Studies Towards the Total Synthesis of (+)-Retronecine and Anthracimycin

Joshua C. Smith

Doctor of Philosophy

University of York

Chemistry

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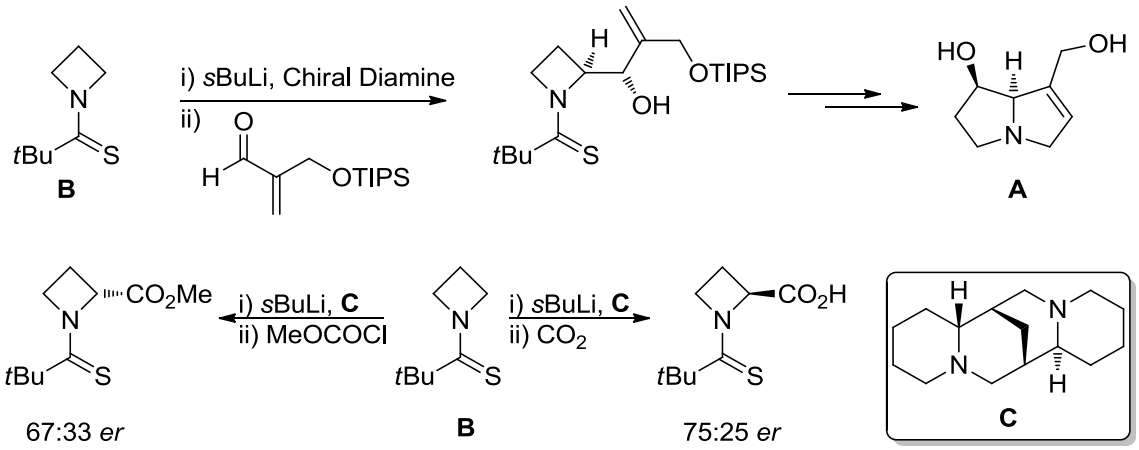
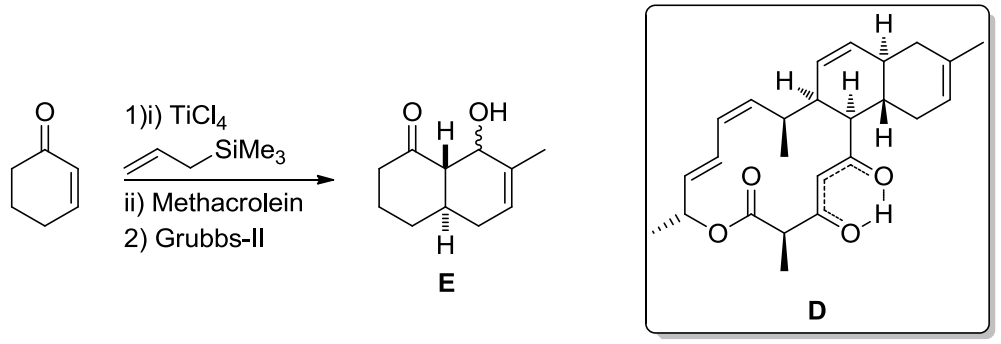
Abstract

This thesis consists of two separate projects. The first project involved an attempted total synthesis of (+)-retronecine **A**, a poisonous pyrrolizidine alkaloid *via* a novel asymmetric α-lithiation-substitution reaction of *N*-thiopivaloyl azetidine **B**, mediated by a chiral diamine.



A total synthesis was not possible and our attention turned towards elucidating the mechanism of enantioinduction. Of particular note was how the use of carbon dioxide and methyl chloroformate as electrophiles gave products with the opposite configuration under otherwise identical reaction conditions (using (–)-sparteine **C**).

Chapter two consists of work undertaken towards a total synthesis of anthracimycin **D**, a potent marine antibiotic. The development of robust methodology was explored for the early stages of the synthesis. In addition, a synthesis of the model decalinone **E**, was developed, *via* a Sakurai-aldol reaction, followed by ring closing metathesis.



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Acknowledgements

As a joint student of two supervisors, I feel fortunate to have been afforded twice the input, ideas and expertise as I would have received were I only a student of one. It has been a privilege to have known and worked with Dr Clarke and Professor O'Brien and despite my occasional brashness, I have the utmost respect for them both.

I would like to thank all members of the PAC and POB groups for their input and suggestions over the years, in particular to Kristaps Ermanis for showing me the ropes in my early days of my PhD, as well as to Peter Rayner for introducing me to the practicalities of organolithium chemistry and his shared experiences of banging one's head against a wall. I would also like to thank the PAC group for the daily banter which, sometimes savage, often silly but always funny, has made day to day life in the lab that bit brighter. Long may the wall of Sam live on.

As is common to all PhD students, this work would not have been possible without a great deal of support from technical staff in the department. I would therefore like to extend my thanks towards Heather Fish for the NMR service, as well as her own unique brand of humour, to Karl Heaton for mass spectrometry, Adrian Whitwood for X-ray services and Steve and Mike from stores and the leeway they afforded myself and the PAC group.

I would like to thank my entire family, in particular my mum and her husband John, without whose love, support and patience this PhD may well never have reached completion. I would also like to make mention of the people I have met at York Vineyard, their friendship and hospitality has been greatly appreciated and I consider all of them to be my extended family.

Lastly but by no means least, I would like to give thanks to our Lord Jesus Christ for the grace and mercy He has shown to me each day, who has brought me through some difficult circumstances and blessed me with opportunities, friendships and success that I can scarcely believe nor deserve. May what little contained herein be for His glory, who is above all others and blessed forever, Amen.

Author's Declaration

The research and results presented herein are, to the best of my knowledge, original except for when due reference has been made to other authors and/or co-workers.

Some of the work in this thesis has been published in the following paper:

"*Mechanistic interrogation of the asymmetric lithiation-trapping of N-thiopivaloyl azetidine and pyrrolidine.*"

Chem. Commun., 2016, **52**, 1354-1357

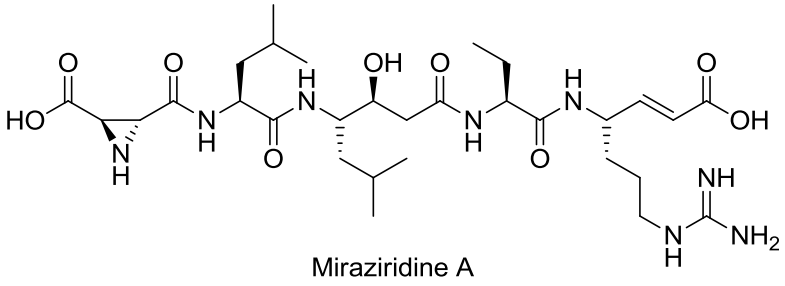
This thesis has not been submitted for any other award at this or any other institution.

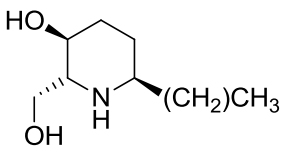
Chapter One: Studies Towards the Total Synthesis of (+)-Retronecine *via* an Azetidine Lithiation-Trapping Reaction

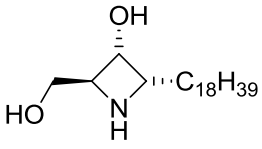
1.1 Introduction to Nitrogen Containing Natural Products

Natural products, assuming that they are chiral, are usually produced as a single enantiomer, given that they are typically made *via* enzymatic catalysis. Despite major advances, efficient methods for asymmetric synthesis remains a challenge in natural product total synthesis, in terms of matching the enantiomeric excesses achieved by the organism that produces it, stepwise efficiency and substrate specificity.

Nitrogen heterocycles are biologically privileged motifs. Many natural products contain at least one substituted nitrogen heterocycle and some selected examples are shown in figure 1.1, including Miraziridine A, a protease inhibitor,[1] Desoxyprosopine, an alkaloid isolated from *Prosopsis africana*,[2] Penazetidine A, a protein kinase C inhibitor,[3] and (–)-Kainic acid, a mammalian neuroexcitory amino acid.[4]







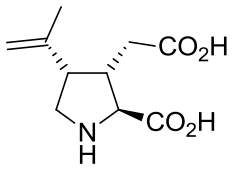
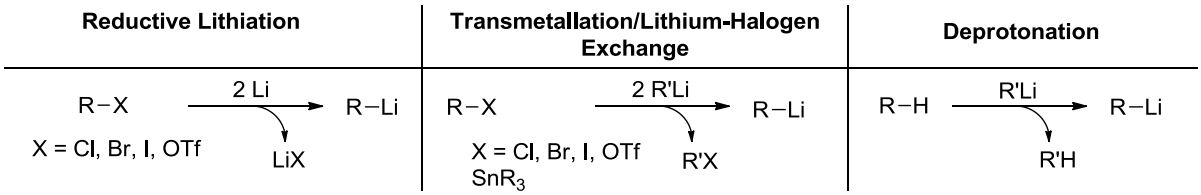


Figure 1.1

Methods for the asymmetric synthesis of α-substituted nitrogen heterocycles are thus important for the synthetic chemist. To date, the asymmetric synthesis of functionalised organolithium reagents remains one of the best, most conceptually simple and fastest ways of accessing enantioenriched α-substituted nitrogen heterocycles.

1.2 α-Lithiation-Substitution of Nitrogen Containing Heterocycles

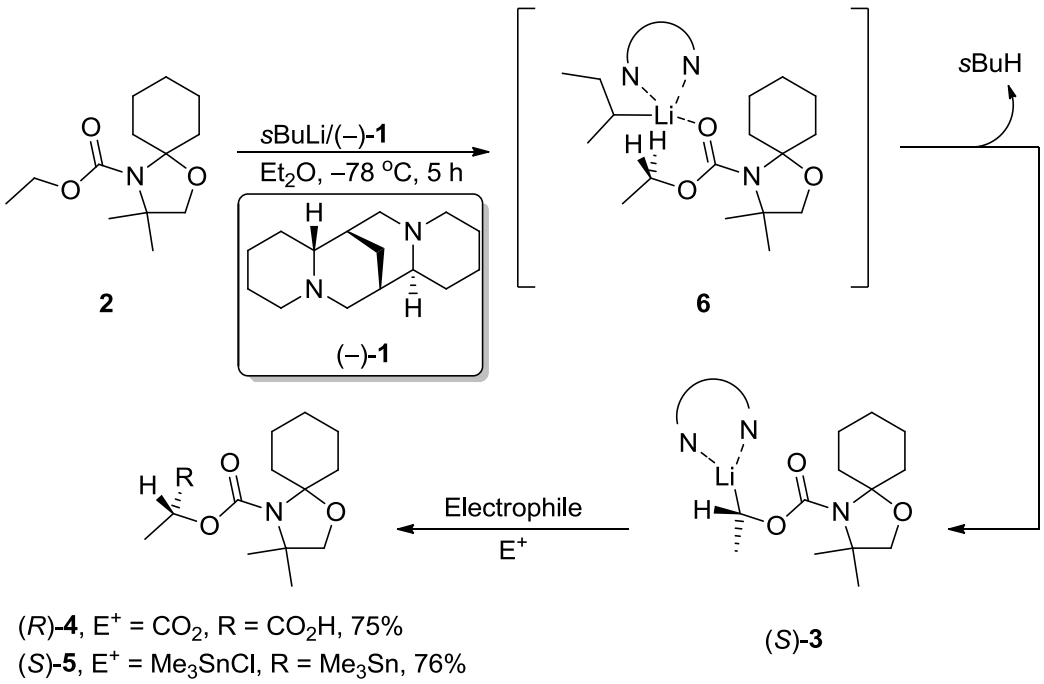
Typically, organolithium reagents are formed *via* three methods: reductive lithiation, transmetallation and deprotonation, summarised in Scheme 1.1.



Scheme 1.1

Ultimately, reductive lithiation remains the only method of generating organolithium reagents *ab initio* but, due to the single electron transfer mechanism of their formation[5] which proceeds *via* an sp^2 planar radical intermediate, any stereogenic centres containing a C–X bond are racemised. Transmetallation also generally suffers from the same problem, although tin-lithium exchange provides a method for retaining the enantioenrichment of the starting stannane.[6] Deprotonation, therefore, remains the most general and most effective method for the formation of enantioenriched α-functionalised organolithium reagents.

The most well utilised method of carrying out asymmetric deprotonations of a substrate is to use a strong base (*s*BuLi or *n*BuLi typically) in the presence of a chiral diamine, with (–)-sparteine (–)-**1**, an alkaloid extracted from *Cytisus scoparius*,[7] being the prime example. Although (–)-sparteine (–)-**1** was used in organometallic chemistry as early as 1968,[8] its potential for asymmetric deprotonations was not realised until 1990, when Hoppe[9] treated cyclic carbamate **2** with *s*BuLi in the presence of (–)-sparteine to form enantioenriched carbamate **3**, which could then be trapped with a variety of electrophiles in high yields and enantioselectivities. The synthesis of α-functionalised carbamates (*R*)-**4** and (*S*)-**5** are shown in Scheme 1.2.

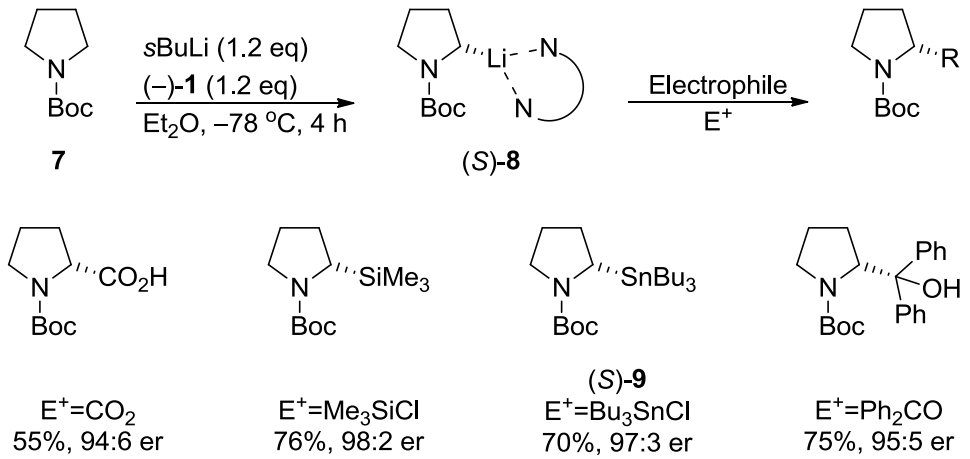


Scheme 1.2

Importantly, the carbamate functional group acts as a directing group and coordinates to the *s*BuLi, forming a pre-lithiation complex **6** consisting of diamine, *s*BuLi and the starting carbamate **2**. Complex **6** can then undergo deprotonation to give the functionalised organolithium. Known as the "complex induced proximity effect", evidence for the pre-lithiation complex was first put forwards by Beak[10] in 1995 and has subsequently been directly observed with some *N*-Boc substrates by *in situ* IR spectroscopy.[11, 12] It is also worth noting, that chiral base mixtures consisting of an alkyllithium and (–)-**1** require a non-coordinating solvent such as Et_2O, toluene or alkanes in order for effective enantioinduction to occur. If THF is used, the product of lithiation-trapping is usually racemic[13-20] which is believed to be due to the solvent out-competing (–)-**1** for ligation to the lithium.[13, 21]

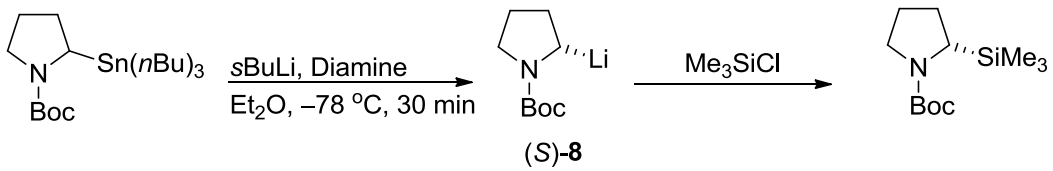
1.2.1 α-Lithiation-Substitution of 5-Membered Nitrogen Containing Heterocycles

Perhaps the most well utilised substrate for α-lithiation-trapping chemistry is the cyclic *N*-Boc pyrrolidine **7**. First reported in 1991,[22] **7** was treated with *s*BuLi in the presence of (–)-**1** to form enantioenriched organolithium (*S*)-**8** and was then trapped with a variety of electrophiles. Some selected examples are shown in Scheme 1.3.



Scheme 1.3

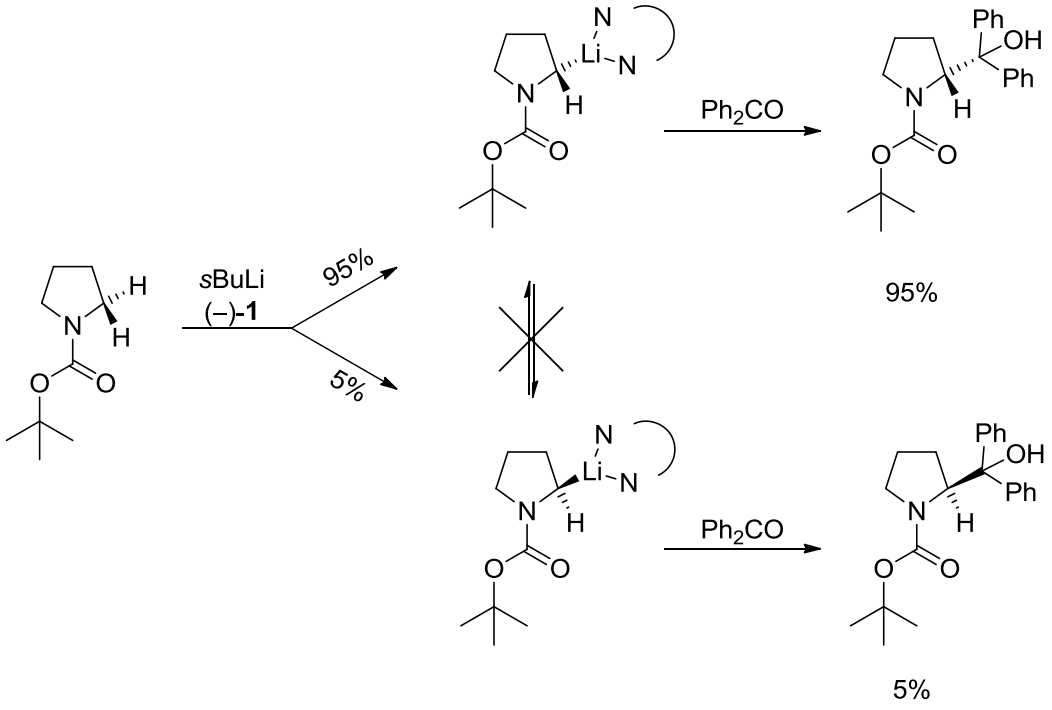
Crucially, Beak also demonstrated that the mechanism of enantioinduction is an enantioselective deprotonation of **7** by the *s*BuLi/(–)-**1** complex, rather than a resolution of racemic organolithium **8** and (–)-**1**. The key experiments are shown in Table 1.1. Enantioenriched stannane (*S*)-**9** (97:3 *er*) was transmetallated to the corresponding organolithium (*S*)-**8** in the presence of TMEDA and then trapped with Me_3SiCl. The product silane had an enantiomeric ratio of 83:17 (Table 1.1, entry 1). In contrast, when racemic **9** was transmetallated to (*S*)-**8** in the presence of (–)-**1**, then trapped with Me_3SiCl, the corresponding silane was effectively racemic (Table 1.1, entry 2).



Entry	SM	Diamine	Product	Yield	*er*
1	(*S*)-**9** 97:3 *er*	TMEDA	(*S*)-**10**	62%	83:17
2	*rac*-**9**	(–)-**1**	(*S*)-**10**	60%	52:48

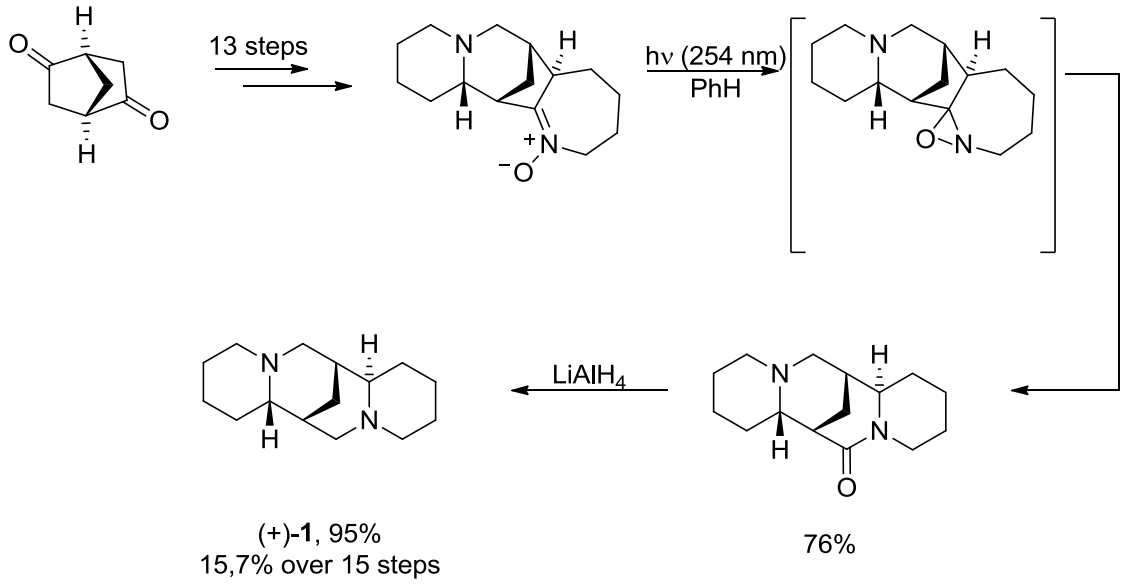
Table 1.1: Demonstration of Configurational Stability of **8**

The results indicate that organolithium **8** is configurationally stable under the reaction conditions *ie.*, it is not able to interconvert to its enantiomer. This means that both the sense of induction and the enantioenrichment of the product must be determined during the deprotonation step (Scheme 1.4). This also explains why the sense of induction does not change and why the overall enantioselectivities do not change significantly with the electrophile that is used.



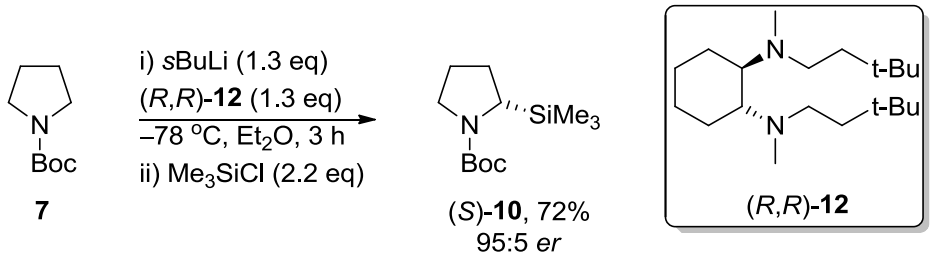
Scheme 1.4

Whilst (–)-sparteine (–)-**1** provides excellent enantioselectivities for products of the opposite enantiomeric series to (*S*)-proline, (+)-sparteine (+)-**1** has been less available commercially. To date, the only enantioselective synthesis of (+)-**1** was reported by Aubé[23] using norbornadione (*S*,*S*)-**11** as starting material. This route gave (+)-sparteine (+)-**1** in 15 steps and 15.7% overall yield (Scheme 1.5).



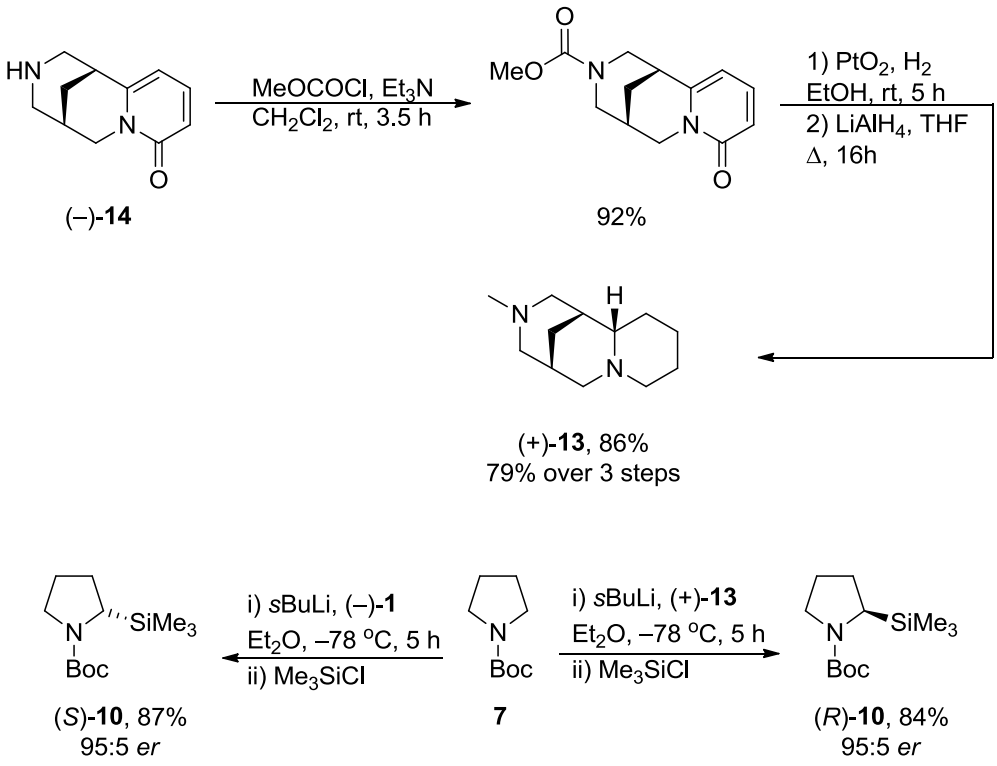
Scheme 1.5

For this reason, chiral diamines that give the opposite sense of induction to (–)-**1** have been investigated. Originally developed as ligands to facilitate the asymmetric addition of organolithium reagents to aromatic imines,[24, 25] diamines (*S*,*S*)-**12** and (*R*,*R*)-**12** have been shown to be effective ligands in the asymmetric α-lithiation-substitution of **7**.[26] For example, *N*-Boc pyrrolidine **7** was treated with *s*BuLi in the presence of (*R*,*R*)-**12** and trapped with Me_3SiCl to give silane (*S*)-**10** in 72% and 95:5 *er* (Scheme 1.6), comparing favourably to the enantioselectivities obtained with (–)-**1**.



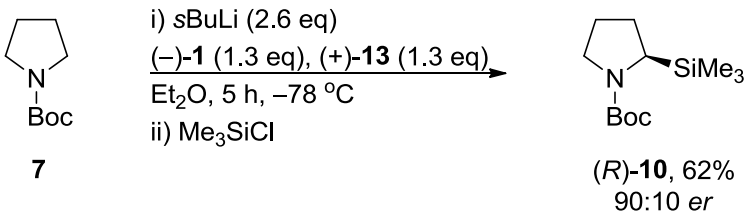
Scheme 1.6

Crucially, racemic *trans*-1,2-diaminocyclohexane is commercially available. Thus, either enantiomer of the desired chiral diamine can be synthesised following resolution with (D)-tartaric acid. (*R*,*R*)-**12** was synthesised *via* two successive alkylations in 60% overall yield.[27, 28] To date, the (+)-sparteine surrogate (+)-**13**, a pseudoenantiomer of (–)-**1** derived from (–)-cytisine (–)-**14**, developed within our group,[29] has shown the greatest promise in terms of matching the yields and enantioselectivities obtained with (–)-**1**. The synthesis of (+)-**13** and a comparison of its use in α-lithiation trapping are shown in Scheme 1.7.



Scheme 1.7

The *s*BuLi/(+)-**13** complex has been demonstrated, *via* a competition experiment, to be significantly more reactive than *s*BuLi/(–)-**1** (Scheme 1.8).[30] Given that the *s*BuLi/(+)-**13** complex and the *s*BuLi/(–)-**1** complex give products with the opposite sense of induction but at similar levels of enantioenrichment, the rate at which each complex lithiates *N*-Boc pyrrolidine **7** will be proportional to the enantioenrichment of the final product. In this case, Me_3SiCl as electrophile gave (*R*)-**10** in 62% yield and an enantiomeric ratio of 90:10, indicating that the *s*BuLi/(+)-**13** complex lithiates *N*-Boc pyrrolidine **7** approximately twenty times faster than does the *s*BuLi/(–)-**1** complex.



Scheme 1.8

Surprisingly, solution phase ^{6}Li and ^{13}C NMR spectroscopy carried out within our group found that the (+)-sparteine surrogate (+)-**13** forms a monomeric *i*PrLi/diamine species **15** (Figure 1.2) in THF.[31] To the best of our knowledge, no other monomeric organolithium species has been directly observed.

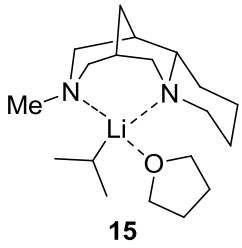


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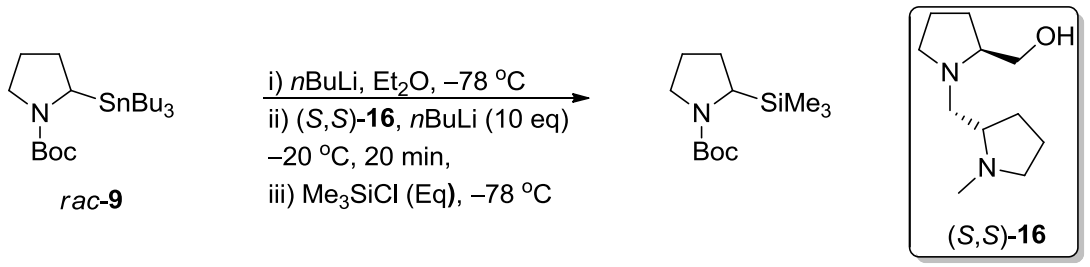
Figure 1.2

Naturally, being able to predictably access both enantiomers of α-substituted pyrrolidines is synthetically useful and both (–)-sparteine (–)-**1** and the (+)-sparteine surrogate (+)-**13** have been used in this manner in several total syntheses.[32-34]

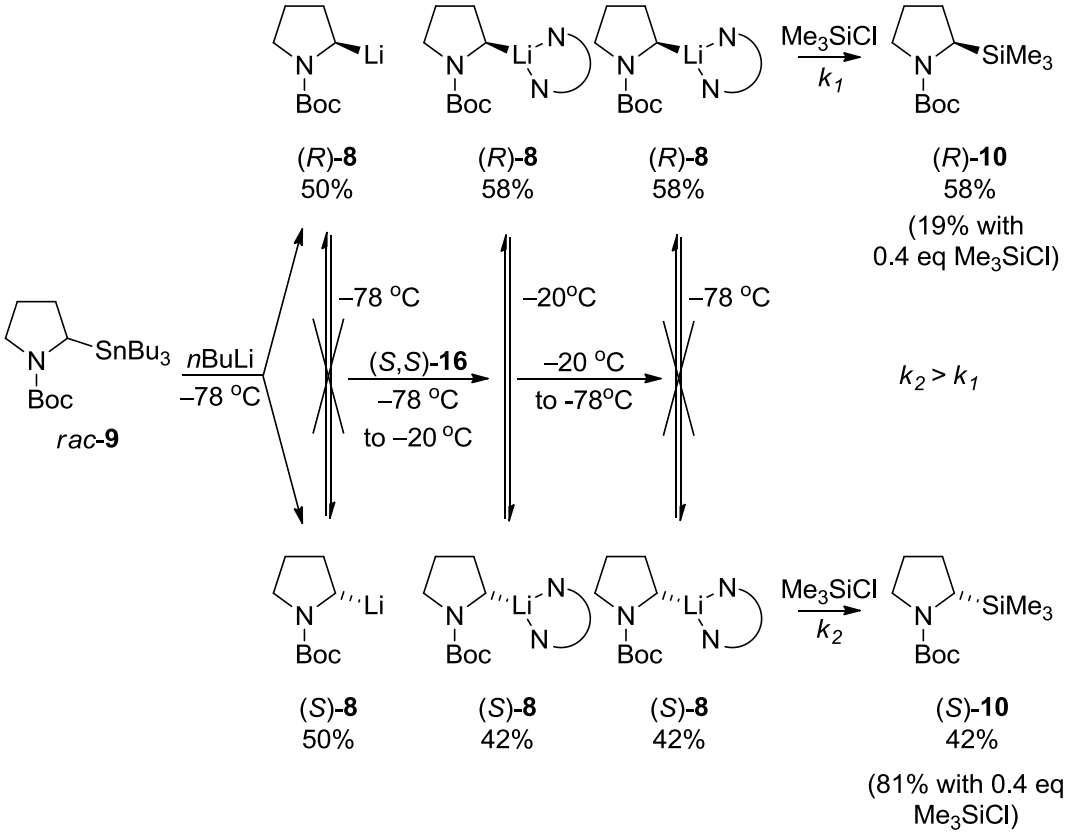
Lithiated *N*-Boc pyrrolidine **8** is known to become configurationally unstable at temperatures above –40 °C.[35] However, provided that the temperature of the reaction remains below this, the mechanism of enantioinduction must remain an enantioselective deprotonation as shown in Scheme 1.4. However, if the temperature is allowed to increase beyond –40 °C, the ratio between the enantiomers of the lithiated intermediate **w**ill be dependent on the equilibrium constant, $K_{eq.}$ In 2006, Coldham[35] formed the racemic organolithium **8** at –78 °C and allowed a resolution by warming the reaction to –20 °C in the presence of (*S*,*S*)-**16**, then re-cooling to –78 °C and trapping with Me_3SiCl (Table 1.2).



Entry	Eq Me_3SiCl	Product	Yield	*er*
1	Excess	(*R*)-**10**	65%	58:42
2	0.4	(*S*)-**10**	39%	19:81

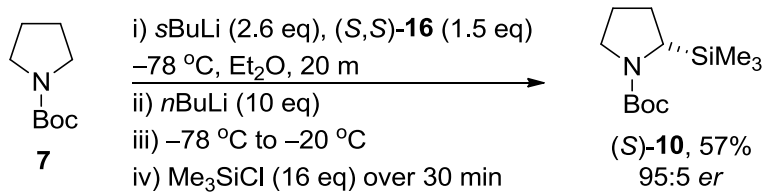
Table 1.2: Results Demonstrating Thermodynamic and Kinetic Resolutions of **8**

The results indicate that chiral diamine (*S*,*S*)-**16** favours a 58:42 thermodynamic ratio of enantiomers, with the (*R*)-lithio-pyrrolidine **8** being the major diastereoisomer. As lithiated pyrrolidine **8** is configurationally stable at –78 °C, the addition of excess Me_3SiCl preserves the thermodynamic ratio of (*R*)-**8** and (*S*)-**8** in the enantiomeric ratio of the product (Scheme 1.9).



Scheme 1.9

Conversely, the addition of substoichometric amounts of Me_3SiCl gives the silane (*S*)-**10** as the major product, with higher enantioselectivities but lower yields. This implies that the (*S*)-lithiopyrrolidine (*S*)-**8**/(*S*,*S*)-**16** complex reacts faster with Me_3SiCl than its diastereoisomer. Coldham was able to optimise the reaction conditions to give silane (*S*)-**10** in 57% yield and 95:5 *er* by the slow addition of excess Me_3SiCl at –20 °C (Scheme 1.10). The presence of 10 equivalents of *n*BuLi was required to maximise *er*s, possibly to increase the rate of interconversion of (*S*)-**8** and (*R*)-**8**.

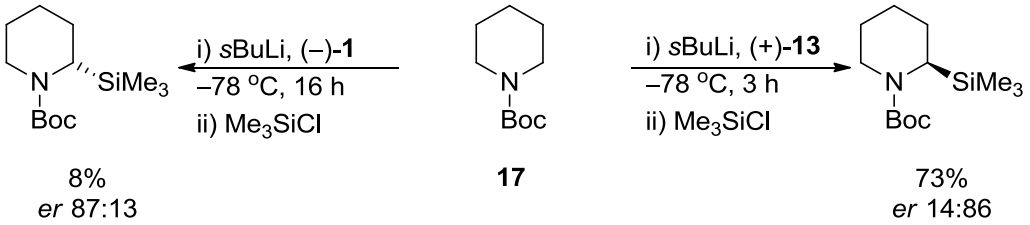


Scheme 1.10

Nonetheless, resolutions of lithiated *N*-Boc pyrrolidine **8** often lack generality due to the poor selectivities offered by thermodynamic resolutions, whilst kinetic resolutions are highly electrophile dependent, both for enantioselectivities and for the overall sense of induction. In contrast, enantioselective deprotonations always proceed with the same sense of induction and enantioselectivities, provided that trapping occurs below the temperature at which the organolithium becomes configurationally unstable.

1.2.2 α-Lithiation-Substitution of 6-Membered Nitrogen Containing Heterocycles

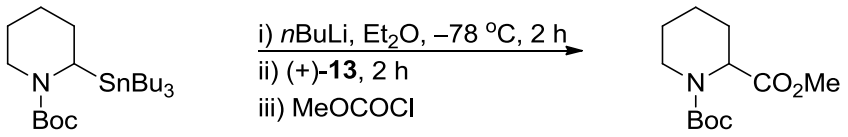
Methodology developed for the asymmetric α-lithiation substitution of *N*-Boc pyrrolidine **7** does not produce equivalent results when applied to the 6-membered ring equivalent *N*-Boc piperidine **17**. Although *N*-Boc pyrrolidine **7** fully lithiates at –30 °C in THF in 5 min, even in the absence of a diamine, *N*-Boc piperidine **17** does not lithiate at all under the same reaction conditions.[36] Even in the presence of (–)-sparteine (–)-**1**, *N*-Boc piperidine **17** only undergoes 10% deprotonation at –78 °C after 6 h using *s*BuLi.[12] It is known that in the case of *N*-Boc pyrrolidine **7** and *N*-Boc piperidine **17**, the equatorial proton is preferentially removed, irrespective of whether a chiral ligand is present.[37, 38] When (–)-**1** is used the chiral diamine, the kinetic energy barrier to deprotonation of the pro-(*S*) proton from **17** is lower than for the pro-(*R*) proton.[39-41] In contrast to (–)-**1**, the use of the (+)-sparteine surrogate (+)-**13** leads to complete deprotonation over 2 h at –78 °C, as confirmed by *in situ* IR spectroscopy.[12] Enantioselectivities are similar to those obtained with (–)-**1** but with the expected opposite sense of induction (Scheme 1.11).[12, 42] As stated previously, (+)-**13** has been shown to form a monomeric *i*PrLi/diamine complex in THF. As lower order alkyllithium species are typically more reactive than their higher order counterparts,[43] it may simply be that due to the increased binding affinity of (+)-**13** relative to (–)-**1**, it is better able to deaggregate the *s*BuLi to a more reactive species that can more readily overcome the kinetic energy barrier of deprotonation.



Scheme 1.11

Despite the difference in relative kinetic barriers, lithiated *N*-Boc piperidine **18** has been demonstrated to be configurationally stable at –78 °C.[12] The mechanism of enantioinduction, provided the temperature is kept at –78 °C, must therefore be an enantioselective deprotonation as is the case with *N*-Boc pyrrolidine **7**. This was formally proven by tin-lithium exchange at –78 °C on racemic stannane **19**. After tin-lithium exchange, (+)-**1** was added and the reaction was incubated at –78 °C for 2 h.

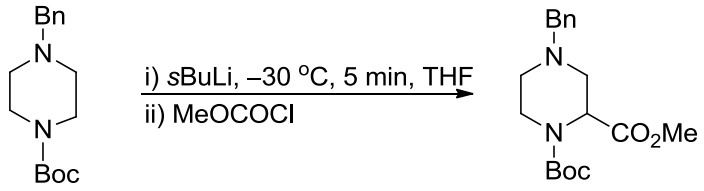
The lithiated intermediate was then trapped with methyl chloroformate to give *rac*-**20**, indicating that enantioinduction does not occur after the deprotonation event (Scheme 1.12).



rac-**19** *rac*-**20**

Scheme 1.12

In contrast to *N*-Boc piperidine **17**, *N*-Boc piperazine **21** lithiates rapidly, even in the absence of a diamine (Scheme 1.13).[36] Although the exact reason for this effect is unknown, two possible explanations for this effect can be suggested. It could be that *N*-Boc piperazine **21** adopts a different conformation to *N*-Boc piperidine **17** and thus allows more facile deprotonation. Alternatively, the electron withdrawing β-nitrogen could lower the pKa of the α-protons in *N*-Boc piperazine **21**.

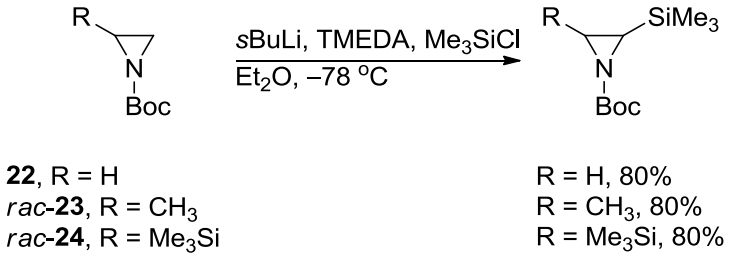


21 83%

Scheme 1.13

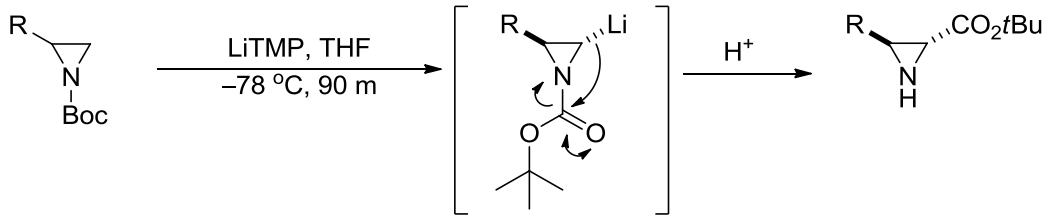
1.2.3 α-Lithiation-Substitution of 3-Membered Nitrogen Containing Heterocycles

Although α-lithiation-substitution chemistry is well established for *N*-Boc pyrrolidine **7** and *N*-Boc piperidine **17**, *N*-Boc aziridines behave differently under similar conditions. In 1994, Beak carried out the first α-lithiation-substitution reaction of *N*-Boc aziridine **22** and the 2-methyl **23** and 2-trimethylsilyl derivatives **24** (Scheme 1.14).[44]



Scheme 1.14

Beak did not comment on the diastereoselectivity of the reaction, although it is likely that the two ring substituents are *trans* to one another, as has been demonstrated on similar substrates.[45-48] It is also worth noting that the substituted aziridine could only be accessed with an *in situ* Me_3SiCl trap. In the original reporrt, Beak did not speculate on why this was the case, although it is now known that 2-lithio-*N*-Boc aziridines rapidly undergo a 1,2-migration to give the corresponding 2-substituted free amine, as demonstrated by Hodgson (Table 1.3).[47]



Entry	R	Yield
1	C_4H_9	90%
2	$(CH_2)_2Ph$	79%
3	CH_2OTBS	90%

Table 1.3: Yields of 1,2-Migration Products on a Variety of *N*-Boc Aziridines

It is unclear why this migration occurs with *N*-Boc aziridines but not with larger ring sizes. A possible reason may be that the nitrogen lone pair does not delocalise into the π^* C=O orbital as efficiently in three-membered ring (Figure 1.3).

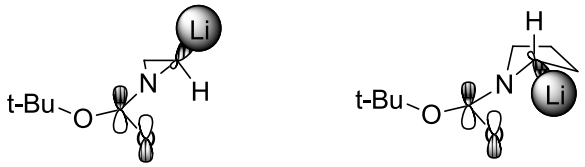
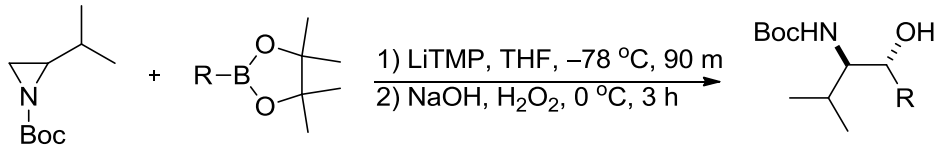


Figure 1.3

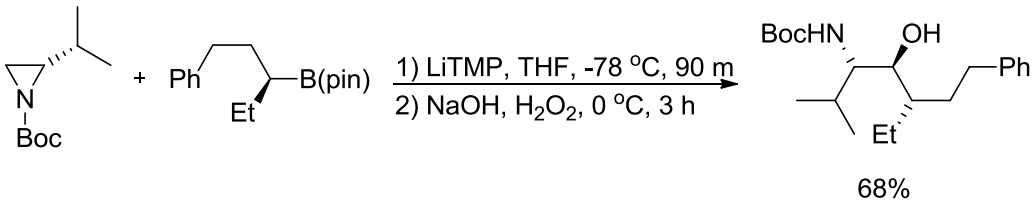
The extra ring strain of *N*-Boc aziridine **22** has been exploited by Aggarwal[46] to stereoselectively gain access to 1,2-amino alcohols (Table 1.4):



Entry	R	Yield (%)
1	Et	76
2	Ph	76
3	CH_2CH_2Ph	73
4	*p*OMeC_6H_4	70

Table 1.4: Lithiation-Boronate Rearrangements of Isopropyl *N*-Boc Aziridine

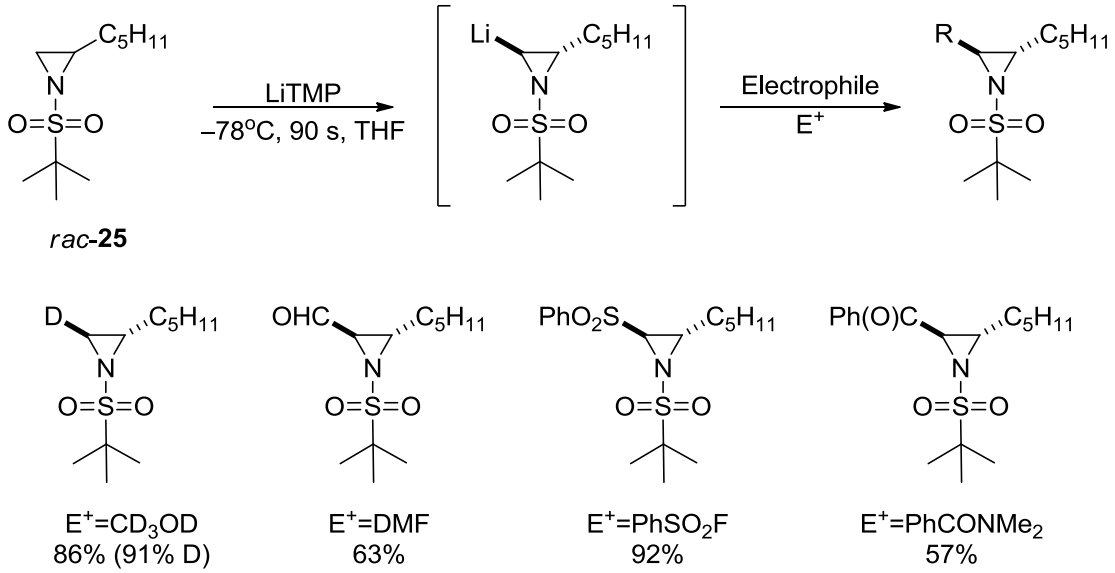
The reaction proceeds diastereoselectively and enantioenriched starting materials retain their original enantioenrichment in the product (Sheme 1.15).



Scheme 1.15

The tendency of the Boc group to migrate largely restricts the applicability of more traditional α-lithiation-substitution chemistry to unreactive electrophiles that can be used for *in situ* trapping *ie.* Me_3SiCl and boronates.

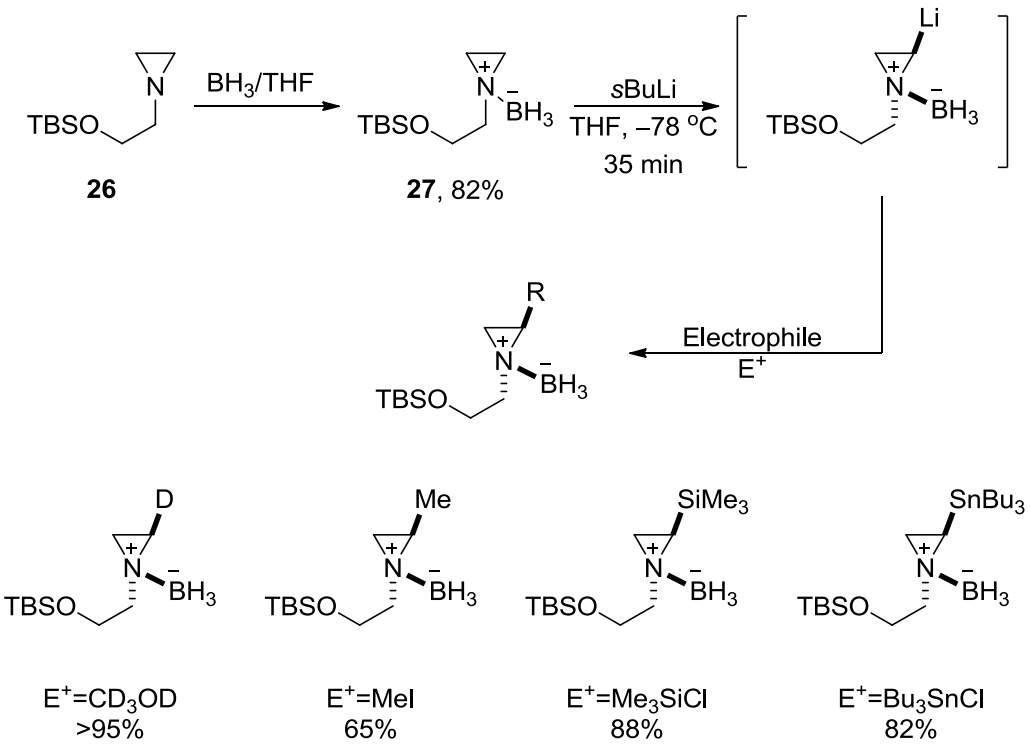
In 2005, Hodgson[49] reported the first successful directed α-lithiation-substitution reaction on racemic aziridine **25** without using utilising an *in situ* electrophilic trap. The Boc group was substituted for a *t*-butyl sulfone directing group, thus avoiding the previously unwanted side reaction of 1,2-migration (Scheme 1.16).



Scheme 1.16

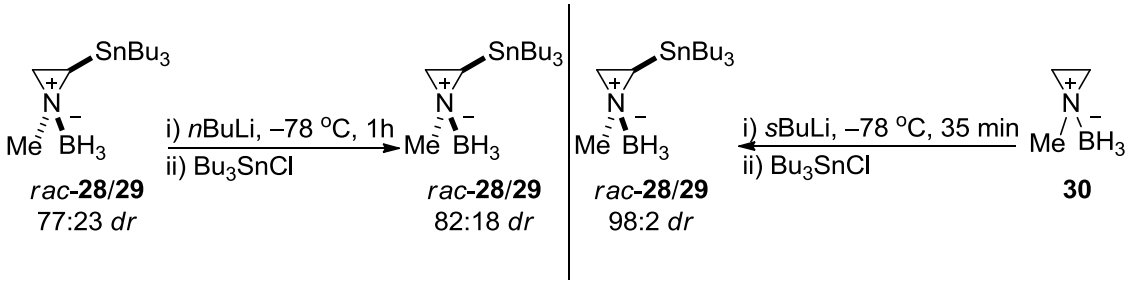
Lithiation is both regioselective and diastereoselective, with the proton *trans* to the alkyl chain being removed and is compatible with a wide range of electrophiles. However, to the best of our knowledge, no asymmetric variant of this reaction has been reported.

In 1997, Vedejs[45] reported the first example of an α-lithiation-substitution reaction on an aziridine without an internal directing group. TBS protected aziridine **26** was treated with borane to give the stable aziridine-borane complex **27** which could then be lithiated with *s*BuLi and trapped with a variety of electrophiles (Scheme 1.17).



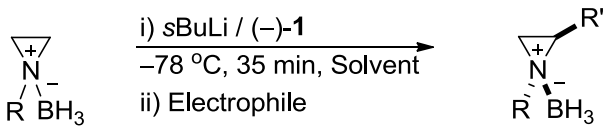
Scheme 1.17

Lithiation occurs *syn* to the boron, although it is likely that this is purely down to sterics, rather than any directing effect from the boron. Crucially, Vedejs demonstrated that the lithiated intermediate is configurationally stable at –78 °C. Tin-lithium exchange on a 77:23 diastereomeric mixture of stannanes *rac*-**28** and *rac*-**29**, followed by trapping with Bu_3SnCl gave re-formed stannanes *rac*-**28** and *rac*-**29** in a largely unchanged 82:18 diastereomeric ratio (Scheme 1.18). When aziridine **30** was lithiated and trapped with Bu_3SnCl, stannanes *rac*-**28** and *rac*-**29** were formed in a 98:2 diasteremeric ratio (Scheme 1.18). The results imply that diastereoselectivity is not due to a resolution of the 2-lithio borane-aziridine, otherwise both experiments would have given an identical diastereomeric ratio.



Scheme 1.18

In 2002, Vedejs[50] reported the first asymmetric α-lithiation substitution reaction on a veriety of aziridine-boranes. The use of (–)-sparteine (–)-**1** as the chiral diamine gave access to 2-substituted aziridines in a consistent *er* of approximately 85:15, although the absolute configuration of the products was not assigned (Table 1.5).



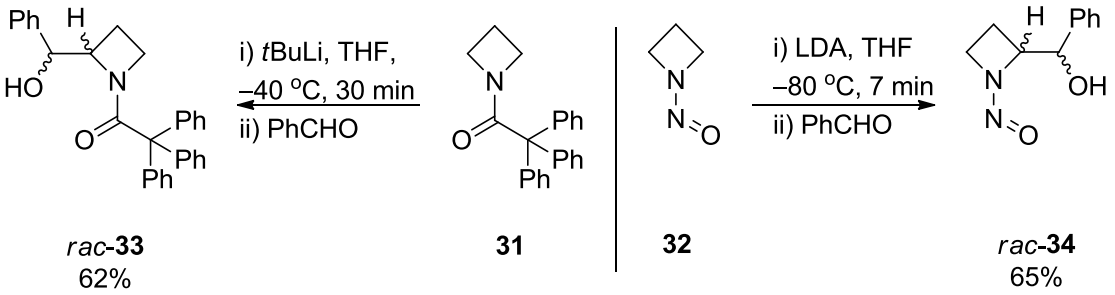
Entry	R	Electrophile	R'	Solvent	Yield	*er*
1	$(CH_2)_2OTBS$	$PhMe_2SiCl$	$PhMe_2Si$	Et_2O	67%	84:16
2	$(CH_2)_2OTBS$	Ph_2CO	$C(OH)Ph_2$	Et_2O	78%	86:14
3	$(CH_2)_2OTr$	Ph_2CO	$C(OH)Ph_2$	PhMe	8%	84:16
4	CH_3	Ph_2CO	$C(OH)Ph_2$	PhMe	65%	85:15

a) Product was isolated as the tertiary amine after treatment with EtOH-CH_2Cl_2

Table 1.5: (–)-**1** Mediated Lithiation-Trapping of Borane-Aziridine Complexes

1.2.4 α-Lithiation-Substitution of 4-Membered Nitrogen Containing Heterocycles

In contrast with 3-,5- and 6-membered rings, lithiation-trapping of the corresponding 4-membered rings, azetidines, has not been as widely explored. Prior to 2010, the only known examples of successful lithiation on an azetidine were reported by Seebach[51, 52] in 1977 and 1981. Azetidines **31** and **32** were lithiated with *t*BuLi and LDA, respectively, and then trapped with benzaldehyde to give product alcohols *rac*-**33** and *rac*-**34** in 62% and 65% yield (Scheme 1.19). The relative stereochemistry of *rac*-**33** and *rac*-**34** was not proven and the diastereoselectivity was not mentioned in either instance. The harsh conditions required to lithiate triphenyl acyl azetidine **31** also mean it is unclear as to whether the carbonyl group acts as a true directing group in the deprotonation step, or whether it is simply due to the electron withdrawing effect of the nitrogen atom.



rac-**33**
62%

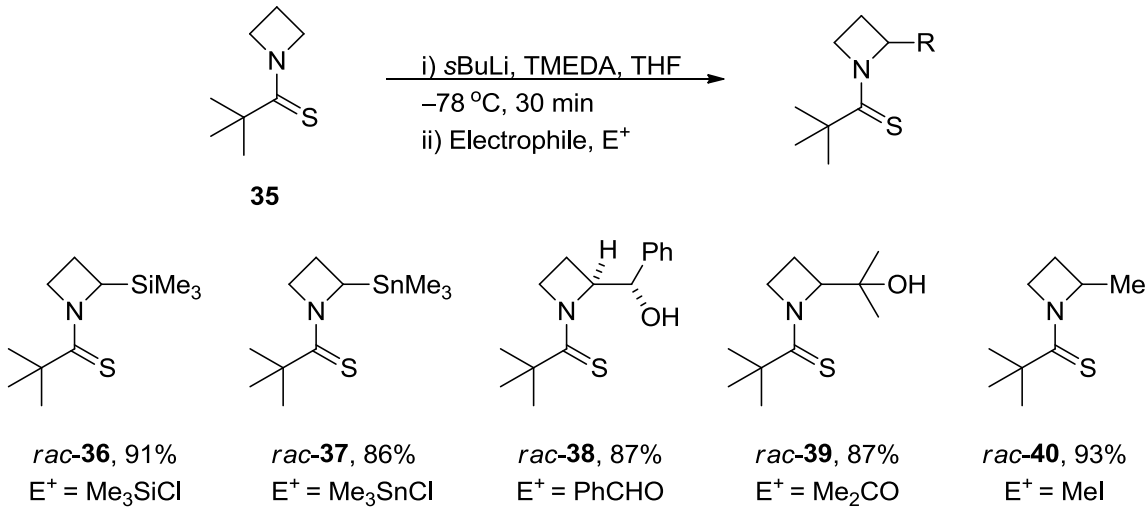
31

32

rac-**34**
65%

Scheme 1.19

More recently, Hodgson[20] reported the first examples of the successful α-lithiation-substitution reaction on azetidine **35** (Scheme 1.20).



35

rac-**36**, 91%
$E^+ = Me_3SiCl$

rac-**37**, 86%
$E^+ = Me_3SnCl$

rac-**38**, 87%
E^+ = PhCHO

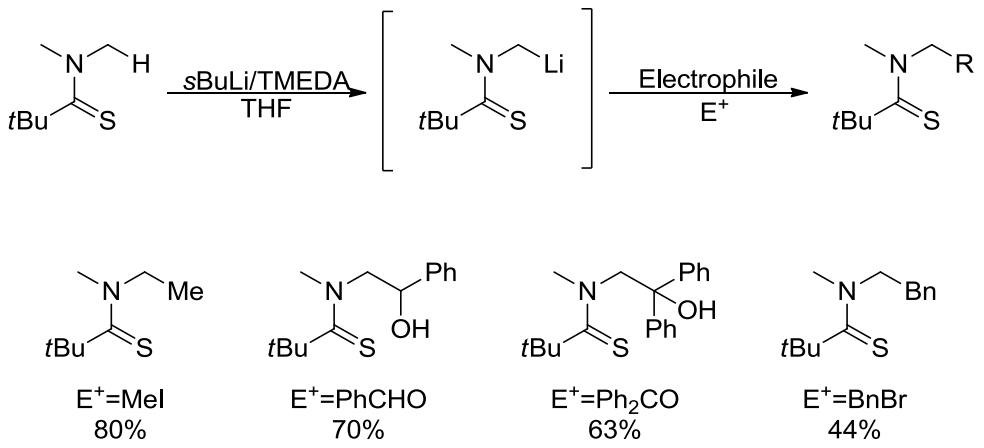
rac-**39**, 87%
$E^+ = Me_2CO$

rac-**40**, 93%
E^+ = MeI

Scheme 1.20

Yields were good with all the electrophiles tested. Interestingly, using benzaldehyde as the electrophile, Hodgson reported that *rac*-**38** was formed as a single diastereoisomer.

Of greater note is that the use of Boc, SO*t*Bu, SO_2*t*Bu and $PO(OEt)_2$ as directing groups either led to decomposition, only partial lithiation or no observable lithiation. Of the protecting groups tested, only the thiopivalamide, first reported by Seebach[53] in 1976 (Scheme 1.21), allowed complete lithiation to occur at the α position.



Scheme 1.21

Use of the thioamide directing group may allow facile deprotonation due to both the longer C=S bond length relative to the C=O bond length and the larger, more diffuse sp^2 p-orbitals containing the lone pairs on the sulfur atom (Figure 1.4). This may allow the reactive carbon centre of *s*BuLi to come into closer proximity to the α-protons and permit efficient deprotonation.[54, 55]

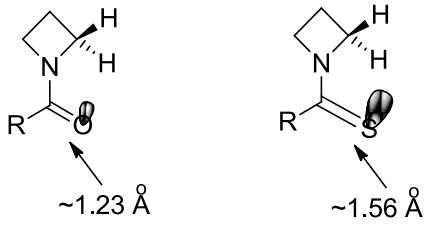
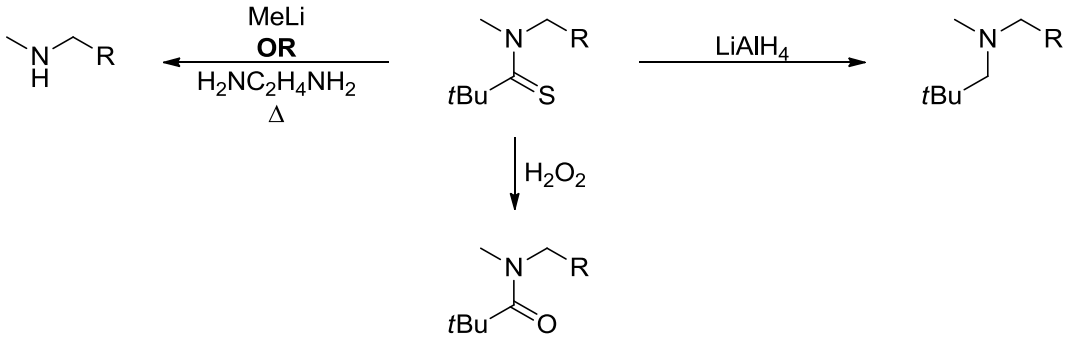


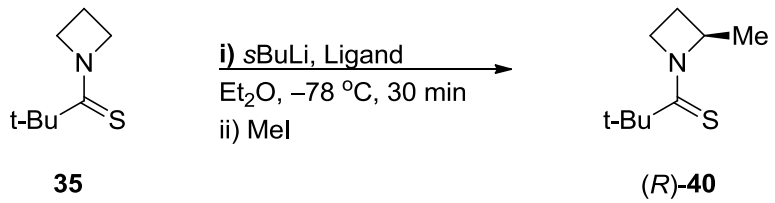
Figure 1.4

The thioamide group is less synthetically useful than the Boc group. However, some useful transformations are possible (Scheme 1.22). For example, the thioamide can be removed with MeLi or refluxing ethylenediamine, oxidised to the corresponding amide using hydrogen peroxide or desulfurised by treatment with $LiAlH_4$.

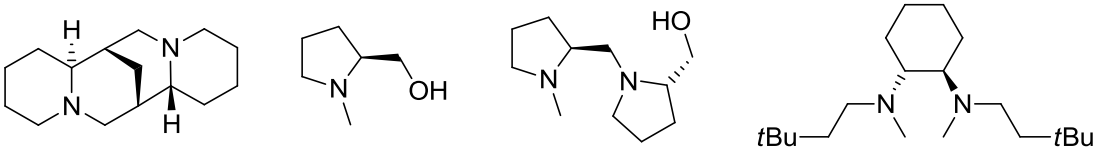


Scheme 1.22

Hodgson also reported the first example of an asymmetric α-lithiation substitution of *N*-thiopivaloyl azetidine **35** (Table 1.6). Of the four ligands tested, (*R*,*R*)-**12** gave the highest enantioselectivity, forming methylated (*R*)-**40** in an 80:20 enantiomeric ratio (Table 1.6, entry 4). The results were intriguing. For example, (–)-**1** which works well with *N*-Boc heterocycles gave low enantioselectivities and no explanation was offered on the mechanism of enantioinduction.



35 (*R*)-**40**

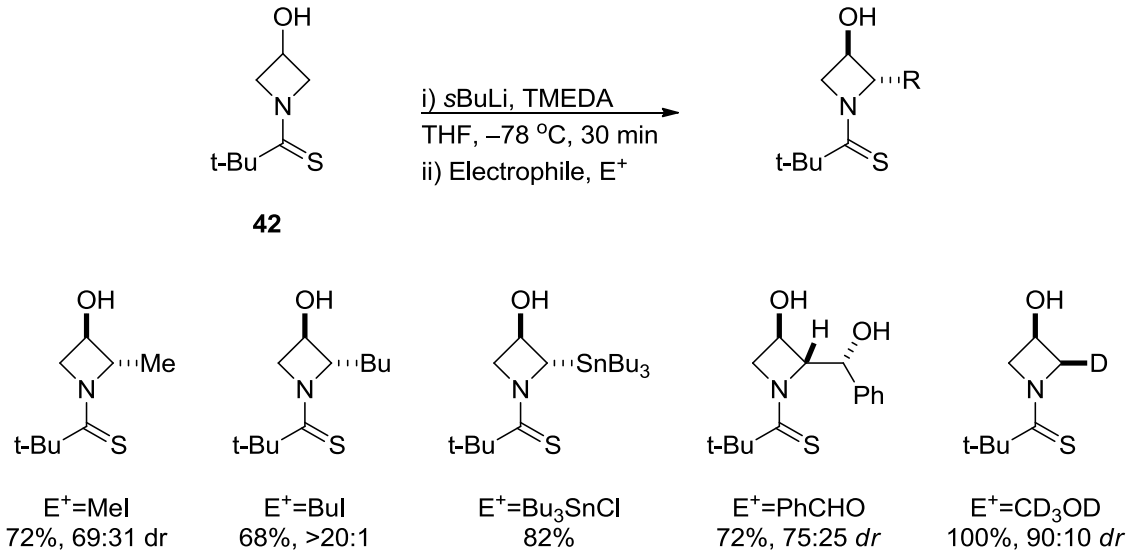


(–)-**1** (*S*)-**41** (*S*,*S*)-**16** (*R*,*R*)-**12**

Entry	Ligand	Conversion	er (*R*:*S*)
1	(–)-**1**	99%	61:39
2	(*S*)-**41**	0%	N/A
3	(*S*,*S*)-**16**	78%	37:63
4	(*R*,*R*)-**12**	96% (isolated)	80:20

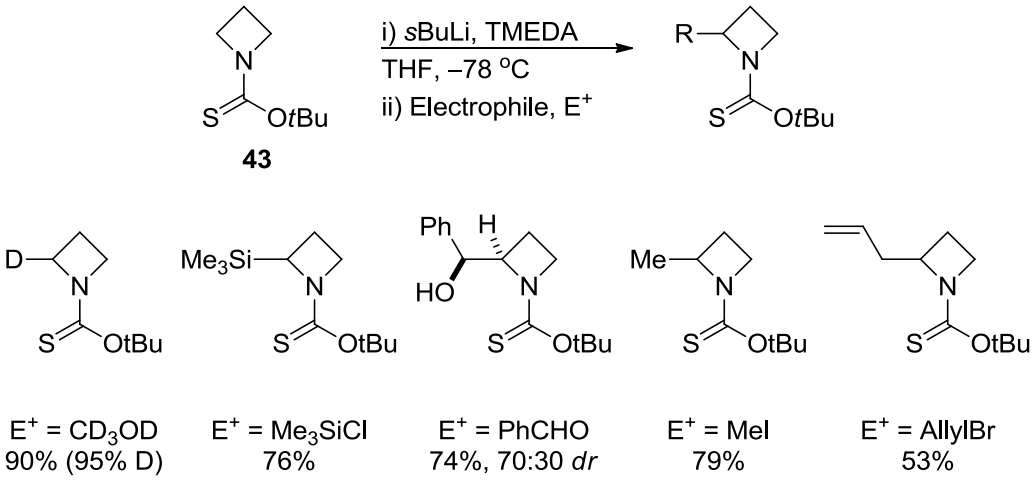
Table 1.6: Optimisation of the Asymmetric Lithiation-Trapping of **35**

Hodgson[56] has also utilised the thiopivaloyl moiety to lithiate azetidinol **42**, under similar conditions used to lithiate **35** (scheme 1.23). For all except deuterium, the electrophile takes the *trans*-position to the hydroxyl group.



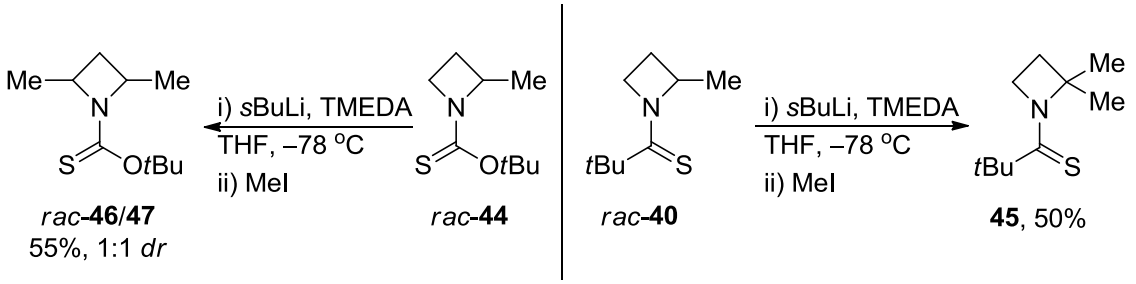
Scheme 1.23

More recently, Hodgson[57] has also reported the use of the *t*-butoxythiocarbonyl group (Botc) to direct lithiation to the α-position of azetidine (Scheme 1.24).



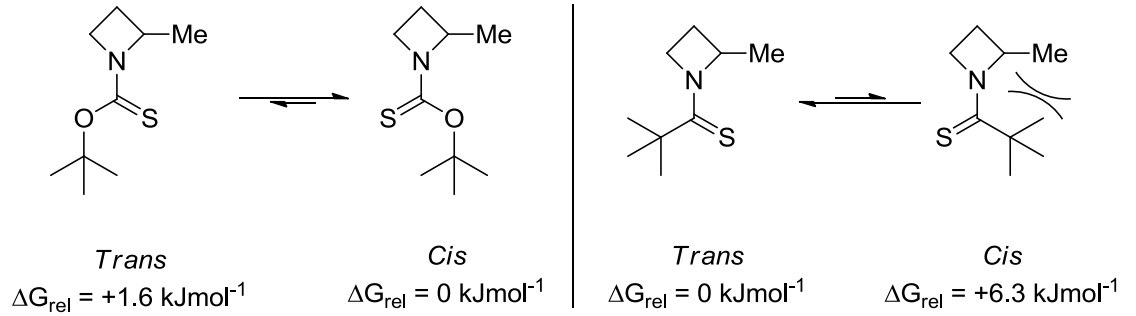
Scheme 1.24

An interesting difference in regioselectivity between thiopivalamide and Botc was observed with methylated azetidines **40** and **44** (Scheme 1.25).[58] Lithiation-trapping of azetidine **40** gives rise to *gem*-dimethyl compound **45**, whereas the analogous reaction on azetidine **44** gives rise to the 2,4-dimethyl compounds *rac*-**46** and *rac*-**47**.



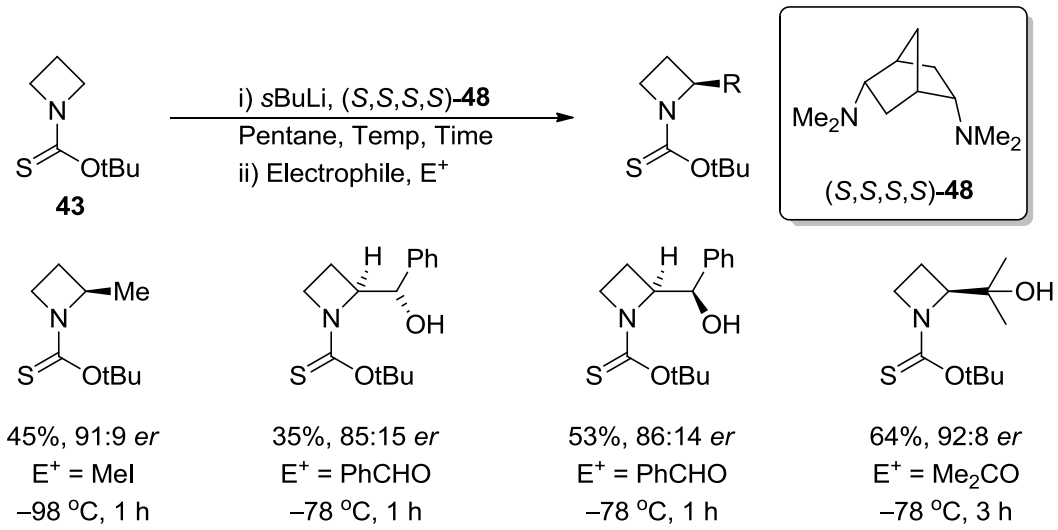
Scheme 1.25

For **40**, the disfavourable steric interaction between the *t*-butyl and methyl groups would be an obvious explanation as to why the *trans* rotamer is favoured (Scheme 1.26). For **44**, the additional C-O bond increases the distance between the *t*-butyl and methyl groups and would thus decrease the disfavourable interaction, although why the *cis* isomer itself is favoured is unclear.



Scheme 1.26

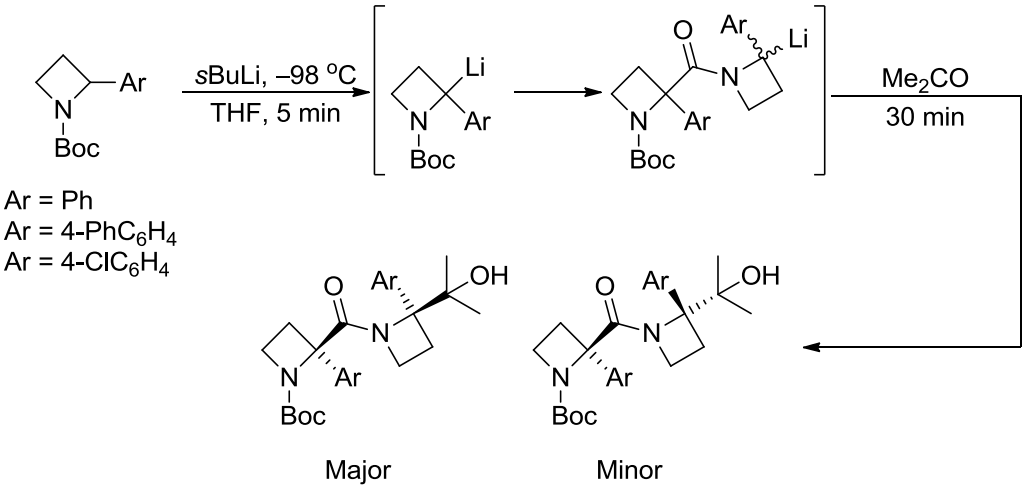
As with azetidine **35**, **43** proved amenable to asymmetric lithiation-trapping with diamine (*S*,*S*,*S*,*S*)-**48**, another diamine initially developed by Alexakis[59] in 2012, proving to be the best ligand, with a maximum *er* of 92:8 obtained with acetone as the electrophile (Scheme 1.27).



