Synthesis and Reactivity of Silylmethylcyclopropanes

Submitted by

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to the University of London as a thesis for the degree of Doctor of Philosophy in Chemistry

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Declaration

The research described in this thesis is, to the best of my knowledge, original, except where due reference is made to other authors and has not been submitted in any part or form for a degree at this or any other university.

Signed_______________________________

Jonathan Dunn

Abstract

Substituted tetrahydrofurans (THFs) are common structural motifs found in natural products. The biological activity and structural complexity of these compounds makes their efficient construction with controlled regio- and stereochemistry a significant challenge in organic synthesis. This thesis is concerned with investigating the use of silylmethylcyclopropanes as precursors for the efficient and practical synthesis of tetrahydrofurans.

The first chapter consists of a review of the relevant literature comprising of four sections. The first section is a brief review of the current methods for the synthesis of tetrahydrofurans with discussions of the advantages and disadvantages of these methods. Next, the concept of donor-acceptor cyclopropanes is introduced and examples of how they have been employed in tetrahydrofuran synthesis are given. The third section outlines the uses of silicon in organic synthesis with particular reference to the physical and electronic influences of silicon on organic molecules. Finally, the chapter concludes with an overview of the application of Lewis acid promoted cycloadditon reactions of allylsilanes and silymethylcyclopropanes to the preparation of tetrahydrofurans.

The second chapter discusses the preparation and purification of unsubstituted silylmethylcyclopropanes outlining various conditions tried and the array of different substituents that may be attached to the silicon. The successful Lewis acid promoted [3+2] cycloaddition reaction of various silylmethylcyclopropanes with α-keto-aldehydes is presented, together with a detailed account of the screening studies of different Lewis acids and aldehydes, and optimisation of reaction conditions. The advantages of having a ketone functionality in the final compound are practically demonstrated by way of several synthetic modifications to produce a range of chemically diverse compounds containing the tetrahydrofuran substructure. The third chapter presents the synthesis of substituted silylmethylcyclopropanes and their attempted cyclisations using the conditions previously developed for unsubstituted silylmethylcyclopropanes.

Following attempts to use Lewis acid-activated aldehydes in [3+2] cycloaddition reactions, and the consequent disadvantage of randomly trialling Lewis acids, chapter four presents our

investigations into the use of NMR spectroscopy as a probe to establish a relative quantitative scale of carbonyl activation with different Lewis acids. Our studies into this method are presented along with the NMR data of several carbonyl-based Lewis bases complexed to the Lewis acids that proved successful in the cycloaddition reactions.

Chapter five provides detailed experimental procedures and characterisation data for the compounds described within this thesis.

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Abbreviations

Ac	Acetyl
Acc	Acceptor group
AIBN	2,2'-Azo*bis*isobutyronitrile
App	Apparent
Aq	Aqueous
Ar	Aromatic
ATP	Adenosine triphosphate
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Br	Broad
Bz	Benzoyl
^{i}Bu	iso-butyl
Cat.	Catalytic
CI	Chemical Ionisation
COSY	Correlation Spectroscopy
CSA	Camphorsulfonic acid
d	Doublet
DCE	1,2-Dichloroethane
de	Diastereomeric excess
DEPT	Distortionless enhancement by polarisation transfer
DET	Diethyl tartrate
DIBAL-H	Diisobutylaluminium Hydride
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	N,N-Dimethylformamide
DMIPS	Dimethylisopropylsilyl
DMPS	Dimethylphenylsilyl
DN	Donor-acceptor number
Don	Donor group
dr	Diastereomeric ratio
DTBB	4,4'-di-*tert*-butylbiphenyl
DTBMS	Di-*tert*-butylmethylsilyl
EDTA	Ethylenediaminetetraacetic acid
ee	Enantiomeric excess

EI	Electron Ionisation
eq.	Equivalent
er	Enantiomeric ratio
ES	Electrospray
FMO	Frontier molecular orbital
GCMS	Gas Chromatography Mass Spectrometry
h	hours
HOMO	Highest occupied molecular orbital
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
HSAB	Hard Soft Acid Base
HWE	Horner-Wadsworth-Emmons
Im	Imidazole
LA	Lewis Acid
LCMS	Liquid Chromatography Mass Spectrometry
LDA	Lithium diisopropylamine
LG	Leaving Group
LHMDS	Lithium hexamethyldisilazide
LRMS	Low Resolution Mass Spectrometry
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
m-CPBA	*meta*-Chloroperoxybenzoic acid
MDIPS	Methyldiisopropylsilyl
MDPS	Methyldiphenylsilyl
Mes	Mesityl (2,4,6-trimethylphenyl)
m/z	Mass to charge ratio
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser effect
NOSEY	Nuclear Overhauser Enhancement Spectroscopy
Nu	Nucleophile
PDC	Pyridinium dichromate
Pg	Protecting group
ppm	Part per million
^{i}Pr	iso-Propyl
q	Quartet
rt	Room Temperature
s	Singlet

t	Triplet
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TDS	Thexyldimethylsilyl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
TMU	*N,N,N’,N’*-Tetramethylurea
Ts	*p*-Toluenesulfonyl
p-TSA	*para*-toluenesulphonic acid
UV	Ultra Violet
v	Frequency
Wt	Weight

Chapter One

1.0 Introduction

The aim of this project was to investigate the synthesis and development of silylmethylcyclopropanes as small organic building blocks, capable of acting as the three-atom component in cycloaddition reactions for the efficient and practical construction of substituted tetrahydrofurans. It was proposed that the two-atom component for the cyclisation would be an aldehyde or ketone activated by a Lewis acid allowing the methodology to be applicable to an array of simple and complex molecules. It would therefore be of value to first review the background to some of the important elements of this work.

After providing a brief review of the current methods for the synthesis of tetrahydrofurans with particular emphasis on cycloaddition reactions, the application of silicon in organic synthesis will be examined. Finally, an overview of Lewis acid promoted cycloaddition reactions of allylsilanes and silylmethylcyclopropanes for the preparation of tetrahydrofurans is discussed. The background and concept of Lewis acids to promote organic reactions is presented later in the thesis (Chapter 4).

1.1 Tetrahydrofurans

Tetrahydrofurans (THFs) consist of a saturated 5-membered ring containing a single etherate oxygen atom. The tetrahydrofuran ring can have different substituents at all four carbon atoms allowing THFs to have a diverse range of chemical and structural variations (Fig. 1.1). The tetrahydrofuran motif is commonly found in an array of biologically active natural products such as polyether antibiotics, *C*-glycosides and acetogenins (Fig. 1.3).[1,2] Although 5-memebered sugars (such as ribose) are covered by the chemical descriptor of a THF, the presence of the hemiacetal and hydroxyl groups makes the chemistry of sugars notably different from THFs containing carbon substituents. This work is interested in carbon substituted THFs and sugars will not be discussed further.

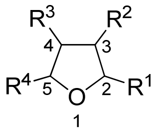
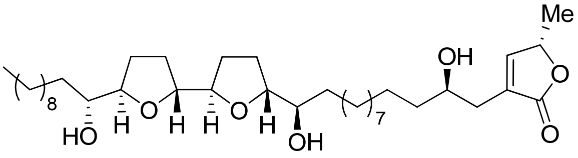


Fig. 1.1 A possible substitution pattern of the tetrahydrofuran motif

1.2 Tetrahydrofurans in Nature

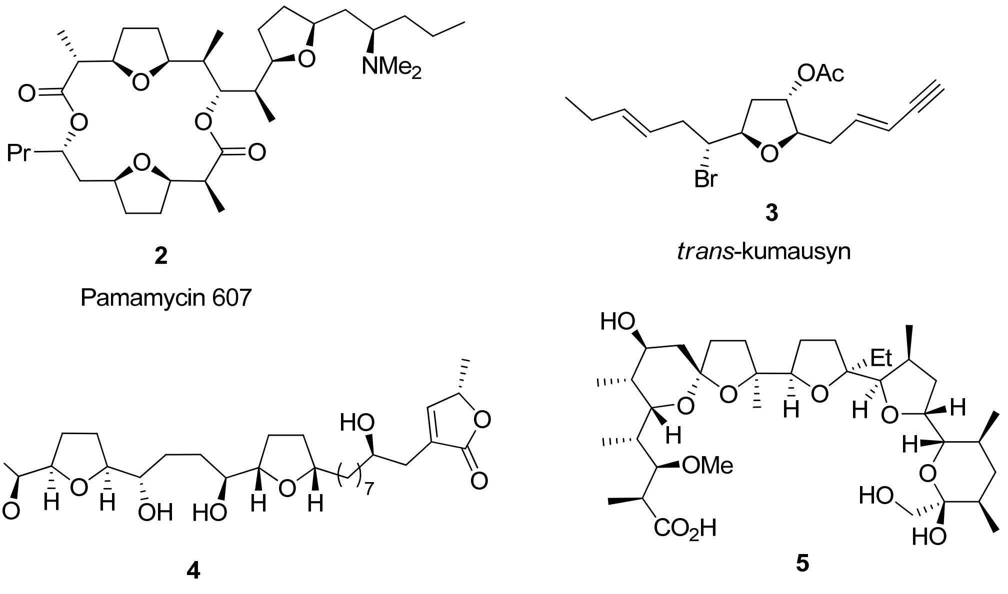
Numerous tetrahydrofuran-containing therapeutic agents possess a varied range of biological activities including antitumour, anthelmintic, antimalarial and antimicrobial activity. One such example of a biologically active molecule is the annonaceous acetogenin, asimicin **1** (Fig. 1.2). Asimicin is a plant metabolite derived from the plant family *Annonaceae* which, along with other members of this family of compounds, shows high cytoxicity. The cytoxicity of these compounds occurs by inhibition of mitochondrial respiratory complex 1, which ultimately results in ATP depletion.[3]



1

Fig. 1.2 Asimicin

In 1979, the bioactive marodiolide Pamamycin 607 was first isolated and classified as a new family type antibiotic active against Gram-positive bacteria, Mycobacteria and Neurospora (Fig. 1.3).[4]



2
Pamamycin 607

3
trans-kumausyn

4
(+)-*cis*-sylvaticin

5
Monensin

Fig. 1.3 Examples of natural products containing single and multiple THF rings; pamamycin 607, Kumausyn, sylvaticin and monensin

Monensin **5** is an ionophore polyether antibiotic produced by a strain of *Streptomyces cinnamonensis*, and exhibits broad-spectrum anticoccoidial activity.[5] Polyether antibiotics generally consist of carbon, hydrogen and oxygen atoms and are distinguished by the terminal carboxylic acid and high density of 5- and 6-membered cyclic ether rings. It is this arrangement of the cyclic ether rings that allows the molecule to complex to metal cations through the Lewis basic oxygen atoms forming a pseudomacrocyclic complex with a hydrophobic exterior around the ion. Monesin's biological activity arises from its ability to transport monovalent and divalent metal ions across lipid membranes by means of the pseudomacrocyclic complex.[6]

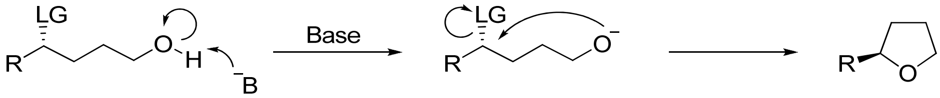
1.3 Synthesis of Substituted Tetrahydrofurans

Owing to the regularity in which the tetrahydrofuran substructure appears in nature and the medicinal potential that many of these compounds show, considerable effort has been devoted towards their synthesis. Presented herein is a short overview of methods that have been used for the stereoselective synthesis of substituted tetrahydrofurans.[7,8,9]

Due to the sheer number of strategies reported, many of the methodologies, particularly those that have been used to synthesise the C-C bond of the tetrahydrofuran ring, such as radical bond formation,[10] olefin metathesis[11] and transition metal catalysed C-C bond forming reactions, have not been included (reviews have recently been published by Wolfe *et al.*[12] and Jalce *et al.*[13]). The following discussion will focus mainly on methods of constructing the tetrahydrofuran ring where the ring closing reaction is the formation of the C-O bond. Tetrahydrofuran synthesis using silicon containing compounds will be discussed in section 1.6.

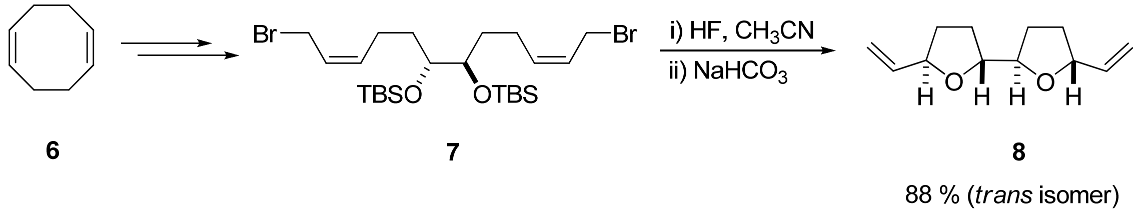
1.3.1 Ether bond formation *via* oxygen nucleophiles

Classical methods for tetrahydrofuran formation use a nucleophilic substitution reaction between an alcohol and a good leaving group as a means to construct the cyclic ether C-O bond (Scheme 1.1). The advantage of performing the nucleophilic substitution intramolecularly is that the chemical outcome is partially controlled by the internal conformational restrictions within the molecule during the transition state. This, along with the orbital requirements of an S_N2-type transition state, insures that a high degree of stereochemical control is achieved.



Scheme 1.1

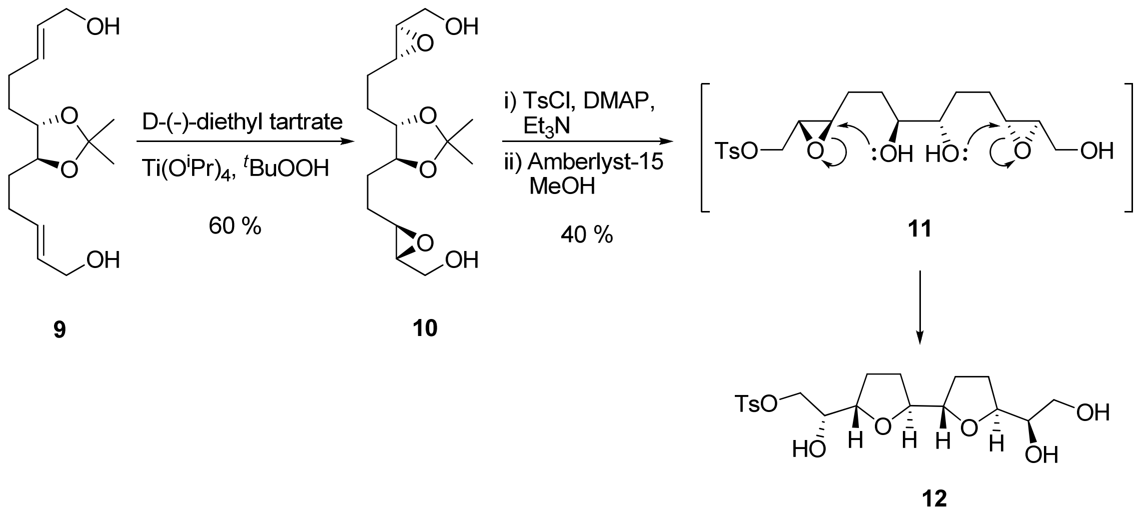
Generally, routes using this methodology involve the stereospecific incorporation and protection of a hydroxyl group followed by inclusion of the desired leaving group. Upon deprotection of the hydroxyl group and under basic conditions the tetrahydrofuran is produced. This strategy is elegantly exemplified by Zhao's double cyclisation to generate the symmetrical vinyl oligo-tetrahydrofuran **8** with 13:1 diastereoselectivity in an 88% isolated yield (Scheme 1.2).[14] The authors propose that the *Z*-olefin produces a higher diastereoselectivity than the *E*-olefin because of hydrogen bonding between the two hydroxyl groups during the transition state.



Scheme 1.2

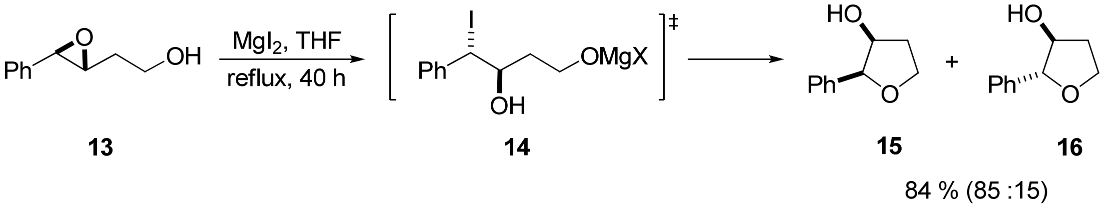
The use of simultaneous ring closure and epoxide opening reactions have been observed to yield substituted tetrahydrofurans with a high degree of stereochemical control. The stereospecific outcome from the epoxide opening reaction produces the *trans* isomer. With careful planning the alcohol and epoxide can both be formed with the correct enantioselectivity so that, upon epoxide opening, one enantiomer is produced in excess. Although the concept was first used by Kishi *et al.* for the synthesis of isolasalocid A,[15] it was the development of the Sharpless asymmetric epoxidation[16] that led to a renewed interest in this method.

In Hoye's synthesis of the *bis*-tetrahydrofuran unit of haxepi-uvaricine,[17] a double Sharpless asymmetric epoxidation is used to facilitate the enantioselective formation of two epoxides. On deprotection of the 1,2-diol, *exo*-mode of attack on the epoxides occurs to afford the double cyclisation product (Scheme 1.3).



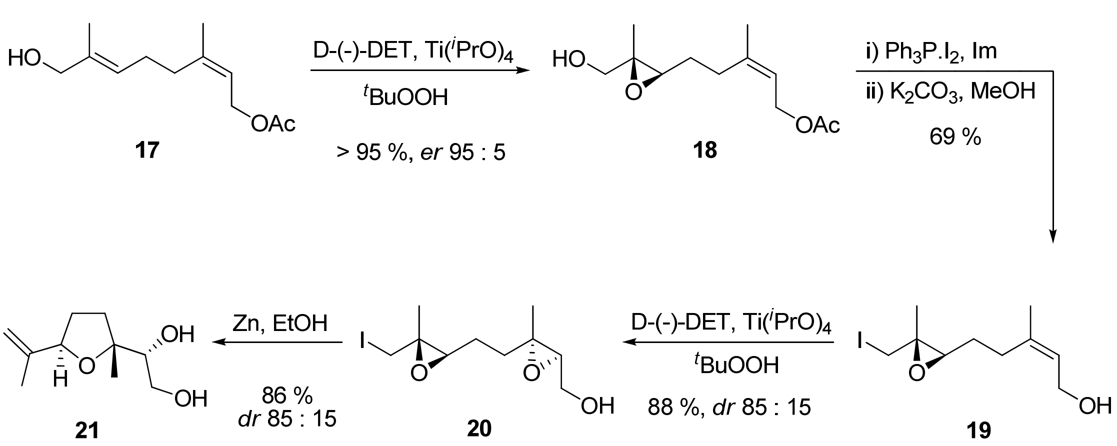
Scheme 1.3

In the majority of intramolecular cycloetherification reactions of epoxides, the *exo*-cyclisation is favoured over the *endo*-cyclisation pathway as the former has better orbital overlap in the transition state.[18] Karikomi has described a procedure that increases the regioselectivity for a 5-*exo*-cyclisation over the 4-*exo*-cyclisation by addition of a magnesium halide. The magnesium halide initially opens the epoxide to form the halohydrin which undergoes a intramolecular nucleophilic substitution reaction with the free hydroxide. The group have taken 4-phenyl-3,4-epoxybutanol and catalytic amounts of magnesium iodide in either THF or diethyl ether, and after 40 hours at reflux, prepared the 2-phenyl-3-hydroxyl tetrahydrofuran in a combined yield of 84 % and a diastereomeric ratio of 85:15 (Scheme 1.4).[19]



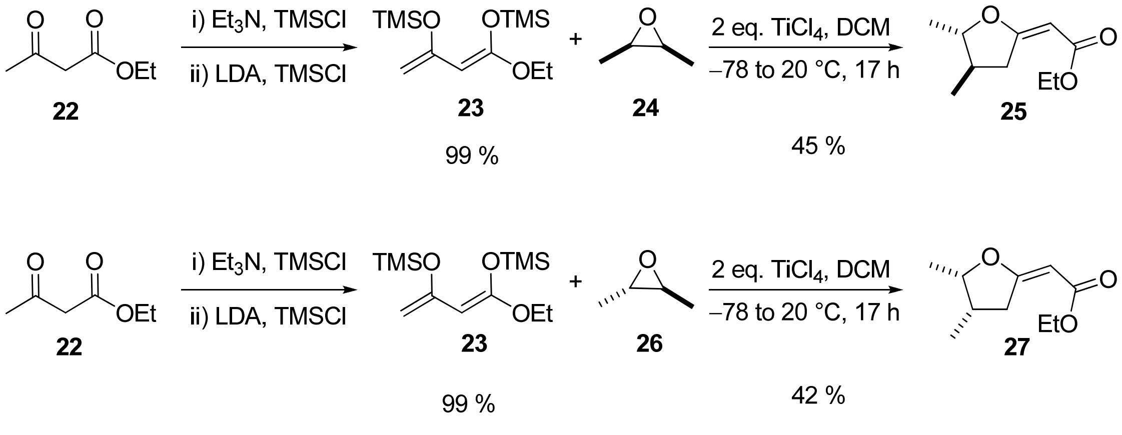
Scheme 1.4

There are a number of examples of oxygen containing functional groups other than hydroxyl groups acting as nucleophiles. Marshall *et al.* have employed epoxides as nucleophilic agents in the synthesis of 2-vinyl-5-(1-hydroxyethyl)-substituted tetrahydrofurans from 1-iodomethyl-1,5-*bis*-epoxides. The treatment of the *bis*-epoxide **20** with metallic zinc in refluxing ethanol furnishes tetrahydrofuran **21** in high yield as a 85:15 mixture of diastereoisomers (Scheme 1.5).[20] These cyclisations are efficient and show high levels of stereospecificity, although lengthy preparation and lack of variation of the precursors limits their use.



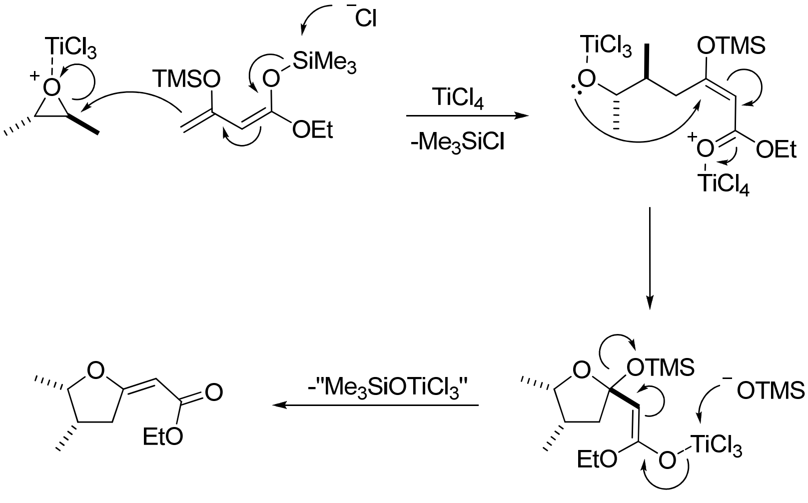
Scheme 1.5

The synthesis of tetrahydrofurans *via* enolate *O*-alkylation has also been achieved. One method published by Langer *et al.* takes advantage of the Lewis acid-mediated cyclisation of 1,3-bis-(trimethylsilyloxy)-1,3-butadienes with substituted epoxides.[21] The 1,3-*bis*-silyl enol ether is an electroneutral equivalent of a 1,3 dicarbonyl dianion which acts as an nucleophile. A Lewis acid is used to increase the activity of the epoxide by associating with the lone pair of electrons on the oxygen. This withdraws electron density from the oxygen which in turn makes the epoxide carbon atoms more electrophilic (Scheme 1.6).



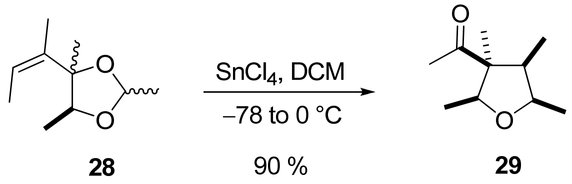
Scheme 1.6

It was observed that the reaction between 1,3-dicarbonyls and *cis*-2,3-butenoxide produced the *E*-configured 2-alkylidenetetrahydrofuran containing the two methyl groups in a *trans* configuration, while the *trans* 2,3-butonoxide gave *E*-configured 2-alkylidenetetrahydrofuran with the two methyl groups having *cis* relative stereochemistry. A mechanism is proposed in Scheme 1.7.



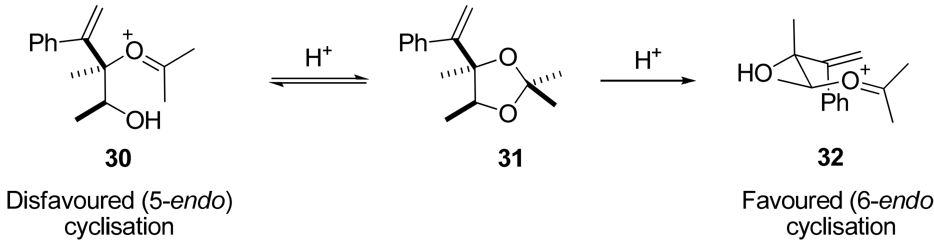
Scheme 1.7

Overman and co-workers have successfully developed the Prins-Pinacol reaction to construct oxacyclic ring systems and in particular tetrahydrofurans from 1-allyl 1,2-diols. Their initial studies began with investigating the rearrangement of allylic acetals in the presence of tin tetrachloride (Scheme 1.8).[22]



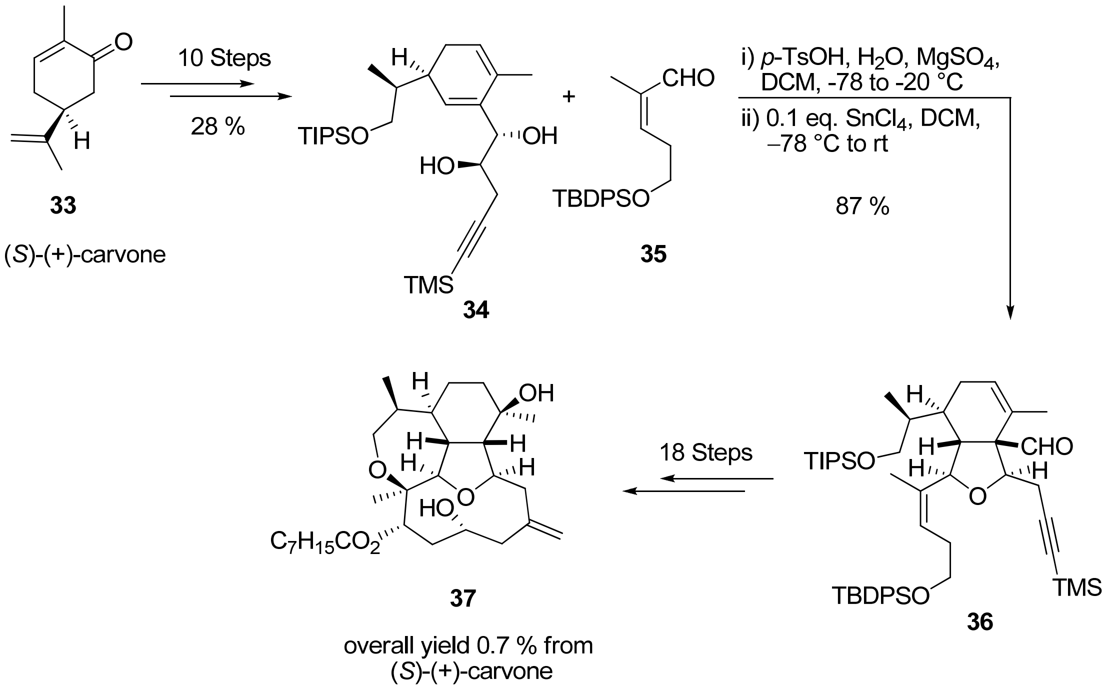
Scheme 1.8

The proposed mechanism for the reaction is a Prins cyclisation of the *E*-oxocarbenium ion generated from the acetal in the presence of the Lewis acid, followed by a Pinacol rearrangement to construct the C-C bond of the tetrahydrofuran. Under the acidic reaction conditions, the acetal can open to form two possible oxocarbenium ions, which would lead to a mixture of products. However, the situation is simplified by only one having the correct geometry to align with the alkene π-system and create the C-C bond (Scheme 1.9).[23]



Scheme 1.9

Further studies led to a range of 1,2-diol precursors, many of which have been applied to target directed synthesis such as briarellin E (Scheme 1.10).[24] The cyclohexadienyl diol precursor was obtained from (*S*)-carvone in 10 steps and an overall yield of the 28 %. Condensation of the diol **34** with the aldehyde **35** in the presence of *p*-TsOH gave the required acetal, which on exposure to $SnCl_4$ gave the desired hexahydroisobenzofuran **36** in 87 % and as a single stereoisomer.

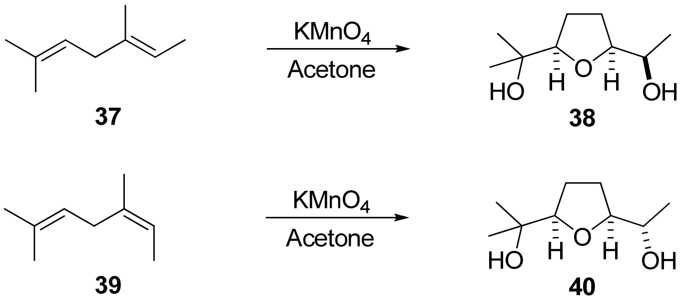


Scheme 1.10

1.3.2 Oxidative cyclisation

Transition metal oxidation cyclisation of alkenes, dienes and polyenes has been employed in the synthesis of several 2,5-disubstituted tetrahydrofurans. Although a number of transition metal oxidants have been reported, $KMnO_4$, RuO_4 and OsO_4 are most commonly utilised in the transformations.

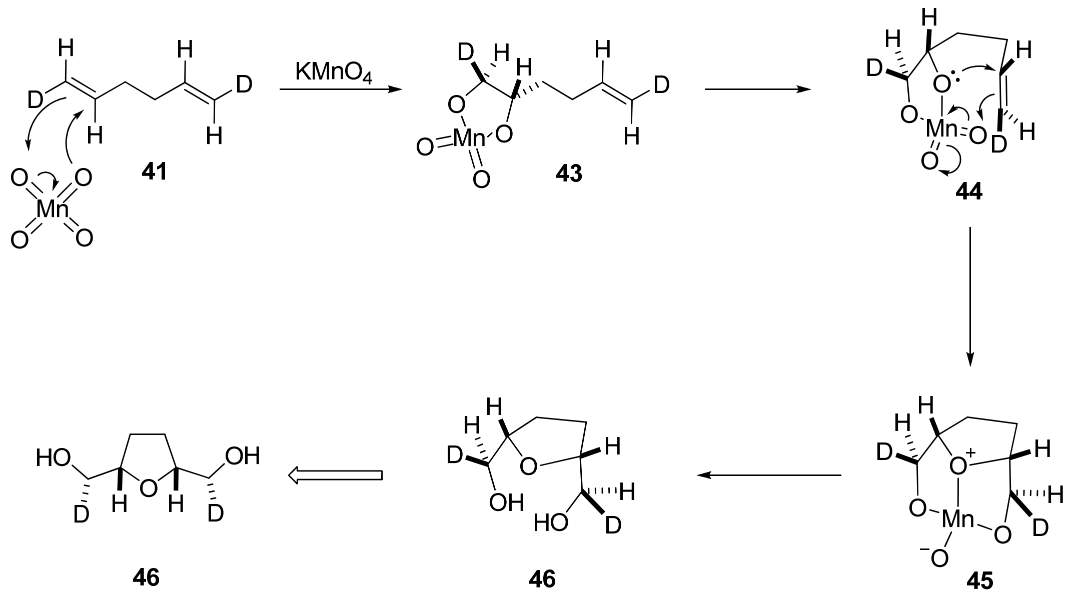
The diastereoselective oxidative cyclisation of 1,5-dienes by $KMnO_4$ to give the corresponding 2,5-*bis*-hydroxylmethyltetrahydrofurans was first reported by Klein and Rojahn (Scheme 1.11).[25]



37 **38** **39** **40**

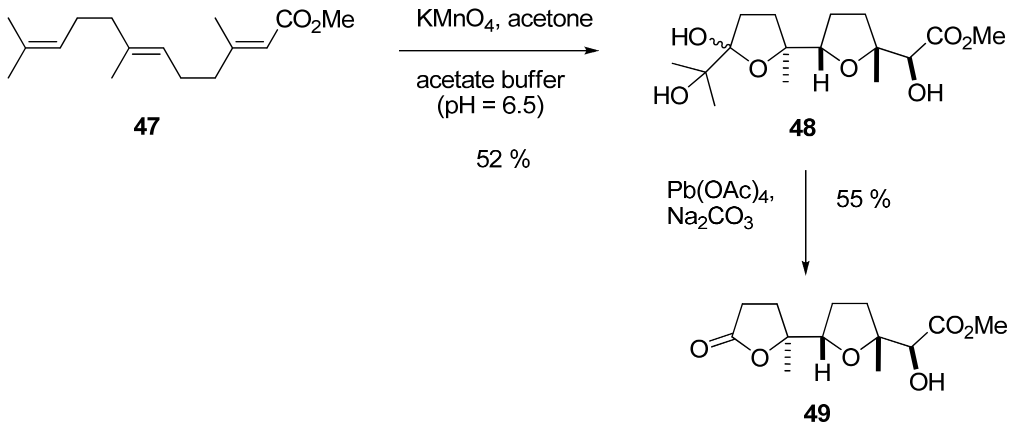
Scheme 1.11

Baldwin showed by synthesis and NMR studies of deuterated 1,5-dienes that the oxidative cycloaddition proceeded with complete stereospecificity and proposed the following mechanism (Scheme 1.12).[26]



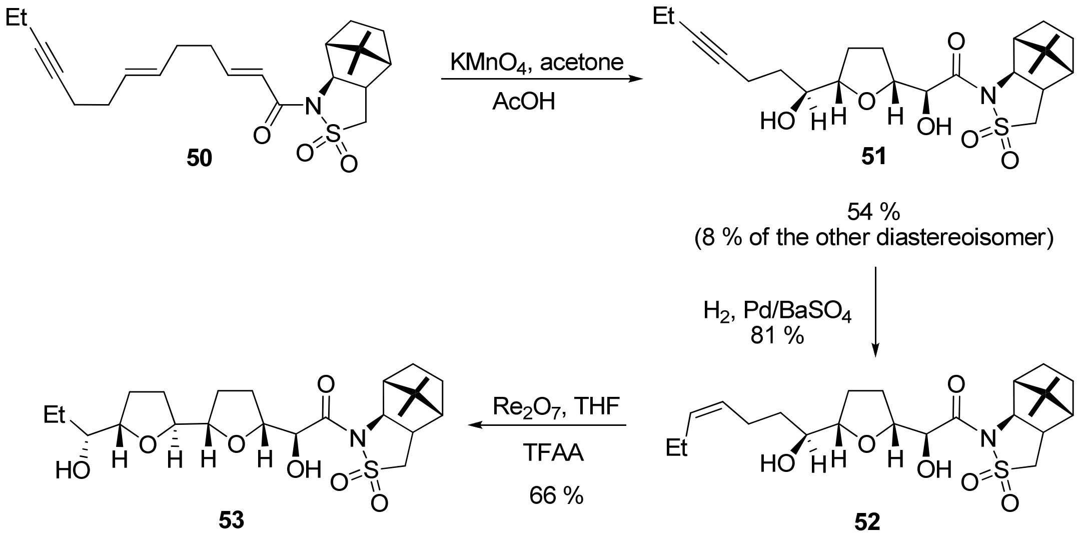
Scheme 1.12

Brown has applied a modified version of the methodology to the synthesis of octahydro-2,2'-bifuranyl systems from 1,5,9-trienes. It was found that the initial cyclisation product was the lactol **48**, which upon treatment with lead acetate formed the lactone **49**.[27] The relative stereochemistry of the 2,5-substituents of the THF ring is always *cis*; however, the geometry of the starting triene determines the relative stereochemistry of the other stereogenic centres (Scheme 1.13).



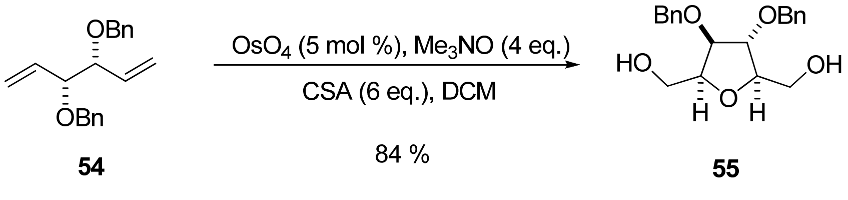
Scheme 1.13

More recently, the group combined the oxidative cyclisation with the use of chiral auxiliaries to provide the corresponding optically enriched tetrahydrofurans (Scheme 1.14). The second *trans*-2,5-disustituted THF ring is formed by a Re_2O_7 oxidative cyclisation.[28]



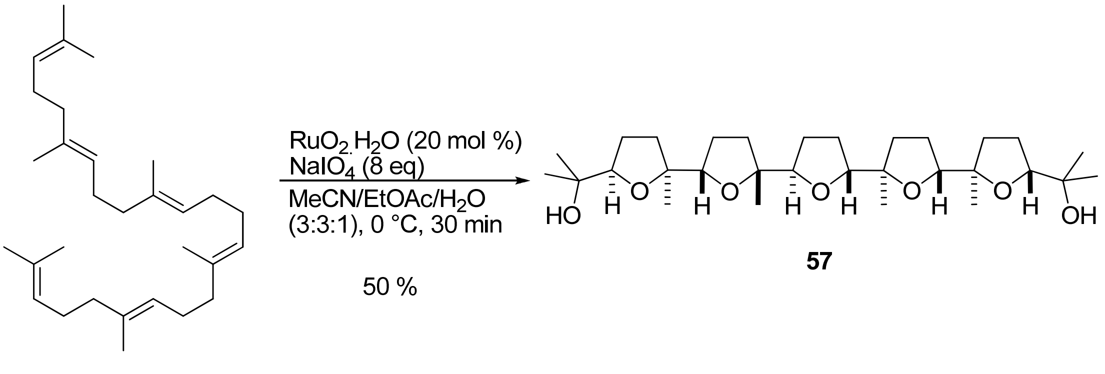
Scheme 1.14

A drawback of these methodologies is the need to use a stoichiometric amount of the metal oxidant and while this is not such a problem with $KMnO_4$, it is a significant disadvantage with more toxic and expensive oxidants. However, several groups have reported conditions to accomplish the oxidation using catalytic quantities of OsO_4 or RuO_4 and a reoxidant. Donohoe *et al.* successfully cyclised the C2-symmetric protected divinyl glycol to the corresponding tetra-substituted THF using catalytic OsO_4 and an amine oxide as the reoxidant under acidic conditions (Scheme 1.15).[29]



Scheme 1.15

Piccialli *et al.* extended the use of oxidative cyclisations to polyenes with the synthesis of the penta-tetrahydrofuranyl **57** from squalene (Scheme 1.16). This single catalytic transformation produces five THF rings, 12 bonds and 10 stereocentres to give the product as a single diastereoisomer in 50 %. Ruthenium tetraoxide is generated *in situ* from $RuO_2.H_2O$ and $NaIO_4$; the sodium periodate is further required as a reoxidant in the catalytic cycle.[30]



56

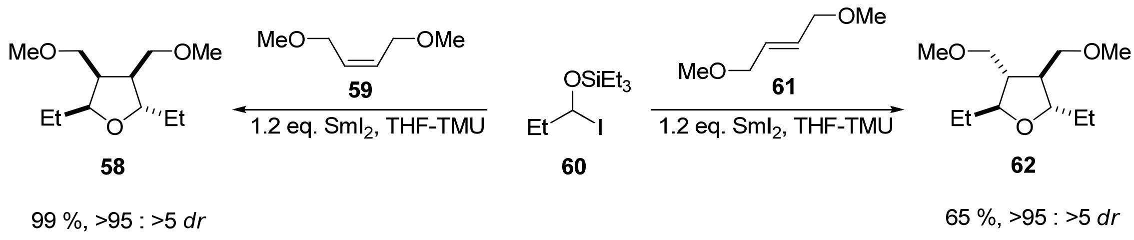
57

Scheme 1.16

1.3.3 Cycloaddition Reactions

Cycloaddition reactions, and in particular [3+2] cycloaddition reactions, are a useful strategy for the stereoselective construction of tetrahydrofurans. Owing to the possibility of generating two or three bonds, two stereocentres, and a ring in a single transformation makes this an efficient and concise route to highly substituted tetrahydrofurans. These reactions take place between two- and three- atom component reagents. Several methods have been developed exploiting carbonyl ylides, epoxides, alkenes and cyclopropanes as the two and three atom-component reagents.[12] A number of methodologies based on epoxides as the three atom-components have been developed. These methods range from transition metal catalysed reactions through to radical based routes. Although the tetrahydrofuran subunit has been assembled with these methods, their flexibility for a range of substituents is still to be improved.[12]

It has been demonstrated that non-stabilised carbonyl ylides generated from iodomethylsilyl ethers can react with unreactive alkene, alkyne and allene dipolarophiles. This [3+2] cycloaddition is limited to the substituents at C2 and C5 being identical (Scheme 1.17).[31]



Scheme 1.17

1.4 Cyclopropanes

Cyclopropanes and their derivatives are useful synthetic intermediates that have frequently been employed as versatile building blocks in organic synthesis. The release of the ring strain (115.5 kJ mol^{-1} of stain energy per mol of cyclopropane), produced from the C-C bonds being forced to adopt bond angles of *ca.* 60 ° in the three membered cycloalkane, results in the relatively high reactivity and provides the thermodynamic driving force for these reactions.[32] Despite the ring strain, cyclopropanes are often chemically inert and require electron-donating or accepting substituents to activate them towards polar reactions. The reactivity of the cyclopropane ring opening towards nucleophiles or electrophiles is greatly dictated by the electronics of the substituents on the ring. An electron donating group activates the ring towards electrophiles while an electron accepting group will increase the ring's susceptibility to nucleophilic attack (Fig. 1.4).[33]

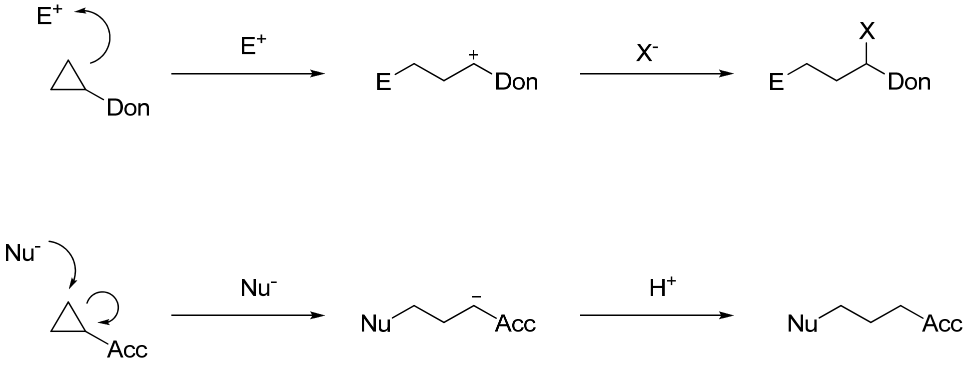
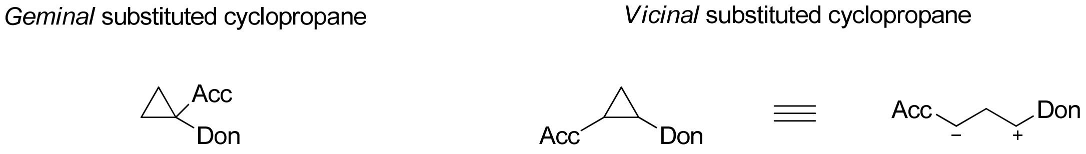


Fig. 1.4 Reactivity of cyclopropanes containing donor and acceptor groups

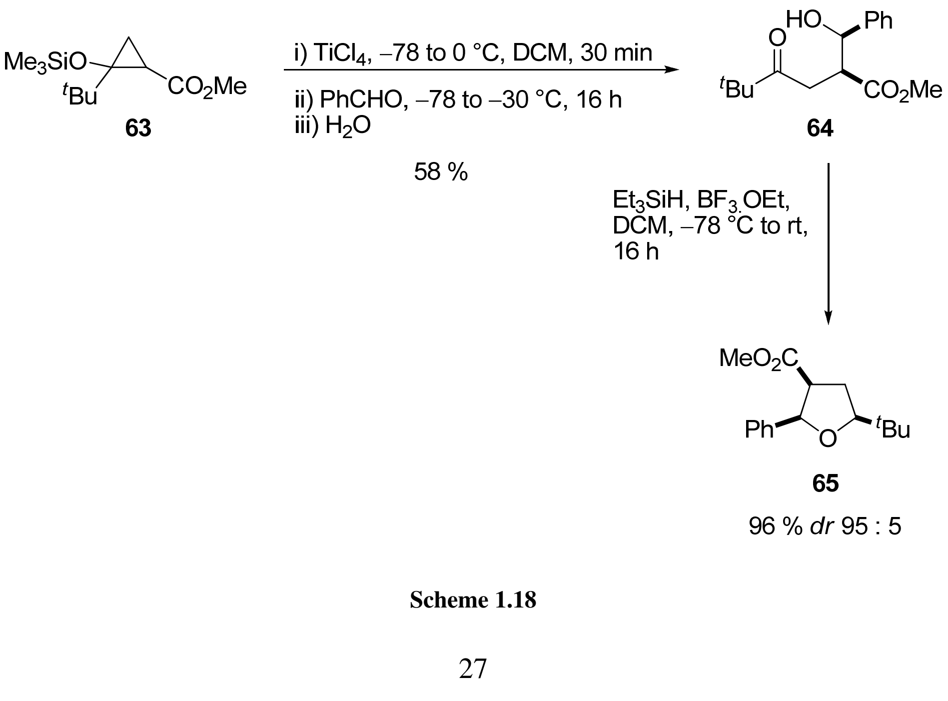
The incorporation of both donor and acceptor groups on the ring has the potential to increase the reactivity of the cyclopropane further. There are two possible arrangements of the donor-acceptor substituents around the ring, vicinal or a geminal. The use of geminal donor-acceptor cyclopropanes in organic chemistry has few examples because of the competing electronic influence of the two substituents.[34] On the other hand, cyclopropanes containing vicinal donor-acceptor substituents have been successfully employed as reagents in organic synthesis.[35] These reagents can be thought of as a 1,3-dipolar synthons capable of acting as three-atom components in cycloaddition reactions (Fig. 1.5).


Geminal substituted cyclopropane

Vicinal substituted cyclopropane

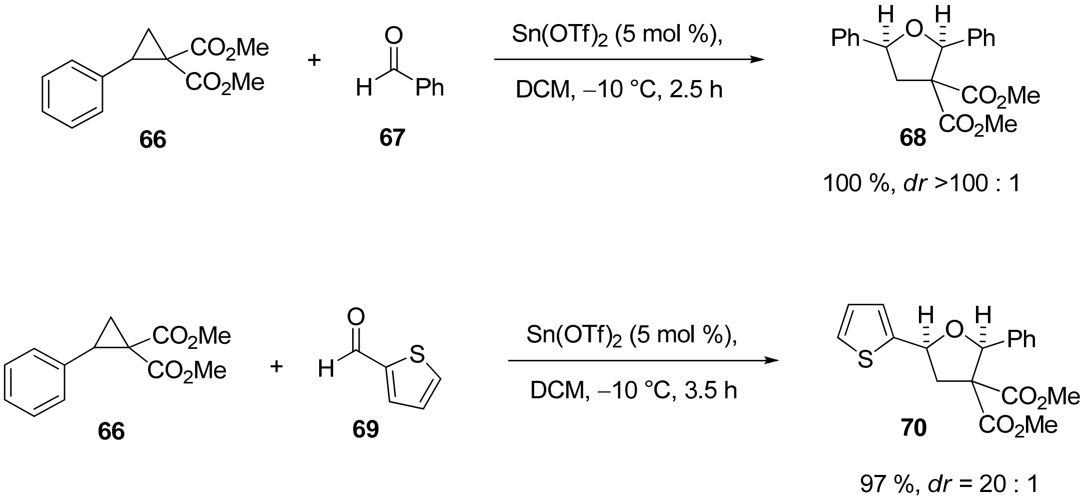
Fig. 1.5 Donor-acceptor substitution patterns around the cyclopropane ring

The acceptor group in the majority of examples is the carbonyl (or malonate) substituent. The synthetic application of cyclopropanes with other acceptor substituents is relatively rare although examples of sulfonyl[36] and phenylsulfinyl[37] acceptor groups have been reported. The two most widely used donating groups are oxygen (usually as the silyl or alkyl ether) and nitrogen substituents (Scheme 1.18).[38] Alternative donating groups that have been utilised in organic synthesis are phenylthio[39] and silylmethyl substituents (see section 1.6.2).



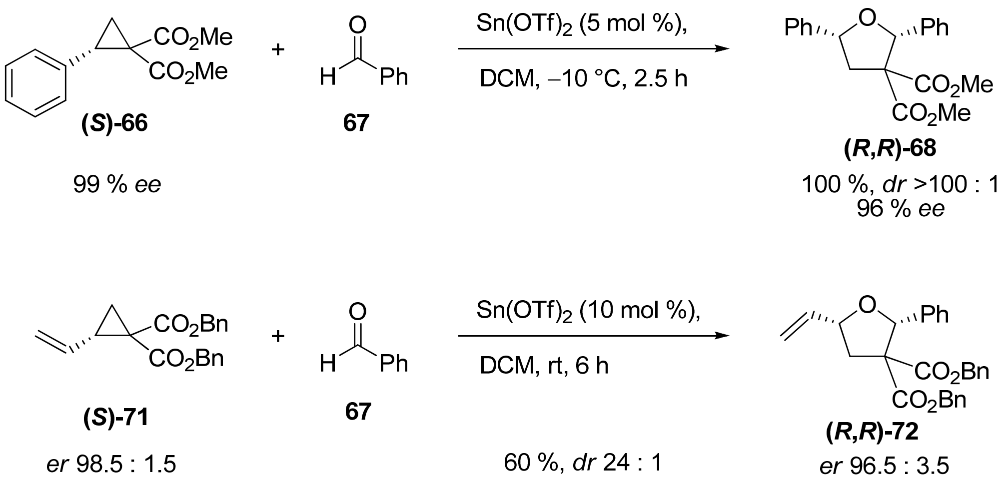
Scheme 1.18

Several groups have employed cyclopropanes as three-atom components in [3+2] annulation reactions to afford tetrahydrofurans. In 2005, Johnson and co-workers reported the use of $Sn(OTf)_2$ as an effective catalyst for the formal [3+2] cycloaddition between a malonate substituted donor-acceptor cyclopropane **66** and a range of aromatic aldehydes. The reaction gave the highest yields when the donor substituent was an sp^2 hybridised substituent (Scheme 1.19).[40]



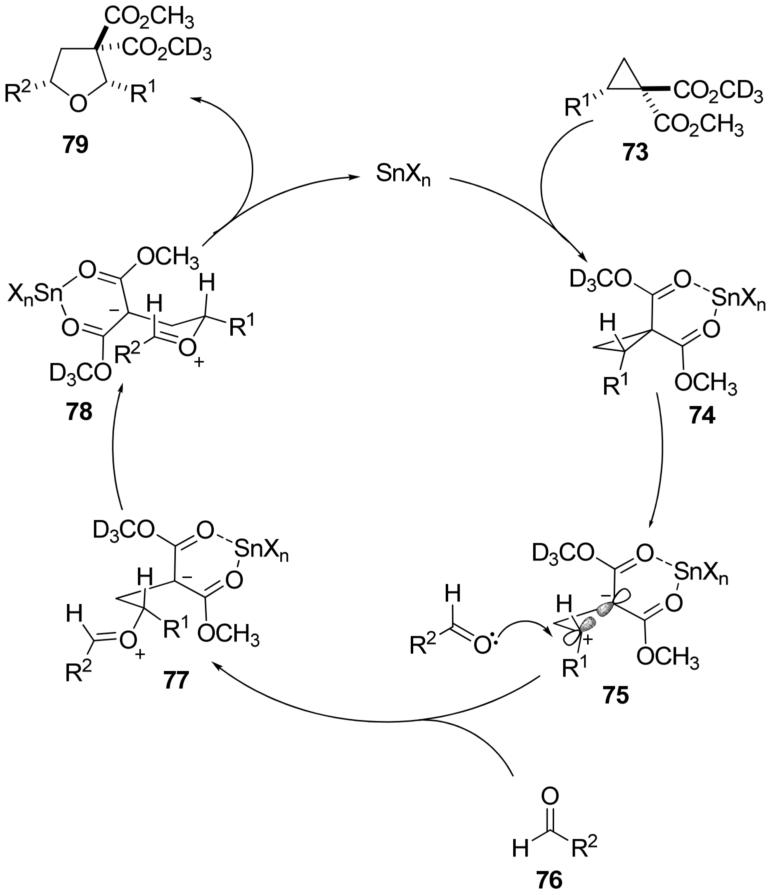
Scheme 1.19

The lower yields and slow rate of reaction from employing alkyl aldehydes were overcome in subsequent publications by using a stronger Lewis acid, $SnCl_4$. The reaction was found to be stereospecific and highly diastereoselective, although the diastereoselectivity was influenced by the aldehyde. Chirality transfer from the cyclopropane controls the stereochemistry of the final THF product (Scheme 1.20).[41]



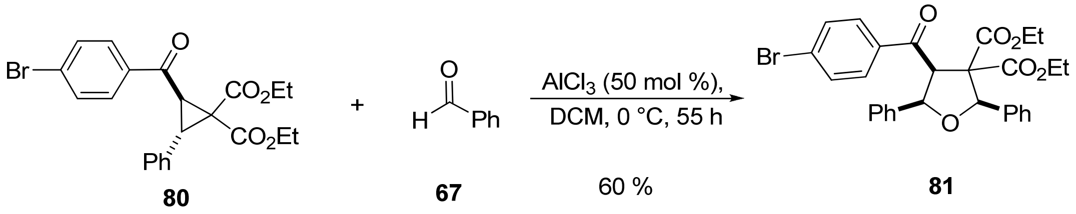
Scheme 1.20

Johnson *et al.* proposed a stereospecific tight ion-pair mechanistic pathway to explain the regio- and stereochemical products of the reaction (Scheme 1.21).[42] The proposed catalytic cycle for the stereospecific cycloaddition begins with the tin catalyst complexing to the carbonyl groups of the malonate activating group, causing the cyclopropane ring to open creating a tight ion-pair intermediate **75**. Addition of the aldehyde produces the more stable *E*-oxocarbenium ion. Rapid rotation of the C-C bond places the R^1 and R^2 substituents in pseudoequatorial positions of an envelope conformation and cyclisation of the enolate on to the carbonyl *E*-oxocarbenium ion yields the observed product.



Scheme 1.21

The application of malonate substituted donor-acceptor cyclopropanes has recently been extended to the preparation of 2,5-diaryl-3,3,4 trisubstituted tetrahydrofurans using $AlCl_3$ to promote the reaction.[43] The presence of electron-donating groups on either the cyclopropane or ketone gave significantly lower yields than phenyl (Scheme 1.22).



Scheme 1.22

It is the properties of cyclopropanes bearing the malonate substituent and the unique mechanistic pathways possible to these precursors that have allowed highly regio- and stereoselective synthetic methodologies to be developed. The work of Johnson and others has shown the potential of malonate substituted donor-acceptor cyclopropanes in the synthesis of substituted THFs. The only limitation of this methodology is that one of the carbons in the final THF will be occupied by the two ester substituents. In some products this may be beneficial while in others the removal of this functionality may be time consuming and difficult.

1.5 Organosilicon Chemistry

Silicon containing compounds have found a number of applications in organic synthesis. By far the three most commonly encountered uses are:

i) protecting groups for alcohols

ii) the formation of silyl enol ethers as stable enolate equivalents

iii) as stabilising and directing groups

The following literature review will focus on the application of silicon in organic synthesis with respect to the ability of silicon substituents to act as stabilising and directing groups in organic molecules and only where the silicon is incorporated in the organic molecule *via* a silicon-carbon bond.

1.5.1 Properties

The relative positions of silicon and carbon in the periodic table led many pioneers of organosilicon chemistry to propose the chemistry of the two elements would be similar. Although there are similarities, such as both have a normal valency of 4 and can form compounds with a tetrahedral geometry, the field of organosilicon chemistry shows some distinct differences to that of carbon, which can be attributed to four factors.[44]

Bond Strength

Much of the chemistry of silicon is dominated by the formation of very strong silicon-oxygen (530 kJ mol^{-1}) and silicon halide bonds (especially the silicon fluoride bond which has a bond dissociation energy value of 690 kJ mol^{-1}). On the other hand, the silicon-silicon bond (310 kJ mol^{-1}) is weaker than the corresponding carbon-carbon (350 kJ mol^{-1}) while silicon π-bonds are usually unstable and are rarely observed in organosilicon chemistry.

Bond Length

The bond length of silicon single bonds to carbon, hydrogen, and oxygen are all significantly longer than their carbon counterparts. The silicon-carbon bond length is 1.89 Å while the typical carbon-carbon bond length is 1.54 Å. The longer Si-C bond length allows reactions to take place at the silicon and α carbon that would be sterically difficult in an all carbon system.

Electronegativity

Although the carbon-silicon bond (320 kJ mol^{-1}) is similar in energy to the carbon-carbon bond (350 kJ mol^{-1}), silicon has a Pauling electronegativity of 1.8 whilst carbon is 2.5. Therefore, the Si-C bond is polarised towards the carbon atom (Fig. 1.6).[45] This uneven distribution of the electron density around the bond makes the silicon more susceptible to nucleophilic attack than the carbon.

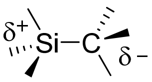
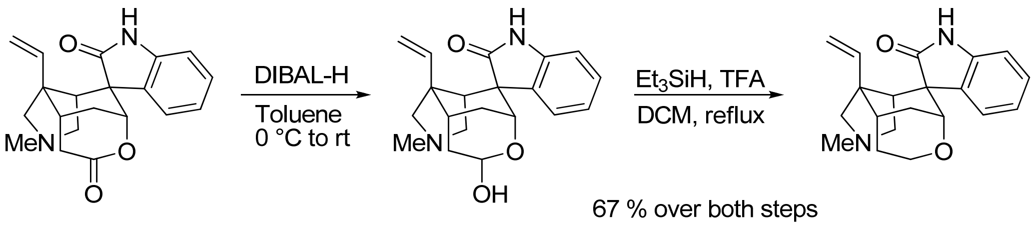


Fig. 1.6 Bond polarisation in a carbon-silicon bond

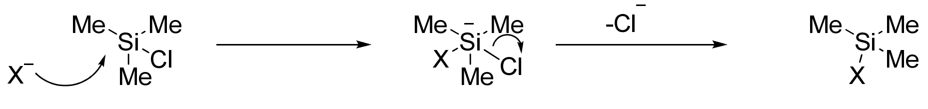
As a result of the silicon-hydrogen bond (300 kJ mol^{-1}) being weaker than carbon-hydrogen bond (410 kJ mol^{-1}) and the electropositivity of silicon, compounds containing silicon-hydrogen bonds, such as Et_3SiH, have been successfully employed as reducing agents in organic synthesis (Scheme 1.23).[46]



Scheme 1.23

Atomic Properties

The final important difference between carbon and silicon is the atomic orbitals available to silicon for bonding. The valency shell electronic configuration of silicon is $3s^2 3p^2 3d^0$, therefore silicon uses the 3s and 3p orbitals for bonding. The higher energy of the 3p orbitals prevents efficient overlap with the 2p bonding orbitals of first row elements, explaining the absence of π-bonding in organosilicon chemistry. The presence of vacant d-orbitals on the silicon allows the silicon atom to expand its valency, such as in the hexafluoro salt $K_2SiF_6^{2-}$. In organosilicon chemistry, the availability of the d orbitals permits the silicon to easily undergo nucleophilic substitution, even at a congested centre. The mechanism for this process is a type of S_N2 reaction (referred to as S_NSi) and proceeds *via* a pentacovalent intermediate (Scheme 1.24).



Scheme 1.24

1.5.2 The α- and β-Effect

The β-effect describes the ability of silicon to stabilise a carbocation or build up of positive charge on the β-carbon in an organic molecule. This has been predominantly attributed to Si-C hyperconjugation with induction and polarisation only contributing a relatively small amount. For the β-effect to take place, the vacant p-orbital must be aligned in the same plane as the α-carbon-silicon bond so that overlap can occur; this results in the β-effect being conformationally dependent (Fig. 1.7).[47] Hyperconjugation may occur with or without movement of the silyl group in the transition state. Movement of the silyl group would, through internal neighbouring group participation, result in the formation of the siliranium cation (TS 2).[33]

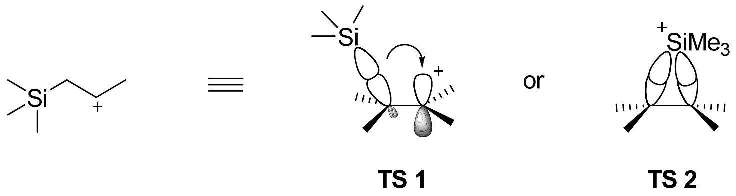
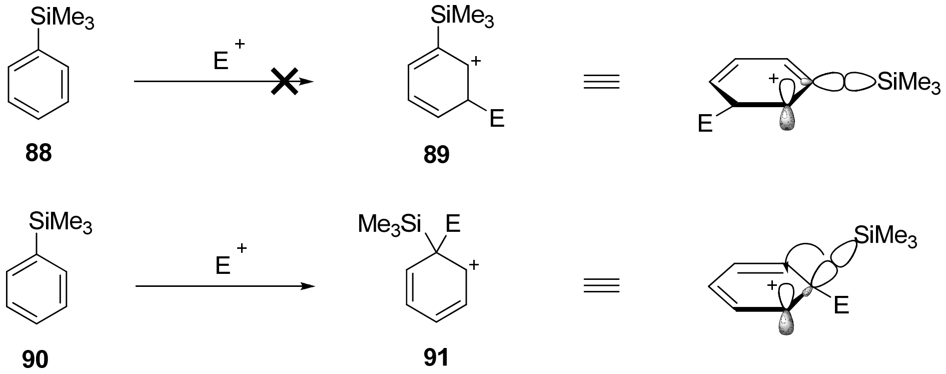


Fig. 1.7 The β-effect: showing the necessary conformation

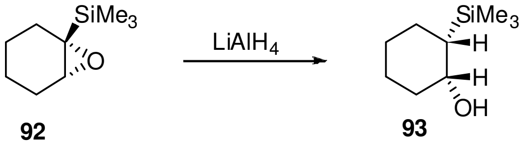
This effect is experimentally observed in the reaction of aryl silanes with electrophiles under Friedel-Crafts conditions. The overall result is that the electrophile replaces the silyl substituent on the aromatic ring. The reaction is known as *ipso*-desilylation (Scheme 1.25). Attack of the carbon bearing the silyl group is favoured as the positive charge formed in the transition state is stabilised by the silyl group.



Scheme 1.25

As well as stabilising a β-carbocation, the silicon atom can stabilise a carbanion at the α-position. This has been attributed to electron donation from the p-type highest occupied molecular orbital (HOMO) of the carbanion into a Si antibonding orbital rather than delocalisation into the empty Si d orbital.[48] Thus, tetramethylsilane can easily be deprotonated by *n*-BuLi to give α-lithiomethyltrimethylsilane. These α-silyl carbanions produced in this manner have been widely employed in the synthesis of heterosubstituted alkenes by the

Peterson alkene synthesis. The α-effect is also observed in the regioselectivity of α,β-epoxysilanes ring opening in the presence of a nucleophile. The observation that the nucleophile bonds to the α-carbon is accounted for by the silicon group stabilising the S_N2 transition state during ring opening (Scheme 1.26).[49]



Scheme 1.26

1.5.3 Silyl groups in Organic Synthesis

A range of silyl groups with different substituents on the silicon atom have been prepared and extensively used in organic synthesis, for example: halosilanes, alkoxysilanes, hydroxysilanes, aminosilanes, and hydrosilanes. The limitation of heterosubstituted organosilanes is that the heteroatom increases the reactivity of the silicon group towards nucleophiles, reducing the tolerance of the silyl group to other reaction conditions. For this reason, silyl groups with alkyl and aryl substituents have been most commonly employed.

The application and development of organosilicon chemistry in organic synthesis stems from three general observations:

i) A silyl group can stabilise a carbocation on a β-carbon and a carbanion on a α-carbon more effectively than an equivalent carbon.

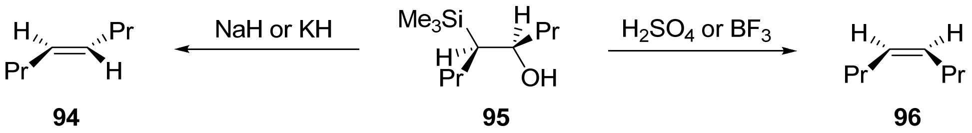
ii) A silyl group is usually displaced from a carbon more easily than a proton is displaced from a corresponding carbon when the nucleophile is an oxygen or halide and there is no steric restraints to inhibit the participation of the silyl group

iii) a silyl group remote from functionality can be relied upon to survive most of the reaction conditions used in modern organic synthesis[50]

From these three general principles organic chemists have built up a range of chemical transformations arising from the incorporation of silicon.

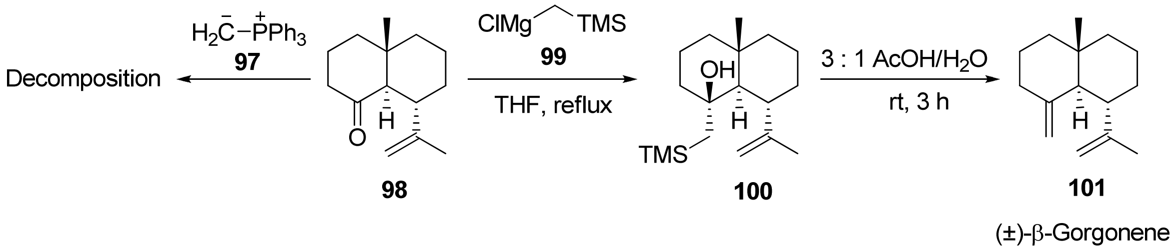
Peterson Reaction

A reaction that takes advantage of silicon's strong affinity for oxygen is the Peterson reaction. The Peterson reaction[51] is a silicon version of the Wittig reaction and is the elimination of trimethylsilanol, from a β-hydroxyalkyltrimethylsilane to yield an alkene. Two distinct mechanistic pathways are observed depending whether the elimination occurs under basic or acidic conditions. This allows the complimentary formation of both *Z*- or *E*-isomers from the same β-hydroxyalkyltrimethylsilane precursor (Scheme 1.27).



Scheme 1.27

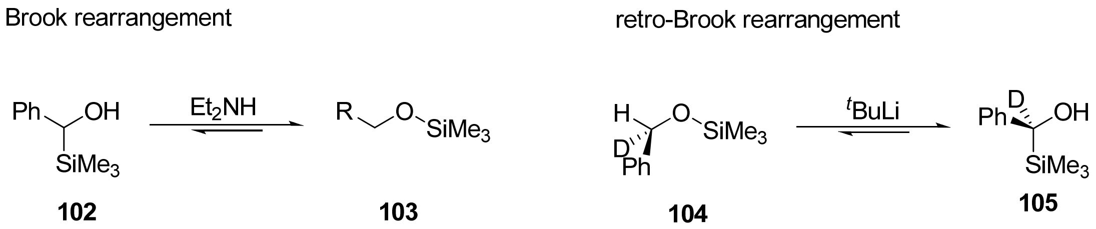
The Wittig reaction has found much greater use in natural product synthesis compared to the Peterson reaction. However, cases have been reported where the silicon based method has proved superior to the phosphorus-based chemistry. In Boeckman's synthesis of (±)-β-gorgonene, the final transformation was a methylenation of ketone **98**. The authors initially attempted this conversion using methylenetriphenylphosphorane but reported that only decomposition occurred under the basic conditions. A successful conversion was achieved using trimethylsilylmethylmagnesium chloride followed by elimination under acid conditions (Scheme 1.28).[52]



Scheme 1.28

Brook Rearrangement

The Brook rearrangement is a stereospecific intermolecular migration of a silyl group from carbon to oxygen that occurs for silylcarbinols in the presence of catalytic amounts of base (Scheme 1.29). The thermodynamic driving force for this reaction is the formation of the Si-O bond. The reaction is in equilibrium and, if a stoichiometric quantity of base is used, the retro-Brook reaction can occur.

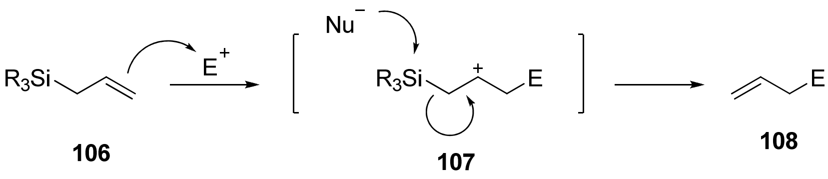


Scheme 1.29

The original Brook rearrangement was specifically a 1,2 anionic migration; however, as other silyl group migrations have been observed, any intramolecular migration of a silyl group from a carbon to oxygen is generally referred to as a Brook rearrangement.[53]

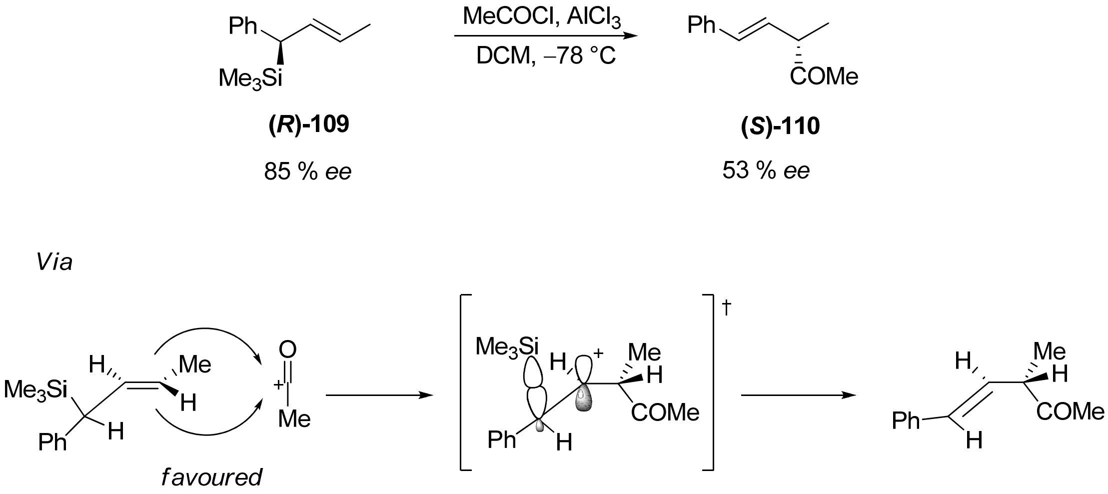
Reactions of Allylsilanes and vinylsilanes

During the last two decades, silicon containing compounds, in particular allyl-, propargyl- and vinylsilanes have become powerful tools in the synthesis of organic molecules.[54] Allylsilanes usually undergo attack by electrophiles at the γ-carbon to form the β-carbocation relative to the silyl group this is followed by elimination to produce the allylic product (Scheme 1.30).



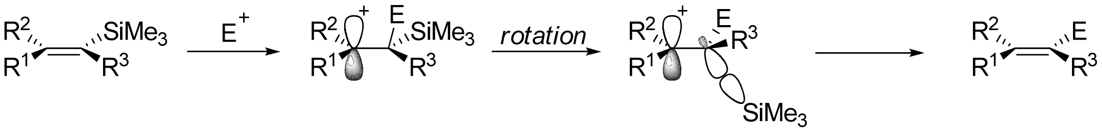
Scheme 1.30

In many cases, the S_E2' reaction shows high stereoselectivity with the resulting *anti* stereochemical relationship between the electrophile and the eliminated silyl group (Scheme 1.31).[55] The observed stereochemistry can be explained in terms of the favoured conformation of the allylsilane during electrophilic addition.



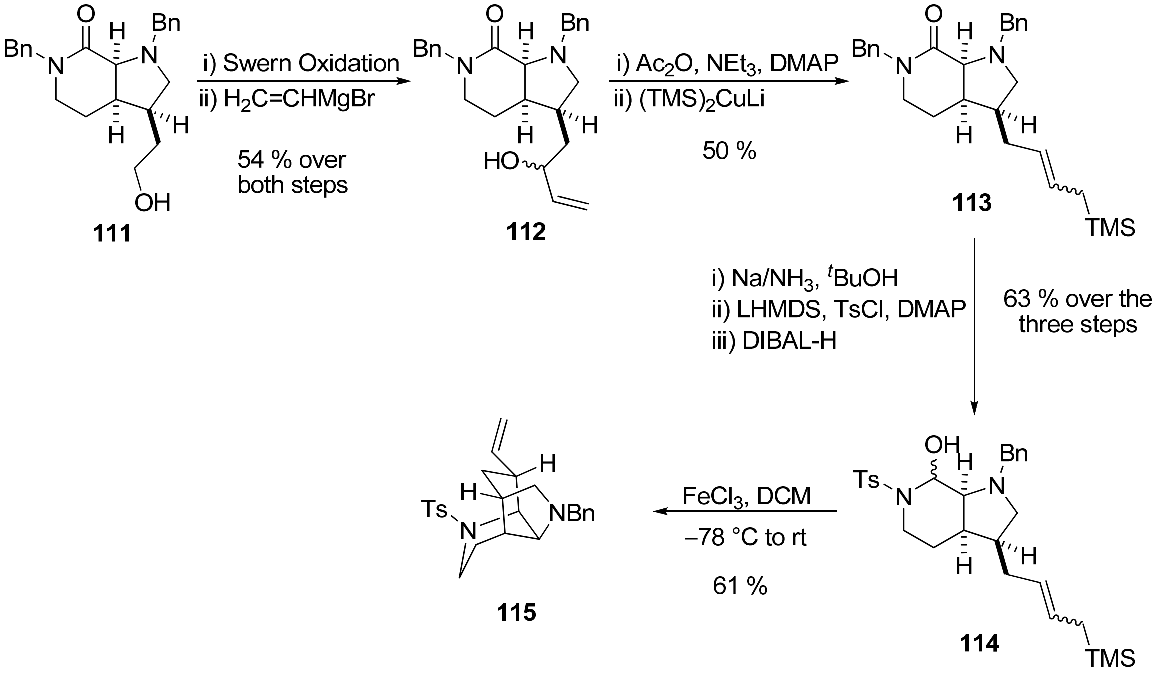
Scheme 1.31

Electrophilic substitution reactions of vinylsilanes take place at the α-carbon and the reaction usually proceeds with retention of configuration because the silyl group will rotate around the carbon bond so as to maximise the stabilisation of the cation in the intermediate (Scheme 1.32).



Scheme 1.32

Weinreb *et al.* elegantly utilised the intramolecular electrophilic substitution reaction of an allylsilane as the pivotal step in the construction of the tricyclic core of the unusual alkaloid sarain A. The electrophile in this case is the *N*-tosyliminium ion generated *in situ* by the reaction of iron (III) chloride and hydroxyl sulphonamide (Scheme 1.33).[56] To incorporate the silicon functionality the group employed a methodology developed by Fleming *et al.* for conversion of an allylic alcohol to allylsilane *via* the acetate leaving group.[57]



Scheme 1.33

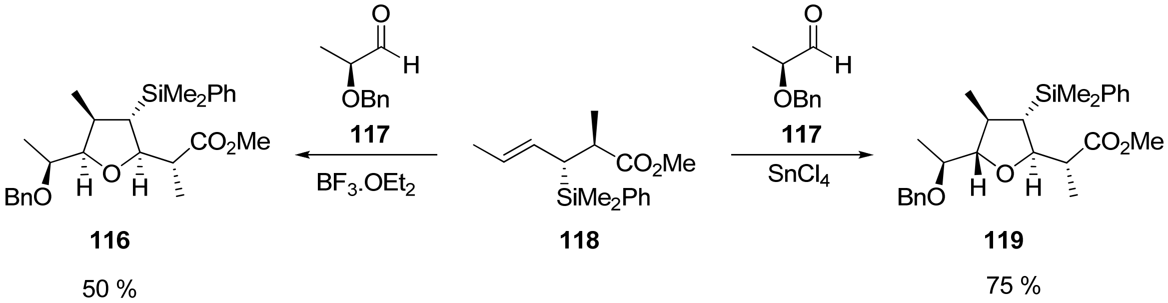
The synthesis of the tricyclic core of sarain A clearly illustrates how silane reagents have been successful in [3+2] annulation processes resulting in high levels of diastereoselectivity and enantiofacial selectivity. Progress in the development of chiral silane reagents capable of enantiotopic selectivity continues to be extensively investigated.[58]

1.6 Silanes in cycloaddition reactions to synthesise tetrahydrofurans

The useful properties of incorporating silicon into organic molecules have led to its employment in constructing many synthetically valuable molecules. As this project aims to look into using silicon containing molecules in the construction of the tetrahydrofuran motif a short review of previous reported methods of synthesising tetrahydrofurans utilising silicon containing precursors will follow.

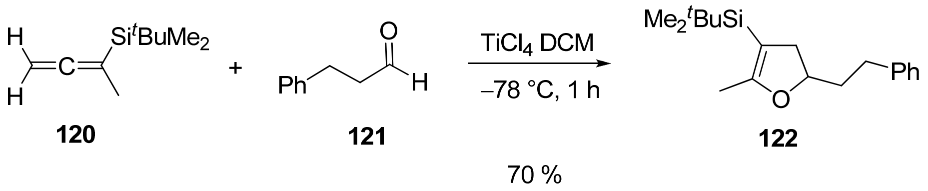
1.6.1 Allylsilanes in formal [3+2] cycloaddition reactions

The synthesis of tetrahydrofurans employing a [3+2] cycloaddition reaction between allylsilanes and achiral aldehydes was initially developed by Panek *et al.* The group have subsequently shown that chiral silanes of the general structure, α-methyl-*E*-crotylsilane, undergo Lewis acid-promoted double stereodifferentiation addition reactions with chiral aldehydes (Scheme 1.34).[59] The diastereofacial selectivity is governed by the choice of Lewis acid and absolute stereochemistry of the crotylsilane. As illustrated in scheme 1.34, where boron trifluoride etherate is used as the Lewis acid, the *cis*-2,5-tetrahydrofuran is produced, while tin tetrachloride yields the *trans* relative stereochemistry. This method requires that a 1,2-silyl shift can take place before the cyclisation can occur.



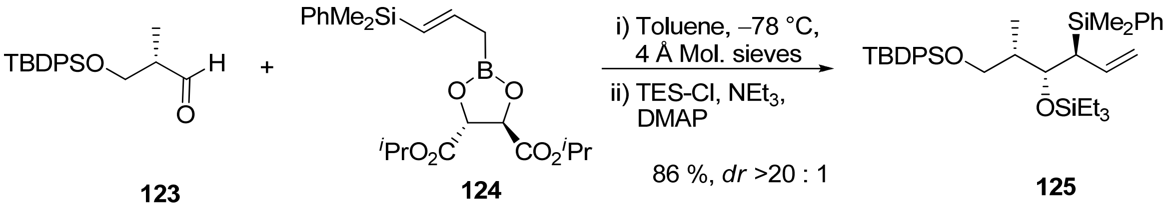
Scheme 1.34

In a similar methodology, Danheiser *et al.* have reported the reaction of allenylsilanes with Lewis acid-activated aldehydes (Scheme 1.35).[60] The drawback of both these approaches is that the syntheses of the pre-requisite allenyl or crotonyl silyl derivatives are not trivial.

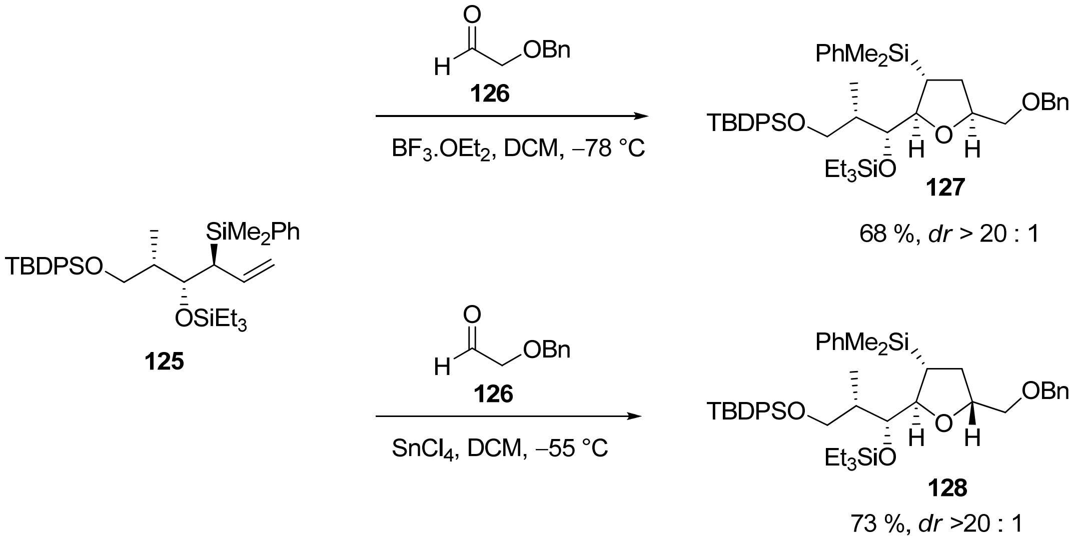


Scheme 1.35

More recently, Roush and co-workers have developed a three component coupling strategy to form 2,3,5-trisubstituted tetrahydrofurans and have consequently shown its practical application in natural product synthesis.[61] The approach uses the tartrate ester derived silylallylboronate **124** in an allylboration sequence with an aldehyde as a direct route to chiral nonracemic allylsilanes.[62] The derived allylsilane reacts in the presence of a Lewis acid-activated aldehyde to produce 2,3,5-trisubstituted tetrahydrofurans *via* a [3+2] annulations (Scheme 1.37).[63] The stereochemistry of the allylsilane is presumably controlled by a chair-like transitions state.

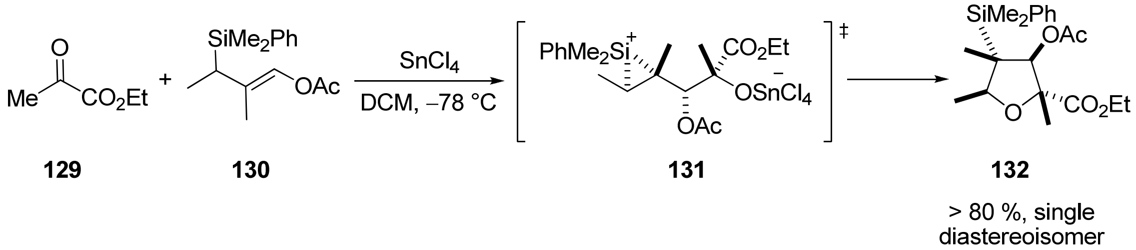


Scheme 1.36



Scheme 1.37

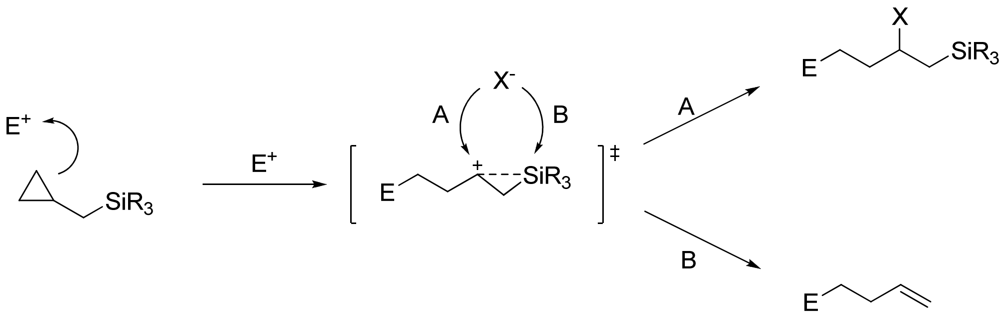
Around the same time Woerpel *et al.* reported the [3+2] annulation reaction of functionalised allylsilanes with α-ketoesters as a means to synthesise highly substituted tetrahydrofurans in 85 % as a single diastereoisomer (Scheme 1.38). The initial step is the nucleophilic addition of the alkene to the Lewis acid-activated carbonyl group. The reaction is then believed to proceed by way of a 1,2-silyl migration from the tertiary β-silyl carbocation to the secondary β-silyl carbocation *via* the siliranium ion **131**. This generates the alkoxide ion intermediate which cyclises to produce the multiply substituted tetrahydrofuran with high stereoselectivity.[64]



Scheme 1.38

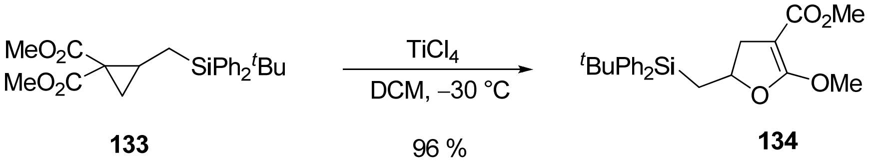
1.6.2 Synthesis of tetrahydrofurans from silylmethylcyclopropane precursors

The silylmethyl substituent attached to a cyclopropane ring can act as a donor group activating the cyclopropane towards ring opening reactions with electrophiles. The silyl group stabilises the positive charge on the β-carbon during the transition state. Depending on the conditions and the counter-ion the carbocation can either eliminate the silyl group to form the alkene or trap the anion (Scheme 1.39).



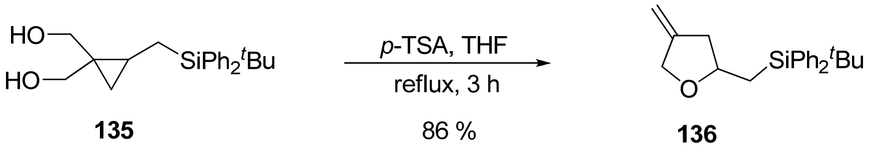
Scheme 1.39

Yadav and co workers have developed a range of annulation reactions with malonate substituted silylmethylcyclopropanes under Lewis acid conditions to generate the 1,3-dipole intermediate as the key step.[65] The group have reported that silylmethylcyclopropanes containing large groups on silicon undergo ring-opening followed by cyclisation to furnish substituted dihydrofurans upon treatment with $TiCl_4$ (Scheme 1.40).[66] This is a donor-acceptor strategy that requires carbonyl functionality adjacent to the ring. The silicon and carbonyl groups define the regioselectivity of the ring opening and are retained in the derived tetrahydrofuran.



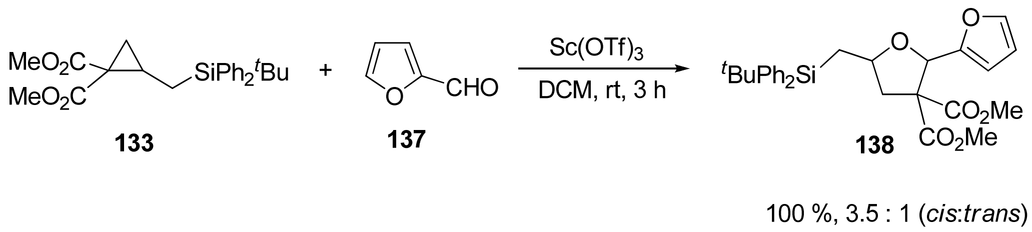
Scheme 1.40

Subsequently the group applied the method to cyclopropyl carbinols as a way to make the 3-methylene-5-methylsilyl tetrahydrofuran along with other oxygen containing saturated heterocycles. In this case it was found that *p*-TSA was effective in promoting the reaction in moderate to high yields (Scheme 1.41).[67]



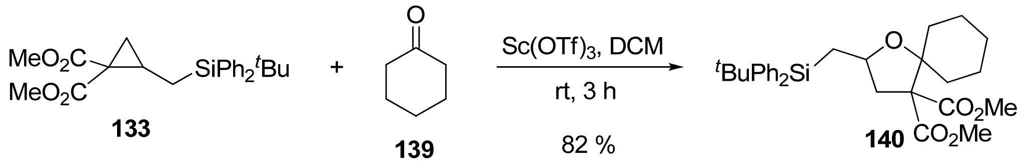
Scheme 1.41

Finally, the group reported that the methodology can be expanded to intermolecular reactions between either aldehydes or ketones and malonate substituted silylmethylcyclopropanes in the presence of Lewis acid (Scheme 1.42).[68]



Scheme 1.42

The *tert*-butyldiphenylsilyl group was the silicon group of choice, as in the previous reactions. It is believed that the high level of diastereoselectivity achieved in the reactions is due to the large size of the substituents on the silicon. The steric bulk of the groups also prevents the elimination of the silyl group during the reaction. The reaction proceeded to yield the 2,5-disubstituted tetrahydrofurans using aldehydes, although it should be noted that only the use of unsaturated or aromatic aldehydes was described. If electron-withdrawing groups were present on the aromatic group then the yield of the reaction was dramatically reduced. The use of ketones produced the 2,2,5-trisubstituted tetrahydrofurans in good yields with cyclic ketones producing the *spiro* derivative (Scheme 1.43).



Scheme 1.43

1.7 Summary

In spite of the fact that an assortment of diverse methodologies for the synthesis of substituted tetrahydrofurans have been developed, many of these routes require difficult and lengthy preparation. Therefore, the need for short, versatile and reliable methodologies with high levels of chemo- and stereoselectivity are still desirable. It is likely that transformations that can construct two or more bonds and stereocentres with a predictable outcome in a single step will prove exceptionally valuable.

Chapter Two

2.0 Results and Discussion

The initial investigation of the reactions of silylmethylcyclopropanes as precursors for five membered heterocycle synthesis began by examining the synthesis of silylmethylcyclopropanes with no additional substituents or functional groups (Fig. 2.1). This would allow the reactivity of the structurally most simple silylmethylcyclopropanes to be established.

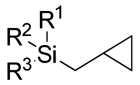


Fig. 2.1 Generic structure of an unsubstituted silylmethylcyclopropane

Once the reactivity of the basic structure had been established, the influence of substituents on either the silicon or cyclopropane ring could be investigated.

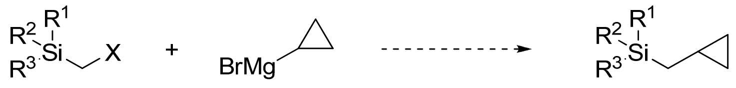
2.1 Synthesis of unsubstituted silylmethylcyclopropanes

2.1.1 Direct coupling

In designing a synthetic route for the preparation of the unsubstituted silylmethylcyclopropanes, the following criteria were desirable: the methodology should permit a selection of different substituents to be incorporated on the silicon while still remaining a robust and short synthesis. The reaction would also need to be efficient on a multi-gram scale as a relatively large quantity of material would be needed for screening experiments. In developing the work further, it would also be convenient if the method allowed the introduction of substituents on the cyclopropane ring.

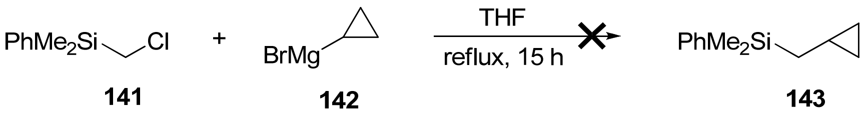
The first route to be explored was the reaction between commercially available cyclopropylmagnesium bromide in THF and a chloromethylsilane. It was envisaged that the

Grignard reagent could be used to couple the cyclopropyl group to the corresponding silylmethyl halide. Although there was no literature precedent for this reaction, it presented a possible synthesis of the silylmethylcyclopropane in one step and would remove the need to make the cyclopropane ring (Scheme 2.1).



