Stereoselective Organoborate Rearrangement Reactions

By

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Declaration

This work has not previously been accepted in substance for any degree and is not being concurrently submitted for candidature for any degree.

Signed: Basil Abdulmahdi Saleh Alabdullah
Date: 29/06/2015

Statement 1

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Acknowledgements

Foremost, I would like to thank my creator (Allah) for making me a curious being who loves to explore His creation and for giving me the opportunity to write this thesis. Without Him, I can do nothing.

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I’d also like to thank University of Basrah for giving me this opportunity to study for my PhD at Cardiff University.
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-5-(dichloromethyl)-5-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
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<tr>
<td>APCI</td>
<td>Atmospheric pressure chemical ionisation</td>
</tr>
<tr>
<td>app</td>
<td>Apparent</td>
</tr>
<tr>
<td>aq</td>
<td>Aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>Unspecified aryl substituent</td>
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<tr>
<td>9-BBN</td>
<td>9-Borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
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<td>b.p.</td>
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<td>BHC</td>
<td>t-Butyl hypochlorite</td>
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<td>br</td>
<td>Broad</td>
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<tr>
<td>d</td>
<td>Doublet</td>
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<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DCME</td>
<td>Dichloromethyl methyl ether</td>
</tr>
<tr>
<td>dd</td>
<td>Doubled doublet</td>
</tr>
<tr>
<td>ddd</td>
<td>Doubled doubled doublet</td>
</tr>
<tr>
<td>decomp</td>
<td>Decomposition</td>
</tr>
<tr>
<td>DEPT</td>
<td>Distortionless Enhancement by Polarisation Transfer</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>dt</td>
<td>Doubled triplet</td>
</tr>
<tr>
<td>e.e.</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>EI+</td>
<td>Electron impact</td>
</tr>
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<td>equiv.</td>
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<td>Et</td>
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<td>EWG</td>
<td>Electron withdrawing group</td>
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<td>g</td>
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<td>High resolution mass spectrometry</td>
</tr>
<tr>
<td>Hz</td>
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</tr>
<tr>
<td>i-Pr</td>
<td>Isopropyl</td>
</tr>
<tr>
<td>lpc</td>
<td>Isopinocamphyl</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>J</td>
<td>Coupling constant (in Hz)</td>
</tr>
<tr>
<td>L</td>
<td>Litre</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
</tr>
<tr>
<td>LiDBB</td>
<td>Lithium-4,4-di-tert-butylbiphenyl radical anion</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>Lithium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>lit.</td>
<td>Literature</td>
</tr>
<tr>
<td>LiTMP</td>
<td>Lithium 2,2,6,6-tetramethylpiperidine</td>
</tr>
<tr>
<td>LR</td>
<td>Low resolution</td>
</tr>
<tr>
<td>m</td>
<td>Multiplet</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>3-Chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>mg</td>
<td>Milligram(s)</td>
</tr>
<tr>
<td>min</td>
<td>Minute(s)</td>
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<td>mL</td>
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<td>mm</td>
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<tr>
<td>mmol</td>
<td>Millimole(s)</td>
</tr>
<tr>
<td>m.p.</td>
<td>Melting point</td>
</tr>
<tr>
<td>MS</td>
<td>Mass spectrometry</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>Sodium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>Normal butyllithium</td>
</tr>
<tr>
<td>NCS</td>
<td>N-Chlorosuccinimide</td>
</tr>
<tr>
<td>NMO</td>
<td>4-Methylmorpholine N-oxide</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>OTf</td>
<td>Trifluoromethanesulfonate</td>
</tr>
<tr>
<td>PDC</td>
<td>Pyridinium dichromate</td>
</tr>
<tr>
<td>pent</td>
<td>Pentet</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
</tr>
<tr>
<td>q</td>
<td>Quartet</td>
</tr>
<tr>
<td>quat C</td>
<td>Quaternary carbon</td>
</tr>
<tr>
<td>R</td>
<td>Undefined group</td>
</tr>
<tr>
<td>r.t.</td>
<td>Room temperature</td>
</tr>
<tr>
<td>sec</td>
<td>Secondary</td>
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<tr>
<td>sept</td>
<td>Septet</td>
</tr>
<tr>
<td>sex</td>
<td>Sextet</td>
</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetra-n-butylammonium fluoride</td>
</tr>
<tr>
<td>tert</td>
<td>Tertiary</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>TFAA</td>
<td>Trifluoroacetic anhydride</td>
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<td>TFEF</td>
<td>Trifluoroethyl formate</td>
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<td>Thexyl</td>
<td>2,3-Dimethyl-2-butyl</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
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<tr>
<td>TMP</td>
<td>2,2,6,6-Tetramethylpiperidine</td>
</tr>
<tr>
<td>TPAP</td>
<td>Tetrapropylammonium perruthenate</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
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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. 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 \(\text{B}_2\text{H}_6\), \(\text{B}_4\text{H}_{10}\), \(\text{B}_5\text{H}_{11}\) and \(\text{B}_{10}\text{H}_{14}\) 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).
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. 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).

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. 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.

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 $\alpha$-pinene leads to only one possible hydroborated isomer, 3 (Scheme 1.3).

Scheme 1.3: Addition of Borane to an $\alpha$-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](image)

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. 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). 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.

**Scheme 1.5**: 1,2-Metallate Rearrangement of Boron ‘Ate’ Complex

**Scheme 1.6**: Selected Examples of 1,2-Metallate Rearrangement
Introduction

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.). Preparation of chiral compounds with well-defined three-dimensional stereochemistry is called asymmetric synthesis. 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. 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 (Ipc₂BH) achieved a very high level of enantioselection in formation of the corresponding alcohols (4) (Scheme 1.7).

![Scheme 1.7: The First Non-Enzymatic Asymmetric Synthesis](image)

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). Also, the past decade has seen the rapid development of homologation and alkylation 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). 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 LiCHCl₂ 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-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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{28}
Scheme 1.9: Effect of Zinc Chloride Addition on the 1,2-Migration

Alkylation of 18 by Grignard reagent R²MgX 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 \((3S,5S)\)-4-methyl-3-heptanol 25 was synthesised by homologation of boronic ester \((4R,5R)\)-,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](image)
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 (3R,5S)-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, (3S,4R) and (3R,4R), 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), which was previously synthesised with high enantiomeric purity and fully characterised by Midland. 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 commercial production of 38.

1.7.1.3 *(2S,3R,1’R)*-Stegobinone (39) and 1’-Epistegobinone (40)

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 extension 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 (2S,3R,1’R)-Stegobinone](image-url)
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: 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:** 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](image)

1.8 **Aggarwal Methodology (Reagent-Control)**

An alternative route to tertiary alcohols involves the Aggarwal methodology. Aggarwal has utilised 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).
Unfortunately, homologation of these ylides with boronic esters was not successful and gave only low enantioselectivity with borinic esters. 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 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). Also, excellent enantioselectivities were achieved when lithiated chiral secondary benzylic carbamates were homologated with boranes and boronic esters (Scheme 1.19).
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. It has been proposed that in the case of boronic esters, the complexation of oxygen with the lithium of the lithiated carbamate 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, thus, the reaction occurs on the face opposite to the lithium face (Scheme 1.20).

Scheme 1.19: Synthesis of the Chiral Secondary and Tertiary Alcohols via Enantioenriched Lithiated Carbamates
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 \( \text{68 (Scheme 1.21).} \) \(^{46} \) Compound \( \text{63} \) was prepared in four steps from propyne. Reaction of lithiated \( \text{63} \) with chloromethylpinacol boronic ester then led to the formation of compound \( \text{64} \). Reaction of \( \text{64} \) with \( \text{60} \) twice gave \( \text{65} \). Compound \( \text{65} \) was then homologated using vinyllithium in the presence of iodine to give \( \text{66} \) containing the carbon skeleton of the target product. Hydroboration/oxidation followed by oxidation with PDC led to \( \text{68} \).
Scheme 1.21: Synthesis of (+)-Faranal, a) t-BuLi/Et₂O, hexane; CICH₂Bpin; b) 60/Et₂O, –78 °C; c) MgBr₂, 40 °C; d) vinyllithium/THF, –78 °C; e) I₂/MeONa, MeOH/r.t.; f) 9-BBN/THF g) H₂O₂/NaOH; h) PDC/DCM

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

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.
Also, more recently, 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-rearrangement; each homologation step produces a new boronic ester, which is ready for another chain extension (Scheme 1.24).
1.9 Blakemore Methodology (Reagent-Control)

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

\textbf{Scheme 1.24}: Iterative Approach to Assembly-Line Synthesis
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.²²

Scheme 1.26: Application of Blakemore’s Method
### 1.10 Catalytic Conjugate Addition

#### 1.10.1 Shibasaki Methodology

Shibasaki, based on seminal work of Hosomi and Miyaura 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).

\[
\text{R}^1\text{R}^2\text{O} + \text{CuPF}_6\cdot 4\text{MeCN (0.1 eq.)} \xrightarrow{\text{84 (0.12 eq.)}} \text{LiO}t-\text{Bu (2 eq.)} \xrightarrow{\text{i-PrOH, DME, r.t.}} \text{Bpin O} \xrightarrow{16-24 \text{ h}} \text{R}^3 \text{R}^1\text{R}^2
\]

**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).
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Introduction

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

More recently, Ma and Song have used a N-heterocyclic carbene copper(I) complex synthesised in situ from triazolium salt 86 and Cu₂O, 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.\textsuperscript{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.\textsuperscript{70–72} Figure 2.1 shows some of the most common bis(oxazoline) ligands used in stereoselective metal catalysis.\textsuperscript{73}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{ligands.png}
\caption{Bis(oxazoline) ligands used in in stereoselective metal catalysis}
\end{figure}

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, \textit{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.\(^7\)

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.\(^7\)

Jadhav and Man reported the first ever examination of bis(oxazoline)-lanthanide complexes in 1997.\(^3\),\(^4\) 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).

