Stereoselective Organoborate Rearrangement Reactions

By

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Abstract

This thesis describes the use of organoborate rearrangement reactions to generate quaternary carbon centres, with the ultimate goal of exploring new procedures for the asymmetric synthesis of chiral quaternary carbon centres.

Chapter One: this chapter contains a historical review of the use of organoboranes in organic synthesis, focusing mainly on the use of boronic esters in asymmetric organic synthesis.

Chapter Two: this chapter focuses on attempts at developing a catalytic method for the generation of quaternary stereocentres using migration reactions of boronic esters with *n*-butyllithium in the presence of chiral catalysts. This study showed that the reaction is stoichiometric in the absence of the Lewis acid. However, there were strong indications of catalytic turn over in some experiments.

Chapters Three and Four: these chapters focus on attempts at designing a chiral version of the DCME reaction using sulfur compounds. **Chapter Three** focuses on attempts at evaluating a heterocyclic system, specifically a dithiane, as a stereocontrol agent in its reaction with trialkylboranes. The study showed that using 2-methoxy-1,3-dithiane-oxide achieved formation of the double and triple migration product but in poor yield. **Chapter Four** contains a detailed investigation into the synthesis and evaluation of non-cyclic sulfur compounds such as sulfoxides, sulfoximines, sulfilimines and sulfones for generation of chiral tertiary alcohols. The study of the reaction of dichloromethyl phenyl sulfoxide with trialkylboranes showed a new type of aldol-like reaction. This reaction was utilised to synthesise a series of new compounds. Also, the study of the reaction of dichloromethyl-*p*-tolyl sulfone with trialkylboranes showed a new type of reaction by replacing the hydrogen with the alkyl group from the trialkylborane. Finally, the study of the reaction of *N*-methyl-*S*-(dichloromethyl)-*S*-phenylsulfoximine with trialkylboranes showed production of the desired triple migration product in moderate to very good yield.

I dedicate this thesis to

Imam Al-Mahdi

Table of Contents

Chapter Five: Future Work

Chapter Six: References

Abbreviations

APCI	Atmospheric pressure chemical ionisation
app	Apparent
aq	Aqueous
Ar	Unspecified aryl substituent
9-BBN	9-Borabicyclo[3.3.1]nonane
Bn	Benzyl
b.p.	Boiling point
BHC	*t*-Butyl hypochlorite
br	Broad
Bu	Butyl
Cat.	Catalytic
CI	Chemical ionisation
Cp	Cyclopentyl
Cy	Cyclohexyl
d	Doublet
DCM	Dichloromethane
DCME	Dichloromethyl methyl ether
dd	Doubled doublet
ddd	Doubled doubled doublet
decomp	Decomposition
DEPT	Distortionless Enhancement by Polarisation Transfer
DMF	*N,N*–Dimethylformamide
DMSO	Dimethyl sulfoxide
dt	Doubled triplet
e.e.	Enantiomeric excess
EI+	Electron impact
equiv.	Equivalent(s)
ES	Electrospray
Et	Ethyl
EWG	Electron withdrawing group

g	Gram(s)
GC	Gas chromatography
h	Hour(s)
HPLC	High performance/pressure liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
i-Pr	Isopropyl
lpc	Isopinocampheyl
IR	Infrared
J	Coupling constant (in Hz)
L	Litre
LDA	Lithium diisopropylamide
LiDBB	Lithium-4,4-di-tert-butylbiphenyl radical anion
LiHMDS	Lithium bis(trimethylsilyl)amide
lit.	Literature
LiTMP	Lithium 2,2,6,6-tetramethylpiperidide
LR	Low resolution
m	Multiplet
m-CPBA	3-Chloroperoxybenzoic acid
Me	Methyl
mg	Milligram(s)
min	Minute(s)
mL	Millilitre(s)
mm	Millimeter(s)
mmol	Millimole(s)
m.p.	Melting point
MS	Mass spectrometry
NaHMDS	Sodium bis(trimethylsilyl)amide
n-BuLi	Normal butyllithium
NCS	*N*-Chlorosuccinimide
NMO	4-Methylmorpholine *N*-oxide

NMR	Nuclear magnetic resonance
OTf	Trifluoromethanesulfonate
PDC	Pyridinium dichromate
pent	Pentet
Ph	Phenyl
ppm	Parts per million
q	Quartet
quat C	Quaternary carbon
R	Undefined group
r.t.	Room temperature
sec	Secondary
sept	Septet
sex	Sextet
t	Triplet
TBAF	Tetra-*n*-butylammonium fluoride
tert	Tertiary
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TFEF	Trifluoroethyl formate
Thexyl	2,3-Dimethyl-2-butyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMP	2,2,6,6-Tetramethylpiperidine
TPAP	Tetrapropylammonium perruthenate
UV	Ultraviolet

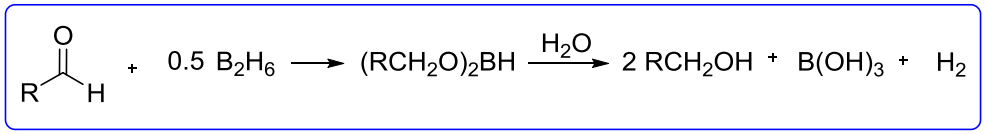
Chapter One
Introduction

1.1 Introduction

Asymmetric synthesis is fast becoming a major aspect of modern organic chemistry. The importance of enantiomerically-pure or enriched compounds in synthetic organic chemistry, natural product chemistry, medicinal chemistry, agricultural chemistry, pharmaceutical and agricultural industries has been one driving force in the investigation of improved control over the stereochemical output of organic reactions.[1] Boranes and boronic esters are among the most widely used reagents in organic synthesis and have been extensively used for asymmetric synthesis. The progress in asymmetric organic synthesis using organoboranes was made mainly by Matteson[2] and Aggarwal[3] who utilised boronic esters and trialkylboranes to establish asymmetric methods to produce chiral secondary and tertiary alcohols. In spite of this progress, the methods are still far from being general for the synthesis of quaternary stereogenic centres. The work described in this thesis is an attempt to develop and optimise general procedures, both catalytically and stoichiometrically, *via* boronic esters and alkylboranes. The following is a literature review on the use of organoboron compounds in asymmetric organic synthesis.

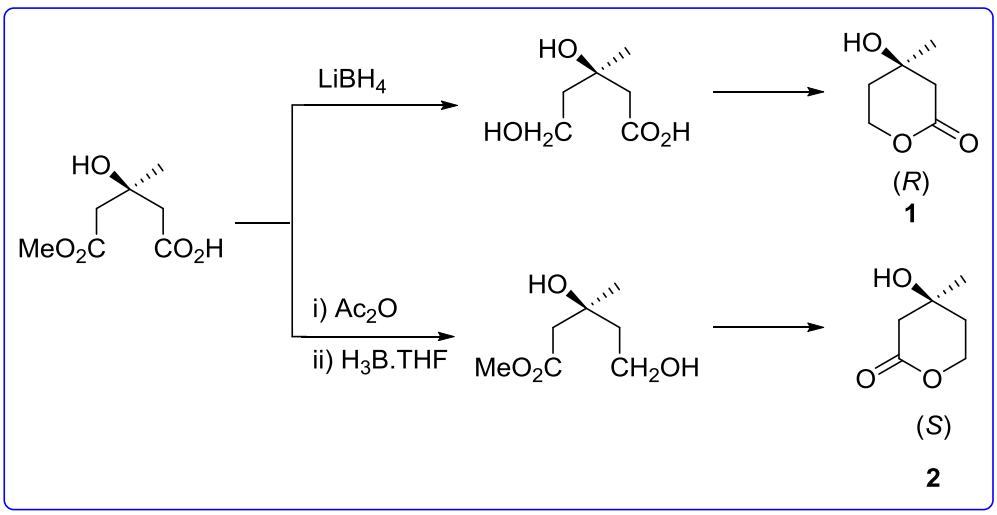
1.2 Boranes as Reducing Agents

The simplest hydrogen compounds of boron, such as B_2H_6, B_4H_{10}, B_5H_{11} and $B_{10}H_{14}$ were first isolated and characterised by Alfred Stock over the period between 1910 – 1930.[4] However, boranes were not examined much as reagents in organic chemistry until 1939.[5] Brown and his colleagues observed that aldehydes and ketones could react with diborane at 0 °C to produce alkoxyboranes and the corresponding alcohols after hydrolysis (**Scheme 1.1**).



Scheme 1.1: Reduction of Aldehydes by Diborane

During and after World War II, Brown was able to prepare several hydride reducing agents. These include the very gentle sodium borohydride, and the more powerful lithium aluminium hydride.[6] This variety gives the organic chemist the ability to reduce most functional groups selectively in the presence of other groups. A good example for the selective reduction is the synthesis of (*R*)-mevalonolactone (**1**) and (*S*)-mevalonolactone (**2**).[7]



Scheme 1.2: Selective Reductions by two Different Borane Reagents

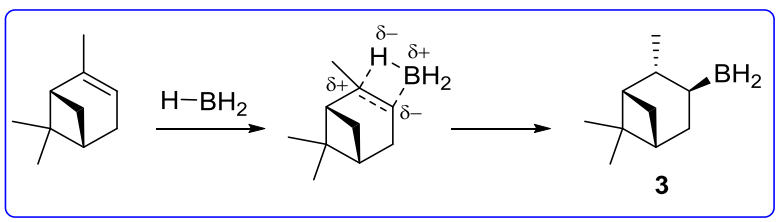
Reduction of a carboxylic acid group can be achieved selectively first by converting the acid into an anhydride derivative and using borane to obtain, after cyclisation, compound **2**. This is because the borane is more effective for reduction of the anhydride than for the ester group. In contrast, the reduction of the ester group in the

presence of the carboxylic acid group can be achieved by using lithium borohydride to produce, after cyclisation, compound **1** (**Scheme 1.2**).

1.3 Alkylboranes

Frankland synthesised the first trialkylborane in 1859 by the reaction of diethylzinc with triethoxyborane. In 1956, the first hydroboration of olefins was recorded in an attempt to enhance the reducing power of sodium borohydride in diglyme by adding anhydrous aluminium chloride to the solution.[8,9] It was observed that this addition led to the hydroboration of olefins present in the substrate. Changing the Lewis acid to boron trifluoride etherate led to more effective hydroboration of olefins in THF. Preparation of complexes of boranes with THF or methyl sulfides, now commercially available in a wide range of different concentrations, made the hydroboration of olefins cleaner, with no production of inorganic salts or other undesirable side products.[10]

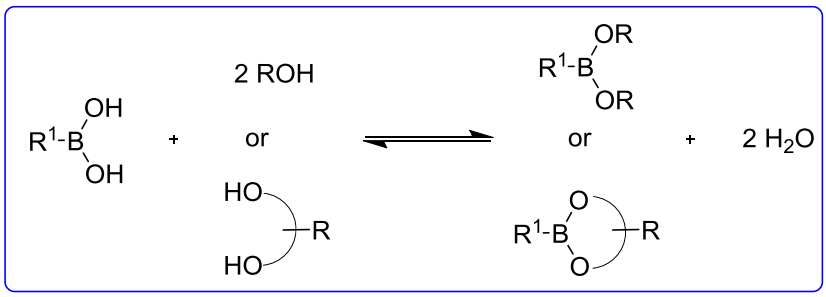
Several interesting features have been observed over the course of the investigation of the hydroboration reaction: first, the addition proceeds to put boron at the least hindered end of a double bond; second, the reaction involves concerted *cis*-addition of the H-B bond and the addition proceeds from the less-hindered face of the double bond; third, there is no rearrangement of the carbon skeleton. These features mean that the outcome of hydroboration is highly predictable. For example, the hydroboration of α-pinene leads to only one possible hydroborated isomer, **3** (**Scheme 1.3**).[11]



Scheme 1.3: Addition of Borane to an α-Pinene

1.4 Boronic Esters[12–14]

Like alkylboranes, boronic esters are broadly useful synthetic intermediates for accomplishing carbon-carbon and carbon-heteroatom bond formations stereoselectively.[2] The boronic esters are easier to handle than boronic acids as they are less polar. They are easily prepared by replacement of the hydroxyl groups of boronic acids by alkoxy, aryloxy or alkylenedioxy groups (**Scheme 1.4**). Because the reaction is in equilibrium, ester formation should be driven by removing the water produced either using azeotropic distillation or, alternatively, a dehydrating agent such as magnesium sulfate or molecular sieves.[12]



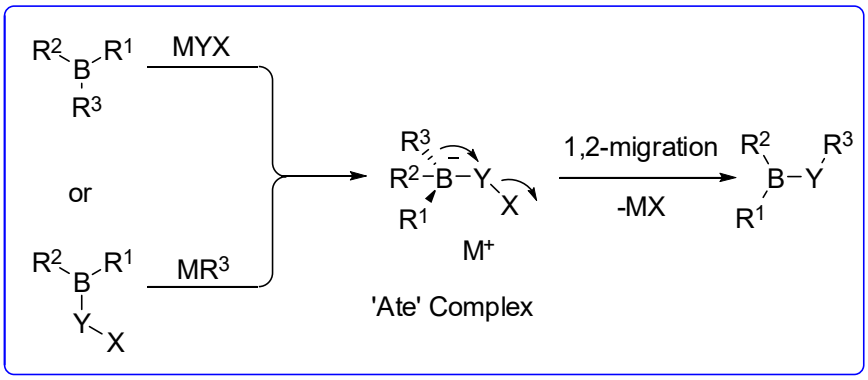
Scheme 1.4: Synthesis of Boronic Esters

Also, synthesis of boronic esters can be achieved by transesterification of smaller dialkyl boronic esters with removal of the more volatile alcohol by-product by distillation driving the exchange process. Air-sensitive alkylboronic acids can be converted into their corresponding cyclic esters by an alternative method which involves treatment of a diol with lithium trialkylborohydrides.[13]

1.5 1,2-Metallate Rearrangement of Boron 'Ate' Complexes

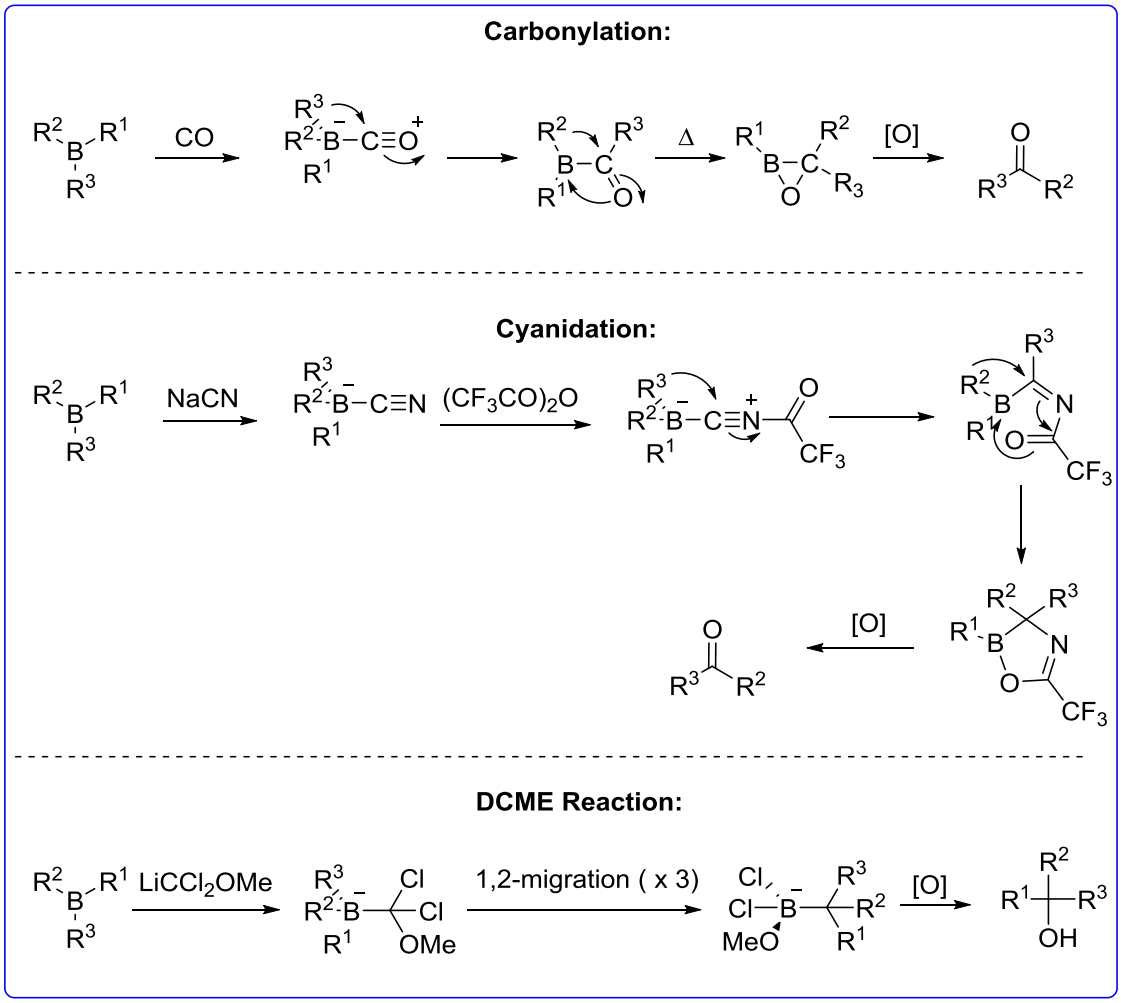
Trialkylboranes and boronic esters are classified as strong electrophiles because boron in such compounds suffers from electron deficiency in the sense of the Lewis octet

theory. The boron atom in these compounds is sp^2 hybridised and the vacant 2*p*-orbital lies at right angles to the three boron-substituent bonds.[15] Addition of nucleophiles, such as carbanions, to a boron compound forms an unstable tetracoordinate 'ate' complex which undergoes a 1,2-metallate rearrangement if one of the substituent groups has a leaving group on the attached carbon atom. 1,2-Migration of one of the groups on boron with concomitant expulsion of the leaving group gives the migrated product. The migration occurs when the alkyl migrating group aligns *anti*-periplanar to the leaving group. This transformation usually takes place with retention of configuration of the alkyl migrating group (**Scheme 1.5**).[2,6,10,11,16]



Scheme 1.5: 1,2-Metallate Rearrangement of Boron 'Ate' Complex

Depending on the reaction conditions and the nature of "YX", which might have one, two or three leaving groups, the reaction can be utilised to achieve one, two or three 1,2-migrations respectively. Subsequent oxidation produces aldehydes, ketones or tertiary alcohols as the products. **Scheme 1.6** shows some selected examples of such transformations.[11]

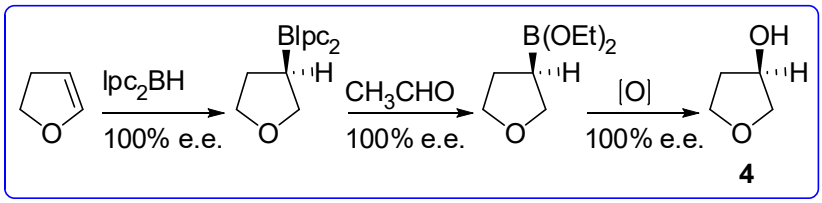


Scheme 1.6: Selected Examples of 1,2-Migration Reactions

1.6 Asymmetric synthesis *via* Organoboranes

The two enantiomers of a chiral compound are differently recognised in biological systems. For many pharmaceuticals, it has been shown that often only one enantiomer has desirable biological activity, such as natural amino acids, which are all L-enantiomers, and the other is either totally inactive or toxic. In order to have a highly biologically active compound, it is highly desirable to synthesise the target compound in an enantiomerically pure form, with 100% enantiomeric excess (% e.e.).[17] Preparation of chiral compounds with well-defined three-dimensional stereochemistry is called asymmetric synthesis.[18–21] Asymmetric syntheses can be classified into two

categories, enantioselective syntheses and diastereoselective syntheses. Enantioselective syntheses can be defined as when a chiral compound is synthesised from its achiral precursor using an enantioselective reagent or catalyst, while diastereoselective synthesis is the formation of a new stereogenic centre influenced by a stereogenic centre already present in the molecule. A vast number of new and increasingly efficient asymmetric synthesis methods have been developed during the last decade.[17] Organoboranes and boronic esters are extensively studied as useful synthetic intermediates since they can be converted into almost every class of functionality present in organic molecules with complete stereospecificity. In 1961, Brown was the first to report a non-enzymatic asymmetric synthesis when hydroboration-oxidation of alkenes using (–)-diisopinocampheylborane (Ipc_2BH) achieved a very high level of enantioselection in formation of the corresponding alcohols (**4**) (**Scheme 1.7**).[22,23]

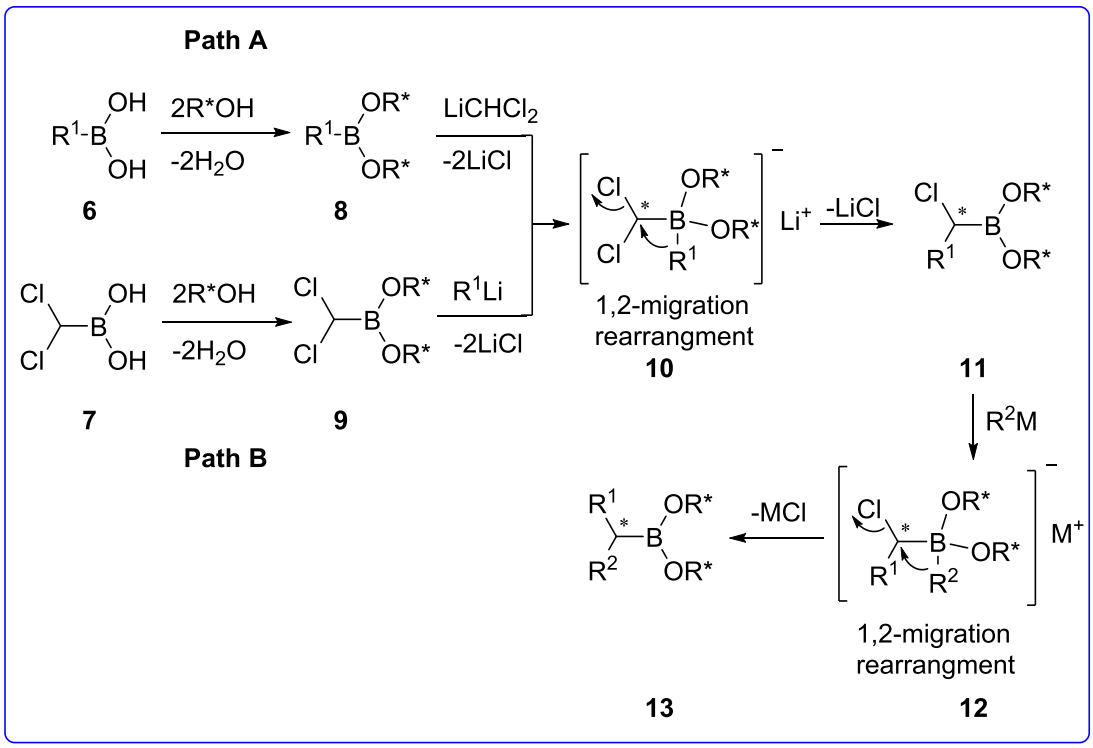


Scheme 1.7: The First Non-Enzymatic Asymmetric Synthesis

However, this method is not appropriate for the synthesis of tertiary alcohols, because hydroboration of a double bond delivers the boron moiety to the less-hindered carbon. Almost twenty years later, Matteson discovered a complementary route to chiral boronic esters (*vide infra*).[24–26] Also, the past decade has seen the rapid development of homologation and alklylation of organoboranes and boronic esters by 1,2-metallate rearrangement. What follows is a description of these discoveries in detail.

1.7 Matteson's Methodology (Substrate-Control)

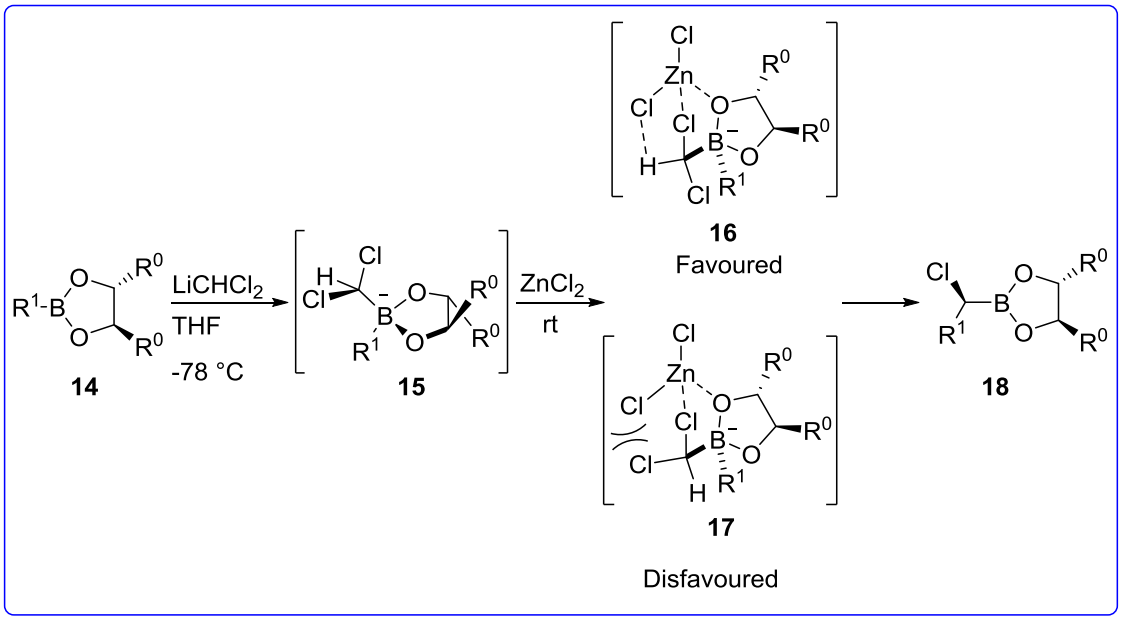
Matteson opened up a wide new field in organoboron chemistry, when he utilised the 1,2-metallate rearrangement of boronic esters to achieve good levels of diastereoselectivity (10:1 to 20:1).[24–26] This diastereoselection could be achieved by three steps; firstly, synthesis of a chiral boronic ester **8** or **9**, which can be obtained by esterification of alkyl boronic acids **6** or (α,α-dichloromethyl)boronic acid **7** with a chiral diol, represented by the two R*OH groups; secondly, homologations either by insertion of a CHCl group from $LiCHCl_2$ into the chiral alkylboronic esters **8** (path A on **Scheme 1.8**) or by addition of organometallic reagents to chiral (α,α-dichloroalkyl)boronic esters **9** (path B on **Scheme 1.8**) followed by 1,2-migration rearrangement of the resulting borate complex **10**; and third, alkylation by reactions of the chiral (α-alkyl)boronic ester **11** with Grignard reagents, which ultimately produce secondary boronic esters **13** *via* **12** (**Scheme 1.8**).



Scheme 1.8: Matteson's Homologation-Alkylation *via* Boronic Esters

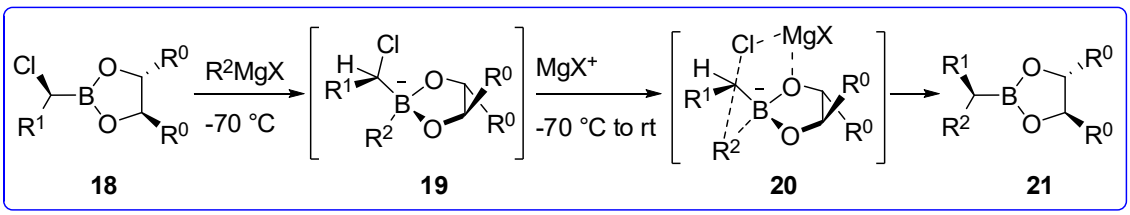
Several observations were made during Matteson's study of such reactions.[27] Use of pinanediol boronic esters meant that the two paths, A and B, did not give the same stereochemical outcome. Path A was more stereoselective than path B. This is presumably because different diastereomeric mixtures of the borate **10** are formed in each case. This issue was tackled by using C_2-symmetric boronic esters, which led to the same diastereomeric 1,2-migration rearrangement for both paths A and B with high diastereoselection**.** The rearrangement takes place when the reaction is warmed to room temperature. The replacement of chloride by an alkyl group, in the third step of alkylation with Grignard reagents, occurs with inversion of the stereochemistry at the carbon atom, and with retention of stereochemistry of the migrating alkyl group (R^2). This homologation-alkylation process can be repeated to prepare several contiguous stereogenic centres. The opposite stereoisomers can be achieved, simply, by changing the order of introduction of the alkyl groups.

More importantly, Matteson discovered that the presence of zinc chloride as a catalyst in the homologation step led to very high diastereoselectivity (≈100:1) in the borate complex rearrangement when warmed to room temperature.[26] The explanation of these results was that the zinc chloride coordinates with the less-hindered oxygen and also with the departing chloride **16** (**Scheme 1.9**). Meanwhile, it is thought that a zinc chloride moiety interacts with the electrophilic C-H, which gives more stabilisation of the proposed transition state. Consequently, zinc chloride both orientates the R^1 group and promotes it to migrate and the coordinated chloride to leave. Midland has demonstrated this favoured transition state by his computational study at the RHF/3-21G level, which showed that the favoured transition state **16** is 52.7 kJ/mol lower in energy than **17.**[28]



Scheme 1.9: Effect of Zinc Chloride Addition on the 1,2-Migration

Alkylation of **18** by Grignard reagent R^2MgX leads to the 'ate' complex **19** (**Scheme 1.10**). Similar to zinc chloride, MgX^+ coordinates to the less hindered oxygen and to the remaining chloride and leads to transition state **20**, which rearranges to produce **21**.



Scheme 10: Effect of Grignard Reagent on the 1,2-Migration

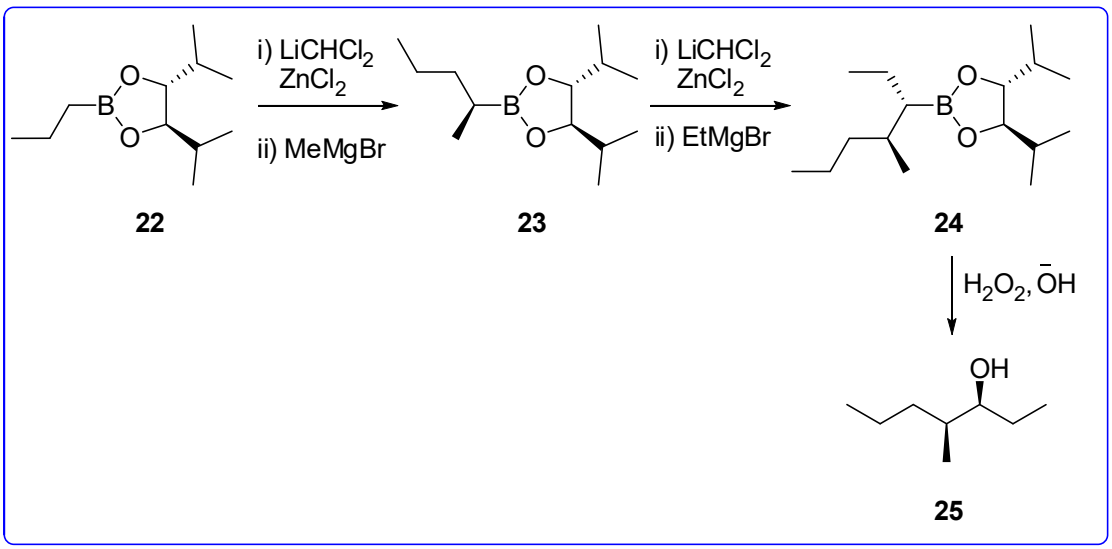
Enantiopure boronic esters could be utilised in this method to install, sequentially, a series of stereocentres. The following is a brief report on application of Matteson's methodology for the synthesis of natural products.

1.7.1 Utilisation of Matteson's Methodology

Matteson has employed his methodology to synthesise several natural products. In the beginning, insect pheromones were chosen as simple targets because they had already been synthesised and fully characterised.

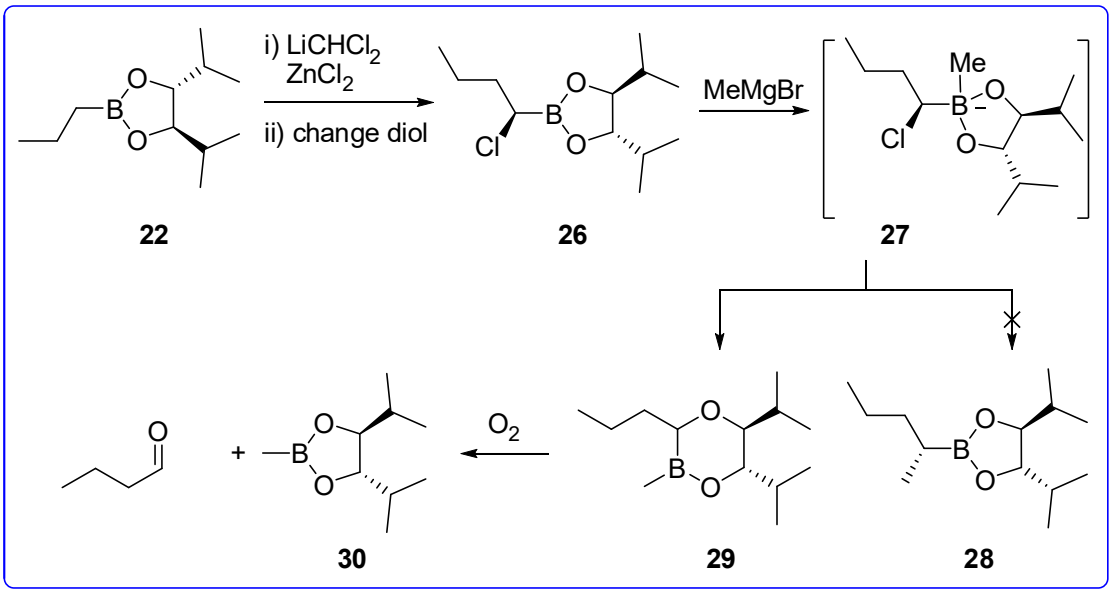
1.7.1.1 Synthesis of Elm Bark Beetle Scolytus Multistriatus and Southeast Asian Ponerine Ant Leptogenys Diminuta Pheromones (25 and 33)

An useful example of the application of Matteson's methodology is the synthesis of elm bark beetle *Scolytus multistriatus* (**25**) and Southeast Asian Ponerine ant *Leptogenys diminuta* (**33**) pheromones.[29–31] High stereoselection was achieved for the two diastereomers of **25** and **33.** The (3*S*,5*S*)-4-methyl-3-heptanol **25** was synthesised by homologation of boronic ester (4*R*,5*R*)-4,5-diisopropyl-2-propyl-1,3,2-dioxaborolane **22** with (dichloromethyl)lithium followed by treatment with zinc chloride and then methylation of the resulting boronic ester with methylmagnesium bromide to produce boronic ester **23**. Homologation of **23** and ethylation with ethylmagnesium bromide produced **24**. Peroxidic oxidation of the boronic ester **24** gave **25** with very high diastereoselectivity (≈700:1) (**Scheme 1.11**).[31]



Scheme 1.11: Synthesis of Elm Bark Beetle Pheromone **25**

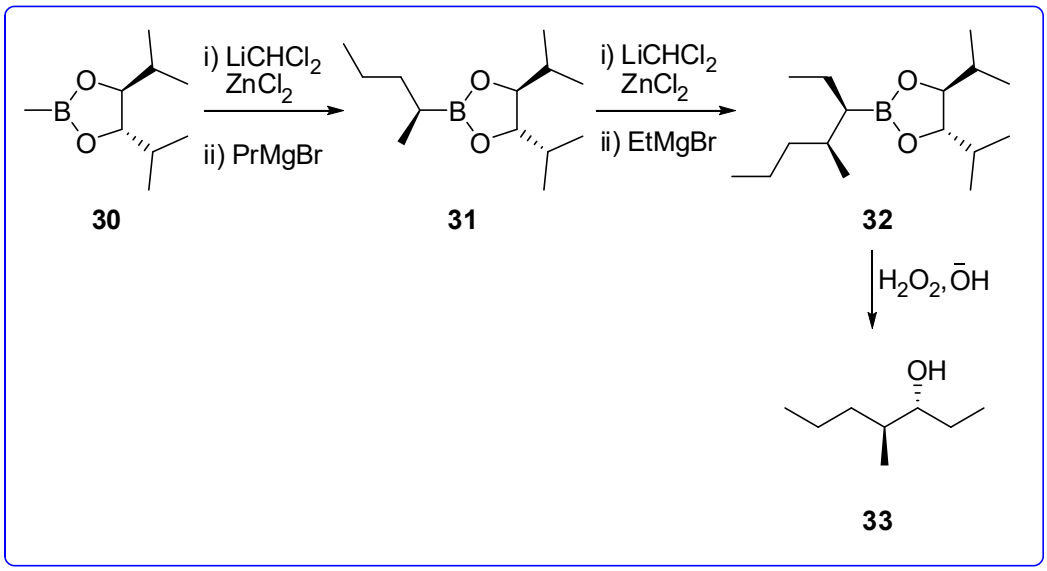
In an attempt to synthesise the Southeast Asian Ponerine ant *Leptogenys diminuta* pheromone **33**, repeating the synthesis and changing the diol stereochemistry before the second homologation/alkylation and oxidising the result, in principle, should give the target product **33**.[29] Contrary to expectations, methylation of **26** failed to produce **28** but produced butyraldehyde and (*S*)-DIPED methylboronate **30** instead, as main products. The separation and characterisation of a very air-sensitive compound **29** led Matteson to suggest that the strong steric interactions of intermediate borate **27** compel oxygen, which is *anti* to Cl, to migrate to form **29** (**Scheme 1.12**).



Scheme 1.12: Possible Effect of Oxygen Migration on the 1,2-Metallate Rearrangement

Alternatively, the (3*R*,5*S*)-4-methyl-3-heptanol **33** was prepared simply by altering the order of addition of the component reagents.[30] Compound **33** was synthesised by homologation of **30** with (dichloromethyl)lithium followed by addition of propylmagnesium bromide to produce **31**, which has the opposite configuration of the chiral auxiliary and same *S*-configuration as **23**. Further homologation with (dichloromethyl)lithium and ethylation with ethylmagnesium bromide followed by

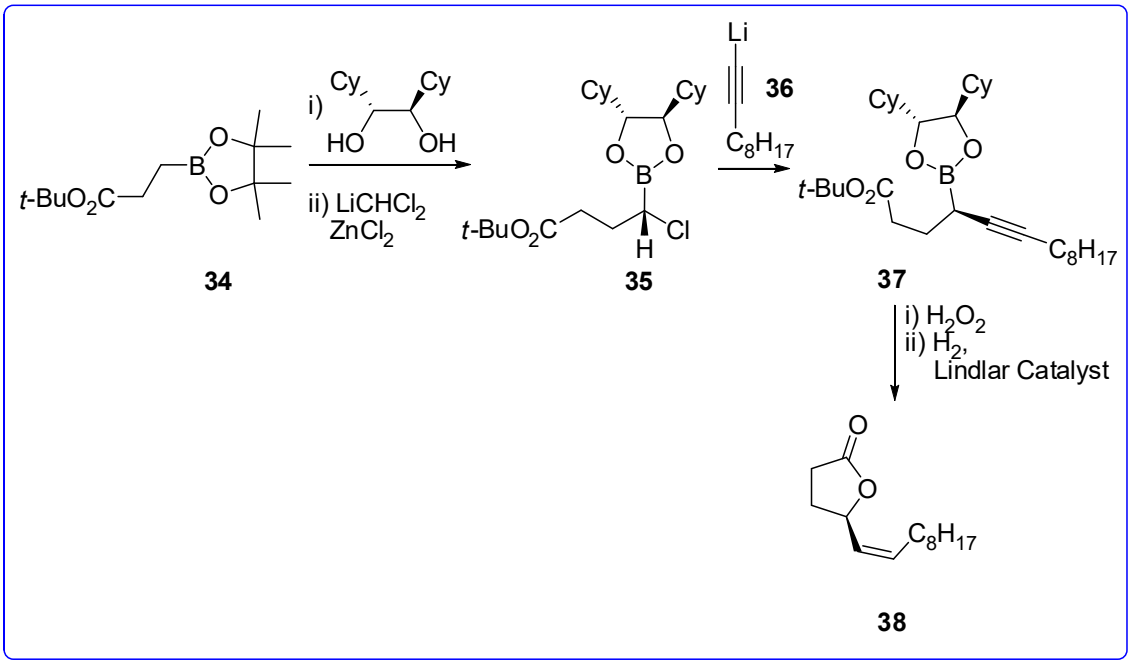
oxidation gave **33** (500:1, **33:25**) (**Scheme 1.13**). Similarly, the two other stereoisomers, (3*S*,4*R*) and (3*R*,4*R*), were synthesised.



Scheme 1.13: Synthesis of Southeast Asian Ponerine Ant Pheromone **33**

1.7.1.2 Japanese Beetle Pheromone Popillia japonica (38)

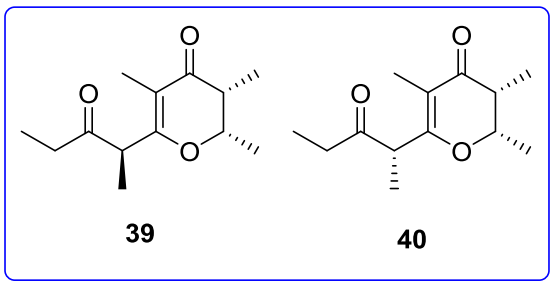
Matteson has also demonstrated homologation/alkylation methodology in the synthesis of Japanese beetle pheromone **38 (Scheme 1.14)**,[32] which was previously synthesied with high enantiomeric purity and fully characterised by Midland.[33] Boronic ester **34** was ester exchanged to give chiral ester and then homologated with (dichloromethyl)lithium in the presence of zinc chloride to produce (α-chloroalkyl)boronic ester **35** as a single diastereoisomer. Compound **35** was alkynylated with lithiated alkyne **36** to produce the desired boronic ester **37** which was readily converted into the target product **38**.



Scheme 1.14: Synthesis of Japanese Beetle Pheromone **38**

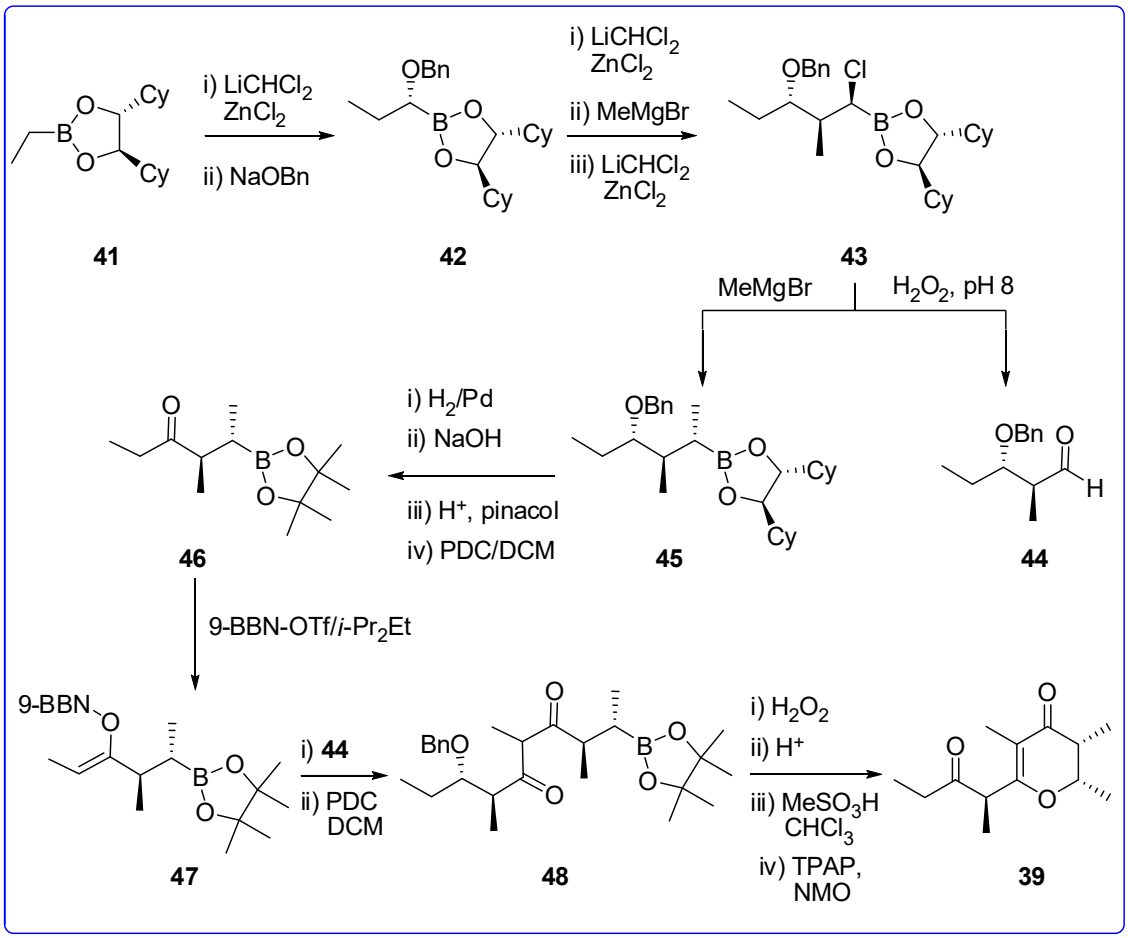
Matteson's synthesis methodology has become an economically competitive route and it has been recently used in commerical production of **38**.[2]

1.7.1.3 (2S,3R,1'R)-Stegobinone (39) and 1'-Epistegobinone (40)[34]



Synthesis of stegobinone (**39**), the pheromone of the Anobiid beetle *Stegobium paniceum*, in high stereochemical purity, is a challenge because the presence of ~3% of the epimer **40** effectively neutralises its attractive effect. The synthesis of the target

compound **39** required the preparation of two key synthetic components, first the aldehyde **44** and second the ketone **46**. The synthesis began with chain extension of boronic ester **41** with (dichloromethyl)lithium followed by nucleophilic displacement of chloride with sodium benzyl oxide to make boronic ester **42**. A second chain extention of **42** with (dichloromethyl)lithium and methylation with methylmagnesium bromide followed by a further homologation with (dichloromethyl)lithium gave the precursor **43** for both intermediates, aldehyde **44** and ketone **46**. The 9-BBN enol ether **47** readily undergoes an aldol condensation with **44** to make **48**, which contains the total carbon skeleton of stegobinone (**Scheme 1.15**).

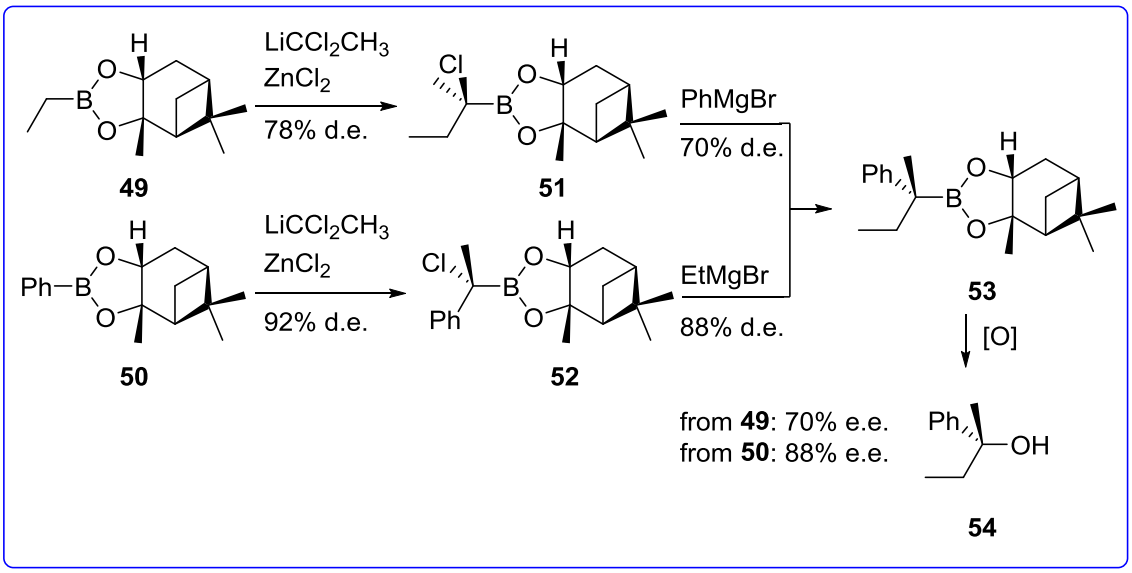


Scheme 1.15: Synthesis of (2*S*,3*R*,1'*R*)-Stegobinone

1.7.1.4 Tertiary Alcohols and Quaternary Stereocentres

Although this methodology is successful in the synthesis of secondary alcohols, limited success has been achieved for the synthesis of tertiary alcohols and quaternary carbon stereocentres.

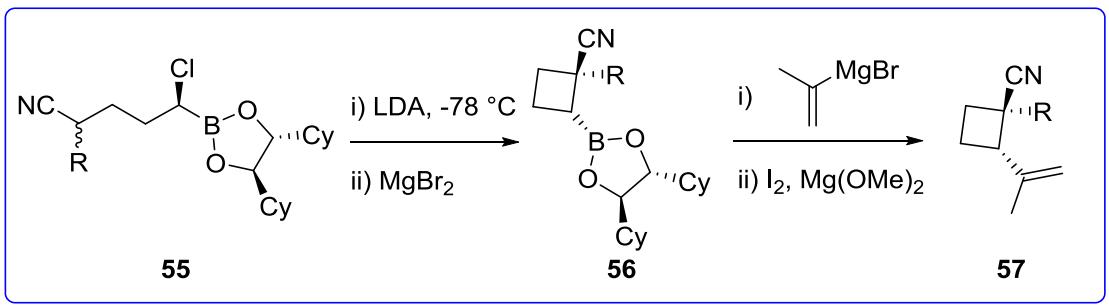
Tertiary Alcohols:[35] Unexpected results were observed in investigation of stereocontrolled assembly of pinanediol (α-chloro-*sec*-alkyl)boronic esters to synthesise tertiary alcohols. In an attempt to synthesise 2-phenyl-2-butanol **54** from two different boronic esters **49** and **50** (**Scheme 1.16**), the two starting materials were homologated with (1,1-dichloroethyl)lithium followed by introduction of the complementary ethyl or phenyl group and peroxidic oxidation. Unexpectedly, compounds **49** and **50** led to different stereochemistry of **51** and **52**, respectively. The two compounds **49** and **50** gave the same stereochemistry of **53** and **54**. The enantiomeric excesses of **54** obtained from **49** and **50** were 70% and 88% respectively.



Scheme 1.16: Synthesis of the Tertiary Alcohol

A number of boronic esters were examined, in an attempt to produce tertiary alcohols, but just a few gave useful stereoselectivity.

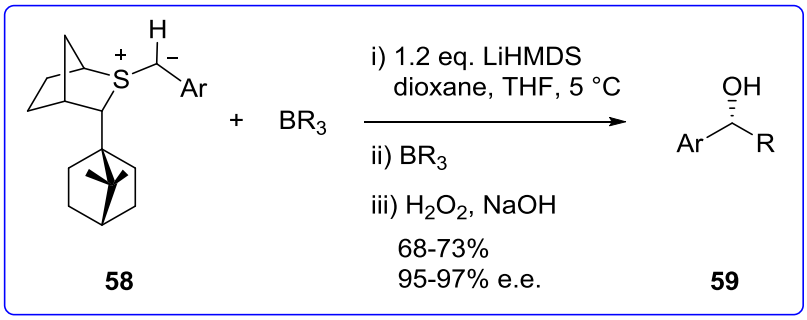
Quaternary Stereocentres:[36] There are few applications of the Matteson method to synthesise quaternary carbon stereocentres. For instance, cyclobutane **57**, containing a quaternary stereocentre, was synthesised in high stereochemical purity by the cyclisation of (1-chloro-4-cyanobutyl)boronic esters **55** to cyclobutane derivatives (**Scheme 1.17**). Compound **55** was converted into **56** by addition of LDA at –78 °C and then addition of magnesium bromide. Reaction of **56** with isopropenylmagnesium bromide followed by iodine yielded **57**.



