A thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy

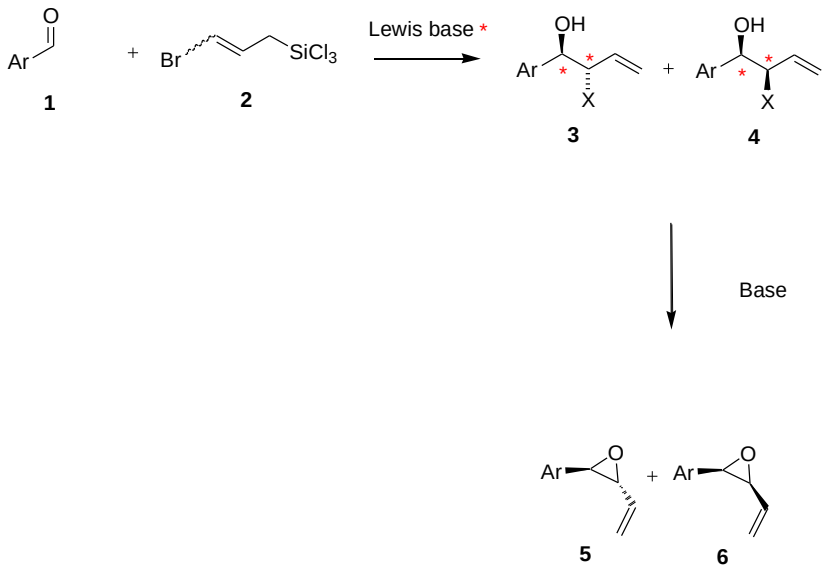
Synthesis of Functionalised Silanes for use in the Asymmetric Allylation Reaction

Claire MacDonald

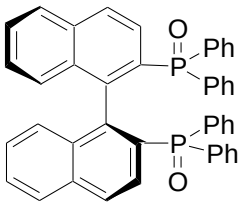
Department of Chemistry
University of Glasgow

Abstract

Asymmetric allylation of aldehydes with allyltrichlorosilane reagents, in recent years, has become a powerful synthetic tool towards the enantioselective construction of homoallylic alcohols. In general, the reaction displays good diastereocontrol. Thus, when the allylation is carried out in the presence of a Lewis base, the homoallylic alcohols *anti*-**3** and *syn*-**4** are stereospecifically obtained from the (*E*)-**2** and (*Z*)-**2** silanes, respectively, indicating that the reaction is likely to proceed via a cyclic, chair-like transistion state.



Herein, the synthesis of isomerically pure allylsilanes **2**, functionalised in the γ-position is reported. This has enabled the range of valuable synthetic intermediates available via the asymmetric allylation reaction of various aromatic aldehydes to be extended. The resultant homoallylic alcohols have two new stereogenic centres. These molecules can now undergo an intramolecular S_N2 reaction to afford the corresponding vinyl epoxides **5** and **6** with retention of the relative stereochemistry.



(*S*) - BINAPO

A variety of chiral Lewis bases, including pyridine N-oxides and phosphine oxides, were synthesised and screened for asymmetric induction. The most notable result was achieved using chiral phosphine oxide BINAPO, which produced the *syn*-homoallylic alcohol **4** in 50 % ee.

Acknowledgement

Firstly I would like to express my gratitude to my family and friends for all their support over the past few years. In particular, I would like to thank my old friend Anna, for providing copious amounts of tea and chocolate throughout our days in the 'west end'. Thanks to Parkie, Caroline, Linsey, Louise, Claire, Nicola and Ching Ching for their valued friendship and lunchtime chat.

I am grateful to Prof Pavel Kocovsky and Prof Andrei Malkov for giving me the opportunity to work within their research group and the Engineering and Physical Sciences Research Council for funding the project.

I would like to thank past and present members of the research group, especially Kveta, Mikhail, Sigitas, Grant and Kenny who made working in the lab an enjoyable experience.

Table of Contents

Abbreviations

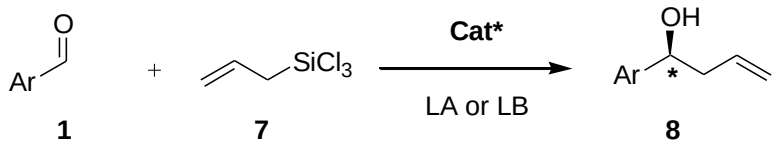
Aq	Aqueous
bs	Broad singlet
°C	Degrees centigrade
cat	Catalytic
CI	Chemical ionisation
d	Doublet
DCM	Dichloromethane
DIPEA	*N,N*-Diisopropylethylamine
DIOP	(4*S*,5*S*)-4,5-Bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
ee	Enantiomeric excess
EI	Electron impact
Equiv/Eq	Equivalents
FAB	Fast Atom Bombardment
h	Hours
HMPA	Hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography
Hz	Hertz
IR	Infrared
LB	Lewis base
m	Multiplet
mmol	Millimole
m-CPBA	Meta-chloroperoxybenzoic acid
MeCN	Acetonitrile
min(s)	Minute(s)
MS	Mass Spectrometry
n-BuLi	*n*-Butyllithium
Naphth	Naphthyl
NMR	Nuclear Magnetic Resonance

PMA	Polymolybdic acid
Py	Pyridine
q	Quartet
rt	Room temperature
t	Triplet
TLC	Thin Layer Chromatography
THF	Tetrahydrofuran
TMS	Trimethylsilyl
UV	Ultraviolet

1 Introduction

1.1 Allylation of Aromatic Aldehydes

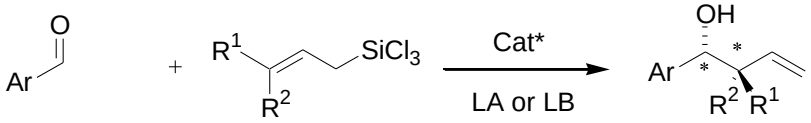
Scheme 1 Sakurai-Hosomi[1] type reaction



1 **7** **8**

The asymmetric allylation reaction of aromatic aldehydes **1** with allyltrichlorosilane is an essential reaction in organic synthesis for C-C bond formation.[1] The resultant homoallylic alcohol **8** is an adaptable subunit that can be readily transformed into a number of useful functionalities. Through the use of various chiral catalysts it is possible to create a new stereogenic centre, as shown in Scheme 1.

Scheme 2 Asymmetric allylation of aldehydes



1 **9** **10**

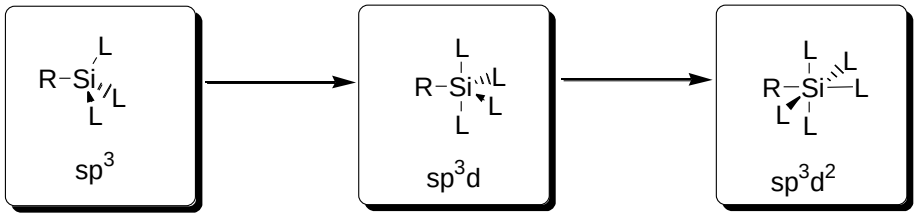
Of course this principle can be extended to allylsilanes substituted at the γ position **9.** This immediately widens the scope of highly functionalized homoallylic products **10**. The formation of this new carbon-carbon bond affords the creation of two new stereogenic centres (Scheme 2).

Asymmetric addition reactions of aldehydes with allylmetal reagents, such as boron and titanium, are well established. If sufficient activation is provided it is possible to extend the range of compounds available for reaction to allylsilanes.

1.2 Use of Silicon Reagents

There are various reactions which utilise silicon as a reactive site. In the formation of a silicon-carbon bond the silane species is tetravalent. However silane intermediates in silicon mediated carbon-carbon bond forming reactions will certainly have a silicon centre possessing a higher coordination number (pentavalent, hexavalent) and these compounds are deemed hypervalent silanes.

Scheme 3 Valency and electron density at silicon in organosilicon compounds



11 **12** **13**

L = negatively charged or neutral ligands
R = H or C

In silicon based C-C bond forming reactions the important factor key to their success is the ability of the coordination number of the silicon atom to be varied. As the number of bonds to silicon increases the electropositivity and consequently Lewis acidity on the atom increases.[1]

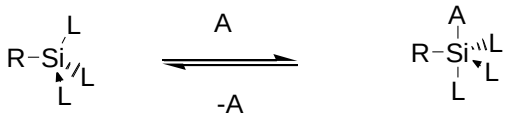
Upon expansion (Scheme **3**; **11** to **13**), and ensuing reduction in the s-character orbital composition at the silicon centre, the electron density decreases. Therefore the electropositivity and Lewis acidity at the silicon centre is increased. These tetravalent and pentavalent Lewis acidic silianes have been exploited in several Lewis acid-catalysed transformations. Once the shell has expanded to incorporate six subsituents it is unlikely for any further extension of the valence shell to occur.[2]

Silicon becomes more positively polarised with the addition of each ligand. As this occurs there is a shift in electron density. While the electron density is

increasing at the ligand, it is decreasing at the silicon centre. The magnitude of this polarization is also dependent on the electronegativity of these ligands.
The property that allows allylsilanes to react in such a way is the ability of silicon to expand its coordination shell.[3] Silicon has the outer electronic configuration $3s^2 3p^2 3d^0$, possessing a vacant d-orbital.[4]

As the silicon centre becomes more saturated with the addition of each chiral Lewis base (A), its lowest unoccupied molecular orbital is significantly lowered (Scheme 4). This decreases the electron density at silicon in **12**. Altered orbital interactions in these extracoordinated systems serve to elongate the Si-R and Si-L bonds and thereby facilitate the transfer of the R group to an acceptor.[3] This distinctive reactivity originates from the increased partial charges at the R moiety and the ligands. Therefore transformations involving a hypervalent silicon centre **11** or **12** generally allow for carbon-carbon as well as carbon-heteroatom bond formation and not carbon-silicon bond formation. Bonds to silicon in tetravalent silicon compounds are substantially less polarised and therefore more covalent. They are more commonly associated with hydrosilation catalysed by transition metals.[3]

Scheme 4 Reversible formation of Lewis acid/Lewis base complex



11 : sp^3 — unreactive Lewis acid

12 : sp^3d — reactive Lewis acid/Lewis base complex

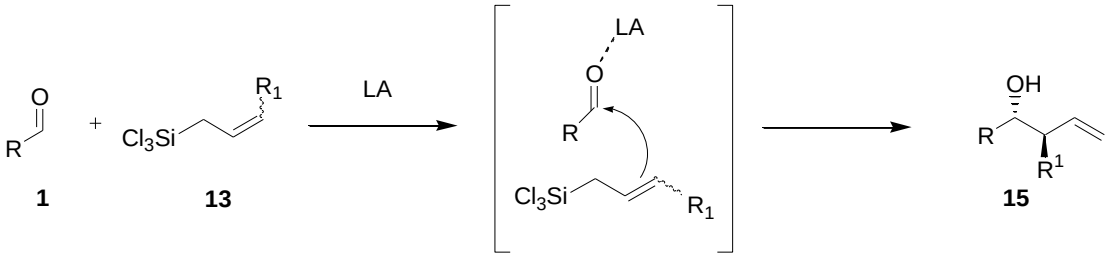
A = activator = chiral Lewis base
L = Cl

1.3 Method of Catalysis

1.3.1 Lewis Acid Catalysis

Due to the poor reactivity of the allylsilanes towards aldehydes, they require some sort of activation in order for the allylation reaction to occur. In the past, the addition was carried out under Lewis acid catalysis.[1] Under Lewis acid catalysis this involves the coordination of the carbonyl group of the aldehyde **1** (electrophile) with a Lewis acid, facilitating nucleophilic attack by the allylsilane **13**, (Scheme **5**). The drawback of using this method of activation is that if the substrate is substituted at the γ-position then there is poor diastereoselectivity as a direct consequence of the open transition state.[5] Ultimately this only produces the anti allylic alcohol **15** so the selectivity in the reaction is lost through the non-rigid transition structure **14**.

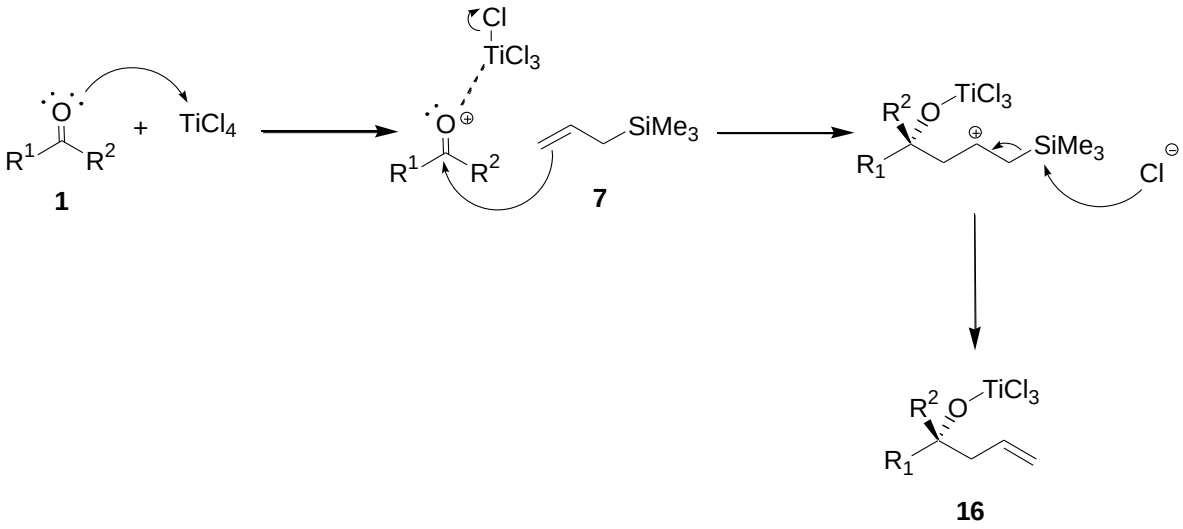
Scheme 5 Allylation reaction under Lewis acid catalysis



1 **13** Open Transistion Structure **14** **15**

From Scheme 6, the reaction is initiated by activation of the electrophile upon coordination of the Lewis acid to the oxygen at the carbonyl group. This increases the electrophilicity of the carbonyl carbon and thus the reactivity of the C=O group. Carbon-carbon bond formation leads to a silyl-stabilised carbocation and subsequent loss of the trimethylsilyl group results in formation of the double bond. From studies conducted on chiral allylsilanes[5] it was concluded that the incoming electrophile attacks the double bond on the surface opposite to the silyl group. The reaction proceeds through an open transition state.

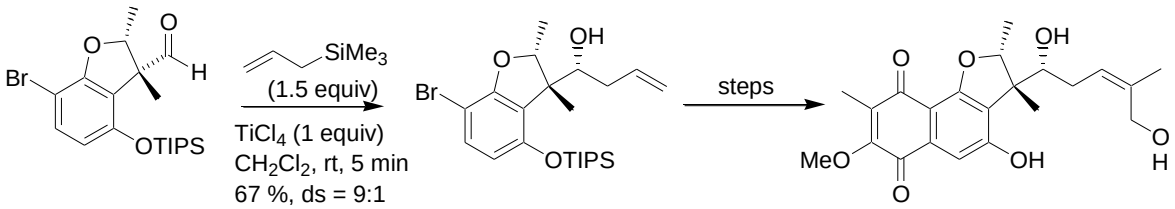
Scheme 6 Mechanism of Lewis acid catalysis



Typically these types of reactions are carried out in dichloromethane under nitrogen atmosphere at temperatures between -78°C and 25 °C. A wide range of Lewis acids can be used in addition to the reactions pioneered with $TiCl_4$, such as $AlCl_3$, $BF_3.OEt_2$, $SnCl_4$ and $EtAlCl_2$.[6,7]

An example of the importance of the Sakuirai allylation has been in its widespread use in total synthesis. Trost *et al* used this transformation as a method of introduction of the homoallylic side chain in a diastereoselective manner, a key step towards the total synthesis of furaquinocin **19** (Scheme 7). It was found that the highest diastereoselectivity was achieved using 1 equivalent of $TiCl_4$ at room temperature.[8]

Scheme 7 Key step towards the synthesis of Furaquinocin A



17 **18** **19** Furaquinocin A

As previously stated there is poor diastereoselectivity through Lewis acid catalysis, due to reaction via an open transition state. However, this can be overcome using a different method of activation: Lewis base catalysis. This mechanistically different conversion allows for the configuration in the homoallylic alcohol to be directly influenced by the starting material.

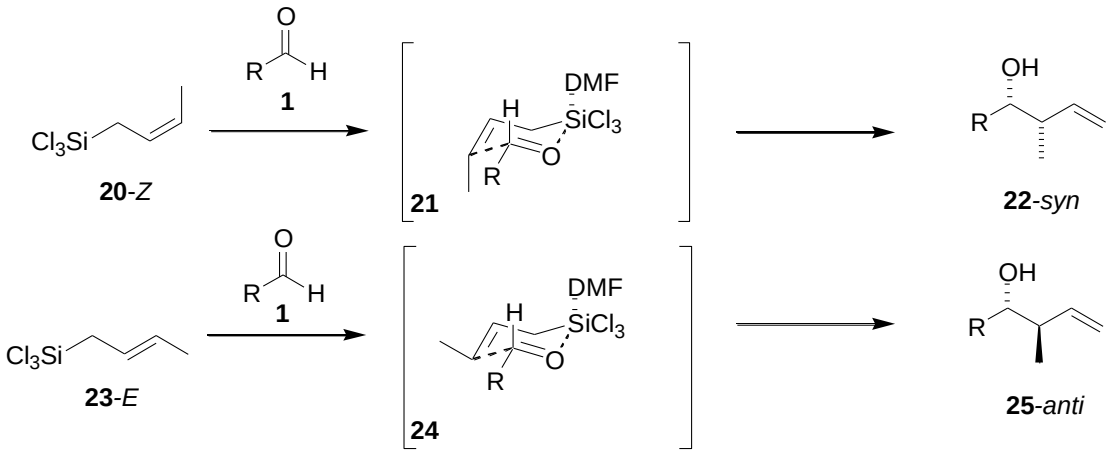
1.3.2 Lewis Base Catalysis

A variety of Lewis basic compounds can be employed as catalysts in this reaction. Common dipolar aprotic solvents; DMF, DMSO, and HMPA are commonly used. In addition, formamides and urea derivatives have also been employed, as they all possess a strongly Lewis basic oxygen atom.

One of the primary illustrations of this was the addition of allylsilane to benzaldehyde using *N,N*-dimethylformamide (DMF) as the Lewis base,[9] without a chiral catalyst. The reaction passes through a six-membered, chair-like, cyclic transition state that has implications for the regio- and diastereoselectivities observed in the products. The proposed transition state was verified by NMR

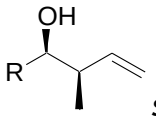
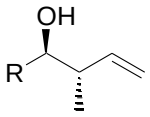
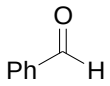
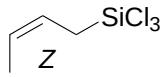
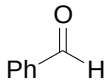
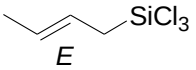
studies carried out by Kobayashi.[9] In these intermediates (**21** and **24**) the silicon atom is coordinated to both the Lewis base and the carbonyl group of the electrophile. The silicate acts as a Lewis acid by activating the carbonyl functionality to nucleophilic attack. Kobayashi *et al*[9] demonstrated that the *syn*-**22** and *anti*-**25** homoallylic alcohols were stereospecifically obtained, under neutral conditions, from the (*Z*)-**20** and (*E*)-**23** crotyltrichlorosilanes respectively.

Scheme 8 Stereospecific formation of homoallylic alcohols in DMF



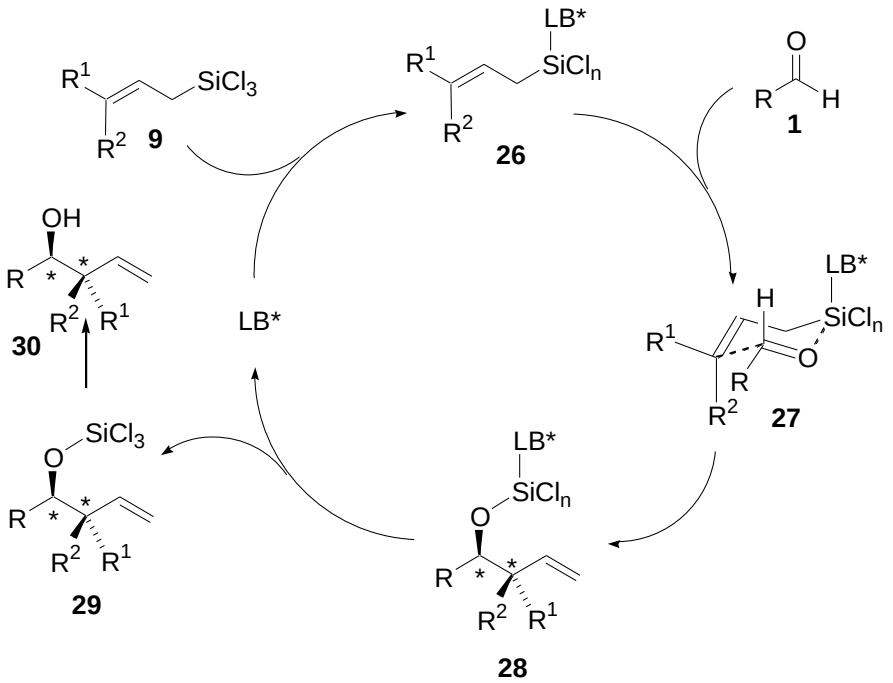
From the data in Table **1**, the reaction of *Z*-crotyltrichlorosilane (*E*/*Z*=<1/99) with benzaldehyde (Scheme 8) gives the product in 82 % yield with a *syn*/*anti* ratio of >99/1.[9] Conversely when *E*-crotyltrichlorosilane (*E*/*Z*=97/3) is employed, the *anti* homoallylic alcohol is the prominent product (89 % yield, *syn*/*anti* >99/1).

Table 1: Stereoselectivity in the Allylation Reaction Promoted by DMF

Benzaldehyde	Crotyltrichlorosilane	 *syn*	 *anti*
	 *Z*	>99	1
	 *E*	3	97

Kobayashi[10] has shown that allyl- and crotyltrichlorosilanes can be successfully employed in additions if DMF is used as the solvent. This is a stereospecfic reaction, with the regiochemistry of the product ultimately determined by the configuration of the starting material.

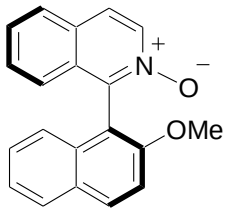
Scheme 9 Lewis base-catalyzed allylation of aldehydes



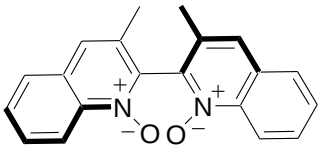
Scheme 9 demonstrates the method of activation by the Lewis base to facilitate the coordination of the silicon species with the aldehyde through a closed transition state **27**. When this occurs the silicon atom becomes more Lewis acidic and allows for coordination to the carbonyl in the cyclic transition state. Upon the transfer of the allylic moiety with the electrophile, **28** is formed. Subsequent release from the Lewis base gives **29**, and detachment of the silicon species affords the homoallylic alcohol **30**. Provided the Lewis base dissociates from silicon in the intermediate **27** at a sufficient rate then it can act as a catalyst rather than a stoichometric reagent.

There is a range of Lewis basic ligands that can be exploited in this reaction although not all are able to act at catalytic levels. For example, pyridine oxazolines, urea derivatives and sulfoxides[11] can influence the reaction but only in stoichometric quantites. Chiral Lewis-basic catalysts regularly employed in the allylation belong to classes such as pyridine *N*-monoxides **31**, pyridine *N,N′*-dioxides **32**, *N,N′,N″*-trioxides **33** and phosphoramides **34**. It should be noted that there is an exception to this generalisation due to the discovery by Iseki that the chiral formamide **35** can facilitate the reaction with aliphatic aldehydes.[12]

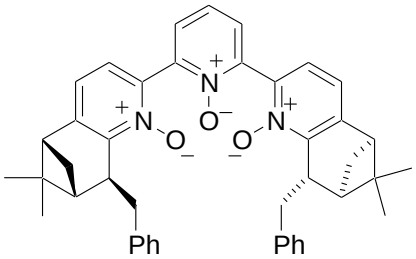
Scheme 10 Lewis base-catalyzed allylation of aldehydes



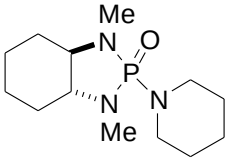
31



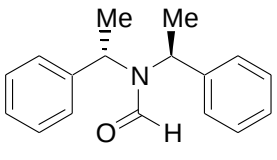
32



33



34

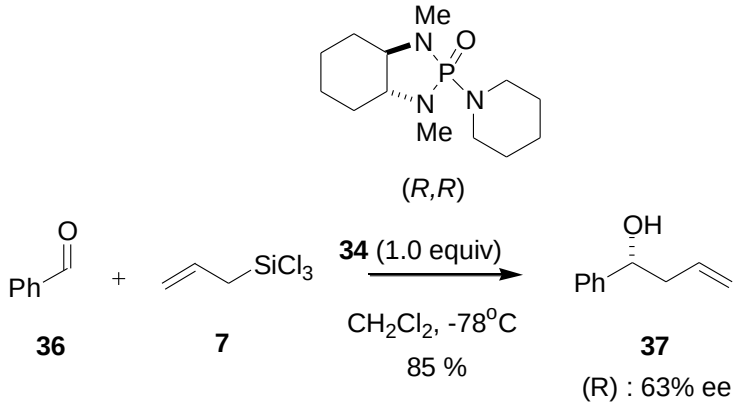


35

1.4 Chiral Additives

The first example of an enantioselective transformation was demonstrated by Denmark[13] where stochiometric amounts of chiral phosphoramide **31** promoted the allylation reaction of aldehyde **32** with allyltrichlorosilane **7** to afford the corresponding homoallylic alcohol **33** with moderate enantioselectivity.

Scheme 11 Phosphoramide catalysed asymmetric allylation of benzaldehyde with allyltrichlorosilane



The piperidine derivative **34** gave alcohol **37** in 85 % yield with 63 % enantiomeric excess. The reaction was carried out using 1 equivalent of catalyst **34**, in CH_2Cl_2 at -78°C over a period of 6 h. This reaction proceeds via a closed transistion structure with a hexacoordinate silicate species. The reaction times were greatly improved in comparison to those observed when DMF was employed as the Lewis base. Phosphine oxides have the ability to produce hypervalent silicates with trichlorosilyl compounds due to their high nucleophilicity originating from the polarisation in the P-O bond (dipole moment of 4.31 D).[14]

Denmark also showed that the addition of *trans* or *cis* allyl-silanes resulted in the formation of the *anti* or *syn* products respectively (Table 2), thus reinforcing the conclusions drawn by Kobayashi stating that the reaction proceeds through a closed cyclic transition state allowing retention of stereochemistry.

Scheme 12 Phosphoramide-catalysed asymmetric allylation of benzaldehyde with crotyltrichlorosilane

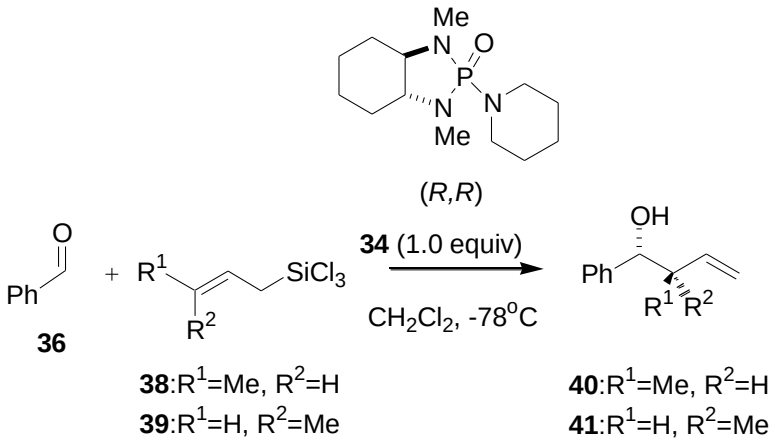
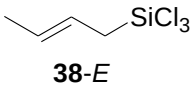
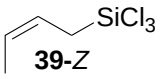


Table 2 Phosphoramide-catalysed asymmetric allylation of benzaldehyde with crotyltrichlorosilane

Crotyltrichloro silane	Yield (%)	ee(%)	*Syn*	*Anti*
 **38**-*E*	68	66	2	98
 **39**-*Z*	72	60	98	2

Subsequent research carried out by Denmark demonstrated that the catalyst loading was proportional to the enantioselectivity observed in the product. From the data in Table 3, it is clear that as the catalyst level is reduced the reaction time increases. When the reaction proceeds with a catalyst loading of 1 equivalent the time for complete conversion is 6 h (Table 3, entry 1). However when the catalyst loading is reduced to 0.1 equivalents the time for the reaction to reach completion was 24 h (Table 3, entry 4). On decreasing the catalyst equivalents from 1 to 0.1, the yield dropped from 81 % (entry 1) to 40 % (entry 4) and the observed enantioselectivity mirrored this trend.[13]

Table 3 Effect of catalyst loading on allylation reaction catalysed by phosphoramide **34**

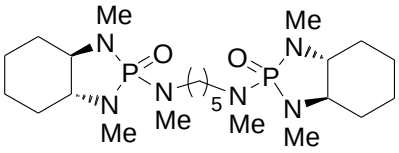
Entry	Catalyst (equiv)	Time (h)	Yield %	ee %
1	1.0	6	81	60
2	0.5	24	78	57
3	0.25	24	74	59
4	0.1	24	40	53

All reactions carried out at -78°C, 0.5 M in each component.