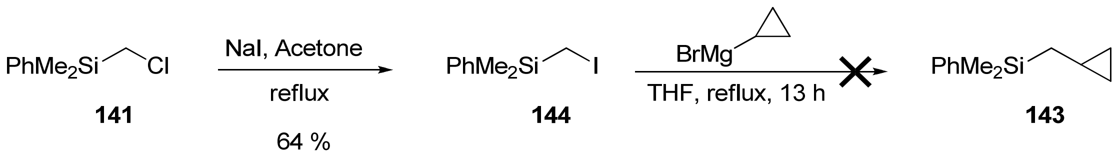
Scheme 2.1

The reaction was performed on a small scale (0.2 mmol) using chloromethyldimethylphenylsilane with cyclopropylmagnesium bromide in THF (Scheme 2.2). The reaction was initially stirred at room temperature and followed by TLC; after 92 h no change had occurred and the reaction was heated at reflux for a further 15 h. After work-up, the material was separated by flash column chromatography to give recovered chloromethyldimethylphenylsilane; none of desired product was observed by ^{1}H NMR.



Scheme 2.2

It was thought that the use of a more reactive electrophile may prove more successful. The reactivity could easily be increased by using a better leaving group than chloride. The iodide was one possible choice as the Finkelstein conversion of a chloride to the iodide is a well-documented procedure.[69] Following the procedure published by Whitmore *et al.*,[70] the iodide was formed from **144** using sodium iodide and dry acetone in moderate yield (Scheme 2.3).



Scheme 2.3

Disappointingly, the subsequent Grignard addition also failed to produce any of the desired cyclopropane **143**. Instead, a mixture of unidentifiable compounds was obtained and analysis by ^{1}H NMR confirmed that no cyclopropyl functionality was present. To confirm the reactivity of the commercial cyclopropylmagnesuim bromide, iodine was used to quench the Grignard reagent with the aim of producing iodocyclopropane. The reaction yielded a small amount of the desired product indicating that some of the Grignard reagent was still active even if some decomposition had also occurred.

Consideration of the electronics of the reaction suggested that there would be a build-up of positive charge on the carbon adjacent to the silicon in the transition state (Fig. 2.2). This would be destabilised by the presence of the electropositive silicon group and could contribute to the failure of this reaction.

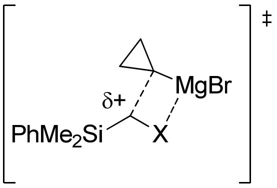
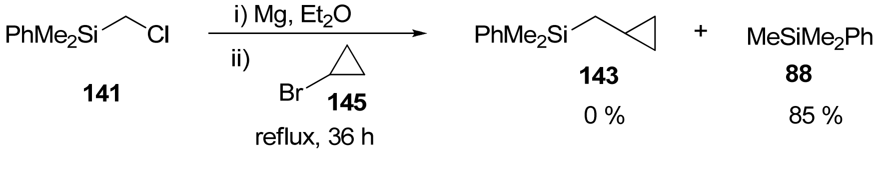


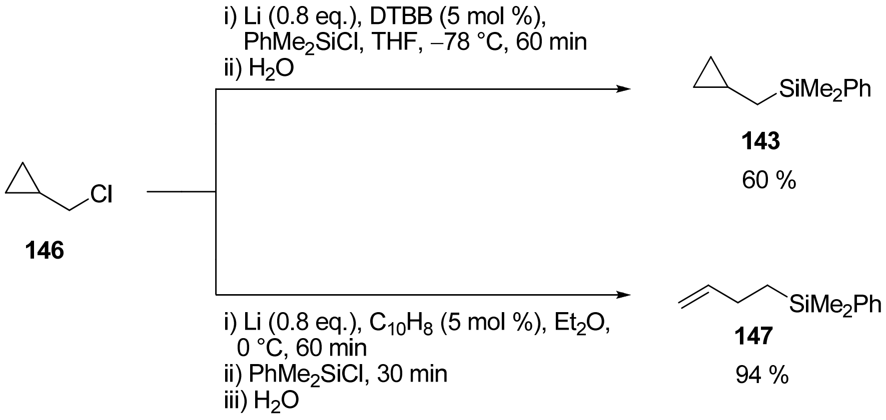
Fig. 2.2 Possible simplified transition state of Grignard coupling

An alternative disconnection was to make the Grignard reagent derived from chloromethylsilane and react it with bromocyclopropane (Scheme 2.4). This route was believed to be more favourable because the silicon would stabilise the negative charge formed at the α-carbon. The Grignard reagent failed to react with the cyclopropyl bromide and upon acidic aqueous work-up, the reduced starting material was recovered in 85 % yield.



Scheme 2.4

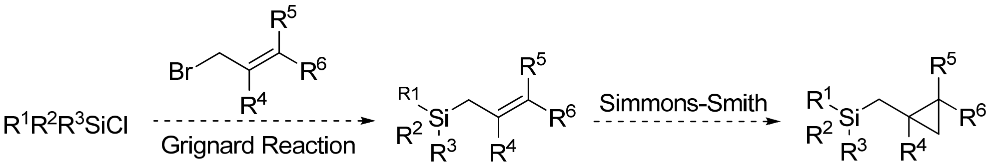
Based on the small number of reactions performed here, it is not possible to state that the reaction holds no potential, but, because of the difficulties encountered, the lack of examples in the literature and the range of alternative approaches available, investigations into an alternative route were undertaken. Since this work was attempted, Yus and co-workers have reported the related direct coupling of cyclopropylmethyllithium and trialkylsilylhalides *via* an arene-catalysed lithiation and subsequent addition reaction using Barbier conditions to give cyclopropylmethylsilanes (Scheme 2.5).[71]



Scheme 2.5

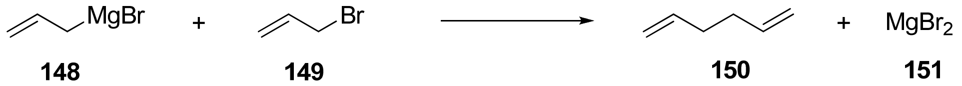
2.1.2 Synthesis of allylsilanes

Several alternative methodologies for the synthesis of unsubstituted silylmethylcyclopropanes have been presented in the literature: the Simmons-Smith reaction (or variations thereof), carbene insertion, ring opening of silacyclopentene[72] and radical addition to methylenecyclopropane.[73] The first two reactions construct the cyclopropane from the corresponding alkene, which in this case would be the corresponding allylsilane. In the later two methods, the desired transformation was reported as a side reaction in low yields as part of mechanistic studies and was not applicable for synthesis. Therefore, the second route we investigated was to use an allylsilane derivative. The alkene would be expected to undergo methylene addition *via* a Simmons-Smith reaction to produce the cyclopropane.[74] The simplest synthetic route to allylsilanes appeared to be a Grignard reaction between the halosilane and allylmagnesium bromide. This route would have a major advantage over other routes as both the substituents on the alkene and silicon could easily be varied (Scheme 2.6).



Scheme 2.6

The preparation of allylic Grignard reagents, in high yields, from allyl halides is documented to be problematic. The difficulty arises because the reactive halide reacts with the Grignard reagent as it forms, resulting in the formation of the homocoupled product. (Scheme 2.7).[75]



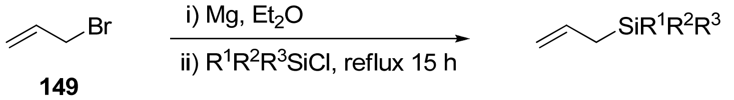
Scheme 2.7

A number of solutions have been established to overcome this problem. One such solution is to use Barbier conditions and form the Grignard reagent in the presence of the electrophile.[76] This results in the Grignard reagent being trapped before it can react with the starting halide. It is generally accepted that the magnesium-carbon bond is formed by a single electron transfer (SET) mechanism, generating a carbon radical at the surface of the metal.[77] In the situation of the reactive allyl halides, the rate of the allyl halide reacting with the magnesium surface is similar to the rate at which it reacts with the freshly formed Grignard reagent. Therefore, increasing the surface area and reactivity of the metallic magnesium reduces the amount of dimerised product formed. For the preparation of many Grignard reagents, commercial magnesium turnings can be sufficiently activated prior to use by either sonication,[78] the addition of an iodine crystal, addition of dibromoethane or using an excess of the starting halide.[79] To access Grignard reagents of very reactive or unreactive halides, Brown and co-workers have shown that magnesium turnings can be conveniently activated by vigorous dry stirring under an atmosphere of nitrogen for 24 h.[75]

Although the unsubstituted allylic Grignard reagent required in this work is commercially available, it was thought advantageous to have a reliable method for the synthesis of allylic Grignard reagents if this synthetic route was to be used for the preparation of more substituted allylsilanes. Initially, trimethylsilyl was used as the silicon group for the synthesis of cyclopropylmethylsilanes but the lack of a UV active chromophore and the low boiling point made it difficult to work with and consequently the dimethylphenylsilyl group was used. In addition to the ease of the handling, the dimethylphenylsilyl had the potential to be of more significant use and versatility as the phenyl substituent offered a synthetic handle to convert the silyl group to the hydroxyl group[80] or remove it completely.[81]

Several of the conditions described above were tested in the synthesis of allyldimethylphenylsilane from allylbromide and magnesium turnings. To compensate for small amounts of dimerised product being formed and consuming the Grignard reagent 2 equivalents of the allyl halide and 2.2 equivalents of magnesium were used. The magnesium was activated by either mechanical activation or addition of iodine; both gave similar yields of the desired product as did performing the reaction under Barbier and Grignard conditions. It was found that if the concentration of the Grignard reagent in THF was higher than 1.4 M, dimerisation became more significant as indicated by formation of a white precipitate ($MgCl_2$). Abel *et al.* reported that cooling Grignard reactions of allylsilanes and allylstannanes to −10 °C before quenching with 10 % *w*/*v* aqueous ammonium chloride solution produced better yields and this work-up was adopted as our standard work-up.[82]

It was found the most successful and convenient method for the synthesis of allylsilanes was based on the procedure reported by Soderquist *et al.* (Scheme 2.8).[83] Allylbromide was added to a suspension of activated magnesium turnings in diethyl ether followed by the chlorosilane and the mixture was heated at reflux temperature. The reaction was cooled to between −10 and 0 °C and quenched with 10 % *w*/*v* aqueous ammonium chloride solution. This method was used effectively for the synthesis of allyltriethylsilane and allyldiphenylmethylsilane.



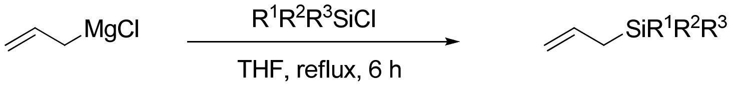
149

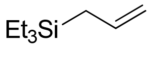
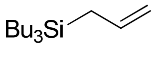
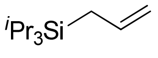
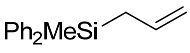
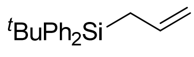
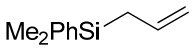
152 R^1, R^2, R^3 = Et 90 %
153 R,$^1R^2$ = Me, R^3 = Ph 59 %

Scheme 2.8

Having found a reliable method for preparing allylsilanes from allyl halides *via* the Grignard reagent, other unsubstituted allylsilanes were synthesised using commercially available Grignard reagent in moderate to high yields (Table 2.1). The allylsilanes were purified by either flash column chromatography using silica gel or reduced pressure distillation.

Table 2.1 Synthesis of allylsilanes using a Grignard methodology

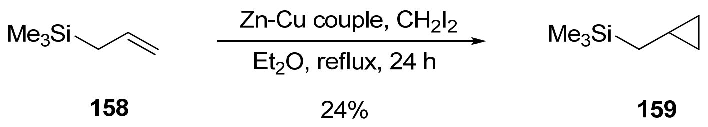


Entry	R^1	R^2	R^3	Product	Yield (%)
1	Et	Et	Et	 **152**	90[a]
2	Bu	Bu	Bu	 **154**	88
3	^{i}Pr	^{i}Pr	^{i}Pr	 **155**	81
4	Me	Ph	Ph	 **156**	59[a]
5	^{t}Bu	Ph	Ph	 **157**	92
6	Me	Me	Ph	 **153**	86

[a] The Grignard reagent was prepared prior to the addition of the chlorosilane from allylbromide and activated magnesium turnings (see experimental for full details).

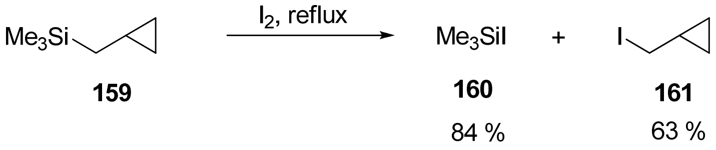
2.1.3 Cyclopropanation of allylsilanes

The next step in the synthetic route was the cyclopropanation of the allylsilanes. A Simmons-Smith reaction was performed on allyltrimethylsilane using commercially available zinc-copper couple (Scheme 2.9) and reaction conditions published in the literature:[84] 1 eq. of allylsilane was heated at reflux temperature in diethyl ether with 1.5 eq. of diiodomethane and 3 eq. of the zinc-copper couple. ^{1}H NMR analysis of the unpurified reaction mixture showed a trace amount of unreacted starting material, a significant number of impurities and the desired product. Purification by distillation gave the desired product in yield of 24 %. Disappointingly, the isolated product was only ever obtained in a yield of between 20-30 % using this method, irrespective of purification by distillation or flash column chromatography. This was slightly lower than the previously reported 38 % yield.[85] Unreacted allylsilane was the only other isolated product of the cyclopropanation reactions although the crude reaction mixtures indicated various silicon species.



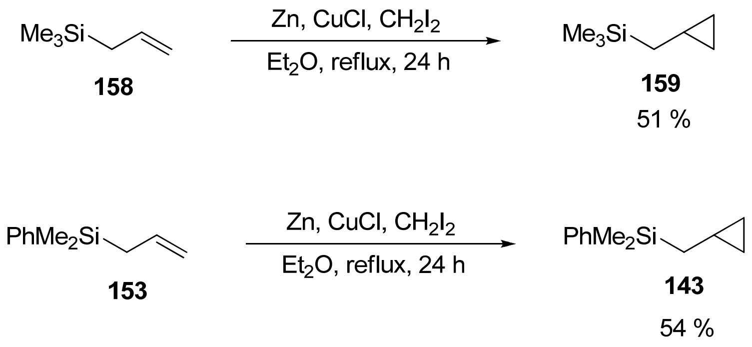
Scheme 2.9

Mironov and co-workers proposed the low yield obtained from the Simmons-Smith reaction was due to free iodide attacking the silicon atom of the product and starting material during the reaction and aqueous work-up.[86] They observed that allyltrimethylsilane underwent cyclopropanation significantly less readily than vinyltrimethylsilane or homoallyltrimethylsilane and that cyclopropyltrimethylsilane reacted with iodine to give iodomethylcyclopropane and iodotrimethylsilane in good yield (Scheme 2.10). Their solution was to carry out the reaction with a non-aqueous work-up, although, in our hands, this method produced similar yields to performing the reaction with an aqueous workup.



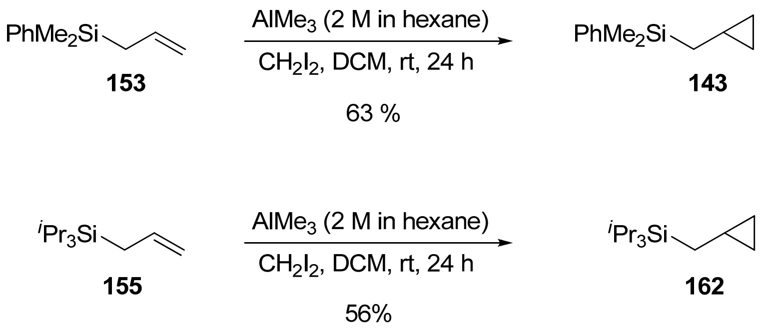
Scheme 2.10

Concerned that the commercial zinc-copper couple had undergone some measure of decomposition, causing the low yields in the cyclopropanation, the couple was freshly prepared according to the method published by Rawson *et al.*[87] Equal molar equivalents of zinc powder and copper chloride in diethyl ether under an inert atmosphere were heated at reflux temperature for 30 min. The alkene and diiodomethane were subsequently added to the reaction mixture and the reaction then performed as before. Utilizing this method of generating the zinc-copper couple *in situ*, cyclopropylmethyltrimethylsilane was synthesised in an improved yield of 51 %. It was anticipated that if, as proposed, the generation of iodine in the reaction mixture was partly responsible for the moderate yield, a more sterically congested silyl group like the dimethylphenylsilyl group would give a better yield. Under identical reaction conditions, cyclopropylmethyldimethylphenylsilane was produced in an overall yield of 54 % from the allylsilane (Scheme 2.11).



Scheme 2.11

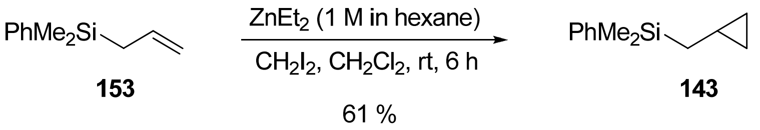
As the original Simmons-Smith reaction generated the desired cyclopropanes in only moderate yields, alternative methods were examined. One method that appeared to offer a good route for the cyclopropanation of allylsilanes was Yamamoto's modified version of the Simmons-Smith reaction which used trimethylaluminium and diiodomethane.[88] The procedure was employed in the cyclopropanation of both allyltriisopropylsilane and allyldimethylphenylsilane to give the desired products in 56 % and 63 % respectively which are comparable to the original method but the crude reaction mixtures were cleaner and easier to purify (Scheme 2.12).



Scheme 2.12

Shortly after the Simmons-Smith reaction was reported, Furukawa and co-workers found that a similar reactive species could be prepared by substituting the Zn/Cu couple with $ZnEt_2$,[89] presumably forming $EtZnCH_2I$ *in situ*, which would be expected to be more reactive than

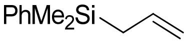
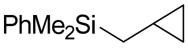
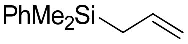
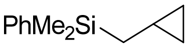
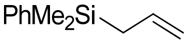
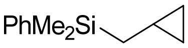
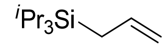
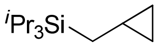
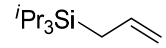
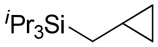
$IZnCH_2I$.[90] The drawback of this method is that it has been reported to be sufficiently exothermic to cause explosions if performed on larger scales.[91] The reaction was performed on a relatively small scale for comparison to the previously outlined methods using allylphenyldimethylsilane as the standard because it is easily synthesised, purified and the starting materials are cheaper than other silanes. The product was obtained in 61 % yield (Scheme 2.13).



Scheme 2.13

Thus in this work three variations of the Simmons-Smith methodology have been examined as routes to converting allylsilanes to the corresponding cyclopropylmethylsilanes: the original method published by Simmons-Smith using the Harrison modification to make the zinc copper couple *in situ*, Furukawa's modification of the original reaction and Yamamoto's method which utilises trimethylaluminium as the metal species. The original Simmons-Smith is a straightforward reaction to perform and one that scales up well. The drawback of the method is that the yields are generally lower and the crude reaction mixture shows more side products. Using Furukawa's method gives cleaner reaction mixtures but has the danger of an explosion on a larger scale. Yamamoto's method of cyclopropanation gives similar yields to the original Simmons-Smith and the product is more easily extracted from the reaction mixture. Table 2.2 shows the yields of the isolated cyclopropanes from the three different methods using the dimethylphenylsilyl group. For two of the methods the allyltriisopropylsilyl group is also shown.

Table 2.2 Summary of different cyclopropanation methodologies used for the synthesis of silylmethylcyclopropane

Allylsilane	Product	Method	Yield (%)
 **153**	 **143**	Simmons Smith[a]	54
 **153**	 **143**	Furukawa[b]	61
 **153**	 **143**	Yamamoto[c]	63
 **155**	 **162**	Simmons Smith	60
 **155**	 **162**	Yamamoto	56

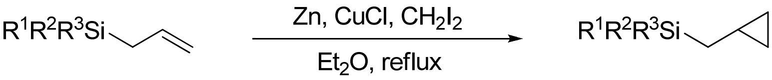
[a] 1 eq. of allylsilane, 2 eq.diiodomethane, 5 eq. of copper chloride and 5 eq. of zinc powder in diethyl ether were heated at reflux temperature for 24 h. [b] 1eq. allylsilane, 5 eq. diiodomethane and 5 eq. of diethyl zinc in DCM were stirred at room temperature for 6 h.[c] 1eq. allylsilane, 2 eq. diiodomethane and 2 eq. of trimethylaluminium in DCM were stirred at room temperature for 24 h.

Owing to the scale of the cyclopropanation reactions (2-10 g), the original Simmons-Smith methodology was usually the most practical route in terms of cost, safety and robustness. It was found that the yield of the Simmons-Smith cyclopropanation could be improved to 71 % with a large excess of reagents and longer reaction times; however, some unreacted alkene always remained. This resulted in the crude reaction mixture containing both the starting material and product which proved exceptionally difficult to separate by distillation or column chromatography. As both compounds were non-polar, purification by flash column chromatography was run eluting with 100 % hexane and often the purification would require the material to be subjected to column chromatography numerous times removing a small amount of pure material each time. This problem was encountered with all the cyclopropanations using the Simmons-Smith reaction and when the reaction was scaled up the problem became more significant.

As allylsilanes are known to undergo cycloaddition reactions, it seemed crucial to have pure cyclopropylmethylsilanes to employ in the following reactions. An effective solution to overcome this purification problem was to use silica gel impregnated with silver nitrate in the flash column chromatography. The application of silver nitrate impregnated silica gel in column chromatography is a known technique for the separation of *cis* and *trans* alkenes.[92] This appeared to be a method that could be applicable to the separation of allylsilanes from cyclopropylmethylsilanes; it was envisaged that the silver would coordinate to the allyl system more than the cyclopropane and the compounds could be separated.

Due to the cost of silver nitrate, several impregnated TLC plates were prepared with various concentrations of silver nitrate to obtain the most effective separation. This was found to be approximately 10-15 wt. % $AgNO_2$:silica; any more than this seemed to make only a small difference. Using this method, the alkene was slightly retained on the silica and a small separation was achieved, allowing the cyclopropane to be eluted from the column first. All column chromatography of the silylmethylcyclopropanes synthesised from allylsilanes was consequently run using a band of approximately 30 % of the total weight of silica impregnated with 10 % silver nitrate above the unmodified silica gel. The unreacted allylsilane could be recycled into another cyclopropanation reaction reducing the amount of waste from the reactions. Table 2.3 summarises the conversion of allylsilanes to cyclopropylmethylsilanes using the best conditions found for the original Simmons-Smith reaction and purified by flash column chromatography using silica gel impregnated with silver nitrate.

Table 2.3 Summary of silylmethylcyclopropanes synthesised using the Simmons-Smith reaction



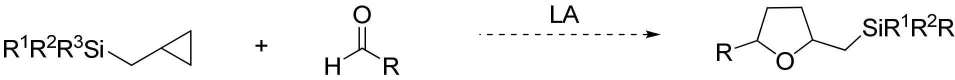
Entry	R^1	R^2	R^3	Product	Isolated yield of cyclopropane (%)	Recovered allylsilane (%)[a]
1	Et	Et	Et	**163**	42	7 (12)[b]
2	Bu	Bu	Bu	**164**	65	9 (13)
3	^{i}Pr	^{i}Pr	^{i}Pr	**162**	77	8 (9)
4	Me	Me	Ph	**143**	82	6
5	Me	Ph	Ph	**165**	71	5
6	^{t}Bu	Ph	Ph	**166**	86	5

[a] In several cases the recovered starting material could not be cleanly separated from the cyclopropane, the value in brackets is the percentage of cyclopropane that eluted with starting material determined by ^{1}H NMR analysis.
[b] The remaining material was identified as hexaethyldisiloxane by GCMS.

2.2 Cycloaddition reactions of silylmethylcyclopropane precursors

2.2.1 Screening reactions

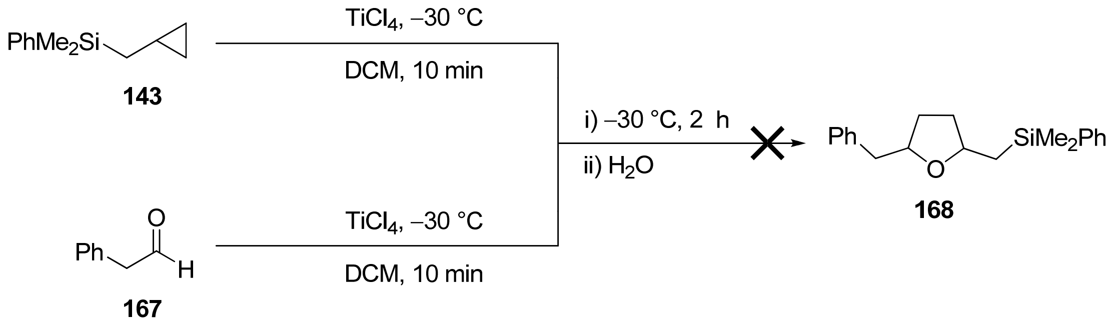
The objective of the screening reactions was to investigate if any cyclisation reaction occurred between a silylmethylcyclopropane and an aldehyde in the presence of a Lewis acid to produce a tetrahydrofuran (Scheme 2.14).



Scheme 2.14

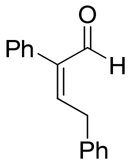
Aldehydes were chosen as the electrophilic partner for several reasons: most importantly, for the preparation of 5 membered cyclic systems, the coupling partner had to be able to contribute one carbon and one oxygen atom to the final product forming the THF. Another reason for using aldehydes is that many methods have been developed for the construction of aldehydes even in the presences of other functional groups, which would broaden the scope and application of any successful method.

Initially, the cyclisation reaction between dimethylphenylsilylmethylcyclopropane **143** and phenylacetaldehyde **167** was attempted. Phenylacetaldehyde was chosen as it is easy to handle, polymerises only slowly and from previous work in the group was found to be fairly reactive.[93] Titanium tetrachloride was selected as the Lewis acid because of the numerous reactions this Lewis acid successfully promotes (Chapter 1). The dimethylphenylsilylmethylcyclopropane **143** and phenylacetaldehyde were activated by addition of the Lewis acid in separate vessels at −30 °C and then combined. After stirring at −30 °C for 2 h, the TLC of the reaction mixture showed many overlapping spots therefore an aqueous work-up was performed and the crude reaction was analysed by ^{1}H NMR spectroscopy. The analysis indicated several silicon containing species and a large amount of unreacted aldehyde were present, whilst the starting cyclopropane had been completely consumed (Scheme 2.15).



Scheme 2.15

On addition of titanium tetrachloride to the cyclopropane the reaction mixture had become a dark red colour. Concerned that the Lewis acid had led to decomposition of the cyclopropane, the reaction was repeated, activating the aldehyde at –78 °C prior to the addition of unactivated cyclopropane. GCMS analysis of the crude reaction mixture revealed a variety of compounds, the major species being the chlorosilane and the aldol condensation product **169**. The mass spectrometry fragmentation patterns of the other compounds suggested polymerised aldehyde.

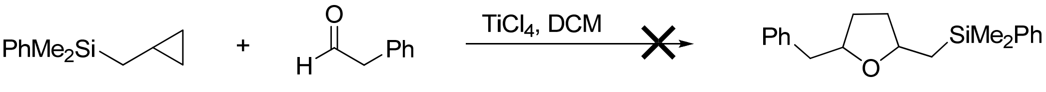


169

Fig. 2.3 Aldol condensation product of phenylacetaldehyde

Numerous efforts at this reaction were attempted, varying the order and temperature that reagents were added and the overall reaction temperature, these are summarised in Table 2.4. The ratio of reagents were 1 : 1.1 : 2 equivalents of cyclopropane : $TiCl_4$: phenylacetaldehyde. The products of these reactions under various conditions were always degradation of starting materials, polymerisation of the aldehyde and aldol products. No cyclopropane was ever recovered or observed in the crude reaction mixtures.

Table 2.4 The cyclisation of cyclopropylmethyldimethylphenylsilane and phenylacetaldehyde with titanium tetrachloride



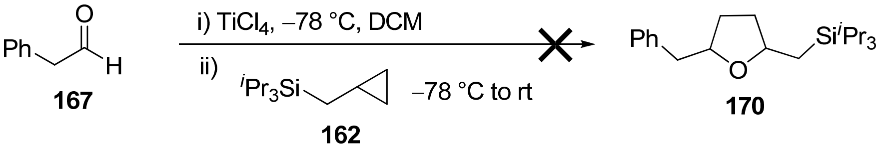
143 **167** **168**

Entry	Order of reagents[a]	Temperature (°C)	Time (h)	Product[b]
1	Aldehyde : cyclopropane : $TiCl_4$	0	2	Decomposition/Aldol
2	Aldehyde : $TiCl_4$: cyclopropane	0	2	Decomposition/Aldol
3	Aldehyde : $TiCl_4$: cyclopropane	−78	2	Aldehyde/Aldol
4	Aldehyde : cyclopropane : $TiCl_4$	−78	2	Decomposition/ Aldehyde
5	Aldehyde : $TiCl_4$ (at 0 °C) : cyclopropane (at −78 °C)	−78	2	Decomposition/Aldol
6	Aldehyde : $TiCl_4$: cyclopropane	−78 to rt	2	Decomposition/Aldol

a All reactions were performed using the following ratio of cyclopropane : $TiCl_4$: phenylacetaldehyde 1 : 1.1 : 2 equivalents.

[b]Products were identified by GCMS and NMR analysis. If there was no evidence by ^1H NMR or GCMS analysis for starting material or the desired THF present in the reaction mixture no purification was attempted.

To assess the effect of the steric properties of the silyl group, the triisopropylsilyl group was next investigated. Pre-mixing the phenylacetaldehyde and $TiCl_4$ in DCM before the addition of the cyclopropane again gave degradation of the starting materials. Due to the strong signals of the isopropyl group dominating the ^1H NMR of the crude reaction mixture, the material was subjected to flash column chromatography to yield several products. The GCMS analysis confirmed that none of the desired product was present.



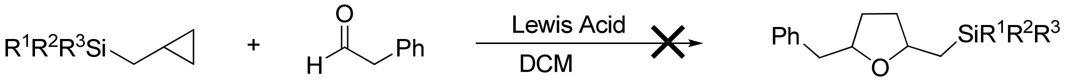
167 **162** **170**

Scheme 2.16

Changing the Lewis acid to boron trifluoride diethyl etherate and performing the reaction in DCM or THF at −78 °C and allowing the reaction to warm to room temperature furnished only the starting material in a recovered yield of 98 % after column chromatography. Indium trichloride is a mild Lewis acid reported to promote organic reactions even in an aqueous medium and has been used previously in the group to promote other silicon containing reactions such as the silyl-Prins reaction.[94] The reaction of cyclopropylmethyldimethylphenylsilane and phenylacetaldehyde with indium trichloride was stirred at room temperature for 24 h, quenched with water and extracted with DCM. By ^{1}H NMR analysis the impure reaction mixture consisted of mostly the unreacted cyclopropane and aldehyde.

Tin tetrachloride is a chelating Lewis acid commonly used in organic synthesis and has been particularly successful for promoting aldol and Mukaiyama aldol reactions in good yields and diastereoselectivities. There are many other examples of reactions that this reagent is able to promote. Activation of phenylacetaldehyde with tin tetrachloride at −78 °C and 0 °C in DCM followed by the addition of either triisopropylsilyl- or dimethylphenylsilyl- methylcyclopropane led to complete consumption of the cyclopropane but none of the desired product was detected from these reactions. The results are summarised in Table 2.5.

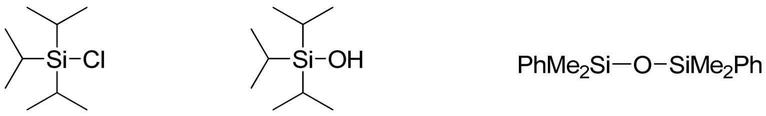
Table 2.5 Attempted Lewis acid promoted cyclisations of silylmethylcyclopropanes



Entry	R^1	R^2	R^3	Lewis Acid	Temp (°C)	Major Product[a]
1	Me	Me	Ph	$TiCl_4$	−78	Disilylether[b] /aldehyde
2	Me	Me	Ph	$TiCl_4$	0	Disilylether[b] /Aldol
3	Me	Me	Ph	$SnCl_4$	−78	Disilylether[b]/aldehyde
4	Me	Me	Ph	$SnCl_4$	0	Disilylether[b]/ Aldol
5	Me	Me	Ph	$BF_3.OEt_2$ (THF)	−78 to 0	Starting material
6	Me	Me	Ph	$BF_3.OEt_2$	−78 to 0	Starting material
7	Me	Me	Ph	$InCl_3$	0 to 21	Starting material
8	^{i}Pr	^{i}Pr	^{i}Pr	$TiCl_4$	−78	Chlorosilane[c]/Aldehyde
9	^{i}Pr	^{i}Pr	^{i}Pr	$TiCl_4$	0	Chlorosilane[c]/Aldol
10	^{i}Pr	^{i}Pr	^{i}Pr	$SnCl_4$	−78	Chlorosilane[c]/Silanol[d]/aldehyde
11	^{i}Pr	^{i}Pr	^{i}Pr	$SnCl_4$	0	Chlorosilane[c]/silanol[d]
12	^{i}Pr	^{i}Pr	^{i}Pr	$BF_3.OEt_2$	−78 to 0	Starting material
13	^{i}Pr	^{i}Pr	^{i}Pr	$InCl_3$	0 to 21	Starting material/Chlorosilane[c]

[a] The major products were identified by GCMS and NMR analysis after an aqueous work-up. If there was no evidence by ^{1}H NMR or GCMS analysis for starting material or the desired THF present in the reaction mixture no purification was attempted. [b] 1,1,2,2-tetramethyl-1,2-diphenyldisiloxane; the condensation product of dimethyl(phenyl)silanol.[c] Chlrortriisopropylsilane [d] Triisopropylsilanol

One feature of these studies was that the cyclopropane was never recovered using $TiCl_4$ or $SnCl_4$ as the Lewis acid, irrespective of the conditions. The crude reaction mixtures often revealed the presence of several silicon containing species (Fig. 2.4). The silicon species were dependent on the silyl group used in the reaction; the triisopropylsilyl group gave a mixture of the chlorosilane and silanol, whilst the dimethylphenylsilyl group gave almost exclusively the 1,1,2,2-tetramethyl-1,2-diphenyldisiloxane **173**.

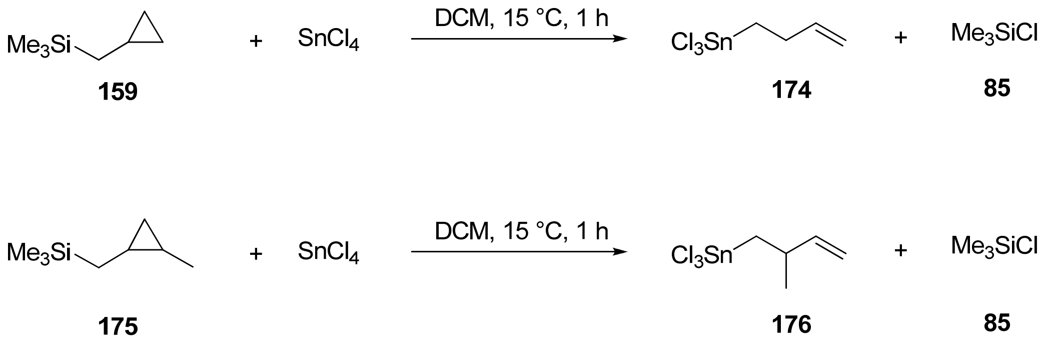


171 **172** **173**

Fig. 2.4 Silicon species observed from the cyclisation reactions

Evidence from the literature that all the silicon species were not products of different sets of transformations but were, in fact, derived from the hydrolysis of the chlorosilane implied that the product of the reaction was the chlorosilane and, upon aqueous work-up, the other derivatives were formed.[95] The likelihood of hydrolysis is increased because, during an aqueous work-up, any Lewis acid remaining from the reaction would decompose to produce a weakly acidic solution. This is consistent with experimental data reported in the literature that described an increase in the rate of hydrolysis of chlorosilanes under acidic conditions.[96] The disilylether **173** is observed with dimethylphenylsilane and the chlorosilane **171** and silanol **172** with the triisopropylsilyl group due to the different rates at which the silyl groups undergo hydrolysis. The rate of hydrolysis of triisopropylsilanes is slower because of the three sterically bulky isopropyl groups on the silicon whilst the dimethylphenylsilylchloride rapidly undergoes hydrolysis followed by condensation.

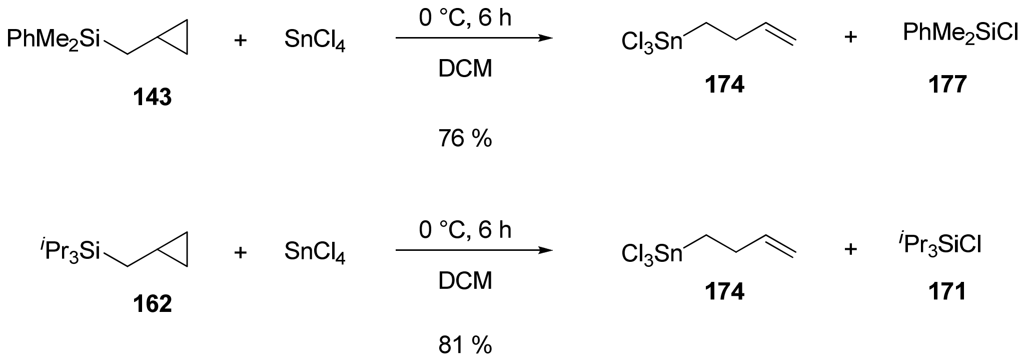
It was uncertain what transformation the cyclopropane fragment was undergoing and what product was formed. The literature offered one possible explanation: in 1987 Ryn *et al.* reported the electrophilic ring opening of trimethylsilylmethyl substituted cyclopropanes with tin tetrachloride to give the corresponding homoallylic tin trichlorides (Scheme 2.17).[97]



Scheme 2.17

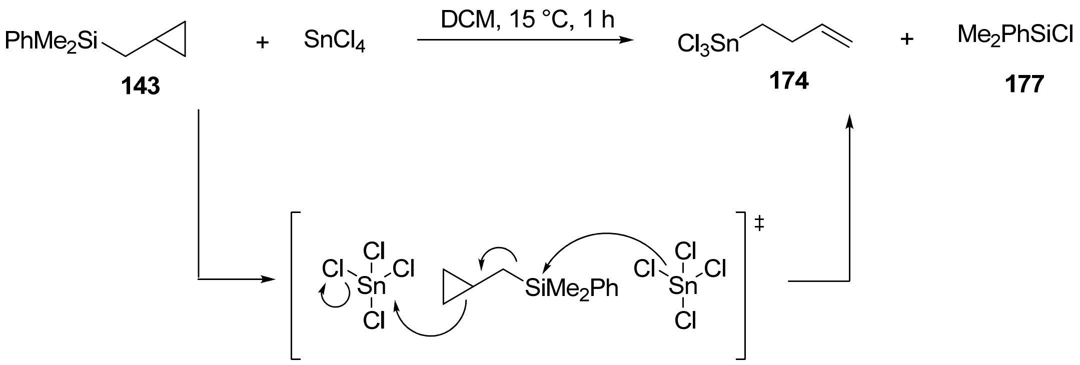
During the study the group examined other substituents on the cyclopropane ring but did not vary the groups on the silicon. The published reaction conditions used shorter reaction times and higher temperatures than our cyclisation reaction but it seemed plausible that other silyl groups would be susceptible to this fragmentation process as well.

To confirm that the degradation products were the homoallylic tin trichloride and the corresponding chlorosilane, each of the silylmethycyclopropanes were stirred with tin tetrachloride in DCM at 0 °C for 6 h then, after removal of the solvent, distilled under reduced pressure. The analysis of the distilled material showed the complete conversion of the cyclopropanes to chlorosilanes and homoallylic tin trichloride. The reaction was repeated and after identification of homoallylic tin trichloride in the crude reaction mixture, an aqueous work-up was carried out. The spectroscopic data of the resulting organic materials were consistent with the previous reactions and revealed that the homoallylic tin trichloride was unstable to aqueous conditions (Scheme 2.18).



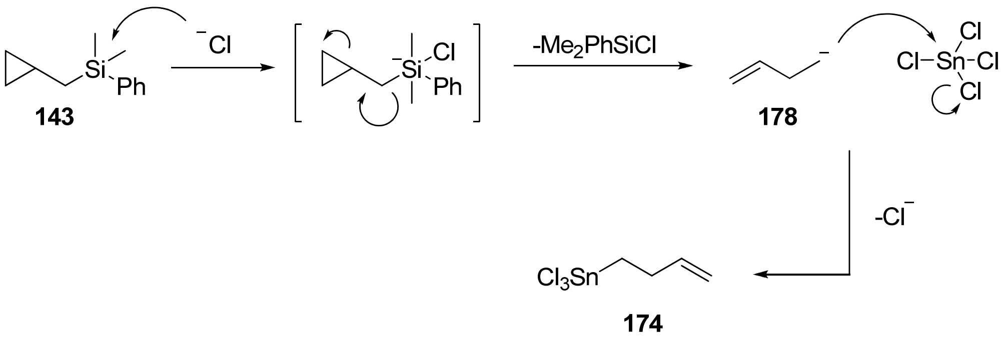
Scheme 2.18

Two types of mechanism can be proposed to account for the observed homoallylic tin trichloride from these reactions. The first is a concerted mechanism where the chlorine-silicon and carbon-tin bonds are formed as the carbon silicon bond breaks (Scheme 2.19).



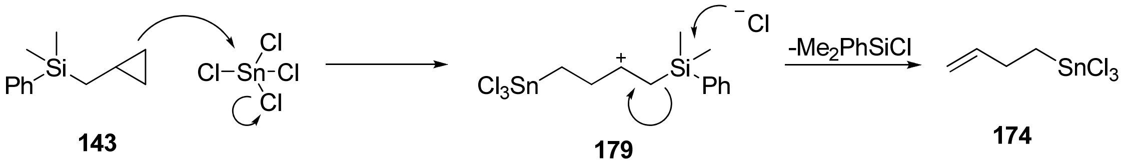
Scheme 2.19

An alternative type of mechanism would be a stepwise mechanism. Two possible sequences of bond breaking and forming steps are feasible: the first possibility is that a chloride ion attacks the silicon atom which is subsequently eliminated from the methylcyclopropyl group to give chlorodimethylphenylsilane and the homoallylic carbanion. This attacks the tin tetrachloride, to form the homoallylic tin trichloride (Scheme 2.20).



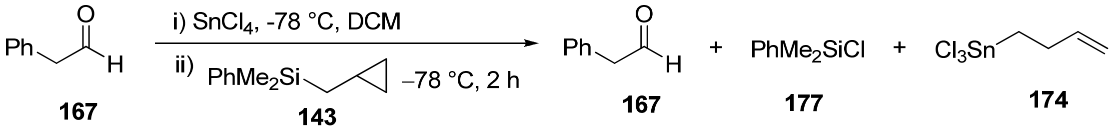
Scheme 2.20

The second possibility is the reverse of the first. The cyclopropane ring could open, forming the tin-carbon bond and the carbocation β to the silicon atom. The silyl group is then eliminated as the chlorosilane and the alkene is formed (Scheme 2.21).



Scheme 2.21

The formation of homoallylic tin trichloride was found to be such a favoured process that repeating the cyclisation reaction of dimethylphenylsilylmethylcyclopropane and phenylacetaldehyde with tin tetrachloride at −78 °C for 2 h with no aqueous work-up gave homoallylic tin trichloride, chlorodimethylphenylsilane and unreacted aldehyde (Scheme 2.22).



Scheme 2.22

The isolation of chlorosilanes from the reactions in which titanium tetrachloride was used as the Lewis acid pointed towards the same process occurring with titanium and presumably forming a titanium homoallylic species. Attempts to observe the formation of the related homoallylic titanium tetrachloride species by either distilling the residue of the reaction or running the experiment in an NMR tube and monitoring by ^{1}H NMR proved unsuccessful.

For the following reactions an aqueous work-up was performed unless otherwise stated and the presence of chlorosilane, silanol, or 1,1,2,2-tetramethyl-1,2-diphenyldisiloxane **173** (when using the dimethylphenylsilyl group) in crude reaction mixture was attributed to ring opening of the cyclopropane with the Lewis acid.

2.2.2 Aldehyde Studies

The results obtained from the attempted cyclisation reactions with $TiCl_4$ and $SnCl_4$ as the Lewis acid indicated that the cyclopropane underwent a reaction with the Lewis acid rather than with the (activated) aldehyde. Hexanal and *para*-nitrobenzaldyde were tested in the cyclisation reaction with dimethylphenylsilylmethylcylopropane at −78 °C and in DCM as the solvent. The reactions of these aldehydes both proved unsuccessful in forming the THF. Decomposition of the starting materials was observed and, in the case of $SnCl_4$ as the Lewis acid, the homoallylic tin trichloride was observed (Table 2.6).

To improve the likelihood that the cyclopropane would react with the aldehyde rather than the Lewis acid, more reactive aldehydes were investigated. Glyoxals **181** and the related glyoxalates **182** are remarkably reactive aldehydes. The presence of the electron-withdrawing carbonyl in glyoxal or the ester functionality in glyoxalates makes the aldehyde more electron deficient and susceptible to nucleophilic attack. In general, they rapidly polymerise when not in solution and exothermically react with water to produce a hydrate. Glyoxal **180** is the simplest of the glyoxals and contains two aldehydes α to each other. Glyoxal **180** and methyl glyoxal are both commercially available as 40 % aqueous solutions. As aqueous solutions are clearly not compatible with Lewis acid reagents, these glyoxals could not be studied. However, the phenyl glyoxal was commercially available as the colourless crystalline monohydrate.


180 **181** **182** **183**

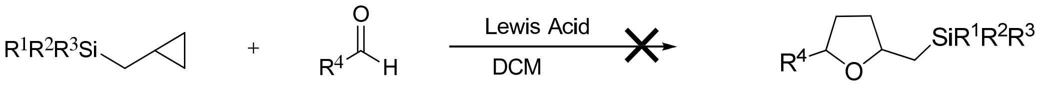
Fig. 2.5

The water from the phenyl glyoxal monohydrate could be removed by distillation under reduced pressure (105-112 °C at 9 mmHg). The distillation of phenyl glyoxal monohydrate was carried out using a Kugelrohr to produce a yellow oil. If the oil was allowed to stand, the neat phenyl glyoxal solidified to a yellow solid or in small quantities reacted with water in the atmosphere to form the monohydrate again. A cyclisation reaction was attempted using phenyl glyoxal, dimethylphenylsilylmethylcyclopropane and tin tetrachloride in DCM at −78 °C. After 4 h at −78 °C a sample was removed and the solvent evaporated under reduced pressure. The homoallylic tin trichloride and chlorosilane were the major products. Repeating the reaction at 0 °C or using titanium tetrachloride at −78 °C failed to give any evidence for the presence of the desired THF. Substituting the dimethylphenylsilylcyclopropane for the triisopropylsilylmethylcyclopropane and repeating the reactions under the same conditions as above were all unsuccessful (Table 2.7, entries 5-9).

Ethyl glyoxalate has found many applications in organic synthesis as a reactive and versatile building block for the construction of complex molecules.[98] Commercially available as a 50 %

solution in toluene, ethyl glyoxalate was investigated in the cyclisation reaction with dimethylphenylsilylcyclopropane using either $TiCl_4$ or $SnCl_4$ to activate the aldehyde. The toluene and trace amounts of water were removed by distillation immediately prior to use in the reaction according to the method reported in the literature.[99] The Lewis acid was added to the aldehyde and allowed to stir, followed by the addition of the cyclopropane at −78 °C. The reaction was then warmed to 0 °C. Both reactions resulted in the decomposition of the starting material with no evidence of the cyclised product. Analysis of an aliquot of the reaction mixture before an aqueous work-up again confirmed the presence of homoallylic tin trichloride when $SnCl_4$ was used (Table 2.7, entries 10 and 11).

Table 2.6 Attempted cyclisation of silylmethylcyclopropanes with a range of different aldehydes

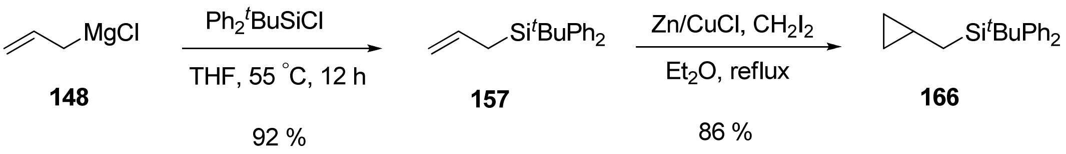


Entry	R^1	R^2	R^3	R^4	Lewis Acid	Temp (°C)	Major Products[a]
1	Me	Me	Ph	$CH_3(CH_2)_4$	$TiCl_4$	−78	Disilylether[b]/Aldol
2	Me	Me	Ph	$CH_3(CH_2)_4$	$SnCl_4$	−78	Disilylether[b]/Aldol
3	Me	Me	Ph	p-$NO_2C_6H_4$	$TiCl_4$	−78	Disilylether[b]/aldehyde
4	Me	Me	Ph	p-$NO_2C_6H_4$	$SnCl_4$	−78	Disilylether[b]/aldehyde
5	Me	Me	Ph	PhCO	$TiCl_4$	−78 to 0	Disilylether[b]
6	Me	Me	Ph	PhCO	$SnCl_4$	−78 to 0	Disilylether[b]
7	Me	Me	Ph	PhCO	$SnCl_4$	0	Disilylether[b]
8	^{i}Pr	^{i}Pr	^{i}Pr	PhCO	$TiCl_4$	−78	Chlorosilane[c]/silanol[d]
9	^{i}Pr	^{i}Pr	^{i}Pr	PhCO	$SnCl_4$	−78	Chlorosilane[c]/silanol[d]
10	Me	Me	Ph	EtO_2C	$TiCl_4$	−78	Disilylether[b]
11	Me	Me	Ph	EtO_2C	$SnCl_4$	−78	Disilylether[b]

[a] The major products were identified by GCMS and NMR analysis after an aqueous work-up. If there was no evidence by ^{1}H NMR or GCMS analysis for starting material or the desired THF present in the reaction mixture no purification was attempted. [b] 1,1,2,2-tetramethyl-1,2-diphenyldisiloxane; the condensation product of dimethyl(phenyl)silanol. [c] Chlrortriisopropylsilane [d] Triisopropylsilanol

2.2.2.1 Cyclisations of *tert*-butyldiphenylsilane with phenyl glyoxal

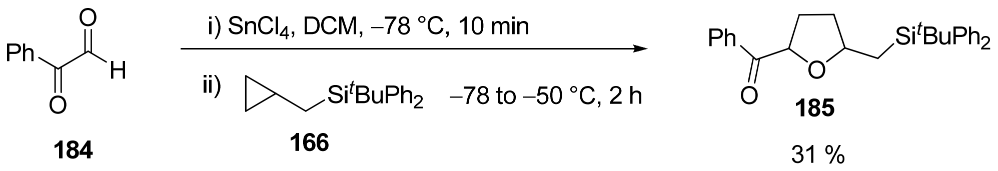
An examination of the literature relating to the cycloaddition of donor acceptor substituted cyclopropanes revealed Yadav and co-workers proposed that the best method to prevent nucleophilic attack at silicon was the incorporation of bulky substituents on the silicon. Accordingly, they used the *tert*-butyldiphenylsilane group in their work.[66] Our own research suggested that the mono-substituted cyclopropanes were undergoing ring opening and nucleophilic attack followed by elimination of the silicon group in the presence of the Lewis acid. In an attempt to prevent nucleophilic attack at the silicon group the bulky *tert*-butyldiphenylsilylmethylcyclopropane was synthesised, according to the methods already outlined (Scheme 2.23).



Scheme 2.23

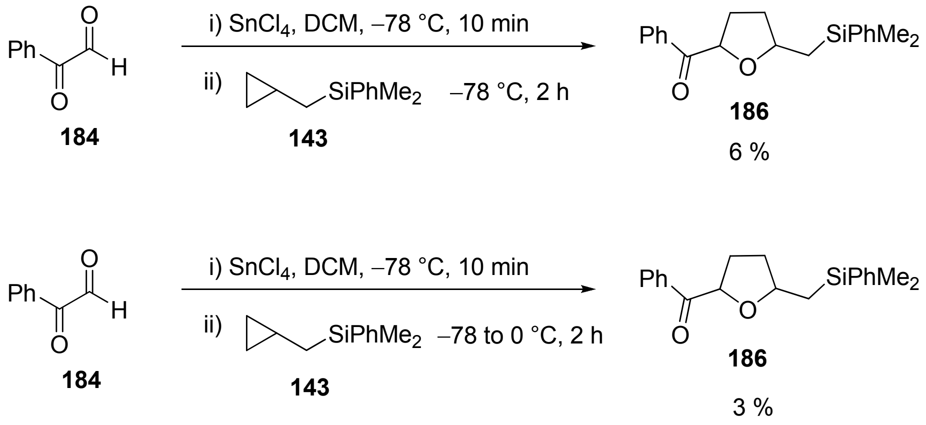
The reaction to form *tert*-butyldiphenylsilylmethylcyclopropane proceeded smoothly and the desired cyclopropane was obtained in an isolated yield of 79 % from the chloro-*tert*-butyldiphenylsilane. Having synthesised the more sterically congested *tert*-butyldiphenylsilylmethylcyclopropane, the compound was tested in the cycloaddition reaction with phenyl glyoxal activated by tin tetrachloride. The tin tetrachloride was added as a solution in DCM to the aldehyde at −78 °C. The reaction was performed at −78 °C being allowed to warm to −50 °C over 1.5 h and was monitored by TLC (Scheme 2.24). An aqueous workup was avoided and the crude reaction mixture was filtered at ambient temperature and concentrated under reduced pressure. The ^1H NMR of the unpurified reaction material was dominated by the methyl signals of the *tert*-butyl group on the silicon but the chromatogram from GCMS analysis did reveal two peaks very close together that had a mass corresponding to the desired product. The material was subjected to column chromatography and the cyclised product was isolated in a yield of 31 %. The reaction was repeated under the same conditions to test the reproducibility and the isolated product after purification was almost identical in yield to the previous reaction (35 %). The reaction was repeated twice more in an attempt to improve the purification using flash column chromatography as the compound showed several close running spots by TLC.

This did not improve the yield and the material needed to be subjected to column chromatography several times to isolate the products.



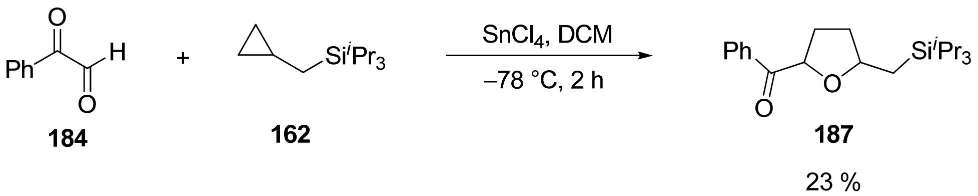
Scheme 2.24

The cycloaddition reactions were also attempted under these conditions with dimethylphenylsilylmethylcyclopropane. This reaction was performed at −78 °C whilst a second reaction was allowed to warm to 0 °C after the reagents were added at −78 °C. A small amount of product was obtained from both reactions (6 % and 3 % respectively). The major product of these reaction was the disilylether (Scheme 2.25).



Scheme 2.25

The lower yield obtained from the cyclisation of dimethylphenylsilylmethylcyclopropane suggested that the steric properties of the silyl group strongly influence the products of the reaction. To confirm this hypothesis, the triisopropylsilylmethylcyclopropane was tested in the reaction. As the triisopropyl (TIPS) group has been reported in the literature to be smaller than the *tert*-butyldiphenyl (TBDPS) group and larger than the dimethylphenyl (DMPS) group, an intermediate yield was expected (Section 2.3.4).[100] Using identical reaction conditions as before, the TIPS substituted cyclopropane gave an isolated yield, after column chromatography, of 23 % (Scheme 2.26).



Scheme 2.26

This confirmed that the steric bulkiness of the groups on the silicon has an effect on the products of the reaction. It appeared that the size of the groups on the silicon affected the rate of nucleophilic attack by the chloride ion at the silicon. Reducing the rate of this reaction increases the amount of the desired THF produced.

Disappointingly, an article outlining the [3+2] cycloaddition reaction of cyclopropylmethylsilanes and α-ketoaldehydes using the same reagents as the ones we had found in the screening reactions was discovered in the literature at this time. The work, published by Akiyama *et al.*, reported the cyclisation of several cyclopropylmethylsilanes in [3+2] cycloaddition reactions with substituted phenylglyoxals. They reported that tin tetrachloride in dichloromethane gave the best yields and that the relative stereochemistry of the tetrahydrofuran is temperature dependent.[101] At −78 °C, a mixture of the *cis* and *trans* substituted tetrahydrofurans was obtained, whilst at 0 °C, the only observed product was the *trans* isomer. There was a conspicuous difference between the yields obtained from our screening reactions and yields reported in the article for the cyclisation reactions at −78 °C and 0 °C. In our hands, the cyclisation of triisopropylsilylmethylcyclopropane and phenylglyoxal at −78 °C gave a yield of 23 % and completely failed at 0 °C, while the paper records yields of 100 % and 83 % at −78 °C and 0 °C respectively. The published article was a communication without any experimental procedures; therefore, no direct comparison of the conditions was possible. A request was made directly to the author for an electronic copy of the supporting information; disappointingly, no response was received.

As it was our intention to develop the method to be applicable to other aldehydes and more substituted cyclopropanes, it was decided that the reaction conditions should be optimised before trying to expand the scope. Since the highest yield obtained from the reaction conditions in the preliminary reactions was 35 % and the purification of the THF was challenging, a program of optimisation was undertaken varying the dilution, temperature, order of addition of the reagents and reaction work-up conditions.

2.2.3 Optimisation Reactions

The cyclisation reaction between triisopropylsilylmethylcyclopropane and phenyl glyoxal was examined in the optimisation reactions. There were several reasons for choosing this silyl group:

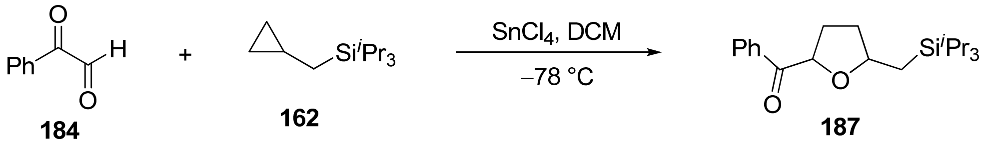
1. The triisopropylsilyl group had given similar yields to the *tert*-butyldiphenylsilyl group but was less problematic and quicker to purify by column chromatography.
2. The dimethylphenylsilylmethylcyclopropane gave such poor yields in the cyclisation that it was difficult to isolate in such small amounts from the other by-products of the reaction.
3. The use of a silyl group that did not contain aromatic protons and had an easily identifiable ^{1}H NMR spectra would simplify interpretation of the cyclised products in the spectra.

The optimisation reactions were performed on a 0.6 mmol scale (with respect to the silylmethylcyclopropane) using the following ratios of reagents: 1 eq. of silylmethylcyclopropane, 1.5 eq. of phenyl glyoxal and 1.1 eq. of $SnCl_4$. All the reagents were added as solutions in DCM. The reactions were followed by TLC although the silylmethylcyclopropane and the chlorosilane produced from the cyclopropane reacting directly with the tin tetrachloride had very similar R_f values (approx. 0.9 in hexane). GCMS was also used to follow the progress of the reactions, although notably the THF product only appeared present in small amounts until an aqueous work-up was carried out. However, the GCMS was valuable for following the consumption of cyclopropane and formation of side products chlorotriisopropylsilane and triisopropylsilanol.

2.2.3.1 Work-up Conditions

The optimisation study began by examining the work-up conditions the THF product could tolerate. In the screening reactions the solvent had been removed under reduced pressure and the residue purified by column chromatography. The problem with this method was that the chromatography was made more difficult because of the tendency of the tin compounds to streak. We were also wary of concentrating any unreacted tin tetrachloride in the reaction mixture as it might lead to decomposition of the desired product. To quench the reaction at −78 °C a 1:1 mixture of acetone and water cooled to −78 °C was added and the reaction then allowed to warm to 0 °C. If the reaction was run at 0 °C it was quenched by addition of water at this temperature. The reaction was then subjected to an aqueous work-up using distilled water and the product extracted with DCM although the formation of emulsions could make the extraction slow. Exchanging water for either acidic (1 M HCl) or basic (saturated $NaHCO_3$) aqueous solutions gave comparable yields (Table 2.7) The aqueous work-up did not improve the yield of the reaction but did make the purification easier so distilled water was used as the standard work-up conditions.

Table 2.7 Summary of the Work-up conditions tested

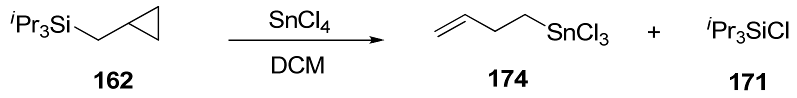


Entry	Work-up Conditions	Yield of isolated THF (%)[a]
1	No work-up (concentrated *in vacuo*)	23
2	1 M HCl	21
3	Sat. $NaHCO_3$ solution	24
4	H_2O	24
5	Acetone/ H_2O (−78 °C)	21

[a] the product extracted with DCM, the solvent was removed under reduced pressure and the pure product was obtained by flash column chromatography of the resulting residue.

2.2.3.2 Order of addition of reagents

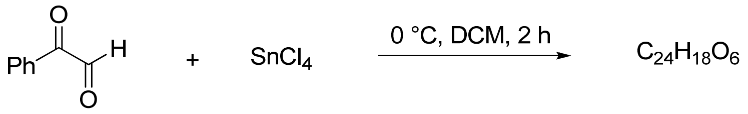
The next stage of the optimisation process was to investigate the order and temperature at which the reagents were combined. The results of the screening reactions indicated that the Lewis acid and cyclopropane could not be mixed together without the aldehyde present otherwise the cyclopropane rapidly underwent ring opening to yield the homoallylic tin trichloride species (Scheme 2.27). This transformation was a strongly favourable reaction even at −78 °C.



162 **174** **171**

Scheme 2.27

Combining the aldehyde and $SnCl_4$ at 0 °C and then cooling the reaction to –78 °C and adding the cyclopropane was found to give 6 % of the THF product. The major product was an aromatic species containing carbonyl functionality with an observed mass of 297 m/z. The compound was suspected to be polymerised aldehyde that had reacted when activated by the $SnCl_4$ at 0 °C. This product was often present by GCMS even if the desired product was obtained in a good yield. This was attributed to the excess aldehyde used, which, once the cyclopropane had been consumed, reacted with itself. Stirring phenyl glyoxal and $SnCl_4$ in DCM at 0 °C for 2 h confirmed that the species was a product of a homocoupling reaction (Scheme 2.28). The compound was isolated by column chromatography but attempts to identify the specific structure were unsuccessful although the mass spectra using chemical ionisation (NH_3) corresponded to a trimer of phenyl glyoxal (402 m/z).



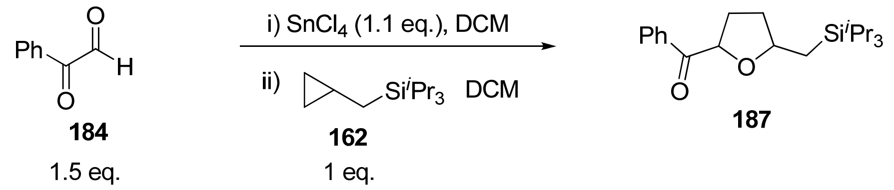
Scheme 2.28

When the phenyl glyoxal and $SnCl_4$ were combined at –78 °C and allowed to stir for 5 min before the addition of the silylmethylcyclopropane this side reaction became negligible at least until after the cyclopropane was consumed. Addition of $SnCl_4$ to the aldehyde at –78 °C followed by the dropwise addition of the silylmethylcyclopropane became the standard method for the rest of the optimisation reactions.

2.2.3.3 Effect of concentration on the cyclisation

In the initial reactions phenyl glyoxal had been examined in the reaction with triisopropylsilylmethylcyclopropane and no product had been obtained. Later when the reaction was repeated using conditions that had successfully given the THF from *tert*-butyldiphenylsilylmethylcyclopropane, the reaction proceeded in a yield of 23 %. It was proposed that the *tert*-butyldiphenylsilylmethylcyclopropane gave the desired THF product because the larger groups on the silicon made it less susceptible to nucleophilic attack. The fact that the triisopropylsilane gave a small amount of product in one of the reactions but not the other indicated that the conditions had changed to make the formation of the desired THF more favourable. The only identifiable difference was that $SnCl_4$ was added as a solution to the reaction that produced the THF. This observation posed the question of whether the reaction was affected by the concentration of the entire reaction or the concentrations in which the tin was added. To understand the influence of concentration on the reaction a series of experiments were undertaken. The recorded yields of the reactions in Table 2.8 are all isolated yields, as, ultimately, we wanted to develop the reaction as a practical synthetic method.

Table 2.8 The effect of concentration on the yield of the cyclisation



Entry	Cyclopropane added in mLs of DCM (mL)	Tin tetrachloride added in mLs of DCM (mL)	Phenyl glyoxal in DCM (mL)	Initial temp (°C)	Temp $SnCl_4$ added (°C)	Temp triisopropylsilylmethylcyclopropane added (°C)	Final Temp (°C)	Time (h)	Yield of THF (%)
1	1	1	2	−78	−78	−78	0	1.5	23
2	1	1	2	−78	−78	−78	−78	1.5	23
3	1	1	2	−78	−78	−78	−78	1.5	21
4	2	1	2	−78	−78	−78	−78	1.5	54
5	2	1	2	−78	−78	−78	−78	2.5	53
6	2	1	2	0	0	0	0	2	8
7	2	1	2	0	0	0	0	1.5	9
8	3	2	2	−78	−78	−78	0	1	63
9	3	2	2	−78	−78	−78	−78	1.5	52
10	3	2	2	−78	−78	−78	−78	1	69
11	3	2	2	−78	−78	−78	0	2	28[a]
12	3	3	3	0	0	0	0	1	13
13	3	3	3	−78	−78	−78	−78	1	65
14	3	3	3	−78	−78	0	0	1	6
15	4	4	4	−78	−78	−78	−78	1	37
16	4	4	4	−78	−78	−78	−78	2.5	45
17	4	4	4	−78	−78	−78	−78	4	50
18	4	4	4	0	0	0	0	2	24

[a] Triisopropylsilylmethylcyclopropane and phenyl glyoxal were mixed before the addition of $SnCl_4$.

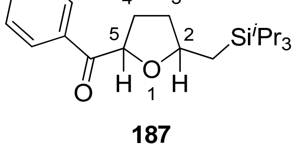
Decreasing the concentration of the reaction, by adding the reagents as more dilute solutions, was observed to improve the yield of the THF as long as the reaction was performed at low temperature. If the concentration decreased below 0.06 M (based on the concentration of cyclopropane) the reaction became slow with unreacted starting material recovered and polymerised aldehyde formed as the major by-product. The optimum concentration (Table 2.8, entry 10) was found to be a concentration of 0.09 M (based on the concentration of cyclopropane) giving the THF in 69 %. Addition of any of the reagents at 0 °C led to a decrease in the yield of the THF (Table 2.8, entries 6, 7 and 14) and the chlorosilane was identified as a major impurity. Having found conditions that gave a good yield the order in which the reagents were combined was re-examined. Adding the tin tetrachloride to a stirred solution of phenyl glyoxal and silylmethylcyclopropane (Table 2.8, entry 11) again gave a lower yield of the THF. To determine whether the higher yields that resulted from reducing the concentration were actually an effect of using a slower rate of addition, the reaction was repeated using a syringe pump set at 24 mL/h for the addition of the cyclopropane. These conditions turned out to be the most successful giving a yield of 81 %. Similar yields could also be achieved by slowly adding the solution dropwise by a hand held syringe.

2.2.4 Stereochemistry of the 2,5 disubstituted THF ring

During the optimisation reactions, when the reaction was run at temperatures below 0 °C, two compounds were always obtained from the reaction which were inseparable by column chromatography. The compounds had the same molecular mass (but slightly different retention times by GCMS), R_f values and similar NMR signals i.e. the same number of carbon environments and a duplication of proton signals. Therefore, based on the spectral evidence, the compounds were diastereoisomers of the THF arising from the *cis*/*trans* relative stereochemical substitution patterns. Initially, the focus of the optimisation reactions was concerned with improving the yield of the reaction but isolation of one diastereoisomer became desirable. As it had already been reported that at 0 °C only the *trans* stereoisomer was obtained, conditions that would allow the reaction to be performed at 0 °C were sought after. During the optimisation all attempts to perform the reaction at 0 °C had given low yields or failed to give any product. ^{1}H NMR and GCMS analysis of the small amounts of the THF obtained at 0 °C indicated that one isomer was the major product. One solution to improve the yield and attain a single isomer was to add the reagents at −78 °C and allow the reaction to warm to 0 °C. The drawback of using these conditions were: longer reaction times due to allowing the reaction to warm from −78 °C to 0 °C, the yields were lower than running the reaction at −78 °C and, although one isomer predominated, traces of the other isomer were often seen by GCMS and NMR analysis.

Having determined that lower concentrations of tin tetrachloride improved the yield a syringe pump was used for the addition of the tin tetrachloride to a mixture of phenyl glyoxal and silylmethylcyclopropane at 0 °C. This method gave the desired product in a yield of 73 % and by ^{1}H NMR as a single diastereoisomer. Another advantage over previous addition sequences was only one solution was required prior to beginning the reaction instead of preparing all the reagents as separate solutions. It should be noted that care must be taken during the addition: if the $SnCl_4$ is added too rapidly the homoallylic tin trichloride forms faster than the THF.

Attempts to assign the relative stereochemistry of the two diastereoisomers of the THF were undertaken. As the THFs were both colourless oils, X-ray crystallography was not an option and the assignment had to rely on nOe studies. In contrast to six membered cyclic systems in which the most energetically stable conformation is usually the chair arrangement, five membered systems have no 'natural' conformation. For cyclopentane the most stable conformation is the envelope although the half chair conformation is similar in energy. The energy barrier between the two conformations is small which allows the molecule to rapidly alternate between them.[102] Due to the rapid changes in the conformations and pseudorotation, resulting from one carbon being out-of-plane in the envelope conformation, five membered rings are conformationally flexible which generally leads to weaker enhancements in nOe experiments as compared to the six membered equivalents.[103] Before running the nOe experiments, assignment of the ^{1}H NMR signals of both the single diastereoisomer and mixture were made with the assistance of 2-D NMR experiments, COSEY and HSQC. The C-5 proton (Fig. 2.6) had distinctly different chemical shifts in the two different diastereoisomers (5.13 and 5.30 ppm) while the C-2 proton signals overlapped with each other (4.23-4.30 ppm).



187

Fig. 2.6 Numbering of the THF ring used for the discussion of the nOe data

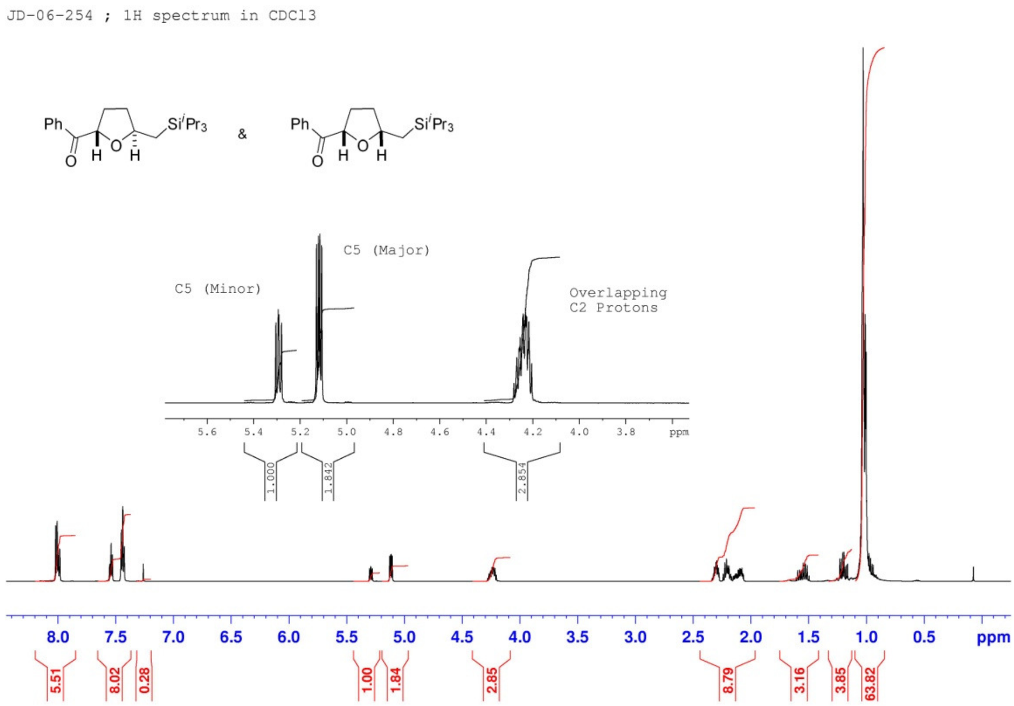


Fig. 2.7 ^{1}H NMR spectrum of the mixture of diastereoisomers of the THF

Irradiation of the signal at 5.30 ppm, assigned as the C-5 proton of the minor diastereoisomer produced an enhancement of the aromatic signal at 7.98-8.02 ppm (1.5 %). This aromatic signal corresponds to the *ortho* protons of the phenyl group and indicates the molecule is in a conformation which twists the phenyl ring towards the C-5 THF proton. Irradiation of the C-5 proton of the major diastereoisomer at 5.13 ppm showed two nOe enhancements one at 4.23-4.30 ppm (0.8 %) and the other at 7.98-8.02 ppm (1.5 %). To confirm this nOe, the C-2 protons of both diastereoisomers (4.23-4.30 ppm) were irradiated and an enhancement of only the signal at 5.13 ppm (0.6 %) was observed. The nOe studies of the single diastereoisomer synthesised at 0 °C verified that no nOe was detectable between the C-5 and C-2 protons (Fig. 2.8).

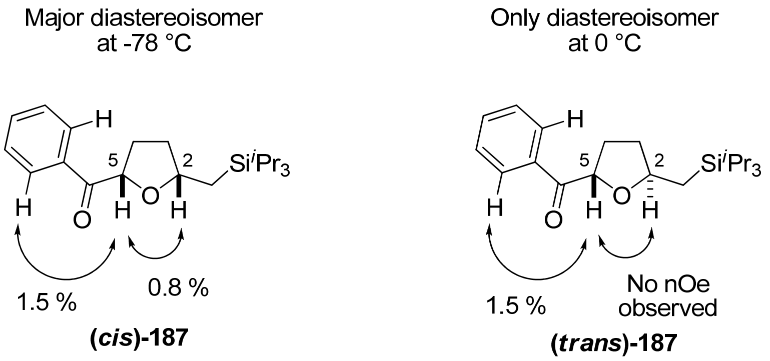


Fig. 2.8 The nOe % enhancements of irradiating the C-5 and C-2 protons

The nOe studies confirmed the relative stereochemistry of the product at 0 °C was the *trans* configuration while at −78 °C a mixture of *cis* and *trans* diastereoisomers were produced in a ratio of 1 :1.6 (*trans*/*cis*) (Fig. 2.9).

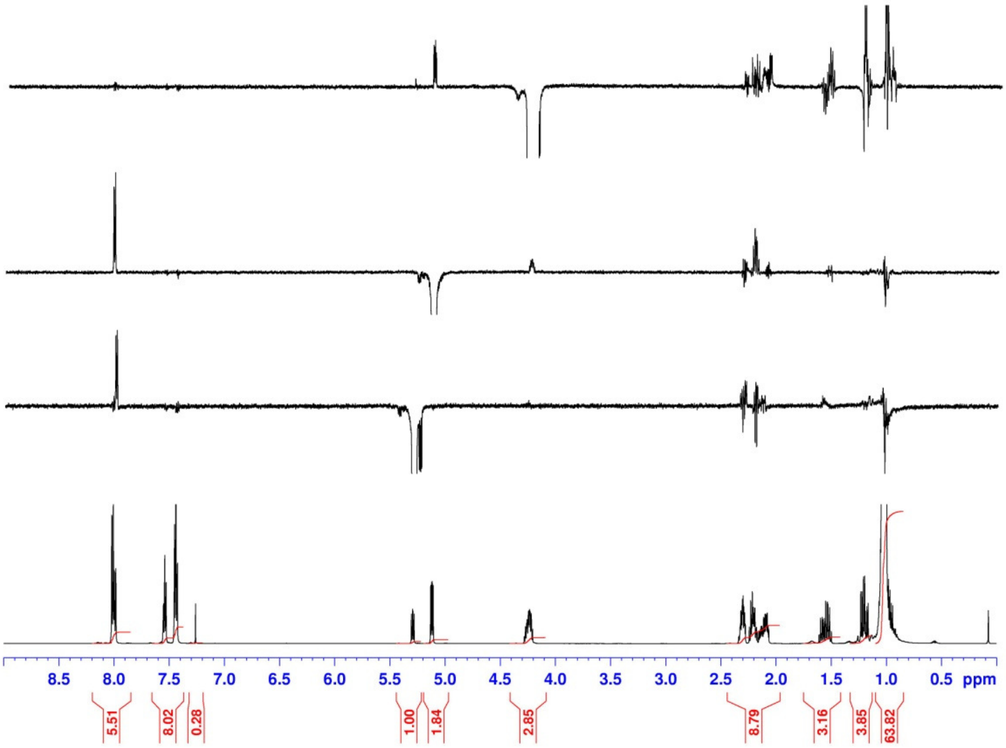
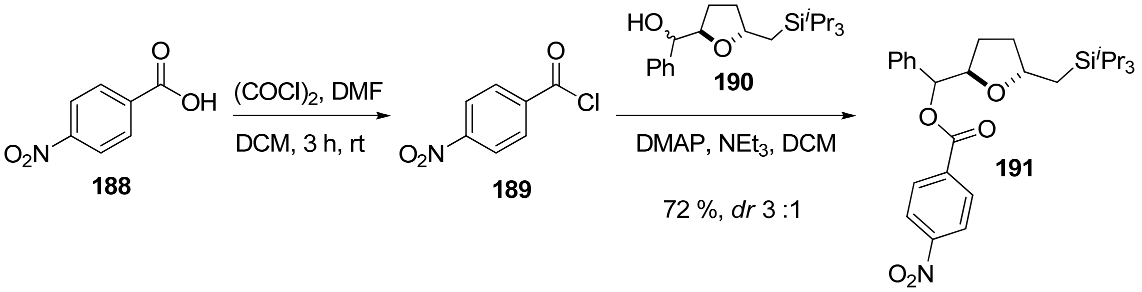


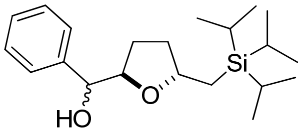
Fig. 2.9 nOe studies of the mixture of diastereoisomers

Throughout this work all the evidence for the relative stereochemistry of the THFs had come from nOe studies, which, because of the flexibility of the five membered ring, only showed a small enhancement upon irradiation. To support the assignment of the relative stereochemistry a X-ray crystal structure was sought. The problem was that the α-keto THFs were all colourless oils. Knowing that *para*-nitrobenzoic ester derivatives are frequently crystalline, the ketone **187** was reduced to the alcohol **190** (full details in section 2.4.4) and reacted with nitrobenzoyl chloride to give **191** (Scheme 2.29).



Scheme 2.29

The ester failed to crystallise even on slow evaporation from a saturated solution. However, after several weeks, the starting alcohol of the triisopropylsilylmethyl THF **190** did crystallise and the X-ray crystal structure was solved (Fig. 2.10).


190

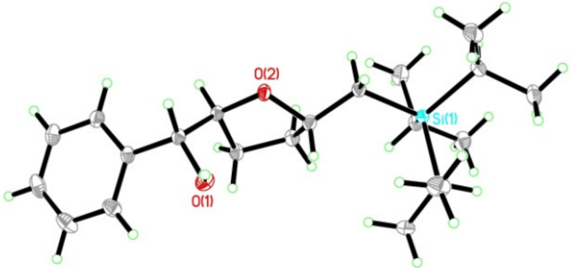


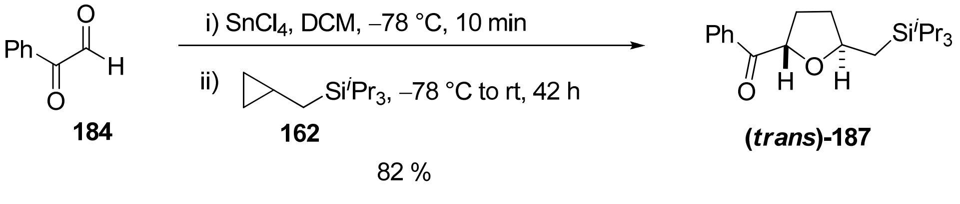
Fig. 2.10 X-ray structure for phenyl-((±)-5-((triisopropylsilyl)methyl)tetrahydrofuran-2-yl)methanol 190

The crystal structure of THF **190** confirmed the *trans* relationship of the C-2 and C-5 substituents and, since the sodium borohydride reduction of the ketone is unlikely to effect the ring stereochemistry, it is reasonable to conclude, in conjunction with the nOe data that the cyclisation step formed the α- keto THF with *trans* relative stereochemistry.

2.2.5 Stability of the THF product

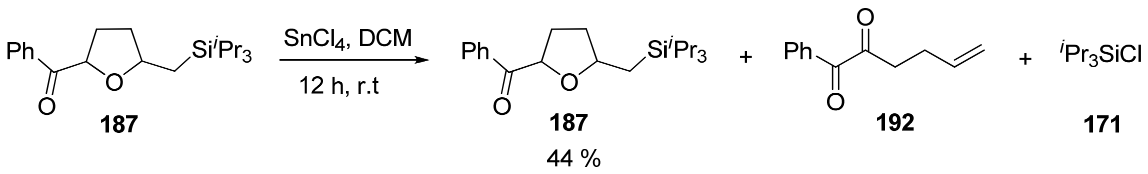
The α-keto THF was relatively unstable; no quantitative measurements were taken on the rate of decomposition but a sample left at room temperature for 12 h would become pale yellow. The colour increased in intensity the longer the sample was left. A crystalline solid was isolated by recrystalisation (petroleum ether 40-60 °C) from the decomposed material and was confirmed to be benzoic acid. Assuming that the carbonyl group of the benzoic acid is the same carbonyl from the THF it seems reasonable to hypothesise that the decomposition could arise from the nucleophilic addition of water followed by fragmentation. Keeping the sample as a solution in chloroform at –30 °C significantly slowed the decomposition process and allowed to the sample to be kept for several days without any evidence of decomposition by ^{1}H NMR analysis.

If the THF was unstable to acidic conditions then it might be unstable to the Lewis acid conditions of the reaction, which could lead to decomposition of the product as it formed. To test the stability of the THF the reaction was setup as usual at –78 °C but allowed to stir at room temperature for 42 h and then worked-up in the standard way. The reaction gave the desired product in good yield (82 %) and as the single *trans* diastereoisomer demonstrating that even at room temperature for long periods of time the THF was stable to the reaction conditions (Scheme 2.30).



Scheme 2.30

If, however, the pre-formed THF was stirred in DCM with tin tetrachloride at room temperature for 12 h using the same concentration and quantities as the optimisation reactions only 44 % of the THF was recovered. The GCMS of the crude material after an aqueous work-up showed the presence of chlorotriisopropylsilane and an aromatic species with a mass of 188 *m/z*, a possible structure may be **192**.



Scheme 2.31

2.2.6 Summary of the optimisation reactions

The following conclusions may be drawn from the optimisation reactions of triisopropylmethylcyclopropane and phenyl glyoxal. Both the order in which the reagents are added and the concentration of the reaction have an important influence on the products obtained. Depending on the reaction conditions two possible side reactions may occur: a polymerisation reaction of the aldehyde and the nucleophilic addition of the cyclopropane to the tin tetrachloride followed by elimination of the silicon. The temperature of the reaction controls the relative stereochemistry of the product, at −78 °C the *cis* diastereoisomer is slightly favoured (1.6 : 1), while at 0 °C only the *trans* diastereoisomer is obtained. The α-keto THF product is stable to mild acidic, basic and neutral aqueous work-up conditions but relatively unstable as a neat sample at room temperature. However, it can be stored for several days at −30 °C as a solution in chloroform.

Two sets of conditions were found to be successful for producing the THF in moderate to good yields:

1) The addition of a solution of tin tetrachloride (0.36 M) to a solution of freshly distilled phenyl glyoxal (0.45 M) at −78 °C. After stirring for 3-5 min a solution of the triisopropylsilylmethylcyclopropane (0.2 M) was added slowly. This could be achieved by syringe pump and generally the yield improved by approximately 5 %, but for ease slow dropwise addition was usually carried out using a hand held syringe. The reaction could be quenched either by wet acetone at −78 °C or with water if the reaction was allowed to warm to 0 °C.

2) To a solution of freshly distilled phenyl glyoxal (1.5 eq.) and triisopropylsilylmethylcyclopropane (0.15 M) in DCM at the desired temperature was added dropwise a solution of tin tetrachloride (0.36 M) in DCM. The reaction was followed by TLC and GCMS and quenched either by wet acetone at −78 °C or water if the reaction was at 0 °C.

2.3 Examining the scope of the reaction

Having optimised the reaction conditions for the cycloaddition between phenyl glyoxal and triisopropylsilylmethylcyclopropane promoted by tin tetrachloride, the scope of the reaction was examined. The scope of the Lewis acid, aldehyde and silyl group that could be used in the reaction were all investigated.

2.3.1 Lewis acid Screening

The objective of the screening reactions was to find which Lewis acids promoted the reaction in similar or better yields than tin tetrachloride. Tin tetrachloride presented three major disadvantages: firstly, it reacted with the cyclopropane to produce homoallylic tin trichloride; secondly, tin compounds are well known to be toxic; and thirdly there are inherent difficulties in handling an air sensitive, corrosive reagent.

Two different reaction arrangements were used for the Lewis acid screening reactions depending on whether the Lewis acid was a solid or liquid (both based on the first condition outlined above):

1) If the Lewis acid was a solid it was transferred to the flask and DCM was added, then cooled to the required temperature. Freshly distilled phenyl glyoxal was added and the mixture was stirred for approx. 5 min before the silylmethylcyclopropane was added.

2) If the Lewis acid was a liquid or in solution then the Lewis acid was added to a solution of phenyl glyoxal cooled to the required temperature. The mixture was stirred for approx. 5 min before the silylmethylcyclopropane was added.

In both arrangements, the reaction was follow by TLC and GCMS, and subjected to an aqueous work-up. If the crude reaction mixture showed significant amounts of product or starting cyclopropane the material was isolated by column chromatography, otherwise the yields quoted were obtained from the GCMS chromatogram. The results of the Lewis acid screening reactions are summarised in Table 2.9 and 2.10.

No Lewis acid with a triflate counter ion afforded any of the desired product and in most cases led to decomposition of the silylmethylcyclopropane (entry 12, 13, 16 and 27). The one exception was $Zn(OTf)_2$ where the starting material was recovered (80 %, entry 32). Brønsted-

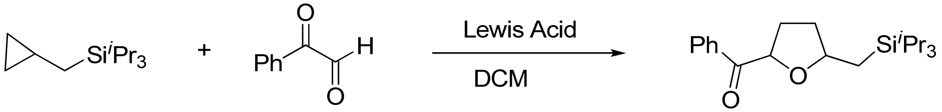
Lowry acids were also ineffective at promoting the reaction (entry 28 and 29). When titanium tetrachloride (entry 8 and 9), aluminium chloride (entry 15), germanium chloride and magnesium bromide were used, only trace amounts of the THF were identified in the crude reaction mixture.

Tin tetrabromide gave a comparable yield of product to tin tetrachloride (entries 5 and 7) although the reaction was slower at −78 °C. With tin tetrachloride the reaction was usually complete after 3 h at −78 °C, whilst using tin tetrabromide the starting silylmethylcyclopropane was recovered in 42 % after 5 h (entry 4). Tin tetrabromide was more difficult to handle than the chloride as it is a crystalline solid at room temperature. For accuracy in the screening reactions a stock solution was prepared from warm tin tetrabromide and DCM and diluted as required.

The only other Lewis acids that promoted the reaction in any significant yield were the zinc halides, in particular zinc bromide, which gave moderate yields of the cyclised product (entry 24). At room temperature, the reaction was slow and starting material was recovered as the major product but when the reaction was heated at reflux temperature for four days with two equivalents of $ZnBr_2$, the THF was obtained in 63 % (entry 24). To determine whether increasing the temperature of the reaction improved the yield, DCE (1,2-dichloroethane) was used as the solvent. Disappointingly, this gave significantly lower yields than DCM (entry 37).

Thus zinc halides and tin (IV) halides are the only Lewis acids to appreciably promote the reaction, although zinc Lewis acids require heating at reflux temperature for longer (4 days) and yielded the desired THF as a 1 : 1 ratio of *cis* and *trans* diastereoisomers. Tin tetrachloride rapidly initiates the reaction at −78 °C and offers control of the relative stereochemistry across the THF ring. For these reasons, it must be concluded that tin tetrachloride is the best Lewis acid to promote this reaction.