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
R^1 & \quad \text{BX}_2 \\
1) & \quad \text{R}^2\text{Li/ML}^* \\
2) & \quad \text{R}^3\text{M} \\
\text{R}^2 & \quad \text{R}^3 \\
\text{R}^1 & \quad \text{BX}_2 \\
\end{align*}
\]

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

**Scheme 2.3:** The Use of ZnEt₂ and Valinol as Chiral Catalyst
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Studies on a Catalytic Borylation Reaction

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.

\[ \text{Yb(OTf)}_3 \cdot \text{Ligand} + \text{LiCl} \xrightarrow{\text{Selective Reaction}} \]

\[ \text{Yb(OTf)}_3 + \text{LiCl} \cdot \text{Ligand} \xrightarrow{\text{Unselective Reaction}} \]

**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 \((4R,4'R)-2,2'-(Propane-2,2-diyl)bis(4-phenyl-4,5-dihydrooxazole)\)

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 \textit{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).

\[ \text{Scheme 2.5: Synthesis of the bis(amide) } 93 \]

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 \textit{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
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Studies on a Catalytic Borylation Reaction

(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 \((\text{NH}_4)_2\text{MoO}_4\)\(^{78}\). 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 Pinacol 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.

![Chemical Structure of 12-Crown-4 (96)]

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.°¹ 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.°² 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.](image)

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). 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. 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.
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

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp./ °C</th>
<th>% e.e.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–78</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>–46</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>–29</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>–15</td>
<td>49</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>48</td>
</tr>
</tbody>
</table>

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 C₇ proton of compound 89 gives a doublet in the §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 C₇ 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 §H NMR peaks of the endo C₇ proton for each diastereoisomer. The calculations were carried out using the iNMR program (Figure 2.4 shows a typical output from the program).³³ The doublet peaks with the higher chemical shift (1.17 ppm, J = 11 Hz) are for the (1S) diastereoisomer while the low chemical shift’s doublet peaks (1.16 ppm, J = 11 Hz) are for the (1R) diastereoisomer.³¹
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. 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((4S)-(−)-4-isopropyl-oxazoline)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.

**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\(_3\)) \(\delta\) 5.28 (1H, s) and 1.27 (12H, s).

\(^{13}\)C NMR (101 MHz; CDCl\(_3\)) \(\delta\) 85.8 and 24.4.
2.6.2 Synthesis of (S)-Pinanediol (1-Chloropentyl)boronate (89)\textsuperscript{74}

![Image of molecule 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 \(-78 \, ^\circ C\). Dry and cold (\(-78 \, ^\circ C\)) 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. \textsuperscript{1}H NMR (400 MHz; CDCl\textsubscript{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. \(\delta\) 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).

\textsuperscript{13}C NMR (125 MHz; CDCl\textsubscript{3}) \(\delta\) 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)\(^75\)

![Chemical Structure of D-Phenylglycinol (92)](image)

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 40 mL) 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\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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)

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.\textsuperscript{85} 127 – 128 °C).

$^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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)

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.

\[ \text{Cl} \text{Cl} \]
\[ \text{O} \text{O} \]

\[ \text{Cl} \text{Cl} \]
\[ \text{O} \text{O} \]

\[ \Delta \]

\[ \text{H NMR (400 MHz; CDCl}_3\text{)} \delta 1.67 (6H, s). \]

\[ \text{C NMR (101 MHz; CDCl}_3\text{)} \delta 172.1, 69.2 \text{ and } 23.2. \]

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

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.

\[ \text{m.p. 128 – 129 °C.} \]
2.6.4.3 **(−)-2,2′-Isopropylidene bis[(4S)-4-phenyl-2-oxazoline] (90)**

![Chemical Structure](image)

2.6.4.3.1 **Method A**

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/H₂O 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.

<table>
<thead>
<tr>
<th>Physical Property</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[a]$_D^{20}$</td>
<td>+169° (c = 1, EtOH)</td>
<td>(lit. $-171.3°$, c = 1, EtOH, for $S$ enantiomer)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^1$H NMR (400 MHz; CDCl$_3$)</td>
<td>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).</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{13}$C NMR (101 MHz; CDCl$_3$)</td>
<td>δ 170.4, 142.4, 128.7, 127.6, 126.7, 75.6, 69.5, 38.9 and 24.5.</td>
<td></td>
</tr>
</tbody>
</table>

2.6.4.4 **Method B**

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((4S)-(−)-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((4S)-(−)-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. 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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Diagram of transition state (R) showing atomic coordinates.
Chapter Two

Studies on a Catalytic Borylation Reaction

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Imaginary frequency 277 cm\(^{-1}\) (intensity 327).
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### Chapter Two

**Studies on a Catalytic Borylation Reaction**

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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-\textit{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 (\textit{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.\textsuperscript{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).

\begin{scheme}
\begin{equation}
\begin{array}{c}
R^3 \quad R^2 \quad B \\
R^1 \quad \text{step 1} \\
\end{array}
\xrightarrow{?} 
\begin{array}{c}
R^3 \quad R^2 \quad C \quad B' \\
R^1 \quad \text{X} \\
\end{array}
\xrightarrow{R^4 \text{CHXM}} 
\begin{array}{c}
R^3 \quad R^2 \quad C \quad B' \\
R^1 \quad \text{X} \\
\end{array}
\xrightarrow{?} 
\begin{array}{c}
R^3 \quad R^2 \quad C \quad B' \\
R^1 \quad \text{X} \\
\end{array}
\xrightarrow{H_2O_2, OH} 
\begin{array}{c}
R^3 \quad R^2 \quad OH \\
R^1 \quad \text{R^4} \\
\end{array}
\xrightarrow{\text{step 3}} 
\begin{array}{c}
R^3 \quad R^2 \quad B' \\
R^1 \quad \text{X} \\
\end{array}
\end{equation}
\end{scheme}

\textbf{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.

![Diagram](image-url)

### 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

![Diagrams](image-url)

The compound 99 has been synthesised before91 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)](image)

**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).\(^{92-95}\)
These studies showed that metallation of such compounds and then addition to trialkylboranes, followed by addition of HgCl₂, 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 R¹ to R³ as a result of their migratory aptitudes, and the leaving groups have different leaving abilities, the stereochemistry could be controlled.
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.\textsuperscript{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.\textsuperscript{102} The reactions of metallated 2-substituted-1,3-dithiane-1-oxide (107) with electrophiles such as D\textsubscript{2}O and benzophenone also gave high stereoselectivity and very good yields.\textsuperscript{101} Organic chemists have recognised that these compounds are excellent strategic elements for synthesis of natural and unnatural products.
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 Triocetylborane

The title compound was prepared by adapting the procedure used by Aggarwal et al. (1991).\textsuperscript{103} The reaction of the trans-2-lithio-1,3-dithiane-1,3-dioxide with various carbonyl compounds was studied previously.\textsuperscript{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.\textsuperscript{104} The solution of lithiated 104 was prepared according to this procedure and cooled to \(-78 \, ^\circ\text{C}\). 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.\textsuperscript{105,106} The resulting solution was transferred to the cold (\(-78 \, ^\circ\text{C}\)) 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. 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.
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.
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).
**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\(_3\)CN\(^+\)) at \(m/z = 350\) (60%) and (M+Na\(^+\)) at \(m/z = 309\) (47%), consistent with the formulae C\(_{15}\)H\(_{21}\)NNaO\(_3\)S\(_2\) and C\(_{13}\)H\(_{18}\)NaO\(_3\)S\(_2\), 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 \(^1\)H NMR spectrum of the crude product, due to the presence of impurities.

**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-\textit{n}-octylborane was chosen for the reaction and \textit{n}-BuLi was used as a base. Tri-\textit{n}-octylborane was prepared as above. The reaction of tri-\textit{n}-octylborane and 109/\textit{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-\textit{n}-octylborane). An alternative procedure was applied to improve the yield by mixing compound 109 and tri-\textit{n}-octylborane before addition of \textit{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 optimising 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.\textsuperscript{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\%), trioclymethanol (118) (6\%) and 1-octanol (117) (69\% of all octyl groups of tri-\textit{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-\textit{n}-Octylborane Using Three Different Alkyl lithium Bases (1.1 equiv.)

<table>
<thead>
<tr>
<th>Base</th>
<th>Dioctylketone GC yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{n}-BuLi</td>
<td>16</td>
</tr>
<tr>
<td>sec-BuLi</td>
<td>28</td>
</tr>
<tr>
<td>tert-BuLi</td>
<td>12</td>
</tr>
</tbody>
</table>

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 \textit{n}-BuLi (16%). The increase of the yield in the sec-BuLi case compared with \textit{n}-BuLi and tert-BuLi could be due to a number of factors – e.g. the sec-BuLi is stronger than \textit{n}-BuLi meanwhile less bulky than tert-BuLi.