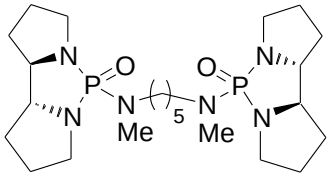
The relationship between the catalyst loading and enantioselectivity, shown in Table 3, led to the conclusion that the reaction can proceed via two pathways. One possible pathway is where two molecules of the catalyst are bound to the chlorosilane, while the less selective pathway involves only one molecule of the catalyst. This competitive alternative pathway is visible at lower catalyst loadings and this could impede the enantiopurity observed in the final product. To prove this hypothesis Denmark carried out a kinetic study to investigate the reaction pathway and observed a positive non-linear effect.[15]

This accounts for the adverse effects observed on the rate and selectivity at low catalytic loadings, with the intervention of the less selective catalyst pathway.[16] To try and minimise the impact of this one-phosphoramide catalyst pathway, Denmark designed a series of bidentate ligands (Figure 1). It was proposed that these ligands could increase the probability of the reaction proceeding through the stereoselective pathway due to the proximity of the second coordination point.

Figure 1 Bisphosphoramide catalysts



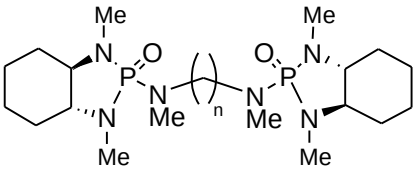
42



43

Denmark designed bidentate catalysts **42** and **43** to test this theory. The structure was determined after an in-depth analysis into the coordination mechanism. By varying the length of the carbon tether between the two phosphoramide units (n = 2, 3, 4, 5 and 6), the chain containing 5 methylene units, **42d**, was found to provide the highest enatioselectivity (72 % ee).

Figure 2 Bisphosphoramide catalyst



42a: n=2, **42b**: n=3
42c: n=4, **42d**: n=5
42e: n=6

To further his understanding of the origin of asymmetric induction and support the design of a more selective catalyst, Denmark proceeded to carry out an investigation into the transition structure of this reaction using NMR spectroscopy and x-ray crystallography. The complexation of phosphoramides and chlorosilanes is very weak via ^{1}H and ^{31}P NMR spectroscopy; thus little information could be obtained. However, analysis of complexes between phosphoramides and $SnCl_4$ are widely established, since Sn exhibits stronger bonding and exhibits similar bonding pattern to Si. This was used as a model to aid the understanding of the formation of the bisphosphoramide·$SiCl_4$ complex.[17] From the chemical shift and coupling constant data observed in the ^{119}Sn NMR experiments, Denmark was able to draw conclusions on the geometry of the two phosphoramides in the hexacoordinate tin complex. The tendency of chelation was highly dependant on concentration and tether length. It was found that bisphosphoramides **42a, 42b,** and **42e** can essentially be considered as bulky monodentate phosphoramides instead of a chelating bisphosphoramide. These catalysts could only achieve the product in racemic form.

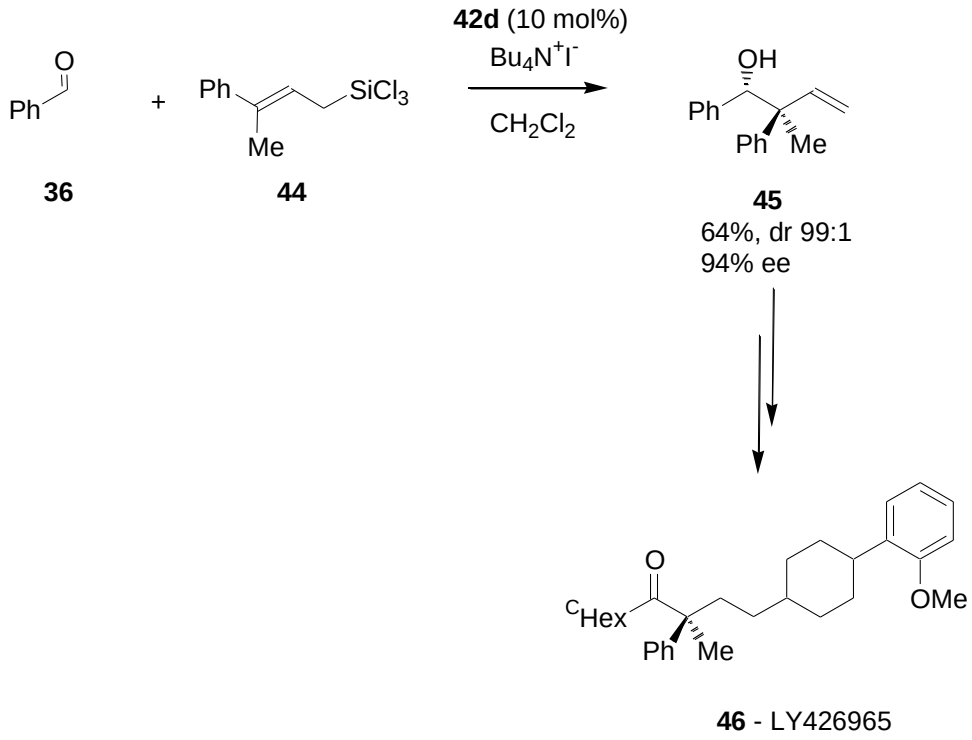
Catalysts **42c** and **42d** containing a tether of four and five methylene units respectively are found to be the most favourable for chelation of phosphoramides, due to the formation of single complexes with $SnCl_4$.[17] However this effect does not correlate to the enantioselectivities. When **42c** was employed as the catalyst, although a single complex was formed, poorer enantioselectivities were observed upon comparison with a monodentate bisphosphoramide. It is proposed the catalyst cannot attain the correct coordination geometry due to the restriction in the orientation of the two phosphoramide groups caused by the tether length and poor flexibility associated with the functional group. In the allylation reaction, bisphosphoramide **42d** gave higher selectivities than the monophosphoramides resulting from the fact that the ligand can bring the chiral information close to the reaction centre.

The X-ray structure of **42** provided information on the coordination geometry of the bisphosphoramide·$SnCl_4$ complexes. Collating this data Denmark concluded that the ligand coordinated in a bidentate manner with the Sn centre having octahedral geometry. It is proposed that the allyl group would be positioned

trans to one of the phosphoramides, furnishing a more nucleophilic centre. At the same time, the aldehyde would coordinate trans to the chloride to increase its electrophilicity. Denmark suggested a hexacoordinate allyltrichlorosilane bisphoramide complex occurs by replacing one of the chloride ions *trans* to the phosphoramide unit with an allyl group.[17] This ionisation of one chloride ion and the coordination of the aldehyde generates a chairlike transition structure.

The allyltion reaction can also be used to construct tertiary carbon stereocentres. Denmark's group accomplished the synthesis of serotonin antagonist LY426965 **42** utilising this reaction as a key step.[5,18]

Scheme 13 Synthetic route to LY426965 **39**



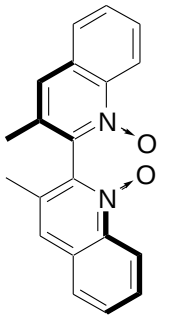
The alcohol **45** was formed in 64 % yield and high enantioselectivity. The addition of 0.2 equiv of *n*-$Bu_4N^+I^-$ slightly improved the reaction yield without affecting the selectivity.[18]

1.5 Catalytic Amounts of Chiral Additives

Chiral pyridine *N*-oxides are used in a diverse array of chemical transformations, specifically tailored to interact with a silicon centre; asymmetric aldol reactions, cyanosilylation and propargylation of aldehydes. Nakajima[19] introduced the chiral bisquinoline *N,N'*-dioxide **32** for the asymmetric allylation of aromatic aldehydes. Amine *N*-oxides can be applied in this field due to their electron-pair donor character to form complexes with a variety of metals.

Since amine *N*-oxides are known to exhibit a significant nucleophilicity toward the silicon atom the predicated success of this class of ligands was justified.
Prepared via the oxidation of 3,3'-dimethyl-[2,2']biquinolinyl with *m*CPBA, the racemic product can be resolved upon complexation with (R)- or (S)- binaphthol, to form the desired homochiral bis-*N*-oxide **32**.

Figure 3 Chiral bisquinoline *N,N'*-dioxide



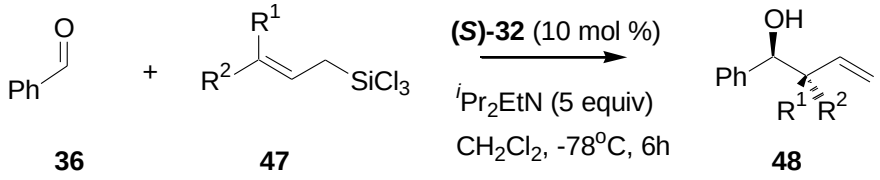
32

The allylation reation with (*S*)-3,3'-dimethyl-2,2'-biquinoline *N,N'*-dioxide **32**, as the chiral catalyst, achieved the homoallylic alcohol in 90 % yield and 71 % ee (reaction carried out at 23°C, 2 h). In this catalyst the *N*-oxide functionalities are embedded within a chiral pocket created by the walls of the biaryl unit.
A major discovery made by Nakajima was that the allylation reaction could be accelerated by the addition of 5 equivalents of diisopropylethylamine (23 °C, 10 min) without affecting the enantioselectivity.[19] This enhancement of the reaction rate made it possible to greatly reduce the reaction temperature, to -

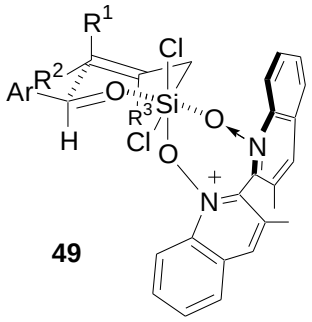
78 °C, and as a consequence, heighten the enantioselectivity to 88% ee. It has been proposed that the reason for this observation is the ability of diisopropylethylamine to promote the dissociation of the ligand from the silicon atom in the product, via ligand exchange, regenerating the catalyst. A variety of other amines were tested; pyridine, triethylamine and diaza[2.2.2]bicyclooctane, but they had a negligible effect on the enantioselectivity of the reaction.[19]

Anti-homoallylic alcohol **48-a** (68 % yield, 86 % ee) was obtained from (*E*)-crotyltrichlorosilane **47** and accordingly the (*Z*)-crotyltrichlorosilane **47** affords the *syn* stereoisomer **48-b** (64 % yield, 84 % ee). On account of these results the following transition state **49** was suggested where the *N*-oxide of the ligand adopts the axial position and coordinates to the silicate.[9] The silicate is coordinated to the aldehyde via a cyclic chair-like transition structure.

Scheme 14 Allylation with chiral bisquinoline *N,N'*-dioxide



36 **47** **48**

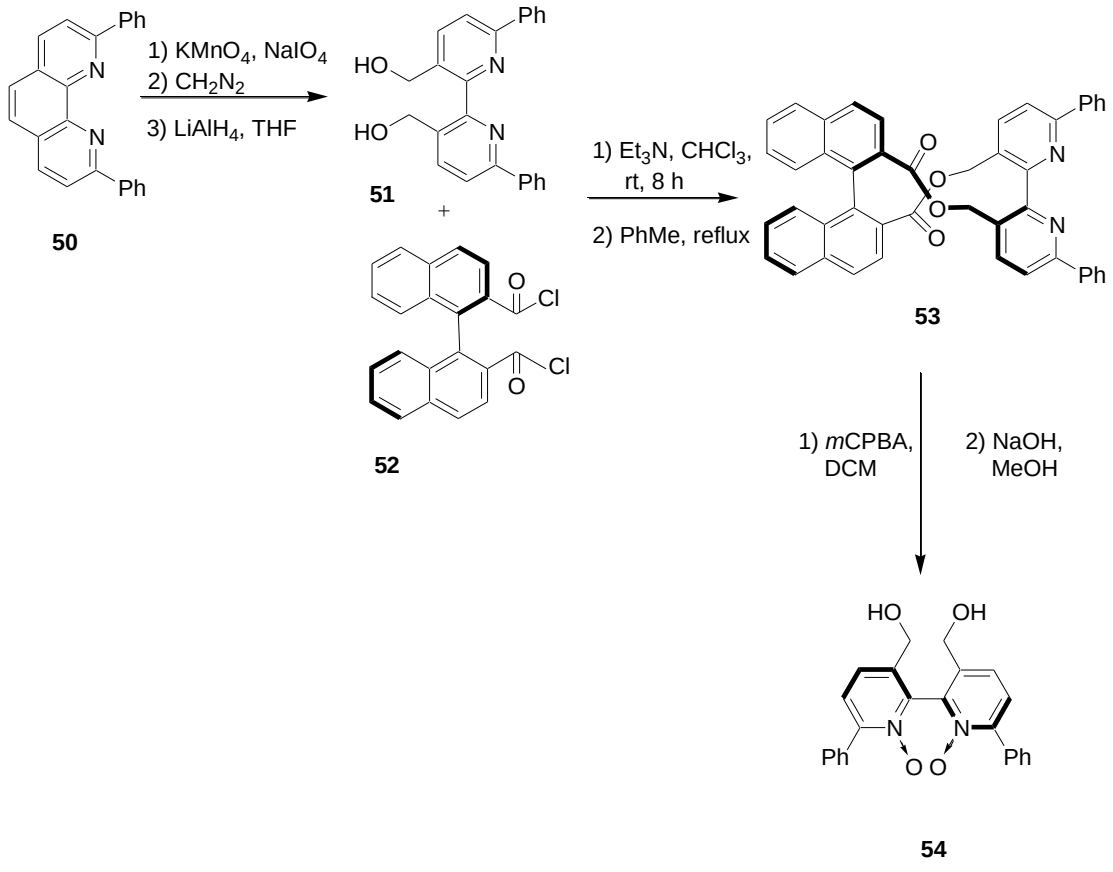


49

Alcohol	R^1	R^2	Yield %	ee %
48-a	H	CH_3	68	86
48-b	CH_3	H	64	84

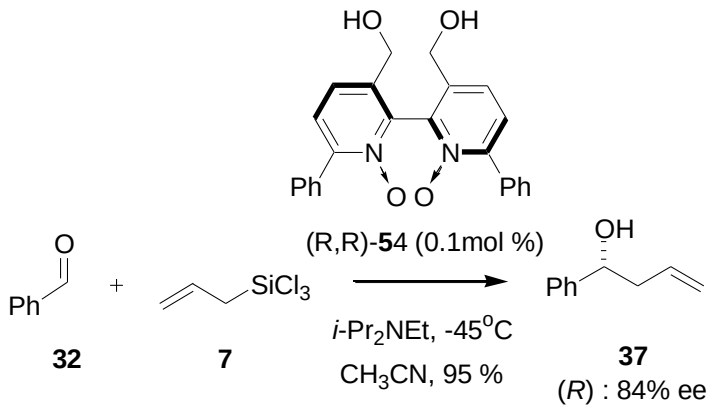
Hayashi[20] presented the chiral catalyst **54** which had significant influence in this field due to the dramatic reduction in catalyst loading. Previously catalysts had been employed at levels between 5 and 10 mol %. Hayashi reduced these down to catalyst loadings of 0.01-0.1 mol %.[3] Following on from the work carried out by Nakajima,[19] Hayashi designed the 2,2'-bipyridine *N,N*'-dioxide ligand **54**. The biaryl axial chirality is achieved upon oxidation of the cyclic diester **53** and therefore affords an enatiomerically pure ligand. The starting material for the formation of this catalyst was 2,9-diphenylphenanthroline **50**. This was converted to the corresponding bipyridine-diol **51** via oxidation with potassium permanganate and sodium periodate followed by esterification. Subsequent reduction with lithium aluminium hydride formed **51**. Which was then coupled with (*R*)-2,2'-bis(chlorocarbonyl)-1,1'-binaphthalene **52** in triethylamine. The more thermodynamically stable diastereoisomer was obtained when the ester was refluxed in toluene and the axial chirality of the bipyridine moiety was established as (*R*). Oxidation of the bipyridine **53** with *m*-chloroperbenzoic acid followed by alkaline hydrolysis gave the enantiomerically pure catalyst **54**.

Scheme 15 Synthetic route to 2,2'-bipyridine *N,N*'-dioxide **54**



It has been concluded that the high catalytic activity is attributed to the phenyl subsituents at the 6 and 6′ positions. It is possible that they could have an effect on the transition state configuration due to π-π stacking between the phenyl group on the catalyst and the aromatic ring of the aldehyde. When different groups (methyl, hydrogen and *tert*-butyl) were incorporated into these positions the rate of allylation was significantly slower or did not take place at all.[21]

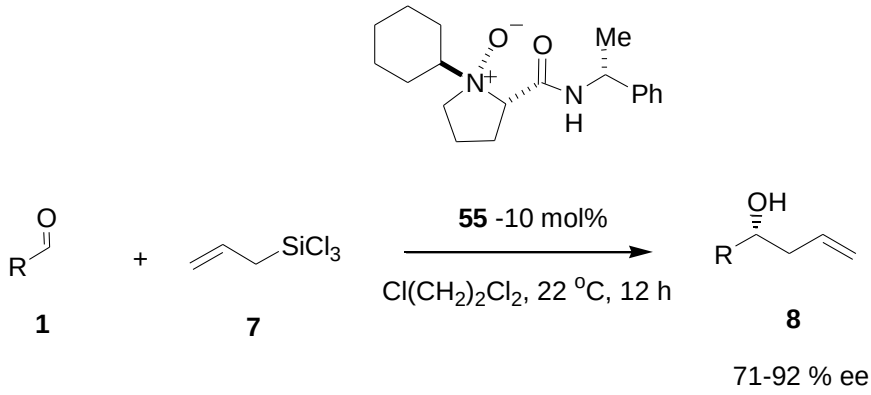
Scheme 16 Allylation with 2,2'-bipyridine *N,N'*-dioxide **54**



Scheme 16 demonstrates that in the presence of 0.1 mol % of catalyst **54**, the allylation of benzaldehyde in acetonitrile, at -45°C, gives alcohol **37** in high yield and with 84 % ee.[21]

The pyridine N-oxide ligands can take other structural forms. It is not necessary for the ligand to have C2-symmetry. Hoveyda and Snapper documented the asymmetric allylation catalysed by novel amino acid based aliphatic *N*-oxide **52**. This organocatalyst exhibits high enantioselectivity at room temperature.[22] The advantage of using amino acid based chiral molecules are that amino acids are available in optically pure form, both antipodes, so it is possible to introduce the chirality at the start of the synthesis, rather than adding an extra step for resolution at the end. It is simple to modify the structure of the amino acid base by introducing new groups through the amide bond linkage. *N*-oxide is easily prepared from optically pure proline in three simple steps, with an overall yield of 60 %.[22]

Scheme 17 Allylation with aliphatic N-oxide **55**

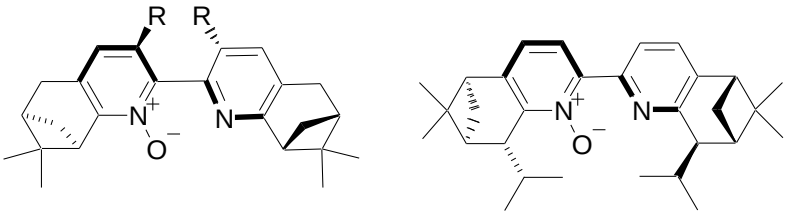


Hoveyda and Snapper[22] screened a range of ligands based on the structure of **55** by varying the substituents at the *C* and *N*-terminus of the modified amino acid. The most favourable results were obtained by ligand **55**. It was found that when the proline *N*-oxide possesses a cyclohexyl substituent the alcohol is achieved in 91 % yield with 87 % ee.

A new class of ligands proved that it was not necessary to have two points of coordination to facilitate the enantioselective allylation reaction. This novel class of monodentate ligands developed by Kocovsky and Malkov not only exhibited high enantioselectivty in the product but also demonstrated unique activity.

Kocovsky and Malkov have documented the synthesis of a range of terpene derived bipyridine *N*-monoxides PINDOX, Me_2PINDOX and *iso*-PINDOX. The annulated terpene units are responsible for the axial chirality that determines the stereochemical influence on the allylation reaction.[23]

Figure 4 PINOX derived catalysts



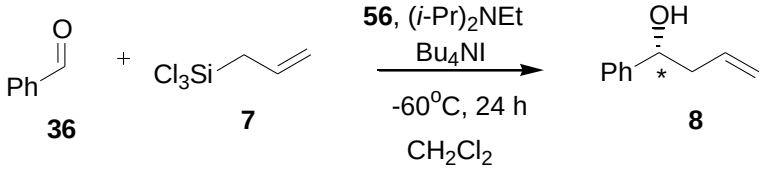
56 R = H
57 R = Me

58

The ligand that achieved the greatest enantioselectivity was Me_2PINDOX **57**. Combining the effects of both central and axial chirality resulting from the added steric bulk due to the two methyl substituents, there is restriction to rotation about the bond between the pyridine units. With no such barrier apparent in the PINDOX **56** and *iso*-PINDOX **58** ligands the activity is a direct result of the coordination to the silicon atom in the allylating agent.

While results with the corresponding dioxide ligand gave poor enantioselectivity (41 % ee) of the *S* enantiomer, the PINOX monoxide ligand gave the *R* enatiomer (scheme 13) in 90 % ee. From mechanistic analysis it is proposed that the *N*-oxide group of (+)**56** activates the allyl silane and restricts the number of diastereoisomeric transition states therefore enabling an enantioselective reaction.

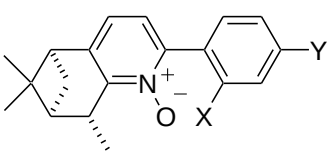
Scheme 18 Allylation with PINOX



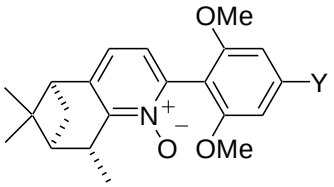
36 **7** **8**

A further advance on this PINOX ligand was to substitute two methyl groups onto the pyridine rings to give Me_2PINOX (+)**57**, this gave 98 % ee at – 60°C.[24] It is thought the effect of the methyl subsituents created a more rigid structure upon coordination at the silicon atom.

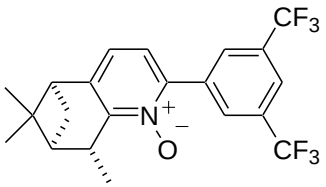
Figure 5 Pyridine *N*-oxide based organocatalysts



(-)59, X = H, Y = H
(+)60, X = OMe, Y = H
(+)61, X = F, Y = H
(-)62, X = H, Y = OMe



(-)63, X = H
(+)64, X = OMe



65

Through the development of these monodenate ligands a number of subsitution patterns on the phenyl ring were explored. Upon comparison of **59**, **60** and **61**, it was found that the *ortho*-fluoro substituted compound **61** proved unsuccessful in the reaction while a more promising result was obtained with the *ortho*-methoxy analogue **60**. This could be explained by a weak coordination from the *ortho*-methoxy group or the electronic effect this group has on the ring. The latter was found to be more probable considering that the catalytic activity can be manipulated in accordance to the nature of substituents on the phenyl ring. To examine this theory a series of ligands with increasing electronic character was synthesised and it was found that the higher the substitution of electron donating groups the more favourable the reaction.

The dimethoxy derivative **63** increases the conversion and enantioselectivity in the product from 68 % ee as observed with **60**, to 80 % ee. This trend was emulated in the trimethoxy ligand, METHOX **64**, achieving 98 % ee (Table 4, entries 4 to 6).[25]

To account for the high reactivity of METHOX **64,** arene-arene interactions between the ligand and the aromatic aldehyde were suggested rather than a second coordination point as with the bidentate ligands. The methoxy substituents increase the electron density of the phenyl moiety and thus, influence the rate of reaction through electronic properties. This theory was supported when the ligand **63**, an electron deficient analoge of METHOX, failed to exhibit the high enantioselectivities of METHOX.[26]

METHOX is a distinctive catalyst since the enantioselectivites were virtually unaffected by low loadings (Table 4, entries 4 to 6) and can work on a wide range of substrates, with negligible differences observed across the range of substituted aromatic aldehydes selected.[25] It is limited to *E*-crotylsilanes, since results have shown that METHOX is ineffective at catalysing the reaction with *Z*-crotyl silanes. Electron deficient aldehydes, e.g *para*-trifluoro-benzaldehyde, gave the product in high yield and 93 % ee (Table 4, entry 7). Similar values were obtained with electron rich aldehyde substrates, *para*-methoxy-benzaldehyde, attained the product in 95 % yield with 96 % ee.

Scheme 19 Allylation with Pyridine *N*-oxide Catalysts

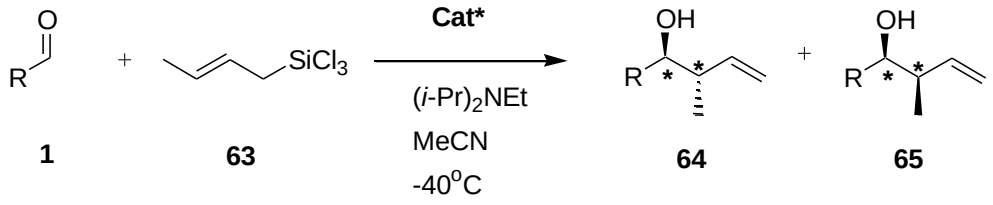


Table 4 Allylation with Pyridine *N*-oxide Catalysts

Entry	Aldehyde R	Silane	Catalyst (mol %)	Solvent	Yield %	ee %
1	Ph	**66** *E*	**60** (10)	CH_2Cl_2	55	68
2	Ph	**66** *E*	**63** (10)	CH_2Cl_2	44	80
3	Ph	**66** *E*	**63** (10)	MeCN	46	80
4	Ph	**66** *E*	**64** (10)	MeCN	≥ 95	96
5	Ph	**66** *E*	**64** (5)	MeCN	≥ 95	96
6	Ph	**66** *E*	**64** (1)	MeCN	68	95
7	4-CF_3-C_6H_4	**66** *E*	**64** (5)	MeCN	86	93
8	4-MeO-C_6H_4	**66** *E*	**64** (5)	MeCN	≥ 95	96
9	2-MeO-C_6H_4	**66** *E*	**64** (5)	MeCN	≥ 95	89

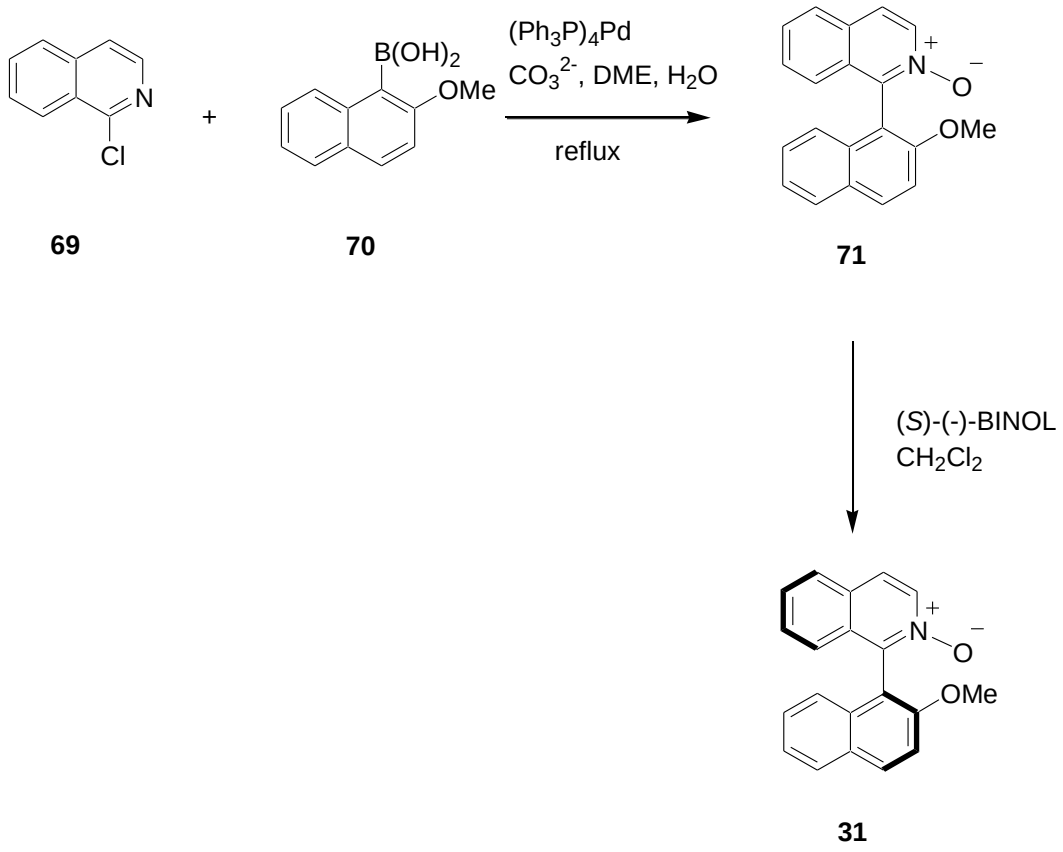
METHOX proved that neither bidentate chelation of silicon to the catalyst nor the presence of a chiral catalyst is a prerequisite for attaining high enantioselectivities in these reactions.