Scheme 1.27

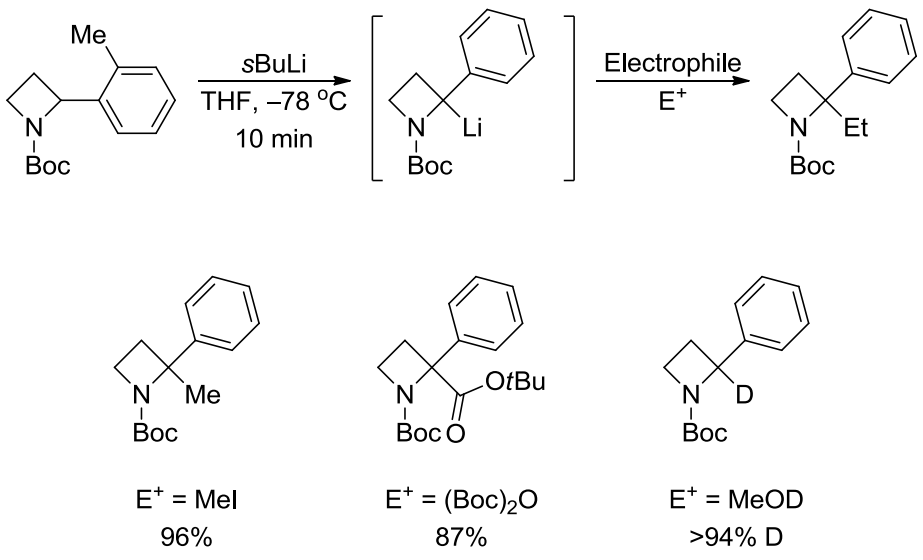
Although Hodgson has reported the first asymmetric α-lithiation-substitution reactions on **35** and **43**, no explanation was offered as to how enantioinduction occurs.

Recently, Luisi[60] investigated the behaviour of various lithiated 2-aryl-*N*-Boc azetidines (Table 1.7). Given that *N*-Boc azetidine was previously proven to be resistant to lithiation by Hodgson, the aromatic ring must therefore significantly acidify the α-hydrogens, most likely *via* delocalisation of the negative charge into the aromatic ring. Treatment of a variety of 4-substituted aromatic *N*-Boc azetidines with *s*BuLi and trapping with acetone gave the self-addition products shown below in Table 1.7. Interestingly, when *ortho*-tolyl-*N*-Boc azetidine was lithiated, the corresponding self addition products were not observed (Scheme 1.28).



Entry	Ar	Yield (%)	*dr*
1	Ph	75	70:30
2	4-PhC_6H_4	78	75:25
3	4-ClC_6H_4	80	70:30

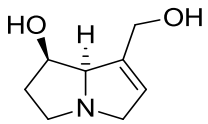
Table 1.7: Results of Self-Addition Reactions of 2-Aryl *N*-Boc Azetidines



Scheme 1.28

1.3 Project Outline

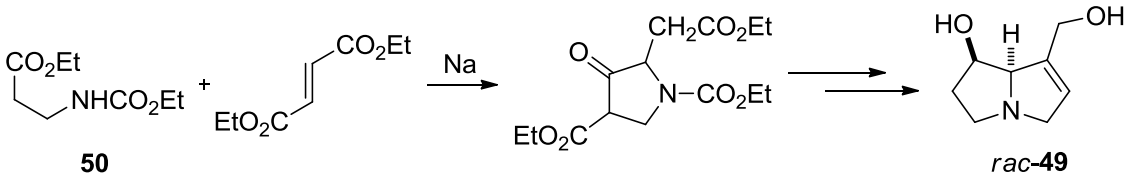
The starting point in this project was the development of an effective lithiation-trapping based synthetic route for the total synthesis of (+)-retronecine (+)-**49** (Figure 1.5), a hepatotoxic pyrrolizidine alkaloid found in *Jacobaea vulgaris*.[61]



(+)-**49**

Figure 1.5

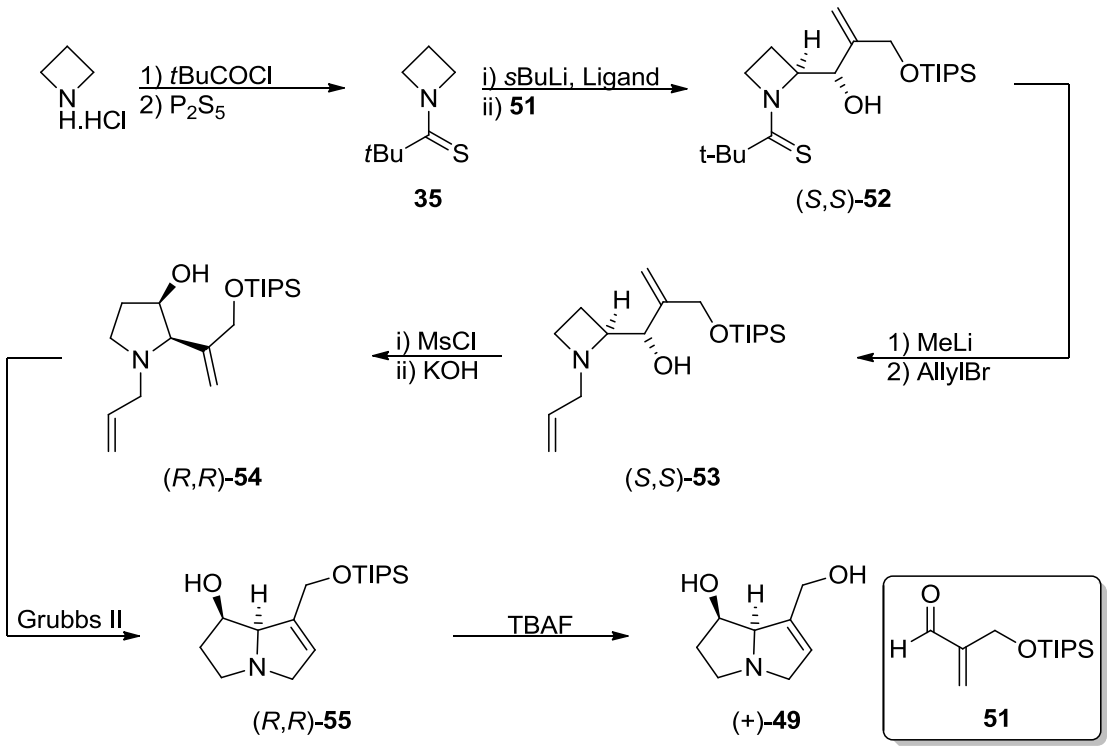
The earliest total synthesis of racemic retronecine was reported in 1962 by Geissman.[62] Starting from carbamate-ester **50**, racemic retronecine was synthesised 0.91% yield and 12 steps (Scheme 1.29).



50 *rac*-**49**

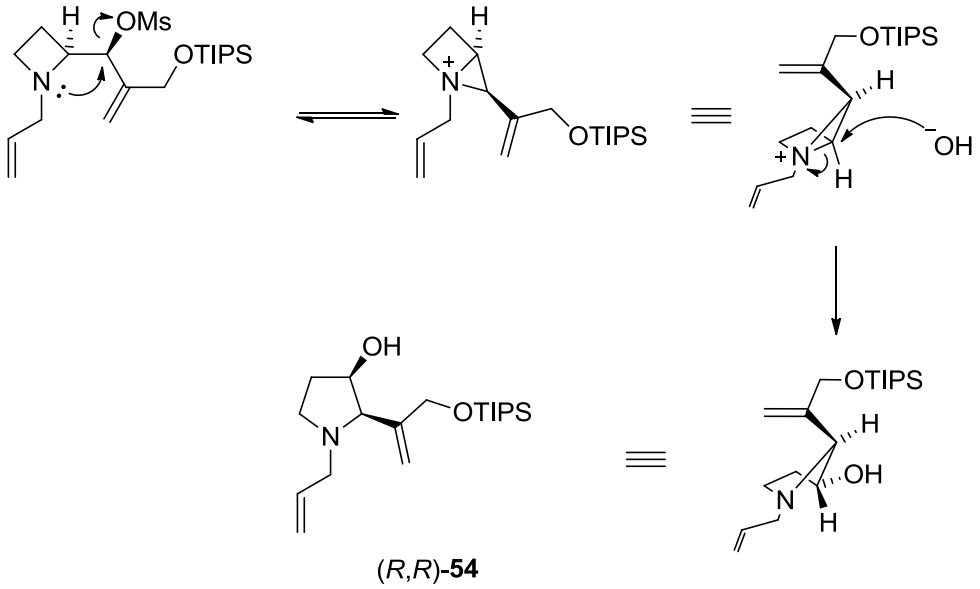
Scheme 1.29

Although (+)-retronecine has been successfully synthesised asymmetrically in several syntheses,[63-68] our proposed synthesis would be only eight steps, comparing favourably to the most recent synthesis by Roche who synthesised (+)-retronecine in 13 steps. Our proposed synthesis would synthesise azetidine **35** by a two step acylation-thiolation reported by Hodgson.[20] This would be followed by an asymmetric lithiation-trapping using an aldehyde such as **51** as the electrophile. If azetidine **35** behaves in a similar manner to *N*-Boc pyrrolidine **7** or *N*-Boc piperidine **17**, then the (+)-sparteine surrogate (+)–**13** should give the product with the correct configuration. Hodgson also reported that when benzaldehyde was used as electrophile, the reaction was completely diastereoselective in favour of the *syn* diastereoisomer **38**. Our proposed synthesis would make use of this diastereoselectivity to control two stereocentres in one step to form (*S*,*S*)-**52** (Scheme 1.30).



Scheme 1.30

From then, methyllithium-mediated deprotection would be followed by alkylation with allyl bromide to give azetidine (*S*,*S*)-**53**, then mesylation and ring expansion would be carried out to give pyrrolidine (*R*,*R*)-**54**. This reaction proceeds by initial mesylation of the alcohol, followed by an intramolecular nucleophilic substitution of the mesylate by the nitrogen lone pair, generating a transient aziridinium species.[69] This would then be ring opened in another nucleophilic substitution reaction with a hydroxide anion to generate the product pyrrolidine (Scheme 1.31). Ring closing metathesis and fluoride deprotection should finally afford (+)-retronecine (+)-**49** in eight linear steps.



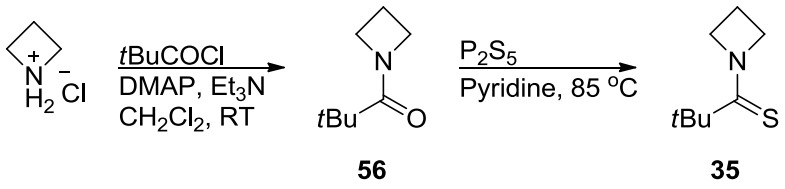
(*R*,*R*)-**54**

Scheme 1.31

In order to carry out an effective synthesis of (+)-retronecine, several mechanistic aspects of the asymmetric α-lithiation-trapping of *N*-thiopivaloyl azetidine **35** needed to be explored. Chapter 1.4 will explore racemic lithiation-trapping of *N*-thiopivaloyl azetidine and the unexpected reactivity of the lithiated intermediate. Chapter 1.5 will then explore the mechanism of asymmetric induction to determine whether enantioinduction occurs *via* an enantioselective deprotonation or a dynamic resolution.

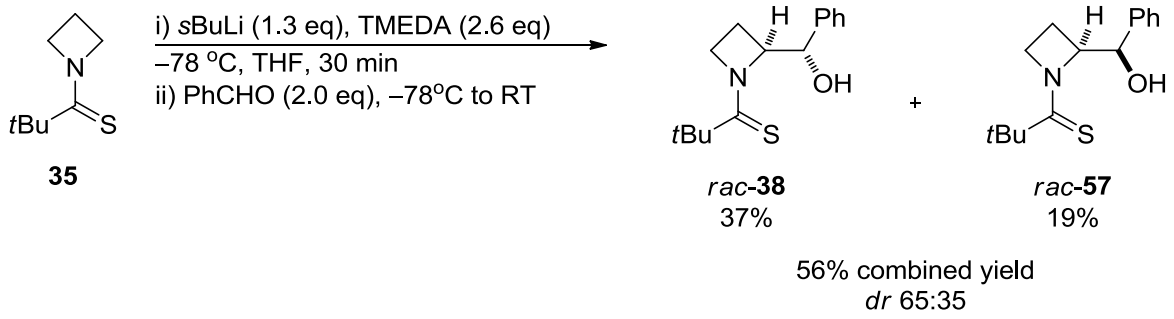
1.4 Racemic Lithiation-Substitution Reactions

To begin with, azetidine thiopivalamide **35** was prepared from azetidine hydrochloride according to the procedure reported by Hodgson.[20] The two-step acylation-thiolation reaction sequence afforded *N*-thiopivaloyl azetidine **35** in an overall yield of 77% (Scheme 1.32). Both the intermediate amide **56** and the thioamide **35** could be purified by vacuum distillation and the reaction sequence worked reliably on a multi-gram scale.



Scheme 1.32

With our ultimate goal being a total synthesis of (+)-retronecine (+)-**49**, understanding the behaviour of the azetidine lithiation-trapping reaction was important, especially for acrolein-type electrophiles which had not been explored previously. Therefore, our first α-lithiation substitution reactions on thioamide **35** were carried out under racemic conditions using *s*BuLi and TMEDA as diamine and benzaldehyde as the electrophilic trapping partner. This was done to explore comparability with Hodgson's results and to gain familiarity with this chemistry. Thus lithiation-substitution with benzaldehyde as electrophile gave a 65:35 mixture of diastereomeric alcohols *syn*-**38** and *anti*-**57** by (^{1}H NMR spectroscopy of the crude reaction mixture). They were readily separated by flash column chromatography to give *syn*-**38** in 37% yield and *anti*-**57** in 19% yield (Scheme 1.33).



Scheme 1.33

The identity and relative stereochemistry of *syn*-**38** and *anti*-**57** were confirmed by X-ray diffraction on a suitable single crystal of each diastereoisomer (Figure 1.6).

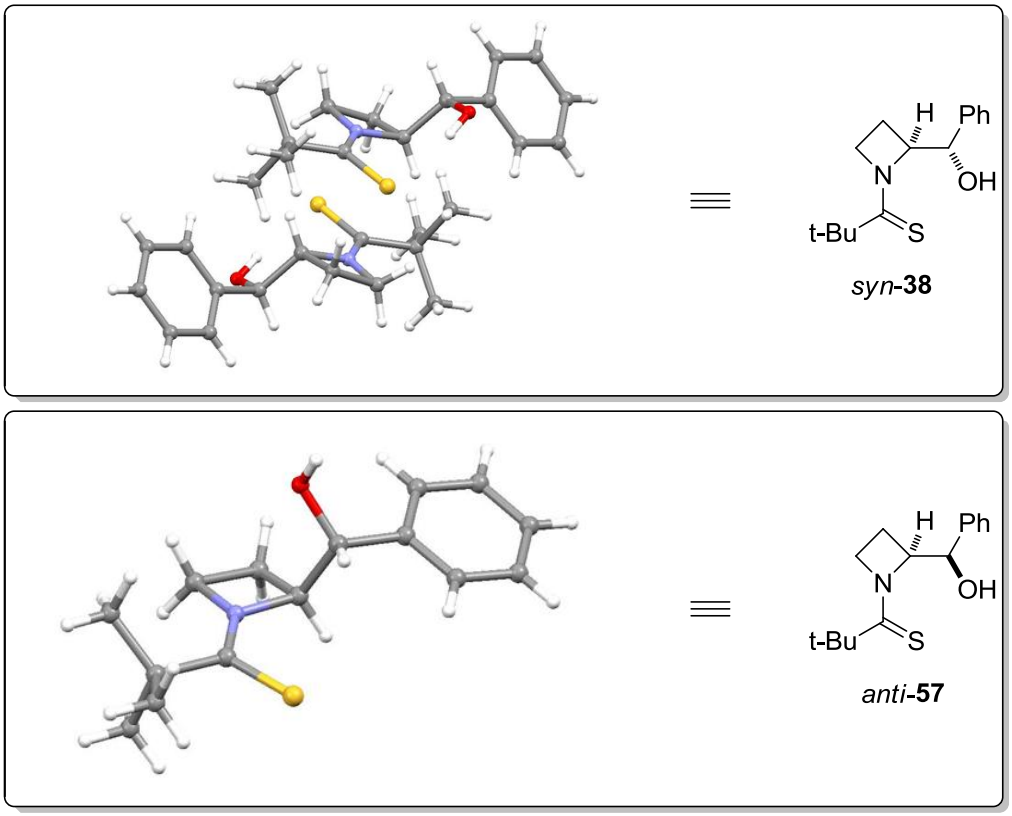
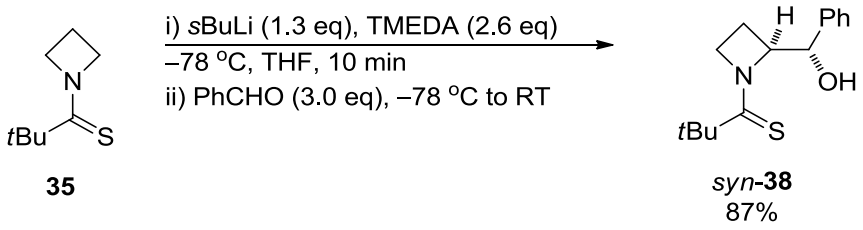


Figure 1.6

Interestingly, Hodgson reported this reaction as being completely diastereoselective for the alcohol *syn*-**38** (Scheme 1.34).

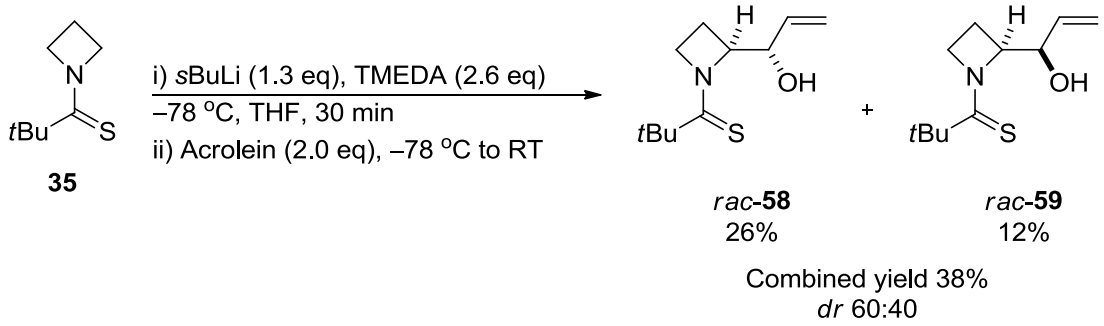


Scheme 1.34

However, in our hands, *anti*-**58** was always observed, even after multiple repeats of the experiment. Upon closer inspection of the supporting information of Hodgson's paper, it is clear that *anti*-**58** was present in the ^{1}H NMR spectrum of *syn*-**38**. Yields of the reaction in our hands were also noticeably lower than that reported by Hodgson.

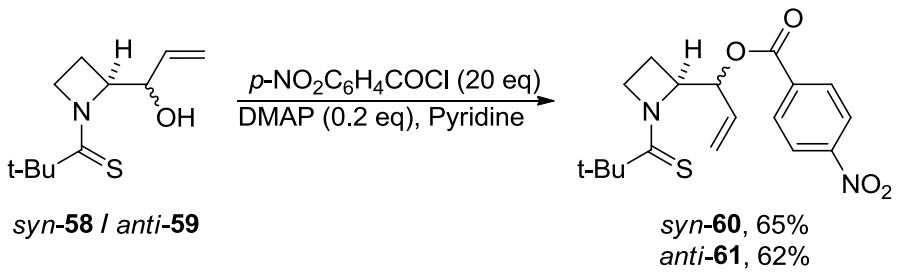
Although the major diastereoisomer (*syn*-**38**) was the same, the presence of the minor diastereoisomer (*anti*-**58**), coupled with the lower than anticipated yields led to a need to develop more robust synthetic methodology before attempting reactions with

protected aldehyde **51** as needed for the total synthesis of (+)-retronecine (+)-**49**. Acrolein possesses both aldehyde and alkene functionality, but is commercially available and would serve as a reasonable model substrate *in lieu* of aldehyde **51**. Thus azetidine thiopivalamide **35** was subjected to α-lithiation-substitution using acrolein as the electrophile (Scheme 1.35).

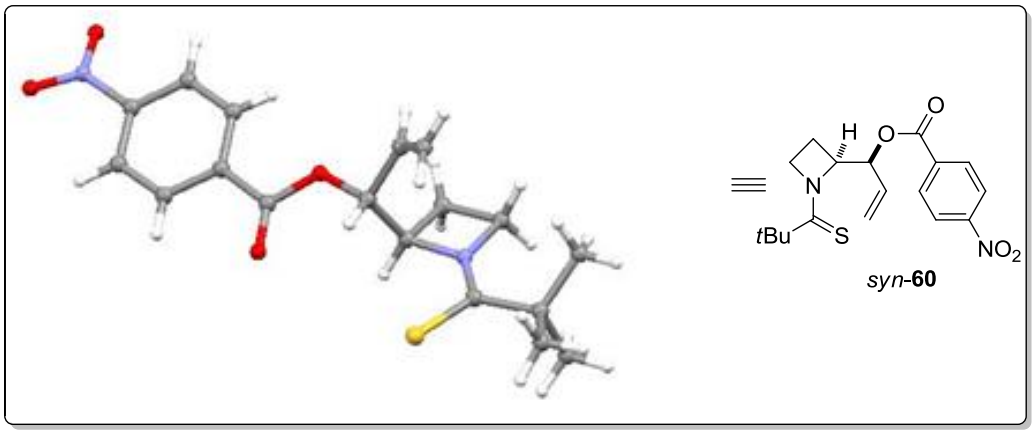


Scheme 1.35

Diastereomeric alcohols *syn*-**58** and *anti*-**59** were formed in a 60:40 diastereomeric ratio (by ^{1}H NMR of the crude reaction mixture) in a disappointing 38% combined yield. The relative stereochemistry of each alcohol was determined by separately acylating each alcohol with *para*-nitrobenzoyl chloride to form the solid *para*-nitrobenzoate esters, then crystallising and subjecting each to X-ray diffraction (Scheme 1.36). The X-ray crystal structures are shown below in Figure 1.7.



Scheme 1.36



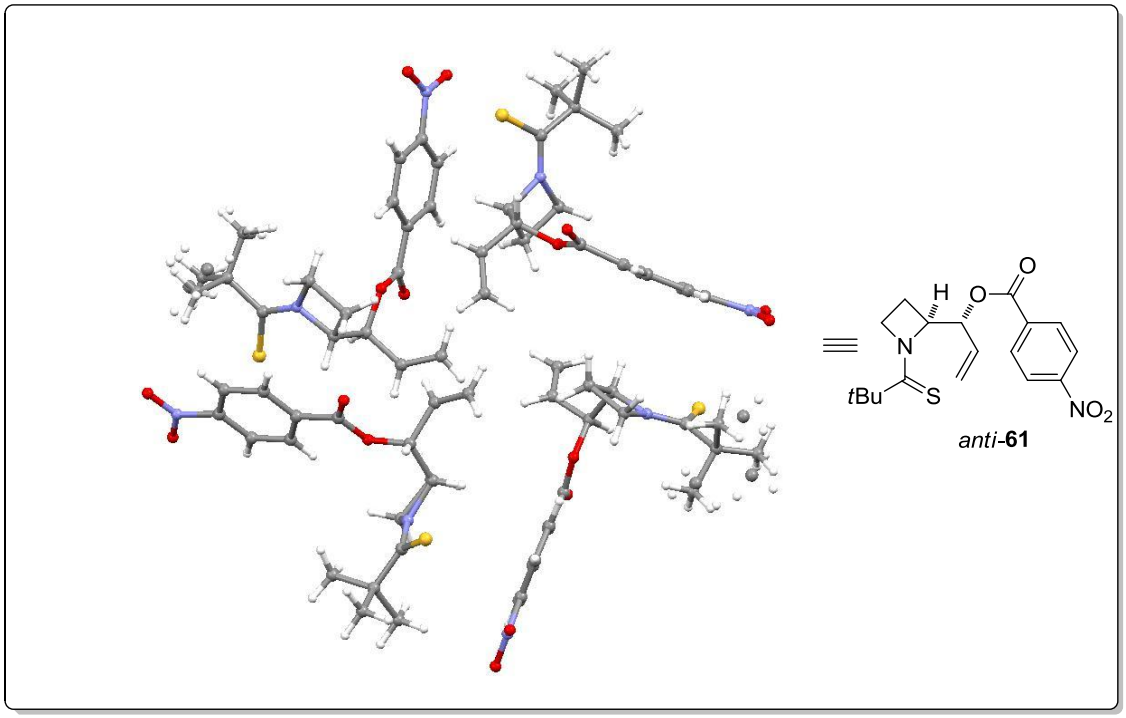
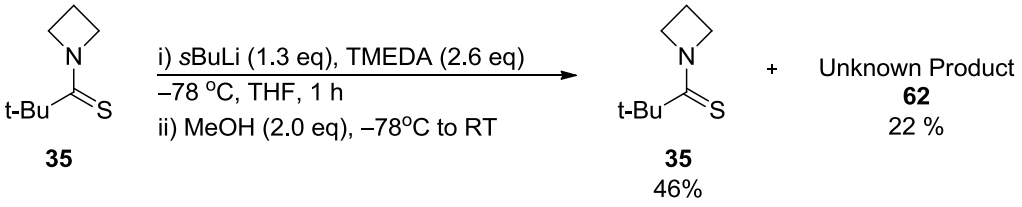


Figure 1.7

Given that neither benzaldehyde nor acrolein possess enolisable protons, it was envisaged that the cause of the low yields would not be due to the trapping step, but rather due to instability of the lithiated intermediate. Hence, we focused our attention on the lithiation step of the reaction and investigated whether or not lithiated azetidine **35** was stable under the reaction conditions.

Thus, azetidine **35** was lithiated at –78 °C in THF, allowed to stir for 1 h and then quenched with methanol (Scheme 1.37). Ideally, **35** should lithiate cleanly to give the lithiated azetidine. If the organolithium is stable, then starting material **35** should be recovered in quantitative yield upon addition of MeOH.



Scheme 1.37

From this experiment, thioamide **35** was recovered in only 46% yield, along with a significant quantity of an unknown product **62**. Based on a HRMS *m/z* value of 258.1345 for the $(M+H)^+$ peak for the unknown product, we calculated a 22% yield. It is also worth noting, that there is still 32% of material that was unaccounted for during this reaction, implying that there is an unknown deleterious reaction pathway.

Unfortunately, we have not been able to definitively confirm the structure of the unknown product **62**. It is useful however, to present the analytical data here and our speculations. The ^{1}H NMR, ^{13}C NMR and DEPT spectra and accompanying data are shown in Figures 1.8, 1.9 and 1.10.

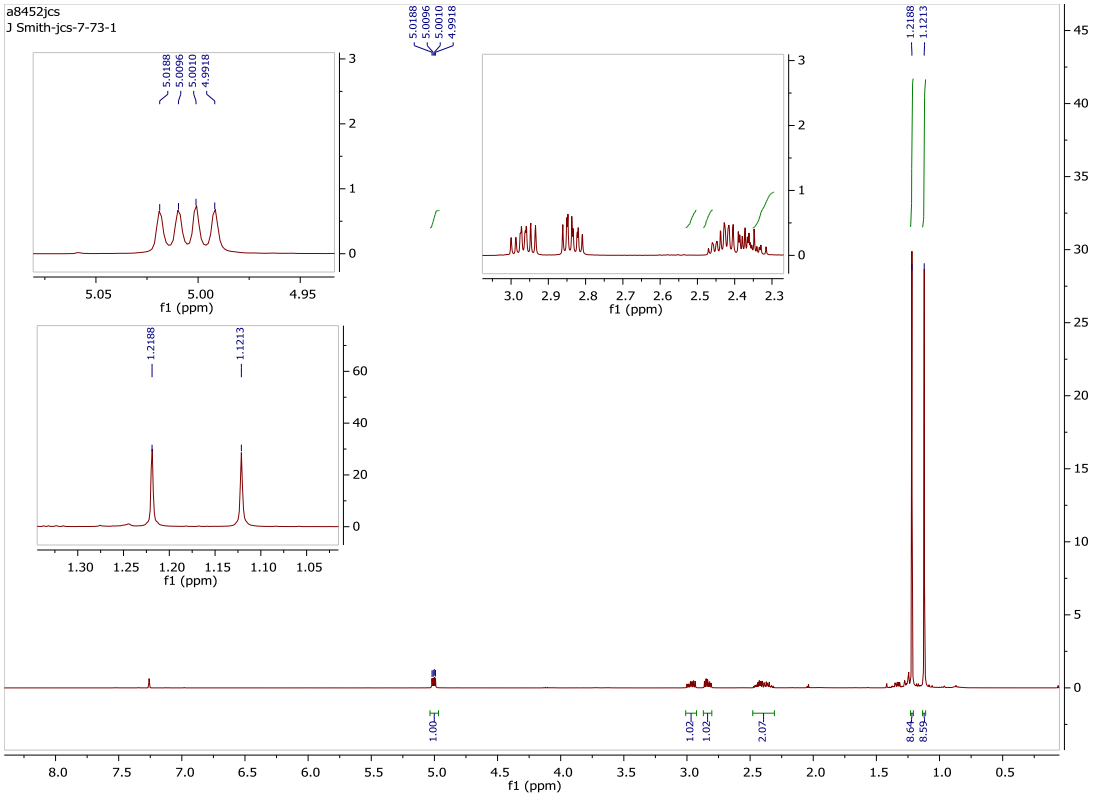


Figure 1.8

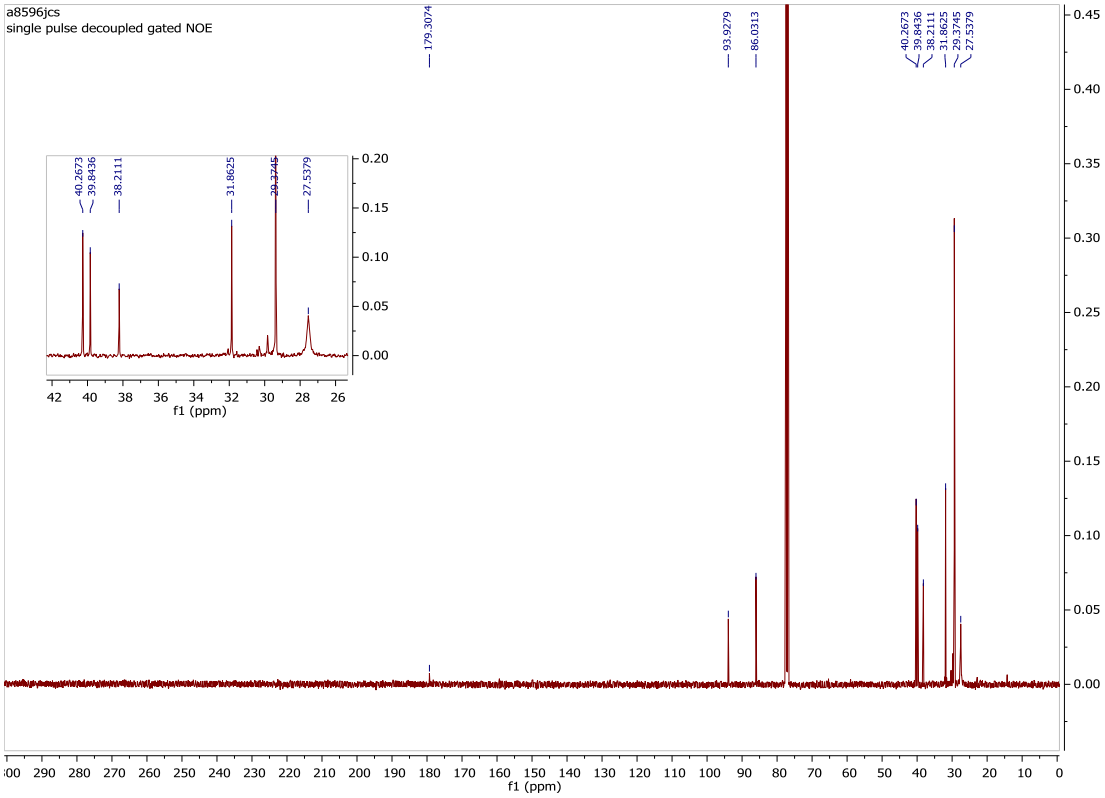


Figure 1.9

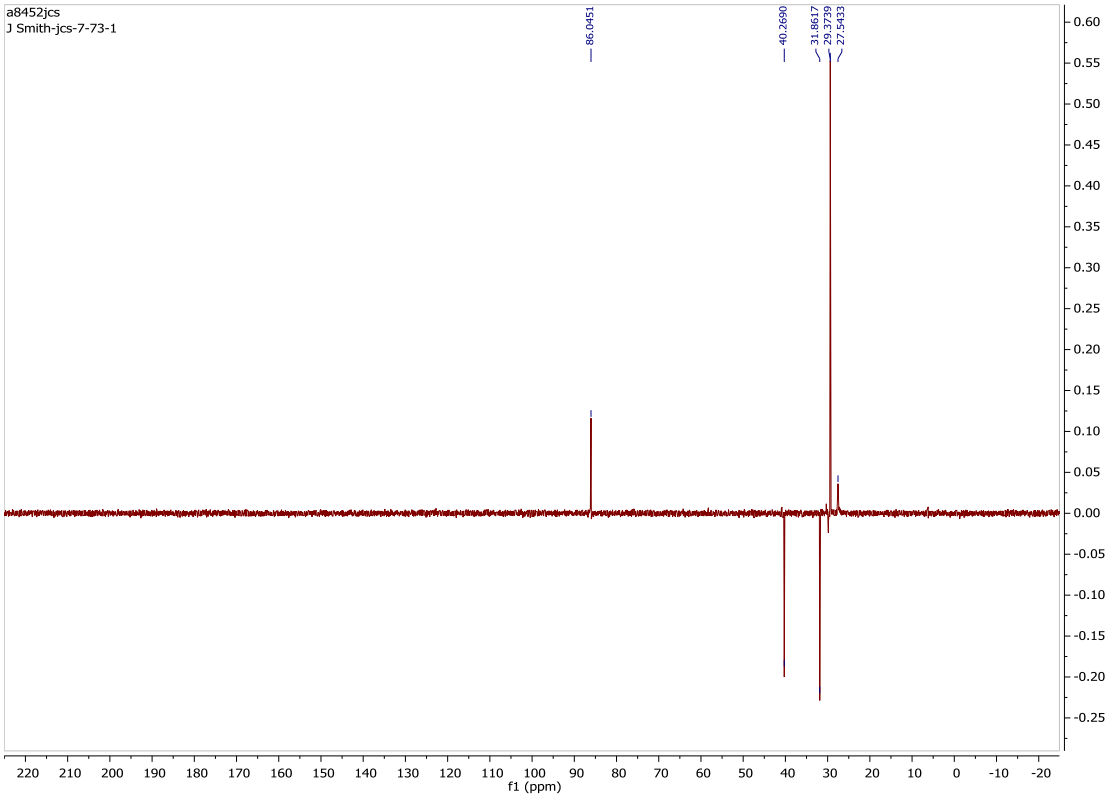


Figure 1.10

Data for unknown product **62**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (dd, J = 7.0, 3.5 Hz, 1H), 2.97 (ddd, J = 11.0, 10.0, 5.0 Hz, 1H), 2.87–2.81 (m, 1H), 2.48–2.31 (m, 2H), 1.22 (s, 9H), 1.12 (s, 9H)

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 179.2, 93.9, 86.0, 40.3, 39.8, 38.2, 31.9, 29.4, 27.5

From the data, the presence of two *t*-butyl groups was clearly seen, each signal in the ^{1}H NMR spectrum integrating for 9H. The presence of the azetidine ring hydrogens, integrating to a total of 5H, is also clearly observed. Initially, we believed this unknown product **62** to be self-addition product **63** (Figure 1.11), akin to what has also been independently observed by Luisi.[60]

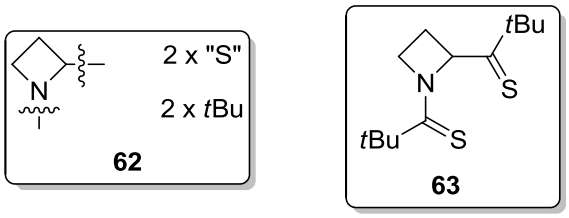
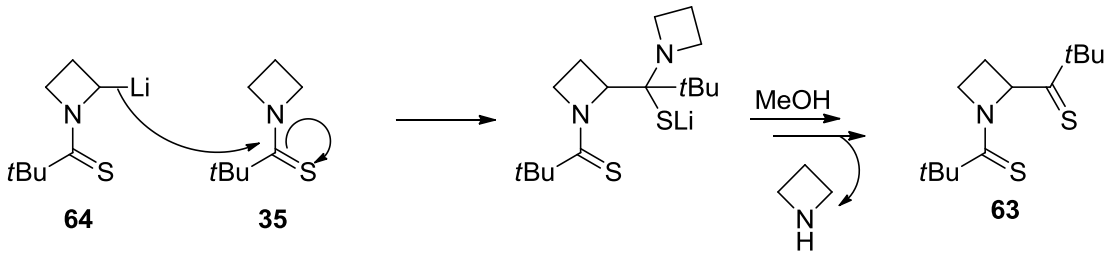


Figure 1.11

We believed that this self-addition product would be formed by attack of lithiated azetidine **64** on unlithiated starting material, followed by collapse of the tetrahedral intermediate upon quenching, expelling a molecule of azetidine and forming self-addition product **63** (Scheme 1.38).



Scheme 1.38

As previously stated, HRMS gave an *m/z* value of 258.1354, as expected for self-addition product **63** and therefore appeared to confirm our initial assignment. However, the ^{13}C NMR spectrum showed the absence of both C=S groups. Thioketones are known to have higher ^{13}C chemical shifts when compared to ketones, typically in the region of 220-280 ppm.[70-72] Thioamides also have higher chemical shifts relative to

amides,[70, 73] the starting azetidine **35** has a ^{13}C chemical shift of 210 ppm, by way of example. However, even when **62** was subjected to wide ^{13}C NMR spectroscopy, scanning between 0-300 ppm, the thioketone and the thioamide peaks were not observed. Also worth noting, is that the methyl carbons in the *t*Bu group responsible for the signal at 27.5 ppm in the ^{13}C NMR spectrum is uncharacteristically broad. Single-bond HMQC NMR experiments confirmed however that this broad peak was indeed caused by the methyl carbon atoms in the *t*Bu group coupling to the methyl hydrogens at δ 1.12 ppm in the ^{1}H NMR (Figure 1.12).

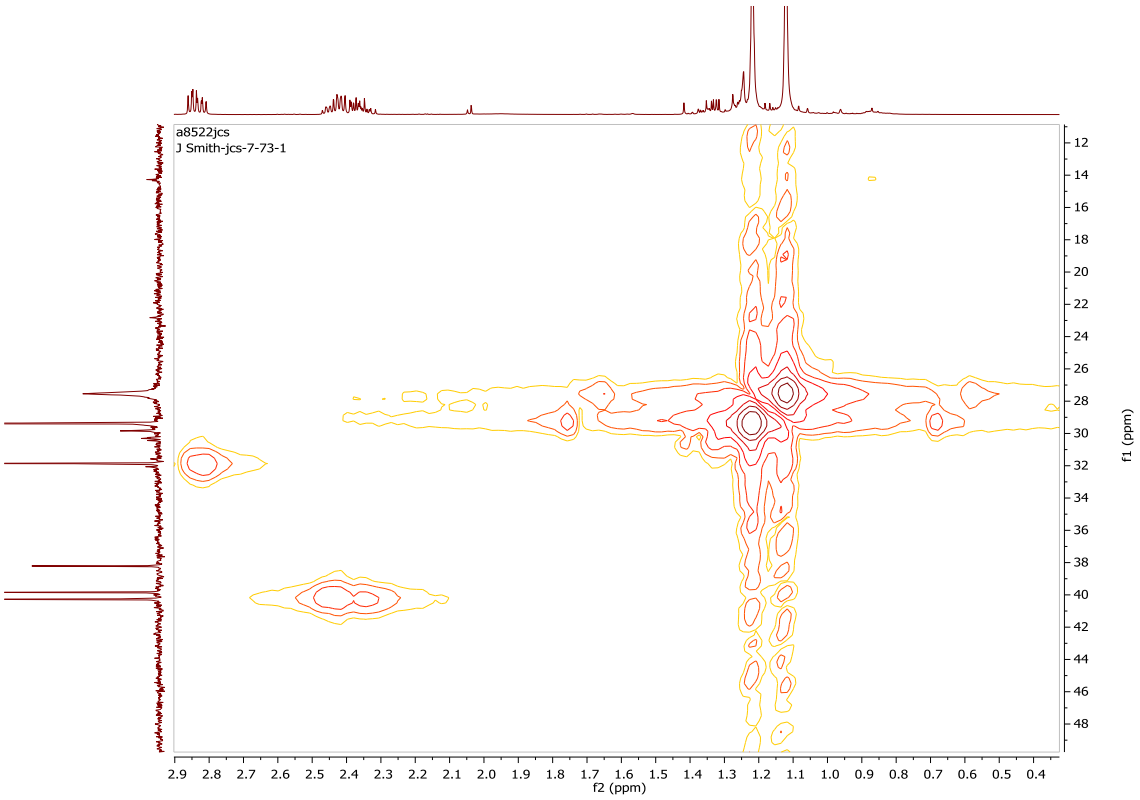


Figure 1.12

Thus, self-addition product **63** could not be the unknown product **62**. This was also confirmed by the isolation of an authentic sample of **63** from other experiments which will be discussed later. By way of comparison, the analytical data for the authentic self-addition product **63** is presented in Figures 1.13, 1.14 and 1.15:

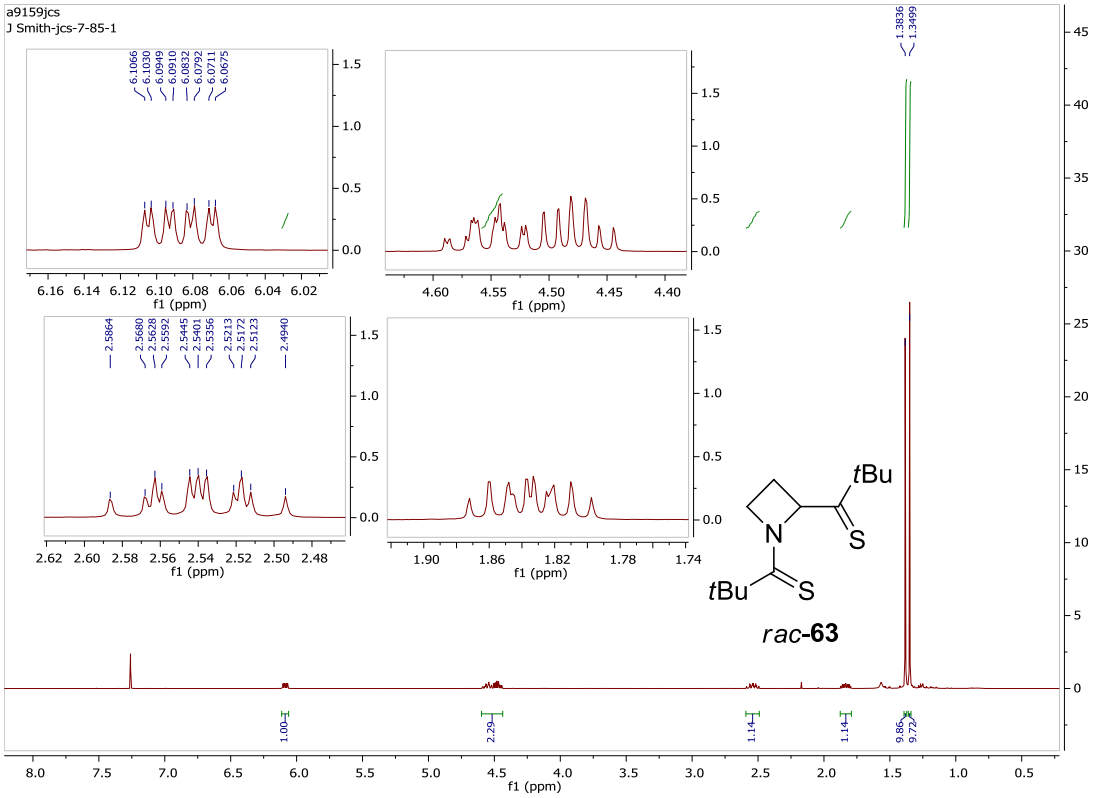


Figure 1.13

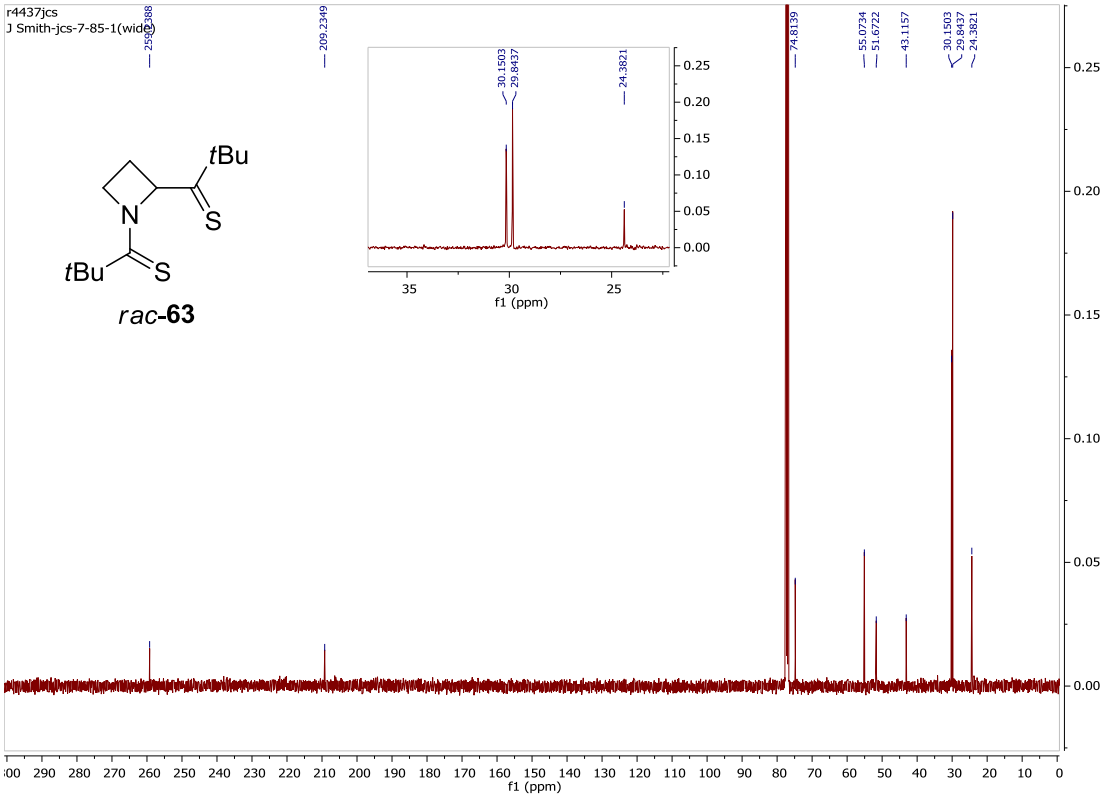


Figure 1.14

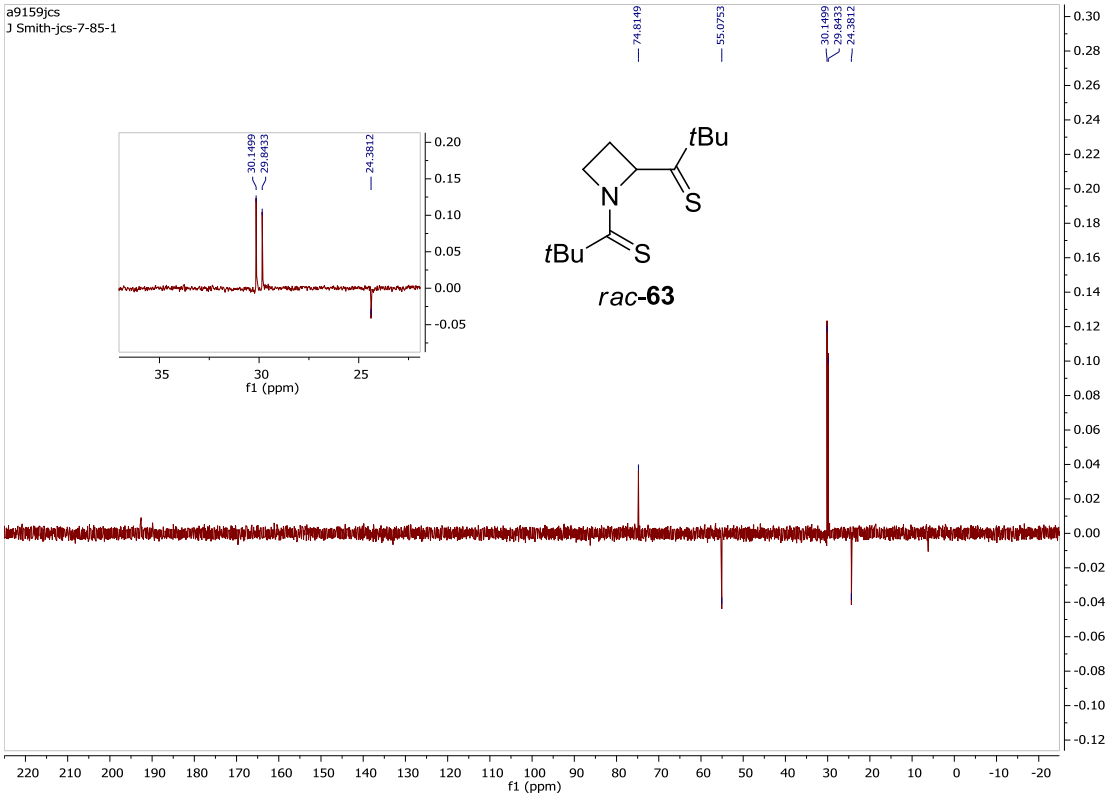


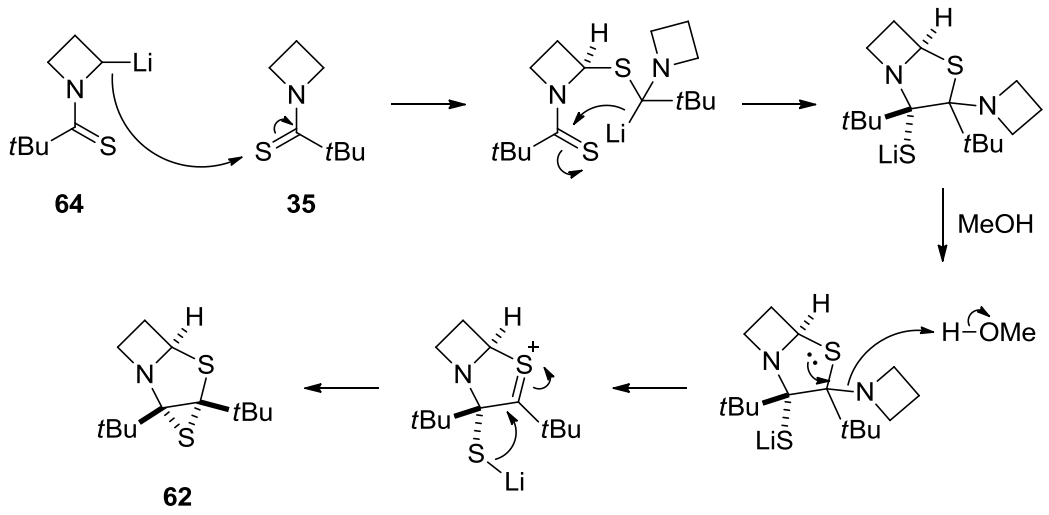
Figure 1.15

Data for **63**:

^{1}H NMR (400 MHz, $CDCl_3$) 6.09 (ddd, J = 9.5, 4.5, 1.5 Hz, 1H, CHN), 4.59–4.51 (m, 1H, CH_AH$_B$N), 4.47 (ddd, J = 9.5, 9.5, 5.0 Hz, 1H, CH$_A$$H_B$N), 2.59–2.49 (m, 1H, C$H_AH_B$), 1.88–1.79 (m, 1H, CH$_A$$H_B$), 1.39 (s, 9H, CMe$_3$), 1.35 (s, 9H, CMe$_3$)

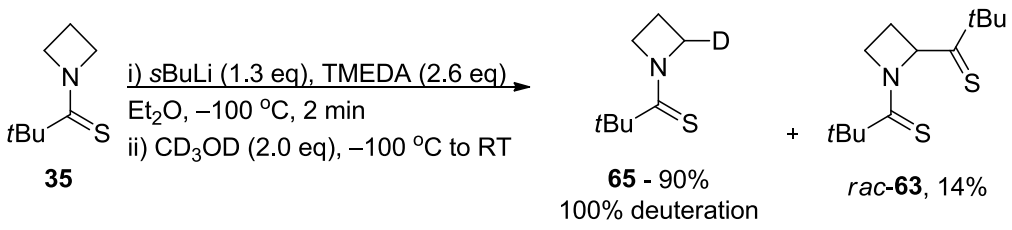
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 259.2 (C=S), 209.2 (NC=S), 74.8 (CHN), 55.0 (CH_2N), 51.7 (CMe$_3$), 43.1 (CMe$_3$), 30.1 (CMe_3), 29.8 (CMe_3), 24.4 (CH_2).

Hitherto however, we have been unable to conclusively determine the identity of product **62**. Scheme 1.39 represents our best suggestion for the structure of unknown compound **62**, as well as the mechanism for its formation. Initial attack of lithiated azetidine **64** on the sulfur atom of the thioamide **35** forms a second organolithium, partially stabilised by the electron withdrawing effect of the nitrogen atom and the α-anion stabilising effect of the sulfur atom. Intramolecular attack of the organolithium on the thioamide group then forms the bicyclic intermediate, followed by expulsion of azetidine upon quenching with methanol. Finally, the sulfide attacks the thioxonium ion to generate the final product **62**.



Scheme 1.39

As we expected that solvent and temperature would affect the formation of the unknown product **62**, we decided to repeat the reaction at –100 °C, reduce lithiation times and change the solvent from THF to Et_2O. Thus, azetidine **35** was lithiated in Et_2O at –100 °C for 2 minutes. In order to determine whether complete lithiation occurs under these conditions, CD_3OD was used as the electrophile rather than MeOH (Scheme 1.40). Under these conditions, starting deuterated azetidine **65** was recovered in 90% yield, with 100% deuteration occuring, as well as 14% of self-addition product *rac*-**63**. The greater than quantitative recovery of starting material was possibly due to a minor amount of contamination from long chain hydrocarbons that occurred during column chromatography.



Scheme 1.40

^{13}C NMR spectroscopy of **63** showed the expected thioketone and thioamide peaks at 259 and 210 ppm respectively. ^{1}H NMR spectroscopy showed 100% deuteration α to the nitrogen atom for **65** and no deuterium incorporation for self-addition product *rac*-**63**. The percentage of deuterium incorporation can be calculated by taking the ratio of the integration value between the CH_2 group and the adjacent CH_2N/CHDN groups

(Figure 1.16). At 0% deuteration, each CH_2N group, as well as the CH_2 group, will integrate to 2H. At 100% deuteration, each CH_2N/CHDN group will integrate to 1.5, whereas the CH_2 group will remain unchanged at 2H. Thus, the observed ratio that can be seen from Figure 1.16 is 1.45:2, implying complete deuterium incorporation. ^{13}C – D coupling could also be clearly observed in the ^{13}C NMR spectrum, with a coupling constant of 23 Hz (Figure 1.17).

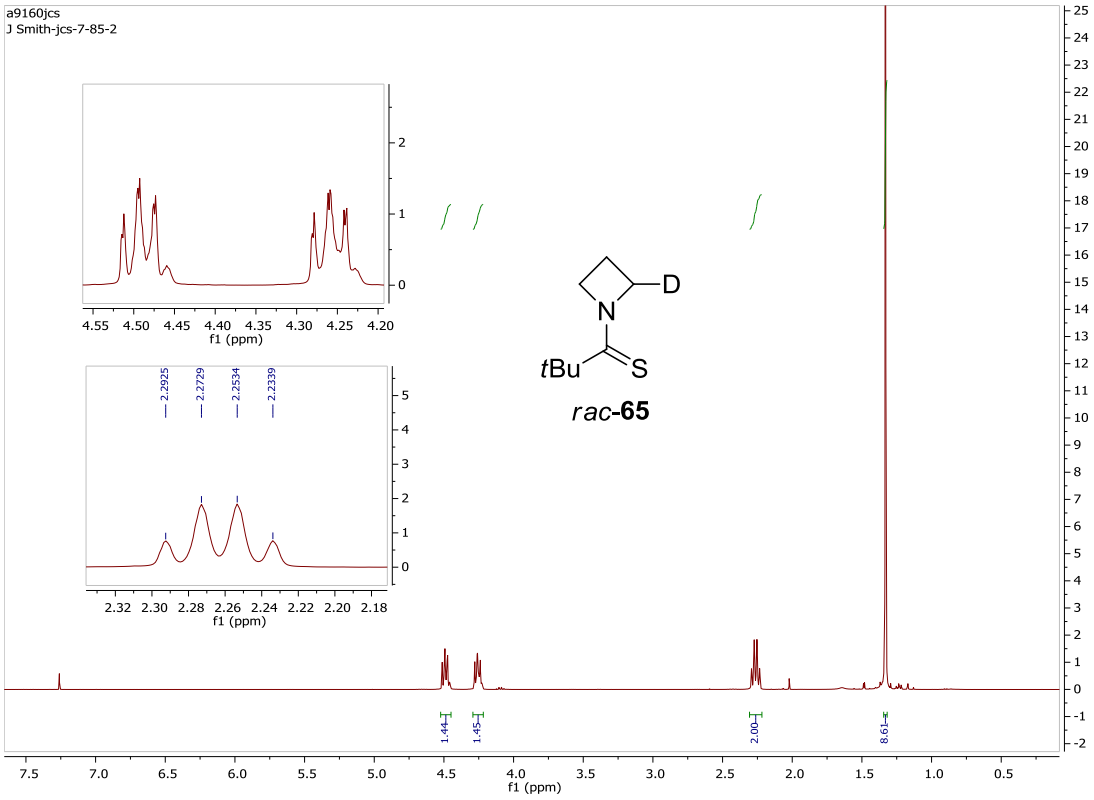


Figure 1.16

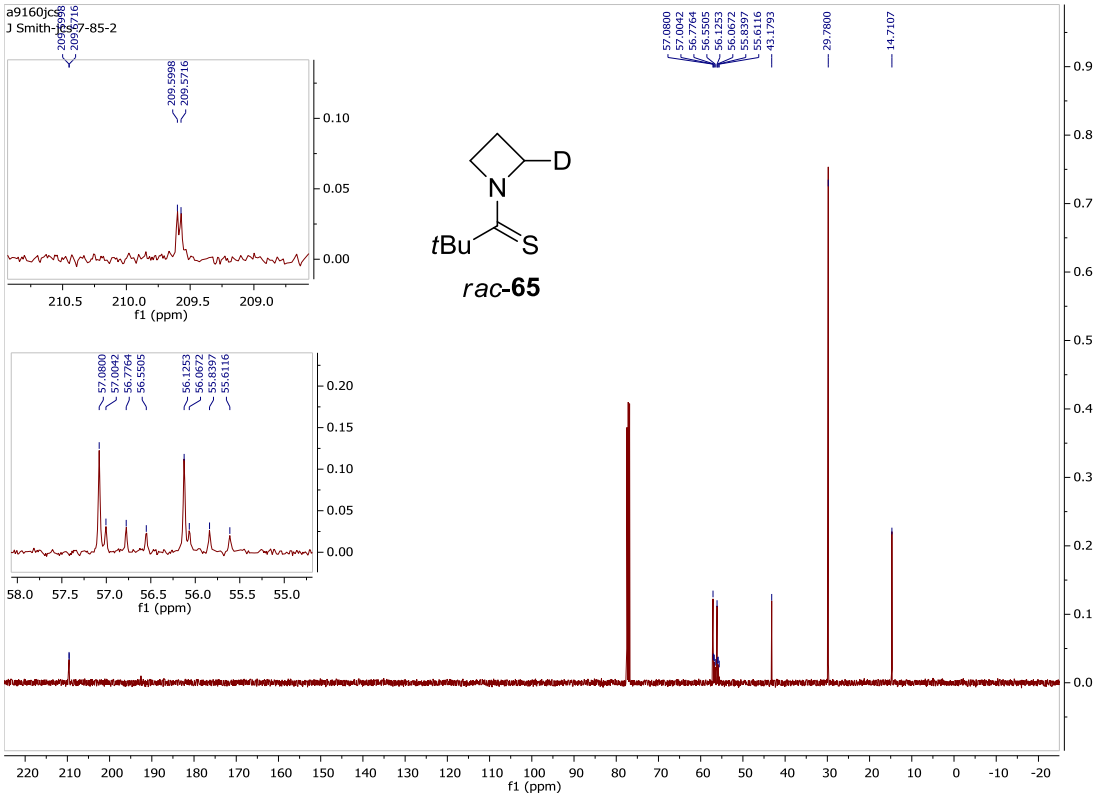
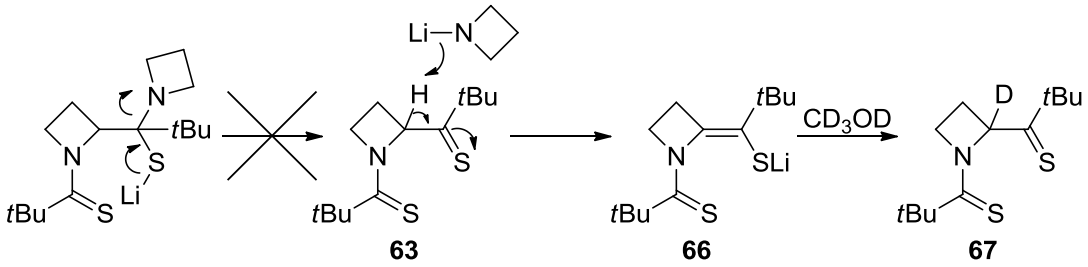


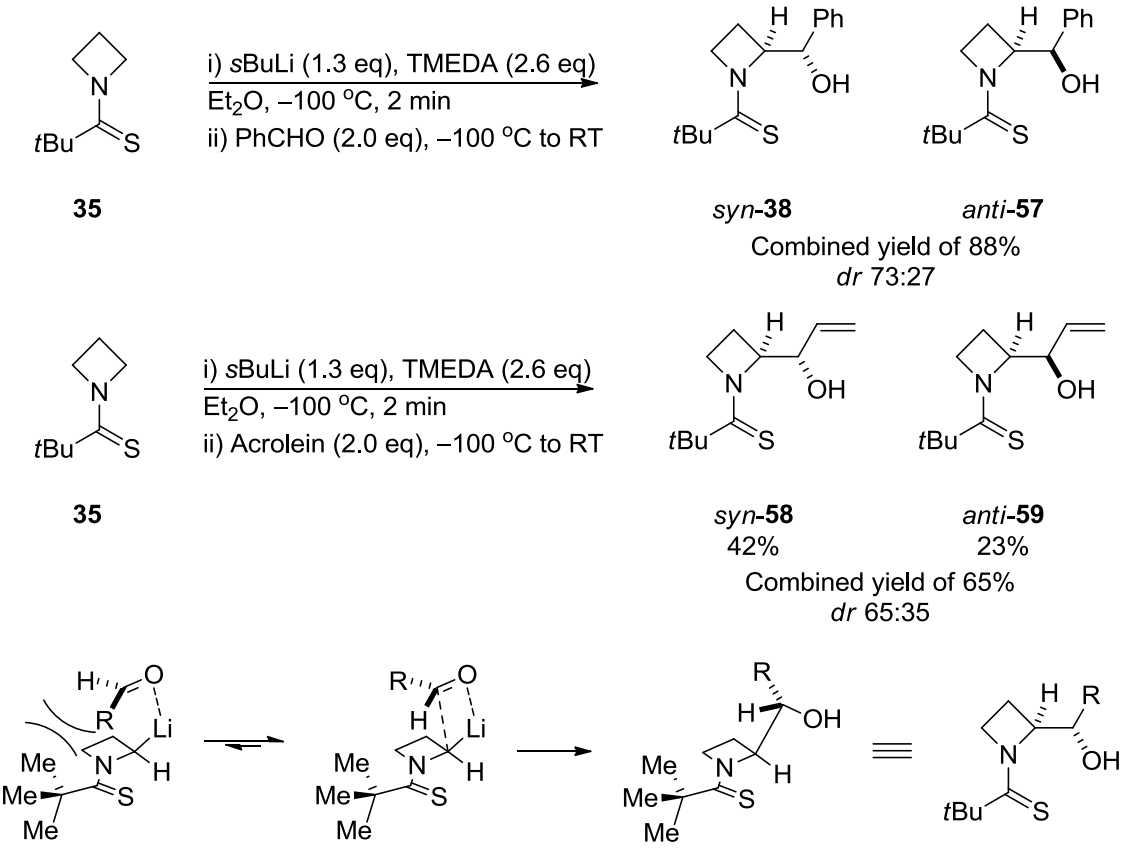
Figure 1.17

These results allowed several conclusions to be drawn. First, azetidine **35** is very easily deprotonated, even at –100 °C. Second, that due to higher recovered yields of the starting material, the extent to which side reactions can compete is substantially lessened. Effectively all material was accounted for and the yield of recovered starting material was almost doubled. Third, the tetrahedral intermediate formed by reaction of **35** with **64** is most likely to be stable under the reaction conditions until the addition of CD_3OD. If the tetrahedral intermediate were to collapse under the reaction conditions, deprotonation of the acidic proton α to the thioketone would occur to generate a thioenolate (Scheme 1.41). Given that deuteration of thioenolate **66** to form deuterated self-addition product *rac*-**67** is not observed, this reaction pathway does not occur. In terms of pKa values, it is also highly unlikely that a sulfur anion (pKa ~10.5) would expel a lithium amide (pKa ~35).



Scheme 1.41

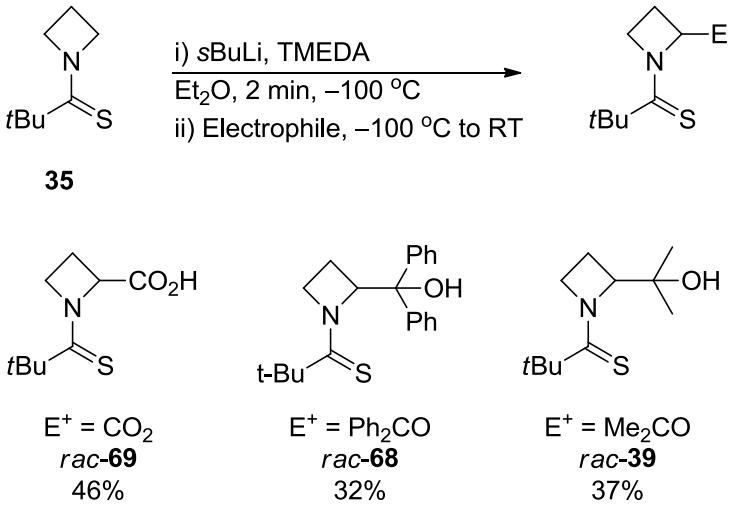
Given as we had identified suitable conditions for the lithiation-trapping of azetidine **35**, the reactions with benzaldehyde and acrolein were carried out under the new lithiation conditions, the results of which are shown in scheme 1.42, along with a tentative explanation of the diastereoselectivity of the reaction: initial coordination of the oxygen atom to the lithium ion serves to tether the electrophile to the organolithium reagent. Trapping could then occur *via* a 2+2 cycloaddition-type mechanism. The lowest energy configuration shown in scheme 1.42 maximises the distance between the bulky R and *t*Bu groups, thereby minimising steric hindrance and lowering the kinetic energy barrier to reaction *via* this configuration.



Scheme 1.42

With benzaldehyde as electrophile, the total yield increased from 56% to 88% and, with acrolein, the total yield almost doubled from 38% to 65%. The diastereoselectivity for both reactions appeared to be relatively unchanged when compared to the results in THF at –78 °C. Of the two electrophiles, acrolein is most chemically similar to protected aldedyde **51**, required for the total synthesis of (+)-retronecine. Yields for acrolein were acceptable and the major diastereoisomer is the same as that required for (+)-retronecine (+)-**49**, though the diastereoselectivity was lower than desired.

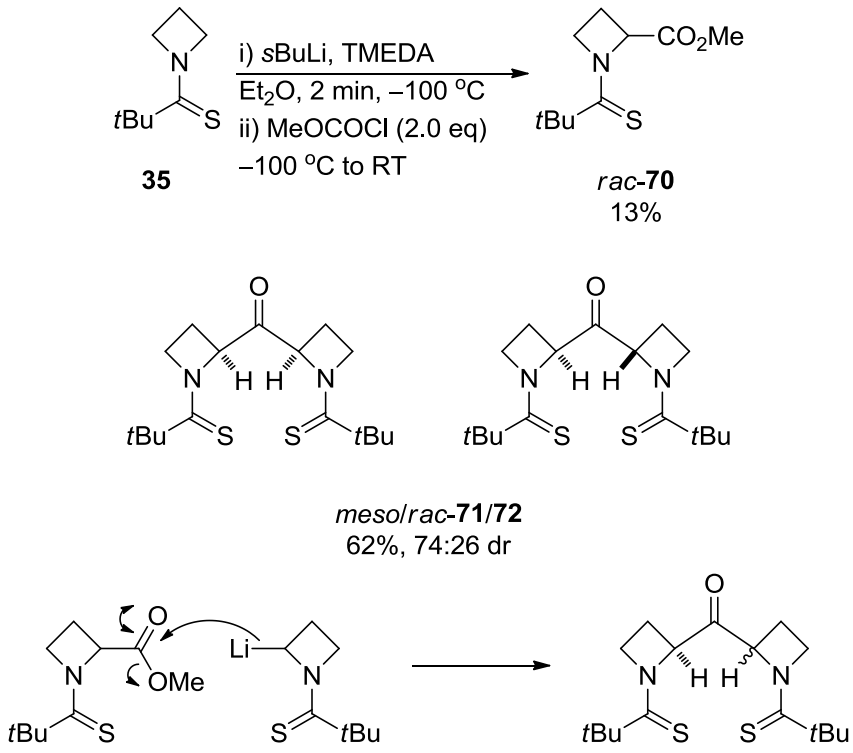
Using our optimised procedure, the reaction was tested on a variety of electrophiles to check for generality and applicability. The electrophiles tested were CO_2, Me_2CO, Ph_2CO (Scheme 1.43), Me_3SiCl (Scheme 1.44) and MeOCOCl (Scheme 1.45). Yields for CO_2, Ph_2CO and Me_2CO were much lower than the yields observed when benzaldehyde or acrolein were used as electrophiles. Benzophenone adduct *rac*-**68** was insoluble in all but halogenated solvents and material was likely lost during flash column chromatography in its purification. Propanone contains enolisable protons, deprotonation of which by lithiated azetidine **64** could have contributed to the low yields observed in this instance.



Scheme 1.43

Lithiation-trapping of azetidine **35** with methyl chloroformate as electrophile gave methyl ester *rac*-**70** in a disappointing 13% yield, with 62% yield of an additional unknown product. HRMS gave an *m/z* value of 363.1534 $(M+Na)^+$, which would be consistent with the self-addition products *meso*/*rac*-**71**/**72** shown in Scheme 1.44. The ^1H NMR, ^{13}C NMR and IR spectra gave results that were consistent with the proposed

structures for *meso*/*rac*-**71**/**72**, with the ketone being a key diagnostic peak in the IR spectrum (1703 cm^{-1}) and the ^{13}C NMR spectrum (δ 204 and 202 ppm). Whilst the relative stereochemistry of the major isomer could not be confirmed, the diastereoselectivity could be ascertained by taking the ratio of integrals for the CHN protons at δ 5.35 and 5.15 ppm in the ^{1}H NMR spectrum of the crude reaction mixture. The ^{1}H NMR and ^{13}C NMR spectra of the purified 81:19 diastereomeric mixture of *meso*/*rac*-**71**/**72** are shown below in Figures 1.18 and 1.19.