Scheme 1.17: Synthesis of a Cyclobutane Containing a Quaternary Stereocentre

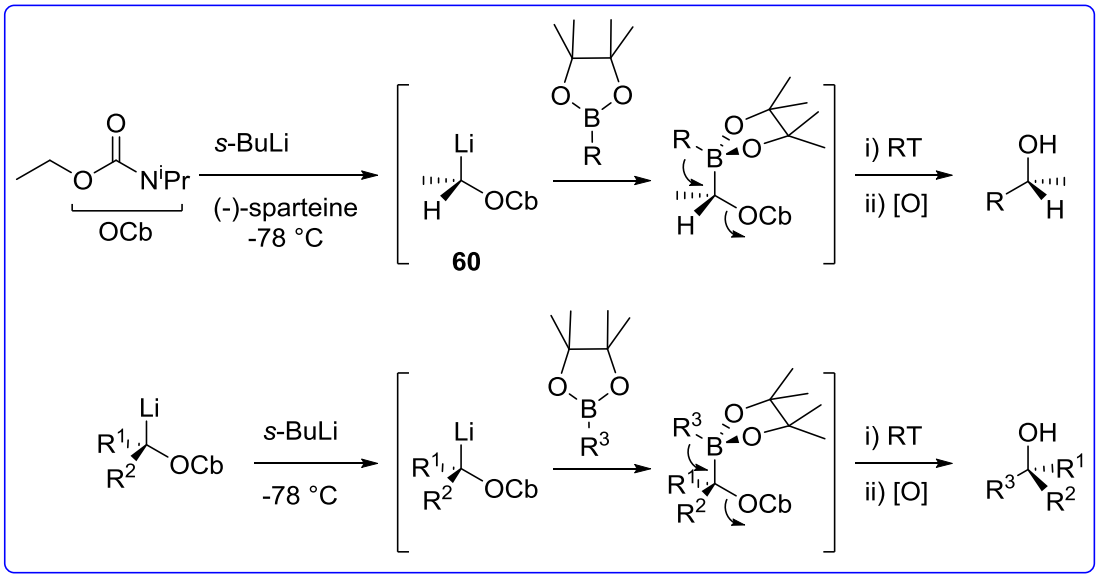
1.8 Aggarwal Methodology (Reagent-Control)

An altenative route to tertiary alcohols involves the Aggarwal methodology. Aggarwal has utlised his chiral sulfur ylides to synthesise a chiral secondary alcohols in high yeild and high e.e. The method involves homologation of chiral aryl sulfur ylides with trialkyl boranes followed by peroxidic oxidation to produce the corresponding alcohols **59** (**Scheme 1.18**).[37–40]



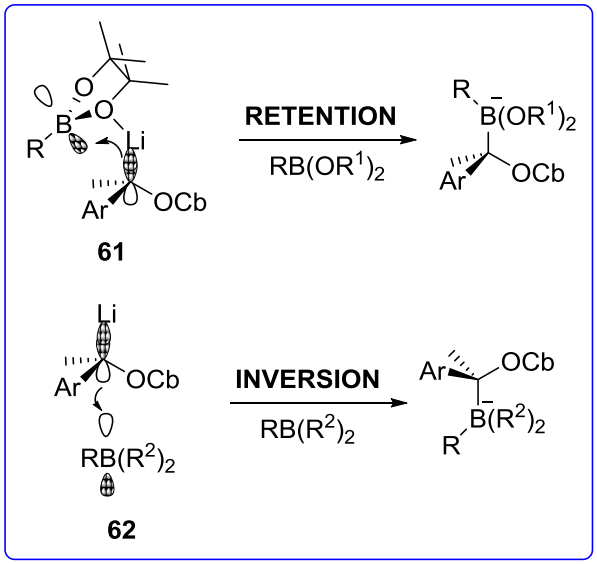
Scheme 1.18: Reactions of Chiral Sulfur Ylides with Boranes

Unfortunately, homologation of these ylides with boronic esters was not successful and gave only low enantioselectivity with borinic esters.[41] Aggarwal turned to the Hoppe carbamates to overcome these limitations. Hoppe discovered that lithiated carbamates derived from primary alcohols could be deprotonated and subsequently trapped with various electrophiles in the presence of sparteine with excellent levels of stereoselectivity. Aggarwal successfully homologated Hoppe-type[42,43] lithiated primary carbamates with boranes and boronic esters in the presence of (–)-sparteine or O'Brien's (+)-sparteine surrogate in good yields and high enantioselectivity (**Scheme 1.19**).[44] Also, excellent enantioselectivies were achieved when lithiated chiral secondary benzylic carbamates were homologated with boranes and boronic esters (**Scheme 1.19**).[3]



Scheme 1.19: Synthesis of the Chiral Secondary and Tertiary Alcohols *via* Enantioenriched Lithiated Carbamates

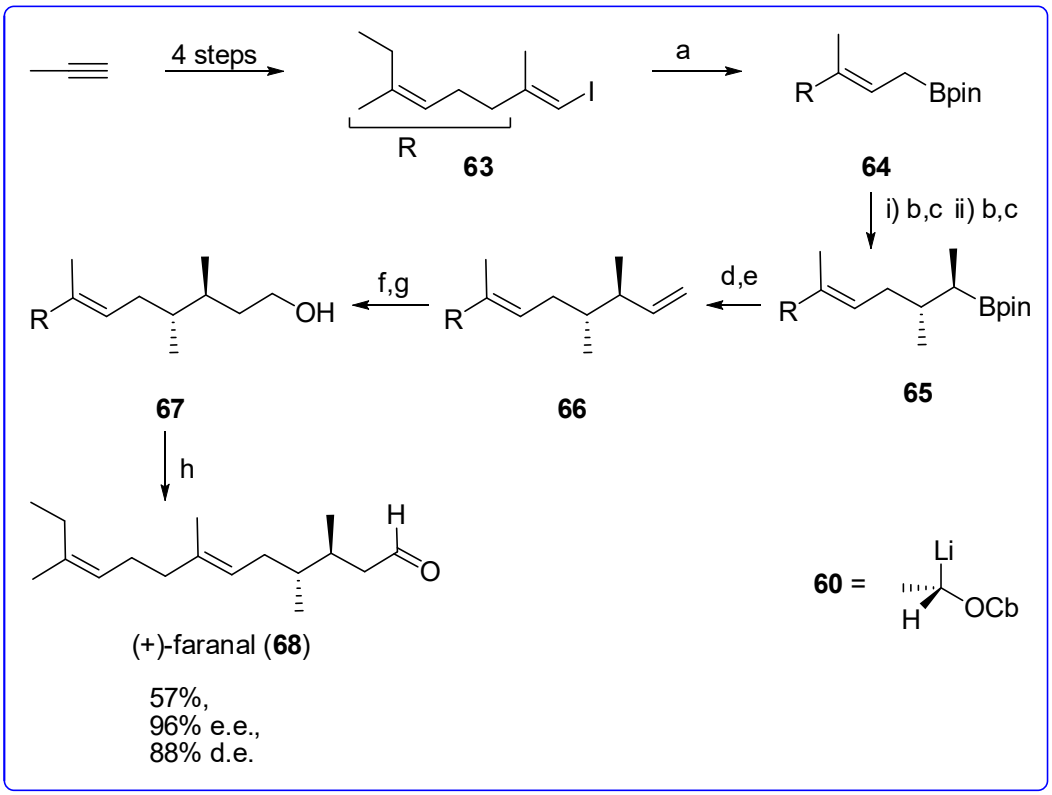
Interestingly, it was observed that the lithiated secondary carbamates complex with boronic esters with retention of stereochemistry, while borylation with boranes takes place with inversion of stereochemistry.[3,45] It has been proposed that in the case of boronic esters, the complexation of oxygen with the lithium of the lithiated carbamate **61** makes the reaction take place on the same face as the lithium. In the case of boranes, such complexation is absent and there is a significant electron density due to the partially flattened nature of the mesomerically stabilised carbanion **62**, thus, the reaction occurs on the face opposite to the lithium face (**Scheme 1.20**).



Scheme 1.20: Retention versus Inversion in the Reactions of Lithiated Carbamates with Boronic Esters and Trialkylboranes Respectively

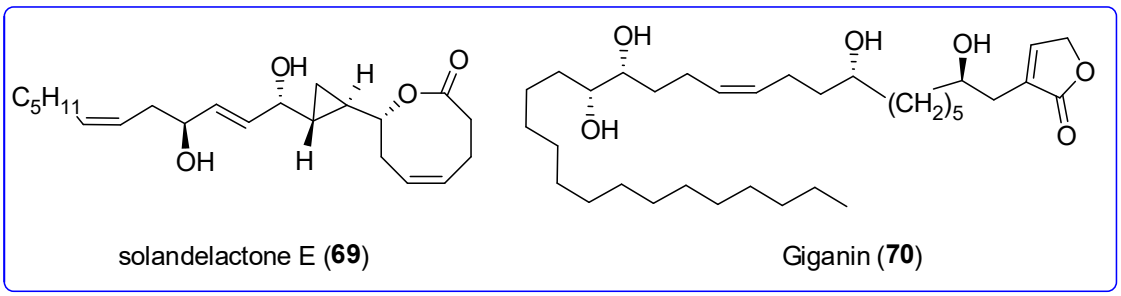
1.8.1 Selected Applications of Aggarwal's Methodology

Aggarwal has elegantly demonstrated the potential of this methodology in the synthesis of numerous natural and unnatural products. This was illustrated in the concise synthesis of insect pheromone (+)-faranal **68** (**Scheme 1.21**).[46] Compound **63** was prepared in four steps from propyne. Reaction of lithiated **63** with chloromethylpinacol boronic ester then led to the formation of compound **64**. Reaction of **64** with **60** twice gave **65**. Compound **65** was then homologated using vinyllithium in the presence of iodine to give **66** containing the carbon skeleton of the target product. Hydroboration/oxidation followed by oxidation with PDC led to **68**.

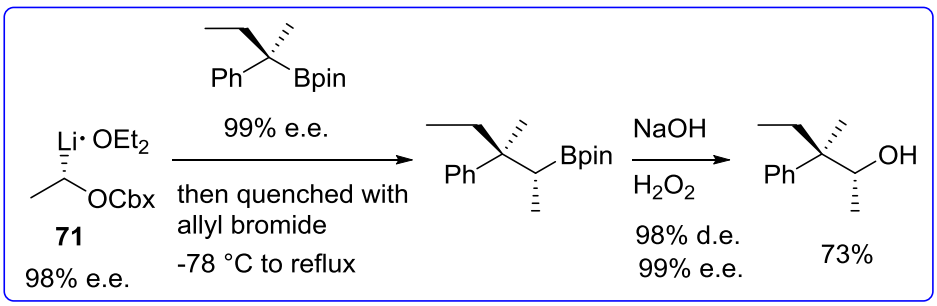


Scheme 1.21: Synthesis of (+)-Faranal, a) *t*-BuLi/Et_2O, hexane; $ClCH_2Bpin$; b) **60**/Et_2O, –78 °C; c) $MgBr_2$, 40 °C; d) vinyllithium/THF, –78 °C; e) I_2/MeONa, MeOH/r.t.; f) 9-BBN/THF g) H_2O_2/NaOH; h) PDC/DCM

Aggarwal further applied the homologation methodology to the asymmetric total synthesis of several natural products such as solandelactone E (**69**)[47] and giganin (**70**).[48]

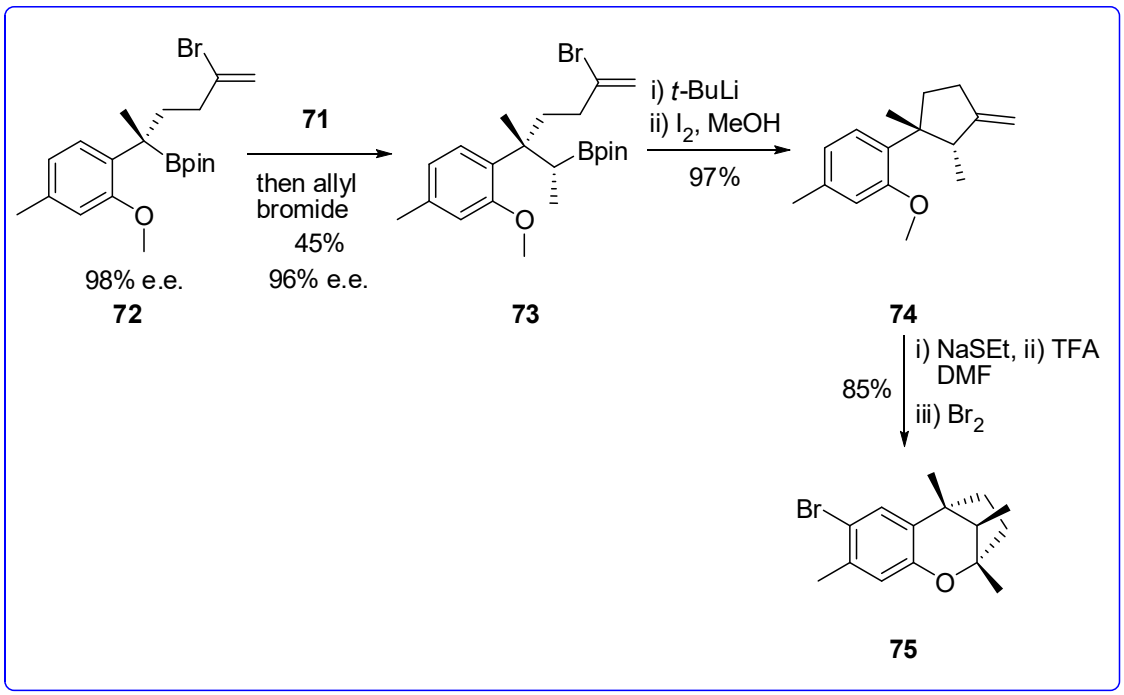


More recently, Aggarwal has developed his methodology for the synthesis of highly challenging aryl-quaternary-tertiary motifs in acyclic systems with full stereocontrol (**Scheme 1.22**).[49]



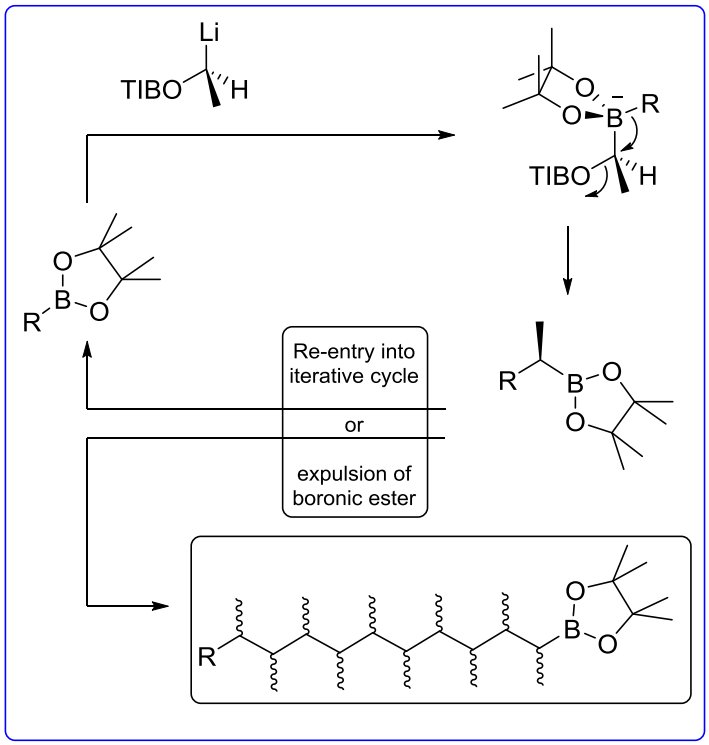
Scheme 1.22: Homologation of Tertiary Boronic Ester

This result was exploited in a concise total synthesis of (–)-filiformin **75** (**Scheme 1.23**). Five steps from bromomethylpinacol boronic ester led to **72** in high enantioselectivity (98% e.e.). Compound **72** was homologated with lithiated carbamate **71** to produce boronic ester **73**, also in high enantioselectivity (96% e.e.). Compound **73** was cyclised to **74** by lithiation/iodination followed by another cyclisation and bromination to give the target product **75**.



Scheme 1.23: Concise Total Synthesis of (–)-Filiformin

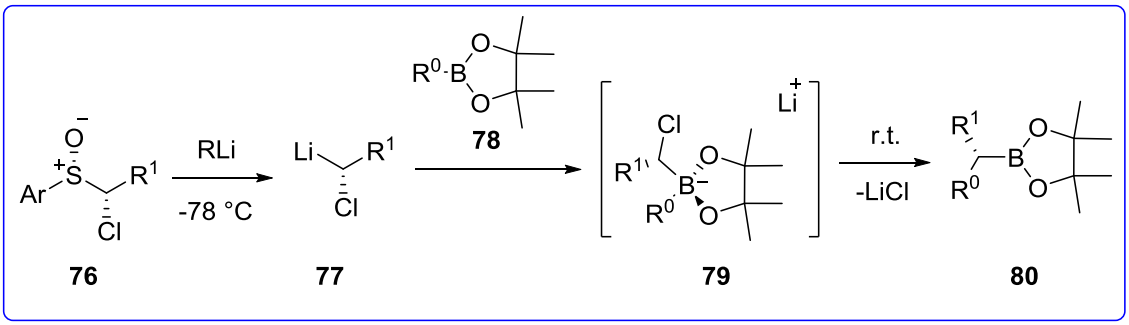
Also, more recently,[50] Aggarwal successfully developed and applied his methodology in the highly stereoselective synthesis of several isomers bearing ten contiguous methyl-substituted carbon atoms. This process relied on α-lithioethyl tri-isopropylbenzoate instead of Hoppe's carbamates, because the former has a superior leaving-ability relative to Hoppe's carbamates. This process involves insertion of α-lithioethyl *tri*-isopropylbenzoate (TIBO) into the carbon-boron bond followed by 1,2-rearrangment; each homologation step produces a new boronic ester, which is ready for another chain extension (**Scheme 1.24**).



Scheme 1.24: Iterative Approach to Assembly-Line Synthesis

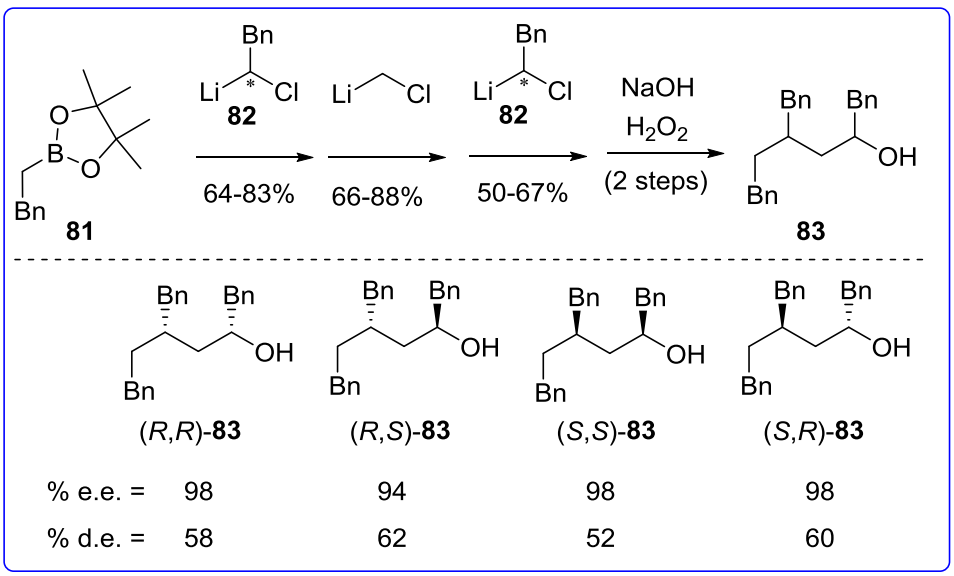
1.9 Blakemore Methodology (Reagent-Control)

Cleavage of asymmetric sulfoxides provides access to asymmetric metal alkyl reagents, which offers a useful methodology.[51] Blakemore's group has prepared asymmetric (α-chloroalkyl)lithium reagents **77** *in situ* from chiral α-chloroalkyl sulfoxides **76** and inserted them into pinacol boronic esters **78** (**Scheme 1.25**).[52] α-Chloroalkyl sulfoxides **76** undergo sulfoxide-lithium exchange to give chloroalkyllithium reagents **77** which then homologate boronic esters *via* ate-complex **79** formation followed by 1,2-metallate rearrangement to produce chiral boronic esters **80**.



Scheme 25: Homologation of Boronic Esters with Lithiated Alkyl Chloride

The successful execution of this method was demonstrated in synthesis of the four stereoisomers of **83** (**Scheme 1.26**). The boronic ester **81** was homologated twice with either the same or different stereoisomers of **82** followed by peroxidic oxidation; the stereoselectivities were moderate to good.[52]

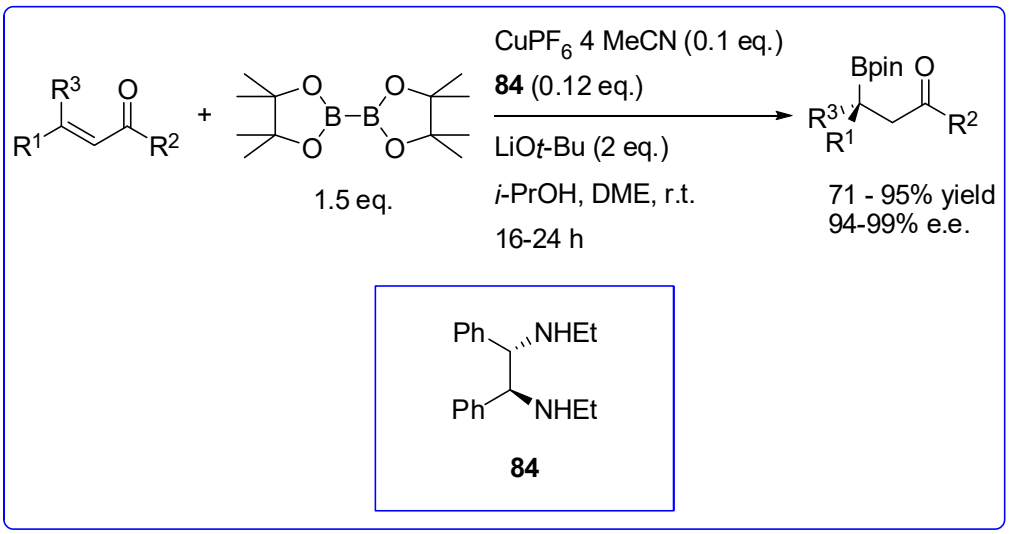


Scheme 1.26: Application of Blakemore's Method

1.10 Catalytic Conjugate Addition

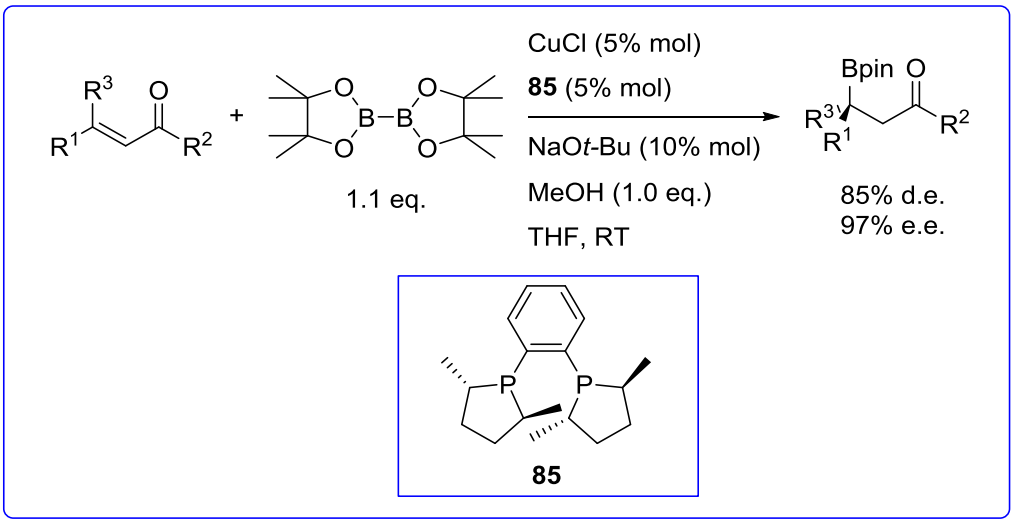
1.10.1 Shibasaki Methodology

Shibasaki,[53] based on seminal work of Hosomi[54] and Miyaura[55,56] who described independently the β-borylation of Michael acceptors, has developed a catalytic conjugate addition process by using a copper(I)-chiral secondary diamine complex to catalyse a conjugate borylation of β,β-disubstituted Michael acceptors in the synthesis of tertiary boronic esters in high yield and enantioselectivity (**Scheme 1.27**).



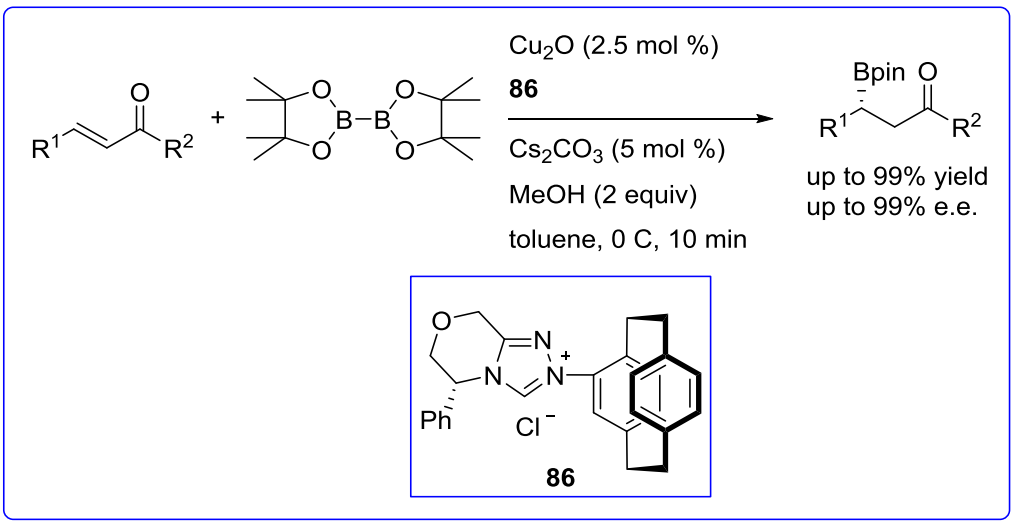
Scheme 1.27: Synthesis of Tertiary Boronic Esters by Shibasaki's Method

Meanwhile, Yun used a different chiral complex, namely the phosphine-copper complex derived from **85**, in the presence of methanol as an additive, to produce tertiary boronic esters in excellent enantioselectivities and high yields (**Scheme 1.28**).[57]



Scheme 1.28: Synthesis of Tertiary Boronic Esters by Yun's Method

More recently,[58] Ma and Song have used a *N*-heterocyclic carbene copper(I) complex synthesised *in situ* from triazolium salt **86** and Cu_2O, as a catalyst in the asymmetric synthesis of secondary boronic esters from acyclic enones (**Scheme 1.29**).



Scheme 1.29: The Asymmetric Synthesis of the Secondary Boronic Esters Using Ma's Catalyst

Chapter Two

Studies on a Catalytic Borylation Reaction

2.1 Aim and Introduction

As was mentioned in the introduction chapter, Matteson and Aggarwal have established powerful substrate-controlled and reagent-controlled methods, respectively, for the asymmetric homologation of boronic esters. However, neither of these two methods has the ability to be a general method for the generation of quaternary stereocentres. The limitation of Aggarwal's method is the requirement of chiral secondary carbamates, so that the method itself is not catalytic (although the carbamates can be produced using catalytic asymmetric processes). The limitation of Matteson's method is the need for stoichiometric auxiliaries.

Meanwhile, great attention has been paid to C_2-symmetric chiral bis(oxazoline)-metal complexes previously.[59–69] This was due to the excellent highly stereoselective reactions which have been achieved by using complexes of such chiral ligands. These reactions include Diels-Alder, Aldol, Mannich, Sakurai-Hosomi, ring opening of epoxides and many other processes.[70–72] **Figure 2.1** shows some of the most common bis(oxazoline) ligands used in stereoselective metal catalysis.[73]

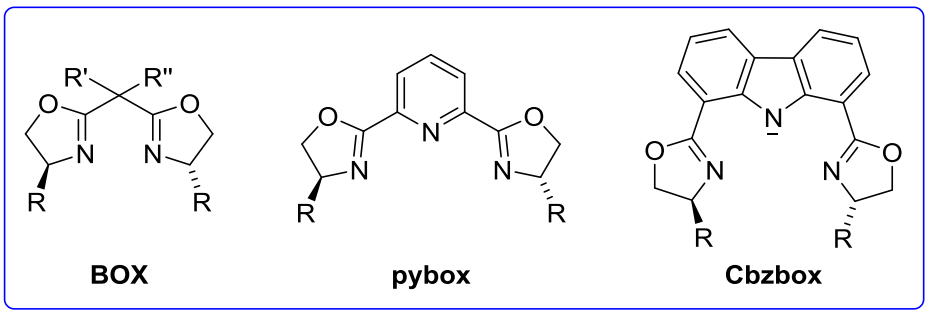


Figure 2.1 : Bis(oxazoline) ligands used in in stereoselective metal catalysis

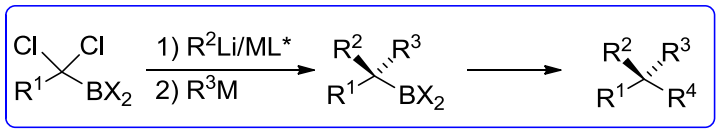
There are a number of factors which make the oxazoline play such a role: first, the moderate chemical hardness of the two nitrogen atoms and their in-plane lone pairs make them able to coordinate with a variety of metal centres, *e.g.* transition and lanthanide metals; second, the relation between the coordinating atom and the position of the chiral centre transfers the chiral information effectively; third, they are

easily prepared in a large variety of structures from relatively inexpensive amino alcohols.[73]

To our knowledge, there is only one study which has attempted to investigate a general catalyst-controlled process using bis(oxazoline)-metal complexes in the borate rearrangement reaction.[74]

Jadhav and Man reported the first ever examination of bis(oxazoline)-lanthanide complexes in 1997.[73,74] However, there have been no reports of improvements to this method since then. This chapter describes the results of attempts to improve this procedure by understanding the reaction as well as the role of Lewis acid and chiral ligand on the stereoselectivity.

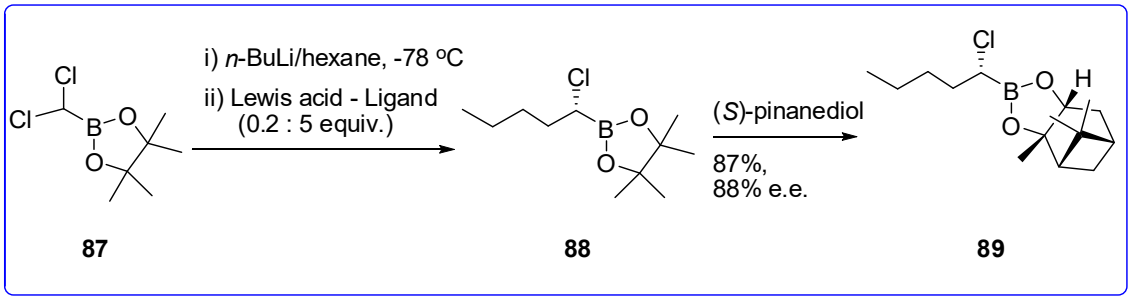
Also, it was proposed, as an eventual goal, to develop this catalytic method for the generation of quaternary stereocentres using migration reactions of alkyl/aryl groups from boron to carbon (**Scheme 2.1**).



Scheme 2.1: Proposed Route for Synthesis of Quaternary Stereocentres

2.2 Summary of the Work by the Jadhav Group

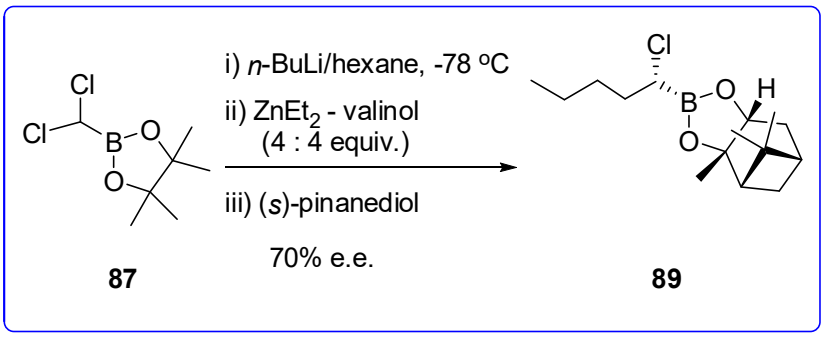
Jadhav reported the reaction of dichloromethylboronic ester **87** with *n*-BuLi, promoted by a chiral ligand and a Lewis acid, to give chloropentylboronic ester **88** with high levels of stereocontrol (**Scheme 2.2**). Because it is not possible to determine the stereoselectivity for the enantiomers of compound **88** directly by ^{1}H NMR spectroscopy, the stereoselectivity of this reaction was determined by conversion of **88** into the pinanediolboronic ester **89**. Jadhav observed that there was no scrambling of stereochemistry when the pinanediol ester was exchanged in the transesterification step.



Scheme 2.2: Reaction of *n*-BuLi with Dichloromethylboronic Ester **87**

In summary, this study reported the following results and fundamental limitations.

1) Initially, the 1,2-migration reaction of the borate complex was examined with chiral Lewis acid derived from valinol and diethylzinc (1 equiv. each). The reaction in THF gave 20% e.e., while using hexane improved the stereoselectivity to 40% e.e.
2) The amount of the chiral ligand influenced the selectivity: by using excess of valinol and diethyl zinc (4 equiv. for each), the stereoselectivity was further improved to 70% e.e. (**Scheme 2.3**).



Scheme 2.3 : The Use of $ZnEt_2$ and Valinol as Chiral Catalyst

3) Using chiral bis(oxazoline) ligands and Lewis acids showed that the presence of a phenyl group on the 4-position of the oxazoline was essential and the optimum pair of chiral ligand and Lewis acid was chosen (**Figure 2.1** red colour).
4) Lanthanide complexes $Yb(OTf)_3$ and $Lu(OTf)_3$ achieved higher stereoselectivity (71% e.e. and 60% e.e. respectively) than transition metal complexes $Zn(OTf)_2$ and $Cu(OTf)_2$ (both 45% e.e.).
5) Excess of the chiral ligand ((*R*,*R*)-bis(oxazoline) **90**, 5 equivalents) and $Yb(OTf)_3$ were needed to reach to 88% e.e.

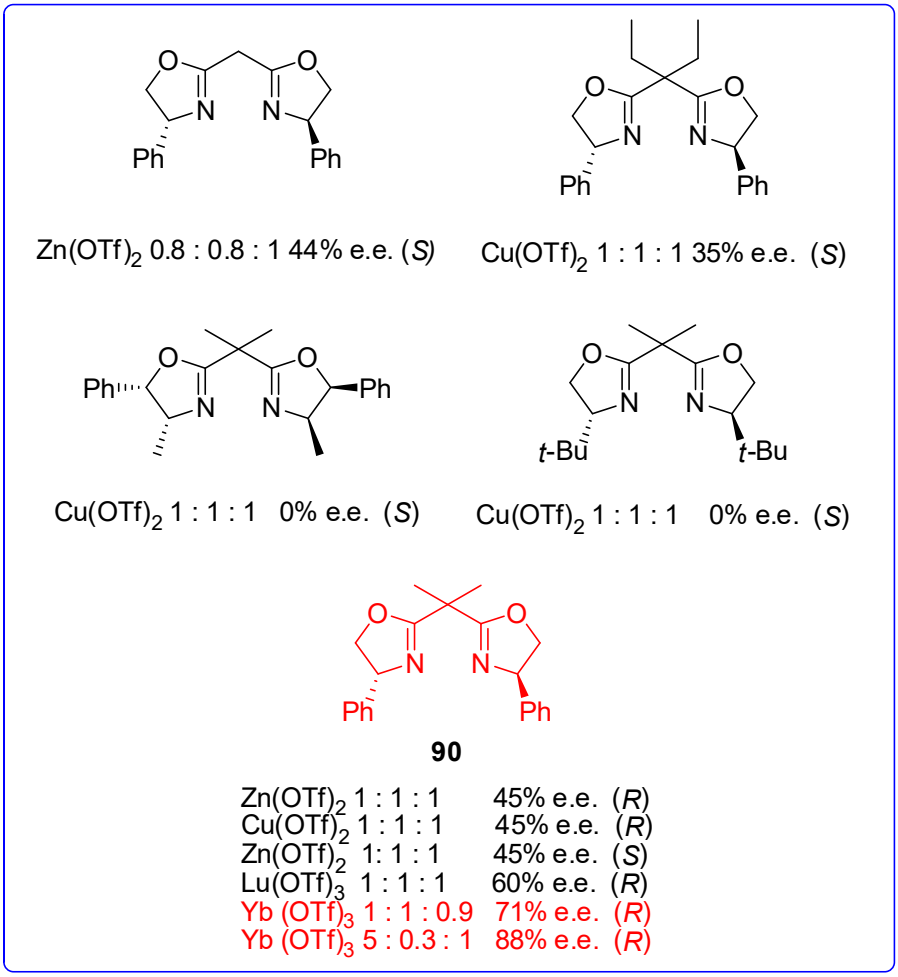


Figure 2.1: The Ratio of Ligand : Lewis Acid : Substrate Used in Jadhav's Study

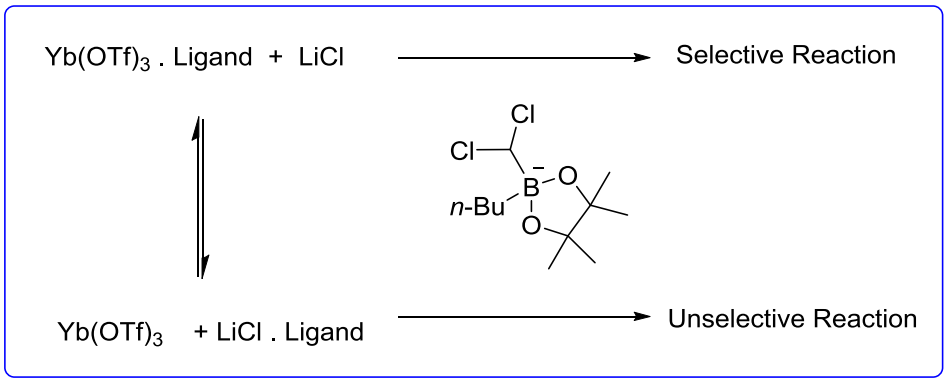
We needed to understand why a large excess of chiral ligand (5 equivalents) was required if we were to be successful in developing a truly catalytic process. Also, the

generality of the reaction had not been established, having only been applied to one substrate. In particular, the reaction had not been applied to the formation of quaternary stereogenic centres.

Jadhav speculated that the large amount of ligand was required because the lithium introduced during the reaction competed with ytterbium for the chiral ligand (**Scheme 2.4**). In the original report, Jadhav stated that:

> *"We were unsuccessful in designing experiments that will allow scavenging of the by-product LiCl without interfering with the chiral catalysis process."*

However, the unsuccessful experiments were not described.



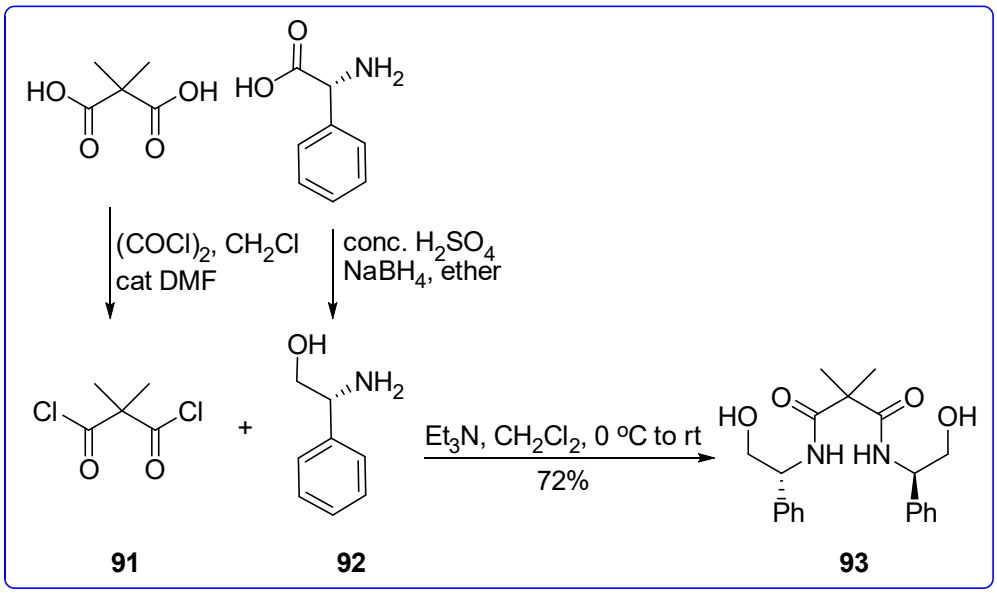
Scheme 2.4: Competition between the Lewis Acid and LiCl to Complex with the Ligand

The requirement for a large excess of the expensive chiral ligand has prevented the procedure from being applicable as a general procedure. To tackle this issue, it was decided that the best method to adopt for this investigation was to scavenge the lithium chloride by use of suitable reagents.

2.3 Results and Discussion

2.3.1 Synthesis of (4*R*,4'*R*)-2,2'-(Propane-2,2-diyl)bis(4-phenyl-4,5-dihydrooxazole)

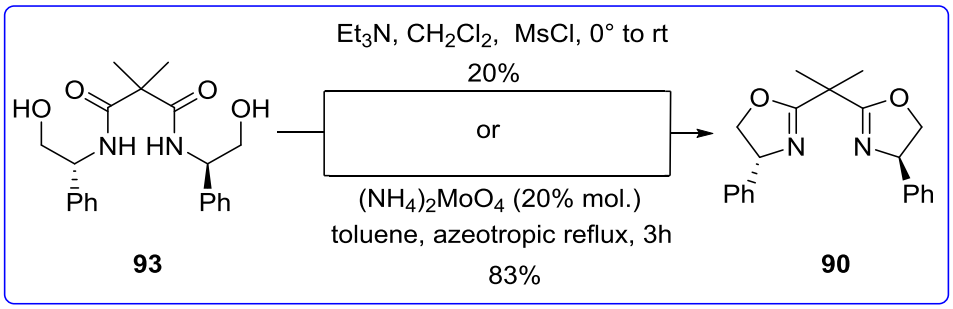
The bis(oxazoline) **90** was prepared in a series of steps. Firstly, D-phenylglycinol **92** was prepared by adopting the procedure used by Abiko and Masamune[75] by treating a mixture of D-phenylglycine in THF with borane which was generated *in situ* from sodium borohydride and a solution of sulfuric acid in diethyl ether. Secondly, bis(amide) **93** was prepared according to the procedure used by Körner and Hiersemann[76] by treating **92** with dimethylmalonyl dichloride (**91**), which was itself prepared according a literature method[76] from the reaction of 2,2-dimethylmalonic acid with oxalyl chloride in the presence of dimethylformamide in catalytic amount (**Scheme 2.5**).



Scheme 2.5: Synthesis of the bis(amide) **93**

Thirdly, for the last step of the cyclisation of compound **93** into the bis(oxazoline) **90**, two methods were used. Initially, the procedure of Dagorne *et al.*[77] was used by treating the bis(amide) **93** with methanesulfonyl chloride in the presence of triethylamine. The reaction proceeded successfully but with unspectacular yields

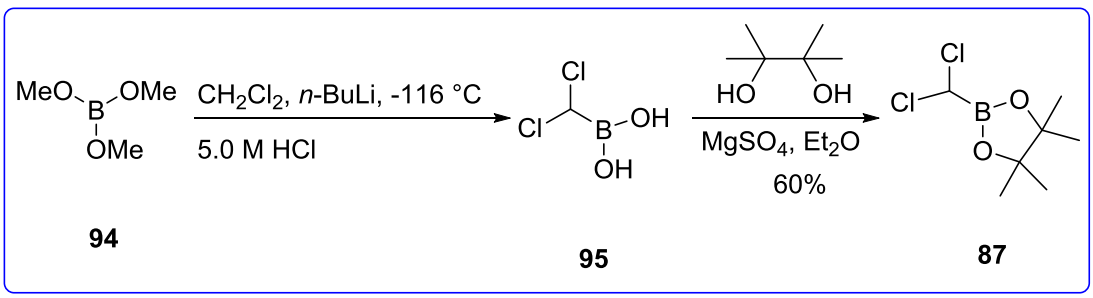
(20%). An alternative route for cyclisation of **93** into **90** was therefore required. After searching further in the literature for cyclisation of compound **93**, a very attractive method of synthesis developed by A. Sakakura**,** *et al* was found. The method involves dehydrative cyclisation of the bis(amide) **93** with 20 mol% of $(NH_4)_2MoO_4$.[78] This method was used for the cyclisation to achieve a very good yield (83%) of **90** (**Scheme 2.6**).



Scheme 2.6: Cyclisation of bis(amide) **93** into bis(oxazoline) **90**

2.3.2 Synthesis of Dichloromethyl Boronic Acid Pincacol Ester

The *title compound* was prepared according to the literature[79] in two steps (**Scheme 2.7**).



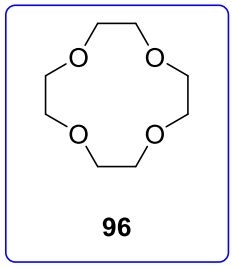
Scheme 2.7: Synthesis of dichloromethylboronic acid pinacol ester (**87**)

Firstly, dichloromethaneboronic acid **95** was prepared according to the procedure used by Rathke *et al.* by addition of trimethyl borate to lithiated dichloromethane at -116 °C

and quenching the resulting mixture with diluted hydrochloric acid. Secondly, esterification of dichloromethaneboronic acid **95** was carried out by heating the compound and pinacol in ether and in the presence of magnesium sulfate at reflux for 5 h.[80]

2.3.3 Scavenging Lithium Chloride

Without knowing what Jadhav actually attempted, we considered methods by which the lithium cations could be scavenged from the reaction. 12-Crown-4 (**96**) has a strong affinity, with good selectivity, for the lithium cation.



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Therefore, a series of experiments was conducted with various amounts of 12-crown-4. To a cold (–78 °C) solution of 1.0 equivalent of the substrate **90** in hexane, *n*-BuLi was added dropwise, followed after 5 minutes by a cold (–78 °C) solution of 12-crown-4 (**96**) in dichloromethane. The solution was stirred for 5 minutes and cold (–78 °C) dichloromethane was added followed by $Yb(OTf)_3$ and bis(oxazoline). The mixture was warmed up over a period of 1 hour at room temperature and then saturated ammonium chloride was added followed by diethyl ether and (*S*)-pinanediol. After 15 minutes, the organic layer was separated and dried over magnesium sulfate. The solvents were removed and the crude product was purified by flash chromatography. The results are depicted in **Figure 2.2**. In these experiments, 0.5 equivalents of ligand and 0.21 equivalents of $Yb(OTf)_3$ were used. With 0.6 equivalents of 12-crown-4, a dramatic increase in stereoselectivity was observed from 21% e.e. to 50% e.e. with these lower loadings of ligand and Lewis acid. Addition of more 12-crown-4 then lowered the stereoselectivity (**Figure 2.2**). In a comparable

experiment in the absence of 12-crown-4, Jadhav observed 55% e.e., but we were never able to reproduce this level of selectivity under these conditions. However, this is an unfair comparison because Jadhav used peak heights in ^{1}H NMR spectra to measure the e.e., while integration of the peaks was used in this study (see section 2.3.9). So, it is not expected that the results would be comparable.

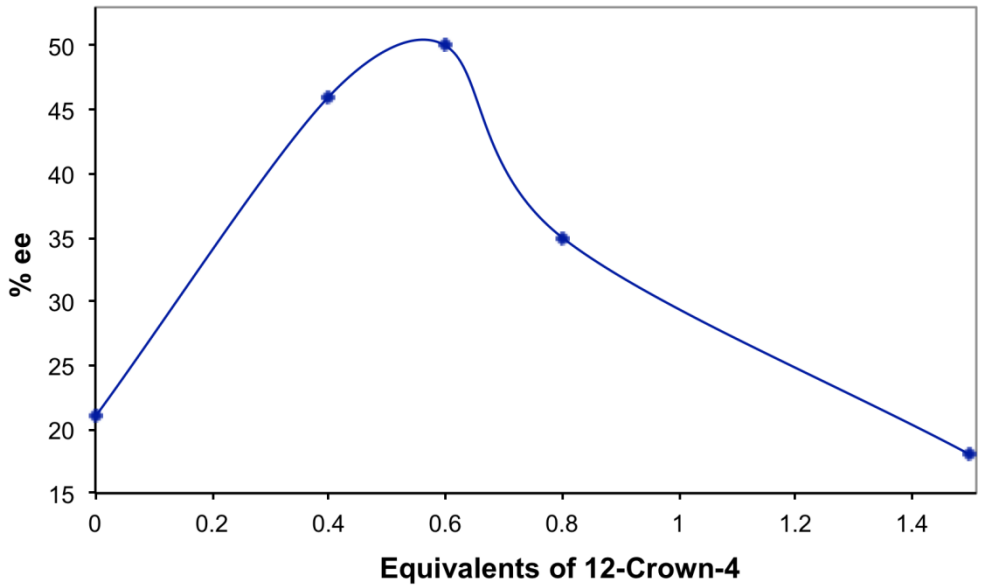


Figure 2.2: The Relationship Between Equivalents of 12-Crown-4 Added and % e.e.

This trend is difficult to understand if the 12-crown-4 is complexing only to lithium. However, complexes of crown ethers with f-block elements, including ytterbium, are well known.[81] We considered the possibility that the improvement in e.e. after 12-crown-4 addition was actually due to the coordination of Yb with the 12-crown-4. This would mean that the stereoselective reaction involving the chiral ligand might actually involve lithium! Complexation of bis(oxazolines) to lithium has been previously used in asymmetric transformations, so that catalysis *via* the lithium complex is entirely plausible.[82] Next, we turned our attention to optimisation of the amount of Lewis acid used.

2.3.4 Evaluating the Influence of Amount of Lewis Acid

The next series of experiments involved variation of the amount of added Lewis acid ($Yb(OTf)_3$). Adding the chiral ligand and the Lewis acid to the reaction as solids might not allow complete dissolution, which could mean that the ytterbium complex was not fully formed. Therefore, in order to obtain reproducible results, and in a change from the procedure reported by Jadhav, the chiral ligand and Lewis acid were premixed in dichloromethane *ex-situ* overnight and this solution was transferred to the reaction mixture by cannula 5 minutes after addition of *n*-BuLi. Surprisingly, as shown in **Figure 2.3**, the level of enantioselectivity increased as the amount of ytterbium triflate was decreased.

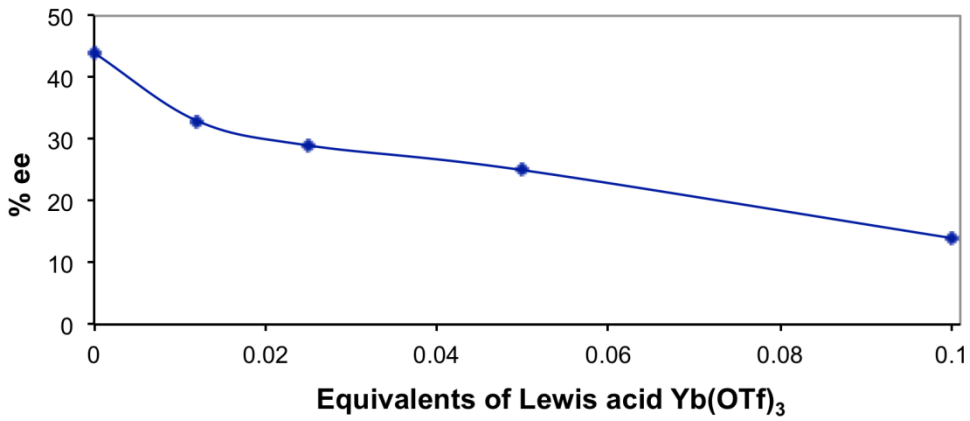


Figure 2.3: The Relationship between Equivalents of Lewis Acid Added and % e.e.

From the data in **Figure 2.3**, it is apparent that the enantioselectivity was the lowest (18% e.e.) when 0.5 equivalents of chiral ligand was premixed with 0.1 equivalents of Lewis acid, while it was the highest (45% e.e.) when no Lewis acid was added. From this, it was clear that the ytterbium triflate was reducing the level of stereoselectivity, presumably by complexing to the bis(oxazoline). Qian and Wang suggested that bis(oxazolines) form complexes with $Yb(OTf)_3$ with a stoichiometry of 1:2 $Yb(OTf)_3$:

bis(oxazoline).[70] Thus, an excess of the chiral ligand was needed because the Lewis acid consumes two equivalents of the amount of the chiral ligand. This result is consistent with the experiments involving addition of crown ether, which showed increasing stereoselectivity, if it is assumed that the crown ether complexes with the $Yb(OTf)_3$ and consequently this allows the chiral ligand to complex with lithium in the transition state.

There are a number of factors which may affect the activity of the bis(oxazoline)-metal complexes; radii, charge density of the metal and the stability of the complexes.[73]
From Jadhav's work, the stereoselectivity obtained from the complexes of transition metals with bis(oxazolines) such as $Zn(OTf)_2$ or $Cu(OTf)_2$ was significantly less than that from $Yb(OTf)_3$: 45% e.e. and 71% e.e. respectively. It seems likely that the complexes of transition metals with bis(oxazolines) are more stable than those of lanthanides. Consequently, the transition metals are stronger competitors with lithium to complex with bis(oxazolines). This might explain why the stereoselectivity was reduced from 71% to 45% when transition metals complexes were used.

2.3.5 Evaluating the Influence of the Amount of Chiral Ligand

To investigate the relationship between the chiral ligand in the absence of Lewis acid and the % e.e., various amounts of chiral ligand were used. The *ex-situ* procedure was carried out in the absence of Lewis acid and the crown ether. A cold (–78 °C) solution of chiral ligand in dichloromethane was transferred to the reaction mixture by cannula 5 minutes after addition of *n*-BuLi and the reaction mixture was stirred for 1 hour at –78 °C. The results are shown in **Figure 2.4**. From **Figure 2.4**, it is clear that the reaction is stoichiometric in ligand. The enantioselectivity rises to approximately 60% e.e. as up to one equivalent of ligand is added, but then does not increase further. Despite many attempts to vary the reaction conditions, we have not managed to achieve catalytic turnover with this reaction.

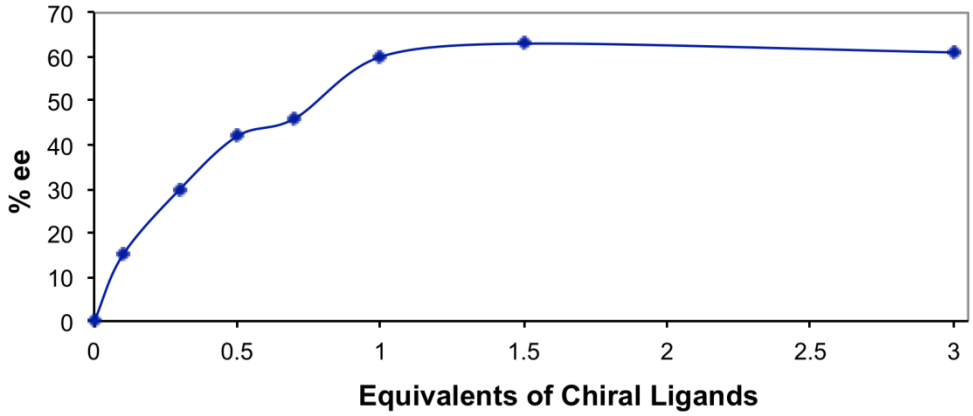


Figure 2.4: The Relationship between Equivalents of Bis(oxazoline) and % e.e.

In order to examine the effect of the crown ether in the absence of the Lewis acid, the reaction was repeated twice by using 0.5 equivalents of chiral ligand and 0.6 and 1 equivalents of the crown ether, respectively. No change was observed in the level of the stereoselectivity. The result shows that in the absence of Lewis acid there is no effect of crown ether on the stereoselectivity, while in the presence of the Lewis acid, ytterbium might prefer to complex with the crown ether and consequently not reduce the stereoselectivity. This also means that the crown ether is not able to sequester lithium cations from this system.

2.3.6 The Reproducibility of the Reaction and the Possibility of Catalytic Turnover

Ytterbium triflate from a fresh bottle had shown good solubility in a dichloromethane solution of the chiral ligand. Also, the results had shown that increasing the amount of ytterbium triflate decreased the stereoselectivity. Using the new bottle and 0.5 equivalents of chiral ligand had given 29% e.e. (**Figure 2.3**). In an attempt to reproduce the same results after one year, 3 mol% of ytterbium triflate from the same bottle was premixed with 0.5 equivalents of chiral ligand and used in the *ex-situ* procedure at -46 °C. Interestingly, the observed stereoselectivity in this experiment was 70% e.e., which is higher than could be achieved in a stoichiometric reaction using 0.5 equivalents of

ligand. This means that some catalytic turnover has been achieved. It is difficult to explain this result because it was found from this study that the presence of ytterbium triflate decreases the level of the stereoselectivity. This result suggests that an as yet unidentified compound could be generated in the old bottle which complexes with bis(oxazoline) to give superior stereocontrol. It is possible that the ytterbium triflate had become contaminated, for example with water. Therefore, to examine this hypothesis, it was decided to assess the reaction using fresh ytterbium triflate as the hydrate. To this end, 5 mol% of ytterbium triflate hydrate from a fresh bottle was premixed with 0.5 equivalents of the chiral ligand and used in the *ex-situ* procedure at –78 °C. Interestingly, the observed stereoselectivity in this experiment was 59% e.e., which is close to that was observed with the use of old ytterbium triflate (70% e.e.), and higher than when a similar amount of new anhydrous ytterbium triflate was used (28% e.e.). This therefore supports the hypothesis that adventitious water is resulting in an increase in e.e. and some catalytic turnover. However, it was not possible to improve the selectivity further.

2.3.7 The Effect of Temperature

In order to investigate the effect of temperature on stereoselectivity in the absence of the Lewis acid, the reactions were repeated at several different temperatures. The solution of the boronic ester **87** in hexane was cooled to the corresponding temperature (see **Table 2.1**) and *n*-BuLi was added. The mixture was stirred for 5 minutes before the addition of a cold (at the corresponding temperature) solution of chiral ligand (0.5 equivalents) by cannula dropwise. The cooling bath was removed and the mixture was warmed up to room temperature over a period of 1 h. The stereoselectivity was measured as before after the usual work up and the results are given in **Table 2.1**.