After identifying the best alkyl lithium 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-\textit{n}-Octylborane Using Various Equivalents of sec-BuLi

<table>
<thead>
<tr>
<th>Equivalents of the sec-BuLi</th>
<th>GC Yield of dioctylketone (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>20</td>
</tr>
<tr>
<td>1.1</td>
<td>28</td>
</tr>
<tr>
<td>1.2</td>
<td>31</td>
</tr>
<tr>
<td>1.4</td>
<td>5</td>
</tr>
<tr>
<td>1.8</td>
<td>0</td>
</tr>
</tbody>
</table>
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.

![Image of compound 119](image_url)

### 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 alkylithium reagents through lithium anion 124 to produce (3-(sec-butylsulfinyl)propyl) (methoxymethyl)sulfane 119 (Scheme 3.14).

Scheme 3.14: Reaction of the Alkyl lithium 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 alkylithium 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 1H 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>
<thead>
<tr>
<th>Base</th>
<th>GC Yield of dioctylketone (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDA</td>
<td>20</td>
</tr>
<tr>
<td>LiTMP</td>
<td>12</td>
</tr>
<tr>
<td>LiHDMS</td>
<td>18</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Equivalent of LDA</th>
<th>GC Yield of dioctylketone (%)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>3</td>
<td>Using 5 equiv. of LDA</td>
</tr>
<tr>
<td>1.1</td>
<td>20</td>
<td>At −78 °C</td>
</tr>
<tr>
<td>1.1</td>
<td>30</td>
<td>At 0 °C</td>
</tr>
</tbody>
</table>

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. 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)

![Chemical Structure](image)

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%).

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

\(^1\)H NMR (400 MHz; CDCl\(_3\)) \(\delta\) 7.35 (1H, s, \(\text{CH}=\text{N}\)), 4.41 (2H, s, -\(\text{NCH}_2\text{S}\)), 3.62 (2H, t, \(J = 6.3\) Hz, \(\text{CH}_2\text{N}\)), 2.87 (2H, t, \(J = 6.3\) Hz, \(\text{CH}_2\text{S}\)) and 1.13 (9H, s, 3 \(\times\) \(\text{CH}_3\)).

\(^{13}\)C NMR (125 MHz; CDCl\(_3\)) \(\delta\) 148.5 (CH), 53.7 (quat C), 50.8 (\(\text{CH}_2\)), 50.2 (\(\text{CH}_2\)), 31.0 (\(\text{CH}_3\)) and 30.5 (\(\text{CH}_2\)).
3.3.2 Preparation of 1,3-Dithiane-1-oxide\textsuperscript{111} (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 \textit{title compound} (0.582 g, 85\%) as a colourless solid.

m.p. 85 – 86 °C (lit.\textsuperscript{111} 86 – 87 °C)

\textsuperscript{1}H NMR (400 MHz; CDCl\textsubscript{3}) \(\delta\) 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).

\textsuperscript{13}C NMR (125 MHz; CDCl\textsubscript{3}) \(\delta\) 52.9, 50.4, 28.3 and 27.1.

3.3.3 Preparation of trans-1,3-Dithiane-1,3-dioxide\textsuperscript{103} (104)

To a suspension of 1,3-dithiane (1.20 g, 10 mmol, 1 equiv.) in MeOH/H\textsubscript{2}O (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. \textsuperscript{103} 170 – 171 °C).

\textsuperscript{1}H NMR (500 MHz; d\textsubscript{6}-DMSO) \(\delta\) 4.34 (2H, s), 3.27 – 3.15 (2H, m), 3.02 – 2.91 (2H, m) and 2.66 – 2.15 (2H, m).

\textsuperscript{13}C NMR (125 MHz; d\textsubscript{6}-DMSO) \(\delta\) 61.8, 47.6 and 14.9.

### 3.3.4 Preparation of 2-Chloro-1,3-dithiane-1,3-dioxide\textsuperscript{102} (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. \textsuperscript{102} 141 - 142 °C)

\textsuperscript{1}H NMR (500 MHz; CDCl\textsubscript{3}) \(\delta\) 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).

\textsuperscript{13}C NMR (125 MHz; CDCl\textsubscript{3}) \(\delta\) 75.3, 45.4, 41.4 and 14.5.
3.3.5 Synthesis of 2-Chloro-1,3-dithiane-1-oxide (108)

1,3-Dithiane-1-oxide (136 mg, 1.0 mmol) was placed 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/Et₂O 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.

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

$^1$H NMR (400 MHz; CDCl$_3$) the individual proton signals of the two isomers overlapped considerably and only the signals for the CHCl 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$_4$H$_7$ClOS$_2$ requires M, 169.9627.
3.3.6 Synthesis of 2-Thiophenyl-1,3-dithiane-1-oxide (110)\(^{112}\)

![Diagram of 2-thiophenyl-1,3-dithiane-1-oxide](image)

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\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 133.9 (CH), 132.8 (quat C), 129.5 (CH), 128.8 (CH), 69.2 (CH), 47.3 (CH\(_2\)), 28.7 (CH\(_3\)) and 24.2 (CH\(_2\)).
3.3.7 Synthesis of 2-Methoxy-1,3-dithiane-1-oxide (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 CHCl₃ (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.

ν<sub>max</sub> (neat) 2935, 2907, 2831, 1424, 1084 and 1029 cm<sup>-1</sup>.

<sup>1</sup>H NMR (400 MHz; CDCl₃), 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).

<sup>13</sup>C NMR (100 MHz; CDCl₃) (major isomer): δ 90.1 (CH), 59.5 (CH₃), 45.2 (CH₂), 29.2 (CH₂) and 22.2 (CH₂); (minor isomer): δ 93.2 (CH), 58.7 (CH₃), 42.2 (CH₂), 31.0 (CH₂) and 23.2 (CH₂).

MS (EI) m/z (%) 166 (M<sup>+</sup>, 68%), 135 (5), 106 (100), 90 (98) and 64 (95); HRMS: Found: M<sup>+</sup>, 166.0125. C₅H₁₀O₂S₂ 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 N₂ 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 ¹H 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

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-\textit{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 (\textbf{114}) (64 mg, 50%) as a colourless oil.

\textsuperscript{1}H NMR (500 MHz; CDCl\textsubscript{3}) \(\delta\) 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).

\textsuperscript{13}C NMR (125 MHz; CDCl\textsubscript{3}) \(\delta\) 180.6 (quat C), 34.3 (CH\textsubscript{2}), 31.9 (CH\textsubscript{2}), 29.3 (CH\textsubscript{2}), 29.2 (CH\textsubscript{2}), 29.2 (CH\textsubscript{2}), 24.8 (CH\textsubscript{2}), 22.8 (CH\textsubscript{2}) and 14.2 (CH\textsubscript{3}).
3.3.10 Reaction of 2-Chloro-1,3-dithiane-1,3-dioxide with tri-n-Octylborane Using HgCl₂

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+CH₃CN]⁺, 60%), 309 ([M+Na]⁺, 47%), 263 (28); HRMS: Found (M+Na)⁺, 309.0606. C₁₃H₁₈NaO₃S₂ 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 Triocetylborane

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.\textsuperscript{113} 48.5 – 49 °C)

\textsuperscript{1}H NMR (400 MHz; CDCl\textsubscript{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).

\textsuperscript{13}C NMR (125 MHz; CDCl\textsubscript{3}) δ 211.7 (quat C), 43.0 (CH\textsubscript{2}), 32.0 (CH\textsubscript{2}), 29.5 (CH\textsubscript{2}), 29.5 (CH\textsubscript{2}), 29.3 (CH\textsubscript{2}), 24.1 (CH\textsubscript{2}), 22.8 (CH\textsubscript{2}) and 14.2 (CH\textsubscript{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.
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The solution then was warmed up to 0 °C for 20 min and used in the reaction. LiTMP and LiHDMSe 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

$n$-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 N₂. 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)

![Chemical Structure](image)

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 CHCl₃ (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. $\nu_{\text{max}}$ (neat) 2927, 1550, 1055, 1026 and 727 cm⁻¹.

$^1$H NMR (400 MHz; CDCl₃) $\delta$ 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).
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$^{13}$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$_9$H$_{20}$O$_2$S$_2$ requires M, 224.0905.

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

2-Methoxy-1,3-dithiane-1-oxide (109) (79 mg, 0.48 mmol) was dissolved in dry THF under nitrogen and cooled to $-78 \degree$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.

$\nu_{\text{max.}}$ (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
(CH₂), 23.6 (CH₂), 23.2 (CH₂), 22.7 (CH₂), 12.0 (CH₃), 11.5 (CH₃), 11.0 (CH₃) and 10.9 (CH₃).

EI-MS m/z (%) 224 (M⁺, 3%), 179 (M⁺-OMe, 10), 163 (20), 148 (46), 107 (72); HRMS: Found: M⁺, 224.0899. C₉H₂₀O₂S₂ requires M, 224.0905.