Scheme 1.44

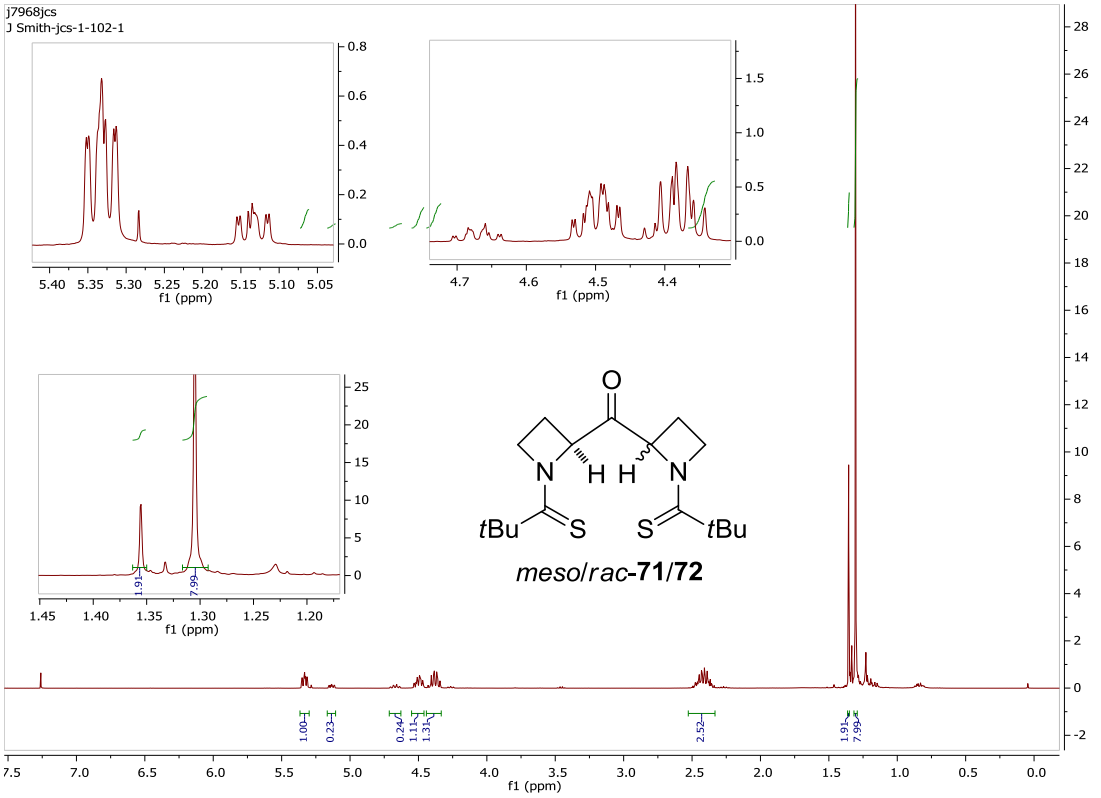


Figure 1.18

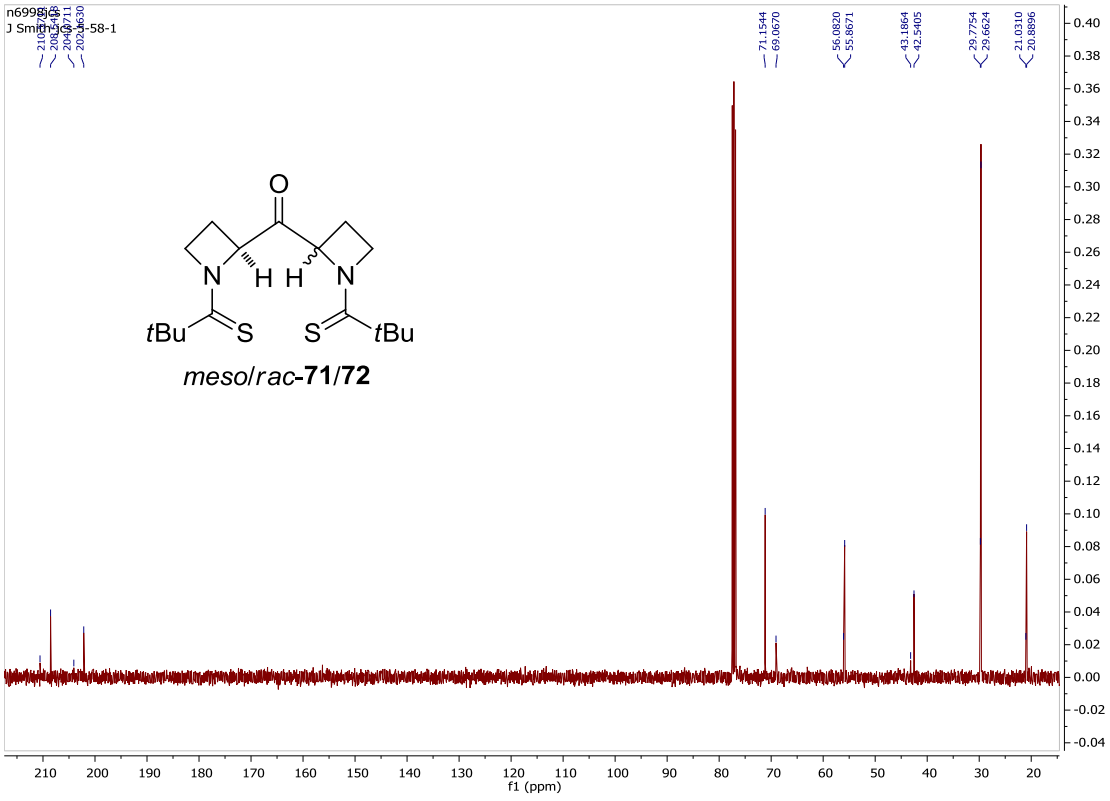
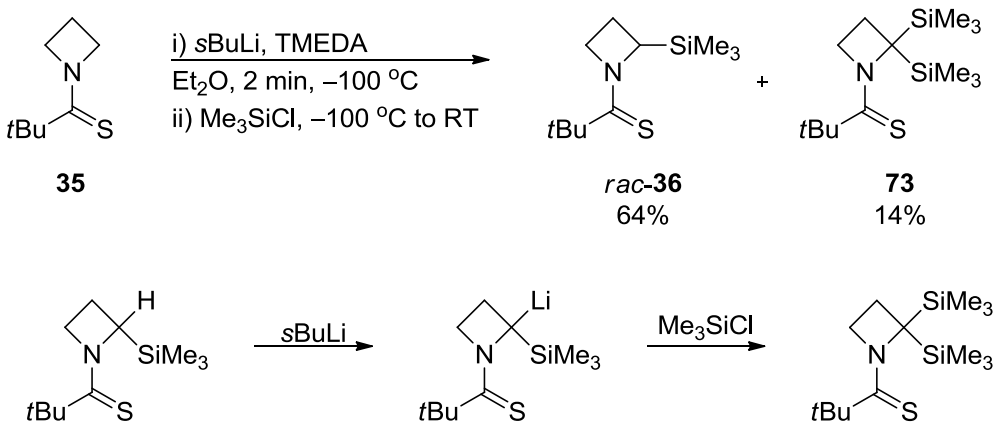


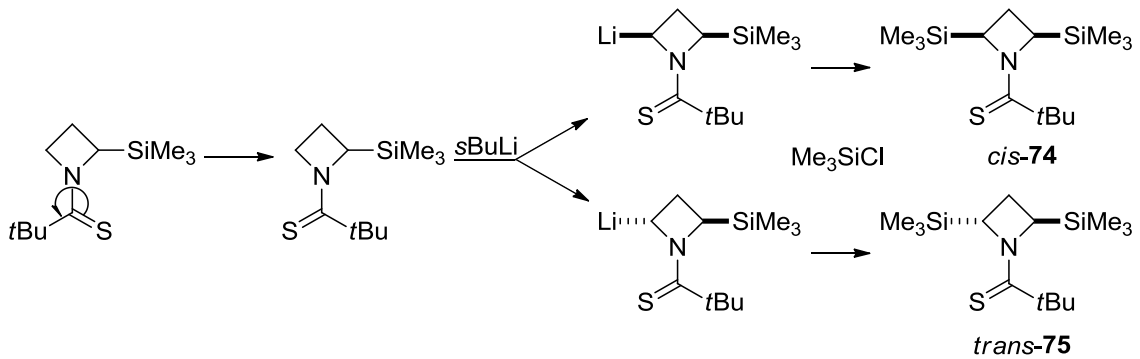
Figure 1.19

Lithiation trapping of azetidine **35** with Me_3SiCl gave the expected α-silyl azetidine *rac*-**36** in 64% yield, as well as 14% of an unknown product with an *m/z* value of 307.1785 $(M+H)^+$, indicating the presence of two Me_3Si substitutions. NMR data, as well as previous literature studies which will be discussed later, confirm that the unknown product is doubly substituted 1,1-disilyl azetidine **73**. This reaction and the mechanism of its formation is shown below in Scheme 1.45.



Scheme 1.45

Theoretically, there are two additional isomers of disilane **73** that could form, *cis*-1,3-disilane **74** and *trans*-1,3-disilane **75** (Scheme 1.46). Hodgson[58] demonstrated in 2015 that the half-life for interconversion of rotamers of azetidine **35** is 13.7 years at –78 °C! As previously discussed, the lone pair on the sulfur atom will direct lithiation to the same side of the azetidine ring. As the reaction temperature is –100 °C, rotameric interconversion followed by lithiation at the 3-position is highly unlikely. Not only that, but the initial silyl substitution serves to acidify the carbon atom it is bonded to *via* the α-anion effect, making deprotonation at the 3-position even less likely.



Scheme 1.46

The ^{1}H NMR spectrum also confirmed that substitution occured to give the 1,1-disilyl product **73** (Figure 1.20). Interconversion of rotamers in the product is likely to be slow on the NMR timescale. Therefore the CHN signals for both 1,3-disilyl azetidines *cis*-**74** and *trans*-**75** would be non-equivalent and each would give its own signal. As can be seen from the ^{1}H NMR spectrum of the obtained product (Figure 1.20), only 1 CH_2N signal is observed, confirming its identity as 1,1-disilyl azetidine **73**. The $C(SiMe_3)_2$ atom in the ^{13}C NMR spectrum also appears as a quarternary centre, further confirming the assignment of **73**.

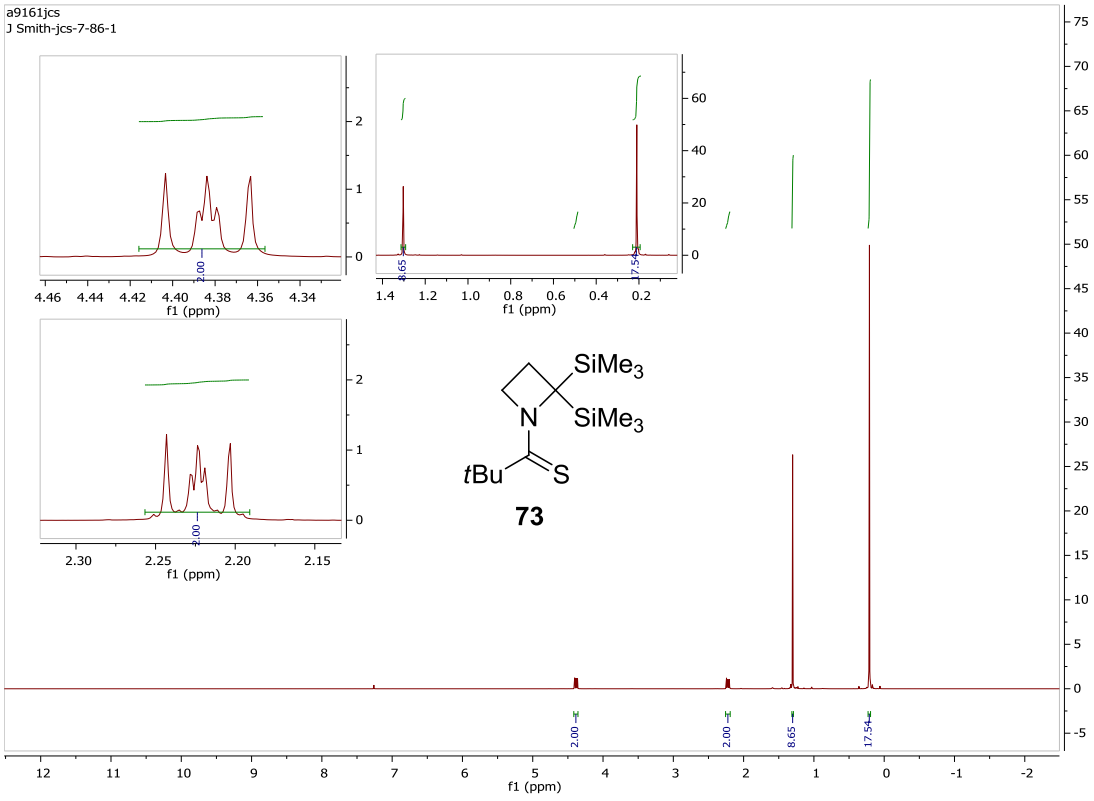


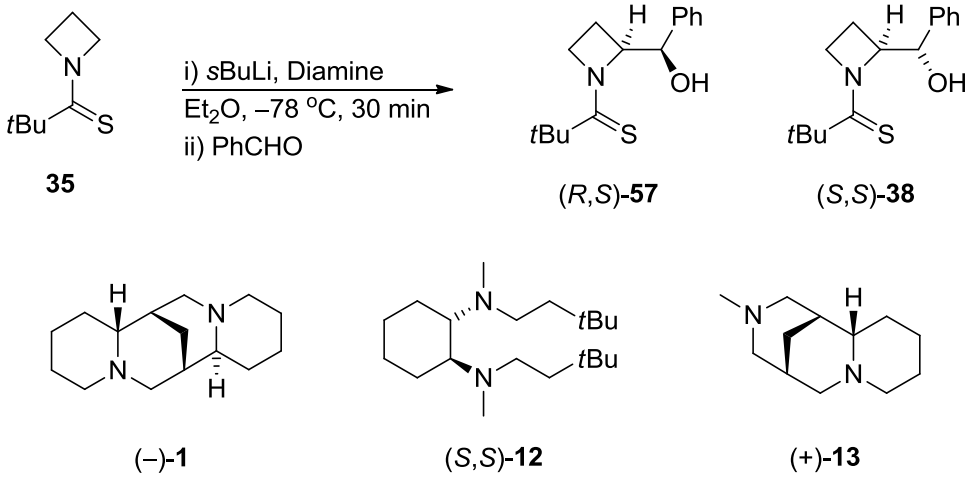
Figure 1.20

In summary, we have carefully studied the racemic lithiation-trapping of azetidine **35**. In particular, new conditions for the lithiation of **35** (*s*BuLi, TMEDA, Et_2O, –100 °C, 2 min) were optimised. With some electrophiles and conditions, various side products were isolated and where possible, characterised.

1.5 Asymmetric α-Lithiation–Substitution Reactions of *N*-Thiopivaloyl Azetidine and Pyrrolidine

1.5.1 Previous Results From Our Group

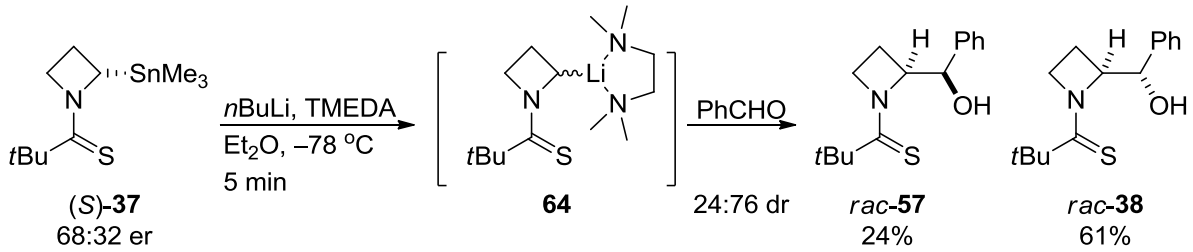
During this time, results obtained within our group[74] casted doubt on the viability of completing an asymmetric synthesis of (+)-retronecine *via* the α-lithiation-trapping methodology. The asymmetric α-lithiation-substitition reaction of azetidine **35** with benzaldehyde was investigated by another member of our group using three separate chiral diamines: (–)-sparteine (–)-**1**, Alexakis' diamine (*S*,*S*)-**12** and the (+)-sparteine surrogate (+)-**13** (Table 1.8). Whilst the yields for the major diastereoisomer were comparable, use of (*S*,*S*)-**12** and (+)-**13** gave effectively racemic product (Table 1.8, entries 2 and 3). The use of (–)-sparteine (–)-**1** as the chiral diamine gave the highest enantioselectivities, though with the opposite configuration to that required for a synthesis of (+)-retronecine.



Entry	Diamine	(*R*,*S*)-**57**		(*S*,*S*)-**38**	
		Yield (%)	er (*R*,*S*):(*S*,*R*)	Yield (%)	er (*S*,*S*):(*R*,*R*)
1	(–)-**1**	9	42:58	75	25:75
2	(*S*,*S*)-**12**	20	65:35	73	53:47
3	(+)-**13**	7	54:46	70	54:46

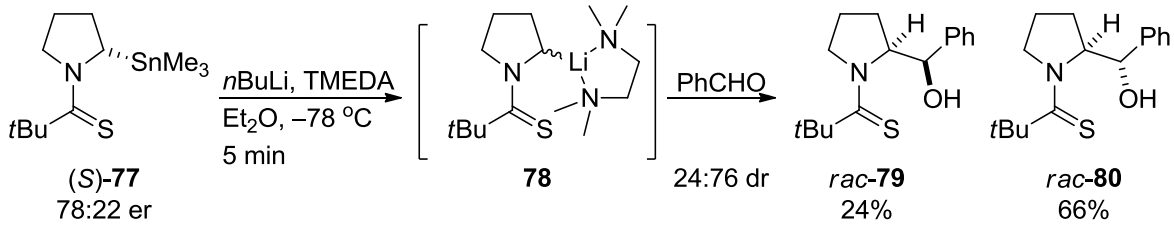
Table 1.8: Role of Chiral Diamine in the Lithiation-Trapping of **35** with Benzaldehyde

Other recent results from within the group included the fact that lithiated azetidine **64** was configurationally unstable at –78 °C. Enantioenriched stannane (*S*)-**37** which had been prepared by an asymmetric lithiation-trapping with (–)-sparteine (–)-**1** was subjected to tin-lithium exchange using *n*BuLi and TMEDA in Et_2O at –78 °C, followed by trapping with benzaldehyde. The benzaldehyde adducts obtained were racemic (Scheme 1.47), thus demonstrating facile interconversion between the enantiomers of lithiated azetidine **64** at –78 °C as lithiated azetidine **64** was left for only 5 minutes before electrophilic trapping.



Scheme 1.47

This result is in stark contrast to *N*-Boc pyrrolidine **7**, *N*-Boc piperidine **17** and borane-aziridine complex **27**, which lithiate to give configurationally stable intermediates at –78 °C. The lithiated species of the corresponding 5-membered analogue, *N*-thiopivaloyl pyrrolidine **76**, was also found to be configurationally unstable at –78 °C. An analogous reaction was performed starting from enantioenriched stannane (*S*)-**77**, followed by tin-lithium exchange and trapping with benzaldehyde (Scheme 1.48). Given that lithiated *N*-Boc pyrrolidine is configurationally stable at –78 °C, it can be concluded that the thiopivalamide directing group is responsible for the configurational instability in the 5- and 4-membered rings.



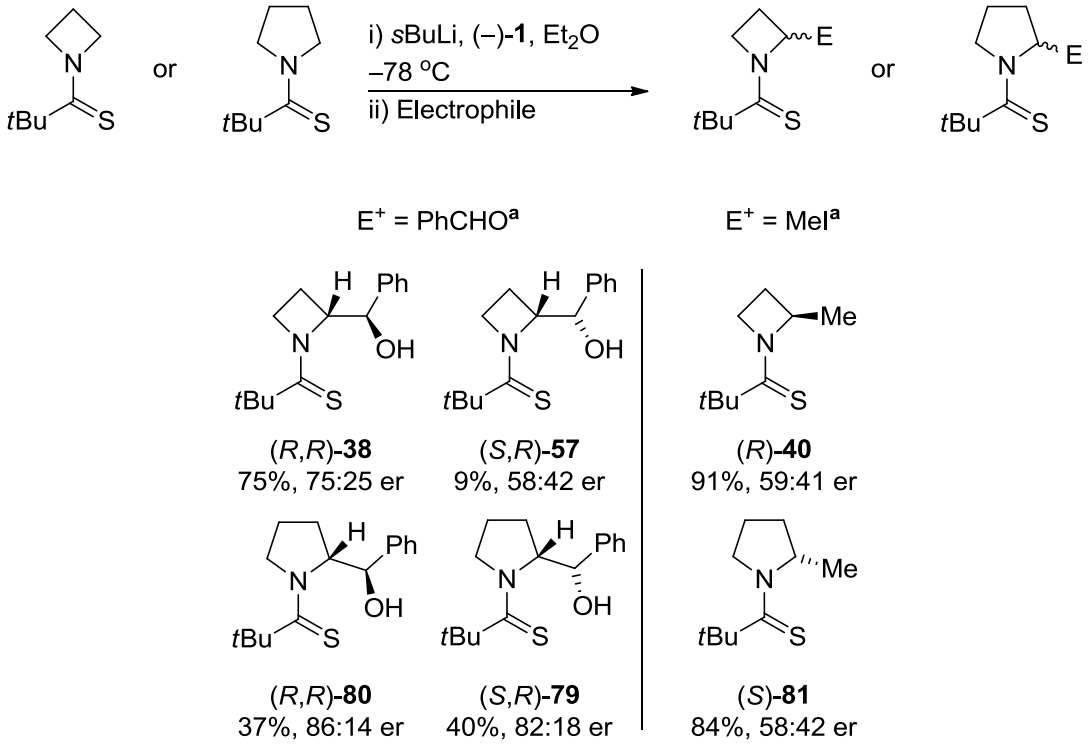
Scheme 1.48

The conclusion from the previous work in the group is that the asymmetric lithiation-trapping of azetidine **35** carried out by Hodgson and us cannot be an enantioselective deprotonation, as this is not possible with configurationally unstable organolithium species. This explains why (–)-sparteine (–)-**1** and the (+)-sparteine surrogate (+)-**13**

give such different results (Table 1.8). The mechanism that accounts for enantioinduction must therefore be either a dynamic thermodynamic resolution (Scheme 1.59) or a dynamic kinetic resolution (Scheme 1.60).

1.5.2 Electrophile Variation in the Asymmetric Lithiation-Substitution of *N*-Thiopivaloyl Azetidine and Pyrrolidine

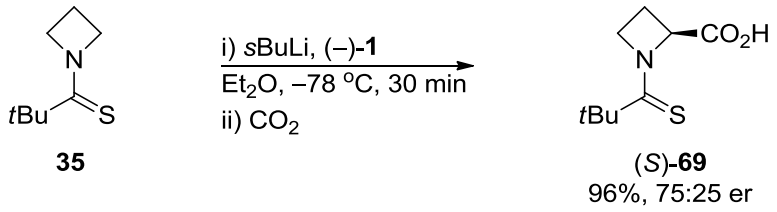
With a lack of precedent for high enantioselectivities in the correct sense for the lithiation–trapping of azetidine **35**, our attention turned away from the planned total synthesis of (+)-retronecine. Instead, research focused on varying the electrophile and diamine in the asymmetric lithiation-trapping reactions, with an ultimate aim to fully explore the scope and limitations of this chemistry. In addition, we wished to clarify the sense of induction with as many electrophiles as possible, as the group's initial results indicated that different electrophiles were giving different absolute configurations under identical conditions for lithiation (Scheme 1.49). Hence, much time and effort was spent developing approaches to proving the absolute configuration of the major products.



Scheme 1.49

As outlined above, lithiation-trapping of azetidine **35** with benzaldehyde and methyl iodide gave products with different absolute stereochemistry, but gave products with the same configuration were obtained for the corresponding pyrrolidine **76**. Therefore, the reaction was repeated using other electrophiles.

To begin with, azetidine **35** was subjected to an asymmetric lithiation-trapping with *s*BuLi/(–)-**1** in Et_2O at –78 °C for 30 minutes, then trapped with carbon dioxide to give the carboxylic acid (*S*)-**69** in 96% yield and 75:25 *er* (Scheme 1.50). Interestingly, under these conditions, self-addition products **62** and **63** were not observed in the ^1H NMR spectrum of the crude reaction mixture. As previously stated, (–)-sparteine (–)-**1** is known to be a much less activating diamine than TMEDA. Not only that, TMEDA is sterically much smaller than (–)-**1**. It is feasible to imagine that the additional steric bulk of (–)-**1** prevents the reactive carbon centre of lithiated azetidine **64** from getting into close proximity to the C=S group to form the self-addition product.



Scheme 1.50

The enantioselectivities of the final product (*S*)-**69** was determined by taking a small quantity (~ 2 mg) of the solid product (*S*)-**69**, forming the methyl ester by treatment with TMS-diazomethane in toluene/MeOH[75, 76] and then subjecting the product ester to chiral stationary phase HPLC. It was noted that when the reaction was repeated under identical conditions, (*S*)-**69** was found to have an *er* of 89:11. When the entirety of both samples were re-dissolved, an aliquot of both solutions taken then separately derivatized to the methyl ester, both samples showed an identical enantiomeric ratio of 75:25. This result led to the realisation that (*S*)-**69** can enantioenrich *via* crystallisation. We wondered whether we could obtain a highly enantioenriched sample suitable for X-ray diffraction by recrystallisation. Indeed, a single recrystallisation of (*S*)-**69** with an *er* of 75:25 from hexane/EtOAc allowed isolation of (*S*)-**69** in with an *er* of 97:3 from the filtrate (*ie*,. racemic crystals of **69** crystallised). From this material, single crystals

suitable for X-ray diffraction were grown and an X-ray structure was obtained, confirming the absolute stereochemistry of (*S*)-**69** (Figure 1.21).

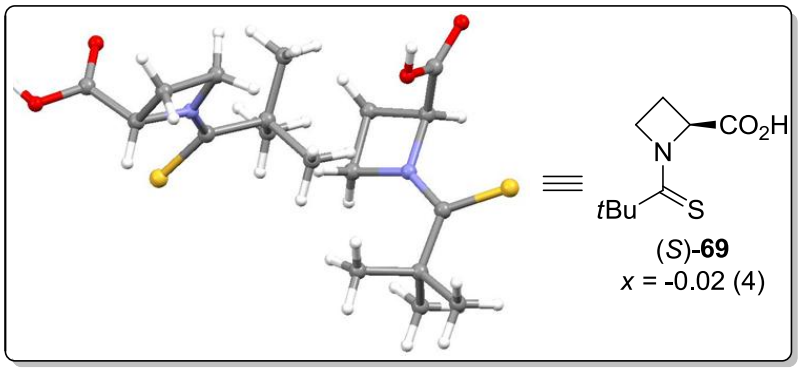
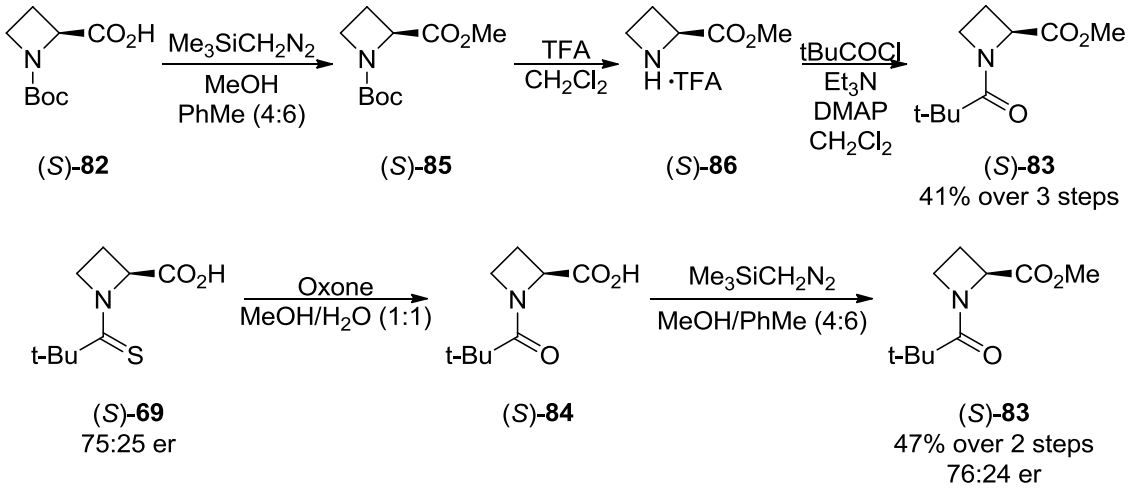


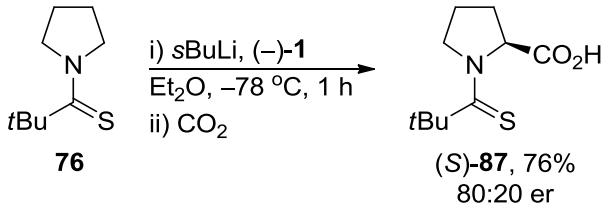
Figure 1.21

Given that the configuration of acid (*S*)-**69** is opposite to the configuration α to nitrogen of benzaldehyde adducts (*R*,*R*)-**38** and (*R*,*S*)-**57** α to the nitrogen, we desired further proof of stereochemistry of acid (*S*)-**69**. Therefore, an independent synthesis from commercially available, enantiomerically pure (*S*)-azetidine carboxylic acid (*S*)-**82** was developed. Enantiomerically pure (*S*)-**82** was esterified to the methyl ester using TMS-diazomethane in toluene/MeOH, the Boc group removed *via* treatment with TFA and the nitrogen acylated with pivaloyl chloride to give enantiomerically pure (*S*)-**83** in an overall yield of 41% over 3 steps (Scheme 1.51). Carboxylic acid (*S*)-**69** with an *er* of 75:25, prepared *via* *s*BuLi/(–)-**1** lithiation-trapping of azetidine **35**, was oxidised to the amide by treatment with oxone in a 1:1 mixture of water/MeOH, then the crude residues esterified to the methyl ester with TMS-diazomethane to give (*S*)-**83** in a 47% yield over 2 steps and an *er* of 76:24. A racemic sample of *rac*-**83** was also prepared *via* the same method from racemic carboxylic acid **69**. Chiral stationary phase HPLC analysis was carried out on *rac*-**83** to find appropriate conditions to separate the two enantiomers. Then, enantiomerically pure (*S*)-**83** was subjected to chiral stationary phase HPLC to determine which of the two peaks in the HPLC trace corresponded to the (*S*)-enantiomer. Finally, (*S*)-**83** of a 76:24 *er* was subjected to chiral stationary phase HPLC to confirm that the major isomer was the (*S*) enantiomer.



Scheme 1.51

We wanted to investigate whether the corresponding pyrrolidine **76** would react with CO_2 to give the corresponding carboxylic acid with the opposite configuration to the products obtained by reaction with benzaldehyde. Pyrrolidine **76** was lithiated using *s*BuLi/(–)-**1** in Et_2O at –78 °C for 1 h, then trapped with CO_2 to give acid (*S*)-**87** in 76% yield and an *er* of 80:20 (Scheme 1.52).



Scheme 1.52

Initial proof of stereochemistry followed the route of the previously established method for (*S*)-**69**. Carboxylic acid (*S*)-**87** was enantioenriched *via* recrystallisation from hexane/EtOAc, with three successive recrystallisations improving the er from 80:20 to 90:10, to 96:4 and finally to 98:2. Single crystals were then grown from this enantioenriched material and submitted for X-ray diffraction, confirming the stereochemical assignment of (*S*)-**87** (Figure 1.22).

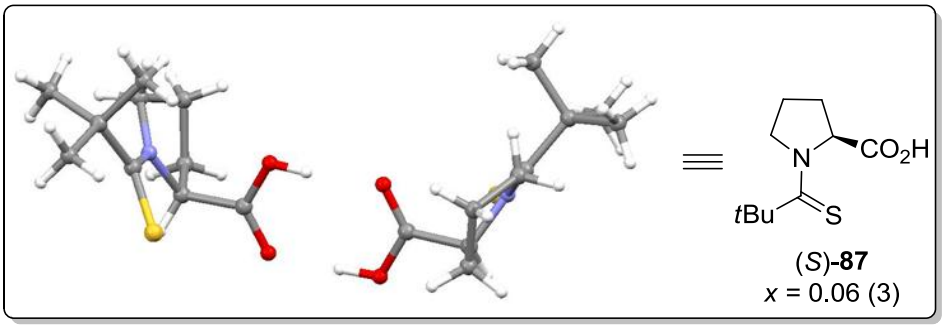
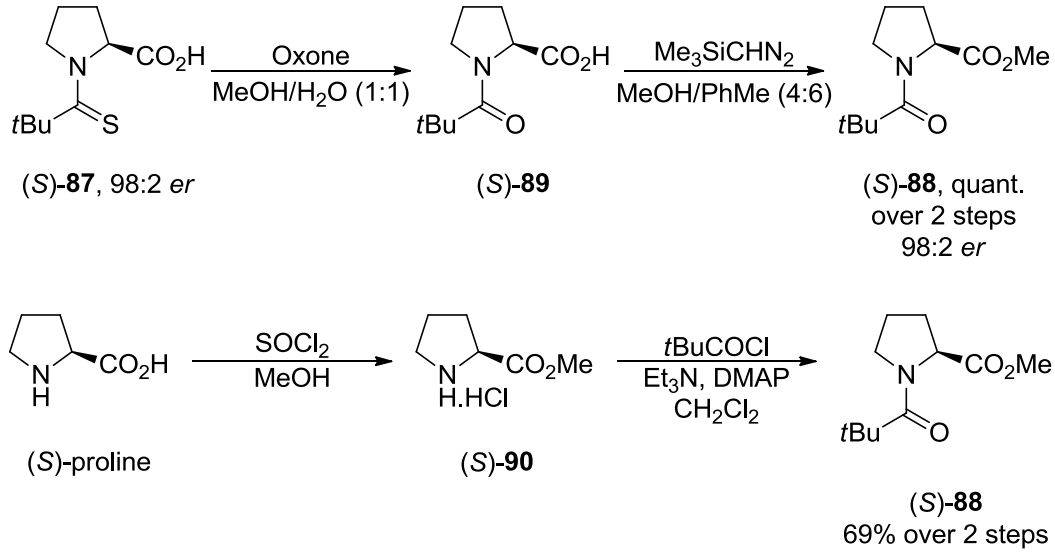


Figure 1.22

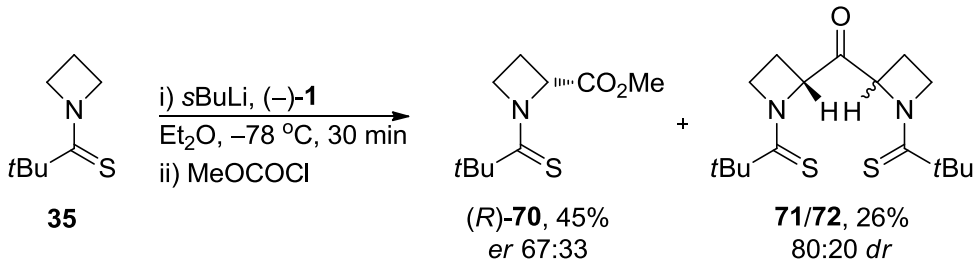
As with the corresponding azetidine acid (*S*)-**69**, a two-step oxidation-esterification procedure was used to form (*S*)-**88** in quantitative yield and 98:2 *er*. Enantiomerically pure (*S*)-proline was subjected to a Fischer esterification[77] to form the methyl ester (*S*)-**90**, then acylated with pivaloyl chloride to form enantiomerically pure (*S*)-**88** in a 69% yield over two steps (Scheme 1.53). A racemic sample of *rac*-**88** was also prepared using the same two step oxidation-esterification procedure using *rac*-**87** as starting material. HPLC analysis of the racemate, the enantiomerically pure (*S*)-**87** and (*S*)-**87** of 98:2 *er* confirmed the original X-ray assignment.



Scheme 1.53

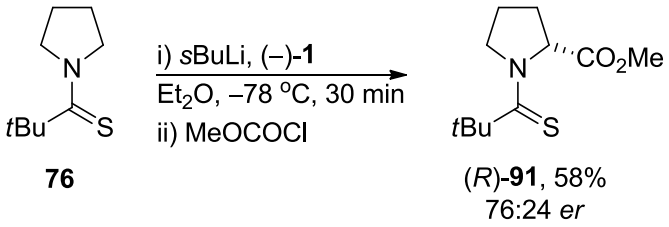
With carbon dioxide as an electrophile having been fully explored, our attention turned to the use of methyl chloroformate as the electrophile. Lithiation of azetidine **35** with *s*BuLi/(–)-**1** in Et_2O at –78 °C for 30 minutes, followed by trapping with methyl chloroformate gave methyl ester (*R*)-**70** in a 45% yield and 67:33 *er*, as well as 26% of

self-addition products **71**/**72** in an 80:20 diastereomeric ratio (Scheme 1.54). Proving the absolute stereochemistry of (*R*)-**70** was trivial, as acid (*S*)-**69** with known stereochemistry had to be derivatized to the corresponding methyl ester (*S*)-**70** prior to HPLC analysis.



Scheme 1.54

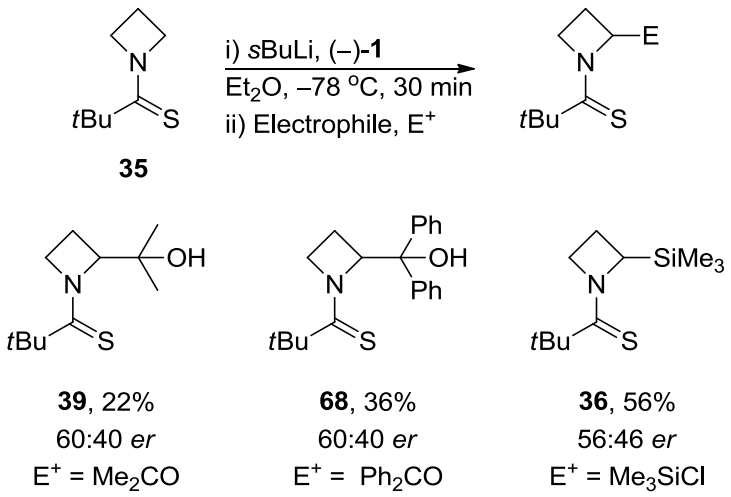
For the corresponding reaction on pyrrolidine **76**, lithiation with *s*BuLi/(–)-**1** in Et_2O at –78 °C for 1 hour, followed by trapping with methyl chloroformate gave (*R*)-**91** in 58% yield and a 76:24 *er* (Scheme 1.55). Curiously, the analogous self-addition products seen in the azetidine system was not observed in the pyrrolidine ring. Proving the absolute stereochemistry was straightforward due to the known stereochemistry of acid (*S*)-**87**.



Scheme 1.55

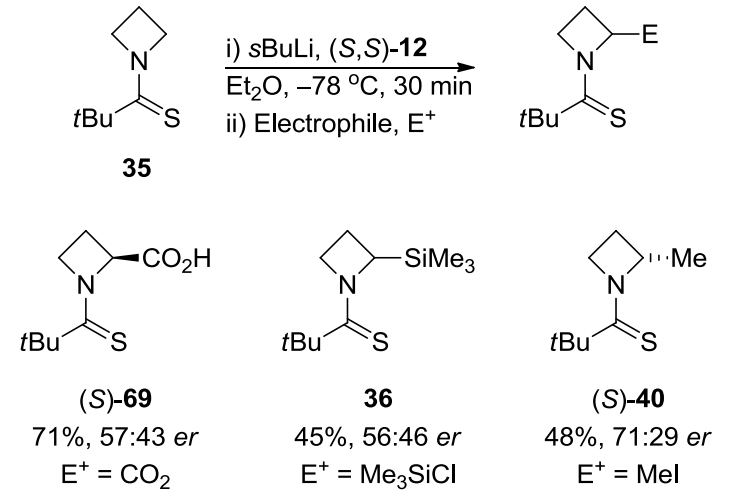
The use of methyl chloroformate as the electrophile gives products with the same configuration α to the nitrogen atom as to those obtained with benzaldehyde as the electrophile. Carbon dioxide, however, appears to react with lithiated azetidine **64** and pyrrolidine **78** with inversion of stereochemistry.

Other electrophiles including benzophenone, acetone and Me_3SiCl were also used in the *s*BuLi/(–)-**1** lithiation-trapping of azetidine **35**. However, enantioselectivities in all instances were poor and the absolute stereochemistry of the adducts were not determined (Scheme 1.56)



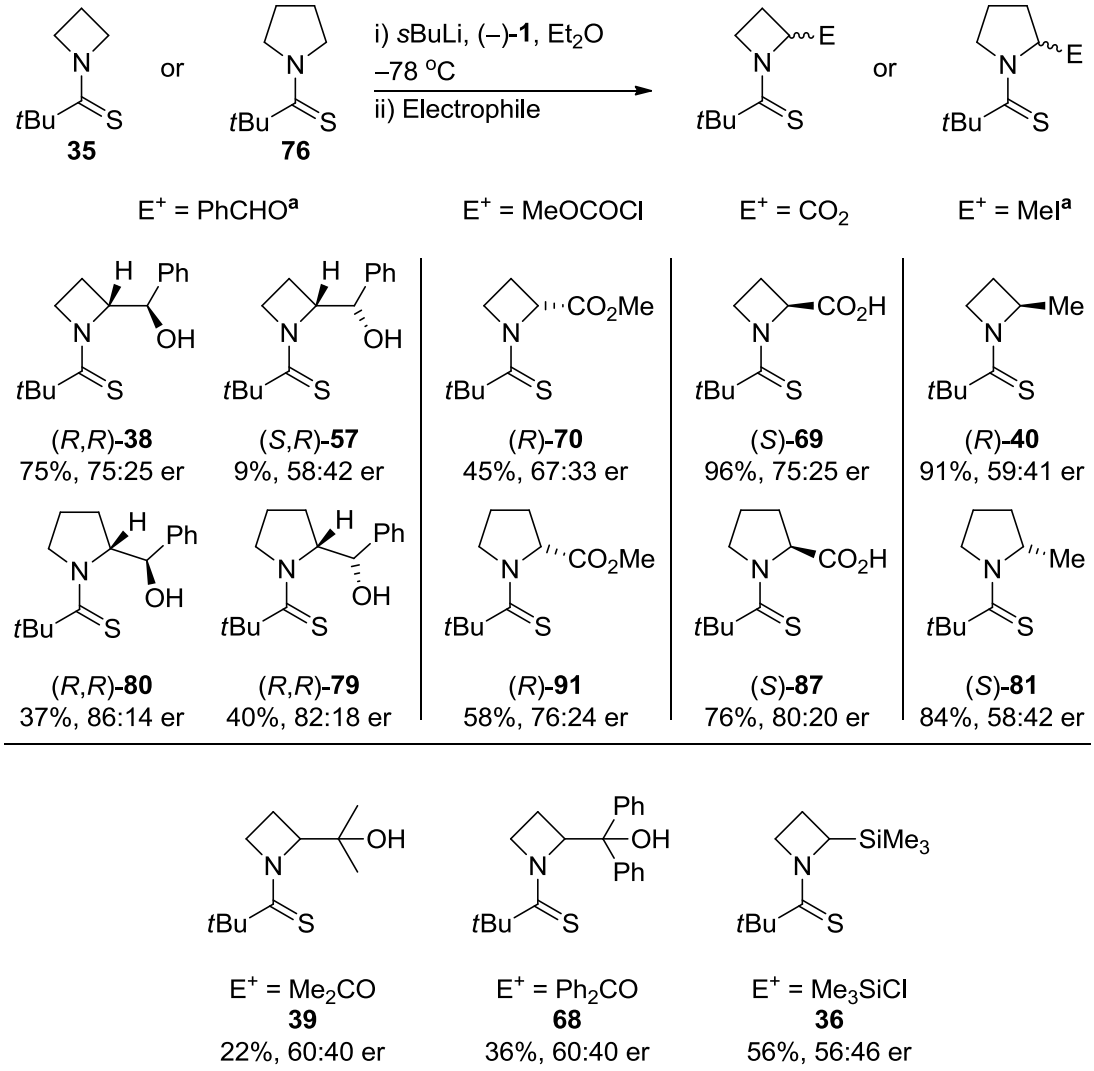
Scheme 1.56

We also briefly investigated the use of (*S*,*S*)-Alexakis' diamine (*S*,*S*)-**12** as a substitute chiral diamine for (–)-**1**. Azetidine **35** was lithiated using *s*BuLi/(*S*,*S*)-**12** in Et_2O at –78 °C for 30 minutes, then trapped using Me_3SiCl, carbon dioxide and methyl iodide (to check reproducibility with Hodgson's results) (Scheme 1.57). The highest enantioselectivities were achieved with the comparatively unreactive electrophile methyl iodide, with carbon dioxide and Me_3SiCl giving almost racemic products.



Scheme 1.57

With enough results in hand, we then attempted to account for the mechanism of enantioinduction in the asymmetric lithiation-trapping of azetidine **35** and pyrrolidine **76**. An overview of the most important results is shown in Scheme 1.58.

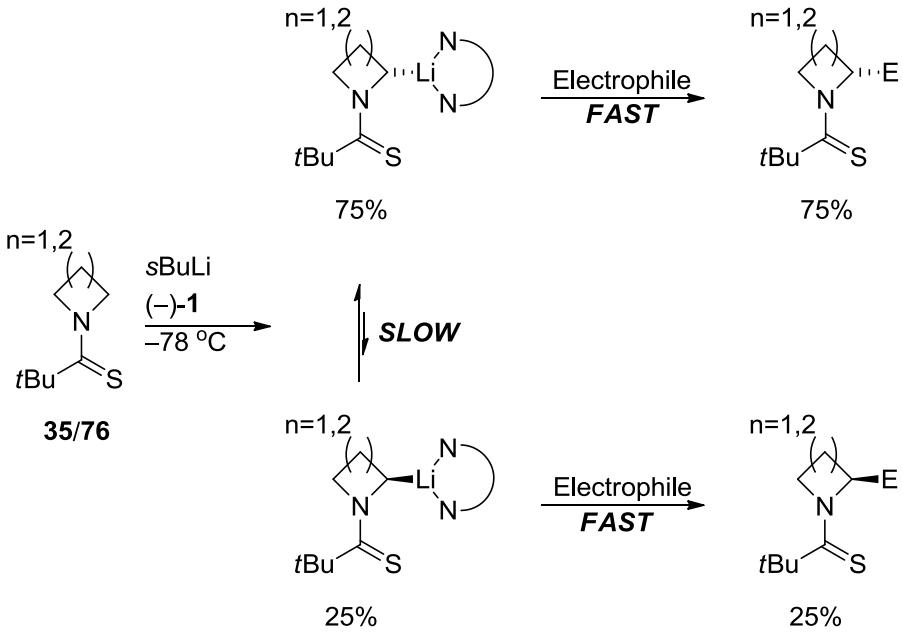


a) P. Rayner, University Of York, Thesis, 2013

Scheme 1.58

The sense of induction in the final products is cleaerly dependent upon the electrophile used. Use of carbon dioxide gives a product of opposite configuration to methyl chloroformate and benzaldehyde. To the best of our knowledge, this is the first example of a non-benzylic C–Li stereocentre reacting with inversion of stereochemistry. Use of methyl iodide as electrophile also gives products of opposite configuration between the 4- and 5- membered rings. Enantioselectivities appear to decrease as the reactivity of the electrophile decreases; benzaldehyde and carbon dioxide give near identical enantioselectivities, methyl chloroformate slightly lower and methyl iodide the lowest. One mechanistic scenario for fast trapping electrophiles such as benzaldehyde, carbon dioxide and methyl chloroformate is shown in Scheme 1.59. At –78 °C, a thermodynamic equilibrium consisting of a 75:25 mixture of diastereomeric lithiated

azetidines is established. With reactive electrophiles, the rate of reaction of each diastereomeric organolithium is faster than the rate of interconversion between the diastereomeric lithiated azetidines. Due to this, the enantiomeric ratio of the products is the same as, or close to, the ratio of diastereoisomers of lithiated azetidines. With less reactive electrophiles such as methyl iodide, the rate of reaction between each of the lithiated azetidines with the electrophile is slower than the rate of interconversion between the diastereoisomers of lithiated azetidine. Due to this, the enantioselectivities in the final product are dependent upon the different rates of reaction between each diastereomeric lithiated azetidine complex and the electrophile. The difference in the sense of induction between methylated products (*R*)-**40** and (*S*)-**81** could be due to the (*R*)-**64** lithiated azetidine and (*S*)-**78** lithiated pyrrolidine being the more reactive diastereomeric complexes.

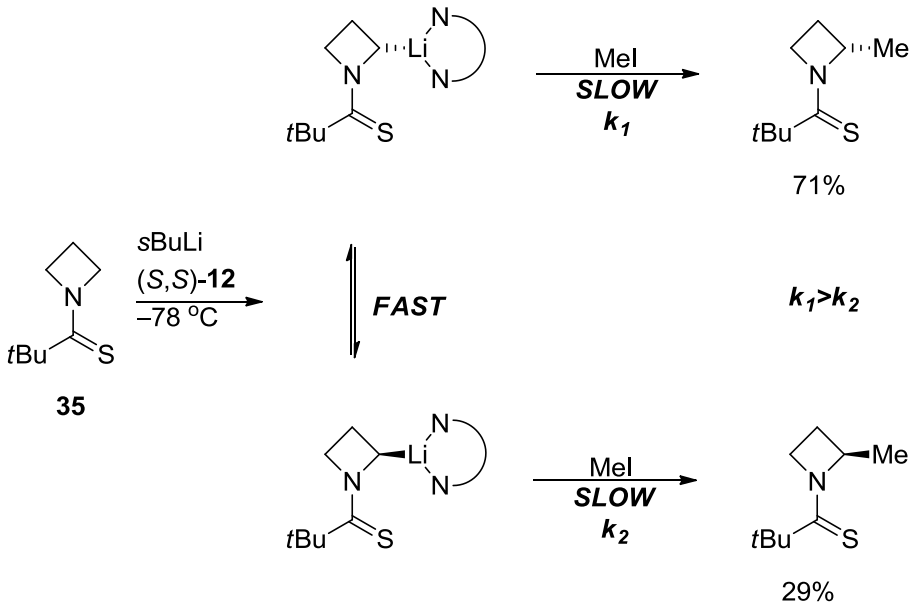


Scheme 1.59

At –78°C, (–)-**1** appears to favour the (*S*) enantiomer of lithiated azetidine **64** in a 75:25 ratio and the (*S*) enantiomer of lithiated pyrrolidine **78** in a 80:20 ratio. This is too low to realistically be synthetically useful.

In contrast to (–)-**1**, (*S*,*S*)-**12** as the chiral diamine appears to give the opposite trend, whereby best enantioselectivities are achieved with methyl iodide, the least reactive electrophile. Carbon dioxide as the electrophile gives (*S*)-**69** in a 57:43 *er*, implying that there is a 57:43 thermodynamic ratio between diastereoisomers of lithiated azetidines.

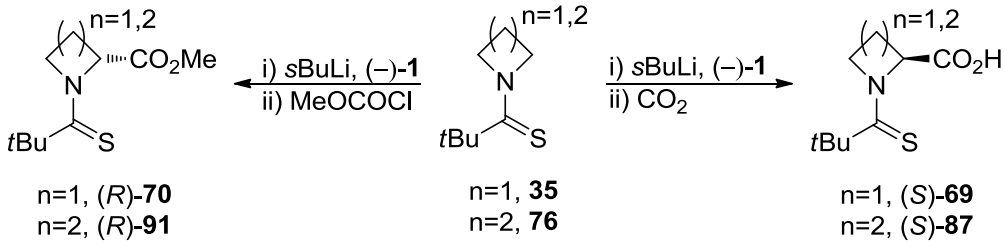
As methyl iodide gives a higher enantioselectivity than carbon dioxide, it would suggest that enantioinduction is due, in this case, to a dynamic kinetic resolution, whereby the rate of reaction between diastereomeric lithiated azetidines is slower than their rate of interconversion (Scheme 1.60).



Scheme 1.60

1.6 Conclusions and Future Work

Azetidine **35** has been shown to lithiate rapidly using *s*BuLi/TMEDA in Et_2O, even at –100 °C, to form a highly reactive TMEDA/lithiated azetidine complex, as demonstrated by deuteration incorporation experiments. Self-addition has been observed as a deletrious side reaction under these racemic conditions, with the isolation of **62** and **63** being proof of this. An optimised procedure for the racemic lithiation-trapping of azetidine **35** has been developed, allowing yields as high as 88% when benzaldehyde is used as the electrophile. Diastereoselectivity for the two aldehyde products was shown to be modest, although the relative stereochemistry of the major diastereoisomer was shown to be correct for our planned synthesis of (+)-retronecine. The difference in the sense of induction of the final products when carbon dioxide and methyl chloroformate are used in the (–)-**1** mediated lithiation-trapping of **35** and **76** is an unexpected result. (Scheme 1.61).



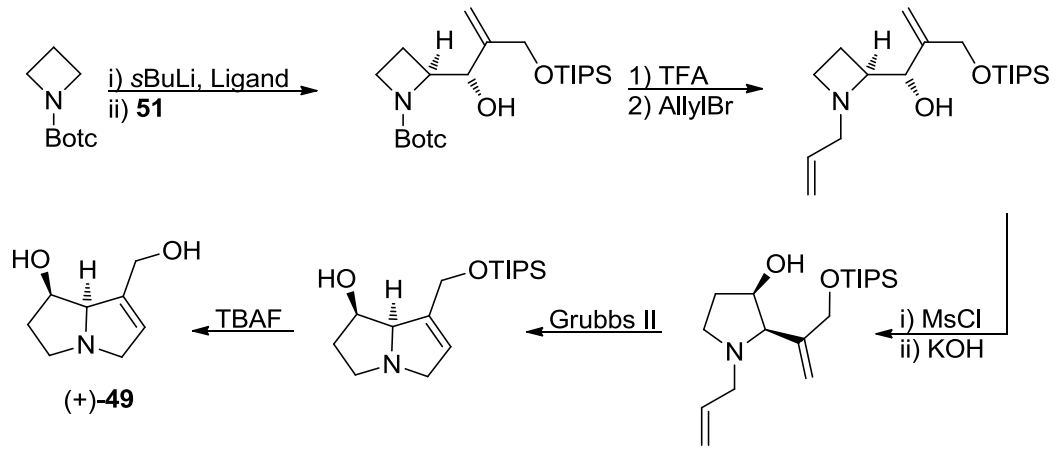
n=1, (*R*)-**70**
n=2, (*R*)-**91**

n=1, **35**
n=2, **76**

n=1, (*S*)-**69**
n=2, (*S*)-**87**

Scheme 1.61

Lithiated azetidine **64** and pyrrolidine **78** are configurationally unstable at –78 °C. The use of (–)-**1** as a chiral diamine favours the formation of the (*S*) enantiomer of lithiated azetidine **64** and pyrrolidine **78** in a 75:25 and 80:20 ratio respectively. Reactive electrophiles are thus most likely to retain this ratio in the final products. (*S*,*S*)-**12** appears to induce enantioselectivity *via* a dynamic kinetic resolution, given that CO_2 gives a product with a lower enantiomeric ratio than with methyl iodide. Overall, the mechanism of enantioinduction is dependent upon both the ligand and the electrophile employed in the reaction. The poor enantioselectivities observed with the (+)-sparteine surrogate (+)-**13** and (*S*,*S*)-Alexakis' diamine (*S*,*S*)-**12** have meant that the asymmetric synthesis of (+)-retronecine was not feasible. Future work could include the use of the Botc group, recently reported by Hodgson,[57] as well as a variety of other chiral diamines to find appropriate conditions to allow an asymmetric total synthesis of (+)-retronecine to be attempted (Scheme 1.62).


i) sBuLi, Ligand
ii) 51
Botc
OTIPS
OH
1) TFA
2) AllylBr
i) MsCl
ii) KOH
Grubbs II
TBAF
HO
H
(+)-49

Scheme 1.62

Chapter Two: Studies Towards the Total Synthesis of Anthracimycin

2.1 Introduction to Antibiotic Resistance

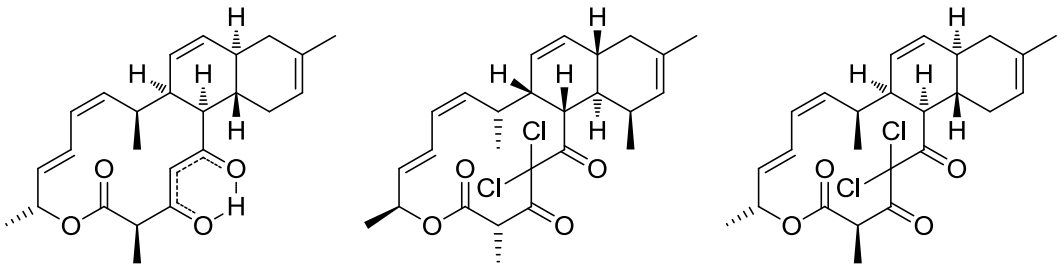
One of the most revolutionary developments in human history has been the discovery of antibiotics; injuries that would have previously been considered a death sentence are now treated as a matter of routine. Nonetheless, as antibiotic use has become more frequent and widespread, so too have resistant strains of bacteria. The centre for disease control (CDC) lists 18 different antibiotic resistant bacteria of varying threat levels, including multi-drug resistant *Neisseria gonorrhoeae*, methicillin-resistant *Staphylococcus aureus* and alarmingly, vancomycin – an antibiotic of last resort – resistant *enteroccoci* and *Staphylococcus aureus*. Indeed, in 2014, the World Health Organisation stated that:[78]

> *"Antimicrobial resistance (AMR) within a wide range of infectious agents is a growing public health threat of broad concern to countries and multiple sectors. Increasingly, governments around the world are beginning to pay attention to a problem so serious that it threatens the achievements of modern medicine. A post-antibiotic era – in which common infections and minor injuries can kill – far from being an apocalyptic fantasy, is instead a very real possibility for the 21st century."*

The problem of antibiotic resistant bacteria is compounded by the fact that there have only been two classes of new synthetic antibiotics discovered within the past sixty years,[79] the fluoroquinolones in 1961 and oxazolodinones in 1955, of which, only the former possess broad spectrum antibiotic activity. Similarly, for natural products with antibiotic activity, there have been only three that have been approved for medical use within the last forty years – daptomycin, quinupristin–dalfopristin and fidaxomicin – and each was deemed to be inappropriate for medical use when first discovered. Suffice to say, the need for new classes of antibiotics is urgent and difficult to overemphasise.

2.2 Introduction to Anthracimycin And Chlorotonil

In 2013, Fenical isolated anthracimycin **92** from a strain of *Streptomyces* found in a sea sponge off the coast of California.[80, 81] Anthracimycin was found to possess significant activity towards *Bacillus anthracis*, methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococci*,[82] as well as a range of other gram positive bacteria. Interestingly, a similar product, chlorotonil **93**, was found in an unrelated bacterium, *Sorangium cellulosum* and was recently discovered to possess potent antimalarial activity.[83, 84] Chlorotonil **93** has an additional methyl group on the decalin ring and a gem-dichloro group. Perhaps most interesting, however, is that is has the opposite configuration to anthracimycin **92** at all remaining stereocentres.



92 **93** **94**

Figure 2.1

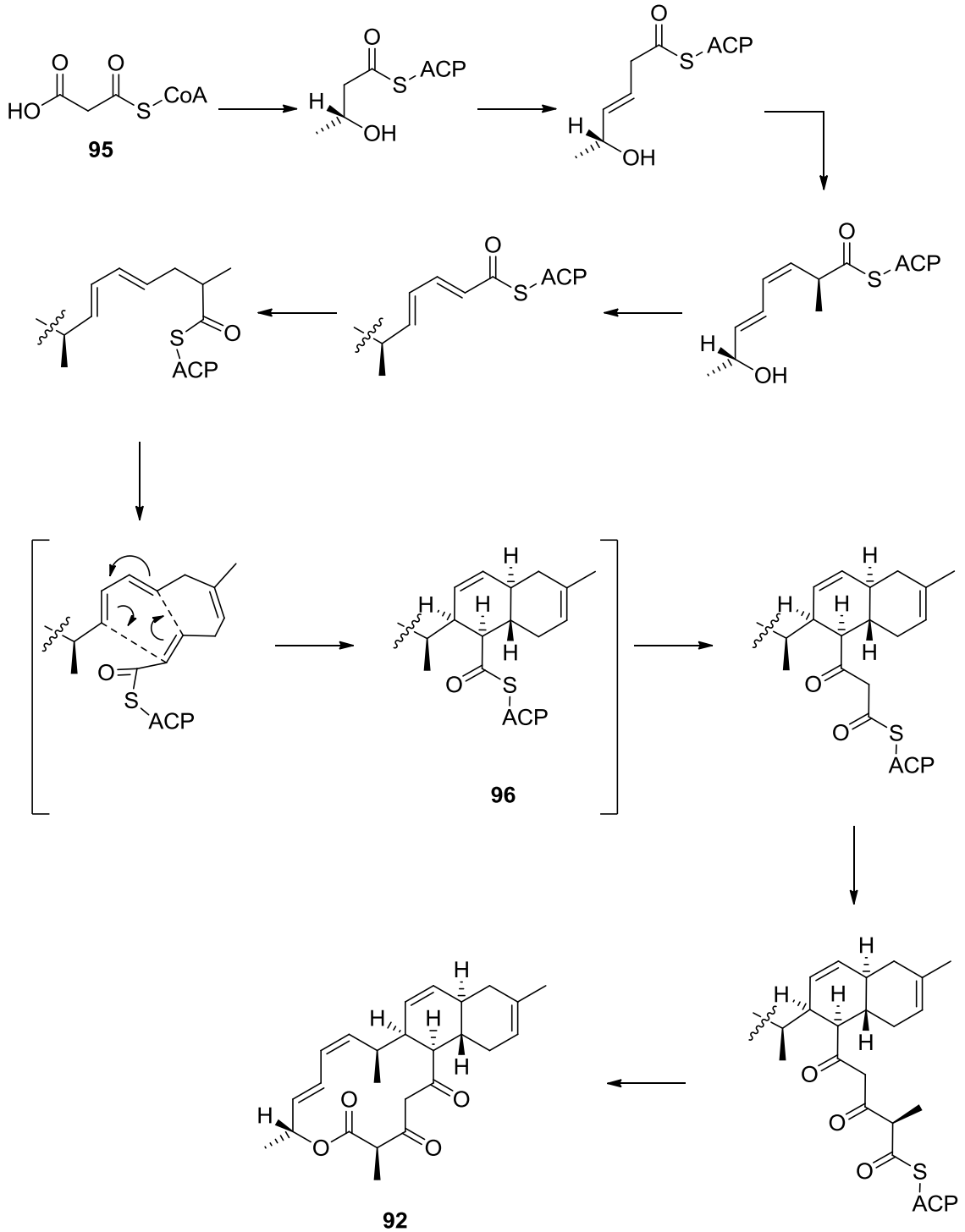
Given the structural similarities between anthracimycin **92** and chlorotonil **93**, anthracimycin was doubly chlorinated with *N*-chlorosuccinimide to give dichloro–anthracimycin **94** and its biological activity tested and compared to anthracimycin. (Table 2.1).[80]

Pathogen	Strain	92 MIC (μg/mL)	94 MIC (μg/mL)
Bacillus anthracis	UM23C1-1	0.03125	0.0625
Staphylococcus aureus	ATCC 13709	0.0625	0.125
Enterococcus faecalis	ATCC 29212	0.125	0.5
Streptococcus pneumoniae	ATCC 51916	0.25	0.25
Escherichia coli	MCR106 *imp*	>128	16
Escherichia coli	MG1655 *tolC*	>128	>128
Haemophilus influenzae	ATCC 31517	>256	32
Haemophilus influenzae	ATCC 31517 KO	4	4
Burkholderia thailandensis	E264 KO	>256	32
Pseudomonas aeruginosa	PAO1 KO	>256	32

Table 2.1: Biological Activity Comparison Between **92** and **94**

Anthracimycin **92** showed potent antibiotic activity towards gram positive bacteria *B. anthracis*, *S. aureus* and *E. faecalis*, yet poor activity towards gram negative bacteria *E. coli*, *H. influenzae*, *B. thailandensis* and *P. aeruginosa*, whereas dichloro-anthracimycin **94** is significantly more potent towards the gram negative bacteria with slightly decreased potency towards gram positive bacteria. It is speculated that dichlorination allows dichloro-anthracimycin **94** to cross the cell barrier more easily, although currently this remains unproven.

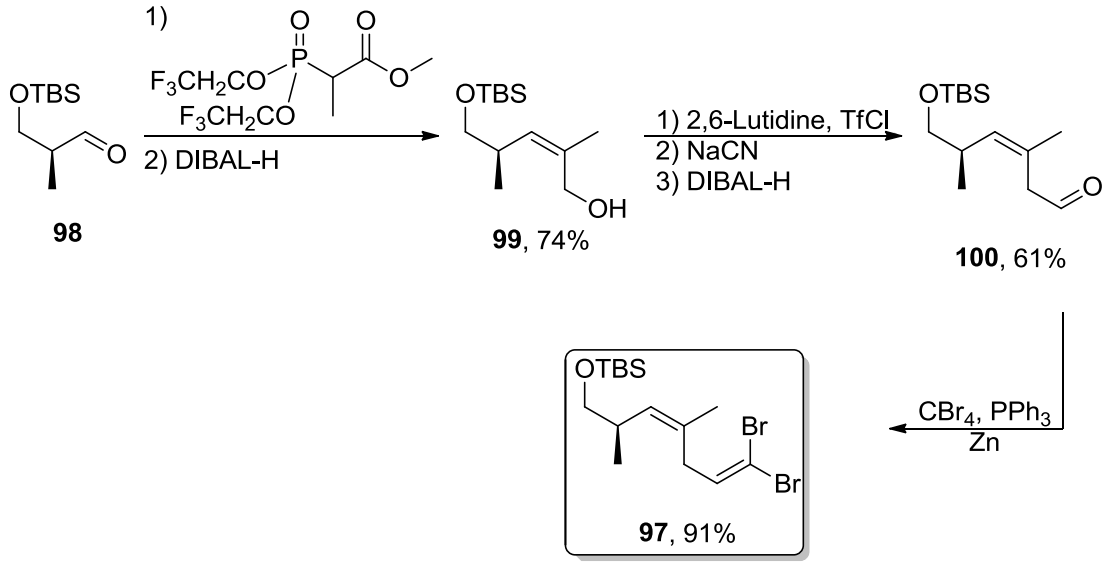
Anthracimycin **92**, unlike most other macrocyclic antibiobiotics, does not exert its biological effects by inhibiting protein synthesis by binding to the 50S ribosomal subunit. In contrast, it interferes with DNA replication, although the specific mechanism by which it does this has yet to be confirmed.[82] Recently, the gene cluster responsible for the biosynthesis of anthracimycin **92** was identified and the enzyme-mediated biosynthetic pathway is shown in Scheme 2.1. Starting from malonyl coenzyme A **95**, the biosynthetic pathway consists of multiple chain elongation reactions, with the key step being the intramolecular Diels-Alder reaction to form the decalin **96** and setting up the correct stereochemistry of four stereocentres.



Scheme 2.1

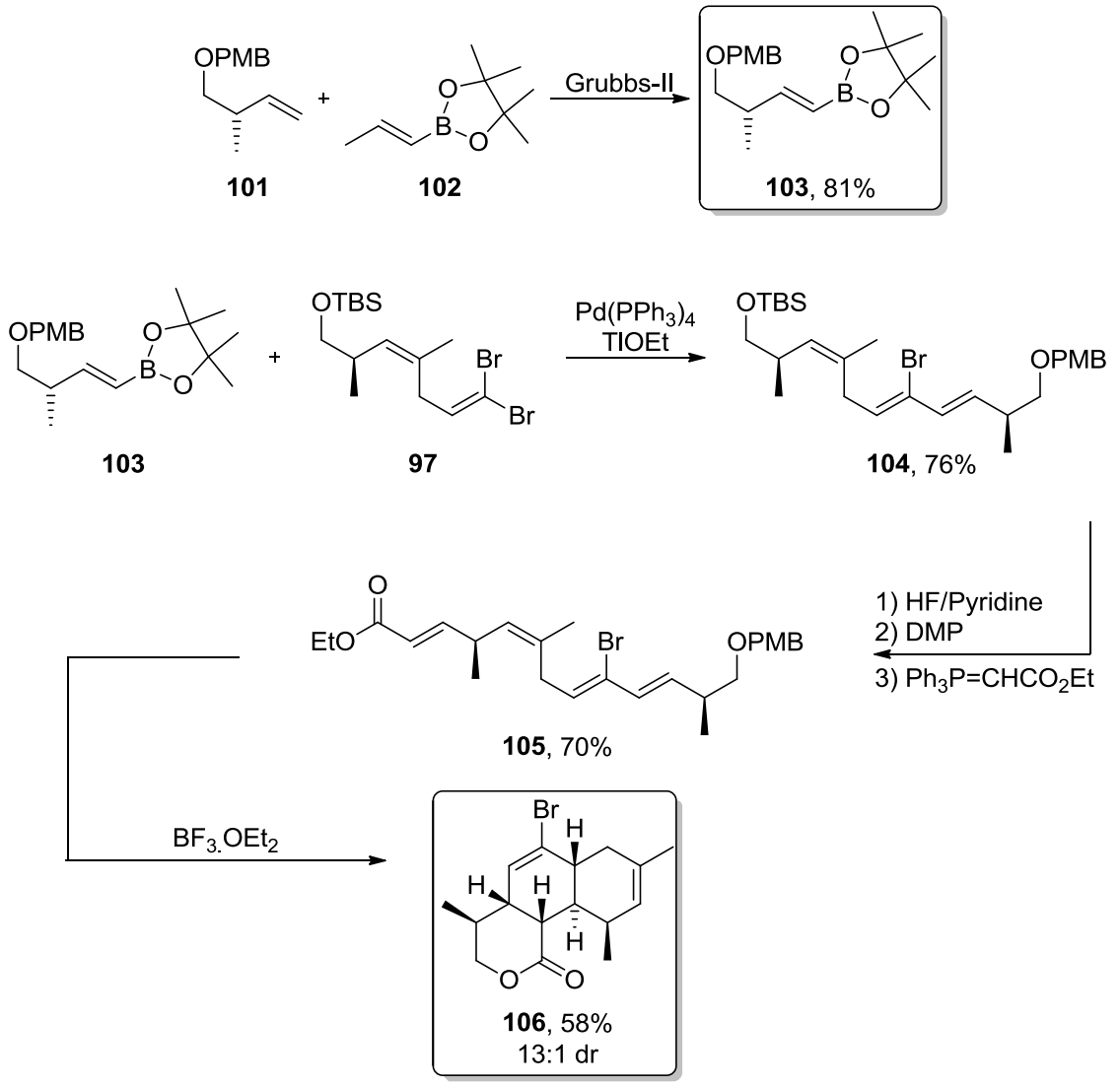
The structurally related chlorotonil **93** on the other hand, is toxic towards all stages of *Plasmodium falciparum*, the organism responsible for causing malaria, with an IC_{50} of between 4-32 nm, depending on strain. The fact that chlorotonil **93** exhibits low toxicity towards mammalian cells makes it an attractive target for medicinal use.

Remarkably, a total synthesis of chlorotonil **93** was reported in 2008, the same year that the natural product was isolated by Kalesse (Schemes 2.2-2.6).[85] Fragment **97** was synthesised from enantioenriched aldehyde **98** *via* a Still-Gennari[86] reaction and reduction to give **99**.[87] Then, a three-step homologation[88] gave aldehyde **100** which was followed by a Corey-Fuchs homologation[89] to give **97** in six steps in an overall yield of 41% (Scheme 2.2) .



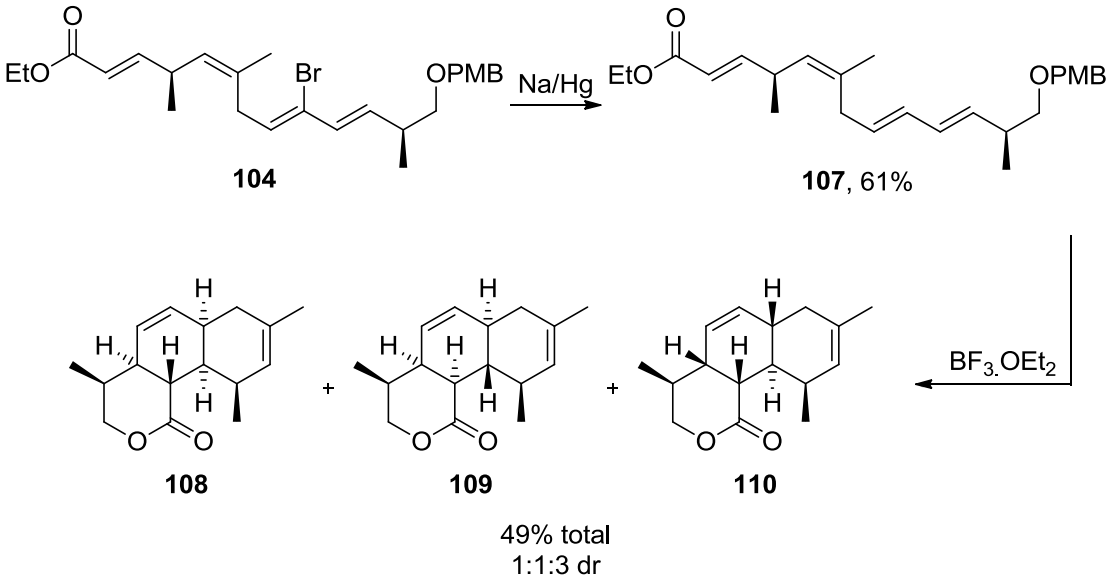
Scheme 2.2

Next, a cross metathesis[90] between PMB-protected alcohol **101** and vinyl boronic ester **102** gave fragment **103** in 81% yield and as a single geometric isomer. Suzuki coupling[91, 92] of **97** with boronic ester **103** gave brominated **104** in 76% yield which was then deprotected, oxidised and subjected to a stabilised Wittig reaction to give **105** in 70% yield over three steps. Finally, a one-pot intramolecular Lewis acid-mediated Diels-Alder reaction, PMB deprotection and lactonisation gave the tricyclic core **106** in 58% yield and a 13:1 diastereomeric ratio (Scheme 2.3).



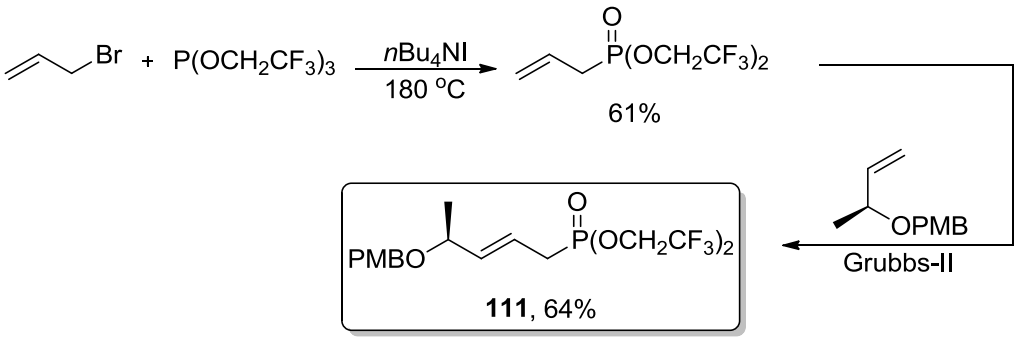
Scheme 2.3

Importantly, the presence of the vinylic bromine atom was necessary for the Diels-Alder step to proceed in high diastereoselectivity. When the same reaction conditions were applied to the debrominated derivative **107**, diastereoisomers **108**, **109** and **110** were isolated in 49% overall yield and a greatly reduced 1:1:3 diastereoselectivity (Scheme 2.4).