Table 2.1: Effect of Temperature on Stereoselectivity Using 0.5 Equivalents of the Chiral Ligand and in the Absence of Lewis Acid

Entry	Temp./ °C	% e.e.
1	–78	40
2	–46	52
3	–29	50
4	–15	49
5	0	48

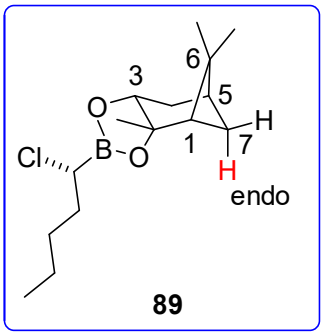
It is apparent from this table that there was almost no significant change in the stereoselectivity when the reaction temperature changed. These results suggest that migration of the butyl group does not occur to a significant extent below 0 °C. Since all of the mixtures would be warming at a similar rate from this point, there would be no significant difference in the results. Therefore, it was thought that running the reaction at low temperature and then warming it up to room temperature at a slow rate might help to increase the chance of high stereoselectivity. To establish whether the slow warming up would give better stereoselectivity, two experiments side by side were carried out at –78 °C, one involving the procedure when the cooling bath is removed after the addition of the chiral ligand and the other with slow warming up, over a period of 5.5 h (the temperature was controlled manually by slow addition of dry ice to an acetone cooling bath). The reaction using slow addition was marginally more selective (43% to 47% e.e.). However, the observed difference in these two experiments was not significant. Another pair of experiments to investigate the effect of fast warming up (the reaction flask was transferred immediately after addition of chiral ligand solution to an oil bath (33 °C)) was set up as well. Again, there was no difference in stereoselectivity between normal warming and fast warming.

2.3.8 The Effect of the Solvent

Jadhav found that using polar solvents such as THF decreased the stereoselectivity significantly compared with non-polar solvent (hexane). They attributed this decrease to the fact that the THF decreases the acidity of the Lewis acid of the chiral catalyst. It is clear from our investigation that the presence of the Lewis acid decreases the stereoselectivity. Thus, the influence of the solvent on the stereoselectivity in the absence of the Lewis acid was needed. An experiment was designed for this purpose. The *ex-situ* reaction procedure was repeated in THF in the absence of the Lewis acid at –78 °C using 0.5 equivalents of the chiral ligand. The stereoselectivity dropped significantly from 44% e.e. (in dichloromethane and hexane) to 18% e.e. This might be attributed to the complexation of the lithium species with the THF instead of the chiral ligand.

2.3.9 Determination of Stereoselectivity

Determination of the stereoselectivity in these reactions is far from trivial. For each isomer, the *endo* C_7 proton of compound **89** gives a doublet in the ^{1}H NMR spectrum in the region of 1.1 ppm.[31] Unfortunately, these peaks for the two diastereoisomers overlap, although integration of the individual peaks is possible. However, there is clearly a significant margin for error in our measurements, although the trends are clearly valid. We cannot compare our levels of stereoselectivity directly with those reported by Jadhav, since he determined the e.e. of **89** by measuring the peak height of the *endo* C_7 proton for each diastereoisomer and the NMR spectra from that study were not published. In the present work, % e.e. measurement of compound **89** was accomplished by line shape analysis and integration of the ^{1}H NMR peaks of the endo C_7 proton for each diastereoisomer. The calculations were carried out using the iNMR program (**Figure 2.4** shows a typical output from the program).[83] The doublet peaks with the higher chemical shift (1.17 ppm, J = 11 Hz) are for the (1*S*) diasteroisomer while the low chemical shift's doublet peaks (1.16 ppm, J = 11 Hz) are for the (1*R*) diasteroisomer.[31]



89

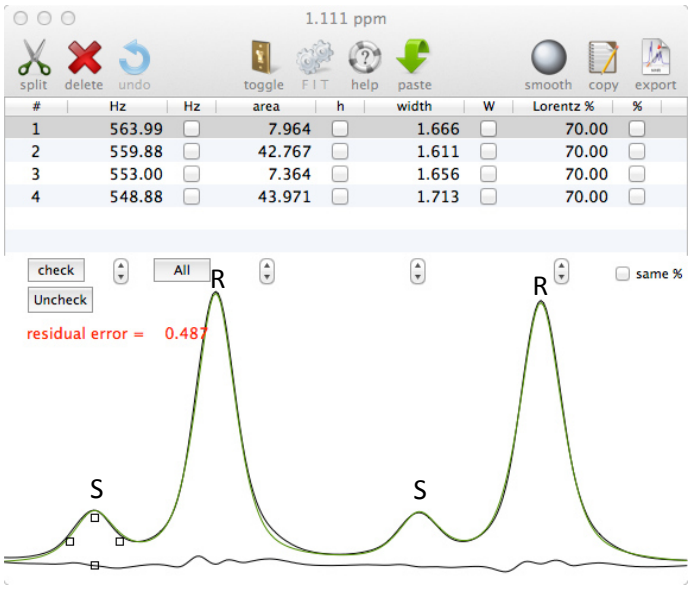


Figure 2.5: Line Fitting of ^{1}H NMR Spectra Using iNMR

2.4 Computational Study

In order to confirm that the lithium complex with the chiral ligand could undergo migration, and to verify the stereoselectivity of the migration product that is expected to predominate, a computational study was also carried out by Dr Mark Elliott.[84] In order to simplify the calculations, the migrating butyl group was replaced with methyl. After extensive conformational analysis, two transition states were located at the RB3LYP/6-31G(d) level of theory. Formation of the (*R*)-enantiomer of compound **88** was reported by Jadhav. The upper transition state in **Figure 2.6** was calculated to be favoured by 26 kJ mol^{-1}. It does indeed favour the observed (*R*)-enantiomer, which is encouraging. The calculations showed that one of the aromatic rings, the right aromatic ring on the **Figure 2.6**, was twisted by 25.4° away from the dichloromethyl

group in (*S*)-enantiomer transition state (lower transition state in **Figure 2.6**) compared to that of the (*R*)-enantiomer transition state. The calculations also showed that the distance between the dichloromethyl group and the *ortho* carbon atom of the aromatic ring was shorter (the distance between the hydrogen and the *ortho* carbon atom was 2.84 Å) for the (*R*)-enantiomer transition state than for the (*S*)-enantiomer transition state (the distance between the non-displaced chlorine and *ortho* carbon atom was 3.65 Å).

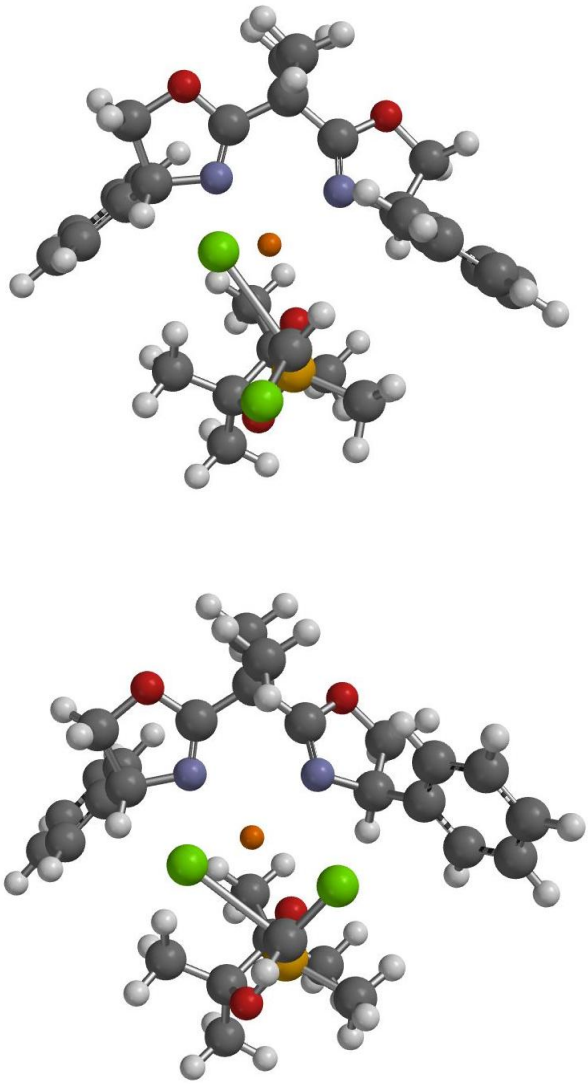
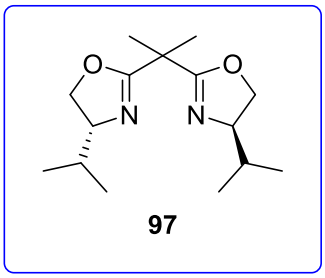


Figure 2.6: Calculated RB3LYP/6-31G(d) Transition States favouring *R* (top) and *S* (bottom) Stereochemistry**.**

In an attempt to verify the importance of the benzene ring in the structure of the chiral ligand experimentally, the *in situ* reaction procedure was repeated using 0.5 equivalents of 2,2-bis((4*S*)-(–)-4-isopropyloxazoline)propane (**97**) and 0.1 equivalents of Lewis acid at –78 °C. The reaction gave a racemic mixture of the product. This finding is in agreement with Jadhav's findings, which showed the same results when the benzene ring was replaced with aliphatic groups. This reflects the importance of the presence and the position of the benzene ring in the bis(oxazoline) structure.



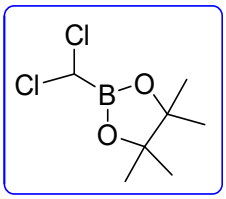
97

2.5 Conclusion

According to this study, it was suggested that most probably the lithium cation coordinates with the chiral ligand to orientate the stereoselectivity. On the other hand, ytterbium competes with lithium in this action. Consequently, the stereoselectivity decreases in the presence of ytterbium triflate. It was initially thought to be possible that the reaction was stoichiometric in the chiral ligand since use of 0.5 equivalent of chiral ligand never resulted in more than 50% e.e. in the absence of ytterbium triflate. However, when aged ytterbium triflate (3% mol) was used with 0.5 equivalents of ligand; high stereoselectivity (70% e.e.) was achieved, which is higher than is possible for a perfectly stereoselective stoichiometric process using only 0.5 equivalents of the chiral ligand, which suggested the possibility of some catalytic turnover.

2.6 Experimental

2.6.1 Synthesis of Dichloromethane Pinacol Boronate (87)[79,80]



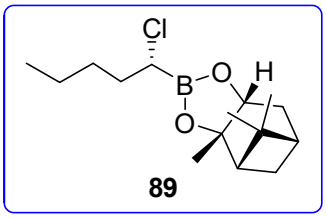
A septum-sealed 250 mL one-neck round-bottomed flask (RBF), was charged with a solution of dichloromethane (1.41 mL, 22 mmol) in THF (40 mL) and immersed in a liquid nitrogen–ethanol bath (–116 °C). *n*-BuLi (1.6 M in hexane, 12.5 mL, 20 mmol) was added dropwise over 8 min. The solution was stirred for 30 min. Trimethoxyborane (2.5 mL, 22 mmol) was added in one portion and the solution was stirred for a further 30 min. Hydrochloric acid (5.0 M, 4.0 mL, 20 mmol) was added to the reaction and the solution was allowed to warm to r.t. The organic layer was separated and dried over magnesium sulfate. The solvent was evaporated under reduced pressure over 1 h to give the crude dichloromethaneboronic acid as a viscous white-light yellow coloured oil.

The crude product was placed in 100 mL two-neck RBF and magnesium sulfate (7.5 g) and pinacol (2.718 g, 23.1 mmol) were added. Diethyl ether (60 mL) was added and the mixture was heated at reflux for 5 h under nitrogen. The organic layer was transferred to another septum-sealed 100 mL RBF and concentrated by flushing with N_2 for 2 hrs. The liquid was transferred to a distillation system and distilled (b.p. 55 – 60 °C, 1 Torr) to give the *title compound* (1.5 g, 32% yield from trimethyl borate) as a colourless oil.

^{1}H NMR (400 MHz; $CDCl_3$) δ 5.28 (1H, s) and 1.27 (12H, s).

^{13}C NMR (101 MHz; $CDCl_3$) δ 85.8 and 24.4.

2.6.2 Synthesis of (*S*)-Pinanediol (1-Chloropentyl)boronate (89)[74]

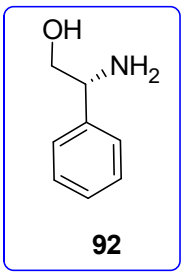


89

To a septum-capped two-neck 50 mL RBF were added pinacol dichloromethaneboronate (211 mg, 1.0 mmol) and dry hexane (1.5 mL). The flask was immersed in a dry ice/acetone bath. *n*-BuLi (0.75 mL, 1.6 M in hexane, 1.2 mmol) was added. The mixture was stirred for 1 hour at –78 °C. Dry and cold (–78 °C) dichloromethane (20 mL) was added by cannula. The mixture was warmed up to room temperature over a period of 1 h. Saturated ammonium chloride solution (20 mL) was added, followed by diethyl ether (25 mL) and *(S)*-pinanediol (171 mg, 1.0 mmol). The reaction mixture was stirred for 15 min. The organic layer was separated and dried over magnesium sulfate. The solvents were evaporated by rotary evaporator to produce the crude product. This was purified by flash column chromatography on silica using dichloromethane to yield a mixture of two diastereomers of the *title compound* (227 mg, 80%) as a colourless oil. ^{1}H NMR (400 MHz; $CDCl_3$) the individual proton signals of the two isomers generally overlapped and only the signals for the *endo* proton attached to carbon 7 could be differentiated. δ 4.36 (2H, dd, *J* = 8.8, 1.8 Hz), 3.50 – 3.39 (2H, m), 2.40 – 2.30 (2H, m), 2.29 – 2.19 (2H, m), 2.08 (2H, t, *J* = 5.5 Hz), 1.96 – 1.77 (8H, m), 1.53 – 1.27 (20H, m), 1.17 (1H of one isomer, d, *J* = 11.0 Hz), 1.16 (1H of the another isomer, d, *J* = 11.0 Hz), 0.90 (6H, t, *J* = 7.2 Hz), 0.84 (6H, s).

^{13}C NMR (125 MHz; $CDCl_3$) δ 86.7, 78.59, 78.58, 51.3, 39.5, 38.32, 38.31, 35.42, 35.40, 34.0, 29.6, 28.6, 27.1, 26.45, 26.44, 24.1, 22.3 and 14.0.

2.6.3 Synthesis of *D*-Phenylglycinol (92)[75]



92

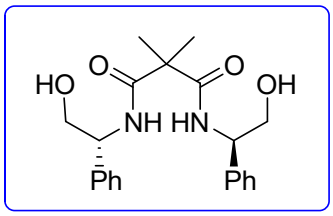
A two-neck 500 mL RBF fitted with a mechanical stirrer and a dropping funnel was charged with $NaBH_4$ (20 g, 0.52 mol) and THF (200 mL). To this stirred suspension, *D*-phenylglycine (30.23 g, 0.20 mol) was added. The flask was cooled to 0 °C, and a solution of (fresh) conc. sulfuric acid (13.2 mL, 0.25 mol) in ether (total volume of 40mL) was added dropwise over 40 min while the reaction mixture was maintained at below 20 °C. The mixture was stirred overnight at room temperature. Methanol (20 mL) was added carefully to remove excess BH_3. The mixture was concentrated to *ca*. 100 mL and sodium hydroxide (5.0 M, 200 mL) was added. The organic solvents were removed under reduced pressure at just below 100 °C. The mixture was heated at reflux for 3 h. The mixture was cooled and filtered through a thin pad of Celite® which was washed with water. The filtrate was diluted with additional water to *ca*. 200 mL and then extracted with dichloromethane (4 x 100 mL), followed by evaporation of the solvent to give a solid crude product. The crude product was recrystallised from ethyl acetate/hexane (1:3) to yield the *title compound* (16 g, 58%) as a colourless solid.

m.p. 73 – 76 °C (lit.[75] 74 – 76 °C).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.41 – 6.98 (5H, m), 3.97 (1H, dd, *J* = 8.3, 4.3 Hz), 3.66 (1H, dd, *J* = 10.8, 4.3 Hz), 3.48 (1H, dd, *J* = 10.8, 8.3 Hz) and 2.24 (3H, br).

^{13}C NMR (101 MHz; $CDCl_3$) δ 142.8, 128.8, 127.6, 126.6, 68.1 and 57.4.

2.6.4 Synthesis of N^1,N^3-bis((*R*)-2-Hydroxy-1-phenylethyl)-2,2-dimethylmalonamide (93)[76]



2.6.4.1 Method A : from diethyl dimethylmalonate and (D)-phenylglycinol

To a 50 mL Schlenk flask, diethyl dimethylmalonate (0.95 mL, 5.0 mmol) and *D*-phenylglycinol (1.372 g, 10.0 mmol) were added. NaH (200 mg, 60% dispersion in mineral oil, 5.0 mmol) was then added to the flask, which was put under vacuum, sealed and heated at 130 – 140 °C (sand bath). After 3 h, the mixture was cooled and the ethanol generated was removed under vacuum. Water (50 mL) was added and the mixture was extracted with dichloromethane (3 × 25 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under vacuum. The yellow viscous crude product was recrystallised from EtOAc/hexane to leave the *title compound* (0.591 g, 32%) as a beige solid.

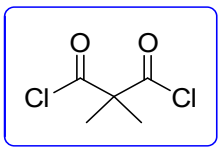
m.p. 128 – 129 °C (lit.[85] 127 – 128 °C).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.40 – 7.24 (10H, m), 7.21 (2H, d, *J* = 7.8 Hz), 5.15 (2H, app. td, *J* = 7.6, 3.9 Hz), 3.93 (2H, dd, *J* = 11.6, 3.9 Hz), 3.78 (2H, dd, *J* = 11.6, 7.4 Hz), 2.23 (2H, br) and 1.53 (s, 6H).

^{13}C NMR (126 MHz; $CDCl_3$) δ 174.2, 138.9, 128.8, 127.8, 126.6, 65.8, 55.9, 50.2 and 23.8.

2.6.4.2 Method B: from 2,2-dimethylmalonic acid and D-phenylglycinol

2.6.4.2.1 Synthesis of 2,2-dimethylmalonyl dichloride (91)[76]



A one-neck 100 mL RBF connected to dropping funnel was charged with 2,2-dimethylmalonic acid (7.5 g, 56.8 mmol, 1.0 equiv.) and DMF (0.57 mL, 7.4 mmol, 0.13 equiv.) in dichloromethane (60 mL). Oxalyl chloride (14.6 mL, 170 mmol, 3.0 equiv.) was added dropwise over 1 h. The reaction mixture was warmed to room temperature, stirred for 18 h and concentrated under reduced pressure. The product was separated from the DMF (which was gathered in the bottom of the flask as a viscous yellow liquid) to afford the dimethylmalonyl dichloride (8.2 g, 86%) as a colourless liquid. The product was used in the next step without further purification.

^{1}H NMR (400 MHz; $CDCl_3$) δ 1.67 (6H, s).

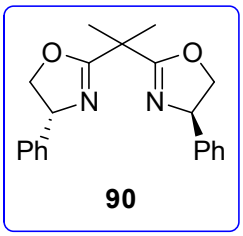
^{13}C NMR (101 MHz; $CDCl_3$) δ 172.1, 69.2 and 23.2.

2.6.4.2.2 Synthesis of N^1,N^3-bis((*R*)-2-hydroxy-1-phenylethyl)-2,2-dimethylmalonamide 93[76]

A solution of *D*-phenylglycinol (4.630 g, 33.75 mmol, 2.25 equiv.) in dichloromethane (15.0 mL) was immersed in an ice-water bath. Triethylamine (10.5 mL, 75 mmol, 5.0 equiv.) was added, followed by a solution of 2,2-dimethylmalonyl dichloride (2 mL, 15.0 mmol, 1.0 equiv.) in dichloromethane (15.0 mL) over a period of 1 h. The reaction mixture was warmed to room temperature, stirred for 35 min and then diluted with dichloromethane (120 mL). The solution was washed with aqueous hydrochloric acid (1.0 M, 18 mL). The organic layer was separated and left in a fume hood for 30 min. to precipitate. The mixture was filtered to give the *title compound* (4.0 g, 72%) as a colourless solid.

m.p. 128 – 129 °C.

2.6.4.3 (–)-2,2'-Isopropylidene bis[(4S)-4-phenyl-2-oxazoline] (90)



90

2.6.4.3.1 Method A[77]:

To an ice-cold solution of the bis(amide) **93** (4.3 g, 11.6 mmol) and triethylamine (5.9 g, 58 mmol) in dichloromethane (75 mL), methanesulfonyl chloride (3.3 g, 29 mmol) was added. The cooling bath was removed and the mixture was stirred for 1 h. The brown solution was washed with a solution of ammonium chloride (20 mL). The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to give an orange solid, which was used in the next step without purification. The bis-mesylated compound was treated with sodium hydroxide (2.0 g, 50 mmol) in a MeOH/H_2O mixture (1:1, 80 mL). The solution was heated at reflux for 2 h, then concentrated to remove methanol and extracted with dichloromethane (3 x 50 mL). The organic layer was dried over magnesium sulfate and concentrated *in vacuo*. The product was purified by column chromatography on silica gel (diethyl ether/hexane, 3:1) to afford the *title compound* (0.8 g, 20%) as a yellow oil.

$[a]^{20}_D$ + 169° (*c*= 1, EtOH) (lit.[86] –171.3°, *c*= 1, EtOH, for *S* enantiomer)

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.35 – 6.96 (10H, m), 5.15 (2H, dd, *J* = 10.1, 7.6 Hz), 4.60 (2H, dd, *J* = 10.1, 8.4 Hz), 4.09 (2H, app. t, *J* = 8.0 Hz) and 1.61 (6H, s).

^{13}C NMR (101 MHz; $CDCl_3$) δ 170.4, 142.4, 128.7, 127.6, 126.7, 75.6, 69.5, 38.9 and 24.5.

2.6.4.4 Method B[78]:

A 100 mL RBF equipped with a Dean-Stark apparatus was charged with a solution of **93** (0.7403 g, 2.0 mmol, 1 eq.) and ammonium molybdate (0.078 g, 0.4 mmol, 0.2 eq.) in toluene (40 mL). The reaction mixture was heated at azeotropic reflux with the

Dean-Stark apparatus to remove water. The colourless solution became darker as the product increased. The mixture was cooled after 3 h and then the solvent was evaporated to leave the crude product. The purification by flash column chromatography on silica using ether / hexane (3:1) afforded the *title compound* (0.5571 g, 83%) as a light yellow oil.

2.6.5 General Procedures of Homologation Reactions

2.6.5.1 In-situ

A 50 mL two-neck flask was charged with pinacol dichloromethaneboronate (211 mg, 1 mmol) and hexane (1.5 mL). A solid-addition tube was charged with $Yb(OTf)_3$ (132 mg, 0.21 mmol) and the apparatus flushed with nitrogen. The mixture was cooled in a dry ice-acetone bath. *n*-BuLi (0.75 mL, 1.6 M in hexane, 1.2 mmol) was added dropwise and the mixture was stirred for 5 min at –78 °C. Cold (–78 °C) dichloromethane (20 mL) was added by cannula followed by $Yb(OTf)_3$ and a solution of bis(oxazoline) **90** (167 mg, 0.5 mmol in dichloromethane (0.5 mL)). The mixture was warmed to room temperature over a period of 1 h. Saturated ammonium chloride solution (20 mL) was added followed by diethyl ether (25 mL) and (*S*)-pinanediol (171 mg, 1.0 mmol). The solution was stirred for 15 min and the aqueous layer was saturated with sodium chloride and extracted with chloroform (3 × 20 mL). The organic layers were combined and dried over magnesium sulfate. Removal of the solvents yielded **89** (220 mg, 78%).

2.6.5.2 Ex-situ

A septum-sealed 50 mL flask was charged with pinacol dichloromethaneboronate (**87**) (211 mg, 1.0 mmol) and dry hexane (1.5 mL). The solution was cooled to –78 °C. *n*-BuLi (0.75 mL. 1.6 M in hexane, 1.2 mmol) was added dropwise and the mixture was stirred for 5 min. Meanwhile, Lewis acid $Yb(OTf)_3$ (132 mg, 0.21 mmol) and bis(oxazoline) **90** (167 mg, 0.5 mmol) were premixed in dry dichloromethane (20 mL) for 12 h and cooled to –78 °C before being added to the reaction mixture 5 min after addition of *n*-BuLi. The mixture was warmed to room temperature over a period of 1 h. Saturated ammonium chloride solution (20 mL) was added, followed by diethyl ether (25 mL) and

(*S*)-pinanediol (171 mg, 1.0 mmol). The solution was stirred for 15 min and the aqueous layer was saturated with sodium chloride and extracted with chloroform (3 × 20 mL). The organic layers were combined and dried over magnesium sulfate. Removal of the solvents yielded **89** (210 mg, 74%).

The % e.e. of the product was determined by line shape analysis and integration of the ^{1}H NMR peaks of the *endo* C_7 proton for each diastereoisomer (the method was detailed in section 2.3.9 and Figure 2.5).

2.6.5.3 Ex-situ: In Absence of the Lewis Acid

A septum-sealed 50 mL flask was charged with pinacol dichloromethaneboronate (**87**) (211 mg, 1.0 mmol) and dry hexane (1.5 mL). The solution was cooled to –78 °C. *n*-BuLi (0.75 mL, 1.6 M in hexane, 1.2 mmol) was added dropwise and the mixture was stirred for 5 min. Meanwhile, bis(oxazoline) **90** (167 mg, 0.5 mmol) was dissolved in dry dichloromethane (20 mL) and cooled to –78 °C before being added to the reaction mixture 5 min after addition of *n*-BuLi. The mixture was warmed to room temperature over a period of 1 h. Saturated ammonium chloride solution (20 mL) was added, followed by diethyl ether (25 mL) and (*S*)-pinanediol (171 mg, 1.0 mmol). The solution was stirred for 15 min and the aqueous layer was saturated with sodium chloride and extracted with chloroform (3 × 20 mL). The organic layers were combined and dried over magnesium sulfate. Removal of the solvents yielded **89** (235 mg, 83%).

2.6.6 Addition of 12-Crown-4 (96)

A 50 mL two-neck flask was charged with pinacol dichloromethaneboronate (211 mg, 1 mmol) and hexane (1.5 mL). A solid-addition tube was charged with $Yb(OTf)_3$ (132 mg, 0.21 mmol) and bis(oxazoline) **90** (167 mg, 0.5 mmol), and the apparatus flushed with nitrogen. The flask was immersed in a dry ice-acetone bath. *n*-BuLi (0.75 mL, 1.6 M in hexane, 1.2 mmol) was added dropwise and the mixture was stirred for 5 min. A cold solution of 12-crown-4 (176 mg, 1.0 mmol) in dichloromethane (1 mL) was added and the mixture was stirred for a further 5 min. Cold (–78 °C) dichloromethane (20 mL) was added by cannula, followed by addition of the mixture of $Yb(OTf)_3$ and bis(oxazoline)

90 from the solid addition tube. The mixture was warmed up to room temperature over a period of 1 h. Saturated ammonium chloride solution (20 mL) was added, followed by diethyl ether (25 mL) and (*S*)-pinanediol (171 mg, 1.0 mmol). The solution was stirred for 15 min and the aqueous layer was saturated with sodium chloride and extracted with chloroform (3 × 20 mL). The organic layers were combined and dried over magnesium sulfate. Removing the solvents yielded **89** (230 mg, 81%).

2.6.7 Testing 2,2-bis((4*S*)-(–)-4-Isopropyloxazoline-2-yl)propane (97)

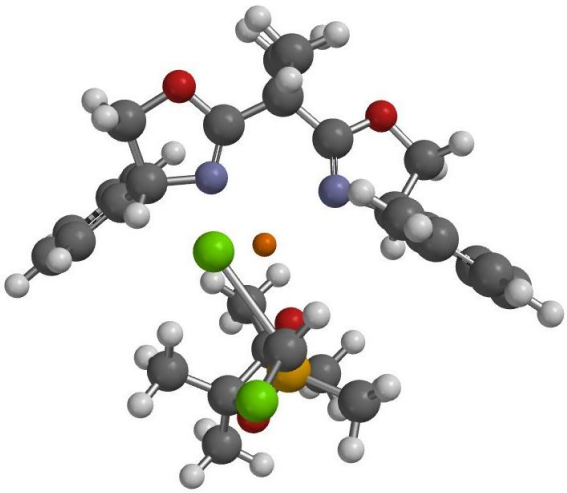
The same two general procedures (*in*- and *ex-situ*) have been applied separately in order to test 2,2-bis((4*S*)-(–)-4-isopropyloxazoline-2-yl)propane (**97**) in the reaction instead of **90**. Quantities: **97** (133 mg, 0.5 mmol), $Yb(OTf)_3$ (62 mg, 0.1 mmol), *n*-BuLi (0.75 mL, 1.6 M in hexane, 1.2 mmol) and (*S*)-pinanediol (171 mg, 1.0 mmol). The purification of the crude product afforded compound **89** (228 mg, 80%, *in-situ* procedure and 222 mg, 78% for *ex-situ* procedure). The product **89** was racemic in both cases.

2.7 Theoretical Methods and Details

The geometries of all transition states were fully optimised using DFT at the B3LYP/6-31G(d) level of theory using Spartan software.[87] All thermal and free energy contributions were calculated at 298.15 K.

2.7.1 Selected Computational Data

2.7.1.1 Transition State (R)



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O	1.014748	-3.785864	1.601101
C	2.109282	-1.680961	1.516012
H	1.942640	-0.881755	2.246138
C	2.117710	-3.074592	2.216525
H	3.031402	-3.646086	2.036858
H	1.922792	-3.022366	3.291474
C	-0.716242	-3.535778	-0.046435
C	-0.059783	-4.374456	-1.180763
H	0.635085	-5.098007	-0.745328
H	0.485236	-3.726420	-1.873734
H	-0.828315	-4.912509	-1.739866
C	-1.567520	-4.460716	0.862937
H	-0.947434	-5.262684	1.268559
H	-2.378296	-4.898736	0.275730
H	-2.001071	-3.900839	1.697986
C	-1.647350	-2.505726	-0.660113
N	-1.762346	-1.261331	-0.394070
O	-2.482946	-3.041632	-1.582445
C	-2.850619	-0.721267	-1.247701
H	-2.401826	0.049594	-1.880868
C	-3.269044	-1.944323	-2.114931
H	-4.324326	-2.210401	-2.019880
H	-3.004407	-1.826342	-3.168665
C	-3.994287	-0.117705	-0.452912
C	-6.191646	0.983374	0.911040
C	-4.603999	1.056793	-0.911278
C	-4.498468	-0.734118	0.700453
C	-5.587190	-0.186156	1.379513
C	-5.697217	1.603998	-0.237061
H	-4.215183	1.548277	-1.800161
H	-4.027368	-1.639914	1.074482
H	-5.963214	-0.671705	2.276785
H	-6.157230	2.516895	-0.606770
H	-7.039800	1.409312	1.440780
C	3.394870	-1.371046	0.764034
C	5.824844	-0.841419	-0.540856
C	4.522660	-0.966915	1.491945
C	3.495053	-1.504004	-0.625447
C	4.704683	-1.237233	-1.273392

C	5.731201	-0.707536	0.846750
H	4.451677	-0.843932	2.571306
H	2.620759	-1.785934	-1.203677
H	4.765141	-1.334083	-2.354144
H	6.595186	-0.390446	1.425001
H	6.762868	-0.631035	-1.047453
B	1.456064	2.466625	-0.052785
O	0.812778	3.730242	0.103631
O	0.705219	1.483320	0.751494
C	-0.140178	2.254416	1.652189
C	-0.423843	3.543723	0.797614
C	2.005122	1.949883	-1.413786
C	-0.711295	4.803538	1.618698
H	-0.849277	5.652130	0.940584
H	0.118356	5.043245	2.288283
H	-1.626307	4.694921	2.213901
C	-1.539112	3.336884	-0.242100
H	-2.528349	3.245624	0.220297
H	-1.349203	2.449368	-0.853727
H	-1.550601	4.201695	-0.913481
C	0.658375	2.550341	2.932493
H	1.036557	1.607038	3.342691
H	0.028977	3.021723	3.695158
H	1.509744	3.207534	2.739044
C	-1.375021	1.431055	2.011957
H	-1.084033	0.537473	2.576922
H	-1.929873	1.108508	1.129279
H	-2.055448	2.014281	2.643065
C	3.172552	2.665325	0.370236
Li	0.036664	-0.110781	-0.242972
H	3.994396	2.142289	-0.124052
Cl	0.259099	0.323133	-2.507988
H	3.341255	3.742213	0.305617
H	3.157352	2.328904	1.412228
Cl	2.427822	3.049525	-2.681151
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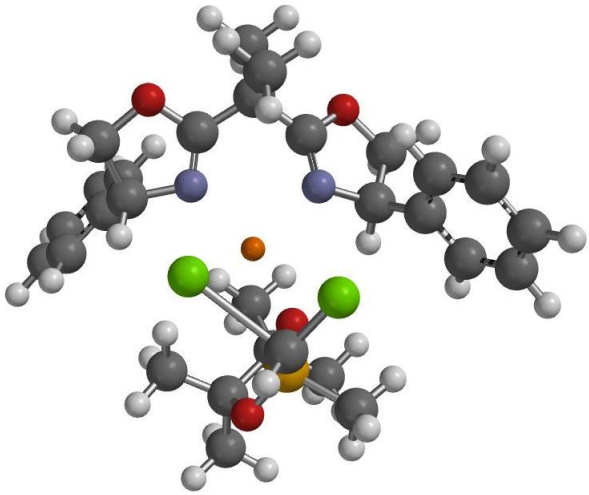
Imaginary frequency 277 cm^{-1} (intensity 327).

2.7.1.2 Transition State (S)



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H	1.804515	-0.127767	1.994791
C	1.890947	-2.256173	2.553894
H	2.814713	-2.785187	2.796462
H	1.385821	-1.952788	3.476024
C	-0.338990	-3.332781	-0.155994
C	0.475284	-3.853902	-1.373529
H	1.293554	-4.491267	-1.021958
H	0.892838	-3.022396	-1.947600
H	-0.173231	-4.443561	-2.026160
C	-0.957889	-4.527442	0.610021
H	-0.172241	-5.211425	0.938702
H	-1.644485	-5.064013	-0.048047
H	-1.507595	-4.192125	1.494895
C	-1.467426	-2.453193	-0.665394
N	-1.698781	-1.222414	-0.407254
O	-2.320925	-3.107841	-1.486523
C	-2.952488	-0.853780	-1.112334
H	-2.723565	-0.008953	-1.765996
C	-3.262945	-2.113029	-1.970347
H	-4.270292	-2.509286	-1.829817
H	-3.061205	-1.954303	-3.032569
C	-4.068480	-0.471756	-0.156553
C	-6.218709	0.205640	1.521999
C	-4.905395	0.606650	-0.468470
C	-4.321535	-1.205716	1.009739
C	-5.387422	-0.869443	1.844029
C	-5.975251	0.943263	0.362716
H	-4.712924	1.188540	-1.366904
H	-3.674951	-2.038730	1.272654
H	-5.567719	-1.445964	2.747880
H	-6.613964	1.784262	0.105895
H	-7.048204	0.468390	2.172978
C	3.511801	-0.966296	1.032730
C	6.184825	-0.785715	0.191020
C	4.357099	0.018678	1.554421
C	4.020784	-1.862718	0.085405
C	5.347407	-1.771840	-0.335355
C	5.686771	0.109633	1.138269
H	3.970324	0.724379	2.286635
H	3.369767	-2.619776	-0.342000
H	5.725999	-2.467412	-1.079849

H	6.328966	0.884300	1.548436
H	7.216961	-0.712234	-0.140781
B	1.117752	2.698142	-0.688856
O	0.220172	3.805187	-0.704500
O	0.706056	1.793614	0.375570
C	-0.137526	2.567541	1.274415
C	-0.791376	3.620315	0.294766
C	1.664671	2.098065	-1.997007
C	-1.084831	4.979350	0.940629
H	-1.506679	5.652734	0.187517
H	-0.177873	5.444864	1.334302
H	-1.813732	4.885286	1.755135
C	-2.062276	3.103959	-0.397099
H	-2.890829	2.966484	0.306442
H	-1.871982	2.166313	-0.925326
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C	0.767485	3.209951	2.337777
H	1.324552	2.421781	2.856630
H	0.181932	3.757353	3.083368
H	1.490116	3.898526	1.893809
C	-1.128204	1.628225	1.960699
H	-0.594123	0.924460	2.610693
H	-1.715703	1.049969	1.245729
H	-1.821382	2.196843	2.591428
C	2.806735	3.382687	-0.605810
Li	0.057274	0.079340	-0.580397
H	3.419816	3.600414	-1.482752
Cl	-0.345597	0.621511	-2.836115
H	2.559802	4.334730	-0.129483
H	1.664803	2.690912	-2.906987
Cl	2.841430	0.816126	-2.089010
H	3.367753	2.714000	0.050652

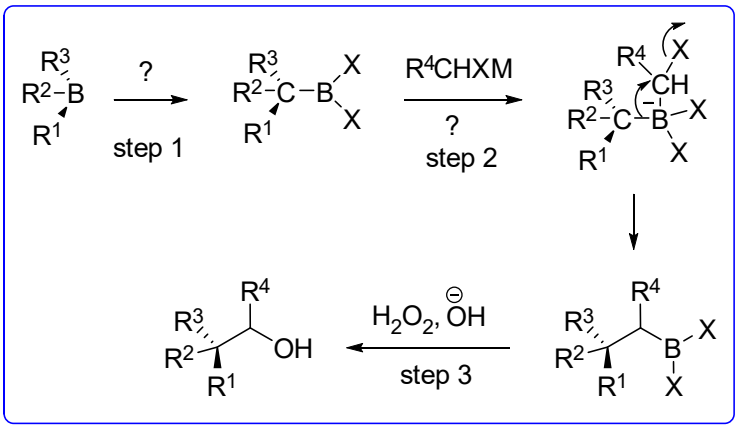
Imaginary frequency 420 cm^{-1} (intensity 404).

Chapter Three

Stoichiometric Studies on Dithiane Derivatives as DCME-like Reagents

3.1 Aims and Introduction

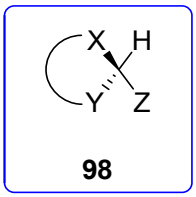
Brown and co-workers found that tri-*n*-butylborane reacts with representative trisubstituted methanes (chloroform, dichlorofluoromethane, chlorodifluoromethane and 1,1-dichloromethyl methyl ether (DCME)) under the influence of lithium triethylcarboxide. They discovered that a wide variety of trialkylboranes containing a tertiary alkyl group (*tert*-butyl or thexyl) readily react with DCME and triethylcarboxide at 25 °C with transfer of all three alkyl groups from boron to carbon in one process (step 1 of **Scheme 3.1**). However, there are no stereoselective examples of the DCME reaction.[88,89] Our goal in this chapter was to design a heterocyclic system as an alternative reagent which influences the three alkyl groups to migrate from boron to carbon in turn and stereoselectively at the first step (**Scheme 3.1**).



Scheme 3.1: The Strategy for Synthesis of Chiral Quaternary Carbon Centres

An alternative reagent to DCME, which has three different leaving groups attached to the central carbon atom, could allow the stereochemistry of the product to be controlled. Essentially, such a system would have to have three main important properties: first, it would need a proton located on the carbon atom that could be removed to generate the corresponding anion; second, groups with different leaving aptitudes in order that the three alkyl groups on boron migrate to the carbon atom in

sequence and as a result are able to influence the stereochemistry of the carbon next to boron; third, it would need to be chiral, and accessible as a single enantiomer. Ideally, the reagent would also have the rigidity imposed by incorporation of the groups into a heterocyclic system such as **98**. In order to begin a study of such ideas, compounds containing just two different leaving groups were first investigated.

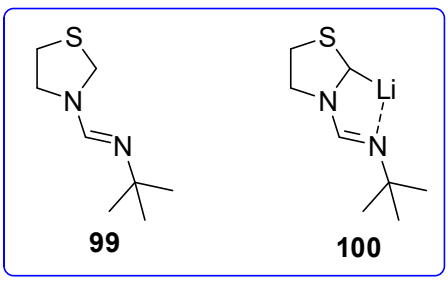


98

3.2 Results and Discussion

3.2.1 Synthesis of 2-Methyl-*N*-(thiazolidin-3-ylmethylene)propan-2-amine (99)

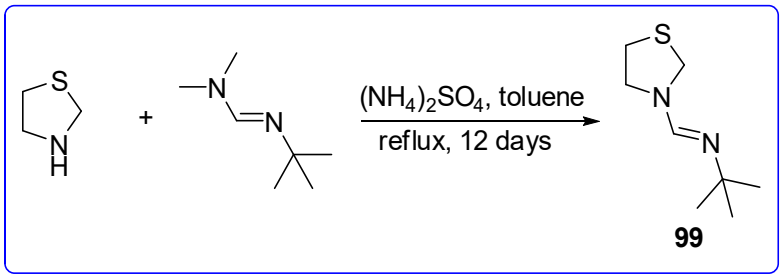
In the beginning, our attention was turned to the formamidine **99**. The compound **99** can provide not only two groups with different leaving aptitudes but also an additional element of stereocontrol by coordination of the lithium atom of its lithiated derivative with the imine nitrogen atom (**100**). Furthermore, more importantly, chiral formamidines have become accessible and they have been used widely in asymmetric organic synthesis.[90]



99 **100**

The compound **99** has been synthesised before[91] but no details of the procedure were given. Nevertheless, the compound **99** was synthesised by heating a mixture of

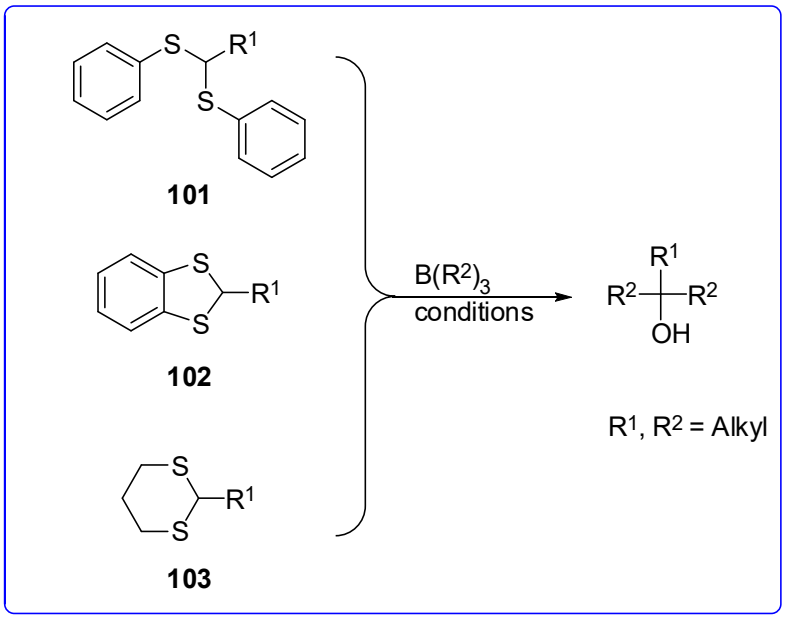
thiazolidine, *N,N*-dimethyl-*N'*-*tert*-butylformamidine and a few crystals of ammonium sulfate as a catalyst in toluene at reflux for 12 days. The conversion according to the ^{1}H NMR spectrum of the crude product was around 40% (**Scheme 3.2**). Unfortunately, the compound could not be purified by column chromatography since it decomposed on the silica gel.



Scheme 3.2: Synthesis of 2-Methyl-*N*-(thiazolidin-3-ylmethylene)propan-2-amine (**99**)

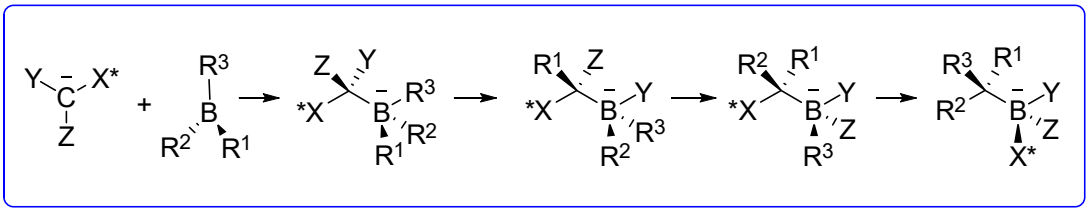
3.2.2 Synthesis of Dithiane Mono- or Di- Sulfoxide and Reactions with Trialkylboranes

Compounds containing sulfur leaving groups could provide the potential to carry stereoselective features. Indeed, several studies have used substituted sulfur compounds to achieve 1,2- boron to carbon migrations (**Scheme 3.3**).[92–95]



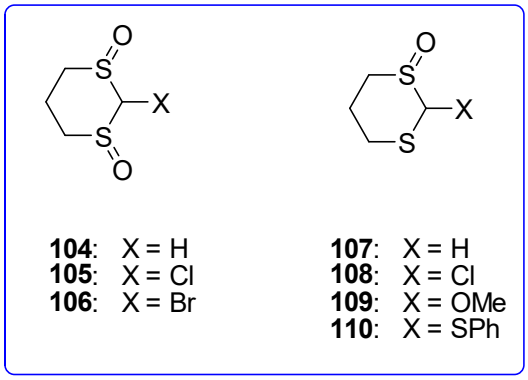
Scheme 3.3: Reactions of 2-Substituted 1,3-Disulfide Compounds with Trialkylboranes

These studies showed that metallation of such compounds and then addition to trialkylboranes, followed by addition of $HgCl_2$, induced two alkyl groups to migrate from boron to carbon. Ultimately, tertiary alcohols were produced since a third alkyl group is already present in the reagent. The aptitude of the sulfide groups to leave in all the above cases is equal. This means that there is no chance of enantiocontrol in the reaction as the two sulfide leaving groups compete to leave without any reagent stereocontrol. In order to introduce stereoselectivity into such a system, one of the leaving groups (X*) must incorporate a chiral unit. A chiral group X* might control the stereochemistry of the borate complex at the addition of anion to trialkylborate step (**Scheme 3.4**). It must then control stereochemistry of the carbon centre by directing the migration of the alkyl groups. Assuming that they migrate in order from R^1 to R^3 as a result of their migratory aptitudes, and the leaving groups have different leaving abilities, the stereochemistry could be controlled.

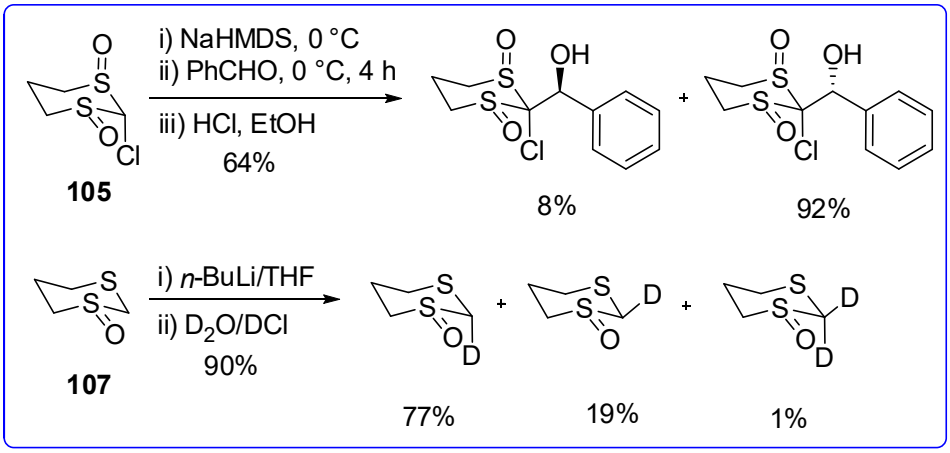


Scheme 3.4: Proposal Pathway for an Asymmetric Version of the DCME Reaction

The stereoselectivity of reactions of metallated 2-substituted-1,3-dithiane-1,3-dioxide (**104-106**) or 1-oxide (**107**) with electrophiles such as ketones, alkyl halides and aldehydes has been studied widely.[96–102]



These studies showed that the sulfoxide groups play a large role in determining the level of stereoselectivity (**Scheme 3.5**). Very high stereoselectivity (≈100:0) has been achieved for the reaction of metallated 2-halogeno-1,3-dithiane 1,3-dioxide (**105** and **106**) with benzaldehydes in moderate to good yield.[102] The reactions of metallated 2-substituted-1,3-dithiane-1-oxide (**107**) with electrophiles such as D_2O and benzophenone also gave high stereoselectivity and very good yields.[101] Organic chemists have recognised that these compounds are excellent strategic elements for synthesis of natural and unnatural products.



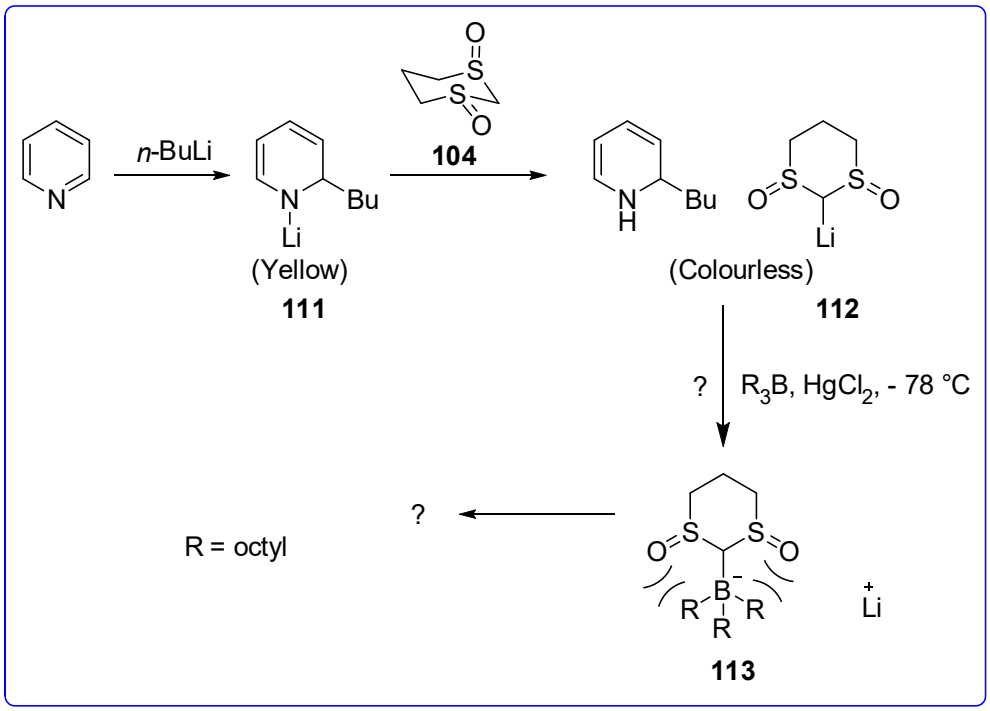
Scheme 3.5: The Stereoselective Reactions of 1,3-Dithiane Mono (**107**) and Di-oxides (**105**)

This drew our attention to the possibility of using such systems as stereocontrol auxiliary elements in reactions with trialkylboranes. To design appropriate thio compounds for such a purpose, three important objectives should be achieved: 1) stereoselective oxidation of one or both of the two sulfur atoms, which will help to orientate the migrating group stereoselectively; 2) insertion of a third leaving group at the carbon atom between the two sulfur atoms, and one with a different migratory aptitude to the sulfide or sulfoxide; and 3) generation of an anion sufficiently stable to survive long enough to react with trialkylboranes. It seemed likely that 2-substituted-1,3-dithiane-1-oxide (**108 – 110**) or *trans* or *cis*-2-sustituted-1,3-dithiane-1,3-dioxide (**105 – 106**) might meet these conditions. An important feature for these compounds would be the stereochemical configurations of the sulfoxide groups. Therefore, a detailed study of the reactions of these and other related systems with trialkylboranes has been undertaken.

The next section describes in greater detail the synthesis of such compounds and the examination of the sulfoxide and sulfide moieties as leaving groups in their reactions with trialkylboranes.

3.2.3 Reaction of *trans*-1,3-Dithiane-1,3-dioxide (104) with Trioctylborane

The *title compound* was prepared by adapting the procedure used by Aggarwal *et al.* (1991).[103] The reaction of the *trans*-2-lithio-1,3-dithiane-1,3-dioxide with various carbonyl compounds was studied previously.[104] The authors observed that the compound **104** could not be dissolved in THF but it was dissolved in pyridine instead. So, to lithiate *trans*-1,3-dithiane-1,3-dioxide, it was dissolved in pyridine, the solution was diluted with THF and then *n*-BuLi was added dropwise to generate 2-lithio-1,3-dithiane-1,3-dioxide **112** (colourless), *via* the transiently-formed lithium amide **111**. After the addition of one equivalent of the *n*-BuLi, an excess of the *n*-BuLi results in persistence of adduct of *n*-BuLi with pyridine **111** (yellow) (**Scheme 3.6**). This acts as an indicator of the completion of the addition of one equivalent; also it could be used to measure the concentration of the *n*-BuLi.[104] The solution of lithiated **104** was prepared according to this procedure and cooled to –78 °C. Among various trialkylboranes, tri-*n*-octylborane was chosen because its one, two and three migration products are all relatively easy to monitor. The tri-*n*-octylborane was prepared in a separate flask according to the literature procedure.[105,106] The resulting solution was transferred to the cold (–78 °C) solution of *trans*-2-lithio-1,3-dithiane-1,3-dioxide by cannula. Oxidising the expected adduct gave no sign of any migration product. Only 1-octanol was obtained even when $HgCl_2$ was used as an electrophile in an attempt to induce rearrangement.

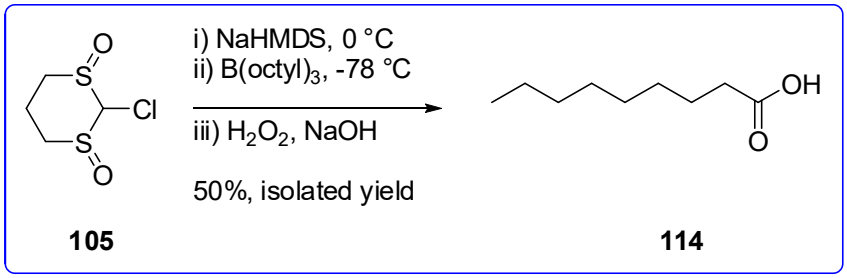


Scheme 3.6: Reaction of *trans*-1,3-Dithiane-1,3-dioxide (**104**) with Trioctylborane

This result may be explained either by no boron-carbon adduct (**113**) having been formed as a result of steric hindrance due to the two sulfoxide groups (**Scheme 3.6**) or by the sulfoxide groups not being good leaving groups. To check whether the adduct was being formed, inserting a good leaving group at position 2 was planned. Therefore, 2-chloro-1,3-dithiane-1,3-dioxide (**105**) was the next target.

3.2.4 Reaction of 2-Chloro-1,3-dithiane-1,3-dioxide (105) with Trioctylborane

The compounds **105** and **106** have been synthesised and their reactions with carbonyl compounds have been studied extensively by Aggarwal and co-workers.[102] In our work, 2-chloro-1,3-dithiane-1,3-dioxide was metallated by following the same procedure, using NaHMDS as a base at 0 °C, and then the addition of the trialkylborane was carried out at –78 °C. Oxidation of the solution with a basic solution of hydrogen peroxide yielded nonanoic acid (**114**) in moderate yield (50%) (**Scheme 3.7**). Also, the GC-MS spectrum showed that there was a trace of dioctyl ketone (two migrations) but it was not promising.