Table 2.9 Summary of the cyclisation reaction using different Lewis acids



Entry	Lewis acid	Conditions	Yield of desired THF (%)	Recovered cyclopropane (%)	Major Products
1	$Ti(O^iPr)_4$	−78 °C / 3 h	0	76	Aldehyde and cyclopropane
2	$Ti(O^iPr)_4$	−78 - 0 °C / 3 h	0	77	Aldehyde and cyclopropane
3	$Ti(O^iPr)_4$	0 °C then reflux / 12 h	0	80	Cyclopropane
4	$SnBr_4$	−78 °C/ 5 h	37	42	Bromotriisopropylsilane/Triisiopropylsilanol
5	$SnBr_4$	−78 - 0 °C/ 5 h	52	15	Bromotriisopropylsilane/Triisiopropylsilanol
6	$SnCl_4$	−78 °C/ 3 h	81	0	Chlorotriisopropylsilane/ Triisiopropylsilanol
7	$SnCl_4$	−78 - 0 °C/ 3 h	73	0	Chlorotriisopropylsilane/ Triisiopropylsilanol
8	$TiCl_4$	−78 °C/ 3 h	~1 (GCMS)	11	Clorotriisopropylsilane
9	$TiCl_4$	−78 - 0 °C/ 3 h	~2 (GCMS)	0	Clorotriisopropylsilane
10	$BF_3.OEt_2$	−78 °C/ 4 h	0	64	Cyclopropane and polymerised aldehyde
11	$BF_3.OEt_2$	−78 - rt/ 4 h	0	0	Polymerised aldehyde
12	$Sc(OTf)_3$	−78 - rt/ 24 h	0	0	Triisopropylsilanol
13	$Sn(OTf)_2$	−78 - rt/24 h	0	0	Triisopropylsilanol
14	$SnCl_2$	−78 °C - reflux/ 30 h	0	41	Cyclopropane
15	$AlCl_3$	−78 - rt/ 4 h	9 (GCMS)	20	Chlorotriisopropylsilane
16	TMSOTf	−78 - 0 °C/ 8 h	0	0	Disilylether/aldehyde
17	$TiCl_2(^iOPr)_2$	−78 - rt/ 4 h	0	27	Cyclopropane

Table 2.10 Summary of the cyclisation reaction using different Lewis acids continued

Entry	Lewis acid	Conditions	Yield of desired THF (%)	Recovered cyclopropane (%)	Major Products
18	$InCl_3$	0 °C - rt / 18 h	0	0	Chlorotriisopropylsilane/triisopropylsilanol
19	$SbCl_5$	−78 °C - rt/ 15 h	0	0	Chlorotriisopropylsilane
20	$SiCl_4$	−78 °C - rt/ 12 h	0	26	Chlorotriisopropylsilane
21	$GeCl_4$	−78 °C - reflux/ 30 h	1 (GCMS)	53	Cyclopropane
22	$ZnBr_2$	−78 °C - rt /5 h	14	35	Cyclopropane and aldehyde
23	$ZnBr_2$	reflux/48 h	15	0	Cyclopropane and aldehyde
24	$ZnBr_2$ (2 eq.)	reflux /96 h	63	0	Bromotriisopropylsilane
25	$FeCl_3$	−78 - 15 °C/ 15 h	0	0	Chlorotriisopropylsilane
26	$InCl_3$	reflux/ 24 h	0	0	Chlorotriisopropylsilane/triisopropylsilanol
27	$Y(OTf)_3$	−78 °C - rt / 48 h	0	12	Cyclopropane/triisopropylsilanol
28	TFA	−78 °C - rt / 24 h	0	25	triisopropylsilanol
29	H_2SO_4	0 °C - reflux / 24 h	0	0	Unknown
30	$MgBr_2.OEt_2$	reflux /16 h	~1 (GCMS)	4	Decomposition
31	$ZnCl_2$	0 °C - reflux / 6 days	31	24	Cyclopropane
32	$Zn(OTf)_2$	0 °C - reflux / 6 days	0	80	Cyclopropane
33	$MgCl_2$	0 °C - reflux / 6 days	0	54	Cyclopropane and aldehyde
34	$CeCl_3$	rt - reflux / 4 days	0	100	No Reaction
35	$AuCl_3$	rt / 4 days	0	100	No Reaction
36	$ZnCl_2$	rt - reflux / 40 h /DCE	34	47	Cyclopropane
37	$ZnBr_2$	rt - reflux / 40 h /DCE	12	14	Polymerised aldehyde
38	ZnI_2	rt - reflux / 40 h /DCE	1-2	6	Polymerised aldehyde

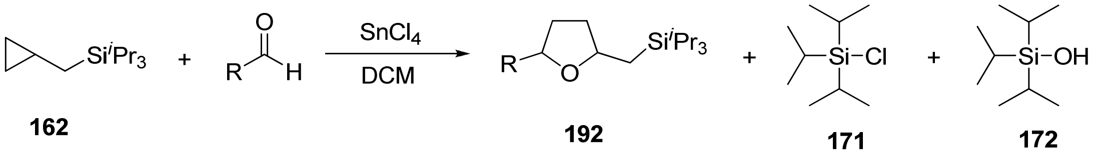
2.3.2 Aldehydes

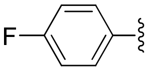
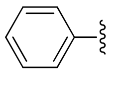
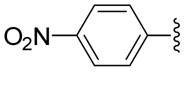
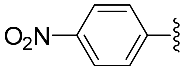
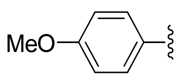
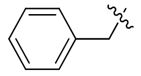
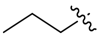
One of the overall aims of this work was to examine the range of aldehydes that could be used in the reaction. Employing the conditions previously optimised for the reaction between triisopropylmethylsilylcyclopropane, phenyl glyoxal and tin tetrachloride, a range of different aldehydes were screened (Table 2.11). Aware that combining tin tetrachloride and silylmethylcyclopropane at 0 °C was likely to cause rapid ring opening of the cyclopropane, the reactions were carried out at −78 °C and, if no reaction was observed by TLC and GCMS, the reaction mixture was allowed to warm. The results are summarised in Table 2.11.

A range of aromatic aldehydes containing either electron-donating or electron-withdrawing substituents at the *para* position were investigated (entries 1-4). None of these aldehydes produced any of the desired THF and the isolated products were always the chlorotriisopropylsilane, triisopropylsilanol and recovered aldehyde. This proved the cyclopropane had reacted directly with the tin tetrachloride. Interestingly, no reaction occurred at −78 °C and even at 0 °C decomposition of the cyclopropane was slow enough that after 3 hours some starting material was observed in the crude reaction mixture of several reactions. Previous reactions had shown that at 0 °C complete consumption of the silylmethylcyclopropane was observed after 1 hour. This implied that the aldehyde was slowing the direct reaction between tin tetrachloride and silylmethylcyclopropane most probably by complexation. To increase the likelihood of the silylcyclopropane reacting with the aldehyde, a large excess of the aldehyde (6 eq.) was employed (entry 4). Disappointingly, ring opening of the cyclopropane was still favoured.

The use of both phenylacetaldehyde and butanal (entries 6 and 7) in the reaction resulted in rapid decomposition of the cyclopropane. GCMS analysis revealed a large number of compounds present in trace amounts but none that corresponded to the desired product.

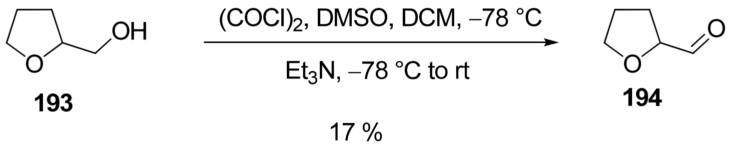
Table 2.11 Attempted cyclisation of triiospropylsilylmethylcyclopropane with a range of aldehydes[a]



Entry	R	Conditions	Yield of **192** (%)	Yield of **171** (%)	Yield of **172** (%)	Yield of **162** (%)
1		−78 °C /2 h then 0 °C/2 h	0	67	16	0
2		−78 °C /2 h then 0 °C/2 h	0	59	8	6
3		−78 °C /2 h then 0 °C/2 h	0	8	13	72
4[b]		−78 °C /2 h then 21 °C/2 h	0	91	3	0
5		−78 °C/ 3.5 h then 0 °C/2 h	0	45	8	33
6		−78 °C/ 2 h then 0 °C/2 h	0	51	44	0
7[c]		−78 °C/ 2 h then 0 °C/2 h	0	54	21	2

[a] The major products were identified by GCMS and NMR analysis after an aqueous work-up. If there was no evidence by ^{1}H NMR or GCMS analysis for starting material or the desired THF present in the reaction mixture no purification was attempted. [b] the reaction was run with six equivalents of aldehyde. [c] no aldehyde was recovered, instead the aldol condensation product was identified.

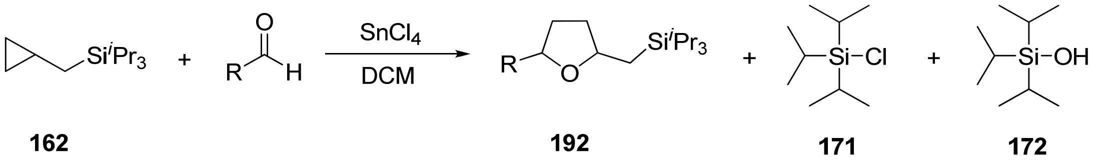
To improve the ability of the aldehyde to coordinate to the tin, aldehydes with chelating groups were examined (Table 2.12). Commercially available 2-furanaldehyde, 5-nitro-2-furanaldehyde and *ortho*-nitrobenzaldehyde (entry 7-9) all proved unsuccessful in the cyclisation reaction. The saturated equivalent of furanaldehyde, tetrahydrofuran-2-carbaldehyde (entry 10), offered a greater degree of conformational flexibility than furanaldehyde. Tetrahydrofuran-2-carbaldehyde was not commercially available and had to be prepared from the racemic tetrahydrofurfuryl alcohol[104] by means of a Swern oxidation (Scheme 2.32).[105] Purification of the aldehyde by reduced pressure distillation following column chromatography was challenging and often had to be repeated which in part accounts for the low yield of this reaction.

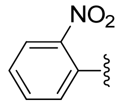
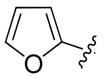
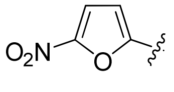
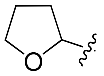
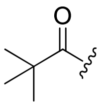
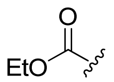


Scheme 2.32

Other methods for the oxidation of the alcohol to the aldehyde such as activated manganese dioxide and pyridinium chlorochromate failed to give the desired aldehyde.

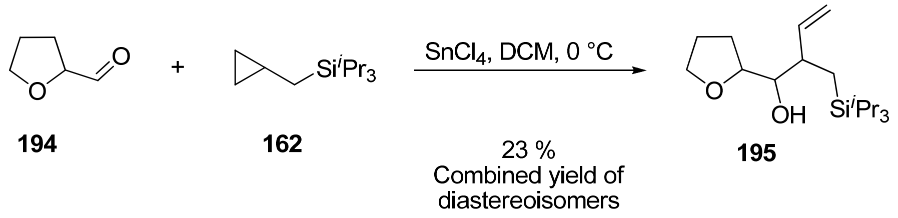
Table 2.12 Attempted cyclisation of triiospropylsilylmethylcyclopropane with a range of aldehydes[a]



Entry	R	Conditions	Yield of **192** (%)	Yield of **171** (%)	Yield of **172** (%)	Yield of **162** (%)
1		−78 °C/ 2 h then 0 °C/2 h	0	93	2	0
2		−78 °C/ 2 h then 0 °C/3 h	0	34	40	12
3[b]		−40 °C/ 2 h then 0 °C/2 h	0	61	26	11
4		−78 to 0 °C/ 6 h	0	26	6	4
5		0 °C	5	63	26	0
6		−78 to 0 °C/2 h	42	11	10	0

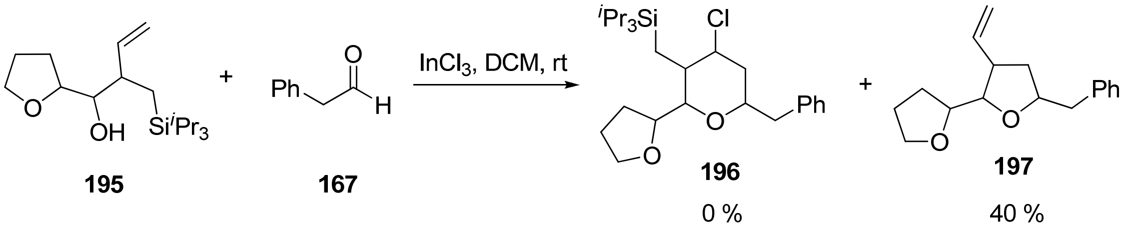
[a]The major products were identified by GCMS and NMR analysis after an aqueous work-up. If there was no evidence by ^{1}H NMR or GCMS analysis for starting material or the desired THF present in the reaction mixture no purification was attempted.[b] the reaction was started at −40 °C because of the poor solubility of the aldehyde at −78 °C

When tetrahydrofuran-2-carbaldehyde was stirred with triisopropylsilylmethylcyclopropane and tin tetrachloride at −78 °C, no reaction occurred. Upon warming to 0 °C and stirring for 2 hours, unreacted aldehyde, cyclopropane and triisopropylsilane derivatives were isolated. When a solution of tin tetrachloride was added to silylmethylcyclopropane and aldehyde at 0 °C two diastereoisomers of the homoallylic alcohol **195** were isolated in a low 23 % yield (Scheme 2.33).



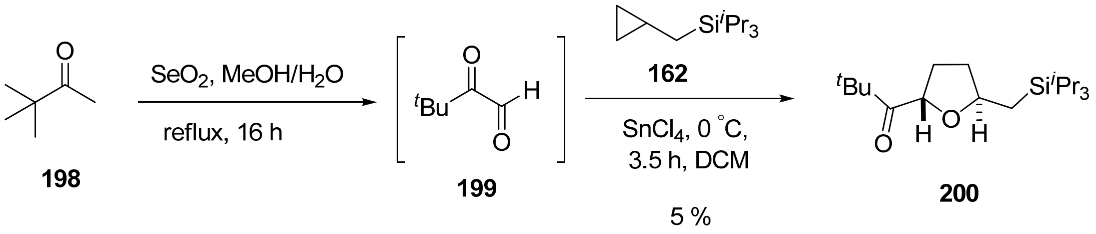
Scheme 2.33

As an interesting aside, other members of our group are interested in the Prins reaction. This is the reaction between a homoallylic alcohol and an aldehyde and is a well documented methodology to access tetrahydropyrans.[106] Curious as to whether the tetrahydrofuran substituted homoallylic alcohol would cyclise, it was reacted with phenylacetaldehyde under indium trichloride promoted Prins cyclisation conditions (Scheme 2.34).[107] Instead of the expected the tetra-substituted tetrahydropyran, a *bis*-tetrahydrofuran product **190** was isolated as a single diastereoisomer. Attempts to identify the relative stereochemistry of the substituents on the ring by nOe studies was inconclusive.



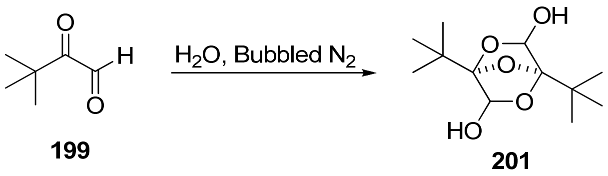
Scheme 2.34

The negative results from using various aldehydes in the reaction suggested that the reaction was only applicable to α-keto aldehydes. Therefore, to test a non-aromatic glyoxal, *tert*-butyl glyoxal was prepared by refluxing pinocolone and selenium dioxide in methanol containing 5 % water for 16 h according to the method of Fuson *et al.* (Scheme 2.35).[108] To avoid decomposition, the unstable product was purified by fractional distillation and used immediately in the cyclisation reaction. The distillate appeared to contain approximately 50 % of the desired glyoxal by NMR analysis. The reaction gave a small amount of the desired THF product, which was confirmed to be the *trans* diastereoisomer by nOe experiments. The reasons for the poor yield is likely to be a combination of using an unknown amount of aldehyde and running the reaction at 0 °C to obtain a single diastereoisomer.



Scheme 2.35

The aldehyde was unstable and therefore the remaining aldehyde from the distillation was poured into water and agitated by bubbling nitrogen through the mixture to synthesise the stable hydrate. Recrystallisation in benzene gave the pure hydrate of the *tert*-butyl glyoxal as white crystalline solid. The X-ray crystal structure confirmed the product as the hydrate and established that the aldehyde had been synthesised prior to hydrolysis. The hydrate could be dehydrated by reduced pressure distillation giving the glyoxal in higher purity than direct distillation of the selenium dioxide reaction mixture.



Scheme 2.36

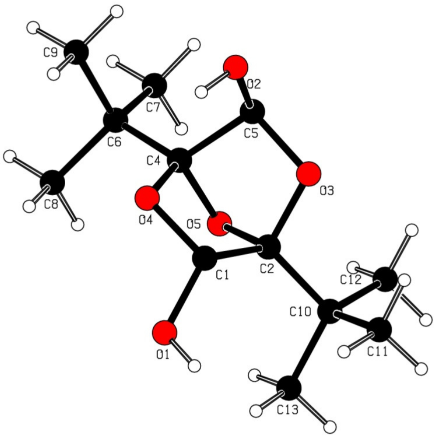
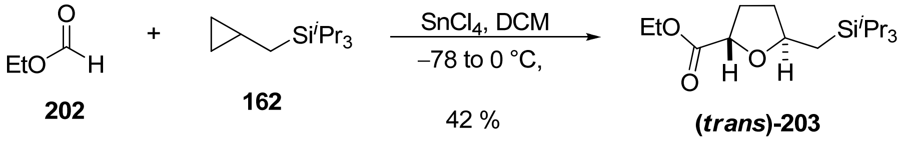


Fig. 2.11 Crystal structure of 201

Due to time restraints and the difficultly of purifying the glyoxal no attempts were made to optimise this reaction, which had shown that a THF could be obtained from the reaction using other (non-aromatic) glyoxals.

Ethyl glyoxalate was also successful in the reaction, producing the desired THF in a moderate yield of 42 %. Again, the reaction was carried out at −78 °C and allowed to warm to 0 °C to obtain the THF as a single diastereoisomer, which by comparison to the THF **183** was assigned as the *trans* diastereoisomer (Scheme 2.37).

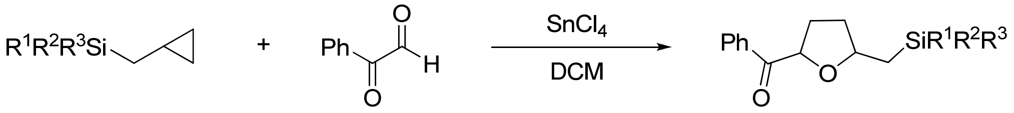


Scheme 2.37

2.3.3 Silyl groups

The *tert*-butyldiphenylsilyl and dimethylphenylsilyl groups had been tested in the cycloaddition reaction using unoptimised conditions and both gave low yields of the desired THF (Section 2.2.2.1). To investigate how different aryl and alkyl substituents on the silicon influenced on the yield and relative stereochemistry, the reaction was examined with a range of silylmethylcyclopropanes using the optimised conditions (Table 2.13). In particular, the synthesis of the THF from dimethylphenylsilylmethylcyclopropane to incorporate the dimethylphenylsilyl group in the THF was of synthetic interest because it can easily be chemically modified.

Table 2.13 Cyclisations using different silylmethylcyclopropanes



Entry	R^1	R^2	R^3	Temperature (°C)	Product	Yield (%)	*dr* (*cis/trans*)
1	Et	Et	Et	−78	**204**	21	2.3 : 1
2	Et	Et	Et	−78 to 0	**204**	53	1 : 10
3	^{n}Bu	^{n}Bu	^{n}Bu	−78	**205**	43	1 : 1.4
4	^{n}Bu	^{n}Bu	^{n}Bu	−78 to 0	**205**	26	1 : 5
5	^{i}Pr	^{i}Pr	^{i}Pr	−78	**187**	81	1.6 : 1
6	^{i}Pr	^{i}Pr	^{i}Pr	−78 to 0	**187**	73	Only *trans*
7	Me	Me	Ph	−78	**186**	53	2.1 : 1
8	Me	Me	Ph	−78 to 0	**186**	17	Only *trans*
9	Me	Ph	Ph	−78	**206**	40	2 : 1
10	Me	Ph	Ph	−78 to 0	**206**	38	1 : 2.4
11	^{t}Bu	Ph	Ph	−78	**185**	66	2.1 : 1
12	^{t}Bu	Ph	Ph	−78 to 0	**185**	72	1 : 1.1

Conditions: A solution of tin tetrachloride in DCM was added to a solution of phenyl glyoxal in DCM at −78 °C. After stirring at this temperature for approx. 5 min a solution of silylmethylcyclopropane in DCM was added. The reaction was either kept at −78 °C or allowed to warm to 0 °C and the product was isolated by column chromatography.

With the exception of the triethylsilyl group (entries 1 and 2) all the reactions carried out at −78 °C gave better yields than those which were allowed to warm to 0 °C. Analysis of the crude reaction mixture of the triethylsilyl reaction (entry 1) showed three compounds: the desired THF, aldehyde and starting cyclopropane. This would suggest that the reaction had not gone to completion because all the tin tetrachloride had been consumed. This anomalous result is likely to be due to decomposition of the tin tetrachloride, otherwise any free tin tetrachloride would have reacted with the silylmethylcyclopropane. The yields of the reaction varied significantly between the different silyl groups and appears to correspond to the size of the substituents on the silicon.

If the silyl groups are arranged in a decreasing order of yield based on an average of the two temperatures the following pattern emerges: TIPS > TBDPS > Bu_3Si ≈ MDPS ≈ DMPS ≈ TES

This order can be compared to the relative stabilities of different trialkylsilyl ethers towards base-catalysed hydrolysis:[109]

DTBMS > TIPS > TDS > TBS ≈ TBDPS > MDIPS > $\mathrm{Bu_3Si}$ > $\mathrm{Pr_3Si}$ > DMIPS ≈ TES > TMS ≈ MDPS ≈ DMPS

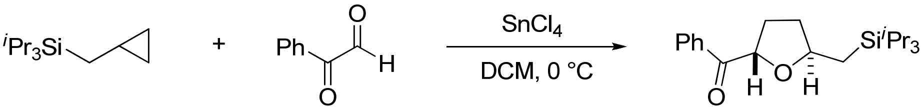
The similarities can be explained if it is assumed the most likely side reaction is addition of the silylmethylcyclopropane to tin tetrachloride and elimination of the silicon by nucleophilic attack of the chloride ion. By comparison, the relative stabilities of different trialkylsilyl ethers towards base-catalysed hydrolysis is a measure of resistance to nucleophilic addition of the hydroxyl ion. Once the silyl group is smaller than the tri-*n*-butylsilyl group all the groups give similar yields and the size of the substituents seems to make only a small difference to the yield.

The relative stereochemical outcome of the different silyl groups follows that of the triisopropylsilyl group; if the reaction is warmed to 0 °C the *trans* diastereoisomer predominates and in some case is the only diastereoisomer detectable. The exception is the TBDPS group (entry 12) which shows equal amounts of the *cis* and *trans* diastereoisomer. If the reaction is quenched at −78 °C, the *cis* diastereoisomer predominates in a ratio of approximately 2 : 1 for all silyl groups except $^n\mathrm{Bu_3Si}$. Presumably, the *cis* diastereoisomer is the kinetic product while the *trans* is the thermodynamic product. A possible reason for only one diastereoisomer being isolated at 0 °C in some case and mixtures in others is that the temperature dependent equilibrium had not been established before the reaction was quenched. The dimethylphenylsilyl group selectively produced the *trans* diastereoisomer at 0 °C, although, disappointingly, the yield was very poor.

2.3.4 Sub-stoichiometric quantities of tin tetrachloride

Having established that tin tetrachloride was the best choice of Lewis acid for the reaction, the use of sub-stoichiometric quantities would be beneficial as it would reduce the amount of toxic material used and is more economical. For the following discussion, as in the previous sections, the number of equivalents is quoted with respect to the silylmethylcyclopropane, which is arbitrarily assigned as 1. Originally, in the reaction 1.1 equivalents of Lewis acid and 1.5 equivalents of aldehyde were used to provide a small excess of activated aldehyde. This ratio had given moderate to good yields of the desired product in the optimisation reactions and had not been changed throughout any of the subsequent work. Sub-stoichiometric quantities of tin tetrachloride were tested in the reaction with triisopropylsilylmethylcyclopropane (Table 2.14) and dimethylphenylsilylmethyl cyclopropane (Table 2.15).

Table 2.14 Cyclisation of triisopropylsilylmethylcyclopropane using sub-stoichiometric quantities of tin tetrachloride

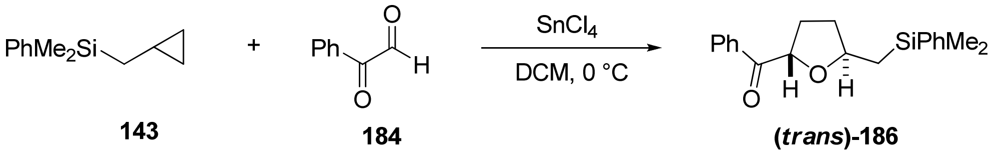


162 **184** **(*trans*)-187**

Entry	Equivalents of $SnCl_4$	Yield (%)
1	1.1	73
2	0.7	85
3	0.6	71
4	0.4	55
5	0.3	46
6	0.2	38

Surprisingly, with sub-stoichiometric amounts of tin tetrachloride, the desired THF was still obtained in good yields, although less than 0.6 eq. gave significantly reduced yields. The cyclopropane starting material was recovered from the reactions using less than 0.5 eq. of tin tetrachloride. It is proposed that, rather than the reaction being catalytic, the tin tetrachloride can coordinate with two molecules of the glyoxal. Therefore, reducing the amount of tin tetrachloride only becomes significant once the no. of moles is less than half that of the aldehyde. This corresponds to an optimum amount of 0.75 eq. and gives a ratio of 2 : 1 of glyoxal to tin tetrachloride.

Table 2. 15 Cyclisation of dimethylphenylsilylmethylcyclopropane using sub-stoichiometric quantities of tin tetrachloride



Entry	Equivalents of $SnCl_4$	Yield (%)
1	1.1	17
2	0.7	71
3	0.6	56
4	0.4	41
5	0.3	29
6	0.2	10

Pleasingly, by using a reduced amount of tin tetrachloride the yield of the *trans* diastereoisomer of THF **182** was considerably improved (71 %). Analysis of the crude reaction mixture showed that the reaction also produced fewer by-products with 0.7 eq. of tin tetrachloride. Accordingly to the above hypothesis that tin coordinates to two molecule of glyoxal then, using 1.1 eq. a small amount of free tin tetrachloride could always have been present in the reaction. This would reduce the yield, of THF especially with more nucleophilic susceptible silyl groups. Alternatively, if it is more favourable for the aldehyde to coordinate in a 1 : 1 complex then a mixture of 1 : 1 and 1 : 2 complexes maybe present in the reaction mixture when more then 0.75 eq. but less than 1.5 eq. are used.

2.3.5 Summary of the scope of the reaction

The best Lewis acid for promoting the reaction between glyoxal and the silylmethylcyclopropanes was tin tetrachloride because it gave high yields of product with some control over the relative stereochemistry. The reaction is usually complete within 3 hours at −78 °C and 1 hour at 0 °C. The optimum quantity of tin chloride was found to be 0.7 eq., which gave comparable yields using triisopropylsilylmethylcyclopropane but improved yields with dimethylphenylsilylcyclopropane and cleaner reactions for both cases. The fact that the reaction gives good or better yields with sub-stoichiometric quantities of Lewis acid may be an indication of the ratio of complexation occurring between the aldehyde and metal. Zinc bromide and zinc chloride both give moderate yields in the reaction but longer reaction times and lack of stereochemical selectivity meant the reaction was not investigated further.

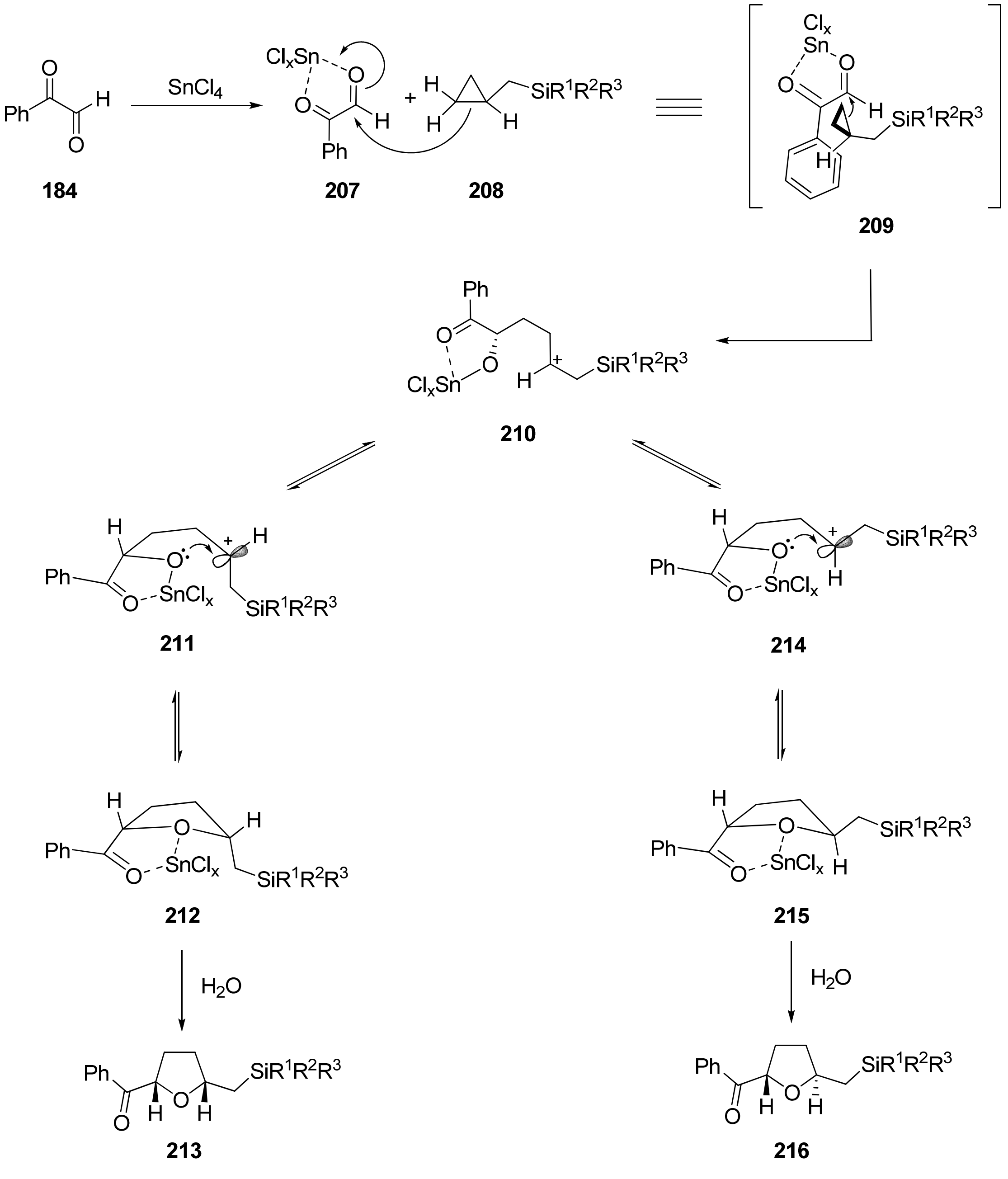
Only aldehydes bearing an α-carbonyl substituent were found to cyclise under the reaction conditions. In all other cases, including aldehydes with other chelating groups, the reactions failed to give the desired THF with ring opening of the silylmethylcyclopropane being the dominant reaction. Using tetrahydrofuran-2-carbaldehyde, the homoallylic alcohol **185** was obtained, although the mechanism of this reaction is unclear. Ethyl glyoxalate gave the desired THF in lower yields than the phenyl glyoxal. *tert*-Butyl glyoxal, gave a low yield of cyclised product which is believed to have been caused by the glyoxal decomposing.

An array of silylmethylcyclopropane containing different alkyl groups on the silicon all gave the cyclised THF product from the reaction. The yield of the reactions was highly dependent on the stability of the silyl group to nucleophilic attack.

2.3.6 Mechanism of cyclisation of silylmethylcyclopropane and glyoxal

From the results of the optimisation reactions and investigating the scope of the reaction, a proposed step-wise mechanism for the reaction is presented in scheme 2.38. In the first step, the tin tetrachloride coordinates to the two carbonyl oxygens of the glyoxal activating the aldehyde to nucleophilic addition **207**. In the next step, the cyclopropane acts as a nucleophilic pseudo π-donor forming the carbon-carbon bond and the silyl stabilised β-carbocation **210**. During the nucleophilic addition, the cyclopropane must approach the carbonyl so that the C-C bond of the cyclopropane aligns with the π* orbital of the C=O bond. To reduce the steric hindrance the bulky methylsilyl group would be expected to be directed away from the glyoxal **209**.

The ring-open of the cyclopropane ring places the 2- and 5- substituents in a *cis* orientation **211**; this is followed by the ring-closing reaction, which appears to be slightly faster than rotation of the C-C bond at −78 °C and gives the *cis* stereoisomer as the major product **212**. However, from the observation that the relative stereochemistry of the THF product is temperature dependent with the *cis* diastereoisomer being the kinetic product and the *trans* diastereoisomer being the thermodynamic product the ring-closing step between the oxygen and the carbocation must be reversible. This allows the ring to open and, *via* rotation around the C-2/C-3 bond, positions the methylsilyl group in a *trans* orientation to the α-keto, which upon ring-closing yields the *trans* stereoisomer **215**. The tin tetrachloride is thought to remain coordinated to the THF and carbonyl oxygen until the reaction is quenched with water.



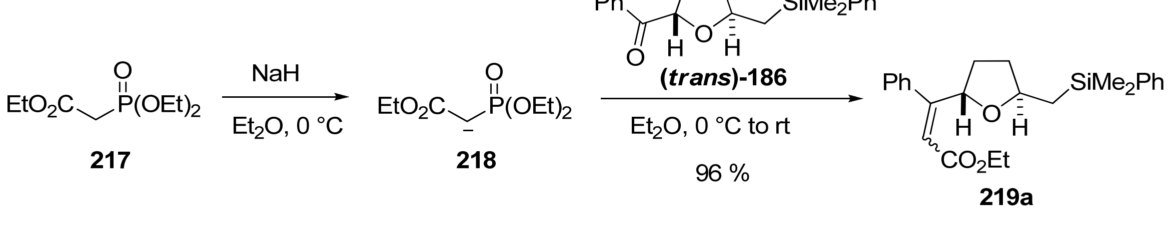
Scheme 2. 38

2.4 Reactions of the 2,5-disubstituted tetrahydrofurans

Having established conditions for the synthesis of 2,5-disubstituted THFs *via* the tin tetrachloride promoted cycloaddition of silylmethylcyclopropanes with glyoxalate or glyoxal, the reactivity of the resulting THFs was investigated. The presence of the α-ketone functionality offered a synthetic handle for further chemical transformations. The feasibility of modifying the ketone to access a range of other THFs bearing different substituents at the α-position was investigated.

2.4.1 Horner-Wadsworth-Emmons

It was envisaged that the α-ketone **186** could be conveniently converted to the tri-substituted alkene using a Wittig type reaction. This synthetic route not only presented a way to synthesise the double bond, allowing the introduction of a wide variety of other functional groups, but also as a means to couple the THF to another molecule. The Horner-Wadsworth-Emmons (HWE) reagent **217** was chosen for the reaction because ylids derived from phosphonium salts with α-stabilising groups have been reported to give lower yields with ketones than phosphonate ylids. The Horner-Wadsworth-Emmons (HWE) reagent also has the practical advantage that the phosphorus by-products are relatively water soluble and are mostly removed by an aqueous work-up. Deprotonation of triethyl phosphonoacetate with sodium hydride in diethyl ether followed by addition of only the *trans* diastereoisomer of THF **186** gave the desired product in a good yield (96 %) and as a 1 : 1.2 mixture of geometric isomers (Scheme 2.39). Separation of the isomers was achieved by column chromatography but identification of the different alkene geometries' by nOe experiments was inconclusive. The nOe study did confirm that no epimisation of the C-5 proton had occurred and the relative stereochemistry of the THF ring was still *trans* (Fig. 2.12).



Scheme 2.39

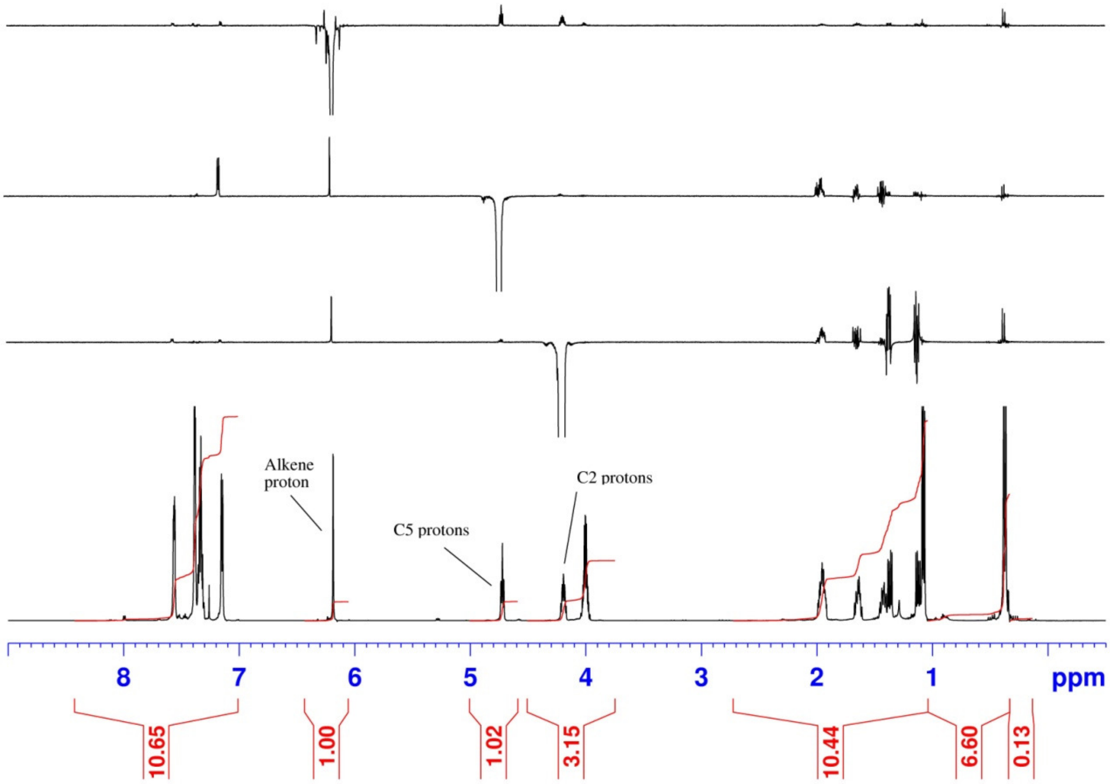
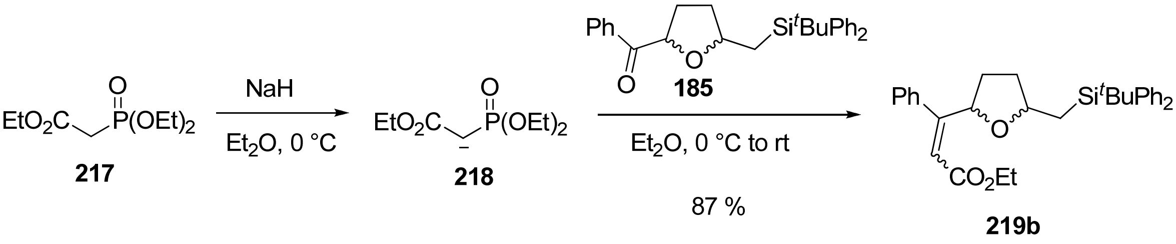


Fig. 2. 12 nOe studies of one of the diastereomer obtained from the Horner-Wadsworth-Emmons reaction showing the *trans* relative stereochemistryhas remained unchanged

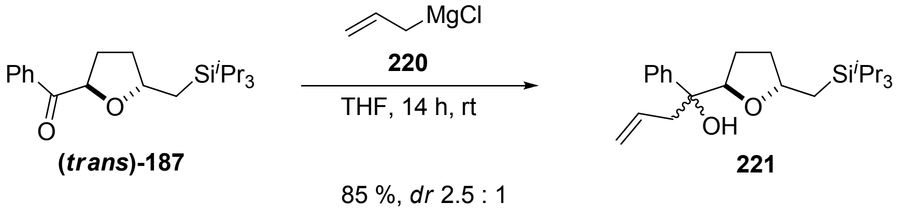
The HWE reaction also proceeded to give good yields when a 1:1 mixture of THF diastereoisomers were employed (87 %) but only partial separation of the four products was possible (Scheme 2.40). Therefore, two mixtures of two compounds were obtained.



Scheme 2.40

2.4.2 Nucleophilic addition

The nucleophilic addition of allylmagniusm chloride to the ketone functionality of the THF was investigated. Treating the *trans* diastereoisomer of the THF **187** with a 2 M solution of allylmagnesium chloride in tetrahydrofuran gave the desired tertiary alcohol **221** in 85 % (Scheme 2.41) as a mixture of diastereoisomers (2.5 : 1).



Scheme 2.41

Nucleophilic addition of the Grignard reagent would be expected to proceed under chelation control through the lone pair of electrons on the THF oxygen. The higher proportion of one diastereoisomer over the other is presumably a result of this chelation control favouring the *anti* arrangement of C-5 proton and hydroxyl group in the product (Fig. 2.13). Unfortunately, assignment of the two diastereoisomers was not possible therefore, the favoured arrangement has not been confirmed.

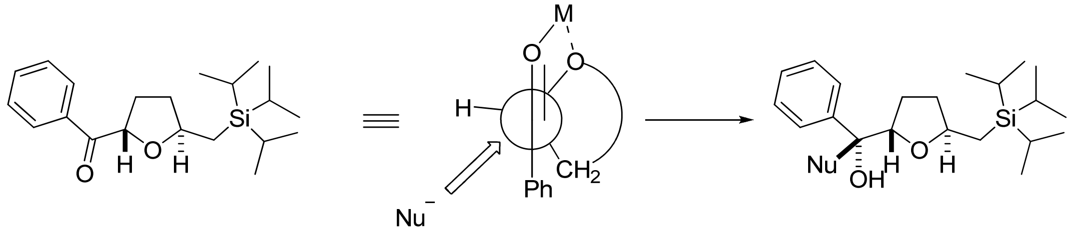
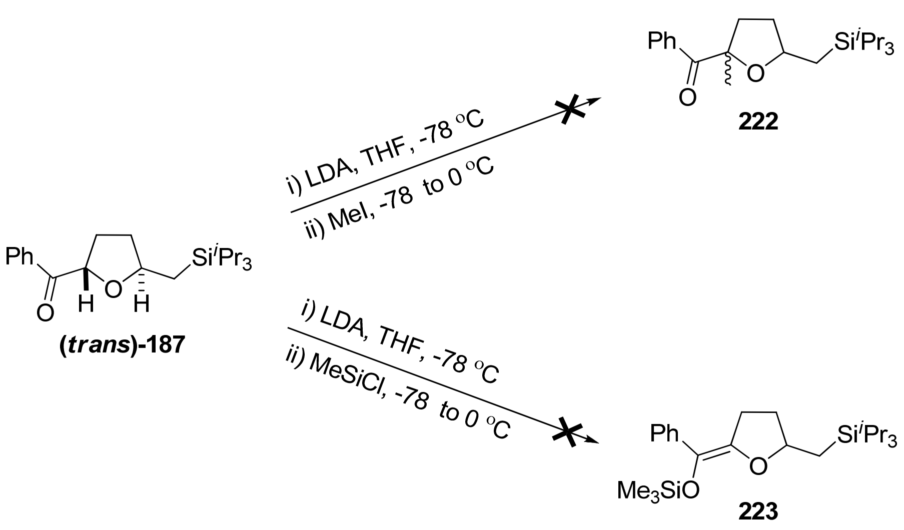


Fig. 2.13 Chelation controlled addition of a nucleophile to the α-ketone functionality on the THF ring

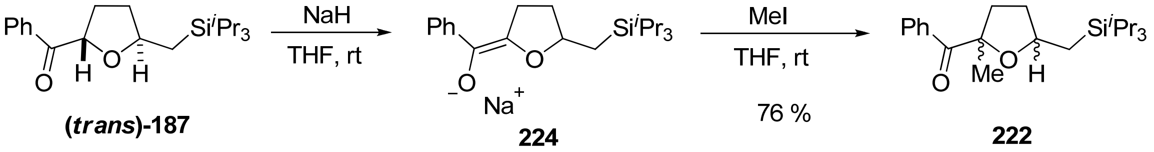
2.4.3 Enolate formation

An alternative method for utilising the ketone functionality to construct a carbon-carbon bond is *via* the enolate and then quenching with a carbon electrophile. The methodology would offer a route to geminal disubstituted THF. The presence of only one enolisable proton removed any chemoselectivity issues, although the enolate would be expected to form as a mixture of the *E* and *Z* isomers, forming a mixture of diastereomers in the product. When lithium diisopropylamine (LDA) was used to generate the enolate and the reaction was quenched with methyl iodide, the starting material decomposed. The reaction was repeated but quenching with TMS-Cl to isolate the silyl-enol-ether and, again, the starting material decomposed to a mixture of unidentifiable products. It may be that LDA is too bulky to remove the C-5 proton and the enolate could not be formed in the reaction. However, as no starting material was recovered from the reactions, this suggested a reaction was occurring.



Scheme 2.42

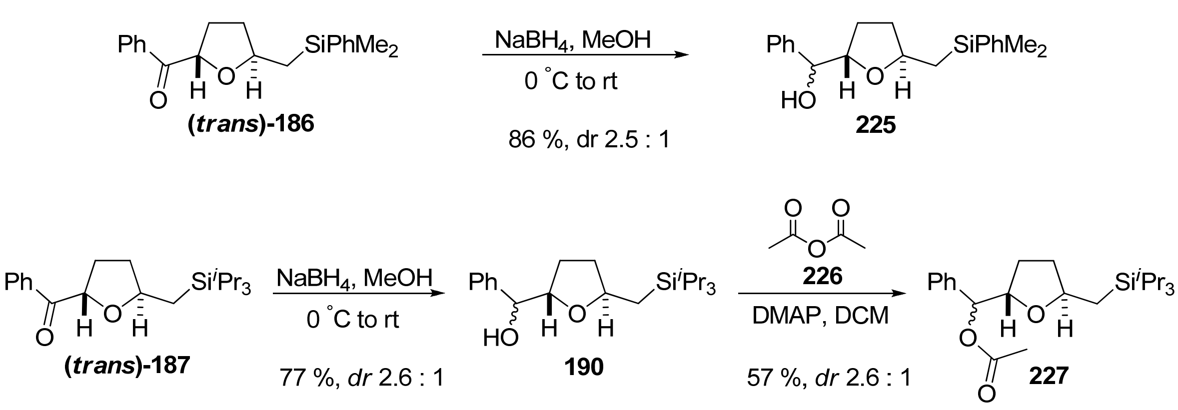
Performing the reaction at room temperature with sodium hydride as the base and quenching with methyl iodide gave the methyl substituted THF **222** in 76 % (Scheme 2.43). Two inseparable diastereoisomers of the product were isolated (1.5 : 1).



Scheme 2.43

2.4.4 Reduction

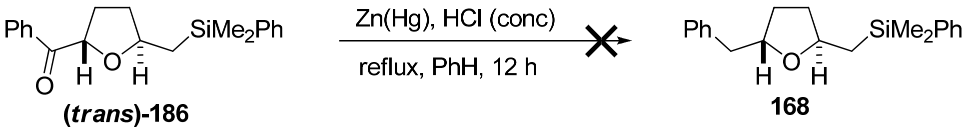
Reduction of the ketone occurred readily using sodium borohydride with both the triisopropyl and dimethylphenyl containing THFs. The resulting secondary alcohol could be converted to the ester **227** in moderate yields from acetic anhydride **226** (Scheme 2.44). Upon removal of the ketone functionality, the molecule was stable enough to be kept at room temperature.



Scheme 2.44

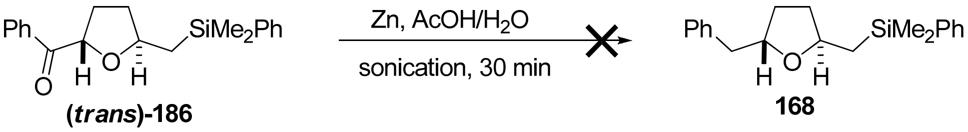
As expected, the diastereomeric ratio of the ester **227** was the same as the starting alcohol **190**. However, it is interesting to note that the products from the reduction with sodium borohydride and the nucleophilic addition with allyl magnesium chloride gave the same diastereomeric ratio (2.5 : 1). Nucleophilic addition of the Grignard reagent would be expected to proceed under chelation control through the lone pair of electrons on the THF oxygen[110] while sodium borohydride is known to be only a weakly chelating reducing agent.[111]

The one-step reduction of the ketone to the methylene group by using Clemmensen reduction conditions resulted in the decomposition of the starting material (Scheme 2.45). Amalgamated zinc was prepared by stirring a 5 % mercuric chloride solution with metallic zinc for 1 h before the reaction.



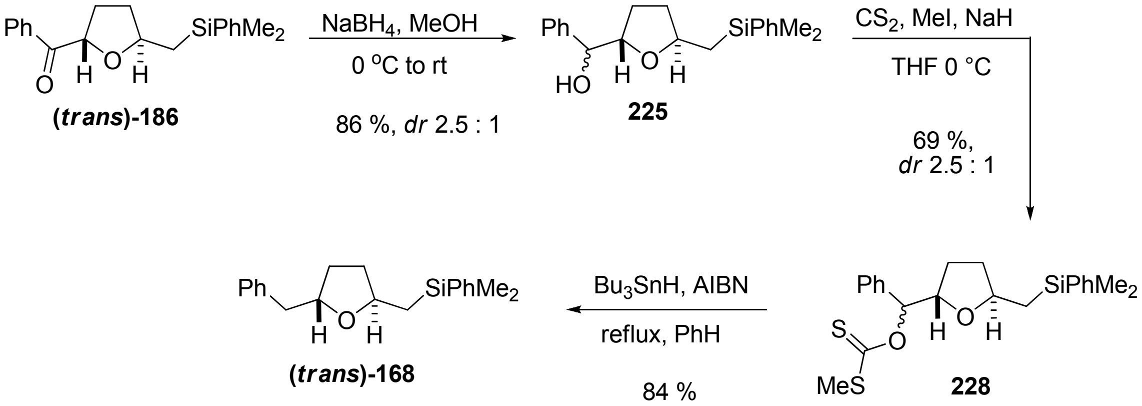
Scheme 2.45

Salvador *et al.* reported a mild ultrasound assisted Clemmensen reduction using the sonochemical conditions with zinc in acetic acid.[112] Application of these conditions also led to degradation of the starting THF (Scheme 2.46).



Scheme 2.46

The THF appeared incompatible with the strongly acid reactions conditions and concerned that the strongly basic conditions of the Wolff-Kishner reduction would also result in decomposition, the one-step approach was abandoned. An alternative route was reduction of the ketone, followed by a Barton-McCombie radical deoxygenation. Conversion of the diastereomeric mixture of alcohols derived from the $NaBH_4$ reduction to the methyl xanthate was achieved with carbon disulfide, methyliodide and sodium hydride in tetrahydrofuran at 0 °C. Treatment of the methyl xanthate with tri-*n*-butyltin and AIBN in toluene at reflux gave the 2,5-disubstituted THF **168** in an overall yield of 50 % from the ketone and as a single diastereoisomer (Scheme 2.47).



Scheme 2.47

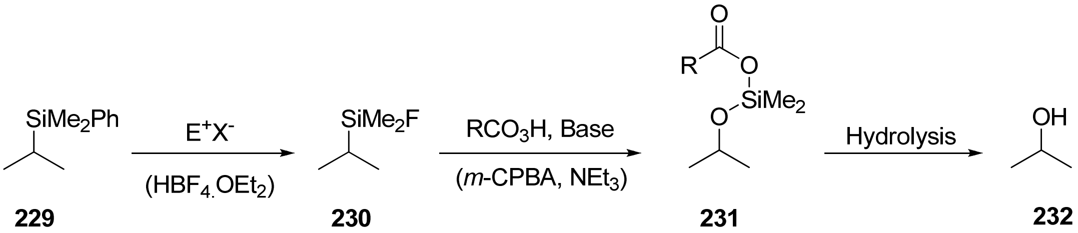
Preparation of the sodium enolate with sodium hydride had previously revealed that the base could potentially epimerise the molecule by deprotonation of the C-5 stereocentre. Confirmation that the *trans* relative stereochemistry around the ring had remained intact during these synthetic modifications was established by nOe experiments.

2.4.5 Oxidation of the Silicon Group

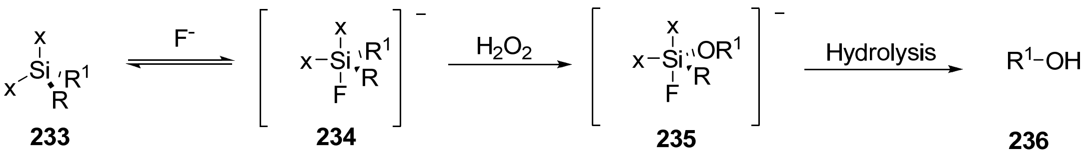
The dual role of the silicon in the reaction was to stabilise any build of positive charge at the β-carbon during the cyclisation step and act as a masked alcohol in the THF product. Being chemically inert to many reactions conditions allows the silyl group to remain present throughout a range of chemical modifications and then be converted to the hydroxyl group when required.

The oxidation of the carbon-silicon bond is a well documented transformation[80] with two complementary methods reported. The Fleming oxidation of dimethylphenyl silanes uses the susceptibility of the phenyl-silicon bond to *ipso* electrophilic aromatic substitution to form a silicon heteroatom bond (usually F) **230**. Oxidation and rearrangement of the newly generated silyl group **230** gives the siloxane species **231**, which upon hydrolysis yields the alcohol **232**. The Tamao-Kumada oxidation is the reaction between a silicon group already containing a heteroatom for example SiR_2Cl, SiR_2OR and SiR_2F and an oxidant such as hydrogen peroxide (Scheme 2.48). The conversion of the silicon-carbon bond to the carbon-oxygen bond occurs stereospecifically with retention of configuration in both methods. Although most examples are a derivative of these two general methods, an array of different conditions have been reported for the oxidation.

Generalised Fleming Oxidation

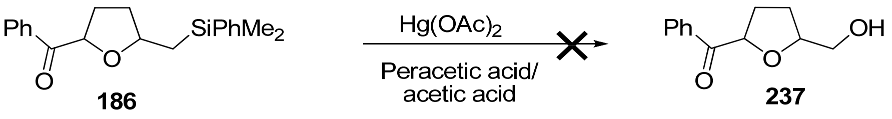


Generalised Tamao-Kumada Oxidation



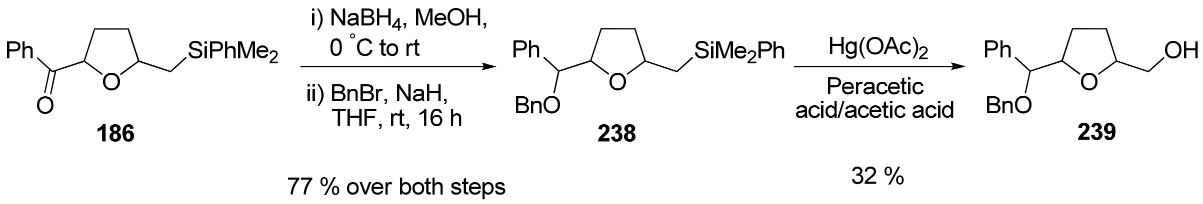
Scheme 2.48

Fleming has reported several methods for the conversion of the phenyldimethylsilyl group using Br^+, Hg^{2+} and H^+ as electrophiles. The advantage of mercuridesilylation or bromodesilylation was the entire reaction could be carried out in one pot with peracetic acid as the oxidant. As a guideline, the group recommended avoiding the bromine based method when a ketone functionality was present in the molecule. Therefore, the one-pot mercury based method was utilised for the transformation (Scheme 2.49).[113]



Scheme 2.49

No product was isolated from the reaction of the α-keto THF with mercuric acetate and peracetic acid. Analysis of the crude reaction showed the presence of several phenyl-mercury species indicating that the electrophilic aromatic substitution had occurred. The presence of the ketone was suspected to be the problem. Therefore, removal of the ketone group by reduction followed by benzyl protection of the resulting alcohol gave THF **238** as a mixture of diastereoisomers. Desilylation of the protected α-hydroxyl THF gave a complex mixture of diastereoisomers. Fortunately, purification by column chromatography gave one diastereoisomer of the desired product in 32 % (Scheme 2.50).



Scheme 2.50

Due to time constraints the reaction could not be optimised or examined further; however, the reaction did prove that the dimethylphenylsilylmethylcyclopropane could cyclise to give the 2,5-disubstituted THF and thereafter the silyl group converted to the hydroxyl group.

2.4.6 Summary

This section of reactions show that the ketone group in the THF is reactive towards a range of standard carbonyl reactions such as reduction, nucleophilic addition and Wittig type chemistry. This allows access to an array of substituents α to the THF ring that would otherwise be difficult to install in the molecule.

The dimethylphenylsilyl group was removed by a Fleming oxidation, although the reaction did not appear to be compatible with the ketone functionality in the molecule. This had to be reduced to the alcohol and protected as the benzyl ether for the reaction to be moderately successful. This reaction was not optimised owing to the lack of time but it has shown that the silicon can be considered as a masked alcohol in these systems.

A small preference for one diastereoisomer was observed in the Grignard addition and reduction reactions. It can reasonably be conceived that, with optimised reaction conditions, this selectivity could be a useful feature of the reaction.

Chapter Three

3. 0 Synthesis of disubstituted silylmethylcyclopropanes

Having established reaction conditions for the cycloaddition reaction of cyclopropylmethylsilanes with α-keto aldehydes, it was decided to investigate novel donor-acceptor cyclopropanes. By the incorporation of an acceptor group in the molecule it was anticipated that the cyclopropanes would be more reactive than the unsubstituted silylmethylcyclopropanes. In accordance with the aims of the work, the donor group would be the silylmethyl moiety. There were a number of possible acceptor or anion stabilising groups that could conceivably be used but, as the ester and geminal diester group had been used extensively in the literature other groups were considered. Two of the most attractive groups were the nitrile and the trialkylsilyl group (making use of the α-effect) and, while not as synthetically versatile, the phenyl group did offer another good stabilising group.

The aim of this aspect of the work was to develop a practical synthetic route that would allow for the gram scale synthesis of the three desired acceptor-donor cyclopropanes (Fig. 3.1). The silicon group chosen for this work was the dimethylphenyl derivative for the practical reasons that this silane was easily available, relatively cheap and could be converted to the hydroxyl group.

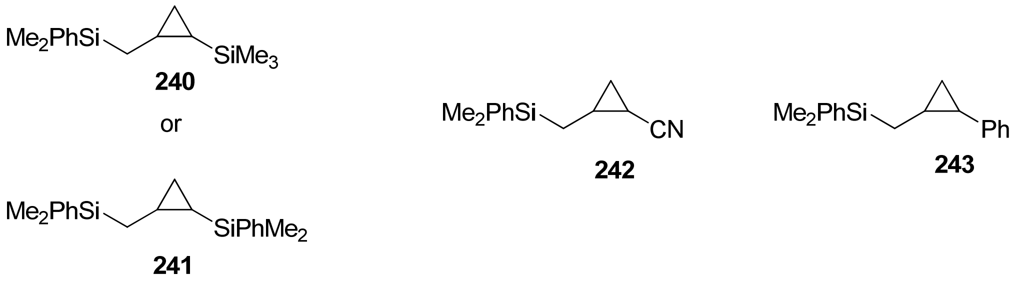
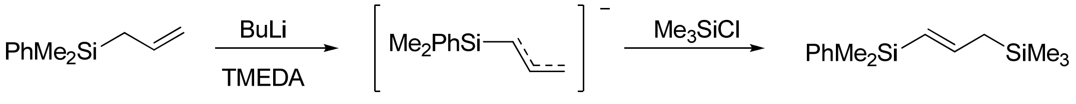


Fig. 3.1 A selection of donor-acceptor cyclopropanes

Due to the success of using the Simmons-Smith reaction for the synthesis of the mono-substituted derivatives, it was considered to be a viable route for the synthesis of the disubstituted cyclopropanes. Therefore, the first disconnection in the retrosynthetic analysis of all three acceptor-donor cyclopropanes was to give the 1,2-substituted alkene.

3.1 Synthesis of 1-dimethylphenylsilyl-3-dimethylphenylsilylpropene

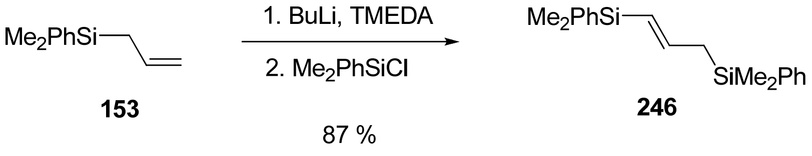
There were two possible methods for the direct synthesis of the 1,3-disilyl substituted allyl system presented in the literature, although neither method had been used for the exact substrates required in this synthesis. The first method was one published by Fleming *et al.* and described the deprotonation of allylsilane using a mixture of *n*-butyllithium and TMEDA to give the allyl anion, which in turn was quenched with chlorotrimethylsilane.[114] Having made the allyldimethylphenylsilane *via* the previously mentioned reaction between the chlorosilane and allylmagnesium bromide, the reaction was performed on this substrate and quenched with chlorotrimethylsilane. Unfortunately, this reaction gave the wrong connectivity *i.e.* 1-dimethylphenylsilyl-3-trimethylsilylpropene **230** (Scheme 3.1).



153 **244** **245**

Scheme 3.1

This problem could have been overcome by using allyltrimethylsilane and quenching with chlorodimethylphenylsilane. Instead, it was decided to quench with chlorodimethylphenylsilane which would result in identical silyl groups at both positions removing the question of which silyl group would end up on C_1 or C_3 (Scheme 3.2).

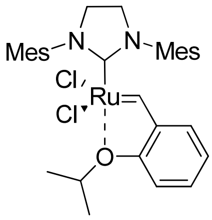


153 **246**

Scheme 3.2

The reaction gave only the *trans* product detected by ^{1}H NMR analysis. No reason for this is suggested in the literature but it is assumed the molecule will orientate itself to reduce the 1,3 allylic strain in the transition state. This method has proved applicable to gram scale synthesis and has been run on a 4 g scale with a yield of 87 %. An important variable in the synthesis is the preparation of the TMEDA which needed to be freshly distilled prior to running the reaction, otherwise the yield of the disubstituted alkene was lower.

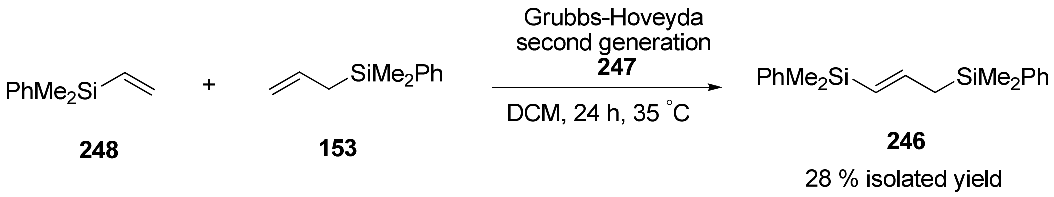
An alternative route for the synthesis of the di-substituted alkene was the cross metathesis between the vinyl- and allylsilanes. The literature contains very few examples of cross metathesis between these two types of substrates. Pietraszuk *et al.* have reported the use of vinyl silanes containing electron withdrawing groups successfully undergoing cross metathesis with allyltrimethylsilane using a Grubbs' second generation catalyst.[115] In the same paper, the group show that vinyltrimethylsilane will undergo cross metathesis when the more reactive Hoveyda–Grubbs' second generation catalyst is used.[116] Previously, the group had reported that using Grubbs' first generation catalyst in the presence of vinylsilanes reduced the catalytic activity and produced a high proportion of by-products.[117]



247

Fig. 3.2 Hoveyda–Grubbs second generation catalyst

Having found Hoveyda–Grubbs second generation catalyst (Fig. 3.2) successful for the cross metathesis between an allylsilane and acrylonitrile, the same catalyst was tested in the reaction between allyldimethylphenylsilane and vinyldimethylphenylsilane (Scheme 3.3). Based on the guidelines for cross metathesis reactions published by Grubbs and co-workers, the reaction was performed using 5 equivalents of the vinylsilane as this was considered to be classified as a type II olefin while the allylsilane was type I.[118] The reaction gave an isolated yield of 28 % and a geometric ratio of 1: 16 (*cis*:*trans*). The major product of the reaction was unreacted starting material that could be recovered by column chromatography.

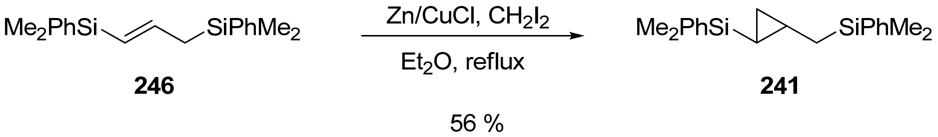


Scheme 3.3

Owing to the low yield, the cost of the catalyst and the quantity of time required to optimise this reaction (if optimisation was possible) to give a yield comparable to the previously mentioned method, this method was not pursued further.

3.2 Synthesis of 1-dimethyl(phenyl)silyl-2-dimethyl(phenyl)silylmethylcyclopropane

The next transformation was to convert the alkene into the cyclopropane. The Simmons-Smith reaction conditions that had been successful previously were employed.

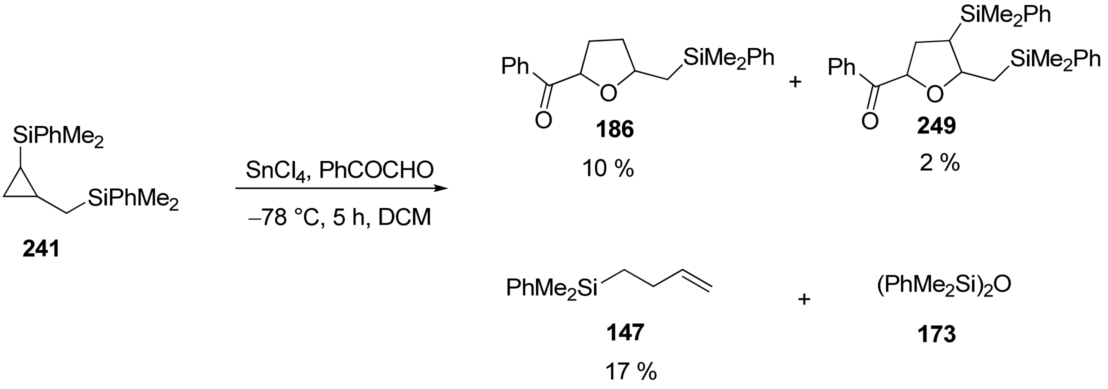


Scheme 3.4

The desired 1,2 substituted cyclopropane was obtained in reasonable yield but the reaction did not go to completion even with longer reaction times. This presented the problem of separating the starting material from the product, both of which had identical R_f values by TLC in 100 % hexane. Consequently, the crude reaction material was subjected to column chromatography using 10 % $AgNO_2$: silica made as previously outlined. Eluting with hexane gave the starting material and pure cyclopropane (98 % pure by GCMS with no alkene present as determined by ^1H and ^{13}C NMR spectroscopy). The yield of the cyclopropanation step was a modest 56 % but could be performed on a large scale, although the purification was difficult, expensive and, in some cases, needed to be repeated several times which resulted in the loss of material.

3.3 Cyclisation of 1-dimethyl(phenyl)silyl-2-dimethyl(phenyl)silylmethylcyclopropane

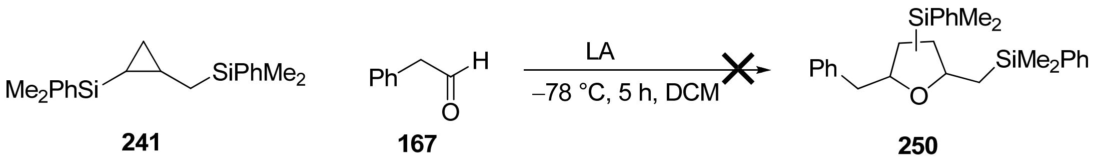
Under the reaction conditions developed for the cyclisation of the silylmethylcyclopropanes with phenyl glyoxal, at –78 °C, the dimethylphenylsilyl substituted silylmethylcyclopropane **241** gave a trace amount of the desired product. After a painstaking purification, 6 mg of the trisubstituted product **242** was isolated (2 %). The very low yield meant there was not enough material to get an infrared spectrum and although the GCMS showed a second diastereoisomer in the chromatogram, it was not visible in the NMR spectra. From analysis of the 2-D NMR spectra, the second silyl group occupied the C-3 position of the THF ring **242** (Scheme 3.5). The main by-products of the reaction were a mixture of starting material and disilylether **173**. Surprisingly, the 2,5-disubstituted THF **186** and homoallylic silane **147** were isolated from the reaction in small amounts, 10 and 17 % respectively.



Scheme 3.5

None of the desired product could be detected when the reaction was carried out at –78 °C and allowed to warm to 0 °C or when tin tetrachloride was added at 0 °C. The disilylether was the major product of reactions using these conditions.

Disappointingly, the second silyl group appeared to make the cyclopropane more susceptible to decomposition with the tin tetrachloride. Therefore, before abandoning this work, cyclisation with phenylacetaldehyde was attempted. None of the desired product was obtained from promoting the reaction with titanium tetrachloride, boron trifluoride or tin tetrachloride (Scheme 3.6).

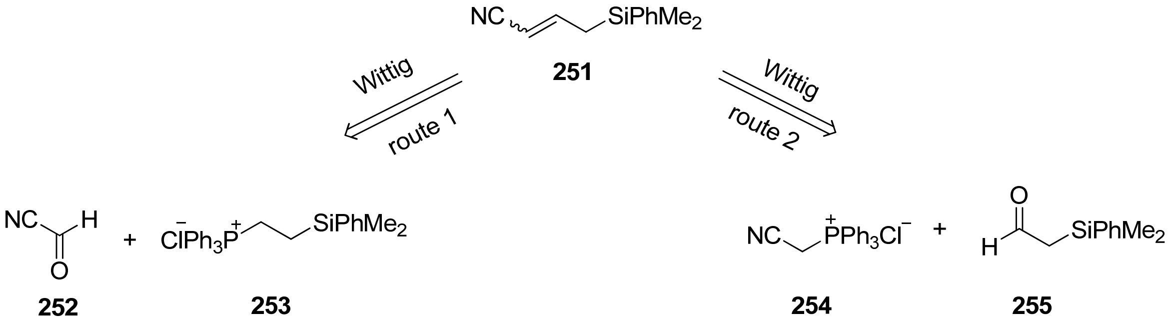

LA = $SnCl_4$, $TiCl_4$, $BF_3.OEt_2$

Scheme 3.6

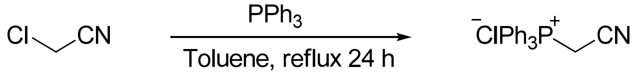
3.4 Synthesis of 4-silylbut-2-enenitrile

3.4.1 Synthesis of 4-silylbut-2-enenitrile *via* the Wittig reaction

With numerous methods available for the synthesis of double bonds, the first approach was to use the Wittig reaction, a well documented and reliable reaction. The retrosynthetic analysis of the desired 1,2 di-substituted cyclopropane, using the Wittig reaction as the first disconnection, is shown below with the two possible Wittig reagents (Scheme 3.7).


Scheme 3.7

It was decided that route 2 would be the easier route to attempt as the literature presented ways of making the α-silyl aldehyde and the phosphonium salt.[119] The formation of the cyanomethylphosphonium chloride **256** was achieved in a good yield (82 %) from the reaction between the triphenylphosphine and chloroacetonitrile in toluene (Scheme 3.8).

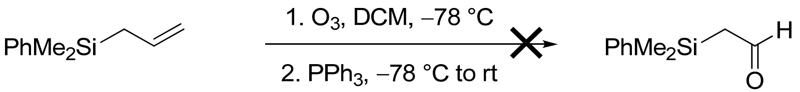


256 **254**

82 %

Scheme 3.8

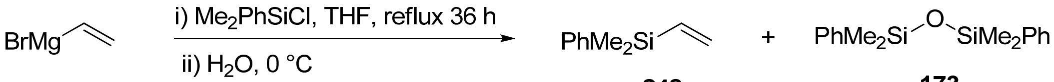
A shorter synthetic route to the aldehyde than the Lewis acid promoted rearrangement of the epoxide **259**, was the ozonolysis of the allylsilane. The reaction was carried out at –78 °C and quenched with triphenylphosphine. However, the crude material revealed none of the desired aldehyde or starting material (Scheme 3.9).



153 **255**

Scheme 3.9

The first step of the synthetic sequence outlined in Scheme 3.10 was the preparation of the vinylsilane **259**. The synthesis of dimethylphenylvinylsilane was initially attempted using the Grignard reaction between vinylmagnesium bromide and chlorodimethylphenylsilane; disappointingly, the reaction failed and disilylether **173** was recovered.

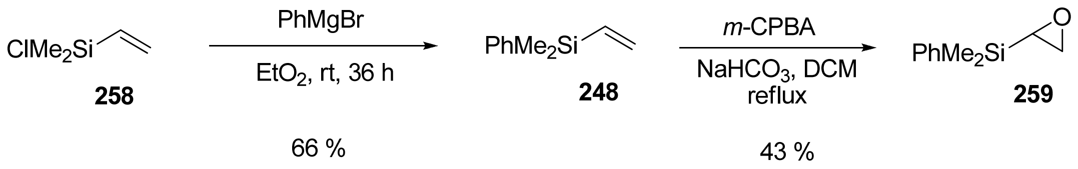


257 **248** **173**

0 % 80 %

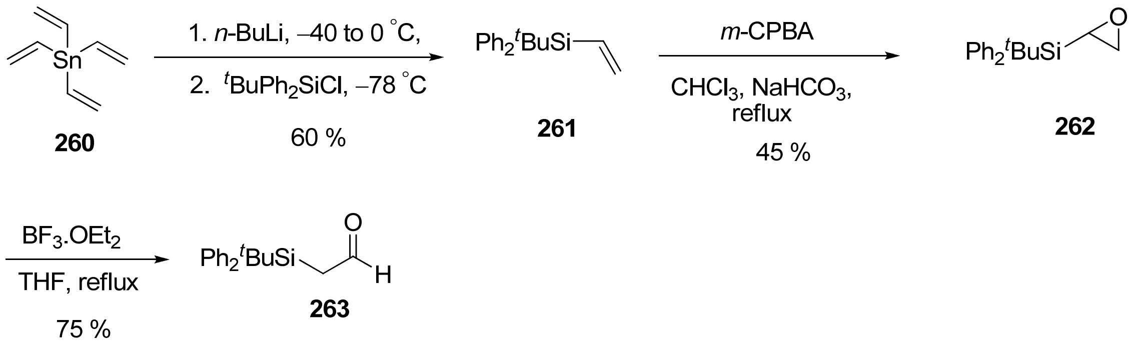
Scheme 3.10

The alternative reaction between chlorodimethylvinylsilane and phenylmagnesium bromide, formed *in situ* from the corresponding halide and magnesium turnings, gave the desired dimethylphenylvinylsilane in 67 %.[120] The conversion of the vinylsilane to the epoxide was achieved using standard *m*-CPBA conditions (Scheme 3.11),[121] although it was found the yield was higher if chloroform was used rather than DCM (74 % and 43 %, respectively). However, the epoxide was difficult to isolate by column chromatography when chloroform was used as the solvent because of an inseparable impurity. This compound was isolated and identified as the ethyl ester of *meta*-chlorobenzoic acid, which is believed to have come from the 1 % ethanol stabiliser that is added to chloroform reacting with *meta*-chlorobenzoic acid, by-product of the epoxidation reaction.



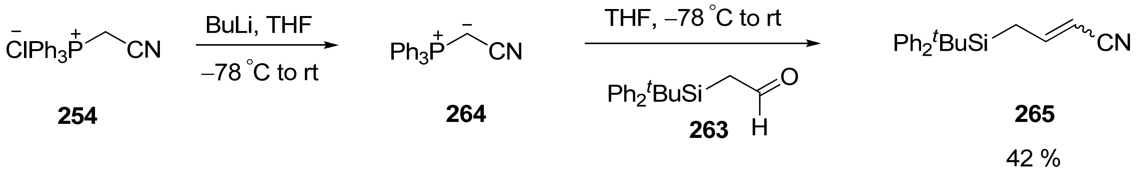
Scheme 3.11

The Lewis acid rearrangement of the epoxide was unsuccessful with MgBr$_2$[122] and InCl$_3$ in toluene and THF. Therefore, it was decided to repeat the reported literature method and use *tert*-butyldiphenylsilane instead. The reaction sequence differed from the synthesis of phenyldimethylsilane, the first step was performed using a mixture of *n*-butyllithium and tetravinyl tin to form tetravinyl lithium *in situ* followed by the addition of *tert*-butylchlorodiphenylsilane to give the desired vinylsilane. The epoxide was again synthesised from *m*-CPBA and in turn underwent Lewis acid-catalysed rearrangement with BF$_3$.OEt$_2$ in THF to give desired the α-silyl-aldehyde (Scheme 3.12).



Scheme 3.12

With the α-silyl-aldehyde in hand the Wittig reaction was undertaken using *n*-BuLi at −78 °C to form the phosphonium ylid. The aldehyde was then added and the reaction was allowed to warm to room temperature (Scheme 3.13).



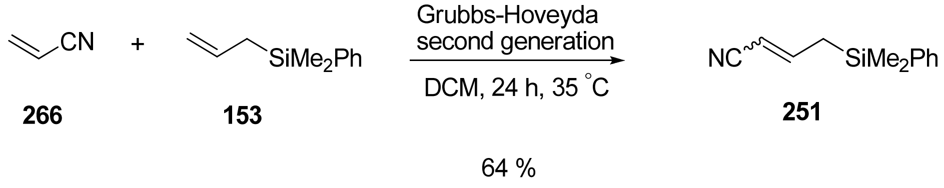
Scheme 3.13

Small amounts of the desired compound were observed in the crude reaction mixture and purification by column chromatography separated the *cis* and *trans* geometric isomers in 14 and 28 % yields. As a consequence of the low yield and difficult purification, this route was not pursued further.

3.4.2 Synthesis of 4-silylbut-2-enenitrile *via* Cross Metathesis

A search of the literature revealed that the cross metathesis between an alkene and acrylonitrile could be problematic with only one related example of an allylsilane being coupled to acrylonitile. In 1995, Crowe *et al.* published the cross metathesis reaction between the allyltrimethylsilane and acrylonitrile using Schrock's molybdenum catalyst ($Mo(CHCMe_2Ph)(NAr)[OCMe(CF_3)_2]_2$). This method required a glove box and a completely inert atmosphere.[123] It appeared that this catalyst had been used because, at the time of the synthesis, cross metastasis was an emerging methodology with only a few catalysts commercially available. During the intervening years, the mechanism of the reaction has been intensely studied and several different catalysts have been reported in many papers on reactivity of various catalysts and ligand systems.

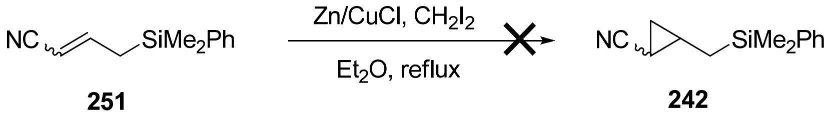
The cross metathesis was attempted using the Hoveyda–Grubbs second generation catalyst (Fig. 3.2). This catalyst was chosen as it is one of the most reactive commercially available catalysts that did not require the reaction to be performed under a rigorously inert atmosphere. The reaction was run in DCM at 35 °C using 10 eq. of acrylonitile and proceeded smoothly to give the desired product after column chromatography in a yield of 64 % and an isomeric ratio of 3.4 : 1 (*trans*:*cis*).



Scheme 3.14

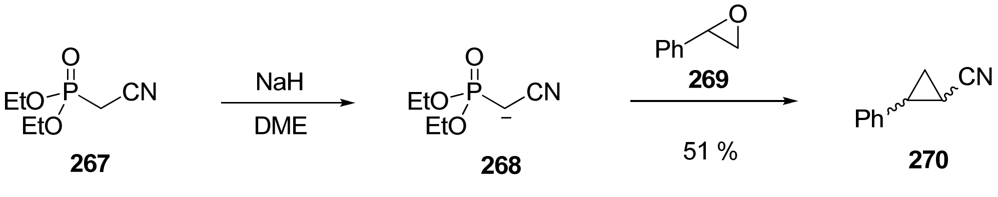
3.5 Synthesis of 2-(silylmethyl)cyclopropanecarbonitrile

Having produced the desired alkene by means of cross metathesis, the cyclopropanation of the 4-silylbut-2-enenitrile was attempted using the standard Simmons-Smith conditions that had been exploited previously. Under these conditions no reaction occurred and the starting material was recovered (Scheme 3.15). It appeared that the conjugated nature of the alkene made it significantly less reactive towards carbanoid insertion in the reaction.



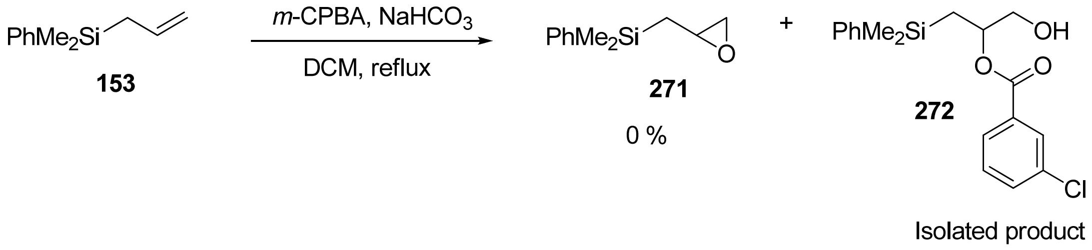
Scheme 3.15

A whole new strategy for the synthesis of nitrile substituted cyclopropanes was needed. An alternative method was a variation of the Wadsworth-Emmons reaction involving the reaction between a phosphonate carbonanion and an epoxide (Scheme 19).[124]



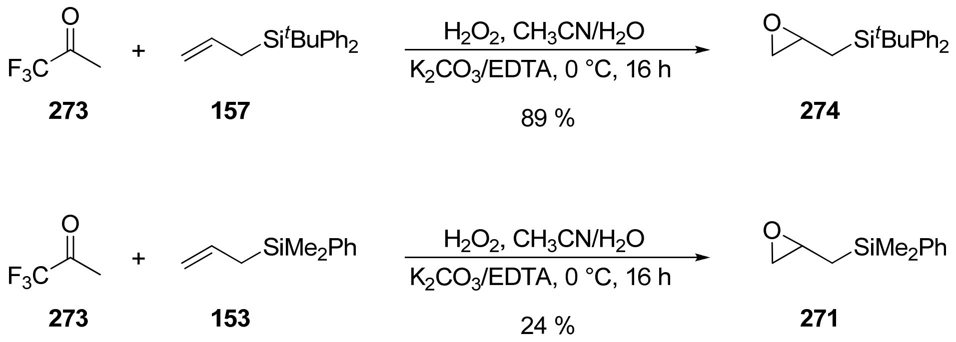
Scheme 3.16

The required epoxide could be derived from epoxidation of allylsilane, although this reaction proved to be more challenging. When *m*-CPBA was used as the oxidant, the acid by-product acted as a nucleophile and ring opening occurred to yield the ester (Scheme 3.17). An alternative epoxidation methodology that did not produce an acid as the by-product was investigated.



Scheme 3.17

The conditions for epoxidation published by Shi *et al.* using trifluoroacetone and hydrogen peroxide cleanly achieved the conversion (Scheme 3.18).[125]



Scheme 3.18

Purification of the dimethylphenylsilyl epoxide was difficult as column chromatography using both silica and alumina and distillation resulted in the epoxide decomposing to what was believed to be either the Brook type rearranged product or the Lewis acid catalysed rearrangement to the aldehyde (Fig. 3.3). The best method of purification was found to be column chromatography using 1-2 % NEt_3 in the solvent system. This improved the yield from 24 % to 61 %.

275

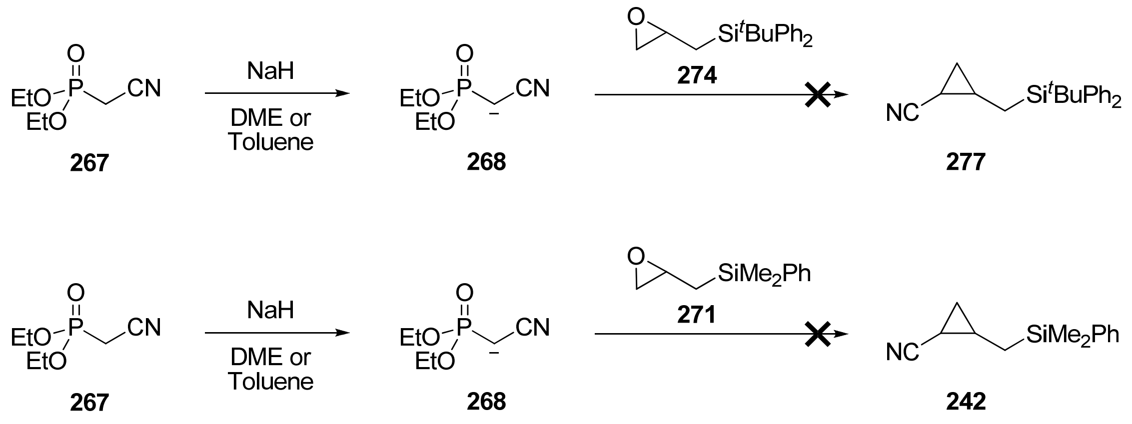
Brook type
rearrangement

276

Possible aldehyde from the
acid catalysed rearrangment

Fig. 3.3

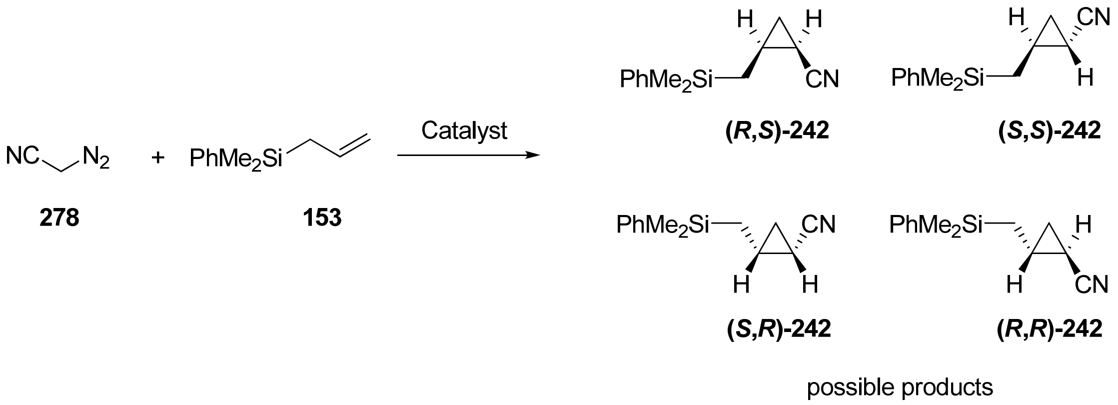
The conversion of the epoxide to the cyclopropane was attempted using diethyl cyanomethylphosphonate and sodium hydride as the base. Disappointingly, the reaction gave none of the product. It was believed that the phosphonate ylide was formed and underwent nucleophilic ring opening of the epoxide (as no starting epoxide was recovered from the reaction) but the reaction did not cyclise at this stage. This hypothesis was supported by the large number of phosphorus species were observed in the crude reaction mixture by ^{31}P NMR. The reaction was tried with toluene and DME as solvents (conditions from the literature)[124] and both dimethylphenyl and *tert*-butyldiphenyl silanes in case the steric restriction around the silicon prevented the cyclisation; however, none of the reactions gave any product.



Scheme 3.19

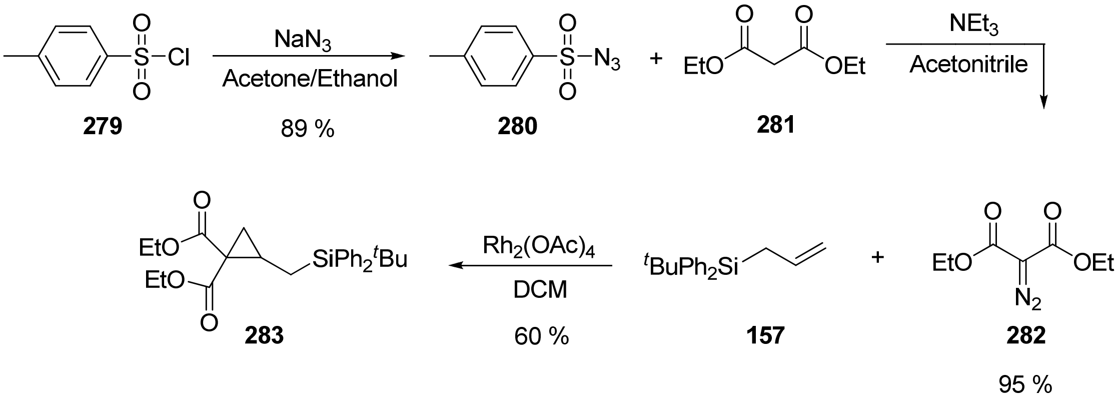
Carbene insertion by the metal catalysed decomposition of diazo compounds is one of the most popular methods of forming cyclopropanes for several reasons, the major being that the metal catalyst can be used to induce chirality in the resulting cyclopropane by the use of chiral ligands. The two drawbacks to the method which had prevented us trying it before were that diazo compounds are inherently explosive, which on larger scale reactions could be a problem and, secondly, the catalyst, although often used in a quantity of 5 mol % or less, is usually rhodium acetate and therefore very expensive. Copper triflate has been employed as a metal catalyst for carbene insertion and has the advantage that it is much cheaper but evidence from the literature suggested that in this specific case rhodium was needed.[126]

It was envisaged that a metal catalysed carbene insertion between diazoacetonitrile and the appropriate allylsilane could form the nitrile substituted cyclopropane (Scheme 3.20).



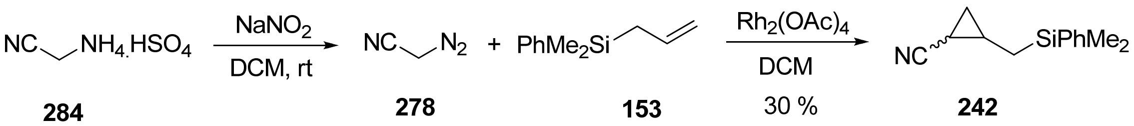
Scheme 3.20

A method of preparing diazoacetonitrile *in situ* from the reduction of the sulphuric acid salt of α-aminoacetonitrile with sodium nitrate in DCM was reported in the literature.[127] Rhodium acetate was used as the catalyst as this had been successful in a previously attempted carbene insertion between diethyl-2-diazomalonate and allyl-tert-butyldiphenylsilane (Scheme 3.21).[66]



Scheme 3.21

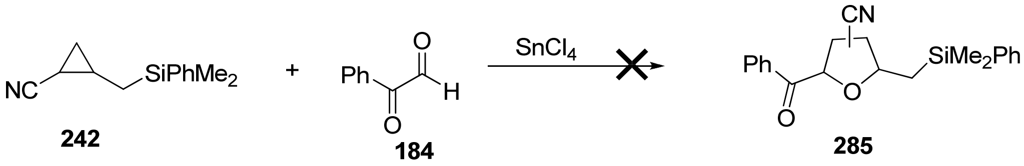
The synthesis of 2-((dimethylphenyl)silylmethyl)-cyclopropanecarbonitrile began with the preparation of a solution of diazoacetonitrile in DCM prepared from the reduction α-aminoacetonitrile bisulfite with sodium nitrate. The reaction mixture was washed with aqueous base to remove any acid present and the resulting yellow/green solution added dropwise, using a syringe pump, to a solution of dimethylphenylallylsilane and rhodium acetate dimer in DCM. The mixture was heated at reflux temperature for 12 h and followed by TLC. The crude material was purified by column chromatography to give the desired product as a 1.6 : 1 ratio of geometric isomers and in a yield of 30 % (Scheme 3.22). The low yield observed in this reaction could be attributed to the unknown concentration of the diazoacetonitrile solution.



Scheme 3.22

3.6 Cyclisation of 2-(silylmethyl)cyclopropanecarbonitrile

Employing the previously optimised conditions for the cyclisation of unsubstituted silylmethylcyclopropanes, the nitrile substituted cyclopropane was reacted with tin tetrachloride and phenyl glyoxal at −78 °C**.** After 5 h at −78 °C no cyclisation had occurred and starting material was recovered in a quantitative yield. The reaction was repeated at 0 °C, after 5 h the TLC showed no change and the reaction was allowed to warm to room temperature. After stirring for 19 h at room temperature, the reaction was then heated at reflux for 48 h. The crude reaction mixture showed none of the cyclised product and the starting material was recovered in 60 % yield (Scheme 3.23).



Scheme 3.23

The nitrile substituted cyclopropane not only appears to be unreactive towards phenyl glyoxal using the previously developed conditions, but also substantially reduced the side reaction between silylmethylcyclopropane and tin tetrachloride. The Lewis basic nature of the nitrogen in the nitrile had been expected to coordinate to the Lewis acid making the ring opening a favourable process. No evidence was found for ring opening of the cyclopropane by nitrile coordination to the tin. The time restraints prevented any further investigations into the results of these reactions.

3.7 Synthesis of 2-phenyl-1-methyl-dimethylphenylsilylcyclopropane

The first route examined for the preparation of the phenyl-substituted allylsilane was *via* the reduction of the corresponding alkyne, this would allow access to either isomer of the alkene. The alkyne could be synthesised by quenching the lithium salt of phenylacetylene with iodomethyl(dimethylphenyl)silane. Reduction using either hydrogen gas with a palladium catalyst or lithium aluminium hydride would give access to either geometric isomer. The last step would be the cyclopropanation of the alkene, which could be achieved by one of the Simmons-Smith conditions.