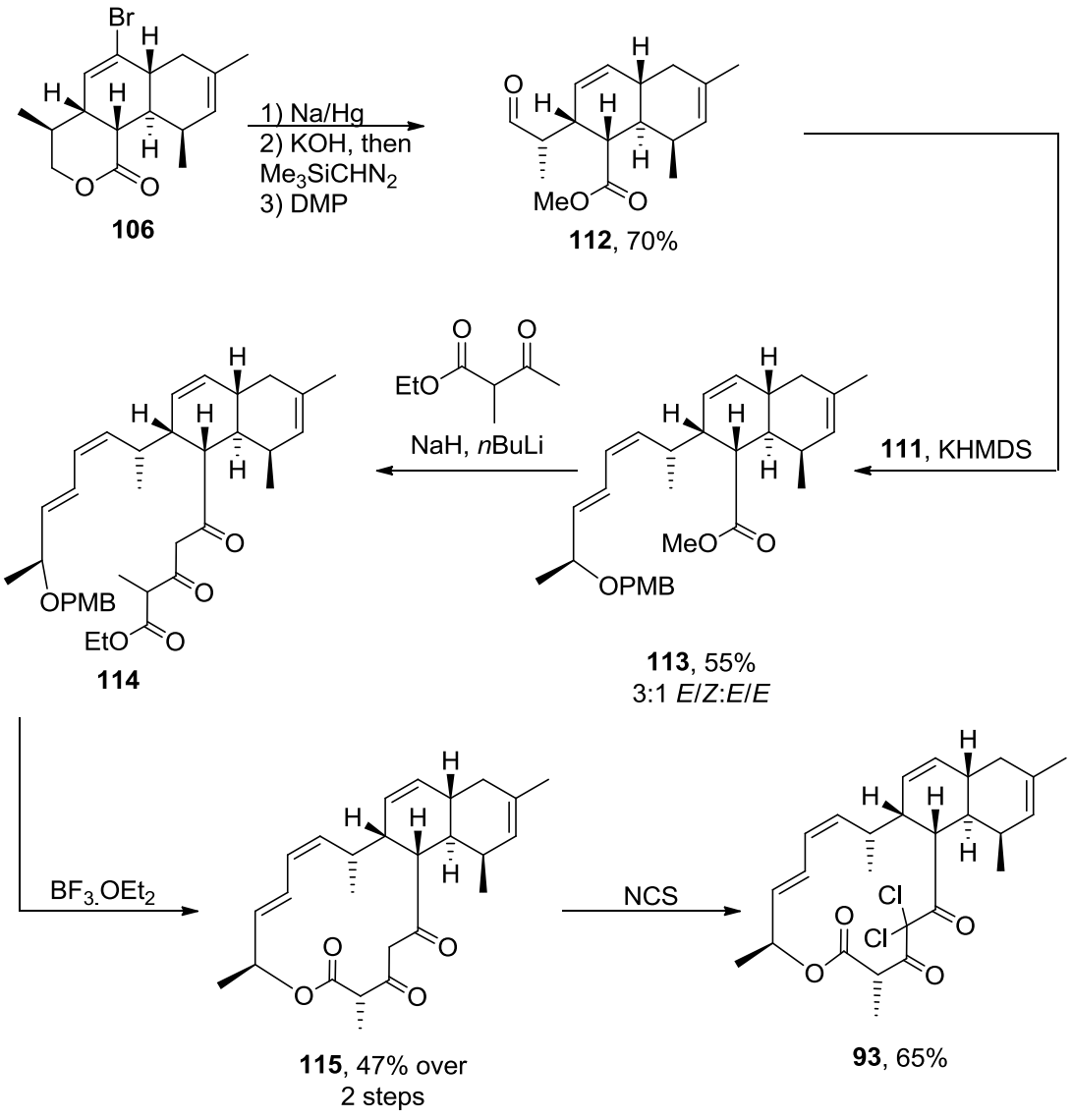
Scheme 2.4

Next, functionalised allyl phosphonate **111** was synthesised in another cross metathesis reaction in 39% overall yield from allyl bromide (Scheme 2.5).



Scheme 2.5

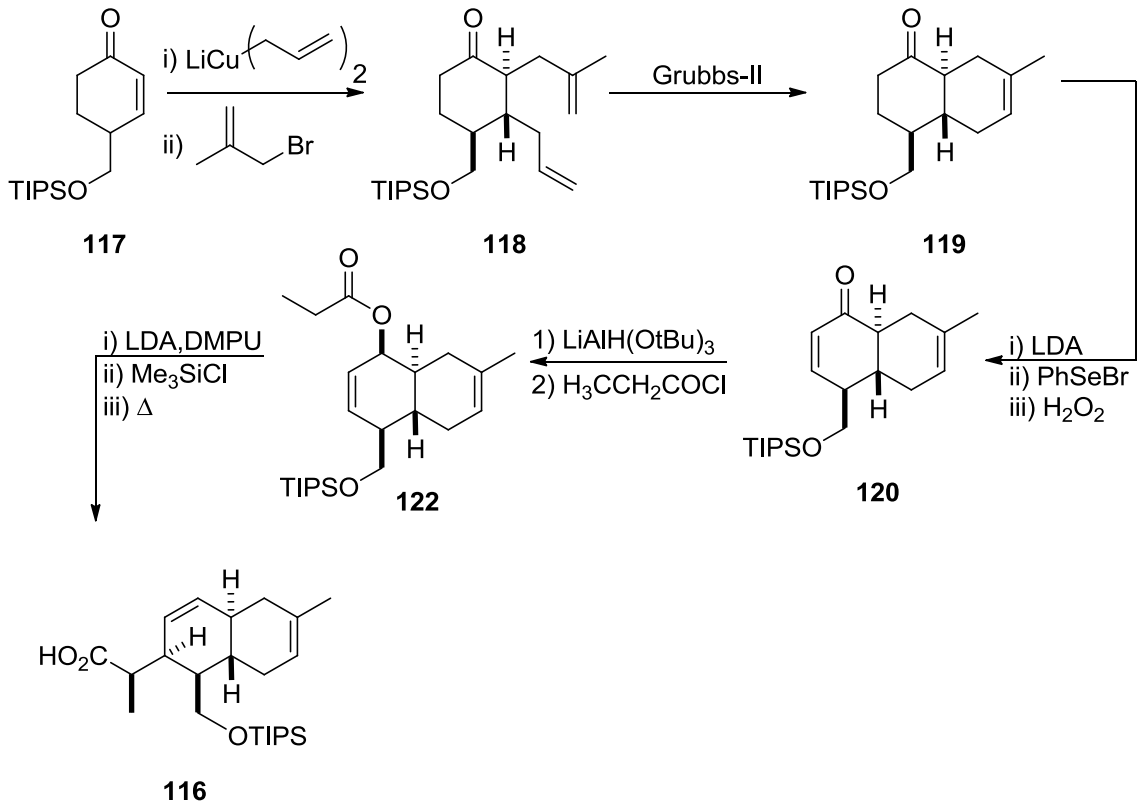
Brominated fragment **106** was then dehalogenated by treatment with sodium amalgam and the lactone opened with potassium hydroxide to give the intermittant carboxylic acid. Then, methylation with TMS-diazomethane,[93] oxidation with DMP gave the aldehyde **112** in a 70% yield over three steps. Next, a second Still-Gennari reaction between **112** and allyl phosphonate **111** gave tetraene **113** in 55% yield and a 3:1 *E*/*Z* to *E*/*E* ratio, followed by a Claisen condensation to give **114**. This was then immediately treated with $BF_3.OEt_2$ to deprotect the PMB ether and affect diastereoselective ring closure to give **115** in 47% yield over two steps. Finally, di-chlorination with NCS gave chlrotonil **93** in 65% yield. The complete synthesis proceeds in 18 linear steps and 1.5% overall yield.


Br
H
H
H
H
O
O
106
1) Na/Hg
2) KOH, then
Me3SiCHN2
3) DMP
O
H
H
H
MeO
O
112, 70%
111, KHMDS
O
O
EtO
NaH, nBuLi
MeO
O
OPMB
113, 55%
3:1 E/Z:E/E
OPMB
O
O
EtO
O
114
BF3.OEt2
NCS
Cl
Cl
O
115, 47% over
2 steps
93, 65%

Scheme 2.6

2.3 Project Outline

Anthracimycin **92** has a very interesting antibiotic profile and has yet to be made synthetically. The development of a total synthesis would allow analogues to be prepared and evaluated for biological activity as antimicrobial agents. Also, given the structure-activity relationship between anthracimycin **92**, di-chloroanthracimycin **94** and chlorotonil **93**, our aim was to develop a racemic synthesis of anthracimycin to allow both enantiomers to be tested for biological activity. As such, all structures presented hereafter will be racemic unless stated otherwise. Our proposed synthesis of the macrocycle follows a similar route to that published by Kalesse for the synthesis of chlorotonil **93**, but includes a new approach to the synthesis of the decalin core **116** and is shown below in Scheme 2.7. Most of our efforts focused on the early steps of this synthesis.

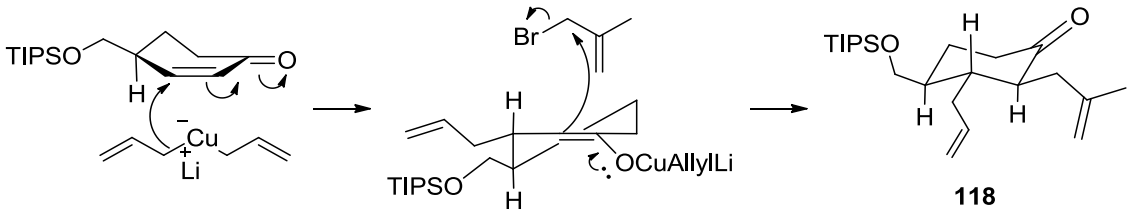


Scheme 2.7

From the starting enone **117**, a stereoselective one-pot 1,4-addition of allyl cuprate, followed by trapping of the intermediate enolate with methallyl bromide is expected to give **118**. Ring closing metathesis, for example, with Grubbs 2nd generation catalyst would then form the desired *trans*-decalin **119**. Next, regioselective formation of the

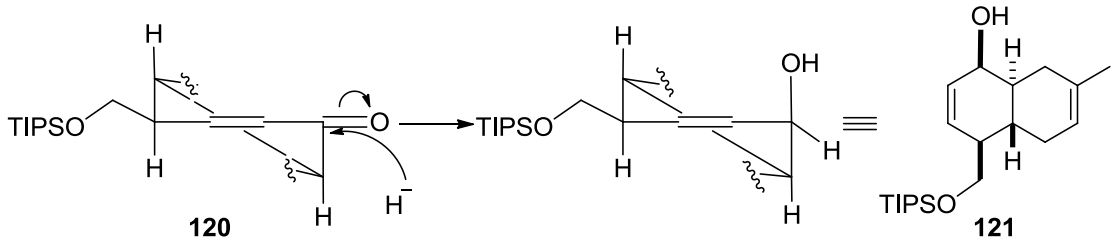
less substituted enolate with LDA, trapping with phenylselenium bromide and oxidative work-up was planned to then give enone **120**. Stereoselective 1,2-reduction should then give alcohol **121** which would then be acylated with proprionyl chloride to give the propionyl ester **122**. The resulting ester would be treated with LDA/DMPU to form the (*E*)-enolate,[94] trapped with Me_3SiCl and then warmed to allow a stereospecific Ireland-Claisen[95] rearrangement to give carboxylic acid **116**.

The relative stereochemistry of the five contiguous stereocentres in carboxylic acid **116** will be controlled in the following ways. First, cyclohexenones such as **117** adopt a relatively flat orientation.[96] The initial addition of allyl cuprate to **117** should therefore occur from the opposite face to the bulky CH_2OTIPS substituent to minimize steric repulsion (Scheme 2.8).[97] This will generate the intermediate enolate. As the allyl group is now closer to the nucleophilic centre, the approach of methallyl bromide to the enolate will occur opposite to it, thus creating diene **118** with all ring substituents adopting equatorial positions.



Scheme 2.8

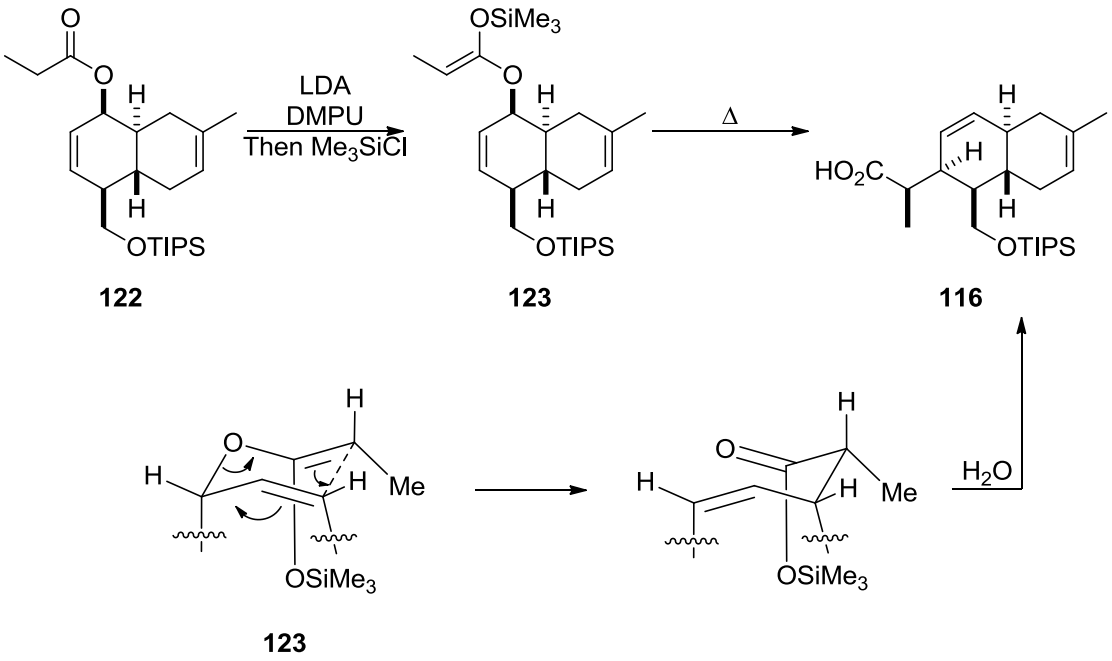
Secondly, reduction of **120** using the sterically bulky $LiAlH(OtBu)_3$ should proceed *via* equatorial attack of hydride to give alcohol **121** with the hydroxyl and CH_2OTIPS groups on the same face (Scheme 2.9).



Scheme 2.9

Thirdly, proprionyl ester **122** will be treated with LDA/DMPU to selectively form the (*E*)-enolate,[94] trapped with Me_3SiCl to form the corresponding (*Z*)-silyl enol ether **123**

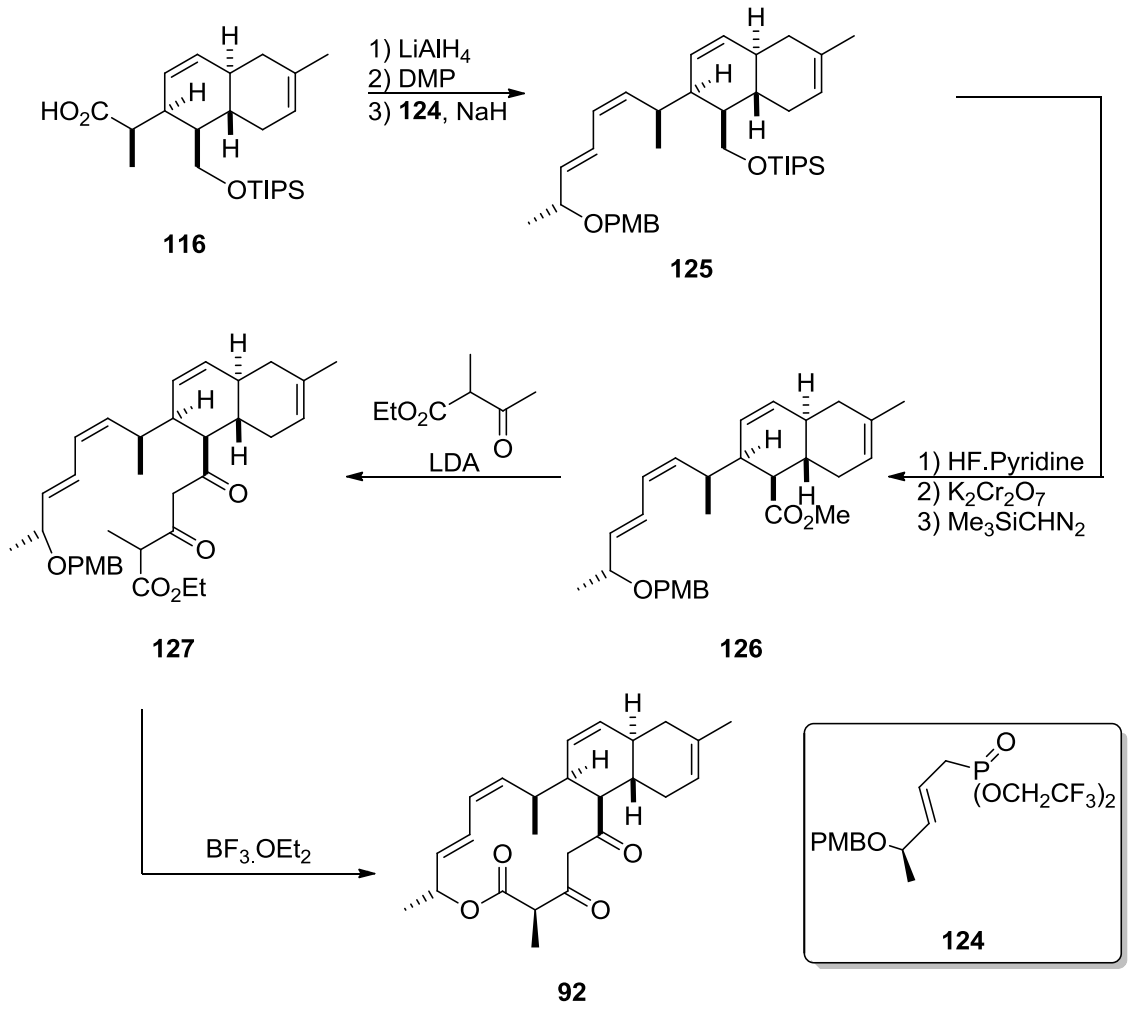
and then warmed to allow a stereospecific Ireland-Claisen[95] rearrangement to give carboxylic acid **116**. The transition state of this reaction is shown in Scheme 2.10. The configuration of the exocyclic methyl group in carboxylic acid **116** will be dependent upon the enolate geometry. Should the Ireland-Claisen rearrangement proceed *via* a different transition state and give the methyl group with the opposite configuration, the corresponding (*E*)-silyl enol ether could be formed by deprotonation with LDA in the absence of DMPU.



Scheme 2.10

The proposed end-game synthesis to take carboxylic acid **116** to anthracimycin **92** is shown below in Scheme 2.11. $LiAlH_4$ reduction of the carboxylic acid, DMP oxidation to the aldehyde and a (*Z*)-selective Still-Gennari olefination using the PMB-protected allyl phosphonate **124** should give the conjugated diene **125**. Next, removal of the TIPS group with hydrogen fluoride in pyridine, Jones oxidation[98] to the carboxylic acid followed by methylation with TMS-diazomethane would give the corresponding methyl ester **126**. At this point, our synthesis follows that of Kalesse.[85] A Claisen condensation of **126** with the dianion formed from ethylacetoacetate, PMB deprotection and diastereselective ring closure by treatment with $BF_3.OEt_2$ should allow access to anthracimycin **92**. Anthracimycin **92** is a pseudo-enantiomer of chlorotonil **93**, apart from the additional methyl group on chlorotonil **93**, anthracimycin **92** possesses the opposite configuration at all remaining stereocentres. It would therefore be reasonable

to assume the ring closing step to form anthracimycin **92** from **127** will place the malonic methyl group in the opposite configuration to chlorotonil **93**.



Scheme 2.11

In this chapter, our efforts exploring the early parts of this proposed route to anthracimycin **92** are described.

2.4 Synthetic Efforts Towards Anthracimycin

2.4.1 Preparation of the Starting Enone

As it is the beginning of a total synthesis, a reliable, scalable synthesis of enone **117** was required. Cyclohexanones with substitution at the 4-position such as **128**, **129**, **130** and **131** are prohibitively expensive to be used as the starting material of a multi-step total synthesis, their per-gram prices from Sigma-Aldrich being shown below in Figure 2.2. Conveniently, the corresponding 1,4-disubstituted aromatic derivative **132**, presents a much more economically viable starting material for the synthesis of TIPS protected enone **117**. Thus, our proposed synthesis began with the hydrogenation of 4-hydroxybenzyl alcohol **132** (Scheme 2.12).

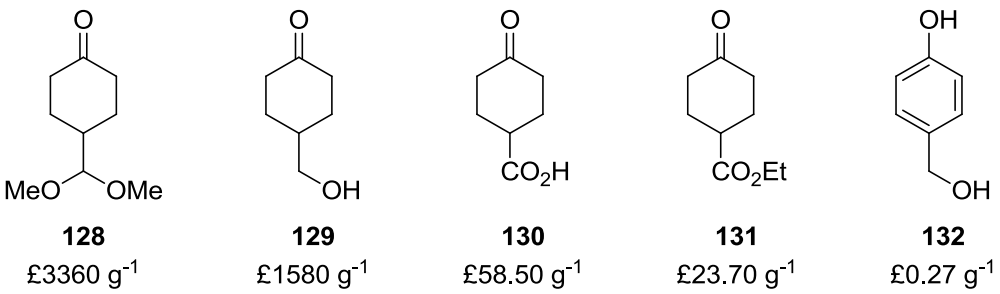
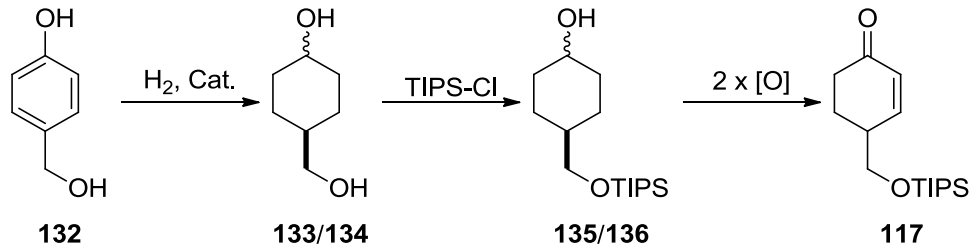


Figure 2.2

With the chosen starting material in hand, our overall aim was to carry out ring hydrogenation, followed by TIPS protection of the primary alcohol. This would be followed by two successive oxidations to get to the desired TIPS protected enone **117** (Scheme 2.12).



Scheme 2.12

Initially, small scale reactions were carried out to find appropriate conditions for the large scale synthesis of enone **117**. Use of Pd/C as a heterogeneous catalyst led to

cleavage at the benzylic C–O position to give *p*-cresol as the major product. Changing the catalyst to PtO_2, known for hydrogenation of aromatic rings,[99] led to isolation of the desired saturated diols **133**/**134** as a 1:2 inseparable mixture of stereoisomers (by ^{1}H NMR spectroscopy) in a combined yield of 58%. The reaction was very slow, requiring five days to reach completion. However, the catalyst loading was very low at 1 mol% and from a practical perspective, very straightforwards, requiring only occasional refreshing of the hydrogen source. The reaction also proved very amenable to scale up due to the robustness of the chemistry and the low cost of starting materials. The results of the multigram synthesis will be presented later.

Heterogenous hydrogenations of alkenes typically proceed from the least hindered face.[100-105] For the purposes of this discussion, the *cis* isomer is assumed to be the major isomer, although this was not definitively assigned due to the difficulty in assigning *J* values for **133**/**134**, with the ^{1}H NMR spectrum shown in Figure 2.3. The stereoselectivity for the reaction was taken by the ratio of the integrals from the signals at approximately δ 3.73 and 3.57 ppm, corresponding to the C*H*(OH) protons.

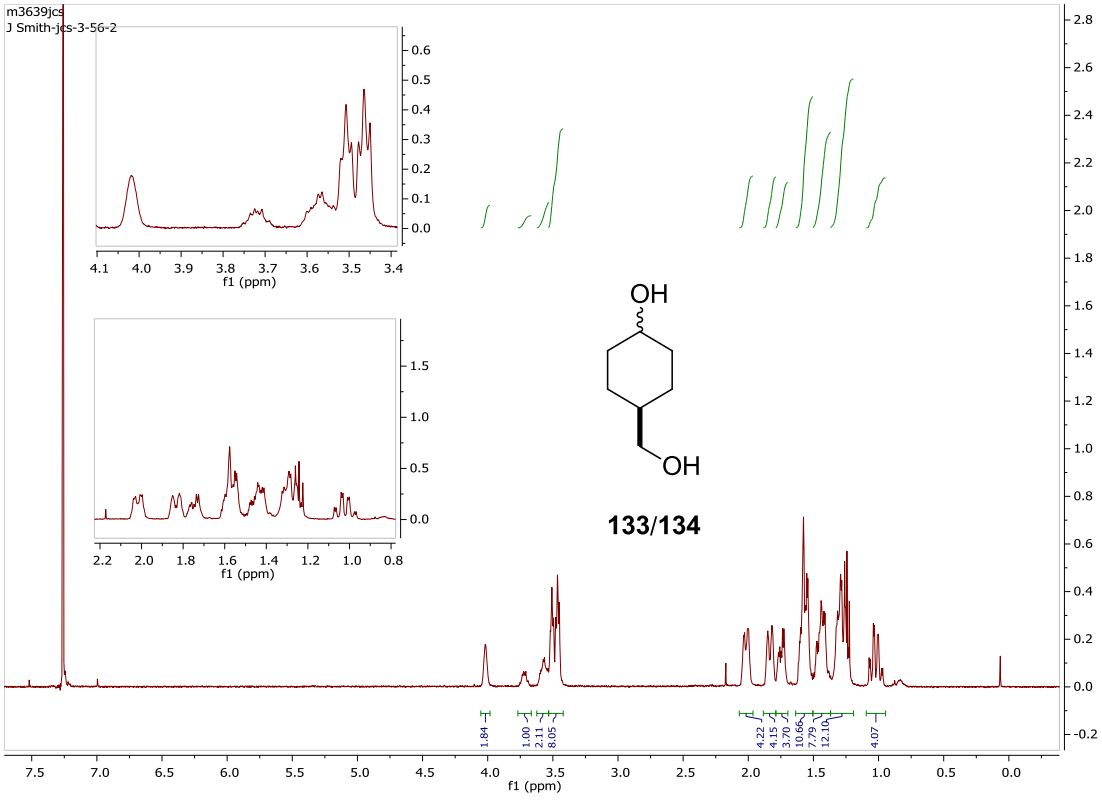
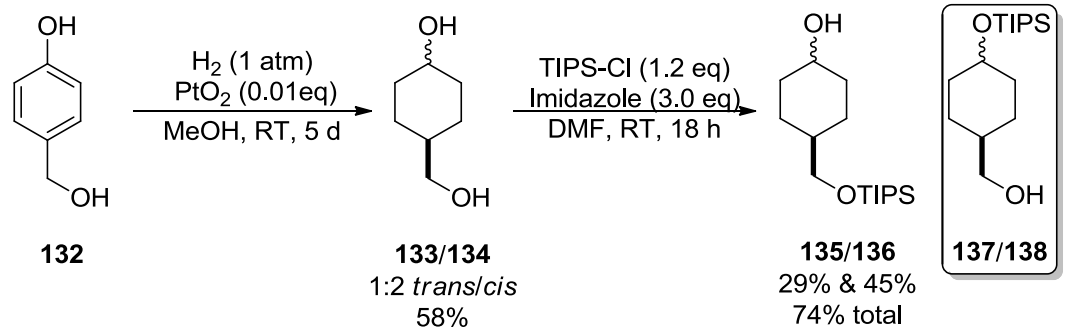


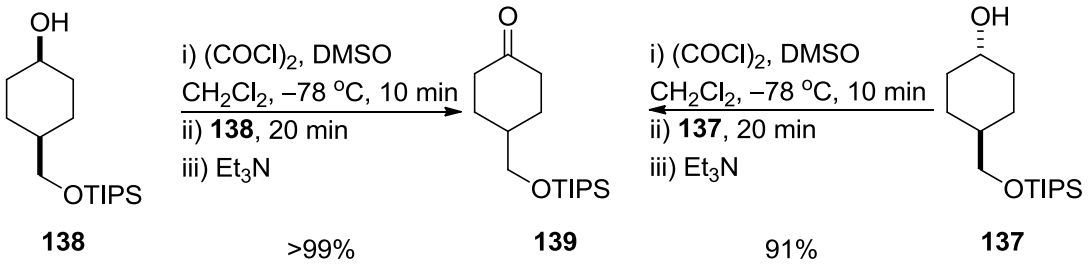
Figure 2.3

Diols **133**/**134** were then selectively protected at the primary alcohol by treatment with TIPS-Cl in a total yield of 74% (Scheme 2.13).



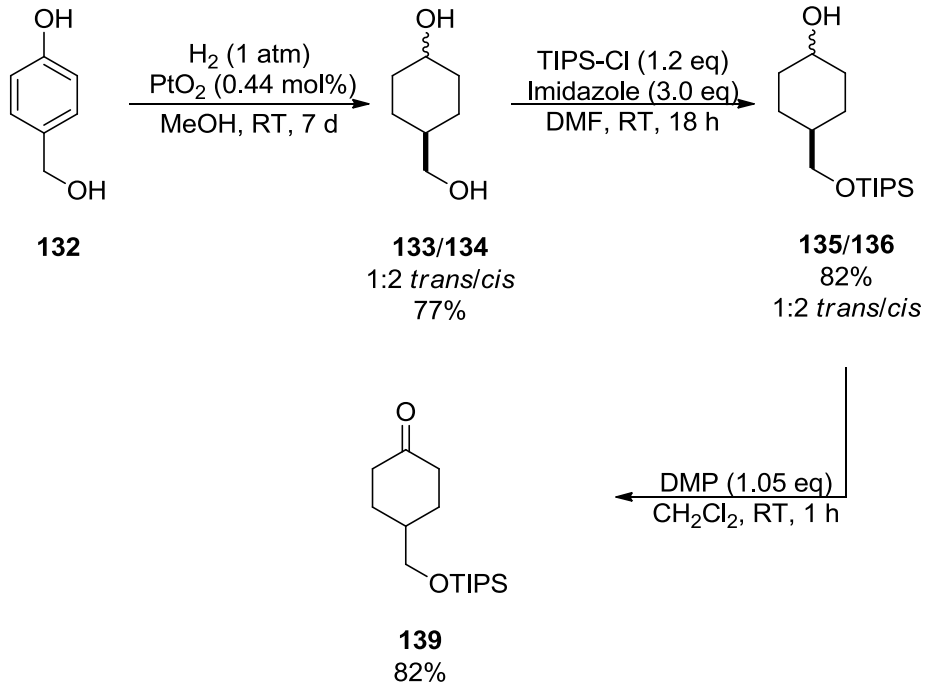
Scheme 2.13

Initially, it was unclear whether or not one of stereoisomers *trans*-**135** and *cis*-**136** were in fact potential regioisomers **137** or **138** (Scheme 2.13). The identity of **135** and **136** was confirmed by independently oxidising a pure sample of each isomer, each giving **139** with identical analytical data (Scheme 2.14).



Scheme 2.14

TIPS protected ketone **139** also proved amenable to a multigram scale synthesis *via* the same route (Scheme 2.15). Yields for the hydrogenation of phenol **132** to give **133**/**134** could be improved to 77% with longer reaction times (7 days) and reduced catalyst loadings (0.44 mol%) with no change in stereoisomeric ratio. Silylation of the primary alcohol also proceeded in a similar fashion upon scale up, with yields of 82% being observed with 2 g of diols **133**/**134** as starting material. Finally, ketone **139** could be formed in 72% *via* a Swern oxidation[106-108] or an improved 82% *via* a Dess-Martin periodinane oxidation.[109, 110]

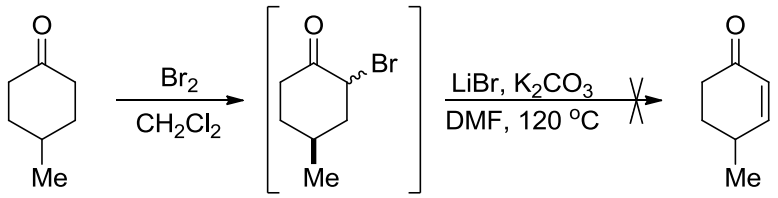


Scheme 2.15

2.4.2 Oxidation of Ketone 139

There are several known methods for the introduction of alkene functionality into ketones to generate the corresponding enones. Most commonly, methods for the oxidation of ketones into enones include α-bromination and elimination,[111] sulfoxide/selenoxide elimination,[112, 113] catalytic oxidation of silyl enol ethers[114] and the use of hypervalent iodine reagents.[115] Not all these methods are equally suited for large scale synthesis. Selenium reagents are both toxic and expensive and the formation of the α-keto selenide intermediate requires large amounts of pyrophoric organolithium reagents. Sulfides are typically formed *via* the same methodology and although the sulfur reagents are usually less toxic, elimination of the sulfoxide requires elevated temperatures which often leads to deletrious side reactions occurring. The Saegusa oxidation, whereby silyl enol ethers are treated with palladium(II) acetate in the presence of a stoichometric oxidant, often requires catalyst loadings in excess of 50 mol%, usually relegating it to late-stage synthesis. For these reasons, robust, scalable methodology for the introduction of the alkene bond into ketone **139** needed to be developed. In order not to waste ketone **139**, commercially available 4-methyl cyclohexenone **140** was used initially in its place.

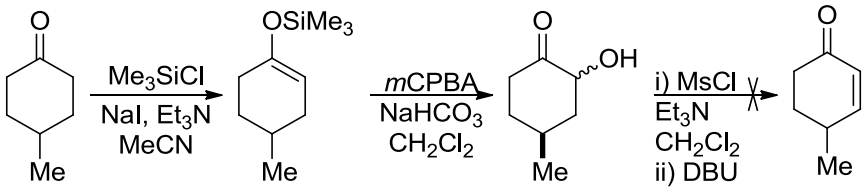
To begin with, cyclohexenone **140** was subjected to a two-step bromination-elimination reaction (Scheme 2.16). Bromination in CH_2Cl_2 proceeded rapidly at room temperature, but bromo-ketones **141**/**142** were found to be unstable and decomposed at room temperature, forming a dark, tarry material over several hours. Attempts to immediately eliminate the crude bromo-ketones **141**/**142** without prior purification, however, failed to give the desired enone **143**.



140 **141/142** **143**

Scheme 2.16

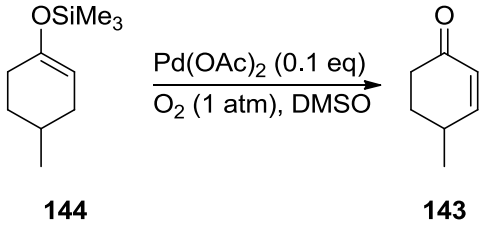
Also investigated was the use of a Rubottom oxidation of silyl enol ether **144**, followed by mesylation and elimination of the α-hydroxy ketones **145**/**146** (Scheme 2.17). Cyclohexenone **140** was converted into the corresponding silyl enol ether **144** by treatment with Me_3SiCl, sodium iodide and triethylamine in acetonitrile in 72% yield after distillation under reduced pressure. Then, reaction of **144** with buffered *m*CPBA, followed by acid-catalysed epoxide opening successfully gave a 57:43 diastereomeric mixture of α-hydroxy ketones **145**/**146** in 41% yield. Unfortunately, attempted mesylation-elimination of **145**/**146** gave rise to a complex mixture of products.



140 **144**, 72% **145**/**146**, 41% 57:43 dr **143**

Scheme 2.17

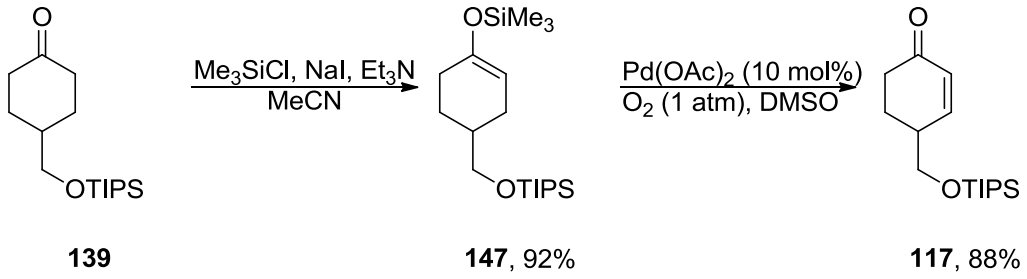
The most promising method attempted was a Saegusa oxidation of silyl enol ether **144** (Scheme 2.18). Although only 25 mg of crude product was obtained from 0.59 g of the starting silyl enol ether **144**, ^{1}H NMR spectroscopic data of the crude material showed complete conversion into enone **143**.



Scheme 2.18

The practical procedure for the isolation of enone **143** involved dilution of the reaction mixture, followed by extraction with hexane. It was envisioned that enone **143** is more soluble in water than in hexane. Due to the large hydrophobic group on ketone **139**, the reaction was repeated on **139**, hoping that the corresponding enone would be preferentially soluble in hexane.

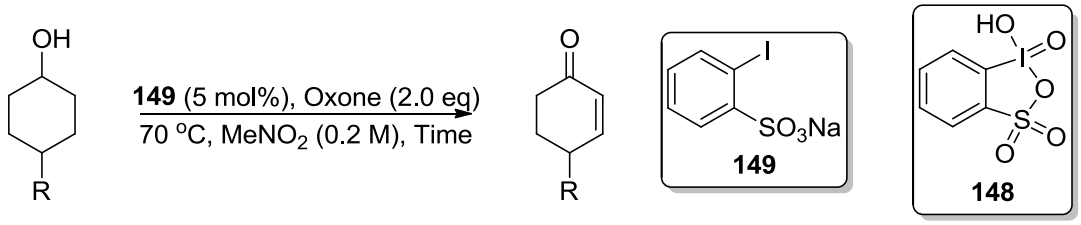
Silyl enol ether **147** was synthesised *via* the same procedure used to synthesise silyl enol ether **144**, initially giving a 54% yield after reduced pressure distillation. Saegusa oxidation of **147** afforded enone **117** in 28% yield over two steps. It is worth noting the low catalyst loadings for the oxidation of **147** and this allowed efficient scale up of the reaction without being prohibitively expensive. On a multi-gram scale, yields of up to 92% were observed for the formation of silyl enol ether **147** and 88% yield for the formation of enone **117**, corresponding to a total yield over two steps of 81% (Scheme 2.19).



Scheme 2.19

Concurrent to these investigations, we also looked into the use of hypervalent iodine reagents to carry out an efficient oxidation of ketone **139** into enone **117**. In 2009, Ishihara[116] first reported the use of the IBX-like analogue, IBS **148** as a catalytic oxidant for the formation of enones from alcohols. Some selected examples are shown in Table 2.2. Unlike IBX, IBS **148** is formed *in situ* from pre-catalyst **149** upon reaction with the

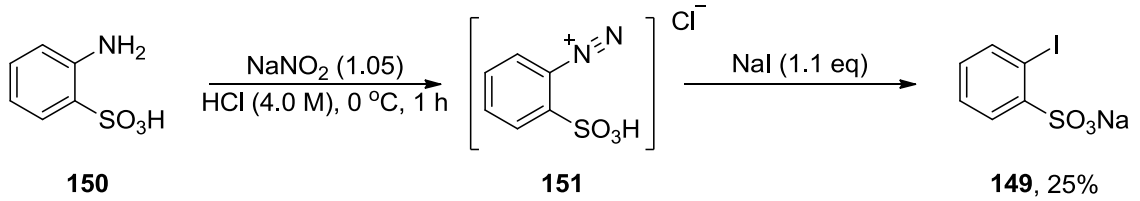
stoichometric oxidant, oxone; the use of nitromethane as a solvent was necessary for adequate conversions.



Entry	R	Time (h)	Yield (%)
1	H	8	82
2	$SiPh_2tBu$	6	88
3	Ph	8	88
4	Me	8	83

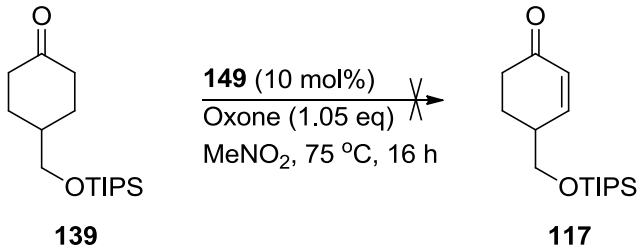
Table 2.2: IBS Mediated Oxidation of 4-Substituted Cyclohexanols

We reasoned that the underlying mechanism was initial oxidation of the alcohol followed by a second oxidation of the ketone. Thus, pre-catalyst **149** was synthesised in a one-pot procedure from amino-sulfonic acid **150** in an overall yield of 25% (Scheme 2.20)



Scheme 2.20

Unfortunately, no reaction was observed when ketone **139** was subjected to the same conditions reported by Ishihara (Scheme 2.21). In retrospect, the analogous reaction should have been attempted on alcohols **135**/**136**, although this was not thought of at the time.



139 **117**

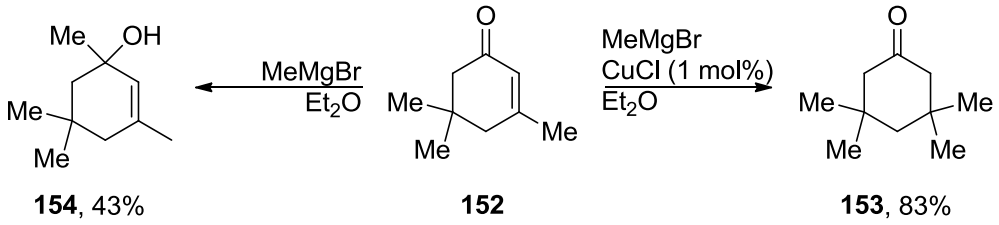
Scheme 2.21

In summary, an efficient gram-scale protocol for the oxidation of ketone **139** into enone **117** was developed, with the highest yields being achieved *via* a Saegusa oxidation of silyl enol ether **147**.

2.5 Investigation of Cuprate Additions

2.5.1 Literature Overview of Cuprate Additions to Enones

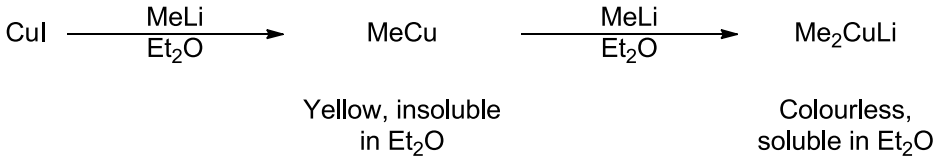
In 1866, Rudolf Böettger reported the discovery of copper(I) acetylide[117] which was prepared by passing acetylene gas through ammoniacal copper(I) chloride. Shock sensitive and explosive when dry, copper(I) acetylide was the first compound discovered to possess a carbon-copper bond. Since then, carbon-copper bond-containing compounds have proved to be of immense synthetic utility. In 1936, Gilman reported that organocopper reagents (RCu) can undergo cross-coupling reactions with organohalides.[118] In 1941, Kharash demonstrated how catalytic quantities of a copper(I) salt could drastically influence the regioselectivity of Grignard reagent additions to enone **152**.[119] For example, the addition of 1 mol% of copper(I) chloride resulted in 1,4-adduct **153** being the major product of the reaction, whilst in the absence of copper salts, 1,2-adduct **154** was isolated in 43% yield (Scheme 2.22).



154, 43% **152** **153**, 83%

Scheme 2.22

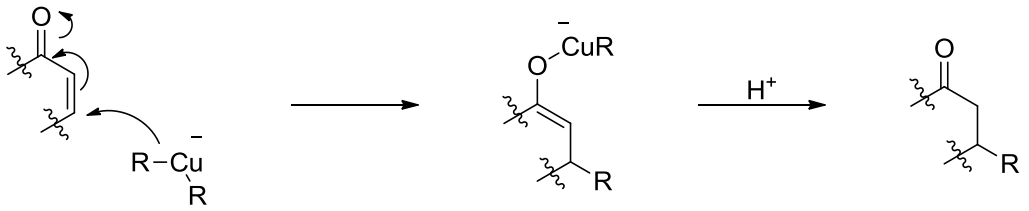
Perhaps the most notable moment in organocuprate chemistry was the 1952 study by Gilman.[120] Treatment of copper(I) iodide with one equivalent of methyllithium produced insoluble methyl copper. Upon treatment with a second equivalent of methyllithium, the solid precipitate redissolved to form the anionic lithium dimethylcuprate (Scheme 2.23).



Scheme 2.23

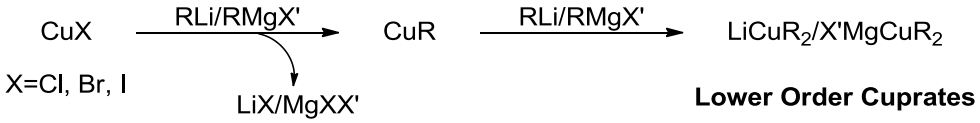
The subsequent work by Corey, House and Whitesides[121-123] firmly established the utility of organocuprates for a range of carbon-carbon forming reactions. In the context of our proposed synthesis, the ability of cuprates to carry out regioselective 1,4-addition to α,β-unsaturated carbonyl compounds, specifically enones, is of prime importance.

Generally, when considering 1,4-additions of cuprates to enones, the mechanism is simplistically considered to be a classical conjugate addition of a nucleophile. This gives an enolate that is then protonated to give the final product (Scheme 2.24).



Scheme 2.24

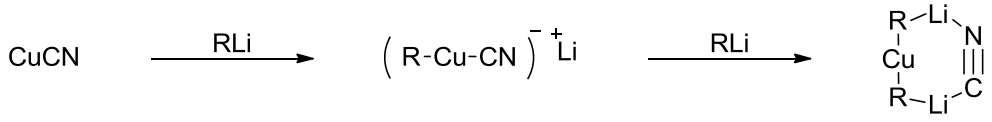
In reality, cuprate chemistry is far more nuanced. The copper(I) salt, with general formula CuX, plays a large role in the identity of the cuprate species. Halides generally form weak bonds with copper, readily dissociating from copper upon treatment with one equivalent of organolithium/Grignard reagent to form the corresponding organocopper reagent (Scheme 2.25). The addition of a second equivalent of organolithium/Grignard reagent then forms the cuprate reagent, also known as "lower order" cuprates.[124]



Scheme 2.25

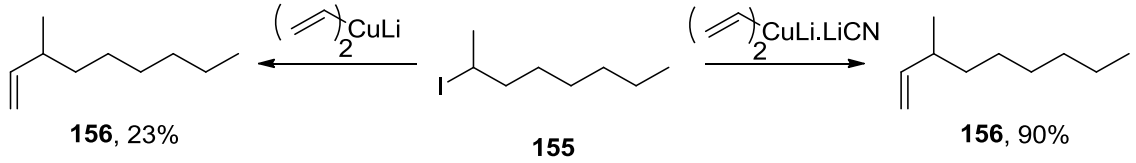
In 1981, Lipshutz[125] suggested the use of a non-transferable ligand on copper, followed by the addition of two equivalents of organolithium reagent to achieve a "higher order" cyanocuprate ($R_2Cu(CN)Li_2$). Although similar higher order cuprates have been characterised in dimethyl sulfide, namely $[Li_3(CuPh_3)(CuPh_2)(SMe_2)_4]$,[126, 127] they have, to date, not been characterised in ethereal solvents and to the best of our knowledge, no cyanocuprate of general formula ($R_2Cu(CN)Li_2$) has ever been characterised. Indeed, NMR,[128-130] EXAFS[131, 132] and IR[133] studies of these cyanocuprates demonstrated that whilst the cyanide ligand is bound to the copper following the addition of a single

equivalent of organolithium reagent, it is not upon addition of a second equivalent (Scheme 2.26). Indeed, ^{15}NMR spectroscopic studies by Bertz[128] demonstrated that the most likely structure of these cyanocuprate reagents was a dialkyl copper species, with bridging Li–CN–Li interactions.



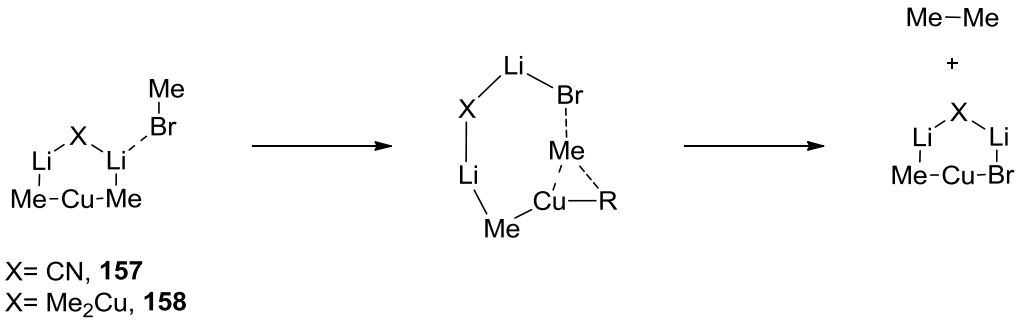
Scheme 2.26

Cyanocuprates can have markedly different reactivities. In 1981, Lipshutz[125] compared the efficiency of the Gilman vinyl cuprate with the higher order cyanocuprate equivalent in an S_N2 reaction with 2-iodooctane **155**. The higher order cyanocuprate gave greatly improved yields of the desired alkene **156** (Scheme 2.27).



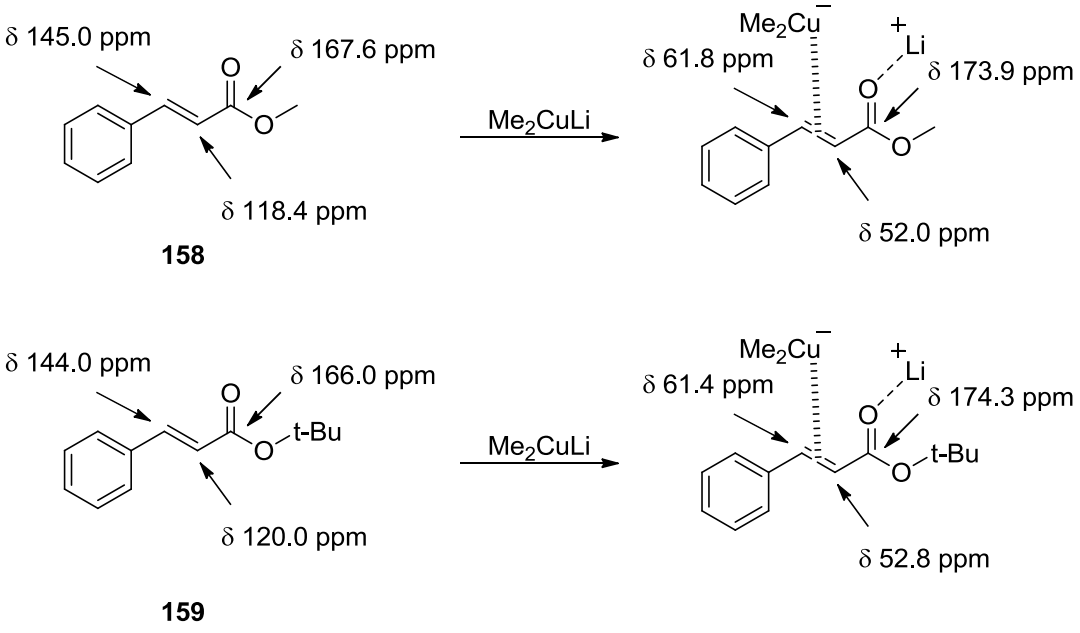
Scheme 2.27

Nakamura[134] offered an explanation for this difference in reactivity with a comparative computational study of the S_N2 reaction of Me_2CuLi/$Me_2CuLi.LiCN$ with MeBr. This study suggested that, firstly, an increased Lewis acidity of the $[Li–CN–Li]^+$ moiety serves to better activate the MeBr to nucleophilic attack and, secondly, that there is a more energetically favourable structural change of the $[Li–CN–Li]^+$ moiety. Indeed, Nakamura calculated the activation energy of reaction with cyanocuprate **157** to be 3.8 kcal mol^{-1} lower than for the Gilman cuprate **158** (Scheme 2.28).



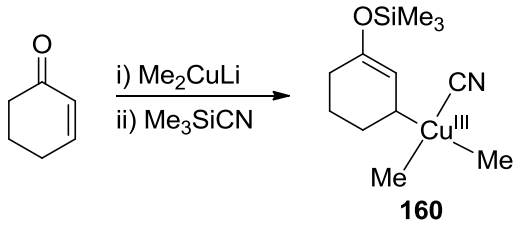
Scheme 2.28

From *in situ* ^{13}C NMR spectroscopic studies of the reaction between Me_2CuLi and methyl and *t*-butyl cinammate **158** and **159**, carried out by Ullenius,[135] it was shown that the initial step of 1,4-addition involved the formation of an η^2 Cu–π complex (Scheme 2.29). Olefinic carbon atoms in both **158** and **159** experience roughly an 80 and 70 ppm upfield shift upon addition of Me_2CuLi (Scheme 2.29). The small downfield shift of the carbonyl carbon atoms was also postulated to be due to co-ordination to the lithium ion, although the precise aggregation state in which it exists is not known and will likely differ depending on cuprate identity, solvent and stoichometry.



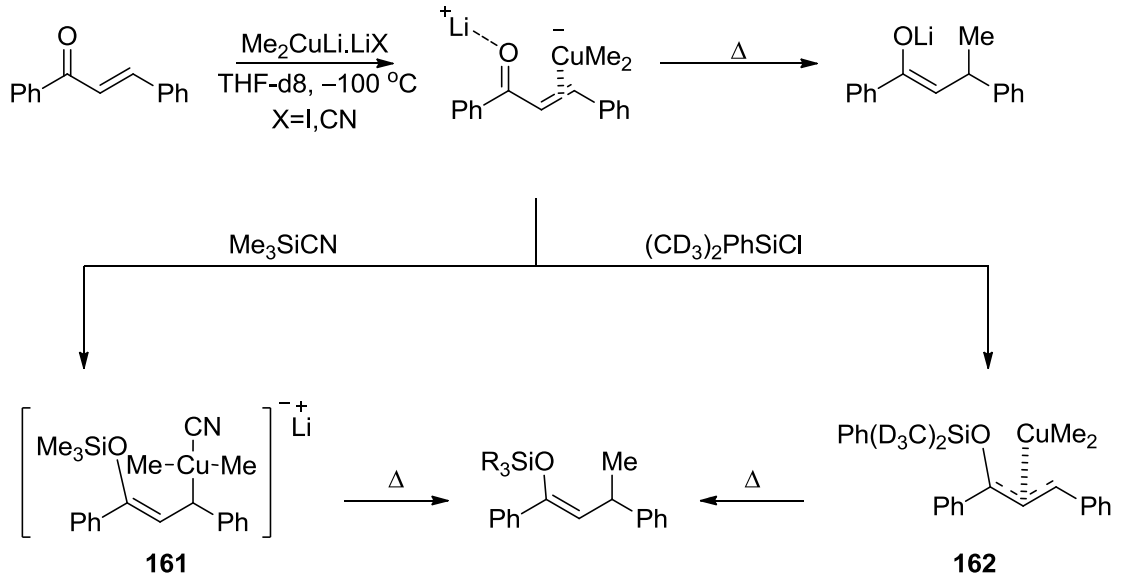
Scheme 2.29

For many years, the existence of a transient Cu(III) species had been speculated to exist.[136, 137] Recently, low temperature, rapid injection ^{13}C NMR spectroscopy provided the first experimental evidence to confirm this idea.[138, 139] The σ-bonded cuprate **160** was observed following the addition of Me_2CuLi to cyclohexenone and Me_3SiCN (Scheme 2.30).



Scheme 2.30

In 2012, Bertz later discovered a key role of the silyl reagent, often used to trap the enolate.[139] Use of Me_3SiCN directly gave the σ-bonded, square planar enolate **161** (Scheme 2.31) whereas addition of $(CD_3)_2PhSiCl$ in fact gave the η^3 allyl π-complex **162**. In both cases, thermal decomposition leads to the formation of the desired 1,4-adduct. The steric bulk of the silyl reagent determines the temperature at which η^3 π-allyl complex **162** undergoes decomposition. The η^3 allyl π-complex derived from the use of Et_3SiCl instead of $(CD_3)_2PhSiCl$, rapidly decomposed at –100 °C, whereas **162** was indefinitely stable at the same temperature. In the absence of a silyl reagent, the η^2 π-allyl complex requires higher temperatures to undergo oxidative addition/reductive elimination. The overall mechanism for cuprate additions to enones, therefore, is the initial formation of a copper η^2 π-complex, followed by an oxidative addition process to form the transient Cu(III) species, then a rate determining reductive elimination type process[140] to form an enolate which can then be quenched (Scheme 2.31).



Scheme 2.31

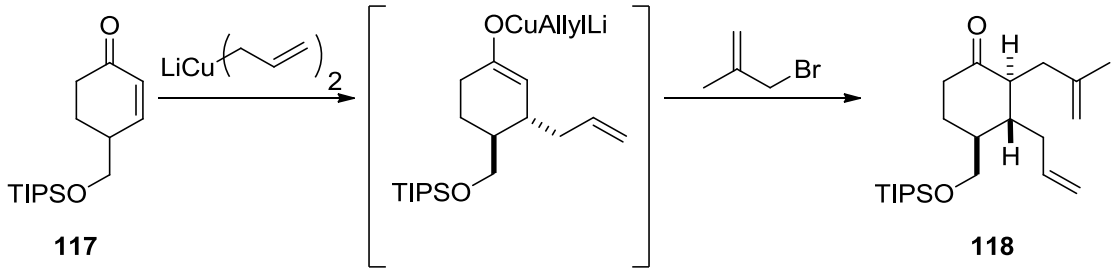
Although there are many examples of 1,4-additions of alkyl and aryl cuprates to enones, there are few successful examples of successful 1,4-addition of allylic cuprates to enones. To the best of our knowledge, there are no reported reactions of successful 1,4-addition of an allylic cuprate to an enone, followed by alkylation of the resulting enolate. In 1989, Lipshutz[141] demonstrated that allylic cuprates exist as the η^1, σ-bonded tautomer, instead of the corresponding π-allyl species (Figure 2.4). Curiously, it was noted that allyl Gilman cuprate $(allyl)_2CuLi$ had to be prepared at –105 °C and

underwent extensive decomposition at –90 °C. The corresponding cyanocuprate, however, was stable at –70 °C.

Figure 2.4

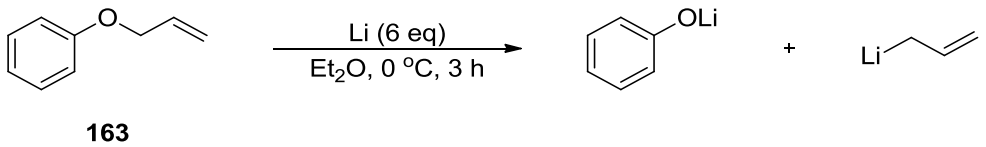
2.5.2 Exploration of Addition of Cuprates to Cyclohexenones

The next stage of our proposed total synthesis of anthracimycin **92** requires the 1,4-addition of allyl cuprate to TIPS-protected enone **117** (Scheme 2.32), with our ultimate aim being to trap the enolate that is formed with methallyl bromide. Our initial studies however, focused on developing effective conditions to allow the 1,4-addition.



Scheme 2.32

Lipshutz generated allyl cyanocuprate $(allyl)_2CuCNLi$ *via* a transmetallation reaction of tetraallyltin and *n*BuLi, followed by addition of the CuCN.LiCl. Reductive lithiation of allyl halides is not typically considered a viable method of accessing allyllithium, due to the propensity of the intermediate allyl radical to homocouple.[142] Nonetheless, due to the toxicity and persistence of stannanes, it was decided to make allyllithium *via* the method reported by Eisch,[142] whereby allyl phenyl ether **163** is treated with lithium metal to generate lithium phenoxide and allyllithium (Scheme 2.32).

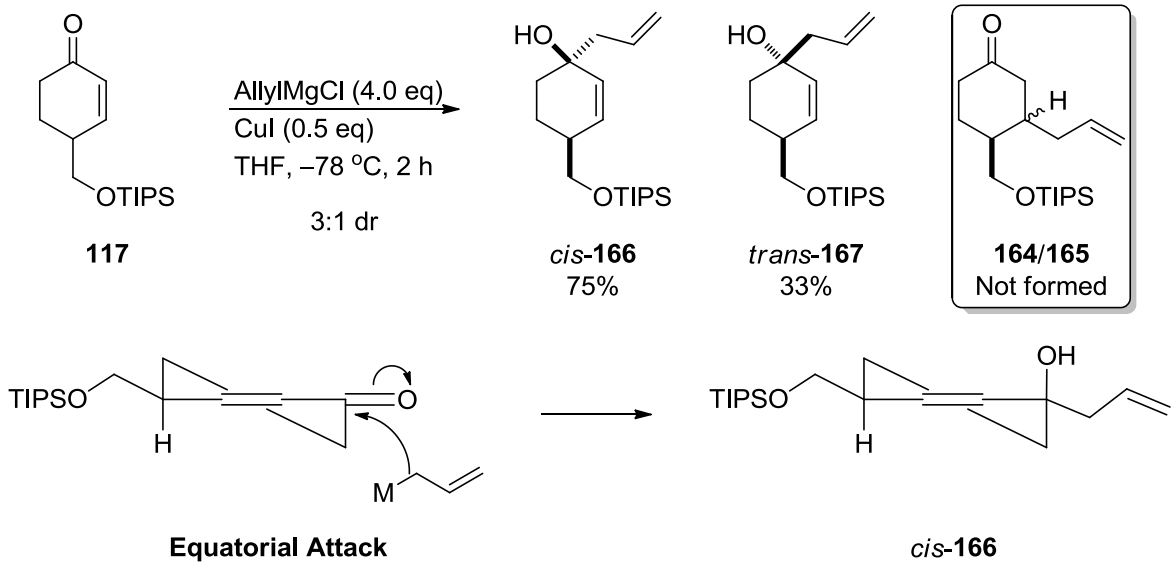


163

Scheme 2.32

However, this reaction proved difficult to reproduce in our hands. Due to being a hetereogeneous reaction, yields were highly dependent on the surface area and the degree of oxidation of the lithium metal. For this reason, allylic cuprates derived from the corresponding Grignard reagent were used in our studies

Our initial experiments began with small scale (20 mg) trial reactions on enone **117**. Thus, enone **117** was treated with 4 equivalents of allylmagnesium chloride and 0.5 equivalents of copper(I) iodide. We expected to see 1,4-adducts **164** and **165**. However, instead, 1,2-adducts **166** and **167** were isolated in quantitative yield and a 3:1 diastereomeric ratio (by ^{1}H NMR spectroscopy of the crude product). The absence of the expected ketone was clearly observed in the IR and ^{13}C NMR spectra, and there was a hydroxyl peak in the IR spectrum. Not only that, an additional two signals in the alkene region were observed in the ^{13}C NMR spectra (Figures 2.5 and 2.6), as well as an additional two protons in the alkene region of the ^{1}H NMR spectra (Figures 2.7 and 2.8). The relative stereochemistry of alcohols **166** and **167** was not definitively assigned, although we assume equatorial attack at the carbonyl to predominate, giving rise to *cis*-**166** as the major product (Scheme 2.33).



Scheme 2.33

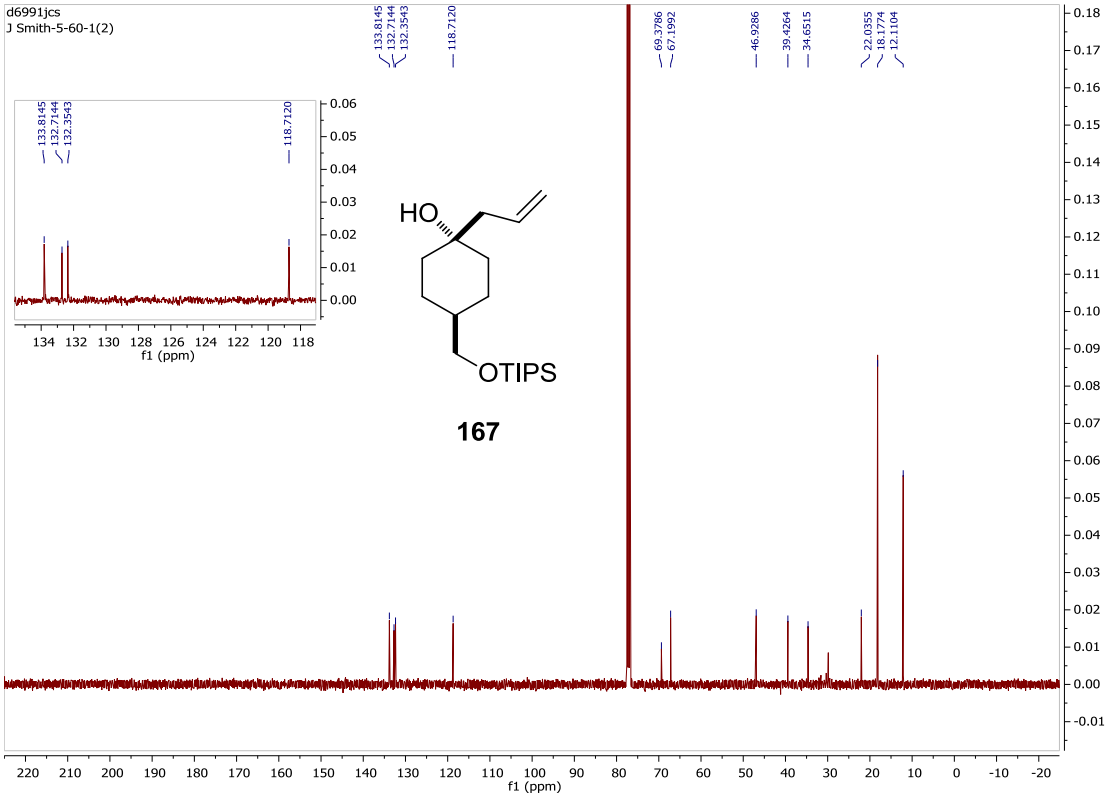


Figure 2.5

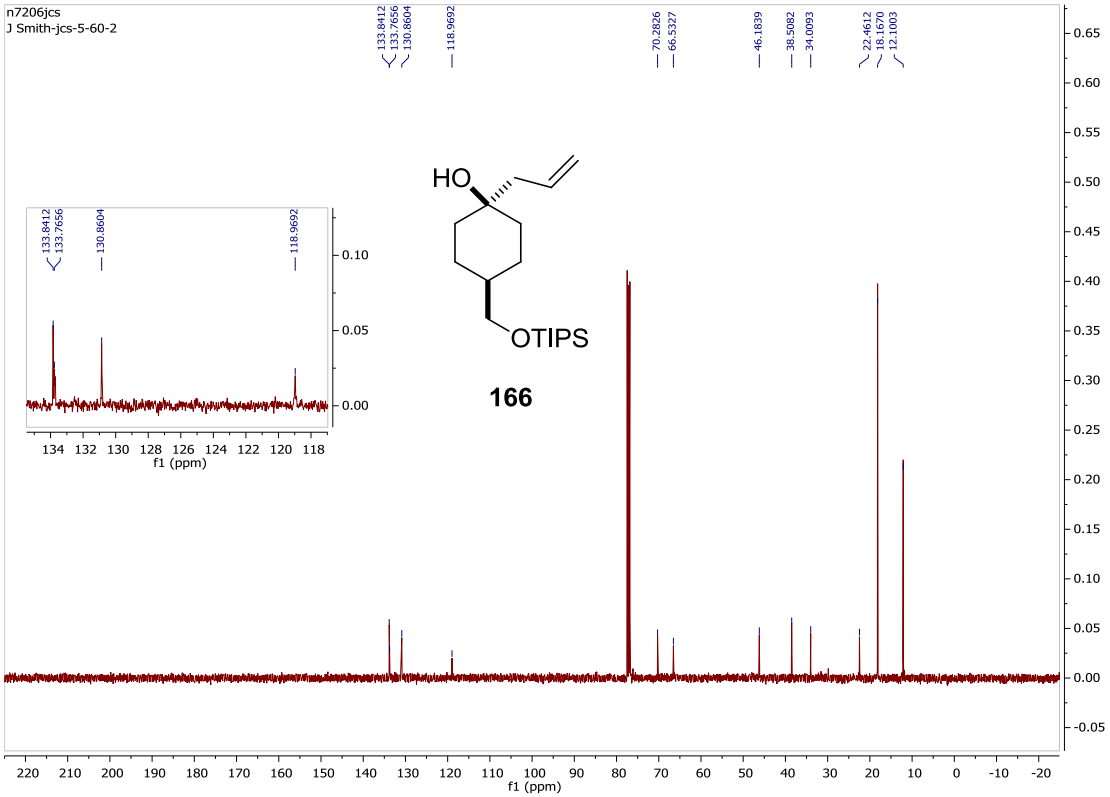


Figure 2.6

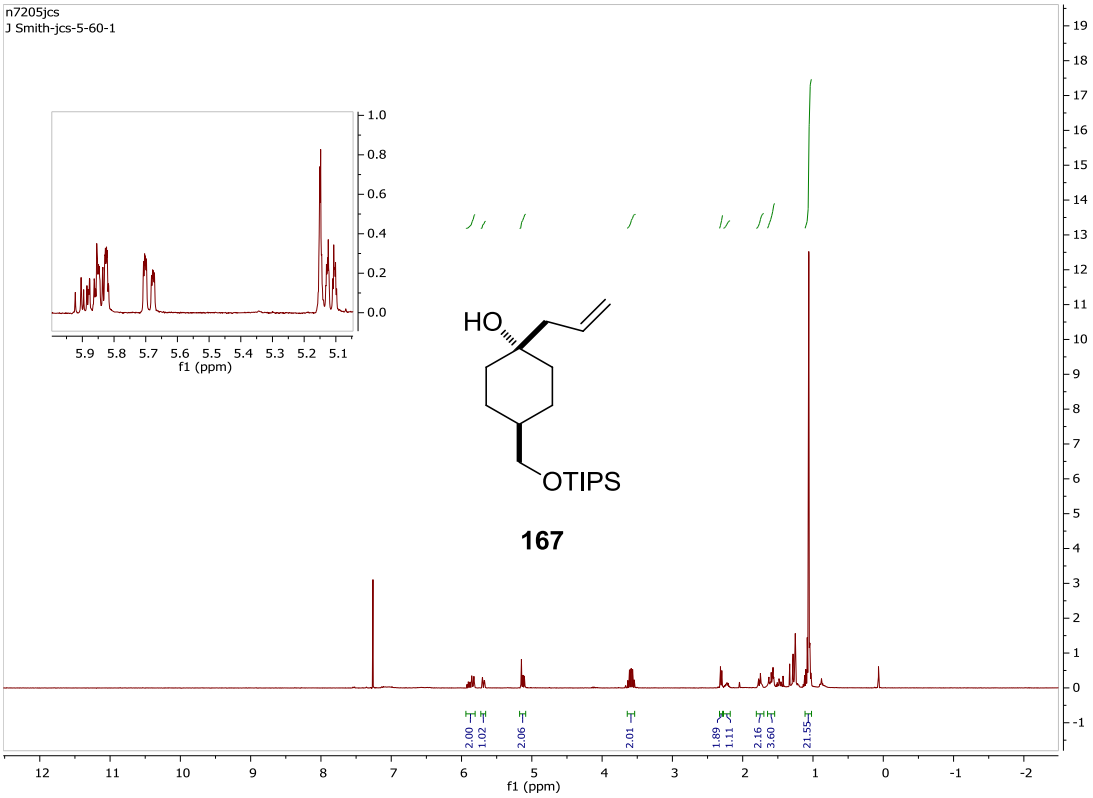


Figure 2.7

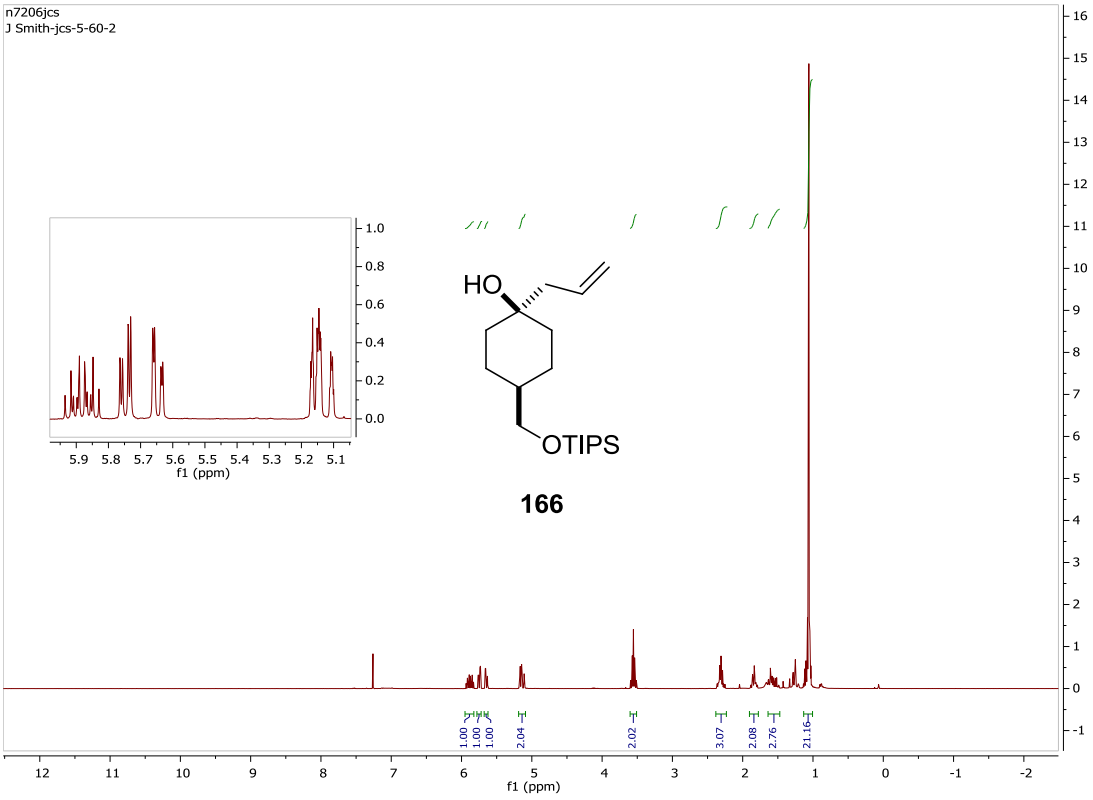
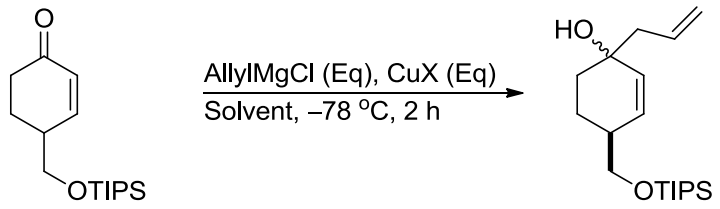


Figure 2.8

In order to find appropriate conditions to affect successful 1,4-addition to enone **117**, we repeated the reaction and investigated the equivalents of allylmagnesium chloride, the identity and equivalents of the copper(I) salt, the solvent and the role of Me_3SiCl as an additive. As mentioned earlier, silyl reagents in 1,4-additions of cuprates to enones serve as Lewis acids, increasing the rate of addition of the cuprate to the enone. Ultimately, however, all reaction conditions effectively gave the same result, namely, direct 1,2-addition to the carbonyl group (Table 2.3).