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

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 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 ($\alpha,\alpha$-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,\textsuperscript{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.\textsuperscript{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.\(^\text{116-118}\) Also, the pure enantiomers of the compound became accessible when Satoh reported the resolution of the compound using menthone.\(^\text{118}\) The synthesis of the sulfoxide 135 was carried out according to the procedure of Satoh (Scheme 4.2)\(^\text{119}\) and used in the borylation reaction.

\[
\text{PhSO}_2\text{Cl} \xrightarrow{\text{NCS, } 0^\circ\text{C}} \text{PhSO}_2\text{Cl}
\]

**Scheme 4.2: Synthesis of Compound 135**

Fresh LDA was first prepared by treating a solution of disopropylamine (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 \(-78^\circ\text{C}\). 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 \(-78^\circ\text{C}\). The peroxidic oxidation of the organoborane product and purification of the products by column chromatography afforded the products from two migrations (dioctyl ketone, \(116, \text{Scheme 4.3}\)) 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.\textsuperscript{11}

The \textsuperscript{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, \textsuperscript{1}H NMR, \textsuperscript{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](image)

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 \(-78^\circ\text{C}\) 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).

\[
\begin{array}{c}
\text{R}_3\text{B} \quad \text{O}^+ \quad \text{O}\quad \text{S}^+ \\
\text{CH}_2\text{S}^- \quad \text{S}^- \\
\end{array}
\]

**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 $\alpha$-chlorosulfoxide compounds to 137/141 were synthesised previously by alkylation of anions derived from chloromethyl aryl sulfoxides with alkyl halides (Scheme 4.7). 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 CHCl 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.
Table 4.1: Preparation of 1-chloroalkyl sulfoxides (137/141) according to Scheme 4.2

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>Yield (%)</th>
<th>Diastereoisomer ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>141a</td>
<td>Et</td>
<td>92</td>
<td>78:22</td>
</tr>
<tr>
<td>141b</td>
<td>n-Bu</td>
<td>88</td>
<td>84:16</td>
</tr>
<tr>
<td>137c</td>
<td>n-Oct</td>
<td>61</td>
<td>84:16</td>
</tr>
<tr>
<td>137d</td>
<td>n-Oct</td>
<td>40</td>
<td>82:18&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>141c&lt;sup&gt;e&lt;/sup&gt;</td>
<td>PhCH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>40</td>
<td>81:19</td>
</tr>
<tr>
<td>141d</td>
<td>Cyclopentyl</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>141e</td>
<td>Ph</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined from the <sup>1</sup>H NMR spectrum of the crude product prior to purification. <sup>b</sup> Isolated yield for the mixture of diastereoisomers. <sup>c</sup> Only around 82% of the R<sub>3</sub>B molecules would be (1-Oct)<sub>3</sub>B because the hydroboration gives ca. 6% of 2-octyl groups. <sup>d</sup> 9-Oct-9-BBN (142) was used in this case. <sup>e</sup> The ratio was measured after column chromatography. <sup>f</sup> Only around 40-50% of the R<sub>3</sub>B molecules would be (PhCH<sub>2</sub>CH<sub>2</sub>)<sub>3</sub>B 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-<i>prim</i>-alkylboranes, <i>i.e.</i> 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-<i>prim</i>-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 \( CHCl \) signals for the two isomers of 141a, major and minor, at \( \approx 4.35 \) ppm and \( \approx 4.45 \) ppm respectively. These were then compared with those reported for 1-chloroethyl phenyl sulfoxide (PhS(O)CHCICH\(_3\), 141f, \( R = Me \)) prepared by methylation of 143 (Scheme 4.7).\(^{131}\)

![Scheme 4.7: Synthesis of compound 141 by alkylation of 143\(^{131}\)](image)

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., 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$_2$O, substituted benzaldehydes and Ph$_2$I$^+$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$_2$O 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$_2$O. 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.
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.

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).

![Figure 4.1. X-ray Structure of 145a(i)](image)

The $^1$H NMR spectrum of this compound showed a singlet at 5.66 ppm due to the CHO 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$_2$O$_2$S, C$_{16}$H$_{17}^{37}$Cl$_{35}$ClO$_2$S and C$_{16}$H$_{17}^{35}$Cl$_2$O$_2$S, 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\textsuperscript{116} as a diastereoisomeric mixture and the chemical shifts of CHO\textsubscript{H} 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\textsuperscript{116} by adding benzaldehyde to a solution of the anion 136 (Scheme 4.11) at \(-78^\circ\text{C}\) 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 CHO\textsubscript{H} protons overlapped in the \textsuperscript{1}H NMR spectrum of the crude product).

\begin{center}
\textbf{Scheme 4.11: Preparation of 146 According to Satoh’s Procedure}
\end{center}

The two diastereoisomers were separated by flash column chromatography and their structures were identified by various spectroscopic and spectrometric techniques (IR, \textsuperscript{1}H, \textsuperscript{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\textsubscript{3} was added to the NMR tube containing the second chromatography fraction of 145a and the resulting mixture was checked again by \textsuperscript{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 CHO 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 CHO 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 CHO 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](image)

The two diastereoisomers of 4-nitrobenzoate derivatives (147) were separated by flash column chromatography (1% EtOAc/CHCl₃) and subjected to full analysis using various spectroscopic and spectrometric techniques, including IR, ¹H, ¹³C 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).
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).

**Figure 4.2: X-Ray Structure and Stereochemistry of the Two Diastereoisomers of 147**
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 CHOH protons, which were distinct from each other, in the 1H 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\(_2\)O (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\(_2\)O](image-url)
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

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Yield of specific diastereoisomer (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Total product yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><em>(i)(RRR)</em> <em>(ii)(RSR)</em> <em>(iii)(RSS)</em> <em>(iv)(RRS)</em></td>
<td></td>
</tr>
<tr>
<td>145a</td>
<td>H</td>
<td>23 2.5 18 14</td>
<td>57.5</td>
</tr>
<tr>
<td>145b</td>
<td>3-OMe</td>
<td>18 - 17 17</td>
<td>52</td>
</tr>
<tr>
<td>145c</td>
<td>4-OMe</td>
<td>18 - 10 17</td>
<td>45</td>
</tr>
<tr>
<td>145d</td>
<td>4-Br</td>
<td>10 4 20 14</td>
<td>48</td>
</tr>
<tr>
<td>145e</td>
<td>4-F</td>
<td>22 8 10 10</td>
<td>50</td>
</tr>
</tbody>
</table>

<sup>a</sup> Amount of pure material isolated after chromatography or calculated by proportion of each component in a fraction after chromatography.<br>
<sup>b</sup> 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.<sup>133–135</sup>
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 diastereoisomers 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. 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.
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

<table>
<thead>
<tr>
<th>Transition State</th>
<th>Diastereoisomer</th>
<th>( G^\circ ) (a.u.)</th>
<th>( \Delta E ) (KJ/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS1 (i) (RRR)</td>
<td>-1794.30314</td>
<td>0 (lowest)</td>
<td></td>
</tr>
<tr>
<td>TS2 (iv) (RRS)</td>
<td>-1794.30308</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>TS3 (iii) (RSS)</td>
<td>-1794.29903</td>
<td>10.8</td>
<td></td>
</tr>
<tr>
<td>TS4 (ii) (RSR)</td>
<td>-1794.28524</td>
<td>47.0</td>
<td></td>
</tr>
</tbody>
</table>

It can be seen from the Table 4.3 that the relative energies agree with the experimental results. The lowest transition state in energy (\( \Delta E = 0 \) KJ/mol) was TS1 which was (i) (RRR) (entry 1), while the highest in energy (\( \Delta E = 47 \) 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 (iii). 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 \( \text{Ph}_2\text{I}^+\text{TfO}^-\), acetic anhydride and acetyl chloride.
Initially, Ph₂I⁺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 Ph₂I⁺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.
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 4.16**: Attempts at Reaction of $135$ with Acetic Anhydride and Acetyl Chloride

![Scheme 4.16](image-url)
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.\textsuperscript{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)\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.

![Scheme 4.18: Reaction of Anion Derived from 153 with Triethylborane](image)

The crude mixture was separated by flash column chromatography. The \textsuperscript{1}H NMR spectrum of the major compound isolated showed ethyl group protons, methyl group protons and aromatic protons without the presence of a CHCl proton (which would be required for a compound analogous to 141). Also, the \textsuperscript{13}C NMR spectrum did not show
a CHCl 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 $\text{C}_{10}\text{H}_{12}^{35}\text{Cl}_{2}\text{O}_{2}\text{S} \ (\text{M+NH}_4)^+$. 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)](image)

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.

