum ether, 1:1); ^{1}H NMR ($CDCl_3$, 300MHz) δ 1.43 (t, *J* = 7.1 Hz, 6H, CH_3 × 2), 4.70 (q, *J* = 7.1 Hz, 4H, CH_2 × 2).

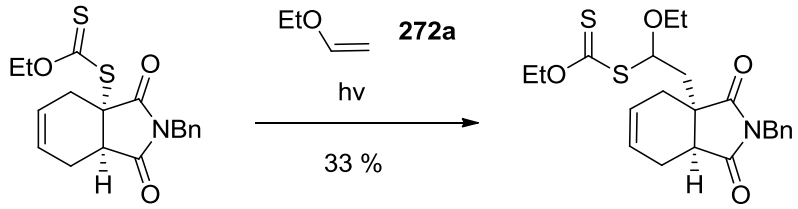
*Synthesis of xanthate **283**.*



278 **283**

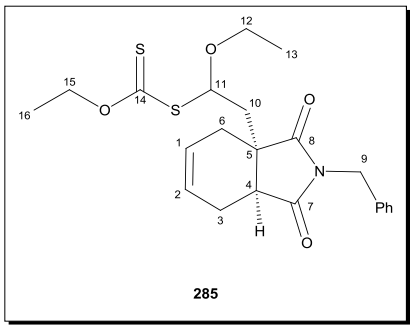
n-butyllithium (0.8 mL, 1.2 mmol, 1.6 M in hexanes) was added dropwise to a solution of di*iso*propylamine hydrochloride (83 mg, 0.6 mmol) in THF (5 mL) at -78 °C. The solution was stirred at -78 °C for 20 min before being warmed to 0 °C and added dropwise to a solution of imide **278** (121 mg, 0.5 mmol) in THF (2.5 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 10 min and then **282** (242 mg, 1.0 mmol) was added in 1 portion and then the mixture was stirred at -78 °C for 50 min before addition of $NH_4Cl_{(aq)}$ (2 mL). The reaction was returned to room temperature and diluted with water (10 mL) and extracted with CH_2Cl_2 (25 mL x 2). The combined organics were washed with Brine (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (2% EtOAc/petroleum ether) to yield **283** as a colourless oil (49 mg, 27%): R_f = 0.38 (4:1, petroleum ether/EtOAc); IR (neat) ν_{max} 2947, 1702, 1389, 1330, 1060, 935, 694, 623 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) δ 1.14 (t, *J* = 7.1, 3H, CH_3), 2.09 (dq, *J* = 3.0, 15.4 Hz, 1H, CH_2), 2.27-2.40 (m, 1H, CH_2), 2.67 (dd, *J* = 6.6, 15.4 Hz, 1H, CH_2), 2.78 (ddd, *J* = 2.5, 6.8, 15.8 Hz, 1H, CH_2), 3.49 (dd, *J* = 2.5, 6.5 Hz, 1H, CH), 4.10 (dq, *J* = 7.1, 10.7 Hz, 1H, Ethyl CH_2), 4.52 (dq, *J* = 7.1, 10.7 Hz, 1H, Ethyl CH_2), 5.05 (d, *J* = 7.1 Hz, 1H, Benzyl CH_2), 5.09 (d, *J* = 7.1 Hz, 1H, Benzyl CH_2), 5.70-5.77 (m, 1H, vinylic CH), 5.92-5.99 (m, 1H, vinylic CH), 7.27-7.37 (m, 5H, Ar CH); MS (ES+) *m/z* 384.1 (M+Na, 100%); HRMS (ES+) found 384.0698. $C_{18}H_{19}NO_3S_2Na$ requires 384.0704.

*Synthesis of xanthate **285**.*



283 **285**

Following a modified literature procedure,[123] a solution of xanthate **283** (89 mg, 0.25 mmol) in ethyl vinyl ether (0.2 mL, 2.46 mmol) under N_2 was irradiated by a sunlamp for 90 min. The solution was extracted with EtOAc (1 mL x 2) and the combined organics were concentrated *in vacuo* to yield a colourless oil. The crude product was purified by flash column chromatography (petroleum ether → 5% EtOAc/petroleum ether) to yield a single diastereomer of **285** as a colourless oil (36 mg, 33 %): R_f = 0.7 (petroleum ether: EtOAc, 1:1); ^{1}H NMR ($CDCl_3$, 400MHz) δ 0.86 (t, *J* = 7.0 Hz, 3H, CH_3-13), 1.43 (t, *J* = 7.1 Hz, 3H, CH_3-16), 1.97 (dq, *J* = 15.1, 2.8 Hz, 1H, ring CH_2), 2.13-2.21 (m, 1H, ring CH_2), 2.31 (d, *J* = 14.4 Hz, 1H, CH_2-10), 2.38 (d, *J* = 14.4 Hz, 1H, CH_2-10), 2.58 (dd, *J* = 15.1, 6.5 Hz, 1H, ring CH_2), 2.63-2.69 (m, 1H, ring CH_2), 2.63-2.69' (m, 1H, CH_2-12), 3.33 (dd, *J* = 7.3, 2.2 Hz, 1H, CH-4), 3.42-3.49 (m, 1H, CH_2-12), 4.59 (d, *J* = 13.8 Hz, 1H, CH_2-9), 4.60-4.67 (m, 2H, CH_2-15), 4.66 (d, *J* = 13.8 Hz, 1H, CH_2-9), 5.42 (dd, *J* = 9.6, 4.2 Hz, 1H, CH-11), 5.78-5.83 (m, 1H, CH-1 or 2), 5.85-5.91 (m, 1H, CH-1 or 2), 7.22-7.31 (m, 3H, Ar CH), 7.40-7.43 (m, 2H, Ar CH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8 (CH_3, C-16), 14.7 (CH_3, C-13), 24.1 (CH_2, ring CH_2), 32.6 (CH_2, ring CH_2), 42.7 (CH_2, C-9), 43.6 (CH_2, C-10), 45.6 (CH, C-4), 65.4 (CH_2, C-12), 70.0 (CH_2, C-15), 89.6 (CH, C-11), 127.5 (CH, vinylic CH), 128.0 (CH, Ar), 128.5 (CH,

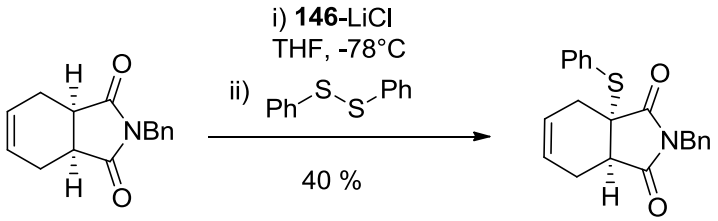


285

vinylic CH), 128.7 (CH, Ar), 129.1 (CH, Ar) 211.2 (C, C-14); MS (ES+) *m/z* 456.1 (M+Na, 29%); HRMS (ES+) found 456.1288. $C_{22}H_{27}NO_4S_2Na$ requires 456.1279.

HMBC and COSY NMR spectra were not recorded. Therefore unambiguous identification of the signals associated with C-1, C-2, C-3 and C-6 was not possible. However all CH and CH_2 signals are accounted for in the ^1H and ^{13}C NMR spectra. Due to obtaining the ^{13}C NMR PENDANT spectrum using a dilute sample, quaternary carbons C-5, C-7, C-8 and the aromatic *ispo* carbon were not observed and are therefore not reported above.

*Synthesis of thioether **286**.*

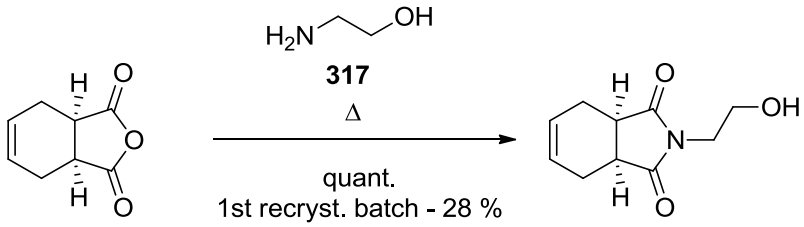


278 **286**

n-Butyllithium (7.5 mL, 12.0 mmol, 1.6 M in hexanes) was added dropwise to a solution of dibenzylethylenediamine (1.4 mL, 6.0 mmol) in THF (20 mL) at -78 °C. The solution was stirred at -78 °C for 30 min before being warmed to 0 °C and added dropwise to a solution of imide **278** (1.21 g, 5.0 mmol) in THF (10 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 40 min and then phenyldisulfide (2.2 g, 10.0 mmol) in THF (5 mL) was added over 1 min. The reaction mixture was stirred at -78 °C for 50 min before addition of $NH_4Cl_{(aq)}$ (10 mL). The mixture was returned to room temperature and diluted with water (50 mL) and extracted with CH_2Cl_2 (4 × 50 mL). The combined organics were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (2 % → 10 %, EtOAc/petroleum ether) to yield **286** as a white solid (695 mg, 40 %): R_f = 0.34 (4:1, petroleum ether/EtOAc); IR (neat) ν_{max} 3046, 2946,

1699, 1390, 1341, 1069, 923, 753, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300MHz) δ 2.21 (dq, *J* = 6.2, 15.1 Hz, 1H, CH_2), 2.28-2.38 (m, 1H, CH_2), 2.63 (ddd, *J* = 2.2, 6.4, 15.7 Hz, 1H, CH_2), 2.80 (dd, *J* = 6.4, 15.1 Hz, 1H, CH_2), 3.04 (dd, *J* = 2.2, 7.4 Hz, 1H, CH), 4.43-4.54 (m, 2H, benzylic CH_2), 5.79-5.93 (m, 2H, vinylic CH), 7.13-7.19 (m, 4H, Ar CH), 7.22-7.33 (m, 4H, Ar CH), 7.36-7.40 (m, 2H, Ar CH); ^{13}C ($CDCl_3$, 100MHz) δ 24.1 (CH_2), 31.0 (CH_2), 42.9 (Benzyl CH_2), 46.9 (CH), 54.8 (C-S), 127.4 (vinylic CH), 127.9 (vinylic CH), 128.5 (Ar CH), 128.7 (Ar CH), 128.8 (Ar CH), 128.9 (Ar C), 129.3 (Ar CH), 130.2 (Ar CH), 135.5 (Ar C), 136.9 (Ar CH), 177.5 (C=O), 178.0 (C=O); MS (ES+) *m/z* 372.1 (M+Na, 100%); HRMS (ES+) found 372.1017. $C_{21}H_{19}NO_2SNa$ requires 372.1034.

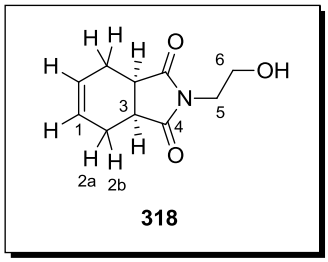
*Synthesis of alcohol **318**.*



277 **318**

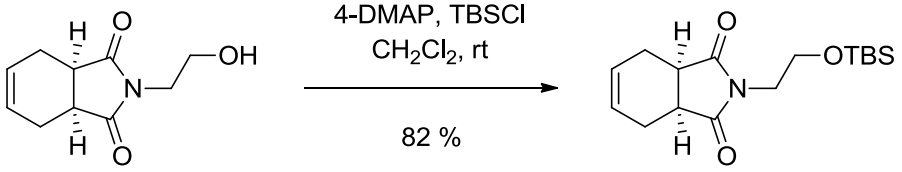
Following a modified literature procedure,[136] a mixture of *cis*-1,2,3,6-tetrahydrophthalic anhydride (**277**) (45.6 g, 300 mmol) and ethanolamine (**317**) (18.1 mL, 300 mmol) was heated at 130 °C for 2 h, before being cooled to room temperature. The resultant precipitate was dissolved in CH_2Cl_2 (200 mL) and washed with $HCl_{(aq)}$ (2 × 50 mL, 2M) and brine (100 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the desired product as a white solid (46.5 g, 80 %). The product was further purified by recrystallisation (Et_2O) to yield **318** as small colourless cuboid crystals which were ground in a pestle and mortar to give a white powder (1st crop - 16.5 g, 28 %): mp 73-75 °C (lit. mp 78-80 °C)[136a]; R_f = 0.1 (Et_2O); IR (neat) ν_{max} 3456, 2948, 1677, 1399, 1327, 1020, 702 cm^{-1}; ^{1}H

NMR ($CDCl_3$, 300 MHz) δ 2.18-2.28 (m, 2H, CH-2a × 2), 2.38-2.41 (br. t, 1H, OH), 2.57-2.64 (m, 2H, CH-2b × 2), 3.11-3.13 (m, 2H, CH-3 × 2), 3.66-3.73 (m, 4H, CH_2-5 & CH_2-6), 5.86-5.94 (m, 2H, CH-1 × 2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.7 (CH_2, C-2), 39.2 (CH, C-3), 42.1 (CH_2, C-5), 60.9 (CH_2, C-6), 127.9 (CH, C-1), 180.9 (C=O, C-4); MS (EI) *m*/*z* 195 (M); HRMS (EI) found 195.089799, requires 195.089543 for $C_{10}H_{13}NO_3$.