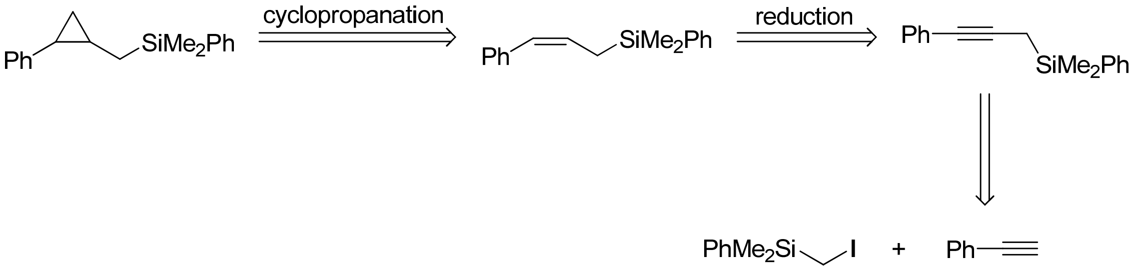
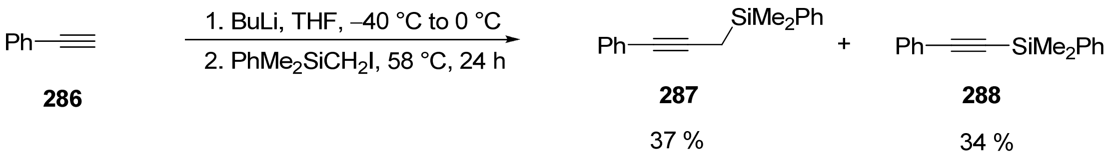


Fig. 3.4 Retrosynthetic analysis of the phenyl substituted silylmethylcyclopropane

Phenylacetylene was deprotonated using *n*-butyllithium at −40 °C, the reactive lithium salt was quenched with iodomethyl(dimethylphenyl)silane **144** prepared from the chloromethylsilane to yield **287** in 37 % following the method by Pornet *et al.*[128] The by-product of the reaction was the silyl substituted alkyne **288** which could only be separated from the desired alkyne **287** by repeatedly subjecting the mixture to column chromatography (Scheme 3.24).



Scheme 3.24

A mixture of the two alkynes was reduced using palladium on carbon but it became apparent that the two species were going to be very difficult to separate at any stage of the synthesis because of the identical functionality. Therefore, another route was examined for the synthesis of the cyclopropane **243**.

The Wittig reaction had been partially successful for the synthesis of the nitrile substituted double bond. It seemed that a similar route could be applicable for the synthesis of the phenyl substituted alkene by using benzaldehyde as the carbonyl species.

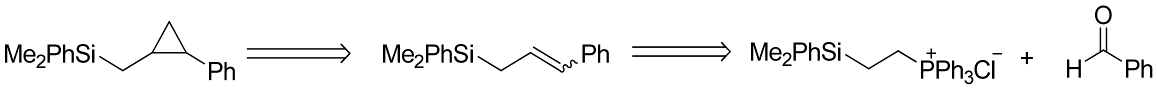
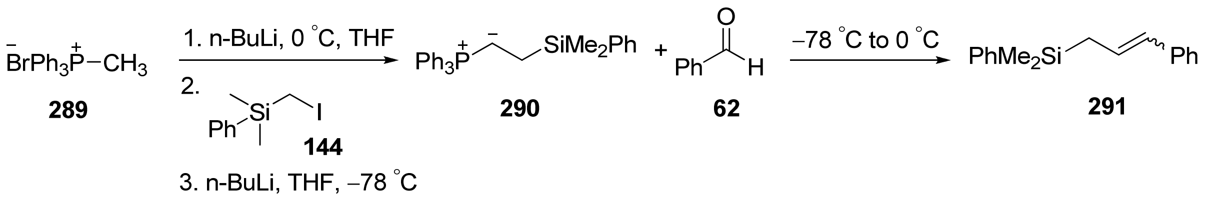


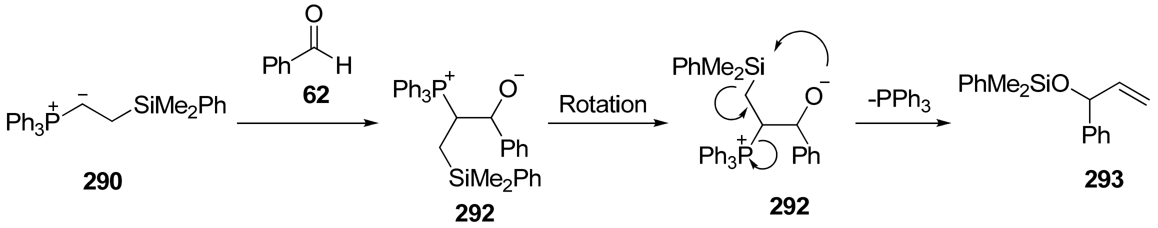
Fig. 3.5 Retrosynthetic analysis of the phenyl substituted silylmethylcyclopropane using the Wittig reaction

A one-pot synthetic route to **278** that involved making the α-silyl-β-phosphonium salt *in situ* was reported in the literature. The synthesis commenced from the commercially available chloromethyl(dimethylphenyl)silane which is converted into iodomethyl(dimethylphenyl)silane using the Finkelstein reaction. The iodomethylsilane was added to a solution of the ylid of methylphosphonium bromide resulting in an S_N2 reaction to elongate the carbon chain by one carbon. A second deprotonation of the newly formed phosphonium salt produced the necessary ylid to react with benzaldehyde (Scheme 3.25).



Scheme 3.25

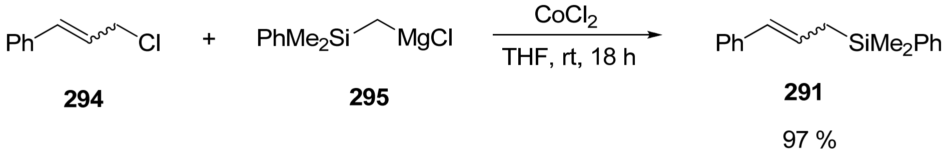
Disappointingly, the main product isolated from the reaction was not the Wittig product, but a Brook-type rearranged species that had eliminated the triphenylphosphine to give the silicon protected α-substituted allyl alcohol (Scheme 3.26). This type of reaction had been reported before and is noted to have been more prevalent when the silicon is bound to a phenyl group.[129]



Scheme 3.26

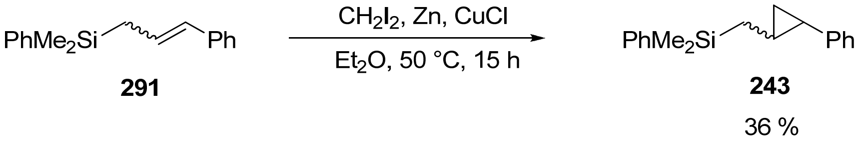
The high affinity of silicon for oxygen has been observed in both attempts to use Wittig type methodology and, owing to the difficulties encountered, was not considered a useful method for this work.

During studies into the cobalt-catalysed Heck-type reactions, Affo *et al.* reported that anhydrous cobalt (II) chloride would catalyse the stereospecific cross-coupling reaction of alkenyl halides and silylmethyl Grignard reagents.[130] The group had shown that the reaction worked well with mono- and geminal di- substituted alkenyl halides. The reaction was initially performed following identical conditions to those reported in the literature; the anhydrous cobalt chloride was prepared by heating the hydrate under a reduced pressure (0.05 mmHg) until it became blue. The dimethylphenylsilylmethylmagnesium chloride was prepared as a 1 M solution in THF from the chloromethyl(dimethylphenyl)silane according to the literature procedure.[131] The reaction between β-bromostyrene (E/Z = 10:1), dimethylphenylsilylmethylmagnesium and cobalt chloride gave the desired allylsilane **291** in 97 % (Scheme 3.27). The ratio of *trans* to *cis* isomers was 10 : 1 by NMR confirming the stereospecific nature of the reaction. The reaction was performed on scales between 1 and 15 mmol and in all cases yields of > 95 % were recorded.



Scheme 3.27

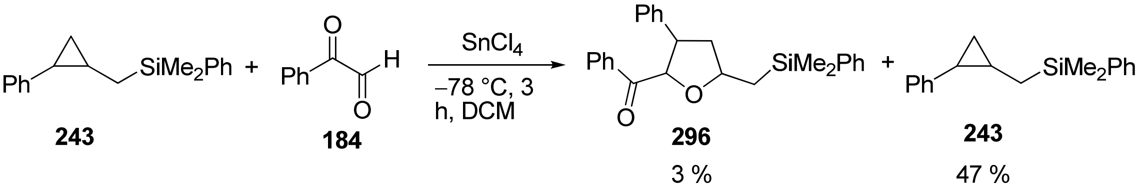
Cyclopropanation of the allylsilane using the Simmons-Smith conditions and purifying with silver nitrate impregnated silica gave the phenyl substituted cyclopropane **243** in 36 % (Scheme 3.28). The low yield of this reaction was attributed to the difficult purification of the silylmethylcyclopropane.



Scheme 3.28

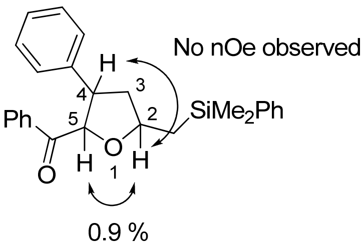
3.8 Cyclisation of the phenyl substituted silylmethylcyclopropane

The cyclisation of the phenyl substituted silylmethylcyclopropane with phenyl glyoxal and tin tetrachloride at −78 °C, yielded a small amount of the tri-substituted THF **296** (3 %). The main product was recovered starting material (47 %) suggesting that the phenyl group reduced the reactivity of the silylmethylcyclopropane towards the Lewis acid and aldehyde at −78 °C.



Scheme 1. 44

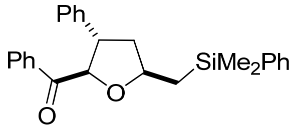
The regiochemistry of the final compound **296** was confirmed by 2D NMR experiments with the phenyl substituent at the C-4 position of the THF ring. The tri-substituted THF was obtained as a single diastereoisomer,



296

Fig. 3.6

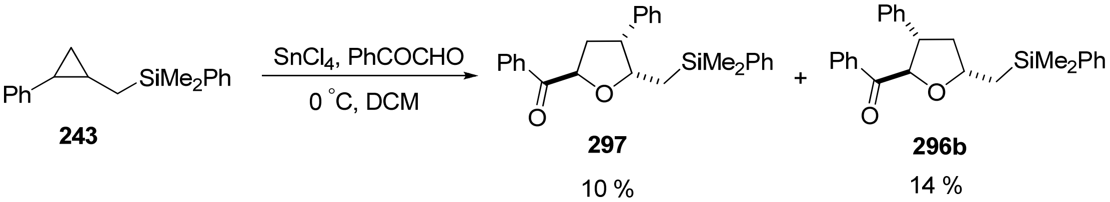
The relative stereochemistry of the substituents around the ring was established by nOe experiments. Irradiation of the C-5 hydrogen produced an enhancement at the C-2 hydrogen (0.9 %) and the coupled C-4 hydrogen (0.7 %), whilst irradiation of the C-2 hydrogen only showed an enhancement of the C-5 hydrogen. The lack of enhancement at the C-2 hydrogen upon irradiation of the C-4 confirmed the *trans* arrangement of substituents at the C-2 and C-4 positions. Therefore, from the nOe experiment the following structure is proposed for the only isolated diastereoisomer of the tri-substituted THF: the 2,5 substituents show a *cis* relationship to each other and *trans* arrangement to the substituent at the C-4 position of the ring (Fig 3.7).



296a

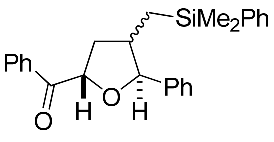
Fig. 3.7

When the reaction of the phenyl substituted silylmethylcyclopropane with phenyl glyoxal and tin tetrachloride was carried out at 0 °C three tri-substituted THFs were isolated in 14, 10 and 3 % yields. The last THF had to be isolated using preparative TLC because of the small amount and difficulty separating it by normal flash column chromatography. All three had different ^{1}H NMR spectra to the previously isolated tri-substituted THF **296a** (Fig 3.7). The other products from the reaction were unreacted cyclopropane, disilyl ether and polymerised aldehyde. Again, using 2D NMR experiments and nOe studies, the proposed structures of the three THFs were a mixture of regio- and stereoisomers. Two of the THFs were regioisomers with the phenyl substituent at either the three or four position of the THF ring (Scheme 3.29). The relative stereochemistry, based on the nOe studies, is proposed to be a *trans* relationship between the substituents at C-2 and C-5, whilst the phenyl substituent appears to be *cis* to the methylsilane substituent and *trans* carbonyl substituent in both regioisomers.



Scheme 3.29

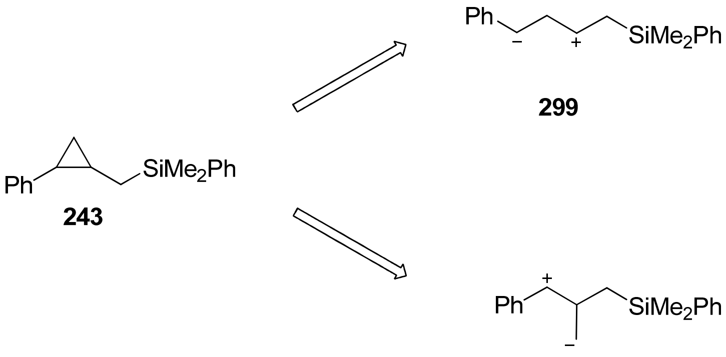
The structure of the third THF **298** is proposed to have the phenyl group at the C-5 position while the methylsilyl substituent is at the four position (Fig 3.8). The nOe data indicated a *trans* relationship between the C-2 and C-5 substituents while the data was ambiguous for the C-4 substituent.



298

Fig. 3.8

The existence of a small amount of **298** would suggest that the cyclopropane has opened with the formation of the carbocation α- to the phenyl group instead of β- to the silyl group (Fig 3.9). This is slightly surprising as, although, the phenyl group can stabilise the positive charge though the π-system, the carbanion has no additional stabilising functionality. The low yield of this product shows that the intermediate is less stable than that with the carbocation β to the silicon atom.



299

243

300

Fig. 3.9

3.9 Summary

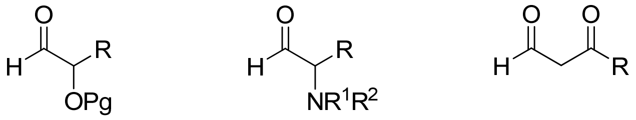
The silyl substituted silylmethylcyclopropane **241** was synthesised from the 1,2-substituted allylsilane by means of a Simmons-Smith reaction using the conditions previously outlined (Section 2.13). The 1,2-substituted allylsilane was most conveniently prepared by deprotonation of the allylsilane and quenching the allylic anion with a chlorosilane. Upon cyclisation with phenyl glyoxal at −78 °C, trace amounts of the tri-substituted and di-substituted THFs were obtained but the majority of the starting material decomposed to the disilylether. Performing the reaction at 0 °C resulted in complete decomposition of the starting material to the disilylether. All attempts to cyclise the silyl substituted silylmethylcyclopropane with phenylacetaldehyde using different Lewis acids were unsuccessful. The silyl substituent on the ring appeared to make the silylmethylcyclopropane more sensitive to decomposition under Lewis acid conditions than the unsubstituted silylmethylcycloproane.

Synthesis of the nitrile substituted silylmethylcyclopropane **242** from the substituted allylsilane *via* a Simmons-Smith reaction was unsuccessful. A rhodium catalysed carbene insertion reaction between diazoacetonitrile and allylsilane produced the desired nitrile substituted silylmethylcyclopropane to test in the cyclisation. No reaction was observed between the nitrile substituted silylmethylcyclopropane and phenyl glyoxal with tin tetrachloride at −78 °C or 0 °C. If the reaction was heated at reflux the starting material decomposed without any of the desired product observed.

The phenyl substituted allylsilane was prepared from β-bromostyrene and dimethylphenylsilylmethylmagnesium chloride *via* a cobalt-catalysed Heck-type reaction in good yield. Cyclopropanation using Simmons-Smith conditions gave the cyclopropane **243** in a moderate yield although the purification was difficult. Cyclisation with phenyl glyoxal produced a small amount of several tri-substituted THF products that were identified as a mixture of regio- and stereoisomers. As with the unsubstituted silylmethylcyclopropanes the temperature of the reaction appeared to influence the relative stereochemistry of the isolated products. The incorporation of the phenyl group on the cyclopropane ring seems to make the cyclopropane more stable to the reaction conditions, although poor yields of the trisubstituted THF were obtained.

Future work arising from chapters two and three

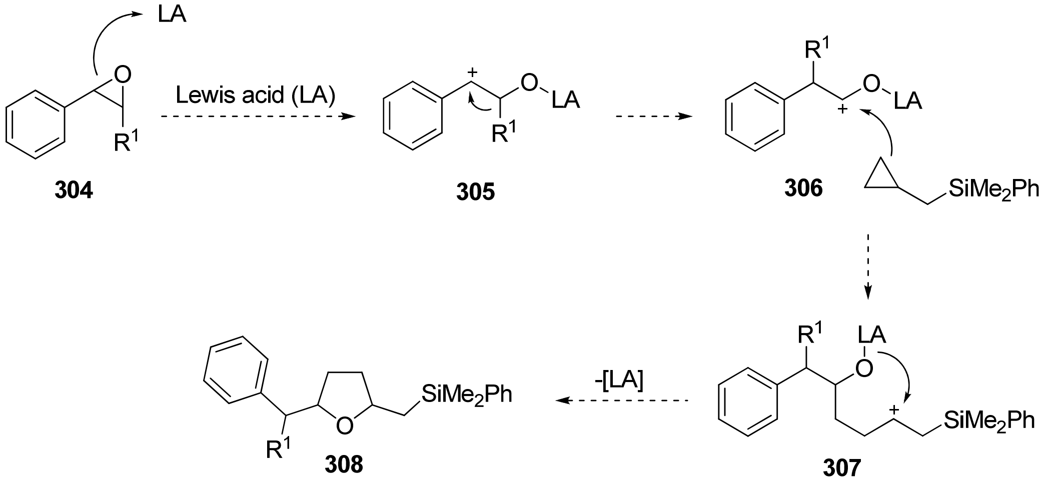
Successful reaction conditions have been developed for the cyclisation of silylmethylcyclopropanes with glyoxals and glyoxalates promoted by tin tetrachloride and to a lesser extent by zinc halides; however, these conditions have not been applicable to other aldehydes. Therefore, the scope of the methodology would need to be extended further before the reaction could be synthetically useful in organic synthesis. One aspect of any future work would be an investigation of other aldehydes containing electron-withdrawing groups or chelating groups such as 1,3-dicarbonyl compounds and α-heteroatom substituents (Fig. 3.10).



301 **302** **303**

Fig. 3.10

Li, amongst others, has reported the use of epoxides as electrophiles in the Lewis acid-promoted Prins reaction with a homoallylic alcohol to form tetrahydropyrans.[132] The proposed mechanism of the reaction is trapping of the carbocation generated by the Lewis acid promoted rearrangement of the epoxide. A similar type of reaction could be envisaged using the cyclopropane to trap the carbocation (Scheme 3.30).



Scheme 3.30

A second aspect of the future work would be to investigate and extend the work with other substituents on the cyclopropane ring. Although the silyl group appears to make the silylmethylcyclopropane more to susceptible to nucleophilic attack, the nitrile and phenyl substituents led to less nucleophilic attack of the starting material. Further work with these substituents as well as a simple methyl substituent would expand the use and offer an insight in to the scope of the reaction. A possible selection of other substituted cyclopropanes are shown in (Fig. 3.11)

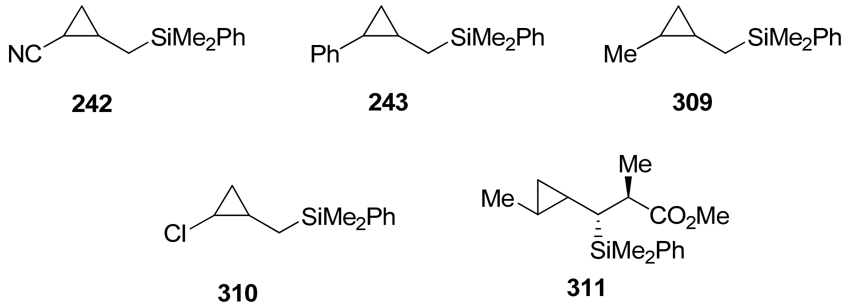
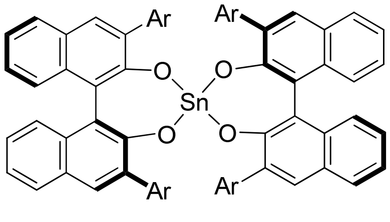


Fig. 3.11

A third aspect of the future work would be to examine whether it is possible to control the absolute stereochemistry of the product. The developed reaction offers some control over the relative stereochemistry of the final 2,5-disubstituted THF (*i.e.* the product can be obtained as only the *trans* isomer). Access to the optically enriched THFs could be achieved by one of two possible strategies, the first is the use of a chiral tin Lewis acid. Kano *et al.* have reported chiral tin (IV) aryloxides prepared from BINOL derivatives (Fig. 3.12) as Lewis acid catalysts for enantioselective Diels–Alder reaction.[133]

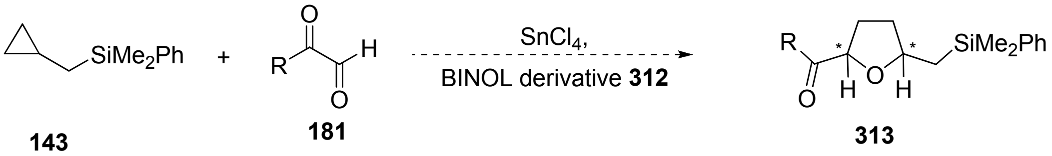


Ar = 3,5-$(CF_3)_2C_6H_3$

312

Fig. 3.12

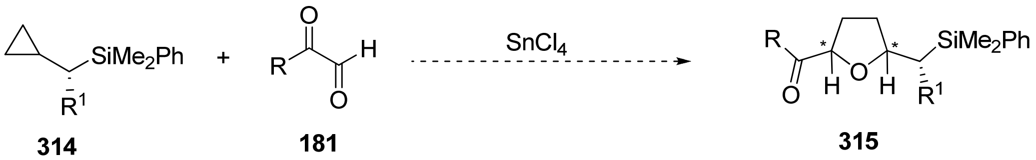
The application of a chiral tin Lewis acid could control the absolute stereochemistry of the two chiral centres in the THF product (Scheme 3.31).



*Absolute stereochemistry contolled by the chiral catalyst

Scheme 3.31

An alternative strategy for controlling the absolute stereochemistry is by asymmetric induction. The enantioselective incorporation of a chrial centre in the silylmethylcyclopropane starting material could conceivably influence the stereochemistry of the product (Scheme 3.32). The only prochiral carbon that could be substituted without substituting the cyclopropane ring is the methylene α- to the silyl group. The relative stereochemistry would be controlled by the reaction conditions while the chiral centre could control the absolute stereochemistry.



*Absolute stereochemistry contolled by the stereochemistry of R^1

Scheme 3.32

Conclusions arising from chapters two and three

The aim of this project was to investigate the use of silylmethylcyclopropanes in a cycloaddition reaction with carbonyl compounds for the construction of substituted tetrahydrofurans. This has been achieved for a limited range of aldehydes containing α-carbonyl group functionality. The reaction between an unsubstituted silylmethylcyclopropane and a glyoxal was efficiently promoted by tin tetrachloride after optimisation of the reaction conditions.

The product of this reaction was the 2,5-disubstituted THF possessing a silylmethyl group and an α-carbonyl group. The relative stereochemistry of the product is partially controlled by the temperature the reaction is performed; at 0 °C the *trans* diastereoisomer is almost exclusively formed while at −78 °C the *cis* diastereoisomer predominates. An array of silylmethylcyclopropanes containing different alkyl and aryl groups on the silicon all gave the cyclised THF product in a range of yields. The Lewis acid reacting directly with the silylmethylcyclopropane and eliminating the silyl group was a competing side reaction and was the major product at higher concentrations.

The ketone functional group retained in the THF product has proved to be a useful synthetic handle; a range of standard carbonyl reactions such as reduction, nucleophilic addition and Wittig type chemistry has allowed access to a selection of THF derivatives. The dimethylphenylsilyl group can be removed by a Fleming oxidation, although the reaction did not appear to be compatible with the ketone functionality in the molecule.

When the silyl and phenyl substituted silylmethylcyclopropanes were tested in the cyclisation reaction with phenyl glyoxal and tin tetrachloride, the tri-substituted THFs were isolated in trace amounts and as mixtures of regio- and stereoisomers. No reaction was observed with the nitrile substituted silylmethylcyclopropane even if the reaction was performed at room temperature.

Chapter Four

4.0 Introduction

During our investigation into the use of Lewis acid-activated aldehydes in cycloaddition reactions it became apparent that, in selecting a Lewis acid for a specific reaction, organic chemists still rely heavily on trial and error. This is because, although having been extensively used in organic synthesis, the nature of Lewis acids is still relatively poorly understood.[134] Most of the Lewis acids that have found success in organic synthesis would be classified as inorganic species usually consisting of a metal or "borderline metal" centre surrounded by the appropriate number of ligands. The following work communicates our studies into classifying Lewis acids by measuring their ability to change the electron distribution in a Lewis base when complexed. Before discussing the experimental work, it is worth recapitulating certain definitions and outlining previous attempts to rationalise Lewis acids by relative acid strengths.

4.1.1 Development of Acid-Base theory

In 1923, the two different acid-base theories that are currently used were proposed: the Brønsted-Lowry theory and the Lewis theory. The Brønsted-Lowry theory published by the Danish chemist J. N. Brønsted and the British chemist T. M. Lowry at approximately the same time defined an acid as follows: "An acid is a species having a tendency to lose a proton, and a base is a species having a tendency to add a proton". The Brønsted-Lowry theory found a large amount of support because of its practical applications and ease of use in quantitative treatment of acids and bases.[135]

First outlined in 1916[136] but later reviewed and expanded in his classic monograph "Valence and The Structure of Atoms and Molecules",[137] Lewis stated: "It seems to me that with complete generality we may say that a *basic substance is one which has a lone pair of electrons which may be used to complete the stable group of another atom,* and that *an acid substance is one which can employ a lone pair from another molecule* in completing the stable group of one of its own atoms. In other words, the basic substance furnishes a pair of electrons for a chemical bond, the acid substance accepts such a pair.".[137] Lewis' definition of acids and bases went fairly unnoticed until 15 years later when, in 1938, Lewis published a more comprehensive paper of acid-base theory.[138]

The modern definition of a Lewis acid is any substance capable of accepting a pair of electrons and a Lewis base is any substance capable of donating a pair of electrons. A base in the Lewis theory is the same as in the Brønsted-Lowry one, namely, a compound with an available pair of electrons, either unshared or in a π-orbital. A Lewis acid, however, is any species with a vacant orbital.[139] Essentially Lewis's definitions of acid-base interactions are founded on the concepts of the octet rule: in covalent bond formation, atoms go as far as possible toward completing their octets by sharing electron pairs.[140] An atom is in its most stable state when it has a full capacity of valence electrons as this leads to an overall lowering in energy of the system. This implies that if the formation of an acid-base complex is favourable, the donor and acceptor atoms have completed their octets through the formation of a dative covalent bond that leads to greater thermodynamic stability. There is an implication of an overall decreased reactivity of the acid and the base (i.e. neutralisation).[141]

In molecular orbital theory, Lewis acids are species with an available Lowest Unoccupied Molecular Orbital (LUMO). Any species with net positive charge is able to behave as a Lewis acid. Lewis bases are species with an available Highest Occupied Molecular Orbital (HOMO). Any species with a net negative charge is able to act as a Lewis base. From this almost purely MO examination of Lewis acids, it can be seen that the concept is easily expanded well beyond the confines of what most organic chemists would think of as an acid-base reaction to encompass substitution reactions of both a nucleophilic and electrophilic nature.[142]

When the Lewis and Brønsted-Lowry theories were first suggested they were thought of as alternative theories; over time this view has slowly changed. The Brønsted-Lowry theory could be described as an important but very specific type of Lewis acid where the proton (H^+) is acting as a Lewis acid and (usually) water is acting as the Lewis base by donation of the non-bonding lone pair of electrons to form the hydroxonium ion. Even though these ideas may be fundamentally closer to the realistic situation, from a practical argument the Brønsted-Lowry theory has the advantage that it is more easily understood and, importantly, it obeys a quantitative relationship.

4.1.2 Selecting a Lewis acid in organic synthesis

The importance of Lewis acids in organic synthesis as both catalysts and promoters has been recognised and extensively reported in the literature.[143] Particularly important is their ability to promote successful carbon-carbon bond forming reactions such as Diels-Alder,[144] aldol,[145] Prins/ene,[146] Friedel-Crafts,[147] Michael reaction,[148] esterification[149] and the Claisen rearrangement[150] to name but a few. Even with such a diverse selection of reactions initiated by Lewis acids, the trial and error method of finding the most appropriate one is still the main method and thus a considerable drawback.

The ability of Lewis acids to affect a chemical reaction can be very varied, as demonstrated by Carlson *et al.* during a computer-assisted study into patterns of reactivity among Lewis acids.[151] The group examined the ability of a selection of Lewis acids to promote three reactions: alkylation of a silyl enol ether, a Friedel-Crafts acylation and a Diels-Alder reaction. The yields of the reactions differed greatly from almost quantitative yields to no observed reaction. This difficulty to predict the success of a Lewis acid in a reaction is a significant drawback, especially when often in chemical synthesis only small amounts of reagents are available and therefore trial and error is time consuming, inefficient, costly and labour intensive.

4.1.3 Relative Lewis acid strength

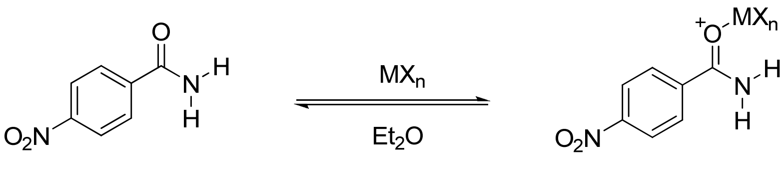
A number of attempts have been made to quantify the relative acid strength of Lewis acids and various theories have been suggested from physical, inorganic, theoretical and organic branches of chemistry, showing the generality of Lewis' theory.[152] One of the original qualitative methods of characterising Lewis acids and bases was to classify them empirically, according to whether they were hard, soft or borderline, as defined by Pearson's method.[153] In what has become known as Hard Soft Acid Base theory (HSAB) Pearson set out the definitions of hard and soft. This theory was supported and expanded as a result of frontier molecular orbital (FMO) treatment of species' interactions by Klopman and Hudson.[154] A Pearson-Klopman HSAB theory may be stated as "Hard [Lewis] Acids prefer to bind to Hard [Lewis] Bases to generate charge-controlled *ionic* complexes and Soft [Lewis] Acids prefer to bind to Soft [Lewis] Bases to generate FMO-controlled *covalent* complexes."[155] Alternative approaches to predicting donor-acceptor reactions include the donor-acceptor number (DN) approach of Gutmann[156] and the E and C equation of Drago.[157]

Frenking *et al.* have investigated the theoretical bond energies and geometries of complexes of BH_3, BF_3, BCl_3, $AlCl_3$ and SO_2 in comparison to experimental gas phase values.[158] Their calculations show that BH_3 binds more strongly than BF_3 to Me_3N and that the change in B-F bond length between the bound and unbound is a useful indication of acceptor-donor strength. It was also found that $AlCl_3$ was the most strongly bound complex studied but with very little covalent character, instead the aluminium was bound through electrostatic interactions.

Previous investigations from the literature to quantify Lewis acid strengths are based on one of two types of measurements; thermodynamic measurements and spectroscopic measurements. Thermodynamic measurements have used the standard heat of formation (ΔH) of the adduct and equilibrium constants to propose orders of acidity for small groups of Lewis acids. There are a small number of reports employing infrared, ultraviolet spectroscopy and nuclear magnetic resonance spectroscopy to measure the change in spectroscopic signals between a bound and unbound Lewis base. However, Satchell *et al.* have reported that no correlation could be found between the shift in carbonyl stretching frequency ($\Delta\upsilon_{C=O}$) and acid strength during a study of phenalen-1-one with a range of acid halides.[159]

4.1.4 NMR Spectroscopic Measurements

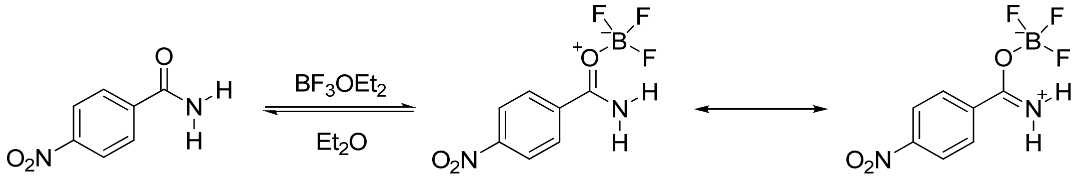
The concept of using NMR analysis as a means of quantifying Lewis acids has been reported previously. The first was by Satchell and Satchell who described an attempt to correlate the difference in chemical shift between the Lewis base and adduct to the equilibrium constant of a Lewis base and a metal halide.[160] The study examined adducts formed from the aromatic amides *m*-methoxybenamide and *p*-nitrobenzamide with a number of metal halides in a diethyl ether solution (Scheme 1).



MX_n = $AsCl_3$, $SbCl_5$, BF_3, $ZnBr_2$, $ZnCl_2$, $GaBr_3$ or $GaCl_3$

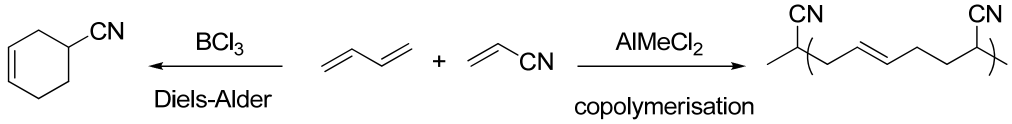
Scheme 4.1

The change in chemical shift of the *cis* and *trans* protons of the amide were measured and compared to the equilibrium constant. The conclusions of this work showed that there did not appear to be a correlation between pK and the chemical shift, but there was a linear relationship between *K* and the chemical shift. Boron trifluoride was seen as an anomalous result in this linear relationship and a six membered species being formed through hydrogen bonding between the fluorines on the boron and nitrogen (amidyl) proton is tentatively suggested (Scheme 2). The resonance positions were independent of the concentrations of the metal halide and adduct. There was no mention of whether the diethyl ether solvent was coordinating to the Lewis acid and if this was a competing factor in the analysis.



Scheme 4.2

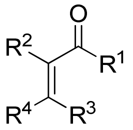
A more detailed NMR analysis of Lewis acid strength was undertaken by Childs *et al.* to investigate the observation that different Lewis acids led to different products in the reaction between acrylonitrile and butadiene (Scheme 3).[161]



Scheme 4.3

The group examined the 1:1 complexes formed from a series of Lewis acids initially using crotonaldehyde as the Lewis base by ^{1}H and ^{13}C NMR. Later studies were expanded to include four different α,β-unsaturated carbonyl functionalities (Table 1). One of the advantages of using α,β-unsaturated carbonyl compounds was that the NMR signals could be comparatively easily and unambiguously assigned.

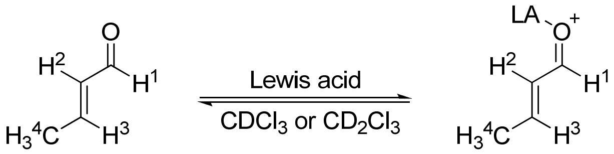
Table 4. 1 Childs' NMR studies into α,β-unsaturated carbonyl compounds



Entry	R^1	R^2	R^3	R^4
1	H	H	H	Me
2	Me	H	H	Me
3	OMe	H	H	Me

The resonances H2-, 3- and 4 of crotonaldehyde all shifted downfield on complexation with the Lewis acid, the chemical shift of the H1 proton appears to change randomly. The magnitude of the change in shift was largest for the H3 and smaller for the H2 and H4. The sticking feature of the ^{13}C chemical shifts is the upfield shift of the C2 carbon, indicating an increase in electron density on the carbon when complexed to the Lewis acid. Linear relationships were found to exist between the change in chemical shift of the carbon and hydrogen atoms at the same position as well as between the carbons and hydrogens along the chain with the exception of the C1 and H1.

Table 4.2 Change in ^{1}H and ^{13}C chemical shifts of crotonaldehyde on complexation with various Lewis acids[a]



Lewis acid	Proton Δδ (ppm)				Carbon Δδ (ppm)			
	H1	H2	H3	H4	C1	C2	C3	C4
BBr_3	0.11	0.93	1.49	0.51				
BCl_3	-0.65	0.85	1.35	0.49	6.8	-3.7	31.7	4.3
$SbCl_5$	0.17	0.78	1.32	0.48	6.9	-4.0	27.6	3.7
$AlCl_3$	-0.20	0.76	1.23	0.47				
$EtAlCl_2$[b,c]	-0.20	0.77	1.25	0.47				
BF_3	-0.27	0.74	1.17	0.44	8.3	-3.3	26.1	3.1
$EtAlCl_2$[b,c,d]	-0.17	0.67	1.15	0.38				
$Et_3Al_2Cl_3$[b,c]	-0.15	0.69	1.14	0.39				
$TiCl_4$	0.03	0.60	1.03	0.36				
Et_2AlCl[b,c]	-0.15	0.55	0.91	0.30	9.4	-2.0	20.1	2.3
$SnCl_4$	0.02	0.50	0.87	0.29	7.8	-2.8	19.2	2.3
Et_3Al	-0.34	0.42	0.63	0.23				

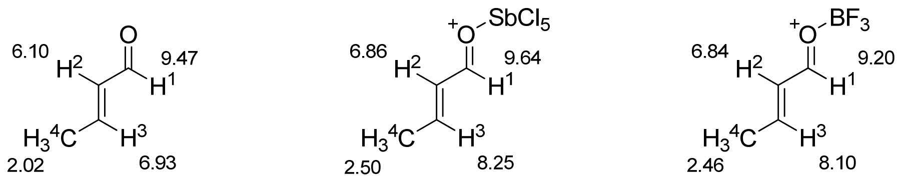
[a] In ppm the chemical shifts of uncomplexed crotonaldehyde are δ_H 9.47 (d, 1H, H1), 6.10 (ddq, 1H, H2), 6.93 (m, 1H, H3), 2.02 (dd, 3H, H4); δ_C 194.7 (C1), 134.4 (C2), 155.2 (C3), 19.0 (C4). As approximately 0.3 M solution in dichloromethane at -20 °C. Δδ is positive for a downfield shift.

[b] At -60 °C the chemical shifts of uncomplexed base: δ_H 9.38 (H1), 1.73 (2-CH,), 6.69 (H3), 1.99 (H4).

[c] Acid written in monomeric form for simplicity.

[d] 2:1 in crotonaldehyde – $EtAlCl_2$

The study revealed a linear relationship existed for the Lewis acid induced chemical shifts of H3, H4, C3 and C4 in all α,β-unsaturated carbonyl compounds. The chemical shift of H1 and C1 appeared to be affected by the local anisotropy while for H2 and C2 it was proposed that two factors were influencing the chemical shifts: through-bond and through-space deshielding. The choice of the Lewis acid changed the magnitude but not the distribution of electron density with H3/C3 showing the greatest difference in chemical shift between the complexed and free base which is expected based on possible resonance forms (Fig. 4.1 and 4.2).



δ_H of H1 > H3 > H2 > H4 in all cases

Fig. 4.1 The chemical shifts (in ppm) of complexed and uncomplexed crotonaldehyde showing the Lewis acid changes the magnitude but not the distribution of electron density.

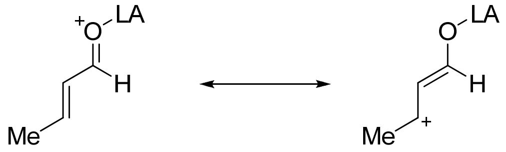


Fig. 4.2 possible resonance forms of complexed crotonaldehyde

Owing to the linear relationship of chemical shifts of all the bases, the work concludes by ranking the Lewis acid by the induced chemical shift of the H3/C3 position to produce a table of relative strength: $BBr_3 > BCl_3 > SbCl_5 > AlCl_3 > BF_3 > AlEtCl_2 > TiCl_4 > SnCl_4 > Et_3Al$. In their follow-up paper the results of the NMR study were compared to calorimetric measurements and no correlation was found.[162]

This NMR procedure has been relatively underused with the exception of Yamamoto and co-workers who used the NMR method of Childs *et al.* in the analysis of the relative strength of their new Lewis acid catalyst.[163] Several other articles on the subject of NMR analysis of Lewis acid-base interactions have appeared in the literature, although these studies were not directly related to Lewis acidity.[164]

4.2 Results and Discussion

The aim of this part of the project was to investigate whether it was possible to establish a relative scale of carbonyl activation of Lewis bases complexed with different Lewis acids using NMR analysis and if the results could be used to predict which Lewis acid would be successful in a particular reaction.

NMR analysis provides a method to determine indirectly the change in electronic distribution within a molecule. If a Lewis base coordinates to a Lewis acid, there must be some degree of electron donation from the Lewis base; a change in electron distribution would result and hence a change in the chemical shift of the Lewis base. It was envisaged that the greater the donation of electron density from the Lewis base, the greater the activation of the carbonyl and hence the larger the change in chemical shift will be.

4.2.1 Butanal

Butanal was selected as the Lewis base for the investigation because it has unambiguous assignable signals in an NMR spectrum and had no other functionality in the molecule. It was important to use an aldehyde molecule that was devoid of functionality other than the carbonyl group as the presence of a second donor site could lead to chelation or two equivalents of Lewis acid interacting with the aldehyde. It was our desire in the initial work to consider only one possible site of donation.

Originally, the NMR experiments were performed using d_2-DCM as the solvent, because DCM is one of the most common solvents for Lewis acid promoted reactions and has been used in our own synthetic work. This was abandoned after some initial experiments because d_2-DCM was awkward to work with (being supplied in 10 mL vials), hydroscopic once opened and expensive at 10 times the cost of $CDCl_3$. Therefore, $CDCl_3$ was used as the solvent. Chloroform and DCM are both low coordinating solvents and have been reported to be unreactive towards Lewis acids.[165] Running the NMR experiment in $CDCl_3$ and DCM gave similar results. The use of other organic solvents such as acetonitrile and tetrahydrofuran are discussed later (section 4.4).

It was expected that the degree of change in the chemical shift of a given proton was likely to be small, therefore it was crucial to have an accurate standard reference. Tetramethylsilane was chosen as the reference although it was uncertain as to whether it would interact with the Lewis acid and influence the results. Therefore, the tetramethylsilane reference was placed in a coaxial NMR tube inside the main NMR tube (Fig. 4.3). This would remain separate from the Lewis acid and base during the NMR experiment and therefore provide the most consistent reference, although a small reduction in resolution might be expected.

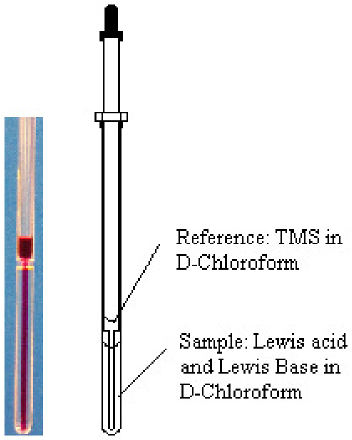


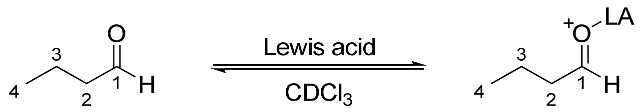
Fig. 4.3 A schematic diagram of the NMR tube with inner coaxial tube next to a photo of the NMR tube with the coaxial tube (the coaxial tube in the photo contains a coloured dye to help it show up)

Initially, the complexes were prepared in the NMR tube by the direct addition of undiluted Lewis acid to a stock solution of the carbonyl compound in $CDCl_3$ at room temperature. This method was abandoned after it was found to frequently give broad signals in the NMR spectra as a result of the solution not being homogeneous and the difficulty of accurately adding small amounts of Lewis acid. Instead, solutions of the aldehyde and Lewis acid were prepared separately then mixed and an aliquot placed in the NMR tube. The coaxial tube containing the reference was rapidly applied to seal the tube and the NMR experiment then run immediately. Aldehydes are known to undergo a number of degradation reactions such as oxidation to the acid, hydrolysis and condensation/dehydration reactions. Therefore, butanal was subjected to a basic wash and purified by distillation over calcium chloride before use. The stock solution of butanal was prepared in an oven dried volumetric flask and kept under an atmosphere of argon. It was found by NMR analysis that, over a period of 24 hours, decomposition began to occur. Therefore, a new stock solution was made freshly from the distillate before use. Interestingly, the distillate was found to decompose at a much slower rate than the solution, which is believed to be a result of the slightly acidic nature of chloroform.

The data obtained from the complexation of equal mole equivalents of butanal and a selection of Lewis acids is presented (Table 2). The values of both the chemical shift (δ_H) and change in chemical shift ($\Delta\delta_H$) of the protons in butanal when complexed to different Lewis acids at room temperature (295 K) are given. The $\Delta\delta_H$ values are calculated by subtracting the chemical shift of the uncomplexed Lewis base from the chemical shift of the complexed Lewis base. Therefore, a negative $\Delta\delta_H$ value represents an upfield shift and a positive value is a downfield shift.

The reference solution was a 10 % mixture of tetramethylsilane in $CDCl_3$. It is worth noting that two chloroform signals are visible in the NMR spectrum, which reveals that the chloroform signal in a solution is affected by solute, and is not an ideal secondary reference for accurate work.

Table 4.3 Change in ^{1}H chemical shifts of butanal on complexation with various Lewis acids[a]



Lewis Acid	δ H1 (ppm)	Δδ H1 (ppm)	δ H2 (ppm)	Δδ H2 (ppm)	δ H3 (ppm)	Δδ H3 (ppm)	δ H4 (ppm)	Δδ H4 (ppm)
Blank	9.76		2.40		1.66		0.96	
$AlCl_3$	9.90	0.13	3.20	0.80	1.88	0.21	1.06	0.10
$TiCl_4$	10.00	0.24	2.96	0.55	1.87	0.21	1.10	0.14
$SnCl_4$	9.83	0.07	2.77	0.37	1.71	0.05	0.95	-0.01
$InCl_3$	9.78	0.01	2.59	0.18	1.72	0.05	0.98	0.02
$BF_3.OEt_2$	9.89	0.13	2.52	0.11	1.70	0.04	1.01	0.05
$ZnBr_2$	9.73	-0.03	2.38	-0.03	1.64	-0.03	0.94	-0.02
$SnBr_4$	9.67	-0.09	2.34	-0.07	1.59	-0.07	0.89	-0.07

a The Lewis acids and base were combined at room temperature and the NMR spectra obtained at room temperature (295 K). All chemical shifts are referenced to an external solution of tetramethylsilane. $\Delta\delta_H = \delta_H$ (complexed Lewis base)-δ_H (Lewis base) Positive values represent a downfield shift negative values represent an upfield shift. All values are stated to 2 decimal places.

The results show that for the Lewis acids $BF_3.Et_2O$, $InCl_3$, $SnCl_4$, $TiCl_4$ and $AlCl_3$ the chemical shifts of the H2 and H3 have moved downfield while in the case of $SnBr_4$ and $ZnCl_2$ the chemical shift of all the protons moved upfield by a small amount. The resonance of H4 tends to show the same trend as the H2 and H3 protons but the magnitude of the change is smaller. The complex-induced chemical shift of H1 appears to vary randomly.

The overall downfield shift is expected as the electron density of the carbonyl group oxygen is reduced as a result of complexation with the Lewis acid. However, the upfield shift of the data for $SnBr_4$ and $ZnCl_2$ suggests that the electron density is in some way increasing across the molecule. It is unclear why this trend is observed for these Lewis acids. As the proton environment increases in distance from the carbonyl group the magnitude of the change in chemical shift decreases.

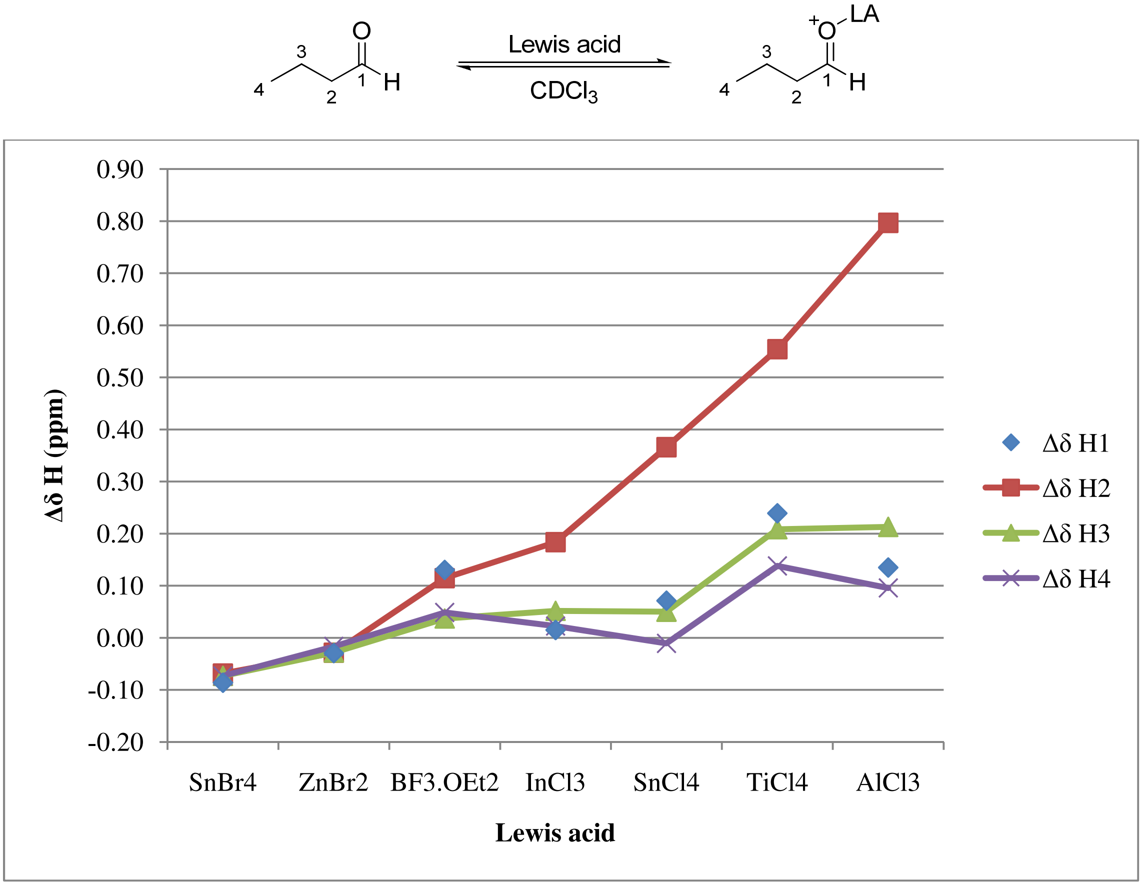


Fig. 4.4 ^{1}H NMR chemical shift difference of equal mole equivalents of butanal with various Lewis acids

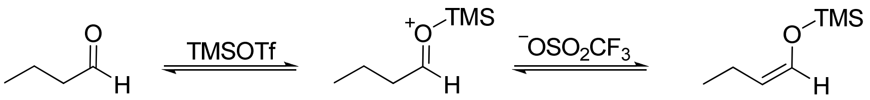
The graph (Fig 4.4) shows how the chemical shift of the protons in butanal change when complexed to 1 equivalent of Lewis acid, for a range of different Lewis acids. The Lewis acids have been arranged in order of increasing change in chemical shift of the H2 hydrogen.

$AlCl_3$, $TiCl_4$, $SnCl_4$ and $BF_3.OEt_2$ reveal similar trends; the chemical shift of the H2 hydrogen is most significantly affected from complexation to the Lewis acid. The shifts of the other hydrogen atoms show a much smaller change and in the case of $InCl_3$ and $BF_3.OEt_2$ the shift is only just detectable. The localised influence of the Lewis acid complexed to the aldehyde can be attributed to the limited donation of electron density from a carbon chain possessing only σ-bonds.

The H1 chemical shift varies randomly and would appear to be an unreliable indicator of the change in electron density upon complexation. As proposed in previous studies the local environment of the H1 is likely to be appreciably effected from being in close proximity to the bound Lewis acid.

The results obtained for the Lewis acids $SnBr_4$ and $ZnBr_2$ appear anomalous for two reasons: the four hydrogen environments show the same amount of change in chemical shift while the chemical shifts of the other Lewis acids clearly suggest a localised affect where the hydrogen atoms further from the carbonyl group experience a weaker effect from complexation. The second anomalous feature is that all the values are negative and thus all the chemical shifts have moved upfield. The magnitude of the change in chemical shift is small and may be an indication that no complexation is occurring and the change in chemical shifts is due to experimental error.

Upon complexation with $BF_3.OEt_2$ the H2 splitting pattern becomes complicated. This coupling appears to be because of the fluorines on the boron interacting with the protons at the C2 position. Trimethylsilyl trifluoromethanesulfonate (TMSOTf) was also tested in this work but the ^{1}H NMR spectrum of the complexed Lewis acid-base adduct contains a number of unexpected signals making the interpretation difficult. To investigate this further, other types of NMR spectra were obtained: ^{13}C, ^{1}H-^{1}H and ^{1}H-^{13}C. These spectra gave support to the idea that there is more than one species present in the sample. Owing to the appearance of a peak at approximately 6.9 ppm, the possibility of the Lewis acid enol forming was considered (Scheme 4.4). This could subsequently lead to an aldol reaction. However, the silyl enol ether of butanal, (1-buten-1-yloxy)trimethylsilane, has been previously been reported in the literature and the reported values for the olefinic protons are 6.11 ppm and 4.49 ppm.[166] No such signals were observed in the NMR spectra and would suggest that the enol is not present (The formation of the Lewis acid enol product was never observed in any of the NMR experiments).



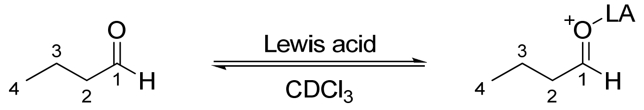
Scheme 4.4

Butanal appeared to undergo a decomposition process in the presence of TMSOTf at room temperature. If TMSOTf was added to the sample at −78 °C no colour change was observed but on transferring the sample to the NMR spectrometer (< 2 min) a yellow colour developed and the NMR confirmed the butanal had decomposed.

Many Lewis acids, being inorganic complexes, are only partially soluble in $CDCl_3$ and the presence of solid in the NMR sample made it impossible to attain a spectrum. Therefore to obtain a NMR spectrum with solid Lewis acids, the Lewis acid was mixed with a solution of Lewis base and then a sample was removed. The NMR spectrum was then obtained of the removed sample not containing solid material. This creates an error and inconsistency in the number of equivalents of Lewis acid that are actually interacting. The reason for including this material was to show than even if the data is inaccurate there is still an interaction occurring. The solubility of $AlCl_3$, $InCl_3$ and $ZnBr_2$ were all problematic.

There is a clear change in chemical shift of H2 from using the different Lewis acids, therefore the ^{13}C NMR data was collected for butanal complexed with several of the Lewis acids to investigate whether the same trend could be observed from the carbon NMR data. This is summarised in Table 4.4.

Table 4.4 Change in ^{13}C chemical shifts of butanal on complexation with various Lewis acids[a]



Lewis Acid	δ C1 (ppm)	Δδ C1 (ppm)	δ C2 (ppm)	Δδ C2 (ppm)	δ C3 (ppm)	Δδ C3 (ppm)	δ C4 (ppm)	Δδ C4 (ppm)
Blank	202.9		45.8		15.6		13.7	
$AlCl_3$	228.8	25.9	46.6	0.8	15.6	-0.1	13.3	-0.4
$TiCl_4$	218.4	15.5	45.5	-0.2	15.8	0.2	13.6	-0.1
$SnCl_4$	215.4	12.5	44.9	-0.9	15.6	0.0	13.4	-0.3
$ZnBr_2$	203.1	0.2	45.6	-0.1	15.6	0.0	13.7	0.0
$SnBr_4$	203.0	0.1	45.7	0.0	15.1	-0.5	13.7	0.0

a The Lewis acids and base were combined at room temperature and the NMR spectra obtained at room temperature (295 K). All chemical shifts are referenced to an external solution of tetramethylsilane. $\Delta\delta_H = \delta_H$ (complexed Lewis base)-δ_H (Lewis base) Positive values represent a downfield shift negative values represent an upfield shift

The Lewis acids have been arranged in order of the largest change in the chemical shift of the C1 carbon. The results show the change in chemical shift of C1 is significant when the aldehyde is complexed to the Lewis acid, whilst the other carbons show only a small change in chemical shift. The ^{13}C chemical shifts of the nuclei further from the bonding site do not follow the same trend; with some moving upfield while others move downfield.

From the H2 ^{1}H NMR and the C1 ^{13}C NMR data the following order of Lewis acids for carbonyl activation is proposed: $AlCl_3 > TiCl_4 > SnCl_4 > InCl_3 > BF_3.OEt > ZnBr_2 \approx SnBr_4$. The similar values obtained for $ZnBr_2$ and $SnBr_4$ may be as a result of the NMR spectrometer not being sensitive enough to detect the small differences.

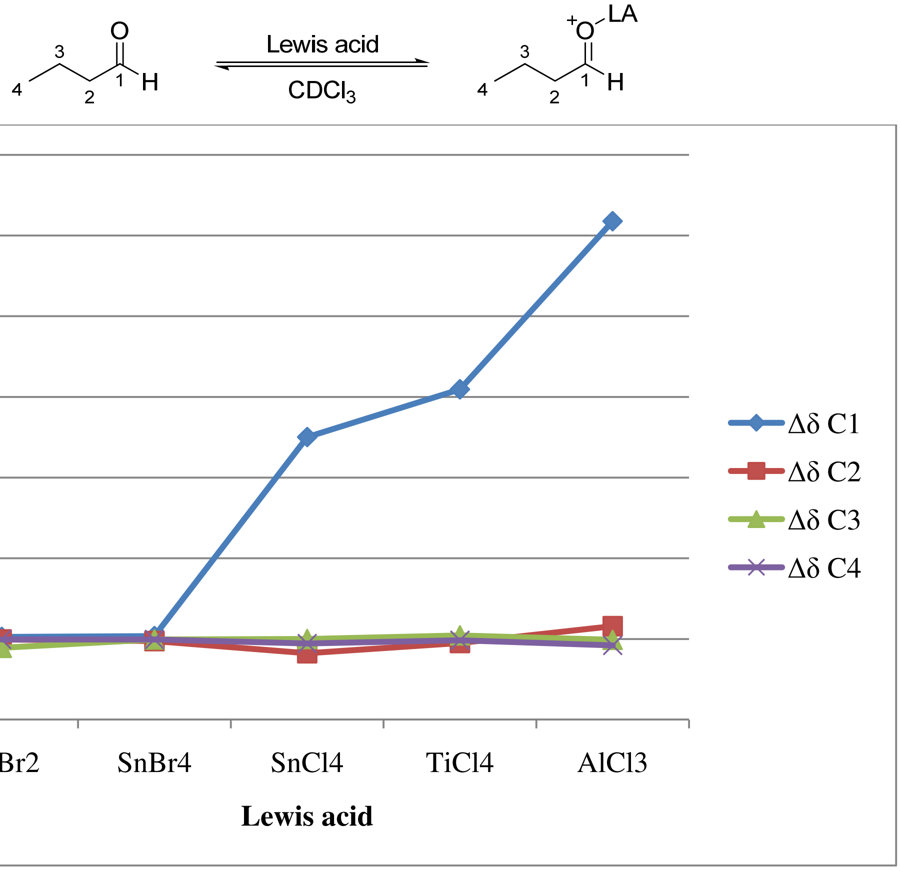


Fig. 4.5 ^{13}C NMR chemical shift difference of carbons in butanal with various Lewis acids

The graph (Fig. 4.5) shows the change in chemical shift of the butanal carbons upon addition of different Lewis acids. Owing to the large difference in Δδ C that C1 displays compared to the other carbons a second graph showing only C2, C3 and C4 has been plotted (Fig. 6). The Δδ C of C1 reveals a strong effect from complexation to the Lewis acid whilst the other carbons feel only a weak effect.

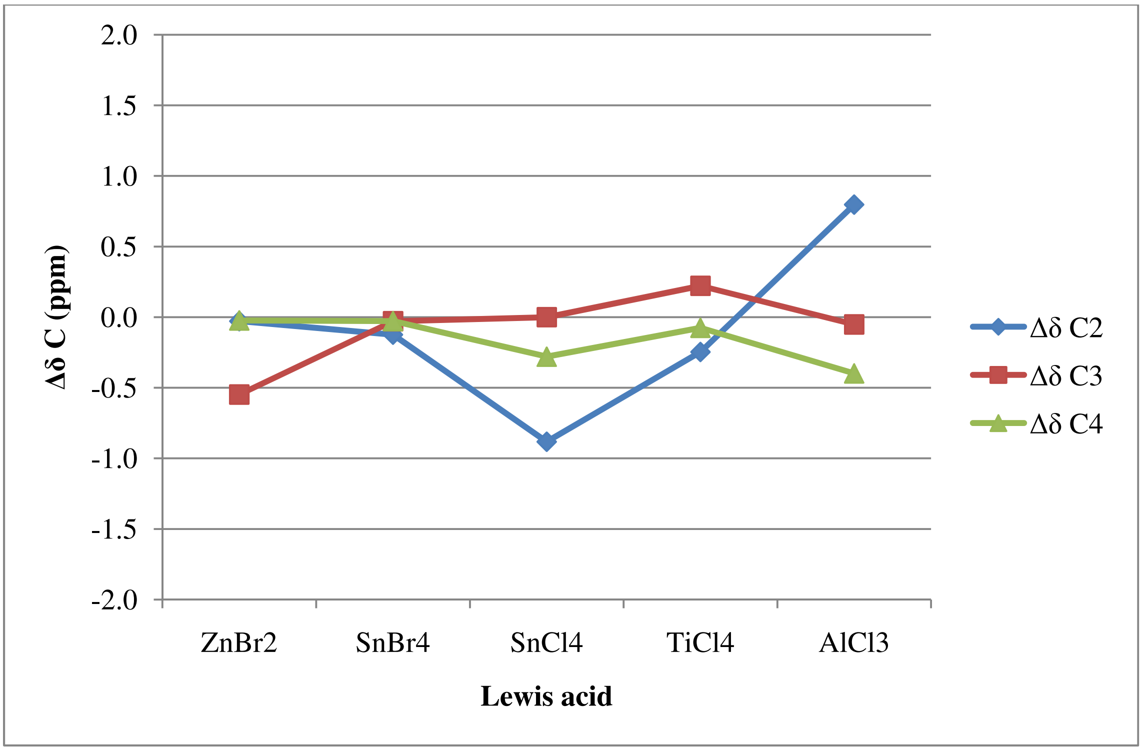
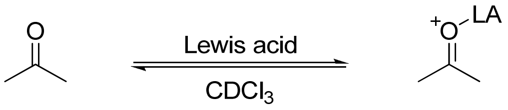


Fig. 4.6 ^{13}C NMR chemical shift difference of the C2, 3 and 4 carbons in butanal with various Lewis acids

4.2.2 Acetone

Given the difficulties of interpreting the spectra of the Lewis acid-activated butanal using BF_3.OEt_2 and TMSOTf, a simpler carbonyl compound was investigated. Acetone produces a very simple single signal in the proton NMR spectrum as all the protons are magnetically and chemically equivalent, therefore the activation of acetone was investigated. It was decided to analyse four of the liquid Lewis acids because it was felt that theses did not raise any solubility problems and therefore, would produce more accurate data. The results of the activation of acetone with different Lewis acids are presented (Table 4.5 and Fig. 6).

Table 4.5 Change in ^{1}H chemical shifts of acetone on complexation with various Lewis acids



Lewis Acid	δ H1 (ppm)	Δδ H1 (ppm)
Blank	2.20	
$TiCl_4$	2.78	0.57
$SnCl_4$	2.45	0.25
BF_3OEt_2	2.29	0.09
TMSOTf	2.21	0.00

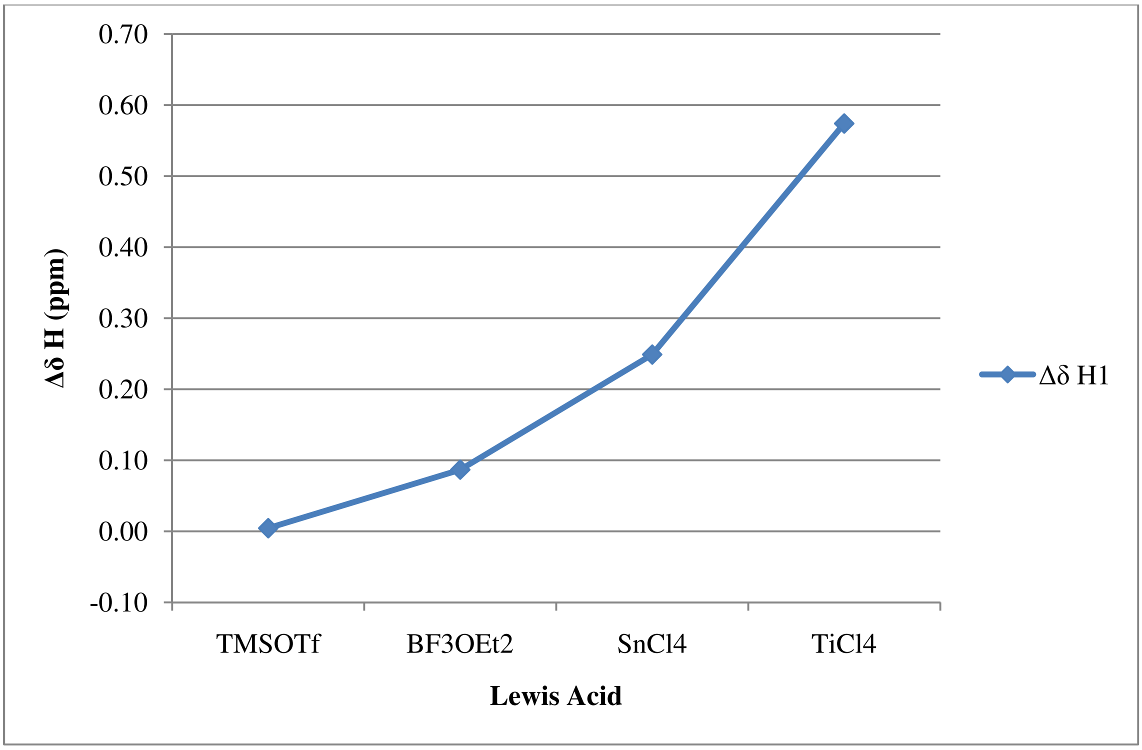


Fig. 4.7 ^{1}H NMR chemical shift difference of equal mole equivalents of acetone with various Lewis acids

The results show that upon complexation the chemical shift of the methyl protons are all shifted downfield. The spectra obtained for all the Lewis acid complexes only showed a single signal although some broadening of the signal was observed. The data acquired for acetone complexed to different Lewis acids supports the order of Lewis acids for carbonyl activation proposed from the butanal experiments: $TiCl_4$ > $SnCl_4$ > $BF_3.OEt_2$ > TMSOTf.

Childs' study into NMR analysis of Lewis acid strength using crotonaldehyde found a consistent change in chemical shift of the proton and carbon resonances within the molecule. If the change in chemical shift of protons (with the exception of H1) were plotted against H3, a linear relationship was obtained. The comparison to the H3 hydrogen was used because the change in chemical shift was greatest for H3. In this study of complexed butanal, a linear relationship was observed for the H2 and H4 protons against the H3, however, the carbon data showed no such correlation (Fig. 4.8 and 4.9).

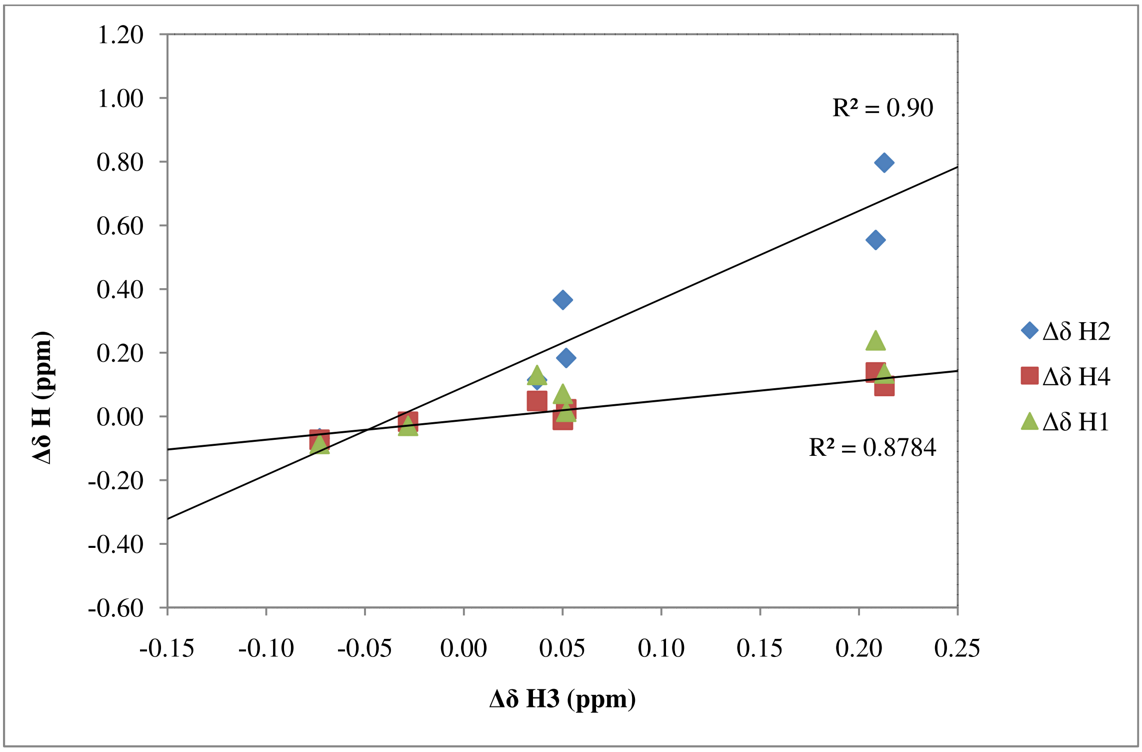


Fig. 4. 8 ^{1}H chemical shift differences of protons of butanal against H3 chemical shift difference on complexation with various Lewis acids

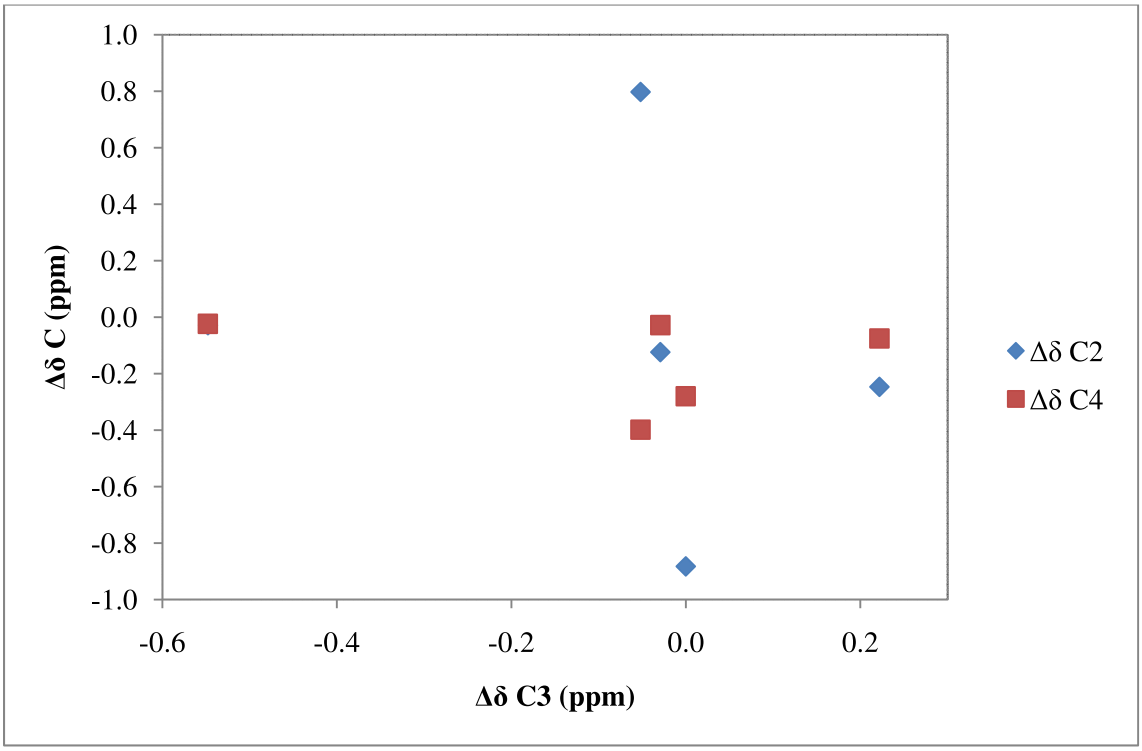
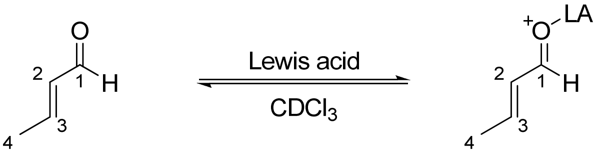


Fig. 4.9 ^{13}**C chemical shift of the carbons of butanal against C3 chemical shift difference on complexation with various Lewis acids**

4.2.3 Crotonaldehyde

To determine whether the linear relationship observed in Child's work was a result of the Lewis base or an operational experimental difference, several experiments were repeated using crotonaldehyde as the Lewis base. The crotonaldehyde was distilled prior to use and the reactions were run in the same way as those using butanal. The results are summarised in Table 6 and 7.

Table 4.6 Change in ^{1}H chemical shifts of crotonaldehyde on complexation with various Lewis acids[a]



Lewis Acid	δ H1 (ppm)	Δδ H1 (ppm)	δ H2 (ppm)	Δδ H2 (ppm)	δ H3 (ppm)	Δδ H3 (ppm)	δ H4 (ppm)	Δδ H4 (ppm)
Blank	9.50		6.14		6.88		2.03	
$AlCl_3$	9.24	-0.25	6.85	0.71	8.15	1.27	2.46	0.43
$TiCl_4$	9.58	0.08	6.61	0.47	7.65	0.77	2.29	0.26
$SnCl_4$	9.45	-0.05	6.52	0.38	7.63	0.76	2.24	0.21
$InCl_3$	9.45	-0.05	6.24	0.10	7.04	0.16	2.07	0.03
$ZnBr_2$	9.46	-0.04	6.18	0.04	6.93	0.05	2.03	0.00

a The Lewis acids and base were combined at room temperature and the NMR spectra obtained at room temperature (295 K). All chemical shifts are referenced to an external solution of tetramethylsilane. $\Delta\delta_H = \delta_H$ (complexed Lewis base)-δ_H (Lewis base) Positive values represent a downfield shift negative values represent an upfield shift

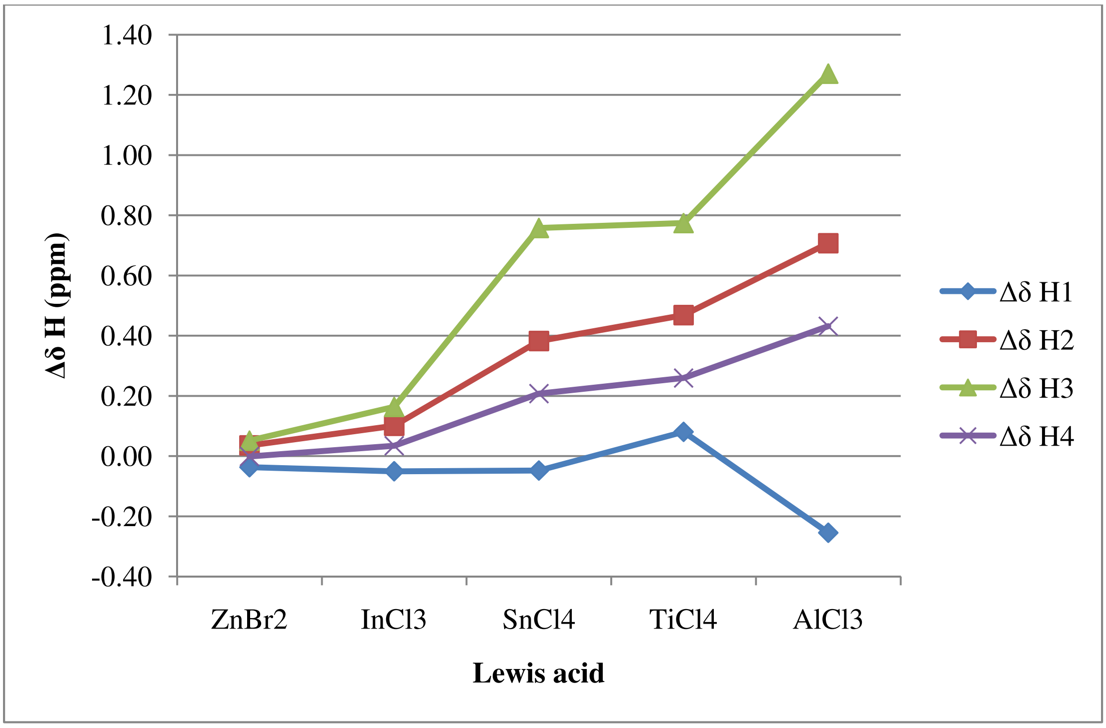


Fig. 4.10 ^{1}H NMR chemical shift difference of hydrogens in crotonaldehyde with various Lewis acids

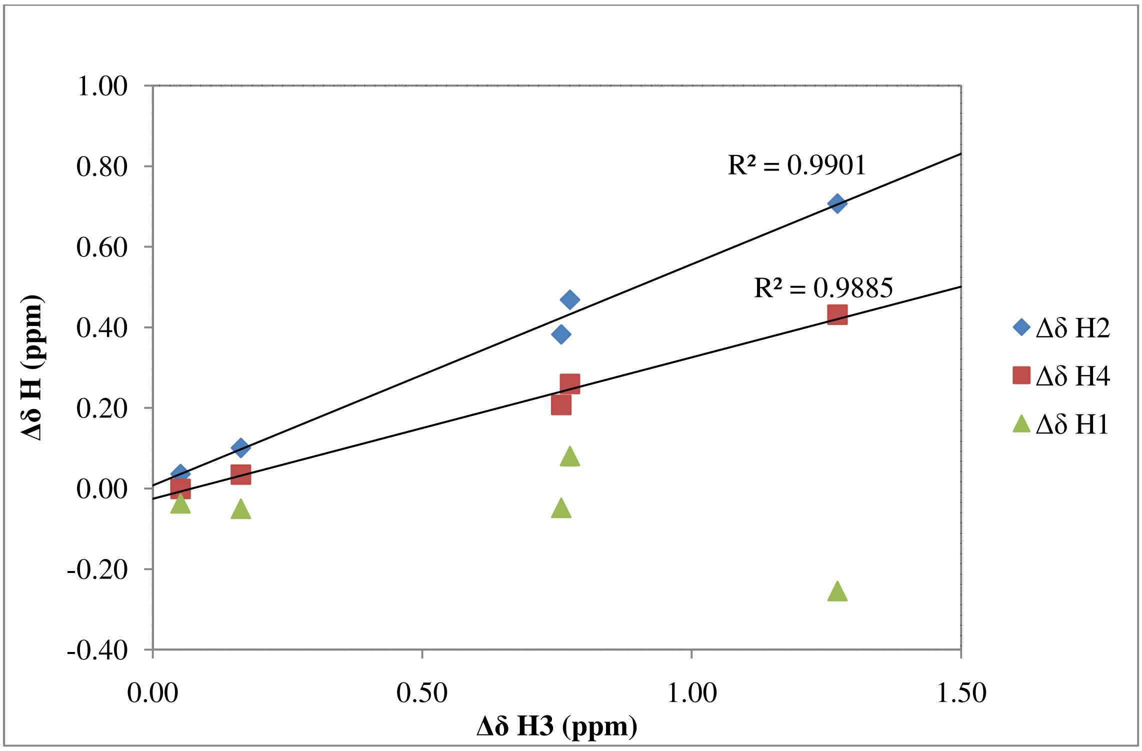
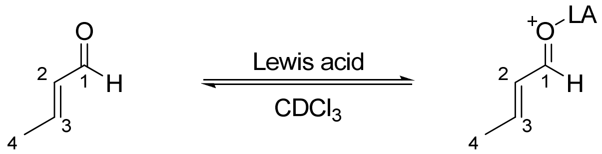


Fig. 4. 11 ^{1}H chemical shift of hydrogens of crotonaldehyde against H3 chemical shift difference on complexation with various Lewis acids

Table 4.7 Change in ^{13}C chemical shifts of crotonaldehyde on complexation with various Lewis acids[a]



Lewis Acid	δ C1 (ppm)	Δδ C1 (ppm)	δ C2 (ppm)	Δδ C2 (ppm)	δ C3 (ppm)	Δδ C3 (ppm)	δ C4 (ppm)	Δδ C4 (ppm)
Blank	194.1		134.6		154.2		18.7	
$AlCl_3$	205.9	11.8	133.0	-1.6	183.2	29.0	22.6	3.9
$TiCl_4$	203.8	9.7	132.5	-2.2	170.1	15.9	20.9	2.1
$SnCl_4$	201.8	7.7	132.1	-2.5	171.6	17.3	21.0	2.2
$InCl_3$	196.8	2.7	134.1	-0.5	158.4	4.2	19.2	0.5
$ZnBr_2$	195.3	1.2	134.4	-0.2	155.9	1.6	18.9	0.1

a The Lewis acids and base were combined at room temperature and the NMR spectra obtained at room temperature (295 K). All chemical shifts are referenced to an external solution of tetramethylsilane. $\Delta\delta_H = \delta_H$ (complexed Lewis base)-δ_H (Lewis base) Positive values represent a downfield shift negative values represent an upfield shift

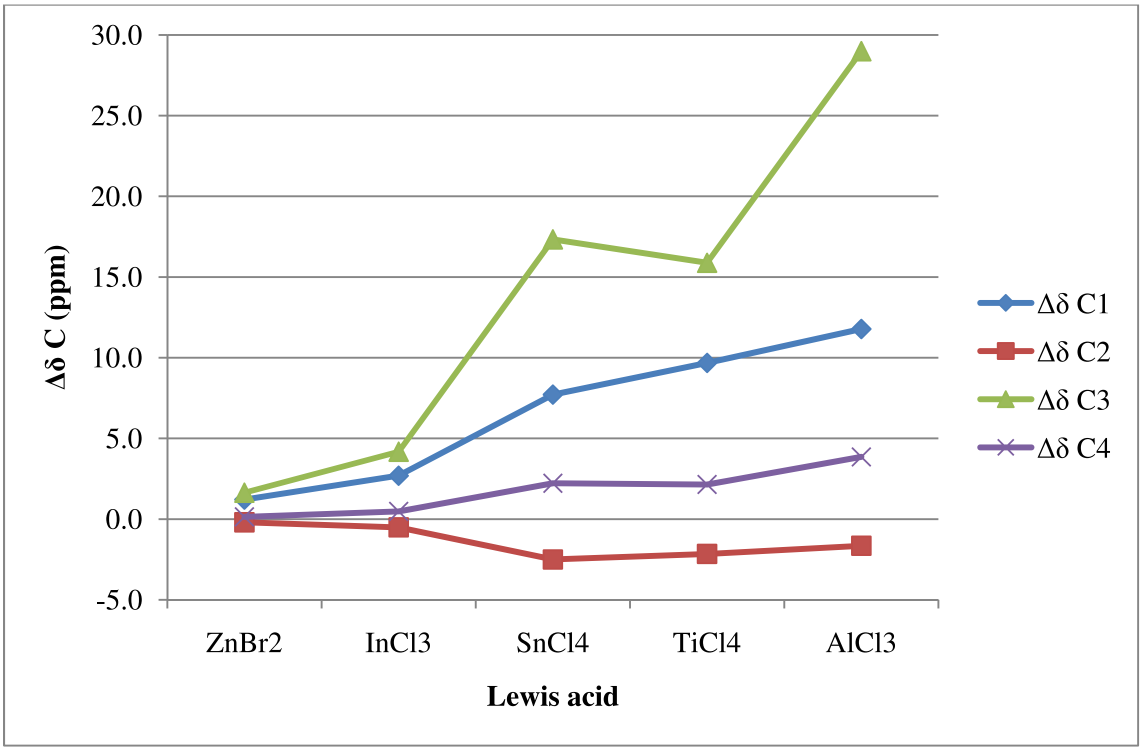


Fig. 4.12 ^{13}C NMR chemical shift difference of the carbons in crotonaldehyde with various Lewis acids

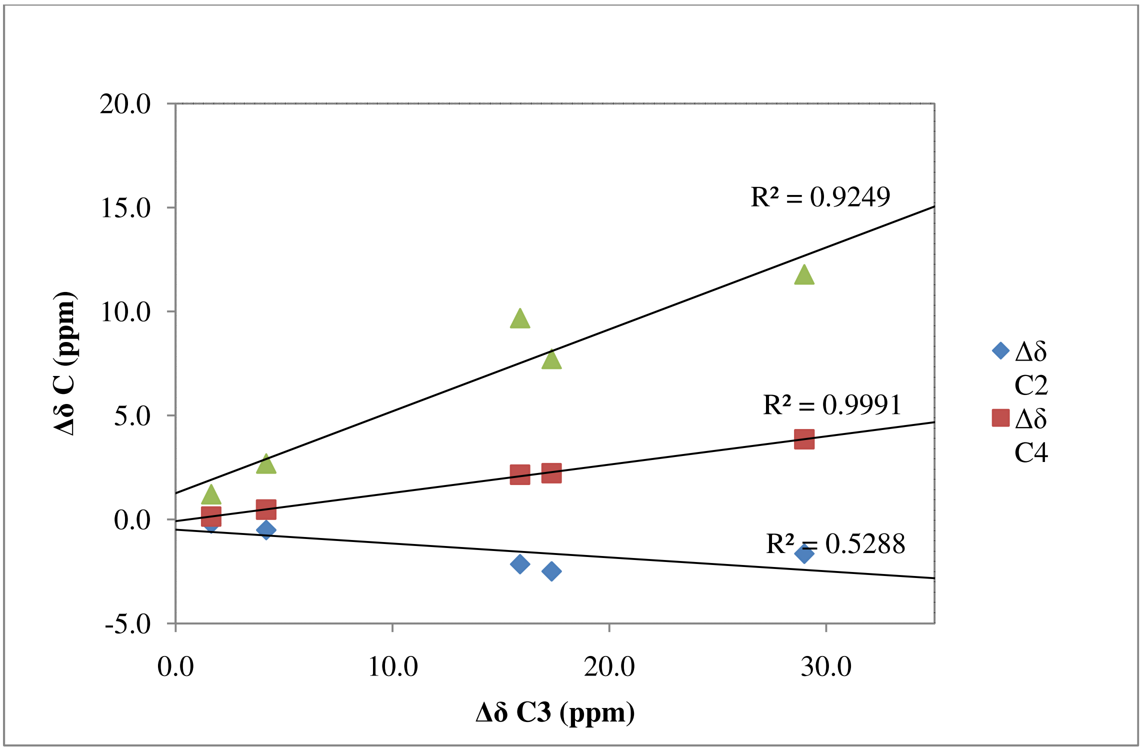


Fig. 4.13 ^{13}**C chemical shift of the carbons of crotonaldehyde against C3 chemical shift difference on complexation with various Lewis acids**

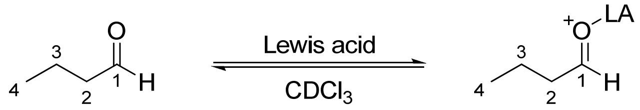
When crotonaldehyde was used in place of butanal a linear relationship between the complex induced chemical shifts for all the carbons and hydrogens except H1 was seen (Fig. 11 and 13). The result showed that the influence of the Lewis acid coordinating to the carbonyl group was more localised in butanal. This work confirms the absence of a linear relationship for the complex induced proton chemical shifts in butanal was a result of the Lewis base used in the original work and not the experimental method. It also demonstrated that the presence of the delocalised π-system in α, β-unsaturated carbonyl compounds allows the transfer of information through the molecule.

The complex induced change in chemical shift obtained for crotonaldehyde complexed with $AlCl_3$, $TiCl_4$ and $SnCl_4$ (for carbon resonances) compare well with the results reported by Childs (Table 2, 6 and 7). The data using crotonaldehyde (Fig. 10 and 12) also supports the order of ability of Lewis acids for carbonyl activation obtained from the butanal and acetone work: $AlCl_3 > TiCl_4 > SnCl_4 > InCl_3 > ZnBr_2$.

4.3 Equivalents of Lewis Acid

The data presented so far was all obtained from mixing equal equivalents of Lewis acid and base and it was assumed that the resulting adduct was a 1 : 1 complex. A single set of signals were seen in the NMR spectra supporting the idea that all the material was complexed. However, when $BF_3.OEt_2$ was used as the Lewis acid the chemical shift of the methylene protons of the diethyl ether and the H2 hydrogens of aldehyde were further downfield than uncomplexed diethyl ether and aldehyde. This was a possible indication that a rapid equilibrium between the complexed and uncomplexed aldehyde was occurring and the observed signals were an average of the two signals. This time averaging position of the signal would be a result of the rate of exchange in the dynamic equilibrium being faster than the NMR time scale. To examine whether it was possible to observe complexed and uncomplexed aldehyde signals at the same time and the effect on the chemical shift of using different ratios of Lewis acid to base, the ^{1}H NMR experiments were repeated for butanal and acetone using a range of equivalents (Table 4.8).