![Chemical structure of 155](image)

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. 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. 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)

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). 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 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.

\[ \text{Scheme 4.19: Preparation of } N\text{-Methyl-S-(dichloromethyl)-S-phenylsulfoximine (156)} \]

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).

\[ \text{Scheme 4.20: Proposed route to 156 from 135} \]
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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Yields of products (%)(^a)</th>
<th>Description of Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oct(_3)COH</td>
<td>Oct(_2)C=O</td>
</tr>
<tr>
<td>1</td>
<td>39</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>81</td>
<td>11</td>
</tr>
</tbody>
</table>

\(^a\) 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 \textit{in situ} by
hydroboration of the corresponding alkenes. Mixed trialkylboranes were prepared according to a literature procedure\textsuperscript{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

<table>
<thead>
<tr>
<th>Alkyl groups of R₁R₂R₃B</th>
<th>Yields of products (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>161</td>
</tr>
<tr>
<td>Et Et Et</td>
<td>-</td>
</tr>
<tr>
<td>Bu Bu Bu</td>
<td>-</td>
</tr>
<tr>
<td>Oct Oct Oct</td>
<td>12(^c)</td>
</tr>
<tr>
<td>Bu(^d) Bu(^d) c-Hex(^d)</td>
<td>-</td>
</tr>
<tr>
<td>Bu(^d) Bu(^d) c-Pent(^d)</td>
<td>-</td>
</tr>
<tr>
<td>Bu(^e) Bu(^e) Ph(^e)</td>
<td>-</td>
</tr>
<tr>
<td>Me(^f) Bu(^f) Ph(^f)</td>
<td>-</td>
</tr>
<tr>
<td>c-Pent c-Pent c-Pent</td>
<td>-</td>
</tr>
<tr>
<td>Ph Ph Ph</td>
<td>-</td>
</tr>
<tr>
<td>Bu c-Hex c-Hex</td>
<td>-</td>
</tr>
<tr>
<td>Oct Oct Thex</td>
<td>-</td>
</tr>
<tr>
<td>Oct 9-BBN 9-BBN</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\) 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 BCl₃, the corresponding cycloalkene and Et₃SiH, followed by 2 equiv. of n-BuLi. \(^e\) The trialkylborane was prepared in situ from PhBCl₂ and 2 equiv. of n-BuLi. \(^f\) The trialkylborane was prepared in situ from PhBCl₂ then sequential addition of 1 equiv. of n-BuLi and 1-equiv. of MeLi; the product was a mixture of PhBBuMe and PhBBu₂. \(^g\) PhC(OH)Bu₂ (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 N₂. By looking at the ¹H 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](image)

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.
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.\textsuperscript{152}

\begin{center}
\textbf{Scheme 4.24:} Reaction of 165 with THF
\end{center}

To avoid this issue it was decided to replace the THF with DCM and the reaction was repeated. The \textsuperscript{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 \textit{t}-butyl hypochlorite at 0 °C (Scheme 4.25). No reaction occurred and only starting materials were observed in the crude reaction mixture.

\begin{center}
\textbf{Scheme 4.25:} Attempted Chlorination of 165 with \textit{t}-BuOCl
\end{center}
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.

\[ \text{Scheme 4.26: Attempts at Chlorination of 168} \]

4.3 Conclusion

In this chapter, the aim was to assess the reaction of three different kinds of anionic reagents derived from Cl$_2$CHX (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 $\beta$-hydroxyalkyl sulfoxides.
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.

Finally, \( S \)-dichloromethyl-\( N \)-methyl-\( S \)-phenyl-sulfoximine anion \( (X = \text{PhSO(NMe)}) \) 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)

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$_3$) $\delta$ 7.86 – 7.74 (2H, m), 7.68 – 7.51 (3H, m) and 6.17 (1H, s).

$^{13}$C NMR (101 MHz; CDCl$_3$) $\delta$ 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 $\mu$L, 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 $-78 ^\circ$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-octanol (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)

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)

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.

\[ \text{CHCl}_3 \text{SOCl} \]

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.

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\[ \text{O} \quad \text{Cl} \]

\[ 141a \]

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\[ \text{O} \quad \text{Cl} \]

\[ 141a \]

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\[ \text{O} \quad \text{Cl} \]

\[ 141a \]

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\[ \text{O} \quad \text{Cl} \]

\[ 141a \]

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\[ \text{O} \quad \text{Cl} \]

\[ 141a \]

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\[ \text{O} \quad \text{Cl} \]

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\[ \text{O} \quad \text{Cl} \]

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\[ \text{O} \quad \text{Cl} \]

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\[ \text{O} \quad \text{Cl} \]

\[ 141a \]

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.

\[ \text{O} \quad \text{Cl} \]

\[ 141a \]
4.4.3.2 1-Chloropentyl Phenyl Sulfoxide (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$_3$) $\delta$ 7.82 – 7.49 (5H of both isomers, m, aromatic CH), 4.53 (1H of minor isomer, dd, $J = 9.5, 4.1$ Hz, CHCl), 4.40 (1H of major isomer, dd, $J = 9.8, 3.0$ Hz, CHCl), 2.31 – 2.21 (1H of minor isomer, m, one of CH$_2$), 2.26 (1H of major isomer, ddddd, $J = 14.3, 8.6, 5.6, 3.0$ 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): $\delta$ 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: $\delta$ 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 (APCI$^+$) $m/z$ 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)

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.

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

$^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 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, CHCl), 4.40 (1H of major isomer, dd, $J$ = 9.8, 3.0 Hz, CHCl), 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): $\delta$ 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: $\delta$ 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, 15%), 234 (20), 125 (100), 78 (100); HRMS: Found: M$^+$, 286.1159. C$_{15}$H$_{23}$S$_{35}$ClO requires M, 286.1158.
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.

\[ \text{141c} \]

\[ \text{13C NMR (126 MHz; CDCl}_3\text{) (major isomer): } \delta 140.9 \text{ (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\text{) and 31.4 (CH}_2\text{). Selected chemical shifts for the minor isomer: } \delta 139.3 \text{ (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\text{) and 31.9 (CH}_2.\text{]}

MS (El) m/z 278 (M\(^{+}\), \(^{35}\)Cl, 5%), 91 (90); HRMS: Found M\(^{+}\), 278.0533. \(^{13}\)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)

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

The above general procedure was followed, but the reaction was quenched with D$_2$O (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$_3$) $\delta$ 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): $\delta$ 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: $\delta$ 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)

\(m\)-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).
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$^1$H NMR (400 MHz; DMSO) $\delta$ 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) $\delta$ 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.

4.4.9 Synthesis of Pinacol n-Butylboronic Ester (152) $^{114}$

$n$-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 $\text{N}_2$ 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$_3$) $\delta$ 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$_3$) $\delta$ 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 (5 mL) before being warmed to room temperature. The organic layer was separated, the aqueous layer was extracted with dichloromethane (3 × 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

\[ R = \text{a)} \text{H, b)} \text{m-OMe, c)} \text{p-OMe, d)} \text{p-Br, e)} \text{p-F,} \]
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

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**

Colourless Solid (72 mg, 23%)
m.p. = 181-182 °C.

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

$^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 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$_3$) $\delta$ 137.3 (quat C), 136.3 (quat C), 132.9 (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. 

$^{16}$C$_{16}$H$_{17}$Cl$_2$O$_2$S requires M, 343.0326.

**Selected crystallographic data:** $^{16}$C$_{16}$H$_{17}$Cl$_2$O$_2$S, FW = 308.80, T = 296(2) K, $\lambda = 1.54184$ Å, Triclinic, P-1, a = 11.2998(3) Å, b = 11.4679(3) Å, c = 12.4272(3) Å, $\alpha$ = 96.840(2)$^\circ$, $\beta = 92.254(2)^\circ$, $\gamma = 104.801(2)^\circ$, V = 1541.78(7) Å$^3$, Z = 4, $\rho_{\text{calc}} = 1.330$ Mg/m$^3$, crystal size = 0.322 x 0.272 x 0.190 mm$^3$, $\mu = 3.442$ mm$^{-1}$, reflections collected = 25725, Independent reflections = 6107, $R_{\text{int}} = 0.0223$, parameters = 365, $R_1 = 0.0332$, w$R_2 = 0.0847$ for $I>2\sigma(I)$ and $R_1 = 0.0396$, w$R_2 = 0.0888$ for all data.
Fraction 2: Mixture of diastereomer 145a(ii) and compound 146a

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

ν<sub>max</sub> (neat) 3348, 3061, 3005, 2931, 2883, 1610, 1444 and 1047 cm<sup>-1</sup>.

<sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>) δ 7.92 - 7.34 (5H of each compound, m, aromatic CH), 5.50 (1H of by-product, d, J = 2.7 Hz, CHO), 5.20 (1H of aldol product, d, J = 8.7 Hz, CHO), 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<sub>2</sub>), 1.28 (1H of aldol product, dq, J = 14.7, 7.1 Hz, one of CH<sub>2</sub>) and 1.07 (3H of aldol product, app. t, J = 7.2 Hz).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) 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), 8.1 (CH<sub>3</sub>.

MS (APCI<sup>+</sup>) m/z (%) 374 ((M+Na+CH<sub>3</sub>CN)<sup>+</sup>, 37 Cl, 40%), 372 ((M+Na+CH<sub>3</sub>CN)<sup>+</sup>, 35 Cl, 100%), 333 ((M+Na)<sup>+</sup>, 37 Cl, 11%), 331 ((M+Na)<sup>+</sup>, 35 Cl, 53%), 228 (13) HRMS: Found (M+Na)<sup>+</sup>, 331.0519. C<sub>16</sub>H<sub>17</sub>ClNaO<sub>2</sub>S requires M, 331.0535.
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Fraction 3: Mixture of two diastereoisomers 145a(iii) and (iv)

![Chemical structure](image)

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

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

$^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 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, CHO), 5.17 (1H of minor isomer, d, $J = 3.3$ Hz, CHO), 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$_3$) $\delta$ 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$_3$CN)$^+$, $^{37}$Cl, 13%), 372 ((M+Na+CH$_3$CN)$^+$, $^{35}$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$_2$S requires M, 331.0536.
4.4.11.1.1 Synthesis of 4-Nitrobenzoate derivatives of Compound 145a(iii) and 145a(iv)

The mixture of two diastereoisomers 145a(iii) and 145a(iv) (94 mg, 0.3 mmol) was dissolved in THF (10 mL). Triethylamine (93 \( \mu \)L, 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.