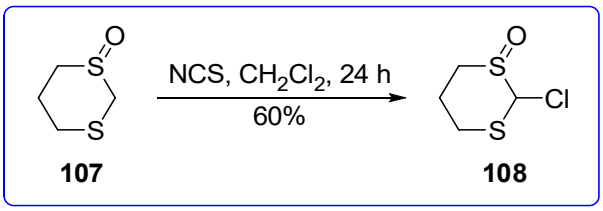
Scheme 3.7: Reaction of 2-Chloro-1,3-dithiane-1,3-dioxide (**105**) with Trioctylborane

Attempts to induce the second or third migration by adding an electrophile ($HgCl_2$) and heating at reflux failed. An implication of this is the possibility that only chlorine was replaced by an octyl group and the sulfoxide groups were not good enough leaving groups. However, even the yield of the one-migration product (carboxylic acid) was not promising. From these experiments, two important points can be concluded: first, the presence of two bulky sulfoxide groups possibly inhibits formation of the boron-carbon adduct, so that the yield of the one-migration product was low; second, the sulfoxide is not a good leaving group because no ketone or tertiary alcohol were produced even when activation by $HgCl_2$ or heating was used.

It seemed likely that a second migration might be achieved if one of the sulfoxide groups could be replaced with sulfide in order to make it more ready to leave. In order to do that, the 2-X-substituted-1,3-dithiane-1-oxide (**108 – 110**) was thought to be a good choice for this purpose.

3.2.5 Synthesis of 2-Chloro-1,3-dithiane-1-oxide (108) and Reaction with Electrophiles

2-Chloro-1,3-dithiane-1-oxide **108** was synthesised from compound **107** using the same method that was detailed for the compound **105** using *N*-chlorosuccinimide as a chlorinating agent (**Scheme 3.8**). The mixture of two diastereomers was isolated in a moderate yield (60%) (58:42 ratio) by column chromatography.



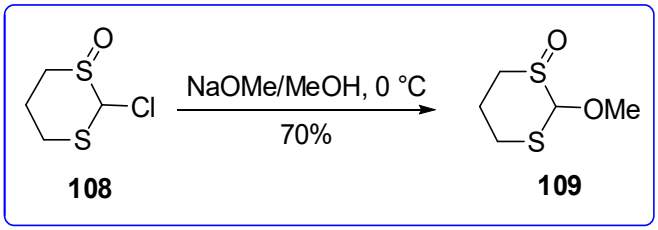
Scheme 3.8: Synthesis of 2-Chloro-1,3-dithiane-1-oxide (**108**)

Before proceeding to examine the compound in 1,2- boron to carbon migration rearrangement, it was decided to conduct a small study of metallation of **108**. Many attempts were carried out to investigate the metallation of **108** and its reactions with electrophiles. The reactions were carried out according to the following procedure: a solution of base was added to a solution of compound **108** at –78 °C, followed by addition of the electrophile (MeI, benzaldehyde or 3,4-dimethoxybenzaldehyde). Different bases (*n*-BuLi, NaHMDS and LDA) and temperatures (0 °C, –78 °C and -100 °C) were investigated in this reaction. Attempts to generate the methylated product, in this way, with iodomethane were not successful. Also, the reaction with benzaldehyde or 3,4-dimethoxybenzaldehyde did not result in identification of any halohydrin products. A possible explanation for these results may be the lack of stability of the metallated derivative of the compound **108**. Thus, to stabilise the anion, manipulation of the structure could be useful. Replacement of the chloride group by an alkoxy group could make the anion more stable. This can be done by substitution of the chloride of **108** with sodium methoxide.

The next part describes the synthesis and evaluation of the reaction of 2-methoxy-1,3-dithiane-1-oxide (**109**).

3.2.6 Synthesis and Reactions of 2-Methoxy-1,3-dithiane-1-oxide (109)

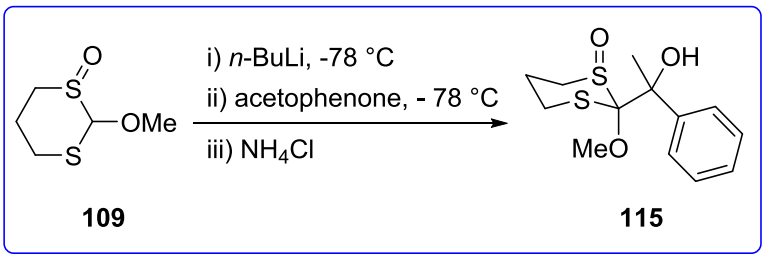
It was decided that the best method to adopt for this synthesis was to add sodium methoxide to a solution of compound **108** in THF at –78 °C. Indeed, the reaction (**Scheme 3.9**) gave diastereomers of 2-methoxy-1,3-dithiane-oxide (**109**) in a moderate yield (70%, 81:19 ratio after purification; the enrichment could be a result of purification) .



108 **109**

Scheme 3.9: Synthesis of 2-Methoxy-1,3-dithiane-1-oxide (**109**)

It was found that the generation of 2-lithio-2-methoxy-1,3-dithiane-1-oxide was easier and the anion was more stable than in the case of **108**. Addition of *n*-BuLi to a solution of the compound in THF at –78 °C, followed by addition of acetophenone, gave the crude product. The low resolution positive ion (ES^+) mass spectrum of the compound showed *pseudo*-molecular ion peaks $(M+Na+CH_3CN)^+$ at *m/z* = 350 (60%) and $(M+Na)^+$ at 309 (47%), consistent with the formulae $C_{15}H_{21}NNaO_3S_2$ and $C_{13}H_{18}NaO_3S_2$, respectively. These assignments were further supported by accurate mass data from the high resolution mass spectrum. Therefore it seemed likely that the desired product **115** (**Scheme 3.10**) had been formed. However, it was difficult to identify the product in the ^1H NMR spectrum of the crude product, due to the presence of impurities.



109 **115**

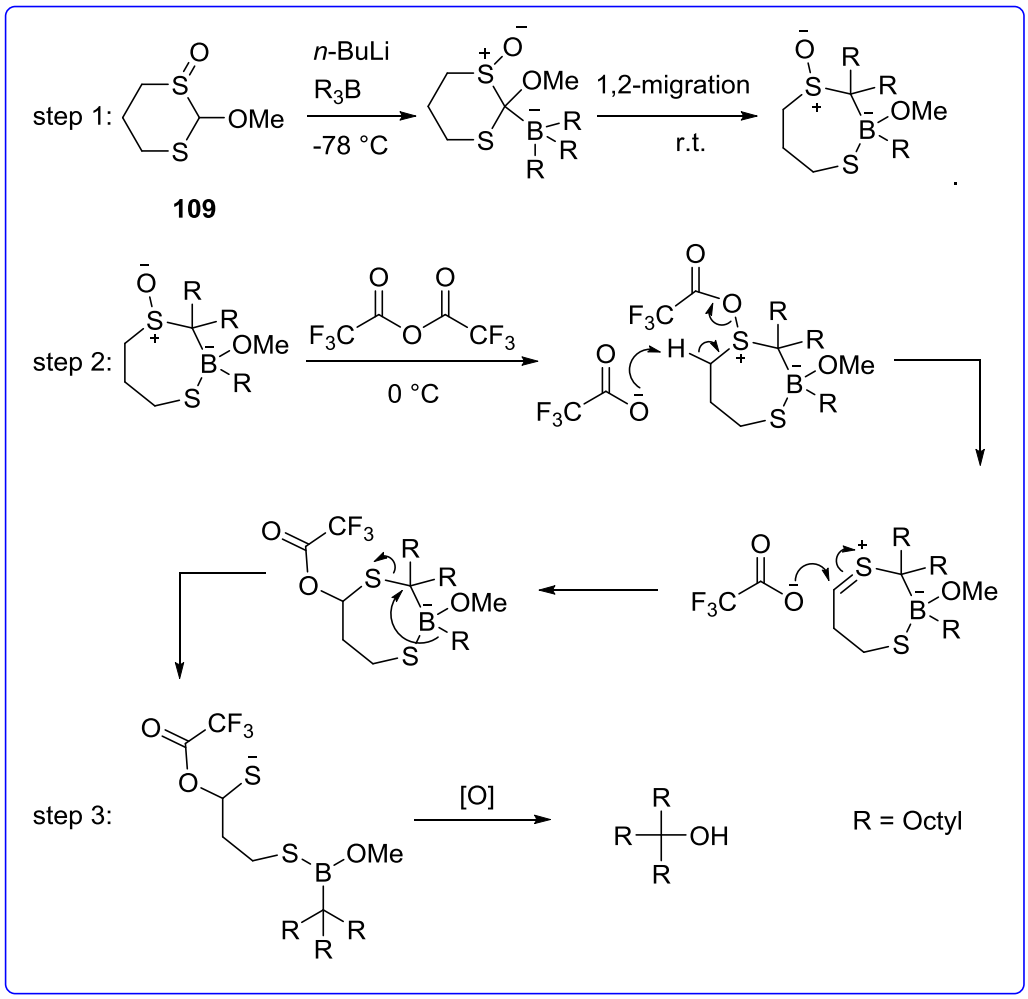
Scheme 3.10: Reactions of 2-Methoxy-1,3-dithiane-1-oxide (**109**) with Acetophenone

It was hard to purify the product by column chromatography, since it decomposed on the silica gel. Other electrophiles: methyl iodide, benzyl bromide and benzophenone, were used to trap the anion but none of their products were separated as a result of similar problems. Nevertheless, the possible formation of compound **115** was encouraging to study the reaction of compound **109** in more detail. It was therefore

worth checking whether the reaction of 2-lithio-2-methoxy-1,3-dithiane-oxide with other electrophiles such as trialkylboranes might take place and lead to boron-to-carbon 1,2-migration reactions.

For the same aforementioned reasons, tri-*n*-octylborane was chosen for the reaction and *n*-BuLi was used as a base. Tri-*n*-octylborane was prepared as above. The reaction of tri-*n*-octylborane and **109**/*n*-BuLi, followed by oxidation gave the desired dioctyl ketone (**116**) and 1-octanol (**117**). The isolated yield of the dioctyl ketone (**116)** was 11% and 1-octanol (**117**) (72% of all octyl groups of tri-*n*-octylborane). An alternative procedure was applied to improve the yield by mixing compound **109** and tri-*n*-octylborane before addition of *n*-BuLi. The yield of dioctyl ketone (**116**) did not improve (13%). The product was purified by flash column chromatography on silica gel and characterised by ^{1}H NMR and ^{13}C NMR spectroscopy. Response factors with respect to a hydrocarbon internal standard (tetradecane) were measured for both products. Thereafter, the yields were determined by GC analysis.

The reaction was repeated and the yield, as measured by GC analysis, was 16%, which required considerable optimisation. Before optimsing the reaction to get high yield, it was worth trying to induce the third alkyl group to migrate. From the reaction of compounds **104** and **105** with trialkylborane, it was concluded that the sulfoxide was not a good leaving group. Also, the evidence from this reaction suggested that sulfides were better leaving groups. So, the third migration might be achievable if the remaining sulfoxide group was converted into a sulfide group. There is a powerful method in the literature that can be used for this purpose. The Pummerer rearrangement is a well known method for conversion of a sulfoxide into a sulfide.[107] The method uses acetic anhydride or TFAA. The same procedure was followed as in the previous experiment, but after warming the reaction solution to room temperature over a period 1 h, TFAA (1.3 equiv.) was added at 0 °C and the mixture was stirred for three hours. The solution was warmed to room temperature and oxidised. The reaction was successful and the product of this reaction was a mixture of dioctyl ketone (**116**) (4%), trioctylmethanol (**118**) (6%) and 1-octanol (**117)** (69% of all octyl groups of tri-*n*-octylborane). A plausible mechanism for this rearrangement is depicted in **Scheme 3.11**.



Scheme 3.11: Induction of the Third Migration *via* Pummerer Rearrangement

Once the third migration was achieved, attempts at the optimisation of the two migration reactions were carried out. The low yield of the dioctyl ketone by using *n*-BuLi might be because the dithiane had not been converted to 2-lithio-2-methoxy-1,3-dithiane-oxide completely. So, in order to optimise the yield of double migrations, it was decided to repeat the reaction using stronger bases such as *sec*- or *tert*-BuLi which might increase the yield. The yields of dioctyl ketone are summarised in **Table 3.1**.

Table 3.1: Reaction of 2-Methoxy-1,3-dithiane-oxide (**109**) with tri-*n*-Octylborane Using Three Different Alkyllithium Bases (1.1 equiv.)

Base	Dioctylketone GC yield (%)
n-BuLi	16
sec-BuLi	28
tert-BuLi	12

Interestingly, *sec*-BuLi improved the yield significantly to 28%. However, it is surprising that with the strongest base (*tert*-BuLi) the yield dropped even further (12%) relative to the *n*-BuLi (16%). The increase of the yield in the *sec*-BuLi case compared with *n***-**BuLi and *tert*-BuLi could be due to a number of factors – e.g. the *sec***-**BuLi is stronger than *n*-BuLi meanwhile less bulky than *tert*-BuLi.

After identifying the best alkyllithium base, many experiments were performed, in attempts to improve the yield using *sec*-BuLi. Manipulation of the stoichiometry of the *sec*-BuLi by using 1.0, 1.1, 1.2 and 1.8 equivalents gave the results summarised in **Table 3.2**/.

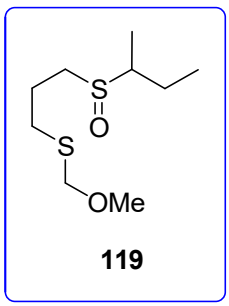
Table 3.2: Reaction of (**109**) with tri-*n*-Octylborane Using Various Equivalents of *sec*-BuLi

Equivalents of the *sec*-BuLi	GC Yield of dioctylketone (%)
1.0	20
1.1	28
1.2	31
1.4	5
1.8	0

It is apparent from this table that the highest yield (31%) was achieved when 1.2 equivalents was used. Decreasing the base to 1.0 equivalents reduced the yield to 20%. Increasing the base to more than 1.2 equivalents decreased the yield as well. Furthermore, it went down to 0% when 1.8 equivalents were used.

Cooling the reaction mixture further to –100 °C did not improve the yield, again giving 31%. To answer the question why the yield was low, it was needed to see whether 2-lithio-2-methoxy-1,3-dithiane-oxide was generated in full conversion. Thus, 2-lithio-2-methoxy-1,3-dithiane-oxide needed to be generated, then quenched by protonation to check whether only the dithiane would be recovered. An experiment was designed for this purpose.

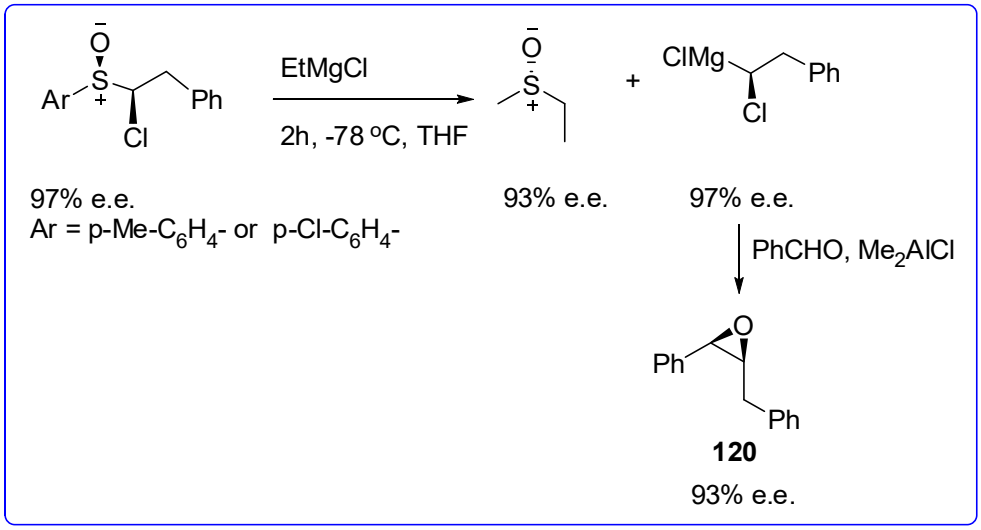
A solution of dithiane **109** in THF was cooled to –78 °C and 1.2 equivalents of *sec*-BuLi were added. When the reaction was quenched with a saturated solution of ammonium chloride, an unknown compound was formed (as seen in the ^{1}H NMR spectrum of the crude product). The product was separated and the structure was confirmed by full characterisation. Surprisingly, the main product, observed, in significant yield (40%) was 1:1 ratio of a mixture of two diastereoisomers of (3-(*sec*-butylsulfinyl)propyl)(methoxymethyl))sulfane (**119**), the result of addition of *sec*-butyllithium to the sulfoxide group.



119

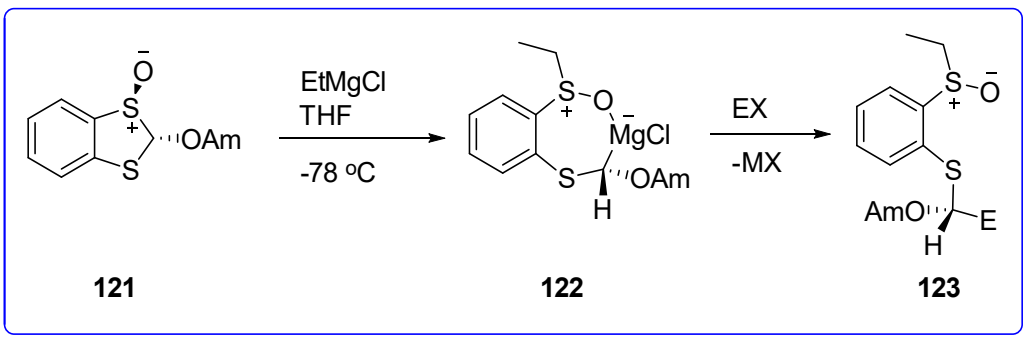
3.2.7 Possible Explanation of Formation of 119

It is well known that sulfoxide/magnesium exchange can be used to generate chiral Grignard reagents. Hoffmann and his co-workers used this method to synthesise the epoxide **120** in high stereoselectivity (93 % e.e.) (**Scheme 3.12**).[51]



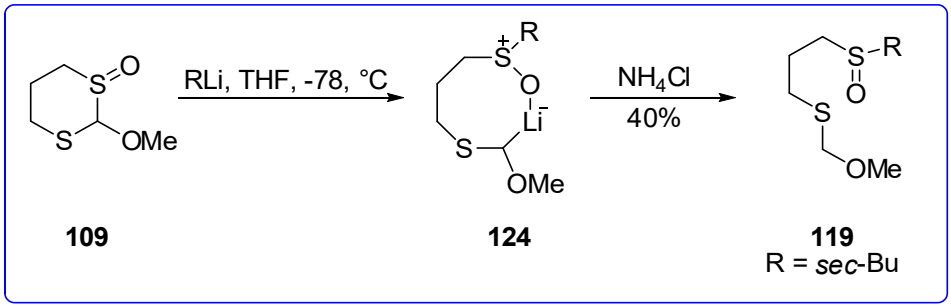
Scheme 3.12: Synthesis of Epoxide Stereoselectively *via* Chiral Grignard Reagents-Sulfoxide/Magnesium Exchange

Recently, Barsamian and Blakemore applied the sulfoxide-ligand exchange to generate α-metallated *S*,*O*-acetal **122** from dithioorthoformate **121** (**Scheme 3.13**).[108]



Scheme 3.13: Application of Sulfoxide-Ligand Exchange

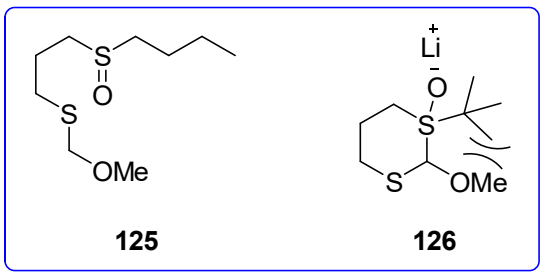
Similarly, in the dithiane case, **109** could undergo this reaction with alkyllithium reagents through lithium anion **124** to produce (3-(*sec*-butylsulfinyl)propyl) (methoxymethyl)sulfane **119** (**Scheme 3.14**).



Scheme 3.14: Reaction of the Alkyllithium with **109**

This provides an explanation for the dramatic dropping of dioctylketone yield to 0% when 1.8 equivalent of *sec*-BuLi was used. Increasing the amount of base favours addition to the sulfoxide rather than deprotonation of the dithiane.

To check whether the other alkyllithium reagents behave similarly to *sec*-BuLi, the experiment was repeated by using *n*-BuLi and *tert*-BuLi respectively. The former gave similar result to the *sec*-BuLi ((3-(butylsulfinyl)propyl) (methoxymethyl)sulfane (**125**), 49%) while the *tert*-BuLi gave only **109** as main product. *tert*-BuLi is sterically hindered and it might not be able to form the intermediate **126** by this mechanism.



Unfortunately, although the *tert*-BuLi does not undergo the sulfoxide-ligand exchange, it did not give a good yield of dioctylketone either (12%). It is possible that the

deprotonation of **109** by this base did not go to complete conversion for the same reason.

The aforementioned issue caused us to turn the attention to looking for an alternative base. It could be solved by using lithium amide bases such as LDA, LiTMP or LiHDMS instead of alkyllithium reagents. Before using these bases, it was necessary to check whether they undergo sulfoxide-ligand exchange.

LDA was chosen for this purpose. LDA was prepared by adding *n*-BuLi to a solution of diisopropylamine in THF at –78 °C and warming it to 0 °C and then added to the solution of **109**. After quenching the reaction with ammonium chloride, the ^{1}H NMR spectrum of the crude product showed that only the starting materials were recovered. This means that such bases do not undergo sulfoxide**-**ligand exchange, so that they might be suitable in the reaction.

Three experiments of reaction of **109** and tri-*n*-octylborane were repeated by using LDA, LiTMP and LiHDMS, respectively, using 1.1 equivalents of each at –78 °C. The GC yields are listed in **Table 3.3**.

Table 3.3: Reaction of **109** with tri-*n*-Octylborane Using Three Bases, LDA, LiTMP and LiHDMS (1.1 equiv.)

Base	**GC Yield of dioctylketone (%)**
LDA	20
LiTMP	12
LiHDMS	18

It is apparent from this table that no increase in the yield was detected, compared to *sec*-BuLi. It is somewhat surprising that no improvement was noted in all cases and the yield has not been increased higher than that obtained when *n*-BuLi was used. In an attempt to make an improvement in the yield, the reaction of **109** with tri-*n*-octylborane was repeated under different conditions and the GC yields are

summarised in **Table 3.4**. The reaction was carried out with two different quantities of LDA (1.1 and 5 equiv.) and at two different temperatures (–78 °C and 0 °C). 1.1 Equivalents of LDA at –78 °C gave only 20% of the dioctylketone. Increasing the LDA to 5 equivalents did not improve the yield but actually decreased it even further down to 5%. The role of temperature was key to improve the yield slightly higher. Running the reaction at a higher temperature (0 °C) improved it to 30%.

Table 3.4: Reaction of **109** with tri-*n*-Octylborane Using LDA

Equivalent of LDA	**GC Yield of dioctylketone (%)**	**Description**
5	3	Using 5 equiv. of LDA
1.1	20	At –78 °C
1.1	30	At 0 °C

Contrary to expectations, the yield did not improve higher than that obtained when *n*-BuLi was used, although the LDA does not undergo sulfoxide-ligand exchange. It is possible that lithium amide bases are not strong enough to deprotonate compound **109** completely. It was thought that using a strong base such as LICKOR might give better deprotonation.

LDA-LICKOR base was prepared according to a literature procedure.[109] After preparing the base, the compound **109** was added to the base, followed by tri-*n*-octylborane. No increase in yield was detected; only 8% GC yield of dioctyl ketone was observed in this reaction.

Replacing the oxygen by sulfur might give a better stability of the lithiated species and might help to improve the yield. The next section describes the synthesis and evaluation of reaction of 2-thiophenyl-1,3-dithiane-1-oxide (**110**) with trialkylboranes.

3.2.8 Synthesis and Reaction of 2-Thiophenyl-1,3-dithiane-1-oxide (110)

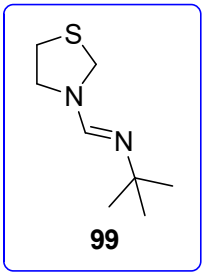
Compound **110** was synthesised using the same method that was detailed for **109**. Sodium thiophenoxide solution was prepared first by dissolving 1.0 equivalents of sodium metal in thiophenol, and this was added to 2-chloro-1,3-dithiane-1-oxide. Two diastereoisomers were obtained (65:35) and one diastereoisomer was isolated from the crude reaction mixture by flash column chromatography (30%). In order to assess the reaction of lithiated **110** with trialkylborane, a reaction of lithiated **110** with tri-*n*-octylborane at –78 °C was conducted and the yields of the alcohol and ketone were monitored by GC. The GC yield showed that 1-octanol was the main product and only 4% of dioctyl ketone was formed. These results were not very encouraging, so the study on these compounds was discontinued at this point.

3.2.9 Conclusion

The work in this chapter was undertaken to design and evaluate a heterocyclic system as a stereocontrol agent in its reaction with trialkylboranes. This study has shown that 2-chloro-1,3-dithiane-1,3-dioxide achieved only one migration in moderate yield. It was also shown that 2-methoxy-1,3-dithiane-1-oxide has achieved two migrations in poor yield and three migrations under the influence of TFAA. It is unfortunate that the yield could not be improved higher than 31%. More broadly, research is also needed to evaluate non-cyclic sulfur compounds such as sulfoxides, sulfoximines, sulfilimines and sulfones. The next chapter describes synthesis and assessment of these compounds.

3.3 Experimental

3.3.1 Preparation of 2-Methyl-*N*-(thiazolidin-3-ylmethylene)propan-2-amine[110] (99)



99

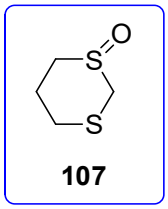
Thiazolidine (0.16 mL, 2.0 mmol), *N,N*-dimethyl-*N'*-*tert*-butyl formamidine (0.32 mL, 2.0 mmol) and ammonium sulfate (*ca*. 50 mg) were mixed in a 50 mL round bottomed flask. The flask was connected to a septum-capped condenser. The equipment was flushed with N_2 for 10 min and toluene (15 mL) was added. The reaction mixture was heated to reflux under nitrogen for 12 days. The solvent was evaporated to yield a colourless oil which was shown to contain a 2:3 mixture of thiazolidine and 2-methyl-*N*-(thiazolidin-3-ylmethylene)propan-2-amine according to ^{1}H NMR spectroscopy. The product mixture was subjected to Kugelrohr distillation at 60 – 65 °C and 1 Torr to give small quantity of the *title compound* (23 mg, 7%).

$\nu_{max.}$ (neat) 3036, 2975, 2919, 2872, 1660, 1387 and 1203 cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.35 (1H, s, C*H*=N-), 4.41 (2H, s, -NCH_2S-), 3.62 (2H, t, *J* = 6.3 Hz, CH_2N), 2.87 (2H, t, *J* = 6.3 Hz, CH_2S) and 1.13 (9H, s, 3 × CH_3).

^{13}C NMR (125 MHz; $CDCl_3$) δ 148.5 (CH), 53.7 (quat C), 50.8 (CH_2), 50.2 (CH_2), 31.0 (CH_3) and 30.5 (CH_2).

3.3.2 Preparation of 1,3-Dithiane-1-oxide[111] (107)



107

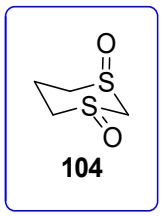
A solution of 1,3-dithiane (0.60 g, 5.0 mmol) in methanol (40 mL) was placed in a 250 mL flask. The flask was immersed in an ice-bath and an aqueous solution (35 mL) of sodium metaperiodate (1.07 g, 5 mmol) was added at such a rate (over approximately 30 min) to keep the temperature below 20 °C**.** The solution was stirred at the same temperature for an additional 30 min. The precipitate was removed by filtration and washed thoroughly with dichloromethane and the resulting solution taken to near dryness on the rotary evaporator. Extraction of the solids with dichloromethane, drying the extract over magnesium sulfate and removal of the solvents gave the *title compound* (0.582 g, 85%) as a colourless solid.

m.p. 85 – 86 °C (lit.[111] 86 – 87 °C)

^{1}H NMR (400 MHz; $CDCl_3$) δ 3.99 (1H, d, *J* = 12.7 Hz), 3.63 (1H, d, *J* = 12.7 Hz), 3.39 - 3.24 (1H, m), 2.71 – 2.43 (4H, m) and 2.32 – 2.10 (1H, m).

^{13}C NMR (125 MHz; $CDCl_3$) δ 52.9, 50.4, 28.3 and 27.1.

3.3.3 Preparation of *trans*-1,3-Dithiane-1,3-dioxide[103] (104)



104

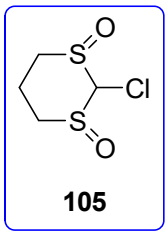
To a suspension of 1,3-dithiane (1.20 g, 10 mmol, 1 equiv.) in MeOH/H_2O (35:3.5 mL), sodium periodate (5.35 g, 25 mmol, 2.5 equiv.) was added in one portion. The mixture

was stirred for 96 h at room temperature. Dimethyl sulfide (0.75 mL, 10 mmol, 1 equiv.) was added and the solution stirred for an additional 30 min. Removing the solvents under vacuum left a white solid product which was extracted with acetone-ethanol (5:1) and then passed through a short pad of silica gel using additional acetone-ethanol (5:1) as eluent. After evaporation of the solvent, the *cis* and *trans* mixture was purified by flash column chromatography on silica gel with acetone as eluent to give the *trans* isomer of the *title compound* (0.94 g, 62%) as a colourless solid, m.p. 171 – 172 °C (lit.[103] 170 – 171 °C).

^{1}H NMR (500 MHz; d_6-DMSO) δ 4.34 (2H, s), 3.27 – 3.15 (2H, m), 3.02 – 2.91 (2H, m) and 2.66 – 2.15 (2H, m).

^{13}C NMR (125 MHz; d_6-DMSO) δ 61.8, 47.6 and 14.9.

3.3.4 Preparation of 2-Chloro-1,3-dithiane-1,3-dioxide[102] (105)



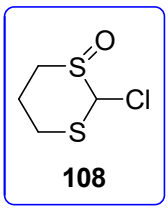
105

Trans-1,3-Dithiane-1,3-dioxide (152 mg, 1.0 mmol) was placed in a 25 mL round bottomed flask. The flask was fitted with a septum and flushed with nitrogen. Dry dichloromethane (10 mL) was added and the substrate was dissolved with stirring. *N*-Chlorosuccinimide (147 mg, 1.1 mmol) was added and the mixture was stirred at room temperature for 23 h. The solvent was evaporated and the product purified by flash column chromatography (silica, 1:9 EtOH/EtOAc) to afford the *title compound* (158 mg, 85%) as a colourless solid, m.p. 139 – 141 °C (lit.[102] 141 - 142 °C)

^{1}H NMR (500 MHz; $CDCl_3$) δ 5.93 (1H, s), 3.46 – 3.08 (3H, m), 2.97 (1H, m), 2.85 – 2.60 (1H, m) and 2.48 – 2.16 (1H, m).

^{13}C NMR (125 MHz; $CDCl_3$) δ 75.3, 45.4, 41.4 and 14.5.

3.3.5 Synthesis of 2-Chloro-1,3-dithiane-1-oxide (108)



108

1,3-Dithiane-1-oxide (136 mg, 1.0 mmol) was place in a 25 mL round bottom flask. The flask was equipped with a septum and flushed with nitrogen. Dry dichloromethane (10 mL) was added and the substrate was dissolved with stirring. *N*-Chlorosuccinimide (147 mg, 1.1 mmol) was added and the mixture was left to stir at room temperature for 23 h. The solvent was evaporated and the product purified by flash column chromatography on silica using 0-10% EtOAc/Et_2O as eluent to give a mixture (58:42 ratio) of diastereomers of the *title compound* (0.103 g, 60%) as a light yellow solid, m.p. 48-70 °C.

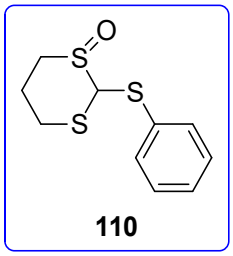
$\nu_{max.}$ (NaCl film) 2995, 2940, 2844 and 1423 cm^{-1}.

^1H NMR (400 MHz; $CDCl_3$) the individual proton signals of the two isomers overlapped considerably and only the signals for the C*H*Cl protons attached to carbon 2 in the two isomers could be reliably differentiated – other assignments are made to give an indication of relative integration of peaks; δ 5.90 (1H of major isomer, s), 5.49 (1H of minor isomer, s), 3.33 – 3.04 (2H of major isomer and 1H of minor isomer, m), 3.04 – 2.89 (1H of major isomer and 1H of minor isomer, m), 2.87 – 2.74 (1H of minor isomer, m), 2.68 – 2.55 (1H of major isomer, m), 2.46 – 2.17 (2H of major isomer and 2H of minor isomer, m) and 1.83 – 1.64 (1H of minor isomer, m).

^{13}C NMR (100 MHz; $CDCl_3$) (major isomer): δ 74.0 (CH), 45.9 (CH_2), 28.9 (CH_2) and 23.1 (CH_2); (minor isomer): 70.2 (CH), 41.0 (CH_2), 29.7 (CH_2) and 23.3 (CH_2).

MS (EI) *m/z* (%) 172 (M^+, ^{37}Cl, 12%), 170 (M^+, ^{35}Cl, 36), 135 (16), 106 (100), 90 (95), 64 (30). HRMS: Found: M^+, 169.9630. $C_4H_7ClOS_2$ requires M, 169.9627.

3.3.6 Synthesis of 2-Thiophenyl-1,3-dithiane-1-oxide (110)[112]



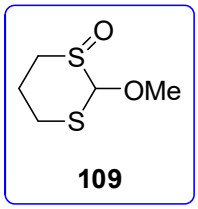
110

Sodium metal (89 mg, 3.9 mmol) was placed in a 25 mL flask and the flask was sealed and flushed with nitrogen for 10 min. Thiophenol was added at room temperature and the solution was stirred until all sodium pieces dissolved in the thiophenol. This solution was added to a solution of 2-chloro-1,3-dithiane-1-oxide (**108**) (0.667 g, 3.9 mmol) in THF (10 mL). The mixture was stirred for 12 h before being saturated with a solution of sodium chloride. The organic layer was separated and the aqueous layer was extracted with chloroform (3 × 20 mL). The organic layers were combined and dried over magnesium sulfate. The solvents were removed to give a mixture of two diastereoisomers of the *title compound* (65:35). One of the two diastereoisomers was separated by flash column chromatography on silica (10% ethyl acetate/diethyl ether), (290 mg, 30%) as a yellow oil.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.75 – 7.60 (2H, m), 7.36 – 7.29 (3H, m), 5.09 (1H, s), 3.20-2.88 (3H, m) and 2.49 – 2.16 (3H, m).

^{13}C NMR (125 MHz; $CDCl_3$) δ 133.9 (CH), 132.8 (quat C), 129.5 (CH), 128.8 (CH), 69.2 (CH), 47.3 (CH_2), 28.7 (CH_2) and 24.2 (CH_2).

3.3.7 Synthesis of 2-Methoxy-1,3-dithiane-1-oxide (109)



109

Sodium metal (14 mg, 0.6 mmol) was placed in a 25 mL flask and the flask was sealed and flushed with nitrogen for 10 min. The flask was immersed in an ice-bath and MeOH (10 mL, excess) was added. After evolution of hydrogen stopped, the solution of sodium methoxide was transferred dropwise by syringe to a cooled (0 °C) and dry solution of 2-chloro-1,3-dithiane-1-oxide (**108**) (103 mg, 0.6 mmol) in THF (4 mL). The mixture was warmed up to room temperature and stirred for 1 h. The solvents were evaporated and the resulting solid was dissolved in $CHCl_3$ (3 × 10 mL) and washed with brine. The organic layer was dried over magnesium sulfate. The solvent was evaporated and the crude product was purified by flash column chromatography on silica gel and 10% EtOAc/diethyl ether to yield two diastereomers (81:19 ratio) of the *title compound* (70 mg, 70%) as a light yellow oil.

$\nu_{max.}$ (neat) 2935, 2907, 2831, 1424, 1084 and 1029 cm^{-1}.

^1H NMR (400 MHz; $CDCl_3$), δ 5.32 (1H of major isomer, s), 5.01 (1H of minor isomer, s) 3.75 (3H of major isomer, s), 3.64 (3H of minor isomer, s), 3.36 (1H of major isomer, td, *J* = 12.8, 2.8 Hz), 3.12 (1H of minor isomer, t, *J* = 6.6 Hz), 3.01-2.95 (1H of each isomer, m), 2.87 – 2.80 (1H of each isomer, m), 2.69 – 2.54 (1H of minor isomer, m) and 2.42 – 2.20 (3H of major isomer and 2H of minor isomer, m).

^{13}C NMR (100 MHz; $CDCl_3$) (major isomer): δ 90.1 (CH), 59.5 (CH_3), 45.2 (CH_2), 29.2 (CH_2) and 22.2 (CH_2); (minor isomer): δ 93.2 (CH), 58.7 (CH_3), 42.2 (CH_2), 31.0 (CH_2) and 23.2 (CH_2).

MS (EI) *m/z* (%) 166 (M^+, 68%), 135 (5), 106 (100), 90 (98) and 64 (95); HRMS: Found: M^+, 166.0125. $C_5H_{10}O_2S_2$ requires M, 166. 0122.

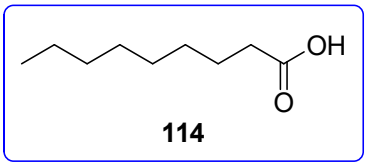
3.3.8 Reaction of *trans*-1,3-Dithiane-1,3-dioxide (104) with Trioctylborane

Solution 1. To a septum-capped 50 mL flask, borane (0.30 mL, 10.0 M in dimethyl sulfide, 3.0 mmol, 1 equiv.) was added, followed by THF (10 mL). The flask was immersed in an ice-bath and 1-octene (1.46 mL, 9.3 mmol, 3.1 equiv.) was added dropwise. The cooling bath was removed and the solution was stirred at room temperature for 1 h. The solution was cooled to –78 °C to be used in the next step.

Solution 2. *Trans*-1,3-dithiane-1,3-dioxide (**104**) (0.457 g, 3.0 mmol) was placed in a 50 mL flask and the flask was sealed with a septum and flushed with N_2 for 10 min. Pyridine (15 mL) was added and the solution was dissolved by heating and then diluted with THF (10 mL). The solution was cooled to 0 °C and *n*-BuLi (1.9 mL, 1.6 M in hexane, 3.0 mmol, 3 equiv.) was added dropwise until permanent appearance of a yellow colour. The solution was cooled to –78 °C.

Solution 1 was transferred by cannula into solution 2 and stirred for 15 min at the same temperature before being allowed to warm to room temperature over a period of 1 h. The solution was oxidised by adding sodium hydroxide (3.0 M, 10 mL) followed by hydrogen peroxide (30% aqueous, 6 mL). The solution was stirred overnight. The aqueous layer was saturated with sodium chloride and extracted with chloroform (2 x 20 mL). The organic layers were combined and washed with saturated aqueous copper sulfate solution (2 x 20 mL). The organic layer was dried over magnesium sulfate and the solvents were evaporated. Only 1-octanol was seen in the ^{1}H NMR spectrum which means either there was no adduct formed between dithiane dioxide and trialkylborane or no migration had taken place.

3.3.9 Reaction of 2-Chloro-1,3-dithiane-1,3-dioxide with Trioctylborane



114

To a septum-capped 25 mL flask, borane (0.08 mL, 10.0 M in dimethyl sulfide, 0.8 mmol, 1 equiv.) was added followed by THF (5 mL). The flask was immersed in an ice-bath and 1-octene (0.40 mL, 2.5 mmol, 3.1 equiv.) was added dropwise. The cooling bath was removed and the solution was stirred at room temperature for 1 h. The solution was cooled to –78 °C to be used in the next step.

NaHMDS (1.0 M in THF, 0.96 mL, 1.2 equiv.) was added to a cooled suspension (0 °C) of 2-chloro-1,3-dithiane-1,3-dioxide (150 mg, 0.8 mmol, 1 equiv.) in THF (6 mL). The mixture was then cooled to –78 °C and the solution of tri-*n*-octylborane was transferred by cannula to it in one portion. The mixture was stirred at the same temperature for 3 h. The mixture was warmed up to room temperature over a period 1 h. The solution was oxidised by adding sodium hydroxide (3.0 M, 10 mL), followed by hydrogen peroxide (30% aqueous, 6 mL) and the solution was stirred overnight. The organic layer was separated and the solvents were removed to give 1-octanol (230 mg, 72%) and there was no sign of any ketone.

The aqueous layer was acidified by concentrated hydrochloric acid and extracted with dichloromethane (3 x 20 mL). Evaporation of the solvent gave nonanoic acid (**114**) (64 mg, 50%) as a colourless oil.

^{1}H NMR (500 MHz; $CDCl_3$) δ 11.09 (1H, br.), 2.34 (2H, t, *J* = 7.5 Hz), 1.68 – 1.58 (2H, m), 1.40 – 1.17 (10H, m) and 0.87 (3H, t, *J* = 7.0 Hz).

^{13}C NMR (125 MHz; $CDCl_3$) δ 180.6 (quat C), 34.3 (CH_2), 31.9 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 24.8 (CH_2), 22.8 (CH_2) and 14.2 (CH_3).

3.3.10 Reaction of 2-Chloro-1,3-dithiane-1,3-dioxide with tri-*n*-Octylborane Using $HgCl_2$

A two necked 50 mL flask equipped with a septum and a magnetic stirrer bar was charged with 2-chloro-1,3-dithiane-1,3-dioxide (150 mg, 0.8 mmol) and THF (6 mL), and fitted with a bent tube with mercuric chloride (0.869 g, 3.2 mmol). The suspension was cooled to 0 °C and NaHMDS (1.0 M soln. in THF, 0.96 mL, 1.2 equiv.) was added. The mixture was then cooled to –78 °C and a solution of tri-*n*-octylborane (0.8 mmol in THF (5 ml)), prepared as in the preceding procedure) was transferred by cannula to it in one portion. The mixture was stirred at the same temperature for 3 h. The mixture was warmed up to room temperature over a period of 1 h. The mixture was cooled again to −78 °C and mercuric chloride was added by turning the bent tube. The mixture was warmed up over a period of 1 h. The mixture was worked up according to the previous procedure to give only 1-octanol (302 mg, 97%).

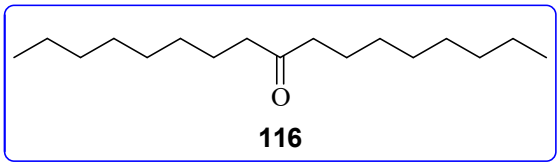
3.3.11 Reaction of 2-Methoxy-1,3-dithiane-1-oxide with Electrophiles

To a cooled solution (–78 °C) of 2-methoxy-1,3-dithiane-1-oxide (75 mg, 0.45 mmol, 1 equiv.) in THF (5 mL), *n*-BuLi (0.31 mL, 1.6 M in hexane, 0.50 mmol, 1.1 equiv.) was added dropwise. The solution was stirred for 5 min, followed by addition of acetophenone (52 μL, 0.45 mmol, 1 equiv.). The solution was stirred for 1 h at –78 °C. The reaction was then quenched by addition of saturated ammonium chloride solution (5 mL). The organic layer was separated and the aqueous layer was extracted with chloroform (3 × 10 mL). The organic layers were combined and dried over magnesium sulfate. Removal of the solvents left the crude product as a colourless oil. Column chromatography failed to isolate the product, which may have decomposed on the silica.

MS (ES^+) *m/z* (%) 350 ($(M+Na+CH_3CN)^+$, 60%), 309 ($(M+Na)^+$, 47%), 263 (28); HRMS: Found $(M+Na)^+$, 309.0606. $C_{13}H_{18}NaO_3S_2$ requires 309.0595.

The same procedure was used with other electrophiles (iodomethane, benzyl bromide and benzophenone).

3.3.12 Reaction of 2-Methoxy-1,3-dithiane-1-oxide with Trioctylborane



116

3.3.12.1 Method A

To a septum-capped 50 mL flask, borane (48 μL, 10.0 M in dimethyl sulfide, 0.48 mmol, 1 equiv.) was added, followed by THF (5 mL). The flask was immersed in an ice-bath and 1-octene (0.23 mL, 1.44 mmol, 3 equiv.) was added dropwise. The cooling bath was removed and the solution was stirred at room temperature over a period of 1 h. The 2-lithio-2-methoxy-1,3-dithiane-1-oxide was prepared separately by adding *n*-BuLi (0.33 mL, , 1.6 M in hexane, 0.53 mmol, 1.1 equiv.) to a solution of compound **109** (80 mg, 0.48 mmol) in THF (5 mL) at –78 °C. The solution then was stirred for 5 min. The solution of tri-*n*-octylborane was added to the anion solution and the mixture was stirred for 1 h. The solution was warmed to room temperature and oxidised by addition of aqueous sodium hydroxide solution (3.0 M, 10 mL), following by hydrogen peroxide (30% aqueous, 6 mL). Purification by flash column chromatography on silica gel (4% EtOAc/hexane) gave dioctyl ketone (14 mg, 11%) as a colourless solid.

m.p. 48 – 49 C (lit.[113] 48.5 – 49 °C)

^{1}H NMR (400 MHz; $CDCl_3$) δ 2.38 (4H, t, *J* = 7.5 Hz), 1.60 – 1.44 (4H, m), 1.34 – 1.16 (20H, m) and 0.87 (6H, t, *J* = 6.9 Hz).

^{13}C NMR (125 MHz; $CDCl_3$) δ 211.7 (quat C), 43.0 (CH_2), 32.0 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 24.1 (CH_2), 22.8 (CH_2) and 14.2 (CH_3).

3.3.12.2 Method B

To a septum-capped 50 mL flask, borane (48 μL, 10.0 M in dimethyl sulfide, 0.48 mmol, 1 equiv.) was added, followed by THF (5 mL). The flask was immersed in an ice-bath and 1-octene (0.23 mL, 1.44 mmol, 3 equiv.) was added dropwise. The cooling bath

was removed and the solution was stirred at room temperature over a period of 1 h. A solution of 2-methoxy-1,3-dithiane-1-oxide (80 mg, 0.48 mmol, 1 equiv.) in THF (5 mL) was added and the mixture was cooled to –78 °C. *n*-BuLi (0.33 mL, 0.53 mmol, 1.1 equiv.) was added dropwise and the solution was stirred for 1 h at the same temperature before being warmed to room temperature over a period of 1 h. The solution was oxidised by adding aqueous sodium hydroxide solution (3.0 M, 10 mL), followed by hydrogen peroxide (30% aqueous, 6 mL) and the solution was stirred overnight. The mixture was saturated with sodium chloride and extracted with chloroform (3 x 20 mL), and the organic layers were combined and dried over magnesium sulfate. The solvents were removed to leave a colourless solid of the crude mixture, which was purified as in the previous procedure to give dioctyl ketone (16 mg, 13%).

For GC yield measurements, after saturation with sodium chloride an accurate weight of tetradecane was added to the total mixture. The yield was then monitored by GC.

3.3.13 Reaction of 2-Thiophenyl-1,3-dithiane-1-oxide with Trioctylborane

Tri-*n*-octylborane (0.59 mmol in THF (5 mL)) was prepared according to the above procedure (Method A, section 3.3.12.1). A solution of 2-thiophenyl-1,3-dithiane-1-oxide (145 mg, 0.59 mmol) in THF (5 mL) was added. The mixture was cooled to –78 °C and *n*-BuLi (0.44 mL, 1.6 M in hexane, 0.70 mmol, 1.2 equiv.) was added dropwise. The solution was stirred for 1 h at the same temperature and 1 h at room temperature. The solution was oxidised by adding aqueous sodium hydroxide solution (3.0 M, 10 mL), followed by hydrogen peroxide (30% aqueous, 6 mL) and the solution was stirred overnight. The mixture was saturated with sodium chloride and an accurate weight of tetradecane was added. The yield was then monitored by GC to indicate 4% of the dioctyl ketone.

3.3.14 Preparation of LDA, LiTMP and LiHDMS

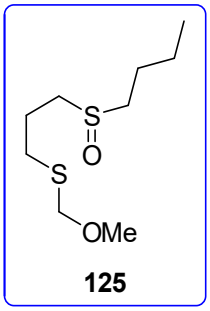
Diisopropylamine (74 μL, 0.53 mmol) was dissolved in dichloromethane (1 mL) and the solution was cooled to –78 °C. *n*-BuLi (0.36 mL, 1.6 M in hexane) was added dropwise.

The solution then was warmed up to 0 °C for 20 min and used in the reaction. LiTMP and LiHDMS were prepared similarly by using the same procedure with the appropriate substrates. The bases were then used in Method B (section 3.3.12.2).

3.3.15 Preparation of LDA-LICKOR Superbase[109]

n-BuLi (0.3 mL, 0.48 mmol) was placed in a septum-capped 10 mL flask and the hexane was stripped off from the solution by flushing it with N_2. Precooled THF (–78 °C) (5 mL), diisopropylamine (67 μL, 0.48 mmol) and potassium *tert*-butoxide (54 mg, 0.48 mmol) were added and the solution was stirred for 15 min at –78 °C.

3.3.16 (3-(Butylsulfinyl)propyl)(methoxymethyl)sulfane (125)



125

2-Methoxy-1,3-dithiane-1-oxide (**109**) (79 mg, 0.48 mmol) was dissolved in dry THF under nitrogen and cooled to –78 °C. *n*-BuLi (0.33 mL, 1.6 M in hexane, 0.52 mmol, 1.1 equiv.) was added dropwise and the solution stirred for 15 min. A saturated solution of ammonium chloride (5 mL) was added and then the solution was warmed to room temperature. The mixture was extracted with $CHCl_3$ (3 x 10 mL) and the extracts were combined and dried over magnesium sulfate. Evaporating the solvent afforded a mixture of two diastereoisomers of the *title compound* (45 mg, 42%) as a colourless oil.

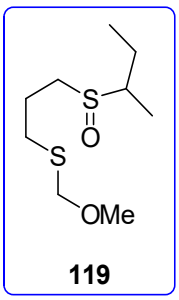
ν_{max}. (neat) 2927, 1550, 1055, 1026 and 727 cm^{-1}.

^1H NMR (400 MHz; $CDCl_3$) δ 4.62 (2H, s), 3.33 (3H, s), 2.56 – 2.84 (6H, m), 2.10 (2H, p, *J* = 7.1 Hz), 1.73 (2H, p, *J* = 7.8 Hz), 1.43 – 1.54 (2H, m) and 0.95 (3H, t, *J* = 7.3 Hz).

^{13}C NMR (100 MHz; $CDCl_3$) δ 75.6 (CH_2), 55.9 (CH_3), 52.4 (CH_2), 51.0 (CH_2), 30.2 (CH_2), 24.7 (CH_2), 23.1 (CH_2), 22.2 (CH_2) and 13.8 (CH_3).

EI-MS *m/z* (%) 224 (M^+, 3%), 179 (M^+-OMe, 48), 163 (58), 148 (63), 107 (85); HRMS: Found: M^+, 224.0899.$C_9H_{20}O_2S_2$ requires M, 224.0905.

3.3.17 (3-(*sec*-Butylsulfinyl)propyl)(methoxymethyl)sulfane (119)



119

2-Methoxy-1,3-dithiane-1-oxide (**109**) (79 mg, 0.48 mmol) was dissolved in dry THF under nitrogen and cooled to –78 °C. *sec*-BuLi (0.37 mL, 1.4 M, 0.52 mmol, 1.1 equiv.) was added dropwise and the solution mixture was stirred for 15 min. A saturated aqueous solution of ammonium chloride (5 mL) was added and then the solution was warmed to room temperature. The mixture as extracted with $CHCl_3$ (3 x 10 mL) and the combined extracts were dried over magnesium sulfate. Evaporating the solvent afforded a mixture of two diastereomers of the *title compound* (55 mg, 51%, 1:1 ratio) as a colourless oil.

$\nu_{max.}$ (neat) 2964, 2926, 2875, 2802, 1423, 1055, 1029, 894 and 749.

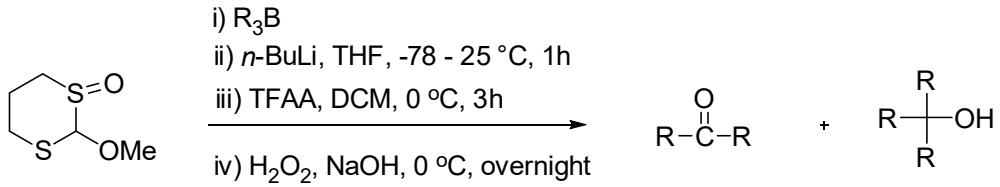
^{1}H NMR (500 MHz; $CDCl_3$) δ 4.57 (2H of each isomer, s), 3.29 (3H of each isomer, s), 2.90 – 2.38 (5H of each isomers, m), 2.15 – 1.96 (2H of each isomer, m), 1.91 – 1.74 (1H of each isomer, m), 1.56 – 1.40 (1H of each isomer, m), 1.22 (3H of minor isomer, d, *J* = 6.9 Hz), 1.14 (3H of major isomer, d, *J* = 6.9 Hz), 1.03 – 0.96 (3H of each isomers, m).

^{13}C NMR (125 MHz; $CDCl_3$) δ 75.61 (CH_2), 75.59 (CH_2), 66.0 (CH_2), 57.3 (CH), 56.6 (CH), 55.9 (CH_3, only one peak was seen for OMe), 47.6 (CH_2), 46.9 (CH_2), 30.2 (CH_2), 23.9

(CH_2), 23.6 (CH_2), 23.2 (CH_2), 22.7 (CH_2), 12.0 (CH_3), 11.5 (CH_3), 11.0 (CH_3) and 10.9 (CH_3).

EI-MS *m/z* (%) 224 (M^+, 3%), 179 (M^+-OMe, 10), 163 (20), 148 (46), 107 (72); HRMS: Found: M^+, 224.0899. $C_9H_{20}O_2S_2$ requires M, 224.0905.

3.3.18 Pummerer Rearrangement in the of Reaction of 2-Methoxy-1,3-dithiane-1-oxide with Trioctylborane



R = octyl

Tri-*n*-octylborane (0.96 mmol, 1 equiv.) in THF (5 mL) was prepared according to the above procedure. The solution was mixed with a solution of 2-methoxy-1,3-dithiane-1-oxide (160 mg, 0.96 mmol, 1 equiv.) in THF (5 mL) and cooled to –78 °C. *n*-BuLi (0.72 mL, 1.47 M, 1.07 mmol, 1.1 equiv.) was added dropwise and the solution was stirred for 1 h at the same temperature before being warmed up to room temperature. The solution was cooled to 0 °C and a solution of TFAA (0.19 mL, 1.36 mmol, 1.4 equiv.) in dichloromethane was added. The mixture was stirred for 3 h and then warmed up to room temperature. The solution was oxidised by adding sodium hydroxide (3.0 M, 10 mL), followed by hydrogen peroxide (30% aqueous, 6 mL) and the solution was stirred overnight. The organic layer was saturated with sodium chloride and extracted with chloroform (3 x 20 mL), the organic layers were combined and dried over magnesium sulfate. The solvents were removed to leave a colourless solid of the crude mixture. The crude product was purified by flash column chromatography on silica gel (4% EtOAc/hexane) to give trioctylmethanol (22 mg, 6%) as a colourless oil, dioctyl ketone (10 mg, 4%) as a colourless solid and (258 mg, 69% of all octyl groups of tri-*n*-octylborane) 1-octanol as a colourless liquid.

3.3.19 Gas Chromatograph (GC) Instrument Details and Conditions

GC measurements were carried out using a Shimadzu GC-2014 gas chromatograph fitted fitted with a ZB-5 column (30 m, 0.32 mm inner diameter, 1.0 μm film thickness). The carrier gas was He at 69.3 kPa, and a split injection mode was used. The oven temperature was increased from 70 to 260 °C at 6 °C min^{-1} and then held for 4 min. Authentic samples of products were used to calculate response factors relative to tetradecane, a known weight of which was added to reaction mixtures to allow quantification of product yields.