117 **166/167**
Yield, dr

Entry	AllylMgCl Equivalents	X	CuX Equivalents	Me_3SiCl Equivalents	Solvent	dr	Yield
1	4	I	0.5	0	THF	3:1	Quant
2	4	I	0.5	0	THF/SMe_2 (95:5)	3:1	Quant
3	4	I	0.5	2.0	THF	3:1	Quant
4	4	I	0.5	2.0	THF/SMe_2 (95:5)	3:1	Quant
5	2.4	I	1.2	0	THF	3:1	Quant[a]
6	2.4	I	1.2	4.0	THF	3:1	Quant[a]
7	2.4	CN	1.2	0	THF	3:1	Quant[a]
8	2.4	CN	1.2	4.0	THF	3:1	Quant[a]

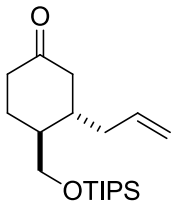
a) Conversion determined by ^1H NMR spectroscopy of the crude product

Table 2.3: Failed 1,4-Additions of Allyl Cuprate to **117**

For all but reaction entries 2 and 4, there were significant issues with copper salt solubility. From a practical perspective, small scale reactions involving copper salts had to use a stock solution of the relevant copper salt, transfer a small aliquot of the solution

into the flask and then evaporate the solvent. The copper salt, upon removal of the solvent, coated itself around the reaction flask and did not re-dissolve upon addition of the Grignard reagent. This likely explained the identical results between reactions, namely, that the uncatalysed reaction between enone **117** and allylmagnesium chloride was taking place.

With these results in hand, our next iteration of experiments varied only the equivalents and identity of the copper salt. Particular attention was paid to ensuring complete dissolution of the copper salt prior to the addition of Grignard reagent. The THF soluble CuCN.2LiCl adduct was used *in lieu* of CuCN, whilst CuI was used in a THF/SMe_2 co-solvent mixture. Under these new reaction conditions, the use of stoichometric amounts of CuI allowed access to 1,4-adducts **164/165** in a 63% yield and a 65:35 mixture of inseparable diastereoisomers (Table 2.4, entry 2), as well as approximately 5% of 1,2-adducts **166**/**167** and 35% of unreacted starting material (by ^{1}H NMR of the crude reaction mixture). The relative stereochemistry was not confirmed. Similar work by Lipshutz[143] on other 4-substituted cyclohexenones would suggest that the *trans*-isomer **164** is favoured (Figure 2.9). The diasteroeomeric ratio was determined by the ratio of the integrals for the C*H*$_2$OTIPS protons in the ^{1}H NMR spectrum, as well as the ratio of the integrals for the H*C*=CH_2 signals in the ^{13}C NMR (Figures 2.10 and 2.11).



164

Figure 2.9

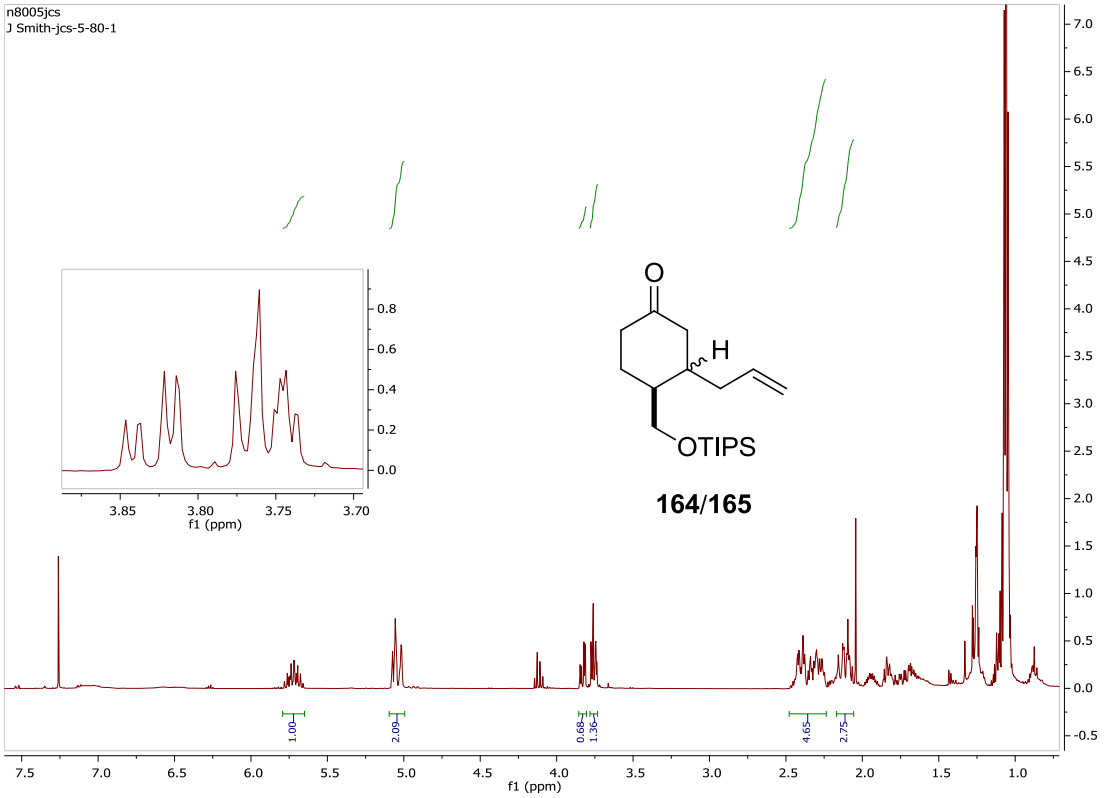


Figure 2.10

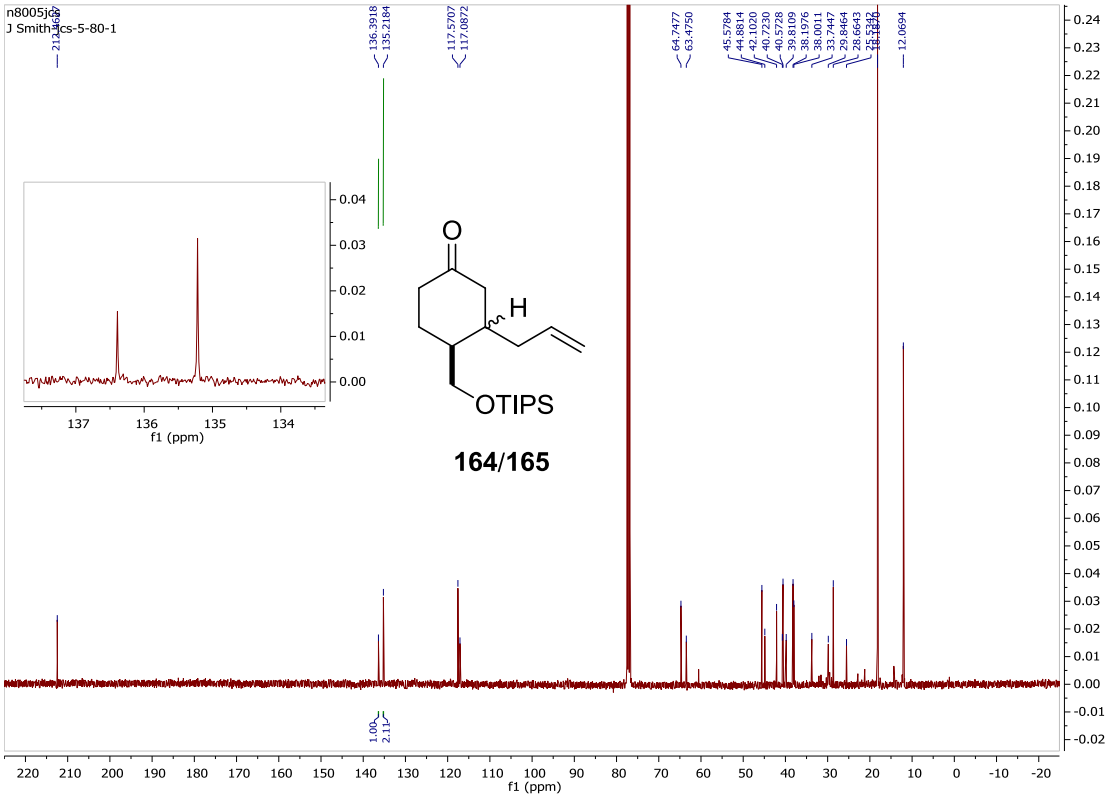
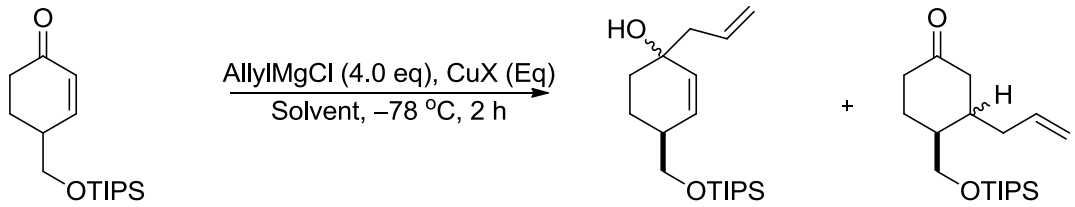


Figure 2.11

Entries 1 and 3 give exclusive access to 1,2-adducts **166**/**167**. This result is not unexpected; copper(I) salts cannot sequester 8 equivalents of Grignard reagent, therefore it could easily be argued that the Grignard reagent itself adds to the carbonyl group much more rapidly than the cuprate can add to the C=C double bond. Nonetheless, entry 4 is worth noting; CuCN is known to be capable of sequestering 2 equivalents of Grignard reagent to form the cyanocuprate, the fact that the 1,2-adduct is exclusively observed demonstrates the atypical reactivity of these allylic cuprate species.



117 | **166/167** Yield, dr | **164/165** Yield, dr

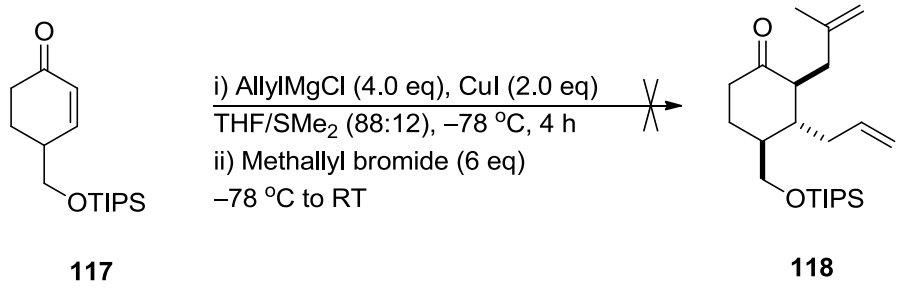
Entry	X	CuX Equivalents	Solvent	dr	Yield of 166/167 (%)	Yield of 164/165 (%)
1	I	0.5	THF/SMe_2 (88:12)	3:1	Quant[a]	/
2	I	2.0	THF/SMe_2 (88:12)	65:35	~5%[a]	63%
3	CN.2LiCl	0.5	THF	3:1	Quant[a]	/
4	CN.2LiCl	2.0	THF	3:1	Quant[a]	/

a) Conversion determined by ^{1}H NMR spectroscopy of the crude product

Table 2.4: Optimisation of Conditions for 1,4-Addition of Allyl Cuprate to **117**

With these new conditions from entry 2 in hand, our attention moved onto attempting to trap the resulting enolate with methallyl bromide. Enone **117** was treated with 4 equivalents of allylmagnesium chloride, 2 equivalents of copper(I) iodide in a THF/SMe_2 (88:12) co-solvent mixture at –78 °C for 4 h to allow complete conjugate addition to occur. Then, methallyl bromide was added to trap the enolate (Scheme 2.34). Unfortunately, no alkylation was observed in the ^{1}H NMR spectrum of the crude reaction mixture. As 12% of the reaction solvent was SMe_2, itself nucleophilic, we

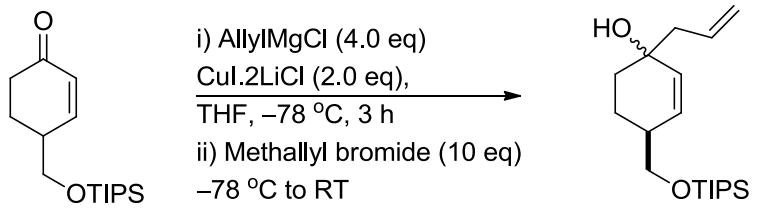
envisioned that it was feasible that alkylation of SMe_2 was out-competing alkylation of the formed enolate.



117 **118**

Scheme 2.34

The inclusion of SMe_2 as a co-solvent was done to solubilise the CuI prior to the addition of the Grignard reagent. In order to ensure complete dissolution of CuI in the absence of SMe_2, the THF soluble CuI.2LiCl adduct was used instead. Unfortunately, the absence of SMe_2 led to a reversal of reactivity, with the 1,2-adducts **166**/**167** being the major products in the ^1H NMR spectrum of the crude reaction mixture (Scheme 2.35).

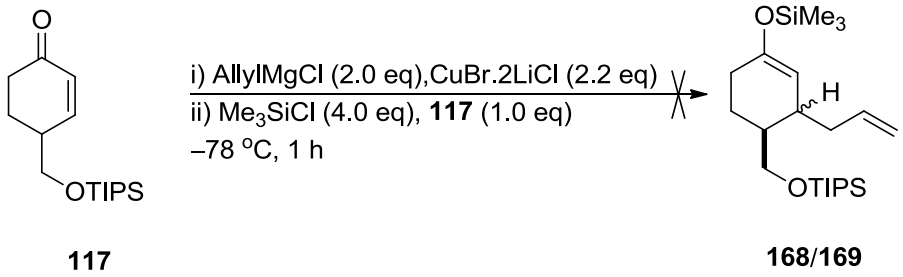


117 **166/167**

Scheme 2.35

Using a similar method reported by Lipshutz,[143] whereby allylcopper was added to various 4-substituted cyclohexenones, we attempted to utilise Lipshutz's conditions and trap the copper enolate as the silyl enol ether, with the idea the we would then alkylate in a separate step. Thus, allylcopper was generated by the addition of 2 equivalents of allylmagnesium chloride to 2.2 equivalents of CuBr.2LiCl in THF, followed by the addition of enone **117** and excess Me_3SiCl (Scheme 2.36). Indeed, the use of allylcopper did give successful 1,4-addition, but despite strictly anhydrous conditions being used for the reaction and the accompanying workup, the intermediate silyl enol

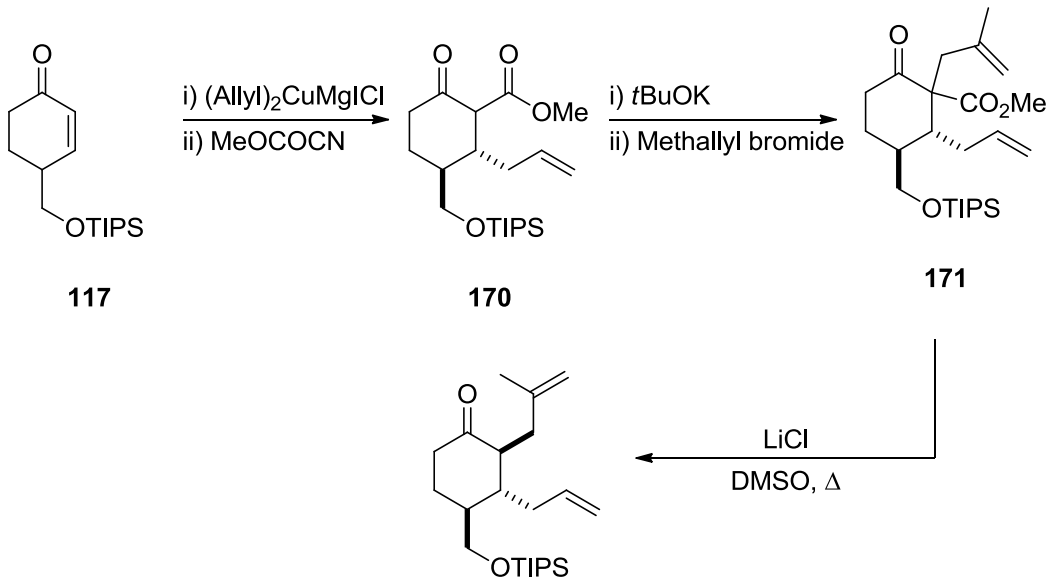
ether could not be isolated. Instead, only 1,4-adducts **164**/**165** were observed in the ^{1}H NMR spectrum of the crude reaction mixture.



117 **168**/**169**

Scheme 2.36

Due to the difficulty of alkylating the intermediate copper enolate or trapping as the silyl enol ether, we briefly investigated whether we could acylate the copper enolate using methyl cyanoformate as the electrophilic quench. The overall strategy would then be to deprotonate **170** to form the malonate, alkylate with methallyl bromide to form the tetra-substituted cyclohexanone **171**, then carry out a Krapcho decarboxylation[144] to gain access to **118** (Scheme 2.37). Given that the Krapcho decarboxylation takes place at elevated temperatures, allowing reversibility of the final enolate quench, we envisioned that the thermodynamic product **118**, with all substitutents adopting an equatorial position, would be preferentially formed.

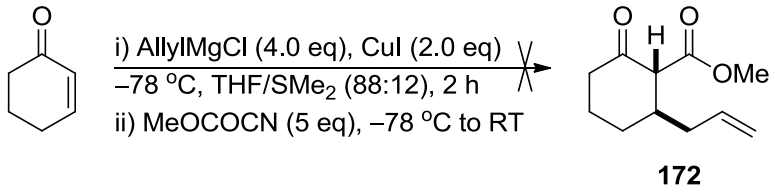


117 **170** **171**

118

Scheme 2.37

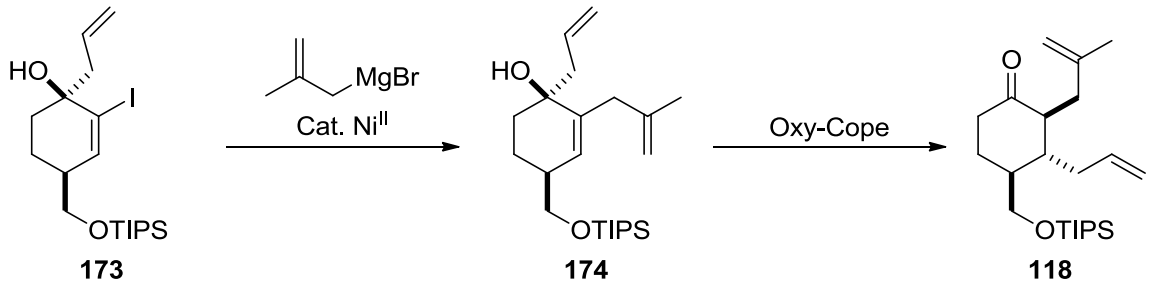
Thus, with this new proposed synthesis, the model substrate cyclohexenone was treated with 4 equivalents of allylmagnesium chloride and 2 equivalents of CuI in THF/SMe_2 (88:12) to affect 1,4-addition, followed by the addition of excess methyl cyanoformate (Scheme 2.38). The reaction, however, gave two products which did not fit with the expected structure and hitherto, have not been positively identified.



Scheme 2.38

Unfortunately, despite our best efforts, we could not realise our intention of cuprate-mediated double addition and, as a result, other methods were explored.

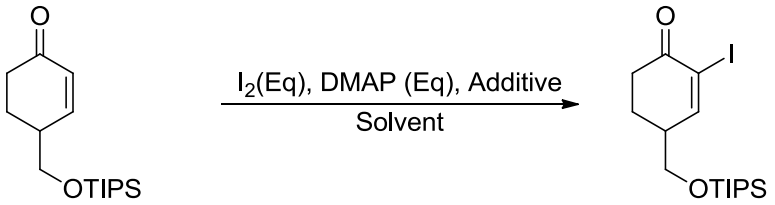
One of the first methods that was briefly investigated is shown in Scheme 2.39. Initially, we planned to carry out a Kumada coupling of iodo-alcohol **173**, obtained from the successful 1,2-addition reactions described previously with methallyl magnesium bromide. This would be followed by an oxy-Cope rearrangement to give the desired tri-substituted ketone **118**. Depending on the conditions for the oxy-Cope reaction, an isomerisation step to give the *trans*-isomer **118** may not be necessary (Scheme 2.39)



Scheme 2.39

In order to obtain access to iodo-alcohol **173**, enone **117** was first subjected to a Baylis-Hilman type iodination. Using the method reported by Taber,[145] TIPS protected enone was treated with iodine and catalytic DMAP in a 1:1 THF/H_2O mixture, using K_2CO_3 as the stoichometric base. These conditions, however, only gave access to iodo-enone **175** in a disappointing 27% yield. Instead, carrying out the reaction in a 1:1 mixture of

$CHCl_3$ and pyridine, the method reported by Felpin,[146] gave iodo-enone **175** in a much improved 86% yield (Table 2.5).

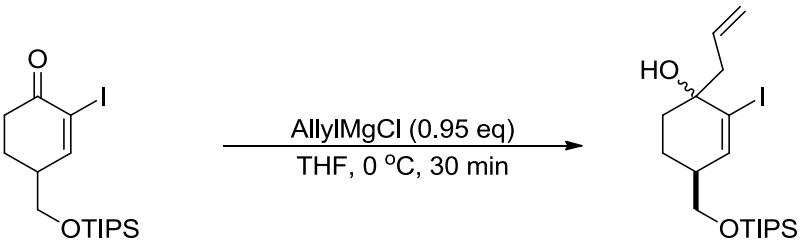


117 **175**

Entry	I_2 Eq	DMAP Eq	Additive	Solvent	Yield (%)
1	1.2	0.02	K_2CO_3 (1.2 eq)	THF/H_2O (1:1)	27
2	2.0	0.2	/	Pyridine:$CHCl_3$ (1:1)	86

Table 2.5: Optimisation of Conditions for the Iodination of **117**

Iodo-enone **175** was then converted into the corresponding tertiary alcohols **173**/**176** by treatment with allyl magnesium chloride, in an overall yield of 90% (Scheme 2.40). The products were formed in a 2:1 diastereomeric ratio, determined by the ratio of the integrals of the IC=C*H* protons in ^{1}H NMR spectrum of the crude reaction mixture at approximately δ 6.60 and 6.50 ppm (Figure 2.12). The relative stereochemistry of the major isomer was not determined.



175 **173**/**176**
90%, 2:1 dr

Scheme 2.40

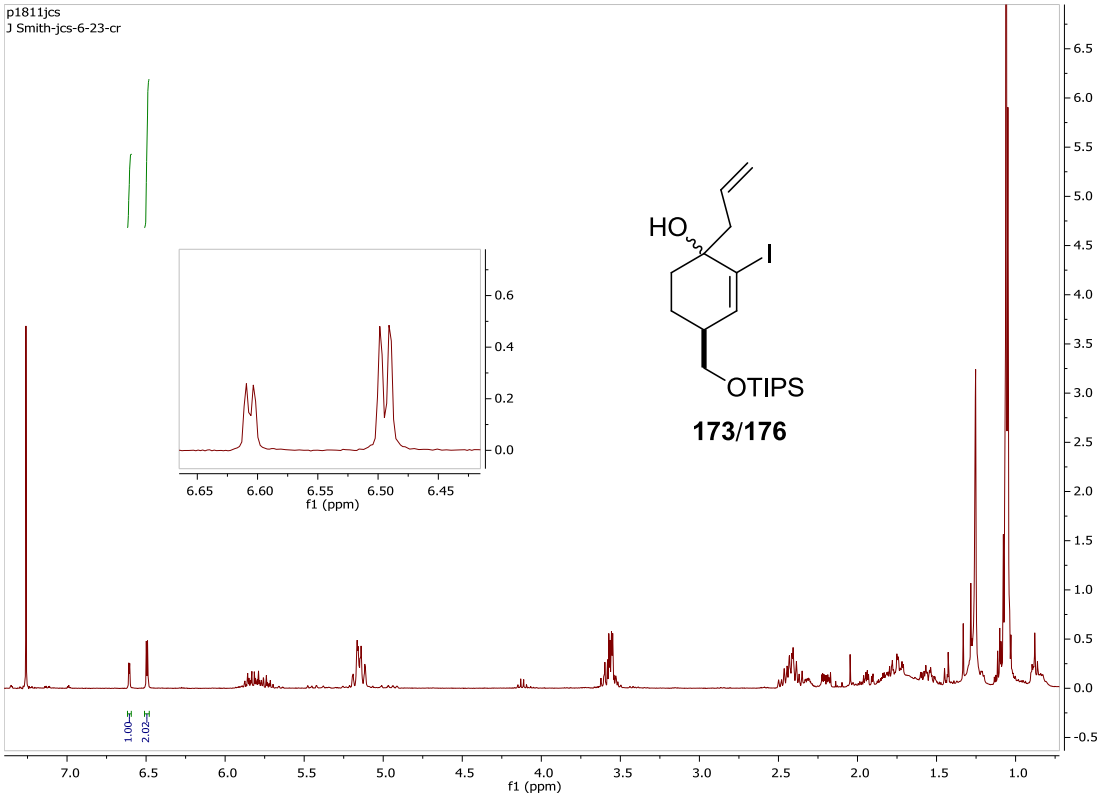
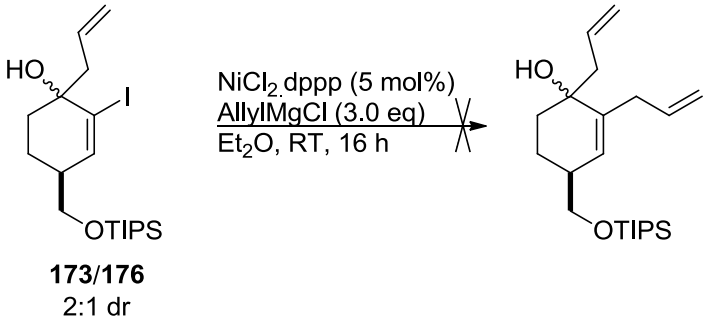


Figure 2.12

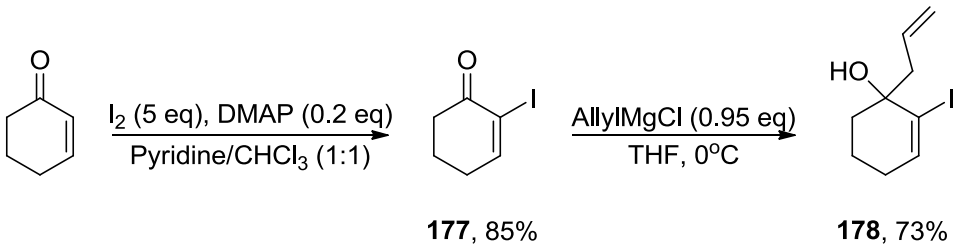
A Kumada coupling using $NiCl_2$.dppp as catalyst on the diastereomeric mixture of **173**/**176** was then attempted using a modified procedure reported by Taber (Scheme 2.41).[145] Due to the difficulty of forming the methallyl Grignard reagent, commercially available allyl magnesium bromide was used *in lieu* for a trial reaction. To our surprise, no reaction was observed, even with 10 times the catalyst loading of the original paper and extended reaction times (Scheme 2.41).



Scheme 2.41

We attempted to repeat Taber's coupling conditions using iodo-alcohol **175** with methyl magnesium bromide and allyl magnesium chloride, to check for reproducibility

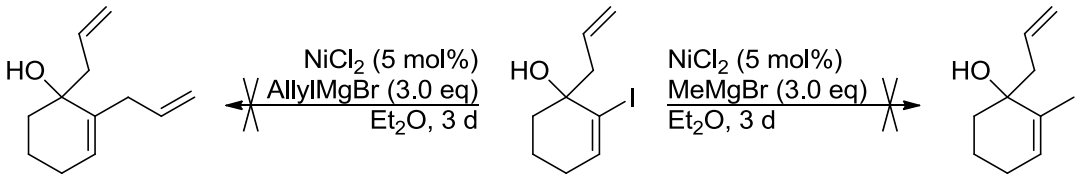
(Scheme 2.42). Cyclohexenone was iodinated to give iodo-enone **177**, then treated with allyl magnesium chloride to give tertiary alcohol **178** in an overall yield of 62% over 2 steps (Scheme 2.42)



177, 85% **178**, 73%

Scheme 2.42

However, as with iodo-alcohols **173**/**176**, neither treatment with methyl magnesium bromide nor allyl magnesium chloride, even with 10 times the reported catalyst loadings and several days reaction time gave the desired alkylated products (Scheme 2.43). As a result, this approach was not investigated further.



178

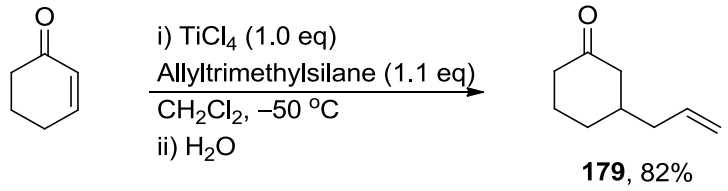
Scheme 2.43

In summary, we were able to develop a novel method for the addition of allyl cuprate to TIPS protected enone **117** in 63% yield. To the best of our knowledge, this is the first reported example of a successful 1,4-addition of an allylic cuprate reagent, of general formula R_2CuMgX_2, to an enone. Unfortunately, we were unable, despite our best efforts, to trap the resultant enolate with any of the electrophiles we tested.

2.6 Synthesis of the Decalin Framework of Anthracimycin

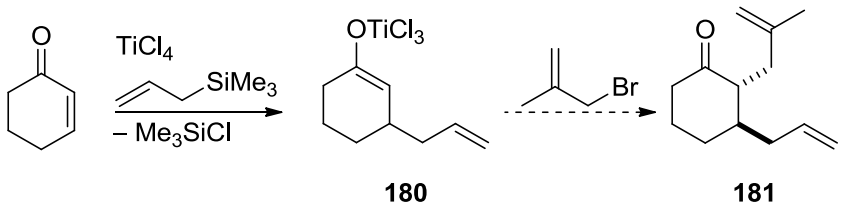
2.6.1 $TiCl_4$-Mediated Addition of Allyltrimethylsilane to Cyclohexenone.

As aforementioned, there is relatively little literature precedent for the addition of allylic cuprates to enones. For the nucleophilic addition of the allylic moiety to enones, the Sakurai reaction is more commonly employed.[147] In this reaction, an enone is treated with allyltrimethylsilane in the presence of $TiCl_4$ to give the 1,4-adduct. For example, it was reported that $TiCl_4$ mediated addition of allyltrimethylsilane to cyclohexenone gave the 1,4-adduct **179** in 82% yield (Scheme 2.44).[148]



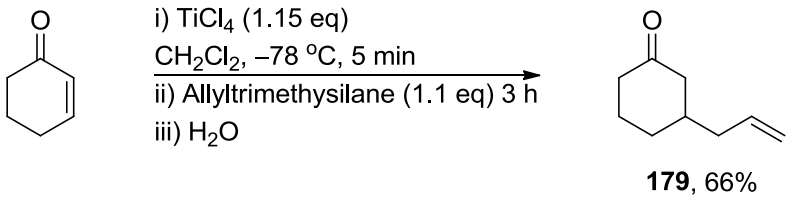
Scheme 2.44

Typically, the titanium enolate is quenched to get access to the 1,4-adduct. We wondered, however, whether titanium enolate **180** could be alkylated with methallyl bromide to gain access to doubly substituted **181** (Scheme 2.45). If this idea could be realised, it would provide a novel alternative to our previously unsuccessful allylic cuprate chemistry.



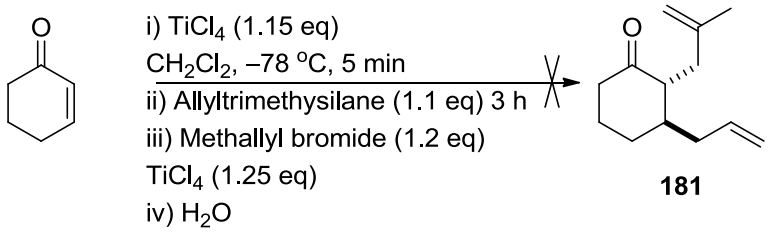
Scheme 2.45

To begin with, cyclohexenone was subjected to treatment with allyltrimethylsilane in the presence of $TiCl_4$. Quenching gave to give access to 1,4–adduct **179** in a 66% yield (Scheme 2.46).



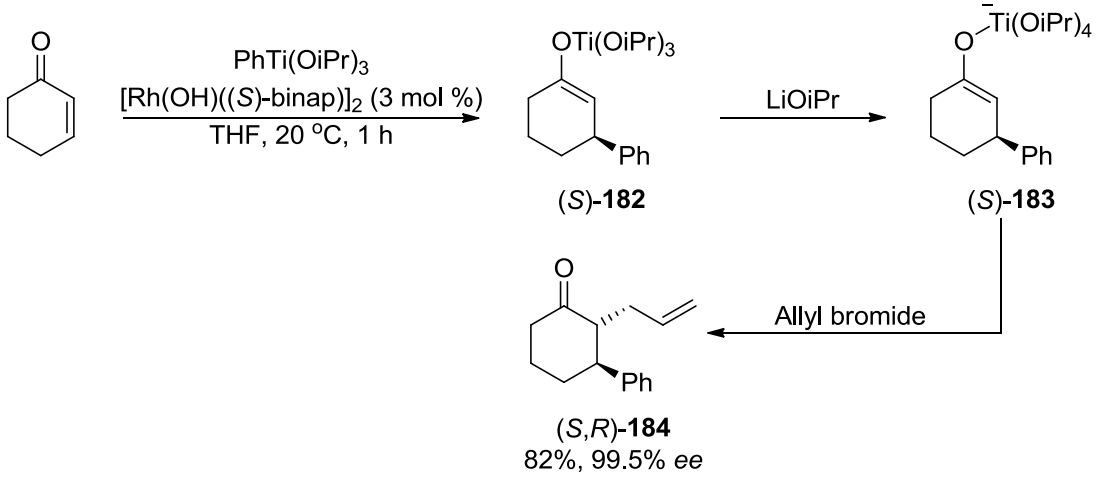
Scheme 2.46

The reaction was then repeated under the same conditions to form the titanium enolate but methallyl bromide was added. Unfortunately no alkylation was observed in the ^{1}H NMR spectrum of the crude product, with only the 1,4-adduct **179** being identified (Scheme 2.47).



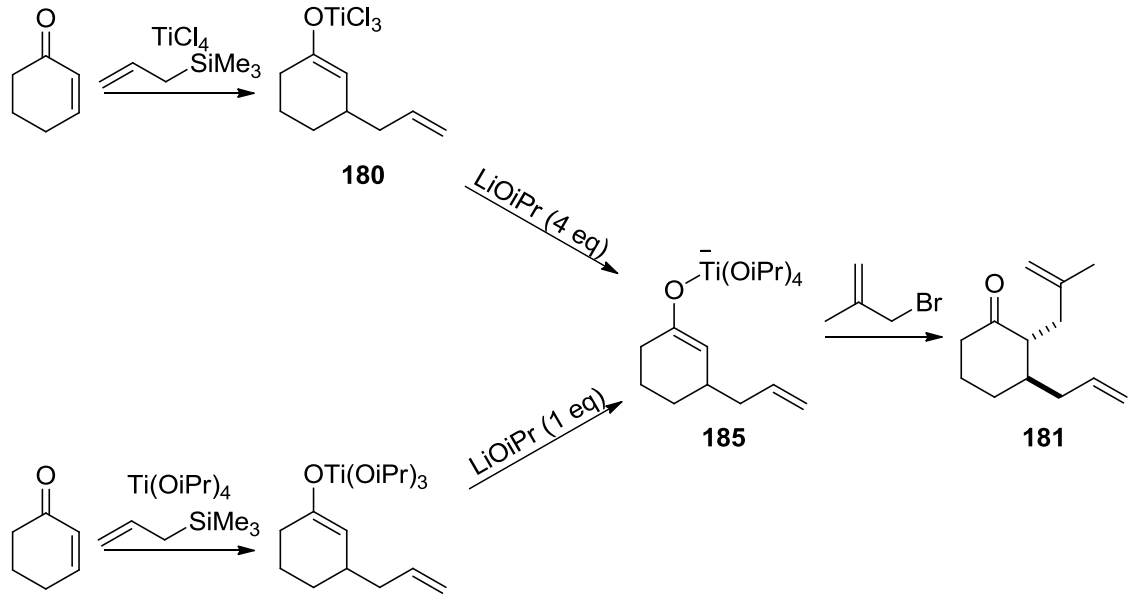
Scheme 2.47

Literature precedent for a similar reaction does, however, exist. In 2002, Hayashi[149] reported the rhodium-catalysed enantioselective addition of a phenyl moiety to cyclohexenone to form the enantioenriched titanium enolate (*S*)-**182**. This was followed by the addition of lithium isopropoxide to form the titanium "ate" complex (*S*)-**183** which was then trapped with allyl bromide to form doubly substituted (*S*,*R*)-**184** in 99.5% *ee* and 82% yield (Scheme 2.48). The diastereoselectivity was not explicity reported, although it is likely that the reaction only gives a single diastereoisomer. The addition of lithium isopropoxide leads to the formation of a more nucleophilic enolate which is sufficiently reactive to undergo allylation.



Scheme 2.48

Given that titanium enolate **180** was insufficiently nucleophilic to attack methallyl bromide, we wondered whether titanium enolate **180** could be converted into the corresponding "ate" complex **185** by treatment with 4 equivalents of LiO*i*Pr and then alkylated with methallyl bromide (Scheme 2.49). Alternatively, use of Ti(O*i*Pr)$_4$ as the Lewis acid for the initial 1,4-addition would require only 1 equivalent of LiO*i*Pr being required for the formation of the "ate" complex **185**. Our plan is set out in Scheme 2.49.

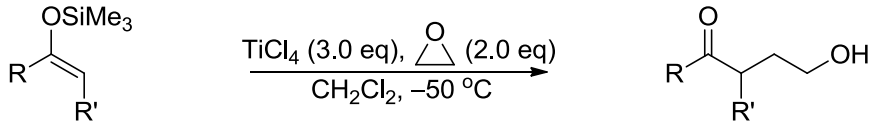


Scheme 2.49

Unfortunately, both avenues did not allow access to doubly alkylated **181**. Ti(O*i*Pr)$_4$ was not sufficiently Lewis acidic to allow 1,4-addition, even when the reaction was carried out at 0 °C, whilst attempted trapping of the "ate" complex **185** *via* $TiCl_4$

mediated addition only gave the 1,4-adduct **179** and no doubly alkylated **181**. With such limited success attempting to directly alkylate these titanium enolates, alternative electrophiles were investigated.

In 2000, Lalic[150] reported the alkylation of several titanium enolates with ethylene oxide to give access to primary alcohols. Selected examples are shown in Table 2.6.



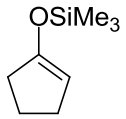
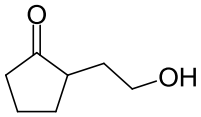
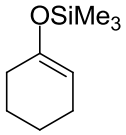
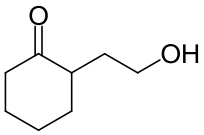
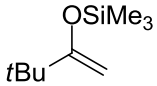
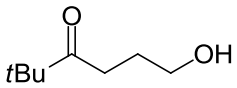
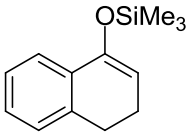
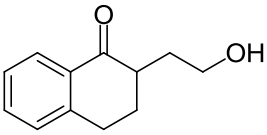
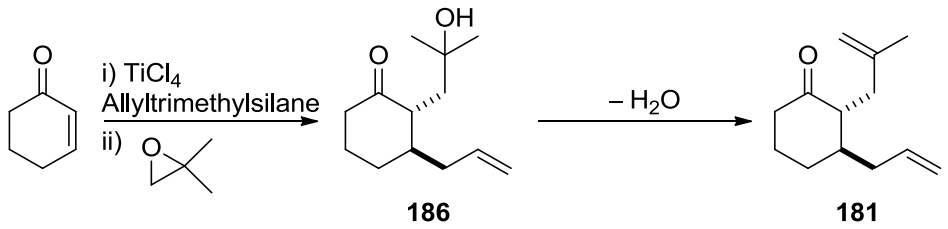
Entry	Starting Material	Product	Yield (%)
1			46
2			55
3			61
4			38

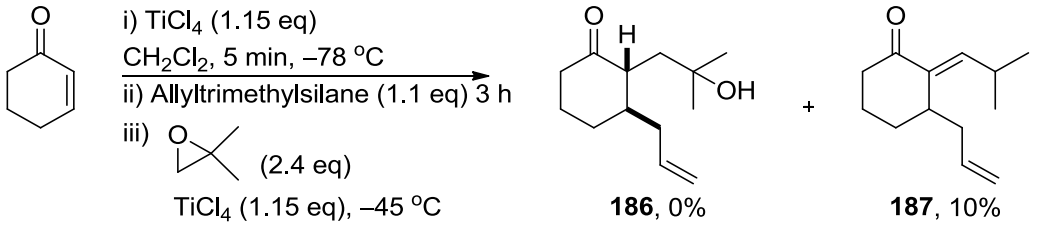
Table 2.6: Alkylation of Titanium Enolates with Ethylene Oxide

Whilst the reaction of ethylene oxide with titanium enolate **180** is of little use towards the synthesis of anthracimycin, we considered that the use of isobutylene oxide could give tertiary alcohol **186** which could then be dehydrated to give doubly alkylated **181** (Scheme 2.50).



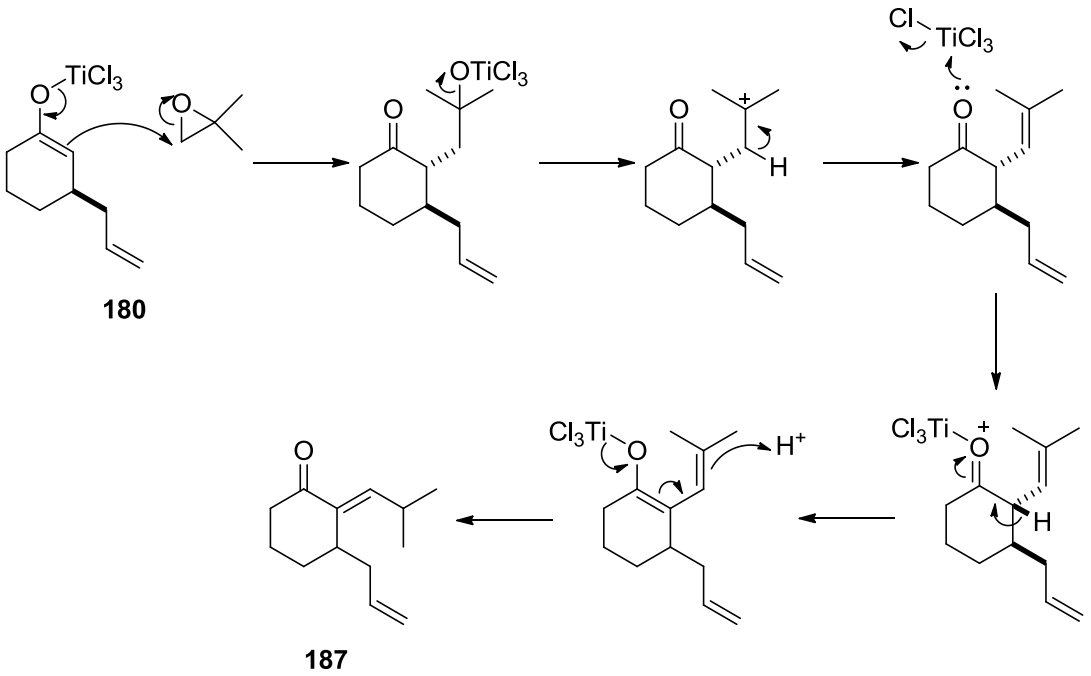
Scheme 2.50

Cyclohexenone, as our model substrate, underwent $TiCl_4$ mediated addition with allyltrimethylsilane to form the intermediate titanium enolate. Then, isobutylene oxide was added as the electrophile. Additional $TiCl_4$ was added to affect the second addition to the epoxide. Expecting to see tertiary alcohol **186**, the reaction instead gave multiple products, one of which was enone **187** and was isolated in 10% yield (Scheme 2.51). The key diagnostic peaks of enone **187** was confirmed by the enone proton at approximately δ 6.20 ppm, as well as the alkene peaks in the ^{13}C NMR spectrum at approximately δ 145 and 139 ppm. The geometry about the enone double bond was not determined.



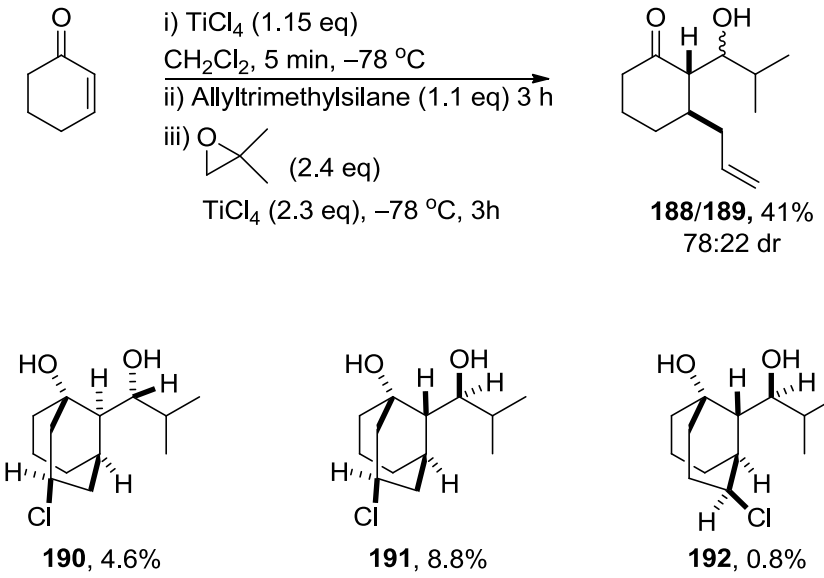
Scheme 2.51

We were initially buoyed by this result. Although enone **187** was not the desired product, it is possible that it could have formed *via* dehydration and isomerisation of tertiary alcohol **186** (Scheme 2.52).



Scheme 2.52

In order to prevent this dehydration-isomerisation sequence, the reaction was repeated but the temperature maintained at –78 °C. To our initial surprise, inseparable diastereomeric alcohols **188**/**189** were isolated in a 41% yield and a 78:22 diastereomeric ratio. After careful chromatography, chlorinated adducts **190**, **191** and **192** were isolated in 4.6, 8.8 and 0.8% yield, respectively (Scheme 2.53). The relative stereochemistry of each was assigned by X-ray crystallography (Figures 2.13, 2.14 and 2.15). These types of products have been observed before in related Prins chemistry.[151]



Scheme 2.53

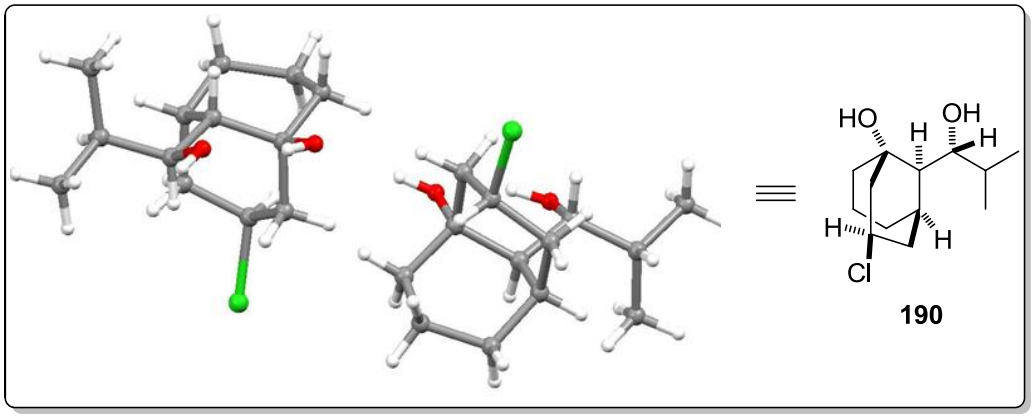


Figure 2.13

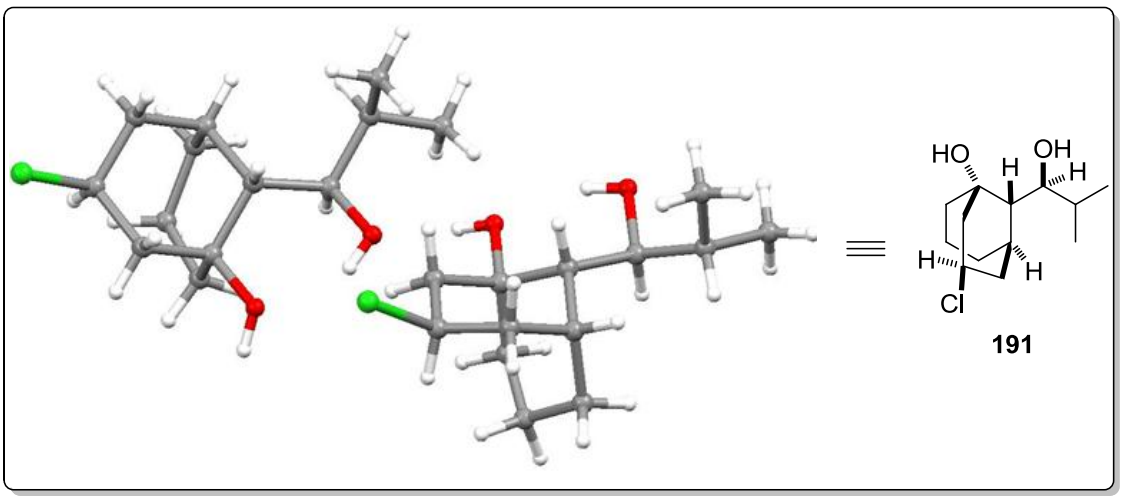


Figure 2.14

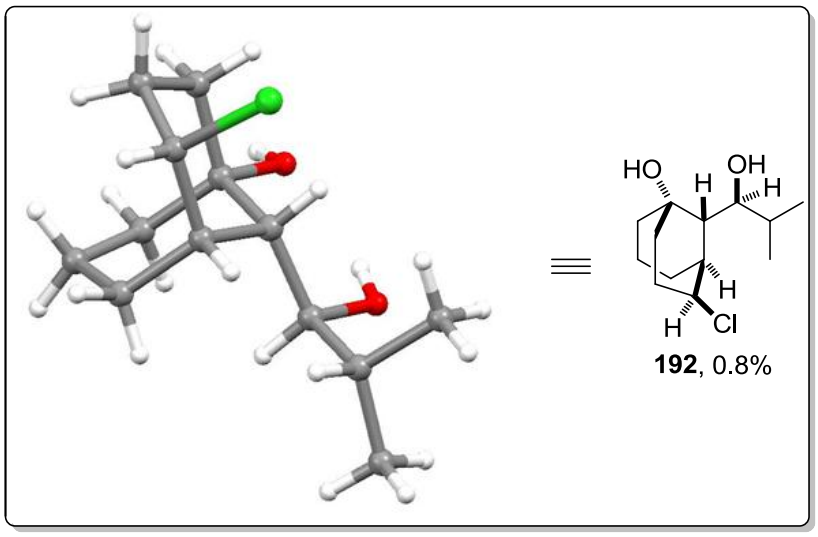
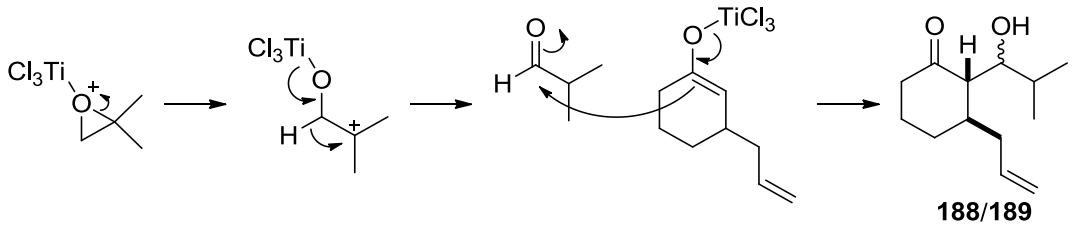


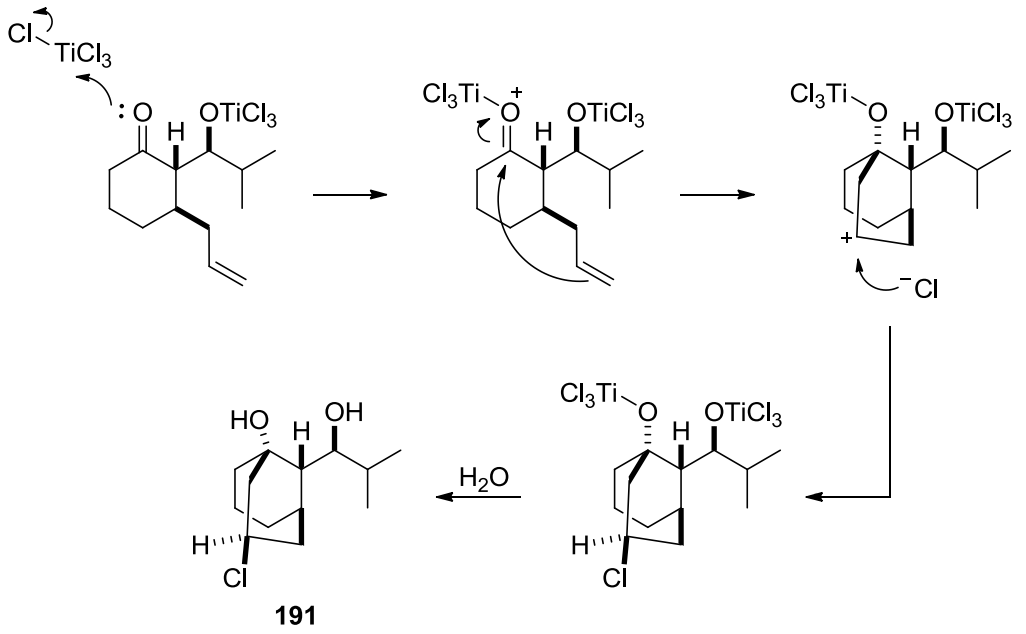
Figure 2.15

Aldol products **188**/**189** appear to have formed *via* a $TiCl_4$ mediated ring opening of isobutylene oxide to form the corresponding tertiary carbocation, followed by an internal hydride shift to form isobutyraldehyde *in situ*, which then acts as the electrophile to trap the titanium enolate **180** (Scheme 2.54). The relative stereochemistry of **188**/**189** was not definitively assigned, although it is likely that the ring substituents are *trans* to one another, with the hydroxyl group carbon atom being the variable stereocentre.



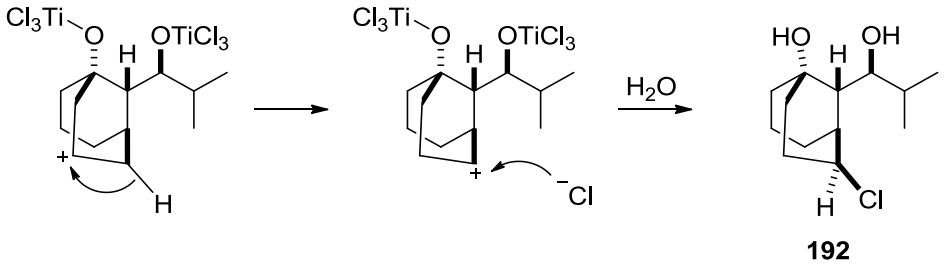
Scheme 2.54

Chlorinated diols **190**, **191** and **192** arise from an intramolecular Prins[152] reaction to form the bicyclic core, followed by trapping of the resultant carbocation with chloride from the least hindered face, itself sourced from $TiCl_4$ (Scheme 2.55).



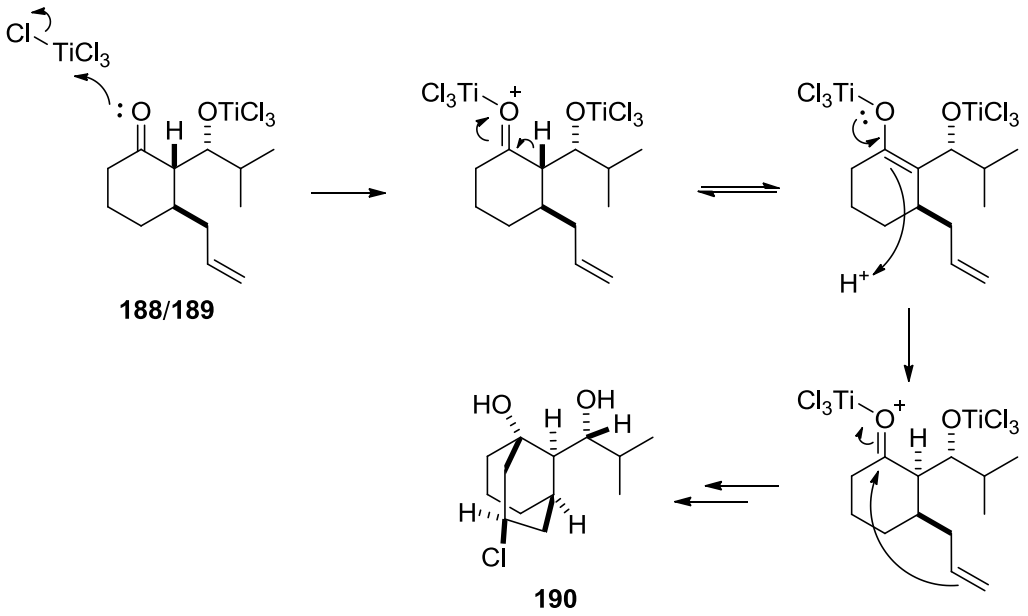
Scheme 2.55

Regioisomer **192** may be formed by a small amount of the intermediate carbocation undergoing a hydride shift before reaction with chloride (Scheme 2.56)



Scheme 2.56

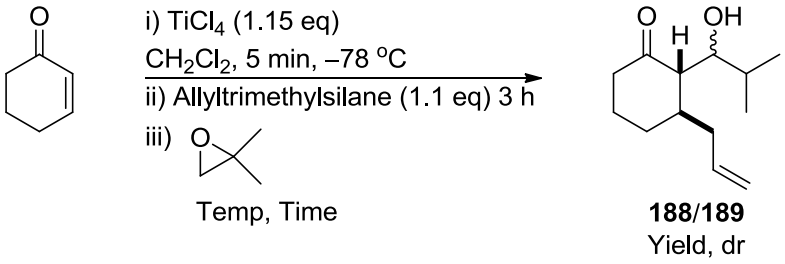
Notably, isomer **190** has a *cis* relationship between the two ring substituents, implying that ketones **188**/**189** must equilibrate to some extent before the Prins cyclisation (Scheme 2.57).



Scheme 2.57

The rearrangement of isobutylene oxide to isobutyraldehyde as shown in Scheme 2.54 is catalysed by $TiCl_4$. In order to avoid this re-arrangement, the reaction was repeated without a second addition of $TiCl_4$ (Table 2.7, entry 1). Unfortunately, this omission of additional $TiCl_4$ did not seem to prevent the rearrangement occuring. Tertiary alcohol **186** was not isolated nor observed in the ^{1}H NMR spectrum of the crude product, instead, keto-alcohols **188**/**189** were isolated in 80% yield and 88:12 dr.

Next, the reaction was repeated at –116 °C, again in an attempt to prevent the rearrangement of the epoxide (Table 2.7, entry 2). Surprisingly, even at such a low temperature, tertiary alcohol **186** was not isolated nor observed in the ^{1}H NMR spectrum of the crude reaction mixture, with keto-alcohols **188**/**189** being isolated in 50% yield and 87:13 dr. Notably, in both experiments, chlorinated diols **190**, **191** or **192** were not observed in the ^{1}H NMR spectrum of the crude product. This would appear to indicate that the Prins cyclisation is dependent upon the second addition of $TiCl_4$.



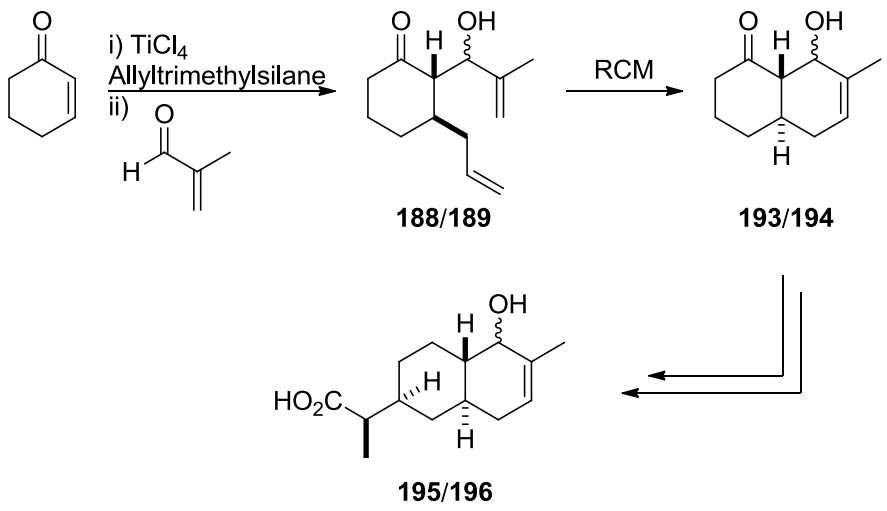
Entry	Temp (°C)	Time (h)	Yield (%)	dr
1	–78	3	80	88:12
2	–116	1	50	87:13

Table 2.7: Reactions of **180** With Isobutylene Oxide

Unfortunately, we were unable to realise our intention of alkylating titanium enolate **180**. The titanium enolate **180** was insufficiently nucleophilic to react with methallyl bromide, whilst attempted alkylation with isobutylene oxide proved impossible due to the extremely facile rearrangement of isobutylene oxide. For this reason, we turned our attention to the use of alternative electrophilic traps for the titanium enolate **180**.

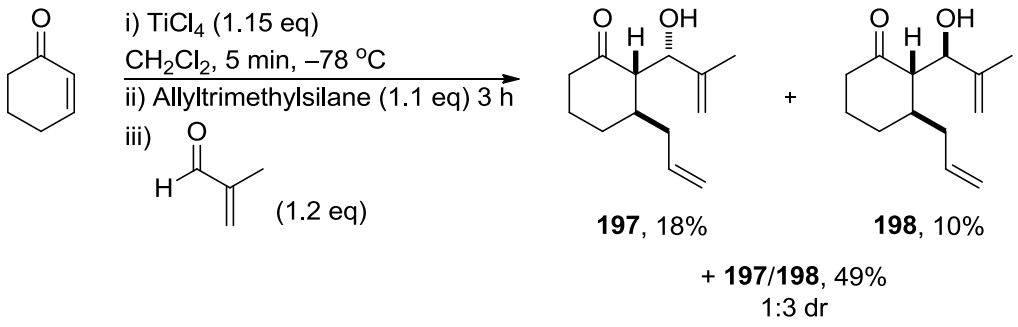
2.6.2 Aldol and Ring Closing Metathesis Route to Decalins

Given how readily isobutylene oxide rearranges to isubutyraldehyde, it appeared extremely unlikely that tertiary alcohol **186** could be accessed *via* this method. Nonetheless, were titanium enolate **180** to be trapped with methacrolein instead of isubutylene oxide, it would allow the desired ring closing metathesis step to deliver the hydroxylated decalins **193**/**194**. Whilst this extra hydroxyl group would need to be removed to gain access to anthracimycin **92**, the functional handle it provides would be useful for late-state functionalisation and the synthesis of structurally related analogues. Our modified synthetic proposal is shown in Scheme 2.58.



Scheme 2.58

Thus, titanium enolate **180** was formed by treatment of cyclohexenone with $TiCl_4$ and allyltrimethylsilane at –78°C. Trapping with methacrolein (Scheme 2.59) gave aldol products **197** and **198** in a 2:3 diastereomeric ratio respectively. After purification, we isolated **197** and **198** with yields of 18% and 10% respectively, as well as 49% of a 1:3 diastereomeric mix of **197** and **198** that co-eluted during chromatography. The diastereomeric ratio was determined by taking the ratio of the integrals of the signals for the C*H*OH protons in the crude ^{1}H NMR spectrum at approximately δ 4.50 and 4.35 ppm (Figure 2.16).



Scheme 2.59

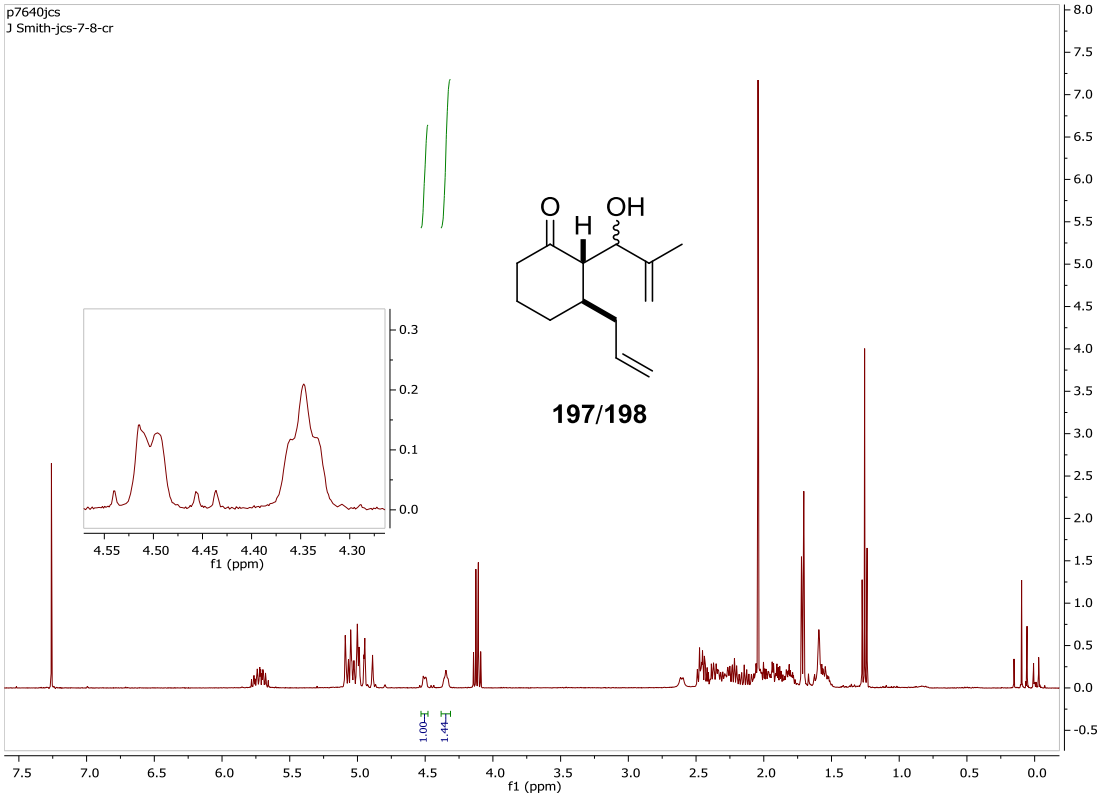
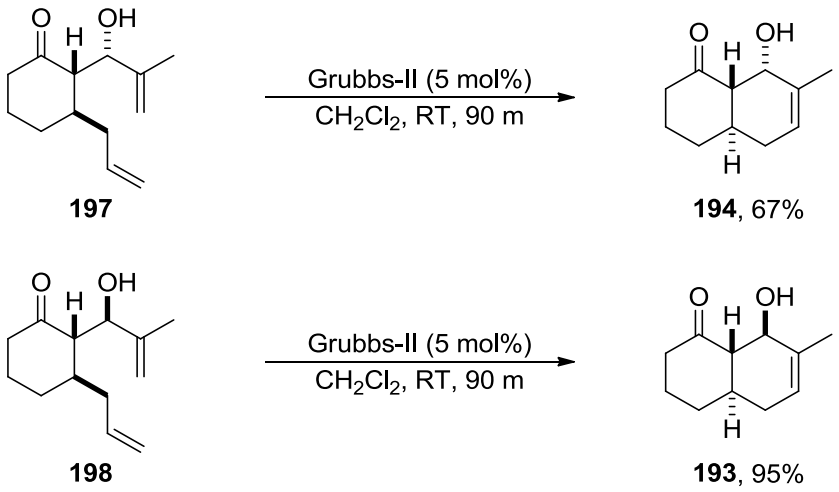


Figure 2.16

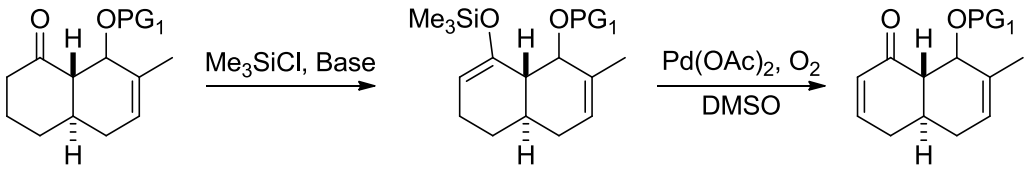
As anticipated, the ring substituents on both **197** and **198** are *trans* to one another, with the hydroxyl group being the variable stereocentre. Our work on proving the relative stereochemistry of aldol products **197** and **198** will be presented later.

Ring closing metathesis of both **197** and **198** proceeded smoothly with just 5 mol% of Grubbs 2nd generation catalyst giving the corresponding decalinones **194** and **193** in 67% and 95% yield respectively (Scheme 2.60). The corresponding work up and purification was straighforwards, requiring only evaporation of the solvent and flash chromatography of the residues.



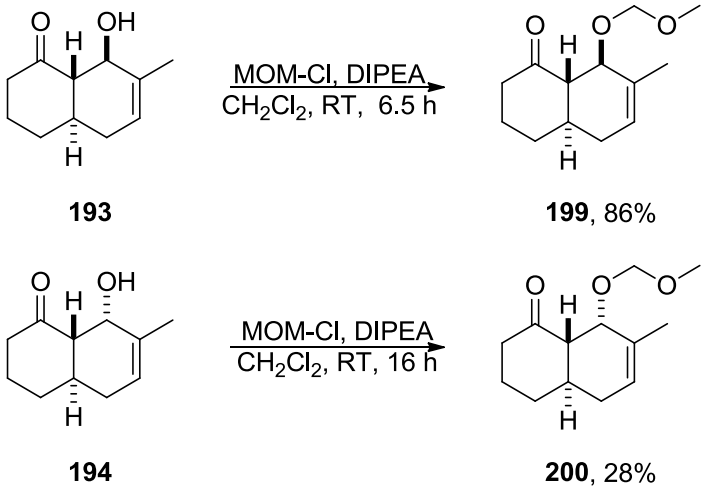
Scheme 2.60

With decalinones **193** and **194** in hand, our attention turned to regioselective oxidation of the ketone to form the less substituted enone (Scheme 2.61). Given our previous success with a Saeugsa oxidation of TIPS protected ketone **139** to enone **117**, we attempted to subject the corresponding silyl enol ethers to the same conditions, hoping for a similar result.



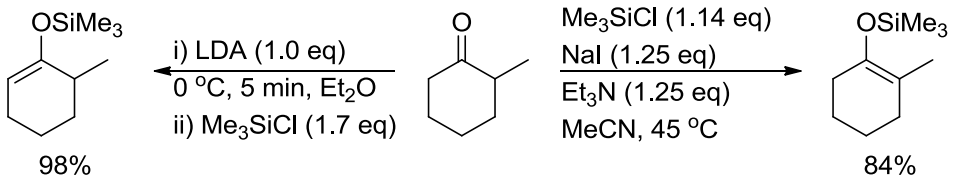
Scheme 2.61

Prior to the formation of the silyl enol ether, the hydroxyl group of decalinones **193** and **194** had to be protected. Thus, **193** and **194** were protected with chloromethyl methyl ether to give the corresponding MOM-protected decalinones **199** and **200** in 86% and 28% yield respectively (Scheme 2.62).



Scheme 2.62

Formation of silyl enol ethers from the corresponding ketones are usually obtained by a kinetic deprotonation with a strong base, typically a lithium amide, followed by addition of the silyl reagent to give the less substituted silyl enol ether. Conversely, if the more substituted silyl enol ether is required, treatment of the ketone with the silyl reagent in the presence of a tertiary amine is commonly employed (Scheme 2.63).[153, 154]

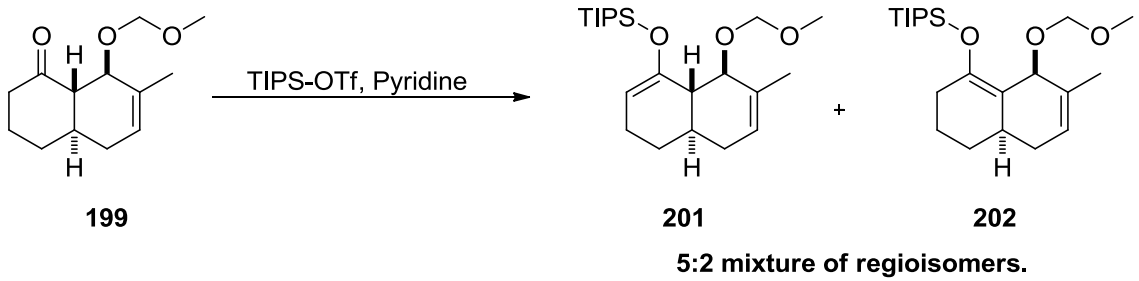


Scheme 2.63

Given the plethora of compounds containing a nitrogen-palladium bond, it is vital that the Saegusa oxidation be performed in the absence of any remaining nitrogen compounds from the formation of the silyl enol ether, as these could diminish the catalytic activity of the palladium(II) acetate. For this reason, initial attempts at forming the silyl enol ether used TIPS-OTf instead of TMS-Cl. The extra steric bulk of the TIPS group serves to increase the stability of the silyl enol ether and should allow chromatographic purification prior to treatment with palladium(II) acetate.

Thus, major decalinone **199** was treated with TIPS-OTf in pyridine to give a 5:2 mixture of regioisomers **201**/**202** (Scheme 2.64). The regioselectivity was confirmed by

the integrals of the C=C*H* protons at approximately δ 5.61 and 5.66 ppm in the ^{1}H NMR of the crude reaction mixture (Figure 2.17).