Table 4.8 Change in ^{1}H chemical shifts of butanal on complexation with various Lewis acids[a]



Lewis Acid	Equivalents	δ H1 (ppm)	Δδ H1 (ppm)	δ H2 (ppm)	Δδ H2 (ppm)	δ H3 (ppm)	Δδ H3 (ppm)	δ H4 (ppm)	Δδ H4 (ppm)
Blank		9.76		2.40		1.66		0.96	
$TiCl_4$	0.1	9.92	0.16	2.66	0.25	1.76	0.09	1.02	0.06
	0.2	9.98	0.22	2.77	0.37	1.79	0.12	1.03	0.07
	0.3	9.99	0.23	2.73	0.32	1.79	0.12	1.04	0.08
	0.4	10.02	0.26	2.87	0.46	1.83	0.16	1.06	0.10
	0.5	10.02	0.26	2.94	0.53	1.86	0.19	1.08	0.12
	0.6	10.02	0.26	2.94	0.53	1.86	0.19	1.08	0.12
	0.8	10.01	0.25	2.96	0.56	1.89	0.23	1.10	0.14
	1	10.00	0.24	2.96	0.55	1.87	0.21	1.10	0.14
	1.5	10.06	0.29	3.04	0.63	1.94	0.28	1.17	0.21
	2.5	10.06	0.30	3.06	0.65	1.97	0.31	1.19	0.23
	3	10.17	0.41	3.17	0.76	2.08	0.42	1.31	0.35
$SnCl_4$	0.1	9.80	0.04	2.50	0.10	1.69	0.03	0.98	0.02
	0.2	9.85	0.09	2.64	0.24	1.72	0.05	0.98	0.02

	0.25	9.84	0.07	2.57	0.17	1.71	0.05	0.98	0.02
	0.3	9.86	0.10	2.72	0.31	1.72	0.06	0.97	0.01
	0.4	9.86	0.10	2.72	0.31	1.73	0.06	0.97	0.01
	0.5	9.89	0.13	2.75	0.35	1.74	0.08	0.98	0.02
	0.6	9.87	0.11	2.77	0.36	1.74	0.07	0.98	0.02
	0.8	9.87	0.11	2.79	0.39	1.74	0.08	0.98	0.02
	1	9.83	0.07	2.77	0.37	1.71	0.05	0.95	-0.01
	1.5	9.88	0.12	2.85	0.44	1.78	0.12	1.02	0.06
	2	9.81	0.05	2.79	0.38	1.73	0.06	0.97	0.01
	3	9.81	0.05	2.80	0.40	1.75	0.08	0.99	0.03
$BF_3.OEt_2$	0.25	9.77	0.01	2.45	0.05	1.69	0.02	0.98	0.02
	0.5	9.77	0.01	2.46	0.01	1.68	0.02	0.97	0.01
	0.75	9.80	0.04	2.49	0.09	1.70	0.04	0.99	0.03
	1	9.89	0.13	2.52	0.11	1.70	0.04	1.01	0.05
	1.5	9.78	0.02	2.49	0.08	1.68	0.01	0.96	0.00
	2	9.85	0.09	2.52	0.11	1.69	0.03	0.97	0.01
	2.5	9.89	0.13	2.55	0.14	1.70	0.04	0.98	0.02
	3	9.85	0.09	2.52	0.12	1.69	0.03	0.97	0.01
$InCl_3$	0.5	9.77	0.01	2.58	0.17	1.71	0.05	0.98	0.02
	1	9.78	0.01	2.59	0.18	1.72	0.05	0.98	0.02
	1.5	9.76	0.00	2.59	0.18	1.70	0.04	0.97	0.01
	2	9.76	0.00	2.58	0.18	1.70	0.03	0.97	0.01
	3	9.76	0.00	2.61	0.21	1.71	0.04	0.97	0.01
$ZnBr_2$	0.5	9.73	-0.03	2.36	-0.04	1.64	-0.03	0.93	-0.03
	0.8	9.74	-0.02	2.39	-0.02	1.65	-0.02	0.94	-0.02
	1	9.73	-0.03	2.38	-0.03	1.64	-0.03	0.94	-0.02
	1.36	9.73	-0.03	2.38	-0.03	1.64	-0.03	0.91	-0.05
	1.86	9.73	-0.03	2.38	-0.03	1.64	-0.03	0.93	-0.03
	3	9.73	-0.03	2.38	-0.03	1.64	-0.03	0.93	-0.03
$AlCl_3$	0.25	9.78	0.02	2.45	0.05	1.69	0.02	0.98	0.02
	0.5	9.79	0.03	2.54	0.13	1.70	0.03	0.98	0.02
	1	9.90	0.13	3.20	0.80	1.88	0.21	1.06	0.10

a The Lewis acids and base were combined at room temperature and the NMR spectra obtained at room temperature (295 K). All chemical shifts are referenced to an external solution of tetramethylsilane. $\Delta\delta_H = \delta_H$ (complexed Lewis base)-δ_H (Lewis base) Positive values represent a downfield shift negative values represent an upfield shift

The results show that upon complexation at any equivalent, the chemical shifts are all shifted downfield by varying amounts with the exception of when $ZnBr_2$ is the Lewis acid. The general trend in the shape of the line indicates with a small addition of Lewis acid the initial change in chemical shift is greatest and as more equivalents are added, less change is observed. The solubility of $AlCl_3$, $InCl_3$ and $ZnBr_2$ were all problematic at all equivalents attempted and even at 1 equivalent a significant amount of $AlCl_3$ did not dissolve and therefore no higher equivalents were tested.

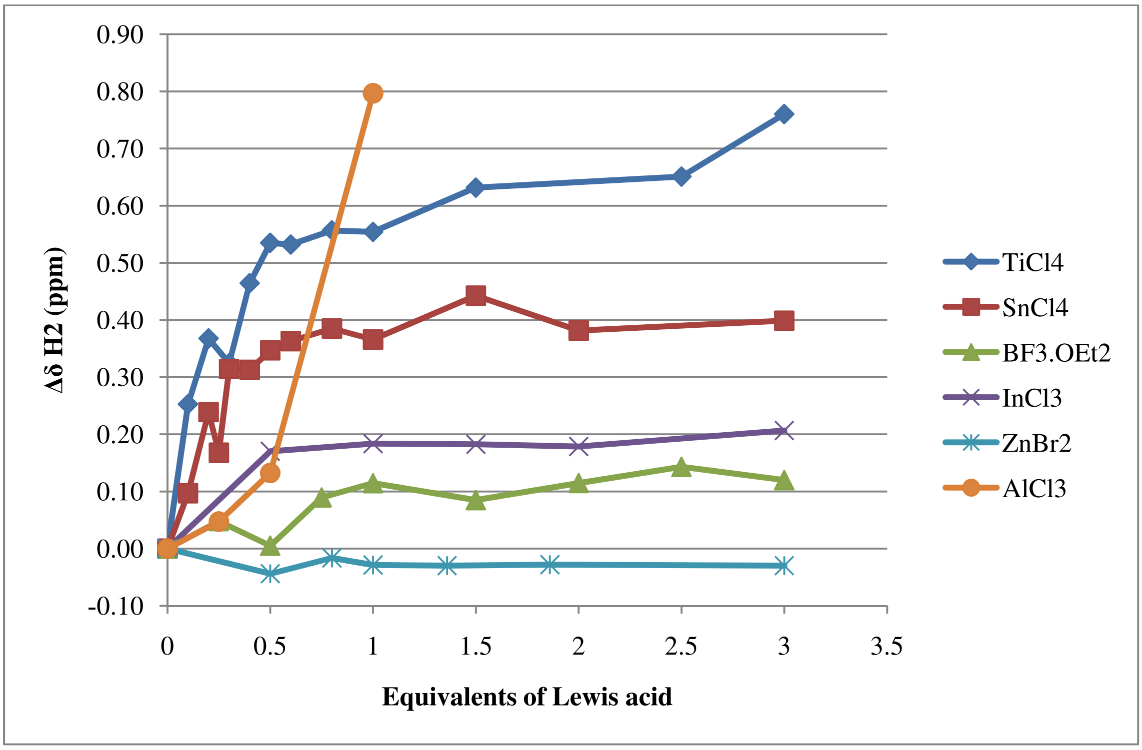
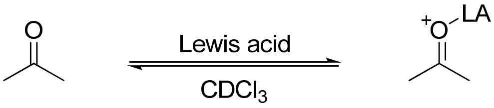


Fig. 4.14 ^{1}H chemical shift difference between the H2 proton in the uncomplexed and the complexed butanal with different Lewis acids at different equivalents

The graph (Fig. 4.14) shows the change in chemical shift of the H2 hydrogen of butanal complexed to different equivalents of different Lewis acids. The greatest change in chemical shift occurs on addition of quantities below 0.75 equivalents of Lewis acid. The addition of more than 1.5 equivalents of Lewis acid results in a small change in chemical shift possibly indicating that the majority of the aldehyde is complexed. With the exception of $AlCl_3$ the amount of change in chemical shift at any given equivalent of Lewis acid reveals $TiCl_4$ complexed to the Lewis base caused the largest change and $ZnBr_2$ the smallest change. The work was repeated with acetone and different equivalents of a range of Lewis acids.

Table 4.9 Change in ^{1}H chemical shifts of acetone on complexation with various Lewis acids[a]



Lewis Acid	Equivalents of Lewis acid	δ H^1 (ppm)	Δδ H^1 (ppm)
Blank	0	2.18	
$TiCl_4$	0.25	2.38	0.20
	0.5	2.73	0.56
	0.75	2.74	0.56
	1	2.78	0.60
	2	2.87	0.69
	3	2.85	0.67
$SnCl_4$	0.25	2.31	0.13
	0.5	2.31	0.14
	0.75	2.45	0.28
	1	2.45	0.28
	1.5	2.44	0.27
	2	2.43	0.25
	3	2.36	0.19
BF_3OEt_2	0.25	2.26	0.09
	0.5	2.30	0.12
	0.75	2.24	0.06
	1	2.29	0.11
	2	2.33	0.15
	3	2.43	0.25
TMSOTf	0.5	2.18	0.00
	1	2.21	0.03
	2	2.22	0.04
	3	2.23	0.05

a The Lewis acids and base were combined at room temperature and the NMR spectra obtained at room temperature (295 K). All chemical shifts are referenced to an external solution of tetramethylsilane. $\Delta\delta_H = \delta_H$ (complexed Lewis base)-δ_H (Lewis base) Positive values represent a downfield shift negative values represent an upfield shift

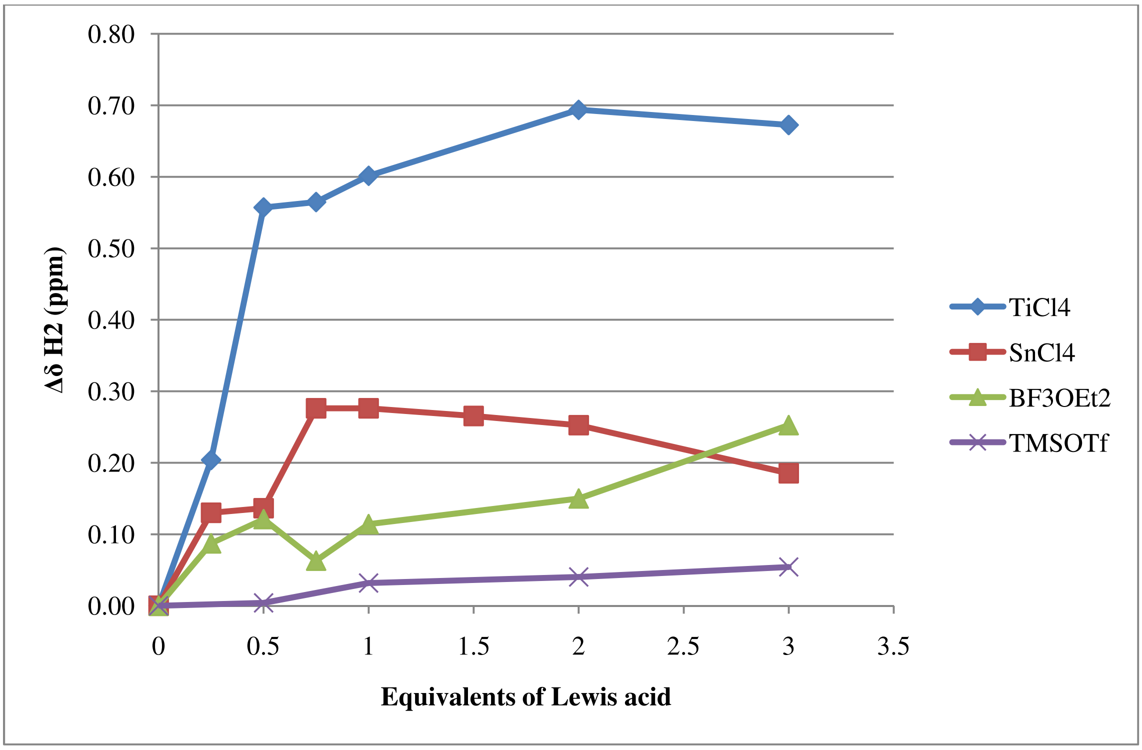


Fig. 4.15 ^{1}H chemical shift difference between the methyl protons in the uncomplexed and the complexed acetone with different Lewis acids at different equivalents

There are several interesting points indicated from the graph; the first is that the change in chemical shift induced from $SnCl_4$ and $TiCl_4$ complexation begins to reduce when the number of equivalents is greater than 2. In the case of $TiCl_4$ the reduction is thought to be a result of the adduct crystallising. After the spectrum had been obtained crystals were observed to have formed on the walls on the NMR tube.

The general trend of the line indicates with a small amount of Lewis acid the initial change in chemical shift is greatest and as more equivalents are added, less change is observed. One possible explanation is that the ratio of Lewis acid coordinating to the Lewis base is changing in the adduct. For example $TiCl_4$ could coordinate to a carbonyl group in several different molar ratios forming a 1:1, 1:2 or 2:2 adduct. At lower concentrations one adduct may be preferred over another but as the ratio of the Lewis acid and base changes so might the preferred adduct structure.

One of the objectives of this part of the work was to investigate whether by using different equivalents of Lewis acid to Lewis base signals of complexed and uncomplexed Lewis base could be observed. It was found that at all equivalents the NMR spectra still showed a single set of signals.

An alternative method for observing the separate signals was to slow the dynamic equilibrium down by cooling the sample. The ^{1}H NMR spectra were taken at −40 °C with 0.5 equivalents of both $TiCl_4$ and $SnCl_4$ (Fig. 4.16). The spectra still showed one set of signals corresponding to the butanal signifying that the rate of the dynamic equilibrium at −40 °C is faster than the NMR time scale.

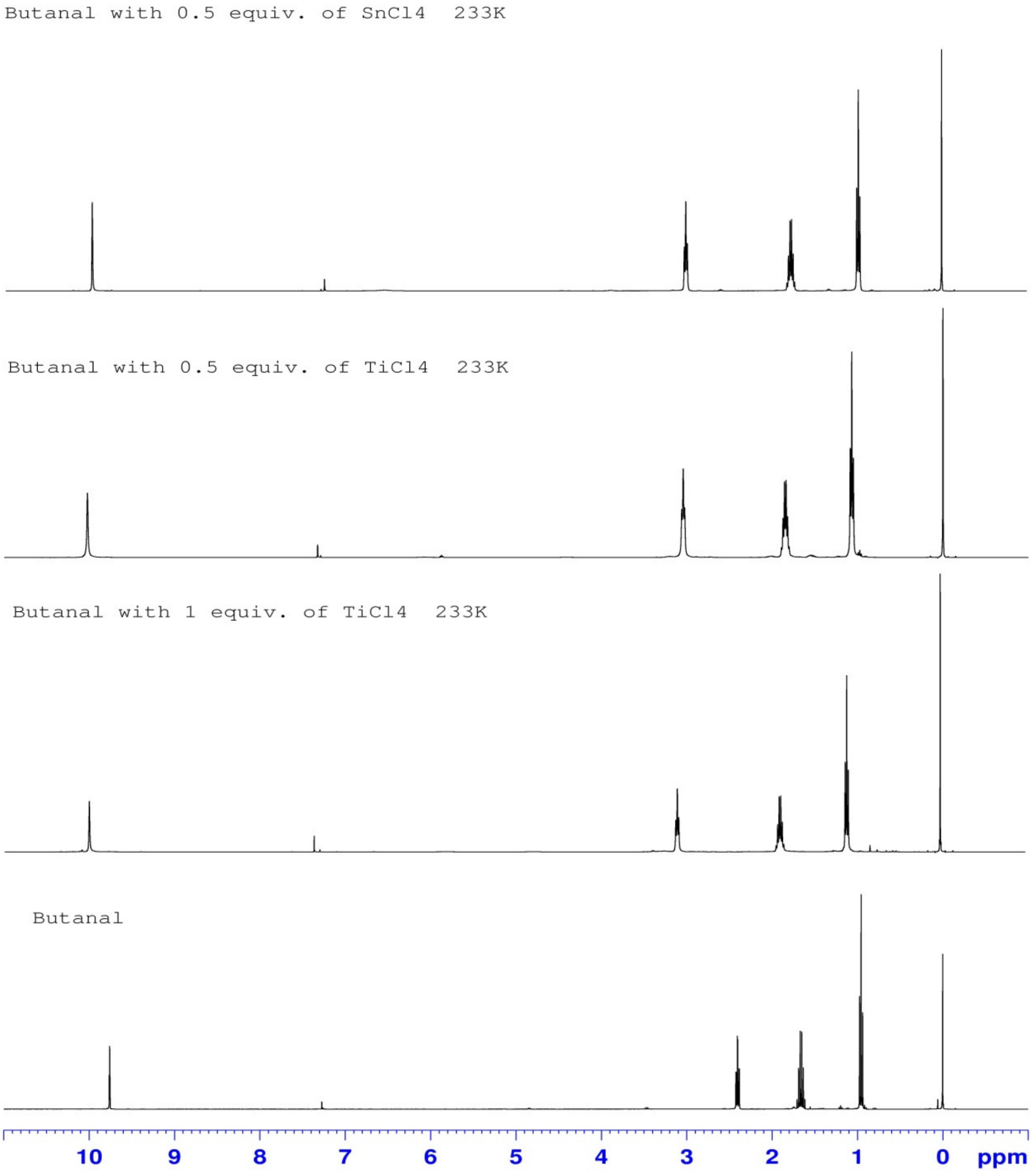


Fig. 4.16

4.3.1 Isolation of $TiCl_4$-acetone complex

As stated in section 4.3, the formation of crystals was observed when $TiCl_4$ was added to acetone at room temperature. Further investigations into the formation of the crystals revealed that, on addition of $TiCl_4$, in amounts greater than 0.75 equivalents, crystals precipitated out of solution. For the lower equivalents of $TiCl_4$, the crystals take longer to form, while at higher equivalents the crystals form within a few minutes. A crystal of the complex has been analysed and X-ray crystallography confirmed a 2:2 complex of $TiCl_4$ and acetone (Fig. 7). This structure has been reported in the literature previously using an alternative method of synthesis.[167]

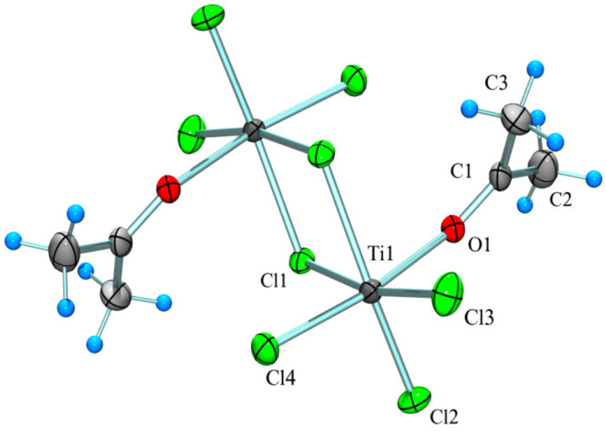


Fig. 4.17 Crystal structure of the 2:2 complex (329) of $TiCl_4$ and acetone

4.4 Alternative solvents

A significant problem was that many of the Lewis acids show only partial solubility in $CDCl_3$ and it was therefore desirable to be able to perform the NMR analysis in an alternative solvent. Both tetrahydrofuran and acetonitrile have successfully been employed as a solvent for Lewis acid promoted reactions. Both these solvents have the ability to act as a Lewis bases, through the lone pair of electrons on hetero-atom and, in the case of the acetonitrile, the π-system has been proposed as a possible coordination site.[168]

Therefore, to establish whether D-8 THF or CD_3CN would be a better solvent for the investigation, several trial experiments were performed. Attempts to measure the chemical shift of butanal or acetone in deuterated acetonitrile or tetrahydrofuran with $TiCl_4$ all proved unsuccessful. On addition of $TiCl_4$, the solvent appeared to complex to the Lewis acid and precipitate was observed in the NMR sample.

Next, $InCl_3$, which had shown only partial solubility in chloroform, was tested in deuterated acetonitrile with butanal. Vigorous stirring was required to dissolve 1 equivalent of $InCl_3$ in a 0.55 M solution of butanal in acetonitrile and more than 1 equivalent could not be fully dissolved.

As deuterated tetrahydrofuran was found to be no better than acetonitrile for dissolving the Lewis acids and $TiCl_4$ proved to be incompatible with both solvents, this work was not explored any further.

4.5 Conclusions

In this chapter, our investigation into the use of NMR spectroscopy to measure the degree of activation a carbonyl compound experiences when complexed to a Lewis acid is presented. It has been demonstrated that NMR spectroscopy can be used to measure changes in the chemical shift between an uncomplexed and a Lewis acid complexed Lewis base.

The ^1H NMR data of three Lewis bases complexed with a small number of Lewis acids commonly used in organic synthesis have been recorded. The ^1H and ^{13}C NMR data of butanal complexed to equal molar quantities of Lewis acid has been measured for a range of Lewis acids. The results showed the H1 chemical shift appeared to be affected by the local anisotropy whilst the H3 and H4 were only weakly influenced by the coordination to the Lewis acid. The complex-induced chemical shift of the H2 hydrogen was more considerable. The ^{13}C NMR signals for the more remote carbon atoms (C2, C3 and C4) were not significantly affected by complexation, however, the C1 resonance showed a large change in chemical shift.

The work was extended to include acetone and crotonaldehyde, which allowed comparisons to be made with Childs' work. The results obtained from this study were comparable to the data reported by Childs where the same Lewis acid and base had been investigated. Attempts to measuring the change in chemical shift of acetone complexed to $TiCl_4$ at room temperature produced a crystalline precipitated, confirmed (by the x-ray crystallography) as a 2:2 complex.

Attempts to observe the complexed and uncomplexed Lewis base in the NMR sample by acquiring the NMR spectra at low temperature (−40 °C) and by the addition of less than one equivalent of Lewis acid proved unsuccessful. This could be because the dynamic equilibrium is faster than the NMR time scale or that the adducts formed are not simple 1 : 1 complexes.

Deuterated chloroform appears to be a good solvent for the studies as it allowed a selection of Lewis acids to be examined, however the solubility of solid Lewis acids in chloroform remains a limitation. Attempts to use solvents other than DCM and chloroform were no better for obtaining the NMR spectra of a wider range of Lewis acids.

From the results obtained for butanal, acetone and crotonaldehyde, for the activation of a carbonyl group the following order of the Lewis acids is proposed: $AlCl_3 > TiCl_4 > SnCl_4 > InCl_3 > BF_3.OEt > TMSOTf > ZnBr_2 \approx SnBr_4$.

The limitation of using NMR spectroscopy (and other spectroscopic method) is that no one solvent dissolves a wide range of Lewis acids. However, the order of Lewis acids is consistent from the experiments with three different Lewis bases indicating the method could be a valuable tool for measuring the relative activation a carbonyl group

4.6 Future work

The NMR studies were undertaken to investigate whether NMR spectroscopy could be used as a predictive tool for the choice of Lewis acid in a reaction. Disappointingly, the cycloaddition reaction between aldehydes without an α-carbonyl group and silylmethylcyclopropanes were unsuccessful therefore, a comparison could not be made between the synthetic work and NMR studies. Therefore, we are interested in expanding the range of Lewis bases used in the NMR study to include 1,2 and 1,3 dicarbonyl compounds as well as other chelating groups.

Another aspect of the future work would be to expand the number of Lewis acids tested in the studies. The original study has only examined what might be described as more classic Lewis acids. The number of Lewis acids that have been used for organic synthesis is very large especially if the variation in possible ligands is also considered. The difficulty with expanding the study to include a wider range of Lewis acids, as mentioned in the previous section, is the insolubility of many Lewis acids in $CDCl_3$ or in fact any one solvent. This makes obtaining a spectra difficult and can create an inconsistency in the ratio of Lewis base to Lewis acids being measured.

Chapter Five: Experimental

5.1 General Experimental Details

Reaction Conditions

All reactions were carried out under an atmosphere of nitrogen or argon unless otherwise stated, using oven or flame-dried glassware and all transfers were performed using either plastic or glass syringes. Degassed solutions were prepared by rapidly bubbling nitrogen gas through the required solvent for approximately 10 min prior to use. Stirring was by internal magnetic follower and all reactions were monitored by tlc.

Solvents

Petroleum ether or petrol refers to the fraction of petroleum ether boiling between 40 °C and 60 °C, unless otherwise stated. Anhydrous THF, diethyl ether, dichloromethane, toluene and DMF were purified using a MBRAUN MB SPS-800 solvent purification system or as follows: dichloromethane and 1,2-dichloroethane were freshly distilled over calcium hydride; THF was distilled over sodium with benzophenone as an indicator; diethyl ether and toluene were dried over sodium wire and distilled. All other solvents were purified by standard procedures[169] or used as supplied from commercial sources.

Reagents

Commercially available reagents were used as supplied unless otherwise stated. Where appropriate, reagents were purified by distillation or recrystallisation. Ethyl glyoxalate was distilled from commercially available 1:1 ethyl glyoxalate toluene solution according to the procedure reported by Evans *et al.*[99] *N*,*N*,*N*,*N*-tetramethylethylenediamine (TMEDA) was purified by distillation over potassium hydroxide under an atmosphere of argon. Mechanically activated magnesium turnings were prepared by vigorous dry stirring with a Teflon-coated stirrer bar for 24 h under an atmosphere of nitrogen as reported in the literature.[75]

Chromatography

Flash column chromatography was carried out using Fluka silica gel 60 (220-240 mesh) (Brockmann 2-3); samples were applied as a concentrated solution in an appropriate solvent. Thin layer chromatography (TLC) was performed on pre-coated aluminium backed plates with either Merck Kieselgel 60 F254 or Merck Aluminium Oxide 60 F254. Visualisation was either by ultraviolet light ($\lambda = 254$ nm) or by staining with acidified aqueous potassium permanganate solution followed by heating. Preparative layer chromatography was performed on pre-coated glass backed plates with Merck silica gel 60 F254 (thickness 1000 μm).

Instrumentation

Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. Low resolution mass spectra were recorded on an Agilent 6890 Series GC System with a 5973 mass spectrometry detector. High and low resolution mass spectra were recorded on a Thermofisher LTQ Orbitrap XL, Finnigan MAT 95 XP, Thermofisher DSQ-II, Agilent 5975C Inert XL GC/MSD or Micromass Quattro II instrument (EPSRC Mass Spectrometry Service, Swansea). Infrared spectra were recorded using either a Shimadzu FTIR-8300 spectrometer, with samples prepared as thin films between NaCl plates or on KBr disks, or on a Perkin Elmer Spectrum 65 FT-IR spectrometer with universal ATR sampling accessory. FTIR spectra were recorded in the range of 600-4000 cm^{-1} and only selected absorbances (ν_{max}) are reported. Elemental analyses (CHN) were obtained using an Exeter Analytical EA44 analyser from the micro analysis service at University College London. X-ray crystal structures were obtained at QMUL using a KAPPA APEX ii DUO diffractometer with dual Cu and Mo Sources and APEX ii CCD area detector.

NMR spectra were recorded on one of the following spectrometers: a JEOL JNM-EX270 operating at 270 MHz (^{1}H), 67.8 MHz (^{13}C) and 109.3 MHz (^{31}P); a Bruker AMX-400 operating at 400 MHz (^{1}H) and 100 MHz (^{13}C) fitted with a variable temperature probe controlled by a Bruker B-VT-2000 controller; a Bruker Avance 400 operating at 400 MHz (^{1}H), 100 MHz (^{13}C), 162 MHz (^{31}P) and 149.2 MHz (^{119}Sn); a Bruker Avance III operating at 400 MHz (^{1}H) and 100 MHz (^{13}C) or a Bruker AV600 operating at 600 MHz (^{1}H) and 150 MHz (^{13}C). Chemical shift values (δ_H and δ_C) are reported as values in parts per million (ppm) relative to either tetramethylsilane or the residual protic solvent as the internal standard reference for ^{1}H NMR spectra and from the solvent peaks for ^{13}C NMR using values from the literature.[170] Coupling constants (J values) are quoted to one decimal place with values in hertz and are quoted twice where possible, each being recorded as observed in the spectrum without averaging. Multiplets are reported over the range at which they appear. ^{1}H NMR data is presented in the form δ_H (integration, multiplicity, coupling constants, assignment). The multiplicity of the signal is designated by the following abbreviations: s-singlet, d-doublet, t-triplet, q-quartet, and m-multiplet. The abbreviation br refers to a broad signal and app refers to apparent. ^{13}C NMR spectra are recorded in the form δ_C (assignment) or (multiplicity, coupling constants, assignment) where appropriate.

Characterisation

Full characterisation of a compound within this experimental chapter includes, but is not limited to, IR, ^{1}H NMR, ^{13}C NMR, low-resolution mass spectra and high-resolution mass spectra data. For compounds that have previously been fully characterised in the literature two or more pieces of spectroscopic data are presented. In many cases assignment of ^{1}H and ^{13}C NMR signals are supported by DEPT and two-dimensional COSY and HSQC experiments. Assignment of relative stereochemistry is based on analysis of nOe studies. On some occasions, it was not possible to obtain all required data; the reasons for this have been alluded to in the main body of this thesis.

5.2 General Experimental Procedures

General Procedure A - Preparation of allylsilanes

A solution of chlorosilane (1 eq.) in anhydrous THF (0.3 mL/mmol) was added cautiously to a stirred solution of allylmagnesium chloride (1.4 eq., 2 M solution in THF) at room temperature under an atmosphere of argon and the resulting mixture stirred at 55 °C for 15 h. The mixture was cooled to 0 °C, quenched with 10 % *w/v* aqueous ammonium chloride solution (1.5 mL/mmol), warmed to room temperature and partitioned between water and diethyl ether. The organic phase was separated and the aqueous phase extracted with diethyl ether. The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The products were purified by flash column chromatography.

General Procedure B - Preparation of (cyclopropylmethyl)silanes

To a stirred suspension of zinc powder (5 eq.) and copper chloride (5 eq.) in anhydrous diethyl ether (5 mL/mmol), which had been heated at reflux temperature for 30 min and allowed to cool to room temperature, was added allylsilane (1 eq.) and diiodomethane (2 eq.). The reaction was heated at reflux temperature for 15 h, cooled to room temperature and filtered through celite washing with diethyl ether (2 mL/mmol). The filtrate was washed with 1 M HCl followed by 10 % *w*/*v* sodium bicarbonate solution until pH 7. The combined aqueous layers were extracted with diethyl ether and the combined organic layers were washed with brine, 10 % *w*/*v* sodium thiosulfate solution, separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the impure product. Purification by flash column chromatography using a mixture of 10 % silver nitrate impregnated silica and standard silica (1 : 3) eluting with hexane gave the desired product.

General Procedure C - Cyclisation of silylmethylcyclopropanes with α-keto-aldehydes

To a stirred mixture of freshly distilled glyoxal or glyoxalate (1.5 eq.) and silylmethylcyclopropane (1 eq.) in anhydrous dichloromethane (9 mL/mmol of silylmethylcyclopropane) cooled to the required temperature (−78 or 0 °C) and under an atmosphere of argon was added, dropwise, a solution of tin tetrachloride (0.8 eq.) in anhydrous dichloromethane (3 mL/mmol of tin tetrachloride). The reaction was stirred at the required temperature and monitored by TLC, after 3 h the reaction was quenched by the addition of wet acetone (1 mL/mmol of silylmethylcyclopropane) if the reaction was performed at −78 °C or water (1 mL/mmol of silylmethylcyclopropane) if the reaction was at 0 °C. The organic layer was separated and the aqueous layer further extracted with dichloromethane. The combined organic phases were washed with brine, separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product as a yellow oil. The products were purified by flash column chromatography.

Typical procedure for the purification of (cyclopropylmethyl)silanes - Preparation of silver nitrate impregnated silica gel.

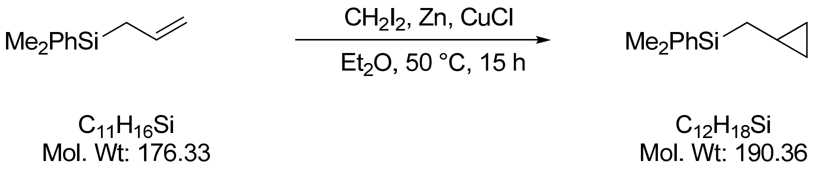
Silver nitrate (3 g) and methanol (300 mL) was stirred vigorously until the all the solid had dissolved. To this solution was added silica gel (30 g) and the resulting mixture stirred for

5 min. The slurry was then transferred to a round bottom flask covered with silver foil and the solvent removed *in vacuo* to give the impregnated silica gel as a bright white powder/gel. The column was made by pre-forming a slurry of silica gel (50 g) in hexane. Once this had settled the silver nitrate impregnated silica gel was added as a slurry in hexane creating a band of silver nitrate impregnated silica at the top of the column. The column was washed with three column lengths of hexane to wash through any residual methanol and run in the usual way.

Procedure for the preparation of aqueous potassium carbonate/EDTA solution

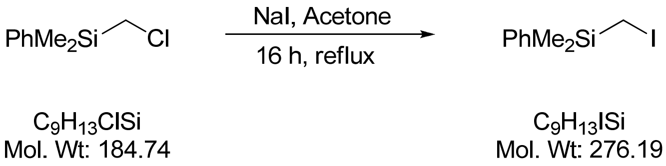
To a 100 mL volumetric flask was added EDTA (0.020 g, 0.069 mmol) and K_2CO_3 (20.70 g, 0.15 mol) which was dissolved in deionised water (100 mL). This produced a 1.5 M solution of K_2CO_3 and a 0.7 mM solution of EDTA, which was used directly in the preceding reactions.

(Cyclopropylmethyl)dimethylphenylsilane (143)



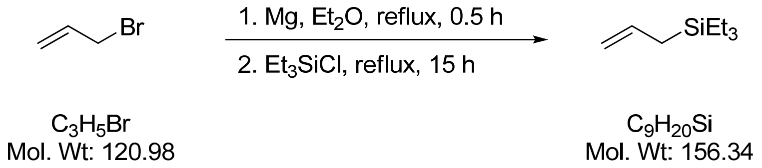
Following the general procedure B, allyldimethylphenylsilane (3.88 g, 22.0 mmol) furnished the impure product as a yellow oil (3.24 g). Purification by flash column chromatography using a mixture of 10 % silver nitrate impregnated silica and standard silica eluting with hexane gave the desired product (2.79 g, 14.7 mmol, 67 %) as a colourless oil; R_f 0.53 [hexane]; ν_{max}(film)/cm^{-1} 3070 (C-H cyclopropyl), 2956, 1426, 1247, 1113, 835; δ_H (400 MHz; $CDCl_3$) −0.03-0.01 (2H, m, CH_2 cyclopropyl), 0.34 (6H, s, 2 × CH_3), 0.43-0.47 (2H, m, CH_2 cyclopropyl), 0.61-0.71 (1H, m, $SiCH_2C\underline{H}$), 0.75 (2H, d, *J* 6.9, $SiC\underline{H}_2CH$),7.36-7.39 (3H, m, Ph), 7.54-7.58 (2H, m, Ph); δ_C (100.6 MHz; $CDCl_3$) −2.6 (2 × CH_3), 6.3 (CH cyclopropyl), 6.6 (2 × CH_2 cyclopropyl), 21.4 ($Si\underline{C}H_2$), 127.8 (2 × *m*-CH, Ph), 128.9 (*p*-CH, Ph), 133.7 (2 × *o*-CH, Ph), 139.9 (C, Ph); LRMS (EI$^+$, *m/z*) 190 ([M]$^+$, 2 %), 175 (9), 135 (100), 105 (12); HRMS (EI$^+$, *m/z*) 190.1173 [M]$^+$, $C_{12}H_{18}Si$ requires 190.1172.

Dimethyl(iodomethyl)phenylsilane (144)



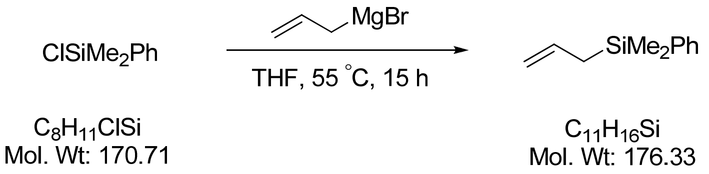
Dimethyl(iodomethyl)phenylsilane was prepared according to the procedure reported by Whitmore *et al.* [70] To a stirred solution of sodium iodide (10.0 g, 66.7 mmol) in dry acetone (60 mL) was added chloromethyldimethylphenylsilane (5.12 g, 5.00 mL, 27.7 mmol) at room temperature. The reaction mixture was heated at reflux temperature for 10 h, after which time the resulting suspension was cooled to room temperature and filtered. The filtrate was partitioned between water (20 mL) and diethyl ether (40 mL) and the aqueous layer further extracted with diethyl ether (2 × 20 mL). The etherate fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the impure product as a yellow oil (7.56 g). Purification by either Kugelrohr distillation or flash column chromatography [silica gel, petroleum ether (40-60 °C)] gave the desired product (7.23 g, 26.2 mmol, 95 %) as a pale yellow oil; bp 119-122 °C/9 mmHg (lit.[171] 97.2 °C/3 mmHg); R_f 0.68 [10 % diethyl ether : petroleum ether (40-60 °C)]; ν_{max}(film)/cm^{-1} 3071, 3017, 2955, 2924, 1427, 1373, 1250, 1111, 1080, 818; δ_H (400 MHz; $CDCl_3$) 0.46 (6H, s, $SiMe_2$), 2.19 (2H, s, $SiCH_2$), 7.36-7.56 (5H, m, Ph); δ_C (100.6 MHz; $CDCl_3$) −13.4 (CH_2), −2.8 (2 × CH_3), 128.1 (2 × CH, Ph), 129.7 (*p*-CH, Ph), 133.8 (2 × CH, Ph), 137.0 (C, Ph); LRMS (EI$^+$, *m/z*) 276 ([M]$^+$,14 %), 261 (37), 149 (100), 135 (100), 119 (21), 105 (29), 91 (29); HRMS (EI$^+$, *m/z*) 275.9826 [M]$^+$, $C_9H_{13}ISi$ requires 275.9826. The spectral data is in good agreement with previously reported values.[172]

Allyltriethylsilane (152)



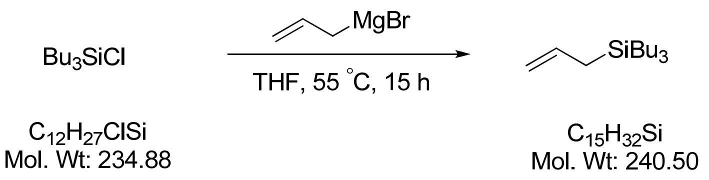
To a stirred suspension of magnesium turnings (1.82 g, 75.0 mmol) in anhydrous diethyl ether (50 mL) under an atmosphere of argon was added several crystals of iodine, upon which the solution turned brown. After 10 min the solution became clear and allylbromide (8.47 g, 6.10 mL, 70.0 mmol) was cautiously added dropwise at a rate sufficient to maintain gentle reflux during the addition. The mixture was stirred for a further 30 min before chlorotriethylsilane (4.06 g, 4.53 mL, 27.0 mmol) was added dropwise at a rate sufficient to maintain gentle reflux. The mixture was heated to reflux temperature for 15 h. After this time, the reaction mixture was cooled to approximately −15 °C and a 10 % *w*/*v* aqueous ammonium chloride solution (90 mL) was added dropwise with efficient stirring over a period of 30 min. Two layers developed and the organic phase was separated. The aqueous phase was extracted with diethyl ether (3 × 20 mL) and the combined organic portions were washed with brine (20 mL), separated, dried ($MgSO_4$) and filtered. The diethyl ether and allylbromide were removed by distillation at atmospheric pressure. Purification of the resulting residue by either Kugelrohr distillation or flash column chromatography [silica gel, hexane] gave the desired product (3.78 g, 24.2 mmol, 90 %) as a colourless oil; bp 81-83 °C/35 mmHg, (lit.[173,174] 37 °C/3 mmHg); R_f 0.75 [hexane]; ν_{max}(film)/cm^{-1} 2953, 2875, 1630 (C=C), 1416, 1237, 1153, 1011, 891; δ_H (400 MHz; $CDCl_3$) 0.54 (6H, q, *J* 8.0, 3 × CH_2), 0.94 (9H, t, *J* 8.0, 3 × CH_3), 1.54 (2H, dt, *J* 8.2 and 1.2, $C\underline{H}_2CH=CH_2$), 4.81 (1H, ddt, *J* 10.1 2.2 and 0.9, $CH_2CH=C\underline{H}_{cis}H_{trans}$), 4.87 (1H, ddt, *J* 16.9 2.2 and 1.4, $CH_2CH=CH_{cis}\underline{H}_{trans}$), 5.81 (1H, ddt, *J* 16.9 10.1 and 8.2, $CH_2C\underline{H}=CH_{cis}H_{trans}$); δ_C (100.6 MHz; $CDCl_3$) 3.3 (3 × CH_2), 7.5 (3 × CH_3), 19.6 ($\underline{C}H_2CH=CH_2$), 112.6 ($CH_2CH=\underline{C}H_2$), 135.6 ($CH_2\underline{C}H=CH_2$); LRMS (EI$^+$, *m/z*) 156 ([M]$^+$, 4 %), 127 (4), 115 (87), 99 (31), 87 (100), 57 (38); HRMS (EI$^+$, *m/z*) 156.1329 [M]$^+$, $C_9H_{20}Si$ requires 156.1329. The data is in good agreement with previously reported values.[175]

Allyldimethylphenylsilane (153)



Following the general procedure A, chlorodimethylphenylsilane (4.27 g, 5.01 mL, 25.0 mmol) furnished the impure product (5.22 g) as a pale yellow oil. Purification by flash column chromatography [silica gel, hexane] afforded the desired product (3.79 g, 21.5 mmol, 86 %) as a colourless oil; R_f 0.49 [hexane]; bp 44-45 °C/0.07 mmHg, (lit.[83] 96-97 °C 14 mmHg); ν_{max}(film)/cm^{-1} 3071, 2956, 1630 (C=C), 1427, 1248, 1195, 890; δ_H (400 MHz; $CDCl_3$) 0.30 (6H, s, $SiMe_2$), 1.77 (2H, dt, *J* 8.1 and 1.0, $C\underline{H}_2CH=CH_2$), 4.86 (1H, ddt, *J* 10.1 2.1 and 1.0, $CH_2CH=C\underline{H}_{cis}H_{trans}$), 4.87 (1H, ddt, *J* 16.9 2.1 and 1.0, $CH_2CH=CH_{cis}\underline{H}_{trans}$), 5.79 (1H, ddt, *J* 16.9 10.1 and 8.1, $CH_2C\underline{H}=CH_2$), 7.35-7.38 (3H, m, Ph), 7.52-7.54 (2H, m, Ph); δ_C (100.6 MHz; $CDCl_3$) −3.3 (3 × CH_3), 23.8 ($\underline{C}H_2CH=CH_2$), 113.6 ($CH_2CH=\underline{C}H_2$), 127.9 (2 × *m*-CH, Ph), 129.1 (*p*-CH, Ph), 133.8 (2 × *o*-CH, Ph), 134.8 ($CH_2\underline{C}H=CH_2$), 138.8 (C, Ph); LRMS (EI$^+$, *m/z*) 176 ([M]$^+$, 7 %), 161 (6), 135 (100), 119 (11), 105 (15), 91 (7); HRMS (EI$^+$, *m/z*) 176.1017 [M]$^+$, $C_{11}H_{16}Si$ requires 176.1016. The data is in good agreement with previously reported values[176]

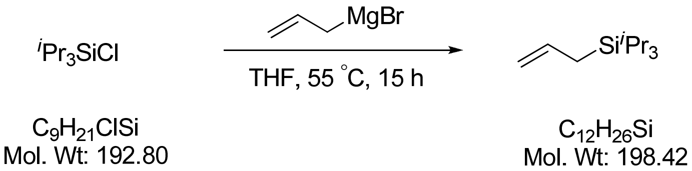
Allyltri-*n*-butylsilane (154)



Following the general procedure A, chlorotributylsilane (4.93 g, 21.0 mmol) furnished the impure product (4.96 g) as a colourless oil. Purification by flash column chromatography [silica gel, hexane] afforded the desired product (4.45 g, 18.5 mmol, 88 %) as a colourless oil; R_f 0.82 [hexane]; ν_{max}(film)/cm^{-1} 2956, 2918, 1630 (C=C), 1195, 890; δ_H (400 MHz; $CDCl_3$) 0.50-0.54

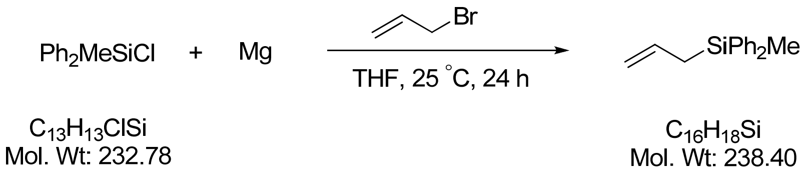
(6H, m, 3 × CH_2 $SiCH_2$), 0.89 (9H, t, *J* 7.0, 3 × CH_3), 1.22-1.37 (12H, m, 6 × CH_2), 1.53 (2H, d, *J* 8.2, $\underline{CH_2}CH{=}CH_2$), 4.80 (1H, dd, *J* 10.1 and 2.2, $CH{=}C\underline{H}_{cis}H_{trans}$), 4.84 (1H, dd, *J* 16.9 and 2.2, $CH{=}CH_{cis}\underline{H}_{trans}$), 5.79 (1H, ddt, *J* 16.9 10.1 and 8.2, $CH_2C\underline{H}{=}CH_{cis}H_{trans}$); δ_C (100.6 MHz; $CDCl_3$) 12.0 (3 × CH_2, $SiCH_2$), 14.0 (3 × CH_3, Bu), 20.7 ($\underline{C}H_2CH{=}CH_2$), 26.2 (3 × CH_2, Bu), 26.9 (3 × CH_2, Bu), 112.6 ($CH_2CH{=}\underline{C}H_2$), 135.7 ($CH_2\underline{C}H{=}CH_2$); LRMS ($EI^+$, *m/z*) 199 ($[M{-}Allyl]^+$, 72 %), 143 (100), 127 (28), 101 (18), 87 (15); HRMS (EI^+, *m/z*) 239.2190 $[M]^+$, $C_{15}H_{32}Si$ requires 239.2189.

Allyltriisopropylsilane (155)



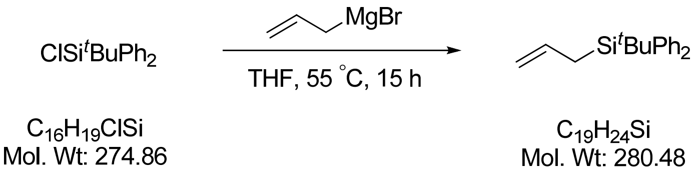
Following the general procedure A, chlorotriisopropylsilane (6.75, 7.92 mL, 35.0 mmol) furnished the impure product (7.17 g) as a pale yellow oil. Purification by flash column chromatography [silica gel, hexane] afforded the desired product (6.52 g, 32.8 mmol, 94 %) as a colourless oil; R_f 0.79 [hexane]; bp 74-79 °C/0.4 mmHg, (lit.[177] 45-50 °C/0.2 mmHg); δ_H (400 MHz; $CDCl_3$) 0.97-1.11 (21H, m, overlapping doublet and septet 3 × ^iPr), 1.64 (2H, dt, *J* 8.2 and 1.2, $\underline{CH_2}CH{=}CH_2$), 4.81 (1H, ddt, *J* 10.0 2.2 and 1.2, $CH_2CH{=}C\underline{H}_{cis}H_{trans}$), 4.92 (1H, ddt, *J* 16.9 2.2 and 1.2, $CH_2CH{=}CH_{cis}\underline{H}_{trans}$), 5.89 (1H, ddt, *J* 16.9 10.0 and 8.2, $CH_2C\underline{H}{=}CH_2$); δ_C (100.6 MHz; $CDCl_3$) 11.2 (3 × CH, ^iPr), 17.5 ($SiCH_2$), 18.8 (6 × CH_3), 112.9 ($CH_2CH{=}\underline{C}H_2$), 136.3 ($CH_2\underline{C}H{=}CH_2$); LRMS ($EI^+$, *m/z*) 198 ($[M]^+$, 3 %), 157 (100), 115 (60), 85 (52). The data is in good agreement with previously reported values.[178]

Allyldiphenylmethylsilane (156)



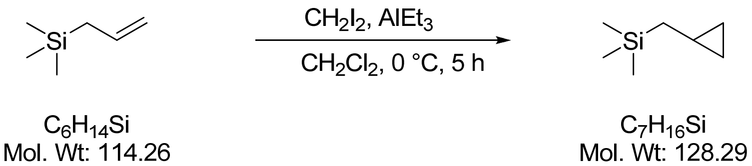
Dimethyl(iodomethyl)phenylsilane was prepared based on the procedure reported by Soderquist *et al.* [83] To a mixture of mechanically activated magnesium turnings (0.36 g, 15.0 mmol) and chloromethyldiphenylsilane (2.79 g, 2.53 mL, 12.0 mmol) in THF (15 mL) was added dropwise allylbromide (1.45 g, 1.01 mL, 12.0 mmol) at a rate to maintain gentle reflux. After being stirred at 25 °C for 15 h, the reaction mixture was poured onto ice. The aqueous layer was extracted with diethyl ether (2 × 20 mL) and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a pale yellow oil (2.90 g). Purification by either Kugelrohr distillation or flash column chromatography [silica gel, hexane] gave the desired product (1.68 g, 7.05 mmol, 59 %) as a colourless oil; bp 115-119 °C/1 mmHg, (lit.[179] 93 °C/0.1 mmHg); R_f 0.23 [hexane]; ν_{max}(film)/cm^{-1} 3069, 2953, 2875, 1629 (C=C), 1427, 1251, 1112, 895; δ_H (400 MHz; $CDCl_3$) 0.59 (3H, s, $SiC\underline{H}_3$), 2.12 (2H, dt, *J* 8.0 and 1.1, $C\underline{H}_2CH{=}CH_2$), 4.89-4.97 (2H, m, overlapping signals $CH_2CH{=}C\underline{H}_2$), 5.83 (1H, ddt, *J* 17.0 10.1 and 8.0, $CH_2C\underline{H}{=}CH_2$), 7.36-7.43 (6H, m, Ar), 7.54-757 (4H, m, Ar); δ_C (100 MHz; $CDCl_3$) −4.7 (2 × CH_3), 22.3 ($\underline{C}H_2CH{=}CH_2$), 114.2 ($CH_2CH{=}\underline{C}H_2$), 128.0 (4 × *m*-CH, Ar), 129.4 (2 × *p*-CH, Ar), 134.2 ($CH_2\underline{C}H{=}CH_2$), 134.7 (4 × *o*-CH, Ar), 136.7 (2 × C, Ar); LRMS (EI$^+$, *m/z*) 238 ([M]$^+$, 2 %), 223 (3), 197 (100), 181 (19), 165 (20), 119 (10), 105 (27); HRMS (EI$^+$, *m/z*) 238.1170 [M]$^+$, $C_{16}H_{18}Si$ requires 238.1172. The data is in good agreement with previously reported values.[180]

Allyl-*tert*-butyldiphenylsilane (157)



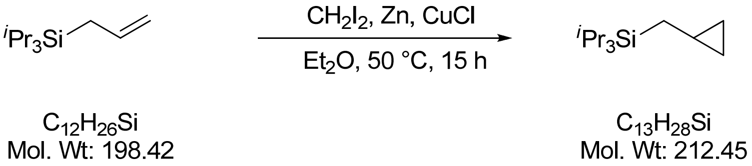
Following the general procedure A, *tert*-butyldiphenylchlorosilane (7.15 g, 6.76 mL, 26.0 mmol) furnished the impure product (7.02 g) as a pale yellow oil. Purification by flash column chromatography [silica gel, hexane] afforded the desired product (6.67 g, 23.8 mmol, 92 %) as a colourless oil; R_f 0.42 [hexane]; ν_{max}(film)/cm^{-1} 2929, 2857, 1630 (C=C), 1427, 1104, 895, 820; δ_H (400 MHz; CDCl$_3$) 1.09 (9H, s, ^{t}Bu), 2.21(2H, dt, *J* 7.8 and 1.2, $C\underline{H}_2CH=CH_2$), 4.82 (1H, ddt, *J* 10.0 2.0 and 1.2, $CH_2CH=C\underline{H}_{cis}H_{trans}$), 4.92 (1H, ddt, *J* 16.9 2.0 and 1.2, $CH_2CH=CH_{cis}\underline{H}_{trans}$), 5.79 (1H, ddt, *J* 16.9 10.0 and 7.8, $CH_2C\underline{H}=CH_{cis}H_{trans}$), 7.35-7.44 (6H, m, Ar), 7.62-7.64 (4H, m, Ar); δ_C (100.6 MHz; CDCl$_3$) 18.6 ($Si\underline{C}(CH_3)_3$), 18.9 ($\underline{C}H_2CH=CH_2$), 28.0 ($SiC(\underline{C}H_3)_3$), 114.7 ($CH_2CH=\underline{C}H_2$), 127.7 (4 × *m*-CH, Ar), 129.2 (2 × *p*-CH, Ar), 134.6 (2 × C, Ar), 134.8 ($CH_2\underline{C}H=CH_2$), 136.16 (4 × *o*-CH, Ar); LRMS (EI$^+$, *m/z*) 280 ([M]$^+$, 1 %), 239 (71), 223 (100), 197 (52), 181 (36), 135 (100), 105 (40); HRMS (EI$^+$, *m/z*) 280.1643 [M]$^+$, $C_{19}H_{24}Si$ requires 280.1642. The data is in good agreement with previously reported values.[181]

(Cyclopropylmethyl)trimethylsilane (159)



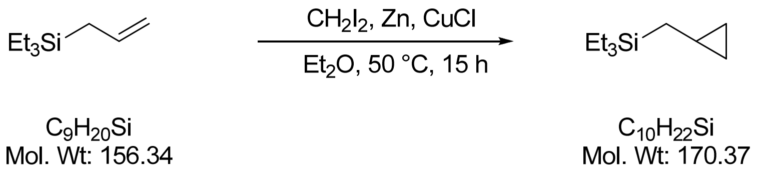
(Cyclopropylmethyl)trimethylsilane was prepared based on the procedure reported by Maruoka *et al.* [88] To a stirred solution of allytrimethylsilane (2.86 g, 25.0 mmol) and diiodomethane (8.04 g, 2.42 mL, 30.0 mmol) in dichloromethane (40 mL) was added at 0 °C a solution of triethylaluminium (30 mL, 30.0 mmol, 1 M solution in *n*-hexane). The mixture was stirred at 0 °C for 5 h. The reaction was diluted with dichloromethane (40 mL) followed by successive treatment with sodium fluoride (4.00 g, 96.0 mmol) and water (1.32 mL, 73.0 mmol) at 0 °C. Vigorous stirring of the resulting suspension was continued at 0 °C for 30 min. The reaction mixture was filtered and the filtrate washed with 10 % *w*/*v* aqueous sodium thiosulphate solution (20 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the impure product as a pale yellow oil. The solvent was removed by short path distillation and purification of the resulting residue by flash column chromatography yielded the desired product (1.66 g, 12.9 mmol, 52 %) as a colourless oil; R_f 0.51 [hexane]; ν_{max}(film)/cm^{-1} 3071 (C-H cyclopropyl), 2956, 1404, 1248, 1013, 835 (Si-C); δ_H (400 MHz; $CDCl_3$) −0.07 to −0.03 (2H, m, CH_2 cyclopropyl), 0.03 (9H, s, $SiMe_3$), 0.42-0.44 (2H, m, CH_2 cyclopropyl), 0.47 (2H, d, *J* 7.0, $SiC\underline{H}_2CH$), 0.57-0.65 (1H, m, CH); δ_C (100.6 MHz; $CDCl_3$) −1.2 (CH_3), 6.36 (CH), 6.43 (2 × CH_2 cyclopropyl), 22.4 ($Si\underline{C}H_2$); LRMS (EI$^+$, *m/z*) 128 ([M]$^+$ 2 %), 113 (71), 85 (25), 73 (100), 55 (5). The data is in good agreement with previously reported values.[85]

(Cyclopropylmethyl)triisopropylsilane (162)



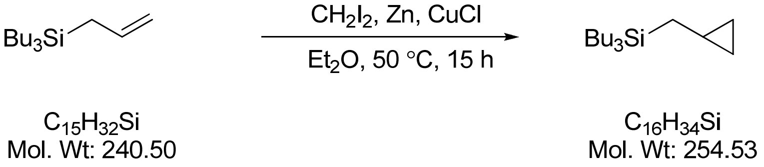
Following the general procedure B, allyltriisopropylsilane (5.77 g, 21.0 mmol) furnished the impure product as a yellow oil (5.04 g). Purification by flash column chromatography using a mixture of 10 % silver nitrate impregnated silica and standard silica eluting with hexane gave the desired product (3.45 g, 16.2 mmol, 77 %) as a colourless oil; R_f 0.88 [hexane]; ν_{max}(film)/cm^{-1} 3074 (C-H cyclopropyl), 2941 (C-H), 1464, 1015, 881 (Si-C); δ_H (400 MHz; $CDCl_3$) 0.00-0.03 (2H, m, CH_2 cyclopropyl), 0.46-0.49 (2H, m, CH_2 cyclopropyl), 0.58 (2H, d, *J* 6.5, $SiC\underline{H}_2CH$), 0.61-0.71 (1H, m, $SiCH_2C\underline{H}$), 1.04-1.12 (21H, m, overlapping signals 6 × CH_3 and 3 × CH, ^iPr); δ_C (100.6 MHz; $CDCl_3$) 6.6 (CH cyclopropyl), 8.0 (2 × CH_2 cyclopropyl), 11.1 (3 × CH, ^iPr), 15.1 ($Si\underline{C}H_2CH$), 19.0 (6 × CH_3); LRMS (EI$^+$, *m/z*) M$^+$ not visible, 169 ([M–^iPr]$^+$, 13 %), 157 (80), 127 (88), 115 (100), 99 (56), 87 (58), 73 (78), 59 (81); HRMS (EI$^+$, *m/z*) 213.2034 [M+H]$^+$, $C_{13}H_{29}Si$ requires 213.2033.

(Cyclopropylmethyl)triethylsilane (163)



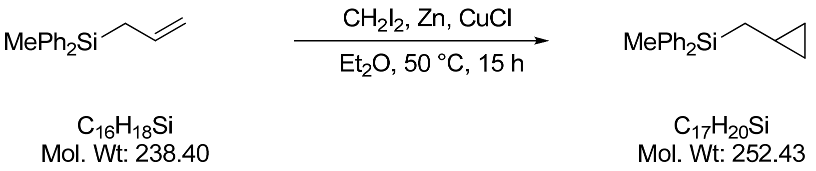
Following the general procedure B, allytriethylsilane (3.78 g, 24.0 mmol) furnished the impure product as a brown oil (2.90 g). Purification by flash column using 10 % silver nitrate impregnated silica and standard silica eluting with hexane gave desired product (1.61 g, 9.45 mmol, 40 %) as a colourless oil; R_f 0.81 [hexane]; ν_{max}(film)/cm^{-1} 3071 (CH cyclopropyl), 2952, 2875, 1457, 1416, 1239, 1013, 891; δ_H (400 MHz; CDCl$_3$) –0.06 to –0.02 (2H, m, CH$_2$ cyclopropyl), 0.41-0.45 (2H, m, CH$_2$ cyclopropyl), 0.49 (2H, d, J 6.9, 3 × CH$_2$), 0.56 (6H, q, J 8.0, 3 × C$\underline{H}_2$CH$_3$), 0.54-0.61 (1H, m, CH cyclopropyl); 0.95 (9H, t, J 8.0, 3 × CH$_3$); δ_C (100.6 MHz; CDCl$_3$) 3.7 (3 × CH$_2$), 6.3 (CH), 6.9 (2 × CH$_2$ cyclopropyl), 7.6 (3 × CH$_3$), 17.3 (SiCH$_2$); LRMS (EI$^+$, *m/z*) 170 ([M]$^+$ 1 %), 141 (34),115 (61), 87 (100), 59 (35); HRMS (EI$^+$, *m/z*) 170.1483 [M]$^+$, $C_{10}H_{22}Si$ requires 170.1485.

(Cyclopropylmethyl)tri-*n*-butylsilane (164)



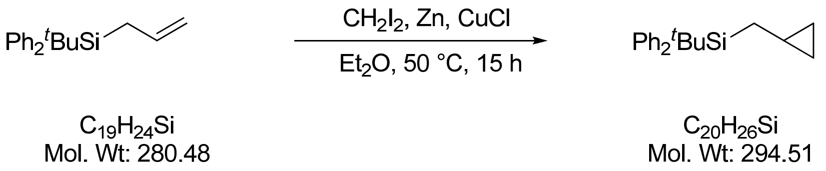
Following the general procedure B, allyltri-*n*-butylsilane (3.78 g, 16.5 mmol) furnished the impure product as a colourless oil (3.78 g). Purification by flash column chromatography using a mixture of 10 % silver nitrate impregnated silica and standard silica eluting with hexane gave the desired product (2.73 g, 10.7 mmol, 65 %) as a colourless oil; R_f 0.93 [hexane]; ν_{max}(film)/cm^{-1} 2918, 1463, 1197 (Si-C), 1081, 886 (Si-C); δ_H (600 MHz; CDCl$_3$) –0.06 to –0.03 (2H, m, CH$_2$ cyclopropyl), 0.42-0.45 (2H, m, CH$_2$ cyclopropyl), 0.49 (2H, d, J 7.0, SiC$\underline{H}_2$CH), 0.54-0.63 (7H, m, $SiCH_2C\underline{H}$ and 3 × CH_2 overlapping signals), 0.89 (9H, t, *J* 7.0, 3 × $C\underline{H}_3$), 1.26-1.36 (12H, m, 6 × $C\underline{H}_2$ Bu); δ_C (100.6 MHz; $CDCl_3$) 6.4 (CH cyclopropyl), 6.9 (2 × CH_2 cyclopropyl), 12.5 (3 × CH_2, Bu), 14.0 (3 × CH_3), 18.3 ($Si\underline{C}H_2CH$), 26.4 (3 × CH_2), 27.1 (3 × CH_2); LRMS (EI^+, *m/z*) 199 ($[M-C_4H_7]^+$, 45 %), 143 (100), 101 (29), 87 (22), 59 (29); HRMS (EI^+, *m/z*) 253.2348 $[M-H]^+$, $C_{16}H_{33}Si$ requires 253.2346.

(Cyclopropylmethyl)(methyl)diphenylsilane (165)



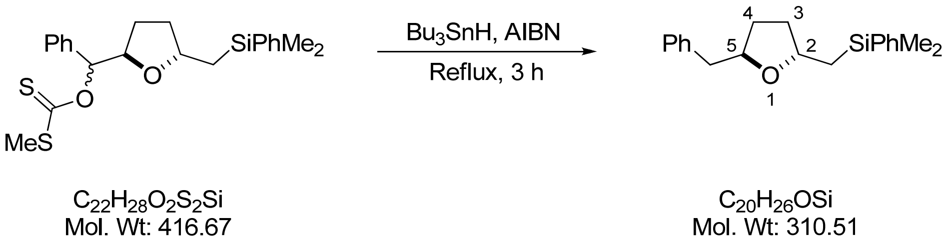
Following the general procedure B, allyl(methyl)diphenylsilane (4.32 g, 18.0 mmol) furnished the impure product as a yellow oil (3.94 g). Purification by flash column chromatography using a mixture of 10 % silver nitrate impregnated silica and standard silica eluting with hexane gave the desired product (3.21 g, 12.7 mmol, 71 %) as a colourless oil; R_f 0.32 [hexane]; ν_{max}(film)/cm^{-1} 3069 (C-H cyclopropyl), 2998 (CH_3), 1427, 1250, 1108, 802, 727, 697; δ_H (400 MHz; $CDCl_3$) 0.01-0.05 (2H, m, CH_2 cyclopropyl), 0.43-0.47 (2H, m, CH_2 cyclopropyl), 0.65 (3H, s, SiMe), 0.68-0.77 (1H, m, CH cyclopropyl), 1.09 (2H, d, *J* 7.0, $SiC\underline{H}_2$), 7.35-7.42 (6H, m, Ar), 7.54-7.60 (4H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) −4.0 ($SiMe_2$), 6.2 (CH cyclopropyl), 6.9 (2 × CH_2 cyclopropyl), 20.0 ($Si\underline{C}H_2$), 127.9 (4 × *m*-CH, Ar), 129.2 (2 × *p*-CH, Ar), 134.7 (4 × *o*-CH, Ar), 137.7 (2 × C, Ar); LRMS (EI^+, *m/z*) 252 ($[M]^+$, 8 %), 237 (4), 224 (13), 197 (100), 181 (13), 165 (11), 105 (20); HRMS (EI^+, *m/z*) 252.1329 $[M]^+$, $C_{17}H_{20}Si$ requires 252.1329.

(Cyclopropylmethyl)-*tert*-butyldiphenylsilane (166)



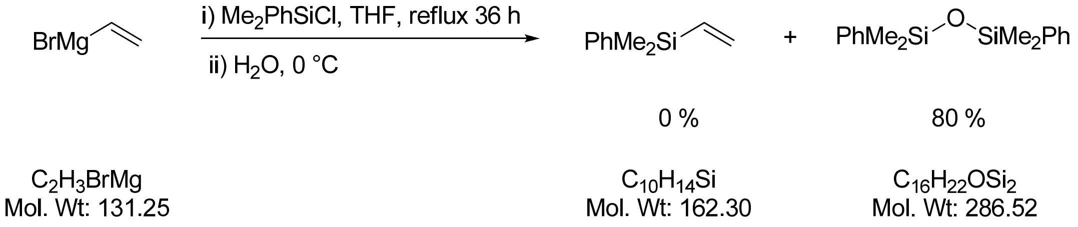
Following the general procedure B, allyl-*tert*-butyldiphenylsilane (3.50 g, 12.5 mmol) furnished the impure product as a colourless oil (3.65 g). Purification by flash column chromatography using a mixture of 10 % silver nitrate impregnated silica and standard silica eluting with hexane gave the desired product (2.16 g, 7.33 mmol, 59 %) as a colourless oil; R_f 0.62 [hexane]; ν_{max}(film)/cm^{-1} 3072, 2929, 2856, 1427, 1103, 818; δ_H (600 MHz; CDCl$_3$) 0.08-0.12 (2H, m, CH$_2$ cyclopropyl), 0.45-0.49 (2H, m, CH$_2$ cyclopropyl), 0.76-0.86 (1H, m, CH cyclopropyl), 1.21 (9H, s, 3 × CH$_3$), 1.31 (2H, d, *J* 6.6, SiC$\underline{H}_2$CH), 7.44-7.54 (6H, m, Ar), 7.79-7.81 (4H, m, Ar); δ_C (100.6 MHz; CDCl$_3$) 6.6 (CH cyclopropyl), 7.9 (2 × CH$_2$ cyclopropyl), 16.7 (Si$\underline{C}$H$_2$CH), 18.2 (Si$\underline{C}$(CH$_3$)$_3$), 28.1 (3 × CH$_3$), 127.6 (4 × *m*-CH, Ar), 129.1 (2 × *p*-CH, Ar), 135.5 (2 × C, Ar), 136.3 (4 × *o*-CH, Ar); LRMS (EI$^+$, *m/z*) M$^+$ not visible, 237 ([M–^{t}Bu]$^+$, 100 %), 197 (54), 183 (100), 159 (62), 135 (100), 105 (44); HRMS (CI$^+$, *m/z*) 312.2141 [M+NH$_4$]$^+$, C$_{20}$H$_{30}$NSi requires 312.2142.

(±)-((5-Benzyltetrahydrofuran-2-yl)methyl)dimethyl(phenyl)silane (168)



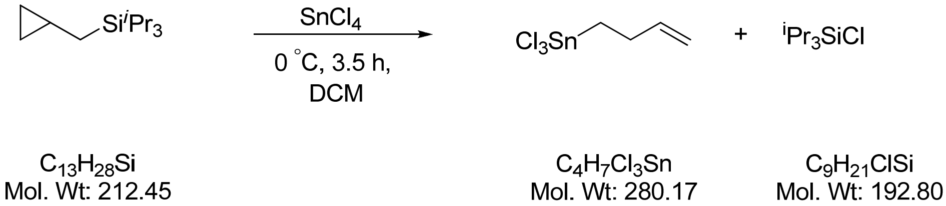
A stirred solution of *O*-(5-((dimethyl(phenyl)silyl)methyl)tetrahydrofuran-2-yl)(phenyl)methyl-*S*-methyl carbonodithioate (0.20 g, 0.48 mmol) and tri-*n*-butyltin hydride (0.67 mL, 2.50 mmol) in toluene (5.5 mL) was degassed with nitrogen. To the reaction mixture at reflux temperature was added portionwise AIBN (3 × 0.005 g, 0.05 mmol, 10 mol %), after 3 h the reaction was cooled and concentrated *in vacuo* to yield the impure product as a yellow oil. Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 10 % diethylether : hexane] afforded the title compound as a single diastereoisomer (0.13 g, 0.40 mmol, 84 %) as a colourless oil (Found: C, 77.1; H, 8.4. $C_{20}H_{26}OSi$ requires C, 77.4; H, 8.4 %); R_f 0.4 [10 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 2957, 1247, 1112, 1074, 835, 819; δ_H (600 MHz; $CDCl_3$) 0.31 (3H, s, $SiCH_3$), 0.33 (3H, s, $SiCH_3$), 1.09 (1H, dd, *J* 14.2 and 8.1, $SiC\underline{H}_aH_b$), 1.32 (1H, dd, *J* 14.2 and 6.3, $SiCH_a\underline{H}_b$), 1.35-1.41 (1H, m, $C\underline{H}_aH_b$ C-3 THF), 1.52-1.58 (1H, m, $C\underline{H}_aH_b$ C-4 THF), 1.90-1.96 (2H, m, overlapping signals $CH_a\underline{H}_b$ C-4 and $CH_a\underline{H}_b$ C-3 THF), 2.67 (1H, dd, *J* 13.5 and 6.8, $PhC\underline{H}_aH_b$), 2.91 (1H, dd, *J* 13.5 and 6.2, $PhCH_a\underline{H}_b$), 4.11 (1H, app tt, *J* 8.2 and 5.8, CH C-2 THF), 4.55 (1H, app dq, *J* 7.9 and 6.4, CH C-5 THF), 7.19-7.21 (3H, m, Ar), 7.26-7.31 (2H, m, Ar), 7.33-7.37 (3H, m, Ar), 7.52-54 (2H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) −2.2 ($SiCH_3$), −1.9 ($SiCH_3$), 24.2 ($SiCH_2$), 32.2 (CH_2, C-4 THF), 35.0 (CH_2, C-3 THF), 42.5 ($PhCH_2$), 76.7 (CH, C-2 THF), 78.9 (CH, C-5 THF), 126.2 (CH, Ar), 127.9 (CH, Ar), 128.3 (CH, Ar), 129.0 (CH, Ar), 129.4 (CH, Ar), 133.8 (CH, Ar), 139.2 (C, Ar), 139.4 (C, Ar); LRMS (EI$^+$, *m/z*): M$^+$ not visible, 295 ([M−Me]$^+$, 2 %), 233 (4), 219 (19), 135 (100), 105 (6), 91 (20), 75 (20); HRMS (ESP, *m/z*) 328.2093 [M+NH$_4$]$^+$, $C_{20}H_{30}ONSi$ requires 328.2091.

1,1,2,2-Tetramethyl-1,2-diphenyldioxane (173)



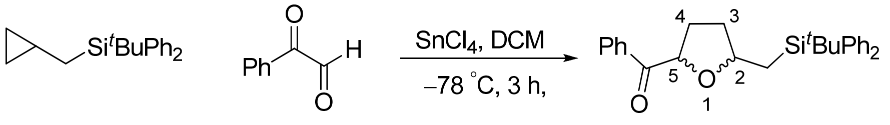
Chlorodimethylphenylsilane (1.71 g, 1.51 mL, 10.0 mmol) was added dropwise to a stirred solution of vinylmagniesm bromide (20.1 mL, 20.0 mmol, 1 M solution in THF) at room temperature and under an atmosphere of nitrogen, the resulting mixture was heated at reflux temperature for 36 h. The mixture was cooled to 0 °C, quenched with 10 % *w*/*v* aqueous ammonium chloride solution (20 mL), warmed to room temperature and partitioned between H_2O and diethyl ether. The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product (1.52 g) as a yellow oil. Purification by flash column chromatography [silica gel, elution 20 % diethylether : petroleum ether (40-60 °C)] afforded the desired product (1.15 g, 4.00 mmol, 80 %) as a colourless oil; R_f 0.78 [20 % diethylether : petroleum ether (40-60 °C)]; δ_H (400 MHz; $CDCl_3$) 0.34 (12H, s, SiMe), 7.34-7.44 (6H, m, Ar), 7.59-7.52 (4H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) 1.1 (4 × CH_3), 127.9 (4 × *m*-CH, Ar), 129.4 (2 × *p*-CH, Ar), 133.2 (4 × *o*-CH, Ar), 140.0 (C, Ar); LRMS (EI^+, *m/z*): 286 ($[M]^+$, 13 %), 271 (100), 255 (14), 193 (58), 135 (27), 89 (4). The spectral data is in good agreement with previously reported data.[119]

But-3-enyltrichlorostannane (174)



To a stirred solution of (cyclopropylmethyl)triisopropylsilane (0.33 g, 1.50 mmol) in anhydrous DCM (1.5 mL) was added dropwise tin tetrachloride (0.39 g, 0.18 mL, 1.50 mmol). The reaction was stirred at room temperature for 16 h during which time the reaction became dark yellow in colour and a white precipitate formed, after this time the solvent was removed under reduced pressure to give an orange residue. Purification by Kugelrohr distillation gave the homoallylic trichlorostannane (0.34 g, 1.21 mmol, 81 %) as a colourless oil; bp 101-103 °C/5 mmHg (lit.[97], 98 °C/3 mmHg); δ_H (400 MHz; $CDCl_3$) 2.49 (2H, t, $J_{H\text{-}H}$ 7.2, $J_{H\text{-}Sn}$ 81.7, CH_2SnCl_3), 2.70 (2H, app q, *J* 6.9, $C\underline{H}_2CH_2SnCl_3$), 5.21-5.28 (2H, m, $CH{=}C\underline{H}_2$), 5.93 (1H, ddt, *J* 17.1 10.2 and 6.5, $C\underline{H}{=}CH_2$); δ_C (100.6 MHz; $CDCl_3$) 28.6 ($SnCH_2$), 32.7 (CH_2), 118.5 ($CH{=}\underline{C}H_2$), 136.6 ($\underline{C}H{=}CH_2$); δ_{Sn}(150 MHz; $CDCl_3$; Me_4Sn) 1.34 (s, $SnCl_3$); LRMS (EI^+, *m/z*): M^+ not visible, 245 ($[M{-}Cl]^+$, 6 %), 225 ($[SnCl_3]^+$, 9), 190 ($[SnCl_2]^+$, 5), 155 ($[SnCl]^+$, 27), 55 ($[\text{homoallyl}]^+$, 100). The data is in good agreement with previously reported literature values.[97]

(±)-2-((*tert*-Butyldiphenylsilyl)methyl)tetrahydrofuran-5-yl)(phenyl)methanone (185)



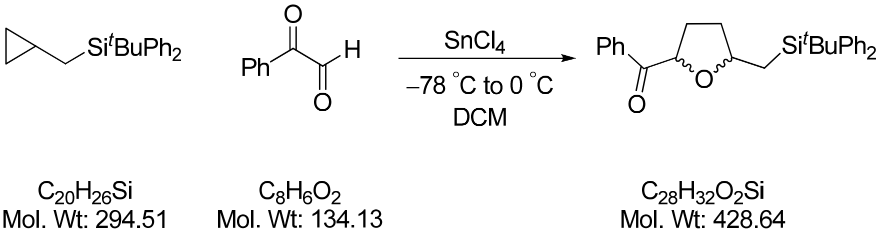
$C_{20}H_{26}Si$
Mol. Wt: 294.51

$C_8H_6O_2$
Mol. Wt: 134.13

$C_{28}H_{32}O_2Si$
Mol. Wt: 428.64

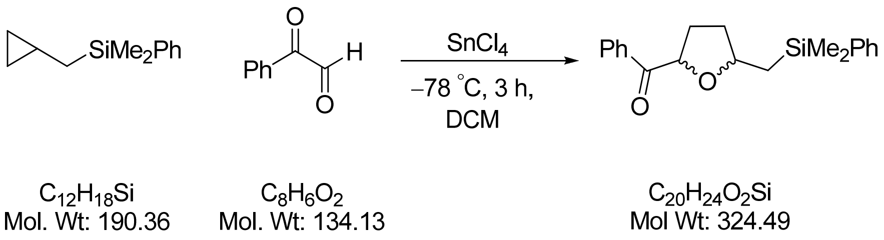
To a stirred solution of freshly distilled phenyl glyoxal (0.12 g, 0.90 mmol) in anhydrous DCM (2 mL) at –78 °C and under an atmosphere of argon was added, dropwise, a solution of tin tetrachloride (0.17 g, 0.08 mL, 0.66 mmol) in anhydrous DCM (2 mL). The resulting mixture was stirred at –78 °C for 5 min followed by the dropwise addition of *tert*-butyl(cyclopropylmethyl)diphenylsilane (0.18 g, 0.60 mmol) in anhydrous DCM (3 mL). The reaction was stirred at –78 °C and monitored by TLC, after 3 h the reaction was quenched by the addition of wet acetone (5 mL), allowed to warm to 0 °C and poured on to H_2O (10 mL). The organic layer was separated and the aqueous layer extracted with DCM (3 × 10 mL). The combined organic phases were washed with brine (10 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product (0.29 g) as a yellow oil. Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 20 % diethyl ether : cyclohexane] afforded the desired product as an inseparable mixture of *cis* and *trans* diastereoisomers (combined yield 0.14 g, 0.33 mmol, 54 %, *dr* (*trans* : *cis*) 1 : 2.1) as a colourless oil; R_f 0.41 [20 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 2930 (C-H), 2857 (C-H), 1691 (C=O), 1448 (C-H), 1228 (Si-C), 1104 (C-O); *cis* diastereoisomer: δ_H (400 MHz; $CDCl_3$) 1.04 (9H, s, $Si\underline{C}(CH_3)_3$), 1.17-1.32 (1H, m, $C\underline{H}_aH_b$ C-3 THF), 1.40-1.47 (1H, m, $CH_a\underline{H}_b$, C-3 THF), 1.58 (1H, dd, *J* 14.5 and 9.8, $SiC\underline{H}_aH_b$), 2.02 (1H, dd, 14.5 and 4.1 $SiCH_a\underline{H}_b$), 2.03-2.08 (2H, m, CH_2 C-4 THF), 4.14 (1H, app tt, 9.5 and 4.8, CH C-2 THF), 5.07 (1H, dd, *J* 8.4 and 5.5, CH C-5 THF), 7.29-7.70 (13H, m, Ar), 7.94-7.96 (2H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) 17.9 ($SiCH_2$), 18.2 ($Si\underline{C}(CH_3)_3$), 29.8 (CH_2, C-4 THF), 33.0 (CH_2, C-3 THF), 79.4 (CH, C-5 THF), 79.6 (CH, C-2 THF), 127.6 (2 × *o*-CH, Ar), 127.7 (2 × *o*-CH, Ar), 128.6 (2 × *m*-CH, -C(=O)Ph), 128.9 (2 × *o*-CH, -C(=O)Ph), 129.3 (2 × *p*-CH, Ar), 133.2 (*p*-CH, -C(=O)Ph), 134.1 (C, Ar), 134.7 (C, Ar), 135.4 (*ipso*-C, -C(=O)Ph), 136.2 (2 × *m*-CH, Ar), 136.3 (2 × *m*-CH, Ar), 198.4 (C=O); *trans* diastereoisomer: δ_H (400 MHz; $CDCl_3$) 1.05 (9H, s, Si $C(CH_3)_3$), 1.17-1.32 (1H, m, $C\underline{H}_aH_b$ C-3 THF), 1.46 (1H, dd, *J* 14.4 and 9.2, $SiC\underline{H}_aH_b$), 1.51-1.56 (1H, m, $CH_a\underline{H}_b$, C-3 THF), 1.95 (1H, dd, *J* 14.4 and 5.0, $SiCH_a\underline{H}_b$), 1.95-2.00 (1H, m, $C\underline{H}_aH_b$ C-4 THF), 2.16 (1H, m, $CH_a\underline{H}_b$ C-4 THF), 4.20 (1H, app tt, 8.9 and 5.2, CH C-2 THF), 5.19 (1H, dd, *J* 8.0 and 7.0, CH C-5 THF), 7.29-7.70 (13H, m, Ar), 7.86-7.88 (2H, m, 2 × *o*-CH Ar); δ_C (100.6 MHz; $CDCl_3$) 18.1 ($SiCH_2$), 18.2 ($Si\underline{C}(CH_3)_3$), 29.4 (CH_2, C-4 THF), 34.0 (CH_2, C-3 THF), 78.6 (CH, C-2 THF), 79.2 (CH, C-5 THF), 127.6 (2 × *o*-CH, Ar), 127.7 (2 × *o*-CH, Ar), 128.5 (2 × *m*-CH, -C(=O)Ph), 128.9 (2 × *o*-CH, -C(=O)Ph), 129.2 (2 × *p*-CH, Ar), 133.1 (*p*-CH, -C(=O)Ph), 134.2 (C, Ar), 134.8 (C, Ar), 135.3 (*ipso*-C, -C(=O)Ph), 136.2 (2 × *m*-CH, Ar), 136.3 (2 × *m*-CH, Ar), 199.2 (C=O); LRMS (EI^+, *m/z*): M^+ not visible, ($[M-{}^tBu]^+$ 18 %), 329 (87), 183 (42), 135 (100), 105 (72), 77 (33); HRMS (CI^+, *m/z*) 446.2512 $[M+NH_4]^+$, $C_{28}H_{36}O_2NSi$ requires 446.2510. Diastereoselectivity calculated by analysis of the ^1H NMR integrals for the C-5 protons of the THF ring, 5.07 *cis* and 5.19 *trans*.

(±)-2-((*tert*-Butyldiphenylsilyl)methyl)tetrahydrofuran-5-yl)(phenyl)methanone (185)



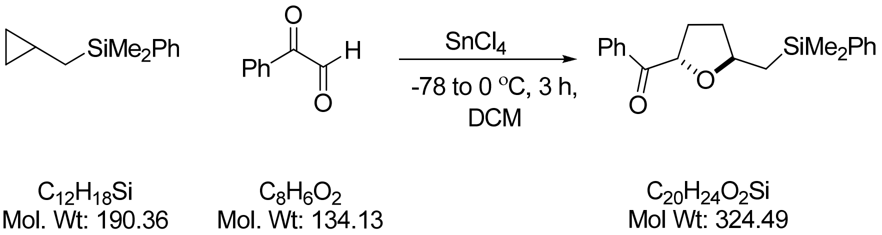
To a stirred solution of freshly distilled phenyl glyoxal (0.12 g, 0.90 mmol) in anhydrous DCM (2 mL) at –78 °C and under an atmosphere of argon was added, dropwise, a solution of tin tetrachloride (0.17 g, 0.08 mL, 0.66 mmol) in anhydrous DCM (2 mL). The resulting mixture was stirred at –78 °C for 5 min followed by the dropwise addition of *tert*-butyl(cyclopropylmethyl)diphenylsilane (0.18 g, 0.60 mmol) in anhydrous DCM (3 mL). The reaction was stirred at –78 °C and monitored by TLC, after 1 h the reaction was allowed to warm to 0 °C and stirred at 0 °C for 1 h. The reaction was quenched by the addition of H_2O (10 mL), the organic layer was separated and the aqueous layer further extracted with DCM (3 x 10 mL). The combined organic phases were washed with brine (10 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product (0.24 g) as a yellow oil. Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 20 % diethyl ethyl : hexane] afforded the desired product as an inseparable mixture of *cis* and *trans* diastereoisomers (combined yield 0.18 g, 0.43 mmol, 72 %, *dr* (*trans* : *cis*) 1 : 1.1) as a colourless oil. Data is in agreement with that previously recorded.

(±)-(2-((Dimethyl(phenyl)silyl)methyl)tetrahydrofuran-5-yl)(phenyl)methanone (186)



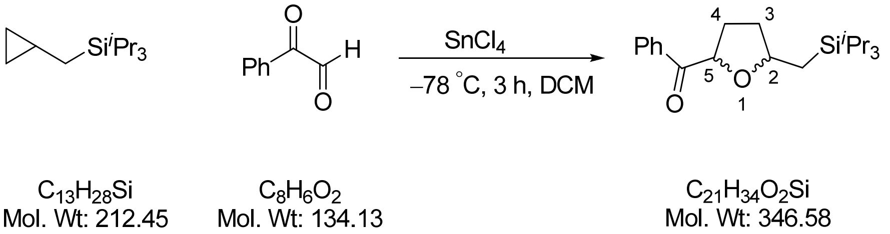
Following the general procedure C, (cyclopropylmethyl)dimethylphenylsilane (0.12 g, 0.60 mmol) and phenyl glyoxal (0.12 g, 0.90 mmol) at −78 °C furnished the impure product (0.27 g) as a yellow oil. Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 20 % diethyl ether : hexane] afforded the desired product as an inseparable mixture of *cis* and *trans* diastereoisomers (combined yield 0.10 g, 0.32 mmol, 53 %, *dr* (*trans* : *cis*) 1 : 1.6) as a colourless oil; R_f 0.22 [20 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 3070, 2957 (C-H), 2886 (C-H), 1692 (C=O), 1451 (C-H), 1429, 1230 (Si-C), 1115 (C-O); *cis* diastereoisomer: δ_H (400 MHz; $CDCl_3$); 0.30 (3H, s, $SiCH_3$), 0.32 (3H, s, $SiCH_3$), 1.21 (1H, dd, *J* 14.2 and 8.5, $SiC\underline{H}_aH_b$), 1.42-1.51 (2H, m, overlapping signals $SiH_a\underline{H}_b$ and $C\underline{H}_aH_b$ C-3 THF), 1.92-2.02 (1H, m, $CH_a\underline{H}_b$ C-3 THF), 2.09-2.33 (2H, m, CH_2 C-4 THF), 4.15 (1H, app tt, *J* 8.7 and 5.8, CH C-2 THF), 5.13 (1H, dd, *J* 8.6 and 5.1, CH C-5 THF), 7.33-7.59 (8H, m, Ar), 8.01-8.04 (2H, m, 2 × *o*-CH Ar); δ_C (100.6 MHz; $CDCl_3$) −2.3 ($SiCH_3$), −2.0 ($SiCH_3$), 23.6 ($SiCH_2$), 29.4 (CH_2, C-4 THF), 33.6 (CH_2, C-3 THF), 78.5 (CH, C-2 THF), 79.2 (CH, C-5 THF), 127.9 (2 × *m*-CH, SiPh), 128.5 (2 × *m*-CH, -C(=O)Ph), 129.0 (2 × *o*-CH, -C(=O)Ph), 129.1 (*p*-CH, SiPh), 133.2 (*p*-CH, -C(=O)Ph), 133.7 (2 × *o*-CH, SiPh), 135.5 (*ipso*-C, -C(=O)Ph), 139.0 (C, SiPh), 198.4 (C=O); *trans* diastereoisomer: δ_H (400 MHz; $CDCl_3$); 0.32 (3H, s, $SiCH_3$), 0.33 (3H, s, $SiCH_3$), 1.12 (1H, dd, *J* 14.2 and 8.1, $SiC\underline{H}_aH_b$), 1.42 (1H, dd, *J* 14.2 and 6.2, $SiH_a\underline{H}_b$), 1.39-1.52 (1H, m, $C\underline{H}_aH_b$ C-3 THF), 1.98 (1H, dddd, *J* 12.1 8.1 5.5 and 3.6, $CH_a\underline{H}_b$ C-3 THF), 2.13 (1H, app dtd, *J* 12.7 8.5 and 6.6, $C\underline{H}_aH_b$ C-4 THF), 2.25 (1H, app dtd, *J* 12.7 8.4 and 3.6, $CH_a\underline{H}_b$ C-4 THF), 4.19 (1H, app tt, *J* 8.4 and 5.9, CH C-2 THF), 5.27 (1H, dd, *J* 8.2 and 6.6, CH C-5 THF), 7.32-7.36 (3H, m, overlapping signals 2 × *o*-CH and *p*-CH Ar), 7.45 (2H, t, *J* 7.6, 2 × *m*-CH Ar), 7.49-7.52 (2H, m, 2 × *m*-CH Ar), 7.56 (1H, app tt, *J* 7.4 and 1.4, *p*-CH Ar), 7.96-7.99 (2H, m, 2 × *o*-CH Ar); δ_C (100.6 MHz; $CDCl_3$) −2.4 ($SiCH_3$), −2.0 ($SiCH_3$), 23.5 ($SiCH_2$), 29.3 (CH_2, C-4 THF), 34.4 (CH_2, C-3 THF), 78.6 (CH, C-2 THF), 79.2 (CH, C-5 THF), 127.9 (2 × *m*-CH, Ar), 128.6 (2 × *m*-CH, -C(=O)Ph), 129.0 (2 × *o*-CH, -C(=O)Ph), 129.0 (*p*-CH, Ar), 133.3 (*p*-CH, -C(=O)Ph), 133.7 (2 × *o*-CH, Ar), 135.3 (*ipso*-C, -C(=O)Ph), 139.1 (C, Ar), 199.4 (C=O); LRMS (EI$^+$, *m/z*): M$^+$ not visible, 309 ($[M{-}CH_3]^+$, 2 %), 267 (5), 239 (10), 219 (16), 135 (100), 105 (21), 77 (15); HRMS (CI$^+$, *m/z*) 342.1878 $[M+NH_4]^+$, $C_{20}H_{28}O_2NSi$ requires 342.1884. Diastereoselectivity calculated by analysis of the ^{1}H NMR integrals for the C-5 protons of the THF ring, 5.13 *cis* and 5.27 *trans*.

(±)-(2-((Dimethyl(phenyl)silyl)methyl)tetrahydrofuran-5-yl)(phenyl)methanone (186)



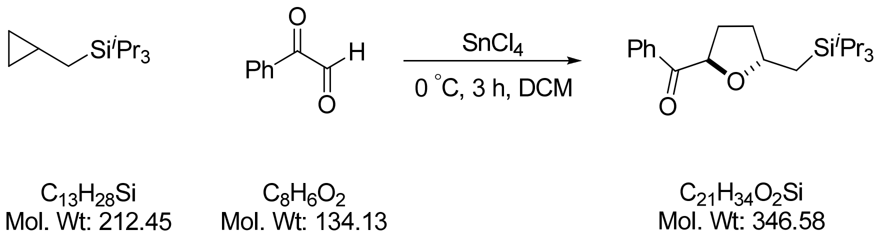
Following the general procedure C, (cyclopropylmethyl)dimethylphenylsilane (0.12 g, 0.60 mmol) and phenyl glyoxal (0.12 g, 0.90 mmol) at 0 °C furnished the impure product (0.26 g) as a yellow oil. Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 20 % diethyl ether : hexane] afforded the desired product as only the *trans* diastereoisomer (0.03 g, 0.11 mmol, 18 %) as a colourless oil; R_f 0.41 [20 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 3070, 2957 (C-H), 2886 (C-H), 1692 (C=O), 1451 (C-H), 1429, 1230 (Si-C), 1115 (C-O); δ_H (400 MHz; $CDCl_3$); 0.32 (3H, s, $SiCH_3$), 0.33 (3H, s, $SiCH_3$), 1.12 (1H, dd, *J* 14.2 and 8.1, $SiC\underline{H}_aH_b$), 1.42 (1H, dd, *J* 14.2 and 6.2, $SiH_a\underline{H}_b$), 1.39-1.52 (1H, m, $C\underline{H}_aH_b$ C-3 THF), 1.98 (1H, dddd, *J* 12.1 8.1 5.5 and 3.6, $CH_a\underline{H}_b$ C-3 THF), 2.13 (1H, app dtd, *J* 12.7 8.5 and 6.6, $C\underline{H}_aH_b$ C-4 THF), 2.25 (1H, app dtd, *J* 12.7 8.4 and 3.6, $CH_a\underline{H}_b$ C-4 THF), 4.19 (1H, app tt, *J* 8.4 and 5.9, CH C-2 THF), 5.27 (1H, dd, *J* 8.2 and 6.6, CH C-5 THF), 7.32-7.36 (3H, m, overlapping signals 2 × *o*-CH and *p*-CH Ar), 7.45 (2H, t, *J* 7.6, 2 × *m*-CH Ar), 7.49-7.52 (2H, m, 2 × *m*-CH Ar), 7.56 (1H, tt, *J* 7.4 and 1.4, *p*-CH Ar), 7.96-7.99 (2H, m, 2 × *o*-CH Ar); δ_C (100.6 MHz; $CDCl_3$) −2.4 ($SiCH_3$), −2.0 ($SiCH_3$), 23.5 ($SiCH_2$), 29.3 (CH_2, C-4 THF), 34.4 (CH_2, C-3 THF), 78.6 (CH, C-2 THF), 79.2 (CH, C-5 THF), 127.9 (2 × *m*-CH, SiPh), 128.6 (2 × *m*-CH, -C(=O)Ph), 129.0 (2 × *o*-CH, -C(=O)Ph), 129.0 (*p*-CH, SiPh), 133.3 (*p*-CH, -C(=O)Ph), 133.7 (2 × *o*-CH, SiPh), 135.3 (*ipso*-C, -C(=O)Ph), 139.1 (C, SiPh), 199.4 (C=O); LRMS (EI$^+$, *m/z*): M$^+$ not visible, 309 ($[M-CH_3]^+$, 2 %), 267 (5), 239 (10), 219 (16), 135 (100), 105 (21), 77 (15); HRMS (CI$^+$, *m/z*) 342.1888 $[M+NH_4]^+$, $C_{20}H_{28}O_2NSi$ requires 342.1884.