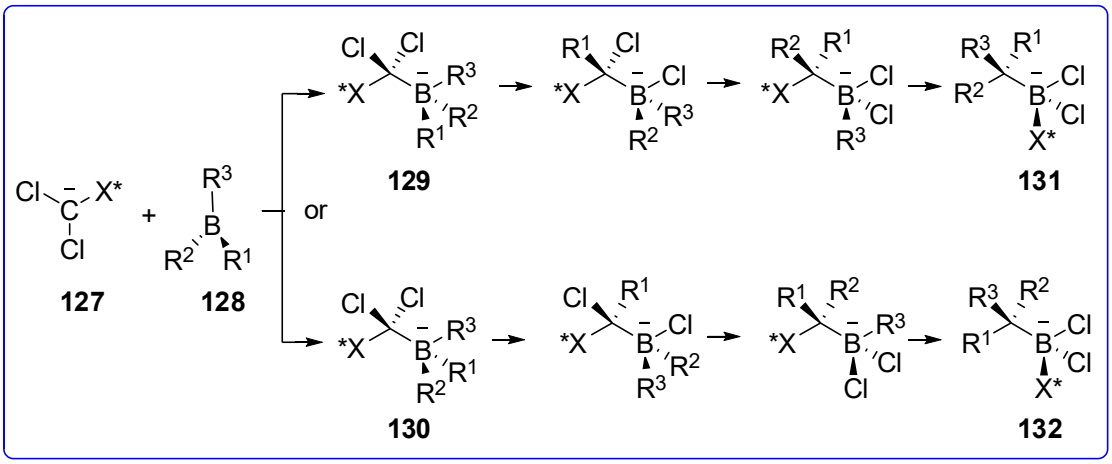
Chapter Four

Stoichiometric Studies on Dichloromethyl Sulfur Compounds as DCME-like Reagents

4.1 Aims and Introduction

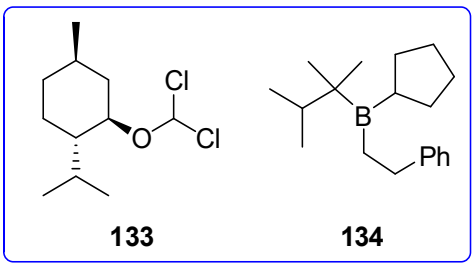
In **Chapter Three**, as part of an attempt to generate a chiral tertiary alkylboron compound, the investigation focused on aspect of incorporation of three different potential leaving groups incorporated into a dithiane ring. However, due to the difficulties encountered in the reactions of dithiane derivatives with trialkylboranes and the poor yields of the migrated products obtained, attention was switched to investigation of an acyclic DCME-like reaction.

As already discussed in **Chapter One** and **Chapter Three**, the DCME reaction allows all three alkyl groups to migrate from boron to a single carbon atom to generate a tertiary alkylboron compound. Having three different alkyl groups in the trialkylborane, in principle, would generate a chiral tertiary alkylboron compound. However, without a chiral group on the starting material (α,α-dichloromethyl methyl ether, DCME), the reaction would not be stereoselective. Replacement of the methoxy group in DCME by a chiral group and reaction of its anion **127** with organoborane compound **128**, which *should* have three significantly different alkyl groups, would give two different diastereoisomeric complexes **129** and **130**. Fundamentally, the two diastereoisomers would have different stabilities and, consequently, rearrange differently, in terms of which diastereotopic chlorine would depart first and/or which alkyl groups were located suitably to displace a particular leaving group. The first migration step would produce an excess of one enantiomer of the final tertiary alkylborane **131** or **132**, which could then either be oxidised to produce a tertiary alcohol or homologated further and then oxidised to produce an alcohol bearing a quaternary carbon centre. The e.e. could then be monitored by HPLC analysis using a chiral column.



Scheme 4.1: Proposed Use of a Chiral DCME-Like Reagent

A previous study, by the Smith group,[114] into such asymmetric DCME-like reactions used compound **133** as a DCME analogue and trialkylboranes as substrates. The chiral menthyloxy group was intended to control the order and stereochemistry of the migration of the alkyl groups. However, when the anion of compound **133** was subjected to a standard DCME-like reaction with trialkylborane **134,** it did not produce the corresponding tertiary alcohol. When less hindered trioctylborane and tricyclopentylborane were used, very low yields of the corresponding tertiary alcohols (5% and 4%, respectively) were obtained.



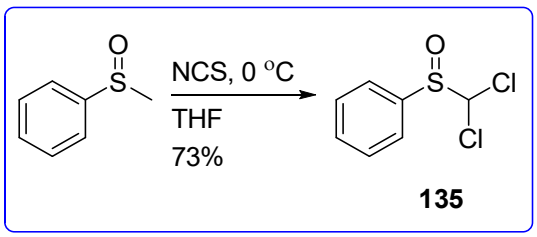
Organosulfur compounds are among the most intensively used chiral auxiliaries in asymmetric organic synthesis.[115] The purpose of the work reported in this chapter was to assess the reaction of organoboranes with anions derived from dichloromethyl

organosulfur compounds, particularly a dichloromethyl sulfoxide, a dichloromethyl sulfone, a dichloromethyl sulfoximine and a dichloromethyl sulfilimine. Here we report successful reactions, behaviours of each anion type as well as some novel reaction mechanisms.

4.2 Results and Discussion

4.2.1 Reaction of Dichloromethyl Phenyl Sulfoxide (135) with Trialkylboranes

Dichloromethyl phenyl sulfoxide (**135**) has become a reagent of choice for many organic transformations.[116–118] Also, the pure enantiomers of the compound became accessible when Satoh reported the resolution of the compound using menthone.[118] The synthesis of the sulfoxide **135** was carried out according to the procedure of Satoh (**Scheme 4.2**)[119] and used in the borylation reaction.

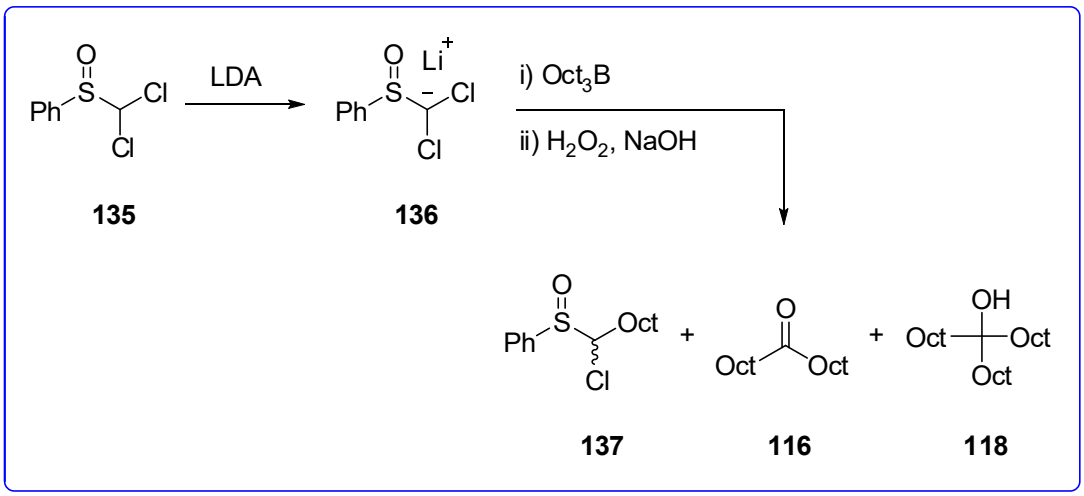


Scheme 4.2: Synthesis of Compound **135**

Fresh LDA was first prepared by treating a solution of diisopropylamine (1.3 equiv.) in dry THF with *n*-BuLi (1.2 equiv.). The anion **136** was prepared by addition of a solution of **135** to the solution of LDA at –78 °C. Meanwhile, a solution of trioctylborane was prepared by hydroboration of 1-octene with borane dimethyl sulfide complex in THF. The solution was then added to the cold solution of anion **136** and stirred at –78 °C. The peroxidic oxidation of the organoborane product and purification of the products by column chromatography afforded the products from two migrations (dioctyl ketone, **116**, **Scheme 4.3**) and three migrations (trioctylmethanol, **118**), but in very low yields, 3% and 1% (6% and 3% GC yield), respectively. The remaining products were an

unknown compound as well as octanol resulting from the oxidation of residual octylboron moieties. All migration products (ketone and alcohols) contained small amount of 2-octyl isomers because of the formation of about 6% of 2-octyl groups during the hydroboration reaction step.[11]

The ^{1}H NMR spectrum of the unknown compound showed two doublet of doublet peaks at 4.53 and 5.40 ppm. It was suggested that these might belong to two different diastereoisomers in 84:16 ratio. Also, there were five protons in the aromatic region as well as a complete number of protons for one octyl group. The unknown compound was fully characterised using IR, ^{1}H NMR, ^{13}C NMR spectroscopy and mass spectrometry. It was concluded that the compound was a diastereoisomeric mixture of 1-chlorononyl phenyl sulfoxides (**137, Scheme 4.3**), isolated in moderate isolated yield (61%).



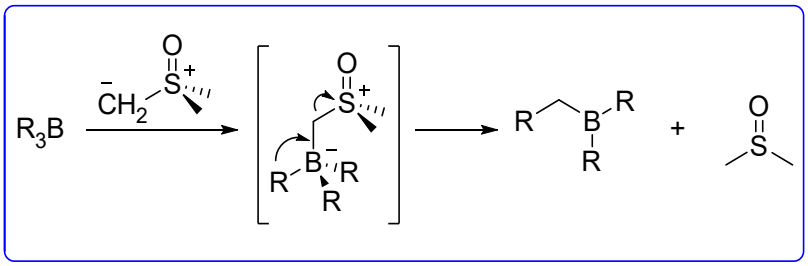
Scheme 4.3: Initial Reaction of the Anion Derived from **135** with Trioctylborane

4.2.2 Attempts at Understanding the Mechanism and Generalisation of the Reaction

It seemed that the product **137** was formed *via* hydrolysis instead of oxidation. In order to confirm this, the reaction was repeated using the same procedure but it was quenched with aqueous ammonium chloride at –78 °C instead of by peroxidic oxidation. The same result was obtained and the same compound isolated in

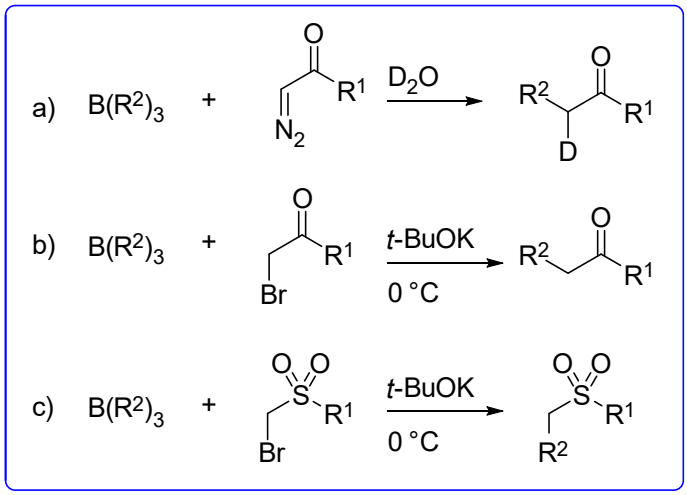
moderate yield (57%). This meant, evidently, that the compound was formed from one alkyl group migration followed by hydrolysis of the organoboron intermediate instead of undergoing second and third migrations.

To the best of our knowledge, there are no known reactions in the literature similar to that forming compound **137** from a substituted sulfoxide and organoboron compounds. There are known reactions of dimethylsulfoxonium ylides with trialkylboranes, but in those reactions, dimethyl sulfoxide behaves as a leaving group (**Scheme 4.4**).[120]



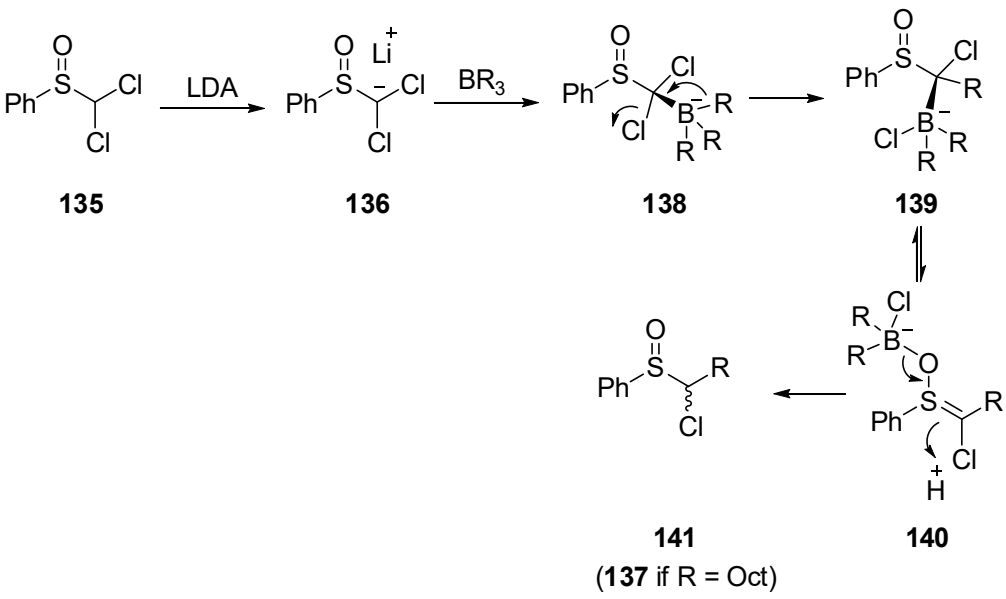
Scheme 4.4: Reaction of Dimethylsulfoxonium Ylides with Trialkylboranes

Reaction of α-chloroalkyl aryl sulfoxides with alkyllithium reagents in the presence of alkylboronic esters leads to lithium-sulfoxide exchange to form α-chloroalkyl aryl lithium species, which then react with boronic esters with homologation.[52,121–125] These reactions were discussed in more detail in **Chapter One** (section 1.9). The formation of homologated carbonyl compounds by reactions of trialkylboranes with diazocarbonyl compounds (**Scheme 4.5a**)[126] or with anions derived from α-bromocarbonyl and related compounds are known reactions (**Scheme 4.5b**).[127,128] Those reactions occur *via* isolable boron enolate intermediates.[129] Also, the reaction of α-bromosulfonyl compounds with trialkylboranes under influence of base leads to a similar reaction (**Scheme 4.5c**).[130]



Scheme 4.5: Homologation Using Carbonyl and Sulfonyl Compounds

Hence, it could reasonably be hypothesised that the reaction under investigation was similar and the mechanism could be as shown in **Scheme 4.6.** Therefore, the boron-containing product of the reaction with a generalised trialkylborane would be **140**, formed by rearrangement of the initially formed intermediate **139**.



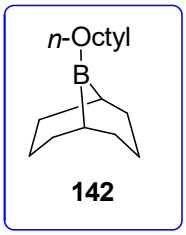
Scheme 4.6: Proposed Mechanism for the Formation of **137**/**141**

Similar α-chlorosulfoxide compounds to **137**/**141** were synthesised previously by alkylation of anions derived from chloromethyl aryl sulfoxides with alkyl halides (**Scheme 4.7**).[131] The importance of such compounds in asymmetric organic synthesis stimulated us to study this reaction in more detail.

A number of questions remain unanswered so far.

1) According to this understanding of the mechanism, can this reaction be generalised in the sense of introducing a wider range of organic groups than is possible by nucleophilic substitution reactions of organic halides?
2) How do the diastereomeric ratios formed in this reaction compare with those synthesised by simple alkylation of the anions derived from chloromethyl sulfoxides (**Scheme 4.7**)?
3) Could the intermediate of type **140** be utilised to react with a wider range of electrophiles?

Several experiments have been designed to help to answer these questions. In order to answer question 1 and for the purpose of synthesis of a range of compounds of type **141**, reactions of **136** with a range of organoboranes, including triethylborane, tributylborane, triphenylborane, tricyclopentylborane, the trialkylborane mixture formed by hydroboration of styrene with borane-dimethyl sulfide, and 9-octyl-9-borabicyclo[3.3.1]nonane (9-Oct-9-BBN, **142**) were carried out. The ratios of the diastereoisomers were determined from the ^{1}H NMR spectra of the crude products prior to purification for all compounds except for compound **137** derived from **142**. In this case, the ratio was determined after column chromatography because the C*H*Cl protons in the ^{1}H NMR spectrum were difficult to integrate due to the presence of impurities. The results are summarised in **Table 4.1**.



142

Table 4.1: Preparation of 1-chloroalkyl sulfoxides (**137**/**141**) according to **Scheme 4.2**

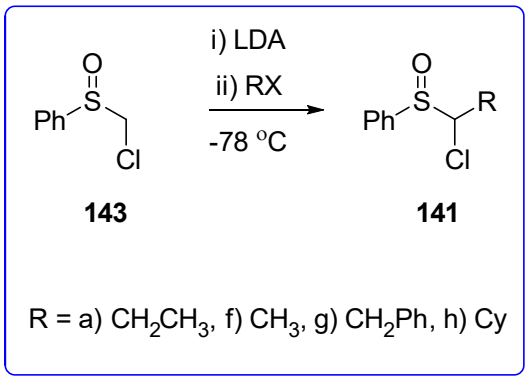
Product	R	Yield (%)[b]	Diastereoisomer ratio[a]
141a	Et	92	78:22
141b	*n*-Bu	88	84:16
137[c]	*n*-Oct[c]	61	84:16
137[d]	*n*-Oct[d]	40	82:18[e]
141c[e]	$PhCH_2CH_2$[f]	40	81:19
141d	Cyclopentyl	0	-
141e	Ph	0	-

[a] Determined from the ^{1}H NMR spectrum of the crude product prior to purification. [b] Isolated yield for the mixture of diastereoisomers. [c] Only around 82% of the R_3B molecules would be $(1\text{-Oct})_3B$ because the hydroboration gives *ca.* 6% of 2-octyl groups. [d] 9-Oct-9-BBN (**142**) was used in this case. [e] The ratio was measured after column chromatography. [f] Only around 40-50% of the R_3B molecules would be $(PhCH_2CH_2)_3B$ because the hydroboration gives *ca.* 20% of 1-phenylethyl groups.

It can be seen from the data in **Table 4.1** that the pure tri-*prim*-alkylboranes, *i.e*. triethylborane and tributylborane, resulted in formation of the expected products in good yield (92% and 88% respectively), while the yields from the impure cases (formed by hydroboration of 1-octene and styrene) were much lower. This is possibly because of the lower proportions of tri-*prim*-alkylboranes present in the mixtures. Compound

9-Oct-9-BBN (**142**) gave 40% of the corresponding product. On the other hand, tricyclopentylborane and triphenylborane gave no comparable products. It can therefore be assumed from these results that only relatively unhindered trialkylboranes take part in this reaction, probably because the initial complexation of the anion with more hindered organoboranes is disrupted.

To answer the second question, the diastereomeric ratios were determined by measuring the relative integrations of the downfield C*H*Cl signals for the two isomers of **141a**, major and minor, at ≈ 4.35 ppm and ≈ 4.45 ppm respectively. These were then compared with those reported for 1-chloroethyl phenyl sulfoxide ($PhS(O)CHClCH_3$, **141f, R = Me**) prepared by methylation of **143** (**Scheme 4.7**).[131]



Scheme 4.7: Synthesis of compound **141** by alkylation of **143**[131]

This alkylation has been reported twice. In work by More and Wemple, the authors reported the synthesis of a series of diastereomeric compounds **141** including R = CH_2CH_3 (**141a**), CH_3 (**141f**), CH_2Ph (**141g**) and cyclohexyl (**141h**). Nevertheless, the diastereomeric ratio was reported only for compound **141f** (R = Me), determined using ^1H NMR data. The chemical shifts for **141f** were at 4.70 ppm (major isomer, 60%) and 4.50 ppm (minor isomer, 40%) ppm. The authors did not determine the stereochemistry of these diastereoisomers.

In another study by Mutterer *et al.*,[132] the same compound **141f** was synthesised by the same method. In this case, the peak at 4.70 ppm corresponded to the minor isomer, although the ratio was not stated.

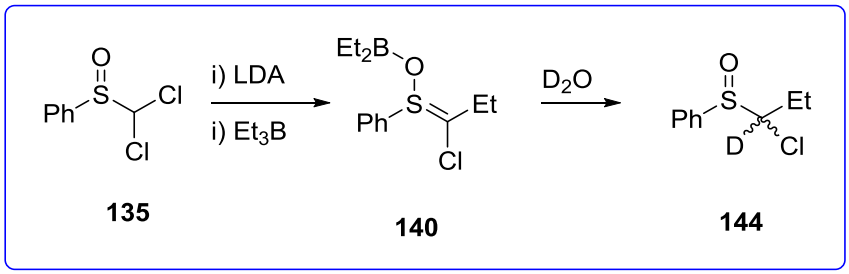
In the present study, the higher chemical shift (4.45 ppm for compound **141a**, R = Et) was for the minor isomer (22%) while the lower chemical shift (4.35 ppm) was for the major isomer (78%). The same trend was observed for all of the other compounds (see **Table 1**). It is clear from these results that the selectivity of the new reaction is better than those of the simple alkylation reactions. However, given the conflicting data in the literature, and the fact that the stereochemistry of the major isomer formed was not determined in those studies, it is impossible to compare the stereochemical outcome properly.

In order to try to answer the third question, trapping of the intermediate **140** formed from the reaction of triethylborane with **136** with a range of electrophiles, including D_2O, substituted benzaldehydes and $Ph_2I^+TfO^-$, was attempted. What follows is a description of these reactions in detail.

4.2.3 Trapping the Intermediate 140 with Electrophiles

4.2.3.1 Reaction of D_2O with the Intermediate 140 (R = Et)

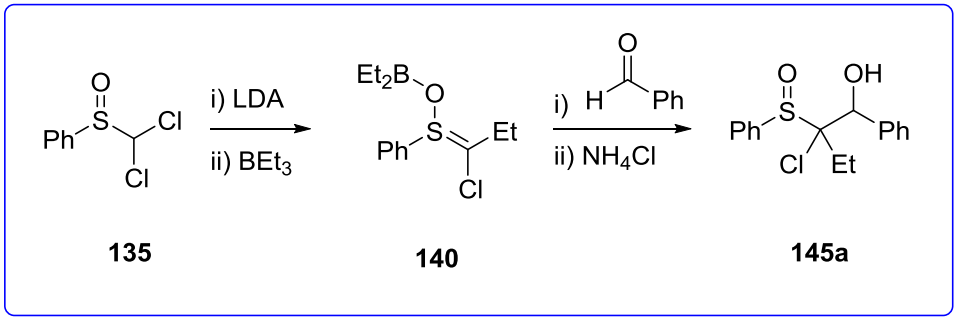
Initially, the intermediate **140** was prepared as in the previous procedure by addition of triethylborane to the anion **136** and stirring the resulting mixture for 1 h at –78 °C, then the intermediate was quenched with D_2O. Work-up and separation of the products by column chromatography gave compound (**144**, **Scheme 4.8**) as a mixture of two diastereoisomers in excellent yield (93%, the ratio was not measured due to overlapping peaks). After this successful reaction our attention was turned to the reaction of **140** with benzaldehydes.



Scheme 4.8: Trapping the Intermediate **140** with D_2O

4.2.3.2 Reaction of Benzaldehyde with the Intermediate 140 (R = Et)

In order to generalise the reaction for a wider range of electrophiles, it was decided to initially examine the reaction of intermediate **140** with benzaldehyde as shown in **Scheme 4.9**.

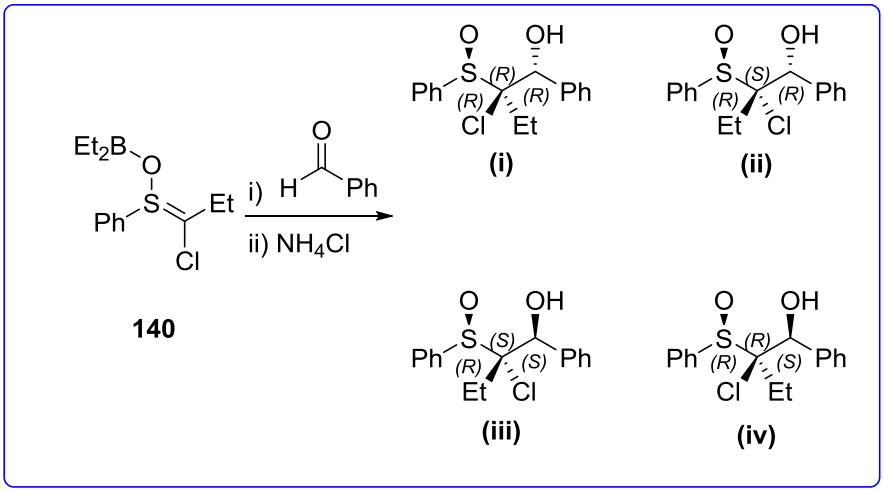


Scheme 4.9: Reactions of the Anion Derived from **135** with Triethylborane and Benzaldehyde

The same procedure used for the synthesis of compound **144** (**Scheme 4.8**) was used but the reaction was quenched with 1 equivalent of benzaldehyde followed by addition of a solution of ammonium chloride. The purification of the crude product gave a complex mixture of what appeared to be several diastereoisomers of aldol-like products **145a** in moderate overall yield (58%). The rest of the material was **141a**,

resulting from the hydrolysis of compound **140**, suggesting that compound **140** did not react fully with benzaldehyde, along with an unknown impurity. Attempts to increase the yield of compound **145a** by stirring the mixture with benzaldehyde for a longer period at –78 °C and/or at room temperature did not help.

In principle, it is possible to get four diastereoisomers from the reaction of **140** with benzaldehyde (**Scheme 4.10**).

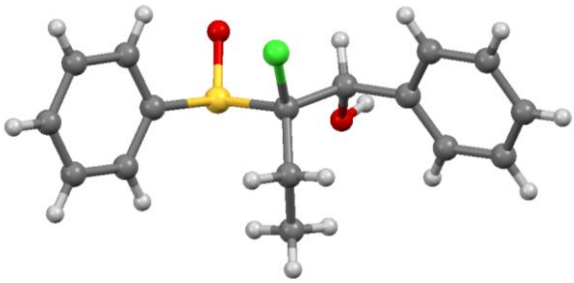


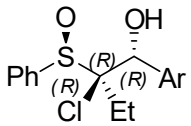
Scheme 4.10: The Four Possible Diastereoisomers of **145a**

Unfortunately, the ^{1}H NMR data were extremely complex. The determination of the ratios of the isomers in the crude product by integration of the ^{1}H NMR spectrum was difficult because the peaks of the isomers overlapped with each other and with the peaks of other impurities. Thus, to determine the structure and stereochemistry for all compounds formed, it was necessary first to separate the products by column chromatography.

The crude product **145a** was purified by flash column chromatography using silica gel and 3% ethyl acetate/chloroform. The first product eluted was the product of hydrolysis of the *pseudo*-enolate, **141a** (18%), followed by the first diastereoisomer of the aldol product **145a** (23%), which was a solid. This compound was recrystallised

from chloroform/petroleum ether and its structure and relative stereochemistry were confirmed by X-ray crystallography as RRR/SSS, (**Figure 4.1**, RRR-enantiomer shown). The X-ray structure determinations were carried out by Dr. Benson Kariuki. This diastereoisomer was therefore shown to be **145a(i)**.



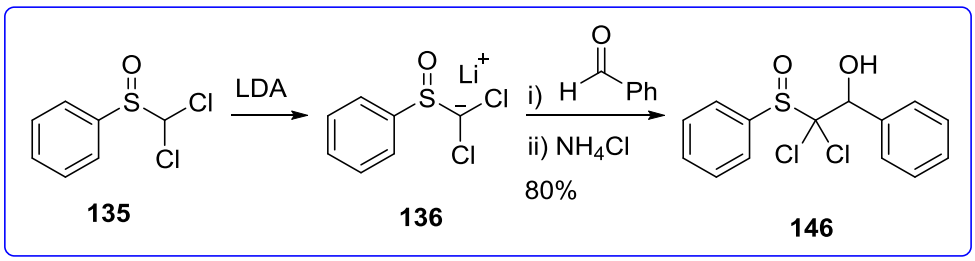


145a(i)

Figure 4.1. X-ray Structure of **145a(i)**

The ^{1}H NMR spectrum of this compound showed a singlet at 5.66 ppm due to the C*H*OH proton, a singlet at 4.96 ppm due to the hydroxyl group proton, a doublet of quartets (J = 15.3, 7.2 Hz) at 3.00 ppm due to one proton of the CH_2 group, a doublet of quartets (J = 15.3, 7.4 Hz) at 2.01 ppm due to the other proton of the CH_2 group and an apparent triplet (J = 7.3 Hz) at 1.3 ppm due to the methyl group protons. It also showed the presence of the ten aromatic protons. The ^{13}C NMR spectrum showed the expected number of resonances. The low resolution negative ion (ES^-) mass spectrum of the compound showed three *pseudo*-molecular ion peaks $(M + Cl)^-$ at m/z = 347 (13%), 345 (67%) and 343 (100%), consistent with the formulae $C_{16}H_{17}{}^{37}Cl_2O_2S$, $C_{16}H_{17}{}^{37}Cl^{35}ClO_2S$ and $C_{16}H_{17}{}^{35}Cl_2O_2S$, respectively. These assignments were further supported by accurate mass data from the high resolution mass spectrum.

The second diastereoisomer to elute (approx. 2.5%) was present as a 1:1 mixture alongside an unknown impurity. It was speculated that this impurity might be a single diastereoisomer of 2,2-dichloro-1-phenyl-2-(phenylsulfinyl)-1-ethanol (**146**) resulting from direct reaction of anion **136** with benzaldehyde. Compound **146** was prepared previously by Satoh[116] as a diastereoisomeric mixture and the chemical shifts of C*H*OH for the two diastereoisomers were reported at 5.44 and 5.46 ppm, which are very close to that for the unknown impurity (5.50 ppm). Thus, to confirm such speculation, it was decided to prepare compound **146** and add it to the NMR tube of this fraction. Compound **146** was prepared according to the procedure used by Satoh[116] by adding benzaldehyde to a solution of the anion **136** (**Scheme 4.11**) at –78 °C and stirring the resulting mixture for 30 minutes. Work-up gave a crude mixture of two diastereoisomers in good yield (80%; 60:40 ratio, measured from the quantities of the two diastereoisomers after separation by column chromatography since the peaks for the C*H*OH protons overlapped in the ^{1}H NMR spectrum of the crude product).



Scheme 4.11: Preparation of **146** According to Satoh's Procedure

The two diastereoisomers were separated by flash column chromatography and their structures were identified by various spectroscopic and spectrometric techniques (IR, ^{1}H, ^{13}C NMR, MS and HRMS). Once pure samples of the two diastereoisomers of compound **146** were obtained, a solution of the less polar diastereoisomer in $CDCl_3$ was added to the NMR tube containing the second chromatography fraction of **145a** and the resulting mixture was checked again by ^{1}H NMR spectroscopy. Indeed,

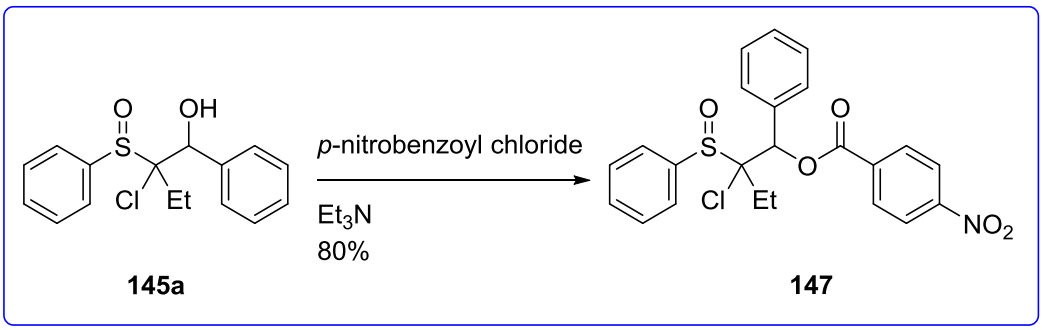
comparison of the ^{1}H NMR spectra before and after the addition showed that the ^{1}H NMR peaks of the added diastereoisomer of compound **146** superimposed on those for the unknown impurity. This verified the hypothesis that the impurity was indeed one diastereoisomer of **146**.

The structure of the diastereoisomer of **145a** present in the second chromatography fraction was investigated by IR, NMR, MS and HRMS spectroscopic/spectrometric data after discounting the signals due to **146**. For example, the ^{1}H NMR spectrum showed a doublet (J = 8.7 Hz) at 5.20 ppm due to the C*H*OH proton, a doublet (J = 8.7 Hz) at 4.92 ppm due to the OH proton, a doublet of quartets (J = 14.7, 7.2 Hz) at 2.39 ppm due to one proton of the CH_2 group, a doublet of quartets (J = 14.7, 7.1 Hz) at 1.28 ppm due to the other proton of the CH_2 group, and an apparent triplet (J = 7.2 Hz) at 1.07 ppm due to the methyl group protons. It also showed the presence of the ten aromatic protons overlapped with those for compound **146**. However, it was difficult to crystallise the diastereoisomer of **145a** because of the contamination with compound **146**; therefore, no X-ray crystal structure could be determined and without that information it was difficult at this stage to assign the stereochemistry of the diastereoisomer.

The last chromatography fraction contained an inseparable but otherwise fairly pure mixture of the third and fourth diastereoisomers of **145a** (total yield 32%, 55:45 ratio). The structures of the diastereoisomers in the mixture were investigated by various spectroscopic and spectrometric techniques including IR, ^{1}H, ^{13}C NMR, MS and HRMS. For the major diastereoisomer, the ^{1}H NMR spectrum showed a doublet (J = 4.0 Hz) at 5.33 ppm due to the C*H*OH proton, a doublet (J = 4.0 Hz) at 3.21 ppm due to the OH proton, a doublet of quartets (J = 15.0, 7.4 Hz) at 1.88 ppm due to one proton of the CH_2 group, a doublet of quartets (J = 15.0, 7.3 Hz) at 1.50 ppm due to the other proton of the CH_2 group, an apparent triplet (J = 7.4 Hz) at 0.95 ppm due to methyl group protons and ten protons in the aromatic region (overlapped with those for the minor diastereoisomer), while the minor diastereoisomer showed a doublet (J = 3.3 Hz) at 5.17 ppm due to the C*H*OH proton, a doublet (J = 3.3 Hz) at 3.63 ppm due to the OH proton, a multiplet at 2.22 – 2.12 ppm due to the CH_2 protons, an apparent triplet (J =

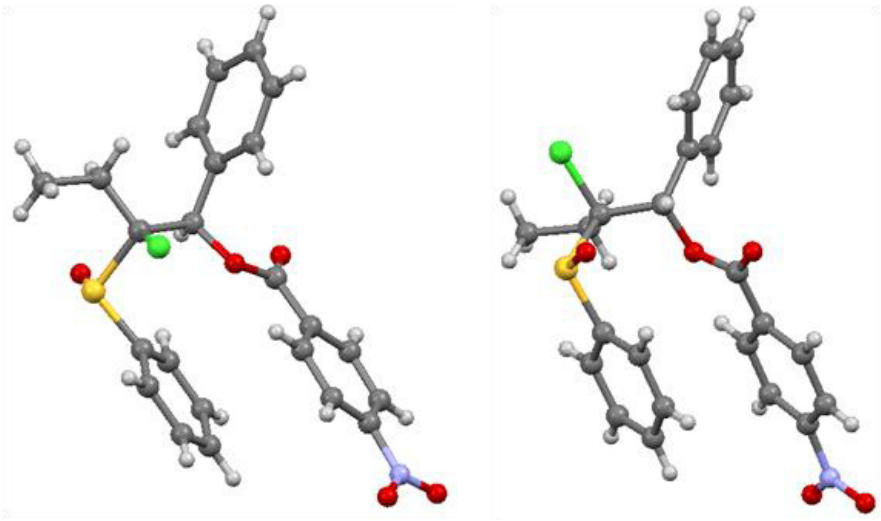
7.5 Hz) at 0.85 ppm due to the methyl group protons and ten protons in the aromatic region (overlapped with those for major diastereoisomer).

In order to separate the last two diastereoisomers and confirm the stereochemistry for both, it was decided to convert the diastereoisomeric mixture into the 4-nitrobenzoate esters by reaction with 4-nitrobenzoyl chloride. Indeed, treatment of a solution of the mixture in THF with 4-nitrobenzoyl chloride in the presence of triethylamine gave the corresponding 4-nitrobenzoate derivatives **147** (80%) (**Scheme 4.12**).



Scheme 4.12: Synthesis of 4-Nitrobenzoate Derivatives of **145a**

The two diastereoisomers of 4-nitrobenzoate derivatives (**147**) were separated by flash column chromatography (1% EtOAc/$CHCl_3$) and subjected to full analysis using various spectroscopic and spectrometric techniques, including IR, ^{1}H, ^{13}C NMR, MS and HRMS. The individual isomers (designated **147a** and **147b**) were recrystallised from chloroform/petroleum ether and then characterised and confirmed by X-ray crystallography (**Figure 4.2**).

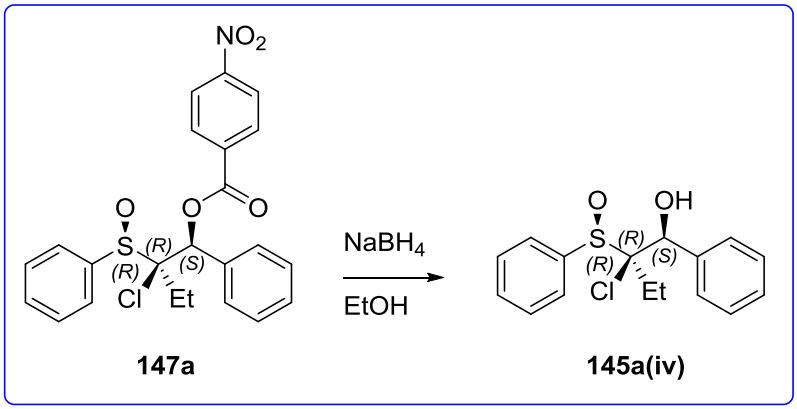


(147a)
(RRS/SSR)

(147b)
(RSS/SRR)

Figure 4.2: X-Ray Structure and Stereochemistry of the Two Diastereoisomers of **147**

The 4-nitrobenzoate derivative **147a** was reduced to give the corresponding diastereoisomer of **145a** (*i.e.* **145a(iv)**, **Scheme 4.13**). Comparison of the ^{1}H NMR spectrum of this compound with that of the crude reaction mixture showed that this was the minor isomer in the original chromatography fraction. The combination of the X-ray crystal structure of **147b** and the ^{1}H NMR spectrum of the final chromatography fraction also allowed assignment of the major diastereoisomer in the fraction as **145a(iii)**.



Scheme 4.13: Reduction of Compound **147a** into **145a(iv)**

Therefore, it was concluded that the major diastereoisomer of **145a** in the final chromatography fraction was RSS/SRR (**145a(iii)**) and the minor diastereoisomer was RRS/SSR (**145a(iv)**). The remaining, as yet uncharacterised, diastereoisomer, *i.e.* the second diastereoisomer to be eluted during column chromatography of the original crude mixture, by a process of elimination, must be **145a(ii)**.

Before attempting to rationalise these results mechanistically, it was felt that more examples of the reaction might provide further insight into the reaction. Consequently, reactions with several other substituted benzaldehydes were undertaken.

4.2.3.3 Reaction of Substituted Benzaldehydes with the Intermediate 140 (R = Et)

Reactions of intermediate **140** were carried out with four substituted benzaldehydes; 3-methoxybenzaldehyde, 4-methoxybenzaldehyde, 4-bromobenzaldehyde and 4-fluorobenzaldehyde were tested using the same procedure that was used for benzaldehyde itself. It was pleasing to see that all of the chosen benzaldehydes reacted to give the desired aldol-like products, albeit as mixtures of diastereoisomers, in combined yields of 45-58% (isolated, following column chromatography).

The stereochemistries of the four diastereoisomers of **145b** - **145f** were assigned by comparison of the chemical shifts and coupling constants for the OH protons to the C*H*OH protons, which were distinct from each other, in the ^{1}H NMR spectra of the separated products. Similar chemical shifts and coupling constants were observed in

the ^{1}H NMR spectra of all of the compounds **145b – 145e** and indeed they were also similar to those in the spectra of the diastereoisomers of **145a**. The stereochemistries of the diastereoisomers of compounds **145b – 145e** could therefore be assigned by analogy with **145a**.

For compounds **145b** and **145c**, three diastereoisomers were isolated after column chromatography. Diastereoisomer **(ii)** was not seen in either case. In terms of compounds **145d** and **145e**, all four diastereoisomers were isolated in the same way as those for compound **145a**, *i.e*. **(i)** was isolated first as a solid followed by **(ii)**, which was contaminated with an analogue of compound **146**, and then a mixture of **(iii)** and **(iv)**.

For all four isomers of compound **145e**, the assignment of the CHO*H* protons was confirmed by ^{1}H NMR deuterium-exchange experiments. **Figure 4.3** shows an example of the spectra of the mixture of diastereoisomers **145e(iii)** and **145e(iv)** before and after addition of D_2O (**Figure 4.3**).

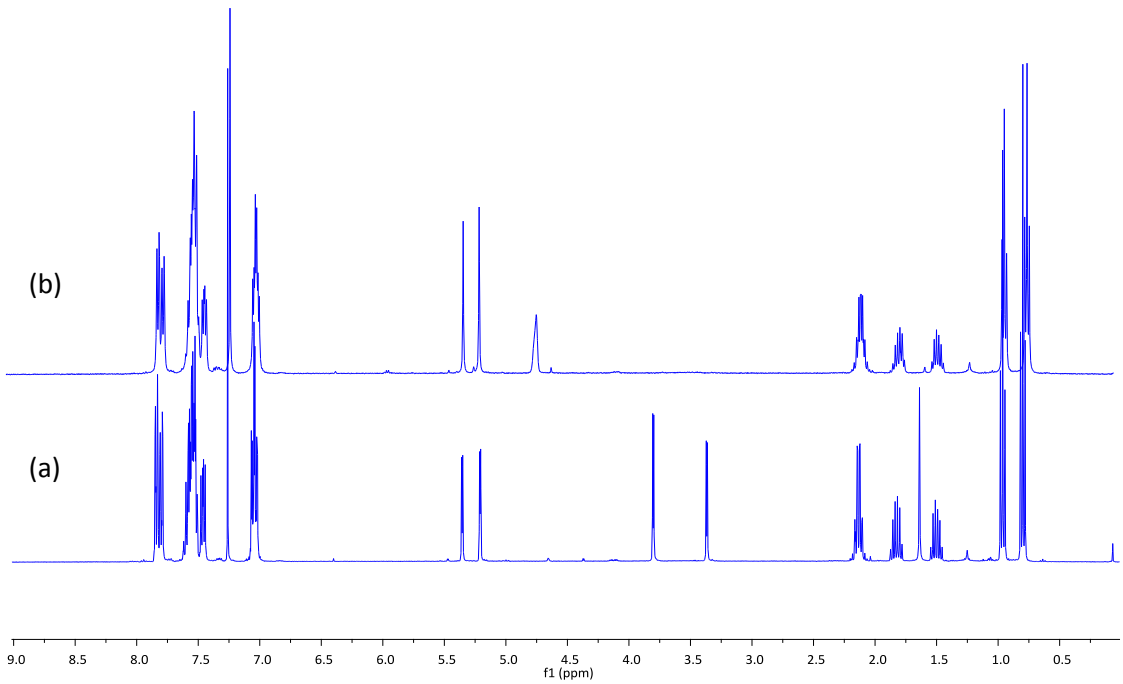
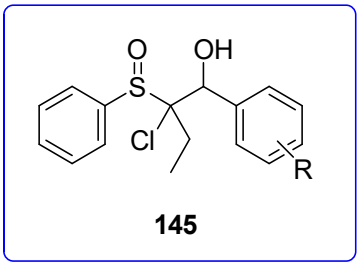


Figure 4.3: ^{1}H NMR spectra of the mixture of **145e(iii)** and **145e(iv)**: (a) before; and (b) after addition of D_2O

The specific diastereoisomer yields and the total product yields for all cases are summarised in **Table 4.2**.

Table 4.2. Diastereoisomers Yields of Compounds of Type **145**



145

Compound	R	Yield of specific diastereoisomer (%)[a]				Total product yield (%)[b]
		(i)(RRR)	(ii)(RSR)	(iii)(RSS)	(iv)(RRS)	
145a	H	23	2.5	18	14	57.5
145b	3-OMe	18	-	17	17	52
145c	4-OMe	18	-	10	17	45
145d	4-Br	10	4	20	14	48
145e	4-F	22	8	10	10	50

[a] Amount of pure material isolated after chromatography or calculated by proportion of each component in a fraction after chromatography. [b] By addition of yields of individual diastereoisomers; yields of crude product prior to chromatography were greater.

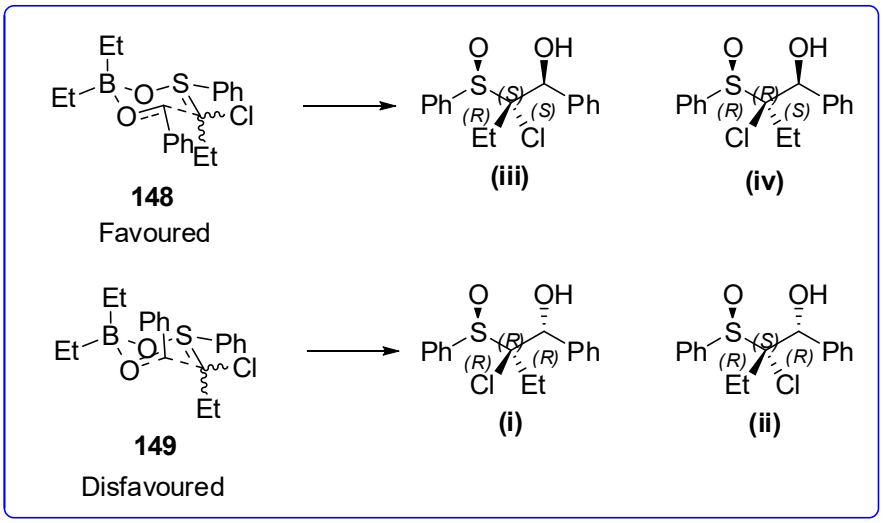
The results in **Table 4.2** showed the formation of at least three diastereoisomers in all cases and all four diastereoisomers in some. These results suggest that the stereocontrol is much less than those for the related aldol reactions of boron enolates.[133–135]

Formation of three diastereoisomers of the aldol-like product in some cases, *i.e.* **145b** and **145c** (**Table 4.2**), and all four in others, in different proportions, raises questions about the selectivity. Discussion of such matters is given in the following section.

4.2.3.4 Considerations Relating to the Selectivity of Reactions of 140 with Aldehydes

It can be seen from the data in **Table 4.2** that the most notable feature was the low relative yield of the RSR diastereoisomer in all cases while the other three diastereomisomers were formed in similar amounts.

In principle, four diastereomers are possible and in several examples all four were formed. If the transition states were to be a tight cyclohexane-like structure **148/149** (**Scheme 4.14**), similar to that involved in reactions of boron enolates with aldehydes, then one might have expected the Ph and Ar groups to be *pseudo*-equatorial in the favoured conformer (**148**), leading to a RS or SR relationship for the configurations of the S atom and the carbon atom bearing the hydroxyl group, with the configuration of the double bond in **140** determining the configuration of the chlorine-bearing carbon atom in **145**. On the other hand, the disfavoured conformer would be **149**, where the Ph group is *pseudo*-equatorial and Ar group is *pseudo*-axial, leading to a RR or SS relationship for the configurations of the S atom and the carbon atom bearing the hydroxyl group. However, computational study was needed to provide more insight into those processes.



Scheme 4.14: Proposed four Diastereoisomers outcome according to Favoured **148** and Disfavoured **149** Cyclohexane-like Transition States

4.2.3.5 Computational Study

In order to confirm the hypothesis depicted in **Scheme 4.14** and to verify the outcome stereochemistry of such hypothesis, a computational study was also carried out by Dr Mark Elliott.[84] After extensive conformational analysis based on cyclohexane-like structure **148/149**, four transition states were located at the RHF/3-21G(d) level of theory and the relative energies are summarised in **Table 4.3** and the corresponding structures are depicted in **Figure 4.4**.

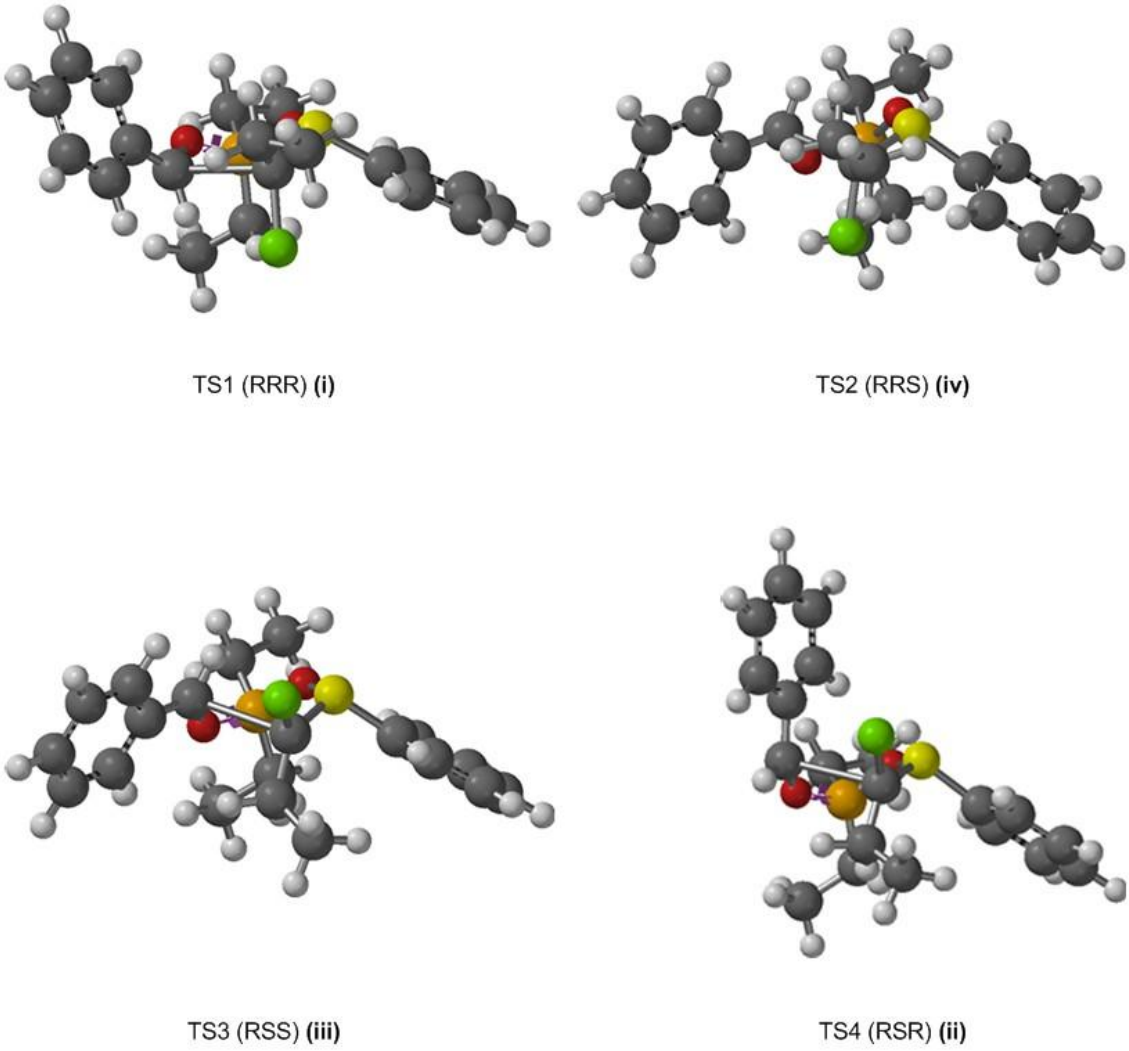


Figure 4.4: Calculated RHF/3-21G(d) TS1 TS2, TS3 and TS4 Transition States

It can be seen from the **Figure 4.4** that the shape of the 6-membered ring of all transition states is not a chair like in the Zimmerman-Traxler model for the aldol transition state, but it is rather more twisted, which means that substituents that are *trans* in the 1 and 3 positions do not need to have one equatorial and one axial. In effect, both can be equatorial.

Table 4.3: Relative Energies of TS1, TS2, TS3 and TS4 Transition States

Transition State	Diastereoisomer	G° (a.u.)	Δ*E* (KJ/mol)
TS1	**(i)** (RRR)	-1794.30314	0 (lowest)
TS2	**(iv)** (RRS)	-1794.30308	0.16
TS3	**(iii)** (RSS)	-1794.29903	10.8
TS4	**(ii)** (RSR)	-1794.28524	47.0

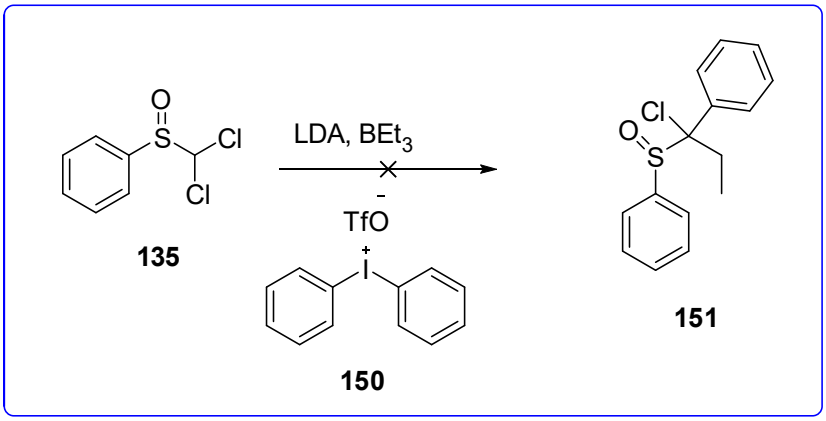
It can be seen from the **Table 4.3** that the relative energies agree with the experimental results. The lowest transition state in energy (ΔE = 0 KJ/mol) was TS1 which was **(i)** (RRR) (entry 1), while the highest in energy (ΔE = 47 KJ/mol) was **(ii)** (RSR) (entry 4). TS4 has the aldehyde phenyl more or less axial (**Figure 4.4**). In contrast, TS1, TS2 and TS3 have this group close to equatorial, which explains the difference in energy calculated. From this, it can be concluded that the two diastereoisomers that share the R stereochemistry at sulfur and the third ("aldehyde") carbon atom are produced from the same transition state as in **Scheme 4.14**, *i.e*. **(i)** and **(ii)** are produced from **149** while **(iii)** and **(iv)** are produced from **148**. The relatively big difference in energy between **(i)** and **(ii)** (47 KJ/mol) allows **(i)** to predominate over **(ii)**. Meanwhile, the small difference in energy between **(iii)** and **(iv)** (10.6 KJ/mol) does not allow either of the two isomers to predominate over the other.

Having successfully produced compounds of type **141** and **145** from intermediate **140**, attention was next turned to the attempted reaction of **140** with a wider range of electrophiles.

4.2.3.6 Attempts at Reaction of Other Types of Electrophiles with Intermediate 140 (R = Et)

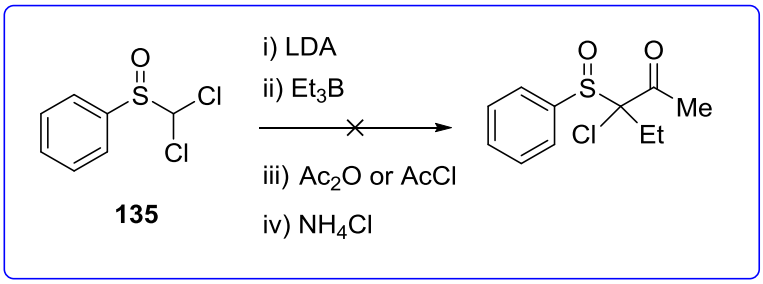
In order to utilise the procedure to include the reaction with some other electrophiles, it was decided to choose various electrophiles including $Ph_2I^+TfO^-$, acetic anhydride and acetyl chloride.