Another monodentate ligand developed by Malkov and Kocovsky was the isoquinoline *N*-oxide QUINOX, **31**. Unlike METHOX **64**, there is a marked distinction in reaction across the aldehyde substrate base. An explorative study of this phenomenon was carried out through collation of kinetic and computational data.[27]

The ligand **31** is formed by the Suzuki-Miyaura coupling of 1-chloroisoquinoline **69** with boronic acid **70** forming the biaryl derivative, whose treatment with *m*-chloroperoxybenzoic acid provided racemic *N*-oxide, in 99 % yield (Scheme 20). This racemate was resolved by cocrystallisation with (*S*)-(−)-2,2′-dihydroxy-1,1′-

binaphthyl (BINOL). This gave a crystalline material containing (*S*)-(—)-BINOL and (+)-**31** in a 1:1 ratio. This was then separated by column chromatography to afford the pure (+)-**31**, 89 % yield and 98 % ee.[28]

Scheme 20 Synthesis of *N*-oxide QUINOX



69 **70** **71** **31**

When QUINOX was used to catalyse the allylation reaction between electron deficient aldehydes and allyltrichlorosilane **2**, the product was formed in good yield with high enantioselectivities (Table 5, entries 3 to 7). However, QUINOX displayed dramatic differences between electron rich and electron poor aldehydes. High enatioselectivity was obtained with electron-poor aldehydes such as *p*-chlorobenzaldehyde which gave the product in 93% ee. While extremely low enantioselectivities were observed with electron-rich aldehydes, *p*-methoxybenzaldehyde gave 16% ee. This data suggested that a different method of activation may be in place and hence the electronic nature of the aldehyde substrate is of high importance for effective use of this ligand.

Scheme 21 Allylation with *N*-oxide QUINOX

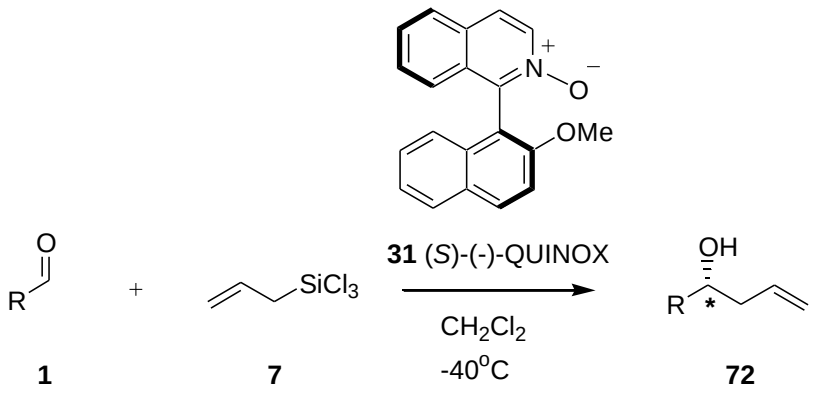


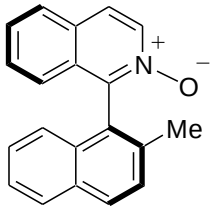
Table 5 Allylation with *N*-oxide QUINOX

Entry	Aldehyde R	Catalyst (mol %)	Time (h)	Solvent	Yield %	ee %
1	Ph	**31** (5)	12	CH_2Cl_2	68	87 (*R*)
2	Ph	**31** (1)	12	CH_2Cl_2	55	87 (*R*)
3	4-Cl-C_6H_4	**31** (5)	2	CH_2Cl_2	65	93 (*R*)
4	2-Cl-C_6H_4	**31** (5)	2	CH_2Cl_2	72	91 (*R*)
5	3-Cl-C_6H_4	**31** (5)	2	CH_2Cl_2	49	95 (*R*)
6	4-F-C_6H_4	**31** (5)	2	CH_2Cl_2	79	91 (*R*)
7	4-CF_3-C_6H_4	**31** (5)	2	CH_2Cl_2	85	96 (*R*)
8	4-MeO-C_6H_4	**31** (5)	18	CH_2Cl_2	70	16 (*R*)
9	2-MeO-C_6H_4	**31** (5)	12	CH_2Cl_2	73	37 (*R*)
10	3-MeO-C_6H_4	**31** (5)	12	CH_2Cl_2	40	80 (*R*)
11	3,5-Me-C_6H_3	**31** (5)	16	CH_2Cl_2	68	81 (*R*)

To assess the electronic effects of the methoxy group in QUINOX it was necessary to synthesise the methyl analogue **73**. The same reactivity pattern across the range of aldehydes was observed but the enantioselectivities were markedly reduced. This shows that the methoxy group not only prevents rotation about the chiral axis but also has an electronic influence. Crotylation

with *cis* and *trans*- crotylsilane is highly diastereoselective suggesting a chair-like transition state, supported by computational data.[28]

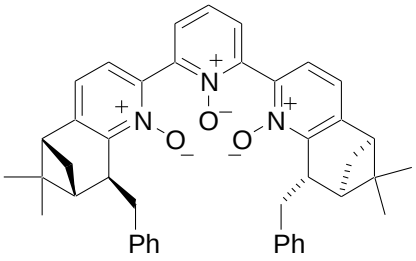
Figure 6 Methyl analogue of QUINOX **73**



(*R*)-(-)-**73**

Kinetic and computational studies lead to the conclusion that the reaction is likely to proceed via a neutral octahedral silicon complex transition state, where only one molecule of the catalyst is coordinated in the rate determining step.

Figure 7 Tri-*N*-oxide catalyst



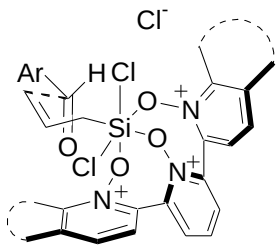
33

Kwong designed the synthesis of 2,2′:6′,2″-terpyridine tri-*N*-oxide ligands.[29] Various structurally modified tri-*N*-oxide ligands were screened and **33** was found to afford the best results. However, an investigation into the effect of temperature on the allyltion reaction gave unexpected results. As the temperature was dropped, from 0 °C to -10 °C or -40 °C, the enantiopurity of the allyltion product was lost. This contradicts the patterns exhibited by other catalysts. Optimal temperature with the tri-*N*-oxide ligand **33** was found to be 0 °C which provided the product in 89% yield and 74% ee.

To assess the reactivity profile, a range of aromatic and aliphatic substrates were screened in the allylation reaction. An interesting trend was discovered upon reaction with aromatic aldehydes. If an electron-donating group was set at the *para*-position the enantioselectivity was adversely affected, reducing to 65% ee. Then again, when an electron-withdrawing group was placed at the *para*-position the enatioselectivity improved to 86% ee with 91% isolated yield. It should be noted that this follows the reactivity pattern observed with QUINOX **31**.

Due to the steric demands from these tri-*N*-oxide ligands the cyclic 6-membered chair-like transition state would be highly improbable. Therefore Kwong suggests the acyclic transition state **76** with the ligand coordinating on a tridentate basis.

Figure 8 Proposed acyclic transition state



74

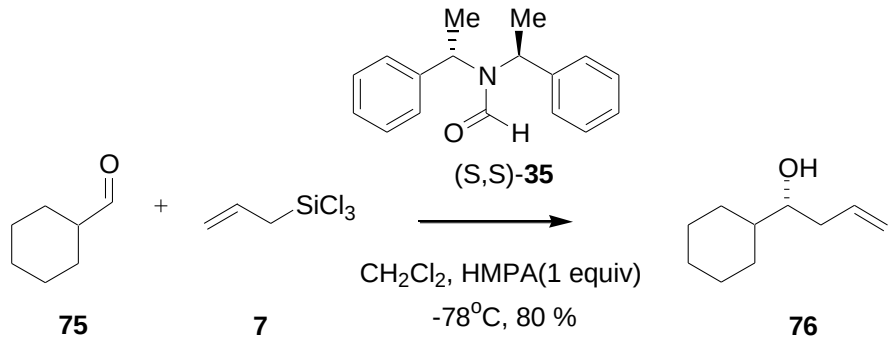
1.5 Allylation Reaction with Aliphatic Aldehydes

The substrate base of the allylation reaction has been limited to aromatic, heteraromatic, and cinnamyl-type aldehydes. However the catalysts that were successful in these reactions failed to have effect on aliphatic aldehydes, as only starting material was recovered. Denmark proposed that, instead of allylation, there could be a different reaction occurring.

Rather than just not reacting, Denmark gathered evidence to prove that instead of allylation, the aldehydes undergo the more favourable reaction with the nucleophilic chloride ion.[30] The silicon atom coordinates to the oxygen of the aldehyde, to form a chlorosilyloxy intermediate. This species is unstable and thus, is hydrolysed upon work-up to reform the staring material.

To overcome this alternative reaction, Denmark added Hg^{2+} to act as chloride scavengers. This did work to some effect, by adding $HgCl_2$ (10 mol %) he achieved the alcohol in 56 % yield.

Scheme 22 Allylation of cyclohexane carboxaldehyde catalysed by chiral formamide **35**



Chiral formamides **35** have had limited success in catalysing the allylation of aldehydes. Developed by Iseki[31], such chiral DMF analogues exhibit poor enantioselectivities on reaction with aromatic aldehydes. Yet, activity in the reaction of aliphatic aldehydes with allylsilane **7** was greatly improved. The allylic alcohol was formed in 81 % yield and 68 % ee. This was further optimised

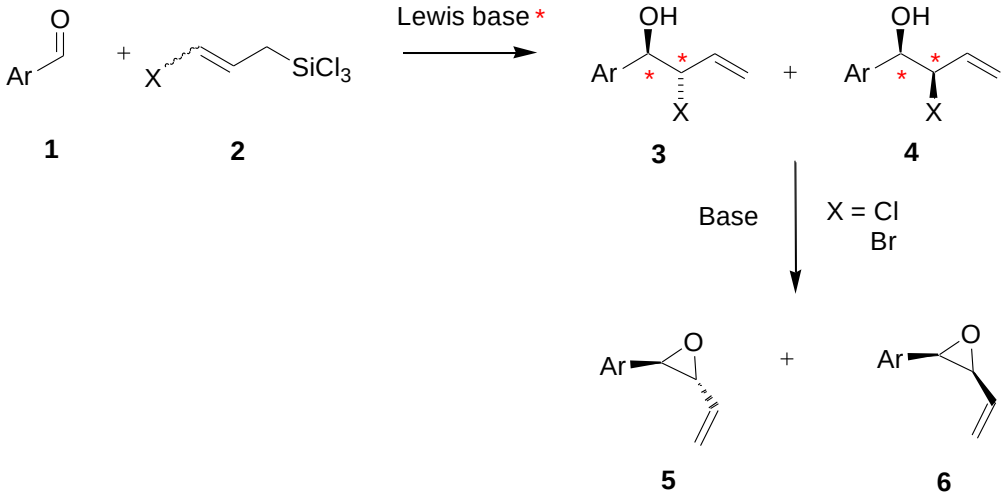
by the addition of 1 equivalent of HMPA to furnish the product **76** in 80 % yield and 98% ee. A major drawback of this transformation was the required reaction time of 2 weeks. However this is one of the few examples of allylation with aliphatic derivatives.[31, 32]

2 Synthesis of Isomerically Pure Allylsilanes

2.1 Introduction

To extend the range of products available via the asymmetric allylation reaction[1] of aromatic aldehydes it was necessary to devise a stereoselective synthesis to produce isomerically pure allylsilanes, functionalised in the γ-position. The resultant homoallylic alcohol possesses two new stereogenic centres. This molecule can now undergo an intramolecular S_N2 reaction to afford the corresponding epoxide with retention of the relative stereochemistry.

Scheme 23

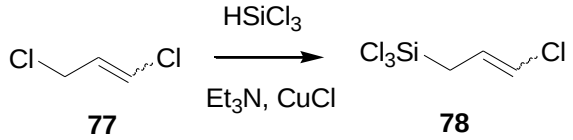


There are very few examples of stereoselective syntheses of the (*E*) and (*Z*) isomers of allylsilane **2,** in the literature. Most of the preceding syntheses of 3-halopropenoic acids were prepared as an isomeric mixture. So deriving a stereoselective synthesis was central to the formation of these homoallylic alcohols.

2.2 Allylation Reaction with Functionalised Allylsilanes

To explore the possibility of the stereoselective synthesis of homoallylic alcohols (**3**, **4**) it was first necessary to establish the reaction in an achiral environment to determine if it is possible to obtain the alcohols stereoselectively via the allylation reaction with these functionalised allylsilanes.

Scheme 24 Formation of Silane

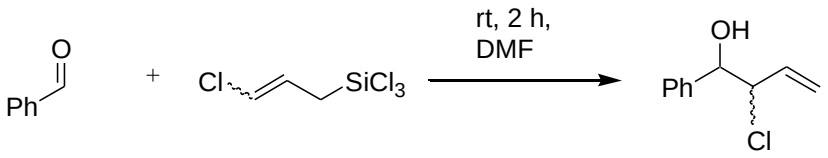


77 **78**

Silane **78** was formed through a copper(I)-chloride hydrosilyation[33] of 1,3-dichloropropene with trichlorosilane in the presence of an equimolar amount of triethylamine.[34] The reaction was carried out at room temperature for 4 h and the product obtained as a mixture of isomers with ratio *cis:trans,* 1:1.3, as determined by ^{1}H NMR. On analysis of the ^{1}H NMR of species **78**, the chemical shift of the CH_2 protons occurs at 2.51 ppm, indicating that the CH_2 is attached to an electropositive atom. In starting material **77**, the signal for the CH_2 protons occurs at 4.05 ppm. Purification of the silane from the allyl chloride by distillation was unsuccessful. However this mixture was taken forward and used in the allylation reaction as the unreacted starting material would have no effect on the outcome of the reaction.

The copper salt used to catalyse the condensation reaction of trichlorosilane with allylic chloride **77** was varied in an effort to improve the efficiency of this step.[33] Other salts such as CuI and CuBr were used in place of CuCl but failed to produce the product in a higher yield.

Scheme 25 Allylation Reaction

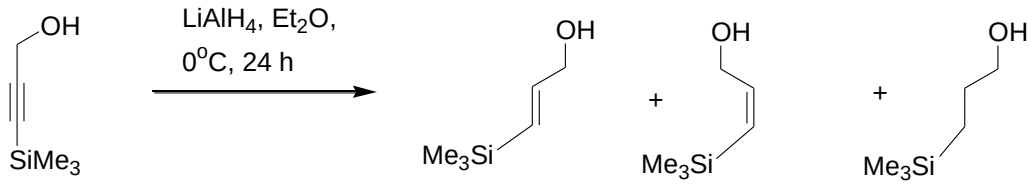


36 **78** **79**

When the silanes **78** were reacted with benzaldehyde the product was obtained as a mixture of diastereoisomers **79** in 62 % yield. The ratio of *syn:anti* isomers was 7:1, as determined by ^{1}H NMR. This reaction served as an ideal model illustrating that the transformation was possible for both isomers in the silane substrate.

It has been documented that alcohol **81** can be prepared directly by reduction of alkyne **80** with $LiAlH_4$[35] or $LiAlH_2(OCH_3)_2$[36] (Scheme 26). However, analysis of the product mixture obtained from the reduction revealed that there was a mixture of three products; the trans alkene **81**, cis alkene **82** and the saturated alcohol **83**. The stereochemistry is dependent on the solvent used.[34] The percentage of trans reduction observed increases with increasing Lewis basicity of solvent and the addition of Lewis acidic cations to the reaction leads to improved selectivity in the product.[37]

Scheme 26

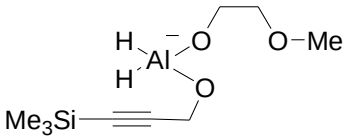


80 **81** **82** **83**

23 : 66 : 11

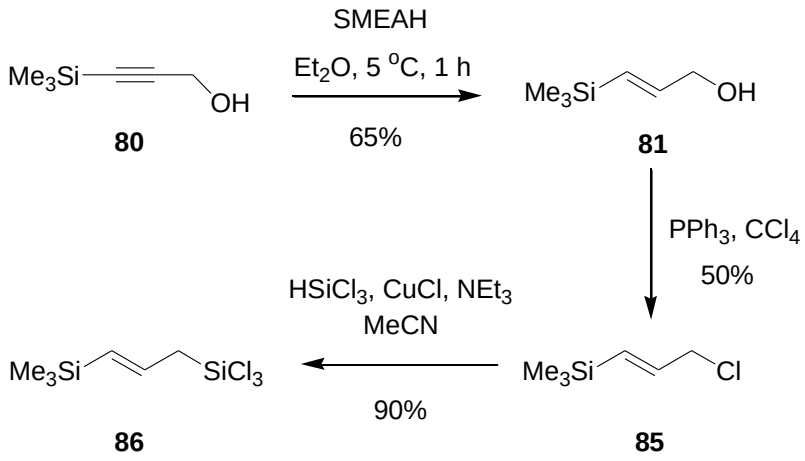
A more stereoseletive and higher yielding reduction was obtained with sodium bis-(2-methoxyethoxy) aluminium hydride (Red-Al or SMEAH).[38] The reaction of **80** took place within 1 h to give **81** exclusively in 65 % yield. Denmark proposed **84** as the active reducing agent.[38]

Figure 9 Proposed Reducing Agent



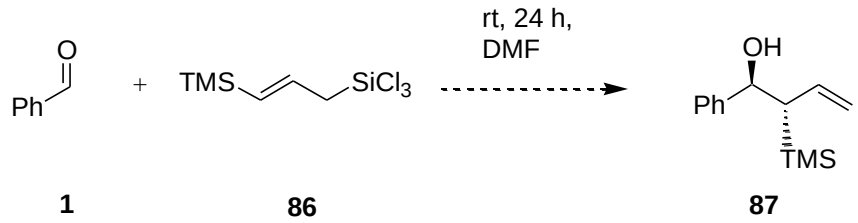
84

Scheme 27 Formation of Allylsilane **86**



This alcohol **81** was then chlorinated to form species **85** using triphenylphosphine in tetrachloromethane, in 50% yield.[39,40] The corresponding allylsilane **86** was formed and used *in situ* for the allylation.[33] Due to the favourable electronic properties of the trimethylsilyl group it was proposed that this would make the silicon centre more susceptible to Lewis basic activation and so facilitate the allylation with the aldehyde.

Scheme 28 Allylation Reaction with Allylsilane **87**



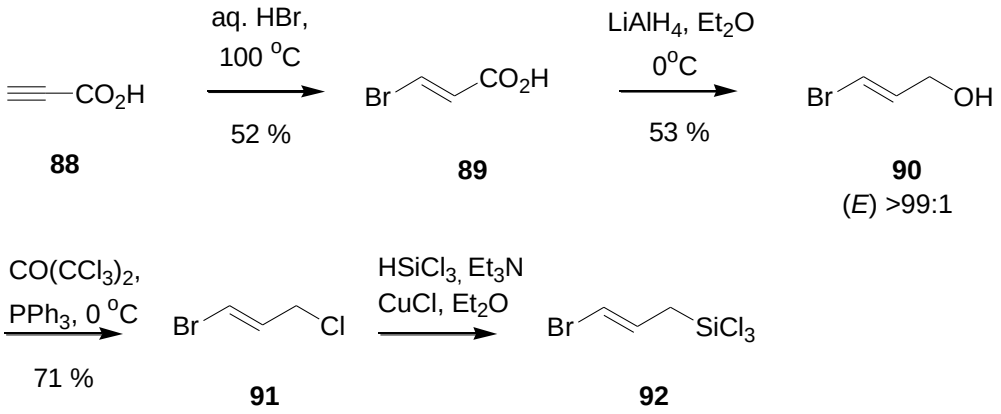
1 **86** **87**

Allylsilane **86** was employed as a substrate in the allylation (Scheme 28). However, the transformation to the homoallylic alcohol was unsuccessful. In an attempt to drive the reaction to completion the solvent medium was varied from DMF to a more potent promoter, the phosphoramide, HMPA.[41] However this also proved unsuccessful as no product was observed. It is possible that the silane **86** decomposed during the reaction.

2.3 Synthesis of Isomerically Pure Allylsilanes

Following on from the synthesis of silane **86**, a selective synthesis of pure *E* and *Z* isomers was devised. Initial attempts to separate *cis* and *trans* isomers of 1,3-dichloropropene by fractional distillation did not result in the isolation of the pure isomer. 3-Halopropenates are usually prepared from the addition of hydrogen halides to propiolates in acetic acid and obtained as an isomeric mixture, with the (*E*) isomer predominating. Hence, to prepare the (*Z*) isomer an alternative route had to be established.[42]

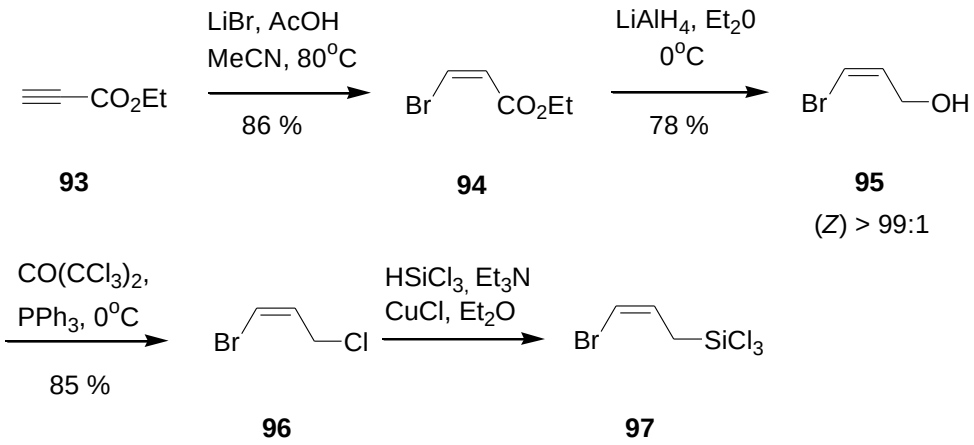
Scheme 29 Formation of (*E*)-3-(Bromoallyl)trichlorosilane **92**



The addition of hydrobromic acid to propiolic acid **91** afforded the *trans*-β-bromoacrylic acid **89**.[43] Subsequent reduction with lithium aluminium hydride gave (*E*)-3-bromoprop-2-en-1-ol **90** as a pure stereoisomer.[43]

Silane **92** was formed through a copper (I) chloride catalysed hydrosilyation[33] of chloride **91** with trichlorosilane in the presence of an equimolar amount of triethylamine. The reaction was carried out at room temperature for 4 h and the product obtained as the pure *E* isomer. A sample of this silane was analysed in solution and then the material was used *in situ* for the allylation reaction.[34] Silane **92** was characterised by the shift of the CH_2 signal in the ^1H NMR spectra on comparison with the ^1H NMR spectra of the allylchloride **91**. In the ^1H NMR spectra of allylchloride **91** the CH_2 signal was observed at 3.92 ppm. After silation, the signal had shifted to 2.26 ppm.

Scheme 30 Formation of (*Z*)-3-(Bromoallyl)trichlorosilane **97**



Ethyl propiolate **93** was readily converted into (*Z*)-bromoacrylate **94** using lithium bromide in acetic acid. Nucleophilic addition of the halide anion to the electron-deficient carbon-carbon triple bond, and simultaneous coordination by the lithium cation to the carbonyl group is proposed to account for the high stereoselectivity observed in this transformation.[44] The ester **94** was then reduced to the alcohol with lithium aluminium hydride at 0 °C, in high yield.

Table 6 Conditions for Chlorination Step

Entry	Conditions	Product yield
1	NCS, PPh_3, DCM, 0 °C→ rt	-
2	$(COCl)_2$, DMF, DCM, 0 °C→ 40 °C	-
3	$SOCl_2$, 85 °C	-
4	PCl_3, Pyridine, -10 °C	22 %
5	$CO(CCl_3)_2$, PPh_3, 0 °C	71 %

The chlorination step (**95** → **96**) proved to be quite problematic. Various methods were screened to make this transformation but with limited success. The allylic substitution was first attempted with *N*-chlorosuccinimide (NCS), but the reaction did not proceed and the alcohol starting material was recovered. Similarly chlorination with thionyl chloride proved unsuccessful, as determined

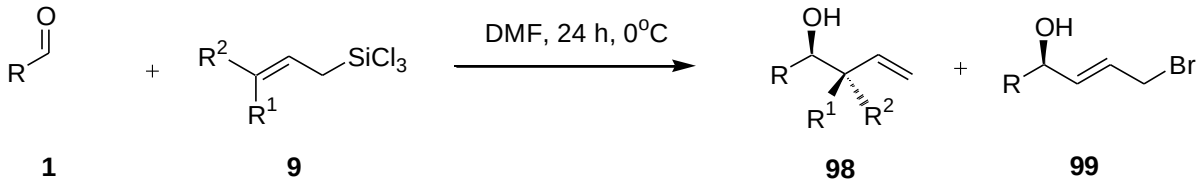
by TLC and ^{1}H NMR. When oxalyl chloride was used the product did form but decomposed during purification via column chromatography. It is proposed that there may be allylic rearrangement occurring and therefore impeding the formation of the desired allyl halide. The reaction of phosphorous trichloride in pyridine with allyl chloride **96** afforded the desired product in a poor yield of 22 % (Table 6, Entry 4).[45]

An alternative procedure using hexachloroacetone as the source of chlorine, allowed the formation of the required allyl chloride in 71 % yield. This provides very mild conditions for the production of allylic chlorides with high regio- and stereoselectivity. Another advantage to this method is the ease of purification via distillation of the product from the reaction mixture, which is possible due to the high boiling point of hexachloroacetone (202 ^{o}C).[46]

2.4 Allylation Reaction with Isomerically Pure Allylsilanes

The allylation reaction with these stereospecific functionalised allylsilanes was carried out with a range of aromatic aldehydes. It has been well documented that the reaction proceeds in a stereospecific manner with minimal isomerisation in the homoallylic alcohol product on condition that the temperature is maintained at 0 ºC or below. Therefore all the allylation reactions, shown in Table 7, were carried out at 0 ºC. DMF was employed as the solvent and Lewis base activator.