(±)-Phenyl(2-((triisopropylsilyl)methyl)tetrahydrofuran-5-yl)methanone (187)



Following the general procedure C, (cyclopropylmethyl)tri*iso*propylsilane (0.13 g, 0.60 mmol) and phenyl glyoxal (0.12 g, 0.90 mmol) at −78 °C furnished the impure product (0.27 g) as a yellow oil. Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 20 % diethyl ether : hexane] afforded the desired product as an inseparable mixture of *cis* and *trans* diastereoisomers (combined yield 0.14 g, 0.40 mmol, 67 %, *dr* (*trans* : *cis*) 1 : 1.6) as a colourless oil; R_f 0.63 [20 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 2947 (C-H), 1690 (C=O), 1430 (C-H), 1230 (Si-C), 1115 (C-O), 885; *cis* diastereoisomer: δ_H (400 MHz; CDCl$_3$) 0.93-1.05 (22H, m, overlapping signals Si(C$\underline{H}$(C$\underline{H}_3$)$_2$)$_3$ and SiC$\underline{H}_a$H$_b$), 1.23 (1H, dd, *J* 12.5 and 6.6, SiCH$_a\underline{H}_b$), 1.46-1.63 (1H, m, C$\underline{H}_a$H$_b$ C-3 THF), 2.05-2.38 (3H, m, overlapping signals CH$_2$ C-4 and CH$_a\underline{H}_b$ C-3 THF), 4.19-4.29 (1H, m, CH C-2 THF), 5.13 (1H, dd, *J* 8.7 and 5.0, CH C-5 THF), 7.42-7.57 (3H, m, Ph), 7.98-8.02 (2H, m, Ph); δ_C (100.6 MHz; CDCl$_3$) 11.4 (SiCH, ^{i}Pr), 16.8 (SiCH$_2$), 18.9 (6 × CH$_3$, ^{i}Pr), 29.2 (CH$_2$, C-4 THF), 34.4 (CH$_2$, C-3 THF), 79.8 (CH, C-2 THF), 79.8 (CH, C-5 THF), 128.6 (2 × *m*-CH, Ph), 129.0 (2 × *o*-CH, Ph), 133.2 (*p*-CH, Ph), 135.4 (C, Ph), 198.3 (C=O); *trans* diastereoisomer: δ_H (400 MHz; CDCl$_3$) 0.96 (1H, dd, *J* 14.4 and 7.5, SiC$\underline{H}_a$H$_b$), 1.02-1.04 (21H, m, overlapping signals 3 × CH and 6 × CH$_3$), 1.20 (1H, dd, *J* 14.4 and 6.6, SiCH$_a\underline{H}_b$), 1.53-1.64 (1H, m, C$\underline{H}_a$H$_b$ C-3 THF), 2.09-2.23 (2H, m, overlapping signals CH$_a\underline{H}_b$ C-3 and C$\underline{H}_a$H$_b$ C-4 THF), 2.27-2.37 (1H, m, CH$_a\underline{H}_b$ C-4 THF), 4.23-4.30 (1H, m, CH C-2 THF), 5.31 (1H, dd, *J* 8.3 and 6.1, CH C-5 THF), 7.45 (2H, app t, *J* 7.7, 2 × *m*-CH, Ph), 7.55 (1H, app tt, *J* 7.4 and 1.4, *p*-CH, Ph), 7.99 (2H, app dd, *J* 8.3 and 1.4, 2 × *o*-CH, Ph); δ_C (100.6 MHz; CDCl$_3$) 11.4 (3 × CH, ^{i}pr), 16.9 (SiCH$_2$), 19.0 (6 × CH$_3$, ^{i}Pr), 29.3 (CH$_2$, C-4 THF), 35.1 (CH$_2$, C-3 THF), 78.7 (CH, C-2 THF), 79.3 (CH, C-5 THF), 128.6 (2 × *m*-CH, Ph), 129.0 (2 × *o*-CH, Ph), 133.2 (*p*-CH, Ph), 135.4 (C, Ph), 199.5 (C=O); LRMS (EI$^+$, *m/z*): M$^+$ not visible, 303 ([M−^{i}Pr]$^+$, 14 %), 261 (100), 241 (7), 157 (22), 105 (30), 77 (22); HRMS (CI$^+$, *m/z*) 347.2405 [M+H]$^+$, $C_{21}H_{35}O_2Si$ requires 347.2401. Diastereoselectivity calculated by analysis of the ^{1}H NMR integrals for the C-5 protons of the THF ring, 5.13 *cis* and 5.30 *trans*.

(±)-(Phenyl(2-((triisopropylsilyl)methyl)tetrahydrofuran-5-yl)methanone (187)

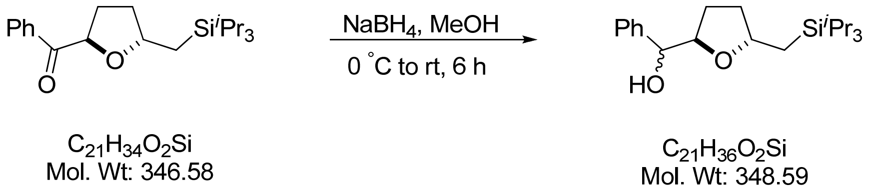


Following the general procedure C, (cyclopropylmethyl)tri*iso*propylsilane (0.13 g, 0.60 mmol) and phenyl glyoxal (0.12 g, 0.90 mmol) at 0 °C furnished the impure product (0.25 g) as a yellow oil. Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 20 % diethyl ether : hexane] afforded the desired product as only the *trans* diastereoisomer (0.14 g, 0.40 mmol, 67 %) as a colourless oil; R_f 0.63 [20 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 2947 (C-H), 1690 (C=O), 1430 (C-H), 1230 (Si-C), 1115 (C-O), 885; *trans*-diastereoisomer: δ_H (400 MHz; $CDCl_3$) 0.96 (1H, dd, *J* 14.4 and 7.5, $SiC\underline{H}_aH_b$), 1.02-1.04 (21 H, m, overlapping signals 3 × CH and 6 × CH_3), 1.20 (1H, dd, *J* 14.4 and 6.6, $SiCH_a\underline{H}_b$), 1.53-1.64 (1H, m, $C\underline{H}_aH_b$ C-3 THF), 2.09-2.23 (2H, m, overlapping signals $CH_a\underline{H}_b$ C-3 and $C\underline{H}_aH_b$ C-4 THF), 2.27-2.37 (1H, m, $CH_a\underline{H}_b$ C-4 THF), 4.23-4.30 (1H, m, CH C-2 THF), 5.31 (1H, dd, *J* 8.26 and 6.1, CH C-5 THF), 7.45 (2H, app t, *J* 7.7, 2 × *m*-CH Ph), 7.55 (1H, app tt, *J* 7.4 and 1.4, *p*-CH Ph), 7.99 (2H, dd, *J* 8.3 and 1.4, 2 × *o*-CH Ph); δ_C (100.6 MHz; $CDCl_3$) 11.4 (3 × CH, ^{i}Pr), 16.9 ($SiCH_2$), 19.0 (6 × CH_3, ^{i}Pr), 29.3 (CH_2, C-4 THF), 35.1 (CH_2, C-3 THF), 78.7 (CH, C-2 THF), 79.3 (CH, C-5 THF), 128.6 (2 × *m*-CH, Ph), 129.0 (2 × *o*-CH, Ph), 133.2 (*p*-CH, Ph), 135.4 (C, Ph), 199.5 (C=O); LRMS (EI$^+$, *m/z*): M$^+$ not visible, 303 ([M–^{i}Pr]$^+$, 14 %), 261 (100), 241 (7), 157 (22), 105 (30), 77 (22); HRMS (CI$^+$, *m/z*) 347.2405 [M+H]$^+$, $C_{21}H_{35}O_2Si$ requires 347.2401.

4-Nitrobenzoyl chloride (189)

To a stirred solution of 4-nitrobenzoic acid (1.00 g, 6.00 mmol) in DCM (10 mL) at room temperature was added oxalyl chloride (1.50 g, 1.05 mL, 12.0 mmol) and DMF (5 drops). The reaction was stirred for 3 h at room temperature and the volatiles removed under reduced pressure to give a crystalline solid. The residue was taken up in DCM (10 mL) to give a 0.6 M solution of 4-nitrobenzoyl chloride in DCM which was used immediately in the next reaction.

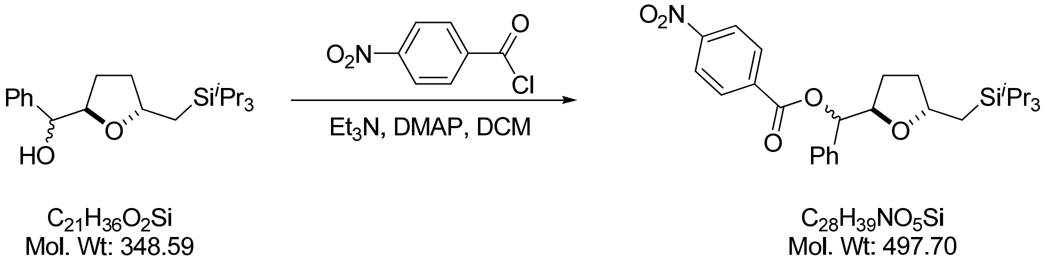
(±)-Phenyl(2-((triisopropylsilyl)methyl)tetrahydrofuran-5-yl)methanol (190)



To a stirred solution of phenyl(2-((triisopropylsilyl)methyl)tetrahydrofuran-5-yl)methanone (0.40 g, 1.16 mmol) in HPLC grade methanol (7.0 mL) at 0 °C was added in one portion $NaBH_4$ (0.11 g, 2.90 mmol). The mixture was stirred at 0 °C until effervescence had ceased then warmed to room temperature and stirred for a further 15 h. The reaction was quenched by the addition of acetic acid (0.1 mL), concentrated to approximately one quarter of the volume under reduced pressure and partitioned between dichloromethane (10 mL) and water (10 mL). The organic phase was separated and the aqueous phase extracted with dichloromenthane (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product (0.33 g) as a cloudy colourless oil. Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 20 %

diethylether : hexane] afforded title compound as an inseparable mixture of the two diastereoisomers (combined yield 0.31 g, 0.89 mmol, 77 %, dr 2.6 : 1) as a colourless oil; R_f 0.29 [20 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 3426 (O-H), 2940, 2864, 1462, 1195, 1027, 881; Major Diastereoisomer: δ_H (400 MHz; $CDCl_3$) 0.94 (1H, dd, *J* 14.5 and 6.8, $SiC\underline{H}_aH_b$), 1.03-1.12 (21H, m, overlapping signals $Si^i\underline{Pr}_3$), 1.12 (1H, dd, *J* 14.5 and 7.4, $SiCH_a\underline{H}_b$), 1.42-1.79 (3H, m, CH_2 C-3 and $C\underline{H}_aH_b$C-4 THF), 2.03-2.15 (1H, m, $CH_a\underline{H}_b$ C-4 THF), 3.06 (1H, d, *J* 1.6, OH), 4.08 (1H, q, *J* 7.4, C-5 THF), 4.19-4.29 (1H, m, overlapping signals C-2 THF), 4.42 (1H, dd, *J* 7.9 and 1.6, $\underline{H}$COH), 7.24-7.39 (5H, m, Ph); δ_C (100.6 MHz; $CDCl_3$) 11.5 (3 × CH Si^iPr_3), 17.7 ($SiCH_2$), 19.0 (6 × CH_3 Si^iPr_3), 28.8 (CH_2, C-4 THF), 36.1 (CH_2, C-3 THF), 77.5 (COH), 77.6 (CH, C-2 THF), 83.0 (CH, C-5 THF), 127.2 (2 × *o*-CH, Ph), 128.0 (*p*-CH, Ph), 128.4 (2 × *m*-CH, Ph), 140.4 (C, Ph); Minor Diastereoisomer: δ_H (400 MHz; $CDCl_3$) 0.92 (1H, dd, *J* 14.4 and 7.9, $SiC\underline{H}_aH_b$), 1.03-1.12 (22H, m, overlapping signals $^i\underline{Pr}_3SiCH_a\underline{H}_b$), 1.42-179 (2H, m, overlapping signals $C\underline{H}_aH_b$ C-3 and $C\underline{H}_aH_b$ C-4 THF), 1.89 (1H, dddd, *J* 12.2, 10.8, 9.1 and 7.6, $CH_a\underline{H}_b$ C-3 THF), 2.03-2.15 (1H, m, $CH_a\underline{H}_b$ C-4 THF), 2.59 (1H, d, *J* 2.5, OH), 4.19-4.29 (2H, m, overlapping signals C-5 and C-2 THF), 4.91 (1H, dd appearing as br t, *J* 2.5, $\underline{H}$COH), 7.24-7.39 (5H, m, Ph); δ_C (100.6 MHz; $CDCl_3$) 11.4 (3 × CH Si^iPr_3), 17.1 (CH_2, $^iPr_3SiCH_2$), 19.0 (6 × CH_3 Si^iPr_3), 26.0 (CH_2, C-4 THF), 35.7 (CH_2, C-3 THF), 74.3 (COH), 78.7 (CH, C-2 THF), 82.2 (CH, C-5 THF), 126.1 (2 × *o*-CH, Ph), 127.4 (*p*-CH, Ph), 128.3 (2 × *m*-CH, Ph), 140.5 (C, Ph); LRMS (EI$^+$, *m/z*): M$^+$ not visible, 305 ($[M-{}^iPr]^+$, 9 %), 287 (3), 263 (6), 241 (24), 157 (100), 131 (68), 103 (86), 75 (50); HRMS (ESP, *m/z*) 366.2822 $[M+NH_4]^+$, $C_{21}H_{40}O_2NSi$ requires 366.2823. Diastereoselectivity calculated by analysis of the ^{1}H NMR integrals for the $\underline{H}$COH proton at 4.42 (major diastereoisomer) and 4.91 ppm (minor diastereoisomer).

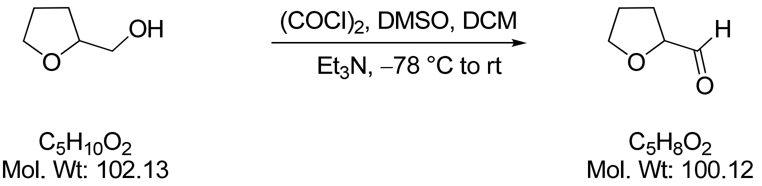
(±)-Phenyl-(2-((triisopropylsilyl)methyl)tetrahydrofuran-5-yl)methyl 4-nitrobenzoate (191)



To a stirred solution of phenyl(5-((triisopropylsilyl)methyl)tetrahydrofuran-2-yl)methanol (0.31 g, 0.89 mmol) in DCM (2 mL) was added a solution of freshly prepared 4-nitrobenzoyl chloride in DCM (0.6 M, 1.70 mL, 1.00 mmol). To the resulting yellow/orange solution was added dropwise triethylamine (0.20 g, 0.30 mL, 2.00 mmol) and DMAP (1 crystal). After 24 h the reaction had become a red/brown colour and was partitioned between water (10 mL) and DCM (10 mL). The organic phase was separated, washed with a 10 % *w*/*v* aqueous sodium hydrogen carbonate solution (10 mL) and the aqueous phase extracted with dichloromenthane (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product as a brown gum. Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 20 % diethylether : hexane] afforded title compound as an inseparable mixture of diastereoisomers (combined yield 0.29 g, 0.64 mmol, 72 %, *dr* 3 : 1) as colourless viscous oils; R_f 0.44 [20 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 2941, 2864, 1727 (C=O), 1529 (N=O), 1463, 1346 (N=O), 1270, 1101, 882; Major Diastereoisomer: δ_H (400 MHz; $CDCl_3$) 0.84-1.08 (23H, m, overlapping signals $\underline{^iPr_3}SiC\underline{H_2}$), 1.45-1.55 (1H, m, C$\underline{H}_aH_b$ C-3 THF), 1.60-1.67 (1H, m, C$\underline{H}_a$H$_b$ C-4 THF), 1.80 (1H, dtd, *J* 12.6 7.5 and 2.3, CH$_a\underline{H}_b$ C-4 THF), 2.02-2.13 (1H, m, CH$_a\underline{H}_b$ C-3 THF), 4.20 (1H, tt, *J* 8.4 and 5.5, CH C-2 THF), 4.46-4.53 (1H, m, CH C-5 THF), 5.89 (1H, d, *J* 8.0, HCO), 7.31-7.46 (5H, m, Ar), 8.23-8.32 (4H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) 11.5 (3 × CH Si^iPr_3), 17.0 ($SiCH_2$), 19.0 (6 × CH_3 Si^iPr_3), 29.4 (CH_2, C-4 THF), 36.3 (CH_2, C-3 THF), 77.7 (CH, C-2 THF), 80.0 (CH, C-5 THF), 80.1 (HCO), 123.5 (CH, Ar), 127.7 (CH, Ar), 128.5 (CH, Ar), 128.7 (CH, Ar), 131.0 (CH, Ar), 136.2 (C, Ar), 137.2 (C, Ar), 150.6 (C, Ar), 164.0 (C=O); Minor Diastereoisomer: δ_H (400 MHz; $CDCl_3$) 0.84-1.08 (23H, m, overlapping signals $\underline{^iPr_3}SiC\underline{H_2}$), 1.45-1.55 (1H, m, C$\underline{H}_aH_b$ C-3 THF), 1.87-1.97 (1H, m, C$\underline{H}_a$H$_b$ C-4 THF), 2.02-2.13 (1H, m, CH$_a\underline{H}_b$ C-3 and CH$_a\underline{H}_b$ C-4 THF), 3.97-4.20 (1H, m, CH C-2 THF), 4.46-4.53 (1H, m, CH C-5 THF), 6.04 (1H, d, *J* 4.4, HCO), 7.31-7.46 (5H, m, Ar), 8.23-8.32 (4H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) 11.4 (3 × CH Si^iPr_3), 17.1 ($SiCH_2$), 19.0 (6 × CH_3 Si^iPr_3), 28.5 (CH_2, C-4 THF), 35.9 (CH_2, C-3 THF), 78.4 (CH, C-2 THF), 79.2 (HCO), 80.0 (CH, C-5 THF), 123.7

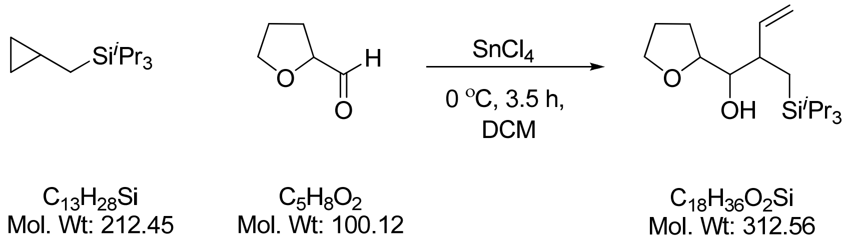
(CH, Ar), 127.5 (CH, Ar), 128.4 (CH, Ar), 128.8 (CH, Ar), 130.9 (CH, Ar), 136.0 (C, Ar), 137.0 (C, Ar), 150.7 (C, Ar), 163.9 (C=O); LRMS (EI$^+$, *m/z*): M$^+$ not visible, 280 (100), 241 (5), 157 (46), 150 (30), 115 (14), 91 (11); HRMS (ESP, *m/z*) 498.2664 [M+H]$^+$, $C_{28}H_{40}O_5NSi$ requires 498.2670. Diastereoselectivity calculated by analysis of the ^{1}H NMR integrals for the $\underline{H}$CO proton at 5.89 (major diastereoisomer) and 6.04 ppm (minor diastereoisomer).

(±)-Tetrahydrofuran-2-carbaldehyde (194)



Tetrahydrofuran-2-carbaldehyde was prepared from commercially availably racemic tetrahydrofurfuryl alcohol according to the method previously reported.[104] To a stirred solution of oxalyl chloride (4.14 g, 2.80 mL, 33.0 mmol) in anhydrous dichloromethane (15 mL) at −78 °C was added dropwise a solution of DMSO (4.29 g, 3.90 mL, 55.0 mmol) in dichloromethane (70 mL). The mixture was stirred for 20 min and then a solution of tetrahydrofurfuryl alcohol (2.64 g, 2.50 mL, 12.9 mmol) in dichloromethane (20 mL) was added dropwise. The mixture was stirred for 10 min and then triethylamine (18 mL) was slowly added dropwise and the reaction was allowed to warm to room temperature. After 1 h stirring at room temperature the reaction mixture was poured onto saturated aqueous ammonium chloride solution (25 mL). The organic layer was separated and the aqueous layer was extracted with DCM (2 × 20 mL). The combined organic layers were washed with brine (20 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the impure product as a pale yellow oil (2.63 g). Purification by flash column chromatography [silica gel, 30 % ethyl acetate : hexane] followed by bulb-to-bulb distillation gave the desired compound (0.23 g, 2.30 mmol, 18 %) as a colourless oil; R_f 0.18 [30 % ethyl acetate : hexane], bp 64-65 °C/23mmHg, (lit.[182] 43-46 °C/15mmHg), ν_{max}(film)/cm^{-1} 2979, 2875, 1731 (C=O), 1461, 1069 (C-O); δ_H (400 MHz; $CDCl_3$) 1.84-2.01 (3H, m, overlapping signals CH_2 and $C\underline{H}_aH_b$ THF), 2.09-2.18 (1H, m, $CH_a\underline{H}_b$ THF), 3.93 (2H, t, *J* 6.6, OCH_2), 4.25 (1H, ddd, *J* 8.4 5.9 and 1.7, OCH), 9.65 (1H, d, *J* 1.7, CHO); δ_C (100.6 MHz; $CDCl_3$) 25.7 (CH_2, C-4), 27.5 (CH_2, C-3), 69.7 (CH_2, C-5), 82.9 (CH), 202.9 (CHO); LRMS (EI$^+$, *m/z*) 101 ([M]$^+$, 2 %), 71 (90), 43 (100), 41 (98), 39 (73); HRMS (EI$^+$, *m/z*) 118.0863 [M+NH$_4$]$^+$, $C_5H_{12}O_2N_1$ requires 118.0863. The data is in good agreement with previously reported values.[104]

1-(Tetrahydrofuran-2-yl)-2-((triisopropylsilyl)methyl)but-3-en-1-ol (195)

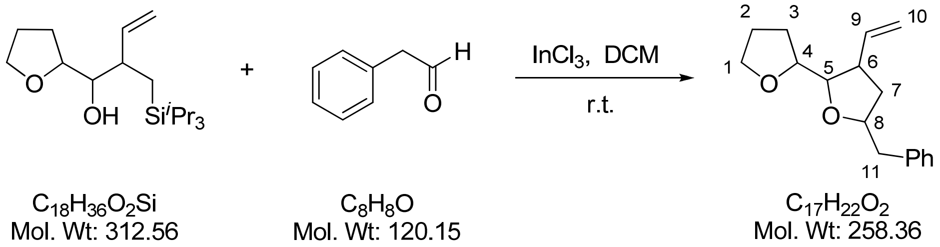


To a stirred solution of tetrahydrofurfuryl aldehyde (0.09 g, 0.90 mmol) and triisopropylsilylmethylcycopropane (0.13 g, 0.61 mmol) in DCM (6 mL) at 0 °C was added dropwise using a syringe pump (rate = 9 mL/h) a solution of tin tetrachloride (0.19 g, 0.73 mmol) in DCM (3 mL). The reaction was allowed to warm to room temperature and monitored by TLC, after 18 h TLC and GCMS analysis showed all the staring material had been consumed and the reaction was quenched by the addition of water (5 mL). The organic layer was separated and the aqueous layer further extracted with DCM (3 × 10 mL). The combined organic phases were washed with brine (10 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product (0.20 g) as a brown oil. Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 20 % ethyl acetate : hexane] afforded a separable mixture of two diastereoisomers of the title compound (combined yield 0.04 g, 0.14 mmol, 23 %) as colourless oils:

Major diastereoisomer (0.04 g, 0.11 mmol, 19 %); R_f 0.25 [20 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 3450 (br), 2941(C-H), 2867 (C-H), 2362, 1465 (O-H bend), 1245 (Si-C), 1059 (C-O), 1000, 883; δ_H (400 MHz; $CDCl_3$); 0.84 (1H, dd, *J* 15.1 and 8.8, SiC$\underline{H}_a$H$_b$), 0.96 (1H, dd, *J* 15.1 and 4.7, SiCH$_a\underline{H}_b$), 1.00-1.08 (21H, m, overlapping signals 3 × CH and 6 × CH_3 ^{i}Pr), 1.48-1.59 (1H, m, C-4/3 THF), 1.82-1.97 (3H, m, C-4/3 THF), 2.31-2.38 (1H, m, C$\underline{H}$CH=CH$_2$), 2.41 (1H, d, *J* 3.0, OH), 3.31 (1H, app dt, *J* 7.3 and 3.2, C$\underline{H}$OH), 3.73-3.84 (3H, m, overlapping signals C-5 and C-2), 4.98 (1H, dd, *J* 17.3 and 2.0, CH=CH$_{cis}\underline{H}_{trans}$), 5.02 (1H, dd, *J* 10.2 and 1.9, CH=C$\underline{H}_{cis}$H$_{trans}$), 5.82 (1H, app dt, *J* 17.3 and 9.8, C$\underline{H}$=CH$_{cis}$H$_{trans}$); δ_C (100.6 MHz; $CDCl_3$) 11.6 (3 × CH$_2$, Si^{i}Pr$_3$), 12.5 (SiCH$_2$), 19.1 (6 × CH$_3$, Si^{i}Pr$_3$), 26.4 (CH$_2$, THF), 27.9 (CH$_2$, THF), 42.6 (SiCH$_2\underline{C}$H), 68.0 (CH$_2$, THF), 78.8 (H$\underline{C}$OH), 80.7 (CH THF), 115.5 (CH=$\underline{C}$H$_2$), 140.7 ($\underline{C}$H=CH$_2$); LRMS (EI$^+$, *m/z*): 269 ([M–^{i}Pr]$^+$, 16 %), 157 (31), 131 (100), 103 (75), 75 (55), 71 (46); HRMS (CI$^+$, *m/z*) 330.2827 [M+NH$_4$]$^+$, $C_{18}H_{40}O_2NSi$ requires 330.2823.

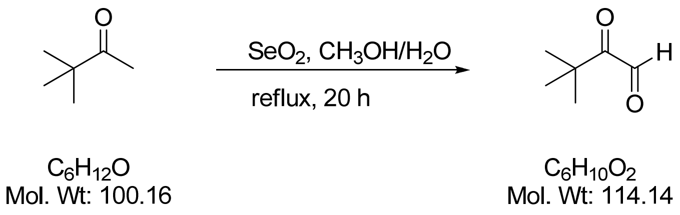
Minor diastereoisomer (0.01 g, 0.03 mmol, 5 %); R_f 0.32 [20 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 3450 (br), 2941(C-H), 2867 (C-H), 2362, 1465 (O-H bend), 1245 (Si-C), 1059 (C-O), 1000, 883; δ_H (400 MHz; $CDCl_3$); 0.67 (1H, dd, *J* 14.9 and 11.2, $SiC\underline{H}_aH_b$), 0.99-1.04 (22H, m, overlapping signals $SiCH_a\underline{H}_b$ and Si^iPr_3) 1.75-1.94 (4H, m, overlapping signals C-3 and C-4 THF), 2.24 (1H, d, *J* 8.2, OH), 2.41 (1H, dddd, *J* 11.2 9.4 6.1 and 2.4, $C\underline{H}CH{=}CH_2$), 3.21 (1H, ddd, *J* 8.2 6.1 and 3.2, $\underline{H}COH$), 3.74-3.86 (1H, m, C-5 THF), 4.01 (1H, td, *J* 7.0 and 3.2, CH C-2 THF), 5.04 (1H, dd, *J* 10.2 and 1.9, $CH{=}C\underline{H}_{cis}H_{trans}$), 5.09 (1H, dd, *J* 17.2 and1.9, $CH{=}CH_{cis}\underline{H}_{trans}$), 5.69 (1H, app dt, *J* 17.2 10.2 and 9.4, $C\underline{H}{=}CH_{cis}H_{trans}$); δ_C (100.6 MHz; $CDCl_3$) 10.5 (CH_2, $SiCH_2CH$), 11.6 (3 × CH Si^iPr_3), 19.1 (CH_3), 19.1 (CH_3), 26.4 (CH_2, THF), 29.3 (CH_2, THF), 44.9 ($SiCH_2C\underline{H}$), 68.9 (CH_2, C-5 THF), 77.8 ($C\underline{H}OH$), 78.4 (CH, C-2 THF), 116.0 ($CH{=}\underline{C}H_2$), 141.8 ($\underline{C}H{=}CH_2$); LRMS (EI$^+$, *m/z*): 269 ([M–^{i}Pr]$^+$, 16 %), 157 (31), 131 (100), 103 (75), 75 (55), 71 (46); HRMS (CI$^+$, *m/z*) 330.2825 [M+NH$_4$]$^+$, $C_{18}H_{40}O_2NSi$ requires 330.2823.

5-benzyl-3-vinyloctahydro-2,2'-bifuran (197)



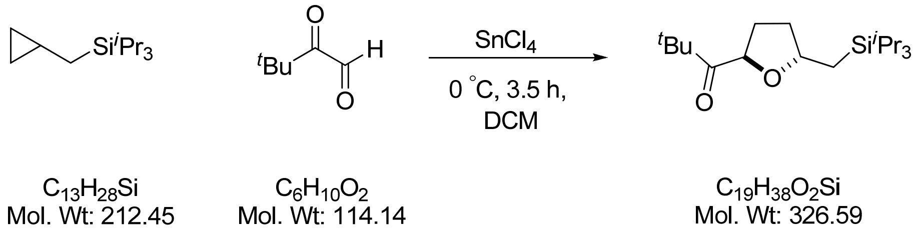
To a solution of phenylacetaldehyde (70.0 mg, 0.60 mmol) in DCM (2 mL) was added in a single portion indium trichloride (45.0 mg, 0.20 mmol) and the resulting mixture was stirred for 1 h at room temperature. After this time a solution of 1-(tetrahydrofuran-2-yl)-2-((triisopropylsilyl)methyl)but-3-en-1-ol (35.0 mg, 0.11 mmol) in DCM (1 mL) was added and the reaction mixture stirred at room temperature for 16 h. The reaction was quenched by the addition of H_2O (5 mL) and the organic layer separated. The aqueous layer was extracted with DCM (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product as a colourless oil (0.10 g). Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 20 % diethylether : hexane] followed by flash column chromatography [silica gel, gradient elution 100 % DCM – 5 % diethyl ether : DCM] afforded the desired product containing trace impurities (15.0 mg, 0.05 mmol, 40 %) as a colourless oil; R_f 0.30 [20 % diethylether : hexane]; ν_{max}(film)/cm^{-1} 3063, 2974, 2940, 2865, 1641, 1603, 1497, 1454, 1067, 1028, 947, 912; δ_H (600 MHz; $CDCl_3$); 1.65-1.72 (2H, m, overlapping signals C-3 and C-7), 1.79-186 (1H, m, C-2), 1.91-1.97 (2H, m, overlapping signals C-2 and C-3), 2.02 (1H, ddd, *J* 12.2 7.7 and 6.4, C-7), 2.76 (1H, dd, *J* 13.4 and 7.6, C-11 CH_2Ph), 2.82-2.88 (1H, m, C-6), 3.11 (1H, dd, *J* 13.4 and 5.6, C-11 CH_2Ph), 3.77-3.81 (2H, m, overlapping signals C-5 and C-1), 3.84-3.87 (1H, m, C-4), 3.92 (1H, dt, *J* 8.1 and 6.7, C-1), 4.14 (1H, dddd, *J* 8.6 7.6 6.4 and 5.6, CH C-8), 4.98-5.03 (2H, m, $CH{=}C\underline{H_2}$), 5.83 (1H, app dt, *J* 17.0 and 9.8 $C\underline{H}{=}CH_2$); δ_C (100.6 MHz; $CDCl_3$) 26.3 (CH_2, C-2), 28.2 (CH_2, C-3), 38.3 (CH_2, C-7), 42.5 (CH_2, C-11), 47.0 (CH, C-6), 68.8 (CH_2, C-1), 79.0 (CH, C-4), 80.4 (CH, C-8), 84.2 (CH, C-5), 115.7 (CH_2, C-10), 126.3 (CH, *p*-CH, Ar), 128.4 (2 × CH, *o*-CH Ar), 129.4 (2 × CH, *m*-CH Ar), 138.6 (CH, C-9), 139.0 (C, Ar); LRMS (EI^+, *m/z*): 258 (M^+, 3 %), 167 ([M^+–Bn], 6), 123 (71), 117 (68), 104 (24), 91 (Bn, 100), 71 (THF, 34); HRMS (EI^+, *m/z*) 258.1614 $[M]^+$, $C_{17}H_{22}O_2$ requires 258.1614.

***tert*-Butylglyoxal (199)**



tert-Butylglyoxal was prepared from commercially available pinacolone as previously reported.[108] A stirred mixture of methanol (6 mL), water (0.3 mL) and selenium dioxide (5.55 g, 50.0 mmol) was gently heated until the selenium dioxide had dissolved and pinacolone (4.90 g, 6.10 mL, 49.0 mmol) was rapidly added. The colourless reaction mixture became yellow then red and finally black after 5 min. The reaction mixture was heated at reflux temperature with vigorous stirring for 20 h, cooled to room temperature and filtered under gravity. The filtrate was distilled under atmospheric pressure and the distillate boiling between 95-125 °C was collected. Purification by fractional distillation using a Vigreux fractionating column gave the desired product (1.20 g, 10.5 mmol, 21 %) as a bright yellow oil; bp 110-115 °C/760 mmHg, (lit.[108] 114-115 °C/760 mmHg). Owing to rapid decomposition of the compound, the material was used immediately.

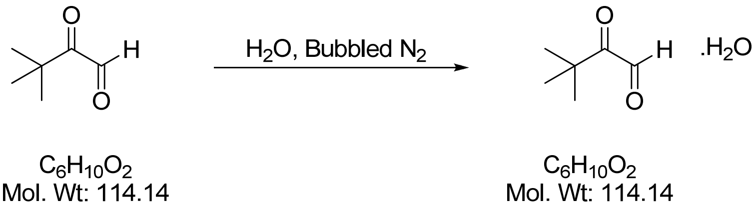
(±)-2,2-Dimethyl-1-(2-((triisopropylsilyl)methyl)tetrahydrofuran-5-yl)propan-1-one (200)



To a stirred solution of freshly distilled *tert*-butyl glyoxal (0.17 g, 1.50 mmol) in anhydrous DCM (2 mL) at 0 °C and under an atmosphere of argon was added, dropwise, a solution of tin tetrachloride (0.17 g, 0.08 mL, 0.66 mmol) in anhydrous DCM (2 mL). The resulting mixture was stirred at 0 °C for 5 min followed by the dropwise addition of a solution of (cyclopropylmethyl)tri*iso*propylsilane (0.13 g, 0.60 mmol) in anhydrous DCM (3 mL). Stirring was continued at 0 °C for 3.5 h and the reaction was monitored by TLC. After this time the reaction was quenched by the addition of H_2O (10 mL), the organic layer was separated and the aqueous layer further extracted with DCM (3 × 10 mL). The combined organic phases were washed with brine (10 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product (0.12 g) as a colourless oil. Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 20 % diethyl ether : hexane] afforded the desired product as only the *trans* diastereoisomer (0.01 g, 0.03 mmol, 5 %) as a colourless oil; R_f 0.67 [20 % diethylether : hexane]; ν_{max}(film)/cm^{-1} 2942 (C-H), 2866 (C-H), 1716 (C=O), 1464, 1059, 883 (Si-C); δ_H (400 MHz; $CDCl_3$); 0.90 (1H, dd, *J* 14.4 and 8.1, SiC$\underline{H}_a$H$_b$), 1.02-1.08 (21H, m, overlapping signals: 6 × CH_3 and 3 × CH), 1.17 (1H, dd, *J* 14.4 and 6.2, SiCH$_a\underline{H}_b$), 1.18 (9H, s, CH_3 ^{t}Bu), 1.49 (1H, m, C$\underline{H}_a$H$_b$ C-3 THF), 1.86-1.95 (1H, m, C$\underline{H}_a$H$_b$ C-4 THF), 2.08-2.21 (2H, m, CH$_a\underline{H}_b$ C-3 and CH$_a\underline{H}_b$ C-4 THF), 4.32 (1H, app tt, *J* 8.1 and 5.7, CH C-2 THF), 4.84 (1H, t, *J* 7.4, CH C-5 THF); δ_C (100.6 MHz; $CDCl_3$) 11.5 (3 × CH, ^{i}Pr), 16.8 ($SiCH_2$), 19.0 (6 × CH_3, ^{i}Pr), 26.4 (CH_3, ^{t}Bu), 30.5 (CH_2, C-4), 35.3 (CH_2, C-3 THF), 40.5 (C, ^{t}Bu), 77.5 (CH, C-5 THF), 78.9 (CH, C-2 THF), 215.9 (C=O); LRMS (EI$^+$, *m/z*): M$^+$

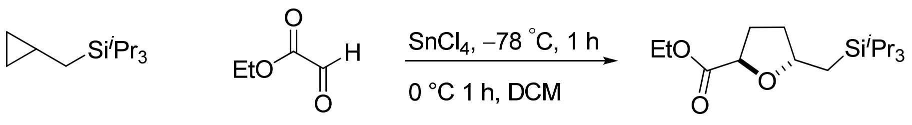
not visible, 283 ([M-^{i}Pr]$^+$, 37 %), 241 (66), 199 (53), 157 (100), 115 (58), 87 (35), 57 (98); HRMS (CI$^+$, *m/z*) 344.2979 [M+NH$_4$]$^+$, $C_{19}H_{42}O_2NSi$ requires 344.2979.

tert-Butylglyoxal dimer hydrate (201)



Owing to rapid decomposition of the compound the material was stored as the hydrate, synthesised as follows: freshly distilled *tert*-butylglyoxal (1.50 g) was added to water (10 mL). Nitrogen was bubbled though the resulting mixture for 2 h and then allowed to stand over night to form pale yellow solid. The reaction mixture was filtered to yield the impure product as a pale yellow solid. Purification by recrystallisation from the minimum amount of hot benzene gave the desired product (0.42 g, 3.68 mmol) as a white crystalline solid; mp 91-93 °C (from C_6H_6) (lit.[108] 91-92 °C); ν_{max}(film)/cm^{-1} 3337 (O-H), 2965 (C-H), 1413, 1368, 1016 (C-O); HRMS (EI$^+$, *m/z*) 264.1802 [M+NH$_4^+$], $C_{12}H_{26}O_5N_1$ requires 264.1805. Crystal structure obtained.

(±)-Ethyl-2-((triisopropylsilyl)methyl)tetrahydrofuran-5-carboxylate (203a)



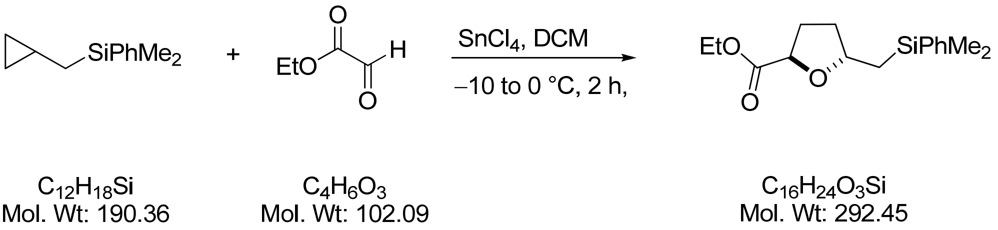
$C_{13}H_{28}Si$
Mol. Wt: 212.45

$C_4H_6O_3$
Mol. Wt: 102.09

$C_{17}H_{34}O_3Si$
Mol. Wt: 314.54

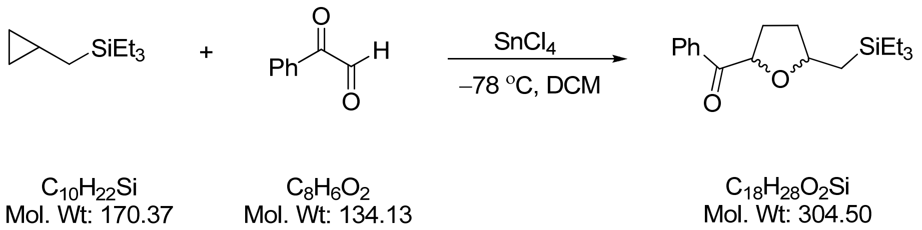
To a stirred solution of freshly distilled ethyl glyoxalate (0.10 g, 0.90 mmol) in anhydrous DCM (2 mL) at −78 °C and under an atmosphere of argon was added, dropwise, a solution of tin tetrachloride (0.17 g, 0.08 mL, 0.66 mmol) in anhydrous DCM (2 mL). The resulting mixture was stirred at −78 °C for 5 min followed by the dropwise addition of a solution of (cyclopropylmethyl)triisopropylsilane (0.13 g, 0.60 mmol) in anhydrous DCM (3 mL). The reaction was stirred at −78 °C and monitored by TLC, after 1 h the reaction was allowed to warm to 0 °C and stirred at 0 °C for 1 h. The reaction was quenched by the addition of H_2O (10 mL), the organic layer was separated and the aqueous layer further extracted with DCM (3 × 10 mL). The combined organic phases were washed with brine (10 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product (0.15 g) as a colourless oil. Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 20 % diethylether : hexane] afforded the desired product as only the *trans* diastereoisomer (0.08 g, 0.25 mmol, 42 %) as a colourless oil; R_f 0.50 [20 % diethylether : hexane]; ν_{max}(film)/cm^{-1} 2940 (C-H), 2865 (C-H), 1752 (C=O), 1735 (C=O), 1264, 1230 (Si-C), 1183 (C-O), 1094 (C-O), 882 (Si-C); δ_H (400 MHz; $CDCl_3$); 0.92 (1H, dd, *J* 14.4 and 8.1, $SiC\underline{H}_aH_b$), 1.00-1.10 (21H, m, overlapping signals: 6 × CH_3 and 3 × CH), 1.18 (1H, dd, *J* 14.4 and 6.1, $SiCH_a\underline{H}_b$), 1.27 (3H, t, *J* 7.1, $OCH_2C\underline{H}_3$), 1.48 (1H, dq, *J* 11.7 and 8.0, $C\underline{H}_aH_b$ C-3 THF), 1.98 (1H, app dtd, *J* 12.6 8.6 and 6.3, $C\underline{H}_aH_b$ C-4 THF), 2.10 (1H, dddd, *J* 11.7 8.0 5.3 and 3.5, $CH_a\underline{H}_b$ C-3 THF), 2.34 (1H, app dtd, *J* 12.5 8.4 and 3.2, $CH_a\underline{H}_b$ C-4 THF), 4.18 (2H, qd, *J* 7.1 and 2.4, $OC\underline{H}_2CH_3$), 4.32 (1H, app tt, *J* 8.3and 5.8, CH C-2 THF), 4.49 (1H, dd, *J* 8.4 and 6.3, CH C-5 THF); δ_C (100.6 MHz; $CDCl_3$) 11.4 (3 × CH, ^{i}Pr), 14.3 ($O CH_2\underline{C}H_3$), 16.7 ($SiCH_2$), 19.0 (6 × CH_3, ^{i}Pr), 30.8 (CH_2, C-4 THF), 34.5 (CH_2, C-3 THF), 60.8 ($O\underline{C}H_2CH_3$), 76.1 (CH, C-5 THF), 78.9 (CH, C-2 THF), 199.5 (C=O); LRMS (EI$^+$, *m/z*): M$^+$ not visible, 271 ([M–^{i}Pr]$^+$, 100 %), 241 (11), 225 (15), 198 (19), 157 (58), 145 (42), 131 (88), 103 (59); HRMS (CI$^+$, *m/z*) 332.2615 [M+NH$_4$]$^+$, $C_{17}H_{38}O_3NSi$ requires 332.2615.

(±)-Ethyl-2-((dimethyl(phenyl)silyl)methyl)tetrahydrofuran-5-carboxylate (203b)



To a stirred solution of freshly distilled ethyl glyoxalate (0.23 g, 2.25 mmol) and (cyclopropylmethyl)dimethylphenylsilane (0.29 g, 1.50 mmol) in anhydrous DCM (15 mL) at −10 °C and under an atmosphere of argon was added dropwise, a solution of tin tetrachloride (0.39 g, 0.18 mL, 1.50 mmol) in anhydrous DCM (6 mL). The resulting mixture was stirred at 0 °C and monitored by TLC. After 3 h the reaction was quenched by the addition of H_2O (10 mL), the organic layer was separated and the aqueous layer further extracted with DCM (3 x 10 mL). The combined organic phases were washed with brine (10 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product (0.38 g) as a colourless oil. Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 10 % diethylether : hexane] afforded the desired product as only the *trans* diastereoisomer (34 mg, 0.11 mmol, 8 %) as a colourless oil; R_f 0.28 [20 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 2957 (C-H), 1749 (C-O), 1732 (C-O), 1427, 1180, 1091, 821 (Si-C); δ_H (600 MHz; $CDCl_3$) 0.33 (3H, s, $SiCH_3$), 0.34 (3H, s, $SiCH_3$), 1.08 (1H, dd, 14.2 and 8.7, $SiC\underline{H}_aH_b$), 1.26 (3H, t, *J* 7.1, $OCH_2C\underline{H}_3$), 1.29-1.38 (1H, m, $C\underline{H}_aH_b$ C-3 THF), 1.39 (1H, dd, *J* 14.2 and 5.7 $SiCH_a\underline{H}_b$), 1.90-1.97 (2H, m, overlapping signals $CH_a\underline{H}_b$ C-3 and $C\underline{H}_aH_b$ C-4 THF), 2.25-2.31 (1H, m, $CH_a\underline{H}_b$ C-4 THF), 4.14-4.26 (3H, m, overlapping signals $OC\underline{H}_2CH_3$ and CH C-2 THF), 4.46 (1H, dd, *J* 8.4 and 6.1, CH C-5 THF), 7.33-7.37 (3H, m, Ph), 7.50-7.55 (2H, m, Ph); δ_C (100.6 MHz; $CDCl_3$) −2.4 ($SiCH_3$), −2.0 ($SiCH_3$), 14.3 ($OCH_2\underline{C}H_3$), 23.4 ($SiCH_2$), 30.7 (CH_2, C-4 THF), 33.8 (CH_2, C-3 THF), 60.8 ($O\underline{C}H_2CH_3$), 76.1 (CH, C-5 THF), 78.8 (CH, C-2 THF), 127.9 (2 × *m*-CH, Ph), 129.1 (*p*-CH, Ph), 133.7 (2 × *o*-CH, Ph), 139.1 (C, Ph) 174.1(C=O); LRMS (EI^+, *m/z*): M^+ not visible, 277 ($[M-Me]^+$, 11 %), 215 (13), 165 (12), 135 (100), 105 (13), 75 (18); HRMS (CI^+, *m/z*) 310.1824 $[M+NH_4]^+$, $C_{16}H_{28}O_3NSi$ requires 310.1833.

(±)-Phenyl(2-((triethylsilyl)methyl)tetrahydrofuran-5-yl)methanone (204)



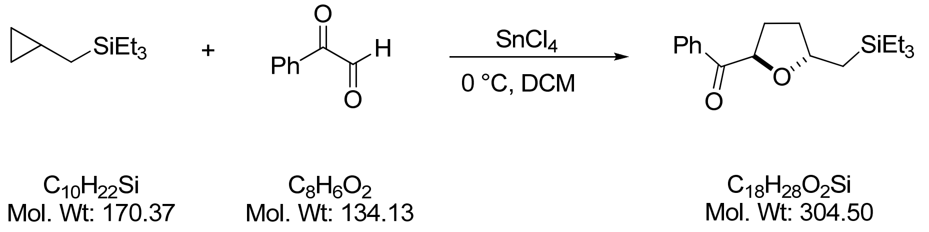
To a stirred solution of freshly distilled phenyl glyoxal (0.12 g, 0.90 mmol) and (cyclopropylmethyl)triethylsilane (0.10 g, 0.60 mmol) in anhydrous DCM (5 mL) at −78 °C and under an atmosphere of argon was added, dropwise, a solution of tin tetrachloride (0.13 g, 0.06 mL, 0.50 mmol) in anhydrous DCM (2 mL). The reaction was stirred at −78 °C and monitored by TLC. After 3 h the reaction was quenched by the addition of wet acetone (5 mL), allowed to warm to 0 °C and poured on to H_2O (10 mL). The organic layer was separated and the aqueous layer further extracted with DCM (3 × 10 mL). The combined organic phases were washed with brine (10 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product (0.16 g) as a yellow oil. Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 10 % diethyl ether : hexane] afforded:

Product 1: the desired product as a mixture of *cis* and *trans* diastereoisomers (combined yield 26.0 mg, 0.09 mmol, 14 %, *dr* (*trans* : *cis*) 0.88 : 1) as a colourless oil; R_f 0.45 [20 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 2909 (C-H), 2951, 2874, 1690 (C=O), 1449, 1228 (Si-C), 1180 (C-O), 1092, 1002; *cis* isomer: δ_H (400 MHz; $CDCl_3$) 0.53 (6H, q, *J* 7.9, 3 × CH_2), 0.91 (9H, t, *J* 7.9, 3 × CH_3), 0.95 (1H, dd, *J* 14.3 and 8.7, SiC$\underline{H}_a$H$_b$), 1.20 (1H, dd, *J* 14.3 and 6.0, SiCH$_a\underline{H}_b$), 1.49 (1H, dq, *J* 12.0 and 9.2, C$\underline{H}_a$H$_b$ C-3 THF), 2.05 (1H, dddd, *J* 12.2 7.7 5.3 and 3.5, CH$_a\underline{H}_b$ C-3 THF), 2.17-2.33 (2H, m, overlapping signals C$\underline{H}_2$ C-4 THF), 4.17 (1H app tt, *J* 8.9 and 5.7,CH C-2 THF), 5.13 (1H, dd, *J* 8.6 and 5.1, CH C-5 THF), 7.43-7.47 (2H, m, 2 × *m*-CH, Ph), 7.50-7.57 (1H, m, *p*-CH, Ph), 8.00-8.03 (2H, m, 2 × *o*-CH, Ph); δ_C (100.6 MHz; $CDCl_3$) 3.9 (3 × CH_2), 7.5 (3 × CH_3), 19.2 ($SiCH_2$), 29.5 (CH_2, C-4 THF), 33.9 (CH_2, C-3 THF), 79.8 (CH, C-2 THF), 79.9 (CH, C-5 THF), 128.6 (2 × *m*-CH, Ph), 129.1 (2 × *o*-CH, Ph), 133.2 (*p*-CH, Ph), 135.6 (C, Ph), 198.5 (C=O); *trans* isomer: δ_H (400 MHz; $CDCl_3$) 0.54 (6H, q, *J* 7.8, 3 × CH_2), 0.88 (1H, dd, *J* 14.1 and 8.4, SiC$\underline{H}_a$H$_b$), 0.93 (9H, t, *J* 7.9, 3 × CH_3), 1.18 (1H, dd, *J* 14.1 and 6.1, SiCH$_a\underline{H}_b$), 1.53 (1H, dq, *J* 11.6 and 8.7, C$\underline{H}_a$H$_b$ C-3 THF), 2.06-2.13 (1H, m, CH$_a\underline{H}_b$ C-3 THF), 2.41-2.22 (1H, m, C$\underline{H}_a$H$_b$ C-4 THF) 2.28-2.36 (1H, m, CH$_a\underline{H}_b$ C-4 THF), 4.19 (1H, app tt, *J* 8.5 and 5.7, CH C-2 THF), 5.29 (1H, dd, *J* 8.2 and 6.4, CH C-5 THF), 7.45 (2H, app t, *J* 7.5, *m*-CH, Ph), 7.53-7.57 (1H, m, *p*-CH, Ph), 7.98-8.00 (2H, m, *o*-CH, Ph);

δ_C (100.6 MHz; $CDCl_3$) 3.9 (3 × CH_2), 7.5 (3 × CH_3), 19.1 ($SiCH_2$), 29.4 (CH_2, C-4 THF), 34.5 (CH_2, C-3 THF), 78.8 (CH, C-2 THF), 79.2 (CH, C-5 THF), 128.6 (2 × *m*-CH, Ph), 129.0 (2 × *o*-CH, Ph), 133.2 (*p*-CH, Ph), 135.4 (C. Ph), 199.5 (C=O); LRMS (EI^+, *m/z*): M^+ not visible, 275 ($[M–Et]^+$, 36 %), 233 (63), 199 (22), 163 (15), 115 (100), 105 (48), 77 (46), 59 (45); HRMS (ESP, *m/z*) 305.1924 $[M+H]^+$, $C_{18}H_{29}O_2Si$ requires 305.1931. Diastereoselectivity calculated by analysis of the ^1H NMR integrals for the C-5 protons of the THF ring, 5.13 *cis* and 5.29 *trans*.

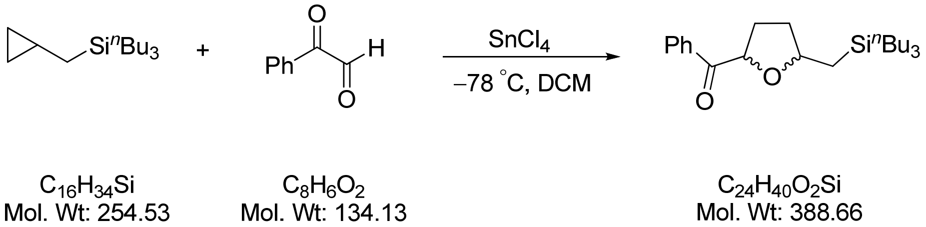
Product 2: the desired product as the single *cis* diastereoisomer (13.0 mg, 0.04 mmol, 7 %) as a colourless oil; R_f 0.45 [20 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 2910 (C-H), 2952, 2874, 1690 (C=O), 1450, 1226 (Si-C), 1175 (C-O), 1090, 1001; δ_H (400 MHz; $CDCl_3$) 0.53 (6H, q, *J* 7.9, 3 × CH_2), 0.91 (9H, t, *J* 7.9, 3 × CH_3), 0.95 (1H, dd, *J* 14.3 and 8.7, $SiC\underline{H}_aH_b$), 1.20 (1H, dd, *J* 14.3 and 6.0, $SiCH_a\underline{H}_b$), 1.49 (1H, dq, *J* 12.0 and 9.2, $C\underline{H}_aH_b$ C-3 THF), 2.05 (1H, dddd, *J* 12.2 7.7 5.3 and 3.5, $CH_a\underline{H}_b$ C-3 THF), 2.17-2.33 (2H, m, overlapping signals $C\underline{H_2}$ C-4 THF), 4.17 (1H, app tt, *J* 8.9 and 5.7, CH C-2 THF), 5.13 (1H, dd, *J* 8.6 and 5.1, CH C-5 THF), 7.43-7.47 (2H, m, 2 × *m*-CH, Ph), 7.50-7.57 (1H, m, *p*-CH, Ph), 8.00-8.03 (2H, m, 2 × *o*-CH, Ph); δ_C (100.6 MHz; $CDCl_3$) 3.9 (3 × CH_2), 7.5 (3 × CH_3), 19.2 ($SiCH_2$), 29.5 (CH_2, C-4 THF), 33.9 (CH_2, C-3 THF), 79.8 (CH, C-2 THF), 79.9 (CH, C-5 THF), 128.6 (2 × *m*-CH, Ph), 129.1 (2 × *o*-CH, Ph), 133.2 (*p*-CH, Ph), 135.6 (C, Ph), 198.5 (C=O); LRMS (EI^+, *m/z*): M^+ not visible, 275 ($[M–Et]^+$, 7 %), 233 (66), 199 (24), 163 (15), 115 (100), 105 (50), 77 (46), 59 (45); HRMS (ESP, *m/z*) 305.1935 $[M+H]^+$, $C_{18}H_{29}O_2Si$ requires 305.1931.

(±)-Phenyl(2-((triethylsilyl)methyl)tetrahydrofuran-5-yl)methanone (204)



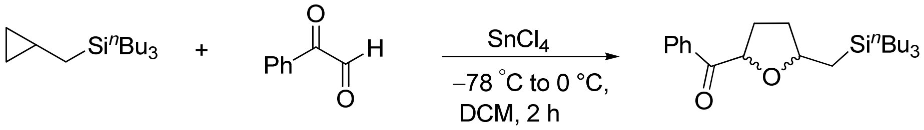
To a stirred solution of freshly distilled phenyl glyoxal (0.12 g, 0.90 mmol) and (cyclopropylmethyl)triethylsilane (0.10 g, 0.60 mmol) in anhydrous DCM (5 mL) at 0 °C and under an atmosphere of argon was added, dropwise, a solution of tin tetrachloride (0.13 g, 0.06 mL, 0.50 mmol) in anhydrous DCM (2 mL). The reaction was stirred at 0 °C and monitored by TLC. After 2 h the reaction was quenched by the addition of water (5 mL), the organic layer was separated and the aqueous layer further extracted with DCM (3 × 10 mL). The combined organic phases were washed with brine (10 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product (0.16 g) as a yellow oil. Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 10 % diethyl ether : hexane] afforded the desired product as an inseparable mixture of *cis* and *trans* diastereoisomers (combined yield 0.10 g, 0.32 mmol, 53 %, *dr* (*trans* : *cis*) 1 : 0.1) as a colourless oil; *trans* isomer: R_f 0.45 [20 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 2952, 2909 (C-H), 2874, 1690 (C=O), 1449, 1229, 1180, 1016, 877; δ_H (400 MHz; $CDCl_3$) 0.54 (6H, q, *J* 7.8, 3 × CH_2), 0.88 (1H, dd, *J* 14.1 and 8.4, SiC$\underline{H}_a$H$_b$), 0.93 (9H, t, *J* 7.9, 3 × CH_3), 1.18 (1H, dd, *J* 14.1 and 6.1, SiCH$_a\underline{H}_b$), 1.53 (1H, dq, *J* 11.6 and 8.7, C$\underline{H}_a$H$_b$ C-3 THF), 2.06-2.13 (1H, m, CH$_a\underline{H}_b$ C-3 THF), 2.41-2.22 (1H, m, C$\underline{H}_a$H$_b$ C-4 THF) 2.28-2.36 (1H, m, CH$_a\underline{H}_b$ C-4 THF), 4.19 (1H, app tt, *J* 8.5 and 5.7, CH C-2 THF), 5.29 (1H, dd, *J* 8.2 and 6.4,CH C-5 THF), 7.45 (2H, app t, *J* 7.5, *m*-CH Ph), 7.53-7.57 (1H, m, *p*-CH Ph), 7.98-8.00 (2H, m, *o*-CH Ph); δ_C (100.6 MHz; $CDCl_3$) 3.9 (3 × CH_2), 7.5 (3 × CH_3), 19.1 ($SiCH_2$), 29.4 (CH_2, C-4 THF), 34.5 (CH_2, C-3 THF), 78.8 (CH, C-2 THF), 79.2 (CH, C-5 THF), 128.6 (2 × *m*-CH, Ph), 129.0 (2 × *o*-CH, Ph), 133.2 (*p*-CH, Ph), 135.4 (C, Ph), 199.5 (C=O); LRMS (EI$^+$, *m/z*): M$^+$ not visible, 275 ([M–Et]$^+$, 11 %), 233 (75), 199 (29), 163 (16), 115 (100), 105 (38), 87 (76), 77 (36), 59 (36); HRMS (ESP, *m/z*) 305.1925 [M+H]$^+$, $C_{18}H_{29}O_2Si$ requires 305.1931.

(±)-Phenyl(2-((tributylsilyl)methyl)tetrahydrofuran-5-yl)methanone (205)



To a stirred solution of freshly distilled phenyl glyoxal (0.12 g, 0.90 mmol) in anhydrous DCM (2 mL) at −78 °C and under an atmosphere of argon was added, dropwise, a solution of tin tetrachloride (0.17 g, 0.08 mL, 0.66 mmol) in anhydrous DCM (2 mL). The resulting mixture was stirred at −78 °C for 5 min followed by the dropwise addition of (cyclopropylmethyl)tri-*n*-butylsilane (0.15 g, 0.60 mmol) in anhydrous DCM (3 mL). The reaction was stirred at −78 °C and monitored by TLC. After 3 h the reaction was quenched by the addition of wet acetone (5 mL), allowed to warm to 0 °C and poured on to H_2O (10 mL). The organic layer was separated and the aqueous layer extracted with DCM (3 × 10 mL). The combined organic phases were washed with brine (10 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product (0.25 g) as a yellow oil. Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 20 % diethyl ether : hexane] afforded the desired product as an inseparable mixture of *cis* and *trans* diastereoisomers (combined yield 0.09 g, 0.26 mmol, 43 %, *dr* (*trans* : *cis*) 1.35 : 1) as a colourless oil; R_f 0.63 [20 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 2920 (C-H), 1691 (C=O), 1449 (C-H), 1228 (Si-C), 1180 (C-O), 1080 (C-O); *trans* diastereoisomer: δ_H (400 MHz; $CDCl_3$) 0.48-0.53 (6H, m, $Si(CH_2)_3$), 0.83-0.97 (10H, m, overlapping signals $SiC\underline{H}_aH_b$ and 3 × CH_3), 1.14-1.34 (13H, m, overlapping signals $SiCH_a\underline{H}_b$ and 6 × CH_2), 1.42-1.56 (1H, m, $C\underline{H}_aH_b$ C-3 THF), 2.01-2.12 (1H, m, $CH_a\underline{H}_b$ C-3 THF), 2.14-2.35 (2H, m, CH_2 C-4 THF), 4.11-4.20 (1H, m, CH C-2 THF), 5.27 (1H, dd, *J* 8.2 and 6.5, CH C-5 THF), 7.42-7.45 (2H, m, 2 × *m*-CH, Ph), 7.51-7.56 (1H, m, *p*-CH, Ph), 7.98-8.02 (1H, m, 2 × *o*-CH, Ph); δ_C (100.6 MHz; $CDCl_3$) 12.7 ($Si(CH_2)_3$), 13.9 (3 × CH_3), 20.1 ($SiCH_2$), 26.2 (3 × CH_2 Bu), 26.9 (3 × CH_2 Bu), 29.2 (CH_2, THF), 34.5 (CH_2, THF), 78.8 (CH, C-2 THF), 79.1 (CH, C-5 THF), 128.6 (2 × *m*-CH, Ph), 128.9 (2 × *o*-CH, Ph), 133.2 (*p*-CH, Ph), 135.4 (C, Ph), 199.3 (CO); *cis* diastereoisomer: δ_H (400 MHz; $CDCl_3$) 0.48-0.53 (6H, m, $Si(CH_2)_3$), 0.83-0.97 (11H, m, overlapping signals $SiCH_2$ and 3 × CH_3), 1.14-1.34 (12H, m, 6 × CH_2), 1.42-1.56 (1H, m,$C\underline{H}_aH_b$ C-3 THF), 2.01-2.12 (1H, m, $CH_a\underline{H}_b$ C-3 THF), 2.14-2.35 (2H, m, CH_2 C-4 THF), 4.11-4.20 (1H, m, CH C-2 THF), 5.12 (1H, dd, *J* 8.6 and 5.1, CH C-5 THF), 7.42-7.45 (2H, m, 2 × *m*-CH, Ph), 7.51-7.56 (1H, m, *p*-CH, Ph), 7.98-8.02 (1H, m, 2 × *o*-CH, Ph); δ_C (100.6 MHz; $CDCl_3$) 12.7 ($Si(CH_2)_3$), 13.9 (3 × CH_3), 20.2 ($SiCH_2$), 26.2 (3 × CH_2 Bu), 26.9 (3 × CH_2 Bu), 29.3 (CH_2, THF), 33.8 (CH_2, THF), 79.7 (CH, C-2 THF), 79.9 (CH, C-5 THF), 128.5 (2 × *m*-CH, Ph), 129.1 (2 × *o*-CH, Ph), 133.1 (*p*-CH, Ph), 135.5 (C, Ph), 198.2 (C=O); LRMS (EI$^+$, *m/z*): M$^+$ not visible, ([M–^{n}Bu]$^+$ 36 %), 289 (100), 199 (9), 171 (68), 143 (26), 105 (32), 77 (20); HRMS (CI$^+$, *m/z)* 389.2870 [M+H]$^+$, $C_{24}H_{41}O_2Si$ requires 389.2870. Diastereoselectivity calculated by analysis of the ^{1}H NMR integrals for the C-5 protons of the THF ring, 5.27 (ppm) and 5.12 (ppm) *trans* and *cis* respectively.

(±)-Phenyl(2-((tributylsilyl)methyl)tetrahydrofuran-5-yl)methanone (205)



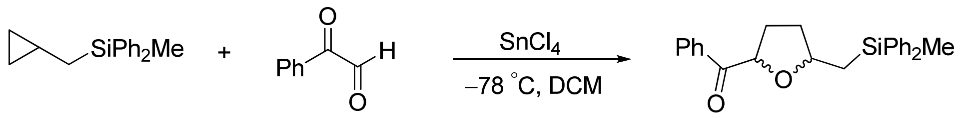
$C_{16}H_{34}Si$
Mol. Wt: 254.53

$C_8H_6O_2$
Mol. Wt: 134.13

$C_{28}H_{32}O_2Si$
Mol. Wt: 428.64

To a stirred solution of freshly distilled phenyl glyoxal (0.12 g, 0.9 mmol) in anhydrous DCM (2 mL) at −78 °C and under an atmosphere of argon was added, dropwise, a solution of tin tetrachloride (0.17 g, 0.08 mL, 0.66 mmol) in anhydrous DCM (2 mL). The resulting mixture was stirred at −78 °C for 5 min followed by the dropwise addition of (cyclopropylmethyl)tri-*n*-butylsilane (0.15 g, 0.60 mmol) in anhydrous DCM (3 mL). The reaction was stirred at −78 °C and monitored by TLC, after 1 h the reaction was allowed to warm to 0 °C and stirred at 0 °C for 1 h. The reaction was quenched by the addition of H_2O (10 mL), the organic layer was separated and the aqueous layer further extracted with DCM (3 × 10 mL). The combined organic phases were washed with brine (10 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product (0.29 g) as a yellow oil. Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 20 % diethyl ether : cyclohexane] afforded an inseparable mixture of diastereoisomers of the desired product (combined yield 0.08 g, 0.19 mmol, 31 %, *dr* (*trans* : *cis*) 11 : 1) as a colourless oil. Data is in agreement with that previously recorded.

(±)-(2-((Methyldiphenylsilyl)methyl)tetrahydrofuran-5-yl)(phenyl)methanone (206)



$C_{17}H_{20}Si$
Mol. Wt: 252.43

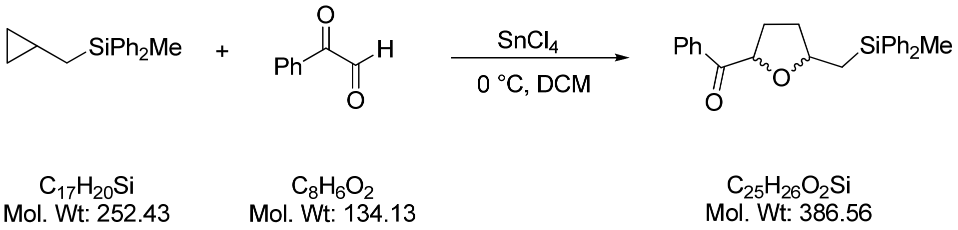
$C_8H_6O_2$
Mol. Wt: 134.13

$C_{25}H_{26}O_2Si$
Mol. Wt: 386.56

To a stirred solution of freshly distilled phenyl glyoxal (0.12 g, 0.90 mmol) and (cyclopropylmethyl)diphenylmethylsilane (0.15 g, 0.60 mmol) in anhydrous DCM (5 mL) at −78 °C and under an atmosphere of argon was added, dropwise, a solution of tin tetrachloride (0.13 g, 0.06 mL, 0.5 mmol) in anhydrous DCM (2 mL). The reaction was stirred at −78 °C and monitored by TLC. After 3 h the reaction was quenched by the addition of wet acetone (5 mL), allowed to warm to 0 °C and poured on to H_2O (10 mL). The organic layer was separated and the aqueous layer further extracted with DCM (3 × 10 mL). The combined organic phases were washed with brine (10 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product (0.34 g) as a yellow oil. Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 10 % diethyl ether : hexane] afforded the desired product as an inseparable mixture of *cis* and *trans* diastereoisomers (combined yield 0.09 g, 0.24 mmol, 40 %, *dr* (*trans* : *cis*) 0.49 : 1) as a colourless oil; R_f 0.27 [20 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 3068 2960, 1688, 1427, 1228, 1110, 873; *cis* diastereoisomer: δ_H (400 MHz; $CDCl_3$) 0.59 (3H, s, SiMe), 1.40-1.51 (1H, m, C$\underline{H}_a$H$_b$ C-3 THF), 1.52 (1H, dd, *J* 14.4 and 8.2, Si$\underline{H}_a$H$_b$), 1.79 (1H, dd, *J* 14.4 and 5.9, SiH$_a\underline{H}_b$), 1.85-1.96 (1H, m, CH$_a\underline{H}_b$ C-3 THF), 2.09-2.28 (2H, m, CH_2 C-4 THF), 4.18 (1H, app tt, *J* 8.7 and 5.7, CH C-2 THF), 5.11 (1H, dd, *J* 8.7 and 5.0, CH C-5 THF), 7.30-7.58 (13H, m, Ar), 8.00 (2H, app d, *J* 8.3, 2 × o-CH Ar); δ_C (100.6 MHz; $CDCl_3$) −3.3 (SiMe), 22.1 ($SiCH_2$), 29.4 (CH_2, C-4 THF), 33.7 (CH_2, C-3 THF), 79.3 (CH, C-2 THF), 79.9 (CH, C-5 THF), 128.0 (4 × *m*-CH, Ar), 128.6 (2 × *m*-CH, Ar), 129.1 (2 × *o*-CH, Ar), 129.3 (2 × *p*-CH, Ar), 133.2 (*p*-CH, Ar), 134.5 (2 × *o*-CH, Ar), 134.6 (2 × *o*-CH, Ar), 135.6 (C, Ar), 137.0 (C, Ar), 199.2 (C=O); *trans* diastereoisomer: δ_H (400 MHz; $CDCl_3$) 0.62 (3H, s, SiMe), 1.40-1.51 (2H, m, overlapping signals SiC$\underline{H}_a$H$_b$ and C$\underline{H}_a$H$_b$, C-3 THF), 1.75 (1H, dd, *J* 14.4 and 6.3, SiH$_a\underline{H}_b$), 1.85-1.96 (1H, m, CH$_a\underline{H}_b$ C-3 THF), 2.09-2.28 (2H, m, CH_2 C-4 THF), 4.25 (1H, app tt, *J* 8.0 and 5.8, CH C-2 THF), 5.23 (1H, dd, *J* 8.2 and 6.6, CH C-5 THF), 7.30-7.58 (13H, m, Ar), 7.94 (2H, app d, *J* 7.4, 2 × *o*-CH Ph) δ_C (100.6 MHz; $CDCl_3$) −3.4 (SiMe), 22.0 ($SiCH_2$), 29.1 (CH_2, C-4 THF), 34.4 (CH_2, C-3 THF), 78.4 (CH, C-2 THF), 79.3 (CH, C-5 THF), 128.0 (4 × *m*-CH, Ar), 128.6 (2 × *m*-CH, Ar), 129.0

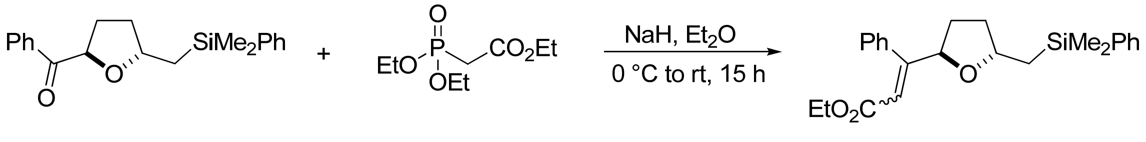
(2 × *o*-CH, Ar), 129.3 (2 × *p*-CH, Ar), 133.2 (*p*-CH, Ar), 134.6 (2 × *o*-CH, Ar), 134.7 (2 × *o*-CH, Ar), 135.4 (C, Ar), 137.1 (C, Ar), 198.3 (C=O); LRMS (EI$^+$, *m/z*): M$^+$ not visible, 309 ([M−Ph]$^+$, 4 %), 281 (11), 197 (100), 137 (19), 105 (21), 77 (13); HRMS (ESP, *m/z*) 404.2031 [M+NH$_4$]$^+$, $C_{25}H_{30}O_2NSi$ requires 404.2040. Diastereoselectivity calculated by analysis of the ^{1}H NMR integrals for the C-5 protons of the THF ring, 5.11 *cis* and 5.23 *trans*.

(±)-(2-((Methyldiphenylsilyl)methyl)tetrahydrofuran-5-yl)(phenyl)methanone (206)



To a stirred solution of freshly distilled phenyl glyoxal (0.12 g, 0.90 mmol) and (cyclopropylmethyl)triethylsilane (0.10 g, 0.60 mmol) in anhydrous DCM (5 mL) at 0 °C and under an atmosphere of argon was added, dropwise, a solution of tin tetrachloride (0.13 g, 0.06 mL, 0.50 mmol) in anhydrous DCM (2 mL). The reaction was stirred at 0 °C and monitored by TLC. After 2 h the reaction was quenched by the addition of water (5 mL), the organic layer was separated and the aqueous layer further extracted with DCM (3 × 10 mL). The combined organic phases were washed with brine (10 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product (0.26 g) as a yellow oil. Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 10 % diethyl ether : hexane] afforded the desired product as an inseparable mixture of *cis* and *trans* diastereoisomers (combined yield 89.7 mg, 0.23 mmol, 38 %, *dr* (*trans* : *cis*) 1 : 0.41) as a colourless oil. Data is in agreement with that previously recorded.

(±)-Ethyl 3-(2-((dimethyl(phenyl)silyl)methyl)tetrahydrofuran-5-yl)-3-phenylacrylate (219a)



$C_{20}H_{24}O_2Si$
Mol Wt: 324.49

$C_8H_{17}O_5P$
Mol. Wt: 224.19

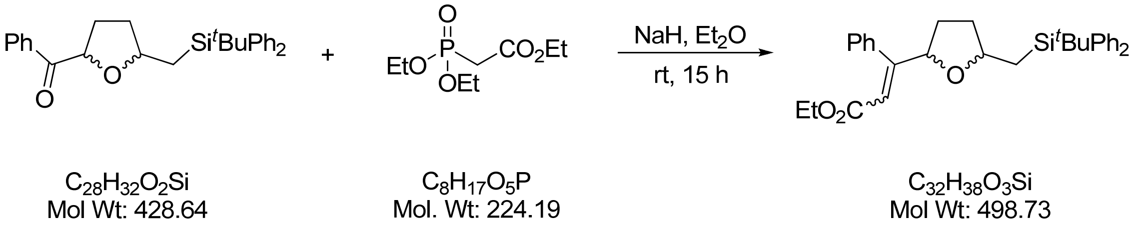
$C_{24}H_{30}O_3Si$
Mol. Wt: 394.58

A 60 % dispersion of sodium hydride in mineral oil (0.02 g, 0.50 mmol) was washed with *n*-hexane (2 × 1 mL), dried under reduced pressure and placed under an atmosphere of argon. Diethyl ether (1 mL) was added and the suspension cooled to 0 °C followed by the dropwise addition of triethyl phosphonoacetate (0.10 g, 0.08 mL, 0.45 mmol). The solution was allowed to warm to room temperature, stirred for a further 15 min followed by the dropwise addition of a solution of (±-5-((dimethyl(phenyl)silyl)methyl)tetrahydrofuran-2-yl)(phenyl)methanone (0.13 g, 0.40 mmol, only *trans* diastereoisomer) in diethyl ether (1.5 mL). The resulting yellow solution was stirred for 15 h at 25 °C and monitored by TLC. After this time, the reaction was quenched with water (10 mL) and the organic layer separated. The aqueous layer was extracted with diethyl ether (3 × 10 mL). The organic fractions were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the impure product as a colourless oil (0.18 g). Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 20 % diethyl ether : hexane] afforded two diastereoisomers of the title compound (combined yield 0.15 g, 0.38 mmol, 96 %) as colourless oils:

Major diastereoisomer: (0.08 g, 0.20 mmol, 51 %); R_f 0.29 [20 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 2957 (C-H), 1724 (C=O), 16.26 (C=C), 1220 (Si-C), 1154 (C-O), 1095 (C-O), 823 (Si-C); δ_H (400 MHz; $CDCl_3$) 0.36 (3H, s, $SiCH_3$), 0.38 (3H, s, $SiCH_3$), 1.08 (3H, t, *J* 7.1, $OCH_2C\underline{H}_3$), 1.12 (1H, dd, *J* 14.2 and 7.8, $SiC\underline{H}_aH_b$), 1.37 (1H, dd, *J* 14.2 and 6.6, $SiCH_a\underline{H}_b$), 1.37-1.46 (1H, m, $C\underline{H}_aH_b$ C-3 THF), 1.59-1.69 (1H, m, $CH_a\underline{H}_b$ C-3 THF), 1.90-2.00 (2H, m, overlapping signals C-3 and C-4 THF), 4.00 (2H, qd, *J* 7.1 and 2.3, $OC\underline{H}_2CH_3$), 4.19 (1H, dtd, *J* 7.8 6.6 and 1.3, CH C-2 THF), 4.72 (1H, ddd, *J* 8.1, 6.9 and 1.4, CH C-5 THF), 6.18 (1H, d, *J* 1.5, $C=C(H)CO_2Et$), 7.13-7.17 (2H, m, Ar), 7.29-7.40 (6H, m, Ar), 7.53-7.58 (2H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) −2.3 ($SiCH_3$), −1.9 ($SiCH_3$), 14.1 ($OCH_2\underline{C}H_3$), 24.0 ($SiCH_2$), 32.0 (CH_2, C-4 THF), 34.9 (CH_2, C-3 THF), 59.9 ($O\underline{C}H_2CH_3$), 78.3 (CH, C-2 THF), 81.3 (CH, C-5 THF), 115.0 ($C=\underline{C}(H)CO_2Me$), 127.6 (2 × *o*-CH, Ar), 127.8 (*p*-CH, Ar), 127.9 (2 × *m*-CH, Ar), 128.0 (2 × *m*-CH, Ar), 129.1 (*p*-CH, Ar), 133.7 (2 × *o*-CH, Ar), 137.9 (C, Ar), 139.1 (C, Ar), 159.8 ($\underline{C}=C(H)CO_2Me$), 166.5 ($C=C(H)\underline{C}O_2Me$); LRMS (EI^+, *m/z*): 394 (M^+, 6 %), 349 ([M^+–OEt], 4), 307 (6), 275 (5), 175 (11), 135 (100) 77 (5); HRMS (ESP, *m/z*) 412.2302 $[M+NH_4]^+$, $C_{24}H_{34}O_3NSi$ requires 412.2302.

Minor diastereoisomer: (0.07 g, 0.18 mmol, 45 %); R_f 0.49 [20 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 2957 (C-H), 1711 (C=O), 1626 (C=C), 1267 (Si-C), 1169 (C-O), 1027 (C-O), 823 (Si-C); δ_H (400 MHz; $CDCl_3$) 0.24 (3H, s, $SiCH_3$), 0.26 (3H, s, $SiCH_3$), 1.05 (1H, dd, *J* 14.3 and 7.7, $SiC\underline{H}_aH_b$), 1.26 (1H, dd, *J* 14.3 and 6.5, $SiCH_a\underline{H}_b$), 1.30 (3H, t, *J* 7.1, $OCH_2C\underline{H}_3$), 1.44 (1H, dddd, *J* 11.6 10.9 8.9 and7.6, $C\underline{H}_aH_b$ C-3 THF), 1.70 (1H, dddd, *J* 12.3 10.9 9.1 and 7.5, $C\underline{H}_aH_b$ C-4 THF), 1.84 (1H, dddd, 11.6 7.5 5.3 and 2.0, $CH_a\underline{H}_b$ C-3 THF), 2.38 (1H, dtd, *J* 12.3 7.2 and 2.0, $CH_a\underline{H}_b$ C-4 THF), 3.80 (1H, dddd, *J* 8.9 7.7 6.5 and 5.4, CH C-2 THF), 4.18 (2H, q, *J* 7.1, $OC\underline{H}_2CH_3$), 5.86 (1H, dd, *J* 9.1 and 7.0, CH C-5 THF), 7.27-7.38 (8H, m, Ar), 7.45-7.47 (2H, m, *o*-CH SiPh); δ_C (100.6 MHz; $CDCl_3$) −2.4 ($SiCH_3$), −1.9 ($SiCH_3$), 14.4 ($OCH_2\underline{C}H_3$), 23.9 ($SiCH_2$), 33.0 (CH_2, C-4 THF), 35.3(CH_2, C-3 THF), 60.3 ($O\underline{C}H_2CH_3$), 76.3 (CH, C-5 THF), 78.1 (CH, C-2 THF), 119.4 ($C{=}\underline{C}(H)CO_2Me$), 127.8 (2 × *m*-CH, Ar), 127.8 (2 × *m*-CH, Ar), 128.1 (*p*-CH, Ar), 128.8 (2 × *o*-CH, Ar), 129.0 (*p*-CH, Ar), 133.7 (2 × *o*-CH, Ar), 139.3 (C Ar), 139.3 (C Ar), 161.9 ($\underline{C}{=}C(H)CO_2Me$), 166.1 ($C{=}C(H)\underline{C}O_2Me$); LRMS ($EI^+$, *m/z*): 394 ($M^+$, 6 %), 349 ($[M^+{-}OEt]$, 4), 307 (6), 275 (5), 175 (11), 135 (100) 77 (5); HRMS (ESP, *m/z*) 395.2036 $[M+H]^+$, $C_{24}H_{31}O_3Si$ requires 395.2037.

Ethyl 3-(2-((tert-butyldiphenylsilyl)methyl)tetrahydrofuran-3-yl)-3-phenylacrylate (219b)

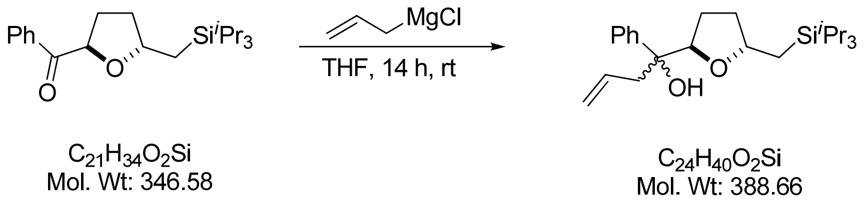


A 60 % dispersion of sodium hydride in mineral oil (0.08 g, 2.00 mmol) was washed with petroleum ether (3 × 2 mL), dried under reduced pressure and placed under an atmosphere of argon. Diethyl ether (3 mL) was added and to the resulting suspension was added dropwise over 1 min a solution of triethyl phosphonoacetate (0.38 g, 0.34 mL, 1.70 mmol) in diethyl ether (3 mL) at −5 °C. The solution was allowed to warm to room temperature, stirred for a further 15 min followed by the dropwise addition of a solution of (5-((tert-butyldiphenylsilyl)methyl)tetrahydrofuran-2-yl)(phenyl)methanone (0.73 g, 1.70 mmol, 1 : 2.1 mixture of *trans*/*cis* diastereoisomers) in diethyl ether (3 mL). The resulting yellow solution was stirred for 15 h at 25 °C and monitored by TLC. The reaction was quenched with water (10 mL) and the organic layer separated. The aqueous layer further extracted with diethyl ether (3 × 10 mL). The etherate fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product as a cloudy colourless oil (0.92 g). Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 20 % diethyl ether : hexane] afforded two products both as inseparable mixtures of diastereoisomers of the desired compound (combined yield 0.74 g, 1.38 mmol, 87 %, product ratio 1.6 : 1) as a colourless oils;

Product 1: (0.45 g, 0.90 mmol, 53 %, *dr* 3 : 1), Colourless oil; R_f 0.38 [20 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 2931, 2856, 1712 (C=O), 1625, 1427, 1268, 1172 (C-O), 1105, 1027, 877, 820; Major diastereoisomer: δ_H (400 MHz; $CDCl_3$); 0.93-1.09 (10H, m, overlapping signals 3 × CH_3 and $C\underline{H}_aH_b$ C-3 THF), 1.17-1.60 (1H, m, overlapping signals $CH_a\underline{H}_b$ C-3 THF),1.26 (1H, dd, *J* 14.5 and 9.9, $SiC\underline{H}_aH_b$), 1.31 (3H, t, *J* 7.1 $OCH_2C\underline{H}_3$), 1.70 (1H, m, $C\underline{H}_aH_b$ C-4 THF), 1.83 (1H, dd, *J* 14.4 and 4.1, $SiCH_a\underline{H}_b$), 2.17 (1H, app dq, *J* 12.7 and 8.5, $CH_a\underline{H}_b$ C-4 THF), 3.96-4.03 (1H, m, CH C-2 THF), 4.21 (2H, q, *J* 7.1, $OC\underline{H}_2CH_3$), 5.66 (1H, app t, *J* 7.7, CH, C-5 THF), 5.90 (1H, d, *J* 0.8, C=CH), 7.58-7.67 (4H, m, Ar), 7.31-7.49 (11H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) 14.3 ($OCH_2\underline{C}H_3$), 17.6 ($SiCH_2$), 18.3 (3 × C, ^{t}Bu), 27.8 (3 × CH_3, ^{t}Bu), 32.3 (CH_2, C-4 THF), 33.5 (CH_2, C-3 THF), 60.2 ($O\underline{C}H_2CH_3$), 75.6 (CH, C-5 THF), 78.4 (CH, C-2 THF), 119.6 ($\underline{C}H$=C), 127.5 (CH, Ar), 127.6 (CH, Ar), 127.7 (CH, Ar), 128.2 (CH, Ar), 128.8 (CH, Ar), 129.2 (CH, Ar), 129.2 (CH, Ar), 134.0 (C, Ar), 134.8 (C, Ar), 136.1 (CH, Ar), 136.2 (CH, Ar), 139.2 (C, Ar), 160.4 ($\underline{C}$=CH), 165.9 (C=O); Minor diastereoisomer: δ_H (400 MHz; $CDCl_3$) 1.04 (9H, s, 3 × CH_3), 1.17-1.60 (4H, m, overlapping signals CH_2 C-3 THF and $C\underline{H}_aH_b$ C-4 THF and $SiC\underline{H}_aH_b$), 1.32 (3H, t, *J* 7.1, $OCH_2C\underline{H}_3$), 1.87 (1H, dd, *J* 14.4 and 4.1, $SiCH_a\underline{H}_b$), 2.30 (1H, app dtd, *J* 12.5 7.2 and 1.9, $CH_a\underline{H}_b$ C-4 THF), 3.81-3.88 (1H, m, CH C-2 THF), 4.20 (2H, q, *J* 7.1, $OC\underline{H}_2CH_3$), 5.81 (1H, d, *J* 1.0, C=CH), 5.91 (1H, app t, *J* 7.7, CH C-5 THF), 7.31-7.49 (11H, m, Ar), 7.58-7.67 (4H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) 14.3 ($OCH_2\underline{C}H_3$), 18.1 ($SiCH_2$), 18.3 (3 × C, ^{t}Bu), 27.8 (3 × CH_3, ^{t}Bu), 33.1 (CH_2, C-4 THF), 34.6 (CH_2, C-3 THF), 60.2 ($O\underline{C}H_2CH_3$), 75.8 (CH, C-5 THF), 78.4 (CH, C-2 THF), 119.3 ($\underline{C}H$=C), 127.6 (CH, Ar), 127.7 (CH, Ar), 127.7 (CH, Ar), 128.0 (CH, Ar), 128.7 (CH, Ar), 129.1 (CH, Ar), 129.2 (CH, Ar), 134.0 (C, Ar), 134.8 (C, Ar), 136.1 (CH, Ar), 136.2 (CH, Ar), 139.1 (C, Ar), 161.9 (C=CH), 165.9 (C=O); LRMS (EI$^+$, *m/z*): 498 ([M]$^+$, 3 %), 441(100), 199 (42), 181 (18), 135 (39), 105 (12); HRMS (ESP$^+$, *m/z*) 499.2656 [M+H]$^+$, $C_{32}H_{39}O_3Si$ requires 499.2663.

Product 2 : (0.29 g, 0.58 mmol, 34 %, *dr* 1.7 : 1), Colourless oil; R_f 0.29 [20 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 2931, 2858, 1722 (C=O), 1648, 1427, 1223, 1155 (C-O), 1103, 1050, 819; Major diastereoisomer: δ_H (400 MHz; $CDCl_3$) 1.02-1.18 (13H, m, overlapping signals 3 × CH_3, $OCH_2C\underline{H}_3$ and $C\underline{H}_aH_b$ C-3 THF), 1.17-1.40 (1H, m, $CH_a\underline{H}_b$ C-3 THF), 1.47-1.55 (1H, m, $SiC\underline{H}_aH_b$), 1.57-1.78 (2H, m, $C\underline{H}_aH_b$ C-4 THF), 2.00 (1H, dd, *J* 14.4 and 4.4, $SiCH_a\underline{H}_b$), 3.97-4.10 (3H, m, overlapping signals $OC\underline{H}_2CH_3$ and CH C-2 THF), 4.49 (1H, dd, *J* 6.0 and 1.5, CH C-5 THF), 6.27 (1H, d, *J* 1.5, C=CH),7.10-7.17 (2H, m, Ar), 7.30-7.46 (9H, m, Ar), 7.66-7.74 (4H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) 14.0 ($OCH_2\underline{C}H_3$), 18.0 ($SiCH_2$), 18.5 (3 × C, ^{t}Bu), 27.9 (3 × CH_3, ^{t}Bu), 31.5 (CH_2, C-4 THF), 32.7 (CH_2, C-3 THF), 59.8 ($O\underline{C}H_2CH_3$), 78.6 (CH, C-2 THF), 81.0 (CH, C-5 THF), 116.0 (C=$\underline{C}$H), 127.6 (CH, Ar), 127.7 (CH, Ar), 127.7 (CH, Ar), 128.7 (CH, Ar), 127.8 (CH, Ar), 129.3 (CH, Ar), 129.3 (CH, Ar), 134.0 (C, Ar), 134.6 (C, Ar), 136.1 (CH, Ar), 136.2 (CH, Ar), 138.0 (C, Ar), 159.3 (C=CH), 166.4 (C=O); Minor diastereoisomer: 1.02-1.18 (12H, m, overlapping signals 3 × CH_3 and $OCH_2C\underline{H}_3$), 1.17-1.40 (1H, m, $C\underline{H}_aH_b$ C-3 THF), 1.47-1.55 (3H, m, overlapping signals $C\underline{H}_aH_b$ C-4 THF, $CH_a\underline{H}_b$ C-3 THF and $SiC\underline{H}_aH_b$), 1.83-1.89 (1H, m, $CH_a\underline{H}_b$ C-4 THF), 1.93 (1H, dd, *J* 14.5 and 4.7, $SiCH_a\underline{H}_b$), 3.97-4.10 (2H, m, $OC\underline{H}_2CH_3$ overlapping signals with other diastereomer), 4.22 (1H, app tt, *J* 9.1 and 4.6, CH C-2 THF), 4.69 (1H, app tt, *J* 7.8 and 1.4, CH C-5 THF), 6.11 (1H, d, *J* 1.5, C=CH), 7.10-7.17 (2H, m, Ar), 7.30-7.46 (9H, m, Ar), 7.66-7.74 (4H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) 14.0 ($OCH_2\underline{C}H_3$), 18.2 ($SiCH_2$), 18.5 (3 × C, ^{t}Bu), 27.9 (6 × CH_3, ^{t}Bu), 32.5 (CH_2, C-4 THF), 34.4 (CH_2, C-3 THF), 59.8 ($O\underline{C}H_2CH_3$), 78.2 (CH, C-2 THF), 81.1 (CH, C-5 THF), 114.9 (C=CH), 127.5 (CH, Ar), 127.6 (CH, Ar), 127.7 (CH, Ar), 127.7 (CH, Ar), 127.9 (CH, Ar), 129.1 (CH, Ar), 129.2 (CH, Ar), 134.0 (C, Ar), 134.8 (C, Ar), 136.1 (CH, Ar), 136.2 (CH, Ar), 137.8 (C, Ar), 159.6 ($\underline{C}$=CH), 166.3 (C=O); LRMS (EI$^+$, *m/z*): 498 ([M]$^+$, 3 %), 441(100), 199 (42), 181 (18), 135 (39), 105 (12); HRMS (ESP$^+$, *m/z*) 516.2918 [M+NH]$^+$, $C_{32}H_{42}O_3NSi$ requires 516.2928.