318

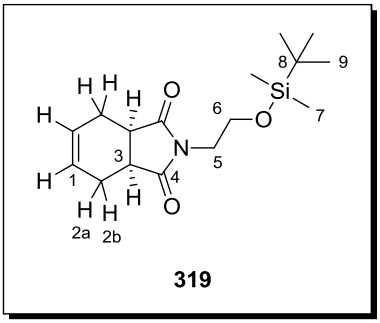
*Synthesis of silyl ether **319**.*



318 **319**

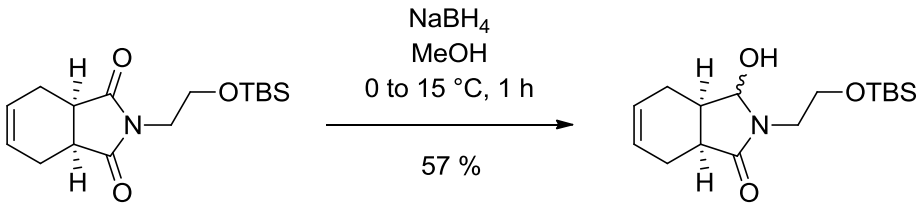
tert-Butyldimethylsilylchloride (966 mg, 6.41 mmol) was added in one portion to a solution of alcohol **318** (1.0 g, 5.13 mmol), imidazole (454 mg, 6.67 mmol) and 4-dimethylaminopyridine (62 mg, 0.51 mmol) in CH_2Cl_2 (25 mL). The reaction mixture was stirred at room temperature for 21 h, diluted with CH_2Cl_2 (25 mL) and filtered. The residue was extracted with CH_2Cl_2 (2 × 25 mL) and the combined organic phases were concentrated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether → 20% Et_2O/petroleum ether) to yield the desired product **319** as a colourless oil (1.3 g, 82 %): R_f = 0.3 (1:1, Et_2O/petroleum ether); IR (neat) ν_{max} 2929, 2856, 1702, 1398, 1109, 837, 778 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.01 (s, 6H, CH_3-7 × 2), 0.85 (s, 9H, CH_3-9 × 3), 2.18-2.30 (m, 2H, CH-2a × 2), 2.55-2.62 (m, 2H, CH-2b × 2), 3.02-3.10 (m, 2H, CH-3 × 2), 3.58-3.63 (m, 2H, CH_2-5), 3.68-3.72 (m, 2H, CH_2-6), 5.84-5.92 (m, 2H, CH-1); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.4 (CH_3, C-7), 18.2 (C, C-8), 23.6 (CH_2, C-2), 25.9 (CH_3, C-9), 39.1

(CH, C-3), 41.2 (CH_2, C-5), 59.3 (CH_2, C-6), 127.8 (CH, C-1), 180.1 (C=O, C-4); MS (ES+) *m/z* 332.3 (M+Na, 100%); HRMS (ES+) found 332.1662, requires 332.1658 for $C_{16}H_{27}NO_3SiNa$.



319

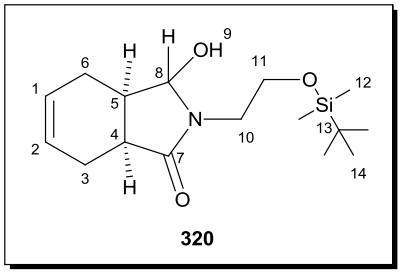
*Synthesis of hydroxylactam **320**.*



319 **320**

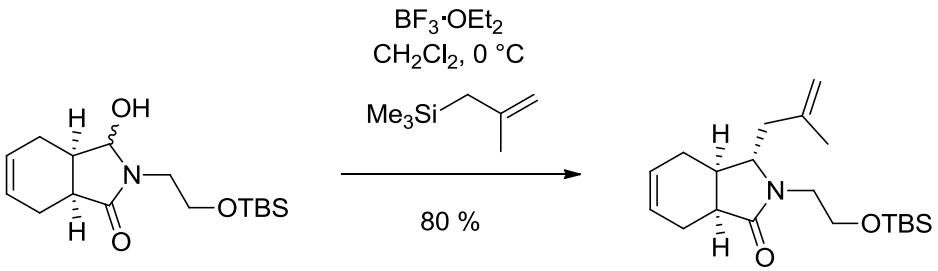
Sodium borohydride (122 mg, 3.24 mmol) was added in small portions over 5 min to a solution of silyl ether **319** (200 mg, 0.65 mmol) in methanol (6 mL) at 0 °C. The reaction was allowed to warm to room temperature over 30 min and quenched with water (2 mL). The mixture was diluted with water (25 mL) and the product was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (3:7, Et_2O:petroleum ether) to yield **320** (inseparable mixture of diastereomers (2:1*)) as a white solid (115 mg, 57 %): R_f = 0.1 (1:1, Et_2O/petroleum ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.06 (s, 3H, CH_3-12*), 0.07 (s, 3H, CH_3-12*), 0.07' (s, 3H, CH_3-12), 0.09 (s, 3H, CH_3-12), 0.87 (s, 9H, CH-14*), 0.89 (s, 9H, CH-14), 1.64-1.73 (m, 1H, CH_2-6), 2.10-2.27 (m, 2H, CH_2-6 & CH_2-3), 2.10-2.27' (m, 3H, CH_2* & CH_2*), 2.32-2.36 (m, 1H, CH_2*), 2.36-2.42 (m, 1H, CH-5), 2.42-2.51 (m, 1H, CH_2-3), 2.46-2.51 (m, 1H, CH-4*), 2.51-2.56 (m, 1H, CH-5*) 2.92-2.97 (m, 1H, CH_2-10), 2.98-3.03 (m, 1H, CH-4), 3.09-3.16 (m, 1H, C-10*), 3.65-3.74 (m, 2H, C-11), 3.65-3.74' (m, 2H, C-11*), 3.78-3.84 (m, 1H, C-

10*), 3.98 (dt, *J* = 14.6, 2.7 Hz, 1H, CH-10), 4.44 (d, *J* = 3.8 Hz, 1H, OH-9*), 4.65 (s, 1H, CH-8), 4.87 (s, 1H, OH-9), 5.04-5.06 (m, 1H, CH-8*), 5.61-5.80 (m, 2H, CH-1 & CH-2), 5.61-5.80' (m, 2H, CH-1* & CH-2*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.6 (CH_3, C-12*), -5.4 (CH_3, C-12), 18.3 (C, C-13), 20.7 (CH_2*), 21.7 (CH_2, C-3), 24.2 (CH_2*), 24.5 (CH_2, C-6), 25.8 (CH_3, C-14), 25.9 (CH_3, C-14*), 34.8 (CH, C-5*), 37.0 (CH), 37.3 (CH), 38.3 (CH, C-4*), 44.0 (CH_2, C-10*), 45.5 (CH_2, C-10), 62.2 (CH_2, C-11*), 62.3 (CH_2, C-11), 85.5 (CH, C-8*), 89.3 (CH, C-8), 124.8 (vinylic CH), 125.1 (vinylic CH*), 126.4 (vinylic CH), 126.5 (vinylic CH*), 176.9 (C=O), 177.5 (C=O*), C-13* was not identified; MS (ES+) *m/z* 334.3 (M+Na, 100%); HRMS (ES+) found 334.1811, requires 334.1814 for $C_{16}H_{29}NO_3SiNa$.



320

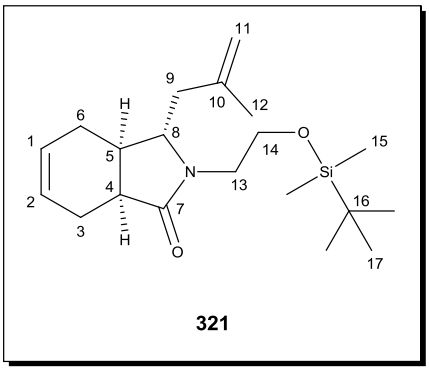
*Synthesis of lactam **321**.*



320 **321**

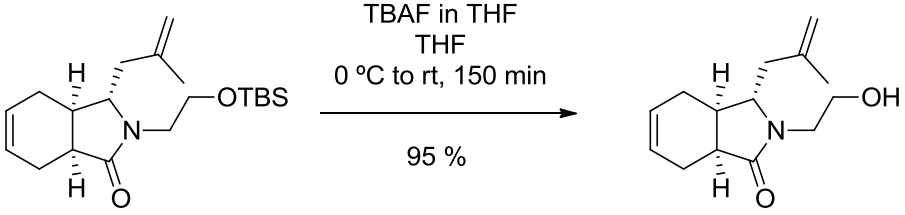
Boron trifluoro diethyl etherate (2.0 mL, 16.05 mmol) was added dropwise to a solution of hydroxylactam **320** (1.0 g, 3.21 mmol) and 2-methylallyltrimethylsilane (5.5 mL, 32.10 mmol) in CH_2Cl_2 (12 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, diluted with sat. $NaHCO_{3\,(aq)}$ (25 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (3:7, Et_2O:petroleum ether) to yield the desired product **321** as a colourless oil (0.8 g, 80 %): R_f = 0.5 (9:1, Et_2O/petroleum

ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.04 (s, 3H, CH_3-15), 0.04 (s, 3H, CH_3-15), 0.88 (s, 9H, CH_3-17), 1.76 (s, 3H, CH_3-12), 1.83-1.92 (m, 1H, CH_2-6), 2.07-2.13 (m, 1H, CH_2-9), 2.09-2.17 (m, 1H, CH_2-6), 2.21-2.26 (m, 1H, CH-5), 2.21-2.30 (m, 1H, CH_2-3), 2.40 (dd, J = 14.1, 4.1 Hz, 1H, CH_2-9), 2.48-2.53 (m, 1H, CH_2-3), 2.72-2.77 (m, 1H, CH-4), 3.00-3.08 (m, 1H, CH_2-13), 3.52 (ddd, J = 9.9, 4.2, 0.8 Hz, 1H, CH-8), 3.71-3.75 (m, 2H, CH_2-14), 3.71-3.76 (m, 1H, CH_2-13), 4.74 (s, 1H, CH_2-11), 4.85 (s, 1H, CH_2-11), 5.67-5.76 (m, 2H, CH-1 & CH-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.36 (CH_3, C-15), -5.30 (CH_3, C-15), 18.3 (C, C-16), 22.1 (CH_2, C-3), 22.8 (CH_3, C-12), 26.0 (CH_3, C-17), 26.9 (CH_2, C-6), 34.0 (CH, C-5), 37.3 (CH, C-4), 39.2 (CH_2, C-9), 43.7 (CH_2, C-13), 62.0 (CH_2, C-14), 63.4 (CH, C-8), 113.3 (CH_2, C-11), 125.5 (CH, C-1), 126.5 (CH, C-2), 142.2 (C, C-10), 176.1 (C=O, C-7).