Initially, $Ph_2I^+TfO^-$ **150** was chosen to introduce an aryl group to the intermediate **140**. The synthesis of diphenyliodonium triflate **150** was carried out according to the procedure of Bielawski and Olofsson[136] by treatment of a solution of *m*-CPBA and iodobenzene in benzene and dichlormethane with triflic acid. Heating the resulting mixture to 40 °C, stirring for 1 h, work-up and purification of the crude product gave pure **150**. Compound **150** was then subjected to the procedure described in the synthesis of **145**. Disappointingly, the reaction with **150** did not give the desired product **151** (**Scheme 4.15**).



Scheme 4.15: Reaction of **135** with Triethylborane and $Ph_2I^+TfO^-$ (**150)**

In an attempt to use the reaction to functionalise the product by introducing aliphatic carbonyl compounds such as anhydride and acid halide, acetic anhydride and acetyl chloride were tested using the reaction procedure described in the synthesis of **145**. A solution of **135** in THF was treated with LDA at –78 °C followed by addition of triethylborane. After 1 hour, the mixture was quenched with the electrophile (acetic anhydride or acetyl chloride) followed by addition of a solution of ammonium chloride (**Scheme 4.16**). Both attempts failed to give the corresponding products.

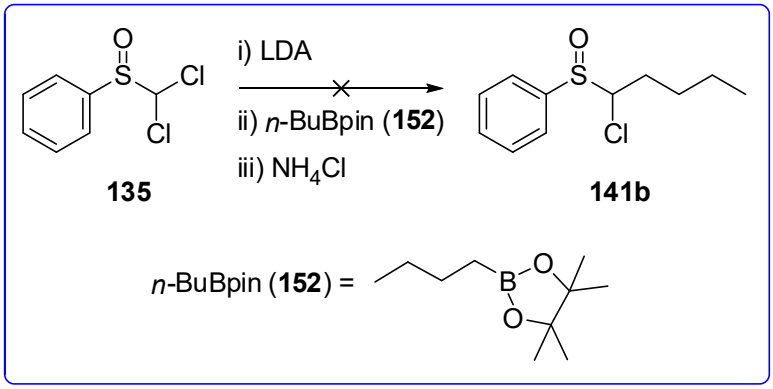


Scheme 4.16: Attempts at Reaction of **135** with Acetic Anhydride and Acetyl Chloride

Due to the results of the reaction of anion **136** with trialkylboranes, the attention was turned to its reaction with boronic esters to determine whether it is possible to produce the corresponding homologated boronic esters or the alcohols from their oxidation.

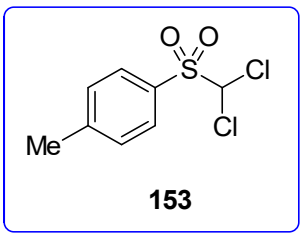
4.2.4 Attempt at Reaction of the Anion 136 with *n*-Butylboronic Acid Pinacol Ester (152)

The drawback of the reaction of trialkylboranes with anion **136** is that it wastes two equivalents of the alkyl group (**Scheme 4.3**), since the boron enolate is hydrolysed to the corresponding borinic acid. To address this issue, it is important to test whether boronic esters react with anion **136** in a manner similar to the reactions with trialkylboranes. Therefore, it was decided to repeat the same procedure but using a boronic ester instead of a trialkylborane. *n*-Butylboronic acid pinacol ester **152** was prepared according to the literature procedure[137] by stirring a solution of pinacol and *n*-butylboronic acid in anhydrous pentane overnight. After work-up, the product was used in the next step without any further purification. Anion **136** was prepared by treatment of a solution of compound **135** in THF with LDA at –78 °C. The boronic ester **152** was added and the mixture was stirred for 1 hour followed by addition of a solution of ammonium chloride. The ^{1}H NMR spectrum of the crude mixture following work-up showed only starting materials and no expected migrated product **141b** (**Scheme 4.17**). This result may be explained by the fact that boronic esters have lower electrophilicity than trialkylboranes.



Scheme 4.17: Attempted Reaction of **135** with *n*-Butylboronic acid

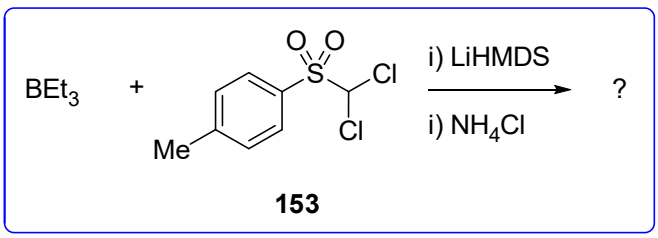
Although the reactions of trialkylboranes with anion **136** had provided some interesting results in the sense of having new reaction types, these reactions did not achieve the aim of producing a tertiary alkylboron compound in high yield. Clearly, the results of these reactions were limited to generation of the product of one migration followed by hydrolysis or by aldol-like reactions with aldehydes. It was thought that the sulfinyl group is not a good leaving group and that the intermediate after the first migration undergoes a rearrangement with the borane moiety. Replacement of the sulfoxide group with a better chiral sulfur leaving group would presumably drive the reaction to the triple migration product. For that reason, it was decided to investigate the reaction of trialkylboranes with an anion derived from compound **153**, which has, instead of a sulfinyl group, a sulfonyl group, which has been shown to act as a good leaving group in recent studies.[138,139]



4.2.5 Reaction of Trialkylborane with Dichloromethyl *p*-Tolyl Sulfone (153)

Compound **153** is not an ideal compound in the sense of that it does not possess the possibility of asymmetric introduction offered by **135**. Also, there was a previous case of a monobromo-substituted sulfone reacting with a trialkylborane that resulted in replacement of bromine by an alkyl group from the trialkylborane (**Scheme 4.5c**)[130] in exactly the same manner as seen with **135**. Nevertheless, compound **153** was thought to be sufficiently different to be worthy of study.

Dichloromethyl *p*-tolyl sulfone **153** was prepared in 40% yield according to the procedure used by Middelbos *et. al.*[140] from sodium *p*-toluenesulfinate, potassium hydroxide and chloroform. The reaction of the anion derived from compound **153** with α,β-enones was studied previously by Ni *et al.*[141] by using lithium bis(trimethylsilyl)amide (LiHMDS) as a base; therefore the LiHMDS was used in this study (**Scheme 4.18**). Initially, compound **153** was mixed with triethylborane in THF as solvent. The mixture was then cooled to –78 °C and LiHMDS was added dropwise. The mixture was stirred for 30 minutes at –78 °C and 90 minutes at room temperature and it was then quenched with aqueous ammonium chloride solution.



153

Scheme 4.18: Reaction of Anion Derived from **153** with Triethylborane

The crude mixture was separated by flash column chromatography. The ^{1}H NMR spectrum of the major compound isolated showed ethyl group protons, methyl group protons and aromatic protons without the presence of a C*H*Cl proton (which would be required for a compound analogous to **141**). Also, the ^{13}C NMR spectrum did not show

a *C*HCl carbon, but instead showed a quaternary carbon atom peak at 101.8 ppm. It was difficult to prove whether the compound contained a sulfoxide or sulfonyl group by NMR spectroscopy. Therefore, more analyses were carried out by X-ray crystallography and mass spectrometry. From the data of these two techniques, it was concluded that the compound was **154**, the yield of which was 46%. Single crystal X-ray diffraction showed the molecule's structure to be as depicted in **Figure 4.5**. Also, the chemical ionisation mass spectrum of **154** showed an intense *pseudo*-molecular ion peak at *m/z* = 284 and the high resolution mass of this peak confirmed its formula as $C_{10}H_{12}{}^{35}Cl_2O_2S$ $(M+NH_4)^+$. The formation of compound **154** formally involves displacement of hydride by the ethyl group of the triethylborane.

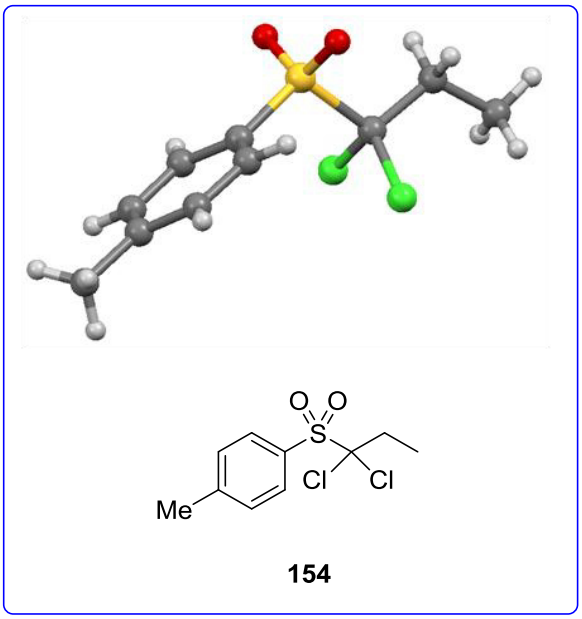
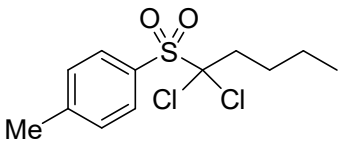


Figure 4.5: X-Ray Structure of 1,1-Dichloro-1-(*p*-tosyl)propane (**154**)

The reaction was also repeated using tri-*n*-butylborane as the trialkylborane to check whether the reaction is applicable for other trialkylboranes. Work-up and separation of the product by column chromatography gave a similar result to that observed in the

formation of compound **154**. 1,1-Dichloro-1-tosylpentane (**155**) was produced in 44% yield.



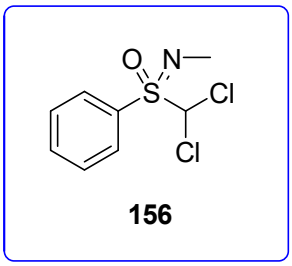
155

The replacement of the hydride by the alkyl group of trialkylboranes means that the process is an oxidation; some other components of the reaction should have been reduced. The yield of the product in each case was less than 50%, which is consistent with half of the original **153** having been reduced. At present, it is unclear what process might be taking place or even whether the reaction is radical or ionic in nature, but it would be interesting to investigate this reaction further in the future. Although, the reaction has provided an interesting new type of reaction, the replacement of the hydride by alkyl group has not provided the goal of generating any of the desired migration products. Therefore, attention was next turned to reaction of an anion derived from a sulfoximine with a trialkylborane.

4.2.6 Reactions with Sulfoximines

Although sulfoximines are isoelectronic with sulfones, the replacement of the oxygen atom by a nitrogen atom causes asymmetry at the tetrahedral sulfur atom in cases where the two other groups are not identical.[142] Generally, sulfoximines are stable compounds which provide a rich and versatile chemistry. Their use in organic synthesis and their applications in medicinal chemistry have been the subject of a number of reviews.[142–144] In this section, the reactions of the anion derived from *N*-methyl-*S*-(dichloromethyl)-*S*-phenylsulfoximine **156** are reported.

4.2.6.1 Attempt at Improving the Yield of N-Methyl-S-(dichloromethyl)-S-phenylsulfoximine (156)

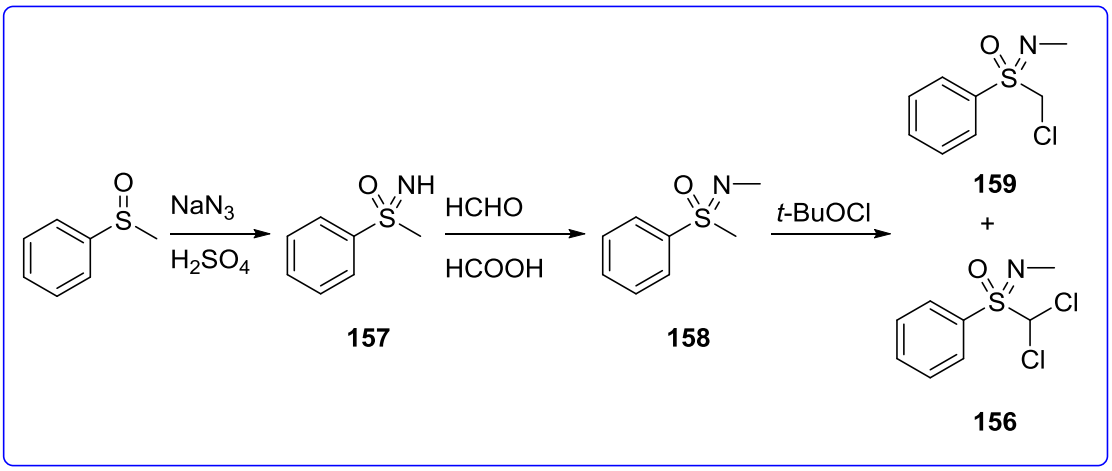


156

To the best of our knowledge, only one report has been published for the preparation of compound **156**, which was produced as a by-product in very poor yield (7%) in an attempted synthesis of the monochloro sulfoximine (**159**) by chlorination of **158** by *t*-butyl hypochlorite (**Scheme 4.18**).[145] It was hoped that it would be possible to optimise the reaction to improve the yield, or find an alternative method to chlorinate **158**.

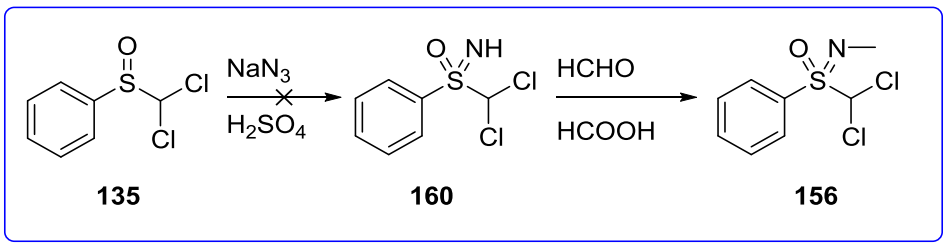
Initially, the sulfoximine **157** was prepared on a relatively large scale (6 grams) according to a literature method[146,147] from methyl phenyl sulfoxide, sodium azide and sulfuric acid. Compound **157** was then methylated using formaldehyde and formic acid to form **158**. Compound **158** was then, firstly, subjected to the same chlorination reaction conditions used by Johnson but with two equivalents of the chlorinating agent being used (**Scheme 4.19**). A solution of **158** in dichloromethane was treated with two equivalents of *t*-butyl hypochlorite in the presence of potassium carbonate and in the absence of light. The mixture was stirred for 1 h at room temperature, to form **159** and **156** as a mixture of products. However, separation by column chromatography gave the two products in 72% (**159**) and 7% (**156**), respectively, a ratio similar to that reported by Johnson. In an attempt to improve the yield of **156**, the reaction was repeated but the reaction mixture was stirred overnight, which led to an increase in the yield slightly to 16% according to the ^{1}H NMR spectra of crude products. Heating the reaction mixture to reflux for 2 hours after addition of *t*-butyl hypochlorite led to improvement of the yield further to 25%, which was the best yield achieved. Heating

the reaction mixture longer caused decomposition of the products instead. Use of a different chlorinating agent, *N*-chlorosuccinimide, failed to form any of the expected chlorinated products.



Scheme 4.19: Preparation of *N*-Methyl-*S*-(dichloromethyl)-*S*-phenylsulfoximine (**156**)

It was thought that if the formation of sulfoximine **156** started from sulfoxide which already contained chlorine atoms (**135**), this might be superior. However, the reaction of sulfoxide **135** with sodium azide and sulfuric acid gave none of the desired product (**Scheme 4.20**).



Scheme 4.20: Proposed route to **156** from **135**

Nevertheless, the compound **156** was prepared, albeit in modest yield, using the procedure shown in **Scheme 4.19** where the reaction mixture was heated to reflux for 2 hours after addition of *t*-butyl hypochlorite. It was therefore available for investigation of its reactions with organoboranes.

4.2.6.2 Exploring and Optimising the Reaction of Sulfoximine 156 with Trioctylborane

In the initial experiment, equimolar amounts of trioctylborane and **156** were dissolved in THF and cooled to –78 °C. LDA was added dropwise to the mixture, which was then allowed to warm to room temperature. The solution was stirred for 1 h at –78 °C and 1 h at room temperature before peroxidic oxidation. Interestingly, work-up and GC analysis of the crude reaction mixture showed the formation of 1-octanol (**117**) (37% of all octyl groups introduced to the system), the product of two alkyl group migrations (dioctyl ketone, **116**, 13%) and the product of three alkyl group migrations (trioctylmethanol, **118**, 39%) (all figures inclusive of 2-octyl isomers).

Having successfully produced the product of three alkyl group migrations, attention was turned to optimisation of the production of the triple migration product. A few attempts at improving the yield of the trioctylmethanol were made and the results are summarised in **Table 4.4**. As can be seen from the table, using 1.5 equivalents of **156** did not increase the amount of trioctylmethanol (entry 2) but increased the amount of dioctyl ketone significantly (from 13% to 29%). Replacement of the THF as solvent by dichloromethane and using 1.5 equivalents of **156** improved the yield of trioctylmethanol significantly to 54% (entry 3). Combining these conditions and stirring the solution mixture for 1 h at –78 °C and overnight at room temperature successfully increased the yield to 81% of the tertiary alcohol along with 11% of dioctyl ketone and 12% of 1-octanol (entry 4).

Table 4.4: Attempts at Optimisation of Reaction Conditions for the Homologation/Oxidation Reaction of **156** with Trioctylborane

Entry	Yields of products (%)[a]			Description of Procedure
	Oct_3COH	$Oct_2C=O$	OctOH[b]	
1	39	13	37	Using 1.0 equiv of **156**, THF as solvent, stirring 1 h at –78 °C and 1h at r.t.
2	40	29	18	1.5 equiv. of **156** but otherwise as above
3	54	13	23	Using DCM but otherwise as in entry 1
4	81	11	12	DCM, 1.5 equiv. of **156** and overnight stirring at r.t.

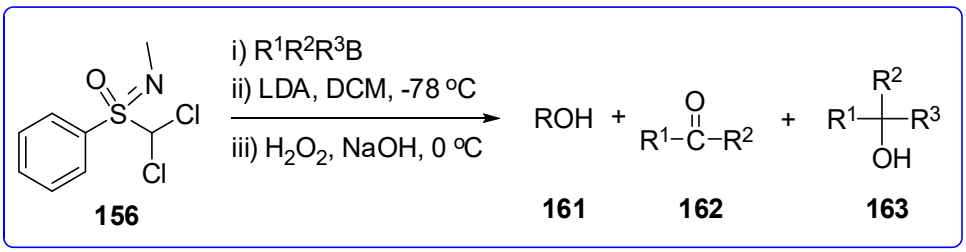
[a] Products yields determined by GC; [b] Proportion as percentage of all octyl groups in trioctylborane

Having successfully optimised the conditions of the reaction to achieve a high yield of the product of the three alkyl group migrations, these conditions were then adopted as standard and the reaction was carried out with a range of trialkylboranes (**Scheme 4.21**).

4.2.6.3 Reaction of Sulfoximine 156 with a Range of Trialkylboranes

Triethylborane, tributylborane and triphenylborane were purchased, while trioctylborane, tricyclopentylborane and tricyclohexylborane were prepared *in situ* by

hydroboration of the corresponding alkenes. Mixed trialkylboranes were prepared according to a literature procedure[148] involving addition of one or two alkyllithium reagents to a chloroborane derivative, which was not optimised and may have given poor yields of mixtures of organoboranes, but the method served to provide mixed organoboranes for testing the outcome of the reactions.



Scheme 4.21: Reactions of Compound **156** with Organoboranes

The results of the reaction of **156** with the organoboranes are summarised in **Table 4.5**.

It can be seen from **Table 4.5** that apart from the more hindered trialkylboranes, all of the reactions gave significant yields of the desired tertiary alcohol. The reaction of triethylborane gave a modest yield, probably due to loss of product through evaporation and/or dissolution in water. With respect to the reaction of butylmethylphenylborane, the low yield (30%) of the triple migration product reflects the poor synthesis of the mixed trialkylborane, which contained a substantial amount of dibutylphenylborane. 5-Phenylnonanol (30%) was also isolated from this reaction, so that the total amount of triple migration products was 60%. With respect to butyldicyclohexylborane, the product tributylmethanol (20%) was observed, which is presumably due to the presence of tributylborane in the butyldicyclohexylborane. However, the more hindered trialkylboranes did not give any of the desired alkyl group migration products.

Table 4.5: Products formed in Reactions According to **Scheme 4.21**

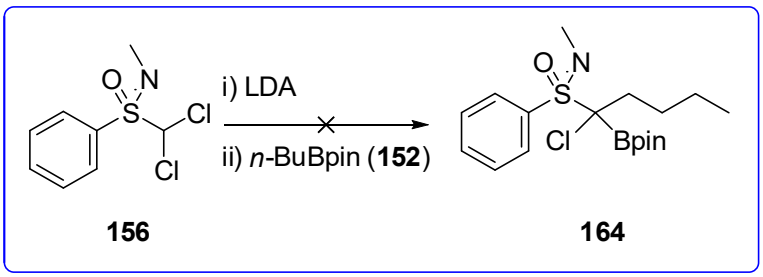
Alkyl groups of $R^1R^2R^3B$			Yields of products (%)[a]		
R^1	**R^2**	**R^3**	**161**	**162**	**163**
Et	Et	Et	-	-	(47)[b]
Bu	Bu	Bu	-	13	(81)
Oct	Oct	Oct	12[c]	11[c]	75[c] (81)
Bu[d]	Bu[d]	*c*-Hex[d]	-	-	73
Bu[d]	Bu[d]	*c*-Pent[d]	-	-	68
Bu[e]	Bu[e]	Ph[e]	-	-	51
Me[f]	Bu[f]	Ph[f]	-	-	30[g]
c-Pent	*c*-Pent	*c*-Pent	-	-	-
Ph	Ph	Ph	-	-	-
Bu	*c*-Hex	*c*-Hex	-	-	20[h]
Oct	Oct	Thex	-	-	-
Oct	9-BBN	9-BBN	-	-	-

[a] Yields of isolated materials by chromatography (GC figures are in parentheses). [b] A significant proportion of the product mixture may have been lost by evaporation during work-up. [c] All compounds contained 2-octyl isomers as a result of the preparation of trioctylborane by hydroboration of 1-octene. [d] The trialkylborane was prepared *in situ* from BCl_3, the corresponding cycloalkene and Et_3SiH, followed by 2 equiv. of *n*-BuLi. [e] The trialkylborane was prepared *in situ* from $PhBCl_2$ and 2 equiv. of *n*-BuLi. [f] The trialkylborane was prepared *in situ* from $PhBCl_2$ then sequential addition of 1 equiv. of *n*-BuLi and 1-equiv. of MeLi; the product was a mixture of PhBBuMe and $PhBBu_2$. [g] $PhC(OH)Bu_2$ (30%) was also isolated. [h] The product observed was tributylmethanol, indicating that the organoborane was a mixture.

Nevertheless, the fact that the mixed organoboranes successfully produced the corresponding tertiary alcohols suggests that the reaction involves three intramolecular organic group transfers, and this opens up a potential process involving asymmetric induction if an appropriate enantiomerically-pure sulfoximine **156** is used in this reaction.

4.2.6.4 Attempted Reaction of the Anion Derived from 156 with Boronic Esters

Due to the success of the reaction of anion derived from sulfoximine **156** with trialkylboranes, it was felt to be worth investigating the reaction of the anion derived from **156** with boronic esters. Therefore, *n*-butylboronic acid pinacol ester (**152**) was chosen as a suitable boronic ester. A mixture of compound **156** and the boronic ester **152** was dissolved in DCM and the solution was cooled to –78 °C. LDA was added and the resulting mixture was stirred overnight (**Scheme 4.22**). A few millilitres of the reaction mixture was taken by syringe and injected into an NMR tube with a septum, and the solvent was removed under a stream of N_2. By looking at the ^{1}H NMR spectrum of the crude products, the experiment showed that only starting materials were observed and none of the desired homologated boronic ester (**164**) had formed, highlighting the lack of reactivity of boronic esters with such anions.



Scheme 4.22: Attempted Reaction of **156** with Boronic Ester **152**

In view of the success in reacting trialkylboranes with the anion derived from compound **156**, it was thought to be interesting to attempt similar reactions with

S-dichloromethyl-*S*-phenyl-*N*-toluenesulfonylsulfilimine (**166**). The first stage was to prepare the compound **166**.

4.2.6.5 Attempted Chlorination of S-Methyl-S-phenyl-N-sulfonylsulfilimines (165)

Sulfilimines are isoelectronic with sulfoxides and they create asymmetry at the tetrahedral sulfur atom when the oxygen atom is replaced by nitrogen and the two carbon groups are not the same (**Figure 4.6**). Their stability and biological activity have abetted a recent growing interest in these compounds.[149–151]

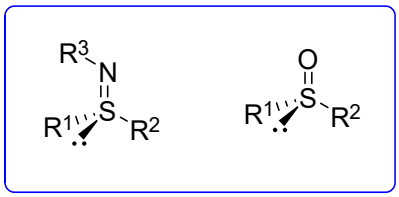
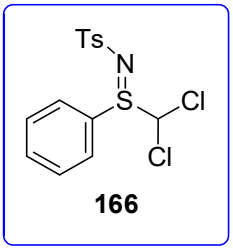


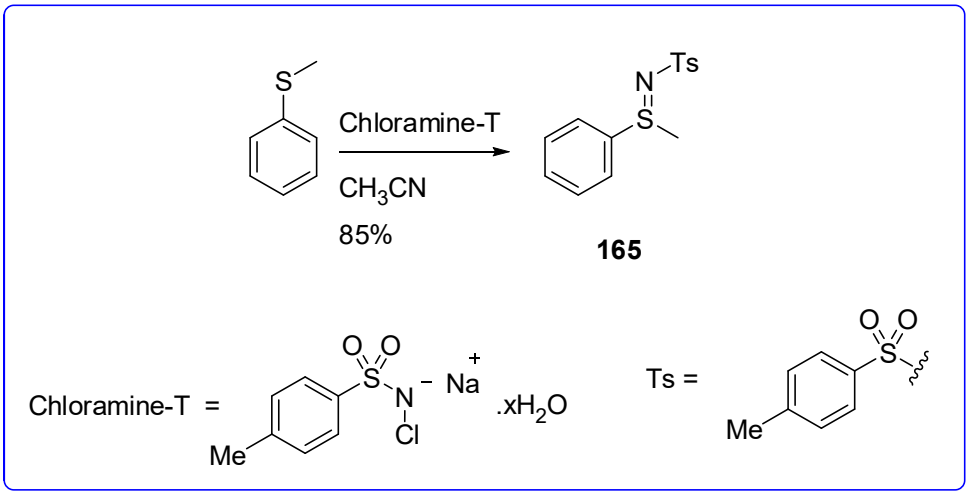
Figure 4.6: Structures of Sulfilimines and Sulfoxides

It was thought that using the anion derived from *S*-dichloromethyl-*S*-phenyl-*N*-toluenesulfonylsulfilimine (**166**) in DCME-like reactions presumably would not form an enolate intermediate, as the sulfilimine group is more hindered than a sulfoxide group. As a result, the reaction of compound **166** with a trialkylborane would probably not undergo a tautomeric rearrangement similar to that of sulfoxides after the first migration (**Scheme 4.6**). This, ultimately, might lead to induction of the second alkyl group migration.



166

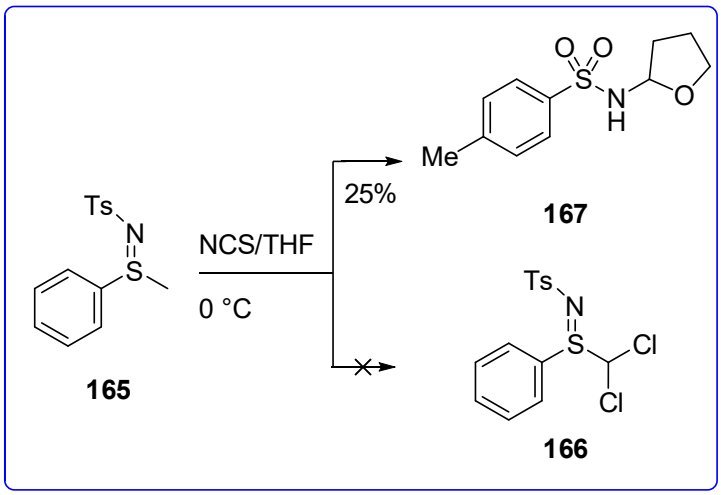
Therefore, synthesis of **166** was attempted. *S*-Methyl-*S*-phenyl-*N*-toluenesulfonylsulfilimine **165** was first prepared by treatment of a solution of thioanisole in acetonitrile with chloramine-T according to a known procedure to give compound **165** in very good yield (85%) (**Scheme 4.23**).[150]



Scheme 4.23: Preparation of *S*-Methyl-*S*-phenyl-*N*-toluenesulfonylsulfilimine (**165**)

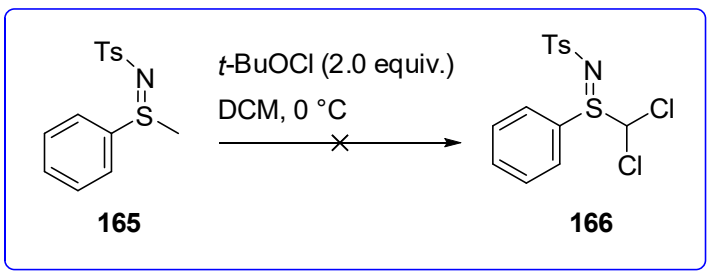
A solution of compound **165** in THF was treated with *N*-chlorosuccinimide (NCS) at 0 °C. The ^{1}H NMR spectrum of the crude product after work-up showed starting material and an unknown compound. The unknown compound was isolated in low yield (25%) by column chromatography and the ^{1}H NMR spectrum showed doublet peaks at 7.72 ppm (J = 8.0 Hz) with integration of two protons and 7.20 ppm (J = 8.0 Hz) with integration of two protons and a singlet at 2.34 ppm with integration of three protons, which seem to be due to the *p*-tosyl group. Also, it showed a doublet at 5.88 ppm (J = 9.0 Hz) for one proton, a multiplet in the range 5.31 – 5.19 ppm due to one proton, a multiplet at 3.69 – 3.49 ppm due to two protons, a multiplet in the range 2.14-1.97 ppm due to one proton and a multiplet at 1.94 – 1.56 ppm due to three protons, which seemed to be due to a 2-substituted tetrahydrofuryl group. Combining these data with ^{13}C NMR data, it was concluded that the compound was **167** resulting from the

reaction of compound **165** with the solvent (**Scheme 4.24**). Indeed, these data were identical to those shown in the literature for compound **167**.[152]



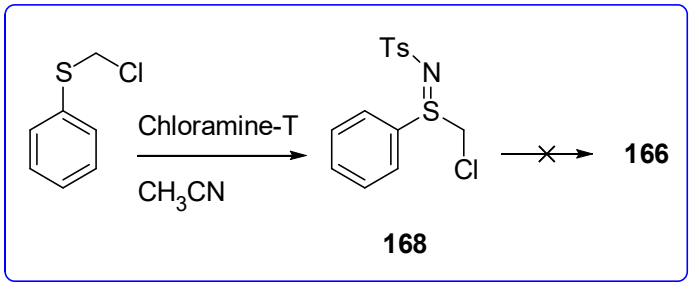
Scheme 4.24: Reaction of **165** with THF

To avoid this issue it was decided to replace the THF with DCM and the reaction was repeated. The ^{1}H NMR spectrum of the crude products showed that no reaction had occurred; only starting materials were observed. Also, a solution of compound **165** in DCM was treated with *t*-butyl hypochlorite at 0 °C (**Scheme 4.25**). No reaction occurred and only starting materials were observed in the crude reaction mixture.



Scheme 4.25: Attempted Chlorination of **165** with *t*-BuOCl

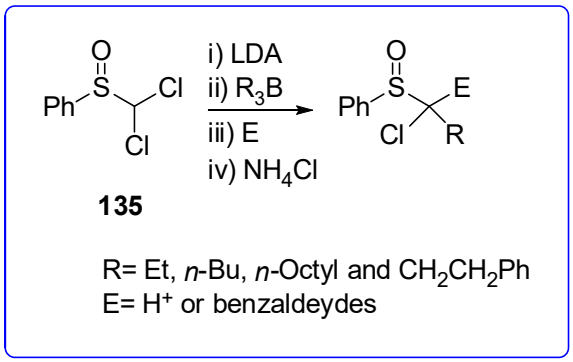
It was thought that the existing chlorine atom in sulfilimine **168** might help to activate the methylene group to further chlorination. Compound **168** can be synthesised from chloromethyl phenyl sulfide, which is commercially available. The compound was synthesised using the same method that was detailed for **165** (**Scheme 4.26**). However, the sulfilimine **168** was subjected to the same two chlorination procedures that were used in attempts to chlorinate compound **165** in DCM without observing the desired product in either case according to the ^{1}H NMR spectra of the crude products. Only starting materials were observed.



Scheme 4.26: Attempts at Chlorination of **168**

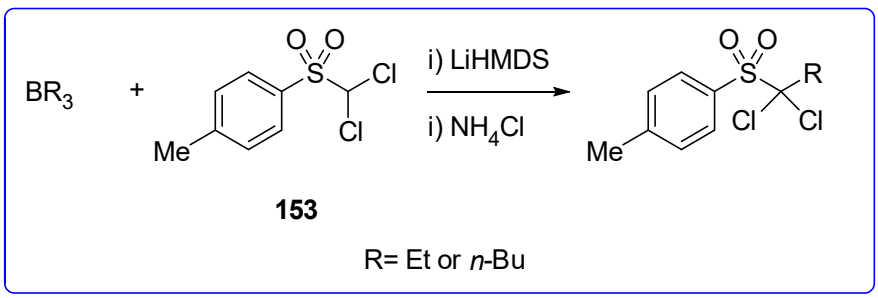
4.3 Conclusion

In this chapter, the aim was to assess the reaction of three different kinds of anionic reagents derived from Cl_2CHX (X = phenylsulfinyl (SOPh), *p*-tosyl and phenylsulfoximinyl (PhSO(NMe)) groups) with trialkylboranes. The three anions were generated and reacted *in situ* with the trialkylboranes and each of the three reagent types showed a different behaviour. Dichloro(phenylsulfinyl)methyl anion (X = SOPh) showed a new kind of reaction involving replacement of one of the chlorine atoms by an alkyl group in a rearrangement reaction, followed presumably by formation and hydrolysis of a boron enolate-like intermediate. The reaction was exploited to produce a series of new compounds by trapping the intermediate with aldehydes to give β-hydroxyalkyl sulfoxides.



Scheme 4.27: Reactions of the Anion Derived from **135** with Triethylborane and Electrophiles

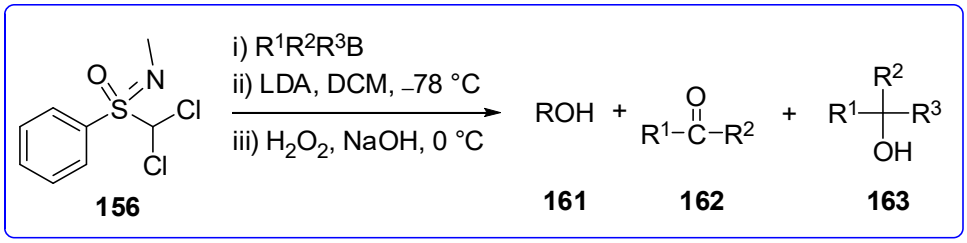
In contrast to the sulfoxide, the reaction of the anion derived from dichloromethyl *p*-tolyl sulfone with a trialkylborane gave the product of the overall replacement of hydride by an alkyl group from the trialkylborane, which is also a new type of reaction.



Scheme 4.28: Reaction of Anion Derived from **153** with Triethylborane

Finally, *S*-dichloromethyl-*N*-methyl-*S*-phenyl-sulfoximine anion (X = PhSO(NMe)) reacted successfully to give the desired tertiary alcohol product of displacement of all three alkyl groups by alkyl groups of a trialkylborane after oxidation. These results

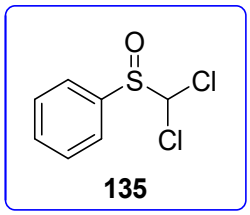
open the way potentially to an asymmetric process influenced by enantiomerically-pure sulfoximines.



Scheme 4.29: Reactions of Compound **156** with Organoboranes

4.4 Experimental

4.4.1 Preparation of Dichloromethyl Phenyl Sulfoxide (135)[119]



135

To a solution of methyl phenyl sulfoxide (1.00 g, 7.13 mmol) in THF (15 mL) at 0 °C, was added *N*-chlorosuccinimide (1.95 g, 14.62 mmol, 2.05 equiv.). The solution was stirred at 0 °C overnight and filtered. The solvent was removed *in vacuo*. The product was purified by flash column chromatography (4:1 petroleum ether/diethyl ether) to afford the *title compound* (1.084 g, 73%) as a colourless oil, R_f = 0.26 (4:1 petroleum ether/diethyl ether).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.86 – 7.74 (2H, m), 7.68 – 7.51 (3H, m) and 6.17 (1H, s).

^{13}C NMR (101 MHz; $CDCl_3$) δ 138.1, 133.2, 129.1, 126.7 and 83.1.

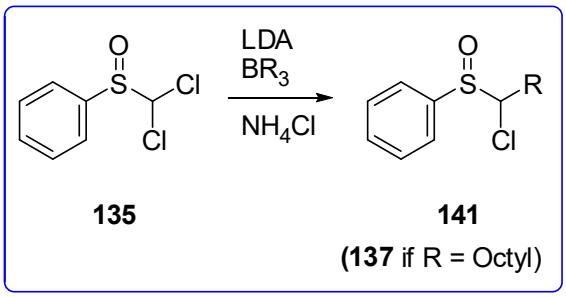
4.4.2 Reactions of Dichloromethyl Phenyl Sulfoxide with Trioctylborane

To a septum-capped 25 mL flask, was added borane (100 μL, 10.0 M in dimethyl sulfide, 1.0 mmol, 1 equiv.), followed by THF (5 mL). The flask was immersed in an ice-bath and 1-octene (0.47 mL, 3.0 mmol, 3 equiv.) was added dropwise. The cooling bath was removed and the solution was left to stir at room temperature for 1 h. The solution was mixed with a solution of dichloromethyl phenyl sulfoxide (**135**) (209 mg, 1.0 mmol, 1 equiv.) in THF (5 mL) and cooled to –78 °C. LDA (1.1 mmol in 2.0 mL of THF, 1.1 equiv.) was added dropwise and the solution was stirred for 1 h at the same temperature. The cooling bath was removed, and the reaction stirred for a further 1 h. The solution was cooled to 0 °C and oxidised by adding sodium hydroxide (3.0 M, 5 mL) followed by aqueous hydrogen peroxide (30% aqueous, 3 mL). After the initial reaction subsided, the mixture was gently warmed and stirred overnight. The aqueous layer was saturated with sodium chloride and tetradecane (221.9 mg) was added. A sample

from the organic layer was taken and injected into the GC machine. The results were: 1-ocatanol (**117**) (55%), dioctyl ketone (**116**) (6%) and trioctylmethanol (**118**) (3%).

The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The organic layers were combined, dried over magnesium sulfate and filtered. The volatile solvents were evaporated under reduced pressure to leave the corresponding alcohol. The crude product was purified by column chromatography on silica gel (5% EtOAc/petroleum ether) to yield 1-octanol (**117**) (188 mg, 48%), dioctyl ketone (**116**) (8 mg, 3%) and trioctylmethanol (**118**) (5 mg, 1%).

4.4.3 General Procedure for Synthesis of 1-Chloroalkyl Phenyl Sulfoxides (141)

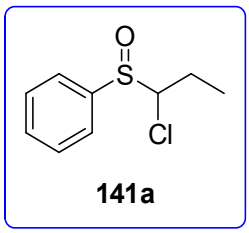


R = a) Et, b) *n*-Bu, c) 2-Phenylethenyl, e) Phenyl

To a cooled (–78 °C) solution of diisopropylamine (91 μL, 0.65 mmol, 1.3 equiv.) in dry THF (5 mL), *n*-BuLi (0.38 mL, 1.6 M in hexane, 0.60 mmol, 1.2 equiv.) was added dropwise. The solution was warmed to 0 °C over a period of 20 min. The solution was cooled again to –78 °C. To this solution was added dichloromethyl phenyl sulfoxide (105 mg, 0.50 mmol, 1.0 equiv.) and the mixture was stirred for 10 minutes. Trialkylborane (0.50 mmol, 1.0 equiv.) was added and the mixture was stirred for 1 h, then the reaction was quenched by addition of saturated ammonium chloride solution (5 mL) before being warmed to room temperature. The organic layer was separated, the aqueous layer was extracted with dichloromethane (3 x 10 mL) and the organic layers were combined and dried over magnesium sulfate. The solvents were evaporated under reduced pressure. The crude product was purified by flash column

chromatography on silica gel (the eluent is indicated in each case) to afford the corresponding sulfoxide.

4.4.3.1 1-Chloropropyl Phenyl Sulfoxide (141a)



141a

According to the general procedure, followed by flash column chromatography (4:1 petroleum ether/diethyl ether), the reaction of triethylborane with dichloromethyl phenyl sulfoxide gave the *title compound* (92 mg, 92%) as a colourless oil as a 78:22 mixture of diastereoisomers.

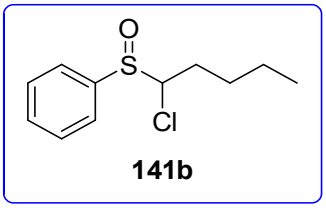
$\nu_{max.}$(neat) 3061, 2974, 2937, 2877, 1444, 1084 and 1049 cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.78 – 7.69 (2H of major isomer, m, aromatic CH), 7.68 – 7.62 (2H of minor isomer, m, aromatic CH), 7.58 – 7.46 (3H of both isomers, m, aromatic CH), 4.46 (1H of minor isomer, dd, *J* = 9.7, 4.1 Hz, C*H*Cl), 4.36 (1H of major isomer dd, *J* = 9.0, 3.1 Hz, C*H*Cl), 2.29 – 2.17 (1H of minor isomer, m, one of CH_2), 2.23 (1H of major isomer, dqd, *J* = 14.6, 7.3, 3.1 Hz, one of CH_2), 1.96 (1H of major isomer, ddq, *J* = 14.6, 9.0, 7.2 Hz, one of CH_2), 1.67 – 1.51 (1H of minor isomer, m, one of CH_2) and 1.20 – 1.09 (3H of both isomers, m, CH_3).

^{13}C NMR (101 MHz; $CDCl_3$) (major isomer): δ 141.2 (quat C), 132.2 (CH), 129.1 (CH), 126.0 (CH), 78.6 (CH), 24.9 (CH_2) and 10.0 (CH_3); (minor isomer): δ 139.3 (quat C), 132.0 (CH), 128.9 (CH), 125.6 (CH), 78.2 (CH), 24.8 (CH_2) and 11.0 (CH_3).

MS ($APCl^+$) *m/z* 205 (MH^+, ^{37}Cl, 10%), 203 (MH^+, ^{35}Cl, 30), 244 (30), 150 (100) and 109 (62); HRMS: Found MH^+, 203.0292. $C_9H_{12}{}^{35}ClOS$ requires M, 203.0297.

4.4.3.2 1-Chloropentyl Phenyl Sulfoxide (141b)



141b

According to the general procedure, followed by flash column chromatography (30% diethyl ether/petroleum ether), the reaction of tributylborane with dichloromethyl phenyl sulfoxide gave the *title compound (*101 mg, 88%) as a colourless oil as a 84:16 mixture of diastereoisomers.

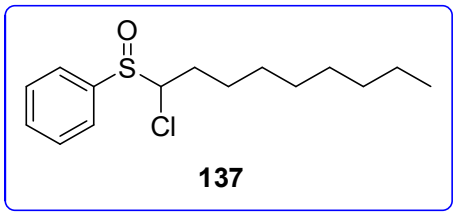
$\nu_{max.}$ (neat) 3057, 2957, 2931, 2862, 1444, 1084 and 1049 cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.82 – 7.49 (5H of both isomers, m, aromatic CH), 4.53 (1H of minor isomer, dd, *J* = 9.5, 4.1 Hz, C*H*Cl), 4.40 (1H of major isomer, dd, *J* = 9.8, 3.0 Hz, C*H*Cl), 2.31 – 2.21 (1H of minor isomer, m, one of CH_2), 2.26 (1H of major isomer, dddd, *J* = 14.3, 8.6, 5.6, 3.0 Hz, one of CH_2), 1.94 (1H of major isomer, app. dtd, *J* = 14.3, 9.9, 4.6 Hz, one of CH_2), 1.78 – 1.22 (4H of major isomer and 5H of minor isomer, m) and 0.90 (3H of both isomers, app. t, *J* = 7.2 Hz, CH_3).

^{13}C NMR (101 MHz; $CDCl_3$) (major isomer): δ 141.3 (quat C), 132.2 (CH), 129.1 (CH), 126.0 (CH), 77.4 (CH), 31.1 (CH_2), 27.7 (CH_2), 22.2 (CH_2) and 13.9 (CH_3). Selected chemical shifts for the minor isomer: δ 131.9 (CH), 128.9 (CH), 125.65 (CH), 76.6 (CH), 30.8 (CH_2), 28.3 (CH_2) and 22.0 (CH_2).

MS ($APCl^+$) *m/z* 233 (MH^+, ^{37}Cl, 10%), 231 (MH^+, ^{35}Cl, 33%), 272 (40), 150 (100); HRMS: Found MH^+, 231.0619. $C_{11}H_{16}{}^{35}ClOS$ requires M, 231.0610.

4.4.3.3 1-Chlorononyl Phenyl Sulfoxide (137)



137

According to the general procedure, followed by flash column chromatography (4:1 petroleum ether/diethyl ether), the reaction of trioctylborane with dichloromethyl phenyl sulfoxide gave the title *compound* (88 mg, 61%) as a colourless oil as a 84:16 mixture of diastereoisomers.

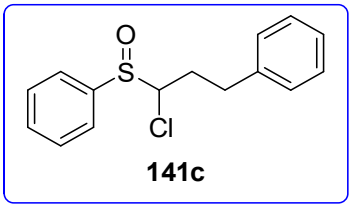
$\nu_{max.}$ (neat) 3063, 2955, 2924, 2854, 1464, 1444 and 1051 cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.80 – 7.70 (2H of major isomer, m, aromatic CH), 7.69 – 7.63 (2H of minor isomer, m, aromatic CH), 7.60 – 7.49 (3H of both isomers, m, aromatic CH), 4.53 (1H of minor isomer, dd, *J* = 9.5, 4.0 Hz, C*H*Cl), 4.40 (1H of major isomer, dd, *J* = 9.8, 3.0 Hz, C*H*Cl), 2.32 – 2.15 (1H of minor isomer, m, one of CH_2), 2.24 (1H of major isomer, dddd, *J* = 14.3, 9.4, 5.8, 3.0, one of CH_2), 1.93 (1H of major isomer, app. dtd, *J* = 14.3, 9.8, 4.5, one of CH_2), 1.83 – 1.05 (12H of major isomer and 13H of minor isomer, m, $(CH_2)_6$) and 0.87 (3H of both isomers, app. t, *J* = 6.9 Hz, CH_3).

^{13}C NMR (101 MHz; $CDCl_3$) (major isomer): δ 141.3 (quat C), 132.2 (CH), 129.1 (CH_2), 126.0 (CH_2), 77.4 (CH), 31.9 (CH_2), 31.3 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 25.6 (CH_2), 22.8 (CH_2) and 14.2 (CH_3). Selected chemical shifts for the minor isomer: δ 131.9 (CH), 129.0 (CH), 125.8 (CH), 76.7 CH), 31.2 (CH_2), 29.2 (CH_2), 28.9 (CH_2) and 26.3 (CH_2).

EI-MS *m/z* (%) 286 (M^+, ^{35}Cl, l5%), 234 (20), 125 (100), 78 (100); HRMS: Found: M^+, 286.1159. $C_{15}H_{23}{}^{35}ClOS$ requires M, 286.1158.

4.4.3.4 1-Chloro-3-phenylpropyl Phenyl Sulfoxide (141c)



141c

According to the general procedure, followed by flash column chromatography (4:1 petroleum ether/diethyl ether), the reaction of tris(2-phenylethyl)borane with dichloromethyl phenyl sulfoxide gave the *title compound* (56 mg, 40%) as a colourless oil as a 81:19 mixture of diastereoisomers.

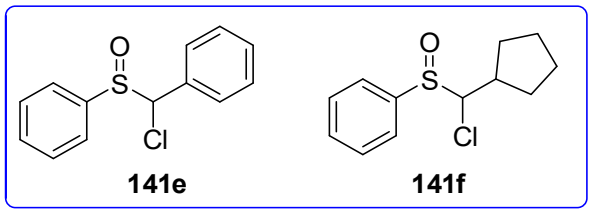
$\nu_{max.}$ (neat) 3061, 3026, 2955, 2930, 2856, 1444, 1085 and 1049 cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.67 – 7.58 (2H of the major isomer, m, aromatic CH), 7.59 – 7.54 (2H of minor isomer, m, aromatic CH), 7.53 – 7.38 (3H of both isomers, m, aromatic CH), 7.27 – 7.04 (5H of both isomers, m, aromatic CH), 4.40 (1H of minor isomer, dd, *J* = 10.3, 3.7 Hz, C*H*Cl), 4.30 (1H of major isomer, dd, *J* = 10.2, 2.8 Hz, C*H*Cl), 3.03 – 2.84 (1H of minor isomer, m, one of CH_2), 2.95 (1H of major isomer, ddd, *J* = 13.9, 9.0, 4.7 Hz, one of CH_2), 2.79 – 2.66 (1H of minor isomer, m, one of CH_2), 2.57 – 2.67 (1H of minor isomer, m , one of CH_2), 2.71 (1H of major isomer, app. dt, *J* = 13.9, 8.2 Hz, one of CH_2), 2.47 (1H of major isomer, dddd, *J* = 14.3, 9.0, 7.8, 2.8 Hz, one of CH_2), 2.15 (1H of major isomer, dddd, *J* = 14.3, 10.2, 8.8, 4.7 Hz, one of CH_2) and 1.91 – 1.77 (1H of minor isomer, m, one of CH_2).

^{13}C NMR (126 MHz; $CDCl_3$) (major isomer): δ 140.9 (quat C), 139.4 (quat C), 132.2 (CH), 129.1 (CH), 128.7 (CH), 128.55 (CH), 126.53 (CH), 125.8 (CH), 76.3 (CH), 32.7 (CH_2) and 31.4 (CH_2). Selected chemical shifts for the minor isomer: δ 139.3 (quat C), 131.9 (CH), 128.9 (CH), 128.8 (CH), 128.57 (CH), 126.62 (CH), 125.7 (CH), 75.2 (CH), 32.4 (CH_2) and 31.9 (CH_2).

MS (EI) *m/z* 278 (M^+, ^{35}Cl, 5%), 91 (90); HRMS: Found M^+, 278.0533. $C_{15}H_{15}{}^{35}ClOS$ requires M, 278.0532.

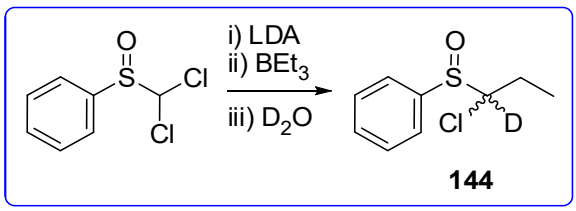
4.4.4 Chloro(phenyl)methyl Phenyl Sulfoxide (141e) and Chloro(cyclopentyl)methyl Phenyl Sulfoxide (141f)



141e **141f**

The general procedure using dichlorophenylborane or triphenylborane in attempts to prepare **141e** failed. Also, the reaction with tricyclopentylborane in an attempt to prepare **141f** failed.

4.4.5 Deuteriation of the Sulfoxide Enolate



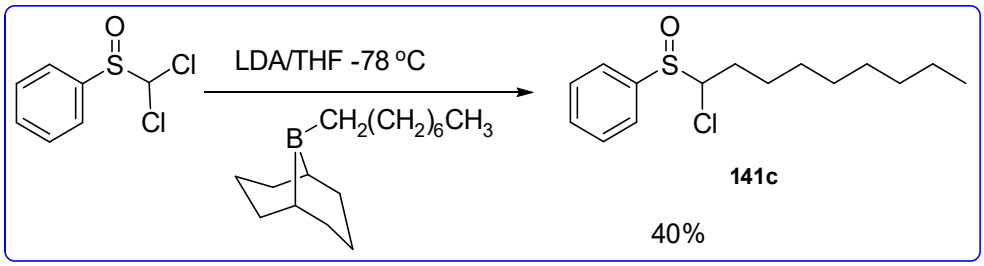
144

The above general procedure was followed, but the reaction was quenched with D_2O (5 mL) and the usual work up was followed to yield two diastereomers of the *title compound* (93 mg, 93%, the ratio was not measured due to overlapping peaks) as a colourless oil.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.79 – 7.70 (2H of major isomer, m, aromatic CH), 7.69 – 7.62 (2H of minor isomer, m, aromatic CH), 7.59 – 7.47 (3H of both isomers, m, aromatic CH), 2.29 (1H of minor isomer, dq, *J* = 14.6, 7.3 Hz, 1H), 2.28 (1H of major isomer, dq, *J* = 14.7, 7.3 Hz, 1H)), 2.01 (1H of major isomer, app. dq, *J* = 14.6, 7.2 Hz, one of CH_2), 1.67 – 1.45 (1H of minor isomer, m, one of CH_2), 1.15 (3H of major isomer, t, *J* = 7.3 Hz) and 1.12 (3H of minor isomer, t, *J* = 7.3 Hz, CH_3).

^{13}C NMR (101 MHz; $CDCl_3$) (major isomer): δ 141.1 (quat C), 132.2 (CH), 129.1 (CH), 126.0 (CH), 78.3 (CD), 24.7 (CH_2) and 10.0 (CH_3); (minor isomer) selected chemical shifts: δ 139.2 (quat C), 131.9 (CH), 129.0 (CH), 125.7 (CH), 24.0 and 11.0 (CH_3).

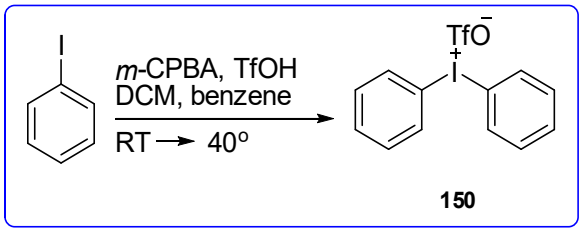
4.4.6 Reaction with *n*-Octyl-9-BBN



The same general procedure was used for this reaction. The *n*-octyl-9-BBN was prepared first and added to the sulfoxide anion. Working up and purifying the crude product afforded **141c** (57 mg, 40%, 82:18 mixture of diastereoisomers).

***n*-Octyl-9-BBN** : 9-BBN dimer (61 mg, 0.25 mmol) was placed in a 5 mL round bottom flask and flushed with nitrogen for 10 minutes. THF (2 mL) was added and the solution was cooled to 0°C. 1-Octene (79 mL, 0.5 mmol) was added dropwise and the solution was allowed to warm to r.t. for 2 h.