Scheme 2.64

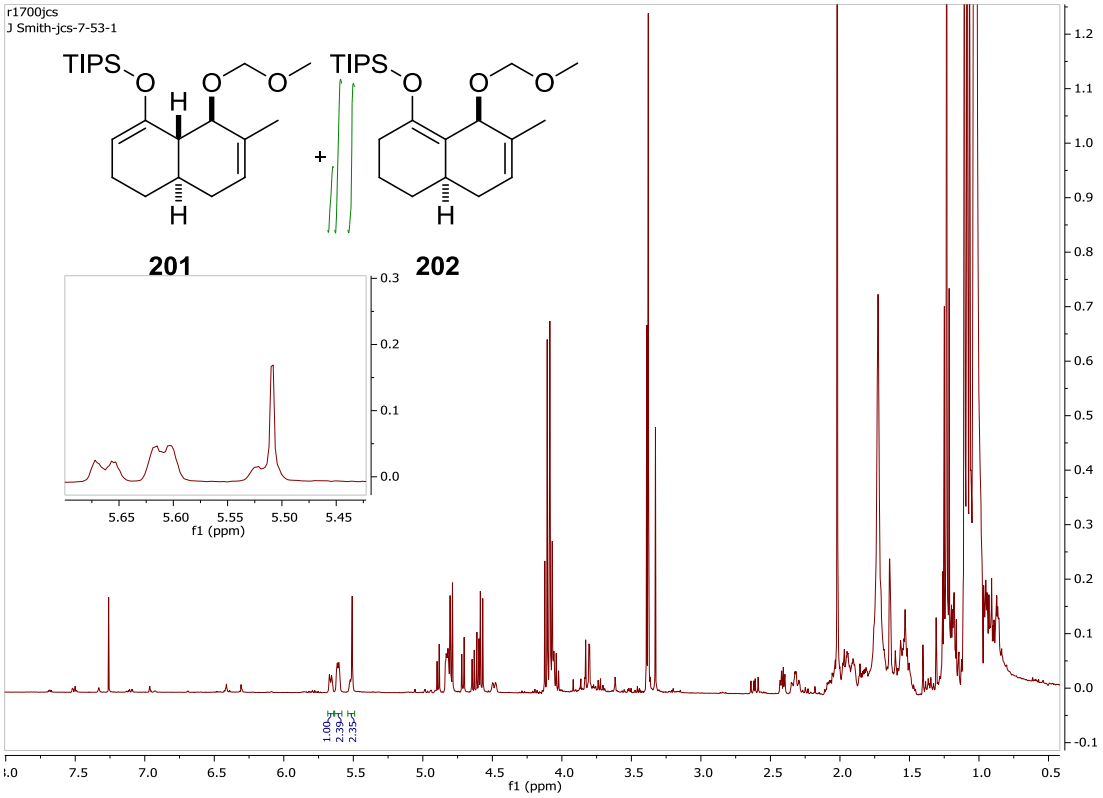
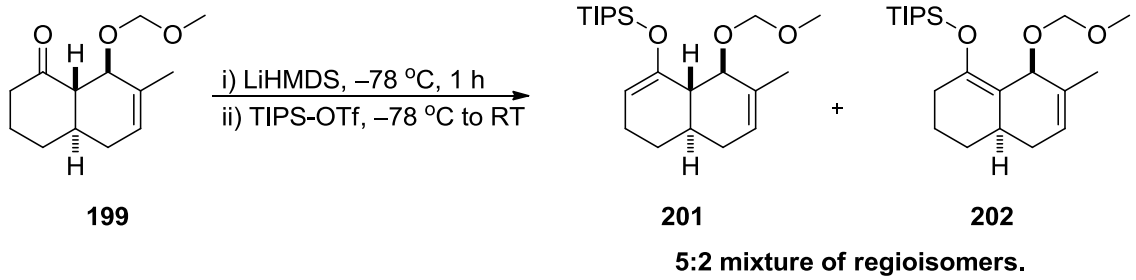


Figure 2.17

The identity of the major regioisomer was not definitively confirmed, although if the signal at approximately δ 5.51 ppm in Figure 2.17 is due to the TIPSOC=C*H* proton, then it would mean that the less substituted regioisomer **201** is favoured.

In an attempt to exclusively form the less substituted silyl enol ether **201**, ketone **199** was treated with LiHMDS at –78 °C in THF for 1 hour, followed by the addition of TIPS-OTf. To our surprise, regioisomers **201** and **202** were again observed to form in a 5:2 mixture (from the ^{1}H NMR spectrum of the crude reaction mixture) (Scheme 2.65).

This unexpected result may be due to deprotonation not occurring at –78 °C prior to the addition of TIPS-OTf and that deprotonation occurs as the reaction mixture begins to warm. The increased temperature at which the deprotonation occurs may therefore account for the decreased regioselectivity of the reaction.

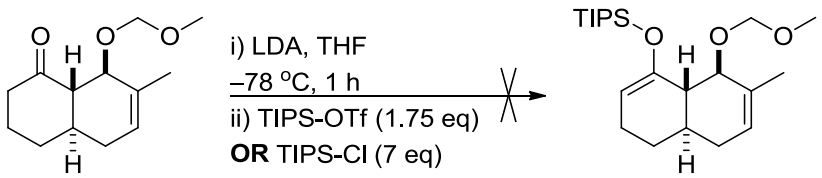


199 **201** **202**

5:2 mixture of regioisomers.

Scheme 2.65

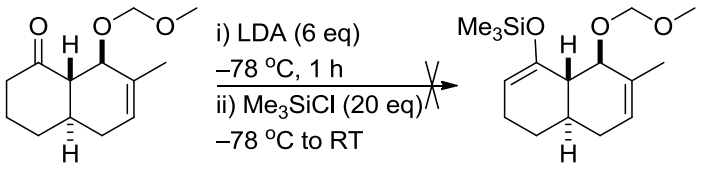
In order to ensure complete deprotonation prior to warming the reaction mixture, the LDA was used as a base instead of LiHMDS. Due to the increased basicity of LDA, complete, regioselective deprotonation should occur at –78 °C. Ketone **199** was therefore treated with LDA at –78 °C for 1 hour in THF, followed by the addition of TIPS-OTF or TIPS-Cl. In both instances, only starting material was observed in the ^{1}H NMR spectrum of the crude reaction mixture (Scheme 2.66). We are not currently able to explain this result.



199 **201**

Scheme 2.66

With our limited success at forming the TIPS-silyl enol ether **201**, we investigated whether or not the use of Me_3SiCl would allow complete regioselective formation of the corresponding silyl enol ether. Treatment of **199** with LDA in THF at –78 °C for 1 hour, followed by trapping with excess Me_3SiCl gave an unknown product (Scheme 2.67).



199 **203**

Scheme 2.67

Initially, we believed this to be the desired silyl enol ether **203**. As can be seen from the ^{1}H NMR spectrum of the crude reaction mixture (Figure 2.18), the signal at approximately δ 5.61 ppm was believed to be the C=C*H* proton, the signal at δ 5.05 ppm was believed to be due to the TIPSOC=C*H* proton and the two signals at δ 5.08 and 4.88 ppm were believed to be the OCH_2OMe protons. The presence of only one set of signals for each of these protons initially led us to believe that **203** had been formed as a single regioisomer.

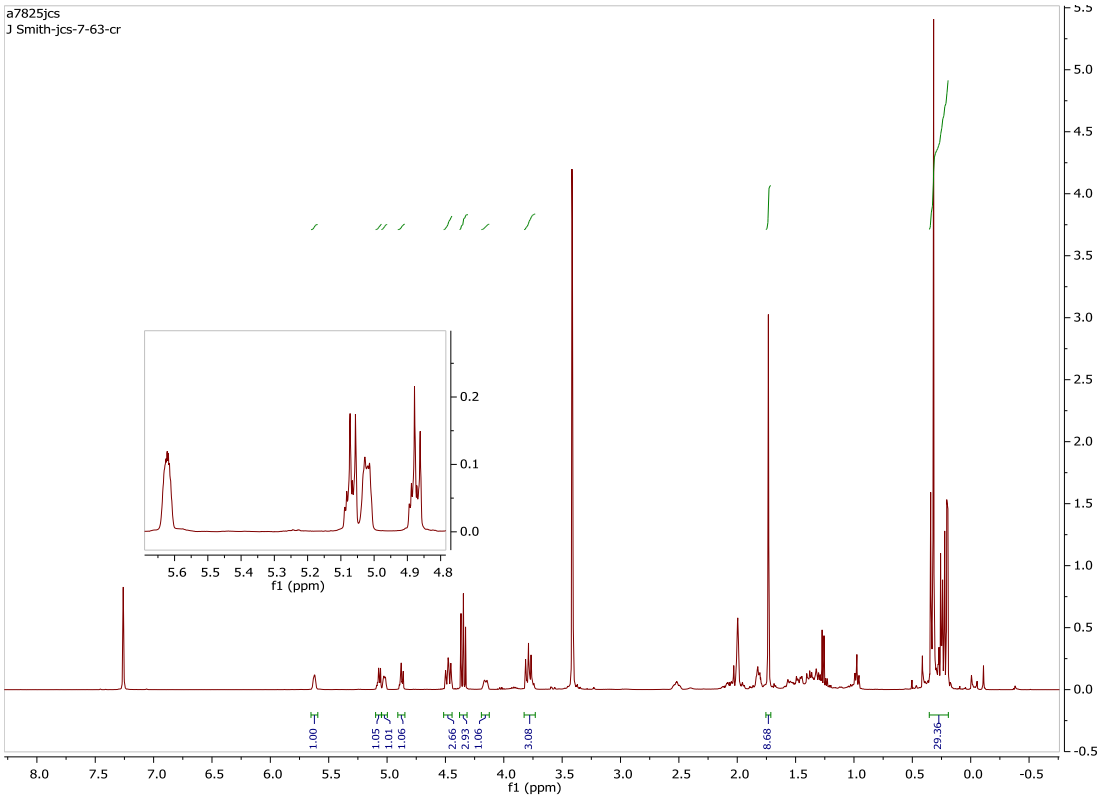


Figure 2.18

Nonetheless, ^{13}C NMR and DEPT NMR experiments cast doubt on our initial sstructure assignment. The signals at δ 172, 167, 153 and 137 ppm all correspond to quarternary carbons (Figure 2.19). As such, its identity remains unknown.

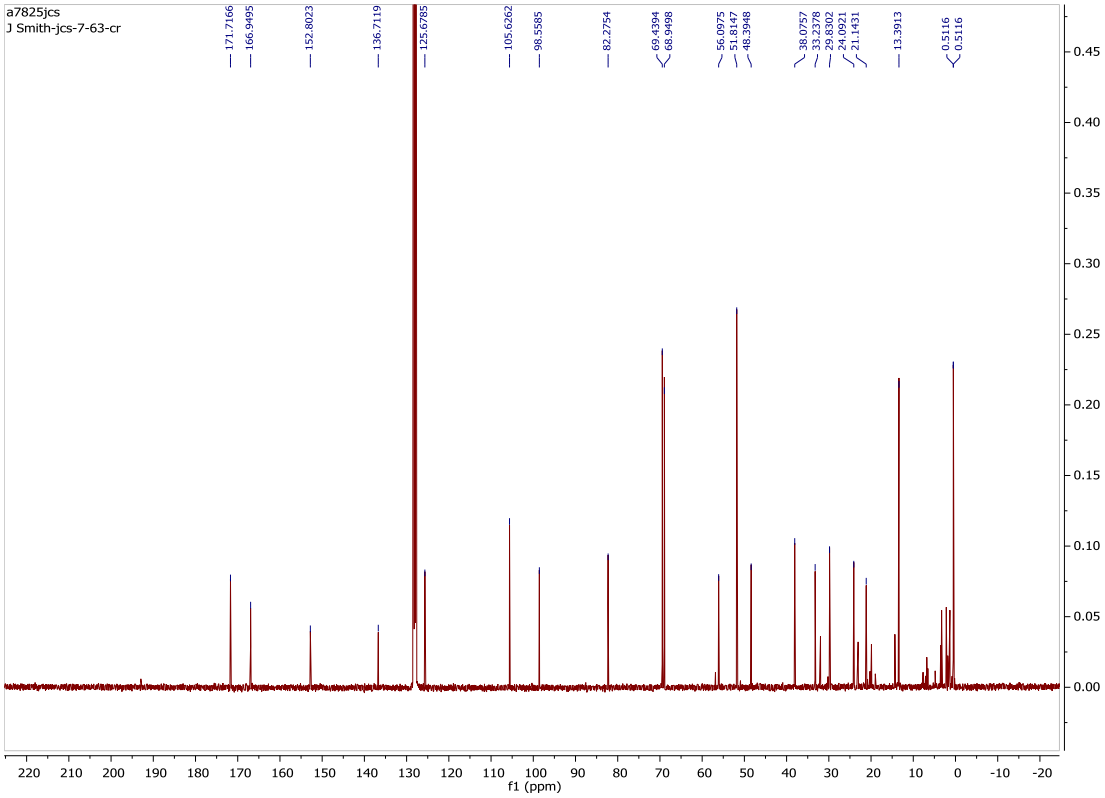
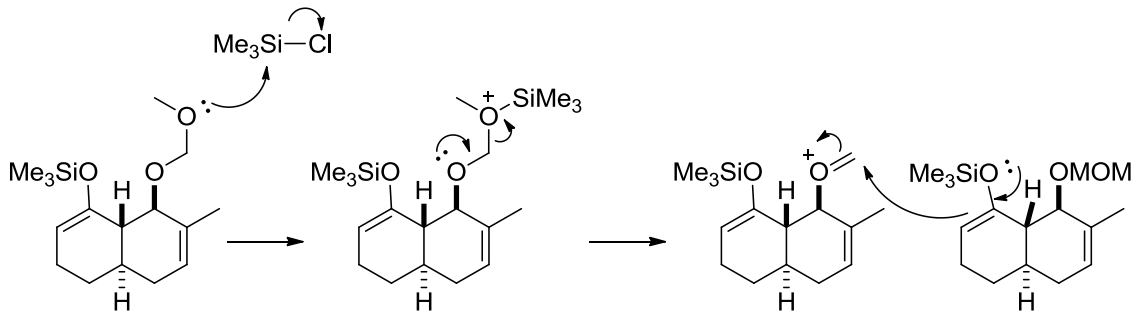


Figure 2.19

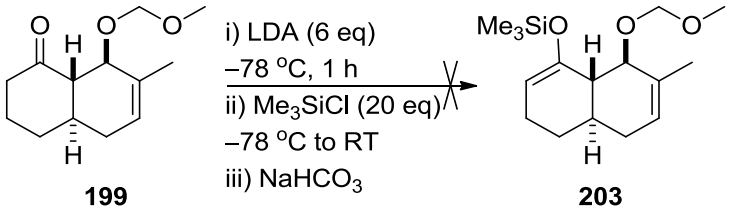
During subsequent repeats of the reaction, it was observed that the reaction mixture would rapidly darken upon concentration. This prevented complete removal of the solvent, excess Me_3SiCl and diisopropylamine. It was thought that Lewis acid-promoted polymerisation of the silyl enol ether could be an explanation (Scheme 2.68) for this observation.



Scheme 2.68

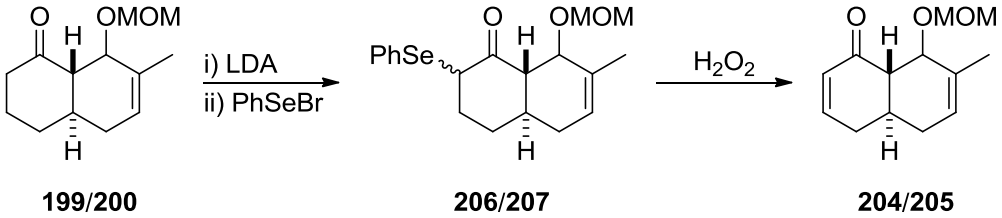
If polymerization akin to that shown in Scheme 2.67 was occurring, we speculated that a rapid wash with aqueous $NaHCO_3$ would be sufficient to neutralize or remove all of the acidic compounds present. Thus, the reaction was repeated, partially concentrated,

diluted into hexane and rapidly washed with saturated aqueous $NaHCO_3$ (Scheme 2.69). Unfortunately, this led to decomposition of the silyl enol ether and only starting material **199** was observed in the ^{1}H NMR spectrum of the crude reaction mixture.



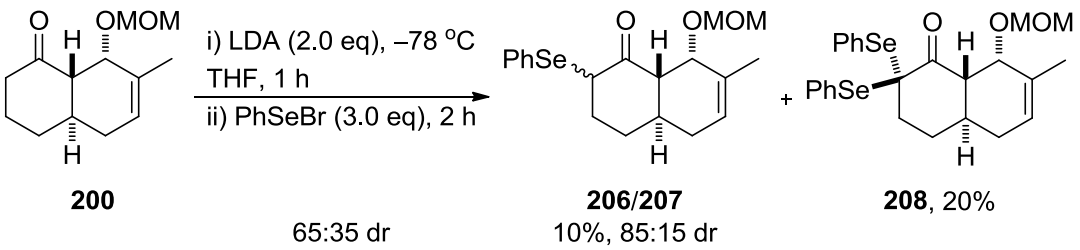
Scheme 2.69

Given our lack of success at oxidising ketone **199** *via* a Saegusa oxidation, we attempted to instead synthesise the corresponding selenide, with the intent to then carry out an oxidation-elimination reaction to gain access to enones **204**/**205** as shown in Scheme 2.70.



Scheme 2.70

Thus, decalinone **200** was deprotonated with LDA in THF at –78 °C for 1 hour and the enolate trapped with PhSeBr to give selenides **206**/**207** in an 65:35 diastereomeric ratio, as determined by the ratio of the integrals of the C=C*H* protons in the ^{1}H NMR spectrum of the crude reaction mixture. After flash chromatography, selenides **206**/**207** were isolated as an 85:15 diastereomeric mixture and a disappointing 10% yield, along with 20% of di-selenide **208**, the identity of which was confirmed by HRMS giving an *m/z* value of 559.0279, as well as a total integration value of 10H for the protons in the aromatic region between δ 7.80–7.30 (Figure 2.20) Presumably formed by a second deprotonation-trapping event on selenides **206**/**207** (Scheme 2.71).



Scheme 2.71

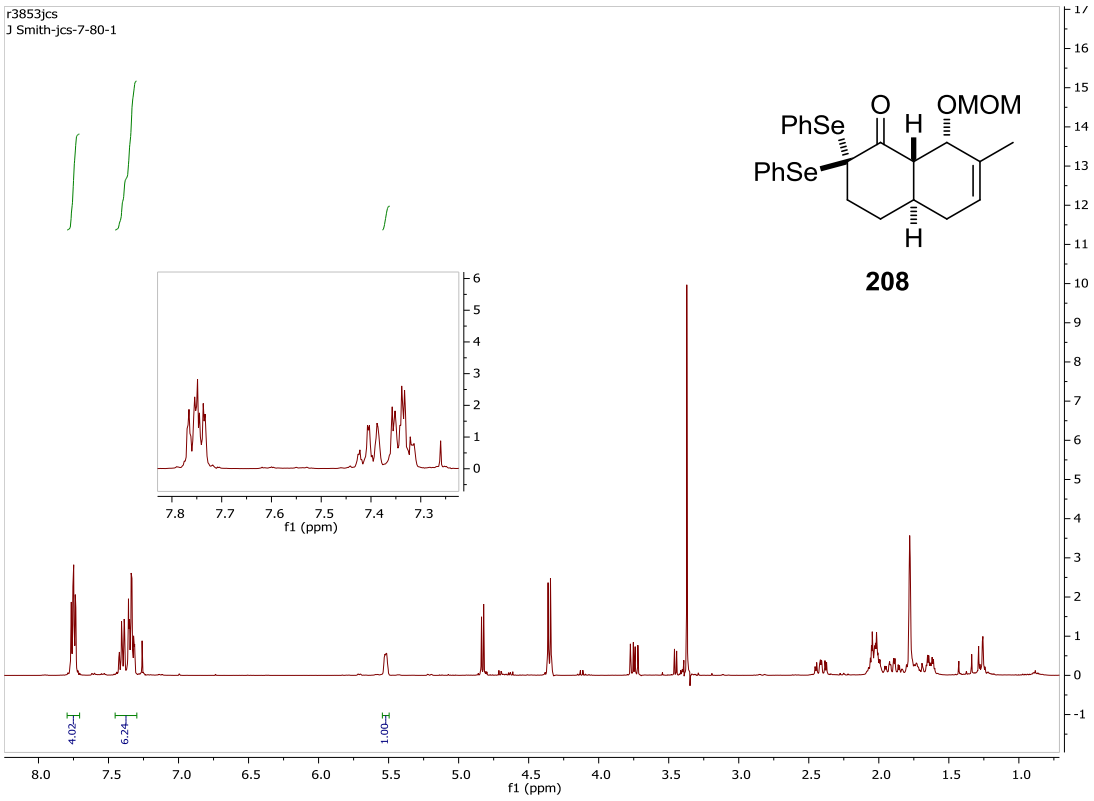
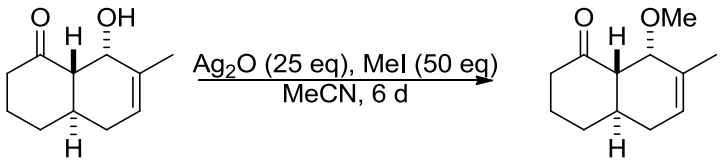


Figure 2.20

As shown earlier in Scheme 2.68, it was speculated that Lewis-acid catalysed polymerisation was occurring with methoxymethyl protected silyl enol ether **203**. Wishing to test this hypothesis, we looked to protect the hydroxyl group of decalinone **194** as a more chemically stable methyl ether. Decalinone **194** was therefore treated with iodomethane and silver oxide in acetonitrile to methylate the hydroxyl group (Scheme 2.72). However, even with vast excesses of reagents and extended reaction times, decalinone methylated decalinone **209** was only formed in 21% yield, with 53% of starting material being recovered.



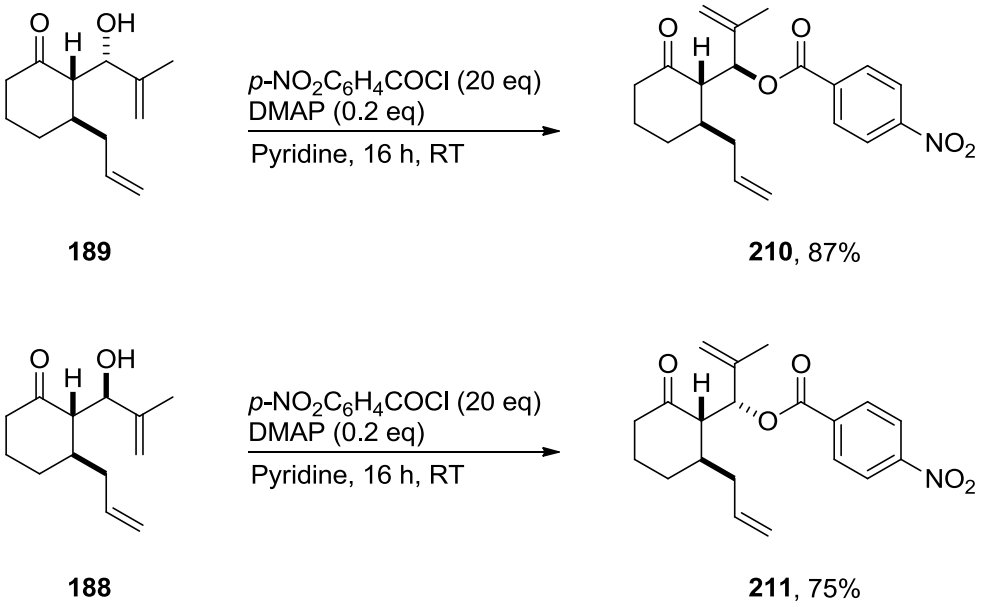
194 **209**, 21%
53% RSM

Scheme 2.72

Whilst we were able to develop methodology for the formation of model decalinones **199** and **200**, oxidation to the corresponding enones *via* a Saegusa oxidation proved much more difficult than anticipated and silyl enol ether **203** could not be isolated. Attempted selenation-oxidation of **200** did not proceed cleanly, giving substantial quantities of di-selenide **208**, as well as low yields of the desired mono-selenides **206**/**207**.

2.6.3 Proof of Relative Stereochemistry of Aldol Products 188 and 189

Attempts to discern the relative stereochemistry of aldol products **188** and **189** directly were problematic, due to the difficulty in assigning *J* values to key diagnostic signals. We therefore looked to derivatise **188** and **189**, both being oils, to a crystalline analogue that could then be subjected to X-ray diffraction after growing suitable single crystals. Thus, aldol products **188** and **189** were acylated with 4-nitrobenzoyl chloride in pyridine with catalytic DMAP to give acylated **210** and **211** in 87% and 75% yield respectively (Scheme 2.73). Both **210** and **211** however, ironically, remained as oils.



Scheme 2.73

Whilst aldol products **188** and **189** were oils, the major decalinone **193** was a waxy solid and eventually, conditions that allowed the growth of a single crystal of adequate quality for X-ray diffraction was grown. The X-ray crystal structure for **193** was thus determined and its relative stereochemistry was proven (Figure 2.21).

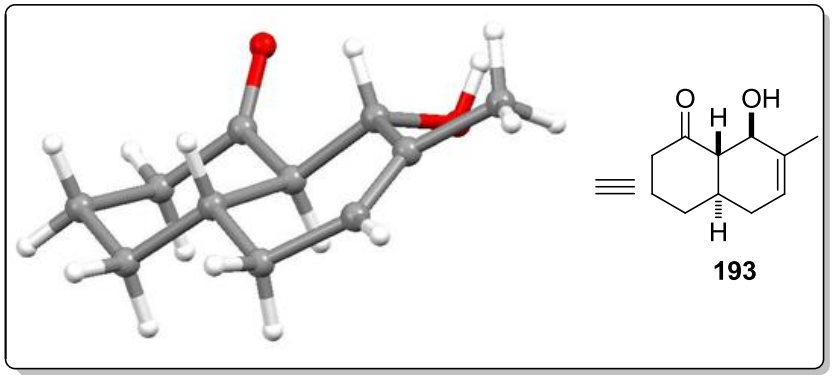
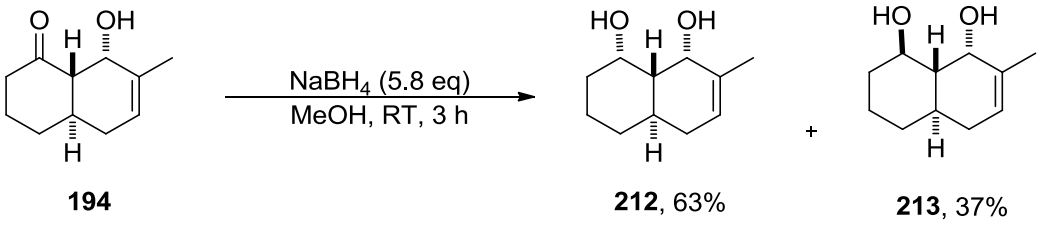


Figure 2.21

Although the relative stereochemistry for the major decalinone **193** had been proven and the *trans* relationship between the ring substituents established, the relative stereochemistry of the minor decalinone was still unknown. Thus, reduction of **194** with $NaBH_4$ in MeOH gave a 63:37 mixture of diasteromeric diols **212**/**213** (by ^1H NMR spectroscopy of the crude reaction mixture) in a 63% and 37% isolated yield (Scheme 2.74).



Scheme 2.74

Whilst the major diol **212** remained as an oil, the minor diol **213** was a well-defined crystalline solid. A suitable single crystal was grown for X-ray diffraction and the relative stereochemistry for **213** was thus proven (Figure 2.22). With the relative stereochemistry of **213** now known and by extension, the relative stereochemistry of the minor decalinone **194** now known, it proved that the variable stereocentre between aldol products **188** and **189** was the hydroxyl group and that the two ring substituents adopt a *trans* relationship between one another.

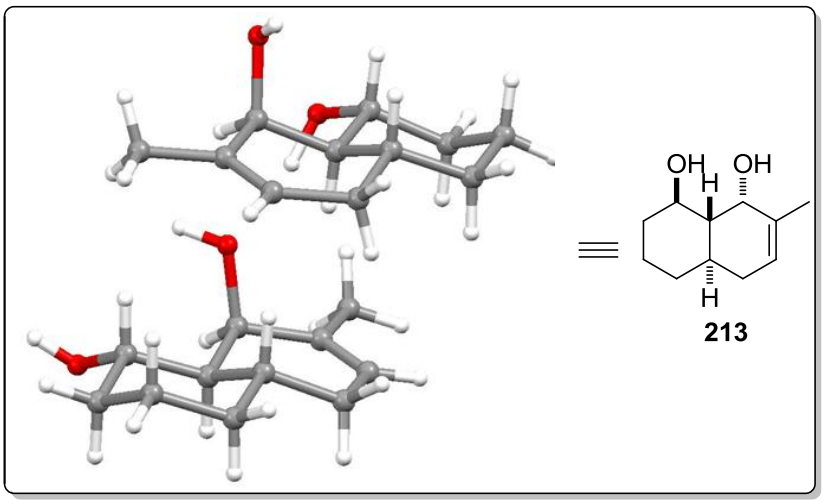


Figure 2.22

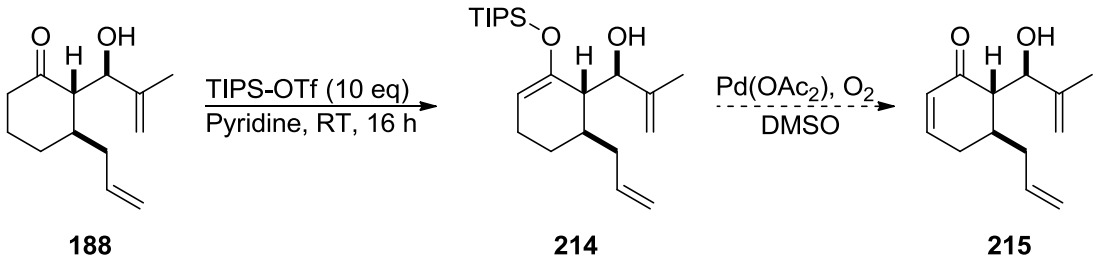
2.7 Conclusions and Future Work

Significant progress has been made at developing methodology suitable for the synthesis of the core of anthracimycin **92** and potential analogues thereof. A robust and scalable route has been developed for the synthesis of the starting enone **117**, as well as for the synthesis of decalinones **193** and **194** *via* titanium enolate chemistry.

The addition of allyl cuprate to TIPS enone **117** was thoroughly investigated. Although conditions for the initial 1,4-addition were discovered, we were unable to trap the enolate with any of the electrophiles that were tested.

Oxidation of decalinone **199** *via* a Saegusa oxidation proved to be more difficult than anticipated, possibly due to the acid-labile nature of the methoxymethyl protecting group. Formation of the α-seleno-ketones **206**/**207** also gave rise to unwanted side product formation including di-selenide **208**.

It was noted in an earlier experiment to TIPS protect the hydroxyl group of aldol product **188**, that the TIPS protected silyl enol ether was formed in 42% yield instead (Scheme 2.74). A Saegusa oxidation at this stage may prove to be a viable alternative to a Saegusa oxidation after the ring closing metathesis step.



188 **214** **215**

Scheme 2.74

Another avenue of research may be to change the protecting group for decalinones **199** and **200** to an acid-stable protecting group in order to prevent polymerisation of the sort speculated in Scheme 2.67 from occurring.

Chapter Three: Experimental Procedures

3.1 General Methods

Water is distilled water. Brine refers to a saturated aqueous solution of NaCl. All non-aqueous reactions were carried out under oxygen-free Ar using flame-dried glassware. Alkyllithiums were titrated against *N*-benzylbenzamide before use.[155] Grignard reagents and allyllithium were titrated against salicylaldehyde phenylhydrazone before use.[156] All diamines and electrophiles were distilled over CaH_2 before use. Et_2O and THF were freshly distilled from sodium and benzophenone ketyl. Petrol refers to the fraction of petroleum ether boiling in the range 40-60 °C.

Flash column chromatography was carried out using Fluka Chemie GmbH silica (220-440 mesh). Thin layer chromatography was carried out using Merck F254 aluminium-backed silica plates. ^1H (400 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded on a Jeol ECX-400 instrument with an internal deuterium lock. Chemical shifts are quoted as parts per million and referenced to $CHCl_3$ (δ_H 7.27), $CDCl_3$ (δ_C 77.0, central line of triplet), PhH (δ_H 7.16), benzene-d6 (δ_C 128.4, central line of triplet), MeOH (δ_H 3.34, central line of quintet) or MeOH-d4 (δ_C 49.2, central line of septet). ^{13}C NMR spectra were recorded with broadband proton decoupling. ^{13}C NMR spectra were assigned using DEPT experiments. Coupling constants (*J*) are quoted in Hertz. IR spectra were recorded on a Perkin-Elmer Spectrum Two infrared spectrophotometer. Melting points were measured on a Stuart Equipment SMP3 melting point apparatus. Electrospray high and low resolution mass spectra were recorded on a Bruker Daltronics microOTOF spectrometer. Chiral stationary phase HPLC was performed on an Agilent 1200 series instrument and a multiple wavelength, UV/Vis diode array detector.

General Procedure A: Racemic *s*BuLi/diamine-mediated lithiation-electrophilic trapping of *N*-thiopivaloyl azetidine 35 and *N*-thiopivaloyl pyrrolidine 76

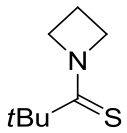
*s*BuLi (1.3 eq of a 1.3 M solution in hexanes) was added rapidly to a stirred solution of *N*-thiopivaloyl azetidine **35** or *N*-thiopivaloyl pyrrolidine **76** (1.0 eq) and TMEDA (2.6 eq.) in Et_2O at −100 °C under N_2. The resulting solution was stirred at −100 °C for 2 min. Then, the electrophile (2.0 eq.) was added and the solution was stirred at −100 °C for 10 min and allowed to warm to rt over the course of 1 h. 2 M $HCl_{(aq)}$ (3 mL) was added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product.

General Procedure B: Asymmetric *s*BuLi/(–)-sparteine mediated lithiation-electrophilic trapping of *N*-thiopivaloyl azetidine 35 and *N*-thiopivaloyl pyrrolidine 76

*s*BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.60 mmol, 1.2 eq.) was added rapidly to a stirred solution of *N*-thiopivaloyl azetidine **35** (77 μL, 79 mg, 0.50 mmol, 1.0 eq) or *N*-thiopivaloyl pyrrolidine **76** (80 μL, 86 mg, 0.5 mmol, 1.0 eq) and (–)-sparteine (–)-**1** (0.14 mL, 141 mg, 0.6 mmol, 1.2 eq) or (*S*,*S*)-Alexakis' diamine (*S*,*S*)-**12** (186 mg, 0.6 mmol, 1.2 eq) in Et_2O (5 mL) at –78 °C under N_2. The resulting solution was stirred at –78 °C for 30 min. Then, the electrophile (2.0 eq) was added and the solution was stirred at –78 °C for 30 min. Then, MeOH (2 mL) was added at –78 °C and the resulting solution was allowed to warm to rt over the course of 1 h. 2 M $HCl_{(aq)}$ (10 mL) was added and the layers were seperated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product.

3.2 Experimental Procedures For Chapter One

N-Thiopivaloyl azetidine 35



35

To a stirred solution of P_2S_5 (1.89 g, 8.50 mmol, 1.2 eq) in pyridine (60 mL) was added amide **56** (1.0 g, 7.08 mmol, 1.0 eq). The resulting solution was heated to 85 °C for 16 h. Then, the reaction mixture was cooled to 0 °C and diluted with water (100 mL) and the pH adjusted to 2-3 with $HCl_{(aq)}$ (12 M) and stirred at room temperature for 3 h. The reaction was diluted with CH_2Cl_2 (100 mL), the layers separated and the aqueous layer washed with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation (approx. 106 °C bp at 0.5 mbar) gave thioamide **35** (0.51 g, 3.26 mmol, 46%) as a bright yellow oil, R_F (8:2 hexane – EtOAc) 0.25; IR (ATR) 2963, 1462, 1434, 1363, 1259, 1142, 1080, 1010, 864, 789, 701, 661, 480 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.51 (dddd, J = 8.0, 8.0, 1.0, 1.0 Hz, 2H, CH_2N), 4.28 (dddd, J = 7.5, 7.5, 1.0, 1.0 Hz, 2H, CH_2N), 2.33–2.24 (m, 2H, CH_2), 1.35 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 209.6 (C=S), 57.1 (CH_2N), 56.2 (CH_2N), 43.2 (CMe_3), 29.8 (CMe_3), 14.9 (CH_2); MS (ESI) *m/z* 158 [$(M+H^+)$, 100], 180 [$(M+Na)^+$, 20]; HRMS *m/z* cacld for $C_8H_{15}NS$ $(M + Na)^+$ 180.0817, found 180.0811 (+3.4 ppm error).

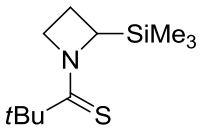
Lab Book Reference: JCS-5-57

To a stirred solution of P_2S_5 (4.57 g, 20.6 mmol, 1.05 eq) in pyridine (60 mL) was added amide **56** (2.76 g, 19.6 mmol, 1.0 eq). The resulting solution was heated to 75 °C for 16 h. Then, the reaction mixture was cooled to 0 °C and diluted with water (100 mL) and the pH adjusted to 2-3 with H_2SO_4 (95% w/w) and stirred at room temperature for 3 h. The reaction was diluted with CH_2Cl_2 (30 mL), the layers separated and the aqueous layer washed with CH_2Cl_2 (5 x 30 mL). The combined organic layers were dried

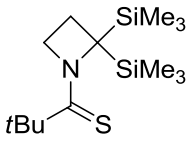
($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2 petroleum ether – EtOAc as eluent gave thioamide **35** (2.83 g, 18.0 mmol, 92%) as a bright yellow oil.

Lab Book Reference: JCS-2-3

Rac-2,2-dimethyl-1-(2-(trimethylsilyl)azetidin-1-yl)propane-1-thione _rac_-36 and 1-(2,2-bis(trimethylsilyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione 73



rac-**36**

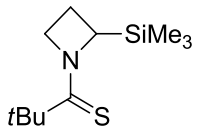


73

Using general method **A**, thioamide **35** (77 μL, 79 mg, 0.5 mmol, 1.0 eq), *s*BuLi (0.5 mL, 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq), TMEDA (0.18 mL, 1.2 mmol, 2.6 eq) and Me_3SiCl (0.130 mL, 0.109 mg, 1.0 mmol, 2.0 eq) as electrophile in Et_2O (5 mL) yielded crude product. Purification by flash column chromatography on silica with 8:2 petroleum ether – EtOAc as eluent gave _rac_-**36** (73 mg, 0.32 mmol, 64%), mp 49–52 °C; R_F (8:2 petroleum ether – EtOAc) 0.44; IR (ATR) 2950, 1474, 1441, 1361, 1244, 1134, 1016, 1110, 1003, 945, 833, 752, 687, 645, 496 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.61 (ddd, J = 11.0, 6.5, 2.0 Hz, 1H, CHN), 4.52–4.39 (m, 2H, CH_2N), 2.47–2.35 (m, 1H, CH_AH_B), 2.10–2.00 (m, 1H, CH_AH_B), 1.33 (s, 9H, CMe_3), 0.18 (s, 9H, $SiMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 206.1 (C=S), 62.2 (CHN), 57.1 (CH_2N), 42.9 (CMe_3), 30.0 (CMe_3), 17.1 (CH_2), –1.30 ($SiMe_3$); MS (ESI) *m/z* 230 [$(M + H)^+$, 100]; HRMS *m/z* calcd for $C_{11}H_{24}NSSi$ $(M+H)^+$ 230.1393, -found 230.1388 (+2.3 ppm error), and di-substituted **73** (21.2 mg, 0.070 mmol, 14%) as a white solid, mp 100.5–102.0 °C; R_F (8:2 petroleum ether – EtOAc) 0.59; IR (ATR) 2950, 1473, 1441, 1391, 1361, 1244, 1193, 1134, 1110, 1017, 1002, 945, 833, 752, 687, 597, 496 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.41–4.36 (m, 2H, CH_2N), 2.26–2.19 (m, 2H, CH_2), 1.30 (s, 9H, CMe_3), 0.21 (s, 18H, $SiMe_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) 203.1 (C=S), 66.9 ($NC(SiMe_3)_2$), 56.0 (CH_2N), 42.4 (CMe_3), 29.9 (CMe_3), 20.2 (CH_2), 0.29 ($SiMe_3$); MS (ESI) 302 [$(M+H)^+$, 100], 324 [$(M+Na)^+$, 50]; HRMS *m/z* calcd for $C_{14}H_{31}NSSi_2$ $(M+H)^+$ 302.1789, found 302.1785 (+0.7 ppm error).

Lab book reference: JCS-7-86

2,2-Dimethyl-1-(2-(trimethylsilyl)azetidin-1-yl)propane-1-thione-36



36, 54:46 *er*

Using general procedure **B**, *s*BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.60 mmol, 1.2 eq), *N*-thiopivaloyl azetidine **35** (77 μL, 79 mg, 0.5 mmol, 1.0 eq) and (–)-**1** (0.14 mL, 141 mg, 0.6 mmol, 1.2 eq) in Et_2O (5 mL) and Me_3SiCl (95 μL, 81 mg, 0.75 mmol, 1.5 eq) gave the crude product. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc as eluent gave silane **36** (64 mg, 0.28 mmol, 56%, 54:46 er by CSP-HPLC) as a white solid; $[\alpha]_D$ +15.6 (*c* 0.52 in EtOAc); CSP-HPLC: Chiralcel OD-H (98:2 Hexane-*i*PrOH, 1.0 mL min^{-1}) 4.7 min (major), 5.9 min (minor).

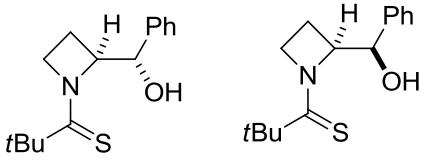
Spectroscopic data consistent with literature values.[20]

Lab Book Reference: JCS-2-11

Using general procedure **B**, *s*BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.60 mmol, 1.2 eq), *N*-thiopivaloyl azetidine **35** (77 μL, 79 mg, 0.5 mmol, 1.0 eq) and diamine (*S*,*S*)-**12** (186 mg, 0.6 mmol, 1.2 eq) in Et_2O (5 mL) and Me_3SiCl (95 μL, 81 mg, 0.75 mmol, 1.5 eq) gave the crude product. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc gave silane **36** (51 mg, 0.22 mmol, 45%, 54:46 er by CSP-HPLC) as a white solid, mp 46–49 °C; $[\alpha]_D$ +19.2 (*c* 1.145 in EtOAc); CSP-HPLC: Chiralcel OD-H (98:2 Hexane-*i*PrOH, 1.0 mL min^{-1}) 5.2 min (major), 6.9 min (minor).

Lab Book Reference: JCS-2-12

***Rac*-1-(2-(hydroxy(phenyl)methyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione *rac*-38 and *rac*-39**



rac-**38** *rac*-**57**

*s*BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq) was added to a stirred solution of thioamide **35** (77 μL, 79 mg, 0.5 mmol, 1.0 eq) and TMEDA (0.20 mL, 0.151 g 1.3 mmol, 2.6 eq) in THF (5 mL) at –78 °C under N_2. After 30 min, benzaldehyde (0.1 mL, 1.0 mmol, 2.0 eq) was added and the resultant solution was allowed to warm to room temperature over 30 m. $HCl_{(aq)}$ (2 M, 3 mL) was added and the reaction mixture was diluted with EtOAc (20 mL). The layers were seperated and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product which ontained a a 65:35 mixture (by ^{1}H NMR of the crude mixture) of diasteromeric alcohols **38** and **57**. Purification by column chromatography through silica with 95:5 – 8:2 petroleum ether – EtOAc as eluent gave *rac*-**57** (25 mg, 0.095 mmol, 19%) as a white solid, mp 130.5–132.2 °C; R_F (8:2 petroleum ether – EtOAc) 0.5; IR (ATR) 3351 (O–H), 2998, 2973, 2931, 2897, 2868, 1481, 1455, 1468, 1432, 1394, 1359, 1276, 1242, 1220, 1206, 1136, 1112, 1065, 1052, 1030, 992, 977, 929, 828, 778, 753, 703, 668, 657, 607, 560, 514, 472 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.41 (m, 2H, PhH), 7.38-7.33 (m, 2H, PhH), 7.32-7.27 (m, 1H, p-PhH), 5.46 (d, *J* = 1.5 Hz, 1H, C*H*OH), 5.25 (dddd, *J* = 9.0, 5.0, 1.5, 1.5 Hz, 1H, CHN), 4.20 (ddd, *J* = 10.0, 10.0, 5.0 Hz, 1H, CH_AH$_B$N), 3.87 (dddd, *J* = 7.5, 7.5, 7.5, 2.0 Hz, 1H, CH$_A$$H_B$N), 2.30 (m, 1H, CH$_AH_B$), 2.11 (m, 1H, CH$_AH_B$), 1.29 (s, 9H, CMe_3); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 211.1 (C=S), 139.6 (*i*-Ph), 128.2 (Ph), 127.7 (Ph), 126.7 (Ph), 73.7 (CHOH), 73.5 (CHN), 56.1 (CH_2N), 43.4 (*C*Me$_3$), 29.5 (C*Me*$_3$), 17.2 (CH_2); MS (ESI) *m/z* 264 [(M+H)$^+$, 60], 286 [(M+Na)$^+$, 100]; HRMS *m/z* calcd for $C_{15}H_{21}NOS$ (M+H)$^+$ 264.1417, found 264.1423 (-3.2 ppm error); CDCC No. 1417066, and *rac*-**38** (49 mg, 0.19 mmol, 37%) as a white solid, mp 132.5–133.2 °C; R_F (8:2 petroleum ether – EtOAc) 0.4; IR (ATR) 3213 (O-H), 2969, 1463, 1367, 1292, 1253, 1219, 1135, 1118, 1078, 1060, 987, 926, 854, 762, 704, 634, 597, 543, 502, 483 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.44-7.40 (m, 2H, PhH), 7.38-7.28 (m, 3H, PhH), 5.31 (d, *J* = 7.5 Hz, 1H, C*H*OH), 5.21 (m, 1H, CHN), 4.29 (ddd, *J* = 10.0, 10.0, 5.5 Hz, 1H, CH_AH$_B$N), 4.15 (m, 1H, CH$_A$$H_B$N), 2.19 (m, 1H, C$H_AH_B$), 1.85 (m, 1H, CH$_A$$H_B$) 1.34 (s, 9H, CMe_3); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 212.3 (C=S), 140.0 (*i*-Ph), 128.4 (Ph), 128.2 (*p*-Ph), 127.4 (Ph), 76.1 (CHOH), 73.9 (CHN), 56.1 (CH_2N), 43.7 (CMe_3), 29.7 (CMe_3), 18.4 (CH_2); MS (ESI) *m/z* 264 [$(M+H)^+$, 10], 286 [$(M+Na)^+$, 100]; HRMS *m/z* calcd for $C_{15}H_{21}NOS$ $(M+Na)^+$ 286.1236, found 286.1234 (+0.4 ppm error), CDCC No. 1417067.

Procedure for growing crystals of *rac*-38 and *rac*-57

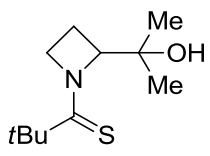
Alcohol *rac*-**57** (Approx 5 mg) was dissolved in the minimum amount of EtOAc. The solution was placed into a small glass vial and placed upright in a sealed vessel containing pentane (~ 20 mL). After several days, suitable crystals had precipitated in the glass vial. These were collected and subjected to X-ray analysis. The same method was used to grow appropriate crystals of diasteromeric alcohol *rac*-**38**.

Lab Book Reference: JCS-1-19, JCS-7-71

Using general method **A**, thioamide **35** (77 μL, 79 mg, 0.5 mmol, 1.0 eq), *s*BuLi (0.50 mL, 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq), TMEDA (0.20 mL, 0.151 g 1.3 mmol, 2.6 eq) and benzaldehyde (0.1 mL, 0.104 g, 1.0 mmol, 2.0 eq) as electrophile in Et_2O (5 mL) yielded crude product containing alcohols *rac*-**57** and *rac*-**38** in a 27:73 ratio respectively. Purification by flash column chromatography with 8:2 petroleum ether – EtOAc gave a mixture of alcohols **57** and **38** (116 mg, 0.44 mmol, 88% combined yield).

Lab book reference: JCS-1-97

***Rac*-1-(2-(2-hydroxypropan-2-yl)azetidin-1-yl)-2,2-dimethylpropane-1-thione 39**



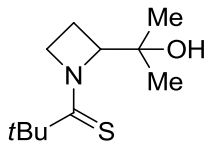
rac-**39**

Using general procedure **A**, *s*BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq), *N*-thiopivaloyl azetidine **35** (77 μL, 79 mg, 0.5 mmol, 1.0 eq) and TMEDA (0.20 mL, 155 mg, 1.3 mmol, 2.6 eq) in Et_2O (7 mL) and freshly distilled, dry acetone (73 μL, 58 mg, 1.0 mmol, 2.0 eq) gave the crude product. Purification by flash column chromatography on silica with 8:2 – 7:3 hexane – EtOAc as eluent gave alcohol *rac*-**39** (40 mg, 0.187 mmol, 37%) as a brown solid, mp 74–77 °C; IR (ATR) 3264 (O–H), 2967, 2924, 1464, 1433, 1402, 1362, 1300, 1255, 1173, 1136, 986, 948, 541, 474 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.00 (br s, 1H, OH), 4.96 (dd, J = 10.0, 6.0 Hz, 1H, CHN), 4.46-4.40 (m, 2H, CH_2N), 2.52–2.41 (m, 1H, CH_AH_B), 1.97-1.87 (m, 1H, CH_AH_B), 1.36 (s, 9H, CMe_3), 1.30 (s, 3H, Me_A), 1.15 (s, 3H, Me_B); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 212.5 (C=S), 79.1 (CHN), 73.3 ($C(Me)_2OH$), 56.3 (CH_2N), 43.8 (CMe_3), 29.8 (CMe_3), 25.7 (Me), 23.2 (Me), 19.5 (CH_2); MS (ESI) *m/z* 238 [$(M+Na)^+$, 85], 216 [$(M+H]^+$, 100]; HRMS *m/z* calcd for $C_{11}H_{22}NOS$ $(M+Na)^+$ 238.1236, found 238.1229 (+3.0 ppm error).

Spectroscopic data consistent with literature values.[20]

Lab Book Reference: JCS-2-6

1-(2-(2-Hydroxypropan-2-yl)azetidin-1-yl)-2,2-dimethylpropane-1-thione 39

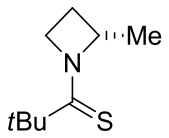


39, 60:40 *er*

Using general procedure **B**, *s*BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.60 mmol, 1.2 eq), *N*-thiopivaloyl azetidine **35** (77 μL, 79 mg, 0.5 mmol, 1.0 eq) and (–)-**1** (0.14 mL, 141 mg, 0.6 mmol, 1.2 eq) in Et_2O (5 mL) and freshly distilled, dry acetone (60 μL, 48 mg, 0.75 mmol, 1.5 eq) gave the crude product. Purification by flash column chromatography on silica with 8:2-7:3 hexane-EtOAc as eluent gave **39** (23 mg, 0.107 mmol, 22%, 60:40 er by CSP-HPLC) as a brown solid, mp 70–75 °C; $[\alpha]_D$ –7.5 (*c* 0.95 in EtOAc); CSP-HPLC: Chiralcel OD-H (98:2 Hexane-*i*PrOH, 1.0 mL min^{-1}) 13.0 min (minor), 14.1 min (major).

Lab Book Reference: JCS-2-7

(*S*)-2,2-Dimethyl-1-(2-methylazetidin-1-yl)propane-1-thione (*S*)-40

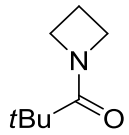


(*S*)-**40**, *er* 71:29

Using general procedure **B**, *s*BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.60 mmol, 1.2 eq), *N*-thiopivaloyl azetidine **35** (77 μL, 79 mg, 0.5 mmol, 1.0 eq) and diamine (*S*,*S*)-**12** (186 mg, 0.6 mmol, 1.2 eq) in Et_2O (5 mL) and methyl iodide (50 μL, 106 mg, 0.75 mmol, 1.5 eq) gave the crude product. Purification by flash column chromatography on silica with 9:1 hexane-EtOAc gave adduct (*S*)-**40** (41 mg, 0.24 mmol, 48%, *er* 71:29 by CSP-HPLC) as a yellow oil, R_F (8:2 petroleum ether – EtOAc) 0.35; IR (ATR) 2962, 2924, 1456, 1425, 1363, 1255, 1139, 1049, 993, 493 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (83:17 mixture of rotamers) δ 4.91–4.78 (m, 0.83H, CHN), 4.91–4.78 (m, 0.13H, CHN), 4.61–4.51 (m, 0.83H, C$H_A$$H_B$N), 4.61–4.51 (m, 0.13H, C$H_A$$H_B$N), 4.45–4.38 (m, 0.83H, CH$_A$$H_B$N), 4.45–4.38 (m, 0.13H, CH$_A$$H_B$N), 2.59–2.47 (m, 0.83H, C$H_A$$H_B$), 2.59–2.47 (m, 0.13H, C$H_A$$H_B$), 1.88–1.79 (m, 0.83H, CH$_A$$H_B$), 1.88–1.79 (m, 0.13H, CH$_A$$H_B$), 1.65 (d, J = 6.5 Hz, 0.39H, CH_3), 1.60 (d, J = 6.5 Hz, 2.49H, CH_3), 1.40 (s, 1.17H, CMe_3), 1.33 (s, 7.47H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 210.5 (C=S), 65.9 (CHN), 55.8 (CH_2N), 43.6 (*C*Me_3), 29.8 (C*Me*$_3$), 23.2 (CH_2), 18.7 (CH_3); $[\alpha]_D$ +4.3 (*c* 0.725 in EtOAc); CSP-HPLC: Chiralcel OD-H (99.9:0.1 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*R*)-**40** 15.1 min, (*S*)-**40** 16.8 min. Spectroscopic data consistent with literature values.[20]

Lab Book Reference: JCS-2-13

***N*-Pivaloyl Azetidine 56**

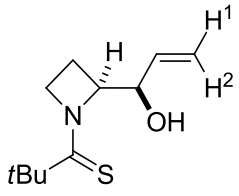


56

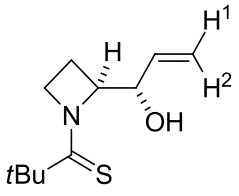
*t*BuCOCl (3.16 mL, 3.10 g, 25.7 mmol, 1.2 eq) was added dropwise to a stirred suspension of azetidine HCl (21.4 mmol, 2.00 g, 1.0 eq), Et_3N (14.9 mL, 10.8 g, 0.11 mol, 5.0 eq), and DMAP (0.52 g, 4.28 mmol, 0.2 eq) in CH_2Cl_2 (50 mL) at 0 °C under N_2 atmosphere over 5 minutes. The resulting solution was then allowed to warm to rt over 16 h. Then, $HCl_{(aq)}$ (2 M, 100 mL) was added, followed by the addition of 50 mL of CH_2Cl_2. The layers were separated and the organic layer was washed with $HCl_{(aq)}$ (2 M, 2 x 20 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation (approx. 80 °C bp at 0.5 mbar) gave **56** (2.54 g, 18.0 mmol, 84%) as a colourless oil; IR (ATR) 2962, 2883, 1809, 1730, 1625 (C=O), 1589 (C=O), 1481, 1413, 1364, 1165, 1043, 1004, 941, 862, 748, 629, 564, 527 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.35 (br s, 2H, CH_2N), 4.00 (br s, 2H, CH_2N), 2.22 (dddd, J = 7.5, 7.5, 7.5, 7.5 Hz, 2H, CH_2), 1.17 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 183.7 (C=O), 177.9 (C=O), 53.4 (CH_2N), 49.2 (CH_2N), 38.6 (CMe_3), 38.5 (CMe_3), 27.2 (CMe_3), 27.1 (CMe_3), 16.0 (CH_2); MS (ESI) *m/z* 142 $[(M+H)^+$, 100], 164 $[(M+Na)^+$, 50]; HRMS *m/z* calcd for $C_8H_{15}NO$ $(M+Na)^+$ 164.1046, found 164.1051 (-3.5 ppm error).

Lab Book Reference: JCS-5-55

Rac-1-(2-(1-hydroxyallyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione _rac_-58 and _rac_-59



rac-**59**



rac-**58**

Using general procedure **A**, *s*BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq), *N*-thiopivaloyl azetidine **35** (0.154 mL, 0.151 g, 1.0 mmol, 1.0 eq) and TMEDA

(0.39 mL, 0.302 g, 2.6 mmol, 2.6 eq) in Et_2O (7 mL) and acrolein (0.134 mL, 0.112 g, 2.0 mmol, 2.0 eq) gave the crude product which contained a 65:35 mixture of diastereomeric alcohols *rac*-**58** and *rac*-**59** (by ^{1}H NMR of the crude reaction mixture). Purification by flash column chromatography on silica with 9:1 hexane – EtOAc as eluent gave alcohol *rac*-**59** (48 mg, 0.23 mmol, 23%) as a pale yellow oil, R_F (8:2 petroleum ether - EtOAc) 0.18; IR (ATR) 3400 (O–H), 2967, 2925, 1464, 1431, 1395, 1363, 1301, 1248, 1219, 1143, 1078, 988, 925, 872, 790, 695, 662, 560, 493 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (ddd, J = 17.0, 10.5, 6.0 Hz, 1H, HC=CH^{1}H^2), 5.42 (ddd, J = 17.0, 1.5, 1.5 Hz, 1H, HC=CH$^1H^2$), 5.27 (ddd, J = 10.5, 1.5, 1.5 Hz, 1H, HC=CH^1H^2), 5.04–4.98 (m, 1H, CHN), 4.70 (br d, J = 4.5 Hz, 1H, CHOH), 4.37–4.31 (m, 2H, CH_2N), 4.27 (br s, 1H, CHOH), 2.43–2.31 (m, 1H, CH_AH$_B$), 2.10–2.00 (m, 1H, CH$_A H_B$), 1.34 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 211.2 (C=S), 135.1 (HC=CH$_2$), 117.3 (HC=CH$_2$), 73.1 (CHOH), 72.9 (CHN), 56.2 (CH_2N), 43.5 (CMe$_3$), 29.7 (CMe_3), 17.7 (CH_2); MS (ESI) *m/z* 214 [(M+H)$^+$, 50], 236 [(M+Na)$^+$, 100]; HRMS *m/z* calcd for $C_{11}H_{19}NOS$ (M+Na)$^+$ 236.1080, found 236.1084 (-2.1 ppm error), and *rac*-**58** (89 mg, 0.42 mmol, 42%) as a pale yellow oil, R_F (8:2 petroleum ether - EtOAc) 0.14; IR (ATR) 3392 (O–H), 3270, 2968, 2927, 1460, 1429, 1395, 1363, 1290, 1248, 1142, 1118, 1055, 992, 926, 872, 811, 701, 662, 511 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (m, 1H, HC=CH^{1}H^2), 5.43 (ddd, J = 17.0, 1.0, 1.0 Hz, 1H, HC=CH$^1H^2$), 5.29 (ddd, J = 10.5, 0.5 Hz, 1H, HC=CH^1H^2), 4.99–4.91 (m, 1H, CHN), 4.81 (br s, 1H, CHOH), 4.73 (dd, J = 7.0, 7.0 Hz, CHOH), 4.47–4.33 (m, 2H, CH_2N), 2.42–2.30 (m, 1H, CH_AH$_B$), 2.03–1.93 (m, 1H, CH$_A H_B$), 1.35 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 212.4 (C=S), 135.7 (HC=CH$_2$), 118.4 (HC=CH$_2$), 75.2 (CHOH), 72.7 (CHN), 56.3 (CH_2N), 43.6 (CMe$_3$), 29.7 (CMe_3), 18.3 (CH_2); MS (ESI) *m/z* 214 [(M+H)$^+$, 40], 236 [(M+Na)$^+$, 100]; HRMS *m/z* calcd for $C_{11}H_{19}NOS$ (M+Na)$^+$ 236.1080, found 236.1080 (-0.3 ppm error).

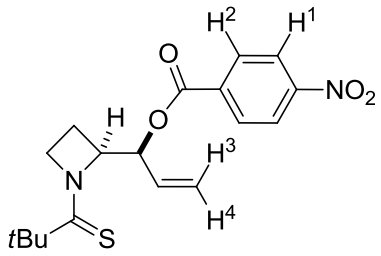
Lab book reference: JCS-7-72

*s*BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.0 eq) was added dropwise over 2 m to a stirred solution of TMEDA (0.39 mL, 0.302 g, 2.6 mmol, 2.6 eq) and *N*-thiopivaloyl azetidine **35** (0.154 mL, 0.151 g, 1.0 mmol, 1.0 eq) in THF (7 mL) at –78 °C under N_2. After 30 minutes, acrolein (0.134 mL, 0.112 g, 2.00 mmol, 2.0 eq) was

added rapidly and the solution was stirred for a further 30 mins at the same temperature. $AcOH_{(l)}$ (2 mL) was added and the solution was allowed to warm to room temperature. $NaHCO_{3(aq)}$ (sat. 10 mL) was added and the layers were separated. The aqueous layer was washed with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were washed with brine (1 x 10 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give crude product which contained a 60:40 mixture of diastereomeric alcohols *rac*-**58** and *rac*-**59**. Purification by flash column chromatography on silica with 9:1 petroleum ether - EtOAc as eluent gave *rac*-**59** (27 mg, 0.124 mmol, 12%) as a pale yellow oil and *rac*-**58** (55 mg, 0.257 mmol, 26%) as a pale yellow oil.

Lab Book Reference: JCS-1-71

Rac-(_S_)-1-((_S_)-1-(2,2-dimethylpropanethioyl)azetidin-2-yl)allyl 4-nitrobenzoate _rac_-60



rac-**60**

4-nitrobenzoylchloride (348 mg, 1.87 mmol, 20 eq) was added in one portion to a stirred solution of alcohol *rac*-**58** (20 mg, 0.094 mmol, 1.0 eq) and DMAP (2.3 mg, 0.019 mmol, 0.2 eq) in pyridine (2 mL) at rt. The resulting solution was stirred at the same temperature for 16 h. Then, the reaction mixture was diluted with EtOAc (50 mL) and washed with $HCl_{(aq)}$ (2 M, 1 x 20 mL), water (1 x 20 mL), $K_2CO_{3(aq)}$ (5% w/w, 1 x 50 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 hexane – EtOAc as eluent gave *rac*-**60** (22 mg, 0.061 mmol, 65%) as a pale yellow solid, mp 103.5–105.5 °C; R_F (7:3 hexane – EtOAc) 0.31; IR (ATR) 3111, 2958, 2926, 2854, 1720 (C=O), 1606, 1525 (N–O), 1462, 1432 (N–O), 1364, 1339, 1316, 1292, 1271, 1173, 1147, 1117, 1106, 1006, 983, 967, 928, 880, 865, 841, 814, 786, 720, 505 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31–8.27 (m, 2H, H^1), 8.22–8.17 (m, 2H, H^2), 6.72 (dd,

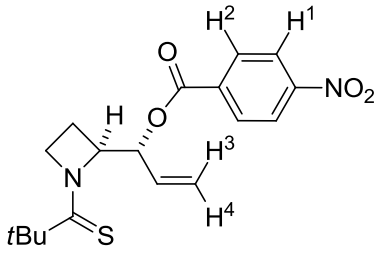
J = 5.5, 5.5 Hz, C*H*OCOOAr), 6.01 (ddd, *J* = 17.0, 10.5, 5.5 Hz, *H*=CH_2), 5.50 (br d, *J* = 17.0 Hz, 1H, H^3), 5.45 (d, *J* = 10.5 Hz, 1H, H^4), 5.18 (ddd, *J* = 9.5, 5.5, 5.5 Hz, 1H, CHN), 4.48–4.35 (m, 2H, CH_2N), 2.54–2.42 (m, 1H, CH_AH_B), 2.38–2.27 (m, 1H, CH_AH_B), 1.32 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 212.1 (C=S), 163.3 (*C*OOAr), 150.7 (*i*-$ArNO_2$), 135.5 (*p*-$ArNO_2$), 130.9 (*m*-$ArNO_2$), 130.6 (H*C*=CH_2), 123.7 (*o*-$ArNO_2$), 120.0 (HC=*C*H_2), 71.5 (*C*HOCOOAr), 67.3 (CHN), 56.6 (CH_2N), 43.5 (*C*Me_3), 29.7 (C*Me*$_3$), 16.6 (CH_2); MS (ESI) *m/z* 363 [$(M+H)^+$, 60], 385 [$(M+Na)^+$, 100]; HRMS *m/z* calcd for $C_{18}H_{22}N_2O_4S$ $(M+H)^+$ 363.1373, found 363.1369 (+0.9 ppm error).

Method For Growing Crystals of *rac*-**60**

A solid sample of *rac*-**60** (approx. 1 mg) was placed in a small glass vial and dissolved in the minimum quantity of EtOAc (approx. 0.05 mL) and placed upright in a sealed vessel containing pentane (approx. 5 mL). After 24 h, crystals suitable for X-Ray analysis had formed on the inner vial.

Lab Book Reference: JCS-7-77

***Rac*-(*R*)-1-((*S*)-1-(2,2-Dimethylpropanethioyl)azetidin-2-yl)allyl 4-nitrobenzoate *rac*-61**



rac-**61**

4-nitrobenzoylchloride (348 mg, 1.87 mmol, 20 eq) was added in one portion to a stirred solution of alcohol *rac*-**59** (20 mg, 0.094 mmol, 1.0 eq) and DMAP (2.3 mg, 0.019 mmol, 0.2 eq) in pyridine (2 mL) at rt. The resulting solution was stirred at the

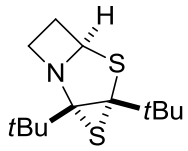
same temperature for 16 h. Then, the reaction mixture was diluted with EtOAc (50 mL) and washed with $HCl_{(aq)}$ (2 M, 1 x 20 mL), water (1 x 20 mL), $K_2CO_{3(aq)}$ (5% w/w, 1 x 50 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 hexane – EtOAc as eluent gave *rac*-**61** (21 mg, 0.058 mmol, 62%) as a pale yellow solid, mp 140.9–143.5 °C; R_F (7:3 hexane – EtOAc) 0.29; IR (ATR) 2971, 2924, 2854, 1723 (C=O), 1608, 1528 (N–O), 1455, 1433 (N–O), 1345, 1319, 1265, 1244, 1205, 1147, 1117, 1102, 1076, 1010, 977, 936, 912, 867, 848, 829, 783, 716, 666, 506 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35–8.30 (m, 2H, H^1), 8.27–8.22 (m, 2H, H^2), 6.89 (dd, J = 5.0, 1.5 Hz, 1H, C*H*ORCOOAr), 5.86 (ddd, J = 16.5, 11.0, 5.0 Hz, 1H, *H*C=CH_2), 5.44 (br d, J = 16.5 Hz, 1H, H^3), 5.36 (br d, J = 11.0 Hz, 1H, H^4), 5.11–5.05 (m, 1H, CHN), 4.46–4.39 (m, 2H, CH_2N), 2.55–2.44 (m, 2H, CH_2), 1.21 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 212.0 (C=S), 163.1 (C=O), 150.8 (C–NO_2), 135.6 (*p*-ArNO_2), 131.1 (H*C*=CH_2), 130.7 (*o*-ArNO_2), 123.9 (*m*-ArNO_2), 118.9 (HC=*C*H_2), 71.8 (*C*HOCOOAr), 68.7 (CHN), 56.6 (CH_2N), 43.7 (*C*Me_3), 29.6 (C*Me*$_3$), 17.0 (CH_2); MS (ESI) *m/z* 363 [$(M+H)^+$, 60], 385 [$(M+Na)^+$, 100]; HRMS *m/z* calcd for $C_{18}H_{22}N_2O_4S$ $(M+H)^+$ 363.1373, found 363.1369 (+0.9 ppm error).

Method For Growing Crystals of *rac*-**61**

A solid sample of *rac*-**61** (approx. 1 mg) was placed in a small glass vial and dissolved in the minimum quantity of EtOAc (approx. 0.05 mL) and placed upright in a sealed vessel containing pentane (approx. 5 mL). After 24 h, crystals suitable for X-Ray analysis had formed on the inner vial.

Lab Book Reference: JCS-7-76

***Rac*-(2*S*,4*R*,6*R*)-2,4-di-tert-butyl-3,5-dithia-1-azatricyclo[4.2.0.02,4]octane *rac*-62**

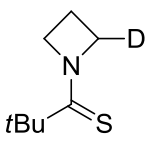


rac-**62**

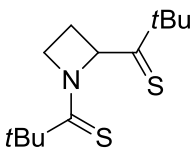
*s*BuLi (1 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq) was added dropwise over 3 m to a stirred solution of TMEDA (0.39 mL, 0.302 g, 2.6 mmol, 2.6 eq) and *N*-thiopivaloyl azetidine **35** (0.151 mL, 0.157 g, 1.0 mmol, 1.0 eq) held at –78 ^{o}C under N_2. The solution was stirred at the same temperature for 1 hour before being quenched by the addition of MeOH (2 mL). The resulting solution was allowed to warm to room temperature and $HCl_{(aq)}$ (2 M, 10 mL) was added. The reaction mixture was diluted with EtOAc (100 mL) and the layers were separated. The organic layer was dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gave *rac*-**62** (28 mg, 0.108 mmol, 22%) as a pale yellow oil, IR (ATR) 2960, 2928, 2867, 1618, 1476, 1460, 1393, 1364, 1263, 1221, 1171, 1127, 1051, 998, 967, 943, 889, 853, 817, 792, 681, 666, 575 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (dd, J = 7.0, 3.5 Hz, 1H, CHN), 2.97 (ddd, J = 11.0, 10.0, 5.0 Hz, 1H, CH_AH$_B$N), 2.87–2.81 (m, 1H, CH$_A$$H_B$N), 2.48–2.31 (m, 2H, CH_2), 1.22 (s, 9H, $(CMe_3)_A$), 1.12 (s, 9H, $(CMe_3)_B$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 179.2, 93.9, 86.0 (CHN), 40.3 (CH_2), 39.8 (CMe$_3$), 38.2 (CMe$_3$), 31.9 (CH_2N), 29.4 ((CMe_3)$_A$), 27.5 ((CMe_3)$_B$); MS (ESI) *m/z* 258 [(M+H)$^+$, 100]; HRMS *m/z* calcd for $C_{13}H_{23}NS_2$ (M+H)$^+$ 258.1345, found 258.1353 (-2.6 ppm error), and RSM (73 mg, 0.46 mmol, 46%). This is a tentatively proposed structure for *rac*-**62**.

Lab book reference: JCS-7-73

***Rac*-d^1-*N*-thiopivaloyl azetidine *rac*-65 and *rac*-1,1'-(azetidine-1,2-diyl)bis(2,2-dimethylpropane-1-thione) *rac*-63**



rac-**65**

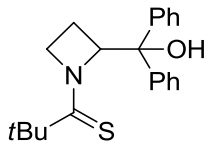


rac-**63**

*s*BuLi (0.5 mL, 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq) was rapidly added to a stirred solution of TMEDA (0.2 mL, 0.151 g, 1.3 mmol, 2.6 eq) and *N*-thiopivaloyl azetidine **35** (77 μL, 79 mg, 0.5 mmol, 1.0 eq) in Et_2O (5 mL) at –100 ^oC under N_2. After 2 min at the same temperature, CD_3OD (36 mg, 40 μL, 1.0 mmol, 2.0 eq) was added rapidly and the solution was allowed to warm to room temperature over 10 m. The solvent was evaporated under reduced pressure to yield the crude product. Purification by flash column chromatography on silica with 7:3 petroleum ether – EtOAc as eluent gave *rac*-**65** (71 mg, 0.45 mmol, 90%, 100% deuteration) as a yellow oil; IR (ATR) 2966, 1464, 1435, 1393, 1362, 1313, 1291, 1255, 1235, 1145, 1093, 1010, 988, 924, 853, 791, 690, 556. 477 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.42–4.34 (m, 1.5H, CH_2N/CHDN), 4.19–4.11 (m, 1.5H, CH_2N/CHDN), 2.16 (dddd, J = 8.0, 8.0, 8.0, 8.0 Hz, 2H, CH_2), 1.23 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (Rotameric mix) δ 209.6 (C=S), 57.1 (CH_2N), 56.8 (t, J = 23.0 Hz, CHDN), 56.1 (CH_2N), 55.8 (t, J = 23.0 Hz, CHDN), 43.2 (CMe_3), 29.8 (CMe_3), 14.7 (CH_2); MS (ESI) *m/z* 159 [$(M+H)^+$, 100], 181 [$(M+Na)^+$, 50]; HRMS *m/z* calcd for $C_8H_{14}DNS$ $(M+Na)^+$ 181.0880, found 181.0877 (-0.6 ppm error), and self-addition product *rac*-**63** (9.1 mg, 35μmol, 14%) as a pink solid, R_F (7:3 hexane – EtOAc) 0.38; mp 104.6–105.3 °C; IR (ATR) 2964, 1465, 1429, 1393, 1363, 1330, 1230, 1192, 1153, 1053, 1032, 1005, 968, 916, 856, 644, 598, 544, 517, 503, 491, 462, 475 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 6.09 (ddd, J = 9.5, 4.5, 1.5 Hz, 1H, CHN), 4.59–4.51 (m, 1H, CH_AH_BN), 4.47 (ddd, J = 9.5, 9.5, 5.0 Hz, 1H, CH_AH_BN), 2.59–2.49 (m, 1H, CH_AH_B), 1.88–1.79 (m, 1H, CH_AH_B), 1.39 (s, 9H, CMe_3), 1.35 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 259.2 (C=S), 209.2 (NC=S), 74.8 (CHN), 55.0 (CH_2N), 51.7 (CMe_3), 43.1 (CMe_3), 30.1 (CMe_3), 29.8 (CMe_3), 24.4 (CH_2); MS (ESI) *m/z* 258 [$(M+H)^+$, 100], 280 [$(M+Na)^+$, 10]; HRMS *m/z* calcd for $C_{13}H_{23}NS_2$ $(M+H)^+$ 258.1345, found 258.1351 (-3.3 ppm error).

Lab book reference: JCS-7-85

***Rac*-1-(2-(Hydroxydiphenylmethyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione *rac*-68**

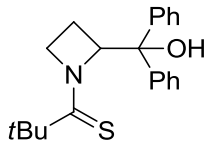


rac-**68**

Using general procedure **A**, *s*BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq), *N*-thiopivaloyl azetidine **35** (77 μL, 79 mg, 0.5 mmol, 1.0 eq) and TMEDA (0.20 mL, 155 mg, 1.3 mmol, 2.6 eq) in Et_2O (7 mL) and a solution of benzophenone (182 mg, 1.0 mmol, 2.0 eq) in Et_2O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica with 95:5-8:2 hexane-EtOAc as eluent gave alcohol *rac*-**68** (55 mg, 0.16 mmol, 32%) as a white solid, mp 191–193 °C; R_F (8:2 petroleum ether – EtOAc) 0.4; IR (ATR) 3163 (O–H), 2961, 2929, 1467, 1395, 1366, 1316, 1287, 1247, 1214, 1060, 1013, 767, 704, 587 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49–7.45 (m, 2H, Ph), 7.38–7.30 (m, 6H, Ph), 7.27–7.24 (m, 2H, Ph), 5.93 (ddd, J = 9.5, 5.0, 1.5 Hz, 1H, CHN), 4.16 (ddd, J = 10.0, 10.0, 4.5 Hz, 1H, CH_AH$_B$N), 3.41–3.32 (m, 1H, CH$_A$$H_B$N), 2.72–2.61 (m, 1H, C$H_AH_B$), 2.11–2.02 (m, 1H, CH$_A$$H_B$), 1.18 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 212.6 (C=S), 144.6 (*ipso*-Ph), 142.6 (*ipso*-Ph), 128.5 (*m*-Ph), 128.1 (*m*-Ph), 127.8 (*p*-Ph), 127.7 (*p*-Ph), 127.5 (*o*-Ph), 127.3 (*o*-Ph), 82.8 (*C*(Ph)$_2$OH), 77.3 (CHN), 56.7 (CH_2N), 43.7 (*C*Me$_3$), 29.7 (C*Me$_3$*), 21.0 (CH_2); MS (ESI) *m/z* 340 [$(M + H)^+$, 100]; HRMS *m/z* calcd for $C_{21}H_{26}NOS$ $(M+H)^+$ 340.1730, found 340.1723 (+2.0 ppm error).