321

Synthesis of alcohol **322**.

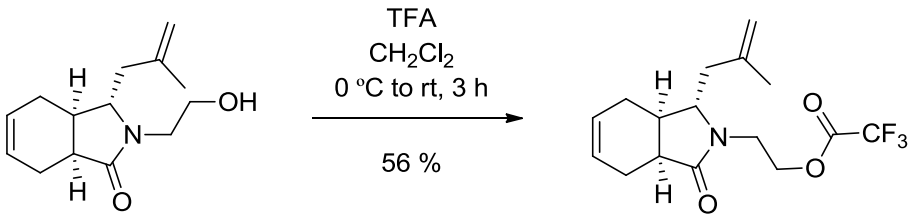


321 **322**

Tetrabutylammonium fluoride (4.2 mL, 4.19 mmol, 1 M soln. in THF) was added dropwise to a solution of lactam **321** (790 mg, 2.26 mmol) in THF (18 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 90 min and then allowed to return to room temperature over 1 h. Water (10 mL) was added and the product was extracted with $CHCl_3$ (3 × 30 mL). The organic phases were combined and washed with water (3 × 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography

(CH_2Cl_2 then 2% MeOH/CH_2Cl_2) to yield the desired product **322** as a colourless oil (508 mg, 95 %): R_f = 0.1 (9:1, Et_2O/ petroleum ether); IR (neat) v_{max} 3362, 2912, 1668, 1429, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.76 (s, 3H, CH_3), 2.13-2.39 (m, 6H), 2.44-2.56 (m, 1H), 2.79-2.85 (m, 1H), 3.19-3.34 (m, 2H), 3.58-3.77 (m, 4H), 4.75-4.78 (m, 1H, vinylic CH_2), 4.86-4.88 (m, 1H, vinylic CH_2), 5.69-5.80 (m, 2H, vinylic CH × 2); MS (ES+) m/z 258.1 (M+Na, 100%); HRMS (ES+) found 258.1467, requires 258.1470 for $C_{14}H_{21}NO_2Na$.

*Synthesis of ester **323**.*

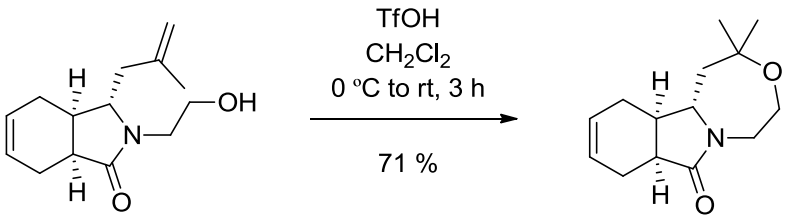


322 **323**

Trifluoroacetic acid (100 μl) was added dropwise to a solution of alcohol **322** (50 mg, 0.21 mmol) in CH_2Cl_2 (1 mL) at 0 °C. The solution was stirred at 0 °C for 1 h and then at room temperature for 2 h before addition of sat. $NaHCO_{3\ (aq)}$ (5 mL). The product was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:1, Et_2O:petroleum ether) to yield undesired product **323** as a colourless oil (39 mg, 56 %): $R_{f\ =}$ 0.1 (1:1, petroleum ether/Et_2O); IR (neat) v_{max} 3388, 2913, 1789, 1672, 1437, 1218, 1165, 895 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.82 (s, 3H, CH_3), 1.92-1.99 (m, 1H, CH_2), 2.10-2.19 (m, 1H, CH_2), 2.22 (dd, *J* = 13.3, 10.2 Hz, 1H, CH_2), 2.25-2.32 (m, 1H, CH_2), 2.34-2.39 (m, 1H, CH_2), 2.43 (m, 1H, CH_2), 2.46-2.49 (m, 1H, CH), 2.58-2.66 (m, 1H, CH_2), 2.70 (d, *J* = 17.0 Hz, 1H, CH_2), 3.34 (dt, *J* = 15.2, 6.3 Hz, 1H, CH_2), 3.68 (s, 3H, CO_2CH_3), 3.76 (app. dd, *J* = 10.0, 3.2 Hz, 1H, CH), 4.04 (dt, *J* = 15.2, 4.3 Hz, 1H, CH_2),

4.43-4.46 (m, 2H, CH_2), 4.75 (s, 1H, vinylic CH_2), 4.86 (s, 1H, vinylic CH_2), 5.52-5.58 (m, 1H, vinylic CH), 5.64-5.69 (m, 1H, vinylic CH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.5 (CH_2), 21.7 (CH_3), 30.2 (CH_2), 37.1 (CH_2), 38.3 (CH_2), 40.1 (C), 41.3 (CH_2), 42.4 (CH), 51.8 (CH_3), 64.1 (CH), 66.3 (CH_2), 114.4 (q, J = 104.5 Hz, C, CF_3) 114.9 (CH_2), 123.9 (CH), 124.7 (CH), 142.2 (C), 157.0 (C=O), 174.1 (q, J = 496.3 Hz, C, C=O); MS (ES+) m/z 354.2 (M+Na, 5 %); HRMS (ES+) found 354.1297, requires 354.1293 for $C_{16}H_{20}F_3NO_3Na$.

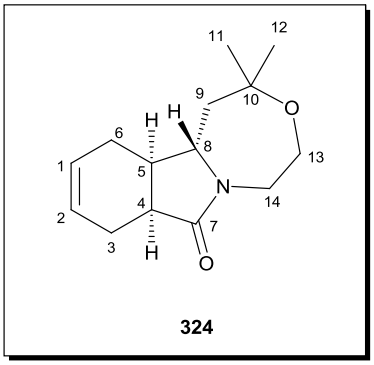
*Synthesis of ether **324**.*



322 **324**

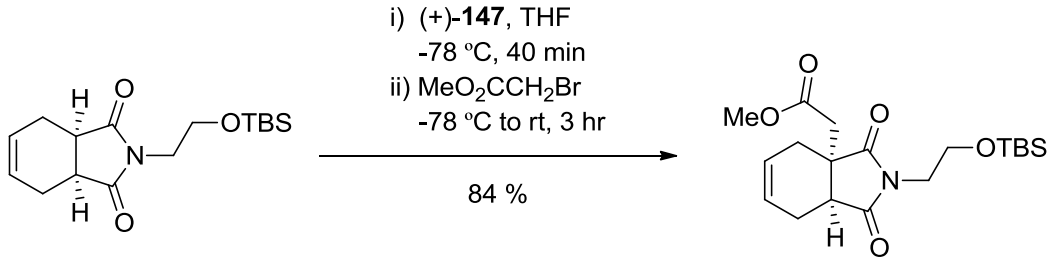
Trifluoromethanesulfonic acid (100 µl) was added dropwise to a solution of alcohol **322** (56 mg, 0.24 mmol) in CH_2Cl_2 (1 mL) at 0 °C under N_2,. The solution was stirred at 0 °C for 1 h and then at room temperature for 2 h before addition of sat. $NaHCO_{3\,(aq)}$ (5 mL). The product was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:9 → 1:1 Et_2O:petroleum ether) to yield the desired product **324** as a colourless oil (40 mg, 71 %): R_f = 0.5 (1:1, petroleum ether/Et_2O); IR (neat) ν_{max} 2917, 1671, 1449, 1427, 1079 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (s, 3H, CH_3-11), 1.26 (s, 3H, CH_3-12), 1.73-1.85 (m, 2H, CH_2-3), 1.78-1.97 (m, 2H, CH_2-9), 1.95-2.09 (m, 2H, CH_2-6), 2.39-2.44 (m, 1H, CH-5), 2.65 (dt, J = 8.2, 4.9 Hz, 1H, CH-4), 2.99-3.05 (m, 1H, CH_2-14), 3.51 (ddd, J = 10.2, 5.3, 0.9 Hz, 1H, CH-8), 3.64-3.67 (m, 2H, CH_2-13), 4.00 (dt, J = 14.2, 2.6 Hz, 1H, CH_2-14), 5.61-5.66 (m, 1H, CH-2), 5.85-5.90 (m, 1H, CH-1); ^{13}C NMR

($CDCl_3$, 100 MHz) δ 21.2 (CH_2, C-3), 22.6 (CH_2, C-6), 27.9 (CH_3, C-11), 28.0 (CH_3, C-12), 39.3 (CH, C-5), 39.8 (CH, C-4), 45.1 (CH_2, C-14), 47.7 (CH_2, C-9), 60.5 (CH, C-8), 61.8 (CH_2, C-13), 74.7 (C, C-10), 125.4 (CH, C-2), 130.0 (CH, C-1), 175.6 (C=O, C-7); MS (ES+) *m/z* 258.1 (M+Na, 100 %), 236.2 (M+1, 11 %); HRMS (ES+) found 258.1474, requires 258.1470 for $C_{14}H_{21}NO_2Na$.



324

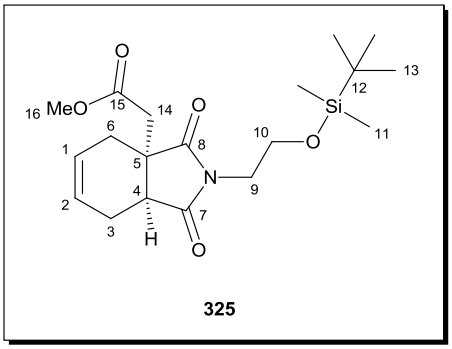
*Synthesis of ester (–)-**325**.*



319 **(–)-325**

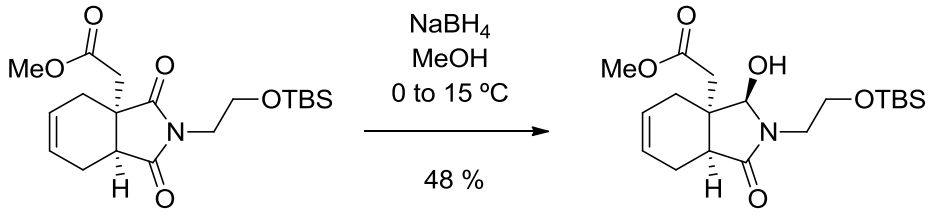
n-Butyllithium (375 μL, 0.6 mmol, 1.6 M solution in hexanes) was added dropwise to a solution of (+)-**178** (252 mg, 0.6 mmol) in THF (6 mL) at -78 °C. The base mixture was stirred at -78 °C for 10 min and then at 0 °C for 20 min. This base solution was then added dropwise over 5 min to a solution of imide **319** (155 mg, 0.5 mmol) in THF (3 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 40 min and then methyl bromoacetate (0.14 mL, 1.5 mmol) was added. The reaction mixture was stirred at -78 °C for a further 2 h before being returned to room temperature over 1 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (2 mL), diluted with water (12 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with brine (15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10 % Et_2O/petroleum ether) to yield **325** as a colourless oil (155 mg, 0.42 mmol, 84 %): R_f = 0.3 (1:1 Et_2O/petroleum ether); $[\alpha]_D^{20}$ = –36.7 (*c* 0.6, $CHCl_3$); IR (neat) ν_{max} 2953, 2856, 1738,

1700, 1107, 837 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.04 (s, 6H, CH_3-11 × 2), 0.86 (s, 9H, CH_3-13 × 3), 2.01 (app. ddd, *J* = 15.4, 5.9, 2.7 Hz, 1H, CH_2-6), 2.20-2.28 (m, 1H, CH_2-3), 2.47 (dd, *J* = 15.4, 6.2 Hz, 1H, CH_2-6), 2.65-2.71 (m, 1H, CH_2-3), 2.68 (d, *J* = 17.0, 1H, CH_2-14), 2.87 (d, *J* = 17.0, 1H, CH_2-14), 2.97 (dd, *J* = 7.0, 2.7 Hz, 1H, CH-4), 3.59-3.63 (m, 2H, CH_2-9), 3.65 (s, 3H, CH_3-16), 3.67-3.70 (m, 2H, C-10), 5.79-5.84 (m, 1H, CH-1), 5.87-5.93 (m, 1H, CH-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.3 (CH_3, C-11), 18.3 (C, C-12), 23.8 (CH_2, C-3), 25.9 (CH_3, C-13), 31.3 (CH_2, C-6), 40.8 (CH_2, C-14), 41.3 (CH_2, C-9), 44.5 (CH, C-4), 45.6 (C, C-5), 52.0 (CH_3, C-16), 59.3 (CH_2, C-10), 126.7 (CH, C-1), 128.4 (CH, C-2), 171.0 (C=O, C-15), 179.0 (C=O, C-7), 181.4 (C=O, C-8); MS (ES+) *m/z* 404.2 (M+Na, 100%); HRMS (ES+) found 404.1870, requires 404.1869 for $C_{19}H_{31}NO_5SiNa$.