4.4.7 Synthesis of Diphenyliodonium Triflate (150) [136]



m-CPBA (0.2465 g, 1.1 mmol) and iodobenzene (0.11 mL, 1.0 mmol) were dissolved in a mixture of benzene (98 mL) and dichloromethane (10 mL). Triflic acid (0.17 mL, 2.0 mmol) was added dropwise. The solution was warmed to 40 °C and stirred for 1 h. The solution was concentrated *in vacuo* while still cold. Diethyl ether (8 mL) was added and the mixture was stirred for 10 minutes then cooled in a freezer for 30 minutes. The colourless oil that precipitated was filtered, washed with cold ether (20 mL) and dried under vacuum to give the *title compound* (0.375 g, 87%) as a pale yellow solid.

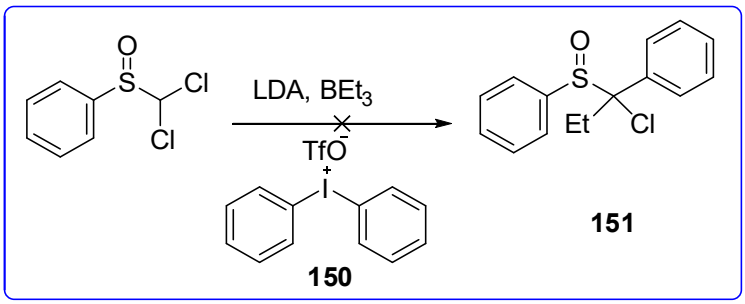
m.p. 177 – 178 °C (lit.[153] 176 – 177 °C).

^{1}H NMR (400 MHz; DMSO) δ 8.29 – 8.11 (4H, m), 7.67 – 7.57 (2H, m) and 7.55 – 7.41 (4H, m).

^{13}C NMR (101 MHz; DMSO) δ 135.2, 132.0, 131.8 and 116.5.

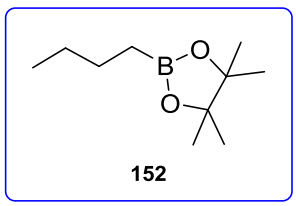
4.4.8 Reaction with Diphenyliodonium Triflate

The procedure used in the reaction of trialkylborane with **135** was followed. Only starting materials were seen.



150 **151**

4.4.9 Synthesis of Pinacol *n*-Butylboronic Ester (152) [114]



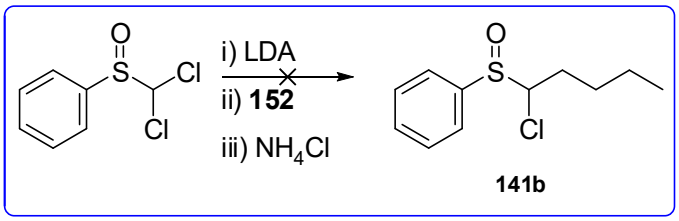
152

n-Butylboronic acid (1.50 g, 14.7 mmol) and pinacol (1.83 g, 15.5 mmol) were placed in a 50 mL round bottom flask, which was flushed with N_2 for 10 minutes. Anhydrous pentane (20 mL) was added and the solution stirred overnight. The solution was dried over magnesium sulfate and the solvents were evaporated to afford the *title compound* (1.2 g, 44%). The product was used for the next step without any further purification.

^{1}H NMR (400 MHz; $CDCl_3$) δ 1.48 – 1.26 (4H, m), 1.23 (12H, s), 0.87 (3H, t, *J* = 7.2 Hz) and 0.70 (2H, t, *J* = 7.7 Hz).

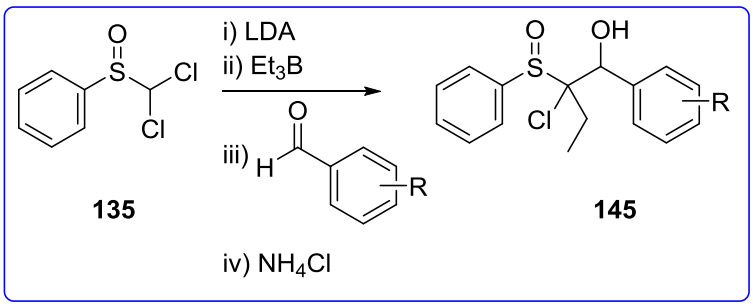
^{13}C NMR (101 MHz; $CDCl_3$) δ 82.6, 25.9, 25.2, 24.5, 24.3 and 13.6.

4.4.10 Reaction of Compound 135 with Boronic Ester



To a cooled (–78 °C) solution of diisopropylamine (91 μL, 0.65 mmol, 1.3 equiv.) in dry THF (5 mL), *n*-BuLi (0.38 mL, 1.6 M in hexane, 0.60 mmol, 1.2 equiv.) was added dropwise. The solution was warmed to 0 °C over a period of 20 min. The solution was cooled again to –78 °C. To this solution, dichloromethyl phenyl sulfoxide (**135**) (105 mg, 0.50 mmol, 1.0 equiv.) was added and the mixture was stirred for 10 minutes. Boronic acid **152** (106 mL, 0.5 mmol, 1.0 equiv.) was added and the mixture was stirred for 1 h, then the reaction was quenched by addition of saturated ammonium chloride solution (5mL) before being warmed to room temperature. The organic layer was separated, the aqueous layer was extracted with dichloromethane (3 x 10 mL) and the organic layers were combined and dried over magnesium sulfate. The solvents were evaporated under reduced pressure. ^{1}H NMR spectrum showed that only starting materials were observed.

4.4.11 Trapping the Sulfoxide Enolate with 3- or 4-R-Substituted Benzaldehydes

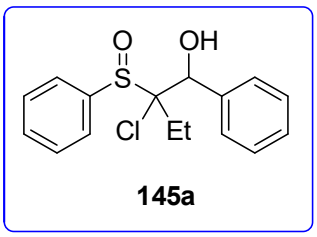


R = a) H, b) *m*-OMe, c) *p*-OMe, d) *p*-Br, e) *p*-F,

4.4.11.1 General Procedure

To a cooled (–78 °C) solution of diisopropylamine (183 μL, 1.3 mmol, 1.3 equiv.) in dry THF (5 mL), *n*-BuLi (0.75 mL, 1.6 M in hexane, 1.2 mmol, 1.2 equiv.) was added dropwise. The solution was warmed to 0 °C over a period of 20 minutes. The solution was cooled to –78 °C. To this solution, a solution of compound **135** (209 mg, 1.0 mmol, 1.0 equiv.) in THF (3 mL) was added and the mixture was stirred for 10 minutes. Triethylborane (1.0 mL, 1.0 M in THF, 1.0 mmol, 1.0 equiv.) was added and stirring was continued for 1 h. The substituted benzaldehyde (1.0 mmol) was added and the mixture was stirred for a further 1 h. The mixture was allowed to warm to 0 °C over a period of 20 minutes and quenched by addition of sat. aqueous ammonium chloride solution (10 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 15 mL); the organic layers were combined and dried over magnesium sulfate. The solvents were evaporated under reduced pressure and the crude material obtained was subjected to silica-gel column chromatography (eluted with a suitable ratio of ethyl acetate/chloroform) to afford the four pure diastereoisomers of the product (except for methoxy substituted products, where only three diastereoisomers were formed).

4.4.11.1.1 Compound 145a

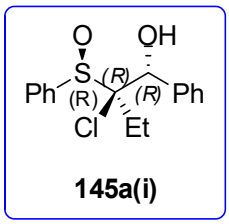


145a

The general procedure was followed. The reaction of triethylborane and benzaldehyde (102 μL, 1.0 mmol) with **135**, followed by flash column chromatography (3% ethyl acetate/chloroform) gave three fractions; fraction 1 contained the **145a(i)** diastereoisomer (72 mg, 23%) as a colourless solid; fraction 2 contained a mixture of two compounds **145a(ii)** and **146a** (16 mg, 5% of the mixture, 1:1 ratio) as a colourless

oil; fraction 3 contained two diastereoisomers **145a(iii)** and **145a(iv)** (100 mg, 32%, 55:45 ratio) as a colourless oil.

Fraction 1



145a(i)

Colourless Solid (72 mg, 23%)

m.p. = 181-182 °C.

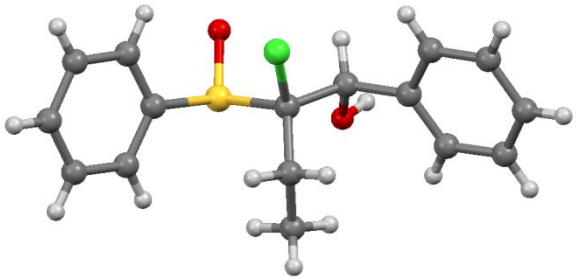
$\nu_{max.}$ (neat) 3201, 3065, 2968, 2937, 2879, 1442 and 1031 cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$) δ 8.04 – 7.87 (2H, m, aromatic CH), 7.75 – 7.54 (3H, m, aromatic CH), 7.27 (5H, app. s), 5.66 (1H, s), 4.96 (1H, s), 3.00 (1H, dq, *J* = 15.3, 7.2 Hz), 2.01 (1H, dq, *J* = 15.3, 7.4 Hz) and 1.30 (3H, app. t, *J* = 7.3 Hz).

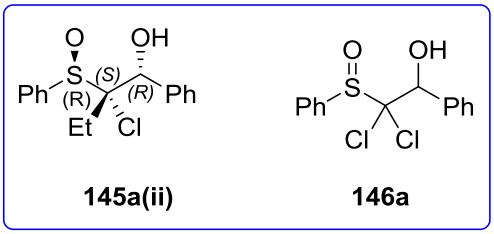
^{13}C NMR (101 MHz, $CDCl_3$) δ 137.3 (quat C), 136.3 (quat C), 132.8 9 (CH), 129.0 (CH), 128.7 (CH), 128.5 (CH), 128.1 (CH), 127.7 (CH), 83.7 (quat C), 78.6 (CH), 23.3 (CH_2) and 8.0 (CH_3).

MS (ES^-) *m/z* (%), 347 (((M+Cl)$^-$, $^{37}Cl_2$, 13%), 345 ((M+Cl)$^-$, $^{37}Cl^{35}Cl$, 67%), 343 ((M+Cl)$^-$, $^{35}Cl_2$, 100%), 313 (74), 255 (65), 223 (82); HRMS: Found (M+Cl)$^-$, 343.0317. $C_{16}H_{17}{}^{35}Cl_2O_2S$ requires M, 343.0326.

Selected crystallographic data: $C_{16}H_{17}ClO_2S$, FW = 308.80, T = 296(2) K, λ = 1.54184 Å, Triclinic, P-1, a = 11.2998(3) Å, b = 11.4679(3) Å, c = 12.4272(3) Å, α= 96.840(2)°, β= 92.254(2)°, γ = 104.801(2)°, V = 1541.78(7) $Å^3$, Z = 4, $\rho_{calc.}$ = 1.330 Mg/m^3, crystal size = 0.322 x 0.272 x 0.190 mm^3, μ = 3.442 mm^{-1}, reflections collected = 25725, Independent reflections = 6107, R_{int} = 0.0223, parameters = 365, R_1 = 0.0332, wR_2 = 0.0847 for I>2σ(I) and R_1 = 0.0396, wR_2 = 0.0888 for all data.



Fraction 2: Mixture of diastereomer **145a(ii)** and compound **146a**



145a(ii) **146a**

Colourless oil (16 mg, 5%, 1:1 mixture of **145a(ii)** and **146a**).

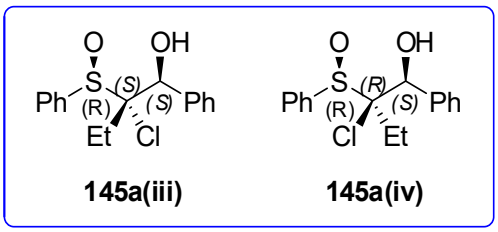
$\nu_{max.}$ (neat) 3348, 3061, 3005, 2931, 2883, 1610, 1444 and 1047 cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.92 - 7.34 (5H of each compound, m, aromatic CH), 5.50 (1H of by-product, d, *J* = 2.7 Hz, C*H*OH), 5.20 (1H of aldol product, d, *J* = 8.7 Hz, C*H*OH), 4.92 (1H of aldol product, d, *J* = 8.7 Hz, OH), 4.15 (1H of by-product, d, *J* = 2.8 Hz, OH), 2.39 (1H of aldol product, dq, *J* = 14.7, 7.2 Hz, one of CH_2), 1.28 (1H of aldol product, dq, *J* = 14.7, 7.1 Hz, one of CH_2) and 1.07 (3H of aldol product, app. t, *J* = 7.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.6 (quat C), 136.8 (quat C), 135.7 (quat C) , 134.4 (quat C), 133.4 (CH), 132.4 (CH), 129.6 (CH), 129.1 (CH), 129.03 (CH), 128.98 (CH), 128.8 (CH), 128.7 (CH), 128.18 (CH), 128.17 (CH), 128.1 (CH), 127.3 (CH), 102.3 (quat C), 80.7 (quat C), 80.2 (CH), 77.9 (CH), 25.6 (CH_2), 8.1 (CH_3).

MS ($APCl^+$) *m/z* (%) 374 ($(M+Na+CH_3CN)^+$, ^{37}Cl, 40%), 372 ($(M+Na+CH_3CN)^+$, ^{35}Cl, 100%), 333 ($(M+Na)^+$, ^{37}Cl, 11%), 331 ($(M+Na)^+$, ^{35}Cl, 53%), 228 (13) HRMS: Found $(M+Na)^+$, 331.0519. $C_{16}H_{17}{}^{35}ClNaO_2S$ requires M, 331.0535.

Fraction 3: Mixture of two diastereoisomers **145a(iii)** and **(iv)**



145a(iii) **145a(iv)**

Colourless oil (100 mg, 32%, 55:45 mixture of diastereoisomers).

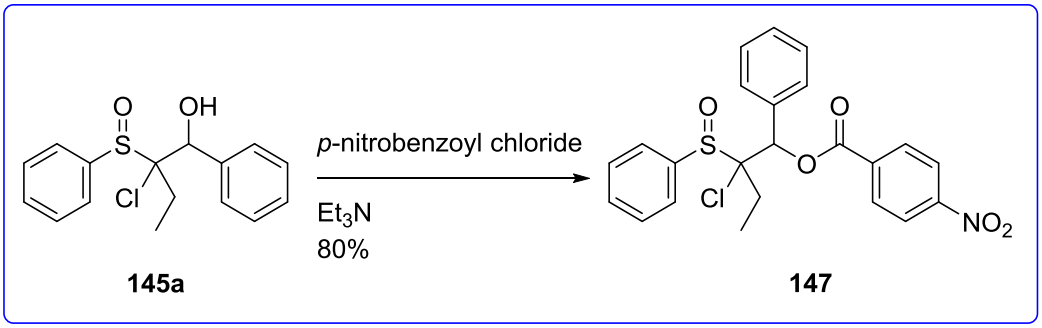
$\nu_{max.}$ (neat) 3338, 3065, 2939, 2879, 1442 and 1020 cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.91 – 7.78 (2H of each isomer, m, aromatic CH), 7.67 – 7.24 (8H of each isomer, m, aromatic CH), 5.33 (1H of major isomer, d, *J* = 4.0 Hz, C*H*OH), 5.17 (1H of minor isomer, d, *J* = 3.3 Hz, C*H*OH), 3.63 (1H of minor isomer, d, *J* = 3.3 Hz, OH), 3.21 (1H of major isomer, d, *J* = 4.0 Hz), 2.22 – 2.12 (2H of minor isomer, m, CH_2), 1.88 (1H of major isomer, dq, *J* = 15.0, 7.4 Hz, one of CH_2), 1.50 (1H of major isomer, dq, *J* = 15.0, 7.3 Hz, one of CH_2), 0.95 (3H of major isomer, app. t, *J* = 7.4 Hz, CH_3) and 0.85 (3H of minor isomer, app. t, *J* = 7.5 Hz, CH_3).

^{13}C NMR (101 MHz; $CDCl_3$) δ 138.8 (quat C), 138.5 (quat C), 138.0 (quat C), 137.8 (quat C), 132.5 (CH), 132.3 (CH), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.7 (CH), 128.4 (CH), 128.3 (CH), 128.0 (CH), 127.4 (CH), 127.2 (CH), 93.5 (quat C), 89.5 (quat C), 78.1 (CH), 75.2 (CH), 27.7 (CH_2), 24.7 (CH_2), 10.1 (CH_3) and 9.3 (CH_3).

MS (ES^+) *m/z* (%) 374 ($(M+Na+CH_3CN)^+$, ^{37}Cl, 13%), 372 ($(M+Na+CH_3CN)^+$, ^{35}Cl, 42%), 333 ($(M+Na)^+$, ^{37}Cl, 37%), 331 ($(M+Na)^+$, ^{35}Cl, 100%), 254 (20); HRMS: Found $(M+Na)^+$, 331.0550. $C_{16}H_{17}{}^{35}ClNaO_2S$ requires M, 331.0536.

4.4.11.1.1.1 Synthesis of 4-Nitrobenzoate derivatives of Compound 145a(iii) and 145a(iv)



145a **147**

The mixture of two diastereoisomers **145a(iii)** and **145a(iv)** (94 mg, 0.3 mmol) was dissolved in THF (10 mL). Triethylamine (93 μL, 0.66 mmol, 2.2 equiv.) was added, followed by DMAP (10 mg, catalytic amount) and *p*-nitrobenzoyl chloride (112 mg, 2 equiv.). The solution was warmed up to room temperature and stirred for 24 h. The reaction was then quenched by saturated sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted with chloroform (2 × 10 mL) and dried over magnesium sulfate. The solvents were removed to yield a mixture of two diastereomers of the **147** (110 mg, 80%). The two diastereomers were separated by flash column chromatography on silica gel (1% EtOAc/$CHCl_3$).

Compound 147a: R_f = 0.21 (1% EtOAc/$CHCl_3$), 60 mg (43%), colourless solid, m.p. 133 – 134 °C.

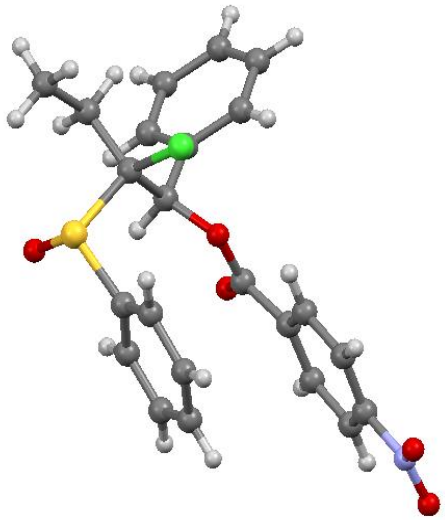
$\nu_{max.}$ (neat) 1728, 1523, 1074 and 1047 cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$) δ 8.32 (2H, d, *J* = 9.0 Hz, aromatic CH), 8.22 (2H, d, *J* = 9.0 Hz, aromatic CH), 7.72 – 7.60 (4H, m, aromatic CH), 7.47 – 7.30 (6H, m, aromatic CH), 6.48 (1H, s, CHO), 2.25 – 2.02 (2H, m, CH_2) and 1.06 (3H, app. t, *J* = 7.5 Hz, CH_3).

^{13}C NMR (101 MHz; $CDCl_3$) δ 162.3 (quat C), 150.6 (quat C), 137.8 (quat C), 134.4 (quat C), 133.9 (quat C), 132.0 (CH), 130.7 (CH), 129.3 (CH), 128.8 (CH), 128.5 (CH), 128.0 (CH), 127.2 (CH), 123.6 (CH), 88.3 (quat C), 77.2 (CH), 27.2 (CH_2) and 9.4 (CH_3).

MS (APCl$^+$) *m/z* (%) 523 ((M+Na+CH_3CN)$^+$, ^{37}Cl, 25%), 521 ((M+Na+CH_3CN)$^+$, ^{35}Cl, 100%), 482 ((M+Na)$^+$, ^{35}Cl, 17%), 480 ((M+Na)$^+$, ^{35}Cl, 58%); HRMS: Found (M+Na)$^+$, 480.0657. $C_{23}H_{20}{}^{35}ClNaO_5S$ requires M, 480.0648.

Selected crystallographic data: $C_{23}H_{20}ClNO_5S$, FW = 457.91, T = 150(2) K, λ = 1.54184, Triclinic, P-1, a = 7.3284(2) Å, b = 12.4907(3) Å, c = 12.9031(4) Å, α= 110.993(2)°, β= 102.930(2)°, γ = 95.432(2)°, V = 1054.73(5) $Å^3$, Z = 2, $\rho_{calc.}$ = 1.442 Mg/m^3, crystal size = 0.261 x 0.235 x 0.155 mm^3, μ = 2.841 mm^{-1}, reflections collected = 16433, Independent reflections = 4150, R_{int} = 0.0187, parameters = 281, R_1 = 0.0303, wR_2 = 0.0819 for I>2σ(I) and R_1 =0.0311, wR_2 = 0.0824 for all data.



Compound 147b: R_f = 0.19 (1% EtOAc/$CHCl_3$), 40 mg (29%) colourless solid

m.p. 127 – 129 °C.

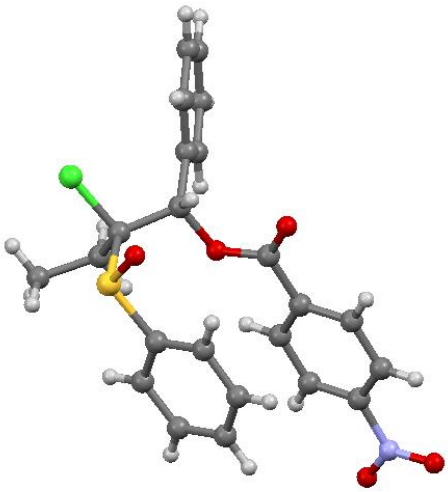
$\nu_{max.}$ (neat) 3053, 2978, 2922, 2854, 1732, 1608, 1442 and 1049 cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$) δ 8.09 (2H, d, *J* = 9.0 Hz, aromatic CH), 7.84 – 7.75 (2H, m, aromatic CH), 7.68 (2H, d, *J* = 9.0 Hz, aromatic CH), 7.54 - 7.40 (2H, m, aromatic CH), 7.38 – 7.29 (3H, m, aromatic CH), 7.23 – 7.09 (2H, m, aromatic CH), 6.98 – 6.80 (1H, m, aromatic CH), 6.44 (1H, s, CHO), 2.19 (1H, dq, *J* = 15.2, 7.0 Hz, one of CH_2), 1.42 (1H, dq, *J* =15.2, 7.3 Hz, one of CH_2) and 1.23 (3H, app. t, *J* = 7.2 Hz, CH_3).

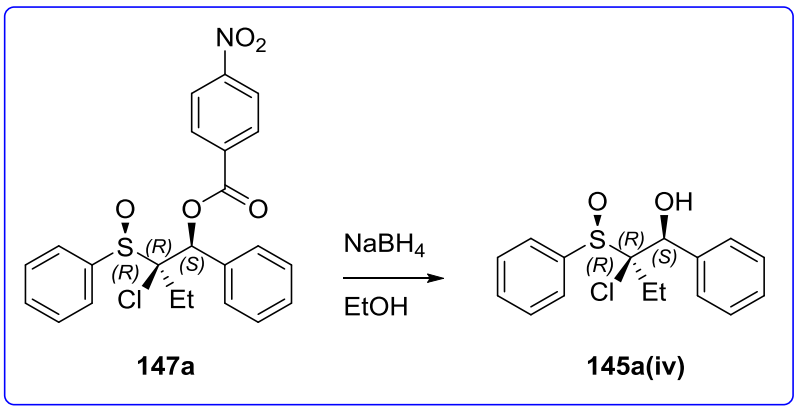
^{13}C NMR (101 MHz; $CDCl_3$) δ 161.6 (quat C), 150.2 (quat C), 138.4 (quat C), 135.0 (quat C), 134.2 (quat C), 130.9 (CH), 130.3 (CH), 129.1 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 126.3 (CH), 122.7 (CH), 88.5 (quat C), 71.8 (CH), 29.6.6 and 8.0 (CH_3).

MS (APCl$^+$) *m/z* 523 ((M+Na+CH_3CN)$^+$, ^{37}Cl, 10%), 521 ((M+Na+CH_3CN)$^+$, ^{35}Cl, 26%), 482 ((M+Na)$^+$, ^{35}Cl, 27%), 480 ((M+Na)$^+$, ^{35}Cl, 100%); HRMS: Found (M+Na)$^+$, 480.0627. $C_{23}H_{20}{}^{35}ClNaO_5S$ requires M, 480.0648.

Selected crystallographic data: $C_{23}H_{20}ClNO_5S$, FW = 457.91, T = 293(2) K, λ = 1.54184, Triclinic, P-1, a = 6.4998(2) Å, b = 7.7680(3) Å, c = 22.2674(8) Å, α= 91.378(3)°, β= 93.748(3)°, γ = 108.174(3)°, V = 1064.75(7) Å^3, Z = 2, $\rho_{calc.}$ = 1.428 Mg/m^3, crystal size = 0.457 x 0.135 x 0.065 mm^3, μ = 2.815 mm^{-1}, reflections collected = 16565, Independent reflections = 4198, R_{int} = 0.0475, parameters =282, R_1 = 0.0728, wR_2 = 0.2281 for I>2σ(I) and R_1 =0.0810, wR_2 = 0.2311 for all data.

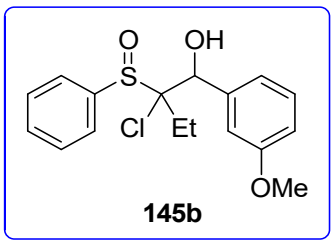


4.4.11.1.1.2 Reduction of the Benzoate Derivative 147a



The benzoate derivative **147a** (27 mg, 0.05 mmol) was dissolved in $CHCl_3$ (1 mL) and added to a solution of sodium borohydride (10 mg) in a mixture of ethanol and $CHCl_3$ (5 mL) dropwise with swirling. The solution was swirled for 15 minutes further. Ice-cold water (5 mL) was added and the solution was neutralised by addition of HCl (2.0 M). The solution was extracted with chloroform (3 × 5 mL) and the chloroform extract was dried over magnesium sulfate. After removal of the solvents, the crude product was purified by flash column chromatography to yield **145a(iv)** (10 mg, 67%) as a colourless oil. While this compound was not analytically pure, it was sufficiently pure to allow the peaks for compound **145a(iv)** in the original mixture of **145a(iii)** and **145a(iv)** to be identified.

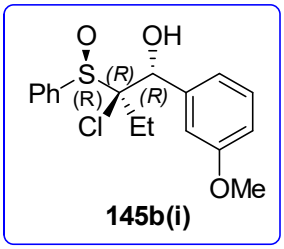
4.4.11.1.2 Compounds 145b



The procedure described in section 4.4.11.1 was followed, involving the reaction of triethylborane and *m*-methoxybenzaldehyde (121 μL, 1.0 mmol) with **135** following by flash column chromatography (3% ethyl acetate/chloroform) gave three fractions; fraction 1 contained diastereoisomer **145b(i)** (60 mg, 18%) as a colourless solid;

fraction 2 contained diastereoisomer **145(iv)** (56 mg, 17%) as a colourless oil; fraction 3 contained diastereoisomer **145(iii)** (56 mg, 17%) as a colourless oil.

Fraction 1:



145b(i)

Colourless solid (60 mg, 18%).

m.p. 177 – 178 °C.

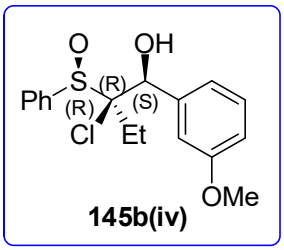
$\nu_{max.}$ (neat) 3242, 2978, 2872 and 1041 cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$) δ 8.00 – 7.91 (2H,m, aromatic CH), 7.68 – 7.65 (3H,m, aromatic CH), 7.18 (1H, t, *J* = 8.1 Hz, aromatic CH), 6.95 – 6.75 (3H, m, aromatic CH), 5.67 (1H, s, , C*H*OH), 4.93 (1H, s, exch., CHO*H*), 3.77 (s, 3H, OCH_3), 2.98 (dq, *J* = 15.5, 7.2 Hz, 1H, one of CH_2), 2.03 (dq, *J* = 15.5, 7.4 Hz, 1H, one of CH_2) and 1.30 (3H, app. t, *J* = 7.3 Hz, CH_3).

^{13}C NMR (101 MHz; $CDCl_3$) δ 159.1 (quat C), 138.8 (quat C), 136.3 (quat C), 132.8 (CH), 129.0 (CH), 128.6 (CH), 128.1 (CH), 121.2 (CH), 114.6 (CH), 113.7 (CH), 83.6 (quat C), 78.5 (CH), 55.4 (CH_3), 23.4 (CH_2) and 8.0 (CH_3).

MS ($APCl^+$) *m/z* (%) 341 (MH^+, ^{37}Cl, 35), 339 (MH^+ with ^{35}Cl, 100), 186 (20), 136 (17); HRMS: Found 339.0819. $C_{17}H_{20}{}^{35}ClO_3S$ requires M, 339.0822.

Fraction 2:



145b(iv)

Colourless oil (56 mg, 17%).

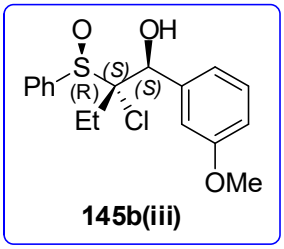
$\nu_{max.}$ (neat) 3296, 3061, 2997, 2957, 2835, 1600, 1442 and 1020 cm^{-1}. ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.87 – 7.71 (2H, m, aromatic CH), 7.57 – 7.38 (3H, m, aromatic, CH), 7.20

(1H, d, *J* = 7.6 Hz, aromatic CH), 7.11 - 7.01 (2H, m, aromatic CH), 6.86 – 6.79 (1H, m, aromatic CH), 5.07 (1H, s, C*H*OH), 3.74 (3H, s, OCH_3), 3.45 (1H, s, OH), 2.16 – 2.06 (2H, m, CH_2) and 0.79 (3H, app. t, *J* = 7.5 Hz, CH_3).

^{13}C NMR (101 MHz; $CDCl_3$) δ 159.3 (quat C), 139.3 (quat C), 138.5 (quat C), 132.3 (CH), 129.0 (CH), 128.7 (CH), 127.5 (CH), 121.0 (CH), 114.4 (CH), 114.3 (CH), 89.5 (quat C), 77.9 (CH), 55.4 (CH_3), 24.9 (CH_2) and 10.1 (CH_3).

MS (APCl$^+$) *m/z* (%) 363 ((M+Na)$^+$, ^{37}Cl, 13%), 361 ((M+Na)$^+$, ^{35}Cl, 36%), 341 (MH$^+$, ^{37}Cl, 20%), 339 (MH$^+$, ^{35}Cl, 56%), 195 (25), 154 (60); HRMS: Found: 361.0636. $C_{17}H_{19}{}^{35}ClNaO_3S$ requires M, 361.0641.

Fraction 3 :



145b(iii)

Colourless oil (56 mg, 17%).

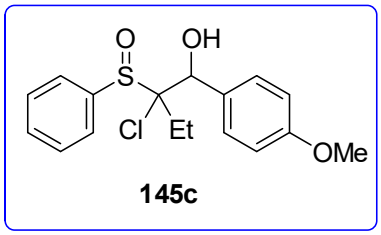
$\nu_{max.}$ (neat) 3356, 3061, 2937, 2883, 2837, 1599, 1442 and 1037 cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.91 – 7.75 (2H, m, aromatic CH), 7.65 – 7.48 (3H, m, aromatic CH), 7.25 (1H, t, *J* = 7.9 Hz, aromatic CH),), 7.09 – 7.00 (2H, m, aromatic CH), 6.92 – 6.84 (1H, m, aromatic CH), 5.31 (1H, d, *J* = 3.8 Hz, C*H*OH), 3.80 (3H, s, OCH_3), 3.14 (1H, d, *J* = 4.0 Hz, OH), 1.91 (1H, dq, *J* = 15.0, 7.4 Hz, one of CH_2), 1.51 (1H, dq, *J* = 15.0, 7.4 Hz, one of CH_2) and 0.98 (3H, app. t, *J* = 7.4 Hz, CH_3).

^{13}C NMR (101 MHz; $CDCl_3$) δ 159.5 (quat C), 139.4 (quat C), 138.7 (quat C), 132.4 (CH), 129.3 (CH), 128.8 (CH), 127.1 (CH), 120.6 (CH), 114.6 (CH), 113.6 (CH), 93.3 (quat C), 74.7 (CH), 55.3 (CH_3), 27.8 (CH_2) and 9.2 (CH_3).

MS (ES$^+$) *m/z* (%) 404 ((M+Na+CH_3CN)$^+$, ^{37}Cl, 35%), 402 ((M+Na+CH_3CN)$^+$, ^{35}Cl, 100%), 363 ((M+Na)$^+$, ^{37}Cl, 33%), 361 ((M+Na)$^+$, ^{35}Cl, 75%), 341 (MH$^+$, ^{37}Cl, 12%), 339 (MH$^+$, ^{35}Cl, 32%), 258 (15), 177 (15); HRMS: Found MH$^+$, 339.0822. $C_{17}H_{20}{}^{35}ClO_3S$ requires M, 339.0822.

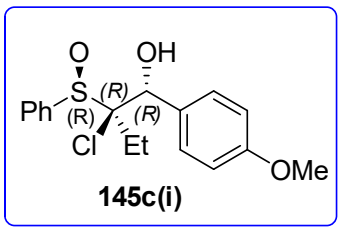
4.4.11.1.3 Compound 145c



145c

The general procedure was followed. The reaction of triethylborane and *p*-methoxybenzaldehyde (121 μL, 1.0 mmol) with **135**, followed by flash column chromatography (3% ethyl acetate/chloroform) gave three fractions; fraction 1 contained diastereoisomer **145c(i)** (60 mg, 18%) as a colourless solid; fraction 2 contained diastereoisomer **145c(iv)** (42 mg, 12%) as a colourless oil; fraction 3 contained a mixture of two diastereoisomers of **145c(iv)** and **145c(iii)** (52 mg, 15%, 2:1 ratio) as a colourless oil.

Fraction 1:



145c(i)

Colourless Solid (60 mg, 18%).

m.p. = 136 – 138 °C.

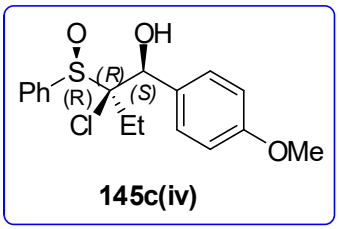
$\nu_{max.}$ (neat) 3327, 3060, 2972, 2935, 2835, 1610, 1442 and 1030 cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.95 (2H, dd, *J* = 8.0, 1.5 Hz, aromatic CH), 7.72 – 7.56 (3H, m, aromatic CH), 7.20 (2H, d, *J* = 8.8, Hz, aromatic CH), 6.80 (2H, d, *J* = 8.8, aromatic CH), 5.61 (1H, s, C*H*OH), 4.91 (1H, s, OH), 3.77 (3H, s, OCH_3), 2.97 (1H, dq, *J* = 15.4, 7.2 Hz, one of CH_2), 2.00 (1H, dq, *J* = 15.4, 7.4 Hz, one of CH_2) and 1.29 (3H, app. t, *J* = 7.3 Hz, CH_3).

^{13}C NMR (101 MHz; $CDCl_3$) δ 159.7 (quat C), 136.3 (quat C), 132.7 (CH), 129.9 (CH), 129.4 (quat C), 129.0 (CH), 128.0 (CH), 113.1 (CH), 84.0 (quat C), 78.3 (CH), 55.3 (CH_3), 23.2 (CH_2) and 8.0 (CH_3).

MS (ES^+) *m/z* (%) 404 ($(M+Na+CH_3CN)^+$, ^{37}Cl, 30%), 402 ($(M+Na+CH_3CN)^+$, ^{35}Cl, 100%), 363 ($(M+Na)^+$, ^{37}Cl, 16%), 361 ($(M+Na)^+$, ^{35}Cl, 50%), 254 (70), 185 (35); HRMS: Found $(M+Na)^+$, 361.0641. $C_{17}H_{19}{}^{35}ClNaO_3S$, requires M, 361.0641.

Fraction 2:



145c(iv)

Colourless oil (42 mg, 12%).

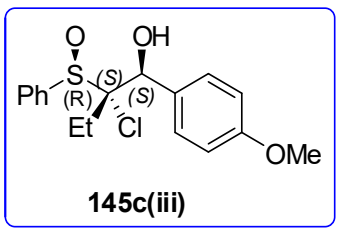
$\nu_{max.}$ (neat) 3311, 3063, 2997, 2931, 2837, 1608, 1442 and 1030 cm^{-1}.

^1H NMR (400 MHz; $CDCl_3$) δ 7.89 – 7.84 (2H, m, aromatic, CH), 7.57 – 7.46 (5H, m, aromatic CH), 6.90 (2H, d, *J* =8.8 Hz, aromatic CH), 5.17 (s, 1H, C*H*OH), 3.82 (3H, s, OCH_3), 3.40 (1H, s, OH), 2.27 – 2.09 (2H, m, CH_2) and 0.84 (3H, app. t, *J* = 7.5 Hz, CH_3).

^{13}C NMR (101 MHz; $CDCl_3$) δ 160.0 (quat C), 138.5 (quat C), 132.2 (CH), 129.9 (CH), 129.8 (quat C), 128.7 (CH), 127.4 (CH), 113.4 (CH), 89.7 (quat C), 77.7 (CH), 55.4 (CH_3), 24.7 (CH_2) and 10.1 (CH_3).

MS ($APCl^+$) *m/z* (%) 339 (MH^+, ^{35}Cl, 3%), 156 (100), 120 (63); HRMS: Found MH^+, 339.0826. $C_{17}H_{20}{}^{35}ClO_3S$ requires M, 339.0822.

Fraction 3: Mixture of diastereomers **145c(iii)** and **146c(iv)**



145c(iii)

Colourless oil. (52 mg, 15%, isomers **(iii)** and **(iv)** in a 2:1 ratio).

$\nu_{max.}$ (neat) 3267, 3063, 2970, 2841, 1606, 1440 and 1030 cm^{-1}.

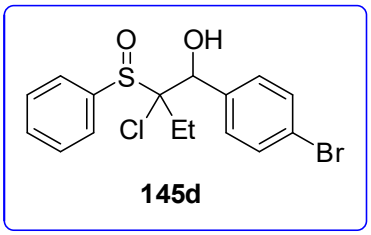
^1H NMR (400 MHz; $CDCl_3$) δ 8.03 – 7.70 (2H of both isomers, m, aromatic CH), 7.69 – 7.32 (5H of both isomers, m, aromatic CH), 6.90 (2H of both isomers, m, aromatic CH), 5.28 (1H of major isomer, s, C*H*OH), 5.13 (1H of minor isomer, s, C*H*OH), 3.81 (3H of minor isomer, s, OCH_3), 3.80 (3H of major isomer, s, OCH_3), 3.52 (1H of minor isomer,

s, OH), 3.23 (1H of major isomer, s, OH), 2.16 (2H of minor isomer, app. q, *J* = 7.5 Hz, CH_2), 1.86 (1H of major isomer, dq, *J* = 15.0, 7.4 Hz, one of CH_2), 1.51 (1H of major isomer, dq, *J* = 15.0, 7.3 Hz, one of CH_2), 0.95 (3H of major isomer, app. t, *J* = 7.4 Hz, CH_3) and 0.86 (3H of minor isomer, app. t, *J* = 7.5 Hz, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) major isomer: δ 159.9 (quat C), 138.8 (quat C), 132.4 (CH), 130.2 (quat C), 129.5 (CH), 128.9 (CH), 127.2 (CH), 113.8 (CH), 93.8 (quat C), 74.9 (CH), 55.4 (CH_3), 27.6 (CH_2) and 9.3 (CH_3). Minor isomer: δ 160.1 (quat C), 138.5 (quat C), 132.2 (CH), 130.2 (quat C), 129.9 (CH), 128.7 (CH), 127.4 (CH), 113.4 (CH), 89.9 (quat C), 77.6 (CH), 55.4 (CH_3), 24.8 (CH_2) and 10.1 (CH_3). Peaks for the OMe and one of the aromatic quaternary carbon atoms were not resolved for both isomers.

MS ($APCl^+$) *m/z* (%) 363 ($(M+Na)^+$, ^{37}Cl, 35%), 361 ($(M+Na)^+$, ^{35}Cl, 100%), 194 (100), 125 (100), 77 (100); HRMS: Found $(M+Na)^+$, 361.0641. $C_{17}H_{19}{}^{35}ClNaO_3S$ requires M, 361.0641.

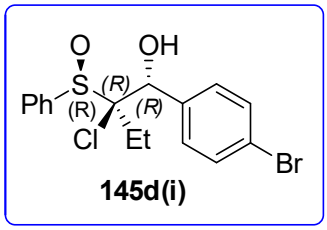
4.4.11.1.4 Compound 145d



145d

The general procedure was followed. The reaction of triethylborane and *p*-bromobenzaldehyde (185 mg, 1.0 mmol) with **135**, followed by flash column chromatography (1% ethyl acetate/chloroform) gave three fractions; fraction 1 contained diastereoisomer **145d(i)** (40 mg, 10%) as a colourless solid; fraction 2 contained a mixture of two compounds **145d(ii)** and **146d** (30 mg, 8% of the mixture, 1:1 ratio) as a colourless oil; fraction 3 contained two diastereoisomers **145d(iii)** and **145d(iv)** (130 mg, 34%, 60:40 ratio) as a colourless oil.

Fraction 1:



145d(i)

Colourless Solid (40 mg, 10%).

m.p. = 156 – 158 °C.

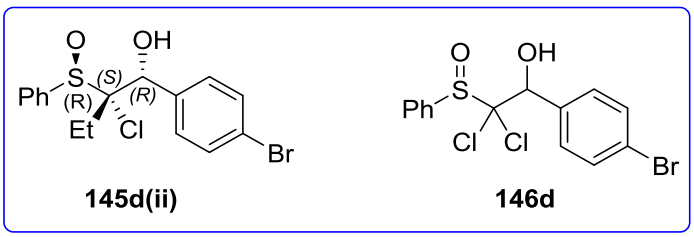
$\nu_{max.}$ (neat) 3225, 3062, 2982, 2924, 2858, 1610, 1442 and 1030 cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.95 (2H, dd, *J* = 8.0, 1.4 Hz, aromatic CH), 7.73 – 7.60 (3H, m, aromatic CH), 7.40 (2H, d, *J* = 8.5 Hz, aromatic CH), 7.16 (2H, d, *J* = 8.5 Hz, aromatic CH), 5.75 (1H, s, C*H*OH), 4.93 (1H, s, OH), 2.98 (1H, dq, *J* = 15.4, 7.2 Hz, one of CH_2), 1.92 (1H, dq, *J* = 15.4, 7.4 Hz, one of CH_2) and 1.29 (3H, app. t, *J* = 7.3 Hz, CH_3).

^{13}C NMR (101 MHz; $CDCl_3$) δ 136.3 (quat C), 136.1 (quat C), 132.9 (CH), 130.9 (CH), 130.4 (CH), 129.1 (CH), 128.0 (CH), 122.7 (quat C), 83.1 (quat C), 78.1 (CH), 23.2 (CH_2) and 7.9 (CH_3).

MS (ES^-) *m/z* (%) 425 ($(M+Cl)^-$, $^{81}Br^{35}Cl^{37}Cl$ and $^{79}Br^{37}Cl^{37}Cl$ combined, 49%), 423 ($(M+Cl)^-$, $^{81}Br^{35}Cl_2$ and $^{79}Br^{37}Cl^{35}Cl$ combined, 100%), 421 ($(M+Cl)^-$, $^{79}Br^{35}Cl_2$, 66%), 197 (27); HRMS: Found $(M+Cl)^-$, 420.9439. $C_{16}H_{16}{}^{79}Br^{35}Cl_2O_2S$ requires M, 420.9431.

Fraction 2: Mixture of diastereomer **145d(ii)** and compound **146d**



145d(ii) **146d**

Colourless oil (30 mg, 8%).

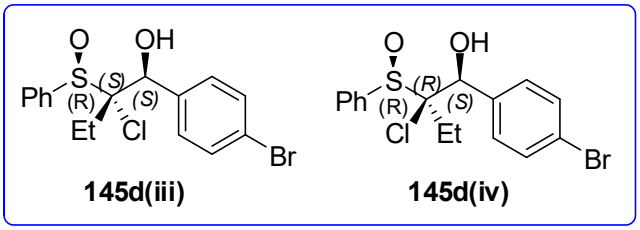
$\nu_{max.}$ (neat) 3344, 3065, 2974, 2939, 2881, 1591, 1444, 1074 and 1010 cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$) δ 8.03 – 7.38 (9H of each compound, m, aromatic CH), 5.49 (1H of by-product, d, *J* = 2.5 Hz, C*H*OH), 5.15 (1H of aldol product, d, *J* = 8.8 Hz, C*H*OH), 5.03 (1H of aldol product, d, *J* = 8.8 Hz, OH), 4.32 (1H of by-product, d, *J* = 2.5 Hz, OH), 2.39 (1H of aldol product, dq, *J* = 14.6, 7.2 Hz, one of CH_2), 1.35 – 1.12 (1H of aldol product, m, one of CH_2) and 1.08 (3H of aldol product, app. t, *J* = 7.2 Hz, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$) chemical shifts for both compounds: δ 137.34 (quat C), 137.29 (quat C), 136.65 (quat C), 134.72 (quat C), 133.56 (CH), 132.57 (CH), 131.36 (CH), 131.23 (CH), 130.80 (CH), 130.70 (CH), 129.06 (CH), 128.76 (CH), 128.16 (CH), 127.23 (CH), 122.95 (quat C), 121.61 (quat C), 93.88 (quat), 85.91 (quat C), 79.78 (CH), 77.64 (CH), 25.50 (CH_2), 8.04 (CH_3).

MS (ES) *m/z* (%) 425 ($(M+Cl)^-$, $^{81}Br^{35}Cl^{37}Cl$ and $^{79}Br^{37}Cl^{37}Cl$ combined, 49%), 423 ($(M+Cl)^-$, $^{81}Br^{35}Cl_2$ and $^{79}Br^{37}Cl^{35}Cl$ combined, 100%), 421 ((M+Cl), $^{79}Br^{35}Cl_2$, 68%), 200 (16), 198 (30); HRMS: Found $(M+Cl)^-$, 420.9430. $C_{16}H_{16}{}^{79}Br^{35}Cl_2O_2S$ requires M, 420.9431.

Fraction 3: Mixture of diastereomers **145d(iii)** and **146d(iv)**



Colourless oil (130 mg, 34%, 60:40 ratio).

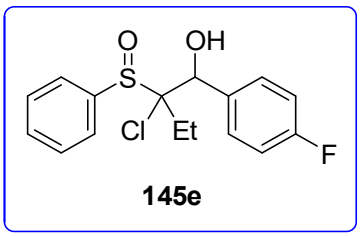
$\nu_{max.}$ (neat) 3306, 3065, 2941, 2883, 1591, 1442 and 1030 cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.85 – 7.73 (2H of each isomer, m, aromatic CH), 7.63 – 7.43 (5H of each isomer, m, aromatic CH), 7.40 (2H of minor isomer, d, *J* = 8.5 Hz), 7.33 (2H of major isomer, d, *J* = 8.4 Hz), 5.28 (1H of major isomer, d, *J* = 3.6 Hz, C*H*OH), 5.08 (1H of minor isomer, d, *J* = 3.3 Hz, C*H*OH), 4.09 (1H of minor isomer, d, *J* = 3.3 Hz, OH), 3.47 (1H of major isomer, d, *J* = 3.6 Hz, OH), 2.16 – 2.06 (2H of minor isomer, m, CH_2), 1.81 (1H of major isomer, dq, *J* = 15.1, 7.4 Hz, one of CH_2), 1.48 (1H of major isomer, dq, *J* = 15.1, 7.3 Hz, one of CH_2), 0.96 (3H of major isomer, app. t, *J* = 7.4 Hz, CH_3), 0.82 (3H of minor isomer, app. t, *J* = 7.5 Hz, CH_3).

^{13}C NMR (101 MHz; $CDCl_3$) chemical shifts for both isomers: δ 138.4 (quat C), 138.1 (quat C), 137.0 (quat C), 137.0 (quat C), 132.6 (CH), 132.3 (CH), 131.5 (CH), 131.1 (CH), 130.4 (CH), 130.0 (CH), 129.0 (CH), 128.8 (CH), 127.4 (CH), 127.2 (CH), 123.1 (quat C), 122.9 (quat C), 93.0 (quat C), 89.4 (quat C), 77.4 (CH), 74.7 (CH), 27.8 (CH_2), 24.8 (CH_2), 10.0 (CH_3) and 9.3 (CH_3).

MS (ES^-) *m/z* (%) 425 $((M+Cl)^-$, $^{81}Br^{35}Cl^{37}Cl$ and $^{79}Br^{37}Cl_2$ combined, 13%), 423 $((M+Cl)^-$, $^{81}Br^{35}Cl_2$ and $^{79}Br^{37}Cl^{35}Cl$ combined, 46%), 421 $((M+Cl)^-$, $^{79}Br\,^{35}Cl_2$, 26%), 299 (100), 255 (62); HRMS: Found $(M+Cl)^-$, 420.9423. $C_{16}H_{16}{}^{79}Br^{35}Cl_2O_2S$ requires M, 420.9431.

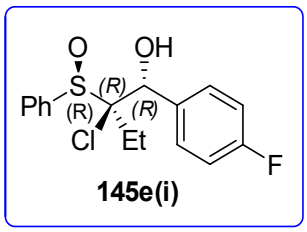
4.4.11.1.5 Compound 145e



145e

The general procedure was followed. The reaction of triethylborane and *p*-fluorobenzaldehyde (108 μL, 1.0 mmol) with **135**, followed by flash column chromatography (5% ethyl acetate/chloroform) gave three fractions; fraction 1 contained diastereoisomer **145e(i)** (70 mg, 22%) as a colourless solid; fraction 2 contained a mixture of two compounds **145e(ii)** and **146e** (56 mg, 17%, 1:1 ratio) as a colourless oil; fraction 3 contained two diastereoisomers **145e(iii)** and **145e(iv)** (64 mg, 20%, 1:1 ratio) as a colourless oil (185 mg, 48%).

Fraction 1



145e(i)

Colourless Solid (70 mg, 22%).

m.p. = 102 – 104 °C.

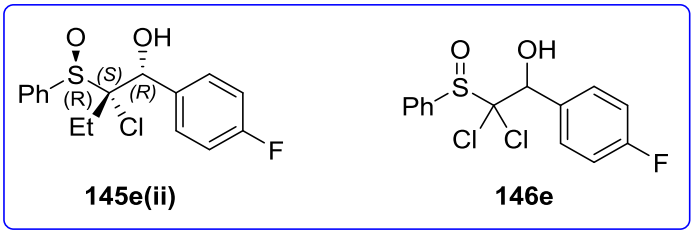
$\nu_{max.}$ (neat) 3321, 3065, 2972, 2924, 2852, 1602, 1442 and 1053 cm^{-1}.

^1H NMR (400 MHz; $CDCl_3$) δ 7.95 (2H,dd, *J* = 8.1, 1.5 Hz,), 7.74 – 7.58 (3H, m, aromatic CH), 7.29 -7.22 (2H, m, aromatic CH), 7.03 – 6.89 (2H, m, aromatic CH), 5.73 (1H, s, C*H*OH), 4.94 (1H, s, OH), 2.99 (1H, dq, *J* = 15.5, 7.2 Hz, one of CH_2), 1.95 (1H, dq, *J* = 15.5, 7.3 Hz, one of CH_2) and 1.30 (3H, app. t, *J* = 7.3 Hz, CH_3).

^{13}C NMR (101 MHz; $CDCl_3$) δ 162.8 (quat C, d, *J* = 247.1 Hz), 136.1 (quat C), 133.0 (CH, d, *J* = 3.2 Hz), 132.9 (CH), 130.4 (CH, d, *J* = 8.2 Hz), 129.1 (CH), 128.0 (CH), 114.7 (CH, d, *J* = 21.5 Hz), 83.4 (quat C), 78.1 (CH), 22.9 (CH_2) and 7.6 (CH_3).

MS (APCl$^+$) *m/z* (%) 392 ((M+Na+CH_3CN)$^+$, ^{37}Cl, 33%), 390 (M+Na+CH_3CN)$^+$, ^{35}Cl, 100%), 329 (MH$^+$, ^{37}Cl, 8%), 327 (MH$^+$, ^{35}Cl, 23%), 165 (78), 150 (93); HRMS: Found MH$^+$, 327.0632. $C_{16}H_{17}{}^{35}ClFO_2S$ requires M, 327.0622.

Fraction 2: Mixture of **145e(ii)** and compound **146e**.



145e(ii) **146e**

Colourless oil (56 mg, 17%).

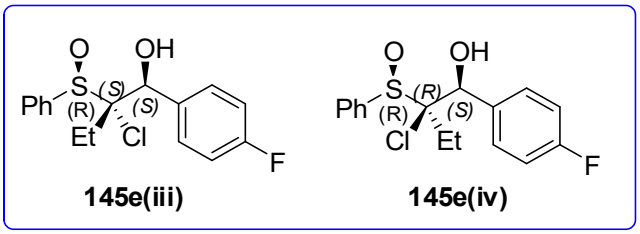
$\nu_{max.}$ (neat) 3346, 3061, 3005, 2941, 1604, 1444 and 1047 cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.84 (2H of one of two compounds, m, aromatic CH), 7.78 – 7.69 (2H of one two compounds, m, aromatic CH), 7.70 – 7.50 (5H of each compound, m, aromatic CH), 7.16 – 7.03 (2H of each compound, m, aromatic CH), 5.51 (1H of by-product, d, *J* = 2.5 Hz, C*H*OH), 5.18 (1H of aldol product, d, *J* = 8.6 Hz, C*H*OH), 5.00 (1H of aldol product, d, *J* = 8.6 Hz, OH), 4.30 (1H of by-product, d, *J* = 2.5 Hz, OH), 2.36 (1H of aldol product, dq, *J* = 14.6, 7.2 Hz, one of CH_2), 1.26 (1H of aldol product, dq, *J* = 14.6, 7.1 Hz, one of CH_2) and 1.07 (3H of aldol product, app. t, *J* = 7.2 Hz, CH_3).

^{13}C NMR (101 MHz; $CDCl_3$) chemical shifts for both compounds: δ 163.5 (d, *J* = 248.4 Hz, quat C), 162.4 (d, *J* = 252.9 Hz, quat C), 137.2 (quat C), 136.8 (quat C), 133.5 (CH), 133.3 (d, *J* = 3.1 Hz, quat C), 132.5 (CH), 131.5 (d, *J* = 3.1 Hz, quat C), 131.0 (d, *J* = 8.4 Hz, CH), 130.71 (d, *J* = 8.2 Hz, CH), 129.0 (CH), 128.7 (CH), 128.1 (CH), 127.2 (CH), 115.2 (d, *J* = 21.7 Hz, CH), 115.0 (d, *J* = 21.5 Hz, CH), 101.7 (quat C), 86.0 (quat C), 79.6 (CH), 77.4 (CH), 25.5 (CH_2) and 8.1 (CH_3).

MS (APCl$^+$) *m/z* (%) 392 (M+Na+CH_3CN)$^+$, ^{37}Cl, 33%), 390 ((M+Na+CH_3CN)$^+$, ^{35}Cl, 100%), 329 (MH$^+$, ^{37}Cl, 8%), 327 (MH$^+$, ^{35}Cl, 37%), 349 (35), 390 (100), 261 (25); HRMS: Found MH$^+$, 327.0638. $C_{16}H_{17}{}^{35}ClFO_2S$ requires M, 327.0622.

Fraction 3: Mixture of two diastereoisomers **145e(iii)** and **145e(iv)**



145e(iii) **145e(iv)**

Colourless oil (64 mg, 20%, 1:1 ratio).