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

\(^1\)H NMR (400 MHz; CDCl\(_3\)) \( \delta \) 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\(_3\)) \( \delta \) 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\(_3\)CN\(^+\), \( ^{37}\)Cl, 25%), 521 ((M+Na+CH\(_3\)CN\(^+\), \( ^{35}\)Cl, 100%), 482 ((M+Na\(^+\), \( ^{35}\)Cl, 17%), 480 ((M+Na\(^+\), \( ^{35}\)Cl, 58%); HRMS: Found (M+Na\(^+\), 480.0657. C\(_{23}\)H\(_{20}\(^{35}\)Cl)NaO\(_5\)S requires M, 480.0648.
**Selected crystallographic data:** \( \text{C}_{23}\text{H}_{20}\text{ClNO}_{5}\text{S}, \text{FW} = 457.91, T = 150(2) \text{ K, } \lambda = 1.54184, \) Triclinic, P-1, \( a = 7.3284(2) \text{ Å}, b = 12.4907(3) \text{ Å}, c = 12.9031(4) \text{ Å}, \alpha = 110.993(2)^\circ, \beta = 102.930(2)^\circ, \gamma = 95.432(2)^\circ, V = 1054.73(5) \text{ Å}^3, Z = 2, \rho_{\text{calc.}} = 1.442 \text{ Mg/m}^3, \) crystal size = 0.261 x 0.235 x 0.155 mm\(^3\), \( \mu = 2.841 \text{ mm}^{-1}, \) reflections collected = 16433, Independent reflections = 4150, \( R_{\text{int}} = 0.0187, \) parameters = 281, \( R_1 = 0.0303, \) \( wR_2 = 0.0819 \) for \( I > 2\sigma(I) \) 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. 
\( \nu_{\text{max}} \) (neat) 3053, 2978, 2922, 2854, 1732, 1608, 1442 and 1049 cm\(^{-1}\).
\(^1\text{H} \) NMR (400 MHz; CDCl\(_3\)) \( \delta 8.09 \) (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\(_3\)).
\(^{13}\text{C} \) NMR (101 MHz; CDCl\(_3\)) \( \delta 161.6 \) (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\(_3\)).
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MS (APCI\(^+\)) \(m/z\) 523 ((M+Na+CH\(_3\)CN\(^+\), \(^{37}\)Cl, 10%), 521 ((M+Na+CH\(_3\)CN\(^+\), \(^{35}\)Cl, 26%), 482 ((M+Na\(^+\), \(^{35}\)Cl, 27%), 480 ((M+Na\(^+\), \(^{35}\)Cl, 100%); HRMS: Found (M+Na\(^+\), 480.0627. 

\(\text{C}_{23}\text{H}_{20}\text{ClNaO}_{5}\text{S}\) requires M, 480.0648.

**Selected crystallographic data:** \(\text{C}_{23}\text{H}_{20}\text{ClNaO}_{5}\text{S}\), FW = 457.91, \(T = 293(2)\) K, \(\lambda = 1.54184\), Triclinic, \(P\)-1, \(a = 6.4998(2)\) Å, \(b = 7.7680(3)\) Å, \(c = 22.2674(8)\) Å, \(\alpha = 91.378(3)\)°, \(\beta = 93.748(3)\)°, \(\gamma = 108.174(3)\)°, \(V = 1064.75(7)\) Å\(^3\), \(Z = 2\), \(\rho_{\text{calc}} = 1.428\) Mg/m\(^3\), crystal size = 0.457 x 0.135 x 0.065 mm\(^3\), \(\mu = 2.815\) mm\(^{-1}\), reflections collected = 16565, Independent reflections = 4198, \(R_{\text{int}} = 0.0475\), parameters =282, \(R_1 = 0.0728\), \(wR_2 = 0.2281\) for \(I > 2\sigma(I)\) and \(R_1 = 0.0810\), \(wR_2 = 0.2311\) for all data.
4.4.11.1.2 Reduction of the Benzoate Derivative 147a

The benzoate derivative 147a (27 mg, 0.05 mmol) was dissolved in CHCl₃ (1 mL) and added to a solution of sodium borohydride (10 mg) in a mixture of ethanol and CHCl₃ (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.

4.4.11.2 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:**

![Chemical Structure](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$_3$) $\delta$ 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, $\text{CH}_2$OH), 4.93 (1H, s, exch., $\text{CHO}_2$H), 3.77 (s, 3H, OCH$_3$), 2.98 (dq, $J$ = 15.5, 7.2 Hz, 1H, one of $\text{CH}_2$), 2.03 (dq, $J$ = 15.5, 7.4 Hz, 1H, one of $\text{CH}_2$) and 1.30 (3H, app. t, $J$ = 7.3 Hz, CH$_3$).

$^{13}$C NMR (101 MHz; CDCl$_3$) $\delta$ 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 (APCI$^+$) m/z (%) 341 (MH$^+$, $^{37}$Cl, 35), 339 (MH$^+$ with $^{35}$Cl, 100), 186 (20), 136 (17); HRMS: Found 339.0819. C$_{17}$H$_{20}$ClO$_3$S requires M, 339.0822.

**Fraction 2:**

![Chemical Structure](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$_3$) $\delta$ 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, CHOH), 3.74 (3H, s, OCH₃), 3.45 (1H, s, OH), 2.16 – 2.06 (2H, m, CH₂) and 0.79 (3H, app. t, J = 7.5 Hz, CH₃).

$^{13}$C NMR (101 MHz; CDCl₃) 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 (CH₃), 24.9 (CH₂) and 10.1 (CH₃).

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. C₁₇H₁₉$^{35}$ClNaO₃S requires M, 361.0641.

**Fraction 3:**

Colourless oil (56 mg, 17%).

$\nu$ max. (neat) 3356, 3061, 2937, 2883, 2837, 1599, 1442 and 1037 cm⁻¹.

$^1$H NMR (400 MHz; CDCl₃) 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, CHOH), 3.80 (3H, s, OCH₃), 3.14 (1H, d, J = 4.0 Hz, OH), 1.91 (1H, dq, J = 15.0, 7.4 Hz, one of CH₂), 1.51 (1H, dq, J = 15.0, 7.4 Hz, one of CH₂) and 0.98 (3H, app. t, J = 7.4 Hz, CH₃).

$^{13}$C NMR (101 MHz; CDCl₃) 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 (CH₃), 27.8 (CH₂) and 9.2 (CH₃).

MS (ES⁺) m/z (%) 404 ((M+Na)+, $^{37}$Cl, 35%), 402 ((M+Na+CH₃CN)+, $^{35}$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. C₁₇H₂₀$^{35}$ClO₃S requires M, 339.0822.
4.4.11.1.3 Compound 145c

The general procedure was followed. The reaction of triethylborane and \( p \)-methoxybenzaldehyde (121 \( \mu \)L, 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:**

Colourless Solid (60 mg, 18%).

m.p. = 136 – 138 °C.

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

\(^1\)H NMR (400 MHz; CDCl\(_3\)) \( \delta \) 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, \( CH(OH) \)), 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\(_3\)) \( \delta \) 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\(_3\)).
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MS (ES\(^{+}\)) m/z (\%) 404 ((M+Na+CH\(_{3}\)CN), \(^{37}\)Cl, 30\%), 402 ((M+Na+CH\(_{3}\)CN), \(^{35}\)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\(_{3}\)S, requires M, 361.0641.

Fraction 2:

![Chemical Structure](image)

Colourless oil (42 mg, 12\%).

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

\(^1\)H NMR (400 MHz; CDCl\(_3\)) \(\delta\) 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, CHO\(_{\text{OH}}\)), 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\(_3\)) \(\delta\) 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\(_{3}\)S requires M, 339.0822.

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

![Chemical Structure](image)

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

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

\(^1\)H NMR (400 MHz; CDCl\(_3\)) \(\delta\) 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, CHO\(_{\text{OH}}\)), 5.13 (1H of minor isomer, s, CHO\(_{\text{OH}}\)), 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, CH₂), 1.86 (1H of major isomer, dq, \(J = 15.0, 7.4\) Hz, one of CH₂), 1.51 (1H of major isomer, dq, \(J = 15.0, 7.3\) Hz, one of CH₂), 0.95 (3H of major isomer, app. t, \(J = 7.4\) Hz, CH₃) and 0.86 (3H of minor isomer, app. t, \(J = 7.5\) Hz, CH₃).

\(^{13}\)C NMR (101 MHz, CDCl₃) major isomer: \(\delta 159.9\) (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 (CH₃), 27.6 (CH₂) and 9.3 (CH₃). Minor isomer: \(\delta 160.1\) (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 (CH₃), 24.8 (CH₂) and 10.1 (CH₃). 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. C₁₇H₁₉\(^{35}\)ClNaO₃S requires M, 361.0641.