325

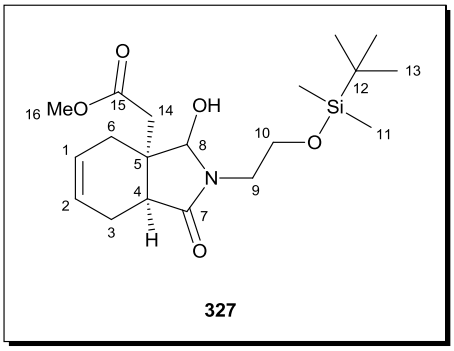
*Synthesis of hydroxylactam **327**.*



325 **327**

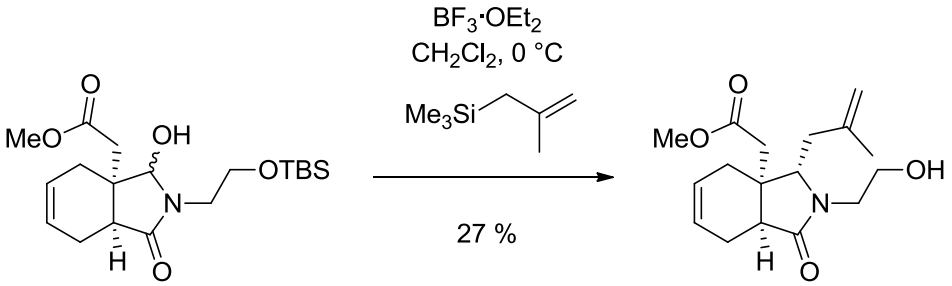
Sodium borohydride (13 mg, 0.35 mmol) was added in small portions to a solution of ester **325** (27 mg, 0.07 mmol) in methanol (1 mL) at 0 °C. The reaction mixture was stirred and warmed gradually to 15 °C over 1 h and then quenched with water (2 mL). The product was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude product. The residue was purified by flash column chromatography to yield the desired product **327** as

a colourless oil (13 mg, 48 %): R_f = 0.25 (4:1, Et_2O/petroleum ether); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.09 (s, 3H, CH_3-11), 0.10 (s, 3H, CH_3-11), 0.90 (s, 9H, CH_3-13 × 3), 1.85-1.93 (m, 1H, CH_2-6), 2.19-2.28 (m, 1H, CH_2-6), 2.19-2.28' (m, 1H, CH_2-3), 2.48 (d, *J* = 14.4 Hz, 1H, CH_2-14), 2.50-2.56 (m, 1H, CH-4), 2.56-2.61 (m, 1H, CH_2-3), 2.59 (d, *J* = 14.4 Hz, 1H, CH_2-14), 3.29-3.38 (m, 1H, CH_2-10), 3.64-3.70 (m, 1H, CH_2-10), 3.67 (s, 3H, CH_3-16), 3.68-3.79 (m, 2H, CH_2-9), 4.42 (d, *J* = 5.6 Hz, 1H, OH), 5.16 (d, *J* = 5.6, 1H, CH-8), 5.65-5.76 (m, 2H, CH-1 & CH-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.4 (CH_3, C-11), -5.4' (CH_3, C-11), 18.4 (C, C-12), 21.5 (CH_2, C-3), 25.8 (CH_2, C-6), 26.0 (CH_3, C-13), 40.4 (CH_2, C-14), 42.2 (C, C-5), 42.9 (CH_2, C-10), 43.7 (CH, C-4), 51.9 (CH_3, C-16), 62.2 (CH_2, C-9), 87.5 (CH, C-8), 124.4 (CH, C-1), 125.2 (CH, C-2), 172.2 (C, C-15), 174.4 (C, C-7); MS (ES+) *m/z* 406.2 (M+Na, 100%); HRMS (ES+) found 406.2030, requires 406.2026 for $C_{19}H_{32}NO_5SiNa$.



327

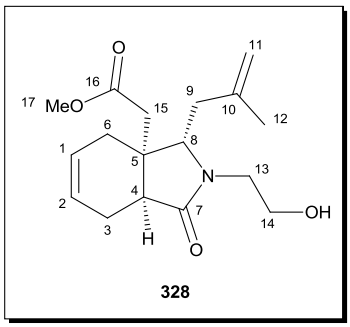
*Synthesis of alcohol **328**.*



327 **328**

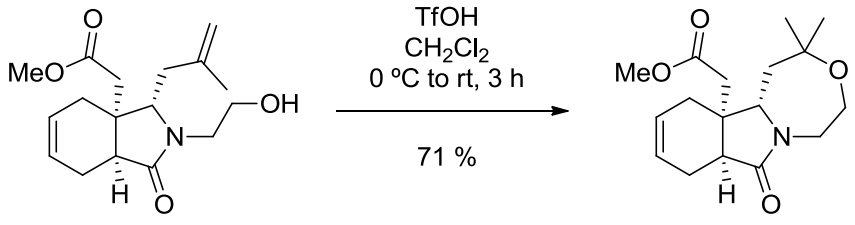
Boron trifluoro diethyl etherate (1.61 mL, 13.05 mmol) was added dropwise to a solution of hydroxylactam **327** (1.0 g, 2.61 mmol) and 2-methylallyltrimethylsilane (4.4 mL, 26.10 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, diluted with sat. $NaHCO_{3\,(aq)}$ (25 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic

phases were washed with brine (25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (3:7, Et_2O:petroleum ether) to yield the desired product **328** as a colourless oil (270 mg, 27 %): R_f = 0.1 (9:1, Et_2O:petroleum ether); IR (neat) ν_{max} 3389, 2950, 1732, 1672, 1433, 1166, 1057 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.81 (s, 3H, CH_3-12), 2.04-2.11 (m, 1H, CH_2-6), 2.11-2.18 (m, 1H, CH_2-3), 2.24 (dd, *J* = 13.3, 9.7 Hz, 1H, CH_2-9), 2.28-2.35 (m, 1H, CH_2-6), 2.33-2.38 (m, 1H, CH_2-9), 2.44 (app. dd, *J* = 17.0, 1.8 Hz, 1H, CH_2-15), 2.51-2.54 (m, 1H, CH-4), 2.57-2.64 (m, 1H, CH_2-3), 2.69 (d, *J* = 17.0 Hz, 1H, CH_2-15), 3.16-3.23 (m, 1H, CH_2-14), 3.67 (s, 3H, CH_3-17), 3.68-3.71 (m, 1H, CH-8), 3.68-3.73 (m, 1H, CH_2-14), 3.69-3.76 (m, 2H, CH_2-13), 4.83 (app. s, 2H, CH_2-11), 5.54-5.60 (m, 1H, CH-1), 5.64-5.69 (m, 1H, CH-2), OH resonance not observed; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.5 (CH_2, C-3), 21.9 (CH_3-12), 30.6 (CH_2, C-6), 36.9 (CH_2, C-15), 38.1 (CH_2, C-9), 40.3 (C, C-5), 42.8 (CH, C-4), 47.8 (CH_2, C-14), 51.7 (CH_3, C-17), 62.0 (CH_2, C-13), 65.3 (CH, C-8), 114.8 (CH_2, C-11), 124.1 (CH, C-1), 124.7 (CH, C-2), 142.1 (C, C-10), 171.9 (C, C-16), 176.6 (C, C-7); MS (ES+) *m/z* 330.0 (M+Na, 100%); HRMS (ES+) found 330.1669, requires 330.1681 for $C_{17}H_{25}NO_4Na$.



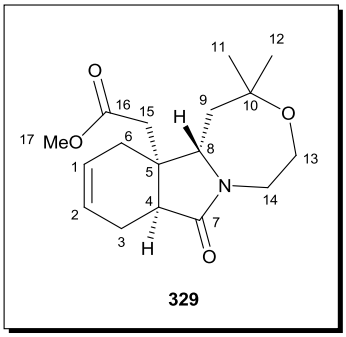
328

*Synthesis of ether **329**.*



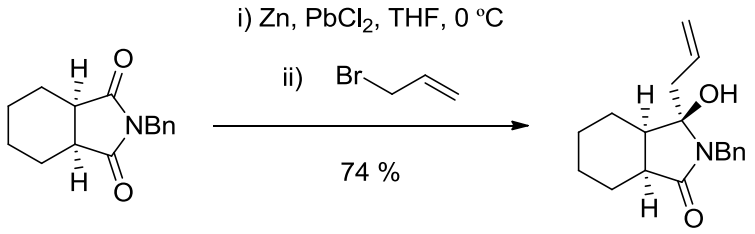
328 **329**

Trifluoromethanesulfonic acid (50 μl) was added dropwise to a solution of alcohol **328** (7 mg, 0.02 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C. The solution was stirred at 0 °C for 1 h and then at room temperature for 2 h before addition of sat. $NaHCO_{3\ (aq)}$ (5 mL). The product was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1:9 → 1:1 Et_2O: petroleum ether) to yield the desired product **329** as a colourless oil (5 mg, 71 %): R_f = 0.5 (1:1 Et_2O/petroleum ether); IR (neat) ν_{max} 2926, 1732, 1685, 1431, 1145, 1081 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20 (s, 3H, CH_3-11), 1.26 (s, 3H, CH_3-12), 1.67-1.71 (m, 1H, CH_2-9), 1.86 (d, *J* = 14.4 Hz, 1H, CH_2-9), 1.94-2.01 (m, 1H, CH_2-6), 2.10-2.17 (m, 1H, CH_2-3), 2.28-2.34 (m, 1H, CH_2-6), 2.32-2.37 (m, 1H, CH_2-15), 2.34-2.36 (m, 1H, CH-4), 2.61-2.68 (m, 1H, CH_2-3), 2.75 (d, *J* = 16.8 Hz, 1H, CH_2-15), 2.89-2.96 (m, 1H, CH_2-14), 3.53-3.60 (m, 1H, CH_2-13), 3.64-3.69 (m, 1H, CH_2-13), 3.67-3.69 (m, 1H, CH-8), 3.68 (s, 3H, OCH_3-17), 4.17 (dt, *J* = 13.9, 2.3 Hz, 1H, CH_2-14), 5.54-5.59 (m, 1H, CH-1), 5.65-5.70 (m, 1H, CH-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.6 (CH_2, C-3), 27.7 (CH_3, C-11), 28.4 (CH_3, C-12), 30.9 (CH_2, C-6), 37.9 (CH_2, C-15), 39.8 (C, C-5), 41.0 (CH_2, C-9), 43.6 (CH, C-4), 44.6 (CH_2, C-14), 51.7 (CH_3, C-17), 62.8 (CH_2, C-13), 63.2 (CH, C-8), 75.0 (C, C-10), 124.1 (CH, C-1), 124.8 (CH, C-2), 171.6 (C=O, C-16), 173.4 (C=O, C-7); MS (ES+) *m/z* 330.2 (M+Na, 100%); HRMS (ES+) found 330.1685, requires 330.1681 for $C_{17}H_{25}NO_4Na$.