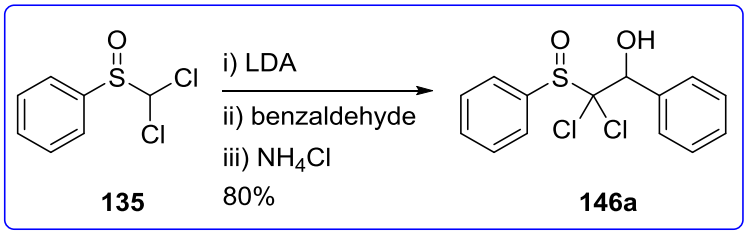
$\nu_{max.}$ (neat) 3323, 3065, 2984, 2941, 2885, 1602, 1442 and 1030 cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.89 – 7.77 (2H of both isomers, m, aromatic CH), 7.63 – 7.41 (5H of both isomers, m, aromatic CH), 7.08 – 7.00 (2H of both isomers, m, aromatic CH), 5.36 (1H of minor isomer, d, *J* = 3.5 Hz, C*H*OH), 5.21 (1H of major isomer, d, *J* = 3.2 Hz, C*H*OH), 3.80 (1H of major isomer, d, *J* = 3.3 Hz, OH), 3.37 (1H of minor isomer, d, *J* = 3.6 Hz, OH), 2.21 – 2.05 (2H of major isomer, m, CH_2), 1.83 (1H of minor isomer, dq, *J* = 15.1, 7.4 Hz, one of CH_2), 1.50 (1H of minor isomer, dq, *J* = 15.1, 7.3 Hz, one of CH_2), 0.96 (3H of minor isomer, app. t, *J* = 7.4 Hz, CH_3) and 0.80 (3H of major isomer, app. t, *J* = 7.5 Hz, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1 (quat C, d, *J* = 247.8 Hz), 163.0 (quat C, d, *J* = 247.7 Hz), 138.5 (quat C), 138.2 (quat C), 133.9 (quat C, d, *J* = 3.3 Hz), 133.6 (quat C, d, *J* = 3.2 Hz), 132.6 (CH), 132.4 (CH), 130.5 (CH, d, *J* = 8.2 Hz), 130.1 (CH, d, *J* = 8.2 Hz), 129.0 (CH), 128.8 (CH), 127.4 (CH), 127.2 (CH), 115.4 (CH, d, *J* = 21.5 Hz), 114.9 (CH, d, *J* = 21.4 Hz), 93.2 (quat C, 89.2 (quat C, 77.4 (CH, 74.7 (CH), 27.9 (CH_2), 24.36 (CH_2), 10.0 (CH_3) and 9.3 (CH_3).

MS ($APCl^+$) *m/z* (%) 392 ($(M+Na+CH_3CN)^+$, ^{37}Cl, 33%), 390 ($(M+Na+CH_3CN)^+$, ^{35}Cl, 100%), 351 ($(M+Na)^+$, ^{37}Cl, 20%), 349 ($(M+Na)^+$, ^{35}Cl, 55%); HRMS: Found $(M+Na)^+$, 349.0435. $C_{16}H_{17}{}^{35}ClFO_2S$ requires M, 349.0441.

4.4.12 Synthesis of 2,2-dichloro-1-phenyl-2-(phenylsulfinyl)-1-ethanol (146a)



135 **146a**

LDA (0.6 mmol) was prepared freshly in THF (5 mL) and cooled in a dry-ice bath. A solution of dichloromethyl phenyl sulfoxide (**135**) (105 mg, 0.5 mmol) in THF (1 mL) was added. After the solution was stirred for 10 minutes, benzaldehyde (51 μL, 0.5 mmol) was added and the solution stirred for 30 minutes further. The solution was extracted into 1:1 ether-toluene (3 × 20 mL) and the extract was dried over magnesium sulfate. The solvents were removed to afford the diastereoisomers of the *title compound* (126 mg, 80%) as a colourless solid. The diastereoisomers were separated by flash column chromatography (4% EtOAc/$CHCl_3$).

The first diastereoisomer: R_f = 0.25 (4% EtOAc/$CHCl_3$), colourless solid (75 mg, 48%).

m.p. 186 – 188 °C.

$\nu_{max.}$ (neat) 3342, 3061, 3011, 1444, 1080 and 1051 cm^{-1}.

^1H NMR (400 MHz; $CDCl_3$) δ 7.89 – 7.81 (2H, m, aromatic CH), 7.69 – 7.52 (5H, m, aromatic CH), 7.42 (3H, dd, *J* = 6.4, 3.7 Hz, aromatic CH), 5.49 (1H, d, *J* = 2.4 Hz, C*H*OH) and 4.12 (1H, dd, *J* = 16.5, 4.9 Hz, OH).

^{13}C NMR (101 MHz; $CDCl_3$) δ 137.5, 135.7, 133.4, 129.6, 129.2, 128.7, 128.2, 128.2, 102.1 and 80.2.

MS ($APCl^+$) *m/z* (%) 382 ($(M+Na+CH_3CN)^+$, $^{37}Cl_2$, 1%), 380 ($(M+Na+CH_3CN)^+$, $^{35}Cl^{37}Cl$, 9%), 378 ($(M+Na+CH_3CN)^+$, $^{35}Cl_2$, 12%), 319 (MH^+, $^{37}Cl^{37}Cl$, 3%), 315 (MH^+, $^{35}Cl_2$, 29%), 317 (MH^+, $^{37}Cl^{35}Cl$, 20%), 315 (MH^+, $^{35}Cl_2$, 29%), 198 (100), 157 (23); HRMS: Found MH^+, 315.0004. requires M, $C_{14}H_{12}{}^{35}Cl_2O_2S$: 315.0013.

The second diastereoisomer: R_f = 0.22 (4% EtOAc/$CHCl_3$), colourless solid (66 mg, 32%).

m.p 193 – 194 °C.

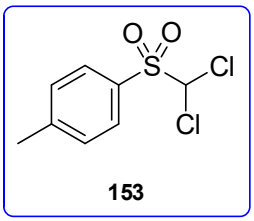
$\nu_{max.}$ (neat) 3244, 1442 and 1043 cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.95 – 7.83 (2H, m, aromatic CH), 7.69 – 7.49 (5H, m, aromatic CH), 7.45 - 7.33 (3H, m, aromatic CH), 5.48 (1H, d, *J* = 5.3 Hz, C*H*OH) and 4.08 (1H, d, *J* = 5.4 Hz, OH).

^{13}C NMR (101 MHz; $CDCl_3$) δ 137.5, 136.1, 133.1, 129.3, 129.2, 128.6, 128.4, 128.1, 102.4 and 77.5.

MS ($APCl^+$) *m/z* (%) 382 ($(M+Na+CH_3CN)^+$, $^{37}Cl_2$, 5%), 380 ($(M+Na+CH_3CN)^+$, $^{35}Cl^{37}Cl$, 20%), 378 ($(M+Na+CH_3CN)^+$, $^{35}Cl_2$, 31%), 319 (MH^+, $^{37}Cl_2$, 4%), 317 (MH^+, $^{35}Cl^{37}Cl$, 17%), 315 (MH^+, $^{35}Cl_2$, 24%), 198 (100), 157 (29); HRMS: Found MH^+, 315.0016. $C_{14}H_{12}{}^{35}Cl_2O_2S$ requires M, 315.0013.

4.4.13 Synthesis of Dichloromethyl-*p*-Tolyl Sulfone (153)[140]



153

p-Toluenesulfinic acid sodium salt dihydrate (8.5 g, 40 mmol) was placed in a 100 mL flask, followed by chloroform (12 mL, 150 mmol), potassium hydroxide (2.8 g, 50 mmol) and water (40 mL). The mixture was stirred and heated to reflux for 12h. The mixture was then extracted into dichloromethane (3 × 20 mL) and dried over magnesium sulfate. The solvents were removed to give the *title compound* (3.81 g, 40%) as a colourless solid.

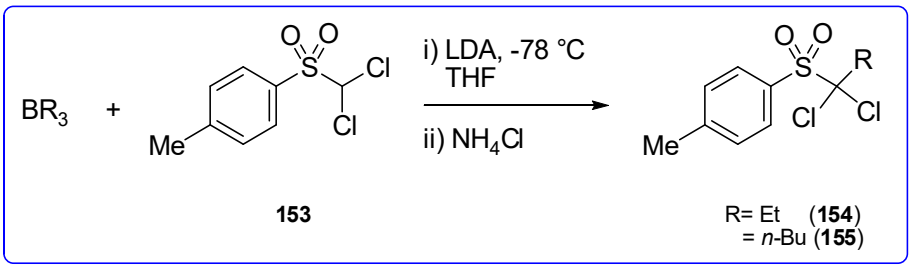
m.p. 89 – 90 °C (lit.[140] 89.5 – 90 °C).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.84 (2H, d, *J* = 8.0 Hz), 7.36 (2H, d, *J* = 8.0 Hz), 6.17 (1H, s) and 2.43 (3H, s).

^{13}C NMR (101 MHz; $CDCl_3$) δ 147.5, 131.6, 130.4, 129.3, 80.3 and 22.3.

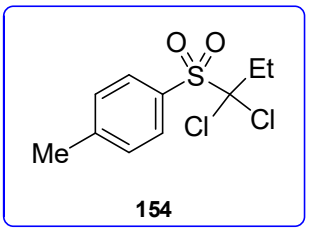
4.4.14 Reactions of Dichloromethyl-*p*-Tolyl Sulfone with Trialkylboranes

4.4.14.1 General Procedure



Dichloromethyl-*p*-tolyl sulfone (**153**) (120 mg, 0.5 mmol) was dissolved in THF (5 mL) and the trialkylborane (0.5 mmol) was added. The mixture was cooled to –78 °C and lithium bis(trimethylsilyl)amide (LiHMDS) (0.6 mL, 1.0 M, 0.6 mmol) was added dropwise. The solution was stirred for 30 minutes at –78 °C and 90 minutes at room temperature. The solution was then quenched with saturated ammonium chloride (5 mL). The organic layer was separated and the aqueous layer was extracted with chloroform (3 × 10 mL). The solution was dried over magnesium sulfate. After the removal of volatile solvents under vacuum, the crude product was further purified by silica column chromatography (5% diethyl ether/petroleum ether) to give the product with yields and data as below.

4.4.14.2 1,1-Dichloro-1-(p-tosyl) propane 154



Colourless solid (62 mg, 46%). R_f = 0.28 (5% diethyl ether/petroleum ether). m.p. = 52 – 54 °C.

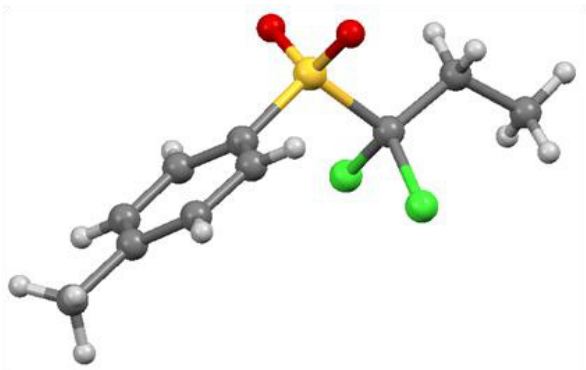
$\nu_{max.}$ (NaCl film) 3069, 2986, 2943, 2883, 1595, 1455, 1334, 1156 and 1076 cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.96 (2H, d, *J* = 8.0 Hz, aromatic CH), 7.40 (2H, d, *J* = 8.0 Hz, aromatic CH), 2.54 (2H, q, *J* = 7.2 Hz, CH_2), 2.49 (3H, s, CH_3) and 1.32 (3H, t, *J* = 7.2 Hz, CH_3).

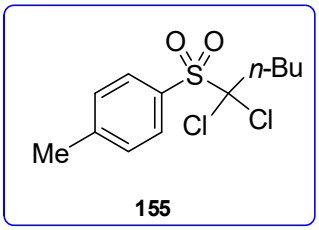
^{13}C NMR (126 MHz; $CDCl_3$) δ 146.5 (quat C), 135.7 (quat C), 132.3 (CH), 129.5 (CH), 101.8 (quat C), 33.4 (CH_2), 21.8 (CH_3) and 8.7 (CH_3).

MS (APCl+) *m/z* (%) 288 ($(M+NH_4)^+$, $^{37}Cl_2$, 15%), 286 ($(M+NH_4)^+$, $^{37}Cl^{35}Cl$, 68%), 284 ($(M+NH_4)^+$, $^{35}Cl_2$, 100%), 250 (8), 214 (13), 119 (100); HRMS: Found $(M+NH_4)^+$, 284.0272. $C_{10}H_{12}{}^{35}Cl_2O_2S$ requires M, 284.0273.

Selected crystallographic data: $C_{10}H_{12}Cl_2O_2S$, FW = 267.1, T = 296(2) K, λ = 1.54184, Monoclinic, P21/n, a = 10.8436(3) Å , b = 17.6380(3) Å, c = 13.1040(3) Å, α= 90°, β = 102.560(2)°, γ = 90°, V = 2446.29(10) Å^3, Z = 8, $\rho_{calc.}$ = 1.451 Mg/m^3, crystal size = 0.885 x 0.146 x 0.056 mm^3, μ = 6.202 mm^{-1}, reflections collected = 20117, Independent reflections = 4902, R_{int} = 0.0289, parameters = 275, R_1 = 0.0339, wR_2 = 0.0920 for I>2σ(I) and R_1 =0.0418, wR_2 = 0.0994 for all data.



4.4.14.3 1,1-Dichloro-1-tosyl pentane 155



155

Colourless solid (65 mg, 44%). R_f = 0.3 (5% diethyl ether/petroleum ether). m.p. = 65 – 67 °C.

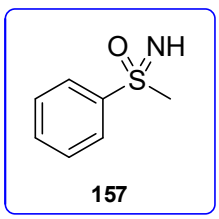
$\nu_{max.}$ (neat) 3068, 2960, 2937, 2874, 1595, 1336, 1155 and 1084 cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.96 (2H, d, *J* = 8.0 Hz, aromatic CH), 7.40 (2H, d, *J* = 8.0 Hz, aromatic CH), 2.57 – 2.41 (5H, m, CH_3 and CH_2), 1.88 – 1.67 (2H, m, CH_2), 1.50 – 1.39 (2H, m, CH_2) and 0.97 (3H, t, *J* = 7.4 Hz, CH_3).

^{13}C NMR (101 MHz; $CDCl_3$) δ 146.5 (quat C), 132.4 (CH), 129.5 (CH), 128.9 (quat C), 100.9 (quat C), 39.1 (CH_2), 26.4 (CH_2), 22.1 (CH_2), 21.9 (CH_3) and 13.9 (CH_3).

MS (APCl$^+$) *m/z* (%) 316 ((M+NH_4)$^+$, $^{37}Cl_2$, 15%), 314 ((M+NH_4)$^+$, $^{37}Cl^{35}Cl$, 64%), 312 ((M+NH_4)$^+$, $^{35}Cl_2$, 100%), 280 (70), 119 (100); HRMS: Found (M+NH_4)$^+$, 312.0583. $C_{10}H_{12}{}^{35}Cl_2O_2S$ requires M, 312.0586.

4.4.15 Synthesis of *S*-Methyl-*S*-phenylsulfoximine(157)[146]



157

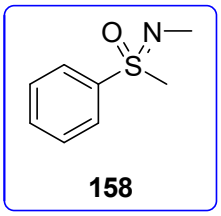
Methyl phenyl sulfoxide (0.7 g, 5 mmol) was dissolved in chloroform (10 mL). Sodium azide (0.360 mg, 5.5 mmol) was added and the flask was immersed in an ice-bath. Sulfuric acid (1.25 mL) was added dropwise. The mixture was then warmed to 45 °C and left to stir overnight. Ice-water (10 mL) was added and the organic layer was separated. The aqueous layer was extracted with chloroform (10 mL). The aqueous

layer was made slightly alkaline (pH ≈ 8.0) with 20% NaOH and extracted into chloroform (3 × 20 mL). After drying and removal of the solvent, a pale yellow oil of the *title compound* (0.571 g, 74%) was obtained as a pure compound.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.93 (2H, m), 7.61 – 7.42 (3H, m), 3.02 (3H, s) and 2.39 (1H, s).

^{13}C NMR (101 MHz; $CDCl_3$) δ 143.6, 133.2, 129.4, 127.8 and 46.3.

4.4.16 Synthesis of *N*,*S*-Dimethyl-*S*-phenylsulfoximine (158)[154]



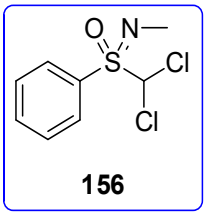
158

A mixture of *S*-methyl-*S*-phenylsulfoximine (0.531 g, 3.42 mmol) and formaldehyde (8 mL, 37% in water) in 90% formic acid (30 mL) was heated at 100 °C for 48 h. Sulfuric acid (21 mL, 2.0 M) was added and the resulting solution was extracted with chloroform (3 × 20 mL). The organic layer was dried over magnesium sulfate and the solvent was removed to leave the *title compound* (0.462 g, 80%) as a colourless oil.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.83 (2H, d, *J* = 7.0 Hz), 7.75 – 7.44 (3H, m), 3.06 (3H, s) and 2.58 (3H, s).

^{13}C NMR (101 MHz; $CDCl_3$) δ 138.7, 133.1, 129.7, 128.9, 45.1 and 29.7.

4.4.17 Synthesis of *N*-Methyl-*S*-(dichloromethyl)-*S*-phenylsulfoximine (156)[145]



156

4.4.17.1 Preparation of t-Butyl Hypochlorite (BHC)[155]*.*

Household bleach solution (500 mL) was placed in a 1L round bottom flask in a dark fume cupboard and the flask was wrapped with aluminium foil. A solution of *t*-butyl alcohol (37 mL, 0.39 mole) in glacial acetic acid (24.5 mL) was added all at once. The solution was stirred for 4 – 5 minutes. The aqueous layer was separated and the organic layer was washed with 10% sodium carbonate (50 mL) and water (50 mL). The organic layer was dried over calcium chloride and then evaporated to yield the *title compound* (20 g, 47%) as a yellow liquid.

4.4.17.2 The Chlorination of **N,S-*dimethyl*-S-*phenylsulfoximine (157)***

A solution of *N*,*S*-dimethyl-*S*-phenylsulfoximine (**157**) (169 mg, 1.0 mmol) in dichloromethane (10 mL) was placed in 25 mL flask, followed by potassium carbonate (207 mg, 1.5 mmol). The flask was wrapped in aluminium foil and immersed in an ice-bath. BHC (0.23 mL, 2 mmol) was added dropwise by syringe. The cooling bath was removed and the mixture was stirred for 1 h, after which it was filtered. The solvents were removed by rotary evaporator to give the crude product. After column chromatography on silica gel (20% diethyl ether/petroleum ether), two products were separated (mono and dichloromethyl products).

***N*-Methyl-*S*-(chloromethyl)-*S*-phenylsulfoximine**: colourless oil (145 mg, 72%), R_f: 0.2 (5:1, petroleum ether/diethyl ether).

^{1}H NMR (400 MHz; $CDCl_3$) δ 8.02 – 7.73 (2H, m), 7.64 – 7.57 (1H, m), 7.55 – 7.47 (2H, m), 4.61 (1H, d, *J* = 12.3 Hz), 4.49 (1H, d, *J* = 12.3 Hz) and 2.79 (3H, s).

^{13}C NMR (101 MHz; $CDCl_3$) δ 135.2, 134.1, 130.2, 129.6, 57.9 and 29.7.

***N*-Methyl-*S*-(dichloromethyl)-*S*-phenylsulfoximine**: colourless solid (19 mg, 7%), R_f: 0.3 (5:1, petroleum ether/diethyl ether). m.p. = 33 – 35 °C.

^{1}H NMR (400 MHz; $CDCl_3$) δ 8.10 – 8.00 (2H, m), 7.74 – 7.57 (1H, m), 7.58 (2H, t, *J* = 7.7 Hz), 6.28 (1H, s) and 3.02 (3H, s).

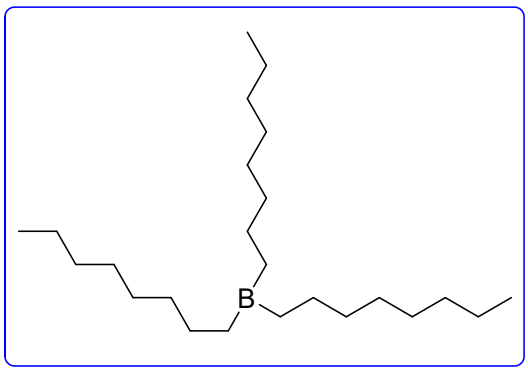
^{13}C NMR (101 MHz; $CDCl_3$) δ 134.2, 135.6, 130.5, 128.9, 80.6 and 29.7.

MS (ES^+) *m/z* (%) 242 (MH^+, $^{37}Cl_2$, 7%), 240 (MH^+, $^{37}Cl^{35}Cl$, 32%), 238 (MH^+, $^{35}Cl_2$, 38%); HRMS: Found MH^+, 237.9851. $C_8H_{10}Cl_2NOS$ requires M, 237.9860.

4.4.18 Reaction of *N*-methyl-*S*-(dichloromethyl)-*S*-phenylsulfoximine with trialkylboranes

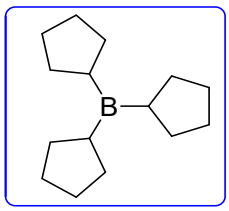
4.4.18.1 Preparation of Trialkylborane

4.4.18.2 Trioctylborane[105,106]



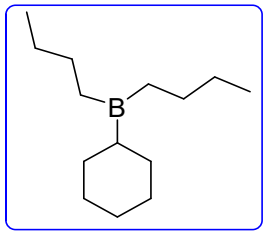
To a septum-capped 50 mL flask, borane (50 μL, 10.0 M in dimethyl sulfide, 0.5 mmol, 1 equiv.) was added, followed by THF (2 mL). The flask was immersed in an ice-bath and 1-octene (0.24 mL, 1.5 mmol, 3 equiv.) was added dropwise. The cooling bath was removed and the solution was left to stir at room temperature for 1 h.

4.4.18.3 Tricyclopentylborane[105,106]



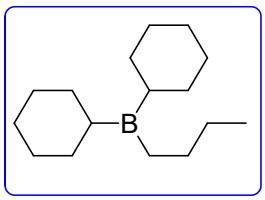
To septum-capped 50 mL flask, borane (50 μL, 10.0 M in dimethyl sulfide, 0.5 mmol, 1 equiv.) was added, followed by THF (2 mL). The flask was immersed in an ice-bath and cyclopentene (132 μL, 1.5 mmol, 3 equiv.) was added dropwise. The cooling bath was removed and the solution was left to stir at room temperature for 1 h.

4.4.18.4 Dibutylcyclohexylborane[148]



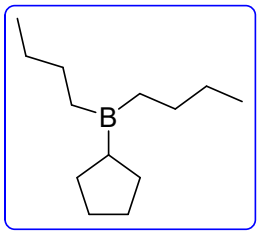
A solution of trichloroborane (0.5 mL, 1.0 M, 0.5 mmol) and cyclohexene (51 μL, 0.5 mmol) in hexane (2 mL) was cooled to –78 °C, and triethylsilane (80 μL, 0.5 mmol) was added dropwise. The solution was stirred for 15 min. The cooling bath was removed and the solution was stirred for 30 min. The mixture was cooled to –78 °C again and *n*-BuLi (0.63 mL, 1.6 M in hexane, 1.0 mmol) was added dropwise. The solution was warmed to r.t. over a period of 1 h.

4.4.18.5 Butyldicyclohexylborane[148]



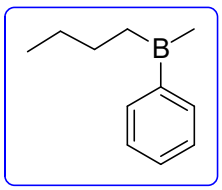
A solution of trichloroborane (0.5 mL, 1.0 M, 0.5 mmol) and cyclohexene and (51 μL, 0.5 mmol) in hexane (2 mL) was cooled to –78 °C, and triethylsilane (80 μL, 0.5 mmol) was added dropwise. The solution was stirred for 15 min. The cooling bath was removed and the solution was stirred for 30 min. A mixture of cyclohexene (51 μL, 0.5 mmol) and triethylsilane (80 μL, 0.5 mmol) in dichloromethane (1 mL) was added and the mixture was stirred for 30 min. The solution was cooled again to –78 °C and *n*-BuLi (0.31 mL, 1.6 M in hexane, 0.5 mmol) was added. The solution was allowed to warm to r.t. over a period of 1 h.

4.4.18.6 Dibutylcyclopentylborane[148]



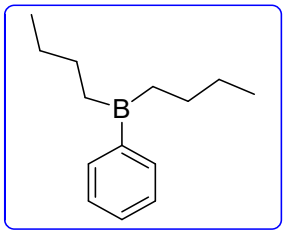
A solution of trichloroborane (0.5 mL, 1.0 M, 0.5 mmol) and cyclopentene (44 μL, 0.5 mmol) in hexane (2 mL) was cooled to –78 °C and triethylsilane (80 μL, 0.5 mmol) was added dropwise. The solution was stirred for 15 min. The cooling bath was removed and the solution was stirred for 30 min. The mixture was cooled to –78 °C again and *n*-BuLi (0.63 mL, 1.6 M in hexane, 1.0 mmol) was added dropwise. The solution was allowed to warm to r.t. over a period of 1 h.

4.4.18.7 Butylmethylphenylborane



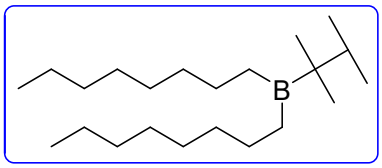
A solution of dichloro(phenyl)borane (65 μL, 0.5 mmol) in dichloromethane (5 mL) was cooled to –78 °C and *n*-BuLi (0.31 mL, 1.6 M in hexane, 0.5 mmol) was added dropwise followed by MeLi (0.31 mL, 1.6 M in hexane, 0.5 mmol). The solution was allowed to warm to r.t. over a period of 1 h. The product was concluded to be a mixture of dibutylphenylborane and butylmethylphenylborane based on the result of the reaction with *N*-Methyl-*S*-(dichloromethyl)-*S*-phenylsulfoximine (**156**).

4.4.18.8 Dibutylphenylborane



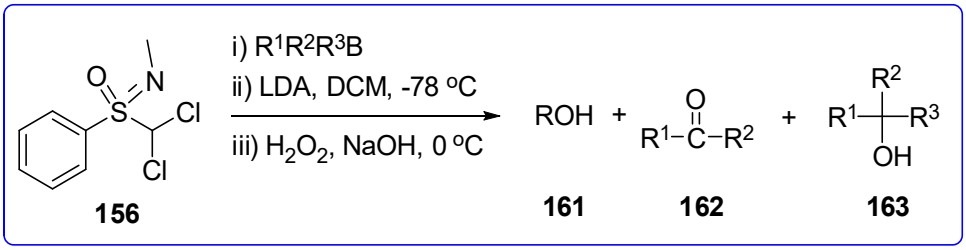
A solution of dichloro(phenyl)borane (65 μL, 0.5 mmol) in dichloromethane (2 mL) was cooled to –78 °C and *n*-BuLi (0.63 mL, 1.6 M in hexane, 1 mmol) was added dropwise. The solution was allowed to warm to r.t. over a period of 1 h.

4.4.18.9 Thexyldioctylborane[3]



The *title compound* was prepared by the dropwise addition of 2,3-dimethyl-2-butene (59 μL, 0.5 mmol) to borane dimethyl sulfide (50 μL, 10.0 M, 0.5 mmol) at 0 °C, and then the reaction mixture was left to stir for 2 h. Dry THF (5 mL) was added, followed by the dropwise addition of 1-octene (157 μL, 1.0 mmol). The solution was stirred for 2 h at 0 °C.

4.4.19 General Procedure of the Reaction of 156 with Organoboranes

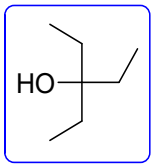


Fresh LDA was prepared by adding *n*-BuLi (0.38 mL, 1.6 M in hexane, 0.60 mmol, 1.2 equiv.) dropwise to a cooled (–78 °C) solution of diisopropylamine (91 μL, 0.65 mmol, 1.3 equiv.) in dry THF (2 mL). The solution then was allowed to warm to 0 °C over a period of 20 min. This solution was added to a solution of *N*-methyl-*S*-(dichloromethyl)-*S*-phenylsulfoximine (119 mg, 0.5 mmol) and a trialkylborane (0.5 mmol) in THF (5 mL) dropwise at –78 °C. The solution was stirred for 1 h at –78 °C and 1h at room temperature. The solution was oxidised by adding sodium hydroxide (3.0 M, 3 mL) followed by hydrogen peroxide (30% aqueous, 3 mL) and the solution was left to stir overnight. The organic layer was separated, and the aqueous layer was saturated with sodium chloride and extracted with dichloromethane (3 x 10 mL). The organic layers were combined, dried over magnesium sulfate and filtered. The volatile solvents were evaporated under reduced pressure to leave the corresponding alcohol. The crude product was purified by column chromatography on silica gel (5% EtOAc/petroleum ether) and the isolated yields were measured.

With respect to GC yield, before working up the reaction solution, the solution was saturated with sodium chloride and tetradecane, as an internal standard, was added and the GC yield of the product was measured.

The reaction was optimised by modification of the procedure using 1.5 equiv. of sulfoximine, changing the solvent to dichloromethane and stirring the reaction solution overnight before oxidation. The yield of trioctylmethanol went up to 81%, see entry 4 in **Table 4.4**.

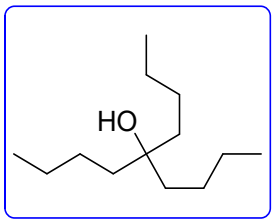
4.4.19.1 3-Ethylpentan-3-ol



Colourless oil (47% GC yield); ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.38 (6H, q, *J* = 7.5 Hz), 1.24 (1H, s) and 0.78 (9H, t, *J* = 7.5 Hz).

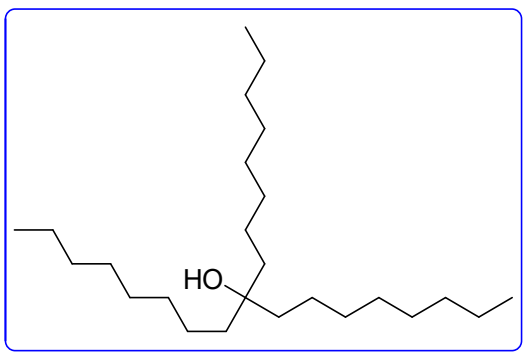
^{13}C NMR (101 MHz; $CDCl_3$) δ 74.8, 30.5 and 7.8.

4.4.19.2 5-Butylnonan-5-ol



Colourless oil (81% GC yield), ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.48 – 1.18 (18H, m), 1.07 (1H, s) and 0.84 (9H, t, *J* = 6.6 Hz). ^{13}C NMR (101 MHz; $CDCl_3$) δ 74.7, 39.3, 25.9, 23.6 and 14.4.

4.4.19.3 9-Octylheptadecan-9-ol

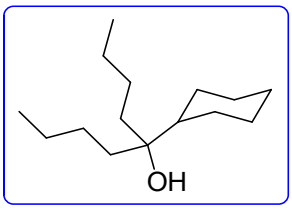


Colourless oil (81% GC yield and 75% isolated yield).

^{1}H NMR (400 MHz; $CDCl_3$) δ 1.50 – 1.03 (43H, m), and 0.88 (9H, t, *J* = 6.9 Hz).

^{13}C NMR (126 MHz; $CDCl_3$) δ 74.5, 39.3, 31.9, 30.3, 29.6, 29.3, 23.5, 22.7 and 14.1.

4.4.19.4 5-Cyclohexyl-5-nonanol



Colourless oil (83 mg, 73%).

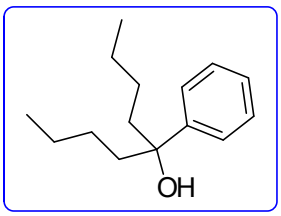
$\nu_{max.}$ (neat) 3477, 2955, 2928, 2854 and 1450 cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$) δ 1.84 – 1.66 (5H, m), 1.54 – 0.97 (19H, m) and 0.91 (6H, t, *J* = 7.0 Hz).

^{13}C NMR (101 MHz; $CDCl_3$) δ 75.5 (quat C), 44.8 (CH), 35.9 (CH_2), 26.7 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 25.2 (CH_2), 23.3 (CH_2) and 14.0 (CH_3).

MS (EI-MS) *m/z* (%): *molecular ion not seen;* 208 ($M^+ - H_2O$, 17%), 151 (38), 109 (72), 69 (94); HRMS: Found ($M^+ - H_2O$), 208.2196. $C_{15}H_{28}$ requires M, 208.2191.

4.4.19.5 5-Phenyl-5-nonanol[156]



Colourless oil (56 mg, 51%).

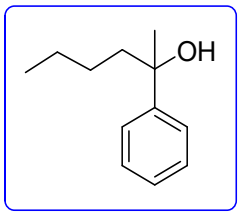
$\nu_{max.}$ (neat) 3419, 2957, 2931, 2860, 1458 and 1078 cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.43 – 7.29 (4H, m), 7.26 – 7.18 (1H, tt, *J* = 7.0, 1.5 Hz), 1.91 – 1.66 (5H, m), 1.37 – 1.15 (6H, m), 1.10 – 0.95 (2H, m) and 0.84 (6H, t, *J* = 7.0 Hz).

^{13}C NMR (101 MHz; $CDCl_3$) δ 146.6 (quat C), 128.1 (CH), 126.3 (CH), 125.4 (CH), 77.1 (quat C), 42.9 (CH_2), 25.7 (CH_2), 23.2 (CH_2) and 14.2 (CH_3).

MS (EI-MS) *m/z* (%): *molecular ion not seen;* 203 (M^+ – OH, 35%), 160 (33), 138 (55), 115 (64); HRMS: Found (M^+ – OH), 203.1800. $C_{15}H_{23}$ requires M, 203.1800.

4.4.19.6 2-Phenyl-2-hexan-2-ol[157]

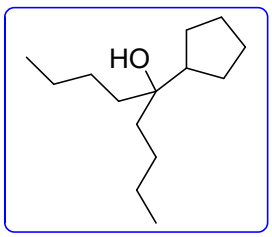


Colourless oil (27 mg, 30%).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.39 – 7.31 (2H, m), 7.29 – 7.20 (2H, m), 7.18 – 7.11 (1H, m), 1.79 (1H, s), 1.77 – 1.64 (2H, m), 1.46 (3H, s), 1.24 – 1.09 (3H, m), 1.08 – 0.95 (1H, m) and 0.76 (3H, t, *J* = 7.1 Hz).

^{13}C NMR (101 MHz; $CDCl_3$) δ 148.2 (quat C), 128.2 (CH), 126.5 (CH), 124.9 (CH), 74.8 (quat C), 44.2 (CH_2), 30.2 (CH_3), 26.2 (CH_2), 23.1 (CH_2) and 14.1 (CH_3).

4.4.19.7 5-Cyclopentylnonan-5-ol



Colourless oil (72 mg, 68%)

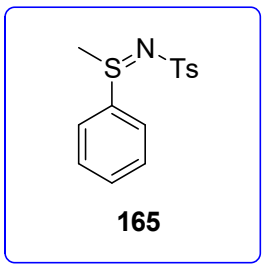
$\nu_{max.}$ (neat) 3485, 2953, 2931, 2864 and 1456 cm^{-1}.

^{1}H NMR (400 MHz; $CDCl_3$) δ 2.08 – 1.82 (1H, m), 1.68 – 1.17 (22H, m), 1.02 (1H, br. exch.) and 0.91 (6H, t, *J* = 7.1 Hz).

^{13}C NMR (101 MHz; $CDCl_3$) δ 75.3 (quat C), 47.6 (CH), 37.5 (CH_2), 26.2 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 23.6 (CH_2) and 14.3 (CH_3).

MS (EI-MS) *m/z* (%): *molecular ion not seen;* 194 ($M^+ - H_2O$, 28%), 137 (35), 95 (76); HRMS: Found ($M^+ - H_2O$), 194.2035. $C_{15}H_{28}$ requires M, 194.2035.

4.4.20 Preparation of *S*-methyl-*S*-phenyl-*N*-sulfonylsulfilimine (165)[150]



165

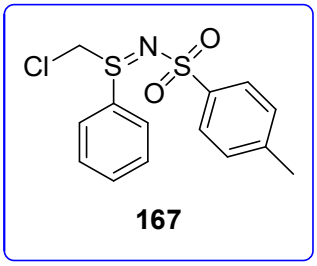
To a solution of thioanisole (0.59 mL, 5.0 mmol) in acetonitrile (25 mL), chloramine-T hydrate (1.69 g, 6.0 mmol) was added. The resulting solution was stirred for 2 h at room temperature. Dichloromethane (40 mL) was added and the solid was removed by filtration. The solvent was removed under reduced pressure to give the crude product as a solid. The product was then recrystallised from methanol:water (9:1) to give the *title compound* (1.246 g, 85%) as a colourless solid.

m.p. 131 – 132 °C (lit.[158] 131.5 – 132 °C)

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.77 – 7.63 (4H, m), 7.57 – 7.42 (3H, m), 7.15 (2H, d, *J* = 8.0 Hz), 2.83 (3H, s) and 2.33 (3H, s).

^{13}C NMR (100 MHz; $CDCl_3$) δ 141.8, 141.3, 136.1, 132.5, 130.1, 129.3, 126.3, 125.9, 39.2 and 21.5.

4.4.21 Preparation of S-(Chloromethyl)-*S*-phenyl-*N*-sulfonylsulfilimine (167)[150]



167

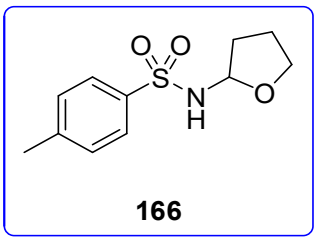
The procedure described in the preceding paragraph was followed, involving the reaction of chloramine-T hydrate with chloromethyl phenyl sulfide (0.67 mL, 5.0 mmol) followed by flash column chromatography (3% ethyl acetate/chloroform) to produce the *title compound* (1.36 g, 83%) as a colourless solid.

m.p. 117 – 118 °C.

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.86 – 7.71 (4H, m), 7.68 – 7.50 (3H, m), 7.20 (2H, d, *J* = 8.5 Hz), 4.67 (1H, d, *J* = 10.2 Hz), 4.47 (1H, d, *J* = 10.2 Hz) and 2.36 (3H, s).

^{13}C NMR (100 MHz; $CDCl_3$) δ 142.2, 140.8, 133.7, 131.3, 130.1, 129.4, 127.5, 126.4, 59.0 and 21.5.

4.4.22 Formation of Tetrahydrofuran-2-yl-tolylsulfonamide (166)[152]



166

To a cooled solution (0 °C) of *S*-methyl-*S*-phenyl-*N*-toluenesulfonylsulfilimine (**165**) (293 mg, 1.0 mmol) in THF (15 mL), was added *N*-chlorosuccinimide (274 mg, 2.05 mmol, 2.05 equiv.). The mixture was stirred at 0 °C overnight and then filtered. The solvent was removed *in vacuo* and the crude product was purified by flash column

chromatography (5% ethyl acetate/chloroform) to give the *title compound* (57 mg, 25%) as a colourless solid.

m.p. 121 – 123 °C. (lit.[159] 121 – 122).

^{1}H NMR (400 MHz; $CDCl_3$) δ 7.72 (2H, d, *J* = 8.0 Hz), 7.20 (2H, d, *J* = 8.0 Hz), 5.88 (1H, d, *J* = 9.0 Hz), 5.31 – 5.19 (1H, m), 3.69 – 3.49 (2H, m), 2.34 (3H, s), 2.18 – 1.96 (1H, m), 1.91 – 1.59 (3H, m).

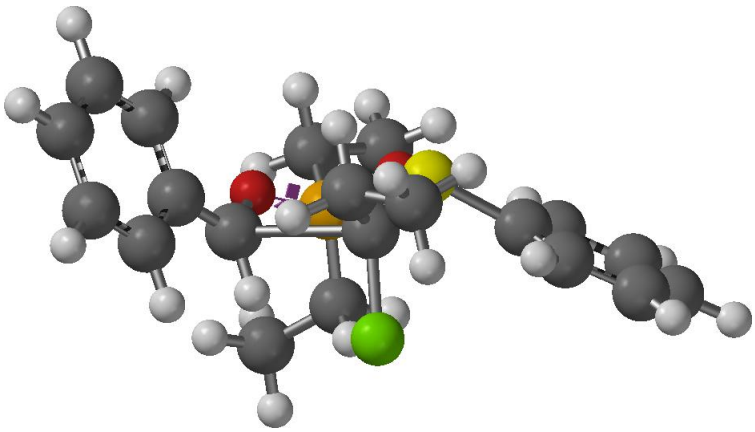
^{13}C NMR (100 MHz; $CDCl_3$) δ 143.3, 138.6, 129.6, 127.1, 85.0, 67.2, 32.6, 24.0 and 21.6.

4.5 Theoretical Methods and Details

The geometries of all transition states were fully optimised at the RHF/3-21G(d) level of theory using Spartan software.[87]

4.5.1 Selected Computational Data

4.5.1.1 Transition State 1 (TS1) Leading to Compound 145a(i)

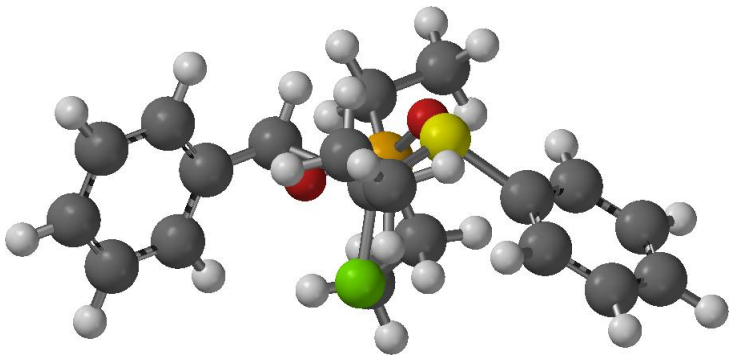


H	3.222311	-1.269648	0.793023
C	3.546614	-0.284932	0.540882
C	4.359756	2.282061	-0.111632
C	2.627043	0.748373	0.495350
C	4.876734	-0.027947	0.258521
C	5.285118	1.252574	-0.065942
C	3.029958	2.032589	0.170507
H	5.588114	-0.828786	0.294869
H	6.316159	1.448491	-0.283463
H	2.314383	2.825886	0.119081
H	4.669241	3.274501	-0.371194
S	0.937774	0.457981	0.991025
O	0.923771	-1.120724	0.879271
C	-0.125243	1.238545	-0.027997
B	0.208015	-2.185346	0.034901
C	0.737614	-2.221342	-1.487780
H	1.784844	-2.520290	-1.468451
H	0.735028	-1.237293	-1.950188
C	0.178075	-3.544867	0.877484

H	-0.312340	-3.358923	1.831533
H	-0.427469	-4.289887	0.362347
C	-0.031119	-3.208217	-2.404434
H	0.051662	-4.223367	-2.033643
H	0.358797	-3.190131	-3.417322
H	-1.088628	-2.963347	-2.453211
C	1.582384	-4.137624	1.149565
H	2.187757	-3.429644	1.705635
H	2.096947	-4.369482	0.221961
H	1.521006	-5.052257	1.731283
C	-1.809548	-0.688198	-0.569166
O	-1.318264	-1.646236	0.080256
Cl	0.297212	1.516308	-1.751047
C	-0.982961	2.350747	0.570040
H	-1.293821	2.041131	1.562607
H	-1.886026	2.435056	-0.019884
C	-0.315796	3.740724	0.653709
H	-1.028903	4.484367	0.995179
H	0.049968	4.044787	-0.319814
H	0.514243	3.726756	1.351832
C	-3.099961	-0.142032	-0.182762
C	-5.555655	0.861513	0.571778
C	-3.740711	0.790088	-0.988418
C	-3.692274	-0.576888	0.997699
C	-4.918289	-0.072824	1.375562
C	-4.971690	1.291673	-0.609066
H	-3.277078	1.120392	-1.898087
H	-3.179419	-1.303049	1.593536
H	-5.377392	-0.402312	2.285563
H	-5.472048	2.011160	-1.224728
H	-6.509045	1.253312	0.866606
H	-1.379705	-0.374050	-1.497801

Imaginary frequency 151 cm^{-1} (intensity 138)

4.5.1.2 Transition State 2 (TS2) Leading to Compound 145a(iv)

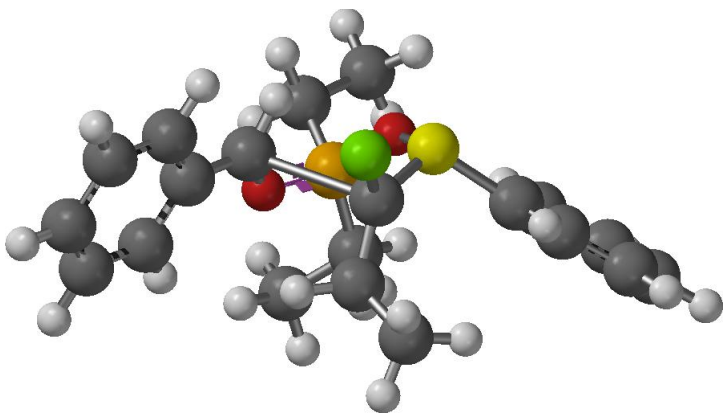


H	3.413270	-0.964258	0.862766
C	3.568060	-0.036047	0.356694
C	3.936079	2.367774	-0.969844
C	2.543379	0.894148	0.297907
C	4.776437	0.240006	-0.255463
C	4.960876	1.439668	-0.920765
C	2.725106	2.098569	-0.357651
H	5.566948	-0.482137	-0.216009
H	5.896090	1.648353	-1.400831
H	1.927014	2.807950	-0.411651
H	4.071465	3.294377	-1.490433
S	1.032900	0.589658	1.195419
O	0.995470	-0.998464	1.184528

C	-0.284304	1.266046	0.448000
B	0.505920	-2.082279	0.199313
C	1.258199	-2.111390	-1.216034
H	2.296123	-2.410906	-1.079213
H	1.286112	-1.120499	-1.661112
C	0.365370	-3.437486	1.051593
H	-0.243594	-3.256731	1.939081
H	-0.157294	-4.195482	0.470613
C	0.592504	-3.081966	-2.224344
H	0.623679	-4.104087	-1.861885
H	1.095880	-3.054417	-3.185735
H	-0.445576	-2.811142	-2.379406
C	1.732810	-4.002913	1.509655
H	2.261127	-3.268728	2.108642
H	2.352313	-4.254875	0.655033
H	1.612304	-4.900588	2.108111
C	-1.722437	-0.882188	0.622062
H	-1.477594	-0.789403	1.661212
O	-1.000733	-1.572023	-0.138068
C	-3.008906	-0.381223	0.180159
C	-5.466182	0.539993	-0.666678
C	-3.881949	0.198453	1.092408
C	-3.367675	-0.501281	-1.156752
C	-4.596202	-0.037416	-1.578714
C	-5.113272	0.657218	0.668909
H	-3.599153	0.286445	2.123784
H	-2.674930	-0.946759	-1.838536
H	-4.875635	-0.120673	-2.609180
H	-5.791932	1.101808	1.368002
H	-6.420575	0.899620	-0.996607
Cl	-0.384292	1.342663	-1.326704
C	-1.038114	2.372975	1.172226
H	-1.039302	2.149156	2.235645
H	-2.069245	2.343924	0.839971
C	-0.485525	3.799185	0.961089
H	-1.120952	4.532046	1.448146
H	-0.445393	4.033807	-0.095647
H	0.512385	3.885920	1.377508

Imaginary frequency 170 cm^{-1} (intensity 153)

4.5.1.3 Transition State 3 (TS3) Leading to Compound 145a(iii)

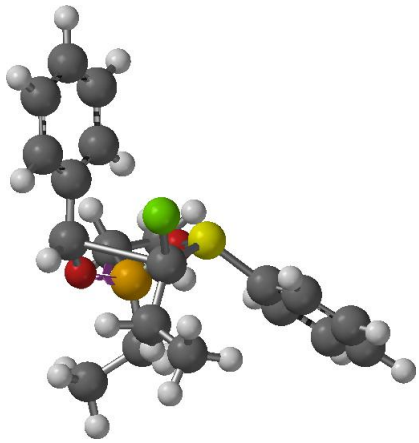


H	3.227832	-1.279588	0.244294
C	3.536405	-0.281035	0.031487
C	4.340226	2.327120	-0.458191
C	2.684742	0.772490	0.299876
C	4.787167	-0.026931	-0.508130
C	5.187922	1.271927	-0.757073

C	3.090734	2.079307	0.075199
H	5.443864	-0.844952	-0.726586
H	6.156547	1.464894	-1.173052
H	2.434643	2.892562	0.314004
H	4.651659	3.336659	-0.636929
S	1.111014	0.536520	1.117703
O	0.988443	-1.048730	1.048283
C	-0.115114	1.286476	0.304610
B	0.362315	-2.129789	0.149484
C	1.039786	-2.306674	-1.298333
H	2.025195	-2.757098	-1.189504
H	1.205969	-1.346800	-1.782614
C	0.165923	-3.430622	1.073491
H	-0.434742	-3.175562	1.948160
H	-0.385127	-4.201740	0.538025
C	0.202825	-3.197239	-2.251935
H	0.081164	-4.195186	-1.845191
H	0.679875	-3.289843	-3.222574
H	-0.783072	-2.772836	-2.399346
C	1.511337	-4.017326	1.569173
H	2.064970	-3.265715	2.120512
H	2.121906	-4.347572	0.734676
H	1.356561	-4.870174	2.222504
C	-1.775697	-0.772188	0.592509
H	-1.464236	-0.600394	1.602691
O	-1.118003	-1.533947	-0.155848
C	-3.059401	-0.246168	0.180648
C	-5.522582	0.713738	-0.600571
C	-3.800605	0.542511	1.051032
C	-3.552640	-0.553745	-1.084243
C	-4.783700	-0.073658	-1.473199
C	-5.034882	1.022321	0.658178
H	-3.407644	0.787990	2.016903
H	-2.963537	-1.166024	-1.734619
H	-5.170127	-0.307134	-2.444267
H	-5.609076	1.634166	1.323180
H	-6.480211	1.087254	-0.904543
C	-0.315698	1.409580	-1.189340
H	0.175017	0.569578	-1.665670
H	-1.374901	1.313205	-1.403701
C	0.186141	2.723650	-1.829285
H	1.264389	2.789590	-1.784757
H	-0.239387	3.578583	-1.318063
H	-0.114452	2.767385	-2.871548
Cl	-0.920690	2.556682	1.291320

Imaginary frequency 168 cm^{-1} (intensity 114)

4.5.1.4 Transition State 4 (TS4) Leading to Compound 145a(ii)



H	2.475561	-1.584998	1.060699
C	2.990161	-0.650814	1.061479
C	4.301305	1.792083	1.116468
C	2.288375	0.520894	0.856285
C	4.359209	-0.598498	1.271766
C	5.015140	0.617448	1.296262
C	2.937964	1.745549	0.900816
H	4.905453	-1.508376	1.420360
H	6.073521	0.654012	1.461713
H	2.381268	2.651672	0.765897
H	4.803071	2.738372	1.146635
S	0.503761	0.559481	0.708918
O	0.214829	-1.013734	0.608138
C	0.035002	1.406093	-0.624799
B	-0.011931	-2.035388	-0.504563
C	1.237902	-2.276738	-1.492751
H	1.942475	-2.948391	-1.002141
H	1.794694	-1.365357	-1.688899
C	-0.671921	-3.363724	0.121748
H	-1.688099	-3.193454	0.469248
H	-0.747763	-4.130046	-0.647422
C	0.835340	-2.903683	-2.851471
H	0.330978	-3.853242	-2.709370
H	1.706265	-3.081291	-3.474478
H	0.162674	-2.244449	-3.385557
C	0.159825	-3.927323	1.303972
H	0.230360	-3.194113	2.099538
H	1.167754	-4.176829	0.985970
H	-0.288909	-4.828609	1.709318
C	-1.929807	-0.292619	-1.286492
O	-1.133659	-1.249135	-1.418352
C	0.656233	1.432188	-2.004832
H	1.160321	0.491780	-2.174530
H	-0.136934	1.493754	-2.745713
C	1.640948	2.593112	-2.271644
H	2.531273	2.487185	-1.667836
H	1.174797	3.543931	-2.045472
H	1.936399	2.598155	-3.316261
Cl	-0.951140	2.853965	-0.232712
C	-2.851300	-0.002027	-0.198184
C	-4.750426	0.616336	1.719956
C	-3.849272	0.930234	-0.468641
C	-2.801646	-0.611536	1.053497
C	-3.749054	-0.300717	2.005169
C	-4.801140	1.234678	0.483476
H	-3.876520	1.417714	-1.423193
H	-2.008505	-1.285485	1.283275
H	-3.705434	-0.764674	2.969419
H	-5.566963	1.951730	0.268036

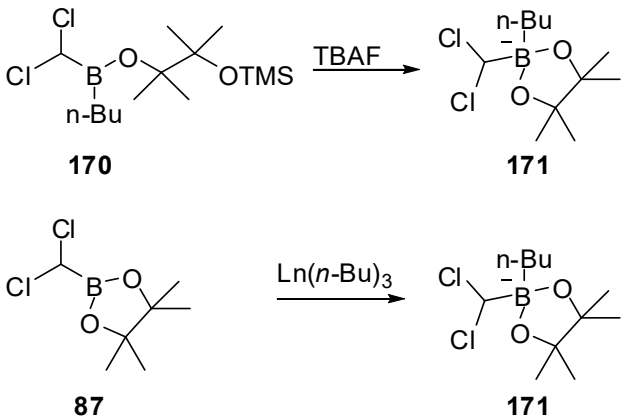
H	-5.483835	0.853558	2.465165
H	-2.071451	0.322616	-2.158937

Imaginary frequency 214 cm^{-1} (intensity 150)

Chapter Five
Future Work

5.1 Future Work

Studies on a Catalytic Borylation Reaction: The study of the reaction of boronic ester **87** with *n*-BuLi showed that the lithium cation coordinates with the chiral ligand to influence the stereoselectivity. Also, high stereoselectivity (70% e.e.) was achieved using a catalytic amount of ytterbium triflate from an old bottle and only 0.5 equivalents of chiral ligand, *i.e.* there was a evidence of some catalytic turnover. To prevent the possible competition between Li and Yb, further research should be undertaken using Yb and other lanthanides in the absence of Li. This can be done by using an unsymmetrical boronic ester **170**, which would undergo cyclisation upon deprotection with tetrabutylammonium floride (TBAF) to give the borate **171**. This would allow us to add lanthanide salts and ultimately study the catalytic process promoted by only one metal. Furthermore, using Ln(*n*-Bu)$_3$ as a source of the *n*-Bu group would provide the borate **171** with a migrating alkyl group directly from lanthanide rather than from Li.



Scheme 5.1: Proposed Future Work

Stoichimetric Studies on Sulfur Compounds in a DCME-Like Reaction: The study of the reaction of trialkylboranes with Cl_2CHX (X = phenylsulfinyl (SOPh), *p*-tosyl and phenylsulfoximinyl (PhSO(NMe)) showed some interesting reactions. The reaction of

dichloromethyl *p*-tosyl sulfone with trialkylboranes showed an interesting outcome by replacing the hydride with an alkyl group from trialkylborane in moderate yields. It would be interesting to explore the mechanism of this reaction, since it presumably does not involve alkyl group migration.

In terms of the reaction of *S*-dichloromethyl-*N*-methyl-*S*-phenyl-sulfoximine (**156**) with trialkylboranes, the reaction worked well with a range of trialkylboranes. However, it was not possible to determine whether there was any stereoselectivity in this reaction. If a boron compound containing only one alkyl group was used successfully, it could be possible to determine the stereoselectivity directly. Although alkylboronic esters were not successful in this respect, other compounds, for example $RBCl_2$, could potentially be used. Alternatively, enantiomerically-pure sulfoximines could be investigated, but this would require an organoborane with three alkyl groups having different migratory aptitudes.

Chapter Six
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6.1 References

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