Scheme 31 Allylation Reaction with Isomerically Pure Allylsilanes



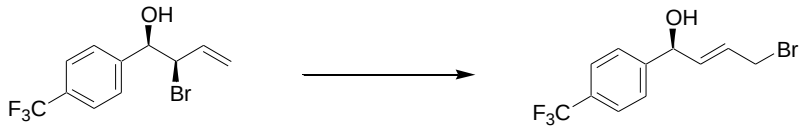
1 **9** **98** **99**

Table 7 Results of Allylation Reaction with Isomerically Pure Allylsilanes

Entry	Aldehyde R	R^1	R^2	% yield	Ratio 98 : 99
1	Ph	Br	H	**98-a** 48	2 : 1
2	4-Cl-C_6H_4	Br	H	**98-b** 31	2 : 1
3	2-Naphthaldehyde	Br	H	**98-c** 38	1 : 1.5
4	4-MeO-C_6H_4	Br	H	**98-d** 31	1 : 3
5	4-CF_3- C_6H_4	Br	H	**98-e** 46	1 : 1
6	Ph	H	Br	**98-f** 36	1 : 3
7	4-Cl-C_6H_4	H	Br	**98-g** 25	1 : 2
8	2-Naphthaldehyde	H	Br	**98-h** -	-
9	4-MeO-C_6H_4	H	Br	**98-i** -	-

The reaction was monitored by TLC and upon analysis, there was an additional product observed which was later isolated on purification by column chromatography. This side product **99** was identified as the allylic rearrangement product.[47,48] It is highly probable that formation of this product is due to the presence of some copper(I) chloride residues from the previous hydrosilyation step catalysing the allylic rearrangement of the homoallylic alcohol **98** to **99**. This obviously impedes the optimal yield available in formation of the product **98**. Ratios of the products from the allylation reaction with isomers of **9** are shown in Table 7**.** It was hoped that the silane could be used *in situ* in the allyltion reaction to avoid any loss via purification upon exposure to the atmosphere.

Scheme 32 Allylation Reaction Product Rearrangement



98-e **99-e**

From the allylation reaction between *p*-trifluromethylbenzaldehyde and allylchlorosilane the side product **99-e** was isolated and analysed by NMR spectroscopy and mass spectrometry. The structure of **99-e** was revealed by the characteristic signal of the alkyl CH_2 group. The ^1H NMR peak for the terminal alkene group in **98-e** occurs at 5.13 ppm. However, this signal was not visible in alcohol **99-e** and a new peak in at 4.02 ppm was observed which is indicative of an alkyl CH_2 with a neighbouring electron withdrawing group.

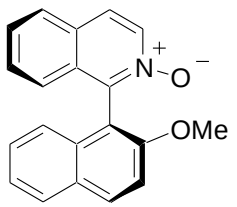
3 Synthesis of Catalysts

3.1 Introduction

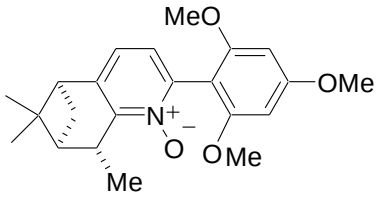
The allylation reaction involves nucleophilic addition to carbonyl derivatives. The enantioselective reaction can be achieved using a variety of Lewis base catalysts.[49] The main classes being; pyridine *N*-oxides, phosphine oxides, formamides and sulfoxides. These Lewis base catalysts all work via attack at the electron deficient silicon atom to form a hypervalent silicate compound which then undergoes a transformation (allylation, alkylation, etc) to release a product and regenerate the ligand.

Figure 10 illustrates a range of chiral catalysts that were synthesised to test their effectiveness in the allylation reaction with allylsilane. It was essential to consider the mode of activation of the ligands. Pyridine *N*-oxides **31** and **64** have one point of coordination whereas the phosphine oxides **100** to **103** have two points of coordination to facilitate the reaction.

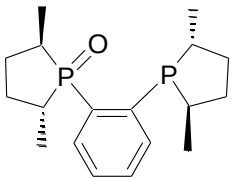
Figure 10 Chiral Catalysts



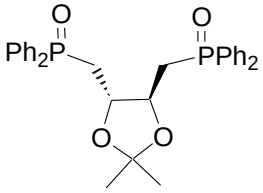
31



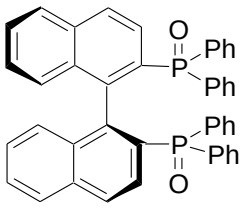
64



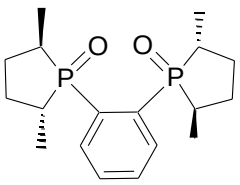
100



101



102

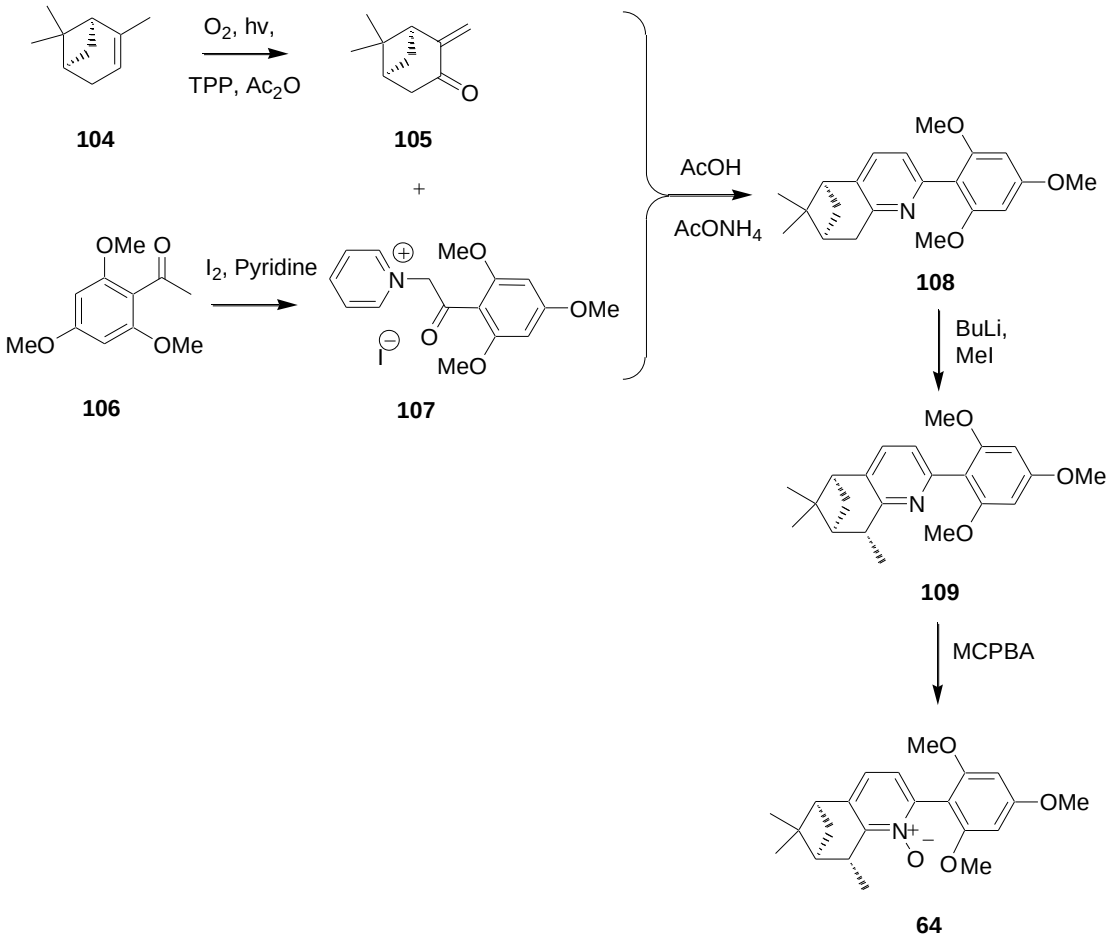


103

3.2 Synthesis of Monodentate Catalysts

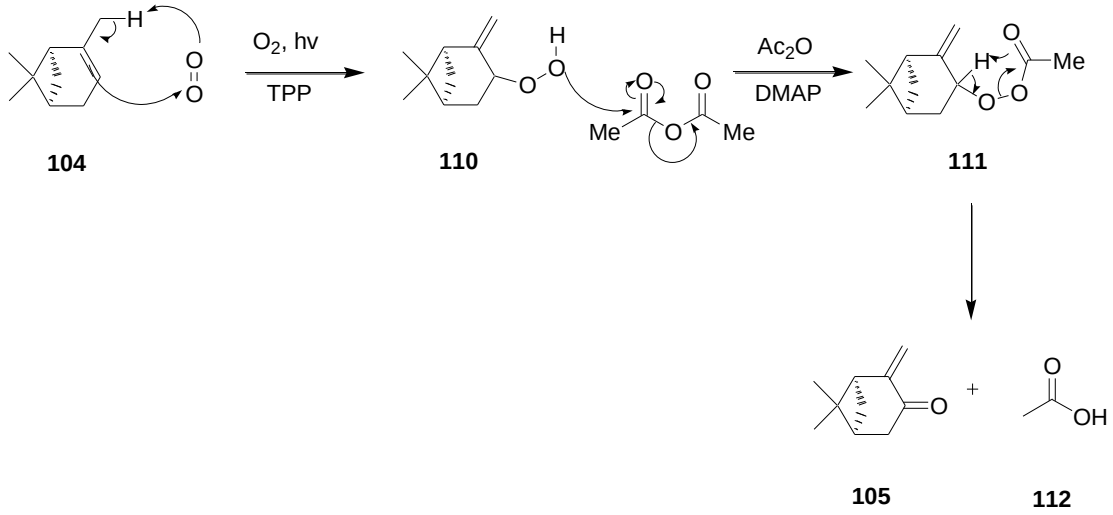
The METHOX[50] catalyst is synthesized from the starting materials, α-pinene **104** and substituted acetophenone **106**. Pinocarvone **105** is obtained via the ene reaction of α-pinene with singlet oxygen. Krohnke salt **107** is formed from the α-iodination of 2,4,6-trimethoxyacetophenone followed by an S_N2 substitution with pyridine. The next step in the reaction sequence is the Krohnke annualtion where the salt can undergo a Michael addition with the α,β-unsaturated enone **105** to give **108**. The pyridine derivative **108** can then be methylated in the benzylic position and subsequent oxidation using *m*-CPBA affords the pyridine *N*-monoxide, METHOX **64**.

Scheme 33 Synthesis of METHOX **64**

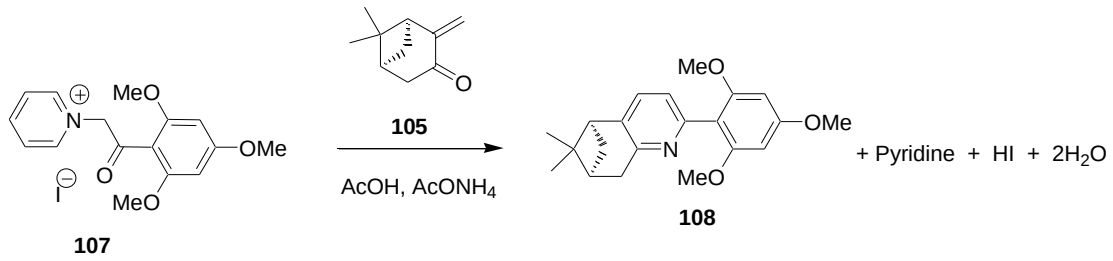


The first step towards the synthesis of METHOX is the ene reaction of α-pinene with singlet oxygen, to afford pinocarvone **105** in high yield. From Scheme 34, the lone pair of electrons on the oxygen extracts a proton from α-pinene **104** resulting in the formation of a new carbon-carbon double bond. This now goes on to attack the remaining oxygen forming a hydroperoxide intermediate **110** which can be transformed to the enone **111** using acetic anhydride and DMAP. In this step the intermediate loses acetic acid to give the desired enone product **105**.[51]

Scheme 34 Mechanism of Ene Reaction

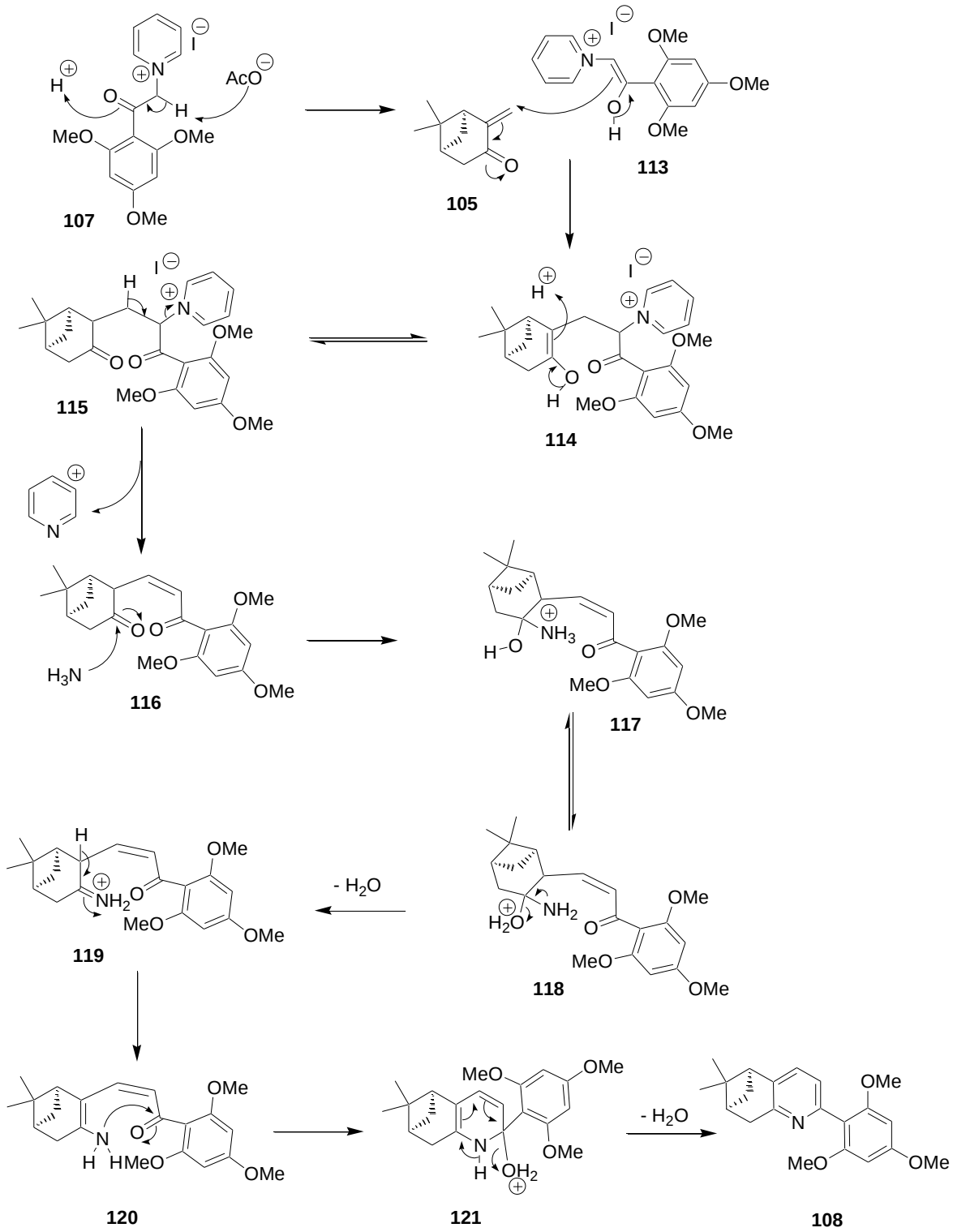


Scheme 35 Kröhnke Annulation



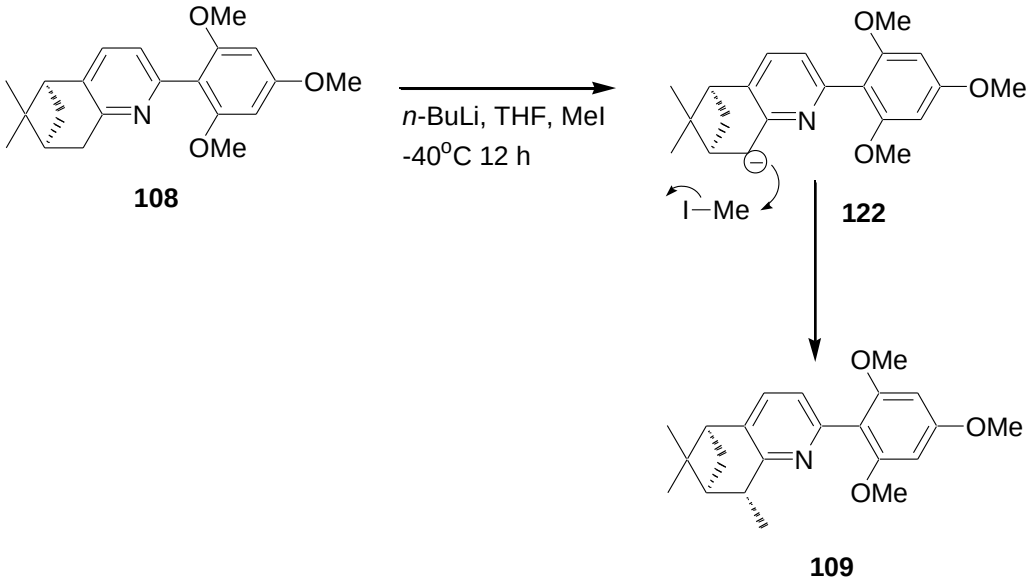
The Kröhnke salt **107** is formed by the α-iodination of the acetophenone **106** in pyridine. Scheme 35 shows the general Kröhnke annulation reaction between a Kröhnke salt and the enone in acetic acid and ammonium acetate to give the pyridine **108**. The mechanism of this transformation is demonstrated in Scheme 36. Enolisation is facilitated by the pyridinium moiety to afford enol **113**, which undergoes Michael addition with the α,ß-unsaturated ketone **105** to form the intermediate **114**. Species **114** rearranges to the corresponding keto form **115** allowing the formation of **116**, following elimination of pyridine. The next stage in the process is imine formation. Ammonia adds to the more reactive carbonyl centre on **116**, the ketone, to form the iminium ion **119**. This imine group then attacks the enone facilitating closure of the ring **121**. The last step in the mechanism involves the elimination of water, allowing full conjugation of the pyridine ring, to generate pyridine **108**.

Scheme 36 Kröhnke Annulation Mechanism



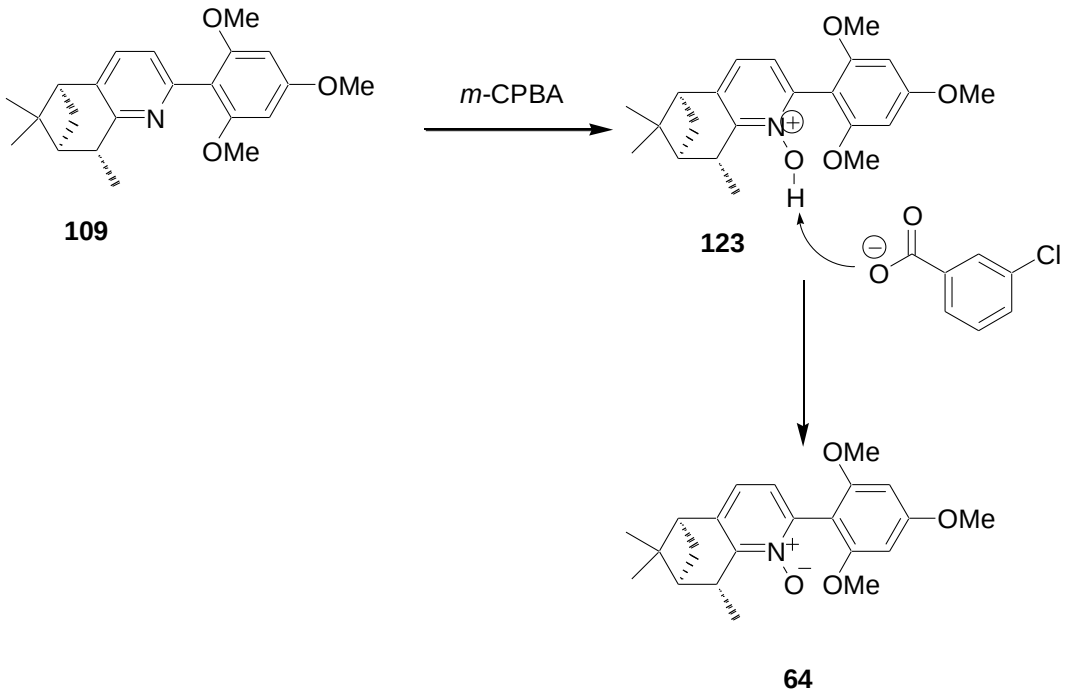
The deprotonation of **108** was achieved using 1.5 equivalents of *n*-BuLi, after several failed attempts using bases such as LDA and bulkier bases such as lithium bistrimethylsilylamide. The resulting anion **122** was quenched with methyl iodide to afford **109**, in 26% yield. The diastereoselectivity achieved in the addition of this new methyl group is due to the steric hindrance caused by the bridge on the ring forcing the methyl group to add from the opposite face.

Scheme 37 Methylation Mechanism



Oxidation of **109** was carried out at room temperature using *m*CPBA for 48 h, giving the pyridine *N*-oxide **64**in 39 % yield. From Scheme 38, the H^+ is transferred to the carbonyl oxygen via a 5-membered cyclic transition state to form the intermediate **123**. The carboxylate anion then abstracts a proton from pyridine intermediate **123**, forming the *N*-oxide **61**.

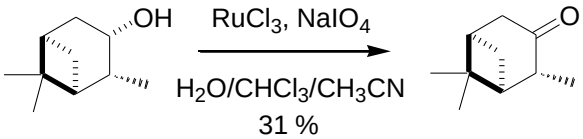
Scheme 38 Mechanism of Oxidation



109 **123** **64**

Due to difficulties encountered in the methylation step it was proposed to start with an alternative α,ß-unsaturated ketone that already had the methyl substituent in place, such as isopinocampheol. Two methods of oxidation were explored. Firstly, (*S*)-(+)-isopinocampheol was oxidised to ketone **129** by sodium periodate in the presence of $RuCl_3$ catalyst.[52]

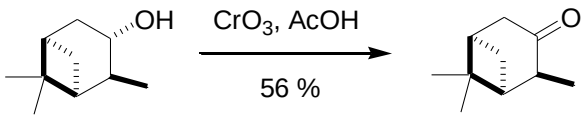
Scheme 39 Oxidation via $RuCl_3$ Catalysis



124 **125**

As a consequence of the low yield an alternative method of oxidation was tested. Chromium troxide in acetic acid was used to oxidise (*S*)-(+)-Isopinocampheol to **125** with an improved yield of 56 %.[53]

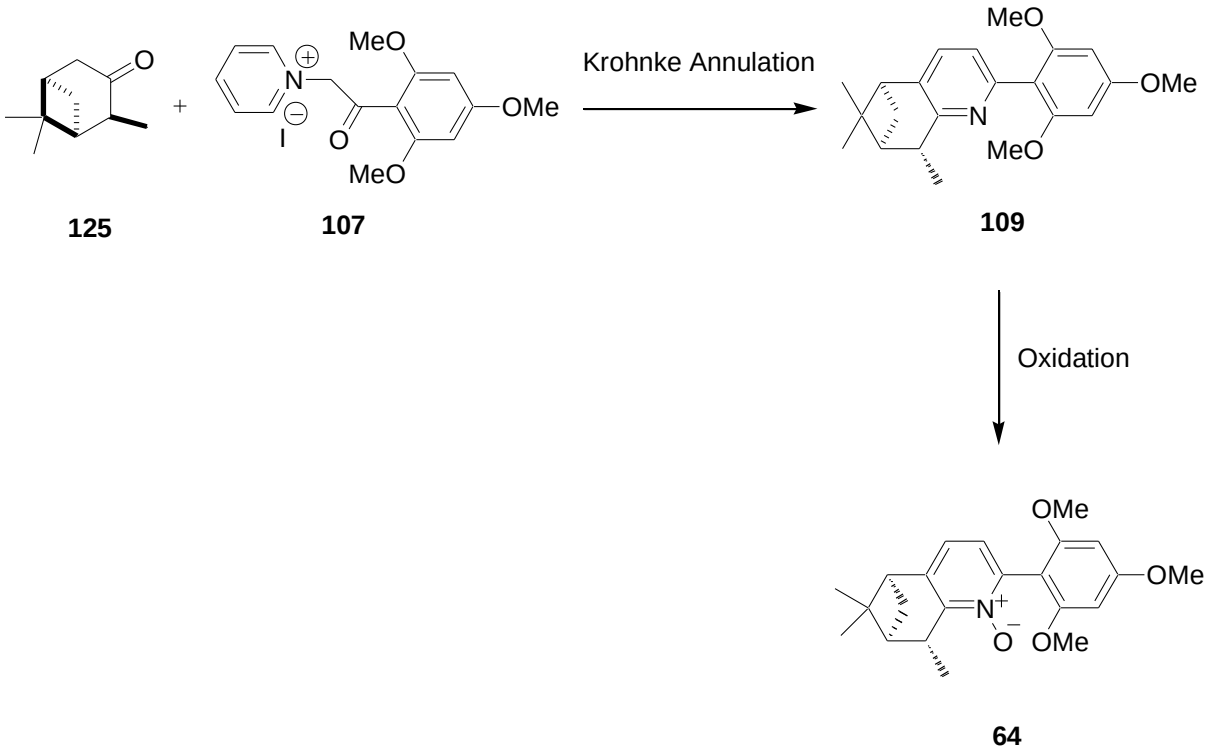
Scheme 40 Oxidation of Alcohol **124**



124 **125**

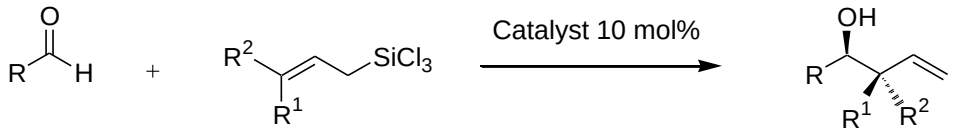
Ketone **125** was then used in a condensation reaction with the Krohnke salt **107** to afford pyridine **109**. This new methodology effectively eliminates a step from the overall synthesis of the ligand.

Scheme 41 Alternative METHOX Synthesis



125 **107** **109** **64**

Scheme 42 Allylation Reaction



1 **2** **98**

Table 8 Allylation Reactions Catalysed by Pyridine *N*-oxide Ligands

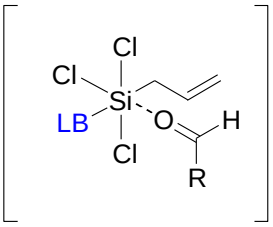
Entry	Catalyst	R	R^1	R^2	Solvent	Temperature	Time	Product
1	**64**	Ph	H	Br	MeCN	-20 °C	24 h	-
2	**64**	Ph	H	Br	MeCN	0 °C	24 h	-
3	**64**	Ph	H	Br	CH_2Cl_2	-20 °C	24 h	-
4	**72**	4-CF_3-C_6H_4	H	Br	CH_2Cl_2	0 °C	24 h	-
5	**72**	4-CF_3-C_6H_4	Br	H	CH_2Cl_2	0 °C	24 h	-

Pyridine *N*-oxides; METHOX **64** and QUINOX **72**, which are known to exhibit significant nucleophilicity towards the silicon atom, were screened in the allylation reaction (Scheme 42). Table 8 charts the reaction conditions tested under asymmetric control. METHOX **64** was tested in the reaction between benzaldehyde and (*E*)(3-Bromoallyl)trichlorosilane at -20 °C and 0 °C. However no product was observed. Similarly, when QUINOX **72** was employed in the allylation reaction between *p*-trifluoromethylbenzaldehyde and bromoallylsilane no product was formed as determined by TLC and NMR. Therefore, it was concluded that monodentate ligands **64** and **72** are not sufficient at catalysing the allylation reaction**.** It was proposed that catalysts with a bidentate mode of activation may be required for the allyltion reaction to occur with such bromoallylsilane substrates **2**.