329

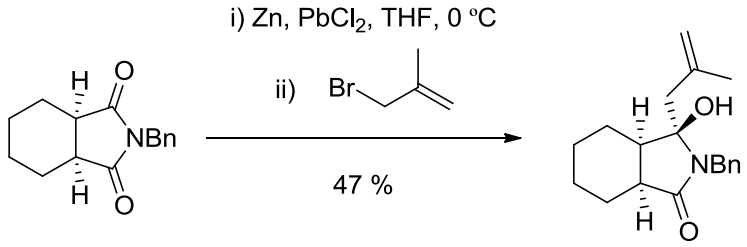
*Synthesis of hydroxylactam **334a**.*



151 **334a**

Following a modified literature procedure,[138] allyl bromide (72 μL, 0.82 mmol) was added dropwise over 5 min to a suspension of imide **151** (100 mg, 0.41 mmol), zinc powder (54 mg, 0.82 mmol) and lead (II) chloride (6 mg, 0.02 mmol) in THF (0.5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 150 min, quenched with sat. $NH_4Cl_{(aq)}$ (1 mL) and then diluted with CH_2Cl_2 (4 mL) and sat. $NH_4Cl_{(aq)}$ (10 mL). The product was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10 % then 50 % Et_2O/petroleum ether) to yield the desired product **334a** (88 mg, 0.31 mmol, 74 %) as a white solid: mp 84-85 °C; R_f = 0.1 (1:1, petroleum ether/Et_2O); ^{1}H NMR (C_6D_6, 300 MHz) δ 0.75-0.92 (m, 2H, CH_2-ring), 1.14-1.41 (m, 5H, CH_2-ring), 1.72 (s, 1H, OH), 1.97-2.02 (m, 1H, CH), 1.97-2.02' (m, 1H, CH_2-allylic), 2.24-2.29 (m, 1H, CH_2-allylic), 2.29-2.37 (m, 1H, CH), 2.29-2.37' (m, 1H, CH_2-ring), 4.30 (d, 1H, J = 15.0 Hz, CH_2-benzylic), 4.57 (d, 1H, J = 15.0 Hz, CH_2-benzylic), 4.80-4.86 (m, 1H, CH_2-vinylic), 4.89-4.92 (m, 1H, CH_2-vinylic), 5.55-5.65 (m, 1H, CH-vinylic), 7.02-7.07 (m, 1H, CH-Ar), 7.12-7.16 (m, 2H, CH-Ar × 2), 7.45-7.47 (m, 2H, CH-Ar × 2), OH resonance not observed; ^{13}C NMR (C_6D_6, 100 MHz) δ 23.2 (CH_2), 23.2' (CH_2), 23.6 (CH_2), 23.6' (CH_2), 40.3 (CH), 40.7 (CH), 41.9 (CH_2, allylic), 42.5 (CH_2, Bn), 91.7 (C), 118.8 (CH_2, vinylic), 127.4 (CH, Ar), 128.7 (CH, Ar), 128.8 (CH, Ar), 133.6 (CH, vinylic), 140.5 (C, Ar), 173.8 (C, C=O); MS (ES+) *m*/*z* 308.2 (M+Na, 100%); HRMS (ES+) found 308.1620, requires 308.1626 for $C_{18}H_{23}NO_2Na$

*Synthesis of hydroxylactam **334b**.*

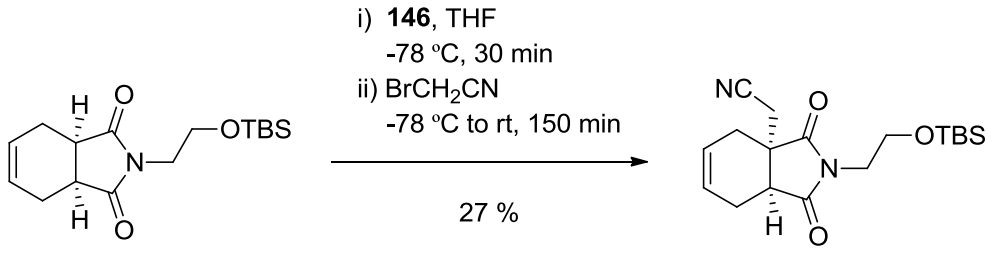


151 **334b**

Following a modified literature procedure,[138] 3-bromo-2-methylpropene (83 μL, 0.82 mmol) was added dropwise over 5 min to a suspension of imide **151** (100 mg, 0.41 mmol), zinc powder (54 mg, 0.82 mmol) and lead (II) chloride (6 mg, 0.02 mmol) in THF (0.5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 150 min, quenched with sat. $NH_4Cl_{(aq)}$ (1 mL) and then diluted with CH_2Cl_2 (4 mL) and sat. $NH_4Cl_{(aq)}$ (10 mL). The product was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (10 % then 50 % Et_2O/petroleum ether) to yield the desired product **334b** (88 mg, 0.20 mmol, 47 %) as a white solid: mp 106-108 °C; R_f = 0.1 (1:1, petroleum ether/Et_2O); ^{1}H NMR (C_6D_6, 400 MHz) δ 0.64-0.74 (m, 1H, CH_2-ring), 0.77-0.88 (m, 1H, CH_2-ring), 1.10 (m, 3H, CH_2-ring), 1.32-1.41 (m, 2H, CH_2-ring), 1.70 (s, 3H, CH_3), 1.79 (s, 1H, OH), 1.99 (d, *J* = 13.9 Hz, 1H, CH_2-allylic), 2.15-2.21 (m, 1H, CH), 2.29 (d, *J* = 13.9, 1H, CH_2-allylic), 2.31-2.35 (m, 1H, CH), 2.42-2.47 (m, 1H, CH_2-ring), 4.22 (d, *J* = 14.9, 1H, CH_2-benzylic), 4.62-4.64 (m, 1H, CH_2-vinylic), 4.67 (d, *J* = 14.9, 1H, CH_2-benzylic), 4.79-4.81 (m, 1H, CH_2-vinylic), 7.03-7.06 (m, 1H, CH-Ar), 7.13-7.17 (m, 2H, CH-Ar × 2), 7.48-7.50 (m, 1H, CH-Ar), OH resonance not observed; ^{13}C NMR (C_6D_6, 100 MHz) δ 23.1 (CH_2), 23.3 (CH_2), 23.4 (CH_2), 23.7 (CH_2), 24.0 (CH_3), 40.4 (CH), 40.9 (CH), 42.6 (CH_2, Bn), 44.9 (CH_2, allylic), 92.1 (C), 115.6 (CH_2, vinylic), 127.4 (CH, Ar), 128.8 (CH, Ar),

128.8 (CH, Ar), 140.7 (C, Ar), 142.2 (C, vinylic), 173.2 (C, C=O); MS (ES+) *m/z* 322.3 (M+Na, 100%); HRMS (ES+) found 322.1771, requires 322.1783 for $C_{19}H_{25}NO_2Na$.

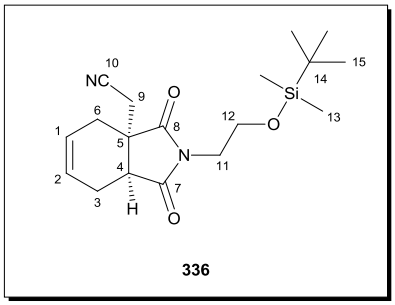
*Synthesis of nitrile **336**.*



319 **336**

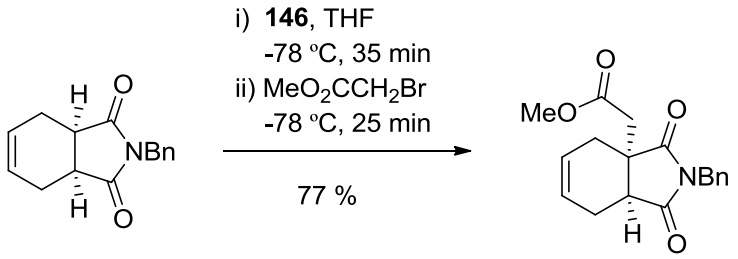
n-Butyllithium (5.34 mL, 8.54 mmol, 1.6 M solution in hexanes) was added dropwise to a solution of dibenzylethylenediamine (**185**) (1 mL, 4.27 mmol) in THF (42 mL) at -78 °C. The base mixture was stirred at -78 °C for 10 min and then at 0 °C for 1 h. This base solution was then added dropwise over 20 min to a solution of imide **319** (1.1 g, 3.56 mmol) in THF (21 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 30 min and then bromoacetonitrile (0.75 mL, 10.68 mmol) was added. The reaction mixture was stirred at -78 °C for a further 30 min and then warmed to 0 °C and stirred for 2 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (10 mL), diluted with water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10 % Et_2O/petroleum ether) to yield **336** as a yellow oil (332 mg, 0.95 mmol, 27 %): R_f = 0.18 (1:1 Et_2O/petroleum ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.02 (d, *J* = 1.0 Hz, 6H, CH_3-13), 0.84-0.86 (m, 9H, CH_3-15), 2.17 (dq, *J* = 15.6, 3.0 Hz, 1H, CH_2-6), 2.29-2.37 (m, 1H, CH_2-3), 2.58 (dd, *J* = 15.6, 6.3 Hz, 1H, CH_2-6), 2.71 (d, *J* = 7.4 Hz, 2H, CH_2-9), 2.75-2.82 (m, 1H, CH_2-3), 2.96 (dd, *J* = 7.1, 2.4 Hz, 1H, CH-4), 3.60-3.63 (m, 2H,

CH_2-11), 3.68-3.72 (m, 2H, CH_2-12), 5.82-5.87 (m, 1H, CH-1), 5.92-5.98 (m, 1H, CH_2-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.4 (CH_3, C-13), 18.2 (C, C-14), 23.6 (CH_2, C-4), 25.8 (CH_2, C-9), 25.9 (CH_3, C-15), 30.6 (CH_2, C-6), 41.7 (CH_2, C-11), 44.6 (CH, C-4), 45.6 (C, C-5), 59.2 (CH_2, C-12), 116.2 (C, C-10), 126.2 (CH, C-1), 128.4 (CH, C-2), 177.3 (C=O, C-7), 179.1 (C=O, C-8); MS (ES+) *m/z* 371.1 (M+Na, 100%); HRMS (ES+) found 371.1765, requires 371.1767 for $C_{18}H_{28}N_2O_3SiNa$.