(±)-1-Phenyl-1-(2-((triisopropylsilyl)methyl)tetrahydrofuran-5-yl)but-3-en-1-ol (221)

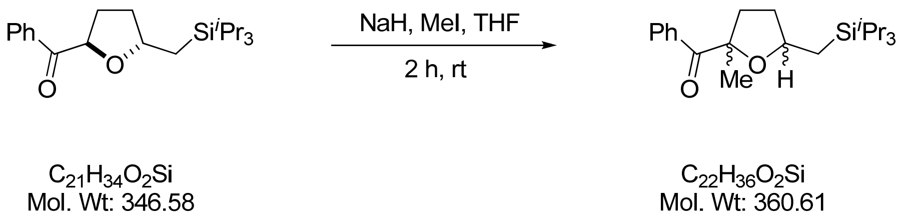


To a stirred solution of phenyl(5-((triisopropylsilyl)methyl)tetrahydrofuran-2-yl)methanone (0.18 g, 0.52 mmol) in THF (3.5 mL) at 0 °C was added a solution of allylmagnesium chloride (2 M solution in THF, 0.32 mL, 0.64 mmol). The mixture was stirred at 0 °C for 1 h then warmed to room temperature and stirred for a further 14 h. The mixture was cooled to 0 °C, quenched with 10 % *w*/*v* aqueous ammonium chloride solution (10 mL), warmed to room temperature and partioned between H_2O and diethyl ether. The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product (0.22 g) as a yellow oil. Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 20 % diethylether : hexane] afforded two diastereoisomers of the title compound (combined yield 0.17 g, 0.44 mmol, 85 %) as colourless oils:

Major diastereoisomer: (0.12 g, 0.31 mmol, 60 %); R_f 0.54 [20 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 3556 (O-H), 2941, 2864, 1640 (C=C), 1463, 1446, 1183, 1066, 881; δ_H (400 MHz; $CDCl_3$) 0.85 (1H, dd, *J* 14.4 and 6.3, SiC$\underline{H}_a$H$_b$), 0.94-1.02 (22H, m, overlapping signals $^i\underline{Pr}_3$SiCH$_a\underline{H}_b$), 1.41-1.51 (1H, m, C$\underline{H}_a$H$_b$ C-3 THF), 1.78-1.88 (1H, m, C$\underline{H}_a$H$_b$ C-4 THF), 1.90-1.99 (2H, m, overlapping signals CH$_a\underline{H}_b$ C-3 and CH$_a\underline{H}_b$ C-4 THF), 2.46 (1H, s, OH), 2.54 (1H, dd, *J* 13.9 and 8.0, C$\underline{H}_a$H$_b$CH=CH$_2$), 2.81 (1H, dd, *J* 13.9 and 6.5 CH$_a\underline{H}_b$CH=CH$_2$), 3.96-4.03 (1H, m, CH C-2 THF), 4.24 (1H, dd, *J* 8.9 and 6.0, CH C-5 THF), 5.03 (1H, dd, *J* 10.2 and 1.0, CH=CH$_{trans}\underline{H}_{cis}$), 5.08 (1H, br d, *J* 17.2, CH=C$\underline{H}_{trans}$H$_{cis}$), 5.55 (1H, dddd, *J* 17.2 10.1 7.8 and 6.6, C$\underline{H}$=CH$_{trans}$H$_{cis}$), 7.23 (1H, br t, *J* 7.0, *p*-CH Ph), 7.32 (2H, br t, *J* 7.5, 2 × *m*-CH Ph), 7.48 (2H, br d, *J* 8.0, 2 × *o*-CH Ph); δ_C (100.6 MHz; $CDCl_3$) 11.4 (3 × CH Si^{i}Pr$_3$), 17.5 (SiCH$_2$), 18.9 (3 × CH$_3$ Si^{i}Pr$_3$), 18.9 (3 × CH$_3$ Si^{i}Pr$_3$), 27.6 (CH$_2$, C-4 THF), 36.3 (CH$_2$, C-3 THF), 43.3 ($\underline{C}$H$_2$CH=CH$_2$), 76.9 (COH), 78.3 (CH, C-2 THF), 84.4 (CH, C-5 THF), 118.9 (CH=C$\underline{H}_2$), 126.3 (2 × *o*-CH, Ph), 126.7 (*p*-CH, Ph), 127.8 (2 × *m*-CH, Ph), 133.5 (C$\underline{H}$=CH$_2$), 143.9 (C, Ph); LRMS (EI$^+$, *m/z*): M$^+$ not visible, 345 ([M–^{i}Pr]$^+$, 27 %), 303 (25), 261 (13), 241 (31), 157 (100), 131 (80), 115 (58), 105 (63), 103 (70), 87 (27), 75 (43); HRMS (ESP, *m/z*) 406.3131 [M+NH$_4$]$^+$, $C_{24}H_{44}O_2NSi$ requires 406.3136.

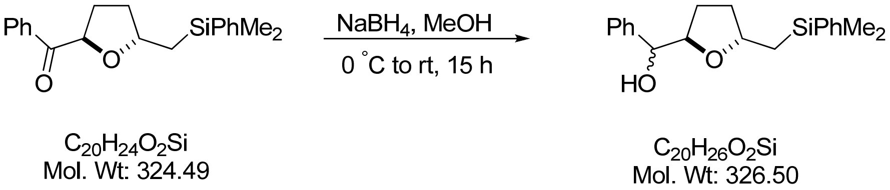
Minor diastereoisomer: (0.05 g, 0.13 mmol, 25 %); R_f 0.68 [20 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 3560 (O-H), 2941, 2864, 1640 (C=C), 1463, 1447, 1179, 1066, 881; δ_H (400 MHz; $CDCl_3$) 0.93 (1H, dd, *J* 14.4 and 6.3, SiC$\underline{H}_a$H$_b$), 1.05-1.13 (22H, m, overlapping signals $^i\underline{Pr}_3$SiCH$_a\underline{H}_b$), 1.35-1.48 (2H, m, C-3/4 THF), 1.63-1.73 (2H, m, C-3/4 THF), 1.93-2.03 (1H, m, C-3/4 THF), 2.41 (1H, s, OH), 2.69 (1H, dd, *J* 14.3 and 6.6, C$\underline{H}_a$H$_b$CH=CH$_2$), 2.81 (1H, dd, *J* 14.3 and 7.8 CH$_a\underline{H}_b$CH=CH$_2$), 4.21-4.28 (2H, m, overlapping signals CH C-2 THF and CH C-5 THF), 4.95-5.04 (2H, m, overlapping signals CH=C$\underline{H}_{trans}\underline{H}_{cis}$), 5.58 (1H, dddd, *J* 17.0 10.2 7.8 and 6.6, C$\underline{H}$=CH$_{trans}$H$_{cis}$), 7.22 (1H, br t, *J* 7.2, *p*-CH Ph), 7.32 (2H, br dd, *J* 8.1 and 7.2, 2 × *m*-CH Ph), 7.38 (2H, br d, *J* 8.1, 2 × *o*-CH Ph); δ_C (100.6 MHz; $CDCl_3$) 11.5 (3 × CH Si^{i}Pr$_3$), 17.6 (SiCH$_2$), 19.0 (6 × CH$_3$ Si^{i}Pr$_3$), 27.7 (CH$_2$, THF), 36.4 (CH$_2$, THF), 45.8 ($\underline{C}$H$_2$CH=CH$_2$), 76.7 (COH), 79.8 (CH, C-2 THF), 84.4 (CH, C-5 THF), 118.1 (CH=C$\underline{H}_2$), 125.3 (2 × *o*-CH, Ph), 126.6 (*p*-CH, Ph), 128.1 (2 × *m*-CH, Ph), 134.1 (C$\underline{H}$=CH$_2$), 142.8 (C, Ph); LRMS (EI$^+$, *m/z*): M$^+$ not visible, 345 ([M–^{i}Pr]$^+$, 20 %), 303 (28), 261 (35), 241 (26), 157 (100), 131 (89), 115 (78), 105 (85), 103 (91), 75 (68); HRMS (ESP, *m/z*) 406.3130 [M+NH$_4$]$^+$, $C_{24}H_{44}O_2NSi$ requires 406.3136.

(±)-(2-Methyl-5-((triisopropylsilyl)methyl)tetrahydrofuran-2-yl)(phenyl)methanone (222)



A 60 % dispersion of sodium hydride in mineral oil (0.03 g, 0.83 mmol) was washed with *n*-hexane (2 x 2 mL), dried under reduced pressure and placed under an atmosphere of argon. The residue was suspened in THF (1.5 mL) followed by the dropwise addition of a solution of phenyl(5-((triisopropylsilyl)methyl)tetrahydrofuran-2-yl)methanone (0.19 g, 0.55 mmol) in THF (1 mL). After effervescense had ceased and the reaction had become yellow, diiodomethane (0.12 g, 0.05 mL, 0.83 mmol) was added and the reaction stirred for 2 h at room temperature and monitored by TLC. The reaction was quenched with 0.1 M HCl (10 mL), neutralised with saturated aqueous sodium hydrogen carbonate solution (10 mL) and the organic layer separated. The aqueous layer was extracted with DCM (3 x 10 mL). The organic fractions were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the impure product as a pale yellow oil (0.16 g). Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 10 % diethylether : hexane] afforded a inseparable diastereoisomeric mixture of compound (combined yield 0.15 g, 0.42 mmol, 76 %, *dr* 1.5 : 1) as a colourless oil; R_f 0.53 [10 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 2941, 2864, 1681, 1462, 1091, 882; Major Diastereoisomer: δ_H (600 MHz; $CDCl_3$) 0.97 (1H, dd, *J* 14.6 and 7.2, $\mathrm{SiC\underline{H}_aH_b}$), 1.92-1.12 (22H, m, overlapping signals ${}^{i}\underline{\mathrm{Pr}}_3\mathrm{SiCH_a\underline{H}_b}$), 1.43 (1H, ddt, *J* 12.1 10.2 and 8.3, $\mathrm{C\underline{H}_aH_b}$ C-4 THF), 1.55 (3H, s, Me) 1.79 (1H, ddd, *J* 12.8 10.2 and 7.5, $\mathrm{C\underline{H}_aH_b}$ C-3 THF), 2.06 (1H, dddd, *J* 12.1 7.6 5.4 and 3.1, $\mathrm{CH_a\underline{H}_b}$ C-4 THF), 2.82 (1H, ddd, *J* 12.8 8.1 and 3.1, $\mathrm{CH_a\underline{H}_b}$ C-3 THF), 4.36 (1H, dddd, *J* 8.9 7.2 6.8 and 5.4, CH C-5 THF), 7.37-7.40 (2H, m, *m*-CH Ph), 7.47-7.51 (1H, m, *p*-CH Ph), 8.19 (2H, dd, *J* 8.4 and 1.3, *o*-CH Ph); δ_C (100.6 MHz; $CDCl_3$) 11.3 (3 × CH $\mathrm{Si}^{i}\mathrm{Pr}_3$), 17.4 ($SiCH_2$), 18.9 (6 × CH_3 $\mathrm{Si}^{i}\mathrm{Pr}_3$), 26.4 ($CH_3$), 35.2 ($CH_2$, C-4 THF), 37.1 ($CH_2$, C-3 THF), 78.8 (CH, C-5 THF), 88.9 (CH, C-2 THF), 127.9 (2 × *m*-CH, Ph), 130.6 (2 × *o*-CH, Ph), 132.4 (*p*-CH, Ph), 135.4 (C, Ph), 203.0 (C=O); Minor Diastereoisomer: δ_H (600 MHz; $CDCl_3$) 1.92-1.12 (22H, m, overlapping signals ${}^{i}\underline{\mathrm{Pr}}_3\mathrm{SiCH_a\underline{H}_b}$), 1.14 (1H, dd, *J* 14.5 and 7.0, $\mathrm{SiCH_a\underline{H}_b}$) 1.59-1.60 (1H, m, C-4 THF), 1.61 (3H, s, Me) 1.83 (1H, ddd, *J* 12.7 9.1 and 5.0, $\mathrm{C\underline{H}_aH_b}$ C-3 THF), 1.98-2.03 (1H, m, $\mathrm{C\underline{H}_aH_b}$ C-4 THF), 2.67 (1H, dt, *J* 12.7 and 8.1, $\mathrm{CH_a\underline{H}_b}$ C-3 THF), 3.94 (1H, m, C-5 THF), 7.37-7.40 (2H, m, *m*-CH, Ph), 7.47-7.51 (1H, m, *p*-CH, Ph), 8.17 (2H, dd, *J* 8.4 and 1.2, *o*-CH Ph); δ_C (100.6 MHz; $CDCl_3$) 11.4 (3 × CH $\mathrm{Si}^{i}\mathrm{Pr}_3$), 17.8 ($SiCH_2$), 18.9 (6 × CH_3 $\mathrm{Si}^{i}\mathrm{Pr}_3$), 27.0 ($CH_3$), 34.7 ($CH_2$, C-4 THF), 36.2 ($CH_2$, C-3 THF), 78.4 (CH, C-5 THF), 88.9 (CH, C-2 THF), 128.0 (2 × *m*-CH, Ph), 130.1 (2 × *o*-CH, Ph), 132.5 (*p*-CH, Ph), 135.2 (C, Ph), 204.9 (C=O); LRMS (EI^+, *m/z*): M^+ not visible, 317 ($[M-{}^{i}Pr]^+$, 70 %), 255 (100), 157 (59), 115 (65), 105 (67), 91 (27), 77 (32); HRMS (ESP, *m/z*) 361.2554 $[M+NH_4]^+$, $C_{22}H_{37}O_2Si$ requires 361.2557. Diastereoselectivity calculated by analysis of the ^1H NMR integrals for the C-5 protons of the THF ring, 4.36 (major diastereoisomer) and 3.94 ppm (minor diastereoisomer).

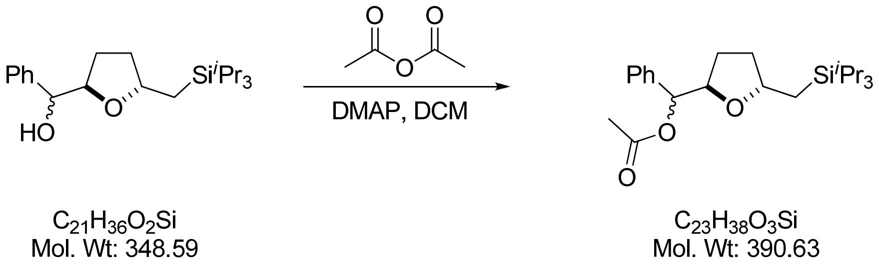
(±)-(2-((Dimethyl(phenyl)silyl)methyl)tetrahydrofuran-5-yl)(phenyl)methanol (225)



The following procedure was carried out on a range of scales from 0.2 mmol to 2 mmol: To a stirred solution of 2-((dimethyl(phenyl)silyl)methyl)tetrahydrofuran-5-yl)(phenyl)methanone (0.13 g, 0.40 mmol) in HPLC grade methanol (3.0 mL) at 0 °C was added in one portion $NaBH_4$ (0.02 g, 0.52 mmol). The mixture was stirred at 0 °C until effervescense had ceased then warmed to room temperature and stirred for a further 2 h. The reaction was quenched by the addition of acetic acid (10 drops), concentrated to approximately one quarter of the volume under reduced pressure and partitioned between dichloromethane (10 mL) and water (10 mL). The organic phase was separated and the aqueous phase extracted with dichloromenthane (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product (0.11 g) as a cloudy colourless oil. Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 30 % diethylether : hexane] afforded title compound as an inseparable mixture of the two diastereoisomers (combined yield 0.11 g, 0.34 mmol, 85 %, *dr* 2.5 : 1) as colourless oils; R_f 0.36 [30 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 3440 (O-H), 2955, 2864, 1452, 1248, 1194, 1026, 833; Major Diastereoisomer: δ_H (400 MHz; $CDCl_3$) 0.38 (3H, s, $SiCH_3$), 0.39 (3H, s, $SiCH_3$), 1.13 (1H, dd, *J* 14.2 and 7.6, $SiC\underline{H}_aH_b$), 1.12 (1H, dd, *J* 14.2 and 6.6, $SiCH_a\underline{H}_b$), 1.37-1.66 (2H, m, $C\underline{H}_aH_b$ C-3 and $C\underline{H}_aH_b$ C-4 THF), 1.73 (1H, dddd, *J* 12.5, 8.2, 7.3 and 2.9, $CH_a\underline{H}_b$ C-4 THF), 1.81-2.02 (1H, m, $CH_a\underline{H}_b$ C-3 THF), 3.03 (1H, d, *J* 2.2, OH), 4.06 (1H, q, *J* 7.4, CH C-5 THF), 4.12-4.20 (1H, m, CH C-2 THF), 4.39 (1H, dd, *J* 7,7 and 2.2, $\underline{H}$COH), 7.25-7.42 (8H, m, Ar), 7.54-7.59 (2H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) −2.2 ($SiCH_3$), −2.0 ($SiCH_3$), 23.7 ($SiCH_2$), 28.6 (CH_2, C-4 THF), 35.2 (CH_2, C-3 THF), 77.3 (COH), 77.5 (CH, C-2 THF), 82.7 (CH, C-5 THF), 127.2 (CH, Ar), 127.9 (CH, Ar), 127.9 (CH, Ar), 128.4 (CH, Ar), 129.1 (CH, Ar), 133.6 (CH, Ar), 139.1 (C, Ar), 140.5(C, Ar); Minor Diastereoisomer: δ_H (400 MHz; $CDCl_3$) 0.35 (3H, s, $SiCH_3$), 0.36 (3H, s, $SiCH_3$), 1.10 (1H, dd, *J* 14.2 and 8.2, $SiC\underline{H}_aH_b$), 1.36 (1H, dd, *J* 14.2 and 6.3, $SiCH_a\underline{H}_b$), 1.37-1.66 (2H, m, $C\underline{H}_aH_b$ C-3 and $C\underline{H}_aH_b$ C-4 THF), 1.81-2.02 (2H, m, $CH_a\underline{H}_b$ C-3 and $CH_a\underline{H}_b$ C-4 THF), 2.62 (1H, d, *J* 2.5, OH), 4.12-4.20 (2H, m, CH C-2 THF and CH C-5 THF), 4.91(1H, br t, *J* 3.1, $\underline{H}$COH), 7.25-7.42 (8H, m, Ar), 7.54-7.59 (2H, m, Ar);

δ_C (100.6 MHz; $CDCl_3$) −2.2 ($SiCH_3$), -2.0 ($SiCH_3$), 24.2 ($SiCH_2$), 25.7 (CH_2, C-4 THF), 35.0 (CH_2, C-3 THF), 74.2 (COH), 78.5 (CH, C-2 THF), 82.0 (CH, C-5 THF),126.1 (CH, Ar), 127.3 (CH, Ar), 128.0 (CH, Ar), 128.2 (CH, Ar), 129.0 (CH, Ar), 133.6 (CH, Ar), 139.1 (C, Ar), 140.5(C, Ar); LRMS (EI^+, *m/z*): M^+ not visible, 219 ($[M{-}BnOH]^+$, 12 %), 135 (100), 107 (7), 75 (13); HRMS (ESP, *m/z*) 344.2039 $[M+NH_4]^+$, $C_{20}H_{30}O_2NSi$ requires 344.2040. Diastereoselectivity calculated by analysis of the ^{1}H NMR integrals for the $\underline{H}$COH proton at 4.39 (major diastereoisomer) and 4.91 ppm (minor diastereoisomer).

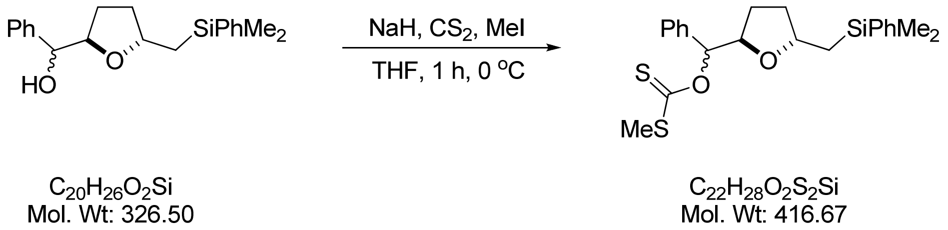
(±)-Phenyl(2-((triisopropylsilyl)methyl)tetrahydrofuran-5-yl)methyl acetate (227)



To a stirred solution of phenyl(2-((triisopropylsilyl)methyl)tetrahydrofuran-5-yl)methanol (0.05 g, 0.14 mmol) in DCM (5 mL) was added acetic anhydride (20.0 µL, 0.21 mmol) and in one portion DMAP (4.00 mg, 0.03 mmol, 20 mol %). The reaction mixture was stirred at room temperature and monitored by TLC. After 15 h the reaction was quenched with a saturated solution of $NaHCO_3$ (3 mL). The organic phase was separated and the aqueous phase extracted with dichloromenthane (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product (0.03 g) as a colourless oil. Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 20 % diethylether : hexane] afforded title compound as an inseparable mixture of the two diastereoisomers (combined yield 31.0 mg, 0.08 mmol, 57 %, *dr* 2.4 : 1) as colourless oils; R_f 0.58 [20 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 2940, 2864, 1742 (C=O), 1462, 1368, 1232, 1022, 882; Major Diastereoisomer: δ_H (400 MHz; $CDCl_3$) 0.91 (1H, dd, *J* 14.5 and 6.7, SiC$\underline{H}_a$H$_b$), 0.99-1.10 (22H, m, overlapping signals $^i\underline{Pr}_3$SiCH$_{\underline{a}}\underline{H}_b$), 1.38-1.48 (1H, m, C$\underline{H}_aH_b$ C-3 THF), 1.50-1.59 (1H, m, C$\underline{H}_a$H$_b$ C-4 THF), 1.67-1.74 (1H, m, CH$_a\underline{H}_b$ C-4 THF), 1.93-2.05 (1H, m, CH$_a\underline{H}_b$ C-3 THF), 2.07 (3H, s, CO_2CH_3), 4.11-4.18 (1H, m, CH C-2 THF), 4.29-4.35 (1H, m, CH C-5 THF), 5.61 (1H, d, *J* 7.9, HCO), 7.27-7.36 (5H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) 11.4

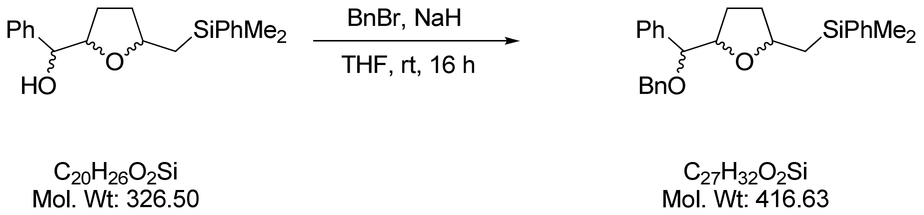
(3 × CH Si^{i}Pr$_3$), 17.0 (SiCH$_2$), 19.0 (6 × CH$_3$ Si^{i}Pr$_3$), 21.4 (CH$_3$, CO$_2$CH$_3$), 29.3 (CH$_2$, C-4 THF), 35.8 (CH$_2$, C-3 THF), 77.5 (CH, C-2 THF), 78.4 (HCO), 79.8 (CH, C-5 THF), 127.7 (CH, Ar), 128.2 (CH, Ar), 128.5 (CH, Ar), 137.9 (C, Ar), 170.4 (C, CO$_2$CH$_3$); Minor Diastereoisomer: δ_H (400 MHz; CDCl$_3$) 0.85 (1H, dd, *J* 14.4 and 7.4, SiC$\underline{H_a}$H$_b$), 0.99-1.10 (22H, m, overlapping signals $^i\underline{Pr}_3$SiCH$_a\underline{H_b}$), 1.38-1.48 (1H, m, C$\underline{H}_a$H$_b$ C-3 THF), 1.79-1.88 (1H, m, C$\underline{H}_a$H$_b$ C-4 THF), 1.93-2.05 (2H, m, CH$_a\underline{H}_b$ C-3 and CH$_a\underline{H}_b$ C-4 THF), 2.10 (3H, s, CO$_2$CH$_3$), 3.97 (1H, dtd, *J* 9.0 7.1 and 5.1, CH C-2 THF), 4.29-4.35 (1H, m, CH C-5 THF), 5.76 (1H, d, *J* 6.6, HCO), 7.27-7.36 (5H, m, Ar); δ_C (100.6 MHz; CDCl$_3$) 11.4 (3 × CH Si^{i}Pr$_3$), 17.0 (SiCH$_2$), 19.0 (6 × CH$_3$ Si^{i}Pr$_3$), 21.4 (CO$_2\underline{C}$H$_3$), 28.4 (CH$_2$, C-4 THF), 35.6 (CH$_2$, C-3 THF), 77.6 (HCO), 78.1 (CH, C-2 THF), 80.0 (CH, C-5 THF), 127.5 (CH, Ar), 128.0 (CH, Ar), 128.2 (CH, Ar), 137.8 (C, Ar), 170.4 (C, CO$_2$CH$_3$); LRMS (EI$^+$, *m/z*): M$^+$ not visible, 331 ([M−CO$_2$Me]$^+$, 2 %), 241 (18), 173 (100), 157 (71), 115 (25), 75 (19); HRMS (ESP, *m/z*) 391.2665 [M+H]$^+$, C$_{20}$H$_{39}$O$_3$Si requires 391.2663. Diastereoselectivity calculated by analysis of the ^{1}H NMR integrals for the $\underline{H}$CO proton at 5.61(major diastereoisomer) and 5.76 ppm (minor diastereoisomer).

O-(2-((dimethyl(phenyl)silyl)methyl)tetrahydrofuran-5-yl)(phenyl)methyl-*S*-methyl carbonodithioate (228)



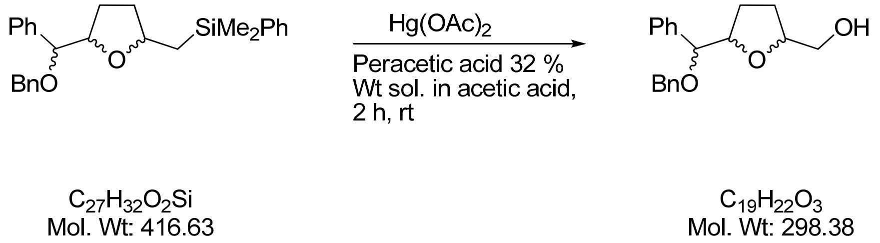
O-(2-((dimethyl(phenyl)silyl)methyl)tetrahydrofuran-5-yl)(phenyl)methyl-*S*-methyl carbonodithioate was prepared according to the procedure reported by Calter *et al.*[183] To a stirred solution of (2-((dimethyl(phenyl)silyl)methyl)tetrahydrofuran-5-yl)(phenyl)methanol (0.41 g, 1.30 mmol) in THF (25 mL) at 0 °C was added carbon disulphide (5.41 mL, 90.0 mmol) and diiodomethane (5.30 mL, 85.0 mmol). The mixture was stirred at 0 °C for 30 min followed by the addition of sodium hydride (60 % suspension in mineral oil, 0.10 g, 2.50 mmol). The reaction was stirred for 1 h at 0 °C and then quenched by the addition of crushed ice (30 g) and allowed to warm to room temperature. The organic layer was separated and the aqueous layer was extracted with DCM (3 × 10 mL). The organic fractions were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the impure product as a yellow oil (0.59 g). Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 10 % diethylether : hexane] afforded the title compound as inseparable mixture of diastereoisomers (combined yield 0.37 g, 0.85 mmol, 69 %, *dr* 2.5 : 1) as a colourless oil; R_f 0.75 and 0.70 [20 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 2954, 2864, 1427, 1209, 1112, 1049, 819; Major Diastereoisomer: δ_H (400 MHz; $CDCl_3$) 0.39 (3H, s, $SiCH_3$), 0.41 (3H, s, $SiCH_3$), 1.14 (1H, dd, *J* 14.4 and 6.9, $SiC\underline{H}_aH_b$), 1.33 (1H, dd, *J* 14.4 and 7.4, $SiCH_a\underline{H}_b$), 1.39-1.49 (1H, m, $C\underline{H}_aH_b$ C-3 THF), 1.60-1.70 (1H, m, $C\underline{H}_aH_b$ C-4 THF), 1.78-1.86 (1H, m, $CH_a\underline{H}_b$ C-4 THF), 1.89-2.07 (1H, m, $CH_a\underline{H}_b$ C-3 THF), 2.59 (3H, s, SCH_3), 4.15 (1H, dtd, *J* 8.9 7.1, 5.2, CH C-2 THF), 4.55 (1H, q, *J* 7.2, C-5 THF), 6.51 (1H, d, *J* 7.1, HCOC), 7.32-7.44 (8H, m, Ar), 7.59-7.61 (2H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) −2.3 ($SiCH_3$), −2.0 ($SiCH_3$), 19.0 (SMe), 23.5 ($SiCH_2$), 29.0 (CH_2, C-4 THF), 35.2 (CH_2, C-3 THF), 77.7 (CH, C-2 THF), 79.7 (CH, C-5 THF), 86.7 ($H\underline{C}OC$), 127.9 (CH, Ar), 128.1 (CH, Ar), 128.5 (2 overlapping CH, Ar), 129.0 (CH, Ar), 133.8 (CH, Ar), 136.7 (CH, Ar), 139.2 (C, Ar), 214.9 ($O\underline{C}S_2Me$); Minor Diastereoisomer: δ_H (400 MHz; $CDCl_3$) 0.34 (3H, s, $SiCH_3$), 0.35 (3H, s, $SiCH_3$), 1.09 (1H, dd, *J* 14.5 and 6.8, $SiC\underline{H_a}H_b$), 1.29 (1H, dd, *J* 14.5 and 7.0, $SiCH_a\underline{H_b}$), 1.39-1.49 (1H, m, $C\underline{H}_aH_b$ C-3 THF), 1.89-2.07 (3H, m, $CH_a\underline{H}_b$ C-3 and CH_2 C-4 THF), 2.59 (1H, s, SCH_3), 4.02-4.09 (1H, m, CH C-2 THF), 4.49 (1H, td, *J* 7.1 and 4.7, CH C-5 THF), 6.61 (1H, d, *J* 4.7, $\underline{H}COC$), 7.32-7.44 (8H, m, Ar), 7.54-7.57 (2H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) −2.4 ($SiCH_3$), −2.3 ($SiCH_3$), 19.1 (SMe), 23.7 ($SiCH_2$), 28.1 (CH_2, C-4 THF), 35.0 (CH_2, C-3 THF), 78.1 (CH, C-2 THF), 80.0 (CH, C-5 THF), 86.1 (COH), 127.6 (CH, Ar), 127.8 (CH, Ar), 128.2 (CH, Ar), 128.4 (CH, Ar), 129.0 (CH, Ar), 133.7 (CH, Ar), 139.2 (C, Ar), 214.9 ($O\underline{C}S_2Me$), one aromatic carbon not visable; HRMS (ESP, *m/z*) 434.1635 $[M+NH_4]^+$, $C_{22}H_{32}O_2NSSi$ requires 434.1638. Diastereoselectivity calculated by analysis of the ^1H NMR integrals for the $\underline{H}COH$ proton at 6.51 (major diastereoisomer) and 6,61 ppm (minor diastereoisomer).

((2-(benzyloxy(phenyl)methyl)tetrahydrofuran-5-yl)methyl)dimethyl(phenyl)silane (238)



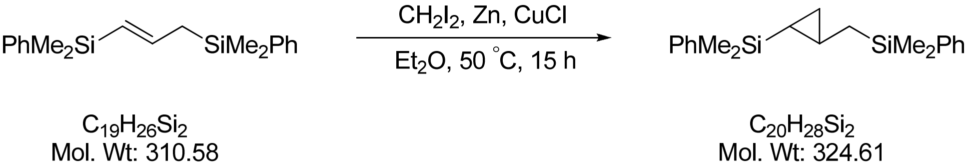
A 60 % dispersion of sodium hydride in mineral oil (12.0 mg, 0.50 mmol) was washed with *n*-hexane (2 × 1 mL), dried under reduced pressure and placed under an atmosphere of argon. To the resulting suspension dissolved in THF (1.5 mL) was added, dropwise, benzyl bromide (0.06 g, 0.04 mL, 0.35 mmol) and a solution of (2-((dimethyl(phenyl)silyl)methyl)-tetrahydrofuran-5-yl)(phenyl)methanol (0.13 g, 0.38 mmol) in THF (1 mL) at room temperature. The resulting solution was stirred for 15 h at 30 °C and monitored by TLC. After this time, the reaction was partitioned between water (10 mL) and DCM (10 mL) and the organic layer separated. The aqueous layer was extracted with DCM (3 × 10 mL). The organic fractions were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the impure product as a colourless oil (0.26 g). Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 20 % diethylether : hexane] afforded the title compound as an inseparable mixture of 4 diastereoisomers (combined yield 0.13 g, 0.31 mmol, 89 %) as a colourless oil; R_f 0.76 [20 % diethyl ether : hexane]; LRMS (EI$^+$, *m/z*): 416 ([M]$^+$, 1 %), 241 (9), 219 (10), 197 (12), 135 (100), 91 (72). Full characterisation of the product was not possible because of the number of diastereoisomers present. The material was used in the next step without further purification.

(±)-(5-(Benzyloxy(phenyl)methyl)tetrahydrofuran-2-yl)methanol (239)



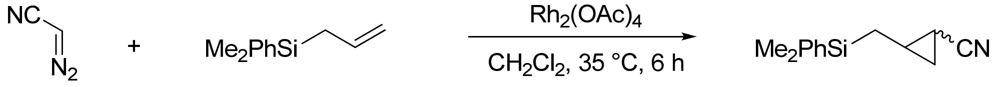
(5-(Benzyloxy(phenyl)methyl)tetrahydrofuran-2-yl)methanol was prepared according to the procedure reported by Fleming *et al.*[113] To a stirred solution of ((5-(benzyloxy(phenyl)methyl)tetrahydrofuran-2-yl)methyl)dimethyl(phenyl)silane (0.12 g, 0.31 mmol) in peracetic acid (30 % *wt* sol. in acetic acid, 3 mL) was added in one portion mercury (II) acetate (0.11 g, 0.35 mmol). The reaction was stirred for 2 h then washed with water (10 mL), sat. NaS_2O_3 (10 mL), sat. $NaHCO_3$ (10 mL) The aqueous layer was extracted with DCM (3 × 10 mL) and the organic fractions were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the impure product as a white solid (0.19 g). Purification by flash column chromatography [silica gel, gradient elution 50 % hexane : diethyl ether – 100 % diethylether] isolated a single diastereoisomer of the title compound (0.03 g, 0.10 mmol, 32 %) as a colourless viscous oil; R_f 0.14 [80 % diethyl ether : hexane]; ν_{max}(film)/cm^{-1} 3439 (O-H), 3062, 3030, 2870, 1495, 1454, 1062 (C-O); δ_H (400 MHz; $CDCl_3$) 1.55-1.67 (3H, m, overlapping signals CH_2 C-4 and $C\underline{H}_aH_b$ C-3 THF), 1.73-1.82 (1H, m, $CH_a\underline{H}_b$ C-3 THF), 2.16 (1H, br s, OH), 3.43 (1H, app dd, *J* 11.1 and 5.1, $C\underline{H}_aH_bOH$), 3.66 (1H, app br d, *J* 11.7, $CH_a\underline{H}_bOH$), 4.04-4.10 (1H, m, CH C-2 THF), 4.24-4.31 (2H, m, overlapping signals CH C-5 THF and $\underline{H}COBn$), 4.34 (1H, d, *J* 12.1 $PhC\underline{H}_aH_bO$), 4.56 (1H, d, *J* 12.1, $PhCH_a\underline{H}_bO$), 7.24-7.39 (10H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) 27.3 (CH_2, C-3 THF), 28.9 (CH_2, C-4 THF), 65.0 (CH_2OH), 70.6 ($Ph\underline{C}H_2O$), 80.1 (CH, C-2 THF), 82.5 (CH, C-5 THF), 84.0 ($\underline{H}COBn$), 127.6 (p-CH, Ar), 127.9 (2 × o-CH, Ar), 128.0 (2 × *o*-CH, Ar), 128.2 (*p*-CH, Ar), 128.4 (2 × *m*-CH, Ar), 128.5 (2 × *m*-CH, Ar), 138.5 (C, Ar), 139.0 (C, Ar); LRMS (EI$^+$, *m/z*): 298 ([M]$^+$, 1 %), 197 (26), 101 (23), 91 (100), 57 (28); HRMS (ESP, *m/z*) 316.1902 [M+NH$_4$]$^+$, $C_{19}H_{26}O_3N$ requires 316.1907.

(±)-((2-(Dimethyl(phenyl)silyl)cyclopropyl)methyl)dimethyl(phenyl)silane (241)



To a stirred suspension of zinc powder (4.29 g , 65.0 mmol) and copper chloride (6.43 g, 65.0 mmol) in anhydrous diethyl ether (100 mL) which had been heated at reflux temperature for 30 min and allowed to cool to room temperature was added 1-dimethyl(phenyl)silyl-3-dimethy(phenyl)silylpropene (4.03 g, 13.0 mmol) and diiodomethane (6.96 g, 2.09 mL, 26.0 mmol). The reaction was heated at reflux temperature for 24 h, cooled to room temperature and filtered through celite washing with diethyl ether (50 mL). The filtrate was washed with 1M HCl (2 x 30 mL) followed by 10 % *w*/*v* aqueous sodium bicarbonate solution until pH 7. The combined aqueous layers were extracted with diethyl ether (3 × 30 mL) and the combine organic layers were washed with brine (20 mL), 10 % *w*/*v* aqueous sodium thiosulphate solution (2 × 20 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the impure product as a colourless oil (4.05 g). Purification by flash column chromatography using a mixture of 10 % silver nitrate impregnated silica and standard silica (1 : 3) eluting with petroleum ether (40-60 °C) gave the desired product (2.35 g, 7.20 mmol, 56 %) as a colourless oil; R_f 0.32 [petroleum ether (40-60 °C]; ν_{max}(film)/cm^{-1} 3068, 3049, 2955, 2896, 1487, 1247, 1113, 828, 806; δ_H (400 MHz; $CDCl_3$) –0.43 (1H, dt, *J* 9.8 and 6.5, SiCH), 0.15 (3H, s, $SiCH_3$), 0.19 (3H, s, $SiCH_3$), 0.30 (3H, s, $SiCH_3$), 0.31 (3H, s, $SiCH_3$), 0.33-0.38 (1H, m, $C\underline{H}_aH_b$ cyclopropyl), 0.46 (1H, td, *J* 7.1 and 3.6, $CH_a\underline{H}_b$ cyclopropyl), 0.63-0.71 (1H, m, $SiCH_2C\underline{H}$), 0.88 (2H, d, *J* 6.8, $SiC\underline{H}_2CH$), 7.34-7.37 (6H, m, Ar), 7.51-7.54 (4H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) –3.6 ($SiCH_3$), –3.3 ($SiCH_3$), –2.6 ($SiCH_3$), –2.5 ($SiCH_3$), 5.7 ($PhMe_2Si\underline{C}H$), 11.1 (CH_2 cyclopropyl), 11.2 ($SiCH_2\underline{C}H$), 22.8 ($Si\underline{C}H_2CH$), 127.8 (2 × *m*-CH, Ar), 127.8 (2 × *m*-CH, Ar), 128.9 (2 × *p*-CH, Ar), 133.7 (2 × *o*-CH, Ar), 133.9 (2 × *o*-CH, Ar), 139.5 (C, Ar), 139.7 (C, Ar); LRMS (EI$^+$, *m/z*): 324 (M$^+$, 23 %), 271 (24), 197 (16), 174 (20), 135 (100), 112 (9); HRMS (EI, *m/z*) 324.1725 [M]$^+$, $C_{20}H_{28}Si_2$ requires 324.1724.

2-((Dimethyl(phenyl)silyl)methyl)cyclopropanecarbonitrile (242)



C_2HN_3
Mol. Wt: 67.05

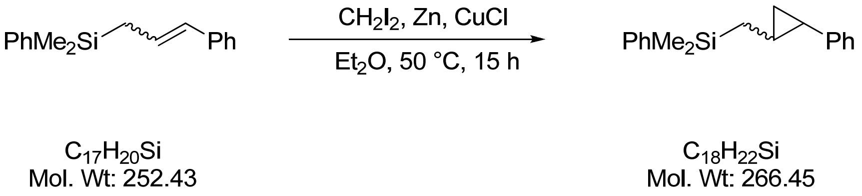
$C_{11}H_{16}Si$
Mol. Wt: 176.33

$C_{13}H_{17}NSi$
Mol. Wt: 215.37

Diazoacetonitrile was prepared according to the procedure reported by Witiak *et. al.*[184] To a suspension of α-aminoacetonitrile bisulfite (3.68 g, 24.0 mmol) in DCM (28 mL) at 0 °C was cautiously added dropwise an aqueous solution of sodium nitrite (4.96 g, 72.0 mmol) in distilled water (22 mL) at a rate that the temperature of the reaction did not rise above 0 °C. During the addition effervescence was observed to occur. The reaction was allowed to stir for 30 min at 0 °C after which time a green solution and precipitate existed. The organic layer was separated and the aqueous layer further extracted with DCM (20 mL). The combined organic phases were washed with 1 % aqueous sodium hydrogen carbonate solution (10 mL), separated, dried ($MgSO_4$), filtered and place under and inert atmosphere. The solution (0.5 M solution of diazoacetinitle in DCM) was used immediately and without purification as diazacetonitrile has been reported to be highly explosive at high concentrations.[185]

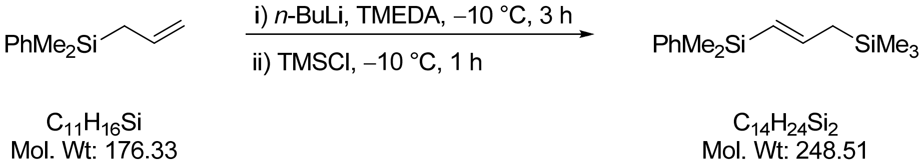
To a stirred mixture of allyldimethylphenylsilane (2.47 g, 14.0 mmol) and dirhodium tetraacetate dihydrate (0.17 g, 0.38 mmol) in degassed DCM (2.4 mL) heated at 35 °C was added using a syringe pump (4 mL/h) diethyl 2-diazomalonate (24.0 mL, 12.0 mmol, 0.5 M solution in DCM). The reaction was heated at 35 °C (oil bath) for 6 h, filtered and concentrated *in vacuo* to give the impure product as a red oil (2.65 g). Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 10 % diethyl ether : hexane] afforded an inseparable mixture of the two geometric isomers the desired (0.73 g, 3.40 mmol, 30 %, *dr* 1 : 0.6) as a colourless oil; R_f 0.20 [10 % diethyl ether - hexane]; ν_{max}(film)/cm^{-1} 3070 (CH cyclopropyl), 2956, 2897, 2233 (C≡N), 1427, 1427, 1250, 1114, 831; major isomer: δ_H (600 MHz; $CDCl_3$) 0.38 (3H, s, SiMe), 0.39 (3H, s, SiMe), 0.65-0.72 (1H, m $C\underline{H}_aH_b$ cyclopropyl), 0.80 (1H, dd, *J* 14.8 and 9.2, $SiC\underline{H}_aH_b$), 1.11 (1H, td, *J* 8.4 and 5.1, $CH_a\underline{H}_b$ cyclopropyl), 1.16-1.23 (1H, m, CHCN), 1.28 (1H, dd, *J* 14.8 and 5.2, $SiCH_a\underline{H}_b$), 1.35-1.41 (1H, m, CH cyclopropyl), 7.36-7.40 (3H, m, Ph), 7.51-7.55 (2H, m, Ph); δ_C (100.6 MHz; $CDCl_3$) −2.9 (SiMe), −2.8 (SiMe), 4.1 (CH cylopropyl), 15.0 ($\underline{C}$HCN cyclopropyl), 15.4 (CH_2 cyclopropyl), 17.3 ($SiCH_2$), 120.9 (CN), 128.0 (2 × *m*-CH, Ph), 129.4 (*p*-CH, Ph), 133.7 (2 × *o*-CH, Ph), 138.1 (C, Ph); minor isomer: δ_H (600 MHz; $CDCl_3$) 0.36 (3H, s, SiMe), 0.37 (3H, s, SiMe), 0.65-0.72 (2H, m, overlapping signals $SiC\underline{H}_aH_b$ and $C\underline{H}_aH_b$ cyclopropyl), 0.90-0.93 (1H, m, CH cyclopropyl), 0.96 (1H, dd, *J* 14.8 and 6.4, $SiCH_a\underline{H}_b$), 1.16-1.23 (1H, m, $CH_a\underline{H}_b$ cyclopropyl), 1.35-1.41 (1H, m, CHCN), 7.36-7.40 (3H, m, Ph), 7.51-7.55 (2H, m, Ph); δ_C (100.6 MHz; $CDCl_3$) −3.1 (SiMe), −2.9 (SiMe), 4.4 (CH cylopropyl), 15.8 (CH_2 cyclopropyl), 18.1 ($\underline{C}$HCN cyclopropyl), 20.4 ($SiCH_2$), 122.0 (CN), 128.1 (2 × *m*-CH, Ph), 129.5 (*p*-CH, Ph), 133.6 (2 × *o*-CH, Ph), 137.9 (C, Ph); LRMS (EI^+, *m/z*): 215 ($[M]^+$, 3 %), 200 (6), 135 (100) 105 (10); HRMS (EI, *m/z*) 215.1127 $[M]^+$, $C_{13}H_{17}NSi$ requires 215.1125.

(±)-Dimethyl(phenyl)((2-phenylcyclopropyl)methyl)silane (243)



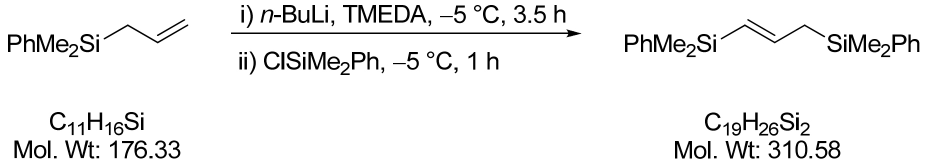
To a stirred suspension of zinc powder (3.96 g, 60.0 mmol) and copper chloride (5.94 g, 60.0 mmol) in anhydrous diethyl ether (90 mL), which had been heated at reflux temperature for 30 min and allowed to cool to room temperature, was added 3-dimethylphenylsilyl-1-phenyl-1-propene (1.57 g, 6.00 mmol) and diiodomethane (6.43 g, 1.93 mL, 24.0 mmol). The reaction was heated at reflux temperature for 48 h, cooled to room temperature and filtered through celite washing with diethyl ether (3 × 30 mL). The filtrate was washed with 1M HCl (2 x 25 mL) followed by 10 % *w*/*v* aqueous sodium bicarbonate solution until pH 7. The combined aqueous layers were extracted with diethyl ether (3 x 30 mL) and the combined organic layers were washed with 10 % *w*/*v* aqueous sodium thiosulphate solution (2 × 20 mL), brine (20 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the impure product as a yellow oil (1.05 g). Purification by flash column chromatography using a mixture of 10 % silver nitrate impregnated silica and standard silica (1 : 1) eluting with hexane gave the desired product (0.58 g, 2.20 mmol, 36 %) as a colourless oil; R_f 0.26 [hexane]; ν_{max}(film)/cm^{-1} 3067 (C-H cyclopropyl), 2999, 2955, 2896, 1605 (Ar-H), 1427, 1248, 1113, 831 (Si-C); δ_H (400 MHz; $CDCl_3$) 0.33 (3H, s, SiMe), 0.34 (3H, s, SiMe), 0.71-0.76 (1H, m, $C\underline{H}_aH_b$ cyclopropyl), 0.86-1.04 (4H, m, overlapping signals $SiC\underline{H}_2$, CH and $CH_a\underline{H}_b$ cyclopropyl), 1.53-1.57 (1H, m, PhC<u>H</u> cyclopropyl), 6.77 (2H, d, *J* 7.8, 2 × *o*-CH Ph), 7.10-7.14 (1H, m, *p*-CH Ph), 7.23 (2H, t, *J* 7.8, 2 × *m*-CH Ph), 7.32-7.37 (3H, m, SiPh), 7.51-7.53 (2H, m, SiPh); δ_C (100.6 MHz; $CDCl_3$) −2.7 (SiMe), −2.6 (SiMe), 18.5 (CH_2 cyclopropyl), 19.7 (CH cyclopropyl), 21.6 ($SiCH_2$), 25.3 (PhC<u>H</u>, cyclopropyl), 125.2 (*p*-CH, Ph), 125.5 (2 × *o*-CH, Ph), 127.9 (2 × *m*-CH, SiPh), 128.3 (2 × *m*-CH, Ph), 129.3 (*p*-CH, SiPh), 133.7 (2 × *o*-CH, SiPh), 139.4 (C, SiPh), 144.0 (C, Ph); LRMS (EI^+, *m/z*): 266 ($[M]^+$, 3 %), 238 (7), 188 (11), 135 (100), 105 (9), 91 (8); HRMS (EI^+, *m/z*) 266.1487 $[M]^+$, $C_{18}H_{22}Si$ requires 266.1485.

***E*-(3-(Dimethyl(phenyl)silyl)allyl)trimethylsilane (245)**



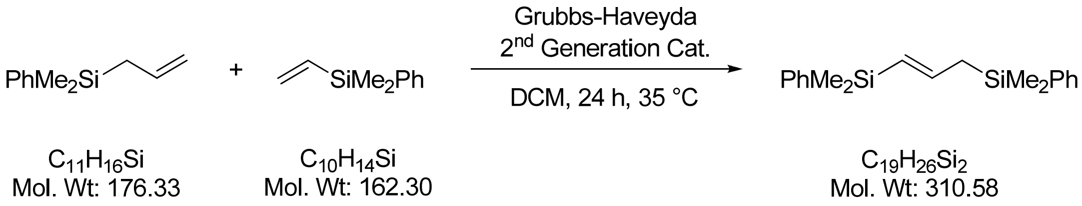
(3-(Dimethyl(phenyl)silyl)allyl)trimethylsilane was prepared according to the procedure reported by Fleming *et al.*[114] Dimethylphenylsilylpropene (1.76 g, 10.0 mmol) was added dropwise to a stirred mixture of freshly distilled *N*,*N*,*N*,*N*-tetramethylethylenediamine (1.75 mL, 11.5 mmol) and *n*-butyllithium (4.00 mL of a 2.5 M solution in hexane, 10.0 mmol) at −10 ºC and the mixture kept at −10 ºC for 3 h. Chlorotrimethylsilane (1.27 mL, 10 mmol) was added and the mixture was kept at −10 ºC for 1h, and then poured into 1 M HCl (10 mL) and extracted with petroleum spirit (40-60 ºC). The extract was washed with 1 M HCl (10 mL, 1M), water (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the impure product as a dark brown oil (2.01 g). Purification by reduced pressure distillation gave the title compound (0.48 g, 1.90 mmol 20 %) as a colourless oil; bp 59-65 °C/0.1 mmHg, (lit.[37] 66-68 °C/0.1 mmHg); δ_H (400 MHz; $CDCl_3$) 0.01 (9H, s, 3 × CH_3), 0.31 (6H, s, 2 × CH_3), 1.69 (2H, dd, *J* 7.9 and 1.2, C<u>H</u>$_2$CH=CH), 5.56 (1H, dt, *J* 18.4 and 1.2, CH_2CH=C<u>H</u>), 6.11 (1H, dt, *J* 18.4 and 7.9, CH_2C<u>H</u>=CH), 7.33-7.37 (3H, m, Ph), 7.51-7.55 (2H, m, Ph); δ_C (100.6 MHz; $CDCl_3$) −2.1 (2 × CH_3), −1.8 (3 × CH_3), 28.8 (CH_2CH=CH), 125.7 (CH_2CH=<u>C</u>H), 127.8 (2 × *m*-CH, Ph), 128.8 (*p*-CH, Ph), 134.0 (2 × *o*-CH, Ph), 139.9 (C, Ph), 139.4 (CH_2C<u>H</u>=CH); LRMS (EI^+, *m/z*): 248 ($[M]^+$, 3 %), 233 (3), 176 (3), 161 (5), 145 (12), 135 (100), 98 (33), 73 (40). The data is in good agreement with previously reported data.[114]

1-Dimethyl(phenyl)silyl-3-dimethy(phenyl)silylpropene (246)



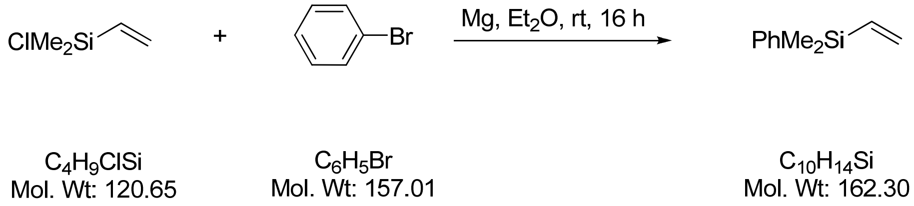
1-Dimethyl(phenyl)silyl-3-dimethy(phenyl)silylpropene was prepared according to the procedure reported by Fleming *et al.*[114] Dimethylphenylsilylpropene (3.52 g, 20.0 mmol) was added dropwise to a stirred mixture of freshly distilled *N*,*N*,*N*,*N*-tetramethylethylenediamine (3.50 mL, 23.0 mmol) and *n*-butyllithium (9.0 mL of a 2.5 M solution in hexane, 22.5 mmol) at −5 °C and the mixture kept at −5 ºC for 3.5 h. Chlorodimethylphenylsilane (3.39 mL, 21.0 mmol) was added dropwise and the mixture was kept at −5 ºC for 1 h (colour changed from orange to yellow), then poured into 1 M HCl (20 mL) and extracted with petroleum spirit (40-60 ºC). The extract was washed with 1 M HCl (20 mL), water (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the impure product as a pale yellow/brown oil (6.02 g). Purification by flash column chromatography [silica gel, hexane] afforded the desired product (5.35 g, 17.0 mmol, 86 %) as a colourless oil; R_f 0.36 [petroleum spirit 40-60 ºC]; ν_{max}(film)/cm^{-1} 3069, 2956, 1603 (C=C), 1486, 1247, 1139, 809; δ_H (400 MHz; $CDCl_3$) 0.29 (6H, s, 2 × CH_3), 0.29 (6H, s, 2 × CH_3), 1.92 (2H, d, *J* 7.8, $C\underline{H}_2CH{=}CH$), 5.57 (1H, d, *J* 18.4, $CH_2CH{=}C\underline{H}$), 6.09 (1H, dt, *J* 18.4 and 7.8, $CH_2C\underline{H}{=}CH$), 7.33-7.40 (6H, m, Ar), 7.47-7.51 (4H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) −3.2 (2 × CH_3), −2.1 (2 × CH_3), 27.9 ($\underline{C}H_2CH{=}CH$), 126.6 ($CH_2CH{=}\underline{C}H$), 127.8 (2 × *m*-CH, Ar), 127.9 (2 × *m*-CH, Ar), 128.9 (*p*-CH, Ar), 129.2 (*p*-CH, Ar), 133.8 (2 × *o*-CH, Ar), 134.0 (2 × *o*-CH, Ar), 138.6 (C, Ar), 139.7 (C, Ar), 145.4 ($CH_2\underline{C}H{=}CH$); LRMS (EI$^+$, *m/z*): 310 (M$^+$, 1 %), 295 (2), 197 (17), 160 (32), 135 (100), 105 (10); HRMS (ESP, *m/z*) 311.1651 [M+H]$^+$, $C_{19}H_{27}Si_2$ requires 311.1646.

1-Dimethyl(phenyl)silyl-3-dimethy(phenyl)silylpropene (246)



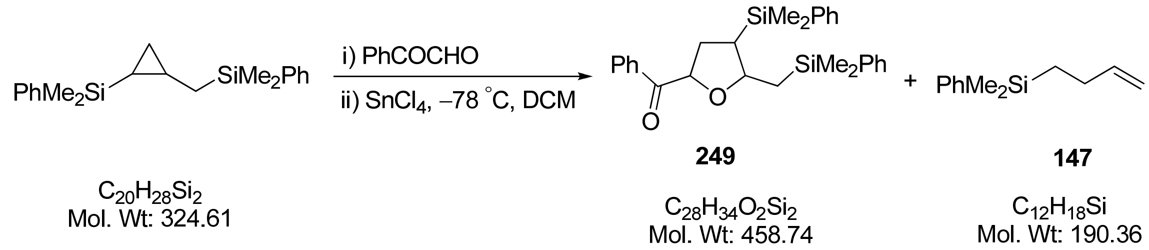
To a stirred mixture of allyldimthylphenylsilane (0.56 g, 3.20 mmol) and vinyldimethylphenylsilane (2.60 g, 16.0 mmol) in argon degassed DCM (10 mL) was added rapidly a solution of (1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium (0.10 g, 0.16 mmol, 10 mol %) in DCM (1 mL). The reaction immediately changed colour from green to brown and was heated at 35 °C and monitored by TLC. After 24 h the reaction was concentrated to approximately one quarter of the volume under reduced pressure and filtered through a pad of silica gel eluting with DCM (2 × 100 mL). The filtrate was concentrated *in vacuo* to yield the impure product as a pale green/brown residue (2.24 g). Purification by flash column chromatography [silica gel, hexane] afforded the desired product (0.27 g, 0.87 mmol, 27 %, *dr* 17:1 *trans*:*cis*) as a colourless oil; R_f 0.34 [petroleum spirit 40-60 ºC]; *trans* isomer: δ_H (400 MHz; $CDCl_3$) 0.29 (6H, s, 2 × CH_3), 0.29 (6H, s, 2 × CH_3), 1.92 (2H, d, *J* 7.8, C$\underline{H}_2$CH=CH), 5.57 (1H, d, *J* 18.4, CH_2CH=C$\underline{H}$), 6.09 (1H, dt, *J* 18.4 and 7.8, CH_2C$\underline{H}$=CH), 7.33-7.40 (6H, m, Ar), 7.47-7.51 (4H, m, Ar); *cis* isomer: 0.31 (6H, s, 2 × CH_3), 0.30 (6H, s, 2 × CH_3), 1.85 (2H, dd, *J* 8.5 and 1.3, C$\underline{H}_2$CH=CH), 5.53 (1H, dt, *J* 13.9, CH_2CH=C$\underline{H}$), 6.46 (1H, dt, *J* 13.9 and 8.5, CH_2C$\underline{H}$=CH), 7.34-7.39 (6H, m, Ar), 7.47-7.58 (4H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) −3.2 (2 × CH_3), −2.1 (2 × CH_3), 27.9 ($\underline{C}H_2$CH=CH), 126.6 (CH_2CH=$\underline{C}$H), 127.8 (2 × *m*-CH, Ar), 127.9 (2 × *m*-CH, Ar), 128.9 (*p*-CH, Ar), 129.2 (*p*-CH, Ar), 133.8 (2 × *o*-CH, Ar), 134.0 (2 × *o*-CH, Ar), 138.6 (C, Ar), 139.7 (C, Ar), 145.4 ($CH_2\underline{C}$H=CH). All other characterisation data the same as above, the ratio of diastereoisomers calculated by analysis of the ^{1}H NMR integrals for the SiCHC$\underline{H}$CH proton at 6.09 ppm (*trans* diastereoisomer) and 6.46 ppm (*cis* diastereoisomer).

Dimethylphenylvinylsilane (248)



Dimethylphenylvinylsilane was prepared *via* a modified procedure from the method reported by Braddock *et al.*[120] To a suspension of Mg (3.10 g, 128 mmol) in diethyl ether (20 mL) at room temperature was added dropwise bromobenzene (8.94 g, 6.00 mL, 56.9 mmol) at a rate to maintain a gentle reflux (addition was complete in approximately 1 h). The reaction mixture was stirred for 15 min at room temperature and a solution of chlorodimethylvinylsilane (6.21 g, 7.10 mL, 50.0 mmol) in diethyl ether (30 mL) was added dropwise and the resulting mixture was stirred at room temperature for 24 h. The reaction was quenched with 10 % *w*/*v* aqueous ammonium chloride solution (40 mL), the organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product (8.61g) as a yellow oil. Purification by reduced pressure distillation gave the desired product (7.54 g, 46.5 mmol, 93 %) as a colourless oil; bp 86-91 °C/15 mmHg (lit.[120], 90-93 °C/40 mmHg); R_f 0.43 [petroleum ether (40-60 °C)]; δ_H (400 MHz; $CDCl_3$) 0.37 (6H, s, 2 × CH_3), 5.78 (1H, dd, *J* 20.2 and 3.8, $CH=CH_{cis}\underline{H}_{trans}$), 6.08 (1H, dd, *J* 14.7 and 3.8, $CH=C\underline{H}_{cis}H_{trans}$), 6.31 (1H, dd, *J* 20.2 and 14.7, $C\underline{H}=CH_{cis}H_{trans}$), 7.37-7.40 (3H, m, Ph), 7.54-7.57 (2H, m, Ph); δ_C (100.6 MHz; $CDCl_3$) −2.8 (2 × CH_3), 128.0 (2 × *m*-CH, Ph), 129.1 (*p*-CH, Ph), 133.0 ($CH=\underline{C}H_2$), 134.1 (2 × *o*-CH, Ph), 138.1 ($\underline{C}H=CH_2$), 138.6 (C, Ph); LRMS (EI^+, *m/z*): 162 ($[M]^+$, 44 %), 147 (100), 135 (30), 121 (45), 105 (45), 91 (11). The spectral data is in good agreement with previously reported data.[120]

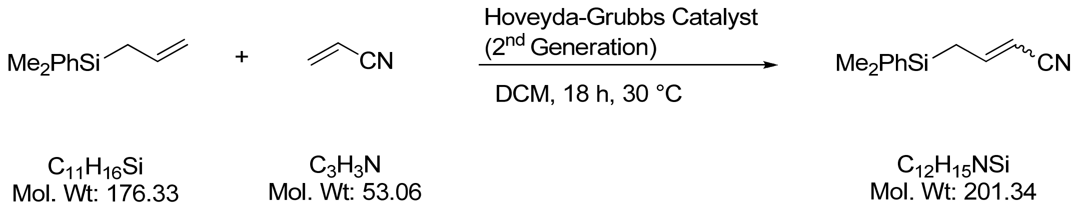
(±)-(4-(dimethyl(phenyl)silyl)-5-((dimethyl(phenyl)silyl)methyl)tetrahydrofuran-2-yl)(phenyl)methanone (249)



To a stirred solution of freshly distilled phenyl glyoxal (0.12 g, 0.90 mmol) in anhydrous DCM (2 mL) at −78 °C and under an atmosphere of argon was added, dropwise, a solution of tin tetrachloride (0.17 g, 0.08 mL, 0.66 mmol) in anhydrous DCM (2 mL). The resulting mixture was stirred at −78 °C for 5 min followed by the dropwise addition of a solution of (±)-((2-(Dimethyl(phenyl)silyl)cyclopropyl)methyl)dimethyl(phenyl)silane (0.19 g, 0.60 mmol) in anhydrous DCM (3 mL). The reaction was stirred at −78 °C and monitored by TLC, after 5 h the reaction was quenched by the addition of wet acetone (5 mL) and allowed to warm to 0 °C and poured on to H_2O (10 mL). The organic layer was separated and the aqueous layer further extracted with DCM (3 × 10 mL). The combined organic phases were washed with brine (10 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product (0.38 g) as a yellow oil. Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 20 % diethyl ether : hexane] afforded the desired product as single diastereoisomer (7 mg, 0.01 mmol, 2 %) as a colourless oil; R_f 0.44 [20 % diethyl ether : hexane]; δ_H (600 MHz; $CDCl_3$); 0.22 (3H, s, $SiCH_3$), 0.27 (3H, s, $SiCH_3$), 0.27 (6H, s, 2 × CH_3), 0.89-0.98 (2H, m, $SiCH_2$), 1.37 (1H, ddd, *J* 12.1 10.6 and 8.2, CH C-4 THF), 2.07 (1H, app td, *J* 12.5 and 7.7, $C\underline{H}_aH_b$ C-3 THF), 2.30 (1H, app dt, *J* 12.8 and 7.9, $CH_a\underline{H}_b$ C-3 THF), 3.96 (1H, ddd, *J* 10.5 8.7 and 4.1 CH C-5 THF), 5.08 (1H, app t, *J* 7.7, CH C-2 THF), 7.29-7.55 (13H, m, Ar), 7.93 (2H, app dd, *J* 8.4 and 1.3, 2 × *o*-CH -C(O)Ph); δ_C (100.6 MHz; $CDCl_3$) −4.2 ($SiCH_3$), −4.0 ($SiCH_3$), −2.4 ($SiCH_3$), −1.8 ($SiCH_3$), 23.4 ($SiCH_2$), 32.8 (CH_2, C-3 THF), 36.7 (CH, C-4 THF), 79.7 (CH, C-2 THF), 80.8 (CH, C-5 THF), 127.7 (CH, Ar), 128.0 (CH, Ar), 128.5 (CH, Ar), 129.2 (CH, Ar), 129.4 (CH, Ar), 133. 1 (CH, Ar), 133.8 (CH, Ar), 133.9 (CH, Ar), 135.6 (C, Ar), 137. 5 (C, Ar), 139.9 (C, Ar), 199.6 (C=O); LRMS (EI^+, *m/z*): M^+ not visible, 353 ($[M{-}PhCO]^+$, 2 %), 239 (2), 209 (26), 135 (100), 105 (8), 67 (25); HRMS (ESI, *m/z*) 476.2429 $[M+NH_4]^+$, $C_{28}H_{38}O_2NSi_2$ requires 476.2436.

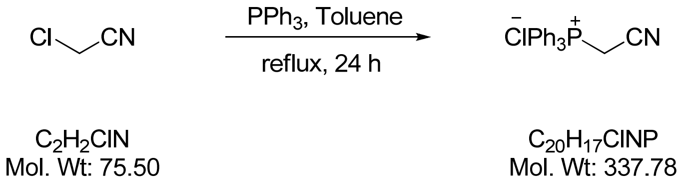
but-3-enyldimethyl(phenyl)silane 147 (0.02 g, 0.12 mmol, 20 %) as a colourless oil; R_f 0.35 [hexane]; δ_H (400 MHz; CDCl$_3$); 0.28 (6H, s, SiMe$_2$), 0.84-0.88 (2H, m, SiCH$_2$), 2.04-2.10 (2H, m, C$\underline{H}_2$CH=CH$_2$), 4.89 (1H, app d, *J* 10.1, CH$_2$CH=C$\underline{H}_{cis}$H$_{trans}$), 4.99 (1H, app dd, CH$_2$CH=CH$_{cis}\underline{H}_{trans}$), 5.88 (1H, ddt, *J* 17.1 10.1 and 6.2, CH$_2$C$\underline{H}$=CH$_2$), 7.35-7.37 (3H, m, SiPh), 7.51-7.56 (2H, m, SiPh); δ_C (100.6 MHz; CDCl$_3$) -2.9 (SiMe$_2$), 14.9 (SiCH$_2$), 28.1 ($\underline{C}$H$_2$CH=CH$_2$), 112.9 (CH$_2$CH=$\underline{C}$H$_2$), 127.9 (2 × *m*-CH, SiPh), 129.0 (p-CH, SiPh), 133.7 (2 × *o*-CH, SiPh), 139.4 (*ipso*-C, SiPh), 141.7 (CH$_2\underline{C}$H=CH$_2$); LRMS (EI$^+$, *m/z*): 190 ([M]$^+$, 4 %), 175 (13), 162 (11), 135 (100), 121 (27), 105 (13). The spectral data is in good agreement with previously reported values.[71, 186]

4-(Dimethyl(phenyl)silyl)but-2-enenitrile (251)



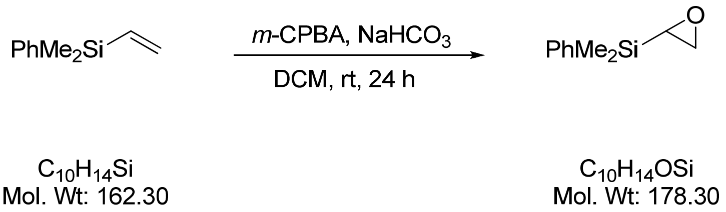
To a stirred solution of dimethylphenylallylsilane (0.56 g, 3.20 mmol) and acyrlonitrile (0.51 g, 0.37 mL, 9.6 mmol) in argon degassed DCM (10 mL) was added a solution of (1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)-ruthenium (0.10 g, 0.16 mmol, 5 mol %) in DCM (1 mL) The reaction immediately changed colour from green to black and was heated at 35 °C and monitored by TLC. After 24 h the solvent was removed *in vacuo* to give the impure product (0.72 g). Purification by flash column chromatography [silica gel, gradient elution 100 % petroleum ether (40-60 °C) - 20 % diethylether : petroleum ether (40-60 °C)] afforded an inseparable mixture of the two geometric isomers of the product (combined yield 0.14 g, 2.00 mmol, 64 %, dr. *cis* : *trans* 1 : 0.3) as a colourless oil: R_f 0.33 [10 % diethylether : petroleum ether (40-60 °C)]; *cis* isomer: δ_H (400 MHz; CDCl$_3$) 0.41 (6H, s, SiMe$_2$), 2.24 (2H, dd, *J* 9.0 and 1.0, SiCH$_2$), 5.15 (1H, dt, *J* 10.8 and 1.0, CH=C$\underline{H}$CN), 6.48 (1H, dt, *J* 10.8 and 9.0, C$\underline{H}$=CHCN), 7.37-7.42 (3H, m, Ph), 7.52-7.55 (2H, m, Ph); δ_C (100.6 MHz; CDCl$_3$) −3.3 (SiMe$_2$), 24.9 (SiCH$_2$), 96.4 (CH=$\underline{C}$HCN), 116.8 (CH=CH$\underline{C}$N), 128.1 (2 × *m*-CH, Ph), 129.7 (*p*-CH, Ph), 133.6 (2 × *o*-CH, Ph), 136.7 (C, Ph), 152.9 ($\underline{C}$H=CHCN); *trans* isomer: δ_H (400 MHz; CDCl$_3$) 0.37 (6H, s, SiMe$_2$), 1.99 (2H, dd, *J* 8.8 and 1.4, $SiCH_2$), 5.08 (1H, dt, *J* 16.1 and 1.4, $CH{=}C\underline{H}CN$), 6.71 (1H, dt, *J* 16.1 and 8.8, $C\underline{H}{=}CHCN$), 7.37-7.42 (3H, m, Ph), 7.48-7.50 (2H, m, Ph); δ_C (100.6 MHz; $CDCl_3$) −3.4 ($SiMe_2$), 25.8 ($SiCH_2$), 97.1 ($CH{=}\underline{C}HCN$), 118.2 ($CH{=}CH\underline{C}N$), 128.2 (2 × *m*-CH, Ph), 129.8 (*p*-CH, Ph), 133.5 (2 × *o*-CH, Ph), 136.4 (C, Ph), 153.9 ($\underline{C}H{=}CHCN$). Diastereomeric ratio calculated by analysis of the ^{1}H NMR integrals for the $C\underline{H}{=}CHCN$ protons, 6.48 (*cis* diastereoisomer) and 6.71 ppm (*trans* diastereoisomer).

(Cyanomethyl)triphenylphosphonium chloride (254)



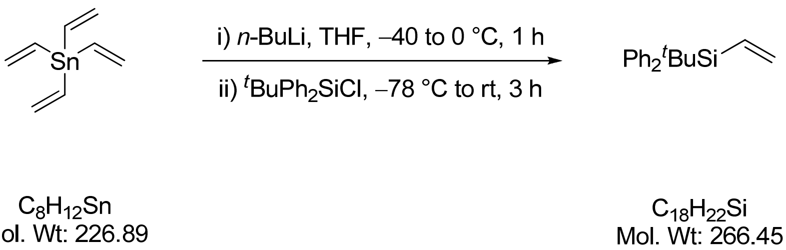
(Cyanomethyl)triphenylphosphonium chloride was prepared based on the procedure reported by Abramovitch *et al.*[187]: A mixture of triphenylphosphine (13.1 g, 50.0 mmol) and toluene (50 mL) were stirred vigorously until the triphenylphosphine had dissolved and chloroacetonitrile (4.56 g, 3.82 mL, 60.0 mmol) was added. The reaction mixture was heated at reflux temperature for 24 h and allowed to cool, (cyanomethyl)triphenylphosphonium chloride precipitated as a white solid. The reaction was filtered washing with petroleum ether (40-60 °C) (3 × 20 mL) and the solid dried under reduced pressure to give the desired product (13.7 g, 40.7 mmol, 81 %) as a white solid; δ_H (270 MHz; $CDCl_3$) 6.71 (2H, d, J_{HP} 16.2, PCH_2), 7.65-7.72 (6H, m, Ar), 7.77-7.83 (3H, m, Ar), 7.97-8.05 (6H, m, Ar); δ_p(109.3 MHz; $CDCl_3$) 22.8 ($[CH_2PPh_3]^+Cl^-$). (Cyanomethyl)triphenylphosphonium chloride was dried prior to use by heating (65 °C) under reduced pressure (0.05 mmHg). The spectral data is in good agreement with previously reported data.[187]

(±)-(Dimethylphenylsilyl)oxirane (259)



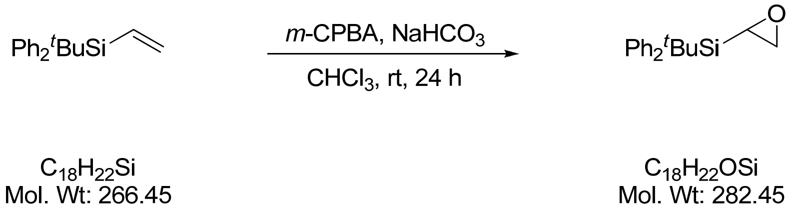
(Dimethylphenylsilyl)oxirane was prepared based on the procedure reported by Barbero *et al.*[121]: To a stirred mixture of *m*-chloroperoxybenzoic acid (2.76 g, 16.0 mmol, 77 %) and sodium hydrogen carbonate (2.70 g, 32.0 mmol) in DCM (30 mL) was added dropwise a solution of dimethylphenylvinylsilane (1.30 g, 8.00 mmol) in DCM (10 mL). The reaction mixture was stirred at room temperature for 24 h then diluted with DCM (60 mL) and washed with saturated aqueous sodium bisulfite (20 mL) and saturated sodium hydrogen carbonate solution (20 mL). The aqueous phase was extracted with DCM (3 × 30 mL) and the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product (2.08 g) as a dark orange oil. Purification by reduced pressure distillation gave the desired product (0.61 g, 3.40 mmol, 43 %) as a colourless oil; bp 45-47 °C/15 mmHg (lit.,[188] 90 °C/7 mmHg); δ_H (400 MHz; $CDCl_3$) 0.31 (3H, s, SiMe), 0.36 (3H, s, SiMe), 2.38 (1H, dd, *J* 5.4 and 4.0, SiCH), 2.57 (1H, dd *J* 5.9 and 4.0, $C\underline{H}_{cis}H_{trans}$ epoxide), 2.94 (1H, t, *J* 5.7, $CH_{cis}\underline{H}_{trans}$ epoxide), 7.35-7.41 (3H, m, Ph), 7.55-7.58 (2H, m, Ph); δ_C (100.6 MHz; $CDCl_3$) −5.4 (SiMe), −5.1 (SiMe), 43.7 (CH epoxide), 44.8 (CH_2 epoxide), 128.1 (2 × *m*-CH, Ph), 129.7 (*p*-CH, Ph), 134.1 (2 × *o*-CH, Ph), 136.1 (C, Ph); LRMS (EI^+, *m/z*): M^+ not visible, 163 ($[M-Me]^+$, 41 %), 135 (100), 121 (85), 104 (39), 91 (21), 77 (30); LRMS (CI^+ (NH_3), *m/z*): 196 ($[M+NH_4]^+$, 96 %), 152 (29), 91 (100); HRMS (ESP, *m/z*) 196.1151 $[M+NH_4]^+$, $C_{10}H_{18}ONSi$ requires 196.1152. The spectral data is in good agreement with previously reported data.[188]

tert-Butyldiphenylvinylsilane (261)



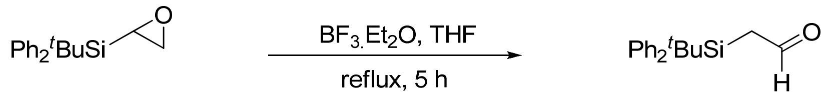
Dimethylphenylvinylsilane was prepared according to the procedure reported by Gerstenberger *et al.*[189] and performed on range of scales from 5 - 60 mmol: To a stirred solution of tetravinyltin (1.00 g, 0.80 mL 4.40 mmol) in anhydrous THF (6 mL) at –40 °C was slowly added dropwise *n*-butyllithium (3.9 mL, 9.7 mmol, 2.5 M solution in hexanes) and the resulting mixture was stirred at –40 °C for 30 min and then 0 °C for 30 min. The resulting vinyllithium solution was cooled to –78 °C and *tert*-butyldiphenylchlorosilane (2.42 g. 2.25 mL, 8.8 mmol) was cautiously added dropwise. The reaction was allowed to warm to room temperature and stirred for 1h then quenched with water (10 mL). The organic phase was separated and the aqueous phase extracted with *n*-hexane (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product (3.34) as a colourless oil. Purification by flash column chromatography [silica gel, elution petroleum ether (40-60 °C)] afforded the desired product (1.33 g, 5.0 mmol, 57 %) as a colourless oil; R_f 0.40 [petroleum ether (40-60 °C)]; δ_H (400 MHz; $CDCl_3$) 1.11 (9H, s, 3 × CH_3), 5.73 (1H, dd, *J* 20.3 and 3.7, $CH=CH_{cis}\underline{H}_{trans}$), 6.29 (1H, dd, *J* 14.8 and 3.7, $CH=C\underline{H}_{cis}H_{trans}$), 6.59 (1H, dd, *J* 20.3 and 14.8, $C\underline{H}=CH_{cis}H_{trans}$), 7.34-7.43 (6H, m, Ar), 7.63 (4H, dd, *J* 7.7 and 1.5, 4 × *o*-CH Ar); δ_C (100.6 MHz; $CDCl_3$) 18.2 (C Si^{t}Bu), 27.8 (3 × CH_3), 127.7 (4 × *m*-CH, Ar), 129.3 (2 × *p*-CH, Ar), 133.6 ($\underline{C}H=CH_2$), 134.1 ($CH=\underline{C}H_2$), 136.4 (4 × *o*-CH, Ar), 136.7 (C, Ar). The spectral data is in good agreement with previously reported data.[189]

(±)-1-*tert*-Butyl(diphenyl)silyl-1,2-epoxyethane (262)



1-*tert*-Butyl(diphenyl)silyl-1,2-epoxyethane was prepared based on the procedure reported by Barbero *et al.*[121]: To a stirred mixture of *m*-chloroperoxybenzoic acid (2.76 g, 16.0 mmol, 77 %) and sodium hydrogen carbonate (2.70 g, 32.0 mmol) in chloroform (80 mL) was added dropwise *tert*-butyldiphenylvinylsilane (2.13 g, 8.00 mmol). The reaction mixture was heated at reflux temperature with vigorous stirring for 24 h. The mixture was allowed to cool to room temperature and washed with saturated aqueous sodium bisulfite (3 × 50 mL), saturated sodium hydrogen carbonate solution (3 × 30 mL), brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product (2.83 g) as a yellow oil. Purification by flash column chromatography [silica gel, elution 10 % diethyl ether- petroleum ether (40-60 °C)] afforded the title compound (1.17 g, 4.10 mmol, 52 %) as a colourless oil; R_f 0.52 [10 % diethyl ether-petroleum ether (40-60 °C)]; δ_H (400 MHz; $CDCl_3$) 1.20 (9H, s, 3 × CH_3), 2.43 (1H, dd, *J* 6.0 and 4.0, CH epoxide), 2.81 (1H, dd, *J* 5.4 and 4.0 $C\underline{H}_aH_b$ epoxide), 2.99 (1H, app t, *J* 5.7, $CH_a\underline{H}_b$ epoxide), 7.34-7.44 (6H, m, Ar), 7.59-7.65 (4H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) 18.8 (C ^{t}Bu), 28.0 (3 × CH_3), 41.4 (CH epoxide), 44.5 (CH_2 epoxide), 127.8 (2 × *m*-CH, Ar), 128.0 (2 × *m*-CH, Ar), 129.7 (*p*-CH, Ar), 129.8 (*p*-CH, Ar), 132.1 (2 × *o*-CH, Ar), 132.6 (2 × *o*-CH, Ar), 136.1 (C, Ar), 136.2 (C, Ar); LRMS (EI^+, *m/z*): M^+ not visible, 225 ($[M-{}^tBu]^+$, 67 %), 183 (100), 105 (31), 77 (12). The spectral data is in good agreement with previously reported data.[121]

***tert*-Butyl(diphenyl)silylacetaldehyde (263)**

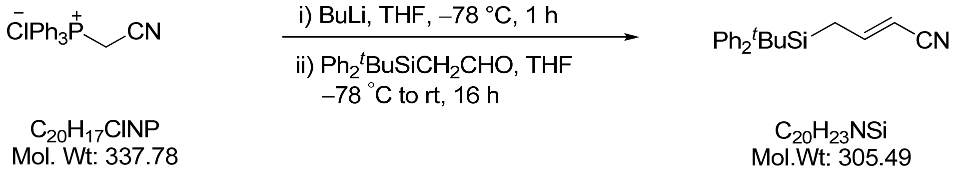


$C_{18}H_{22}OSi$
Mol. Wt: 282.45

$C_{18}H_{22}OSi$
Mol. Wt: 282.45

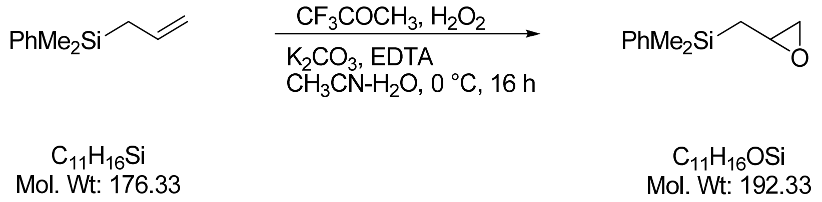
tert-Butyl(diphenyl)silylacetaldehyde was prepared according to the procedure reported by Barbero *et al.*[121] To a stirred solution of 1-*tert*-Butyl(diphenyl)silyl-1,2-epoxyethane (0.90 g, 3.30 mmol) in anhydrous THF (35 mL) was added $BF_3.Et_2O$ (0.52 g, 0.47 mL, 3.70 mmol) and the resulting mixture heated at reflux temperature for 5 h. The reaction mixture was quenched by addition to a saturated aqueous sodium hydrogen carbonate solution (30 mL). The organic phase was washed with water (20 mL), brine (3 × 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product (2.77 g) as a yellow oil. Purification by flash column chromatography [silica gel, gradient elution petroleum ether (40-60 °C) to 10 % diethyl ether : petroleum ether (40-60 °C)] afforded the title compound (0.72 g, 2.50 mmol, 77 %) as a colourless oil; R_f 0.21 [10 % diethyl ether-petroleum ether (40-60 °C)]; δ_H (400 MHz; $CDCl_3$) 1.10 (9H, s, 3 × CH_3), 2.82 (2H, d, *J* 4.3, $C\underline{H}_2CHO$), 7.37-7.45 (6H, m, Ar), 7.61-7.65 (4H, m, Ar), 9.59 (1H, t, *J* 4.3, CHO); δ_C (100.6 MHz; $CDCl_3$) 18.9 (C ^{t}Bu), 27.5 (3 × CH_3), 34.4 ($\underline{C}H_2CHO$), 128.1 (2 × *m*-CH, Ar), 130.0 (*p*-CH, Ar), 132.8 (C, Ar), 135.9 (2 × *o*-CH, Ar), 200.6 (CHO); LRMS (EI^+, *m/z*): M^+ not visible, 225 ($[M-{}^tBu]^+$, 100 %), 183 (56), 105 (11), 77 (4). The spectral data is in good agreement with previously reported data.[121]

4-(*tert*-Butyldiphenylsilyl)but-2-enenitrile (265)



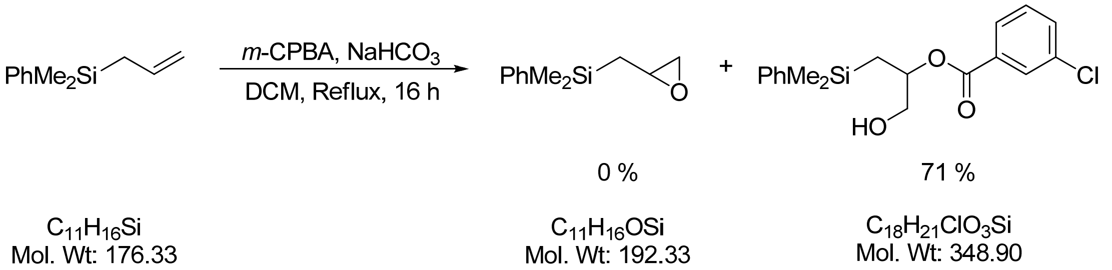
To a stirred suspention of (cyanomethyl)triphenylphosphonium chloride (1.35 g, 4.00 mmol) in anhydrous THF (25 mL) was added *n*-butyllithium (1.60 mL, 4.00 mmol, 2.5 M solution in hexanes) at −78 °C. The resulting bright yellow solution was stirred at −78 °C for 1 h, a solution of *tert*-butyl(diphenyl)silylacetaldehyde (0.40 g, 1.40 mmol) in THF (20 mL) was added dropwise and the reaction was stirred at −78 °C for 1 h, warmed to room temperature and stirred for 16 h. The reaction was poured into water (30 mL) and extracted with diethyl ether (30 mL) and DCM (3 × 20 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a brown oil (1.88 g) containing a precipitate. The crude residue was triturated (diethyl ether-petroleum ether, 3:7, 40 mL) and the filtrate was concentrated *in vacuo* to give the impure products as a yellow oil. Purification by flash column chromatography [silica gel, gradient elution 100 % petroleum ether (40-60 °C) – 10 % diethyl ether : petroleum ether (40-60 °C)] afforded the two geometric isomers of the product (combined yield 0.18 g, 0.59 mmol, 42 %, *trans* : *cis* 1 : 0.5) as colourless oils: *trans* isomer (0.12 g, 0.39 mmol, 28 %); R_f 0.33 [10 % diethylether : petroleum ether (40-60 °C)]; δ_H (400 MHz; $CDCl_3$) 1.08 (9H, s, 3 × CH_3), 2.36 (2H, dd, *J* 8.6 and 1.4, $SiCH_2$), 4.98 (1H, dt, *J* 16.1 and 1.4, $CH{=}C\underline{H}CN$), 6.69 (1H, dt, *J* 16.1 and 8.6, $C\underline{H}{=}CHCN$), 7.37-7.46 (6H, m, Ar), 7.53-7.56 (4H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) 18.7 (C, Si^tBu), 20.6 ($SiCH_2$), 27.8 (3 × CH_3), 98.2 ($CH{=}\underline{C}HCN$), 118.1 ($CH{=}CH\underline{C}N$), 128.1 (4 × *m*-CH, Ar), 129.7 (2 × *p*-CH, Ar), 132.6 (2 × C, Ar), 135.9 (4 × *o*-CH, Ar), 153.8 ($\underline{C}H{=}CHCN$); *cis* isomer: (0.06 g, 0.20 mmol, 14 %); R_f 0.37 [10 % diethylether : petroleum ether (40-60 °C)]; δ_H (400 MHz; $CDCl_3$) 1.11 (9H, s, 3 × CH_3), 2.60 (2H, dd, *J* 8.7 and 1.3, $SiCH_2$), 5.06 (1H, dt, *J* 10.8 and 1.3, $CH{=}C\underline{H}CN$), 6.40 (1H, dt, *J* 10.8 and 8.7, $C\underline{H}{=}CHCN$), 7.37-7.46 (6H, m, Ar), 7.60-7.63 (4H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) 18.7 (C, Si^tBu), 19.5 ($SiCH_2$), 27.7 (3 × CH_3), 97.6 ($CH{=}\underline{C}HCN$), 116.9 ($CH{=}CH\underline{C}N$), 128.0 (4 × *m*-CH, Ar), 129.8 (2 × *p*-CH, Ar), 132.8 (2 × C, Ar), 136.0 (4 × *o*-CH, Ar), 152.9 ($\underline{C}H{=}CHCN$); LRMS (EI^+, *m/z*) 305 ($[M]^+$, 13 %), 248 (46), 197 (30), 181 (19), 135 (100), 105 (28); HRMS (ESP, *m/z*) 323.1942 $[M+NH_4]^+$, $C_{20}H_{27}N_2Si$ requires 323.1938.

(±)-Dimethyl(oxiran-2-ylmethyl)(phenyl)silane (271)



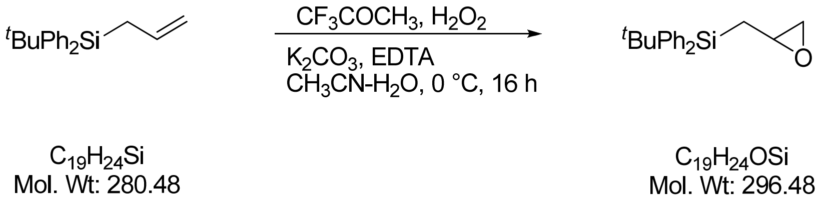
Dimethyl(oxiran-2-ylmethyl)(phenyl)silane was prepared according to to the method published by Shi *et. al.*[125] To a mixture of allyldimethylphenylsilane (1.23 g, 7.00 mmol) and trifluoroacetone (0.24 g, 0.18 mL, 2.10 mmol) in acetonitrile (12 mL) and aqueous potassium carbonate (1.5 M in 7 × 10^{-4} M EDTA, 12 mL) was added H_2O_2 (30 %, 2.80 mL, 28.0 mmol) at 0 °C. The reaction was stirred at 0 °C for 12 h, extracted with diethyl ether (3 × 20 mL) and the organic fractions washed with 1 M sodium bisulfite (2 × 20 mL), brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product as a colourless oil (1.11 g). Purification by flash column chromatography [silica gel, gradient elution 100 % petroleum ether (40-60 °C) – 10 % diethylether : petroleum ether (40-60 °C) buffered with 1 % NEt_3] afforded the desired product (0.55 g, 2.90 mmol, 41 %) as a colourless oil; R_f 0.44 [20 % diethylether : petroleum ether (40-60 °C) buffered with 1 % NEt_3]; ν_{max}(film)/cm^{-1} 3047 (C-H epoxide), 2956, 2917, 1479, 1427, 1249, 1112 (C-O), 833; δ_H (400 MHz; $CDCl_3$) 0.37 (3H, s, SiMe), 0.38 (3H, s, SiMe), 0.85 (1H, dd, *J* 14.2 and 8.2, $SiC\underline{H}_aH_b$), 1.41 (1H, dd, *J* 14.2 and 5.1, $SiCH_a\underline{H}_b$), 2.37 (1H, dd, *J* 5.0 and 2.8, $CH_{trans}\underline{H}_{cis}$ epoxide), 2.73 (1H, ddd, *J* 5.0, 4.1 and 0.9, $C\underline{H}_{trans}H_{cis}$ epoxide), 2.98 (1H, dddd, *J* 8.2 5.1 4.1 and 2.8, $SiCH_2C\underline{H}$), 7.36-7.39 (3H, m, Ph), 7.51-7.55 (2H, m, Ph); δ_C (100.6 MHz; $CDCl_3$) −2.5 (SiMe), −2.4 (SiMe), 20.5 ($SiCH_2$), 48.8 (CH_2, epoxide), 50.4 ($SiCH_2\underline{C}H$), 128.0 (2 × *m*-CH, Ph), 129.4 (*p*-CH, Ph), 133.6 (2 × o-CH, Ph), 138.3 (C, Ph); LRMS (EI^+, *m/z*): M^+ not visible, 177 ($[M-CH_3]^+$ 69 %), 159 (17), 135 (100), 121 (35), 115 (62), 100 (47), 91 (16); LRMS (CI^+ (NH_3), *m/z*): 210 ($[M+NH_4]^+$ 100 %), 177 (12), 114 (11); HRMS was not possible due to the instability of the material.