3.3 Synthesis of Bidentate Catalysts

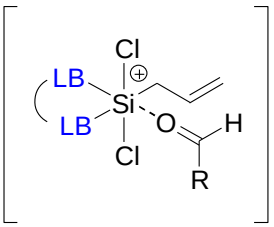
The method of coordination of the ligand to the silicon centre is crucial in achieving the enantioselective reaction. Figure 11 demonstrates that when a monodentate ligand is employed then this forms a neutral hexacoordinate silicon species **126.** However no reaction is observed when these ligands are implemented in the allylation reaction (ligands **64**, **72**). We can therefore conclude that this class of ligand is not sufficient for activation with our functionalised silanes **92** and **97**. However, when a bidentate ligand is employed, the intermediate possesses a cationic silicon centre **127** which is more inclined to form the six membered transition state required for successful reaction and formation of the homoallylic alcohol.

Figure 11 Hexacoordinate Silicon



126

neutral hexacoordinate silicon



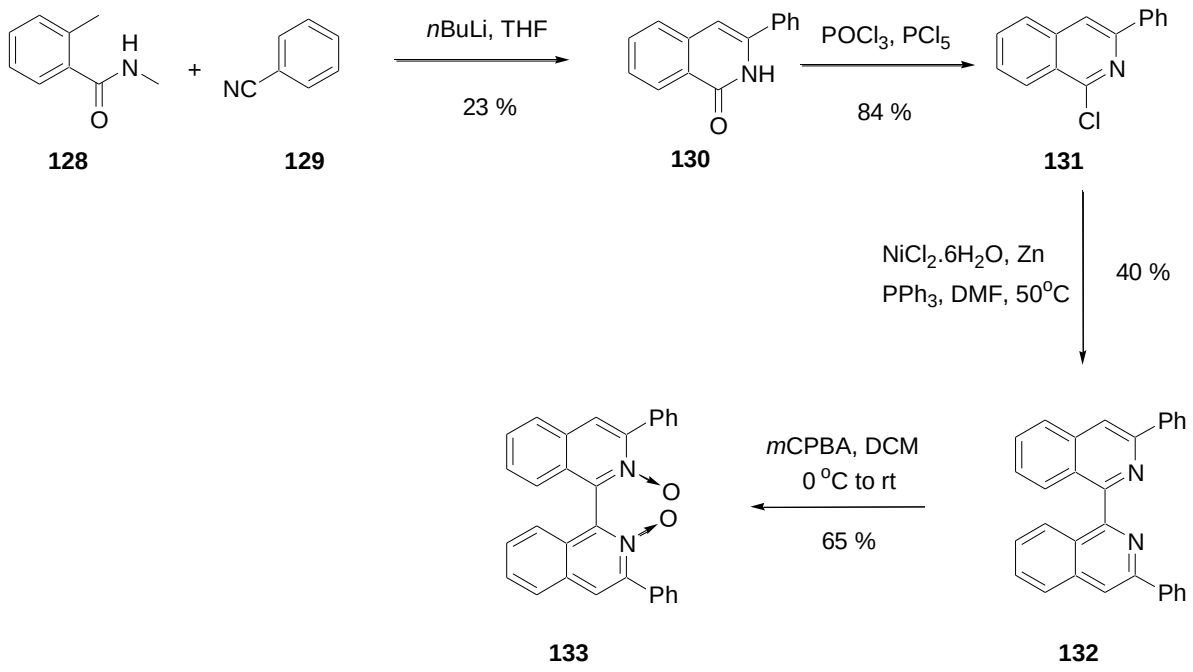
127

cationic hexacoordinate silicon

3.3.1 Synthesis of Pyridine *N*-Oxides

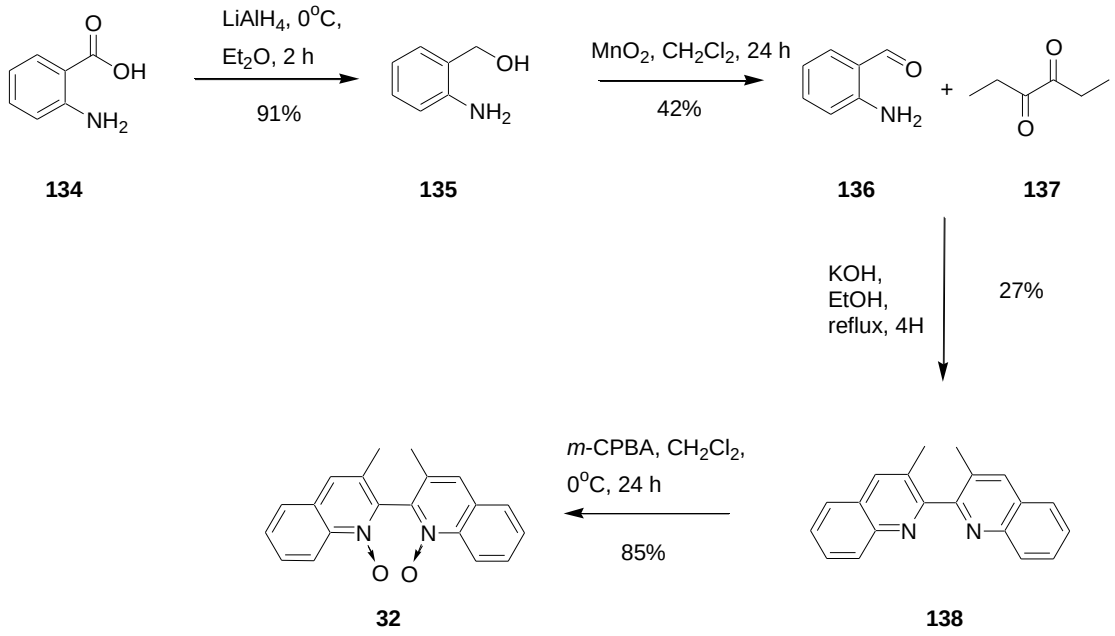
One such bidentate ligand is the pyridine-derived organocatalyst **133.**[54] The coupling reaction of *N*-methyl-*o*-toluamide **128** with benzonitrile **129** was accomplished via a dilithio species using *n*-BuLi. Isoquiolone **130** was chlorinated using phosphonyl chloride and the transformation occurred in high yield, 84 %. To form the biisoquinoline unit requires the homo-coupling of the halopyridine **131** in the presence of $NiCl_2(PPh_3)_2$. Subsequent oxidation of **132** with *m*CPBA in dichloromethane gave the dioxide **133** in 65 % yield.

Scheme 43 Formation of Biisoquinoline Dioxide **133**

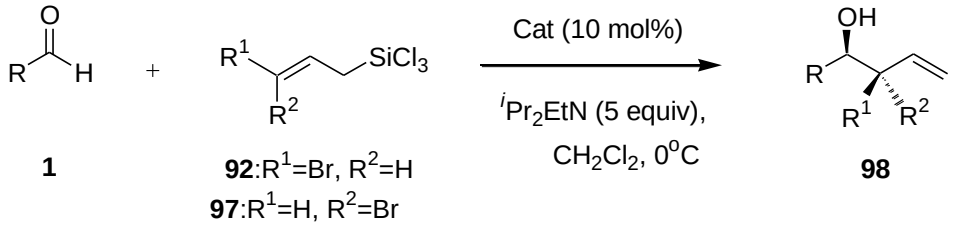


Nakajima[55] prepared the biquinoline *N,N'*-dioxide in three steps from anthranilic acid. Firstly, anthranilic acid **138** was reduced to the corresponding alcohol by reduction with lithium aluminium hydride, in virtually quantitative yield.[56] Next the alcohol was oxidised under neutral conditions with manganese dioxide[57], to give the aldehyde **140**.[58] The following reaction of 2-aminobenzaldehyde with 3,4-hexanedione gave the biquinoline **142** after recrystallisation from ethyl acetate-hexane mixture.[59] Oxidation with *m*-CPBA gave the racemic ligand **143** in 85% yield.[55]

Scheme 44 Synthesis of Biquinoline *N,N'*-dioxide **32**



Scheme 45 Allylation Reaction



The bidentate *N*-oxide ligands **133** and **32** were screened in the allylation reaction (Scheme 45) with the isomerically pure functionalised silanes **95**, **100**. However, they did not prove effective in catalysing the reaction and no product was formed. Therefore, our focus was drawn to another class of bidenate ligand; the phosphine oxides.

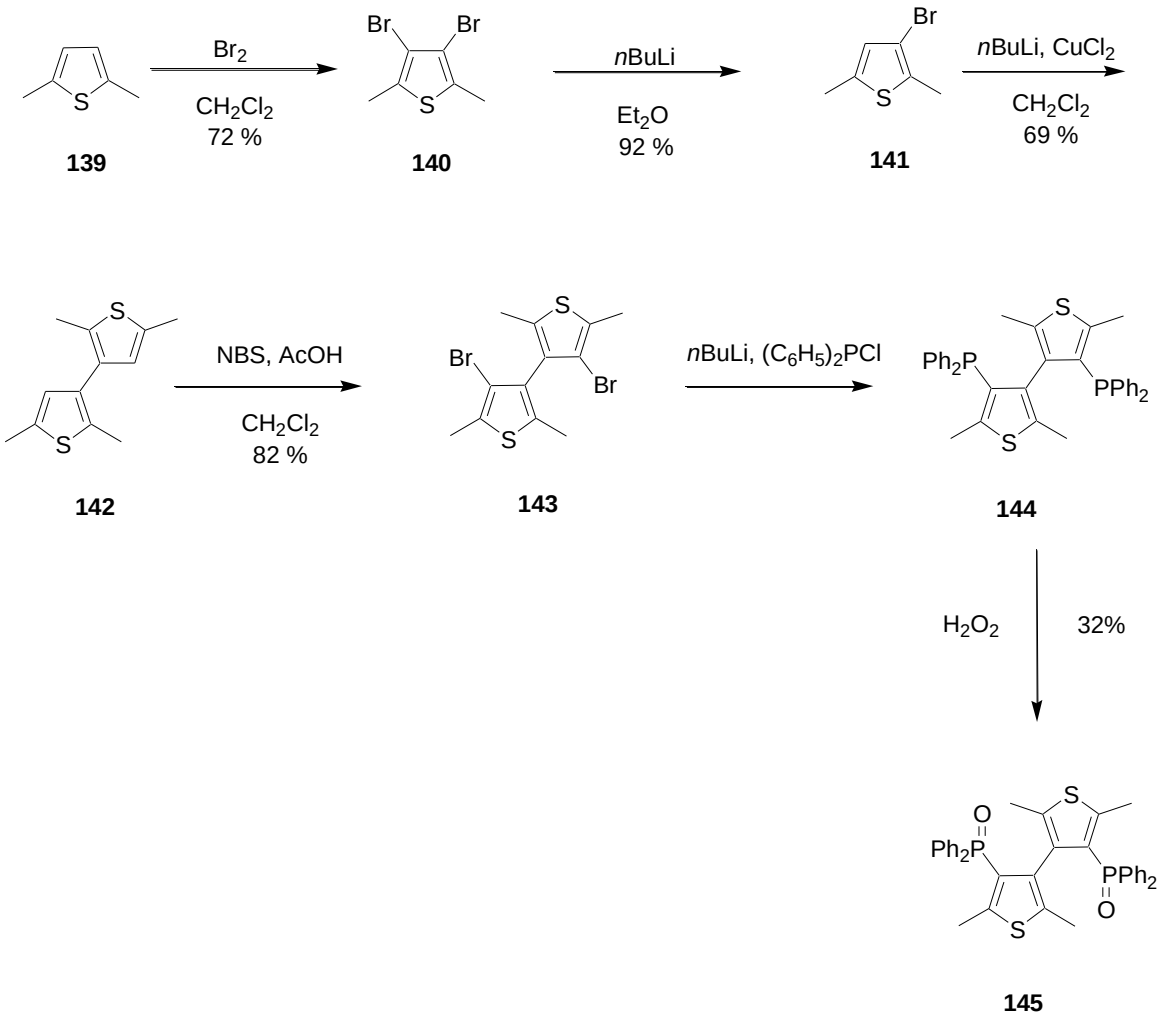
3.3.2 Synthesis of Phosphine Oxides

The chiral biheteroaromatic diphosphine oxide, (*S*)-TetraMe-BITIPO **145**, has shown high enatioselectivity in the reaction of benzaldehyde with allyltrichlorosilane, exhibiting up to 95% ee.[60] The diphenylphosphine group is in the electron-rich β-position of the thiophene ring and it has two coordination sites. Reaction of (*S*)-TetraMe-BITIPO **145** with allyltrichlorosilane forms the cationic hexacoordinate silicon species **127**. Upon consideration of these factors we proposed that (*S*)-TetraMe-BITIPO **145** could contribute to a highly enantioselective reaction with our functionalised silanes.

(*S*)-TetraMe-BITIPO **145** can efficiently promote the addition of allyltrichlorosilane to both electron-deficient and electron-rich aromatic aldehydes. On assessment, catalysis of the allylation of 4-NO_2-benzaldehyde with allyltrichlorosilane gave the product in 51% yield and 93% ee, while reaction of 4-MeO-benzaldehyde gave 95% yield, in 91% ee. Electron-poor aldehydes react slower than electron-rich aldehydes but both with similar high enantioselectivities.[60] Evaluation of the reaction with an 80:20 mixture of (*E*)- and (*Z*)-crotyltrichlorosilane gave the diastereoisomeric alcohols in an *anti*/*syn* mixture of 83/17. Due to this information it is plausible that the reaction involves a six-membered cyclic transition state.

Depicted in Scheme 46 is the synthesis of TetraMe-BITIPO. From the inexpensive starting material, dimethyl thiophene **139**, bromination[59,61] with bromine in CH_2Cl_2 afforded the dibromo compound **140,** in 72 % yield.[62] Following lithium-halogen exchange 3-bromo-2,5-dimethylthiophene **146** was formed in a yield of 92 %. The next step in the synthesis was transmetallation with *n*-BuLi to give the intermediate 2,5-dimethyl-3-thienyllithium.[63] This species can then undergo copper catalysed oxidative coupling to give 2,2',5,5'-tetramethyl-3,3'-bithiophene **142**. [64] Dibromination with NBS affords **143** in 82 % yield. Subsequent reaction of this dibromide with 2 equiv of *n*-butyllithium and quenching with chlorodiphenylphosphine formed the intermediate **144**.[65,66] Oxidation with hydrogen peroxide afforded the bidentate ligand **145** in 32 % yield.[67]

Scheme 46 Synthesis of TetraMe-BITIPO **145**



Nakajima *et al*[59] performed the asymmetric allylation reaction using catalytic quantities of chiral phosphine oxide **102**. This class of ligand is widely applied in Rh (I)-catalysed asymmetric hydrogenation of functionalised olefins.[68] Due to the polarisation of the P-O bond, the phosphine oxides possess a highly nucleophilic centre allowing the ligand to behave as a Lewis base.[69] These axially chiral phosphine oxides are derived from commercially available chiral phosphines.[70] Nakajima discovered that the addition of a combination of diisopropylethylamine and tetrabutylammonium iodide is essential to accelerate the catalytic cycle.

Scheme 47 Allylation Catalysed with (*S*)-BINAPO

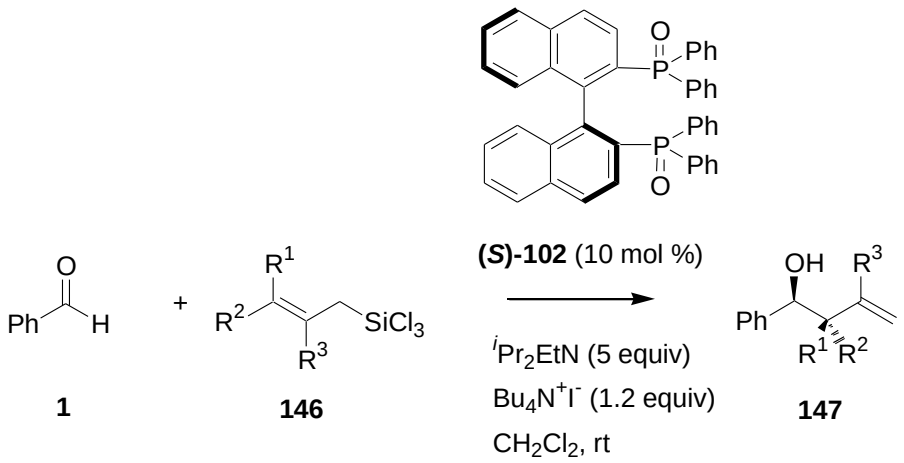


Table 9 Results of Allylation Reaction with BINAPO

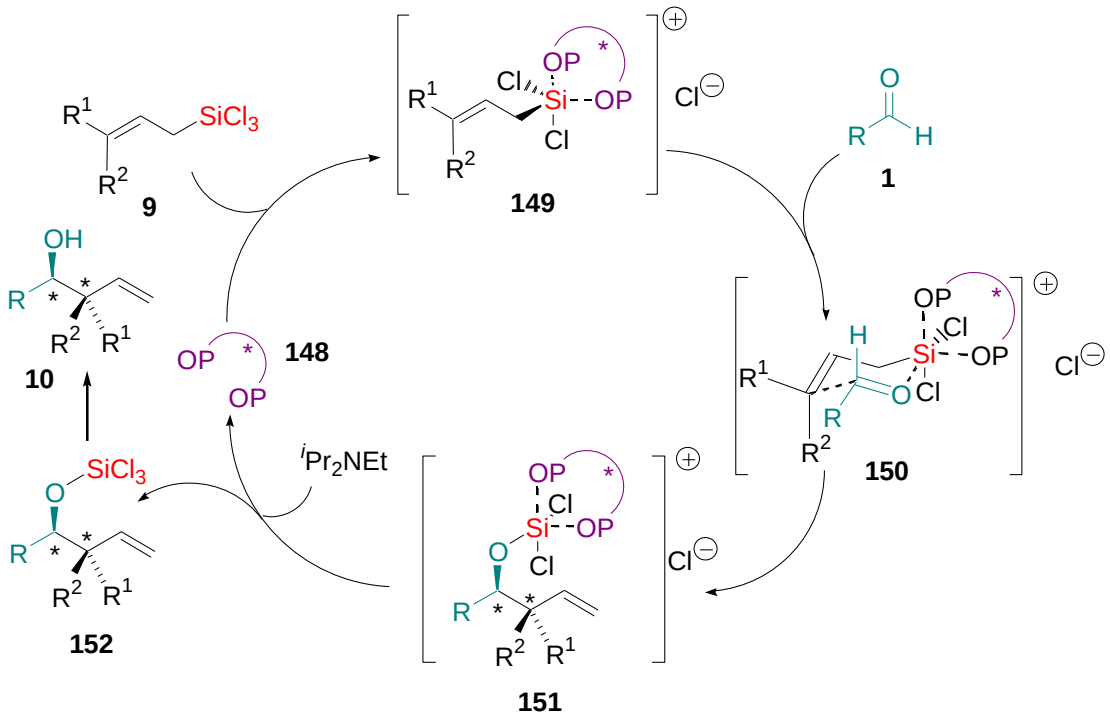
Entry	R^1	R^2	R^3	Time (h)	Yield %	ee %
1	H	H	H	4	92	43
2	CH_3	H	H	4	92	4
3	H	CH_3	H	2	87	46

Work was carried out to examine the effect of substituted silanes on the allylation reaction of benzaldehyde. Nakajima found that the enantioselectivity obtained is strongly dependent on the substitution pattern in the allylsilane molecule (Scheme 47). It is clear from the data in Table 9, when allylsilane or *trans*-crotylsilane were used, similar enantioselectivities were observed but *cis*-crotylsilane gave only 4 % ee.[69] So the orientation of the group at R^1 greatly affects the enantioselectivity. The BINAPO gave *anti*-products from (*E*)-silanes and *syn*-product from (*Z*)-silanes.

Scheme 48 denotes the proposed mechanism for the allylation reaction as catalysed by the chiral bidentate phosphine oxide ligand, determined by ^{31}P NMR studies.[71] The bidentate Lewis base binds to the allyltrichlorosilane to give **149,** a pentacoordinate silicon complex. This electrophilic silicon is attacked by the aldehyde to form the closed six-membered transition state **150**. Upon the

transfer of the allylic moiety with the electrophile, **151** is formed. Subsequent regeneration of the Lewis base **148** gives **152**, and detachment of the silicon species gives the homoallylic alcohol **10**.

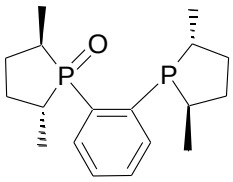
Scheme 48 Bidentate Catalytic Scheme



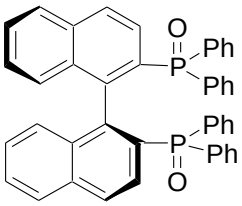
3.4 Application of Phosphine Oxides in the Asymmetric Allylation Reaction

A series of phosphine oxide ligands (159 – 163) were prepared by the oxidation of commercially available chiral phosphines with *m*-CPBA (Figure 13).[69] These ligands were screened along with the TetraMe-BITIPO ligand **145** for activation in the allylation reaction with bromosilanes **92** and **97**.

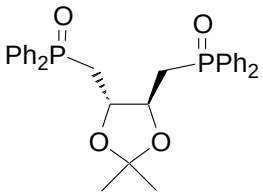
Figure 13 Phosphine Oxide Ligands



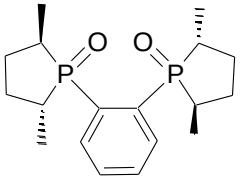
100



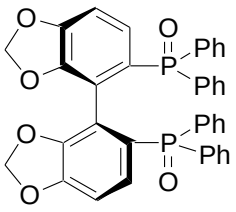
102



101

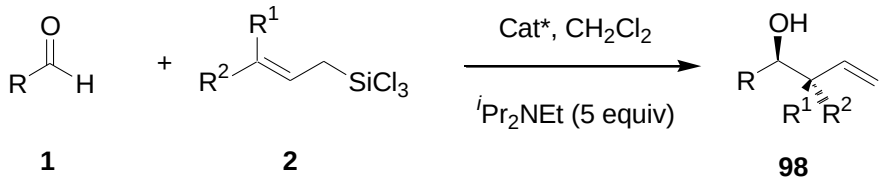


103



153

Scheme 49 Allylation Reaction with Phosphine Oxide Ligands



1 **2** **98**

Table 10 Results of Allylation Reaction with Phosphine Ligands

Entry	R	R^1	R^2	Catalyst (mol %)	Temp (°C)	Yield %	ee %
1	Ph	Br	H	**145** (20)	0	**98-a** -	-
2	Ph	H	Br	**100** (20)	0	**98-b** -	-
3	Ph	H	Br	**100** (20)	-20	**98-c** 23	29
4	Ph	Br	H	**101** (10)	-20	**98-d** 17	18
5	Ph	H	Br	**102** (10)	0	**98-e** -	-
6	Ph	Br	H	**102** (10)	-20	**98-f** 34	50
7	4-CF_3-C_6H_4	Br	H	**102** (10)	-10	**98-g** 22	43
8	Ph	H	Br	**103** (10)	-20	**98-h** 10	15
9	Ph	Br	H	**103** (10)	-20	**98-i** 43	25
10	Ph	H	Br	**153** (10)	-20	**98-j** -	-
11	Ph	Br	H	**153** (10)	-20	**98-k** -	-

Table 10 shows the results obtained upon the allylation reaction promoted by chiral phosphine oxides. When employed in the allylation reaction with functionalised silanes **2** they exhibited poor to moderate enantioselectivities, ranging from 15 to 50 % ee. All the transformations proceeded in a stereoselective manner with the *syn*-**98** and *anti*-**98** being obtained from the (*Z*)-**2** and (*E*)-**2** respectively.

TetraMe-BITIPO **145** and (*S*)-SEGPHOS **153** both failed to activate the silane towards reaction with benzaldehyde. (*R*,*R*)-MeDUPHOS **100** afforded the *anti*-

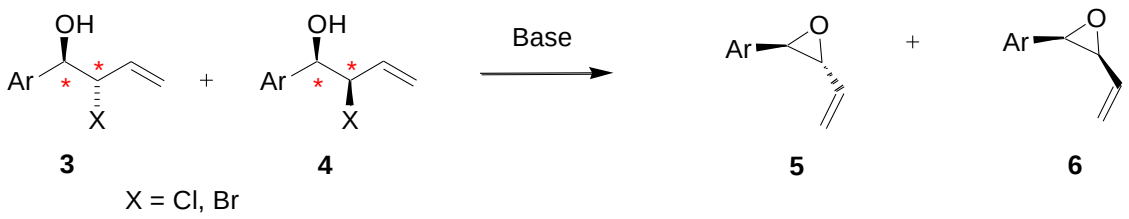
alcohol in 29 % ee (Table 10, entry 3). (*R*,*R*)-**103** promoted the formation of the *anti*-alcohol-**98c** in 15 % ee and the *syn*-alcohol in 25 % ee at -20 °C. The most notable result was achieved using (*S*)-BINAPO-**102**, where upon reaction with *Z*-silane **2** the *anti*-alcohol-**98f** was formed in 50 % ee. This level of enantioselectivity is relatively high in the context of previously published work by Nakajima when carrying out the allylation reaction with crotylsilanes.[72] However, the enantioselectivity displayed upon reaction of (*S*)-BINAPO-**102** with the *Z*-silane was not replicated when the *E* isomer was employed. No product was observed by TLC.

4 Formation of Epoxides

4.1 Introduction

The resultant homoallylic alcohols **4** and **5**, from the asymmetric allylation reaction, possess two new stereogenic centres. These molecules can undergo an intramolecular S_N2 reaction resulting in the formation of the corresponding vinyl epoxides **6** and **7**. This transformation proceeds with retention of the relative stereochemistry. Vinyl epoxides are important starting materials for the preparation of a variety of biologically active products and hence are useful intermediates in synthesis.[73, 74] There are many different synthetic routes to obtain vinyloxiranes, most involving elimination of a leaving group vicinal to the hydroxyl function. The difficulties lie in the stereoselective building of the precursor. However, as described earlier, we have developed a streoselective route to form homoallylic alcohols, functionalised in the γ-position.

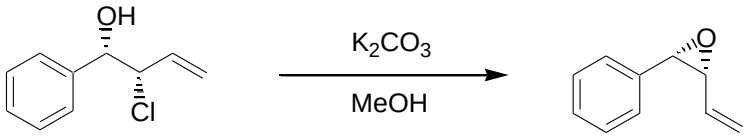
Scheme 50 Epoxide Formation



4.2 Formation of Epoxide from Homoallylic Alcohol

The cyclisation of 1,2-chlorohydrin to the corresponding epoxide has been previously described in the literature.[75,76] Cozzi and his colleagues published a synthesis of the alcohol **154** via a Cr(Salen) complex promoted enantioselective addition of 1,3-dichloropropene to aromatic aldehydes in the presence of Mn. This 1,2-*syn*-chlorohydrin **154** was used as a key intermediate towards the synthesis of *cis*-vinyl epoxide **155**. The base used to perform this cyclisation was potassium carbonate in MeOH.[77] The reaction was left for 3h at rt to yield the vinyl epoxide **155**.

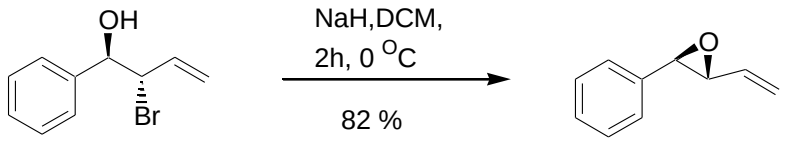
Scheme 51



154 **155**

We attempted to emulate this procedure and apply it to the homoallylic alcohol **98-f**. When this reaction was carried out no product was observed. After work-up and anaylsis by NMR, only starting material was recovered. Another commonly used method is the reaction of an allylic alcohol with sodium hydride.[78] A solution of **98-f**, in DCM, was cooled to 0 °C and 2 equivalents of NaH was added. The reaction was monitored by TLC anaylsis, and deemed complete after 2 h. The pure *trans*-epoxide **156** was obtained in 82 % yield, following aqueous work-up, with no further purification necessary.[79]

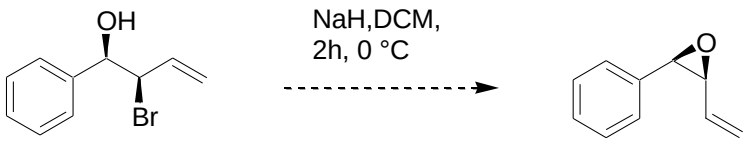
Scheme 52



98-f **156**

Despite the success of the cyclisation with the *anti*-homoallylic alcohol **98-f**, when the *syn*-homoallylic alcohol **98-a** was treated under the same reaction conditions the reaction failed to produce the corresponding *cis*-epoxide **157**. Instead only starting material was recovered.