Lab Book Reference: JCS-2-2

1-(2-(Hydroxydiphenylmethyl)azetidin-1-yl)-2,2-dimethylpropane-1-thione 68



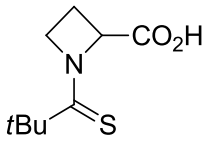
68, 60:40 *er*

Using general procedure **B**, *s*BuLi (0.5 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq), *N*-thiopivaloyl azetidine **35** (77 μL, 79 mg, 0.5 mmol, 1.0 eq) and (–)-**1** (0.14 mL, 141 mg, 0.6 mmol, 1.2 eq) in Et_2O (7 mL) and a solution of benzophenone (182 mg,

1.0 mmol, 2.0 eq) in Et_2O (0.5 mL) gave the crude product. Purification by flash column chromatography on silica eluting with 95:5-8:2 hexane-EtOAc as eluent gave alcohol **68** (61 mg, 0.18 mmol, 36%, 60:40 er by CSP-HPLC) as a white solid, mp 179–183 °C; $[\alpha]_D$ +23.6 (*c* 0.85 in $CHCl_3$). CSP-HPLC: Chiralcel OD-H (98:2 Hexane-*i*PrOH, 1.0 mL min^{-1}) 7.7 min (minor), 12.8 min (major).

Lab Book Reference: JCS-2-10

Rac-1-(2,2-Dimethylpropanethioyl)azetidine-2-carboxylic acid _rac_-69

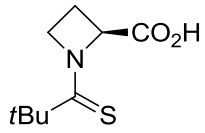


rac-**69**

*s*BuLi (0.50 mL of a 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq) was added rapidly to a stirred solution of *N*-thiopivaloyl azetidine **35** (77 μL, 79 mg, 0.5 mmol, 1.0 eq) and TMEDA (0.2 mL 0.151 g, 1.3 mmol, 2.6 eq) in Et_2O (7 mL) at –100 °C under N_2. The resulting solution was stirred at –100 °C for 2 min. Then, dry CO_2 (generated from solid CO_2 flushed through $CaCl_2$ and added into the reaction *via* cannula) was bubbled through the reaction mixture for 10 min at –100 °C and then allowed to warm to rt over 1 h. The reaction mixture was diluted with Et_2O (10 mL) and extracted with water (6 x 5 mL). The aqueous layer was acidified to pH < 2 with 2 M $HCl_{(aq)}$ and extracted with CH_2Cl_2 (6 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give acid *rac*-**69** (47 mg, 0.23 mmol, 46%) as an off white solid, IR (ATR) 2968, 2924, 2867, 2638 (CO_2H), 2554 (CO_2H), 1705 (C=O), 1455, 1421, 1397, 1365, 1339, 1294, 1254, 1223, 1198, 1164, 1045, 1031, 1005, 931, 825, 780, 721, 680, 655, 563, 537, 528 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.07 (dd, J = 9.0, 5.0 Hz, 1H, CHN), 4.62 (ddd, J = 9.5, 9.5, 9.5 Hz, 1H, CH_AH$_B$N), 4.49 (ddd, J = 9.5, 9.5, 5.5 Hz, 1H, CH$_A$$H_B$N), 2.64-2.53 (m, 1H, C$H_AH_B$), 2.46-2.35 (m, 1H, CH$_A$$H_B$), 1.34 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 212.0 (C=S), 173.8 (CO_2H), 66.5 (CHN), 56.5 (CH_2N), 43.3 (*C*Me_3), 29.6 (CMe_3), 19.0 (CH_2); MS (ESI) material degraded during analysis.

Lab Book Reference: JCS-2-5

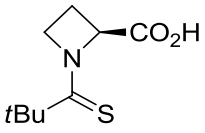
(*S*)-1-(2,2-Dimethylpropanethioyl)azetidine-2-carboxylic acid (*S*)–36



(*S*)-**69**, 75:25 *er*

*s*BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq) was added to a stirred solution of *N*-thiopivaloyl azetidine **35** (77 μL, 79 mg, 0.5 mmol, 1.0 eq) and (–)-**1** (0.14 mL, 141 mg, 0.6 mmol, 1.2 eq) in Et_2O (5 mL) at –78 °C under N_2. The resulting solution was stirred at –78 °C for 30 min. Then, dry CO_2 (generated from solid CO_2 flushed through $CaCl_2$ and added into the reaction *via* cannula) was bubbled through the reaction mixture for 10 min at –78 °C and then allowed to warm to rt over 1 h. The reaction mixture was diluted with Et_2O (10 mL) and extracted with water (6 x 5 mL). The aqueous layer was acidified to pH < 2 with 2 M $HCl_{(aq)}$ and extracted with CH_2Cl_2 (6 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give acid (*S*)-**69** (97 mg, 0.48 mmol, 96%, 75:25 er by CSP-HPLC of the methyl ester) as an off white solid, mp 126–139 °C; $[\alpha]_D$ –62.2 (*c* 0.93 in EtOAc); CSP-HPLC of the methyl ester: Chiralcel OD-H (98:2 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*)-**69** 14.3 min, (*R*)-**69** 18.2 min.

Lab Book Reference: JCS-2-15



(*S*)-**69** *er* 57:43

*s*BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq) was added to a solution of *N*-thiopivaloyl azetidine **35** (77 μL, 79 mg, 0.5 mmol, 1.0 eq) and (*S*,*S*)-**12** (178 mg, 0.6 mmol, 1.2 eq) in Et_2O (5 mL) at –78 °C under N_2. The resulting solution was stirred at –78 °C for 30 min. Then, dry CO_2 (generated from solid CO_2 flushed through $CaCl_2$ and added into the reaction *via* cannula) was bubbled through the reaction mixture for 10 min at –78 °C and then allowed to warm to rt over 1 h. The

reaction mixture was diluted with Et_2O (10 mL) and extracted with water (6 x 5 mL). The aqueous layer was acidified to pH < 2 with 2 M $HCl_{(aq)}$ and extracted with CH_2Cl_2 (6 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give acid (*S*)-**69** (71 mg, 0.36 mmol, 71%, 57:43 er by CSP-HPLC of the methyl ester) as an off white solid. CSP-HPLC of the methyl ester: Chiralcel OD-H (98:2 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*)-**69** 14.5 min, (*R*)-**69** 18.3 min.

Lab Book Reference: JCS-3-69

Determination of *er* of acid (*S*)-69:

The entirety of solid (*S*)-**69** was dissolved in CH_2Cl_2 (~ 10 mL) and a small aliquot (~ 0.2 mL) of this solution was evaporated under reduced pressure. The residue was dissolved in MeOH/toluene (4:6 v/v, 2 mL) and, to this stirred solution, was added Me_3SiCHN_2 (2.0 M solution in Et_2O) dropwise until the yellow colour persisted. Glacial AcOH (5 mL) was then added to destroy excess Me_3SiCHN_2 and the solvent was evaporated under reduced pressure. The residue was dissolved in HPLC grade hexane (~ 2 mL) and subjected to HPLC analysis.

Enantioenrichment of (*S*)-69

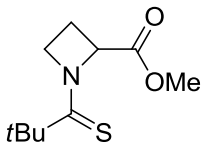
A stirred solution of acid (*S*)-**69** (60 mg, 75:25 er) in hexane (approx. 2 mL) was gently heated until boiling. Then, boiling EtOAc was added until the solids just dissolved and the solution was allowed to slowly cool to rt. Then, the solution was cooled to 0 °C for 30 min. The formed crystals were collected by filtration through a piece of cotton wool in a pipette to give acid (*S*)-**69** (29 mg, 50.1:49.9 er by CSP-HPLC). The filtrate was evaporated under reduced pressure to give acid (*S*)-**69** (30 mg, 97:3 er) as a white solid, CSP-HPLC of the methyl ester: Chiralcel OD-H (98:2 Hexane-*i*PrOH, 1 mL min^{-1}) (*S*)-**69** 13.5 min, (*R*)-**69** 17.4 min.

Method for growing crystals of acid (*S*)-69

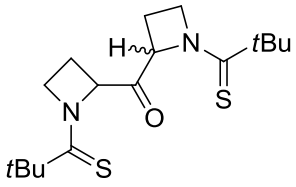
Acid (*S*)-**69** (30 mg, 97:3 er) was dissolved in the minimum amount of EtOAc. The solution was placed into a small glass vial and placed upright in a sealed vessel containing pentane (~ 20 mL). After several days, suitable crystals had precipitated in the glass vial. These were collected and subjected to X-ray analysis.

CCDC No: 1417069

***Rac*-methyl 1-(2,2-dimethylpropanethioyl)azetidine-2-carboxylate *rac*-70 and *rac*-bis(1-(2,2-dimethylpropanethioyl)azetidin-2-yl)methanone *rac*-71/72**



rac-**70**



rac-**71/72**

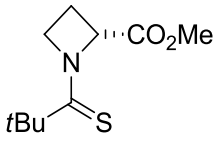
Using general method **A**, thioamide **35** (77 μL, 79 mg, 0.5 mmol, 1.0 eq), *s*BuLi (0.5 mL, 1.3 M solution in hexanes, 0.65 mmol, 1.3 eq), TMEDA (0.18 mL, 1.2 mmol, 2.6 eq) and methyl chloroformate (80 μL, 95 mg, 1.0 mmol, 2.0 eq) as electrophile in Et_2O (5 mL) yielded the crude product containing alcohols **71** and **72** in a 26:74 ratio. Purification by flash column chromatography with 95:5 petroleum ether - EtOAc gave *rac*-**70** (13.6 mg, 0.063 mmol, 13%); R_F (8:2 petroleum ether - EtOAc) 0.14; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02–4.96 (m, 1H, CHN), 4.68–4.59 (m, 1H, CH_AH$_B$N), 4.52–4.43 (m, 1H, CH$_A$$H_B$N), 3.75–3.73 (m, 3H, CO_2Me), 2.59–2.48 (m, 1H, CH_AH$_B$), 2.24–2.14 (m, 1H, CH$_A$$H_B$), 1.35–1.33 (m, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 211.6 (C=S), 170.0 (*C*O_2Me), 65.9 (CHN), 56.1 (CH_2N), 52.4 (CO_2CH_3), 43.1 (*C*Me_3), 29.6 (C*Me*$_3$), 19.1 (CH_2). and ketones **70/71** as a 19:81 inseperable mixture of diastereomers (53 mg, 0.156 mmol, 62%); R_F (8:2 hexane – EtOAc) 0.33; IR (ATR) 2959, 1703 (C=O), 1464, 1430, 1393, 1360, 1337, 1299, 1252, 1230, 1144, 1090, 1004, 984, 830, 724, 665, 551, 511, 477 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (Major) δ 5.38–5.32 (m, 1H, CHN), 4.56–4.47 (m, 1H, CH_AH$_B$N), 4.43–4.34 (m, 1H, CH$_A$$H_B$N), 2.53–2.34 (m, 2H, CH_2), 1.32 (s, 9H, CMe_3); (Minor) δ 5.18–5.12 (m, 1H, CHN), 4.73–4.64 (m, 1H, CH_AH$_B$N), 4.45–4.37 (Assumed, m, 1H, CH$_A$$H_B$N), 2.52–2.33 (Assumed, m, 2H, CH_2), 1.37 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (Major) δ 208.5 (C=S), 202.2

(C=O), 71.2 (CHN), 55.9 (CH_2N), 42.5 (CMe_3), 29.7 (CMe_3), 20.9 (CH_2); (Minor) δ 210.6 (C=S), 204.1 (C=O), 69.1 (CHN), 56.1 (CH_2N), 43.2 (CMe_3), 29.8 (CMe_3), 21.0 (CH_2); MS (ESI) *m/z* 341 [$(M+H)^+$, 60], 363 [$(M+Na)^+$, 100]; HRMS *m/z* calcd for $C_{17}H_{28}N_2OS_2$ $(M+Na)^+$ 363.1535, found 363.1534 (0.0 ppm error).

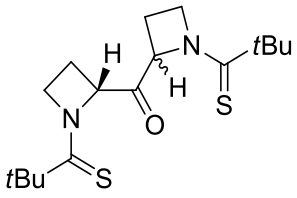
Spectroscopic data consistent with literature values.[20]

Lab book reference: JCS-1-102

(*R*)-Methyl 1-(2,2-dimethylpropanethioyl)azetidine-2-carboxylate (*R*)-70 and ((*R*)-1-(2,2-dimethylpropanethioyl)azetidin-2-yl)(1-(2,2-dimethylpropanethioyl)azetidin-2-yl)methanone (*R*)-71/72



(*R*)-**70** *er* 67:33

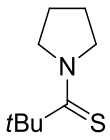


(*R*)-**71/72**

Using general procedure **B**, *s*BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.60 mmol, 1.2 eq), *N*-thiopivaloyl azetidine **35** (77 μL, 79 mg, 0.5 mmol, 1.0 eq) and (–)-**1** (0.14 mL, 141 mg, 0.6 mmol, 1.2 eq) in Et_2O (5 mL) and methyl chloroformate (60 μL, 71 mg, 0.75 mmol, 1.5 eq) gave the crude product which contained an 80:20 mixture of diastereomeric ketones (*R*)-**71**/**72**. Purification by flash column chromatography on silica with 8:2 to 7:3 hexane-EtOAc as eluent gave (*R*)-**70** (48 mg, 0.225 mmol, 45%, 67:33 er by CSP-HPLC) as a pale yellow oil, $[\alpha]_D$ +45.5 (*c* 0.52 in EtOAc); CSP-HPLC: Chiralcel OD-H (98:2 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*)-**70** 12.7 min, (*R*)-**70** 13.8 min and double addition products (*R*)-**71/72** (22 mg, 64.6 μmol, 26%) as an inseperable 81:19 mixture (by ^1H NMR) of diastereoisomers, mp 145–157 °C (with decomposition); $[\alpha]_D$ +295.5 (*c* 0.49 in EtOAc).

Lab Book Reference: JCS-5-58

***N*-thiopivaloyl pyrrolidine 76**

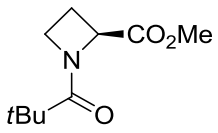


76

Amide **216** (10.6 g, 68.5 mmol, 1.0 eq) in pyridine (10 mL) was added dropwise over 5 min to a stirred solution of P_2S_5 (16.0 g, 71.9 mmol, 1.05 eq) in pyridine (180 mL) at rt. The resulting solution was then stirred at 75°C for 16 hours. Then, the reaction mixture was cooled to RT and water (200 mL) was added. The solution was adjusted to pH = 2-3 with H_2SO_4 (95% w/w) and the resulting solution was allowed to stir at room temperature for 2 hours. The reaction mixture was extracted with CH_2Cl_2 (6 x 30 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation (approx. 105°C bp at 0.35 mbar) gave **76** (11.0 g, 64.3 mmol, 94%) as a bright yellow oil, R_F (95:5 petroleum ether – EtOAc) 0.3; IR (ATR) 2956, 2876, 1468, 1441, 1412, 1393, 1359, 1323, 1257, 1211, 1169, 1149, 1092, 1046, 1015, 967, 926, 873, 845, 798, 697, 666, 475 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.95 (dd, *J* = 7.0, 7.0 Hz, 2H, CH_2N), 3.82 (dd, *J* = 6.5, 6.5 Hz, 2H, CH_2N), 2.03 (dddd, *J* = 6.5, 6.5, 6.5, 6.5 Hz, 2H, CH_2), 1.90 (dddd, *J* = 7.0, 7.0, 7.0, 7.0 Hz, 2H, CH_2), 1.42 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) 209.0 (C=S), 58.0 (CH_2N), 53.1 (CH_2N), 43.9 (CMe_3), 30.6 (CMe_3), 27.6 (CH_2), 23.3 (CH_2); MS (ESI) *m/z* 172 [$(M+H)^+$, 100], 194 [$(M+Na)^+$, 85]; HRMS *m/z* calcd for $C_9H_{17}NS$ $(M+Na)^+$ 194.0974, found 194.0973 (+0.3 ppm error).

Lab Book Reference: JCS-1-40, JCS-5-56

(*S*)-Methyl 1-pivaloylazetidine-2-carboxylate (*S*)-83

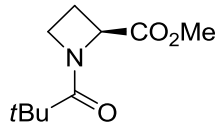


(*S*)-**83**

Me_3SiCHN_2 (0.15 mL of a 2.0 M solution in Et_2O, 0.30 mmol, 1.2 eq) was added dropwise to a stirred solution of acid (*S*)-**82** (50 mg, 0.248 mmol, 1.0 eq) in MeOH/toluene (4:6, 3 mL) at rt. After 5 min, glacial AcOH (4 mL) was added and the

solvent was evaporated under reduced pressure to give the crude ester (57 mg) as a colourless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.60 (dd, J = 9.0, 5.5 Hz, 1H, CHN), 4.01 (ddd, J = 8.5, 8.5, 6.0 Hz, 1H, CH_AH$_B$N), 3.87 (ddd, J = 8.5, 8.5, 5.5 Hz, 1H, CH$_A$$H_B$N), 3.76 (s, 3H, CO_2Me), 2.54-2.43 (m, 1H, CH_AH$_B$), 2.16 (dddd, J = 11.0, 8.5, 5.5, 5.5 Hz, 1H, CH$_A$$H_B$), 1.40 (s, 9H, CMe_3). Freshly distilled TFA (0.57 mL, 0.855 g, 7.50 mmol, 30 eq) was added to a stirred solution of the crude methyl ester (57 mg) in CH_2Cl_2 (5 mL) at rt. The resulting solution was stirred at rt for 48 hours. Then, the solvent was evaporated under reduced pressure to give the crude TFA salt (88 mg) as a yellow oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (dd, J = 9.0, 9.0 Hz, 1H, CHN), 4.24 (ddd, J = 10.0, 10.0, 10.0 Hz, 1H, CH_AH$_B$N), 4.10 (ddd, J = 10.0, 10.0, 6.5 Hz, 1H, CH$_A$$H_B$N), 3.84 (s, 3H, CO_2Me), 2.97-2.86 (m, 1H, CH_AH$_B$), 2.75-2.63 (m, 1H, CH$_A$$H_B$). Pivaloyl chloride (0.15 mL, 150 mg, 1.24 mmol, 5 eq) was added to a stirred solution of the crude TFA salt (88 mg), Et_3N (0.35 mL, 251 mg, 2.48 mmol, 10 eq) and DMAP (6.1 mg, 0.05 mmol, 0.2 eq) in CH_2Cl_2 (5 mL) at rt under N_2. The resulting solution was stirred at rt for 48 hours. Then, 2 M $HCl_{(aq)}$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was absorbed onto a plug of silica and eluted with 80 mL of EtOAc-pentane (1:1) to give the crude product. Purification by dry column flash chromatography through 13 cm of silica in a 2 cm diameter flash column, eluting with 50 mL aliquots of 5% increasing polarity of EtOAc-pentane (95:5 to 70:30) as eluent gave amido-ester (*S*)-**83** (6.8 mg, 34.1 μmol, 13.7% over 3 steps from (*S*)-**82**, >99:1 er by CSP-HPLC) in the sixth fraction as a pale yellow oil, IR (ATR) 2959, 1744 (C=O), 1631 (C=O), 1573, 1435, 1407, 1381, 1362, 1281, 1242, 1199, 1179, 1159, 1135, 1065, 1025, 980, 933, 881, 756, 632 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (br s, 1H, CHN), 4.48 (br s, 1H, CH_AH$_B$N), 4.30 (br s, 1H, CH$_A$$H_B$N), 3.76 (s, 3H, CO_2Me), 2.61-2.48 (m, 1H, CH_AH$_B$), 2.22-2.13 (m, 1H, CH$_A$$H_B$), 1.20 (s, 9H, CMe_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 172.0 (C=O, CO_2Me), 123.6 (NC=O), 60.1 (CHN), 52.4 (CO_2*Me*), 29.8 (CH_2N), 27.1 (C*Me*$_3$), 20.4 (CH_2), 14.3 (*C*Me$_3$); MS (ESI) *m/z* 200 [(M + H)$^+$, 100], 222 [(M + Na)$^+$, 65]; HRMS *m/z* calcd for $C_{10}H_{18}NO_3$ (M + Na)$^+$ 222.1101, found 222.1097 (+1.7 ppm error); $[\alpha]_D$ –78.5 (c 0.34 in EtOAc); CSP-HPLC: Chiralcel OD-H (98:2 Hexane – *i*PrOH, 1.0 mL min^{-1}) (*S*)-**83** 26.2 min. A second portion of (*S*)-**83** (13.3 mg, 66.8 μmol, 26.9% over 3 steps of lesser purity) was isolated from the fifth fraction.

Lab Book Reference: JCS-4-84, JCS-4-80, JCS-4-81

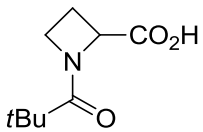


(*S*)-**83**, 76:24 *er*

Oxone (142 mg, 0.46 mmol, 5.1 eq) was added to a stirred solution of acid (*S*)-**69** (18.6 mg, 0.092 mmol, 75:25 *er*, 1.0 eq) in MeOH/water (1:1, 5 mL) at rt. The resulting solution was stirred at rt for 72 hours. Then, the reaction mixture was diluted with EtOAc (50 mL) and washed with water (2 x 5 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product (15.9 mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04 (dd, J = 8.5, 7.0 Hz, 1H, CHN), 4.45–4.29 (m, 2H, CH_2N), 2.55–2.45 (m, 1H, CH_AH_B), 2.22–2.13 (m, 1H, CH_AH_B), 1.23 (s, 9H, CMe_3). The residues were dissolved in MeOH/toluene (4:6 v/v, 3 mL) and to this stirred solution was added Me_3SiCHN_2 (2.0 M in Et_2O) dropwise at rt until the yellow colour persisted (~0.05 mL). The resulting solution was stirred at rt for 5 min. Then, glacial AcOH (5 mL) was added to destroy excess Me_3SiCHN_2 and the solvent was evaporated under reduced pressure to give (*S*)-**83** (6.9 mg, 0.044 mmol, 47% over 2 steps, 76:24 er) as a pale yellow oil that did not require further purification, $[\alpha]_D$ –79.0 (c 0.35 in EtOAc); CSP-HPLC: Chiralcel OD-H (98:2 Hexane – *i*PrOH, 1.0 mL min^{-1}) (*S*)-**83** 25.6 min, (*R*)-**83** 47.4 min.

Lab Book Reference: JCS-5-20, JCS-5-21

Rac-1-pivaloylazetidine-2-carboxylic acid _rac_-84



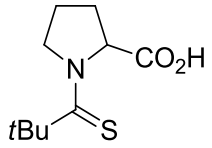
rac-**84**

Oxone (154 mg, 0.50 mmol, 5 eq) was added to a stirred solution of acid *rac*-**84** (20 mg, 0.1 mmol, 1.0 eq) in MeOH/water (1:1, 2 mL) at rt. The resulting solution was stirred at rt for 72 hours. Then, the reaction mixture was diluted with EtOAc (50 mL) and washed

with water (2 x 5 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product (22 mg). A sample of this solid was then derivatized to the methyl ester using the same procedure as for the enantioenriched material.

Lab Book Reference: JCS-5-32

Rac-1-(2,2-dimethylpropanethioyl)pyrrolidine-2-carboxylic acid _rac_-87

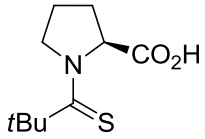


rac-**87**

_s_BuLi (1.0 mL of a 1.3 M solution in hexanes, 1.3 mmol, 1.3 eq) was added to a solution of _N_-thiopivaloyl pyrrolidine **76** (0.16 mL, 171 mg, 1.0 mmol, 1.0 eq) and TMEDA (0.2 mL, 155 mg, 1.3 mmol, 1.3 eq) in Et_2O (10 mL) at –78 °C under N_2. The resulting solution was stirred at –78 °C for 30 min. Then, dry CO_2 (generated from solid CO_2 flushed through $CaCl_2$ and added into the reaction _via_ cannula) was bubbled through the reaction mixture for 10 min at –78 °C and then allowed to warm to rt over 1 h. The reaction mixture was diluted with Et_2O (10 mL) and extracted with water (6 x 5 mL). The aqueous layer was acidified to pH < 2 with 2 M $HCl_{(aq)}$ and extracted with CH_2Cl_2 (6 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give acid _rac_-**87** (184 mg, 0.86 mmol, 86%) as an off white solid, mp 153.0–154.5 °C (with decomposition); IR (ATR) 2978, 2869 (CO_2H), 2646 (CO_2H), 2553 (CO_2H), 1703 (C=O), 1474, 1416, 1368, 1336, 1297, 1272, 1225, 1173, 1152, 1090, 1058, 1021, 929, 915, 871, 804, 692, 61, 597, 502 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.25-5.13 (m, 1H, CHN), 4.06-3.98 (m, 1H, CH_AH$_B$N), 3.96-3.88 (m, 1H, CH$_A$$H_B$N), 2.31-1.99 (m, 4H, CH_2CH_2), 1.43 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) 211.8 (C=S), 175.2 (CO_2H), 66.6 (CHN), 53.3 (CH_2N), 43.9 (_C_Me$_3$), 30.5 (C_Me_$_3$), 27.9 (CH_2), 26.1 (CH_2); MS (ESI) _m/z_ 216 [$(M + H)^+$, 55], 238 [$(M + Na)^+$, 100]; HRMS _m/z_ calcd for $C_{10}H_{17}NO_2S$ $(M+Na)^+$ 238.0872, found 238.0878 (-2.2 ppm error).

Lab Book Reference: JCS-2-29

(*S*)-1-(2,2-Dimethylpropanethioyl)pyrrolidine-2-carboxylic acid (*S*)-87



(*S*)-**87**, 80:20 *er*

*s*BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.6 mmol, 1.2 eq) was added to a solution of *N*-thiopivaloyl pyrrolidine **76** (80 μL, 86 mg, 0.5 mmol, 1.0 eq) and (–)-sparteine (0.14 mL, 141 mg, 0.6 mmol, 1.2 eq) in Et_2O (5 mL) at –78 °C under N_2. The resulting solution was stirred at –78 °C for 30 min. Then, dry CO_2 (generated from solid CO_2 flushed through $CaCl_2$ and added into the reaction *via* cannula) was bubbled through the reaction mixture for 10 min at –78 °C and then allowed to warm to rt over 1 h. The reaction mixture was diluted with Et_2O (10 mL) and extracted with water (6 x 5 mL). The aqueous layer was acidified to pH < 2 with 2 M $HCl_{(aq)}$ and extracted with CH_2Cl_2 (6 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give acid (*S*)-**87** (79 mg, 0.37 mmol, 74%, 80:20 er by CSP-HPLC of the methyl ester) as an off white solid. CSP-HPLC of the methyl ester: Chiralcel OD-H (98:2 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*)-**87** 11.6 min, (*R*)-**87** 12.9 min. X-ray crystallography analysis of enantioenriched (*S*)-**87**, 98:2 *er* proved the absolute stereochemistry to be (*S*). $[\alpha]_D$ of 98:2 material -23.9 (c 0.095 in EtOAc).

Determination of er of acid (*S*)-87:

The entirety of solid (*S*)-**87** was dissolved in CH_2Cl_2 (~ 10 mL) and a small aliquot (~ 0.2 mL) of this solution was evaporated under reduced pressure. The residue was dissolved in MeOH/toluene (4:6 v/v, 2 mL) and, to this stirred solution, was added Me_3SiCHN_2 (2.0 M solution in Et_2O) dropwise until the yellow colour persisted. Glacial AcOH (5 mL) was then added to destroy excess Me_3SiCHN_2 and the solvent was evaporated under reduced pressure. The residue was dissolved in HPLC grade hexane (~ 2 mL) and subjected to HPLC analysis.

Enantioenrichment of (*S*)-87

A stirred solution of acid (*S*)-**87** (80 mg, 80:20 er) in hexane (~ 2 mL) was gently heated until boiling. Then, boiling EtOAc was added until the solids just dissolved and the solution was allowed to slowly cool to rt. Then, the solution was cooled to 0 °C for 30 min. The formed crystals were collected by filtration through a piece of cotton wool in a pipette to give *rac*-acid **87** (21 mg). The filtrate was evaporated under reduced pressure to give acid (*S*)-**87** (59 mg, 90:10 er) as a white solid. The solid was then recrystallized again using the same procedure to give *rac*-acid **87** (9.9 mg) and (*S*)-**87** (49.5 mg, 96:4 er), then a third time to give *rac*-acid **87** (4.4 mg) and (*S*)-**87** (44.1 mg, 98:2 er) as a white solid. CSP-HPLC of the methyl ester: Chiralcel OD-H (98:2 Hexane-*i*PrOH, 1 mL min^{-1}) (*S*)-**87** 11.6 min, (*R*)-**87** 12.9 min.

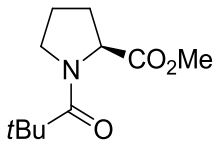
Method for growing crystals of acid (*S*)-87

Acid (*S*)-**87** (44.1 mg, 98:2 er) was dissolved in the minimum amount of EtOAc. The solution was placed into a small glass vial and placed upright in a sealed vessel containing pentane (~ 20 mL). After several days, suitable crystals had precipitated in the glass vial. These were collected and subjected to X-ray analysis.

CCDC No: 1417068

Lab Book Reference: JCS-2-28, JCS-3-72, JCS-2-29

(*S*)-Methyl 1-pivaloylpyrrolidine-2-carboxylate (*S*)-88

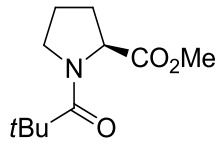


(*S*)-**88** *er* 98:2

Oxone (18 mg, 0.059 mmol, 5 eq) was added to a stirred solution of acid (*S*)-**87** (5 mg, 11.9 μmol, 1.0 eq, 98:2 er) in MeOH/water (1:1 v/v, 1 mL) at rt. The resulting solution was stirred at rt for 72 h. Then, the reaction was diluted with EtOAc (50 mL) and

washed with water (2 x 5 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product (7.2 mg), ^{1}H NMR (400 MHz, $CDCl_3$) 4.68–4.61 (br m, 1H, CHN), 3.74–3.69 (m, 2H, CH_2N), 2.15–1.87 (m, 4H, CH_2CH_2), 1.29 (s, 9H, CMe_3). The residues were redissolved in MeOH/toluene (4:6 v/v, 2 mL) and Me_3SiCHN_2 (2.0 M soln in Et_2O) was added dropwise at rt until the yellow colour persisted (~0.03 mL). The resulting solution was stirred at rt for 5 min. Then, glacial AcOH (5 mL) was added to destroy excess Me_3SiCHN_2 and the solvent was evaporated under reduced pressure to give the crude product. Purification on silica with 80 mL of 1:1 EtOAc – pentane gave (*S*)-**88** (2.6 mg, 0.012 mmol, 102% over 2 steps, 98:2 er), ^{1}H NMR (400 MHz, $CDCl_3$) 4.52–4.45 (br m, 1H, CHN), 3.82–3.66 (m, 2H, CH_2N), 3.72 (s, 3H, CO_2Me), 2.17–2.01 (m, 2H, CH_2), 2.00–1.81 (m, 2H, CH_2), 1.23 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.9 (C=O), 173.5 (C=O), 60.9 (CHN), 52.1 (CH_2N), 48.2 (CO_2*Me*), 38.8 (*C*Me_3), 27.9 (CH_2), 27.3 (C*Me*$_3$), 26.1 (CH_2); [α] -14.5 (c 0.13 in EtOAc). Chiralcel OD-H (98:2 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*)-**88** 13.1 min, (*R*)-**88** 17.8 min.

Spectroscopic data consistent with literature values.[157]



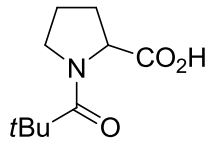
(*S*)-**88**

To a stirred solution of (*S*)-proline (2 g, 17.4 mmol, 1.0 eq) in MeOH (30 mL) was added thionyl chloride (2.53 mL, 4.13 g, 34.8 mmol, 2.0 eq) dropwise at 0 °C. The resulting solution was stirred at 0 °C for 2 h. Then, the solvent was evaporated under reduced pressure to give the crude product (2.97 g). The crude product (0.59 g) was suspended in CH_2Cl_2 (10 mL). To this was added DMAP (74 mg, 0.60 mmol), Et_3N (2.10 mL, 1.53 g, 15.1 mmol) and pivaloyl chloride (0.58 mL, 546 mg, 4.53 mmol) at 0 °C under N_2. The resulting solution was allowed to warm to rt over 4 h. Then, the reaction was diluted with EtOAc (50 mL) and washed with 2 M HCl (2 x 20 mL), K_2CO_3 (10% w/w, 1 x 30 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product. Purification on a plug of silica with 200 mL of 8:2 hexane – EtOAc gave (*S*)-**88** (509 mg, 2.39 mmol, 69% over 2 steps) as a pale

red oil, [α] -47.2 (c 1.025 in EtOAc); CSP-HPLC: Chiralcel OD-H (96:4 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*)-**88** 13.3 mins.

Lab Book Reference: JCS-5-4, JCS-4-90, JCS-5-28, JCS-5-10, JCS-6-38, JCS-6-39

Rac-1-pivaloylpyrrolidine-2-carboxylic acid _rac_-89

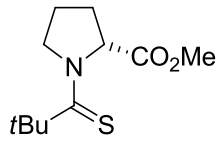


rac-**89**

Oxone (178 mg, 0.58 mmol, 5 eq) was added to a stirred solution of acid *rac*-**89** (25 mg, 0.116 mmol, 1.0 eq) in MeOH/water (1:1, 2 mL) at rt. The resulting solution was stirred at rt for 48 hours. Then, the reaction mixture was diluted with EtOAc (50 mL) and washed with water (2 x 5 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product (21 mg). A sample of this solid was then derivatized to the methyl ester using the same procedure as for the enantioenriched material.

Lab Book Reference: JCS-5-30

(*R*)-Methyl 1-(2,2-dimethylpropanethioyl)pyrrolidine-2-carboxylate (*R*)-91



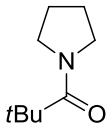
(*R*)-**91** *er* 76:24

Using general procedure **B**, *s*BuLi (0.46 mL of a 1.3 M solution in hexanes, 0.60 mmol, 1.2 eq), *N*-thiopivaloyl pyrrolidine **76** (0.084 mL, 86 mg, 0.5 mmol, 1.0 eq) and (–)-**1** (0.14 mL, 141 mg, 0.6 mmol, 1.2 eq) in Et_2O (5 mL) and methyl chloroformate (60 μL, 71 mg, 0.75 mmol, 1.5 eq) gave the crude product. Purification by flash column chromatography on silica with 8:2 hexane-EtOAc as eluent gave (*R*)-**91** (67 mg, 0.29 mmol, 58%, 76:24 er by CSP-HPLC) as a waxy solid, ^1H NMR (400 MHz, $CDCl_3$) δ 5.11 (dd, J = 8.5, 5.0 Hz, CHN), 4.04–3.90 (m, 2H, CH_2N), 3.71 (s, 3H, CO_2Me), 2.30–

2.10 (m, 2H, CH_2), 2.07–1.90 (m, 2H, CH_2), 1.42 (s, 9H, CMe_3); ^{13}C NMR δ 211.6 (C=S), 171.5 (CO_2Me), 68.6 (CHN), 53.4 (CH_2N), 52.3 (CO_2Me), 43.8 (CMe_3), 30.4 (CMe_3), 28.0 (CH_2), 26.1 (CH_2); $[\alpha]_D$ +25.3 (*c* 1.075 in EtOAc). CSP-HPLC: Chiralcel OD-H (98:2 Hexane-*i*PrOH, 1.0 mL min^{-1}) (*S*)-10.6 min, (*R*)-11.8 min.

Lab Book Reference: JCS-5-59

_N_-pivaloyl pyrrolidine 216



216

Trimethylacetyl chloride (1.10 mL, 9.13 mmol, 1.0 eq) was added dropwise over 10 m to a stirred solution of pyrrolidinium hydrochloride (1.0 g, 9.13 mmol, 1.0 eq), Et_3N (6.41 mL, 46 mmol, 5.0 eq) and DMAP (0.22 g, 1.83 mmol, 0.2 eq) in CH_2Cl_2 (20 mL) at 0°C under N_2. The resulting solution was allowed to warm to rt over 16 hours. Then, $HCl_{(aq)}$ (2M, 30 mL) was added and the layers were seperated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were dried ($MgSO_4$) and the solvent evaporated under reduced presure to give the crude product. Purification by filtration through a small plug of silica with 7:3 petroleum ether – EtOAc as eluent gave **216** (1.10 g, 7.12 mmol, 78%) as a colourless oil that crystallised upon standing, R_F (7:3 petroleum ether – EtOAc) 0.4; IR (ATR) 2969, 2874, 1718, 1599 (C=O), 1479, 1408, 1383, 1363, 1341, 1257, 1214, 1113, 1043, 1028, 981, 950, 919, 876, 862, 755, 744, 731, 604, 581, 556, 524, 475, 453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.53 (br s, 4H, CH_2N), 1.84 (br s, 4H, CH_2), 1.24 (s, 9H, CMe_3); ^{13}C (100.6 MHz, $CDCl_3$) δ 176.6 (C=O), 48.0 (CH_2N), 39.1 (CMe_3), 27.6 (CMe_3), 27.2 (CH_2); MS (ESI) *m/z* 156 $[(M+H)^+$, 60], 178 $[(M+Na)^+$, 100]; HRMS *m/z* calcd for $C_9H_{17}NO$ $(M+Na)^+$ 178.1202, found 178.1204 (-0.6 ppm error).

Lab Book Reference: JCS-1-8

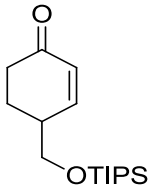
Trimethylacetyl chloride (9.1 mL, 73.9 mmol, 1.05 eq) was added dropwise over 5 m to a stirred solution of pyrrolidine (5.8 mL, 70.4 mmol, 1.0 eq), Et_3N (49 mL, 0.35 mol, 5.0 eq) and DMAP (1.72 g, 14.1 mmol, 0.2 eq) in CH_2Cl_2 (200 mL) at 0°C under N_2. The resulting solution was allowed to slowly warm to rt over 16 hours. Then, $HCl_{(aq)}$ (2M, 250 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic layers were dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product. Purification by filtration through a small plug of silica with 7:3 petroleum ether – EtOAc as eluent gave **216** (10.6 g, 68.5 mmol, 97%) as a colourless oil that crystallised upon standing.

Lab Book Reference: JCS-1-38

3.3 Experimental Procedures For Chapter Two

All compounds listed hereafter were synthesised racemically unless otherwise stated.

4-(((Triisopropylsilyl)oxy)methyl)cyclohex-2-enone 117



117

Ketone **139** (100 mg, 0.35 mmol, 1.0 eq) in MeCN (1.5 mL) was added dropwise over 5 min to a stirred solution of NaI (105 mg, 0.70 mmol, 2.0 eq), Et_3N (178 mg, 0.24 mL, 1.76 mmol, 5.0 eq) and Me_3SiCl (152 mg, 0.18 mL, 1.40 mmol, 4.0 eq) in MeCN (1.5 mL) at rt under N_2. The resulting solution was then heated to 45 °C and stirred for 16 h before the solvent and excess reagents were evaporated under reduced pressure. The residues were triturated with dry hexane (3 x 20 mL), filtered through celite and the solvent evaporated under reduced pressure to give the crude silyl enol ether. Distillation under reduced pressure gave the intermediate racemic silyl enol ether (68 mg, 0.19 mmol, 54%) as a colourless oil which was used immediately. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86-4.82 (m, 1H, *H*C=CH_2), 3.62-3.51 (m, 2H, CH_2C=O), 2.15-1.94 (m, 3H, CH_2 and CH), 1.87-1.66 (m, 3H, CH_2 and CH), 1.42-1.30 (m, 1H, CH), 1.09-1.03 (m, 21H, Si(*i*Pr)$_3$), 0.176 (s, 9H, $SiMe_3$). $Pd(OAc)_2$ (4.2 mg, 18.1 μmol, 0.1 eq) was added to a stirred solution of silyl enol ether (65 mg, 0.181 mmol, 1.0 eq) in dry DMSO (5 mL) at rt. The reaction vessel was then evacuated and backfilled with dry O_2 at 1 atm and stirred at rt for 16 h. Then, the reaction was diluted with water (100 mL), extracted with hexane (4 x 20 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica eluting with 9:1 hexane – EtOAc as eluent gave **117** (28 mg, 98.0 μmol, 28% over 2 steps) as a colourless oil, R_F (9:1 petroleum ether – EtOAc) 0.28; IR (ATR) 2942, 2891, 2856, 1681 (C=O), 1463, 1418, 1390, 1252, 1209, 1184, 1110, 1068, 995, 918, 881, 865, 842, 784, 766, 749, 681, 659, 514 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (ddd, J = 10.0 2.5, 1.5 Hz, 1H, *H*C=CHCO), 6.04 (dd, J = 10.0, 2.5 Hz, 1H, HC=C*H*CO), 3.71 (m, 2H,

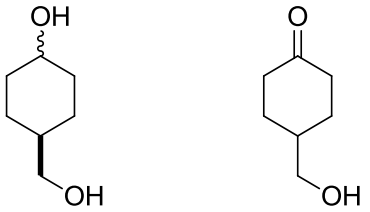
C*H*$_2$OSi(*i*Pr)$_3$), 2.66-2.57 (m, 1H, C*H*$_A$H$_B$CO), 2.53 (ddd, *J* = 16.5, 4.5, 4.5 Hz, 1H, CH$_A$*H*$_B$CO), 2.42-2.33 (m, 1H, C*H*$_A$H$_B$), 2.13-2.03 (m, 1H, CH$_A$*H*$_B$), 1.78 (dddd, *J* = 13.0, 13.0, 10.0, 4.5 Hz, 1H, CH), 1.10-1.03 (m, 21H, Si(*i*Pr)$_3$); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 200.1 (C=O), 152.3 (H*C*=CHCO), 130.1 (HC=*C*HCO), 66.1 (CH_2), 39.6 (CH), 36.9 (CH_2), 25.6 (CH_2), 18.1 (CH_3), 12.0 (*C*H(CH_3)$_2$); MS (ESI) *m/z* 283[$(M+H)^+$, 5], 305 [$(M+Na)^+$, 100]; HRMS *m/z* calcd for $C_{16}H_{30}O_2Si$ $(M+Na)^+$ 305.1907, found 305.1900 (+2.3 ppm error).

Lab Book Reference: JCS-5-43, JCS-5-44

Me_3SiCl (2.90 g, 3.34 mL, 26.3 mmol, 4.0 eq) was added to a stirred solution of ketone **139** (1.87 g, 6.58 mmol, 1.0 eq), Et_3N (3.33 g, 4.59 mL, 32.9 mmol, 5.0 eq) and NaI (1.97 g, 13.2 mmol, 2.0 eq) in MeCN (56 mL) at rt under N_2. The resulting solution was then heated to 45 °C and stirred for 16 h before the solvent and excess reagents were evaporated under reduced pressure. The residues were triturated with dry hexane (3 x 50 mL), filtered through celite and the solvent evaporated under reduced pressure to give the crude silyl enol ether. Distillation under reduced pressure gave the intermediate racemic silyl enol ether (2.16 g, 6.06 mmol, 92%) as a colourless oil which was used immediately. $Pd(OAc)_2$ (137 mg, 0.61 mmol, 0.1 eq) was added to a stirred solution of silyl enol ether (2.16 g, 6.06 mmol, 1.0 eq) in dry DMSO (50 mL) at rt. The reaction vessel was then evacuated and backfilled with dry O_2 at 1 atm and stirred at rt for 16 h. Then, the reaction was diluted with water (450 mL) and extracted with hexane (6 x 50 mL). TLC analysis of the water/DMSO layer indicated that product enone had remained in solution. The aqueous layer was then saturated with NaCl and re-extracted with hexane (3 x 50 mL). The combined organic layers were then dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product. Purification by distillation under reduced pressure gave enone **117** (1.51 g, 5.35 mmol, 81% over 2 steps) as a colourless oil.

Lab Book Reference: JCS-5-46 and JCS-5-48

4-(hydroxymethyl)cyclohexanol 133/134 and 4-(hydroxymethyl)cyclohexanone 129



133/134 **129**

A solution of 4-hydroxybenzylalcohol (2.0 g, 16.1 mmol, 1.0 eq) and PtO_2 (37 mg, 0.16 mmol, 1 mol%) in MeOH (20 mL) was evacuated and backfilled with N_2 twice, then evacuated and backfilled with H_2 gas at 1 atm. The resulting solution was stirred for 7 days at room temperature before being filtered through celite and the solvent evaporated under reduced pressure. Purification by flash column chromatography through silica with 1:1 – 9:1 EtOAc – Hexane as eluent gave a 56:44 inseperable mix of **134** and **133** (393 mg, 3.02 mmol, 19%) as a white, waxy solid, R_F (1:1 hexane – EtOAc) 0.05; IR (ATR) 3284 (O–H), 2923, 2859, 1448, 1362, 1296, 1200, 1126, 1097, 1048, 1023, 976, 932, 898, 820, 690, 597, 506 cm^{-1}; ^1H NMR (400 MHz, MeOH-d4) δ 3.86 (dddd, J = 2.5, 2.5, 2.5, 2.5 Hz, 0.44H, C*H*OH), 3.43 (dddd, J = 11.0, 11.0, 4.5, 4.5 Hz, 0.56 H, C*H*OH), 3.36 (d, J = 6.0 Hz, 0.88H, CH_2OH), 3.31 (d, J = 6.5 Hz, 1.12H, CH_2OH), 1.96–1.87 (m, 1H, 0.5 x CH_2), 1.82–1.73 (m, 1H, 0.5 x CH_2), 1.71–1.61 (m, 1H, CH), 1.56–1.30 (m, 4H, 2 x CH_2), 1.26–1.14 (m, 1H, 0.5 x CH_2), 1.01–0.88 (m, 1H, 0.5 x CH_2); ^{13}C NMR (100.6 MHz, MeOH-d4) (Major) δ 71.7 (CHOH), 68.2 (CH_2OH), 40.9 (CH), 35.8 (CH_2), 28.9 (CH_2); (Minor) δ 67.8 (CHOH), 67.7 (CH_2OH), 40.3 (CH), 32.7 (CH_2), 24.7 (CH_2); MS (ESI) 153 [$(M+Na)^+$, 100]; HRMS *m/z* calcd for $C_7H_{14}O_2$ $(M+Na)^+$ 153.0886, found 153.0882 (+2.8 ppm error), and keto-alcohol **129** (36 mg, 0.28 mmol, 1.7%) as a colourless oil, R_F (1:1 hexane – EtOAc) 0.11; IR (ATR) 3386 (O–H), 2927, 2866, 1704 (C=O), 1615, 1517, 1448, 1421, 1331, 1240, 1167, 1085, 1034, 1006, 972, 938, 917, 820, 597, 496, 458 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.55 (d, J = 6.5 Hz, CH_2OH), 2.44–2.27 (m, 4H, 2 x CH_2), 2.21–2.06 (m, 3H, 2 x C$H_A$$H_B$ and OH), 2.00–1.88 (m, 1H, CH), 1.42 (dddd, J = 13.0, 13.0, 13.0, 5.0 Hz, 2H, 2 x $CH_A$$H_B$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 212.5 (C=O), 66.8 (CH_2OH), 40.5 (CH_2), 38.7 (CH), 29.2 (CH_2); MS (ESI) *m/z* 151 [(M+Na), 100]; HRMS *m/z* calcd for $C_7H_{12}O_2$ $(M+Na)^+$ 151.0730, found 151.0729 (0.0 ppm error).

Lab Book Reference: JCS-7-79

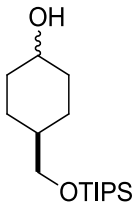
A solution of 4-hydroxybenzylalcohol (1.01 g, 8.14 mmol, 1.0 eq) and PtO_2 (20 mg. 0.081 mmol, 1 mol%) in MeOH (40 mL) was evacuated and backfilled with N_2 twice, then evacuated and backfilled with H_2 gas at 1 atm. The resulting solution was stirred for 5 days at room temperature, then filtered through celite and the solvent evaporated under reduced pressure. Purification by flash column chromatography through silica with 7:3 – 9:1 EtOAc – hexane as eluent gave a 2:1 inseperable mix of **134/133** (0.62 g, 4.73 mmol, 58%) as a white, waxy solid.

Lab Book Reference: JCS-3-56

A solution of 4-hydroxybenzylalcohol (5.0 g, 40.3 mmol, 1.0 eq) and PtO_2 (40 mg. 0.176 mmol, 0.44 mol%) in MeOH (50 mL) was evacuated and backfilled with N_2 twice, then evacuated and backfilled with H_2 gas at 1 atm. The resulting solution was stirred for 7 days at room temperature, then filtered through celite and the solvent evaporated under reduced pressure. Purification by flash column chromatography through silica with 7:3 – 9:1 EtOAc – hexane as eluent gave a 2:1 inseperable mix of **134**/**133** (4.17 g, 31.2 mmol, 77%) as a white, waxy solid.

Lab Book Reference: JCS-3-66

4-(((Triisopropylsilyl)oxy)methyl)cyclohexanol 135/136



135/136

Triisopropylsilyl chloride (214 mg, 1.11 mmol, 0.24 mL, 1.0 eq) was added dropwise to a stirred solution of a 2:1 diastereomeric mixture of alcohols **134**/**133** (170 mg, 1.11 mmol, 1.0 eq) and imidazole (114 mg, 1.67 mmol, 1.5 eq) in DMF (5 mL) at rt. The resulting solution was stirred for 16 h. Then, additional triisopropylsilyl chloride (2 mL of a 0.11 M soln in DMF, 0.22 mmol, 0.2 eq) and imidazole (114 mg, 1.67 mmol, 1.5 eq) was added and the resulting solution was stirred for a further 2 h at rt. The reaction

mixture was diluted with EtOAc (100 mL) and washed with HCl (2 M, 2 x 10 mL), water (3 x 10 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography with 19:1 to 4:1 hexane – EtOAc gradient elution gave **135** (91 mg, 0.32 mmol, 29%) as a colourless oil, R_F (1:1 hexane – EtOAc) 0.8; IR (ATR) 3345 (O–H), 2923, 2890, 2864, 1463, 1383, 1254, 1137, 1111, 1090, 1064, 1031, 1013, 995, 979, 959, 950, 937, 813, 679, 658, 640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.03–3.97 (m, 1H, C*H*OH), 3.52 (d, J = 6.0 Hz, CH_2OSi(iPr)$_3$), 1.77–1.68 (m, 2H, CH_2) 1.61–1.50 (m, 4H, 2 x CH_2), 1.46–1.32 (m, 3H, CH_2 and CH), 1.13–1.00 (m, 21H, OSi(iPr)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 68.1 (CHOH), 67.2 (CH_2OSi(iPr)$_3$), 39.6 (CH), 32.2 (CH_2), 23.6 (CH_2), 18.2 (CH(*C*H$_3$)$_2$), 12.1 (*C*H(CH$_3$)$_2$); MS (ESI) *m/z* 309 [(M+Na)$^+$, 100]; HRMS *m/z* calcd for $C_{16}H_{34}O_2Si$ (M+Na)$^+$ 309.2220, found 309.2213 (+2.2 ppm error), and **136** (141 mg, 0.49 mmol, 45%) as a colourless oil; R_F (1:1 hexane – EtOAc) 0.7; IR (ATR) 3331 (O–H), 2928, 2864, 1462, 1383, 1361, 1249, 1204, 1114, 1083, 1066, 1012, 995, 949, 918, 881, 802, 787, 775, 680, 658, 513, 465 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 3.55 **(**dddd, J = 11.0, 11.0, 4.5, 4.5 Hz, 1H, C*H*OH), 3.48 (d, J = 6.0 Hz, CH_2OSi(iPr)$_3$), 2.03–1.94 (m, 2H, CH_2) 1.86–1.77 (m, 2H, CH_2), 1.51–1.38 (m, 2H, CH_2), 1.31–1.18 (m, 3H, CH_2 and CH) 1.11–0.95 (m, 21H, OSi(iPr)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 71.4 (CHOH), 68.5 (CH_2OR), 39.9 (CH), 35.3 (CH_2), 27.9 (CH_2), 18.2 (CH(*C*H$_3$)$_2$), 12.1 (*C*H(CH$_3$)$_2$); MS (ESI) *m/z* 309 [(M+Na)$^+$, 100]; HRMS *m/z* calcd for $C_{16}H_{34}O_2Si$ (M+Na)$^+$ 309.2220, found 309.2214 (+2.0 ppm error).

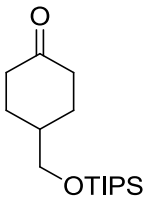
Lab Book Reference: JCS-3-76

Triisopropylsilyl chloride (2.97 g, 15.4 mmol, 3.29 mL, 1.0 eq) was added dropwise to a stirred solution of a 2:1 diastereomeric mixture of alcohols **134**/**135** (2.0 g, 15.4 mmol, 1.0 eq) and imidazole (2.62 g, 38.5 mmol, 1.5 eq) in DMF (50 mL) at rt. The resulting solution was stirred for 16 h. Then, additional triisopropylsilyl chloride (594 mg, 3.08 mmol, 0.66 mL, 0.2 eq) was added and the resulting solution was stirred for a further 2 h at rt. The reaction mixture was concentrated in a hard vacuum, then diluted with EtOAc (200 mL) and washed with HCl (2 M, 2 x 50 mL), water (3 x 20 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 hexane –

EtOAc as eluent gave a 2:1 mixture (by ^{1}H NMR) of alcohols **136**/**135** (3.60 g, 12.6 mmol, 82%).

Lab Book Reference: JCS-3-79

4-(((Triisopropylsilyl)oxy)methyl)cyclohexanone 139



139

Triisopropylsilyl chloride (0.31 mL, 276 mg, 1.43 mmol, 1.5 eq) was added to a stirred solution of ketone **129** (122 mg, 0.95 mmol, 1.0 eq) and imidazole (162 mg, 2.38 mmol, 2.5 eq) in CH_2Cl_2 (3 mL) at rt. After 16 h, MeOH (2 mL) was added and the resulting solution was stirred for a further 1 h. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2 hexane – EtOAc as eluent gave protected ketone **139** (240 mg, 0.84 mmol, 89%) as a colourless oil, R_F (8:2 hexane – EtOAc) 0.50; IR (ATR) 2942, 2891, 2865, 1716 (C=O), 1463, 1383, 1366, 1329, 1247, 1202, 1168, 1120, 1103, 1067, 996, 920, 881, 826, 789, 750, 679, 658, 597, 497, 463 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.60 (d, J = 6.5 Hz, 2H, CH_2OR), 2.44–2.28 (m, 4H, 2 x $CH_2C(O)$), 2.14–2.06 (m, 2H, 2 x CH_AH$_B$), 2.00–1.87 (m, 1H, CH), 1.46 (dddd, J = 13.0, 13.0, 13.0, 5.0 Hz, 2H, 2 x CH$_A$$H_B$), 1.11–1.02 (m, 21H, Si(iPr)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 212.5 (C=O), 67.4 (CH_2OR), 40.7 ($CH_2C(O)$), 39.2 (CH), 29.3 (CH_2), 18.2 (CH_3), 17.8 ($CH(CH_3)_2$); MS (ESI) 307 [(M+Na)$^+$, 100]; HRMS *m/z* calcd for $C_{16}H_{32}O_2Si$ (M+Na)$^+$ 307.2064, found 307.2064 (-0.1 ppm error).

Lab Book Reference: JCS-7-84

Anhydrous DMSO (31.3 mg, 28 μL, 0.40 mmol, 1.25 eq) was added to a stirred solution of oxalyl chloride (48.7 mg, 32 μL, 0.38 mmol, 1.2 eq) in anhydrous CH_2Cl_2 (3 mL)

under N_2 at –78 °C. The resulting solution was stirred at the same temperature for 10 min, followed by the dropwise addition of **135** (91 mg, 0.32 mmol, 1.0 eq) in CH_2Cl_2 (1 mL). After 30 m, Et_3N (162 mg, 0.22 mL, 1.6 mmol, 5 eq) was added dropwise and the resulting solution was allowed to warm to rt over 1 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with $HCl_{(aq)}$ (2M, 2 x 10 mL), water (1 x 10 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give ketone **139** (83 mg, 0.29 mmol, 91%) as a pale yellow oil.

Lab Book Reference: JCS-3-77

Anhydrous DMSO (47.9 mg, 44 μL, 0.61 mmol, 1.25 eq) was added to a stirred solution of oxalyl chloride (74.6 mg, 49 μL, 0.59 mmol, 1.2 eq) in anhydrous CH_2Cl_2 (5 mL) under N_2 at –78 °C. The resulting solution was stirred at the same temperature for 10 min, followed by the dropwise addition of **136** (141 mg, 0.49 mmol, 1.0 eq) in CH_2Cl_2 (1 mL). After 30 m, Et_3N (248 mg, 0.34 mL, 2.45 mmol, 5 eq) was added dropwise and the resulting solution was allowed to warm to rt over 1 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with $HCl_{(aq)}$ (2M, 2 x 10 mL), water (1 x 10 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give ketone **139** (139 mg, 0.49 mmol, Quantitative) as a pale yellow oil.

Lab Book Reference: JCS-3-78

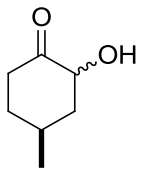
DMSO (1.13 g, 1.03 mL, 14.5 mmol, 1.15 eq) was added dropwise over 5 min to a stirred solution of oxalyl chloride (1.76 g, 1.17 mL, 13.8 mmol, 1.1 eq) in anhydrous CH_2Cl_2 (100 mL) under N_2 at –78 °C. The resulting solution was stirred at the same temperature for 10 min, followed by the dropwise addition of a 2:1 mix of **136**/**135** (3.60 g, 12.6 mmol, 1.0 eq) dissolved in CH_2Cl_2 (10 mL). After 30 min, Et_3N (6.36 g, 8.76 mL, 62.85 mmol, 5 eq) was added dropwise over 5 m and the resulting solution was allowed to warm to rt over 1 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with $HCl_{(aq)}$ (2M, 2 x 50 mL), water (1 x 20 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product. The residues were distilled under vacuum (approx. 140°C at 0.8 mbar) to give ketone **139** (2.57 g, 9.04 mmol, 72%) as a colourless oil.

Lab Book Reference: JCS-3-82

A 2:1 mixture of **136**/**135** (3.30 g, 11.5 mmol, 1.0 eq) in CH_2Cl_2 (5 mL) was added to a stirred solution of DMP (5.12 g, 12.1 mmol, 1.05 eq) in anhydrous CH_2Cl_2 (50 mL) under N_2 at rt. The resulting solution was stirred at the same temperature for 1 hour before being quenched with aqueous $NaHCO_3$ (50 mL). The biphasic mixture was stirred rapidly for 3 hours and the precipitated solids were removed by filtration through celite. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product. The residues were distilled under vacuum to give ketone **139** (2.67 g, 9.39 mmol, 82%) as a colourless oil.

Lab Book Reference: JCS-3-93

2-Hydroxy-4-methylcyclohexanone 145/146



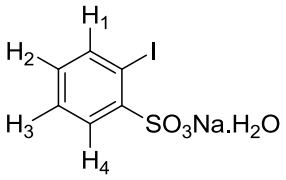
145/146

4-methylcyclohexanone (1.0 g, 8.92 mmol, 1.10 mL, 1.0 eq) was added dropwise to a stirred solution of Me_3SiCl (3.88 g, 35.7 mmol, 4.53 mL, 4.0 eq), Et_3N (4.51 g, 44.6 mmol, 6.22 mL, 5.0 eq) and NaI (2.67 g, 17.8 mmol, 2.0 eq) in dry MeCN (20 mL) at rt under N_2. The resulting solution was heated at 45 °C for 16 h. Then, the solvent, excess Me_3SiCl and Et_3N were evaporated under reduced pressure. The residues were then triturated with dry hexane (3 x 30 mL), filtered through celite and the solvent was evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation under reduced pressure gave the intermediate racemic silyl enol ether (1.19 g, 6.46 mmol, 72%) as a colourless oil which was used immediately. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84-4.81 (m, 1H, *H*C=CH_2), 2.15-1.94 (m, 3H, CH_2 + CH), 1.75-1.57 (m, 3H, CH_2 + CH), 1.37-1.24 (m, 1H, CH), 0.96 (d, J = 6.5 Hz, 3H, CH_3), 0.19 (s, 9H, $SiMe_3$).

m-CPBA (821 mg of a 77% sample, dissolved in 10 mL of CH_2Cl_2, dried over $MgSO_4$ and diluted to 20 mL, 3.56 mmol, 1.1 eq) was added dropwise over 15 min to a stirred solution of this silyl enol ether (615 mg, 3.35 mmol, 1.0 eq) and $NaHCO_3$ (546 mg, 6.50 mmol, 1.94 eq) in dry CH_2Cl_2 (5 mL) at 0 °C under N_2. The reaction was allowed to warm to rt over the course of 2 h and stirred for a further 14 h. Then, $HCl_{(aq)}$ (2 M, 20 mL) was added and stirred vigorously for 2 h at rt before the layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with $K_2CO_{3(aq)}$ (5% w/w, 1 x 10 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product which contained a 57:43 mixture of diastereomeric keto-alcohols **145**/**146** (by ^{1}H NMR spectroscopy of the crude reaction mixture). Purification by flash column chromatography on silica eluting with 9:1-7:3 hexane - EtOAc as eluent gave a 50:50 mixture of diastereomeric keto-alcohols (by ^{1}H NMR spectroscopy of the isolated material) **145**/**146** (176 mg, 1.37 mmol, 41%) as a white solid, mp 90.5–103.1 °C; R_F (7:3 petroleum ether – EtOAc) 0.21; IR (ATR) 3381 (O-H), 2924, 1963, 1724 (C=O), 1454, 1377, 1310, 1272, 1250, 1209, 1162, 1134, 1060, 1026, 987, 919, 840, 806, 751, 670, 529, 503 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (1:1 mix of inseparable diastereoisomers) δ 4.30 (dd, J = 11.5, 6.5 Hz, 0.5H, C*H*OH), 4.14 (ddd, J = 12.0, 7.0, 1.0 Hz, 0.5H, C*H*OH), 3.57 (br s, 0.5H, OH), 3.46 (br s, 0.5H, OH), 2.62-2.32 (m, 3H, CH_2 + CH), 2.27-2.17 (m, 1H, CH), 2.07-1.96 (m, 1H, CH), 1.90-1.83 (m, 1H, CH), 1.72-1.64 (m, 1H, CH), 1.22 (d, J = 7.0 Hz, 1.5H, CH_3), 1.00 (d, J = 6.5 Hz, 1.5H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (mix of diastereoisomers) δ 212.1 (C=O), 211.8 (C=O), 74.4 (CHOH), 71.9 (CHOH), 44.7 (CH_2), 42.2 (CH_2), 38.5 (CH_2), 35.6 (CH_2), 35.3 (CH_2), 33.1 (CH_2), 30.3 (CH), 27.4 (CH), 21.1 (CH_3), 18.0 (CH_3); MS (ESI) *m/z* 279 [$(M_2+Na)^+$, 100]; HRMS *m/z* calcd for $C_{14}H_{24}O_4$ $(M_2+Na)^+$ 279.1567, found 279.1556 (+3.8 ppm error).

Lab Book Reference: JCS-5-39 and JCS-5-40

Sodium 2-iodobenzenesulfonate hydrate 149



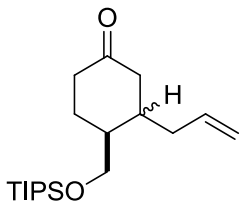
149

$NaNO_2$ (2.09 g, 30.3 mmol, 1.05 eq) in H_2O (10 mL) was added dropwise over 1 h to a stirred solution of aniline-2-sulfonic acid (5.0 g, 28.9 mmol, 1.0 eq) in $HCl_{(aq)}$ (6M, 20 mL) at 0 °C. After 1 h, NaI (4.76 g, 31.2 mmol, 1.1 eq) in H_2O (10 mL) was added dropwise over 10 m and the reaction mixture was stirred at the same temperature for 1 h. The reaction mixture was then allowed to warm to rt over 1 h, then heated to 50 °C for 12 h. Then, the reaction mixture was cooled to 0 °C and the solids were removed by filtration. The retentate was recrystallized from EtOH to give **149** as a brown crystalline solid (2.37 g, 7.31 mmol, 25%), IR (ATR) 3510 (O-H), 3440 (O-H), 1643, 1563, 1428, 1231, 1194, 1137, 1104, 1058, 1033, 1004, 761, 750, 733, 706, 647, 597, 550, 495 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 8.11 (d, J = 7.0 Hz, 1H, H_4), 7.99 (dd, J = 8.0, 2.0 Hz, 1H, H_1), 7.50 (ddd, J = 8.0, 8.0, 1.5, Hz, 1H,H_2), 7.21 (ddd, J = 8.0, 8.0, 1.5 Hz, 1H, H_3); ^{13}C NMR (100.6 MHz, D_2O) δ 144.7 (CSO_3Na), 142.1 (CH_4), 132.4 (CH_1), 128.5 (CH_2), 128.3 (CH_3), 90.9 (CI).

Spectroscopic data consistent with literature values.[116]

Lab Book Reference: JCS-5-23

3-Allyl-4-(((triisopropylsilyl)oxy)methyl)cyclohexanone 164/165



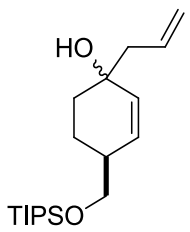
164/165

Allylmagnesium chloride (0.14 mL of a 0.2 M solution in THF, 0.284 mmol, 4.0 eq) was added dropwise over 5 m to a solution of copper (I) iodide (0.71 mL of a 0.2 M solution in SMe_2, 0.142 mmol, 2.0 eq) and THF (4 mL) at –78 °C. After 30 min, enone

117 (20 mg, 0.071 mmol, 1.0 eq) dissolved in THF (1 mL) was added dropwise over 5 min. The resulting solution was allowed to stir at the same temperature for 2 h before being quenched by the addition of aqueous NH_4Cl (sat. 2 mL). The reaction mixture was allowed to warm to rt and was diluted with EtOAc (60 mL) and washed with a mix of NH_4Cl (sat. 3 mL) and water (7 mL) three times, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the crude product which contained a 65:35 mix of diastereomeric ketones **164**/**165** (by ^{1}H NMR of the crude product). Purification by flash column chromatography with 19:1 to 9:1 hexane – EtOAc as eluent gave a 65:35 mix of ketones **164**/**165** (14.5 mg, 44.7 μmol, 63%) as a colourless oil, IR (ATR) 2938, 2925, 2866, 1717 (C=O), 1463, 1113, 995, 914, 882, 680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78–5.65 (m, 1H, *H*C=CH_2), 5.08–5.00 (m, 2H, HC=C*H*$_2$), 3.86–3.80 (m, 0.7H, CH_2OR), 3.78–3.73 (m, 1.4H, CH_2OR), 2.47–2.24 (m, 4H, 2 x CH_2), 2.18–2.06 (m, 3H, CH_2 and CH), 1.98–1.90 (m, 1H, CH), 1.87–1.65 (m, 2H, CH_2), 1.11–1.02 (m, 21H, Si(*i*Pr)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) (Major) δ 212.5 (C=O), 135.2 (H*C*=CH_2), 117.6 (HC=*C*H_2), 64.7 (CH_2OR), 45.6 (*C*H_2C(O)), 42.1 (CH), 40.6 (*C*H_2C(O)), 38.2 (CH), 38.0 (CH_2), 28.7 (CH_2), 18.2 (CH_3), 12.1 (H*C*(CH_3)$_2$); (Minor) δ 212.5 (C=O), 136.4 (H*C*=CH_2), 117.1 (HC=*C*H_2), 63.5 (CH_2OR), 44.9 (*C*H_2C(O)), 40.7 (CH), 39.8 (*C*H_2C(O)), 38.0 (CH), 33.7 (CH_2), 25.5 (CH_2), 18.2 (CH_3), 12.1 (H*C*(CH_3)$_2$); MS (ESI) *m/z* 325 [(M+H)$^+$, 5], 347 [(M+Na)$^+$, 100]; HRMS *m/z* calcd for $C_{19}H_{36}O_2Si$ (M+Na)$^+$ 347.2377, found 347.2375 (-0.3 ppm error).

Lab Book Reference: JCS-5-80

1-Allyl-4-(((triisopropylsilyl)oxy)methyl)cyclohex-2-enol 166 and 167



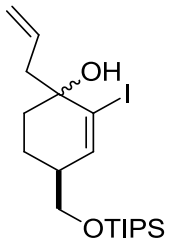
166/**167**

Allyl magnesium chloride (0.14 mL of a 2.0 M solution in THF, 0.28 mmol, 4.0 eq) was added dropwise over 5 min to a stirred solution of CuI (6.8 mg, 36 μmol, 0.5 eq) in THF

(6.8 mL) at –78 °C under N_2. After 30 m, a solution of enone **117** (20 mg, 71 μmol, 1.0 eq) in dry THF (1 mL) was added dropwise over 5 min and stirred at the same temperature for 2 h. Then, $NH_4Cl_{(aq)}$ (sat. 1 mL) was added and the reaction mixture was allowed to warm to rt over 10 m. The reaction mixture was diluted with EtOAc (50 mL) and washed with $H_2O/NH_4Cl_{(aq)}$ (20 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product which contained a 3:1 mixture of **166**/**167** (by ^{1}H NMR spectroscopy of the crude reaction mixture). Purification by flash column chromatography on silica eluting with 9:1 hexane – EtOAc as eluent gave **167** (7.6 mg, 0.023 mmol, 33%) as a colourless oil, R_F (9:1 hexane – EtOAc) 0.27; IR (ATR) 3388 (O–H), 2921, 2865, 1493, 1463, 1453, 1382, 1249, 1107, 1068, 1012, 994, 912, 881, 787, 759, 659, 696, 681, 539 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93-5.81 (m, 2H, *H*C=CH_2 and C(OH)*H*C=CH), 5.71–5.67 (m, 1H, C(OH)HC=C*H*), 5.16-5.09 (m, 2H, HC=C*H*$_2$), 3.63–3.54 (m, 2H, CH_2OR), 2.32-2.29 (m, 2H, allylic CH_2), 2.27-2.18 (m, 1H, allylic CH), 1.80-1.70 (m, 2H, CH_2), 1.52-1.41 (m, 2H, CH_2), 1.08-1.02 (m, 21H, OSi(*i*Pr)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) 133.8 **(**H*C*=CH_2), 132.7 (C(OH)H*C*=CH), 132.4 (C(OH)HC=*C*H), 118.7 (HC=*C*H_2), 69.4 (C(OH)), 67.2 (*C*H_2OR), 46.9 (allylic CH_2), 39.4 (allylic CH), 34.7 (CH_2), 22.0 (CH_2), 18.2 (CH_3), 12.1 (*C*H(CH_3)$_2$); MS(ESI) 347 [(M+Na)$^+$, 100]; HRMS *m/z* calcd for $C_{19}H_{36}O_2Si$ (M+Na)$^+$ 347.2377, found 347.2368 (+2.2 ppm error), and **166** (17.3 mg, 0.053 mmol, 75%), R_F (9:1 hexane – EtOAc) 0.17; IR (ATR) 3385 (O–H), 2941, 2926, 2865, 1463, 1453, 1383, 1249, 1104, 1069, 1011, 996, 911, 881, 786, 755, 697, 681, 657, 644 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 5.94–5.82 (m, 1H, *H*C=CH_2), 5.75 (dd, *J* = 10.0, 3.0 Hz, 1H, C(OH)*H*C=CH), 5.64 (dd, *J* = 10.0, 2.0 Hz, 1H, C(OH)HC=C*H*), 5.18–5.09 (m, 2H, HC=C*H*$_2$), 3.60–3.50 (m, 2H, CH_2OR), 2.37–2.24 (m, 3H, allylic CH_2 and allylic CH), 1.89–1.78 (m, 2H, C(OH)C*H*$_2$), 1.63–1.48 (m, 2H, CH_2), 1.14–1.02 (m, 21H, Si(*i*Pr)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) 133.8 (H*C*=CH_2), 133.8 (C(OH)H*C*=CH), 130.8 (C(OH)HC=*C*H), 118.9 (HC=*C*H_2), 70.3 (COH), 66.5 (CH_2OR), 46.2 (allylic *C*H_2), 38.5 (allylic CH), 34.0 (CH_2), 22.5 (CH_2), 18.2 (CH_3), 12.1 (H*C*(CH_3)$_2$); MS (ESI) *m/z* 347 [(M+Na)$^+$, 100]; HRMS *m/z* calcd for $C_{19}H_{36}O_2Si$ (M+Na)$^+$ 347.2377, found 347.2367 (+2.7 ppm error).

Lab Book Reference: JCS-5-60

1-Allyl-2-iodo-4-(((triisopropylsilyl)oxy)methyl)cyclohex-2-enol 173 and 174



173/176

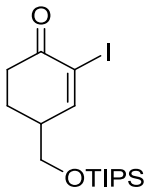
Allylmagnesium chloride (16 μL of a 1.7 M solution in THF, 27 μmol, 0.95 eq) was added in one portion to a stirred solution of iodo-enone **175** (11.6 mg, 28 μmol, 1.0 eq) in THF (2 mL) at 0 °C under N_2. After 30 mins, $HCl_{(aq)}$ (2 M, 10 mL) was added and the reaction mixture was diluted with EtOAc (50 mL) and the layers separated. The organic layer was washed with brine (1 x 10 mL), dried ($MgSO_4$) and the solvent evaporated to give the crude product which contained a 1:2 mix of diastereomeric alcohols **176**/**173** (by ^{1}H NMR of the crude mixture). Purification by flash column chromatography on silica with 9:1 hexane – EtOAc gave alcohol **176** (2.9 mg, 6.4 μmol, 23%), R_F (9:1 hexane – EtOAc) 0.32; IR (ATR) 3458 (O–H), 2924, 2864, 1463, 1384, 1365, 1116, 1000, 919, 882, 790, 982 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (br s, 1H, IC=CH), 5.81–5.68 (m, 1H, *H*C=CH_2), 5.21–5.12 (m, 2H, HC=C*H*$_2$), 3.63–3.51 (m, 2H, CH_2OSi), 2.42 (d, J = 8.0 Hz, 2H, C*H*$_2$CH=CH_2), 2.03–1.70 (m, 5H, 2 x CH_2 and CH), 1.11–1.00 (m, 21H, Si(*i*Pr)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) 144.2 (IC=*C*H), 133.1 (H*C*=CH_2), 119.1 (HC=*C*H$_2$), 73.4 (COH), 66.1 (CH_2OSi), 48.3 (CH_2), 43.9 (CH), 32.9 (CH_2), 29.9 (CH_2), 18.2 (CH_3), 12.1 (*C*HMe_2); MS (ESI) *m/z* 473 [(M+Na)$^+$, 100]; HRMS *m/z* calcd for $C_{19}H_{35}IO_2Si$ (M+Na)$^+$ 473.1343, found 473.1322 (+4.4 ppm error) and alcohol **173** (2.3 mg, 5.1 μmol, 18%), R_F (9:1 hexane – EtOAc) 0.27; IR (ATR) 3459 (O–H), 2925, 2865, 1462, 1384, 1117, 998, 916, 884, 687 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 6.49 (d, J = 3.0 Hz, 1H, IC=CH), 5.88–5.76 (m, 1H, *H*C=CH_2), 5.18–5.09 (m, 2H, HC=C*H*$_2$), 3.60–3.51 (m, 2H, CH_2OSi), 2.52–2.33 (m, 3H, CH_2 and C*H*$_A$H$_B$), 2.23–2.15 (m, 1H, CH), 1.92–1.70 (m, 3H, CH_2 and CH$_A$*H*$_B$), 1.10–1.00 (m, 21H, Si(*i*Pr)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) 142.7 (IC=*C*H), 133.0 (H*C*=CH_2), 119.1 (HC=*C*H$_2$), 73.5 (COH), 66.0 (CH_2OSi), 45.6 (CH_2), 43.4 (CH), 32.6 (CH_2), 29.9 (CH_2), 18.1 (CH_3), 12.1 (*C*HMe_2); MS (ESI) material degraded during analysis, and a 22:78 mix of diastereomeric alcohols **176**/**173** (6.2 mg, 13.8 μmol, 49%, combined total yield of 90%).