1-(Dimethyl(phenyl)silyl)-3-hydroxypropan-2-yl 3-chlorobenzoate (272)



To a stirred mixture of *meta*-chloroperoxybenzoic acid (70 %, 1.81 g, 10.5 mmol) and sodium hydrogen carbonate (1.18 g, 14.0 mmol) in dichloromethane (100 mL) was added allyldimethylphenylsilane (1.25 g, 7.09 mmol). The resulting mixture was heated to reflux temperature until all the starting material was consumed (16 h) as determined by TLC. The reaction mixture was washed with saturated sodium bisulfite (20 mL), saturated sodium hydrogen carbonate (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the impure product as a pale yellow oil (2.04 g). Purification by flash column chromatography [silica gel, gradient elution 100 % hexane - 40 % diethylether : petroleum ether (40-60 °C)] followed by flash column chromatography [silica gel, elution 100 % dichloromethane] afforded the title compound (1.73 g, 4.90 mmol, 71 %) as a colourless oil; R_f 0.25 [dichloromethane]; ν_{max}(film)/cm^{-1} 3439 (O-H), 2954, 1715 (C=O), 1427, 1288, 1252, 1113, 826; δ_H (400 MHz; $CDCl_3$) 0.35 (6H, s, $SiMe_2$), 1.26 (1H, dd, *J* 14.7 and 6.7, $\mathrm{SiC\underline{H}_aH_b}$), 1.42 (1H, dd, *J* 14.7 and 8.0, $\mathrm{SiCH_a\underline{H}_b}$), 1.79 (1H, br s, OH), 3.36 (1H, dt, *J* 12.1 and 6.3, $\mathrm{C\underline{H}_aH_bOH}$), 3.72 (1H, ddd, *J* 12.1 6.2 and 3.2, $\mathrm{CH_a\underline{H}_bOH}$), 5.31 (1H, dtd, *J* 8.0 6.6 and 3.2, $\mathrm{SiCH_2C\underline{H}}$), 7.29-7.37 (4H, m, Ar), 7.48-7.52 (3H, m, Ar), 7.78 (1H, dt, *J* 7.8 and 1.2, Ar), 7.86 (1H, t, *J* 1.8 Ar); δ_C (100.6 MHz; $CDCl_3$) −2.4 (SiMe), −2.2 (SiMe), 18.7 ($SiCH_2$), 66.9 (CH_2OH), 75.2 ($\mathrm{SiCH_2\underline{C}H}$), 127.9 (CH, Ar), 128.1 (CH, Ar), 129.4 (CH, Ar), 129.7 (CH, Ar), 129.8 (CH, Ar), 132.0 (C, Ar), 133.1 (CH, Ar), 133.5 (CH, Ar), 134.5 (C, Ar), 138.1 (C, Ar), 165.5 (C=O); LRMS (EI$^+$, *m/z*): M$^+$ not visible, 275 (14), 213 (18), 177 (18), 156 (10), 139 (54), 135 (100), 111 (23); HRMS (ESP, *m/z*) 366.1290 $[M+NH_4]^+$, $C_{18}H_{25}O_3NClSi$ requires 366.1287.

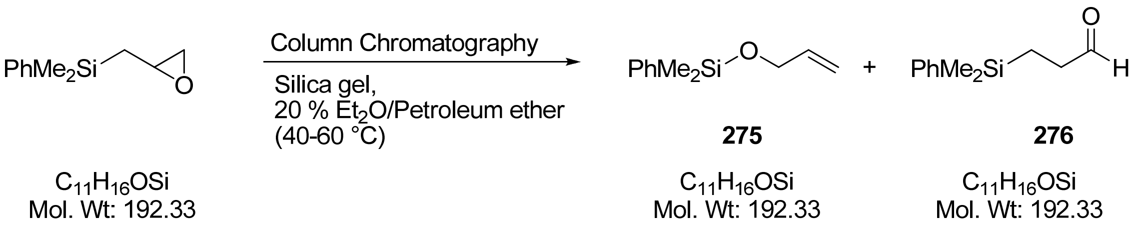
(±)-*tert*-Butyl(oxiran-2-ylmethyl)diphenylsilane (274)



tert-Butyl(oxiran-2-ylmethyl)diphenylsilane was prepared according to the method published by Shi *et. al.*[125] To a mixture of allyl(*tert*-butyl)diphenylsilane (1.26 g, 4.49 mmol) and trifluoroacetone (0.09 g, 0.07 mL, 0.80 mmol) in acetonitrile (10 mL) and aqueous potassium carbonate (1.5 M in 7×10^{-4} M EDTA, 10 mL) was added H_2O_2 (30 %, 1.80 mL, 18.0 mmol) at 0 °C. The reaction was stirred at 0 °C for 12 h, extracted with diethyl ether (3 × 10 mL) and the organic fractions washed with 1 M sodium bisulfite (2 × 10 mL), brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product as a colourless oil (1.60 g). Purification by flash column chromatography [silica gel, elution 20 % diethylether : petroleum ether (40-60 °C)] afforded the desired product (1.19 g, 4.01 mmol, 89 %) as a colourless oil; R_f 0.53 [20 % diethylether : petroleum ether (40-60 °C)]; ν_{max}(film)/cm^{-1} 3046 (C-H epoxide), 2929, 2857, 1471, 1188, 1104 (C-O), 938, 821; δ_H (400 MHz; $CDCl_3$) 1.08 (9H, s, 3 × CH_3), 1.12 (1H, dd, *J* 14.5 and 9.0, $SiC\underline{H}_aH_b$), 1.93 (1H, dd, *J* 14.5 and 4.0, $SiCH_a\underline{H}_b$), 2.27 (1H, dd, *J* 4.8 and 2.8, $C\underline{H}_aH_b$ of epoxide), 2.55 (1H, ddd, *J* 4.8 4.0 and 1.0, $CH_a\underline{H}_b$ of epoxide), 2.98 (1H, dtd, *J* 9.0 4.0 and 2.8, CH epoxide), 7.34-7.45 (6H, m, Ar), 7.60-7.65 (4H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) 15.9 ($SiCH_2$), 18.1 (C, ^{t}Bu), 27.8 (3 × CH_3), 49.5 (CH_2, epoxide), 50.6 (CH, epoxide), 127.8 (2 × *m*-CH, Ar), 127.9 (2 × *m*-CH, Ar), 129.5 (*p*-CH, Ar), 129.5 (*p*-CH, Ar), 134.0 (C, Ar), 134.3 (C, Ar), 135.9 (2 × *o*-CH, Ar), 136.0 (2 × o-CH, Ar); LRMS (EI$^+$, *m/z*): M$^+$ not visible, 239 (85), 221 (19), 197 (11), 181 (29), 161 (100), 117 (21), 105 (29); HRMS (ESP, *m/z*) 314.1938 $[M+NH_4]^+$, $C_{19}H_{28}ONSi$ requires 314.1935. The compound is unstable and was observed to decompose; over 14 days stored at 5 °C the compound changed from 92 % pure to 46 % pure, as determined by GCMS analysis.

Allyloxydimethyl(phenyl)silane (275) and 3-(Dimethyl(phenyl)silyl)propanal (276)

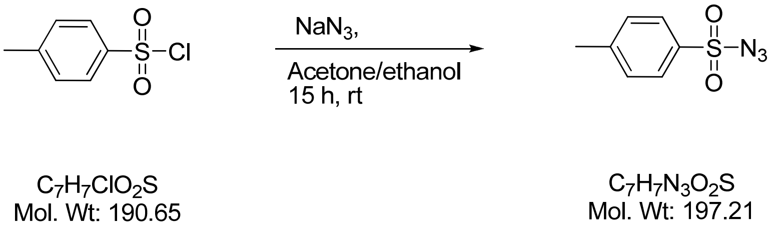
From column chromatography without the triethylamine buffer and during reduced pressure distillation the following reaction was observed to occur:



Allyloxydimethyl(phenyl)silane 275 still containing impurities (0.29 g, 1.50 mmol, 25 %) as a colourless oil; R_f 0.78 [20 % diethylether : petroleum ether (40-60 °C)]; ν_{max}(film)/cm^{-1} 3069, 2957, 2924, 2855, 1646 (C=C), 1251, 1116, 826; δ_H (400 MHz; $CDCl_3$) 0.41 (6H, s, $SiMe_2$), 4.16 (2H, dt, J 4.9 and 1.7, $C\underline{H}_2CH=CH_2$), 5.10 (1H, dq, J 10.4 and 1.7, $CH_2CH=C\underline{H}_{cis}H_{trans}$), 5.27 (1H, dq, J 17.1 and 1.7, $CH_2CH=C\underline{H}_{cis}H_{trans}$), 5.93 (1H, ddt, J 17.1 10.4 and 4.9, $CH_2C\underline{H}=CH_{cis}H_{trans}$), 7.36-7.42 (3H, m, Ph), 7.59-7.62 (2H, m, Ph); δ_C (100.6 MHz; $CDCl_3$) −1.5 (2 × CH_3), 64.2 (OCH_2), 114.8 ($CH_2CH=\underline{C}H_2$), 128.0 (2 × *m*-CH, Ph), 129.8 (*p*-CH, Ph), 133.6 (2 × *o*-CH, Ph), 137.2 ($CH_2\underline{C}H=CH_2$), 137.8 (C, Ph); LRMS (EI$^+$, *m/z*): M$^+$ not visible, 177 ([M-CH_3]$^+$ 60 %), 159 (29), 135 (44), 121 (42), 117 (18), 99 (100), 91 (14), 75 (27). The spectral data is in good agreement with previously reported data.[190]

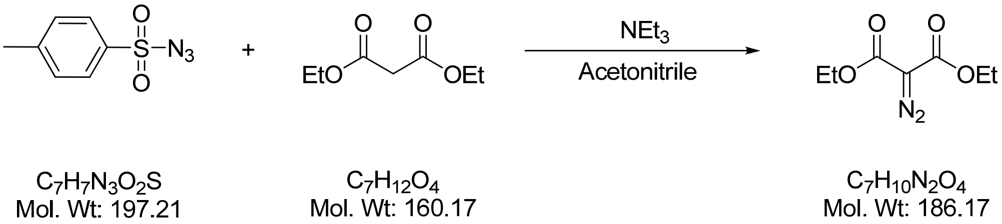
3-(Dimethyl(phenyl)silyl)propanal 276 containing impurities (0.12 g, 0.60 mmol, 12 %) as a pale yellow oil: R_f 0.44 [20 % diethylether : petroleum ether (40-60 °C)]; ν_{max}(film)/cm^{-1} 3070, 2955, 2922, 1722 (C=O), 1427, 1249, 1113, 832; δ_H (400 MHz; $CDCl_3$) 0.31 (3H, s, SiMe), 0.31 (3H, s, SiMe), 0.99-1.04 (2H, m, $SiCH_2$), 2.36-2.41 (2H, m, $C\underline{H}_2CHO$), 7.36-7.38 (3H, m, Ph), 7.49-7.53 (2H, m, Ph), 9.72 (1H, br q, J 1.6, CHO); δ_C (100.6 MHz; $CDCl_3$) −3.1 ($SiMe_2$), 7.6 ($SiCH_2$), 38.5 (CH_2CHO), 128.1 (2 × *m*-CH, Ph), 129.4 (*p*-CH, Ph), 133.7 (2 × *o*-CH, Ph), 138.1 (C, Ph), 202.9 (CHO); LRMS (EI$^+$, *m/z*): M$^+$ not visible, 177 ([M-CH_3]$^+$ 49 %), 159 (13), 135 (100), 121 (27), 107 (11), 105 (20), 99 (44), 91 (8). The spectral data is in good agreement with previously reported data.[191]

Tosyl Azide (280)



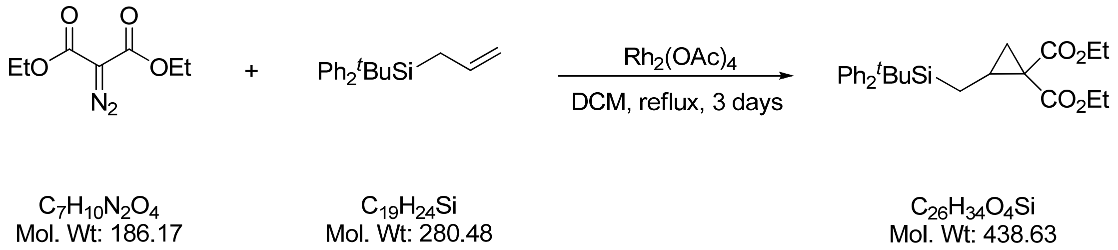
Tosyl azide was prepared according to the procedure reported by McElwee-White *et al.*[192] To a stirred solution of sodium azide (4.80 g, 73.0 mmol) in 95 % ethanol (20 mL) was added a solution of *p*-toluenesulfonyl chloride (13.3 g, 67.0 mmol) in acetone (56 mL). A precipitate formed immediately and the supernatant liquid became orange. The reaction mixture was stirred at room temperature for 15 h under an inert atmosphere, filtered and concentrated *in vacuo* to give an oil. The residue was diluted with DCM (30 mL), washed with water (2 × 20 mL) and the combined aqueous layers extracted with DCM (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the product (11.8 g, 59.6 mmol, 89 %) as a colourless oil; δ_H (270 MHz; $CDCl_3$) 2.46 (3H, s, CH_3), 7.39 (2H, d, *J* 8.5, Ar), 7.81(2H, d, *J* 8.5, Ar); δ_C (66.7 MHz; $CDCl_3$) 22.0 (CH_3), 127.7 (2 × CH, Ar), 130.5 (2 × CH, Ar), 135.7 (C, Ar), 146.4 (C, Ar). The data is in good agreement with previously reported data[193]

Diethyl 2-diazomalonate (282)



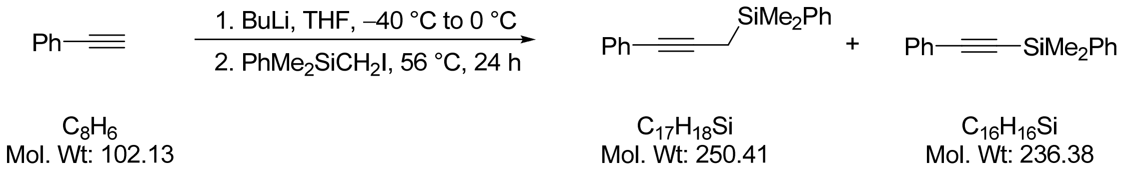
To a stirred solution of diethyl malonate (2.00 g, 1.90 mL, 12.0 mmol) and *p*-toluenesulfonyl azide (2.60 g, 13.0 mmol) in anhydrous acetonitrile (30 mL) was added dropwise over 0.5 h neat triethylamine (1.40 g, 1.90 mL, 14.0 mmol) at 0 °C. The reaction was allowed to stir at room temperature for 24 h, diluted with DCM (30 mL) and the organic layer was separated. The aqueous layer extracted with DCM (3 × 20 mL) and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a dark orange oil (4.52 g). The residue was triturated (diethyl ether-petroleum ether, 1:1) and the solvent removed under reduced pressure to give the impure product as a an orange oil (2.32 g). Purification by flash column chromatography [silica gel, 20 % ethyl acetate-petroleum ether (40-60 °C)] afforded the desired (2.24 g, 12.0 mmol, 99 %) as a yellow oil which solidified on cooling (5 °C); R_f 0.45 [20 % ethyl acetate-petroleum ether (40-60 °C)]; δ_H (400 MHz; $CDCl_3$) 1.31 (6H, t, *J* 7.1, $OCH_2C\underline{H}_3$), 4.30 (4H, q, *J* 7.1, $OC\underline{H}_2CH_3$); δ_C (100.6 MHz; $CDCl_3$) 14.5 ($OCH_2\underline{C}H_3$), 61.7 ($O\underline{C}H_2CH_3$), 161.2 (2 × $\underline{C}O_2Et$). The data is in good agreement with previously reported values.[194]

(±)-Diethyl 2-((tert-butyldiphenylsilyl)methyl)cyclopropane-1,1-dicarboxylate (283)



Diethyl 2-((tert-butyldiphenylsilyl)methyl)cyclopropane-1,1-dicarboxylate was prepared based on the method published by Yadav *et. al.*[62] To a stirred mixture of allyl-*tert*-butyldiphenylsilane (1.12 g, 4.00 mmol) and dirhodium tetraacetate dihydrate (43.0 mg, 0.09 mmol) in anhydrous chloroform (0.5 mL) heated at reflux temperature was added over a period of 10 h using a syringe pump a solution of diethyl 2-diazomalonate (0.37 g, 2.00 mmol) in anhydrous chloroform (2 mL). The reaction mixture was stirred at reflux temperature for a further 12 h, cooled to room temperature and the solvent removed *in vacuo*. Purification of the residue by flash column chromatography [silica gel, 20 % diethyl ether-petroleum ether (40-60 °C)] gave the desired product (0.53 g, 1.20 mmol, 60 %) as a colourless oil; R_f 0.33 [20 % ethyl acetate-petroleum ether (40-60 °C)]; ν_{max}(film)/cm^{-1} 3058, 2930. 2857, 1720 (C=O), 1427, 1207, 1101, 820; δ_H (400 MHz; CDCl$_3$) 0.78 (1H, dd, *J* 14.7 and 11.7, $SiC\underline{H}_aH_b$), 1.04 (9H, s, 3 × CH$_3$), 1.10-1.16 (2H, m, CH$_2$ cyclopropyl), 1.19 (3H, t, *J* 7.2, $OCH_2C\underline{H}_3$), 1.31 (3H, t, *J* 7.1, $OCH_2C\underline{H}_3$), 1.64 (1H, dd, *J* 14.7 and 2.7, $SiCH_a\underline{H}_b$), 1.86-1.94 (1H, m, CH cyclopropyl), 4.02-4.17 (2H, m, $OC\underline{H}_2CH_3$), 4.18-4.34 (2H, m, $OC\underline{H}_2CH_3$), 7.33-7.43 (6H, m, Ar), 7.60-7.65 (4H, m, Ar); δ_C (100.6 MHz; CDCl$_3$) 10.2 (SiCH$_2$), 14.2 ($OCH_2\underline{C}H_3$), 14.5 ($OCH_2\underline{C}H_3$), 18.3 (3 × C), 23.4 (CH$_2$ cyclopropyl), 25.5 (CH cyclopropyl), 27.9 (3 × CH$_3$), 35.6 (C cyclopropyl), 61.3 ($O\underline{C}H_2CH_3$), 61.4 ($O\underline{C}H_2CH_3$), 127.7 (2 × *m*-CH, Ar), 127.8 (2 × *m*-CH, Ar), 129.4 (*p*-CH, Ar), 134.0 (C, Ar), 134.2 (C, Ar), 136.1 (2 × *o*-CH, Ar), 136.2 (2 × *o*-CH, Ar), 168.5 ($\underline{C}O_2Et$), 170.5 ($\underline{C}O_2Et$); LRMS (EI$^+$, *m/z*): 381 ([M-^{t}Bu]$^+$, 72 %), 263 (11), 227 (13), 183 (34), 135 (100), 105 (19); HRMS (EI, *m/z*) 439.2302 [M+H]$^+$, $C_{26}H_{35}O_4Si$ requires 439.2299.

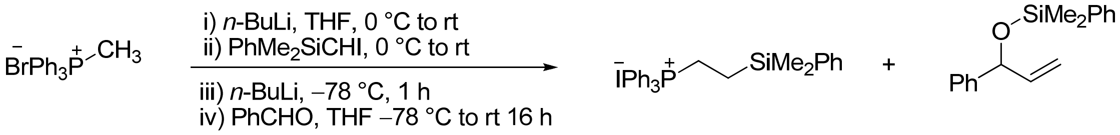
Dimethyl(phenyl)(3-phenylprop-2-ynyl)silane (287)



Dimethyl(phenyl)(3-phenylprop-2-ynyl)silane was prepared according to the method previously reported.[195] To a stirred solution of phenylacetylene (1.02 g,1.09 mL, 10.0 mmol) in THF (11 mL) at –40 ºC was added dropwise butyllithium (5.00 mL of a 2.5 M solution in hexanes, 12.5 mmol) upon which the reaction mixture became a dark yellow colour. The reaction mixture was stirred at –40 ºC for 15 min then allowed to slowly warm to 0 ºC, (Iodomethyl)dimethylphenylsilane (2.70 g, 10.0 mmol) was added and the reaction turned a black colour. The reaction was heated at 56 ºC for 24 hours cooled to room temperature and quenched by the addition of H_2O (10 mL). The organic layer was separated and the aqueous layer extracted with diethyl ether (3 × 20 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product as a yellow oil (2.60 g). Purification by flash column chromatography [silica gel, petroleum ether (40-60 °C)] afforded the desired product (0.85 g, 3.43 mmol, 34 %) as a colourless oil; R_f 0.18 [petroleum ether (40-60 °C)]; ν_{max}(film)/cm^{-1} 3069, 2957, 2208 (C≡C), 1491, 1250, 1115, 816; δ_H (400 MHz; $CDCl_3$) 0.65 (6H, s, $SiMe_2$), 2.14 (2H, s, $SiCH_2$), 7.43-7.60 (8H, m, Ar), 7.80-7.82 (2H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) –3.6 ($SiMe_2$), 7.4 ($SiCH_2$), 80.0 (C≡C), 88.1 (C≡C), 124.8 (C, Ar), 127.2 (CH, Ar), 128.3 (CH, Ar), 129.5 (CH, Ar), 131.4 (CH, Ar), 133.8 (CH, Ar), 137.7 (C, Ar); LRMS (EI$^+$, *m/z*): 250 (M$^+$, 63 %), 235 (16), 221 (16), 135 (100), 115 (87), 105 (70), 89 (30), 77 (18); HRMS (EI, *m/z)* 250.1166 [M]$^+$, $C_{17}H_{18}Si$ requires 250.1172.

Dimethyl(phenyl)(phenylethynyl)silane 288 (0.87 g, 3.7 mmol, 37 %) as a pale yellow oil; R_f 0.22 [petroleum ether (40-60 °C)]; δ_H (400 MHz; $CDCl_3$) 0.52 (6H, s, $SiMe_2$), 7.27-7.57 (8H, m Ar), 7.70-7.74 (2H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) -0.7 (2 × CH_3), 92.2 (C≡C), 106.9 (C≡C), 128.1 (CH, Ar), 128.4 (CH, Ar), 128.8 (CH, Ar), 129.6 (CH, Ar), 132.2 (CH, Ar), 133.9 (CH, Ar), 137.2 (C, Ar), 138.7 (C, Ar); LRMS (EI$^+$, *m/z*): 236 (M$^+$, 18 %), 221 (100), 178 (17), 135 (50), 129 (21), 115 (14), 105 (36), 91 (15), 77 (21); HRMS (CI, *m/z)* 237.1091 [M+H]$^+$, $C_{16}H_{17}Si$ requires 237.1094. The data is in good agreement with previously reported data.[196]

Dimethyl(phenyl)(1-phenylallyloxy)silane (290) and 2-Dimethyl(phenyl)silylethylidentriphenylphosphonium iodide (293):



293 **290**

$C_{19}H_{18}BrP$
Mol. Wt: 357.22

$C_{28}H_{30}IPSi$
Mol. Wt: 552.50

$C_{17}H_{20}OSi$
Mol. Wt: 268.43

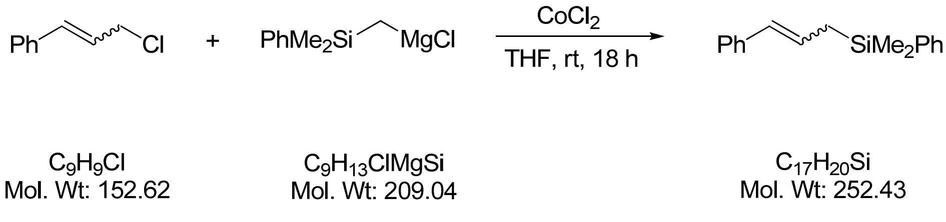
Based on the procedure reported by Mohan *et al.*[197]: Prior to the reaction methyltriphenylphosphonium bromide was dried (60 °C/0.03 mmHg) for 30 min and (iodomethyl)dimethylphenylsilane was freshly distilled. To a stirred suspension of methyltriphenylphosphonium bromide (3.39 g, 9.40 mmol) in anhydrous THF (15 mL) was added *n*-butyllithium (4.00 mL, 10.0 mmol, 2.5 M solution in hexanes) at 0 °C. The mixture was warmed to room temperature, stirred for 1 h, recooled to 0 °C and (Iodomethyl)dimethylphenylsilane (3.00 g, 10.8 mmol) was added over 10 min. The reaction was allowed to warm to room temperature, stirred for 1 h, cooled to −78 °C, treated with *n*-butyllithium (4.00 mL, 10.0 mmol, 2.5 M solution in hexanes) and stirred at room temperature for 1.5 h. The reaction was cooled to −78 °C and a solution of benzaldehyde (1.10 g, 1.07 mL, 10.3 mmol) in THF (8 mL) was added. After 0.5 h the mixture was allowed to warm slowly to room temperature and was stirred for 16 h. The reaction was quenched by pouring into saturated aqueous ammonium chloride solution (30 mL) and extracted with diethyl ether (3 × 30 mL) and then DCM (20 mL) to extract the precipitate.

Dimethyl(phenyl)(1-phenylallyloxy)silane **290**: The etherate fraction was washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil (4.42 g). Flash column chromatography [silica gel, elution 10 % dichloromethane-petroleum ether (40-60 °C)] followed by stirring with copper chloride and filtering through a silica plug to remove the triphenylphosphine impurity gave the title compound (0.82 g, 3.10 mmol, 33 %) as a colourless oil; R_f 0.21 [10 % dichloromethane-petroleum ether (40-60 °C)]; ν_{max}(film)/cm^{-1} 3068 (CH alkene), 3027, 2958, 2856, 1640 (w, C=C), 1428, 1116, 1060, 989, 922, 827; δ_H (400 MHz; $CDCl_3$) 0.35 (3H, s, SiMe), 0.39 (3H, s, SiMe), 5.10 (1H dt, *J* 10.2 and 1.2, CH=C$\underline{H}_{cis}H_{trans}$), 5.17 (1H, d, *J* 6.0 C$\underline{H}$CH=CH$_{cis}H_{trans}$), 5.49 (1H, dt, *J* 17.0 and 1.2, CHCH=CH$_{cis}\underline{H}_{trans}$), 5.97

(1H, ddd, *J* 17.0 10.2 and 6.0, CHC<u>H</u>=$CH_{cis}H_{trans}$), 7.22-7.43 (8H, m, Ar), 7.58 (2H, dd, *J* 7.6 and 1.6, 2 × *o*-CH of SiPh); δ_C (100.6 MHz; $CDCl_3$) −0.9 (SiMe), −0.7 (SiMe), 76.3 (C<u>H</u>OSi), 114.2 (CH=CH_2), 126.4 (2 × *m*-CH, Ph) 127.3 (*p*-CH, Ph), 127.9 (2 × *m*-CH, SiPh), 128.4 (2 × *o*-CH, Ph), 129.7 (*p*-CH, SiPh), 133.7 (*o*-CH, SiPh), 138.0 (C, SiPh), 141.3 (CH=CH_2), 143.3 (C, Ph); LRMS (EI^+, *m/z*) 268 (14), 253 (15), 190 (63), 175 (35), 135 (98), 117 (100), 105 (18), 91 (34), 75 (29); HRMS (ESP, *m/z*) 286.1624 $[M+NH_4]^+$, $C_{17}H_{24}ONSi$ requires 286.1622.

2-Dimethyl(phenyl)silylethylidentriphenylphosphonium iodide **293**: The DCM fraction was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a gray solid (2.16 g). Purification by recrystallisation from the minimum amount of hot DCM gave the desired product (1.86 g, 3.40 mmol, 36 %) as a white crystalline solid; δ_H (400 MHz; $CDCl_3$) 0.40 (6H, s, $SiMe_2$), 0.83-0.90 (2H, m, $SiCH_2$), 3.23-3.31 (2H, m, CH_2PPh_3), 7.28-7.41 (5H, m, Ar), 7.52-7.77 (15H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) −3.4 ($SiMe_2$), 7.98 (CH_2, d, J_{CP} 8.1, $SiCH_2$), 18.5 (CH_2, d, J_{CP} 46.5, PCH_2), 117.6 (C, d, J_{CP} 85.2, 3 × *ipso*-C PPh_3), 128.1 (2 × *m*-CH, SiPh), 129.6 (*p*-CH, SiPh), 130.5 (CH, d, J_{CP} 12.4, 6 × *o*-CH, PPh_3), 133.6 (CH, d, J_{CP} 9.7, 6 × *m*-CH, PPh_3), 133.6 (2 × *o*-CH, SiPh), (2 × C Ar), 135.1 (CH, d, J_{CP} 2.9, 3 × *p*-CH, PPh_3), 136.3 (C, SiPh); δ_P(162 MHz, $CDCl_3$) 26.4 ($[CH_2PPh_3]^+$); HRMS (ESP, *m/z*) 425.1845 $[M-I]^+$, $C_{28}H_{30}PSi$ requires 425.1849.

(*E*/*Z*)-3-dimethylphenylsilyl-1-phenyl-1-propene (291)



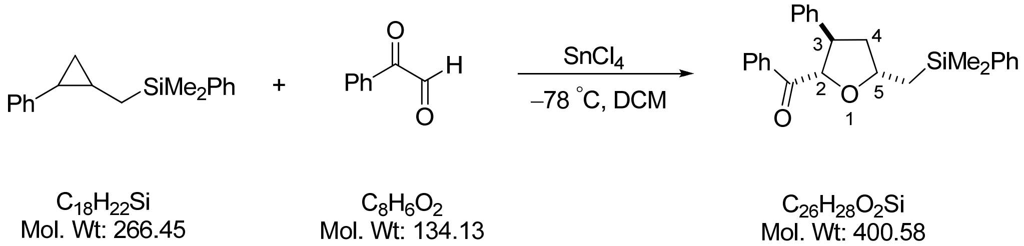
Preparation of anhydrous cobalt (II) chloride: Cobalt chloride hexahydrate (approx 2 g) was weighed into a 25 mL flask, placed under vacuum (0.05 mmHg) and gently heated with a heat gun. The red solid was observed to "bump" as the water was removed and change to a bright blue solid. The anhydrous cobalt (II) chloride was placed under nitrogen and used immediately.

Preparation of dimethylphenylsilylmethylmagnesium chloride[198]: To a stirred suspension of magnesium turnings (2.26 g, 93.0 mmol) in THF (19 mL) was added dropwise neat 1,2-

dibromoethane (0.82 g, 0.40 mL, 4.52 mmol). After effervescence had subsided (chloromethyl)dimethylphenylsilane (3.70 g, 3.60 mL, 20.0 mmol) was added at such a rate to maintain a gentle reflux during the course of the addition. The reaction mixture was allowed to stir for 15 min at room temperature to give a light gray solution of dimethylphenylsilylmethylmagnesium chloride (approx. 1 M in THF).

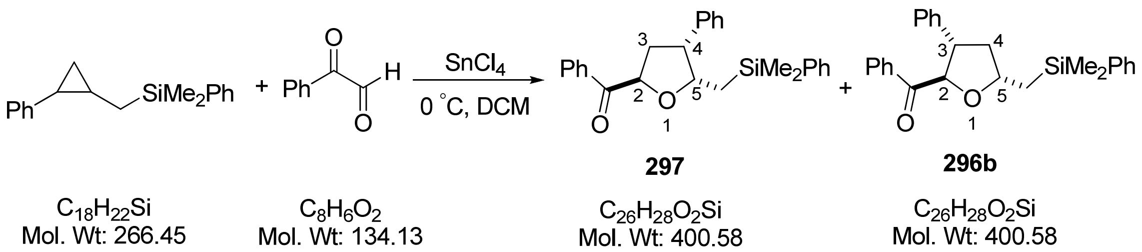
Preparation of (*E*/*Z*)-3-dimethylphenylsilyl-1-phenyl-1-propene based on the procedure reported by Affo *et. al.*[130] To a blue solution of anhydrous cobalt (II) chloride (0.31 g, 2.40 mmol) and β-bromostyrene (2.20 g, 1.55 mL, 12.0 mmol, *E*/*Z* =1: 0.1) in THF (12 mL) was added dropwise a solution of dimethylphenylsilylmagnesium chloride (18.0 mL, 18.0 mmol, 1 M solution in THF) at 0 °C. During the addition the reaction mixture became a brown colour. The ice bath was removed and the reaction allowed to stir at room temperature over 18 h then partitioned between saturated aqueous ammonium chloride solution (30 mL) and ethyl acetate (20 mL). The organic phase was separated and the aqueous phase extracted with ethyl acetate (3 × 20 mL). The combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product as a brown oil (4.25 g). Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 2 % diethyl ether : hexane] afforded the desired product (3.08 g, 12.0 mmol, 98 %, *trans* : *cis* 1 : 0.1) as a mixture of isomers and as a colourless oil; R_f 0.19 [hexane]; ν_{max}(film)/cm^{-1} 3023, 2955, 1640 (C=C), 1427, 1248, 1113, 813; *trans* isomer: δ_H (400 MHz; $CDCl_3$) 0.37 (6H, s, $SiMe_2$), 1.95 (2H, d, *J* 6.8, $SiCH_2$), 6.22-6.32 (2H, m, C$\underline{H}$=C$\underline{H}$), 7.18-7.21 (1H, m, Ar), 7.28-7.32 (4H, m, Ar), 7.39-7.43 (3H, m, Ar), 7.57-7.59 (2H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) −3.2 ($SiMe_2$), 23.2 ($SiCH_2$), 125.7 (CH, Ar), 126.4 (CH, Ar), 127.3 (CH=CH), 128.0 (CH, Ar), 128.6 (CH, Ar), 129.1 (CH=CH), 129.2 (CH, Ar), 133.8 (CH, Ar), 138.5 (C, Ar), 138.7 (C, Ar); *cis* isomer: δ_H (400 MHz; $CDCl_3$) 0.35 (6H, s, $SiMe_2$), 2.11 (2H, dd, *J* 9.0 and 1.1, $SiCH_2$), 5.75 (1H, dt, *J* 11.7 and 9.0, $CH_2C\underline{H}$=CH), 6.39 (1H, d, *J* 11.7, CH_2CH=C$\underline{H}$), 7.19-7.41 (8H, m, Ar), 7.51-7.56 (8H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) −3.0 ($SiMe_2$), 18.8 ($SiCH_2$), 126.3 (CH, Ar), 127.7 (CH=CH), 127.8 (CH, Ar), 128.2 (CH=CH), 128.4 (CH, Ar), 128.7 (CH, Ar), 129.2 (CH, Ar), 133.7 (CH, Ar), 138.2 (C, Ar), 138.7 (C, Ar); LRMS (EI^+, *m/z*): 252 ($[M]^+$, 9 %), 135 (100), 115 (9) 105 (15), 91 (6); HRMS (EI, *m/z*) 252.1331 $[M]^+$, $C_{17}H_{20}Si$ requires 252.1331. Diastereoselectivity calculated by analysis of the ^1H NMR integrals for the $SiC\underline{H}_2$ protons at 1.95 (*E*-diastereoisomer) and 2.11 ppm (*Z*-diastereoisomer). The spectral data is in good agreement with previously reported data.[199]

(±)-(5-((dimethyl(phenyl)silyl)methyl)-3-phenyltetrahydrofuran-2-yl)(phenyl)methanone (296a)



To a stirred solution of freshly distilled phenyl glyoxal (0.12 g, 0.90 mmol) in anhydrous DCM (3 mL) at −78 °C and under an atmosphere of argon was added, dropwise, a solution of tin tetrachloride (0.17 g, 0.08 mL, 0.66 mmol) in anhydrous DCM (3 mL). The resulting mixture was stirred at −78 °C for 5 min followed by the dropwise addition of a solution of dimethyl(phenyl)((2-phenylcyclopropyl)methyl)silane (0.16 g, 0.60 mmol) in anhydrous DCM (3 mL). The reaction was stirred at −78 °C and monitored by TLC, after 5 h the reaction was quenched by the addition of wet acetone (5 mL) and allowed to warm to 0 °C and poured on to H_2O (10 mL). The organic layer was separated and the aqueous layer further extracted with DCM (3 × 10 mL). The combined organic phases were washed with brine (10 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product (0.25 g) as a yellow oil. Purification by flash column chromatography [silica gel, gradient elution 100 % hexane – 20 % diethyl ether : hexane] followed by flash column chromatography [silica gel, gradient elution 60 % dichloromethane : hexane] afforded the desired product as single diastereoisomer (0.02 g, 0.04 mmol, 7 %) as a colourless oil; R_f 0.48 [60 % dichloromethane : hexane]; δ_H (600 MHz; $CDCl_3$); 0.28 (3H, s, $SiCH_3$), 0.30 (3H, s, $SiCH_3$), 1.24 (1H, dd, *J* 14.3 and 8.0, $SiC\underline{H}_aH_b$), 1.48 (1H, dd, *J* 14.3 and 6.5, $SiH_a\underline{H}_b$), 2.01 (1H, app dt, *J* 12.7 and 8.7, $C\underline{H}_aH_b$ C-4 THF), 2.14 (1H, ddd, *J* 12.6 6.3 and 4.8, $CH_a\underline{H}_b$ C-4 THF), 3.84 (1H, app dt, *J* 8.9 and 5.1, CH C-3 THF), 4.50 (1H, app tt, *J* 7.8 and 6.5, CH C-5 THF), 5.14 (1H, d, *J* 5.5, CH C-2 THF), 7.20-7.41 (10H, m, Ar), 7.50-7.53 (3H, m, Ar), 7.92-7.93 (2H, m, Ar); δ_C (100.6 MHz; $CDCl_3$) −2.3 ($SiCH_3$), −2.0 ($SiCH_3$), 24.2 ($SiCH_2$), 42.5 (CH_2 C-4 THF), 47.4 (CH C-3 THF), 79.3 (CH C-5 THF), 86.6 (CH C-2 THF), 126.9 (CH, Ar), 127.6 (CH, Ar), 127.9 (CH, Ar), 128.5 (CH, Ar), 128.9 (CH, Ar), 129.1 (CH, Ar), 129.3 (CH, Ar), 133.3 (CH, Ar), 133.7 (CH, Ar), 135.6 (C, Ar), 139.0 (C, Ar), 142.9 (C, Ar), 197.5 (C=O); LRMS (EI^+, *m/z*): M^+ not visible, 295 ($[M-PhCO]^+$, 12 %), 277 (4), 239 (5), 135 (100), 105 (13), 91 (10), 77 (15); HRMS (ESI, *m/z*) 418.2195 $[M+NH_4]^+$, $C_{26}H_{32}O_2NSi$ requires 418.2197.

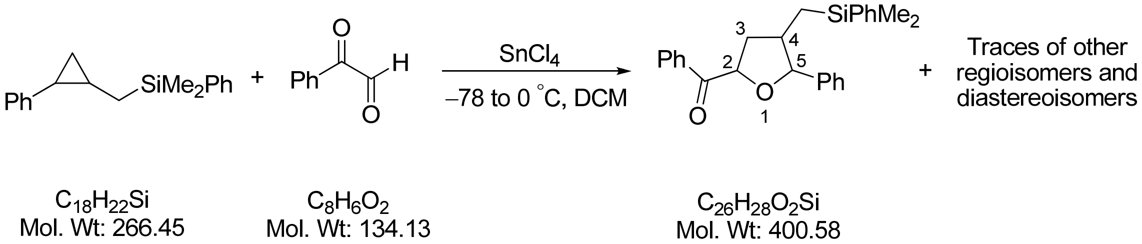
(±)-(5-((dimethyl(phenyl)silyl)methyl)-4-phenyltetrahydrofuran-2-yl)(phenyl)methanone (297) and (±)-(5-((dimethyl(phenyl)silyl)methyl)-3-phenyltetrahydrofuran-2-yl)(phenyl)methanone (296b)



To a stirred solution of freshly distilled phenyl glyoxal (0.12 g, 0.90 mmol) and dimethyl(phenyl)((2-phenylcyclopropyl)methyl)silane (0.16 g, 0.60 mmol) in anhydrous DCM (6 mL) at 0 °C and under an atmosphere of argon was added, dropwise, a solution of tin tetrachloride (0.01 g, 0.04 mL, 0.36 mmol) in anhydrous DCM (3 mL). The reaction was stirred at 0 °C and monitored by TLC. After 3 h the reaction was quenched by the addition of water (5 mL), the organic layer was separated and the aqueous layer further extracted with DCM (3 × 10 mL). The combined organic phases were washed with brine (10 mL), separated, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the impure product (0.26 g) as a yellow oil. Purification by flash column chromatography [silica gel, 50 % dichloromethane : hexane] afforded product **297** (yield 0.02 g, 0.06 mmol, 10 %) as a colourless oil; R_f 0.48 [50 % dichloromethane : hexane]; δ_H (400 MHz; $CDCl_3$) 0.21 (3H, s, $SiCH_3$), 0.28 (3H, s, $SiCH_3$), 1.04-1.06 (2H, m, $SiCH_2$), 2.50 (1H, ddd, *J* 13.0 10.6 and 7.2, $C\underline{H}_aH_b$ C-3 THF), 2.67 (1H, dt, *J* 13.1 and 8.4, $CH_a\underline{H}_b$ C-3 THF), 2.95 (1H, q, *J* 9.4, CH C-4 THF), 4.00 (1H, ddd, J 9.4 7.3 and 5.9, CH C-5 THF), 5.38 (1H, dd, *J* 8.1 and 7.3, CH C-2 THF), 7.17-7.61 (13H, m, Ar), 8.04 (2H, app dd, *J* 8.1 and 0.9, Ar); δ_C (100.6 MHz; $CDCl_3$) −2.5 ($SiCH_3$), −1.9 ($SiCH_3$), 20.4 ($SiCH_2$), 37.2 (CH_2, C-3 THF) 55.3 (CH, C-4 THF), 78.7 (CH, C-2 THF), 84.3 (CH, C-5 THF), 127.0 (CH, Ar), 127.7 (CH, Ar), 128.8 (CH, Ar), 129.2 (CH, Ar), 133.4 (CH, Ar), 133.7 (CH, Ar), 135.4 (C, Ar), 139.6 (C, Ar), 140.0 (C, Ar), 198.9 (C=O); LRMS (EI^+, *m/z*): M^+ not visible, 323 ($[M-Ph]^+$, 1 %), 296 (10), 239 (4), 135 (60), 117 (100), 105 (40), 91 (10), 77 (21); HRMS (ESP, *m/z*) 418.2196 $[M+NH_4]^+$, $C_{26}H_{28}O_2NSi$ requires 418.2197.

(±)-(5-((dimethyl(phenyl)silyl)methyl)-3-phenyltetrahydrofuran-2-yl)(phenyl)methanone 296b (0.03 g, 0.09 mmol, 14 %) is a colourless oil; R_f 0.35 [50 % dichloromethane : hexane]; δ_H (600 MHz; CDCl$_3$) 0.31 (3H, s, SiCH$_3$), 0.33 (3H, s, SiCH$_3$), 1.24 (1H, dd, *J* 14.3 and 8.0, SiC$\underline{H}_a$H$_b$), 1.52 (1H, dd, *J* 14.2 and 6.2, SiCH$_a\underline{H}_b$), 1.78 (1H, app dt, *J* 12.2 and 10.3, C$\underline{H}_a$H$_b$ C-4 THF), 2.44 (1H, ddd, *J* 12.3 7.8 and 4.8, CH$_a\underline{H}_b$ C-4 THF), 3.78 (1H, dt, *J* 10.3 and 7.4, CH C-3 THF), 4.29 (1H, dddd, *J* 10.3 7.7 6.4 and 4.8, CH C-5 THF), 5.19 (1H, d, *J* 6.8, CH C-2 THF), 7.20-7.39 (10H, m, Ar), 7.48-7.52 (3H, m, Ar), 7.30 (2H, app dd, *J* 8.3 and 1.0, Ar); δ_C (100.6 MHz; CDCl$_3$) -2.2 (SiCH$_3$), -2.0 (SiCH$_3$), 23.2 (SiCH$_2$), 45.2 (CH$_2$, C-4 THF) 48.3 (CH, C-3 THF), 79.3 (CH, C-5 THF), 86.1 (CH, C-2 THF), 126.9 (CH, Ar), 127.8 (CH, Ar), 127.9 (CH, Ar), 128.4 (CH, Ar), 128.9 (CH, Ar), 129.1 (CH, Ar), 129.3 (CH, Ar), 133.3 (CH, Ar), 133.7 (CH, Ar), 135.4 (C, Ar), 138.9 (C, Ar), 142.6 (C, Ar), 198.5 (C=O); LRMS (EI$^+$, *m/z*): M$^+$ not visible, 295 ([M-PhCO]$^+$, 18 %), 277 (4), 239 (5), 135 (100), 105 (19), 91 (8), 77 (14); HRMS (ESI, *m/z*) 418.2190 [M+NH$_4$]$^+$, $C_{26}H_{32}O_2NSi$ requires 418.2197.

(±)-(4-((dimethyl(phenyl)silyl)methyl)-5-phenyltetrahydrofuran-2-yl)(phenyl)methanone (298)



To a stirred solution of freshly distilled phenyl glyoxal (0.12 g, 0.90 mmol) and dimethyl(phenyl)((2-phenylcyclopropyl)methyl)silane (0.16 g, 0.60 mmol) in anhydrous DCM (6 mL) at –78 °C and under an atmosphere of argon was added, dropwise, a solution of tin tetrachloride (0.01 g, 0.04 mL, 0.36 mmol) in anhydrous DCM (3 mL). The reaction was stirred and allowed to warm to 0 °C and monitored by TLC. After 2 h at 0 °C the reaction was quenched by the addition of water (5 mL), the organic layer was separated and the aqueous layer further extracted with DCM (3 × 10 mL). The combined organic phases were washed with brine (10 mL), separated, dried (MgSO$_4$), filtered and concentrated *in vacuo* to give the impure product (0.22 g) as a yellow oil. Purification by flash column chromatography [silica gel, gradient elution, 100 % hexane – 10 % diethyl ether : hexane] followed by preparative TLC

[60 % dichloromethane : hexane] afforded product (7.00 mg, 0.02 mmol, 3 %) as a colourless oil; *R*$_f$ 0.19 [60 % dichloromethane : hexane]; δ_H (400 MHz; CDCl$_3$) 0.21 (3H, s, SiCH$_3$), 0.23 (3H, s, SiCH$_3$), 0.75 (1H, dd, *J* 14.7 and 11.3, SiC$\underline{H}_a$H$_b$), 0.99 (1H, dd, *J* 14.7 and 2.8, SiCH$_a\underline{H}_b$), 1.85 (1H, ddd, *J* 12.3 10.8 and 8.7, C$\underline{H}_a$H$_b$ C-3 THF), 2.18 (1H, m, CH C-4 THF), 2.45 (1H, dt, *J* 12.6 and 7.4, CH$_a\underline{H}_b$ C-3 THF), 4.50 (1H, d, *J* 9.1, CH C-5 THF), 5.44 (1H, t, *J* 8.0, CH C-2 THF), 7.25-7.56 (13H, m, Ar), 7.98 (2H, app d, *J* 8.1, Ar); δ_C (100.6 MHz; CDCl$_3$) −2.4 (SiCH$_3$), −2.0 (SiCH$_3$), 16.9 (SiCH$_2$), 38.2 (CH$_2$, C-3 THF) 44.9 (CH, C-4 THF), 79.9 (CH, C-2 THF), 90.1 (CH, C-5 THF), 127.1 (CH, Ar), 128.0 (CH, Ar), 128.1 (CH, Ar), 128.5 (CH, Ar), 128.7 (CH, Ar), 129.0 (CH, Ar), 129.2 (CH, Ar), 133.4 (CH, Ar), 133.6 (CH, Ar), 135.4 (C, Ar), 138.7 (C, Ar), 140.2 (C, Ar), 199.0 (C=O).

5.3 Experimental details concerned with the NMR studies

For the NMR studies, all spectra were recorded using either deuterated dichloromethane (DCM) or deuterated chloroform ($CDCl_3$) as the solvent. Chemical shifts are quoted relative to tetramethylsilane and to an accuracy of ± 0.01 ppm. All reactions were carried out under an atmosphere of argon unless otherwise stated. All glassware, syringes and needles were oven dried and allowed to cool in a desiccators containing either anhydrous $CaCl_2$ or silica gel prior to use. Commercially available deuterated solvents were used as supplied and stored over activated 4Å molecular sieves.

Reagents

The Lewis bases, which were all commercially available materials, were used as purchased unless otherwise stated. All commercially available Lewis acids were used as purchased and stored under either nitrogen or argon at the recommended temperature.

Purification of Butyraldehyde: To a solution of butyraldehyde (50mL) in diethyl ether (50 mL) was added saturated sodium bicarbonate solution (100mL) and allowed to stir vigorously for 10 min. After this time the mixture was transferred to a separating funnel, the aqueous fraction was separated and the organic washed with water (3 × 20 mL) and brine (20 mL). The organic fraction was dried ($MgSO_4$), filtered and concentrated under reduced pressure until approximately half the volume remained. The remaining mixture was fractionally distilled over anhydrous $CaCl_2$ and under an atmosphere of argon. The fractions collected (70-75 ºC) with no diethyl ether or impurities by ^{1}H NMR analysis were kept at room temperature under an inert atmosphere.

Preparation of the Lewis base stock solution: To an oven dried volumetric flask (5 ml, ± 0.02 ml) cooled in an atmosphere of argon was added either freshly distilled or highly pure commercial Lewis base (2.77 mmol, ± 0.03 mmol) using a 4 d.p. analytical balance. After the addition of deuterated $CDCl_3$ the flask is flushed with argon and sealed with a glass stopper and parafilm.

Preparation of NMR samples: the NMR samples were prepared using the following general procedure: To an oven dried round bottom flask equipped with a magnetic follower and rubber septum containing Lewis base stock solution under an atmosphere of argon either heated or cooled to the required temperature was added the require amount of Lewis acid. The mixture was stirred until the reagent had dissolved (or a maximum of 5 min). A portion (0.5 ml) of the mixture was transferred to the NMR and the coaxial tube was immediately fitted and the NMR spectrum acquired at 295 ± 1 ºK (machine accuracy of ± 0.1 ºK) unless otherwise stated.

5.4 Crystallographic data

X-ray crystallographic data for compound **190**

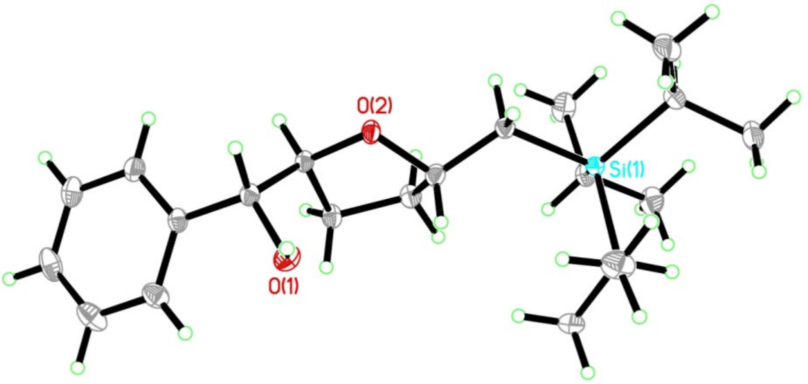


Table 1. Crystal data and structure refinement for JDTHF1 for cu_jd466_0m

Identification code	JDTHF1	
Chemical formula	$C_{21}H_{36}O_2Si$	
Formula weight	348.59	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.14 x 0.34 x 0.36 mm	
Crystal habit	colorless Block	
Crystal system	monoclinic	
Space group	C 1 2/c 1	
Unit cell dimensions	a = 30.9404(12) Å	$\alpha = 90°$
	b = 7.5968(3) Å	$\beta = 123.9090(10)°$
	c = 21.0505(8) Å	$\gamma = 90°$
Volume	4106.4(3) $Å^3$	
Z	8	
Density (calculated)	1.128 Mg/cm^3	
Absorption coefficient	0.124 mm^{-1}	
F(000)	1536	
Theta range for data collection	1.59 to 30.50°	
Index ranges	-43<=h<=44, -10<=k<=10, -30<=l<=29	
Reflections collected	24306	
Independent reflections	6227 [R(int) = 0.0183]	
Max. and min. transmission	0.9828 and 0.9566	

Structure solution technique	direct methods	
Structure solution program	SHELXS-97 (Sheldrick, 2008)	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-97 (Sheldrick, 2008)	
Function minimized	$\Sigma\ w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	6227 / 0 / 224	
Goodness-of-fit on F^2	1.037	
Δ/σ_{max}	0.002	
Final R indices	5539 data; $I>2\sigma(I)$	R1 = 0.0329, wR2 = 0.0883
	all data	R1 = 0.0379, wR2 = 0.0920
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0488P)^2+2.4654P]$ where $P=(F_o^2+2F_c^2)/3$	
Largest diff. peak and hole	0.548 and -0.192 eÅ^{-3}	
R.M.S. deviation from mean	0.046 eÅ^{-3}	

Table 2. Atomic coordinates and equivalent isotropic atomic displacement parameters (Å^2) for JDTHF1.

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U(eq)
C1	0.70744(3)	0.67422(11)	0.38827(4)	0.01452(15)
C2	0.72070(3)	0.84653(11)	0.36500(4)	0.01429(15)
C3	0.75381(3)	0.82334(12)	0.33198(5)	0.01662(16)
C4	0.79278(3)	0.97503(12)	0.36870(5)	0.01784(16)
C5	0.80260(3)	0.98354(12)	0.44797(5)	0.01566(15)
C6	0.82524(3)	0.15022(11)	0.49487(5)	0.01469(15)
C7	0.67252(3)	0.55929(11)	0.31856(5)	0.01499(15)
C8	0.62334(3)	0.61805(13)	0.25951(5)	0.02011(17)
C9	0.59115(4)	0.51244(14)	0.19594(5)	0.02352(19)
C10	0.60767(4)	0.34661(14)	0.19061(5)	0.0250(2)
C11	0.65659(5)	0.28796(13)	0.24882(6)	0.0269(2)
C12	0.68877(4)	0.39326(12)	0.31257(5)	0.02118(18)
C13	0.94198(3)	0.04361(12)	0.57435(5)	0.01696(16)
C14	0.93935(4)	0.89812(13)	0.52171(6)	0.02202(18)
C15	0.94011(4)	0.96282(14)	0.63960(6)	0.0266(2)
C16	0.91185(3)	0.42230(12)	0.58947(5)	0.01814(16)
C17	0.88808(4)	0.42515(16)	0.63680(6)	0.0296(2)

C18	0.97132(4)	0.44444(14)	0.64279(5)	0.02365(19)
C19	0.89015(3)	0.29426(12)	0.43516(5)	0.01685(16)
C20	0.84824(4)	0.43323(14)	0.38773(6)	0.0252(2)
C21	0.94284(4)	0.36204(14)	0.45407(6)	0.02442(19)
O1	0.75460(2)	0.58604(9)	0.44274(4)	0.01928(13)
O2	0.75058(2)	0.95818(8)	0.43149(3)	0.01601(12)
Si1	0.892134(8)	0.22479(3)	0.523139(12)	0.01207(6)

Table 3. Bond lengths (Å) for JDTHF1.

C1-O1	1.4234(10)	C1-C7	1.5212(11)
C1-C2	1.5318(12)	C1-H1	1.0
C2-O2	1.4455(10)	C2-C3	1.5354(11)
C2-H2	1.0	C3-C4	1.5296(12)
C3-H3A	0.99	C3-H3B	0.99
C4-C5	1.5216(12)	C4-H4A	0.99
C4-H4B	0.99	C5-O2	1.4578(10)
C5-C6	1.5156(12)	C5-H5	1.0
C6-Si1	1.8932(8)	C6-H6A	0.99
C6-H6B	0.99	C7-C12	1.3894(13)
C7-C8	1.3963(12)	C8-C9	1.3926(12)
C8-H8	0.95	C9-C10	1.3874(15)
C9-H9	0.95	C10-C11	1.3863(15)
C10-H10	0.95	C11-C12	1.3933(13)
C11-H11	0.95	C12-H12	0.95
C13-C15	1.5346(13)	C13-C14	1.5348(13)
C13-Si1	1.8921(9)	C13-H13	1.0
C14-H14A	0.98	C14-H14C	0.98
C14-H14B	0.98	C15-H15A	0.98
C15-H15B	0.98	C15-H15C	0.98
C16-C17	1.5337(13)	C16-C18	1.5392(13)
C16-Si1	1.9034(9)	C16-H16	1.0
C17-H17A	0.98	C17-H17B	0.98
C17-H17C	0.98	C18-H18A	0.98
C18-H18B	0.98	C18-H18C	0.98
C19-C20	1.5323(13)	C19-C21	1.5354(12)
C19-Si1	1.8935(9)	C19-H19	1.0

C20-H20A	0.98	C20-H20B	0.98
C20-H20C	0.98	C21-H21A	0.98
C21-H21B	0.98	C21-H21C	0.98
O1-H1A	0.84		

Table 4. Bond angles (°) for JDTHF1.

O1-C1-C7	111.36(7)	O1-C1-C2	108.82(7)
C7-C1-C2	110.78(6)	O1-C1-H1	108.6
C7-C1-H1	108.6	C2-C1-H1	108.6
O2-C2-C1	109.41(6)	O2-C2-C3	106.13(6)
C1-C2-C3	114.34(7)	O2-C2-H2	108.9
C1-C2-H2	108.9	C3-C2-H2	108.9
C4-C3-C2	102.81(7)	C4-C3-H3A	111.2
C2-C3-H3A	111.2	C4-C3-H3B	111.2
C2-C3-H3B	111.2	H3A-C3-H3B	109.1
C5-C4-C3	101.83(7)	C5-C4-H4A	111.4
C3-C4-H4A	111.4	C5-C4-H4B	111.4
C3-C4-H4B	111.4	H4A-C4-H4B	109.3
O2-C5-C6	108.25(7)	O2-C5-C4	102.41(6)
C6-C5-C4	119.13(7)	O2-C5-H5	108.9
C6-C5-H5	108.9	C4-C5-H5	108.9
C5-C6-Si1	118.80(6)	C5-C6-H6A	107.6
Si1-C6-H6A	107.6	C5-C6-H6B	107.6
Si1-C6-H6B	107.6	H6A-C6-H6B	107.0
C12-C7-C8	118.64(8)	C12-C7-C1	120.69(8)
C8-C7-C1	120.67(8)	C9-C8-C7	120.75(9)
C9-C8-H8	119.6	C7-C8-H8	119.6
C10-C9-C8	120.17(9)	C10-C9-H9	119.9
C8-C9-H9	119.9	C11-C10-C9	119.35(9)
C11-C10-H10	120.3	C9-C10-H10	120.3
C10-C11-C12	120.54(9)	C10-C11-H11	119.7
C12-C11-H11	119.7	C7-C12-C11	120.55(9)
C7-C12-H12	119.7	C11-C12-H12	119.7
C15-C13-C14	110.17(8)	C15-C13-Si1	112.04(6)
C14-C13-Si1	114.48(6)	C15-C13-H13	106.5
C14-C13-H13	106.5	Si1-C13-H13	106.5

C13-C14-H14A	109.5	C13-C14-H14C	109.5
H14A-C14-H14C	109.5	C13-C14-H14B	109.5
H14A-C14-H14B	109.5	H14C-C14-H14B	109.5
C13-C15-H15A	109.5	C13-C15-H15B	109.5
H15A-C15-H15B	109.5	C13-C15-H15C	109.5
H15A-C15-H15C	109.5	H15B-C15-H15C	109.5
C17-C16-C18	109.65(8)	C17-C16-Si1	114.46(7)
C18-C16-Si1	112.62(6)	C17-C16-H16	106.5
C18-C16-H16	106.5	Si1-C16-H16	106.5
C16-C17-H17A	109.5	C16-C17-H17B	109.5
H17A-C17-H17B	109.5	C16-C17-H17C	109.5
H17A-C17-H17C	109.5	H17B-C17-H17C	109.5
C16-C18-H18A	109.5	C16-C18-H18B	109.5
H18A-C18-H18B	109.5	C16-C18-H18C	109.5
H18A-C18-H18C	109.5	H18B-C18-H18C	109.5
C20-C19-C21	109.15(8)	C20-C19-Si1	112.54(6)
C21-C19-Si1	112.92(6)	C20-C19-H19	107.3
C21-C19-H19	107.3	Si1-C19-H19	107.3
C19-C20-H20A	109.5	C19-C20-H20B	109.5
H20A-C20-H20B	109.5	C19-C20-H20C	109.5
H20A-C20-H20C	109.5	H20B-C20-H20C	109.5
C19-C21-H21A	109.5	C19-C21-H21B	109.5
H21A-C21-H21B	109.5	C19-C21-H21C	109.5
H21A-C21-H21C	109.5	H21B-C21-H21C	109.5
C1-O1-H1A	109.5	C2-O2-C5	109.44(6)
C13-Si1-C6	111.23(4)	C13-Si1-C19	109.36(4)
C6-Si1-C19	110.04(4)	C13-Si1-C16	109.25(4)
C6-Si1-C16	108.26(4)	C19-Si1-C16	108.66(4)

Table 5. Torsion angles (°) for JDTHF1.

O1-C1-C2-O2	-61.53(8)	C7-C1-C2-O2	175.74(6)
O1-C1-C2-C3	57.34(9)	C7-C1-C2-C3	-65.40(9)
O2-C2-C3-C4	-17.97(9)	C1-C2-C3-C4	-138.68(7)
C2-C3-C4-C5	36.10(8)	C3-C4-C5-O2	-41.27(8)
C3-C4-C5-C6	-160.60(7)	O2-C5-C6-Si1	-178.02(5)
C4-C5-C6-Si1	-61.73(9)	O1-C1-C7-C12	-2.19(11)
C2-C1-C7-C12	119.06(9)	O1-C1-C7-C8	177.39(7)
C2-C1-C7-C8	-61.36(10)	C12-C7-C8-C9	0.12(13)
C1-C7-C8-C9	-179.47(8)	C7-C8-C9-C10	0.08(14)
C8-C9-C10-C11	-0.49(15)	C9-C10-C11-C12	0.69(16)
C8-C7-C12-C11	0.08(14)	C1-C7-C12-C11	179.67(9)
C10-C11-C12-C7	-0.49(15)	C1-C2-O2-C5	115.54(7)
C3-C2-O2-C5	-8.29(9)	C6-C5-O2-C2	157.98(7)
C4-C5-O2-C2	31.30(8)	C15-C13-Si1-C6	-50.07(8)
C14-C13-Si1-C6	76.31(7)	C15-C13-Si1-C19	-171.81(7)
C14-C13-Si1-C19	-45.43(8)	C15-C13-Si1-C16	69.37(7)
C14-C13-Si1-C16	-164.25(6)	C5-C6-Si1-C13	-54.24(7)
C5-C6-Si1-C19	67.11(7)	C5-C6-Si1-C16	-174.27(6)
C20-C19-Si1-C13	176.52(6)	C21-C19-Si1-C13	-59.35(8)
C20-C19-Si1-C6	54.07(7)	C21-C19-Si1-C6	178.19(6)
C20-C19-Si1-C16	-64.31(7)	C21-C19-Si1-C16	59.82(8)
C17-C16-Si1-C13	-92.50(8)	C18-C16-Si1-C13	33.64(8)
C17-C16-Si1-C6	28.77(8)	C18-C16-Si1-C6	154.90(6)
C17-C16-Si1-C19	148.26(7)	C18-C16-Si1-C19	-85.61(7)

Table 6. Anisotropic atomic displacement parameters (Å^2) for JDTHF1.

The anisotropic atomic displacement factor exponent takes the form:

$$-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	0.0131(3)	0.0164(4)	0.0133(3)	-0.0008(3)	0.0068(3)	-0.0009(3)
C2	0.0129(3)	0.0155(4)	0.0131(3)	-0.0019(3)	0.0064(3)	-0.0020(3)
C3	0.0178(4)	0.0192(4)	0.0144(3)	-0.0030(3)	0.0099(3)	-0.0037(3)
C4	0.0190(4)	0.0199(4)	0.0177(4)	-0.0025(3)	0.0121(3)	-0.0033(3)

C5	0.0130(3)	0.0182(4)	0.0168(3)	-0.0018(3)	0.0090(3)	-0.0017(3)
C6	0.0140(3)	0.0159(4)	0.0151(3)	-0.0016(3)	0.0087(3)	-0.0015(3)
C7	0.0157(4)	0.0169(4)	0.0140(3)	-0.0018(3)	0.0094(3)	-0.0039(3)
C8	0.0156(4)	0.0221(4)	0.0201(4)	-0.0037(3)	0.0084(3)	-0.0024(3)
C9	0.0180(4)	0.0293(5)	0.0176(4)	-0.0029(3)	0.0064(3)	-0.0064(4)
C10	0.0325(5)	0.0243(5)	0.0162(4)	-0.0052(3)	0.0123(4)	-0.0120(4)
C11	0.0399(6)	0.0175(4)	0.0214(4)	-0.0037(3)	0.0159(4)	-0.0022(4)
C12	0.0255(4)	0.0177(4)	0.0175(4)	-0.0004(3)	0.0102(3)	0.0008(3)
C13	0.0151(4)	0.0157(4)	0.0178(4)	0.0003(3)	0.0078(3)	0.0019(3)
C14	0.0221(4)	0.0181(4)	0.0260(4)	-0.0016(3)	0.0135(4)	0.0041(3)
C15	0.0340(5)	0.0231(5)	0.0210(4)	0.0066(3)	0.0143(4)	0.0069(4)
C16	0.0192(4)	0.0152(4)	0.0185(4)	-0.0033(3)	0.0096(3)	-0.0012(3)
C17	0.0293(5)	0.0340(5)	0.0323(5)	-0.0158(4)	0.0213(4)	-0.0051(4)
C18	0.0215(4)	0.0248(5)	0.0213(4)	-0.0070(3)	0.0099(4)	-0.0068(3)
C19	0.0178(4)	0.0176(4)	0.0166(4)	-0.0002(3)	0.0105(3)	-0.0034(3)
C20	0.0234(4)	0.0242(5)	0.0210(4)	0.0082(3)	0.0081(4)	-0.0021(4)
C21	0.0235(4)	0.0284(5)	0.0278(4)	-0.0011(4)	0.0183(4)	-0.0064(4)
O1	0.0172(3)	0.0237(3)	0.0150(3)	0.0029(2)	0.0078(2)	0.0022(2)
O2	0.0136(3)	0.0195(3)	0.0170(3)	-0.0061(2)	0.0098(2)	-0.0048(2)
Si1	0.01173(10)	0.01164(11)	0.01295(10)	-0.00047(7)	0.00696(8)	-0.00032(7)

Table 7. Hydrogen atomic coordinates and isotropic atomic displacement parameters (Å^2) for JDTHF1.

	x/a	y/b	z/c	U(eq)
H1	0.6885	0.7029	0.4129	0.017
H2	0.6876	0.9081	0.3264	0.017
H3A	0.7718	0.7080	0.3466	0.02
H3B	0.7322	0.8335	0.2755	0.02
H4A	0.8252	0.9488	0.3716	0.021
H4B	0.7777	1.0864	0.3403	0.021
H5	0.8249	0.8815	0.4789	0.019
H6A	0.8264	1.1348	0.5425	0.018
H6B	0.8006	1.2473	0.4658	0.018

H8	0.6117	0.7314	0.2627	0.024
H9	0.5578	0.5541	0.1561	0.028
H10	0.5857	0.2740	0.1475	0.03
H11	0.6683	0.1751	0.2452	0.032
H12	0.7221	0.3512	0.3523	0.025
H13	0.9770	1.1001	0.5986	0.02
H14A	0.9670	0.8119	0.5522	0.033
H14C	0.9440	0.9500	0.4833	0.033
H14B	0.9054	0.8396	0.4961	0.033
H15A	0.9076	0.8967	0.6181	0.04
H15B	0.9417	1.0568	0.6727	0.04
H15C	0.9698	0.8834	0.6696	0.04
H16	0.8984	1.5290	0.5560	0.022
H17A	0.8993	1.3203	0.6694	0.044
H17B	0.8500	1.4261	0.6023	0.044
H17C	0.8998	1.5309	0.6689	0.044
H18A	0.9794	1.5538	0.6720	0.035
H18B	0.9862	1.4492	0.6121	0.035
H18C	0.9862	1.3444	0.6781	0.035
H19	0.8811	1.1877	0.4021	0.02
H20A	0.8569	1.5419	0.4176	0.038
H20B	0.8144	1.3896	0.3746	0.038
H1	0.6885	0.7029	0.4129	0.017
H2	0.6876	0.9081	0.3264	0.017
H3A	0.7718	0.7080	0.3466	0.02
H3B	0.7322	0.8335	0.2755	0.02
H4A	0.8252	0.9488	0.3716	0.021

Table 8. Hydrogen bond distances (Å) and angles (°) for JDTHF1.

	Donor-H	**Acceptor-H**	**Donor-Acceptor**	**Angle**
O1-H1A···O2#1	0.84	1.93	2.7606(9)	172.6

Symmetry transformations used to generate equivalent atoms:
#1 -x+3/2, -y+3/2, -z+1

X-ray crystallographic data for compound **201**

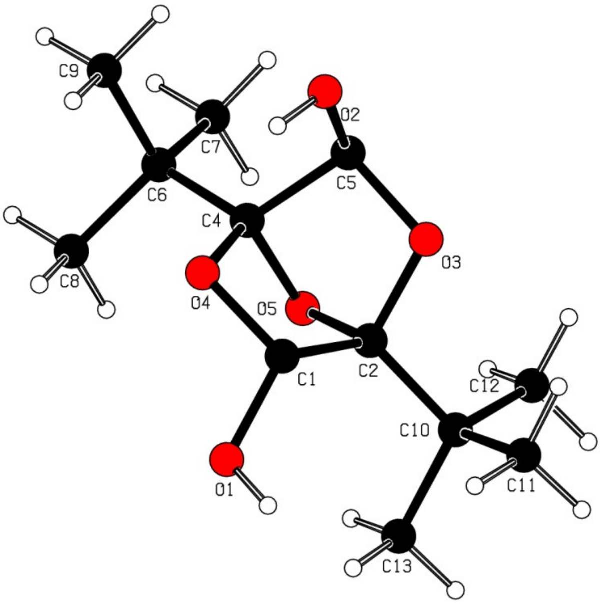


Table 1. Crystal data and structure refinement for cu_jd466_0m

Identification code	cu_jd466_0m	
Empirical formula	C12 H20 O5	
Formula weight	244.28	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system		
Space group		
Unit cell dimensions	a = 23.0005(6) Å	α= 90°.
	b = 6.3458(2) Å	β= 100.560(2)°.
	c = 18.7061(7) Å	γ = 90°.
Volume	2684.04(15) Å^{3}	
Z	8	
Density (calculated)	1.209 Mg/m^{3}	
Absorption coefficient	0.778 mm^{-1}	
F(000)	1056	
Crystal size	0.10 x 0.01 x 0.01 mm^{3}	
Theta range for data collection	4.81 to 65.92°.	
Index ranges	-26<=h<=26, -7<=k<=6, -13<=l<=22	

Reflections collected	6985
Independent reflections	2245 [R(int) = 0.0377]
Completeness to theta = 65.92°	96.0 %
Max. and min. transmission	0.9923 and 0.9262
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2245 / 0 / 162
Goodness-of-fit on F^2	1.164
Final R indices [I>2sigma(I)]	R1 = 0.0776, wR2 = 0.2062
R indices (all data)	R1 = 0.0792, wR2 = 0.2073
Largest diff. peak and hole	0.833 and -0.413 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for cu_jd466_0m.

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	2035(1)	1832(5)	5563(2)	21(1)
C(2)	1502(1)	2349(5)	5929(2)	21(1)
C(4)	1185(1)	2870(5)	4811(2)	20(1)
C(5)	1260(1)	5109(5)	5157(2)	26(1)
C(6)	780(2)	2505(5)	4085(2)	25(1)
C(7)	147(2)	3135(6)	4141(2)	34(1)
C(8)	795(2)	172(6)	3887(2)	36(1)
C(9)	995(2)	3852(6)	3501(2)	40(1)
C(10)	1466(2)	1594(5)	6689(2)	26(1)
C(11)	2000(2)	2432(6)	7223(2)	38(1)
C(12)	894(2)	2453(6)	6891(2)	33(1)
C(13)	1452(2)	-817(5)	6724(2)	32(1)
O(1)	2269(1)	-232(4)	5628(1)	30(1)
O(2)	1660(1)	6400(4)	4880(1)	31(1)
O(3)	1472(1)	4614(3)	5901(1)	25(1)
O(4)	1786(1)	2212(3)	4816(1)	23(1)
O(5)	1017(1)	1692(3)	5384(1)	19(1)

Table 3. Bond lengths [Å] and angles [°] for cu_jd466_0m.

C(1)-O(1)	1.413(4)	C(1)-O(4)	1.432(4)
C(1)-C(2)	1.544(4)	C(2)-O(5)	1.427(4)
C(2)-O(3)	1.439(4)	C(2)-C(10)	1.518(5)
C(4)-O(5)	1.418(4)	C(4)-O(4)	1.441(4)
C(4)-C(6)	1.517(5)	C(4)-C(5)	1.558(4)
C(5)-O(2)	1.400(4)	C(5)-O(3)	1.423(4)
C(6)-C(8)	1.528(5)	C(6)-C(7)	1.532(5)
C(6)-C(9)	1.537(5)	C(7)-H(7A)	0.9800
C(7)-H(7B)	0.9800	C(7)-H(7C)	0.9800
C(8)-H(8A)	0.9800	C(8)-H(8B)	0.9800
C(8)-H(8C)	0.9800	C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800	C(9)-H(910)	0.9800
C(10)-C(11)	1.529(5)	C(10)-C(13)	1.532(5)
C(10)-C(12)	1.535(5)	C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800	C(11)-H(11C)	0.9800
C(12)-H(12A)	0.9800	C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800	C(13)-H(13A)	0.9800
C(13)-H(13B)	0.9800	C(13)-H(13C)	0.9800
O(1)-H(1)	0.8400	O(2)-H(2)	0.8400
O(1)-C(1)-O(4)	108.5(2)	O(1)-C(1)-C(2)	118.7(3)
O(4)-C(1)-C(2)	100.9(2)	O(5)-C(2)-O(3)	103.9(2)
O(5)-C(2)-C(10)	114.0(2)	O(3)-C(2)-C(10)	109.7(3)
O(5)-C(2)-C(1)	101.7(2)	O(3)-C(2)-C(1)	103.5(2)
C(10)-C(2)-C(1)	122.1(3)	O(5)-C(4)-O(4)	103.7(2)
O(5)-C(4)-C(6)	112.9(2)	O(4)-C(4)-C(6)	113.1(2)
O(5)-C(4)-C(5)	101.0(2)	O(4)-C(4)-C(5)	103.3(2)
C(6)-C(4)-C(5)	120.9(3)	O(2)-C(5)-O(3)	111.1(3)
O(2)-C(5)-C(4)	114.2(3)	O(3)-C(5)-C(4)	101.4(2)
C(4)-C(6)-C(8)	109.2(3)	C(4)-C(6)-C(7)	109.5(3)
C(8)-C(6)-C(7)	109.4(3)	C(4)-C(6)-C(9)	109.1(3)
C(8)-C(6)-C(9)	110.0(3)	C(7)-C(6)-C(9)	109.6(3)
C(6)-C(7)-H(7A)	109.5	C(6)-C(7)-H(7B)	109.5

H(7A)-C(7)-H(7B)	109.5	C(6)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5	H(7B)-C(7)-H(7C)	109.5
C(6)-C(8)-H(8A)	109.5	C(6)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	109.5	C(6)-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8C)	109.5	H(8B)-C(8)-H(8C)	109.5
C(6)-C(9)-H(9A)	109.5	C(6)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5	C(6)-C(9)-H(910)	109.5
H(9A)-C(9)-H(910)	109.5	H(9B)-C(9)-H(910)	109.5
C(2)-C(10)-C(11)	109.0(3)	C(2)-C(10)-C(13)	111.1(3)
C(11)-C(10)-C(13)	109.9(3)	C(2)-C(10)-C(12)	108.4(3)
C(11)-C(10)-C(12)	109.8(3)	C(13)-C(10)-C(12)	108.6(3)
C(10)-C(11)-H(11A)	109.5	C(10)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5	C(10)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5	H(11B)-C(11)-H(11C)	109.5
C(10)-C(12)-H(12A)	109.5	C(10)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5	C(10)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5	H(12B)-C(12)-H(12C)	109.5
C(10)-C(13)-H(13A)	109.5	C(10)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5	C(10)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5	H(13B)-C(13)-H(13C)	109.5
C(1)-O(1)-H(1)	109.5	C(5)-O(2)-H(2)	109.5
C(5)-O(3)-C(2)	105.1(2)	C(1)-O(4)-C(4)	105.4(2)
C(4)-O(5)-C(2)	95.7(2)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3)for cu_jd466_0m. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	20(2)	9(1)	34(2)	-1(1)	8(1)	0(1)
C(2)	21(2)	11(1)	30(2)	-2(1)	5(1)	-1(1)
C(4)	22(2)	12(1)	28(2)	3(1)	12(1)	2(1)
C(5)	28(2)	9(2)	44(2)	3(1)	19(1)	0(1)
C(6)	34(2)	20(2)	24(2)	0(1)	10(1)	2(1)
C(7)	31(2)	39(2)	31(2)	-1(2)	2(2)	7(2)
C(8)	49(2)	24(2)	33(2)	-6(2)	7(2)	3(2)
C(9)	57(2)	36(2)	29(2)	6(2)	14(2)	-2(2)
C(10)	29(2)	21(2)	27(2)	-1(1)	1(1)	-1(1)
C(11)	45(2)	31(2)	34(2)	-2(2)	-7(2)	-2(2)
C(12)	41(2)	31(2)	28(2)	4(1)	14(2)	5(2)
C(13)	38(2)	22(2)	34(2)	5(1)	4(2)	0(2)
O(1)	32(1)	17(1)	42(1)	3(1)	8(1)	4(1)
O(2)	36(1)	16(1)	43(2)	2(1)	16(1)	0(1)
O(3)	31(1)	11(1)	35(1)	-4(1)	8(1)	-3(1)
O(4)	23(1)	13(1)	35(1)	0(1)	12(1)	1(1)
O(5)	21(1)	13(1)	23(1)	1(1)	7(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for cu_jd466_0m.

	x	y	z	U(eq)
H(7A)	17	2313	4526	51
H(7B)	-116	2855	3676	51
H(7C)	136	4639	4255	51
H(8A)	1202	-248	3872	54
H(8B)	547	-62	3408	54
H(8C)	644	-671	4252	54
H(9A)	969	5348	3622	60
H(9B)	746	3574	3027	60
H(910)	1406	3493	3482	60
H(11A)	2364	1843	7101	58

H(11B)	1968	2019	7719	58
H(11C)	2011	3973	7190	58
H(12A)	897	3997	6871	49
H(12B)	866	1998	7385	49
H(12C)	553	1915	6548	49
H(13A)	1124	-1348	6358	47
H(13B)	1397	-1262	7209	47
H(13C)	1826	-1384	6626	47
H(1)	2488	-375	6036	45
H(2)	1931	5656	4766	46

Table 6. Torsion angles [°] for cu_jd466_0m.

O(1)-C(1)-C(2)-O(5)	-85.2(3)
O(4)-C(1)-C(2)-O(5)	33.1(3)
O(1)-C(1)-C(2)-O(3)	167.2(3)
O(4)-C(1)-C(2)-O(3)	-74.5(3)
O(1)-C(1)-C(2)-C(10)	43.1(4)
O(4)-C(1)-C(2)-C(10)	161.3(3)
O(5)-C(4)-C(5)-O(2)	153.1(3)
O(4)-C(4)-C(5)-O(2)	46.1(3)
C(6)-C(4)-C(5)-O(2)	-81.6(4)
O(5)-C(4)-C(5)-O(3)	33.6(3)
O(4)-C(4)-C(5)-O(3)	-73.5(3)
C(6)-C(4)-C(5)-O(3)	158.9(3)
O(5)-C(4)-C(6)-C(8)	-60.1(3)
O(4)-C(4)-C(6)-C(8)	57.2(3)
C(5)-C(4)-C(6)-C(8)	-179.7(3)
O(5)-C(4)-C(6)-C(7)	59.7(3)
O(4)-C(4)-C(6)-C(7)	177.0(3)
C(5)-C(4)-C(6)-C(7)	-60.0(4)
O(5)-C(4)-C(6)-C(9)	179.6(3)
O(4)-C(4)-C(6)-C(9)	-63.1(3)
C(5)-C(4)-C(6)-C(9)	60.0(4)
O(5)-C(2)-C(10)-C(11)	-178.8(3)
O(3)-C(2)-C(10)-C(11)	-62.8(3)

C(1)-C(2)-C(10)-C(11)	58.5(4)
O(5)-C(2)-C(10)-C(13)	59.9(4)
O(3)-C(2)-C(10)-C(13)	176.0(3)
C(1)-C(2)-C(10)-C(13)	-62.8(4)
O(5)-C(2)-C(10)-C(12)	-59.4(3)
O(3)-C(2)-C(10)-C(12)	56.7(3)
C(1)-C(2)-C(10)-C(12)	177.9(3)
O(2)-C(5)-O(3)-C(2)	-121.7(3)
C(4)-C(5)-O(3)-C(2)	0.1(3)
O(5)-C(2)-O(3)-C(5)	-33.8(3)
C(10)-C(2)-O(3)-C(5)	-156.1(2)
C(1)-C(2)-O(3)-C(5)	72.0(3)
O(1)-C(1)-O(4)-C(4)	125.8(2)
C(2)-C(1)-O(4)-C(4)	0.3(3)
O(5)-C(4)-O(4)-C(1)	-34.1(3)
C(6)-C(4)-O(4)-C(1)	-156.7(2)
C(5)-C(4)-O(4)-C(1)	70.9(3)
O(4)-C(4)-O(5)-C(2)	54.2(2)
C(6)-C(4)-O(5)-C(2)	176.9(2)
C(5)-C(4)-O(5)-C(2)	-52.5(2)
O(3)-C(2)-O(5)-C(4)	54.6(3)
C(10)-C(2)-O(5)-C(4)	174.1(3)
C(1)-C(2)-O(5)-C(4)	-52.6(2)

Table 7. Hydrogen bonds for cu_jd466_0m [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2)...O(1)#1	0.84	2.12	2.895(3)	153.0
O(2)-H(2)...O(4)	0.84	2.22	2.679(3)	114.8

Symmetry transformations used to generate equivalent atoms:
#1 -x+1/2,-y+1/2,-z+1

X-ray crystallographic data for compound **329**

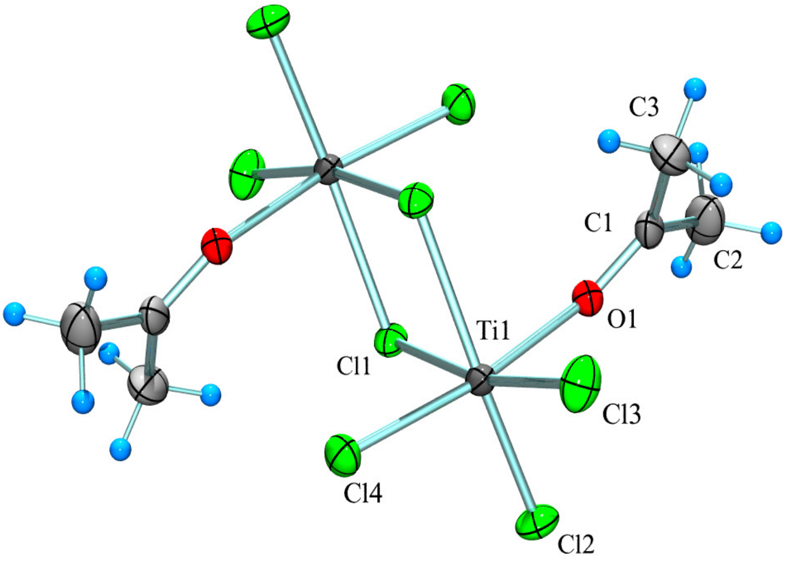


Table 1. Crystal data and structure refinement for jd-ticl$_4$

Identification code	jd-ticl4	
Empirical formula	$C_6 H_{12} Cl_8 O_2 Ti_2$	
Formula weight	495.56	
Temperature	160(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 10.719(2) Å	□= 90°.
	b = 12.290(3) Å	□= 91.28(2)°.
	c = 6.759(2) Å	□ = 90°.
Volume	890.2(4) Å^3	
Z	2	
Density (calculated)	1.849 Mg/m^3	
Absorption coefficient	2.086 mm^{-1}	
F(000)	488	
Crystal size	0.3 x 0.1 x 0.1 mm^3	
Theta range for data collection	2.52 to 24.97°.	
Index ranges	-12<=h<=12, 0<=k<=14, 0<=l<=8	
Reflections collected	1694	
Independent reflections	1552 [R(int) = 0.0605]	

Completeness to theta = 24.97°	99.5 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1552 / 0 / 84
Goodness-of-fit on F^2	1.013
Final R indices [I>2sigma(I)]	R1 = 0.0670, wR2 = 0.1639
R indices (all data)	R1 = 0.0814, wR2 = 0.1787
Largest diff. peak and hole	1.161 and -0.954 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3)

for jd-ticl$_4$.

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	795(4)	2704(4)	-7(8)	29(1)
C(2)	1098(6)	3423(5)	-1649(9)	47(2)
C(3)	-12(5)	3120(5)	1588(10)	44(2)
Cl(1)	803(1)	-395(1)	-1779(2)	23(1)
Cl(2)	3428(1)	322(1)	473(2)	35(1)
Cl(3)	1765(1)	1201(1)	4317(2)	36(1)
Cl(4)	1487(1)	-1354(1)	2771(2)	35(1)
O(1)	1237(3)	1781(3)	37(5)	24(1)
Ti(1)	1470(1)	318(1)	1505(1)	21(1)

Table 3. Bond lengths [Å] and angles [°] for jd-ticl$_4$.

C(1)-O(1)	1.229(6)
C(1)-C(3)	1.488(8)
C(2)-H(2B)	0.9800
C(3)-H(3A)	0.9800
C(3)-H(3C)	0.9800
Cl(1)-Ti(1)	2.4765(15)
Cl(3)-Ti(1)	2.2057(16)
O(1)-Ti(1)	2.067(3)

C(1)-C(2)	1.461(8)
C(2)-H(2A)	0.9800
C(2)-H(2C)	0.9800
C(3)-H(3B)	0.9800
Cl(1)-Ti(1)#1	2.4487(14)
Cl(2)-Ti(1)	2.2270(15)
Cl(4)-Ti(1)	2.2256(16)
Ti(1)-Cl(1)#1	2.4487(14)
O(1)-C(1)-C(2)	119.0(5)
O(1)-C(1)-C(3)	122.0(5)
C(2)-C(1)-C(3)	119.0(5)
C(1)-C(2)-H(2A)	109.5
C(1)-C(2)-H(2B)	109.5
H(2A)-C(2)-H(2B)	109.5
C(1)-C(2)-H(2C)	109.5
H(2A)-C(2)-H(2C)	109.5
H(2B)-C(2)-H(2C)	109.5
C(1)-C(3)-H(3A)	109.5
C(1)-C(3)-H(3B)	109.5
H(3A)-C(3)-H(3B)	109.5
C(1)-C(3)-H(3C)	109.5
H(3A)-C(3)-H(3C)	109.5
H(3B)-C(3)-H(3C)	109.5
Ti(1)#1-Cl(1)-Ti(1)	100.73(5)
C(1)-O(1)-Ti(1)	149.0(4)
O(1)-Ti(1)-Cl(3)	89.93(11)
O(1)-Ti(1)-Cl(4)	171.11(11)
Cl(3)-Ti(1)-Cl(4)	97.07(7)
O(1)-Ti(1)-Cl(2)	87.24(10)
Cl(3)-Ti(1)-Cl(2)	98.65(6)
Cl(4)-Ti(1)-Cl(2)	97.07(6)
O(1)-Ti(1)-Cl(1)#1	83.85(10)
Cl(3)-Ti(1)-Cl(1)#1	92.26(5)
Cl(4)-Ti(1)-Cl(1)#1	90.37(5)
Cl(2)-Ti(1)-Cl(1)#1	165.90(7)
O(1)-Ti(1)-Cl(1)	81.28(10)
Cl(3)-Ti(1)-Cl(1)	168.34(6)
Cl(4)-Ti(1)-Cl(1)	91.03(6)

Cl(2)-Ti(1)-Cl(1)	88.61(6)
Cl(1)#1-Ti(1)-Cl(1)	79.27(5)

Symmetry transformations used to generate equivalent atoms:
#1 -x,-y,-z

Table 4. Anisotropic displacement parameters ($Å^2 x 10^3$)for jd-ticl$_4$.

The anisotropic displacement factor exponent takes the form: $-2\pi^2$[$h^2a^{*2}U^{11}$ + ... + 2 h k a* b* U^{12}]

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	24(2)	20(3)	44(3)	-6(2)	-12(2)	-2(2)
C(2)	48(4)	36(3)	56(4)	16(3)	-19(3)	-8(3)
C(3)	32(3)	30(3)	68(4)	-15(3)	1(3)	4(3)
Cl(1)	18(1)	26(1)	26(1)	-3(1)	3(1)	-1(1)
Cl(2)	16(1)	42(1)	48(1)	-1(1)	3(1)	1(1)
Cl(3)	42(1)	39(1)	27(1)	-2(1)	-4(1)	-12(1)
Cl(4)	33(1)	25(1)	46(1)	12(1)	-11(1)	-1(1)
O(1)	23(2)	19(2)	32(2)	-1(1)	-3(1)	-2(2)
Ti(1)	16(1)	19(1)	27(1)	3(1)	-2(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2 x 10^3$) for jd-ticl$_4$.

	x	y	z	U(eq)
H(2A)	1516	4076	-1133	71
H(2B)	328	3632	-2362	71
H(2C)	1652	3043	-2553	71
H(3A)	-285	2511	2409	65
H(3B)	-743	3483	996	65
H(3C)	460	3639	2411	65

Table 6. Torsion angles [°] for jd-ticl$_4$.

C(2)-C(1)-O(1)-Ti(1)	175.8(5)
C(3)-C(1)-O(1)-Ti(1)	-2.6(9)
C(1)-O(1)-Ti(1)-Cl(3)	-41.8(6)

C(1)-O(1)-Ti(1)-Cl(4)	100.2(8)
C(1)-O(1)-Ti(1)-Cl(2)	-140.5(6)
C(1)-O(1)-Ti(1)-Cl(1)#1	50.5(6)
C(1)-O(1)-Ti(1)-Cl(1)	130.5(6)
Ti(1)#1-Cl(1)-Ti(1)-O(1)	-85.34(10)
Ti(1)#1-Cl(1)-Ti(1)-Cl(3)	-43.9(3)
Ti(1)#1-Cl(1)-Ti(1)-Cl(4)	90.18(5)
Ti(1)#1-Cl(1)-Ti(1)-Cl(2)	-172.76(6)
Ti(1)#1-Cl(1)-Ti(1)-Cl(1)#1	0.0

Symmetry transformations used to generate equivalent atoms:
#1 -x,-y,-z

Chapter Six

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