Scheme 53



98-a **157**

5 Conclusions

Through the development of isomerically pure allylsilanes (**92**, **97**) functionalised in the in the γ-position, we have demonstrated that it is possible to prepare the corresponding homoallyic alcohols in a stereoselctive manner.

Different classes of chiral catalysts were synthesised and screened for activity in the allylation reaction. These can be categorised based on their method of activation. The monodentate ligands failed to achieve the homoallylic alcohol species (Table 8). This led to the exploration of ligands with a bidentate mode of activation. A variety of bidentate ligands were synthesised, ranging from *N*-oxides to phosphine oxides to achieve an enantioselective reaction. The latter group proved to be the most effective at promoting the reaction and imparting chirality in the product. (*S*)-BINAPO **102** exhibited the most promising enantioselectivity of 50 % ee (Table 10) in the homoallylic alcohol product when reacted with (*Z*)-3-bromo-allyltrichlorosilane.

It can be envisaged that further optimisation of this process would be possible through the design and synthesis of other phosphine oxide based ligands employing the bidentate activation mode. The cyclisation of the anti-homoallylic alcohol **98-f** to form the trans-epoxide **156** was achieved upon reaction with base. However, additional exploration is required for the cyclisation of the syn-homoallylic alcohol **98-a** which would give the corresponding cis-epoxide **157**.

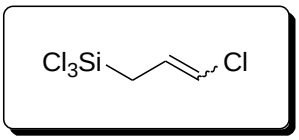
Experimental

General Methods

All reactions were performed under an atmosphere of dry, oxygen-free nitrogen (or argon where specified) in oven-dried glassware twice evacuated and filled with the nitrogen. Room temperature refers to ambient room temperature (20-22^{o}C); 0^{o}C refers to an ice slush bath. Heated experiments were conducted using thermostatically controlled oil baths. All solvents for the reactions were of reagent grade and were dried and distilled immediately before use. Solvents and solutions were transferred by syringe-septum and cannula techniques. Petroleum ether refers to the fraction boiling in the range of 40-60 ^{o}C. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. The identity of the products prepared by different methods was checked by comparison of their NMR, IR, and MS data and by the TLC behaviour. Reactions were monitored by Thin Layer Chromatography using aluminium backed silica gel 60 (F254) plates, visualised using UV254/286 nm and PMA, Dragendorf, Ninhydrin dips as appropriate. Flash chromatography was carried out using 60 A silica gel as the stationary phase.

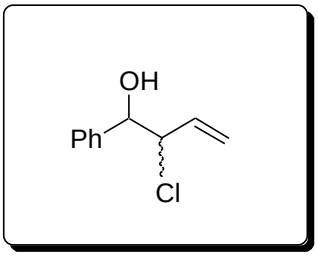
The NMR spectra were recorded in $CDCl_3$, ^{1}H at 400 MHz and ^{13}C at 100.6 MHz on a Bruker Spectrospin 400 (400 MHz) spectrometer. Chemical shifts are reported in δ units, parts per million with chloroform-d_1 ((δ 7.26, ^{1}H; δ 77.0, ^{13}C) as internal standard unless otherwise indicated. Coupling constants (J) are measured in Hz and are unadjusted. Various 2D-techniques and DEPT experiments were used to establish the structures and to assign the signals. Infra-red (IR) spectra were obtained on a Shimadzu FTIR-8400S spectrometer using attenuated total reflectance (ATR) so that the IR spectrum of the compound (solid or liquid) could be directly detected (thin layer) without any sample preparation. The mass spectra (EI, CI and/or FAB) were measured on a Jeol JMS700 spectrometer. Melting points were determined on a Kofler block and are uncorrected. Optical rotations were recorded in $CHCl_3$ at 25 °C unless otherwise indicated, with an error of ≤ ± 0.1. The $[\alpha]_D$ values are given in 10^{-1}

deg cm^3 g^{-1}. Enantiomeric excess was determined by chiral HPLC analysis (using a Hewlett Packard Agilent 1100 Series quaternary pump, vacuum degasser, diode array detector, manual injector and Hewlett Packard ChemStation). The chiral GC and HPLC methods were calibrated with the corresponding racemic mixtures. (+)-DIOP was purchased from Aldrich with $[\alpha]_D$ + 25 (*c* = 2.3; $CHCl_3$).



(3-Chloroallyl)trichlorosilane 78

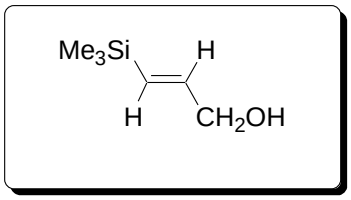
Into a three-neck round bottom flask, copper (I) chloride (0.25 g, 2.4 mmol), triethylamine (6.6 mL, 47.6 mmol) and diethyl ether (30 mL) were stirred in an argon atmosphere. 1,3-Dichloropropene **77** (4.4 mL, 47.6 mmol) and trichlorosilane (5.3 mL, 52.4 mmol) were added dropwise simultaneously via an addition funnel and the mixture was stirred at room temperature for 4 h. The white precipitate was filtered off using a closed tubing system. The filtrate was then distilled at over 230 ^{o}C and the desired product **78** (3.24 g g) was obtained as an oil. This material was used for further transformations without additional purification; *cis*/*trans* mixture (1:1.3); ^{1}H NMR (400 MHz, $CDCl_3$) (*cis*) δ 2.51 (dd, *J* = 8.4, 1.2 Hz, 2H), 5.71-5.84 (m, 1H), 6.20 (d, *J* = 7.2 Hz, 1H); (*trans*) δ 2.54 (dd, *J* = 8, 1.2 Hz, 2H), 5.71-5.84 (m, 1H), 6.04 (d, *J* = 13.2 Hz, 1H).[33,34]



2-Chloro-1-phenylbut-3-en-1-ol 79

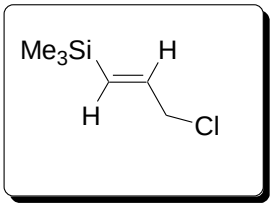
Trichloro(3-chloroallyl)silane **78** (100 μL, $6.6x10^{-4}$ mmol) and benzaldehyde (56 μL, $5.3x10^{-4}$ mmol) were dissolved in DMF (2 mL) and stirred at room temperature for 2 h. Saturated aqueous sodium hydrogen carbonate (8 mL) was added to quench the reaction and the aqueous layer was extracted with ether (3 × 10mL). The ether layer was washed with brine and water (2 × 10 mL) successively and then dried with Na_2SO_4. The solvent was evaporated *in vacuo* and the crude product was purified by chromatography on a column of silica gel (15 × 1.5 cm), eluting with a mixture of petroleum ether and ethyl acetate (8:1)

to afford the chlorohydrin **79** syn:anti 1:1 (7.8 mg, 62% as a colourless oil): ^{1}H NMR (*syn*) δ 2.81 (d, *J* = 3.6 Hz, 1H), 4.56 (dd, *J* = 8.1 Hz, 7.2 Hz, 1H), 4.70 (dd, *J* = 7.2 Hz, 3.3 Hz, 1H), 5.10-5.28 (m, 2H), 5.78-5.90 (m, 1H), 7.3-7.6 (m, 5H); (*anti*) δ 2.54 (d, *J* = 3.2 Hz, 1H), 4.80 (m, 1H), 4.90 (d, *J* = 4.6 Hz, 1H), 5.20-5.40 (m, 2H), 5.92-6.00 (m, 1H), 7.3-7.6 (m, 5H), in accordance with the literature data.[80]



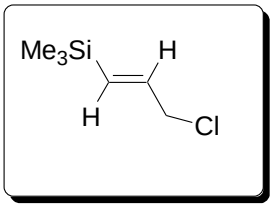
(*E*)-3-Trimethylsilyl-2-propen-1-ol 81

A 3.4 *M* solution of sodium bis(2-methoxyethoxy)aluminium hydride (SMEAH) (4.9 mL, 25.0 mmol) in anhydrous ether (10 mL) was transferred into a three-necked round-bottomed flask fitted with a thermometer and N_2 inlet. The SMEAH solution was cooled to around 3 ^{o}C in an ice bath and then a solution of 3-trimethylsilyl-2-propyn-1-ol **80** (2.28 mL, 15.6 mmol) in ether (8 mL) was added dropwise, while the temperature was maintained at 0-5 ^{o}C. After complete addition the ice bath was removed and the reaction was complete within 1 h. The reaction mixture temperature was reduced to 0 ^{o}C and quenched by the addition of 3.6 M sulfuric acid (10 mL). The aqueous phase was extracted with ether (2 × 20 mL) and the combined ether layers were washed with water (2 × 10 mL), saturated sodium chloride (10 mL) and dried ($MgSO_4$) and concentrated *in vacuo*. Distillation at 121 ^{o}C afforded (*E*)-3-trimethylsilyl-2-propene-1-ol **81** (3.91 g, 65%) as a clear liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 9H), 1.44 (s, 1 H), 4.10 (dd, *J* = 4.4, 1.6 Hz, 2 H), 5.83 (dt, *J* = 18.8, 1.6 Hz, 1 H), 6.13 (dt, *J* = 18.8, 4.4 Hz, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 0.3 (CH_3), 66.9 (CH_2), 130.9 (CH), 146.1 (CH); MS (CI), *m/z* (%) 131.2 (M+H, 65), 113.1 (89), 79.1 (33) in accordance with the literature data.[38]



Trimethyl(3-chloro-1-propenyl)silane 85

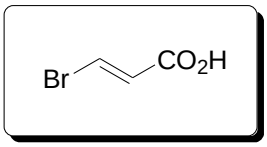
3-Trimethylsilyl-2-propen-1-ol **81** (1.95 g, 14.99 mmol) was added to a mixture of triphenylphosphine (3.93 g, 14.99 mmol) and tetrachloromethane (2.89 mL, 29.98 mmol) and heated under nitrogen. At 40 °C, triphenylphosphine dissolved and as the temperature reached 80 °C, a white solid, triphenylphosphine oxide, precipitated. The solution was heated at 85 °C for 1 h and then cooled to room temperature. Hexane was added and the white solid was removed by filtration. The hexane solution was evaporated *in vacuo* and the residue was passed through a plug of silica gel (10 g) with hexane. The resulting solution was evaporated *in vacuo* to afford trimethyl(3-chloro-1-propenyl)silane **85** (860 mg, 40%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 9H), 3.99 (dd, *J* = 6.0, 1.2 Hz, 2 H), 5.83 (d, *J* = 18.0, 1.2 Hz, 1 H), 6.01 (dt, *J* = 18.0, 5.6 Hz, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 0.1 (CH_3), 48.9 (CH_2), 136.3 (CH), 141.9 (CH) in accordance with the literature data.[39]



Trimethyl(3-chloro-1-propenyl)silane 85

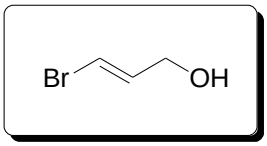
DMF (1.25 mL, 13.99 mmol) was added dropwise to a stirred solution of oxalyl chloride (1.32 mL, 15.14 mmol) in CH_2Cl_2 (50 mL) at 0 °C and the resulting white suspension was allowed to warm to room temperature and after a period of 10 min was recooled to 0 °C. 3-Trimethylsilyl-2-propene-1-ol **81** (1.84 g, 14.15 mmol) was added in one portion and the resulting solution was heated at reflux for 24 h and then cooled to room temperature, poured onto saturated aqueous

NaCl (150 mL), and the product was extracted into ether (2 × 150 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to furnish the product **85** (1.04 g, 50%) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 9H), 3.99 (dd, *J* = 6.0, 1.2 Hz, 2 H), 5.83 (dd, *J* = 18.0, 1.2 Hz, 1 H), 6.01 (dt, *J* = 18.0, 5.6 Hz, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 0.1 (CH_3), 48.9 (CH_2), 136.3 (CH), 141.9 (CH) in accordance with the literature data.[45]



(E)-3-Bromoacrylic acid 89

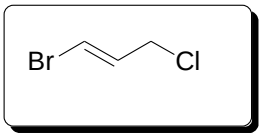
A solution of propiolic acid (25.0 g, 357 mmol) in 48% aqueous hydrobromic acid (20 mL) was stirred at 100 °C (preheated bath) for 2 h and then allowed to cool overnight. The precipitate was isolated by filtration and washed with cold water to afford the acid **89** (40.34 g, 75%) as a white crystalline solid: mp 108-110 °C (lit. gives 121 °C)[43]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (d, *J* = 14.0 Hz, 1H), 7.78 (d, *J* = 14.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 128.1 (CH), 129.9 (CH), 168.9 (C); MS (EI), *m/z* (%) 149.9 (60), 132.9 (40), 71.0 (100); HRMS (EI) 149.9316 ($C_3H_3O_2{}^{79}Br$ requires 149.9318) in accordance with the literature data.[43]



(E)-3-Bromo-2-propen-1-ol 90

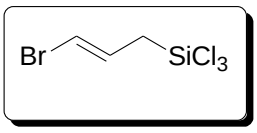
A solution of (*E*)-3-bromoacrylic acid **89** (30.0 g, 199 mmol) in dry ether (150 mL) was added dropwise to a stirred mixture of $LiAlH_4$ (7.54 g, 199 mmol) in dry ether (450 mL) under argon at 0 °C and then stirred at this temperature for 2 h. The reaction was quenched at 0 °C by addition of sodium sulphate decahydrate until no more gas was given off. The mixture was then filtered through celite and concentrated *in vacuo* to afford the alcohol **90** (16.50 g, 62 %) a colourless

oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84 (s, 1H), 4.06-4.10 (m, 2H), 6.33-6.42 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 63.0 (CH_2), 107.9 (CH), 136.5 (CH); MS (CI), *m/z* (%) 137, 135 (M^+-1, 75), 121, 119 (100); IR 3316 (O-H), 1622 (C=C) cm^{-1}in accordance with the literature data.[42]



(*E*)-1-Bromo-3-chloropropene 91

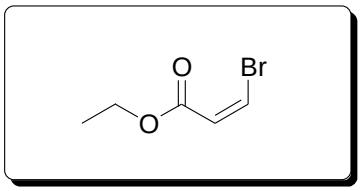
In a round bottomed flask, a solution of (*E*)-1-bromo-3-chloropropene **90** (3.0 g, 22.1 mmol) in hexachloropropanone (8.4 mL, 55.2 mmol) was cooled to 0 °C and a slight excess (10%) of Ph_3P (6.4 g, 24.3 mmol) was added in small portions over 20 minutes. The exothermic reaction was maintained at or below 15 °C. When the addition was complete, the mixture was allowed to warm to room temperature over a period of 10 min. The crude product was purified by flash distillation into a dry ice-acetone cooled receiver, under reduced pressure (76 torr) at 56 °C to give a clear product **91** (2.39 g, 71 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (dd, *J* = 7.1, 1.1 Hz, 2H), 6.18 (dt, *J* = 13.6, 7.1 Hz 1H), 6.31 (dt, *J* = 13.6, 1.1 Hz, 1H); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ 43.6 (CH_2), 110.8 (CH), 133.0 (CH) in accordance with the literature data.[81]



(*E*)(3-Bromoallyl)trichlorosilane 92

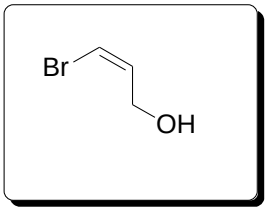
A three-neck round bottomed flask was charged with copper(I) chloride (80 mg, 0.77 mmol), triethylamine (2.15 mL, 15.4 mmol) and ether (20 mL) and the mixture was stirred in an argon atmosphere at room temperature. (*E*)-1-Bromo-3-chloropropene **91** (2.39 g, 15.4 mmol) and trichlorosilane (1.71 mL, 16.92 mmol) were combined and added dropwise and the resulting mixture was stirred

at room temperature for 4 h. The white precipitate was filtered off using a closed tubing system. A sample was taken and the solvent was evaporated for recording an NMR spectrum. The product **92** was carried through to the next stage: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 (dd, *J* = 7.2, 0.8 Hz, 2H), 6.03 – 6.16 (m, 2H); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ 27.7 (CH_2), 111.8 (CH), 124.4 (CH).[45]



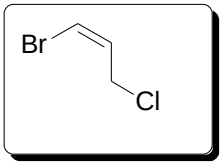
Ethyl (Z)-3-Bromoacrylate 94

Lithium bromide (27.66 g, 319 mmol), acetic acid (18.20 mL, 319 mmol), ethyl propiolate **93** (25.0 g, 255 mmol) were added to acetonitrile (250 mL), under an argon atmosphere. The mixture was stirred under reflux and upon analysis by TLC it was deemed complete after 12 h. The reaction mixture was then left to cool, after which time water (100 mL) was added and the mixture was cautiously neutralised with solid potassium carbonate, added in portions. The organic layer was separated and the aqueous layer extracted with ether (3 × 100 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to afforded (*Z*)-3-bromoacrylic acid ethyl ester **94** (41.98 g, 92%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.2 Hz, 3H), 4.17 (q, *J* = 7.2 Hz, 2H), 6.55 (d, *J* = 8.4 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.2 (CH_3), 60.8 (CH_2), 121.2 (CH), 124.5 (CH), 164.0 (C) in accordance with the literature; MS (CI), *m/z* (%) 181 (M+H, 100)/179 (M+H, 100), 101 (50); HRMS (CI) 178.9703 ($C_5H_8O_2{}^{79}Br$ requires 178.9708). [44]



(Z)-3-Bromo-2-propen-1-ol 95

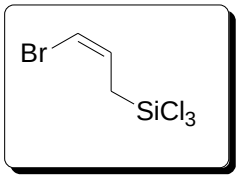
A solution of ethyl (*Z*)-3-bromoacrylate **94** (5.0 g, 27.9 mmol) in dry ether (16 mL) was added dropwise to a stirred mixture of $LiAlH_4$ (0.71 g, 18.62 mmol) in dry ether (60 mL) under argon at 0 ^oC over a period of 20 min and the reaction mixture was stirred at this temperature for 1 h. The reaction was quenched upon addition of solid sodium sulfate decahydrate, the mixture was then filtered through a pad of celite, and the solvent was evaporated to give (*Z*)-3-bromo-2-propen-1-ol **95** (2.94 g, 77%) as a colourless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.73 (s, 1H), 4.25-4.28 (m, 2H), 6.22 (dt, *J* = 7.2, 1.6 Hz, 1H), 6.30 (dt, *J* = 7.2, 4.4 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 63.0 (CH_2), 107.9 (CH), 135.5 (CH) MS (EI), *m/z* (%) 135.0 (M^+-1, 70), 97.1 (30); HRMS (EI) 136.9528 (C_3H_5OBr requires 136.9558); IR 3323 (O-H), 1622 (C=C) cm^{-1}in accordance with the literature data.[42]



(*Z*)-1-Bromo-3-chloropropene 96

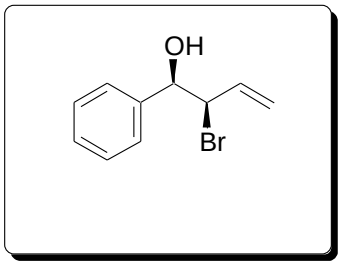
Triphenylphosphine (9.10 g, 34.69 mmol) was added in small portions over 20 minutes to a solution of (*Z*)-3-bromo-2-propen-1-ol **95** (4.32 g, 31.5 mmol) in hexachloropropanone (12.0 mL, 78.8 mmol) at 0 °C and the reaction mixture was allowed to warm to room temperature over a period of 10 min. The crude product was purified by flash distillation into a dry ice-acetone cooled receiver, under reduced pressure [76 Torr] at 48 °C to afford the pure product **96** (3.41 g, 85 %) as a colourless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 4.22 (dd, *J* = 7.1, 0.8 Hz, 2H), 6.36 (dd, *J* = 7.2, 7.1 Hz, 1H), 6.43 (dt, *J* = 7.2, 0.8 Hz, 1H); ^{13}C-NMR (100.6

MHz, $CDCl_3$) δ 40.7 (CH_2), 112.2 (CH), 130.6 (CH) in accordance with the literature data.[81]



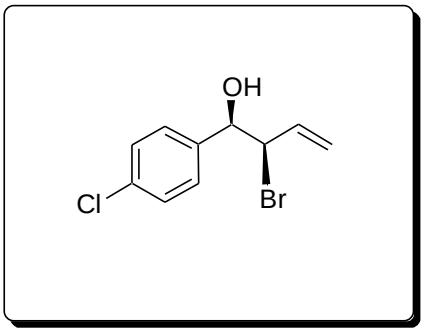
(*Z*)-(3-Bromoallyl)trichlorosilane 97

A three-neck round bottomed flask was charged with copper(I) chloride (64 mg, 0.64 mmol), triethylamine (0.89 mL, 6.43 mmol) and ether (15 mL) and the mixture was stirred in an argon atmosphere. (*Z*)-1-Bromo-3-chloro-propene **96** (1.0 g, 6.43 mmol) and trichlorosilane (0.71 mL, 7.08 mmol) were combined and added dropwise. After 4 h, the white precipitate (Et_3NHCl) was filtered off using a closed tubing system. A sample was taken and the solvent was evaporated for NMR, while the bulk of the product **97** was carried through to the next stage: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 (dd, *J* = 7.1, 0.8 Hz, 2H), 6.10 (dd, *J* = 7.2, 7.1 Hz, 1H), 6.37 (dt, *J* = 7.2, 0.8 Hz, 1H); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ 27.7 (CH_2), 111.8 (CH), 124.4 (CH).[45]



(±)-2-Bromo-1-phenylbut-3-en-1-ol 98-a

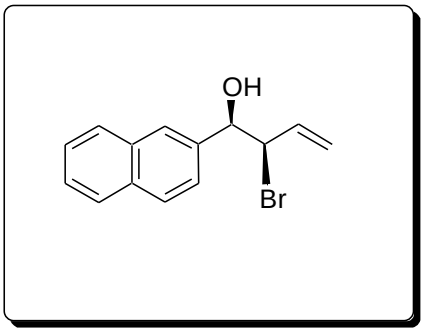
(*Z*)-(3-Bromoallyl)trichlorosilane **97** (730 mg, 2.87 mmol) was added dropwise to a solution of benzaldehyde (310 mg, 2.87 mmol) in DMF (5 mL) at 0 °C and the resulting mixture was left to stir at this temperature for 24 h. Saturated aqueous sodium hydrogen carbonate (5 mL) was added to quench the reaction and the mixture was extracted with ether (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over Na_2SO_4 and evaporated. The crude product was purified by chromatography on a column of silica gel (15 × 1 cm) with a mixture of petroleum ether and ethyl acetate (6:1) to give pure **98-a** (310 mg, 48 %) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) (*syn*) δ 2.82 (d, *J* = 4.0 Hz, 1H), 4.72 – 4.80 (m, 2H), 5.06 (d, *J* = 12.0 Hz, 1H), 5.17 (d, *J* = 16.0 Hz, 1H), 5.92-6.01 (m, 1H), 7.28-7.41 (m, 5H).



(±)-2-Bromo-1-(4-chlorophenyl)but-3-en-1-ol 98-b

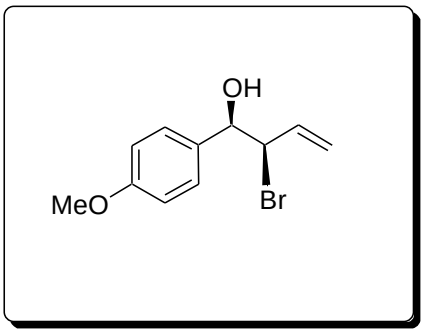
(*Z*)-(3-Bromoallyl)trichlorosilane **97** (500 mg, 1.97 mmol) and *p*-chloro-benzaldehyde (250 mg, 1.79 mmol) were dissolved in DMF (5mL) and the mixture was stirred at 0°C for 24 h. Saturated aqueous sodium hydrogen carbonate (8 mL) was added to quench the reaction and the mixture was extracted with ether (3 × 10mL). The ethereal layer was washed with brine and water (2 × 10 mL)

successively, dried with Na_2SO_4, and the solvent was evaporated. The crude product was purified by chromatography on a column of silica gel (15 × 1 cm), eluting with a mixture of petroleum ether and ethyl acetate (8:1) to afford the alcohol **98-b** (68 mg, 25 %) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) (*syn*) δ 2.80 (d, *J* = 3.6 Hz, 1H), 4.45 (dd, *J* = 7.6, Hz, 1H), 4.77 (dd, *J* = 7.2, 3.6 Hz, 1H), 5.10 (d, *J* = 10, 1H), 5.10 (d, *J* = 16.8, 1H), 5.95 (dt, *J* = 16.8, 10 Hz, 1H), 7.29-7.37 (m, 4H) in accordance with the literature data.[75]



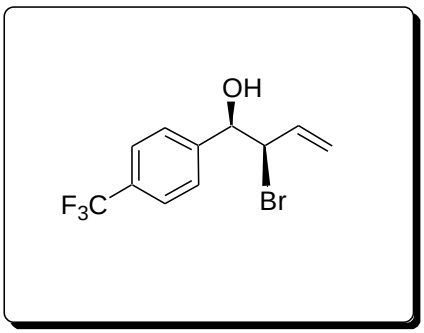
(±)-2-Bromo-1-(naphthalen-2-yl)but-3-en-1-ol 98-c

(*Z*)-3-(Bromoallyl)trichlorosilane **97** (500 mg, 1.97 mmol) was added dropwise to a solution of 2-naphthaldehyde (310 mg, 1.97 mmol) in DMF (5 mL) at 0 °C and the resulting mixture was left to stir at this temperature for 24 h. Saturated aqueous sodium hydrogen carbonate (5 mL) was added to quench the reaction and the mixture was extracted with ether (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over Na_2SO_4 and evaporated. The crude product was purified by chromatography on a column of silica gel (15 × 1 cm) with a mixture of petroleum ether and ethyl acetate (6:1) to give pure **98-c** (160 mg, 38 %) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) (*syn*) δ 2.89 (d, *J* = 4.0 Hz, 1H), 4.84-4. 86 (m, 1H), 4.97 (dd, *J* = 8, 4 Hz, 1H), 5.04 (d, *J* = 10 Hz, 1H), 5.15 (d, *J* = 16.8 Hz, 1H), 6.02 (dt,*J* = 16.8, 10.4 Hz, 1H), 7.41-7.43 (m, 3H), 7.74-7.78 (m, 4H) in accordance with the literature data.[75]



(±)-2-Bromo-1-(4-methoxyphenyl)but-3-en-1-ol 98-d

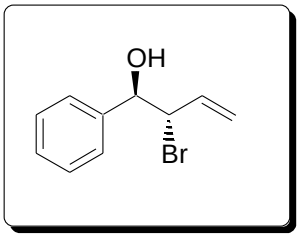
(*Z*)-(3-Bromoallyl)trichlorosilane **97** (500 mg, 1.97 mmol) and *p*-methoxybenzaldehyde (0.23 mL, 1.97 mmol) were dissolved in DMF (5mL) and the mixture was stirred at 0°C for 24 h. Saturated aqueous sodium hydrogen carbonate (8 mL) was added to quench the reaction and the mixture was extracted with ether (3 × 10mL). The ethereal layer was washed with brine and water (2 × 10 mL) successively, dried with Na_2SO_4, and the solvent was evaporated. The crude product was purified by chromatography on a column of silica gel (15 × 1 cm), eluting with a mixture of petroleum ether and ethyl acetate (8:1) to afford the alcohol **98-d** (157 mg, 31 %) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) (*syn*) δ 2.67 (d, *J* = 4.0 Hz, 1H), 3.75 (s, 3H), 4.62-4.65 (m, 2H), 4.97 (d, *J* = 12.0 Hz, 1H), 5.01 (d, *J* = 16.0 Hz, 1H), 5.83-5.92 (m, 1H), 6.82-6.92 (m, 2H), 7.19 (t, *J* = 9.2 Hz, 2H).[75]