### 4.4.11.1.4 Compound 145d

![Compound 145d](image)

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.
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Fraction 1:

![Chemical Structure](image)

Colourless Solid (40 mg, 10%).

m.p. = 156 – 158 °C.

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

$^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_{16}$Br$^{35}$Cl$_2$O$^2$S requires M, 420.9431.

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

![Chemical Structures](image)

Colourless oil (30 mg, 8%).

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

$^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 8.03 – 7.38 (9H of each compound, m, aromatic CH), 5.49 (1H of by-product, d, $J = 2.5$ Hz, CHO), 5.15 (1H of aldol product, d, $J = 8.8$ Hz, CHO), 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$_3$).

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\[ \delta 137.34 \text{(quat C)}, 137.29 \text{(quat C)}, 136.65 \text{(quat C)}, 134.72 \text{(quat C)}, 133.56 \text{(CH)}, 132.57 \text{(CH)}, 131.36 \text{(CH)}, 131.23 \text{(CH)}, 130.80 \text{(CH)}, 130.70 \text{(CH)}, 129.06 \text{(CH)}, 128.76 \text{(CH)}, 128.16 \text{(CH)}, 127.23 \text{(CH)}, 122.95 \text{(quat C)}, 121.61 \text{(quat C)}, 93.88 \text{(quat)}, 85.91 \text{(quat C)}, 79.78 \text{(CH)}, 77.64 \text{(CH)}, 25.50 \text{(CH}_2\text{)}, 8.04 \text{(CH}_3\text{)}. \]

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

\[
\text{Ph} S (S) \quad \text{OH} \\
\text{Et} Cl \quad \text{Br} \\
145d(iii) \\
\text{Ph} S (R) \quad \text{OH} \\
\text{Et} Cl \quad \text{Br} \\
145d(iv)
\]

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

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

\[ \delta 7.85 - 7.73 \text{(2H of each isomer, m, aromatic CH)}, 7.63 - 7.43 \text{(5H of each isomer, m, aromatic CH)}, 7.40 \text{(2H of minor isomer, d, } J = 8.5 \text{ Hz)}, 7.33 \text{(2H of major isomer, d, } J = 8.4 \text{ Hz)}, 5.28 \text{(1H of major isomer, d, } J = 3.6 \text{ Hz, CHOH}), 5.08 \text{(1H of minor isomer, d, } J = 3.3 \text{ Hz, CHOH}), 4.09 \text{(1H of minor isomer, d, } J = 3.3 \text{ Hz, OH}), 3.47 \text{(1H of major isomer, d, } J = 3.6 \text{ Hz, OH}), 2.16 - 2.06 \text{(2H of minor isomer, m, CH}_2\text{)}, 1.81 \text{(1H of major isomer, dq, } J = 15.1, 7.4 \text{ Hz, one of CH}_2\text{)}, 1.48 \text{(1H of major isomer, dq, } J = 15.1, 7.3 \text{ Hz, one of CH}_2\text{)}, 0.96 \text{(3H of major isomer, app. t, } J = 7.4 \text{ Hz, CH}_3\text{)}, 0.82 \text{(3H of minor isomer, app. t, } J = 7.5 \text{ Hz, CH}_3\text{).}
\]

\[ \delta 138.4 \text{(quat C)}, 138.1 \text{(quat C)}, 137.0 \text{(quat C)}, 137.0 \text{(quat C)}, 132.6 \text{(CH)}, 132.3 \text{(CH)}, 131.5 \text{(CH)}, 131.1 \text{(CH)}, 130.4 \text{(CH)}, 130.0 \text{(CH)}, 129.0 \text{(CH)}, 128.8 \text{(CH)}, 127.4 \text{(CH)}, 127.2 \text{(CH)}, 123.1 \text{(quat C)}, 122.9 \text{(quat C)}, 93.0 \text{(quat C)}, 89.4 \text{(quat C)}, 77.4 \text{(CH)}, 74.7 \text{(CH)}, 27.8 \text{(CH}_2\text{)}, 24.8 \text{(CH}_2\text{)}, 10.0 \text{(CH}_3\text{)} \text{ and } 9.3 \text{(CH}_3\text{).}
\]
MS (ES\textsuperscript{−}) m/z (%) 425 ((M+Cl)\textsuperscript{−}, \textsuperscript{81}Br\textsuperscript{35}Cl\textsuperscript{37}Cl and \textsuperscript{79}Br\textsuperscript{37}Cl\textsuperscript{2} combined, 13%), 423 ((M+Cl)\textsuperscript{−}, \textsuperscript{81}Br\textsuperscript{35}Cl\textsuperscript{2} and \textsuperscript{79}Br\textsuperscript{37}Cl\textsuperscript{35}Cl combined, 46%), 421 ((M+Cl)\textsuperscript{−}, \textsuperscript{79}Br\textsuperscript{35}Cl\textsuperscript{2}, 26%), 299 (100), 255 (62); HRMS: Found (M+Cl)\textsuperscript{−}, 420.9423. C\textsubscript{16}H\textsubscript{16}\textsuperscript{79}Br\textsuperscript{35}Cl\textsuperscript{2}O\textsubscript{2}S requires M, 420.9431.

4.4.11.5 Compound 145\textsubscript{e}

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

Fraction 1

Colourless Solid (70 mg, 22%).
m.p. = 102 – 104 °C.
ν\textsubscript{max.} (neat) 3321, 3065, 2972, 2924, 2852, 1602, 1442 and 1053 cm\textsuperscript{−1}.
\textsuperscript{1}H NMR (400 MHz; CDCl\textsubscript{3}) \textdelta 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, CHO\textsubscript{OH}), 4.94 (1H, s, OH), 2.99 (1H, dq, J = 15.5, 7.2 Hz, one of CH\textsubscript{2}), 1.95 (1H, dq, J = 15.5, 7.3 Hz, one of CH\textsubscript{2}) and 1.30 (3H, app. t, J = 7.3 Hz, CH\textsubscript{3}).
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$^{13}$C NMR (101 MHz; CDCl$_3$) $\delta$ 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 (APCI$^+$) m/z (%) 392 ((M+Na+CH$_3$CN)$^+$, $^{37}$Cl, 33%), 390 (M+Na+CH$_3$CN)$^+$, $^{35}$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}$ClFO$_2$S requires M, 327.0622.

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

Colourless oil (56 mg, 17%).

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

$^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 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, CHO), 5.18 (1H of aldol product, d, $J = 8.6$ Hz, CHO), 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: $\delta$ 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, qua C), 132.5 (CH), 131.5 (d, $J = 3.1$ Hz, qua 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 (APCI$^+$) m/z (%) 392 (M+Na+CH$_3$CN)$^+$, $^{37}$Cl, 33%), 390 ((M+Na+CH$_3$CN)$^+$, $^{35}$Cl, 100%), 329 (MH$^+$, $^{37}$Cl, 8%), 327 (MH$^+$, $^{35}$Cl, 23%), 349 (35), 390 (100), 261 (25); HRMS: Found MH$^+$, 327.0638. C$_{16}$H$_{17}$$^{35}$ClFO$_2$S requires M, 327.0622.
Fraction 3: Mixture of two diastereoisomers 145e(iii) and 145e(iv)

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

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

$^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 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, CHO$_2$), 5.21 (1H of major isomer, d, $J$ = 3.2 Hz, CHO$_2$), 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$_3$) $\delta$ 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 (APCI$^+$) $m/z$ (%) 392 ([(M+Na+CH$_3$CN)$^+$, $^{37}$Cl, 33%), 390 ((M+Na+CH$_3$CN)$^+$, $^{35}$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$_2$S requires M, 349.0441.
4.4.12 Synthesis of 2,2-dichloro-1-phenyl-2-(phenylsulfinyl)-1-ethanol (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 x 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/CHCl₃).

**The first diastereoisomer:** R<sub>f</sub> = 0.25 (4% EtOAc/CHCl₃), colourless solid (75 mg, 48%).

m.p. 186 – 188 °C.

ν<sub>max</sub> (neat) 3342, 3061, 3011, 1444, 1080 and 1051 cm<sup>-1</sup>.

<sup>1</sup>H NMR (400 MHz; CDCl₃) δ 7.89 – 7.81 (2H, m, aromatic CH), 7.69 – 7.52 (5H, m, aromatic CH), 7.42 (3H, dd, <i>J</i> = 6.4, 3.7 Hz, aromatic CH), 5.49 (1H, d, <i>J</i> = 2.4 Hz, CHO<sub>H</sub>) and 4.12 (1H, dd, <i>J</i> = 16.5, 4.9 Hz, OH).

<sup>13</sup>C NMR (101 MHz; CDCl₃) δ 137.5, 135.7, 133.4, 129.6, 129.2, 128.7, 128.2, 128.2, 102.1 and 80.2.