336

*Synthesis of ester **342**.*

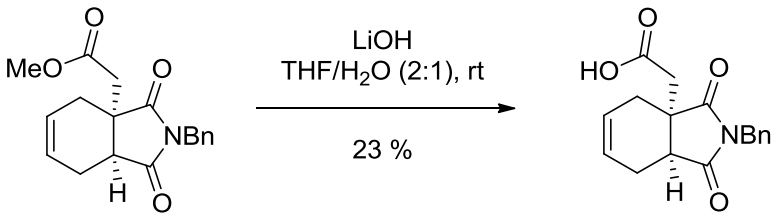


278 **342**

n-Butyllithium (0.8 mL, 1.12 mmol, 1.4 M solution in hexanes) was added dropwise to a solution of dibenzylethylenediamine (**185**) (263 μL, 1.12 mmol) in THF (9 mL) at -78 °C. The base mixture was stirred at -78 °C for 10 min and then at 0 °C for 25 min. This base solution was then added dropwise over 5 min to a solution of imide **278** (180 mg, 0.75 mmol) in THF (4.5 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 35 min and then methyl bromoacetate (1.0 mL, 10.88 mmol) was added. The reaction mixture was stirred at -78 °C for a further 25 min before being quenched with sat. $NH_4Cl_{(aq)}$ (5 mL) and returned to room temperature. The reaction mixture was diluted with sat. $NH_4Cl_{(aq)}$ (20 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash

column chromatography (20 % Et_2O/petroleum ether) to yield **342** as a colourless oil (181 mg, 0.42 mmol, 77 %): R_f = 0.15 (1:1, E_2O/petroleum ether); IR (neat) ν_{max} 2952, 1697, 1433, 1399, 1344, 1168, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.99 (ddd, *J* = 15.3, 5.9, 2.8 Hz, 1H, CH_2), 2.19-2.27 (m, 1H, CH_2), 2.47 (dd, *J* = 15.3, 6.3 Hz, 1H, CH_2), 2.67 (d, *J* = 16.8 Hz, 1H, CH_2), 2.67-2.74 (m, 1H, CH_2), 2.90 (d, *J* = 16.8 Hz, 1H, CH_2), 3.00 (dd, *J* = 6.9, 2.6 Hz, 1H, CH), 3.51 (s, 3H, CH_3), 4.61 (d, *J* = 14.4, 1H, CH_2), 4.67 (d, *J* = 14.4, 1H, CH_2), 5.76-5.81 (m, 1H, CH), 5.86-5.93 (m, 1H, CH), 7.22-7.32 (m, 5H, CH × 2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.8 (CH_2), 31.6 (CH_2), 40.7 (CH_2), 42.6 (CH_2), 44.6 (CH), 45.8 (C), 51.9 (CH_3), 126.8 (CH, vinylic), 127.7 (CH, Ar), 128.4 (CH, Ar), 128.6 (CH, Ar), 128.7 (CH, Ar), 135.9 (C, Ar), 170.8 (C, C=O), 178.9 (C, C=O), 181.2 (C, C=O); MS (ES+) *m/z* 336.3 (M+Na, 100%); HRMS (ES+) found 336.1208, requires 336.1212 for $C_{18}H_{19}NO_4Na$.

*Synthesis of acid **343**.*

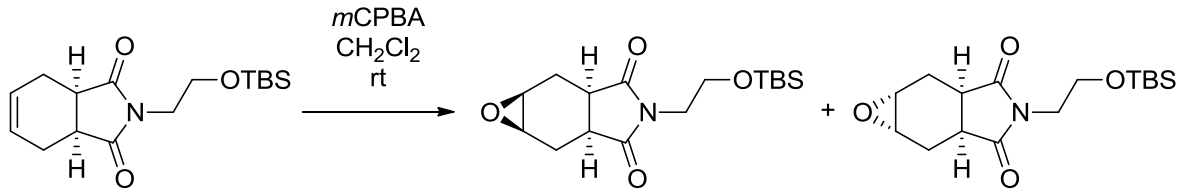


342 **343**

A solution of lithium hydroxide (41 mg, 0.98 mmol) in water (4.5 mL) was added dropwise to a solution of ester **342** (77 mg, 0.25 mmol) in THF (9 mL). The reaction mixture was stirred at room temperature for 30 min and then acidified with 2M $HCl_{(aq)}$. The product was extracted with Et_2O (4 × 25 mL) and the combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (1:1, Et_2O/petroleum ether) to yield the desired product **343** (17 mg, 0.06 mmol, 23 %) as a colourless oil: R_f = 0.1 (1:1, Et_2O/petroleum

ether); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.00 (ddd, *J* = 15.4, 6.0, 2.7 Hz, 1H, CH_2), 2.19-2.26 (m, 1H, CH_2), 2.47, (dd, *J* = 15.4, 6.3 Hz, 1H, CH_2), 2.69-2.75 (m, 1H, CH_2), 2.72 (d, *J* = 17.4 Hz, 1H, CH_2), 2.96 (d, *J* = 17.4 Hz, 1H, CH_2), 3.01 (dd, *J* = 6.8, 2.6 Hz, 1H, CH), 4.60 (d, *J* = 14.4 Hz, 1H, CH_2), 4.66 (d, *J* = 14.4 Hz, 1H, CH_2), 5.76-5.82 (m, 1H, CH), 5.88-5.94 (m, 1H, CH), 7.21-7.31 (m, 5H, CH × 5), COOH resonance not observed; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.7 (CH_2), 31.6 (CH_2), 40.3 (CH_2, CH_2CO_2H), 42.9 (CH_2, Bn), 44.6 (CH), 45.5 (C), 126.6 (CH, vinylic), 127.8 (CH, Ar), 128.3 (CH, Ar), 128.6 (CH, Ar CH), 128.7 (CH, vinylic), 135.7 (C, Ar), 175.2 (C, C=O), 178.8 (C, C=O), 181.2 (C, C=O); MS (ES+) *m*/*z* 322.3 (M+Na, 100%); HRMS (ES+) found 322.1061, requires 322.1055 for $C_{17}H_{17}NO_4Na$.

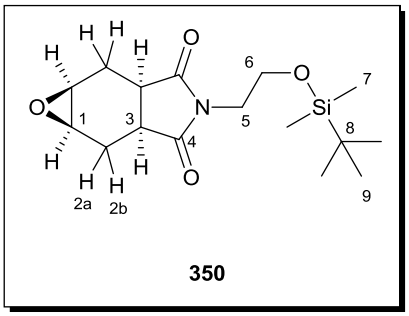
*Synthesis of epoxides **350** & **351**.*



319 **350**, 57 % **351**, 17 %

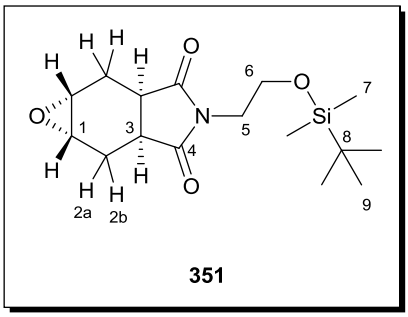
Following a modified literature procedure,[144] *meta*-chloroperoxybenzoic acid (230 mg, 0.97 mmol) was added to a solution of imide **319** (200 mg, 0.65 mmol) in CH_2Cl_2 (6 mL) at room temperature, and the mixture was stirred at room temperature for 17 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) (to dissolve the precipitate which formed) and washed with $Na_2S_2O_{3\,(aq)}$ (15 mL, 15 % w/v), sat. $NaHCO_{3\,(aq)}$ (20 mL) and brine (20 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the crude products (4:1). The residue was purified by flash column chromatography (Et_2O/petroleum ether, 1:1) to give **350** (120 mg, 57 %) and **351** (35 mg, 17 %) as white solids.

Epoxide **350**: R_f = 0.1 (1:1, Et_2O/petroleum ether); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.03 (s, 6H, CH_3-7 × 2), 0.85 (s, 9H, CH_3-9), 2.12-2.19 (m, 2H, CH_2-2a), 2.69-2.77 (m, 2H, CH_2-2b), 2.72-2.77 (m, 2H, CH-3), 3.14-3.17 (m, 2H, CH-1), 3.62-3.66 (m, 2H, CH_2-5), 3.71-3.75 (m, 2H, CH_2-6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.3 (CH_3, C-7 × 2), 18.3 (C, C-8), 22.5 (CH_2, C-2), 25.9 (CH_3, C-9 × 3), 35.4 (CH, C-3), 41.2 (CH_2, C-5), 50.7 (CH, C-1), 59.2 (CH_2, C-6), 180.3 (C=O, C-4); MS (ES+) *m/z* 348.3 (M+Na, 100%); HRMS (ES+) found 348.1612, requires 348.1607 for $C_{16}H_{27}NO_4NaSi$.



350

Epoxide **351**: R_f = 0.15 (1:1, Et_2O/petroleum ether); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.01 (s, 6H, CH_3-7 × 2), 0.84 (s, 9H, CH_3-9 × 3), 1.85-1.97 (m, 2H, CH_2-2a), 2.58-2.68 (m, 2H, CH_2-2b), 2.87-2.98 (m, 2H, CH-3), 3.24-3.28 (m, 2H, CH-1), 3.60-3.64 (m, 2H, CH_2-5), 3.72-3.76 (m, 2H, CH_2-6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.3 (CH_3, C-7 × 2), 18.3 (C, C-8), 23.3 (CH_2, C-2), 25.9 (CH_3, C-9 × 3), 35.3 (CH, C-3), 40.9 (CH_2, C-5), 49.3 (CH, C-1), 59.2 (CH_2, C-6), 179.7 (C=O, C-4).



351

Appendix A – X-ray Crystal Structure Data for Compound **188**.

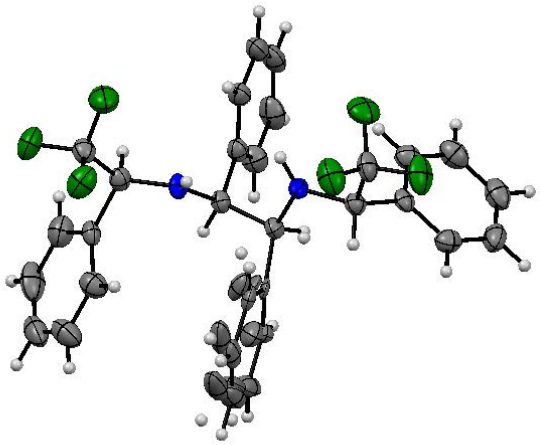


Table A1. Crystal data and structure refinement for diamine **188**.

Identification code	**188**	
Empirical formula	$C_{30}H_{26}F_6N_2$	
Formula weight	528.53	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C 2/c	
Unit cell dimensions	a = 16.3579(6) Å	α= 90°.
	b = 22.9058(14) Å	β= 112.064(3)°.
	c = 15.2548(9) Å	γ = 90°.
Volume	5297.2(5) $Å^3$	
Z	8	
Density (calculated)	1.325 Mg/m^3	
Absorption coefficient	0.107 mm^{-1}	
F(000)	2192	
Crystal size	0.40 x 0.16 x 0.10 mm^3	
Theta range for data collection	2.99 to 25.03°.	

Index ranges	-18<=h<=19, -27<=k<=27, -18<=l<=17
Reflections collected	25807
Independent reflections	4664 [R(int) = 0.0804]
Completeness to theta = 25.03°	99.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9894 and 0.9584
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4664 / 191 / 398
Goodness-of-fit on F^2	1.063
Final R indices [I>2sigma(I)]	R1 = 0.0685, wR2 = 0.1568
R indices (all data)	R1 = 0.0990, wR2 = 0.1718
Largest diff. peak and hole	0.538 and -0.476 e.$Å^{-3}$

Notes:

The phenyl ring C17-C22/C17'-C22' is disordered over two positions at an occupancy ratio of 50 (4):50 (4).

The hydrogen atoms were fixed as riding models.

Appendix B – X-ray Crystal Structure Data for Compound **197**.

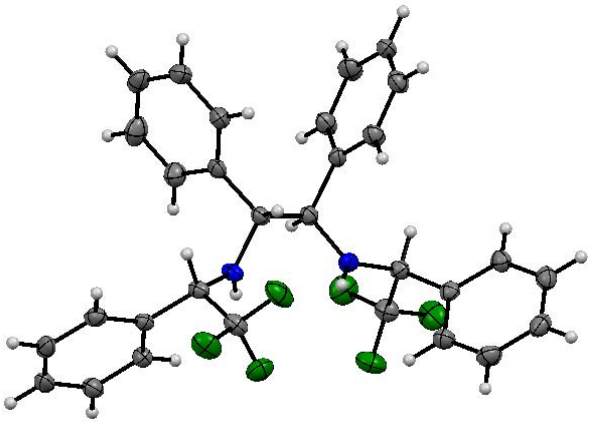


Table B1. Crystal data and structure refinement for diamine **197**.