(±)-2-Bromo-1-(4-trifluoromethylphenyl)but-3-en-1-ol 98-e

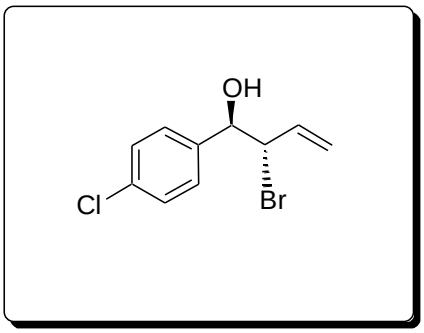
(*Z*)-(3-Bromoallyl)trichlorosilane **97** (500 mg, 1.97 mmol) and *p*-trifluoromethylbenzaldehyde (0.23 mL, 1.97 mmol) were dissolved in DMF (5mL)

and the mixture was stirred at 0°C for 24 h. Saturated aqueous sodium hydrogen carbonate (8 mL) was added to quench the reaction and the mixture was extracted with ether (3 × 10mL). The ethereal layer was washed with brine and water (2 × 10 mL) successively, dried with Na_2SO_4, and the solvent was evaporated. The crude product was purified by chromatography on a column of silica gel (15 × 1 cm), eluting with a mixture of petroleum ether and ethyl acetate (8:1) to afford the alcohol **98-e** (280 mg, 46 %) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) (*syn*) δ 2.75 (d, *J* = 4.0 Hz, 1H), 4.62 (dd, *J* = 9.2, 7 Hz, 1H), 4.75 (dd, *J* = 7, 4 Hz, 1H), 5.00-5.11 (m, 2H), 5.86-5.89 (m, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.2 (C), 63.0 (CH), 76.5 (CH), 76.7 (C), 119.9 (CH_2), 125.4 (CH), 125.4 (CH), 127.2 (CH), 134.6 (CH), in accordance with the literature data.[75]



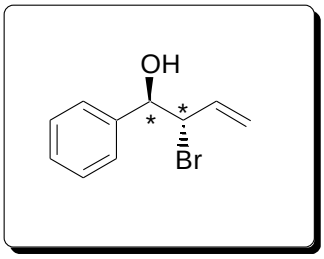
(±)-2-Bromo-1-phenyl-but-3-en-1-ol 98-f

(*E*)-(3-Bromoallyl)trichlorosilane **92** (250 mg, 0.98 mmol) and benzaldehyde (0.09 mL, 0.89 mmol) were dissolved in *N*,*N*-Dimethylformamide (DMF) (5 mL) and stirred at 0°C for 24 h. Saturated aqueous sodium hydrogen carbonate (5 mL) was then added to quench the reaction, and the mixture was extracted with ether (3 × 10 mL). The ethereal layer was washed with brine and water (2 × 10 mL), dried with Na_2SO_4, and evaporated *in vacuo*. The crude product was purified by chromatography on a column of silica gel (15 × 1cm), eluting with a mixture of petroleum ether and ethyl acetate (8:1) to afford the alcohol **98-f** (49 mg, 36%) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) (*anti*) δ 2.60 (d, *J* = 3.2 Hz, 1 H), 4.76 (dd, *J* = 9.6, 4.4 Hz, 1H), 5.04 (d, *J* = 4.4, 1H), 5.16-5.23 (m, 2H), 5.93 – 6.13 (m, 1H), 7.31 - 7.4 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 67.4 (CH), 76.9 (CH), 120.1 (CH_2), 126.8 (CH), 128.2 (CH), 128.3 (CH), 133.3 (CH), 139.2 (C).[75]



(±)-2-Bromo-1-(4-chlorophenyl)but-3-en-1-ol 98-g

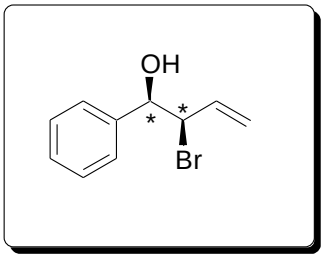
(*E*)-(3-Bromoallyl)trichlorosilane **92** (250 mg, 0.89 mmol) and *p*-chloro-benzaldehyde (130 mg, 0.89 mmol) were dissolved in DMF (5mL) and the mixture was stirred at 0°C for 24 h. Saturated aqueous sodium hydrogen carbonate (8 mL) was added to quench the reaction and the mixture was extracted with ether (3 × 10mL). The ethereal layer was washed with brine and water (2 × 10 mL) successively, dried with Na_2SO_4, and the solvent was evaporated. The crude product was purified by chromatography on a column of silica gel (15 × 1 cm), eluting with a mixture of petroleum ether and ethyl acetate (8:1) to afford the alcohol **98-g** (68 mg, 25 %) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) (*anti*) δ 2.51 (s, 1H), 4.45 (dd, *J* = 8.4, 4.8 Hz, 1H), 4.84 (d, *J* = 4.8 Hz, 1H), 5.10-5.18 (m, 2H), 5.75-5.89 (m, 1H), 7.19-7.25 (m, 4H) in accordance with the literature data.[75]



2-Bromo-1-phenylbut-3-en-1-ol 98-c

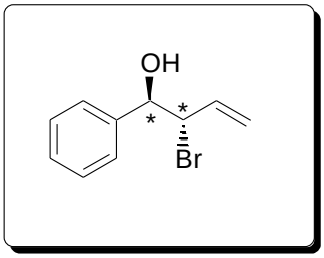
(3-Bromoallyl)trichlorosilane **92** (65 mg, 0.26 mmol) was added to a solution of (*R*, *R*)-**100** (15 mg, 0.05 mmol), diisopropylethylamine (0.2 mL, 1.16 mmol) and benzaldehyde (53 mg, 0.23 mmol) in DCM (5 mL) under argon at –20 °C and the mixture was stirred at -20 °C overnight. The reaction was quenched by the

addition of saturated aqueous sodium hydrogen carbonate (1 mL) and the aqueous layer was extracted with ether (3 × 10 mL). The ethereal layer was washed with brine (2 x 10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by chromatography on a column of silica gel (15 × 1 cm) with a petroleum ether–ethyl acetate mixture (6:1) to give product **98-c** (16 mg, 23 %) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) (*anti*) δ 2.49 (d, *J* = 3.2 Hz, 1H), 4.65 (dd, *J* = 10, 4.4 Hz 1H), 4.83 (m, 3H), 5.95-6.01 (m, 1H), 7.25 – 7.29 (m, 5H); Chiral HPLC (Chiralcel IB, flow rate: 0.5 mL/min, hexane:isopropyl alcohol = 99:1; t_{minor} = 40.41 min, t_{major} = 44.81 min) showed 29 % ee.



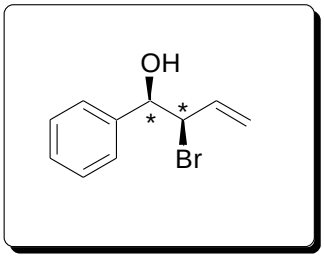
2-Bromo-1-phenylbut-3-en-1-ol 98-d

(3-Bromoallyl)trichlorosilane **97** (140 mg , 0.54 mmol) was added to a solution of **(+)-101** (27 mg, 0.05 mmol), diisopropylethylamine (0.4 mL, 2.5 mmol) and benzaldehyde (53 mg, 0.50 mmol) in DCM (2 mL) under argon at –20 ^{o}C and the mixture was stirred at -20 ^{o}C overnight. The reaction was quenched by the addition of saturated aqueous sodium hydrogen carbonate (1 mL) and the aqueous layer was extracted with ether (3 × 5mL). The ethereal layer was washed with brine (2 x 5 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by chromatography on a column of silica gel (15 × 1 cm) with a petroleum ether–ethyl acetate mixture (6:1) to give product **98-d** (22.3 mg, 17 %) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) (*syn*) δ 2.69 (d, *J* = 3.6 Hz, 1H), 4.63-4.71 (m, 2H), 4.97 (d, *J* = 10 Hz, 1H), 5.16 (d, *J* = 16.8 Hz, 1H), 5.83-5.90 (m, 1H), 7.22-7.44 (m, 5H),; Chiral HPLC (Chiralcel IB, flow rate: 0.5 mL/min, hexane:isopropyl alcohol = 99:1; t_{minor} = 53.35 min, t_{major} = 46.53 min) showed 18 % ee.



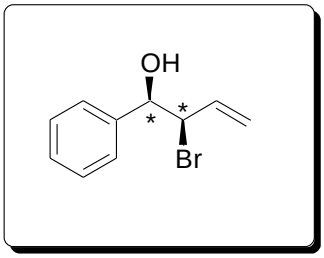
2-Bromo-1-phenylbut-3-en-1-ol 98-e

(3-Bromoallyl)trichlorosilane **92** (65 mg , 0.26 mmol) was added to a solution of **(*R*, *R*)**-**103** (8 mg, 0.02 mmol), diisopropylethylamine (0.20 mL, 1.16 mmol) and benzaldehyde (25 mg, 0.23 mmol) in DCM (5 mL) under argon at –20 ^{o}C and the mixture was stirred at -20 ^{o}C overnight. The reaction was quenched by the addition of saturated aqueous sodium hydrogen carbonate (1 mL) and the aqueous layer was extracted with ether (3 × 10mL). The ethereal layer was washed with brine (2 x 10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by chromatography on a column of silica gel (15 × 1 cm) with a petroleum ether–ethyl acetate mixture (6:1) to give product **98-e** (10 mg, 10 %) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) (*anti*) δ 2.50 (s, 1H), 4.66 (dd, *J* = 10, 4.4 Hz 1H), 5.05-5.130 (m, 3H), 5.95-6.03 (m, 1H), 7.24-7.30 (m, 5H); Chiral HPLC (Chiralcel IB, flow rate: 0.5 mL/min, hexane:isopropyl alcohol = 99:1; t_{minor} = 43.42 min, t_{major} = 47.16 min) showed 15% ee.



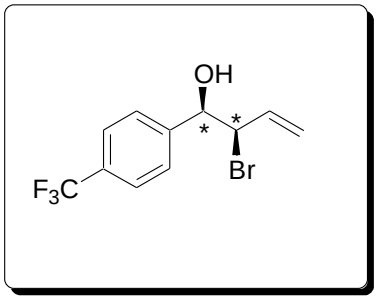
2-Bromo-1-phenylbut-3-en-1-ol 98-f

(3-Bromoallyl)trichlorosilane **97** (140 mg , 0.55 mmol) was added to a solution of **(*R*, *R*)**-**103** (17 mg, 0.05 mmol), diisopropylethylamine (0.44 ml, 2.5 mmol) and benzaldehyde (53 mg, 0.5 mmol) in DCM (2 mL) under argon at –20 ^{o}C and the mixture was stirred at -20 ^{o}C overnight. The reaction was quenched by the addition of saturated aqueous sodium hydrogen carbonate (1 mL) and the aqueous layer was extracted with ether (3 × 10mL). The ethereal layer was washed with brine (2 x 10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by chromatography on a column of silica gel (15 × 1 cm) with a petroleum ether–ethyl acetate mixture (6:1) to give product **98-f** (54.2 mg, 43 %) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) (*syn*) δ 2.67 (d, *J* = 3.6 Hz, 1H), 4.63-4.71 (m, 2H), 4.97 (d, *J* = 10.4 Hz, 1H), 4.97 (d, *J* = 16.8 Hz, 1H), 5.86-5.92 (m, 1H), 7.24 – 7.30 (m, 5H); Chiral HPLC (Chiralcel IB, flow rate: 0.5 mL/min, hexane:isopropyl alcohol = 99:1; t_{minor} = 43.60 min, t_{major} = 41.25 min) showed 25% ee.



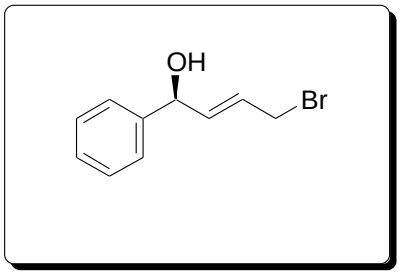
2-Bromo-1-phenylbut-3-enol 98-h

(3-Bromoallyl)trichlorosilane **97** (86 mg , 0.34 mmol) was added to a solution of **(*S*)-102** (20 mg, 0.03 mmol), diisopropylethylamine (197 mg, 1.53 mmol) and benzaldehyde (33 mg, 0.31 mmol) in DCM (2 mL) under argon at –20 ^{o}C and the mixture was stirred at -20 ^{o}C overnight. The reaction was quenched by the addition of saturated aqueous sodium hydrogen carbonate (1 mL) and the aqueous layer was extracted with ether (3 × 10mL). The ethereal layer was washed with brine (2 x 10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by chromatography on a column of silica gel (15 × 1 cm) with a petroleum ether–ethyl acetate mixture (6:1) to give product **98-h** (31 mg, 34 %) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) (*syn*) δ 2.70 (d, *J* = 3.2 Hz, 1H), 4.63 – 4.71 (m, 2 H), 4.98 (d, *J* = 10 Hz, 1H), 5.05 (d, *J* = 16.8 Hz, 1H), 5.01-5.11 (m, 2H), 5.82-5.91 (m, 1H), 7.21-7.26 (m, 5H); Chiral HPLC (Chiralcel IB, flow rate: 0.5 mL/min, hexane:isopropyl alcohol = 99:1; t_{minor} = 40.30 min, t_{major} = 42.84 min) showed 50% ee**.**



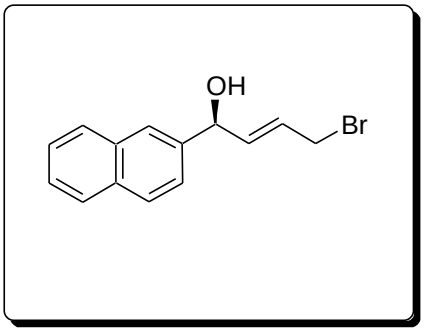
2-Bromo-1-(4-trifluoromethylphenyl)but-3-en-1-ol 98-i

(3-Bromoallyl)trichlorosilane **97** (140 g , 0.55 mmol) was added to a solution of **(*S*)-102** (32 mg, 0.05 mmol), diisopropylethylamine (0.44 mL, 2.5 mmol) and trifluoromethylbenzaldehyde (87 mg, 0.50 mmol) in MeCN (2 mL) under argon at –10 °C and the mixture was stirred at -10 °C overnight. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (1 mL) and the aqueous layer was extracted with ether (3 × 10mL). The ethereal layer was washed with brine (2 x 10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by chromatography on a column of silica gel (15 × 1 cm) with a petroleum ether–ethyl acetate mixture (6:1) to give product **98-i** (17 mg, 22 %) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) (*syn*) δ 2.75 (d, *J* = 4 Hz, 1H), 4.62 (dd, *J* = 8 Hz, 4 Hz, 1H), 4.76 (dd, *J* = 8 Hz, 4 Hz, 1H), 5.01-5.11 (m, 2H), 5.82-5.91 (m, 1H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.53 (d, *J* = 8.1 Hz, 2H); Chiral HPLC (Chiralcel IB, flow rate: 0.75 mL/min, hexane:isopropyl alcohol = 98:2; t_{minor} = 18.51 min, t_{major} = 19.45 min) showed 43% ee.



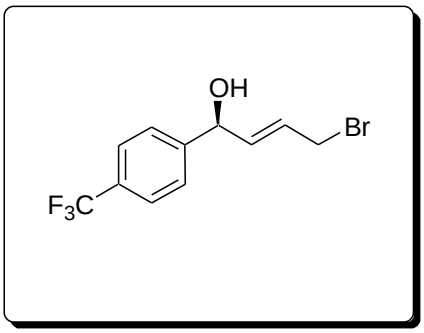
4-Bromo-1-phenylbut-3-en-1-ol 99-a

Isolated side product from the formation of homoallylic alcohol **98-a**, (96 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (d, *J* = 6.8 Hz, 2 H), 5.28 (d, *J* = 5.6 Hz, 1H), 5.89 – 6.06 (m, 2H), 7.21 - 7.35 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 44.4 (CH_2), 73.9 (CH), 126.4 (CH), 126.6 (CH), 128.0 (CH), 128.7 (CH), 136.6 (CH), 142.2 (C).[47]



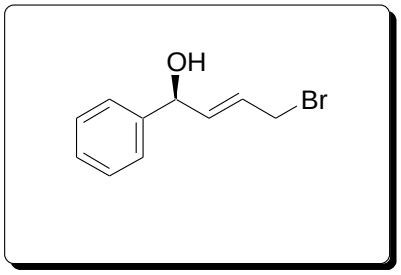
4-Bromo-1-(naphthalen-2-yl)but-3-en-1-ol 99-c

Isolated rearrangement product from the formation of homoallylic alcohol **98-c** (250 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (d, *J* = 6 Hz, 2 H), 5.35 (d, *J* = 5.2 Hz, 1H), 5.81 – 6.04 (m, 2H), 7.39 - 7.44 (m, 3H), 7.69 - 7.72 (m, 4H).[47]



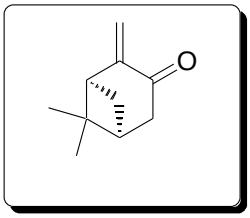
4-Bromo-1-(4-trifluoromethylphenyl)but-3-en-1-ol 99-e

Isolated rearrangement product from the formation of homoallylic alcohol **98-e** (250 mg, 41 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (d, *J* = 4.4 Hz, 1 H), 4.01 (dd, *J* = 5.2, 3.2 Hz, 1H), 5.25 (d, *J* = 3.2 Hz , 2H), 5.82 – 5.91 (m, 2H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 44.0 (CH_2), 73.5 (CH), 76.7 (C), 125.6 (CH), 125.7 (CH), 126.6 (CH), 127.6 (CH), 134.7 (CH).[47]



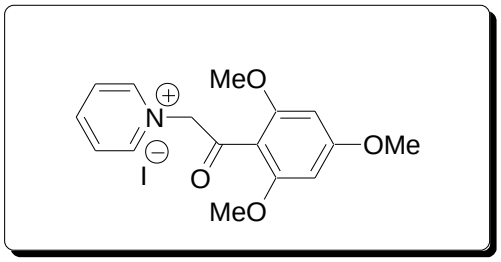
4-Bromo-1-(phenyl)but-3-en-1-ol 99-f

Isolated side product from the formation of homoallylic alcohol **98-f** (120 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 (d, *J* = 8 Hz, 2 H), 5.18 (d, *J* = 4.8 Hz, 1H), 5.81 – 5.91 (m, 2H), 7.21 - 7.35 (m, 5H).[47]



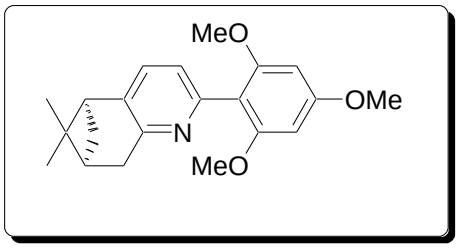
Pinocarvone 105

Into a solution of (+)-α-pinene **104** (10.4 mL, 66.57 mmol) in DCM (150 mL), the following reactants were added: acetic anhydride (6.3 mL, 66.57 mmol), pyridine (3.4 mL, 44.60 mmol), DMAP (2.20 g, 17.97 mmol) and TPP (5 mg, 9×10^{-2} mmol), turning the solution purple. Oxygen was bubbled moderately through the solution while irradiated using a UV lamp (546nm). Cold water was circulated through the well that encapsulates the UV lamp for 24 h. The resulting brown solution was diluted with CH_2Cl_2 (150 mL) and washed with saturated aqueous $NaHCO_3$ solution until basic (3 × 50 mL). The organic layer was then washed with 1M HCl (2 × 35mL) until it turned lime green and the aqueous washes became acidic, followed by washing with saturated aqueous $CuSO_4$ (2 × 50 mL) and saturated NaCl (2 × 50 mL). The organic layer was dried with $MgSO_4$ and concentrated *in vacuo* to give pinocarvone **105** (8.39g, 84%) as a deep red oil (no further purification required[14]): $[\alpha]_D$ -46.8 (*c* 1.0, CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74 (s, 3H), 1.20 (d, *J* = 11.6 Hz, 1 H), 1.30 (s, 3H), 2.14 (m, 1H), 2.45 (dd, *J* = 18.8, 3.2 Hz, 1H), 2.62 (m, 2H), 2.70 (t, J = 5.6 Hz), 4.74 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.5 (CH_3), 25.0 (CH_3), 31.4 (CH_2), 37.5 (CH), 39.8 (C), 41.5 (CH_2), 47.4 (CH), 116.4 (alkene CH_2), 148.1 (C), 198.9 (C=O) in accordance with the literature data.[51]



1-[2-(2',4',6'-Trimethoxyphenyl)-2-oxo-ethyl]-pyridinium Iodide 107

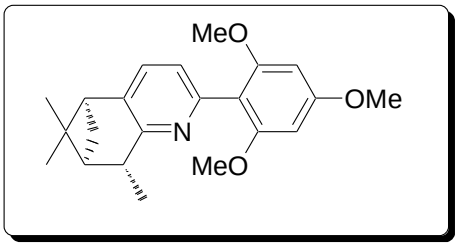
2,4,6-Trimethoxyacetophenone **106** (5.0 g, 23.78 mmol) was heated in pyridine (10 mL) until a clear solution was obtained. Crystalline iodine (7.16 g, 28.24 mmol) was added portionwise and the resulting solution was refluxed for 1 h and then cooled to room temperature. The brown precipitate was filtered and washed with absolute pyridine to give the pale yellow Krohnke salt **107** (5.6 g, 82%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 3.88 (s, 6H), 6.09 (s, 2H), 6.33 (s, 2H), 8.02 (t, *J* = 7.2 Hz, 2H), 8.43 (t, *J* = 8.0 Hz, 1H), 8.92 (d, *J* = 8.0 Hz, 2H) in accordance with the literature data;[50] MS (FAB), *m/z* (%) 288.1 ($M^{\cdot+}$, 100), 195.5 (9), 79.0 (5.5); HRMS(FAB) 288.1233 ($C_{16}H_{18}O_4N$ requires 288.1236).



(+)-5-(2',4',6'-Trimethoxyphenyl)-10,10-dimethyl-6-azatricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene 108

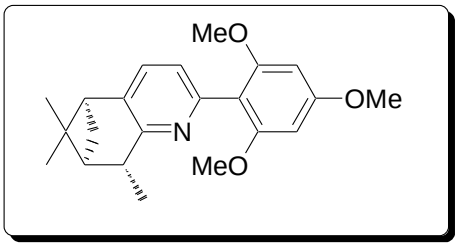
Anhydrous ammonium acetate (50 g) was heated in acetic acid (50 mL) at 110 °C until it dissolved. Krohnke salt **107** (9.0 g, 22.3 mmol) was then added and the mixture was left at 110 °C until the Krohnke salt had dissolved. Pinocarvone **105** (3.08 g, 20.5 mmol) was added and the solution was stirred at 110 °C for 48 h. Aqueous NaOH (1M) was then added and the mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with brine (15 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to afford an oil

that was purified by flash chromatography on a column of silica gel (15 × 1 cm) using a mixture of petroleum ether and ethyl acetate (1:5) to give the pure product **108** (1.82 g, 26%) as as a yellow solid: mp 110-113 °C (lit. gives 98-100 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.62 (s, 3H), 1.32 (d, *J* = 9.2 Hz, 1H), 1.39 (s, 3H), 2.27-2.31 (m, 1H), 2.59 (dt, *J* = 9.2, 5.6 Hz, 1H), 2.69 (t, *J* = 5.6 Hz, 1H), 3.13 (d, *J* = 2.8 Hz, 2H), 3.62 (s, 6H), 3.76 (s, 3H), 6.17 (s, 2H), 6.92 (d, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H); in accordance with the literature data;[50] MS (EI), *m*/*z* (%) 339.1 ($M^{\cdot+}$, 100), 324.1 (76), 296.1 (25), 44 (58); HRMS (EI) 339.1831 ($C_{21}H_{25}O_3N$ requires 339.1834).[50]



(+)-5-(2',4',6'-Trimethoxyphenyl)-8,10,10-trimethyl-6-azatricyclo[7.1.1.$0^{2,7}$]undeca-2(7),3,5-triene 109

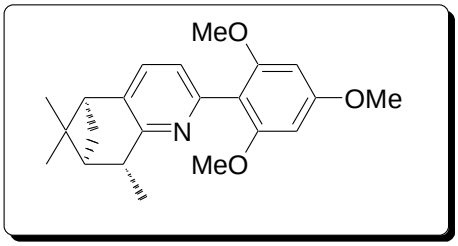
A solution of *n*-butyllithium (1.6 M in hexane, 0.48 mL, 4.55 mmol) was added dropwise to a solution of diisopropylamine (0.57 mL, 5.01 mmol) in THF (5 mL) at -40 °C and the mixture was warmed to 0 °C. After a period of 30 mins the mixture was cooled back to -40 °C where a solution of pyridine derivative **108** (1.03 g, 3.03 mmol) in THF (10 mL) was added dropwise, turning the solution dark red. The mixture was stirred at this temperature for 2 h and subsequently methyl iodide (0.29 mL, 4.55 mmol) was added dropwise and the mixture was left to stir overnight at room temperature. Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, washed with brine (10 mL), dried with $MgSO_4$ and the solvent was removed under reduced pressure. From NMR data analysis, only starting material was retrieved.



(+)-5-(2',4',6'-Trimethoxyphenyl)-8,10,10-trimethyl-6-azatricyclo[7.1.1.$0^{2,7}$]undeca-2(7),3,5-triene 109

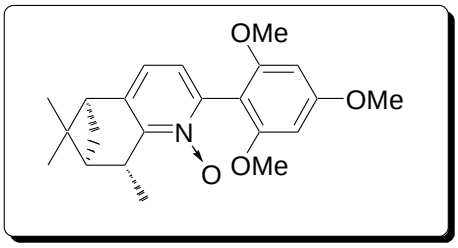
Pyridine derivative **108** (70 mg, 0.21 mmol) was dissolved in of THF (5 mL) and cooled to 0°C. Lithium bistrimethylsilylamide (52 mg, 0.31 mmol) was added and the reaction mixture was left to stir for 2 h at room temperature. Methyl iodide (0.19 mL, 0.31 mmol) was added dropwise and the mixture was left to stir

overnight, at this temperature. Water (5 mL) was added to the reaction and the organic layer was extracted with diethyl ether (3 × 5 mL). The organic portions were combined and rinsed with brine (10 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure. From NMR data analysis; only starting material was retrieved.