MS (APCI⁺) m/z (%) 382 ((M+Na+CH₃CN)<sup>+</sup>, <sup>37</sup>Cl₂, 1%), 380 ((M+Na+CH₃CN)<sup>+</sup>, <sup>35</sup>Cl<sup>37</sup>Cl, 9%), 378 ((M+Na+CH₃CN)<sup>+</sup>, <sup>35</sup>Cl<sub>2</sub>, 12%), 319 (MH<sup>+</sup>, <sup>37</sup>Cl<sup>37</sup>Cl, 3%), 315 (MH<sup>+</sup>, <sup>35</sup>Cl<sub>2</sub>, 29%), 317 (MH<sup>+</sup>, <sup>37</sup>Cl<sup>35</sup>Cl, 20%), 315 (MH<sup>+</sup>, <sup>35</sup>Cl<sub>2</sub>, 29%), 198 (100), 157 (23); HRMS: Found MH<sup>+</sup>, 315.0004. requires M, C<sub>14</sub>H<sub>12</sub><sup>35</sup>Cl<sub>2</sub>O<sub>2</sub>S: 315.0013.

**The second diastereoisomer:** R<sub>f</sub> = 0.22 (4% EtOAc/CHCl₃), colourless solid (66 mg, 32%).

m.p 193 – 194 °C.

ν<sub>max</sub> (neat) 3244, 1442 and 1043 cm<sup>-1</sup>.  

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**Chapter Four: Stoichiometric Studies on Dichloromethyl Sulfur Compounds ...**
1H NMR (400 MHz; CDCl₃) 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, CHOHH) and 4.08 (1H, d, J = 5.4 Hz, OH).

13C NMR (101 MHz; CDCl₃) δ 137.5, 136.1, 133.1, 129.3, 129.2, 128.6, 128.4, 128.1, 102.4 and 77.5.

MS (APCI⁺) m/z (%) 382 ((M+Na+CH₃CN)⁺, 36Cl₂, 5%), 380 ((M+Na+CH₃CN)⁺, 35Cl³Cl, 20%), 378 ((M+Na+CH₃CN)⁺, 35Cl₂, 31%), 319 (MH⁺, 37Cl₂, 4%), 317 (MH⁺, 35Cl³Cl, 17%), 315 (MH⁺, 35Cl₂, 24%), 198 (100), 157 (29); HRMS: Found MH⁺, 315.0016. C₁₄H₁₂³5Cl₂O₂S requires M, 315.0013.

4.4.13 Synthesis of Dichloromethyl-p-Tolyl Sulfone (153)

\[
\text{SO}_2\text{Cl} \quad \text{Cl} \\
\text{153}
\]

*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. 89.5 – 90 °C).

1H NMR (400 MHz; CDCl₃) 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).

13C NMR (101 MHz; CDCl₃) 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.

\( \nu_{\text{max.}} \) (NaCl film) 3069, 2986, 2943, 2883, 1595, 1455, 1334, 1156 and 1076 cm\(^{-1}\).
$^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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 (APCI+) $m/z$ (%) 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$_{12}$Cl$_2$O$_2$S requires M, 284.0273.

Selected crystallographic data: C$_{10}$H$_{12}$Cl$_2$O$_2$S, FW = 267.1, $T$ = 296(2) K. $\lambda$ = 1.54184, Monoclinic, P21/n, a = 10.8436(3) Å, b = 17.6380(3) Å, c = 13.1040(3) Å, $\alpha$ = 90°, $\beta$ = 102.560(2)°, $\gamma$ = 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$^3$, $\mu$ = 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 $I>2\sigma(I)$ and $R_1$ = 0.0418, $wR_2$ = 0.0994 for all data.
4.4.14.3 1,1-Dichloro-1-tosyl pentane 155

![Chemical Structure](image)

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

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

$^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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 (APCI$^+$) 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}$Cl$_2$O$_2$S requires M, 312.0586.

4.4.15 Synthesis of S-Methyl-S-phenylsulfoximine(157)$^{146}$

![Chemical Structure](image)

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$_3$) $\delta$ 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$_3$) $\delta$ 143.6, 133.2, 129.4, 127.8 and 46.3.

**4.4.16 Synthesis of N,S-Dimethyl-S-phenylsulfoximine (158)$^{154}$**

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$_3$) $\delta$ 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$_3$) $\delta$ 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)$^{145}$**
4.4.17.1 Preparation of t-Butyl Hypochlorite (BHC)\textsuperscript{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).

\textbf{N-Methyl-S-(chloromethyl)-S-phenylsulfoximine:} colourless oil (145 mg, 72%), \textit{Rf}: 0.2 (5:1, petroleum ether/diethyl ether).

\textsuperscript{1}H NMR (400 MHz; CDCl\textsubscript{3}) \(\delta\) 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).

\textsuperscript{13}C NMR (101 MHz; CDCl\textsubscript{3}) \(\delta\) 135.2, 134.1, 130.2, 129.6, 57.9 and 29.7.

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

\textsuperscript{1}H NMR (400 MHz; CDCl\textsubscript{3}) \(\delta\) 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).

\textsuperscript{13}C NMR (101 MHz; CDCl\textsubscript{3}) \(\delta\) 134.2, 135.6, 130.5, 128.9, 80.6 and 29.7.

MS (ES\textsuperscript{*}) \(m/z\) (%) 242 (MH\textsuperscript{+}, \textsuperscript{37}Cl\textsubscript{2}, 7%), 240 (MH\textsuperscript{+}, \textsuperscript{37}Cl\textsuperscript{35}Cl, 32%), 238 (MH\textsuperscript{+}, \textsuperscript{35}Cl\textsubscript{2}, 38%); HRMS: Found MH\textsuperscript{+}, 237.9851. \textit{C}_{8}\textit{H}_{10}\textit{Cl}_{2}\textit{NOS} 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 $\mu$L, 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 $\mu$L, 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 $\mu$L, 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

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

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.
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.

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 Thexyldioctylborane³

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 1 h 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$_3$) $\delta$ 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$_3$) $\delta$ 74.8, 30.5 and 7.8.

4.4.19.2 5-Butynonan-5-ol

Colourless oil (81% GC yield), $^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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).
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$^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 1.50 – 1.03 (43H, m), and 0.88 (9H, t, $J$ = 6.9 Hz).

$^{13}$C NMR (126 MHz; CDCl$_3$) $\delta$ 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

![Chemical structure of 5-Cyclohexyl-5-nonanol](image)

Colourless oil (83 mg, 73%).

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

$^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_2$O, 17%), 151 (38), 109 (72), 69 (94); HRMS: Found (M$^+$ – H$_2$O), 208.2196. C$_{15}$H$_{28}$ requires M, 208.2191.

### 4.4.19.5 5-Phenyl-5-nonanol$^{156}$

![Chemical structure of 5-Phenyl-5-nonanol](image)

Colourless oil (56 mg, 51%).

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

$^1$H NMR (400 MHz; CDCl$_3$) $\delta$ 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).

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13C NMR (101 MHz; CDCl3) δ 146.6 (quat C), 128.1 (CH), 126.3 (CH), 125.4 (CH), 77.1 (quat C), 42.9 (CH2), 25.7 (CH2), 23.2 (CH2) and 14.2 (CH3).
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. C15H23 requires M, 203.1800.

4.4.19.6 2-Phenyl-2-hexan-2-ol157

 Colourless oil (27 mg, 30%).

1H NMR (400 MHz; CDCl3) 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).

13C NMR (101 MHz; CDCl3) δ 148.2 (quat C), 128.2 (CH), 126.5 (CH), 124.9 (CH), 74.8 (quat C), 44.2 (CH2), 30.2 (CH3), 26.2 (CH2), 23.1 (CH2) and 14.1 (CH3).

4.4.19.7 5-Cyclopentyl-nonan-5-ol

 Colourless oil (72 mg, 68%)

νmax. (neat) 3485, 2953, 2931, 2864 and 1456 cm⁻¹.

1H NMR (400 MHz; CDCl3) 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).
13C NMR (101 MHz; CDCl₃) δ 75.3 (quat C), 47.6 (CH), 37.5 (CH₂), 26.2 (CH₂), 26.0 (CH₂), 25.8 (CH₂), 23.6 (CH₂) and 14.3 (CH₃).

MS (EI-MS) m/z (%): molecular ion not seen; 194 (M⁺ – H₂O, 28%), 137 (35), 95 (76); HRMS: Found (M⁺ – H₂O), 194.2035. C₁₅H₂₈ requires M, 194.2035.

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

![](image)

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)

¹H NMR (400 MHz; CDCl₃) 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).

¹³C NMR (100 MHz; CDCl₃) 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)\textsuperscript{150}

![Diagram of 167](image)

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\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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)\textsuperscript{152}

![Diagram of 166](image)

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 \textit{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\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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)
### Imaginary frequency 151 cm\(^{-1}\) (intensity 138)

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

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Chapter Four: Stoichiometric Studies on Dichloromethyl Sulfur Compounds

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

4.5.1.3 Transition State 3 (TS3) Leading to Compound 145a(iii)
Chapter Four: Stoichiometric Studies on Dichloromethyl Sulfur Compounds...

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

**Stoichiometric Studies on Sulfur Compounds in a DCME-Like Reaction**: The study of the reaction of trialkylboranes with Cl₂CHX (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
References
6.1 References


(84) The calculations were carried out by Dr. Mark Elliott.


(87) Spartan ’10, Wavefunction Inc., Irvine, CA, USA.