Identification code	**197**	
Empirical formula	$C_{30}H_{26}F_6N_2$	
Formula weight	528.53	
Temperature	120(2) K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P $2_12_12_1$	
Unit cell dimensions	a = 6.5937(1) Å	α = 90°.
	b = 16.3505(2) Å	β = 90°.
	c = 24.2581(2) Å	γ = 90°.
Volume	2615.27(6) $Å^3$	
Z	4	
Density (calculated)	1.342 Mg/m^3	
Absorption coefficient	0.925 mm^{-1}	
F(000)	1096	
Crystal size	0.40 x 0.28 x 0.22 mm^3	

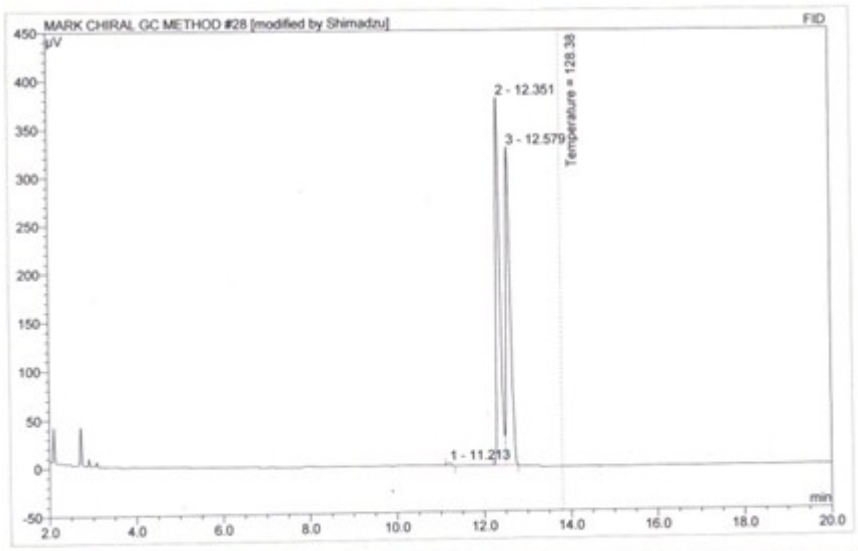
Theta range for data collection	6.53 to 70.03°.
Index ranges	-7<=h<=7, -18<=k<=19, -29<=l<=28
Reflections collected	20196
Independent reflections	4843 [R(int) = 0.0237]
Completeness to theta = 70.03°	98.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8224 and 0.7086
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4843 / 0 / 343
Goodness-of-fit on F^2	1.046
Final R indices [I>2sigma(I)]	R1 = 0.0309, wR2 = 0.0824
R indices (all data)	R1 = 0.0315, wR2 = 0.0830
Absolute structure parameter	0.06(8)
Largest diff. peak and hole	0.439 and -0.398 e.$Å^{-3}$

Notes:

The absolute structure has been determined from the diffraction data. Centres C(2) and C(23) are *S* while centres C(9) and C(16) are *R*.

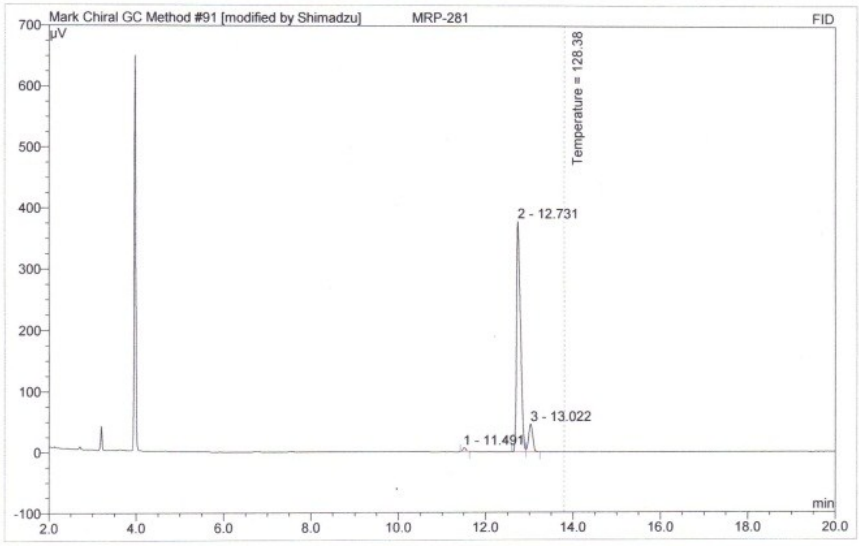
The hydrogen atoms have been fixed as riding models.

Appendix C – Example Chiral GC Chromatograms for **34**.



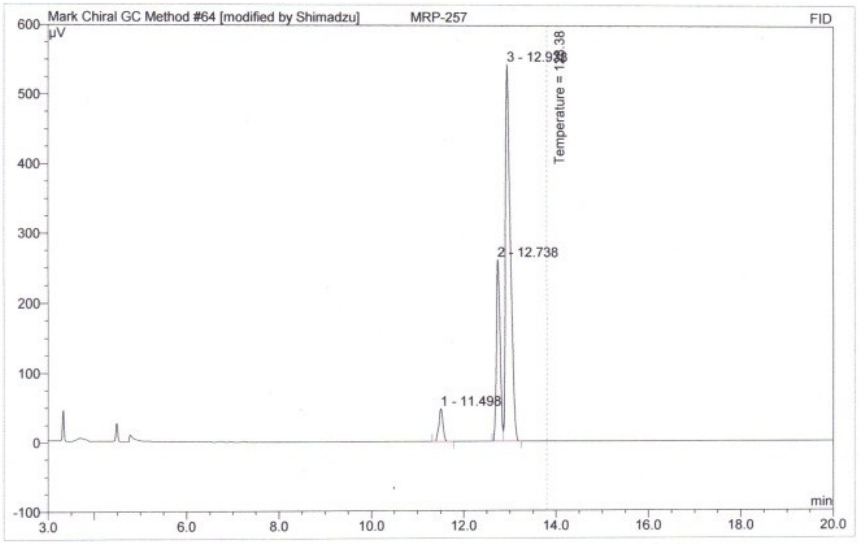
No.	Ret.Time min	Peak Name	Height µV	Area µV*min	Rel.Area %	Amount	Type
1	11.21	n.a.	3.00	0.36	0.46	n.a.	BMB*
2	12.35	n.a.	383.00	39.00	50.20	n.a.	BM *
3	12.58	n.a.	332.00	38.34	49.34	n.a.	MB*
Total:			718.00	77.70	100.00	0.000	

Figure C1: Chiral GC chromatogram of a racemic sample of enol silane **34** synthesised using LDA-LiCl (Table 7.1, Entry 2). Peak 1 – ketone 1, peak 2 – enol silane (*S*)-**34** and peak 3 – enol silane (*R*)-**34**.



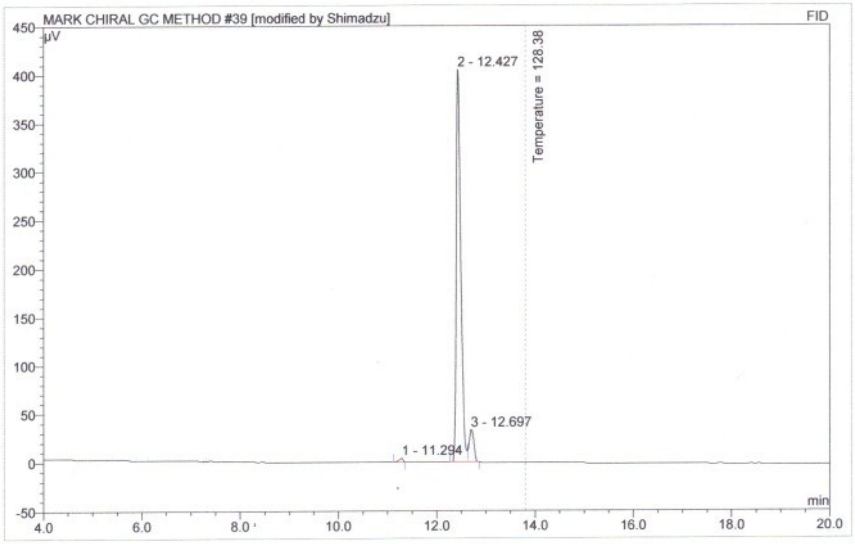
No.	Ret.Time min	Peak Name	Height µV	Area µV*min	Rel.Area %	Amount	Type
1	11.49	n.a.	6.00	0.48	1.07	n.a.	BMB*
2	12.73	n.a.	381.00	39.67	87.75	n.a.	BM *
3	13.02	n.a.	46.00	5.05	11.18	n.a.	MB*
Total:			433.00	45.21	100.00	0.000	

Figure C2: Chiral GC chromatogram of a sample of enol silane (*S*)-**34** with 79 % ee synthesised using (*R*)-**122**-LiCl (Table 7.1, Entry 10). Peak 1 – ketone **1**, peak 2 – enol silane (*S*)-**34** and peak 3 – enol silane (*R*)-**34**.



No.	Ret.Time min	Peak Name	Height µV	Area µV*min	Rel.Area %	Amount	Type
1	11.50	n.a.	47.00	4.69	4.88	n.a.	BMB*
2	12.74	n.a.	263.00	24.35	25.35	n.a.	BM *
3	12.94	n.a.	544.00	67.03	69.77	n.a.	MB*
Total:			854.00	96.07	100.00	0.000	

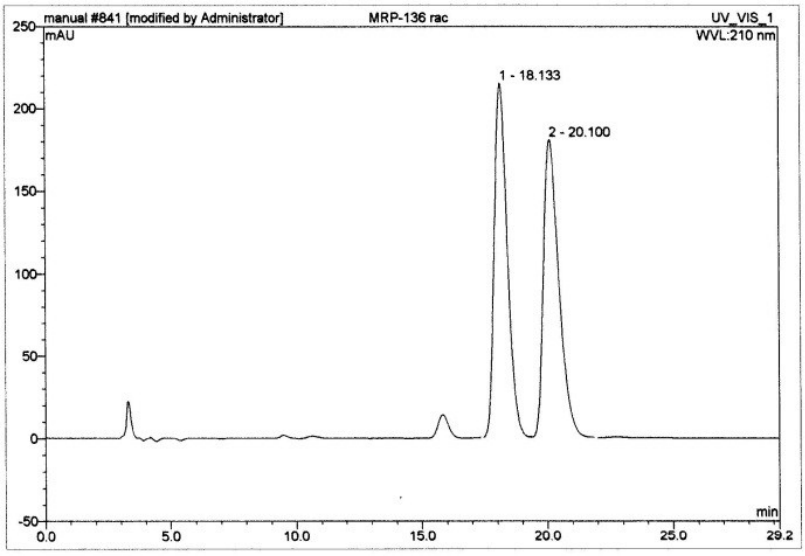
Figure C3: Chiral GC chromatogram of a sample of enol silane (*R*)-**34** with 46 % ee synthesised using (+)-**147** (Table 7.1, Entry 11). Peak 1 – ketone **1**, peak 2 – enol silane (*S*)-**34** and peak 3 – enol silane (*R*)-**34**.



No.	Ret.Time min	Peak Name	Height µV	Area µV*min	Rel.Area %	Amount	Type
1	11.29	n.a.	4.00	0.37	0.77	n.a.	BMB*
2	12.43	n.a.	405.00	43.50	91.43	n.a.	BM *
3	12.70	n.a.	33.00	3.71	7.80	n.a.	MB*
Total:			442.00	47.58	100.00	0.000	

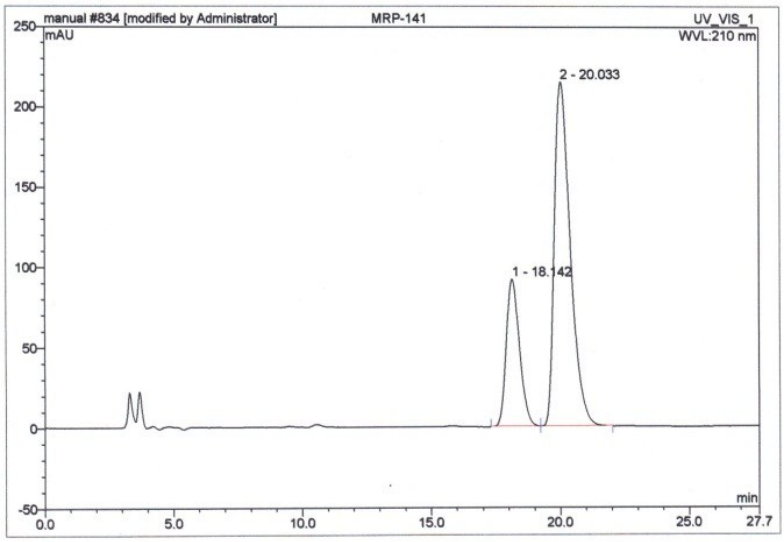
Figure C4: Chiral GC chromatogram of a racemic sample of enol silane (*S*)-**34** with 84 % ee synthesised using a mixture of LDA-LiCl and (*R*)-**186** (Table 7.3, Entry 6). Peak 1 – ketone **1**, peak 2 – enol silane (*S*)-**34** and peak 3 – enol silane (*R*)-**34**.