Lab Book Reference: JCS-6-23

Allylmagnesium chloride (0.48 mL of a 1.7 M solution in THF, 0.81 mmol, 1.2 eq) was added dropwise over 2 mins to a stirred solution of iodo-enone **175** (281 mg, 0.68 mmol, 1.0 eq) in THF (3 mL) at 0 °C under N_2. After 30 mins, $HCl_{(aq)}$ (2 M, 10 mL) was added and the reaction mixture was diluted with EtOAc (50 mL). The layers were separated and the organic layer was washed with brine (1 x 10 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product which contained a 1:2 mix of diastereomeric alcohols **176**/**173** (by ^{1}H NMR of the crude product). Purification by flash column chromatography gave a 1:2 mix of alcohols **176**/**173** (260 mg, 0.57 mmol, 84%).

Lab Book Reference: JCS-6-33

2-Iodo-4-(((triisopropylsilyl)oxy)methyl)cyclohex-2-enone 175



175

Iodine (106 mg, 0.42 mmol, 1.2 eq) was added to a stirred solution of enone **117** (100 mg, 0.35 mmol, 1.0 eq), K_2CO_3 (58 mg, 0.42 mmol, 1.2 eq) and DMAP (850 μg, 7 μmol, 2 mol%) in THF/H_2O (1.4 mL, 1:1 v/v) at 0 °C in one portion. The resulting solution was allowed to warm to room temperature over 16 h with stirring. Then, EtOAc (50 mL) was added and the resulting solution was washed with $Na_2S_2O_3$ (5% w/w, 1 x 20 mL), HCl (2M, 1 x 20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography eluting with 9:1 petroleum ether – EtOAc gave **175** (39 mg, 95 μmol, 27%) as a pale yellow oil, R_F (19:1 hexane – EtOAc) 0.27; IR (ATR) 2941, 2890, 2864, 1690 (C=O), 1586, 1462, 1417, 1382, 1309, 1249, 1182, 1114, 1098, 1068, 995, 919, 881, 802, 781, 719, 680, 659, 526 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 2.5 Hz, 1H, C=CH), 3.72 (dddd, J = 10.0, 10.0,

10.0, 6.5 Hz, 2H, CH_2OSi), 2.82 (16.5, 4.5, 4.5 Hz, 1H, C$H_A$$H_B$C(O)), 2.77–2.69 (m, 1H, $CH_A$$H_B$C(O)), 2.61–2.51 (m, 1H, ½ CH_2), 2.19–2.10 (m, 1H, ½ CH_2), 1.93–1.81 (m, 1H, CH), 1.16–1.03 (m, 21H, Si(*i*Pr)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 192.6 (C=O), 161.1 (IC=*C*H), 104.5 (I*C*=CH), 65.5 (CH_2OSi), 44.0 (*C*H_2C(O)), 35.8 (CH_2), 25.8 (CH), 18.2 (CH_3), 12.1 (*C*H(CH_3)$_2$); MS (ESI) *m/z* 431 [$(M+Na)^+$, 100]; HRMS *m/z* calcd for $C_{16}H_{29}IO_2Si$ $(M+Na)^+$ 431.0874, found 431.0855 (+4.4 ppm error).

Lab Book Reference: JCS-6-1, JCS-5-93

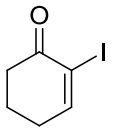
Iodine (91 mg, 0.36 mmol, 2.0 eq) in $CHCl_3$ (1 mL) and pyridine (1 mL) was added over 5 m to a stirred solution of enone **117** (50 mg, 0.177 mmol, 1.0 eq) and DMAP (4.3 mg, 35μmol, 0.2 eq) in $CHCl_3$ (1 mL) and pyridine (1 mL) at 0 °C. The resulting solution was allowed to warm to rt over 16 h before being diluted with EtOAc (50 mL) and washed with $HCl_{(aq)}$ (2 M, 2 x 10 mL), $Na_2S_2O_3$ (10% w/w, 20 mL) and water (20 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product. Purification through a small plug of silica with 100 mL of 9:1 hexane – EtOAc as eluent gave iodo-enone **175** (62 mg, 0.15 mmol, 86%) as a pale yellow oil.

Lab Book Reference: JCS-6-21

Iodine (449 mg, 1.77 mmol, 2.0 eq) in $CHCl_3$ (5 mL) and pyridine (5 mL) was added to a stirred solution of enone **117** (250 mg, 0.885 mmol, 1.0 eq) and DMAP (21 mg, 0.177 mmol, 2.0 eq) in $CHCl_3$ (5 mL) and pyridine (5 mL) at 0 °C under N_2. The resulting solution was allowed to warm to rt over 16 h before being diluted with EtOAc (150 mL), washed with HCl (2M, 2 x 50 mL), $Na_2S_2O_3$ (10% w/w, 1 x 50 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 hexane – EtOAc as eluent gave iodo-enone **175** (281 mg, 0.68 mmol, 77%) as a pale yellow oil.

Lab Book Reference: JCS-6-31

2-Iodocyclohex-2-enone 177



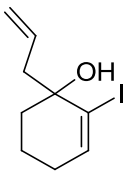
177

Iodine (15 g, 59 mmol, 1.9 eq) were added to a stirred solution of DMAP (254 mg, 2.08 mmol, 0.07 eq) in $CHCl_3$/pyridine (1:1 v/v, 40 mL) at 0 °C. To this solution was added cyclohexenenone (3 g, 3.02 mL, 31.2 mmol, 1.0 eq) in one portion and the reaction mixture was removed from the cooling bath and allowed to warm to rt. After 16 h, the reaction mixture was diluted with EtOAc (150 mL) and washed with $HCl_{(aq)}$ (2 M, 3 x 30 mL), $Na_2S_2O_3$ (10% w/w, 30 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gave iodo-enone **177** (5.86 g, 26.4 mmol, 85%) as a waxy, yellow solid, R_F (9:1 hexane – EtOAc) 0.19; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, J = 4.5, 4.5 Hz, 1H, IC=CH), 2.66 (dd, J = 7.0, 7.0 Hz, 2H, C(O)CH_2), 2.44 (ddd, J = 6.0, 6.0, 4.5 Hz, 2H, CH_2CH=CI), 2.08 (dddd, J = 6.0, 6.0, 6.0, 6.0 Hz, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 192.3 (C=O), 159.6 (IC=*C*H), 104.0 (I*C*=CH), 37.4 (CH_2), 30.1 (CH_2), 23.0 (CH_2).

Spectroscopic data consistent with literature values.[145]

Lab Book Reference: JCS-6-41

1-Allyl-2-iodocyclohex-2-enol 178



178

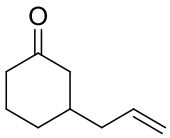
Allylmagnesium chloride (3.04 mL of a 1.7 M solution in THF, 5.18 mmol, 1.15 eq) was added dropwise over 5 mins to a stirred solution of iodo-enone **177** (1.0 g, 4.50 mmol, 1.0 eq) in THF (20 mL) at 0 °C under N_2. After 10 m, $HCl_{(aq)}$ (2 M, 12 mL) was added and the reaction mixture was diluted with EtOAc (150 mL). The layers were separated and the organic layer washed with brine (10 mL), dried ($MgSO_4$) and the

solvent evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 hexane – EtOAc gave **178** (0.87 g, 3.29 mmol, 73%) as a colourless oil, R_F (hexane – EtOAc) 0.28; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (dd, J = 4.0, 4.0 Hz, 1H, IC=CH), 5.83–5.71 (m, 1H, HC=CH_2), 5.19–5.15 (m, 1H, HC=CH_AH$_B$), 5.14–5.12 (m, 1H, HC=CH$_A$$H_B$), 2.44–2.40 (m, 2H, CH_2), 2.08–1.97 (m, 2H, CH_2), 1.90–1.83 (m, 2H, CH_2), 1.79–1.65 (m, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.0 (IC=CH), 133.0 (CH=CH_2), 119.1 (CH=CH$_2$), 111.9 (IC=CH_2), 73.1 (COH), 47.3 (CH_2), 34.3 (CH_2), 29.8 (CH_2), 19.0 (CH_2).

Spectroscopic data consistent with literature values.[145]

Lab Book Reference: JCS-6-44

3-Allylcyclohexanone 179



179

$TiCl_4$ (1.13 g, 0.66 mL, 5.98 mmol, 1.15 eq) was added dropwise over 5 min to a stirred solution of cyclohexenone (0.5 g, 5.20 mmol, 0.50 mL, 1.0 eq) in CH_2Cl_2 (10 mL) at –78 °C under N_2. After 5 min, allyltrimethylsilane (0.65 g, 0.91 mL, 5.72 mmol, 1.10 eq) was added and stirred for 1.5 h. The reaction mixture was then warmed to –30 °C and held there for 30 min. TLC analysis showed the presence of starting material. The reaction mixture was re-cooled to –78 °C and a further aliquot of $TiCl_4$ (1.13 g, 0.66 mL, 5.98 mmol, 1.15 eq) and allyltrimethylsilane (0.65 g, 0.91 mL, 5.72 mmol, 1.10 eq) was added and stirred for a further 1.5 h. The reaction mixture was allowed to warm to room temperature and stirred for 2 h, then, citric acid (aq. 10% w/w, 10 mL) was added and the reaction mixture was diluted with EtOAc (50 mL). The layers were separated and the organic layer washed with citric acid (aq. 10% w/w, 2 x 10 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 to 8:2 hexane – EtOAc gradient elution gave **179** (223 mg, 1.61 mmol, 31%) as a pale yellow oil of reasonable purity, R_F (9:1 hexane – EtOAc) 0.25; IR (ATR) 3076, 2926, 2865, 1709 (C=O), 1640, 1447, 1420,

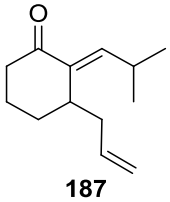
1345, 1310, 1287, 1224, 1182, 1056, 995, 959, 912, 866, 752, 665, 618, 597, 516 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79–5.67 (m, 1H, *H*C=CH_2), 5.06–4.99 (m, 2H, HC=C*H*$_2$), 2.44–2.31 (m, 2H, CH_2), 2.29–2.19 (m, 1H, CH), 2.13–1.97 (m, 4H, CH_2 and CH_2), 1.94–1.79 (m, 2H, CH_2), 1.70–1.57 (m, 1H, CH), 1.41–1.28 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 212.0 (C=O), 135.8 (H*C*=*C*H$_2$), 117.0 (HC=*C*H$_2$), 47.9 (CH_2), 41.5 (CH_2), 40.9 (CH_2), 38.9 (CH), 31.0 (CH_2), 25.3 (CH_2); MS (ESI) *m/z* 161 [$(M+Na)^+$, 100]; HRMS *m/z* calcd for $C_9H_{14}NaO$ $(M+Na)^+$ 161.0937, found 161.0940 (-1.9 ppm error).

Lab Book Reference: JCS-6-58

$TiCl_4$ (1.13 g, 0.66 mL, 5.98 mmol, 1.15 eq) was added dropwise over 5 min to a stirred solution of cyclohexenone (0.5 g, 5.20 mmol, 0.50 mL, 1.0 eq) in CH_2Cl_2 (10 mL) at –78 °C under N_2. After 5 min, allyltrimethylsilane (0.65 g, 0.91 mL, 5.72 mmol, 1.10 eq) was added and stirred for 3 h. Citric $acid_{(aq)}$ (10% w/w, 10 mL) was added dropwise at –78 °C and the reaction mixture was allowed to warm to room temperature. The reaction mixture was diluted with EtOAc (50 mL) and the layers seperated. The combine organic layers were dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 to 8:2 hexane – EtOAc gradient elution gave **179** (0.47 g, 3.41 mmol, 66%) as a colourless oil.

Lab Book Reference: JCS-6-62

3-Allyl-2-(2-Methylpropylidene)cyclohexanone 187



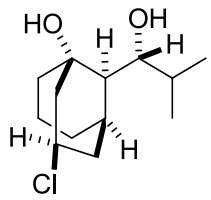
187

$TiCl_4$ (0.57 g, 3.0 mmol, 0.33 mL, 1.15 eq) was added dropwise over 1 m to a stirred solution of cyclohexenone (0.25 g, 0.25 mL, 2.60 mmol, 1.0 eq) in CH_2Cl_2 (5 mL) at –

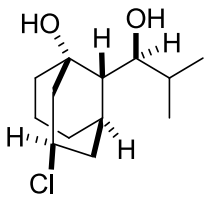
78 °C under N_2. After 2 min, allyltrimethylsilane (0.33 g, 0.46 mL, 2.86 mmol, 1.1 eq) was added dropwise over 5 m and the resulting solution was stirred at the same temperature for 2 h. Then, isobutylene oxide (0.56 mL, 448 mg, 6.24 mmol, 2.4 eq) was added over 2 min, followed by the immediate addition of $TiCl_4$ (1.14 g, 0.66 mL, 6.0 mmol, 2.3 eq). The temperature was raised to –45 °C. After 2 h, $HCl_{(aq)}$ was added (2 M, 20 mL) and the reaction mixture was diluted with EtOAc (50 mL). The layers were separated and the organic layer washed with $HCl_{(aq)}$ (2 M, 20 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica gave with 95:5 hexane – EtOAc as eluent gave **187** (52 mg, 0.27 mmol, 10%) as a colourless oil, R_F (9:1 hexane – EtOAc) 0.32; IR (ATR) 3076, 2958, 2931, 2868, 1687 (C=O), 1616, 1465, 1448, 1414, 1383, 1362, 1305, 1246, 1139, 1097, 1076, 1040, 996, 910, 838, 826, 684, 636, 593, 560, 497 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.22 (d, J = 10.5 Hz, 1H, C=CH), 5.77–5.66 (m, 1H, *H*C=CH_2), 5.06–4.98 (m, 2H, HC=C*H*$_2$), 2.60–2.46 (m, 2H, CH_2), 2.34–2.26 (m, 1H, CH), 2.20–2.00 (m, 2H, CH_2), 1.93–1.64 (m, 5H, CH_2), 1.02 (d, J = 7.0 Hz, 3H, CH_3), 0.98 (d, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 203.1 (C=O), 145.2 (C=*C*H), 138.6 (*C*=CH), 136.3 (H*C*=CH_2), 116.8 (HC=*C*H$_2$), 40.5 (CH_2), 39.0 (CH_2), 35.9 (CH), 27.4 (CH_2), 26.9 (CH), 22.7 (CH_3), 22.4 (CH_3), 18.8 (CH_2); MS (ESI) *m/z* 193 [$(M+H)^+$, 10], 215 [$(M+Na)^+$, 100]; HRMS *m/z* calcd for $C_{13}H_{20}O$ $(M+Na)^+$ 215.1406, found 215.1413 (-3.0 ppm error).

Lab Book Reference: JCS-6-76

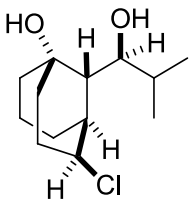
3-Allyl-2-(1-hydroxy-2-methylpropyl)cyclohexanone 188/189, (1*R*,3*R*,5*R*,9*R*)-3-chloro-9-((*R*)-1-hydroxy-2-methylpropyl)bicyclo[3.3.1]nonan-1-ol 190, (1*R*,3*R*,5*R*,9*S*)-3-chloro-9-((*S*)-1-hydroxy-2-methylpropyl)bicyclo[3.3.1]nonan-1-ol 191 and (1*R*,4*S*,5*S*,9*S*)-4-chloro-9-((*S*)-1-hydroxy-2-methylpropyl)bicyclo[3.3.1]nonan-1-ol 192



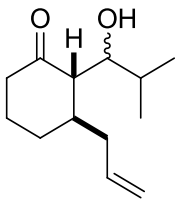
190



191



192



188/189

$TiCl_4$ (0.66 mL, 1.14 g, 6.0 mmol, 1.15 eq) was added over 30 seconds to a stirred solution of cyclohexenone (0.50 mL, 0.50 g, 5.2 mmol, 1.0 eq) in CH_2Cl_2 (10 mL) at –78 °C under N_2. After 30 seconds, allyltrimethylsilane (0.92 mL, 0.66 g, 5.8 mmol, 1.1 eq) was added over 30 seconds and the resulting solution was stirred at the same temperature for 3 h. Then, isobutylene oxide (1.12 mL, 0.91 g, 12.6 mmol, 2.4 eq) was added in one portion, followed by the immediate addition of $TiCl_4$ (1.32 mL, 2.28 g, 12.0 mmol, 2.3 eq). The resulting solution was allowed to stir at –78 °C for 3 h. Then, $NaHCO_{3(aq)}$ (sat. 20 mL) was added and the reaction mixture was diluted with EtOAc (100 mL). $NaHCO_{3(aq)}$ (sat. 30 mL) was added and the layers were separated. The organic layer was washed with additional $NaHCO_{3(aq)}$ (sat. 20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 80:20 mixture of diastereomeric keto-alcohols **188**/**189** (by ^{1}H NMR of the crude reaction mixture. Purification by flash column chromatography on silica using 8:2 to 7:3 hexane – EtOAc gradient elution gave a 78:22 mixture of keto-alcohols **188**/**189** (448 mg, 2.13 mmol, 41%) as a colourless oil, R_F (7:3 hexane – EtOAc) 0.32; IR (ATR) 3458 (O–H), 2959, 2931, 2871, 1696 (C=O), 1468, 1388, 1367, 1336, 1309, 1279, 1249, 1211, 1173, 1139, 1065, 1043, 994, 913, 857, 793, 769, 748, 641, 618, 601, 538, 501 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81–5.63 (m, 1H, $HC{=}CH_2$), 5.09–4.98 (m, 2H, $HC{=}CH_2$), 3.83 (ddd, *J* = 11.0, 7.0, 3.5 Hz, 0.23 H, C*H*OH), 3.55 (br s, 0.78 H, OH), 3.44–3.36 (m, 0.22 H, OH), 3.30 (ddd, *J* = 11.0, 8.5, 3.0 Hz, 0.78 H, C*H*OH), 2.67 (d, *J* = 11.0 Hz, 0.78 H, C(O)C*H*), 2.43–2.25 (m, 4.22 H, C(O)C*H* and 2 x CH_2) 2.18–2.08 (m, 2H, CH_2) 2.06–1.79 (m, 3H, CH_2 and CH) 1.76–1.62 (m, 1H, $HC(CH_3)_2$), 0.99–0.94 (m, 3H, $HC(CH_3)_A(CH_3)_B$), 0.88 (d, *J* = 6.5 Hz, 0.66 H, $HC(CH_3)_A(CH_3)_B$), 0.80 (d, *J* = 6.5 Hz, 2.34 H, $HC(CH_3)_A(CH_3)_B$); ^{13}C NMR (100.6 MHz, $CDCl_3$) (Major)**:** 216.2 (C=O), 135.1 ($HC{=}CH_2$), 117.7 ($HC{=}CH_2$), 75.6 (CHOH), 56.1 (C(O)*C*H), 42.8 (CH_2), 40.9 (CH), 37.5 (CH_2), 32.1 (CH), 29.8 (CH_2), 26.1 (CH_2), 20.1 (CH_3), 19.2 (CH_3); (Minor) *δ* 214.3 (C=O), 136.5 ($HC{=}CH_2$), 117.1 ($HC{=}CH_2$), 74.9 (CHOH), 59.8 (C(O)*C*H), 41.1 (CH_2) 37.6 (CH_2), 37.4 (CH), 31.4 (CH), 25.2 (CH_2), 22.8 (CH_2), 20.6

(CH_3), 15.2 (CH_3); MS (ESI) m/z 233 [$(M+Na)^+$, 100]; HRMS m/z calcd for $C_{11}H_{22}O_2$ $(M+Na)^+$ 233.1512, found 233.1511 (+0.4 ppm error), chlorinated diol **190** (59 mg, 0.24 mmol, 4.6%) as a white, crystalline solid, mp 145.5–147.5 °C; R_F (7:3 hexane – EtOAc) 0.29; IR (ATR) 3234 (O–H), 2916, 1468, 1347, 1313, 1285, 1230, 1198, 1124, 1075, 986, 938, 889, 860, 832, 804, 737, 661, 597, 576, 542, 521 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.68–4.58 (m, 1H, CHCl), 4.09 (d, J = 10.0 Hz, 1H, C*H*OH), 4.00 (br s, 1H, OH), 2.89 (br s, 1H, OH), 2.31 (d, J = 9.0 Hz, 2H, (Cl)CCH_2C(OH)), 2.15 (br s, 1H, CH), 1.99 (ddd, J = 14.0, 7.0, 2.0 Hz, 1H, CH_AH$_B$), 1.91–1.82 (m, 2H, CH$_A$$H_B$ and C*H*$(CH_3)_2$), 1.80–1.58 (m, 7H, 3 x CH_2 and CH), 1.05 (d, J = 7.0 Hz, 3H, $(CH_3)_A$), 0.87 (d, J = 7.0 Hz, 3H, $(CH_3)_B$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 75.5 (CHOH), 74.3 (COH), 55.6 (CHCl), 48.4 ((Cl)C*C*H_2C(OH)), 41.6 (CH_2), 37.1 (CH_2), 34.2 (CH), 31.9 (CH_2), 28.7 (*C*$(CH_3)_A(CH_3)_B$), 22.8 (CH_2), 20.2 ($(CH_3)_A$), 13.5 ($(CH_3)_B$); MS (ESI) *m/z* 269 [$(M+Na)^+$, 100], 271 [$(M+Na)^+$, 25]; HRMS *m/z* calcd for $C_{13}H_{23}O_2{}^{35}Cl$ $(M+Na)^+$ 269.1279, found 269.1280 (-0.6 ppm error), chlorinated diol **191** (113 mg, 0.46 mmol, 8.8%) as a white, crystalline solid, mp 138.0–140.5°C; R_F (7:3 hexane – EtOAc) 0.23; IR (ATR) 3234 (O–H), 2952, 2920, 2870, 1472, 1445, 1384, 1366, 1351, 1316, 1303, 1289, 1266, 1224, 1197, 1178, 1130, 1116, 1088, 1068, 1011, 985, 966, 933, 917, 881, 860, 829, 806, 786, 731, 662, 608, 598, 574, 542, 518 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.69–4.59 (m, 1H, CHCl), 4.03 (d, J = 10.0 Hz, 1H, C*H*OH), 3.74 (OH), 2.95 (OH), 2.44–2.38 (m, 1H, (Cl)CCH_AH$_B$C(OH)), 2.28–2.21 (m, 1H, CH_ACH$_B$), 2.19–2.13 (m, 1H, CH), 2.05–1.62 (m, 10H, 3 x CH_2, (Cl)CCH$_A$$H_B$C(OH), CH$_A$$H_B$, C*H*$(CH_3)_A(CH_3)_B$ and (OH)CC*H*), 1.03 (d, J = 7.0 Hz, 3H, $(CH_3)_A$), 0.88 (d, J = 7.0 Hz, 3H, $(CH_3)_B$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 75.0 (CHOH), 74.0 (C(OH)), 55.2 (CHCl), 53.0 ((Cl)CCH_AH$_B$C(OH)), 48.4 ((OH)C*C*H), 44.3 (CH$_A$H$_B$), 34.2 (CH), 33.8 (CH_2), 28.8 (*C*H$(CH_3)_A(CH_3)_B$), 23.9 (CH_2), 22.1 (CH_2), 20.3 ($(CH_3)_A$), 13.6 ($(CH_3)_B$); MS (ESI) MS (ESI) *m/z* 269 [$(M+Na)^+$, 100], 271 [$(M+Na)^+$, 25]; HRMS *m/z* calcd for $C_{13}H_{23}O_2{}^{35}Cl$ $(M+Na)^+$ 269.1279, found 269.1272 (+2.7 ppm error), and chlorinated diol **192** (10.3 mg, 42 μmol, 0.81%) as a white, crystalline solid, mp 188.0–191.0 °C; R_F (7:3 hexane – EtOAc) 0.13; IR (ATR) 3271 (O–H), 2924, 2866, 1737, 1471, 1456, 1368, 1354, 1310, 1286, 1259, 1244, 1228, 1211, 1179, 1129, 1101, 1081, 1067, 1008, 991, 934, 922, 909, 867, 846, 743, 715, 691, 661, 597, 585, 559, 530, 492 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 4.36–4.32 (m, 1H, CHCl), 4.09 (dd, J = 10.0, 1.5 Hz, C*H*OH), 3.45 (br s, 1H, OH), 3.19 (br s, 1H, OH), 2.50–2.37 (m, 1H, (OH)CC*H*), 2.36–2.30 (m, 2H, CH_2), 2.13–2.00 (m, 3H, CH_2 and CH_AH$_B$), 1.92–1.68 (m, 6H, CH$_A$$H_B$,

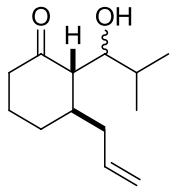
C*H*$(CH_3)_A(CH_3)_B$, and 2 x CH_2), 1.43–1.36 (m, 1H, CH), 1.04 (d, *J* = 7.0 Hz, 3H, $((CH_3)_A)$, 0.93 (d, *J* = 7.0 Hz, 3H, $((CH_3)_B)$; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 75.1 (CHOH), 73.1 (COH), 64.2 (CHCl), 42.3 (CH), 41.8 (CH), 37.6 (CH_2), 34.0 (CH_2), 32.4 (CH_2), 28.5 (*C*H$(CH_3)_A(CH_3)_B$), 23.4 (CH_2), 20.9 (CH_2), 20.3 $((CH_3)_A)$, 13.2 $((CH_3)_B)$; MS (ESI) *m/z* 269 $[(M+Na)^+$, 100], 271 $[(M+Na)^+$, 25]; HRMS *m/z* calcd for $C_{13}H_{23}O_2{}^{35}Cl$ $(M+Na)^+$ 269.1279, found 269.1284 (-1.8 ppm error).

Method For Growing Crystals of **190-192**

A solid sample of **190** (approx. 5 mg) was placed in a small glass vial and dissolved in the minimum quantity of EtOAc (approx. 0.05 mL) and placed upright in a sealed vessel containing pentane (approx. 20 mL). After 24 h, crystals suitable for X-Ray analysis had formed on the inner vial. The same procedure was used for growing crystals of diols **191** and **192**

Lab Book Reference: JCS-6-84

3-Allyl-2-(1-hydroxy-2-methylpropyl)cyclohexanone 188/189



188/189

$TiCl_4$ (0.66 mL, 1.14 g, 6.0 mmol, 1.15 eq) was added over 10 s to a stirred solution of cyclohexenone (0.50 mL, 0.50 g, 5.2 mmol, 1.0 eq) in CH_2Cl_2 (10 mL) under N_2 at –78 °C. After 30 s, allyltrimethylsilane (0.92 mL, 0.66 g, 5.8 mmol, 1.1 eq) was added dropwise over 2 m. After 3 h, the temperature was reduced to –116 °C ($N_{2(l)}$/EtOH), followed by the dropwise addition of isobutylene oxide (1.12 mL, 0.91 g, 12.6 mmol, 2.4 eq) over 2 m. The resulting solution was stirred at the same temperature for 1 h before being quenched by the addition of $NaHCO_{3(aq)}$ (sat. 20 mL) and diluted with EtOAc (100 mL). $NaHCO_{3(aq)}$ (sat. 30 mL) was added and the layers were separated. The organic layer was washed with $NaHCO_{3(aq)}$ (sat. 20 mL), dried ($MgSO_4$) and the

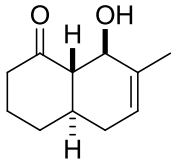
solvent evaporated under reduced pressure to give the crude product which contained an 87:13 mix of diastereomeric keto alcohols **188**/**189** (by ^{1}H NMR of the crude reaction mixture). Purification by flash column chromatography on silica with 9:1 to 7:3 hexane – EtOAc as eluent gave a mixture of keto alcohols **188**/**189** (549 mg, 2.61 mmol, 50%, 86:14 dr) as a colourless oil. Chlorinated diols **190**, **191** and **192** were not observed.

Lab Book Reference: JCS-6-86

$TiCl_4$ (0.66 mL, 1.14 g, 6.0 mmol, 1.15 eq) was added over 10 s to a stirred solution of cyclohexenone (0.50 mL, 0.50 g, 5.2 mmol, 1.0 eq) in CH_2Cl_2 (10 mL) under N_2 at –78 °C. After 30 s, allyltrimethylsilane (0.92 mL, 0.66 g, 5.8 mmol, 1.1 eq) was added dropwise over 2 m. After 3 h, isobutylene oxide (0.56 mL, 0.45 g, 6.3 mmol, 1.2 eq) was added dropwise over 2 m. The reaction vessel was then placed into an ice bath and stirred at the same temperature for 3 h before being quenched with $NaHCO_{3(aq)}$ (sat. 10 mL) and diluted with EtOAc (60 mL). The layers were separated and organic layer was washed with $NaHCO_{3(aq)}$ (sat. 3 x 25 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product which contained an 88:12 mix of diastereomeric keto alcohols **188**/**189** (by ^{1}H NMR of the crude reaction mixture). Purification by flash column chromatography on silica with 8:2 to 75:25 hexane – EtOAc as eluent gave a 91:9 mixture of keto alcohols **188**/**189** (839 mg, 4.0 mmol, 80%, 91:9 dr) as a colourless oil. Chlorinated diols **190**, **191** and **192** were not observed.

Lab Book Reference: JCS-7-3

8-Hydroxy-7-methyl-3,4,4a,5,8,8a-hexahydronaphthalen-1(2H)-one 193



193

Hoveyda-Grubbs 2nd generation catalyst (12 mg, 0.019 mmol, 0.1 eq) was added in one portion to a stirred solution of aldol product **198** (40 mg, 0.19 mmol, 1.0 eq) in CH_2Cl_2 (5 mL) at rt under N_2. After 3 h, the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 hexane–EtOAc as eluent gave decalin **193** (21 mg, 0.12 mmol, 61%), mp 62.5–63.5 °C; R_F (7:3 hexane–EtOAc) 0.21; IR (ATR) 3341 (O–H), 2967, 2925, 2886, 2866, 2854, 1702 (C=O), 1463, 1452, 1430, 1378, 1343, 1328, 1308, 1281, 1262, 1202, 1180, 1168, 1160, 1119, 1093, 1076, 1062, 1037, 1019, 958, 939, 897, 857, 841, 811, 780, 579, 523, 489 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.41–5.37 (m, 1H, C=CH), 4.41 (d, J = 9.5 Hz, 1H, C*H*OH), 3.24 (br s, 1H, CHO*H*), 2.49–2.42 (m, 1H, CH), 2.40–2.29 (m, 1H, CH), 2.25–2.17 (m, 1H, CH), 2.16–2.03 (m, 2H, 2 x CH), 2.00–1.93 (m, 1H, CH), 1.92–1.85 (m, 1H, CH), 1.84–1.77 (m, 1H, CH), 1.76–1.73 (m, 3H, CH_3), 1.70–1.63 (m, 1H, CH), 1.53–1.45 (m, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 214.3 (C=O), 135.5 (*C*=CH), 122.2 (C=*C*H), 69.0 (CHOH), 58.6 (C(O)*C*HCH(OH)), 42.1 (CH_2), 39.0 (CH), 33.3 (CH_2), 31.9 (CH_2), 25.6 (CH_2), 19.1 (CH_3); MS (ESI) *m/z* 203 [$(M+Na)^+$, 100]; HRMS *m/z* calcd for $C_{11}H_{16}O_2$ $(M+Na)^+$ 203.1043, found 203.1039 (+2.0 ppm error).

Lab Book Reference: JCS-7-11

Grubbs 2nd generation catalyst (10 mg, 12 μmol, 0.05 eq) was added in one portion to a stirred solution of aldol product **198** (50 mg, 0.24 mmol, 1.0 eq) in CH_2Cl_2 (10 mL) at rt under N_2. After 90 mins, the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 hexane–EtOAc as eluent gave decalin **193** (41 mg, 0.23 mmol, 95%) as a white solid.

Lab Book Reference: JCS-7-46

Grubbs 2nd generation catalyst (31 mg, 36 μmol, 0.05 eq) was added in one portion to a stirred solution of aldol product **198** (150 mg, 0.72 mmol, 1.0 eq) in CH_2Cl_2 (30 mL) at rt under N_2. After 90 mins, the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 hexane–EtOAc as eluent gave decalin **193** (115 mg, 0.64 mmol, 89%) as a white solid.

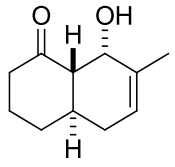
Lab Book Reference: JCS-7-51

Method for growing crystals of **193:**

A solid sample of **193** (approx. 5 mg) was placed in a small glass vial and dissolved in the minimum quantity of *i*PrOH (approx. 0.05 mL) and placed upright in a sealed vessel containing water (approx. 10 mL). After 24 h, crystals suitable for X-Ray analysis had formed on the inner vial.

Lab Book Reference: JCS-7-44

(4*R*,8*S*,8*S*)-8-hydroxy-7-methyl-3,4,4,5,8,8-hexahydronaphthalen-1(2H)-one 194



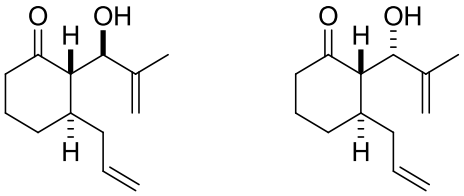
194

Grubbs 2nd generation catalyst (10 mg, 12 μmol, 0.05 eq) was added in one portion to a stirred solution of aldol product **197** (50 mg, 0.24 mmol, 1.0 eq) in CH_2Cl_2 (10 mL) at rt under N_2. After 90 mins, the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 hexane–EtOAc as eluent gave decalin **194** (29 mg, 0.16 mmol, 67%) as a pale yellow oil, R_F (7:3 hexane – EtOAc) 0.26; IR (ATR) 3535 (O–H), 2929, 2865, 1695 (C=O), 1449, 1374, 1336, 1317, 1299, 1241, 1206, 1179, 1146, 1124, 1091, 1080, 1039, 1016, 969, 931, 891, 868, 840, 805, 780, 710, 535 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.56–5.51 (m, 1H, C=CH), 4.32 (br s, 1H, C*H*OH), 3.25 (d, J = 3.0 Hz, 1H, CHO*H*), 2.47–2.41(m, 1H, CH), 2.40–2.34 (m, 1H, 0.5 x CH_2), 2.30–2.22 (m, 1H, 0.5 x CH_2), 2.19–2.11 (m, 2H, CH_2), 2.11–2.02 (m, 1H, 0.5 x CH_2), 2.02–1.94 (m, 1H, 0.5 x CH_2), 1.92–1.82 (m, 1H, 0.5 x CH_2), 1.82–1.78 (m, 3H, CH_3), 1.76–1.69 (m, 1H, CH), 1.50–1.38 (m, 1H, 0.5 x CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 214.6 (C=O), 134.0 (*C*=CH), 124.7 (C=*C*H), 66.3 (CHOH), 56.3 (C(O)*C*H), 42.6 (C(O)*C*H_2), 34.1 (CH_2), 33.4 (CH), 32.0 (CH_2),

25.7 (CH_2), 21.4 (CH_3); MS (ESI) *m/z* 203 [$(M+Na)^+$, 100]; HRMS *m/z* calcd for $C_{11}H_{16}O_2$ $(M+Na)^+$, 203.1043, found 203.1043 (-0.2 ppm error).

Lab Book Reference: JCS-7-46

(2*S*,3*R*)-3-Allyl-2-((*R*)-1-hydroxy-2-methylallyl)cyclohexanone 198 and (2*S*,3*R*)-3-Allyl-2-((*S*)-1-hydroxy-2-methylallyl)cyclohexanone 197



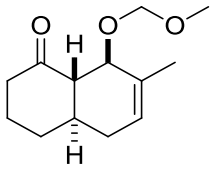
198 **197**

$TiCl_4$ (1.14 g, 0.66 mL, 6.0 mmol, 1.15 eq) was added dropwise over 5 m to a stirred solution of cyclohexenone (0.5 g, 0.5 mL, 5.2 mmol, 1.0 eq) in CH_2Cl_2 (10 mL) at –78 °C under N_2. After 5 min, allyltrimethylsilane (0.66 g, 0.92 mL, 5.8 mmol, 1.1 eq) was added dropwise over 5 min and the resulting solution was stirred at the same temperature for 3 h. Then, methacrolein (0.44 g, 0.51 mL, 6.24 mmol, 1.2 eq) was added dropwise over 5 m and the reaction mixture was stirred at the same temperature for a further 2 h. $NaHCO_{3(aq)}$ (sat. 30 mL) was added at –78 °C and the reaction mixture was allowed to warm to rt over 5 m before being being diluted with EtOAc (150 mL) and the layers separated. The organic layer was washed with $NaHCO_{3(aq)}$ (sat. 3 x 25 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product which contained a 40:60 ratio of diastereomeric alcohols **197**/**198** (by ^{1}H NMR of the crude mixture. The presence of the remaining 2 possible diastereoisomers was not observed). Purification by flash column chromatography on silica with 7:3 hexane – EtOAc as eluent gave **197** (198 mg, 0.95 mmol, 18%) as a colourless oil, R_F (7:3 hexane – EtOAc) 0.3; IR (ATR) 3423 (O–H), 3075, 2928, 1697 (C=O), 1641, 1450, 1374, 1308, 1236, 1107, 1028, 995, 907, 762 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77–5.65 (m, 1H, *H*C=CH_2), 5.06–4.97 (m, 3H, C=CH_2 and C=C$H_A$$H_B$), 4.90–4.87 (m, 1H, C=C$H_A$$H_B$), 4.50 (dd, *J* = 6.0, 6.0 Hz, 1H, C*H*OH), 2.47–2.36 (m, 3H, CH_2/CH), 2.32–2.15 (m, 3H, CH_2/CH), 2.06–1.95 (m, 2 H, CH_2/CH), 1.94–1.76 (m, 2H, CH_2/CH), 1.72 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 213.9 (C=O), 145.6 (*C*=CH_2), 136.2

(H*C*=CH_2), 117.3 (H_2*C*=C), 113.5 (H_2*C*=CH), 75.4 (CHOH), 58.3 (C(O)*C*H), 41.4 (CH_2), 38.1 (CH_2), 37.1 (CH_2), 26.7 (CH_2), 22.9 (CH_2), 18.2 (CH_3); MS (ESI) *m/z* 231 [$(M+Na)^+$, 100]; HRMS *m/z* calcd for $C_{13}H_{20}O_2$ $(M+Na)^+$ 231.1356, found 231.1350 (+2.4 ppm error), and **198** (110 mg, 0.53 mmol, 10%) as a colourless oil, R_F (7:3 hexane – EtOAc) 0.15; IR (ATR) 3334 (O–H), 3078, 2967, 2922, 2870, 1711 (C=O), 1642, 1439, 1374, 1339, 1308, 1246, 1229, 1164, 1132, 1100, 1042, 1028, 1016, 992, 964, 860, 836, 772. 725, 673, 637, 593, 564, 513, 487, 466 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80–5.68 (m, 1H, *H*C=CH_2), 5.12–4.94 (m, 4H, HC=C*H*$_2$ and C=C*H*$_2$), 4.36 (dd, *J* = 7.0, 7.0 Hz, 1H, C*H*OH), 2.66–2.63 (1H, C(CO)C*H*), 2.51–2.41 (m, 2H, CH_2/CH), 2.40–2.32 (m, 1H, CH_2/CH), 2.28–2.19 (m, 1H, CH_2/CH), 2.17–2.11 (m, 1H, CH_2/CH), 2.10–1.77 (m, 4H, CH_2/CH), 1.71 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 214.8 (C=O), 145.6 (*C*=CH_2), 135.4 (H*C*=CH_2), 117.7 (C=*C*H_2), 112.9 (HC=*C*H_2), 74.4 (CHOH), 57.3 (C(O)*C*H), 41.2 (CH_2), 39.7 (CH), 37.6 (CH_2), 27.6 (CH_2), 24.5 (CH_2), 18.1 (CH_3); MS (ESI) *m/z* 231 [$(M+Na)^+$, 100]; HRMS *m/z* calcd for $C_{13}H_{20}O_2$ $(M+Na)^+$ 231.1356, found 231.1358 (-1.1 ppm error), and a 1:3 mixture of diasteromeric alcohols **197**/**198** (0.54 g, 2.59 mmol, 50%) in a combined overall yield of 78%.

Lab Book Reference: JCS-7-8

(4*S*,8*S*,8*S*)-8-(methoxymethoxy)octahydronaphthalen-1(2H)-one 199



199

Methoxymethyl chloride (64 μL, 68 mg, 0.84 mmol, 30 eq) was added in one portion to a stirred solution of decalin **193** (5 mg, 27.8 μmol, 1.0 eq) and DIPEA (0.22 mL, 162 mg, 1.25 mmol, 45 eq) in CH_2Cl_2 (0.25 mL) at rt. After 3 h and 45 m, MeOH (1 mL) was added and the reaction mixture was stirred at rt overnight. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 hexane–EtOAc as eluent gave **199** (1.4 mg, 6.2 μmol, 22%) as a pale yellow oil, R_F (7:3 hexane–EtOAc) 0.32; IR (ATR) 2924, 2858,

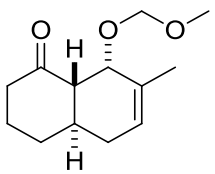
1714 (C=O), 1451, 1366, 1306, 1205, 1186, 1151, 1079, 1030, 966, 925 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54 (d, J = 5.5 Hz, 1H, C=C*H*), 4.91 (d, J = 7.0 Hz, 1H, OCH_AH$_B$OMe), 4.67 (d, J = 7.0 Hz, OCH$_A$$H_B$OMe), 4.51 (d, J = 8.0 Hz, C*H*(OMOM)), 3.35 (s, 3H, OCH_3), 2.63 (dd, J = 12.5, 8.5 Hz, 1H, C(O)C*H*), 2.46–2.40 (m, 2H, CH_2), 2.14–2.03 (m, 2H, CH_2), 2.00–1.81 (m, 2H, CH_2), 1.76–1.72 (br s, 3H, CH_3), 1.72–1.62 (m, 3H, CH_2 + CH); ^{13}C NMR (100.6 MHz, $CDCl_3$ 211.3 (C=O), 134.3 (*C*=CH), 124.6 (C=*C*H_2), 97.4 (O*C*H_2OMe), 74.5 (*C*HOMOM), 58.8 (C(O)*C*H), 56.3 (OCH_3), 42.8 (CH_2), 41.7 (CH), 33.0 (CH_2), 32.9 (CH_2), 27.3 (CH_2), 20.4 (CH_3); MS (ESI) *m/z* 247 [$(M+Na)^+$, 100]; HRMS *m/z* calcd for $C_{13}H_{20}O_3$ $(M+Na)^+$ 247.1305, found 247.1307 (-1.4 ppm error).

Lab Book Reference: JCS-7-47

Methoxymethyl chloride (0.24 mL, 257 mg, 3.20 mmol, 5 eq) was added in one portion to a stirred solution of decalin **193** (115 mg, 0.64 mmol 1.0 eq) and DIPEA (1.10 mL, 827 mg, 6.40 mmol, 10 eq) in CH_2Cl_2 (3 mL) at rt. After 6 h and 20 min, MeOH (2 mL) was added and the reaction mixture was stirred at rt overnight. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 hexane–EtOAc as eluent gave **199** (123 mg, 0.55 mmol, 86%) as a pale yellow oil.

Lab Book Reference: JCS-7-52

(4*R*,8*S*,8*S*)-8-(Methoxymethoxy)-7-methyl-3,4,4,5,8,8-hexahydronaphthalen-1(2H)-one 200



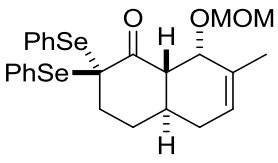
200

Methoxymethyl chloride (0.32 mL, 340 mg, 4.22 mmol, 2.0 eq) was added to a stirred solution of decalinone **194** (381 mg, 2.11 mmol, 1.0 eq) and DIPEA (1.10 mL, 818 mg,

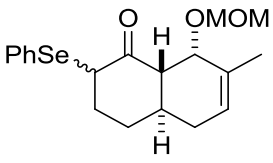
6.33 mmol, 3.0 eq) in CH_2Cl_2 (3 mL) at rt under N_2. The resulting solution was allowed to stir at the same temperature for 16 h. Then, MeOH (2 mL) was added and stirred for a further 16 h. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica eluting with 8:2 hexane – EtOAc gave protected decalinone **200** (131 mg, 0.58 mmol, 28%) as a colourless oil, R_F (8:2 hexane – EtOAc) 0.30; IR (ATR) 2923, 2823, 1707 (C=O), 1448, 1371, 1341, 1319, 1276, 1245, 1208, 1180, 1149, 1128, 1092, 1025, 980, 920, 893, 871, 776, 704, 617, 596, 533 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.51–5.47 (m, 1H, C=CH), 5.02 (d, J = 7.0 Hz, 1H, OCH_AH$_B$OMe), 4.58 (d, J = 7.0 Hz, 1H, CH$_A$$H_B$OMe), 4.19 (d, J = 2.5 Hz, 1H, C*H*OMOM), 3.34 (s, 3H, OMe), 2.46 (ddddd, J = 16.0, 2.0, 2.0, 2.0, 2.0 Hz, 1H, CH_AH$_B$), 2.37–2.17 (m, 3H, CH$_A$$H_B$, C$H_CH_D$ and CH), 2.09–2.02 (m, 1H, C(O)C*H*), 2.01–1.92 (m, 2H, CH_EH$_F$ and CH_GH$_H$), 1.88–1.65 (m, 5H, CH$_C$$H_D$, CH$_3$ and CH$_E$$H_F$), 1.43–1.29 (m, 1H, CH$_G$$H_H$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 210.1 (C=O), 134.0 (*C*=CH), 125.2 (C=*C*H), 98.7 (O*C*H$_2$OMe), 74.2 (*C*HOMOM), 56.4 (C(O)*C*H), 55.8 (OMe), 41.8 (CH$_A$H$_B$), 34.2 (CH$_C$H$_D$), 32.1 (CH), 31.7 (CH$_G$H$_H$), 23.8 (CH$_E$H$_F$), 21.6 (CH$_3$); MS (ESI) *m/z* 247 [(M+Na)$^+$, 100]; HRMS *m/z* calcd for $C_{13}H_{20}O_3$ (M+Na)$^+$ 247.1305, found 247.1301 (+1.3 ppm error).

Lab Book Reference: JCS-7-83

(4*R*,8*S*,8*S*)-8-(methoxymethoxy)-7-methyl-2-(phenylselanyl)-3,4,4,5,8,8-hexahydronaphthalen-1(2H)-one 206/207 and (4*R*,8*S*,8*S*)-8-(methoxymethoxy)-7-methyl-2,2-bis(phenylselanyl)-3,4,4,5,8,8-hexahydronaphthalen-1(2H)-one 208



208



206/207

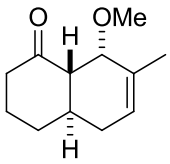
*n*BuLi (0.62 mL of a 2.47 M soln in hexanes, 1.54 mmol, 2.0 eq) was added dropwise over 2 m to a stirred solution of diisopropylamine (0.18 mL, 129 mg, 1.28 mmol, 2.5 eq) in THF (2 mL) under N_2 at –78 °C. After 30 min, decalinone **200** (115 mg, 0.51 mmol, 1.0 eq) in THF (2 mL) was added dropwise over 5 min and the resulting solution was stirred at the same temperature for 1 h. Then, phenylselenium bromide (361 mg, 1.53

mmol, 3.0 eq) was added in THF (2 mL) over 30 s and the resulting solution was stirred at the same temperature for 2 h before being quenched with K_2CO_3 (10% w/w, 3 mL), diluted with EtOAc (70 mL), washed with K_2CO_3 (10% w/w, 2 x 20 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product which contained a 60:40 mixture of diastereomeric selenides **206**/**207** (by ^{1}H NMR of the crude reaction mixture). Purification by flash column chromatography on silica with 9:1 hexane – EtOAc as eluent gave an 85:15 mix of diastereomeric selenides **206**/**207** (19 mg, 50.3 μmol, 10%) as a yellow oil, R_F (8:2 hexane – EtOAc) 0.31; IR (ATR) 3052, 2921, 2871, 1688 (C=O), 1670, 1576, 1474, 1436, 1351, 1291, 1260, 1238, 1215, 1169, 1146, 1110, 1095, 1079, 1061, 1028, 999, 923, 859, 812, 795, 745, 735, 690, 672, 660, 622, 552, 531, 472 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (Major) δ 7.55–7.51 (m, 2H, *m*-PhH), 7.30–7.24 (m, 3H, *p*-PhH and *o*-PhH), 5.59–5.54 (m, 1H, C=CH), 4.81 (d, J = 6.5 Hz, 1H, OCH_AH$_B$OMe), 4.50 (d, J = 6.5 Hz, 1H, OCH$_A$$H_B$OMe), 4.47 (d, J = 8.5 Hz, 1H, C*H*OMOM), 3.99–3.96 (m, 1H, C*H*SePh), 3.50 (dd, J = 13.0, 8.5 Hz, 1H, C(O)C*H*), 3.29 (s, 3H, OCH_3), 2.32–2.16 (m, 2H, CH_{2A}), 2.11–1.98 (m, 2H, CH_{2B}), 1.79–1.68 (m, 6H, CH_3, CH_{2C} and CH); ^{1}H NMR (Minor, some signals unassigned) δ 7.79–7.74 (m, 2H, *m*-PhH), 7.43–7.33 (m, 3H, *p*-PhH and *o*-PhH), 5.73 (d, J = 6.0 Hz, 1H, C=CH), 4.70 (d, J = 6.5 Hz, 1H, CH_AH$_B$OMe), 4.59 (d, J = 6.5 Hz, 1H, CH$_A$$H_B$OMe), 3.04 (s, 3H, OCH_3), 1.71 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) (Major) δ 208.2 (C=O), 134.5 (*C*=CH), 134.2 (*m*–Ph), 129.4 (*o*–Ph), 128.8 (*i*–Ph), 128.1 (*p*-Ph), 124.6 (C=*C*H), 97.4 (O*C*H$_2$OMe), 74.2 (*C*HOMOM), 56.4 (OCH_3), 53.7 (C(O)*C*H), 51.1 (*C*HSePh), 41.2 (CH), 32.6 (CH_{2B}), 32.4 (CH_{2A}), 29.1 (CH_{2C}), 20.6 (CH_3); ^{13}C NMR signals unobservable for minor diastereoisomer; MS (ESI) *m/z* 403 [(M+Na)$^+$, 100]; HRMS *m/z* calcd for $C_{19}H_{24}O_3{}^{80}Se$ (M+Na)$^+$ 403.0784, found 403.0799 (-4.1 ppm error), doubly substituted **208** (54 mg, 0.10 mmol, 20%) as a yellow solid, mp 126–128 °C; R_F (8:2 hexane – EtOAc) 0.39; IR (ATR) 2921, 1699 (C=O), 1578, 1477, 1438, 1371, 1344, 1294, 1265, 1211, 1191, 1151, 1079, 1040, 1023, 921, 849, 810, 791, 739, 690, 670, 598, 543, 459 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78–7.72 (m, 4H, *m*–PhH), 7.44–7.30 (m, 6H, *o*–PhH and *p*-PhH), 5.54–5.50 (m, 1H, C=CH), 4.83 (d, J = 6.5 Hz, 1H, OCH_AH$_B$OMe), 4.35 (d, J = 6.5 Hz, 1H, OCH$_A$$H_B$OMe), 4.37–4.32 (underneath doublet at 4.35, 1H, C*H*OMOM), 3.75 (dd, J = 13.5, 8.5 Hz, 1H, C(O)C*H*), 3.37 (s, 3H, OCH_3), 2.46–2.36 (m, 1H, CH_AH$_B$), 2.07–1.98 (m, 3H, CH$_A$$H_B$ and CH_2), 1.78 (m, 4H, CH_3 and CH), 1.67–1.60 (m, 1H, CH_{AA}H$_{BB}$), 1.28–1.24 (m, 1H, CH$_{AA}$$H_{BB}$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 204.9 (C=O), 138.2 (*m*-Ph), 136.8 (*m*-Ph), 134.8 (*C*=CH), 129.6 (*p*-Ph),

129.13 (*p*-Ph), 129.07 (*o*-Ph), 128.8 (*o*-Ph), 127.9 (*i*-Ar), 127.4 (*i*-Ar), 124.0 (C=*C*H), 98.9 (O*C*H_2OMe), 75.9 (*C*HOMOM), 64.5 (*C*$(SePh)_2$), 56.6 (OCH_3), 54.4 (C(O)*C*H), 41.0 (CH_AH_B), 40.4 (CH), 32.6 (CH_2), 30.2 ($CH_{AA}H_{BB}$), 20.7 (CH_3); MS (ESI) *m/z* 559 [$(M+Na)^+$, 100]; HRMS *m/z* calcd for $C_{19}H_{24}O_3{}^{80}Se$ $(M+Na)^+$ 559.0266, found 559.0279 (-1.3 ppm error) and a 62:38 mix of selenides **206**/**207** (60:40 dr) and doubly substituted **208** (24 mg).

Lab Book Reference: JCS-7-80

(4*R*,*8S*,8*S*)-8-methoxy-7-methyl-3,4,4,5,8,8-hexahydronaphthalen-1(2H)-one 209



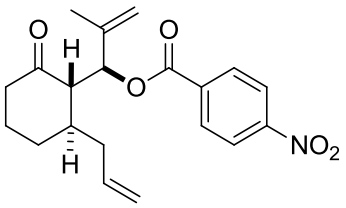
209

Iodomethane (0.17 mL, 397 mg, 2.8 mmol, 8.3 eq) was added in one portion to a stirred suspension of decalin **194** (60 mg, 0.336 mmol, 1.0 eq) and silver (I) oxide (642 mg, 2.8 mmol, 8.3 eq) in MeCN (1 mL) at rt. After 24 h, a further portion of iodomethane (0.34 mL, 792 mg, 5.6 mmol, 16.6 eq) and silver(I) oxide (1.28 g, 5.6 mmol, 16.6 eq) was added. After 3 d, a further portion of iodomethane (0.5 mL, 1.16 g, 8.24 mmol, 24.4 eq) was added and the resulting solution was stirred at rt for 2 d before the solvent and excess reagent were evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 8:2 hexane – EtOAc as eluent gave methylated decalin **209** (13.7 mg, 70.5 μmol, 21%) as a colourless oil, R_F (8:2 hexane – EtOAc) 0.34; IR (ATR) 2924, 2824, 1709 (C=O), 1448, 1371, 1340, 1318, 1278, 1245, 1216, 1179, 1130, 1092, 1061, 1042, 974, 915, 893, 873, 835, 775, 616, 531 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.48–5.43 (m, 1H, C=CH), 3.94 (d, J = 2.5 Hz, C*H*OMe), 3.62 (s, 3H, OMe), 2.49 (ddddd, J = 16.0, 2.5, 2.5, 2.5, 2.5 Hz, 1H, C$H_{eq}$$H_{ax}$C(O)), 2.30–1.91 (m, 7H, $CH_{eq}H_{ax}$, 2 x CH and 2 x CH_2), 1.86–1.72 (m, 5H, CH_3 and CH_2); ^{13}C (100.6 MHz, $CDCl_3$) δ 210.2 (C=O), 134.6 (*C*=CH), 124.2 (C=*C*H), 76.0 (*C*HOMe), 61.5 (OCH_3), 56.3 (C(O)*C*H), 41.8 (C(O)*C*H_2), 34.2 (CH_2), 32.4 (CH), 31.6 (CH_2), 23.7 (CH_2), 24.4 (CH_3); MS (ESI) *m/z* 217 [$(M+Na)^+$, 100]; HRMS *m/z*

calcd for $C_{12}H_{18}O_2$ $(M+Na)^+$ 217.1199, found 217.1197 (+2.6 ppm error), and RSM (32 mg, 0.18 mmol, 53%) as a colourless oil.

Lab Book Reference: JCS-7-74

(*S*)-1-((1*S*,2*R*)-2-Allyl-6-oxocyclohexyl)-2-methylallyl 4-nitrobenzoate 210

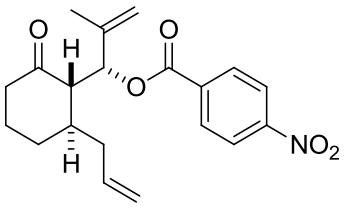


210

Para-nitrobenzoyl chloride (53 mg, 0.29 mmol, 3.0 eq) was added in one portion to a stirred solution of alcohol **197** (20 mg, 0.096 mmol, 1.0 eq) in pyridine (3 mL) at rt. After 16 h, a further portion of *para*-nitrobenzoyl chloride (353 mg, 1.90 mmol, 20 eq) was added and the resulting solution was stirred at rt for a further 16 h. Then, the reaction mixture was diluted with EtOAc (150 mL) and washed with $HCl_{(aq)}$ (2 M, 30 mL), water (2 x 20 mL), $K_2CO_{3(aq)}$ (10% w/w, 2 x 20 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 hexane – EtOAc as eluent gave **210** (30 mg, 84.0 μmol, 87%) as a bright yellow oil, R_F (7:3 hexane – EtOAc) 0.47; IR (ATR) 2926, 1724 (C=O), 1710 (C=O), 1608, 1526 (N–O), 1451, 1410, 1378, 1347, 1319, 1267 (N–O), 1097, 1014, 916, 872, 850, 783, 718, 565, 505 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 9.0 Hz, 2H, *o*-ArH-NO_2), 8.20 (d, J = 9.0 Hz, 2H, *m*-ArH-NO_2), 6.02 (d, J = 9.5 Hz, 1H, C*H*OCOAr), 5.73–5.62 (m, 1H, *H*C=CH_2), 5.11–4.96 (m, 4H, HC=CH_2 and C=CH_2), 2.83 (br d, J = 9.5 Hz, 1H, C(O)C*H*), 2.49–2.39 (m, 1H, C$H_A$$H_B$C(O)), 2.37–2.29 (m, 1H, C$H_A$$H_B$C(O), 2.21–2.03 (m, 4H, CH_2 and 2 x CH), 1.97–1.83 (m, 2H, CH_2), 1.80 (s, 3H, CH_3), 1.66–1.57 (m, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) 210.2 (C=O), 163.8 (*C*O_2Ar), 150.8 (*i*-ArNO_2), 140.9 (*p*-ArNO_2), 135.8 (H*C*=CH_2), 135.4 (*C*=CH_2), 130.9 (*o*-Ar-NO_2), 123.8 (*m*-Ar-NO_2), 117.4 (HC=*C*H_2), 116.2 (C=*C*H_2), 77.4 (H*C*OCOAr), 57.4 (C(O)*C*H), 40.5 (C(O)*C*H_2), 37.3 (CH), 37.1 (CH_2), 25.1 (CH_2), 22.4 (CH_2), 17.3 (CH_3); MS (ESI) 380 [$(M+Na)^+$, 100]; HRMS *m/z* calcd for $C_{20}H_{23}NO_5$ $(M+Na)^+$ 380.1468, found 380.1460 (+ 2.7 ppm error).

Lab Book Reference: JCS-7-15

(*R*)-1-((1*S*,2*R*)-2-allyl-6-oxocyclohexyl)-2-methylallyl 4-nitrobenzoate 211

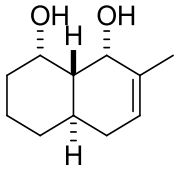


211

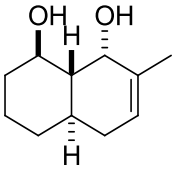
Para-nitrobenzoyl chloride (56 mg, 0.28 mmol, 3.0 eq) was added in one portion to a stirred solution of alcohol **198** (21 mg, 0.10 mmol, 1.0 eq) in pyridine (3 mL) at rt. After 16 h, a further portion of *para*-nitrobenzoyl chloride (373 mg, 2.0 mmol, 20 eq) was added and the resulting solution was stirred at rt for a further 16 h. Then, the reaction mixture was diluted with EtOAc (150 mL) and washed with $HCl_{(aq)}$ (2 M, 30 mL), water (2 x 20 mL), $K_2CO_{3(aq)}$ (10% w/w, 2 x 20 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 7:3 hexane – EtOAc as eluent gave **211** (27 mg, 76 μmol, 75%) as a bright yellow oil, R_F (7:3 hexane – EtOAc) 0.42; IR (ATR) 2937, 1722 (C=O), 1716 (C=O), 1608, 1526 (N–O), 1439, 1411, 1347, 1320, 1268 (N–O), 1171, 1100, 1051, 1014, 995, 943, 915, 873, 859, 841, 784, 718, 600, 567, 506 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27–8.23 (m, 2H, 2 x *o*-ArH-NO_2), 8.16–8.12 (m, 2H, 2 x *m*-ArH-NO_2), 5.99 (d, J = 10.5 Hz, 1H, C*H*OCOAr), 5.75–5.62 (m, 1H, C*H*=CH_2), 5.27–5.04 (m, 4H, CH=CH_2 and C=CH_2), 2.77 (d, J = 10.5 Hz, 1H, C(O)C*H*), 2.61 (ddd, J = 14.0, 12.5, 7.0 Hz, 1H, CH), 2.31–2.24 (m, 1H, CH), 2.13–1.83 (m, 6H, 3 x CH_2), 1.74 (s, 3H, CH_3), 1.66–1.58 (m, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 211.5 (C=O), 163.8 (*C*O_2Ar), 150.8 (*i*-ArNO_2), 139.9 (*p*-ArNO_2), 135.5 (H*C*=CH_2), 135.3 (*C*=CH_2), 131.0 (*o*-ArNO_2), 123.7 (*m*-ArNO_2), 118.0 (HC=*C*H_2), 117.9 (C=*C*H_2), 78.9 (H*C*OCOAr), 56.0 (C(O)*C*H), 39.3 (C(O)*C*H_2), 37.8 (CH), 37.1 (CH_2), 24.8 (CH_2), 22.5 (CH_2), 16.9 (CH_3); MS (ESI) *m/z* 380 [$(M+Na)^+$, 100]; HRMS *m/z* calcd for $C_{20}H_{23}NO_5$ $(M+Na)^+$ 380.1468, found 380.1461 (+2.2 ppm error).

Lab Book Reference: JCS-7-14

(1*S*,4*R*,8*S*,8*R*)-7-methyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene-1,8-diol 212 and (1*R*,4*R*,8*S*,8*R*)-7-methyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene-1,8-diol 213



212



213

$NaBH_4$ (13 mg, 0.35 mmol, 5.8 eq) was added in one portion to a stirred solution of decalinone **194** (11 mg, 60 μmol, 1.0 eq) in MeOH (1 mL) at rt. After 3 h, the reaction was diluted with EtOAc (30 mL) and washed with $HCl_{(aq)}$ (2 M, 1 x 5 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product which contained a 63:37 mix of diastereomeric alcohols **212** and **213** respectively. Purification by flash column chromatography on silica using 7:3 to 1:1 hexane–EtOAc gradient elution gave **212** (7 mg, 38 μmol, 63%) as a colourless oil, R_F (1:1 hexane – EtOAc) 0.33; IR (ATR) 3307 (O–H), 2926, 2864, 1417, 1357, 1326, 1274, 1172, 1125, 1107, 1086, 1045, 1001, 939, 661, 597 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.53–5.49 (m, 1H, C=CH), 4.32–4.27 (m, 1H, C*H*OH), 4.08 (d, J = 3.0 Hz, 1H, C*H*(OH)C=CH), 2.26–2.16 (m, 1H, CH(OH)C*H*), 2.05–1.95 (m, 1H, CH/CH_2), 1.92–1.84 (m, 1H, CH/CH_2), 1.79–1.77 (m, 3H, CH_3), 1.71–1.55 (m, 2H, CH/CH_2), 1.54–1.41 (m, 2H, CH/CH_2), 1.34–1.23 (m, 2H, CH/CH_2), 1.07–0.93 (m, 1H, CH/CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 134.7 (*C*=CH), 125.7 (C=*C*H), 73.7 (CHOH), 70.3 (*C*H(OH)C=CH), 45.8 (CH(OH)*C*H), 34.0 (CH_2), 33.9 (CH_2), 33.8 (CH_2), 24.9 (CH), 21.2 (CH_2), 19.4 (CH_3); MS (ESI) *m/z* 205 [$(M+Na)^+$, 100]; HRMS *m/z* calcd for $C_{11}H_{18}O_2$ $(M+Na)^+$ 205.1199, found 205.1193 (+2.2 ppm error) and diol **213** (4.1 mg, 22.5 μmol, 37%) as a white solid, mp 113.0–116.0 °C; R_F (1:1 hexane – EtOAc) 0.17; IR (ATR) 3323 (O–H), 2923, 2858, 1449, 1400, 1109, 1046, 1008, 920, 847, 793 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.55–5.51 (m, 1H, C=CH), 4.15 (d, J = 3.5 Hz, 1H, HC=CC*H*OH), 3.81 (ddd, J = 10.5, 10.5, 4.5 Hz, 1H, C*H*OH), 2.16–2.12 (m, 1H, CH_AH_B), 2.06–1.99 (m, 1H, CH_CH_D), 1.81 (m, 3H, CH_3), 1.79–1.71 (m, 3H, CH_EH_F, CH_GH_F and CH_AH_B), 1.46–1.31 (m, 4H, CH_CH_D, 2 x CH, CH_EH_F), 1.03–0.93 (m, 1H, CH_GH_F); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 134.7 (*C*=CH), 125.1 (C=*C*H), 70.2 (CHOH), 68.8 (HC=C*C*HOH), 51.0

(CH(OH)*C*H), 35.5 (CH_CH_D), 33.3 (CH_AH_B), 33.1 (CH_GH_F), 30.0 (CH), 23.7 (CH_EH_F), 21.5 (CH_3); MS (ESI) *m/z* 205 [$(M+Na)^+$, 100]; HRMS *m/z* calcd for $C_{11}H_{18}O_2$ (M+Na) 205.1199, found 205.1192 (+3.1 ppm error).

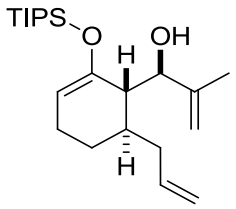
Lab Book Reference: JCS-7-50

<u>Method for growing crystals of 213:</u>

The entirety of **213** (4 mg) was placed in a small glass vial and dissolved in the minimum quantity of EtOAc (approx. 0.05 mL) and placed upright in a sealed vessel containing pentane (approx. 20 mL). After 24 h, crystals suitable for X-Ray analysis had formed on the inner vial.

Lab Book Reference: JCS-7-50

(*R*)-1-((1*S*,6*R*)-6-Allyl-2-((triisopropylsilyl)oxy)cyclohex-2-en-1-yl)-2-methylprop-2-en-1-ol 214



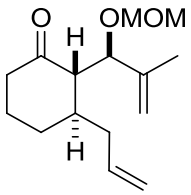
214

Triisopropylsilyl triflate (0.30 mL, 1.10 mmol, 10 eq) was added in one portion to a stirred solution of keto-alcohol **198** (21 mg, 0.11 mmol, 1 eq) in pyridine (3 mL) at rt. After 16 h, the reaction mixture was diluted with EtOAc (60 mL), washed with $HCl_{(aq)}$ (2M, 1 x 50 mL), water (2 x 50 mL), $NaHCO_3$ (sat. 50 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 hexane – EtOAc as eluent gave **214** (16.7 mg, 0.046 μmol, 42%) as a colourless oil, R_F (9:1 hexane – EtOAc) 0.44; IR (ATR) 3529 (O–H), 3074, 2943, 2927, 2894, 2867, 1736, 1716, 1666, 1641, 1494, 1463, 1437, 1415, 1383, 1368, 1331, 1317, 1289, 1274, 1246, 1191, 1167, 1069, 1012, 995, 970, 899, 881, 823, 767, 682, 657, 555, 506, 465 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ

5.79–5.68 (m, 1H, SiOC=C*H*), 5.04–4.87 (m, 5H, HC=CH_2 and C=CH_2), 4.18 (d, *J* = 10.0 Hz, 1H, C*H*OH), 3.97 (br s, 1H, OH), 2.06–1.97 (m, 5H, 2 x CH_2 and CH), 1.71 (s, 3H, CH_3), 1.64–1.50 (m, 2H, CH_2), 1.42–1.34 (m, 1H, CH), 1.14–1.04 (m, 21H, Si(*i*Pr)$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 151.0 (COSi(*i*Pr)$_3$), 145.6 (*C*=CH_2), 137.5 (H*C*=CH_2), 116.3 (C=*C*H_2), 114.4 (HC=*C*H_2), 103.6 (H*C*=COSi(*i*Pr)$_3$), 81.8 (CHOH), 45.1 (HOHC*C*H), 37.0 (CH_2), 21.8 (CH_2), 19.9 (CH_2), 18.2 (HC(*C*H_3)$_2$), 16.1 (H*C*(CH_3)$_2$), 12.7 (CH_3); MS (ESI) *m/z* 387 [(M+Na)$^+$, 100]; HRMS *m/z* calcd for $C_{22}H_{40}O_2Si$ (M+Na)$^+$ 387.2690, found 387.2685 (+1.7 ppm error).

Lab Book Reference: JCS-7-33

(2*S*,3*R*)-3-allyl-2-((*R*)-1-(methoxymethoxy)-2-methylallyl)cyclohexanone 217



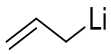
217

Chloromethylmethyl ether (0.32 mL, 348 mg, 4.4 mmol, 30 eq) was added dropwise to a stirred solution of aldol product **198** (30 mg, 0.14 mmol, 1.0 eq) and DIPEA (0.75 mL, 560 mg, 4.4 mmol, 30 eq) in CH_2Cl_2 (3 mL) at rt. The resulting solution was stirred at rt for 16 h before the addition of EtOH (3 mL). After 2 h at rt, the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with 9:1 to 8:2 hexane – EtOAc gradient elution gave **216** (29 mg, 0.11 mmol, 80%) as a colourless oil, R_F (7:3 hexane – EtOAc) 0.34; IR (ATR) 3075, 2936, 1714 (C=O), 1641, 1439, 1376, 1309, 1249, 1221, 1153, 1091, 1052, 1024, 912, 767, 718, 629, 576, 509 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70–5.58 (m, 1H, *H*C=CH_2), 5.12–4.98 (m, 4H, HC=CH_2 and C=CH_2), 4.59 (d, *J* = 7.0 Hz, 1H, OCH_AH$_B$OMe), 4.51 (d, *J* = 11.0 Hz, 1H, C*H*OMOM), 4.37 (d, *J* = 7.0 Hz, 1H, OCH$_A$$H_B$OMe), 3.25 (s, 3H, OCH_3), 2.65 (ddd, *J* = 13.0, 13.0, 7.0 Hz, 1H, C(O)CH_AH$_B$), 2.50 (br d, *J* = 11.5 Hz, 1H, C(O)C*H*), 2.34–2.26 (m, 1H, C(O)CH$_A$$H_B$), 2.07–1.77 (m, 6H, CH/$CH_2$), 1.59 (s, 3H, CH_3), 1.55–1.48 (m, 1H, 0.5 x CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 212.8 (C=O), 141.1 (*C*=CH_2), 140.0 (H*C*=CH_2), 118.0 (C=CH_2), 117.4

(C=CH_2), 93.0 (O*C*H_2OMe), 80.4 (H*C*OMOM), 56.7 (C(O)*C*H), 56.0 (OCH_3), 38.8 (C(O)*C*H_2), 37.8 (CH), 37.0 (CH_2), 24.4 (CH_2), 22.6 (CH_2), 15.8 (CH_3); MS (ESI) *m/z* 275 [$(M+Na)^+$, 100], HRMS *m/z* calcd for $C_{15}H_{24}O_3$ $(M+Na)^+$ 275.1618, found 275.1616 (+0.5 ppm error).

Lab Book Reference: JCS-7-35

Allyllithium



Allyl phenol ether (0.69 mL, 671 mg, 5 mmol, 1 eq) was added over 3 h *via* syringe pump to a vigorously stirred suspension of lithium metal (208 mg, 30 mmol, 6 eq) in Et_2O (10 mL) at 0 °C under argon. The resulting solution was stirred for a further 2 h at 0 °C, then titrated against a solution of 2-hydroxybenzaldehyde phenylhydrazone (49 mg, 0.23 mmol, 0.61 mL of allyllithium required, 0.38 M, 4.05 mmol, 81%).

JCS-6-50

List Of Abbreviations

Ac	Acetyl
Aq	Aqueous
Bn	Benzyl
Boc	Tertiary-butyloxycarbonyl
Botc	Tertiary-butyloxythiocarbonyl
br	Broad
Bu	Butyl
Bz	Benzoyl
CIPE	Complex induced proximity effect
cm^{-1}	Wavenumber
CSP-HPLC	Chiral stationary phase high pressure liquid chromatography
δ	Chemical shift
d	Doublet
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
E^+	Electrophile
ESI	Electrospray ionisation
eq	Equivalents
er	Enantiomeric ratio
Et	Ethyl
g	Gram(s)
h	Hour
HRMS	High resolution mass spectrometry
Hz	Hertz

*i*Pr	Isopropyl
IR	Infrared
J	Coupling constant in hertz
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazide
M	Molar
M^+	Parent ion
m	Multiplet
*m*CPBA	*meta*-chloroperbenzoic acid
Me	Methyl
mg	Milligram
min	Minutes
mL	Millilitre
mol	Mole
MOM	Methoxymethyl ether
mp	Melting point
MS	Mass spectrometry
Ms	Mesyl
m/z	Mass to charge ratio
*n*Bu	Normal-butyl
NCS	*N*-chlorosuccinimide
NMR	Nuclear magnetic resonance
Ph	Phenyl
PMB	*para*-methoxybenzyl
ppm	Parts per million
Pr	Propyl
R	Undefined group

R_F	Retention factor
RSM	Recovered starting material
rt	Room temperature
s	Singlet
*s*Bu	Secondary-butyl
TBS	Tertiary-butyldimethylsilyl
TBDMS	Tertiary-butyldimethylsililyl
TIPS	Triisopropylsilyl
*t*Bu	Tertiary-butyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine

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