Appendix D – Example Chiral HPLC Chromatograms for **156**.



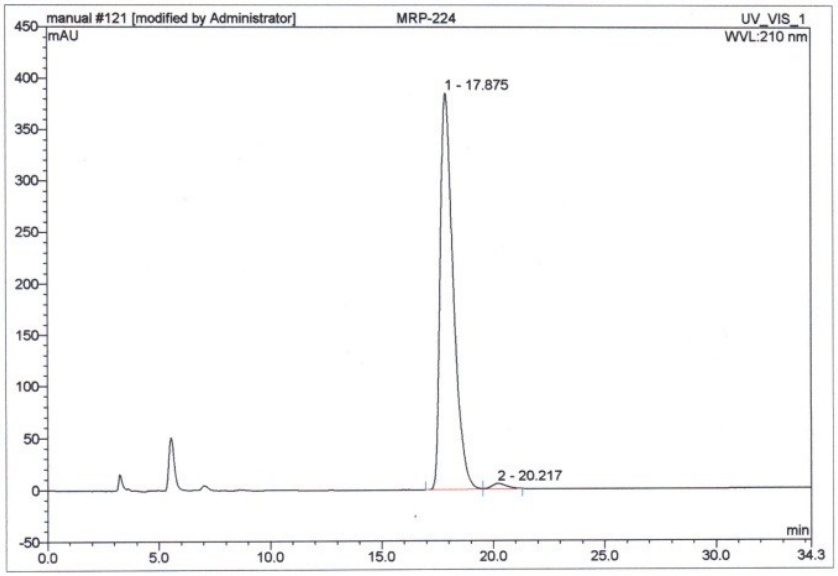
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	18.13	n.a.	214.940	129.443	49.92	n.a.	BM
2	20.10	n.a.	180.507	129.858	50.08	n.a.	MB
Total:			395.447	259.301	100.00	0.000	

Figure D1: Chiral HPLC chromatogram of a racemic sample of ester **156** synthesised using LDA-LiCl (Table 7.5, Entry 2). Peak 1 – (–)-**156**, peak 2 – (+)-**156**.



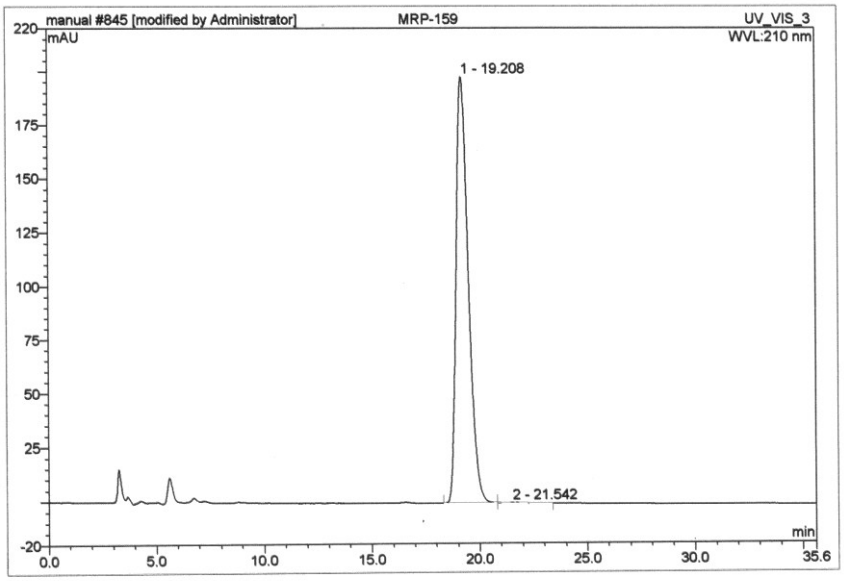
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	18.14	n.a.	92.895	55.432	26.23	n.a.	BM
2	20.03	n.a.	215.653	155.882	73.77	n.a.	MB
Total:			308.548	211.314	100.00	0.000	

Figure D2: Chiral HPLC chromatogram of a sample of ester (+)-**156** with 48 % ee synthesised using (*R*)-**122**-LiCl (Table 7.5, Entry 6). Peak 1 – (–)-**156**, peak 2 – (+)-**156**.



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	17.88	n.a.	386.920	263.072	98.49	n.a.	BM
2	20.22	n.a.	5.227	4.040	1.51	n.a.	MB
Total:			392.147	267.111	100.00	0.000	

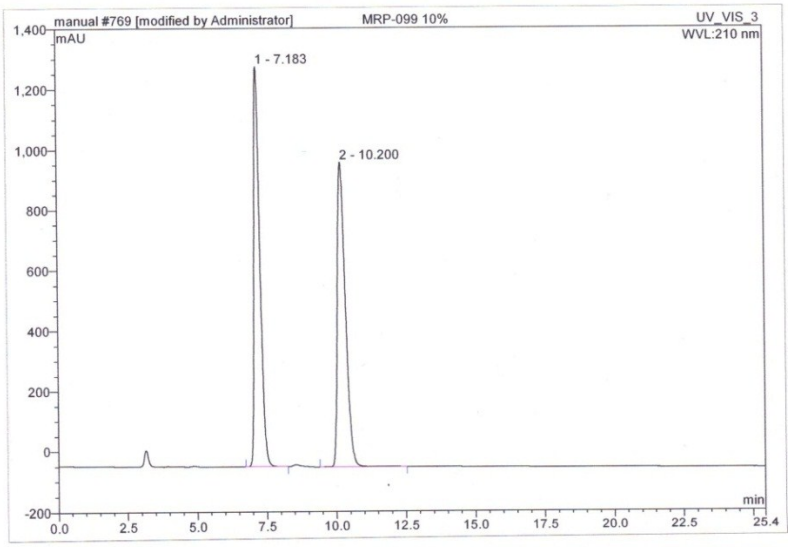
Figure D3: Chiral HPLC chromatogram of a sample of ester (–)-**156** with 97 % ee synthesised using (+)-**147**-LiCl (Table 7.5, Entry 8). Peak 1 – (–)-**156**, peak 2 – (+)-**156**.



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	19.21	n.a.	198.432	129.857	99.99	n.a.	BMB
2	21.54	n.a.	0.115	0.011	0.01	n.a.	BMB*
Total:			198.547	129.868	100.00	0.000	

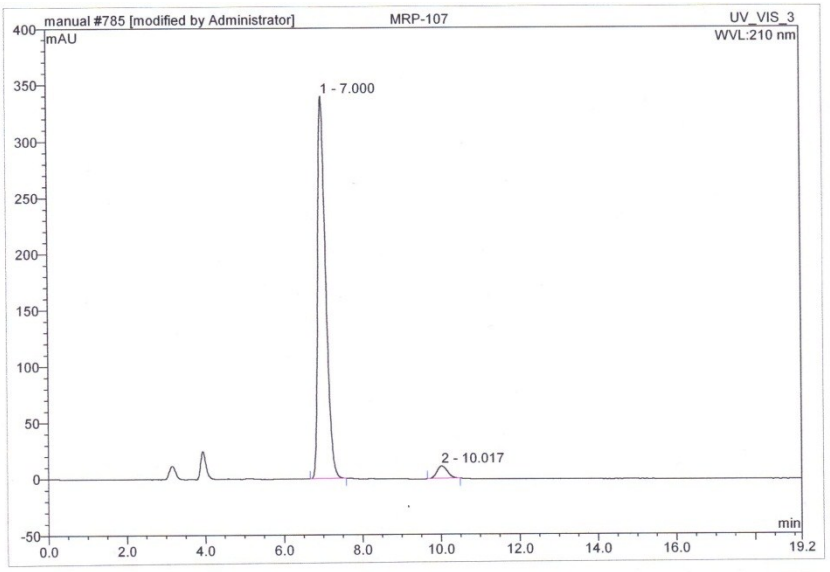
Figure D4: Chiral HPLC chromatogram of a sample of ester (–)-**156** with 99 % ee synthesised using (+)-**147**-LiCl (Table 7.6, Entry 2). Peak 1 – (–)-**156**, peak 2 – (+)-**156**.

Appendix E – Example Chiral HPLC Chromatograms for **165**.



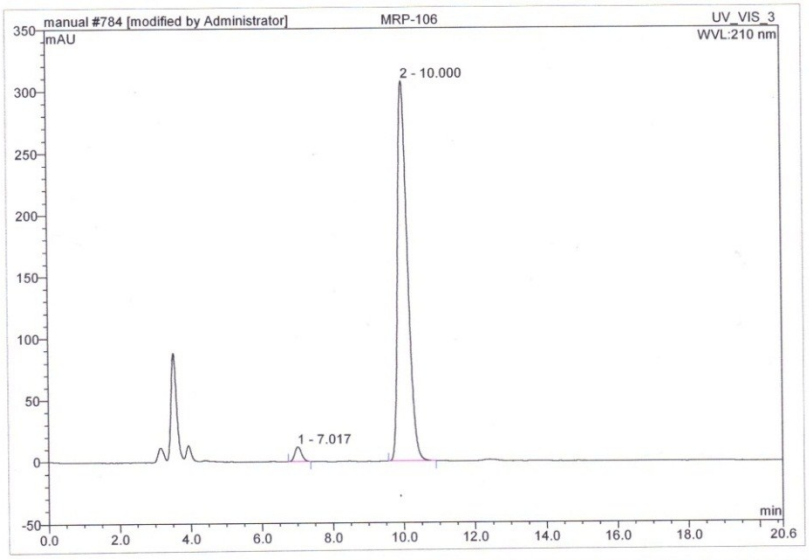
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7.18	n.a.	1325.570	329.632	49.47	n.a.	BMB*
2	10.20	n.a.	1010.566	336.658	50.53	n.a.	BMB
Total:			2336.136	666.290	100.00	0.000	

Figure E1: Chiral HPLC chromatogram of a racemic sample of ester **165** synthesised using LDA-LiCl (Table 7.8, Entry 1). Peak 1 – (–)-**165**, peak 2 – (+)-**165**.



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7.00	n.a.	339.809	78.851	95.86	n.a.	BMB
2	10.02	n.a.	11.047	3.409	4.14	n.a.	BMB
Total:			350.856	82.259	100.00	0.000	

Figure E2: Chiral HPLC chromatogram of a sample of ester (–)-**165** with 92 % ee synthesised using (*R*, *R*)-**19** (Table 7.8, Entry 3). Peak 1 – (–)-**165**, peak 2 – (+)-**165**.



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7.02	n.a.	11.992	2.711	2.69	n.a.	BMB
2	10.00	n.a.	307.776	98.128	97.31	n.a.	BMB
Total:			319.768	100.839	100.00	0.000	

Figure E3: Chiral HPLC chromatogram of a sample of ester (+)-**165** with 95 % ee synthesised using (+)-**147** (Table 7.8, Entry 4). Peak 1 – (–)-**165**, peak 2 – (+)-**165**.

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