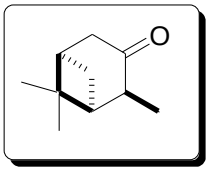
(+)-5-(2',4',6'-Trimethoxyphenyl)-8,10,10-trimethyl-6-azatricyclo[7.1.1.$0^{2,7}$]undeca-2(7),3,5-triene 109

Butyl lithium (0.48 mL, 4.43 mmol) was added dropwise to a solution of the pyridine derivative **108** (1 g, 2.95 mmol) in THF (10 mL), turning the solution dark red. This was left to stir for 1 h at –40 °C. Methyl iodide was then added dropwise and the temperature was raised to 0 °C. The reaction mixture was left at this temperature overnight, after which time the reaction mixture had turned a cloudy yellow colour. Water (15 mL) was then added and the product was extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined and washed with brine(15 mL) and dried ($MgSO_4$), and the solvent was removed *in vacuo* to afford **109** (0.28 g, 26%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.64 (s, 3H), 1.31 (d, *J* = 7.2 Hz, 2H), 1.35 (s, 3H), 2.07-2.08 (m, 1H), 2.47 (dt, *J* = 9.2, 5.6 Hz, 1H), 2.68 (t, *J* = 5.6 Hz, 1H), 3.15-3.17 (m, 1H), 3.64 (s, 6H), 3.82 (s, 3H), 6.17 (s, 2H), 6.88 (d, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 7.2 Hz, 1H) in accordance with the spectrum of an authentic sample.[50]



(+)-5-(2',4',6'-Trimethoxyphenyl)-8,10,10-trimethyl-6-azatricyclo[7.1.1.0^{2,7}]undeca-2,4,6-triene 6-oxide 64

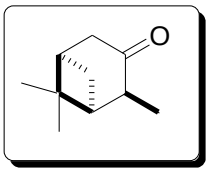
m-Chloroperoxybenzoic acid (*m*-CPBA) (20.9 mg, 0.12 mmol) was added portion-wise to a solution of the pyridine derivative **109** (39 mg, 0.11 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 12 h. After this time the mixture was diluted with ether (10 mL) and washed successively with saturated aqueous $NaHCO_3$ (3 × 5 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The resulting crude product was purified by chromatography on a column of silica gel (15 × 1 cm) with a mixture of petroleum ether and ethyl acetate (3:5) to isolate the *N*-oxide **64** (26 mg, 39%) as a white powder: mp 114-116 °C (lit. 112-113 °C)[50]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.61 (s, 3H), 1.35 (s, 3H), 1.38-1.49 (m, 4H), 2.06-2.13 (m, 1H), 2.44-2.51 (m, 1H), 2.70 (t, *J* = 5.6 Hz, 1H), 3.63-3.70 (m, 6H), 3.77 (s, 3H), 6.31-6.34 (m, 2H), 6.75 (d, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 1H); MS (EI) *m/z* (%) 370.4 (M + H$^{\cdot}$, 95), 354.1 (90), 338.4 (15) in accordance with the spectrum of an authentic sample.[50]



2,6,6-Trimethylbicycloheptan-3-one 125

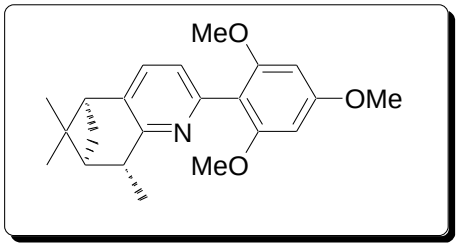
A mixture of (*S*)-(+)-isopinocampheol **124** (0.5 g, 3.24 mmol), sodium periodate (2.77 g, 12.97 mmol) and ruthenium trichloride hydrate (15 mg, 2.2 mol %) in CH_2Cl_2 (7 mL), acetonitrile (7 mL) and water (10 mL) was stirred at room

temperature for 4 h. The reaction was quenched with water (15 mL) and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by chromatography on a column of silica gel (12 × 1 cm) with a mixture of petroleum ether and ethyl acetate (9:1), to give ketone **125** (0.15 g, 31%) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (s, 3H), 1.11-1.18 (m, 2H), 1.14 (d, *J* = 7.2 Hz, 3H), 1.25 (s, 3H), 1.98-2.07 (m, 1H),2.40-2.47 (m, 1H), 2.52-2.61 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.8 (CH_3), 21.9 (CH_3), 27.0 (CH_3), 34.5 (CH_2), 39.0 (CH), 39.2 (C), 44.8 (CH_2), 45.0 (CH), 51.3 (CH), 215.2 (C=O) in accordance with the literature data.[52,53]



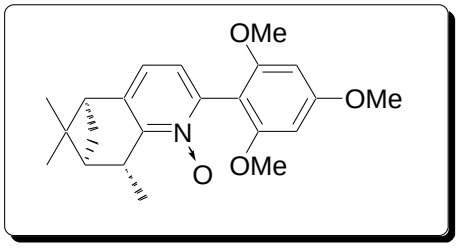
2,6,6-Trimethylbicycloheptan-3-one 125

Chromium (VI) oxide (0.31 g, 3.09 mmol) was added to a solution of (*S*)-(+)-isopinocampheol **124** (0.5 g, 4.02 mmol) in acetic acid (10 mL) and the resulting mixture was left to stir at room temperature for 24 h. The reaction was quenched with addition of water (15 mL) and aqueous $NaHCO_3$ (10 mL) and the product was extracted into CH_2Cl_2 (3 × 15 mL). The organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by chromatography on a column of silica gel (20 × 2 cm) with a mixture of petroleum ether and ethyl acetate (15:1), to give the product **125** (0.27 g, 56%) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (s, 3H), 1.02-1.18 (m, 2H), 1.14 (d, *J* = 7.2 Hz, 3H), 1.25 (s, 3H), 1.97-2.01 (m, 1H),2.03-2.08 (m, 1H), 2.52-2.61 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.8 (CH_3), 21.9 (CH_3), 27.0 (CH_3), 34.5 (CH_2), 39.0 (CH), 39.2 (C), 44.8 (CH_2), 45.0 (CH), 51.3 (CH), 215.2 (C=O) in accordance with the literature data.[52,53]



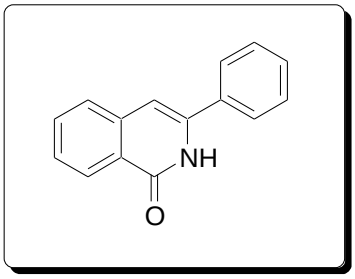
(+)-5-(2',4',6'-Trimethoxyphenyl)-8,10,10-trimethyl-6-azatricyclo[7.1.1.$0^{2,7}$]undeca-2(7),3,5-triene 109

Anhydrous ammonium acetate (11.2 g, 14.5 mmol) was heated to reflux in acetic acid (12 mL) at 110 °C until the compound had completely dissolved. Krohnke salt **108** (1.93 g, 4.8 mmol) was then added and the mixture was left to stir at this temperature until the Krohnke salt dissolved. The ketone **125** (0.66 g, 4.4 mmol) was added and the solution was stirred at 110 °C for 48 h. Aqueous NaOH (1M) (15 mL) was then added and the mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine (15 mL), and dried over $MgSO_4$. The solvent was removed in vacuo to afford an oil that was purified via flash chromatography on a column of silica gel (15 × 1 cm) using a mixture of petroleum ether and ethyl acetate (3:5), to furnish **109** (0.23 g, 16%) as a white powder: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.61 (s, 3H), 1.30 (d, *J* = 6.8 Hz, 1H), 1.34 (s, 3H), 2.04-2.07 (m, 1H), 2.46 (dt, *J* = 9.6, 5.6 Hz, 1H), 2.66 (t, *J* = 5.6 Hz, 1H), 3.15-3.16 (m, 2H), 3.61 (s, 6H), 3.83 (s, 3H), 6.12 (s, 2H), 6.89 (d, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H) in accordance with the spectrum of an authentic sample.[50]



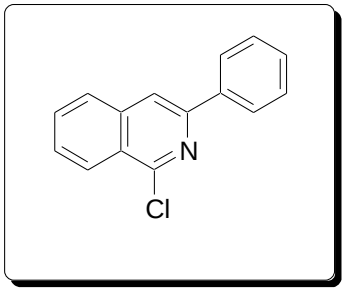
(+)-5-(2',4',6'-Trimethoxyphenyl)-8,10,10-trimethyl-6-azatricyclo[7.1.1.$0^{2,7}$]undeca-2,4,6-triene 6-oxide 64

m-Chloroperoxybenzoic acid (*m*CPBA) (0.14 g, 0.8 mmol) was added portion-wise to a solution of the pyridine derivative **109** (0.23 g, 0.7 mmol) in CH_2Cl_2 (10 mL) at 0 °C and the mixture was warmed to room temperature, where it was stirred for 12 h. The reaction mixture was then diluted with ether (10 mL) and washed successively with saturated aqueous $NaHCO_3$ (3 × 8 mL) and brine (10 mL). The organic solution was dried (Na_2SO_4) and the solvent was evaporated in vacuo. The resulting crude product was purified by chromatography on a column of silica gel (10 × 1 cm) with a mixture of petroleum ether and ethyl acetate (10:1) and then (3:5) to isolate the product **64** (0.11 g, 46%) as a white powder: mp 108-110 °C (lit. gives112-113 °C)[50] ; $[\alpha]_D$ +164.2 (*c* 0.5, CH_2Cl_2) (lit. gives $[\alpha]_D$ +8.6 (*c* 1.0, CH_2Cl_2)) [50]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.61 (s, 3H), 1.35 (s, 3H), 1.38-1.49 (m, 4H), 2.06-2.13 (m, 1H), 2.44-2.51 (m, 1H), 2.70 (t, *J* = 5.6 Hz, 1H), 3.63-3.70 (m, 6H), 3.77 (s, 3H), 6.31-6.34 (m, 2H), 6.75 (d, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 1H); MS (EI) *m*/*z* (%) 369.1 ($M^{\cdot+}$, 6), 338.1 (100), 310.1 (12), 63 (41); HRMS (EI) 369.1942 ($C_{22}H_{27}O_4N$ requires 369.1940) in accordance with the spectrum of an authentic sample.[50]



3-Phenyl-2*H*-isoquinolinone 130

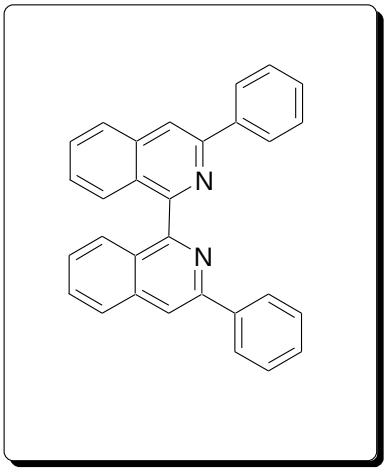
n-BuLi (2.5 M, 39.4 mL) was added dropwise to a solution of *N*-methyl-*o*-toluamide **128** (5 g, 33.52 mmol) in THF (125 mL) at –20 °C and the reaction mixture was left at this temperature for 1.5 h. Thereafter it was cooled to –50 °C and a solution of benzonitrile (5.6 mL, 54.63 mmol) in THF (10 mL) was added. The mixture was left to stir at room temperature for 30 min and then heated at 40 °C for a further 17 h. Upon completion, the reaction was quenched with water, dried with MgSO4 and the solvent was removed under reduced pressure. The crude product was recrystallised with EtOAc and CH_2Cl_2 mixture to afford **130** (1.7g, 23 %) as a white solid: mp 208 – 210 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 1H), 7.51-7.74 (m, 8H), 8.44 (d, *J* = 8.8 Hz, 1H), 8.78 (bs, 1H); MS (EI) *m/z* (%) 221.1 (M, 12), 84.0 (83), 49.0 (100) HRMS (EI) 221.0838 ($C_{15}H_{11}NO$ requires 221.2584) in accordance with the literature data.[82]



1-Chloro-3-phenylisoquinoline 131

Solid PCl_5 (1.58 g, 7.59 mmol) was added to a solution of 3-phenyl-2*H*-isoquinolinone **130** (1.68 g, 7.59 mmol) in phosphoryl chloride (15 mL) and the mixture was heated to 120 °C for 2 h, then left to cool to room temperature and quenched by pouring onto ice. The resultant precipate was isolated by filtration

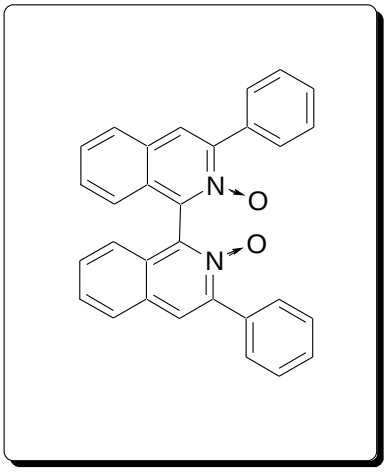
and washed with conc. aqueous ammonia solution until the aqueous phase was basic. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), the organic phases were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by recrystalisation from hexane:ethyl acetate to give the product, 1-chloro-3-phenylisoquinoline **131** (1.52 g, 84 %) as a white solid: mp 75-78°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (tt, *J* = 7.3, 1.2 Hz, 1H), 7.52-7.56 (m, 2H), 7.70 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.78 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 8.05 (s, 1H), 8.13-8.16 (m, 2H), 8.37 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 116.3 (CH), 126.0 (C), 126.5 (CH), 126.9 (2 × CH), 127.4 (CH), 128.3 (CH), 128.8 (2 × CH), 129.0 (CH), 131.3 (CH), 138.0 (C), 138.7 (C), 150.3 (C), 151.3 (C) in accordance with an authentic sample.[54]



3,3'-Diphenyl-[1,1']-biisoquinolinyl 132

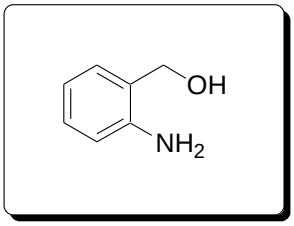
Zinc powder (50 mg, 0.81 mmol) was added to a stirred, deep blue solution of nickel(II) chloride hexahydrate ($NiCl_2.6H_20$) (193 mg, 0.81 mmol) and triphenylphosphine (854 mg, 3.25 mmol) in DMF (5 mL), under nitrogen at 50 °C. After 1 h, the colour of the mixture had changed to red brown. 1-Chloroisoquinoline **131** (195 mg, 0.81 mmol) was added and the progress of the reaction was monitored by TLC. After 3.5 h, all of the staring material was consumed. The mixture was then poured into a dilute ammonia solution and extracted with chloroform (3 × 15 mL), the organic layers were combined, washed with H_2O (3 × 15 mL), dried with $MgSO_4$, and evaporated. The resulting

crude product was purified by chromatography on a column of silica gel (15 × 1 cm) with a mixture of petroleum ether and ethyl acetate (2:1) to isolate the product **132** (35 mg, 40%) as a white solid: mp 175-176 °C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.44 (m, 2H), 7.48-7.52 (m, 6H), 7.75 (t, *J* = 7.6 Hz, 2H), 8.02 (t, *J* = 8 Hz, 4H), 8.21-8.23 (m, 4H), 8.28 (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 116.9 (4 × CH), 127.2 (2 × CH), 127.2 (2 × CH), 127.4 (2 × CH), 127.6 (2 × CH), 128.5 (4 × CH), 128.8 (2× CH), 130.4 (2 × CH), 138.0 (2 × C), 139.6 (2 × C), 149.9 (2 × C), 157.9 (4 × C) in accordance with an authentic sample.[54]



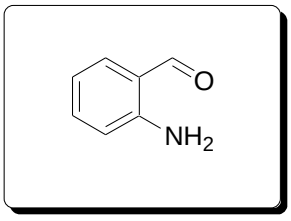
3,3'-Diphenyl-[1,1']-biisoquinolinyl 2,2'-dioxide 133

m-CPBA (66 mg, 0.4 mmol) was added to a solution of 3,3'-diphenyl-[1,1']-biisoquinolinyl **132** (27 mg, 0.05 mmol) in CH_2Cl_2 (5 mL) at 0 °C, the mixture was left to warm to room temperature and then stirred at this temperature for 48 h. The reaction was quenched by the addition of water (5 mL). The mixture was partitioned between CH_2Cl_2 and water, the aqueous layer was extracted with CH_2Cl_2 and the combined fractions were dried over $MgSO_4$ and concentrated *in vacuo* to give the product **133** (14 mg, 65%) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.39 (m, 2H), 7.51-7.57 (m, 2H), 7.81-7.83 (m, 2H), 8.01 (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 123.4 (2 × CH), 125.5 (2 × CH), 127.3 (2 × CH), 128.0 (2 × CH), 128.6 (4 × CH), 128.7 (2 × C), 129.0 (2 × C), 129.4 (2 × CH), 129.7 (2 × CH), 130.1 (4 × CH), 132.6 (2 × C), 138.9 (2 × C), 147.5 (2 × C) in accordance with an authentic sample.[54]



2-Aminobenzyl alcohol 135

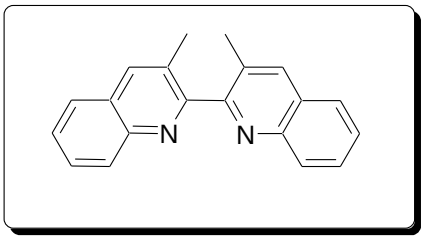
Anthranilic acid **134** (10 g, 72.92 mmol) was added to a solution of $LiAlH_4$ (6.6 g, 175 mmol) in ether (400 mL) which had been cooled to 0 °C. The reaction mixture was stirred at this temperature for 2 h and then quenched by the addition of Na_2SO_4 until no more hydrogen gas evolved. Once quenched, this mixture was passed through a pad of celite and evaporated *in vacuo* to leave **135** (8.15 g, 91%) as a yellow solid: mp 71-78 °C; ^{1}H NMR (400 MHz, CDCl3) δ 7.17 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 1H), 6.75 (t, *J* = 7.6, 7.2 Hz, 2H), 4.72 (s, 2H), 4.22 (broad s, 2H); ^{13}C NMR (100.6 MHz, CDCl3): δ 146.0 (C), 129.5 (CH), 129.2 (CH), 124.8 (C), 118.2 (CH), 116.1 (CH), 64.5 (CH2); MS (EI), m/z (%) 123.0 (100), 105.0 (92), 83.9 (61) in accordance with the literature data;[56] HRMS (EI) 123.0684 (C_7H_9ON requires 123.0683).



2-Aminobenzaldehyde 136

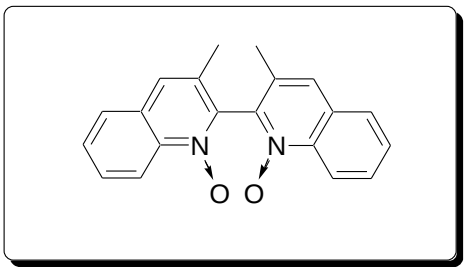
MnO_2 (2.12 g, 24.36 mmol) was added to a solution of 2-aminobenzyl alcohol **135** (1 g, 8.12 mmol) in anhydrous CH_2Cl_2 (50 mL) under an argon atmosphere and the mixture was stirred at room temperature for 24 h. The mixture was then filtered through a pad of silica (5 g) and the filtrate was concentrated to afford the pure product **136** (0.79 g, 81 %) as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.48 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.32 (dt, *J* = 7.2, 1.6 Hz, 1H), 6.75 (dt, *J* = 7.2, 0.8 Hz, 1H), 6.66 (d, *J* = 8.3 Hz, 1H), 6.10 (broad s, 2H); ^{13}C NMR

(100.6 MHz, $CDCl_3$) δ 116.0 (CH), 116.6 (CH), 118.9 (C), 135.2 (CH), 135.8 (CH), 149.9 (C), 194.1 (CH); MS (EI), *m/z* (%) 121.0 (80), 93.0 (100), 66.0 (35) in accordance with the literature data;[58] HRMS (EI) 121.0528 (C_7H_7ON requires 121.0529).



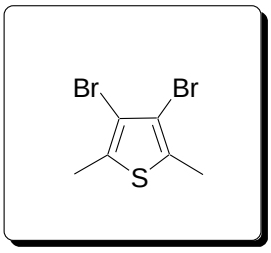
3,3′-Dimethyl-2,2′-biquinoline 138

A solution of potassium hydroxide (50 mg) in ethanol (3 mL) was added to a solution of 2-aminobenzaldehyde **136** (0.67 g, 5.53 mmol) and 3,4-hexanedione **137** (0.32 g, 2.77 mmol) in absolute ethanol (30 mL) and the resulting solution was heated under argon to reflux for 4 h. The solvent was evaporated *in vacuo*, the residual crude oil was diluted with CH_2Cl_2 (20 mL) and washed with water (2 × 10 mL). The organic fractions were combined and dried with $MgSO_4$ and evaporated to give crude **138** (780 mg, 27%). Purification via chromatography on a column of silica (20 × 1 cm) with a mixture of petroleum ether and ethyl acetate (2:1), followed by recrystalisation from a hexane:ethyl acetate mixture (2:1), gave pure **138** (210 mg, 27%) as yellow needles: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.0 Hz, 4H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.62 (t, *J* = 8.0 Hz, 2H), 7.50 (t, *J* = 8.0, 2H), 2.26 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.1 (CH_3), 126.8 (CH), 126.9 (CH), 128.2 (C), 128.9 (CH), 129.3 (CH), 129.5 (C), 136.9 (CH), 146.4 (C), 159.1 (C); MS (EI), *m/z* (%) 284.7 (M+H) (100), 283.7 (13) in accordance with the literature data;[59] HRMS (EI) 285.1392 ($C_{20}H_{16}N_2$ requires 285.1387).



(±)-3,3′-Dimethyl-2,2′-biquinoline N,N′-dioxide 32

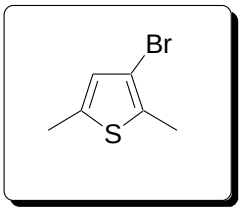
m-Chloroperbenzoic acid (70%, 91 mg, 0.53 mmol) was added portion-wise to a solution of biquinoline **32** (60 mg, 0.21 mmol) in CH_2Cl_2 (5 mL) at 0 °C and the mixture was stirred at room temperature for 24 h. The reaction mixture was then successively washed with sat. $NaHCO_3$ (3 × 10 mL) and brine (10 mL) and dried over Na_2SO_4. The solvent was evaporated *in vacuo* to afford the ligand **32** (57 mg, 85 %) as a opaque needles: mp 255-260 °C (lit. gives 270 °C)[Error! Bookmark not defined.]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 8.0 Hz, 2H), 7.88-7.65 (m, 8H), 2.28 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.9 (CH_3), 120.1 (CH), 125.2 (CH), 127.4 (CH), 129.1 (CH), 129.3 (CH), 130.2 (C), 131.7 (C), 140.4 (C) in accordance with the literature data.**Error! Bookmark not defined.**



3,4-Dibromo-2,5-dimethylthiophene 140

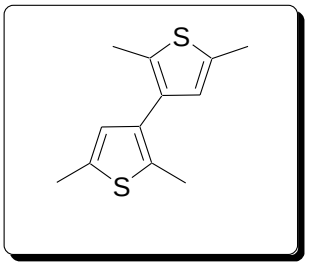
Bromine (0.91 mL, 17.83 mmol) was added to a solution of 2,5-dimethylthiophene **139** (1 g, 8.91 mmol) in CH_2Cl_2 (30 mL) over a period of 15 min and the resulting dark mixture was stirred at room temperature for 18 h. The excess of bromine was reduced with a 20% aqueous solution of $Na_2S_2O_3$ and the organic phase was washed with $NaHCO_3$ (aq) and water and dried using Na_2SO_4. The crude product was recrystalised from a mixture of ethanol and chloroform (9:1) to give pure **140** (1.75 g, 72%) as white needles: mp 44-45 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.8 (CH_3), 110.6 (C), 130.4 (C); MS (EI), *m/z* (%) 269.8 (93), 190.9 (100), 110.0 (64) in accordance with the literature data;[61] HRMS (EI) 269.8533 ($C_6H_6Br_2S$ requires 269.8536).



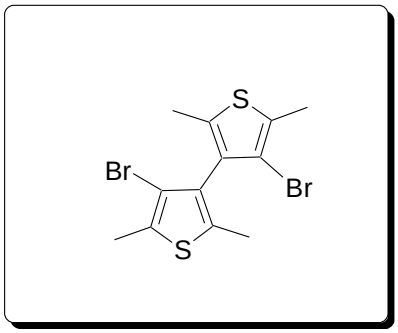
3-Bromo-2,5-dimethylthiophene 141

n-BuLi in hexane (1.6 M, 27 mL, 38.30 mmol) was added dropwise to a solution of 3,4-dibromo-2,5-dimethylthiophene **140** (9.4 g, 34.8 mmol) in anhydrous ether (100 mL) at –70 °C, under argon atmosphere and the resulting mixture was vigorously stirred for 45 min. Water (5.5 mL) was then added dropwise and the mixture was stirred at –70 °C for a further 1 h. The mixture was then warmed to room temperature, washed with water (2 × 50 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford **141** (6.13 g, 92%) as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 2.32 (s, 3H), 6.48 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.5 (CH_3), 15.3 (CH_3), 107.9 (C), 127.6 (CH), 131.6 (C), 136.9 (C); MS (EI) *m/z* (%) 192.0 (83), 111.0 (100) in accordance with the literature data.[83]



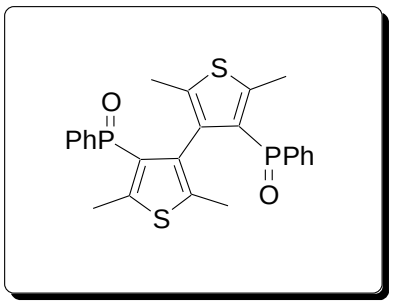
2,2',5,5'-Tetramethyl-3,3'-bithiophene 142

A solution of *n*-BuLi (1.6 M) in hexane (3.6 mL, 5.75 mmol) was added dropwise to a solution of 3-bromo-2,5-dimethylthiophene **141** (1 g, 5.23 mmol) at –70 °C in anhydrous ether (20 mL), the mixture was stirred for 15 min, and then allowed to warm to -55 °C. Copper(II) chloride (0.70 g, 5.23 mmol) was added in portions so that the temperature was maintained below -45 °C. The mixture was stirred at -45 °C for 1 h and then warmed to room temperature where it was left to stir for a further 24 h. The reaction was quenched by the addition of water (5 mL) and the organic phase was separated. The water phase and the inorganic solid material were extracted with ether (20 mL), the combined organic phases were dried over $MgSO_4$ and filtered through a pad of silica gel (10 g). The filtrate was concentrated to give the dimer **142** (0.79 g, 69%) as an oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 6H), 2.40 (s, 6H), 6.55 (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.5 (CH_3), 15.3 (CH_3), 107.9 (C), 127.6 (CH), 131.6 (C), 136.9 (C); MS (EI), *m/z* (%) 220.0 (100), 206.9 (78), 179.0 (38) in accordance with the literature;[64] HRMS (EI) 222.0537 ($C_{12}H_{14}S_2$ requires 222.0527).



4,4'-Dibromo-2,2',5,5'-tetramethyl-3,3'-bithiophene 143

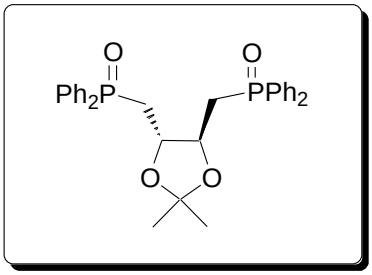
Hydroquinone (1 mg) and *N*-bromosuccinimide (0.76 g, 4.3 mmol) was added and in portions to a solution of 2,2',5,5'-tetramethyl-3,3'-bithiophene **142** (0.48 g, 2.15 mmol) in a 1:1 mixture of acetic acid-chloroform (15 mL) at 0 °C (ice water bath). The reaction was complete within a few minutes, and the solution was diluted with water. The organic layer was separated and was then washed with water, sodium carbonate solution and once more with water. The organic layer was then dried over Na_2SO_4 and the solvent was evaporated *in vacuo* to afford the product **143** (0.66 g, 82 %) as an oil; 1H NMR (400 MHz, CDCl3) δ 2.19 (s, 6H), 2.38 (s, 6H), ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.4 (CH_3), 15.1 (CH_3), 111.4 (C), 130.1 (C), 132.7 (C), 1134.7 (C) in accordance with the literature data.[66]



4,4'-Bis(diphenylphosphinyl)-2,2',5,5'-tetramethyl-3,3'-bithiophene 145

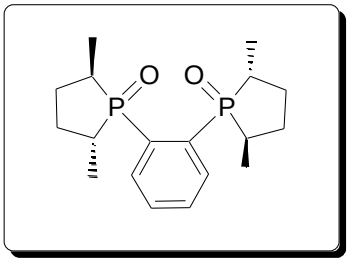
n-BuLi (3.3 mL, 1.6 M solution in hexane, 5.34 mol) was added dropwise to a solution of 4,4'-dibromo-2,2',5,5'-tetramethyl-3,3'-bithiophene **143** (1.0 g, 2.63 mol) in THF (30 mL) at -60°C, under argon. The mixture was stirred at this temperature for 10 min after which diphenylphosphinous chloride (0.96 ml, 5.37

mol) was added and the mixture was stirred for an addition 1 h. The mixture was then allowed to warm to room temperature and concentrated under reduced pressure. The residue was diluted with water and the product was extracted into CH_2Cl_2. A 35% aqueous solution of H_2O_2 (10 mL) was added to the organic layer at 0°C and and the mixture was stirred at room temperature for 1 h. The mixture was then diluted with water (10 mL), the organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified via chromatography on a column of silica (15 × 1) with a mixture of ethyl acetate, CH_2Cl_2, and Et_3N (3:7:0.1) to afford pure (±)-**145** (0.52 g, 32%) as a solid; mp 155-158 °C (lit. gives 140 °C)[67], ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66 (s, 6H), 2.30 (s, 6H), 7.3-7.7 (m, 20 H), MS (EI), *m/z* (%) 623.1 (M+H), 393.0 (63), 313.2 (100) in accordance with the literature.[67]



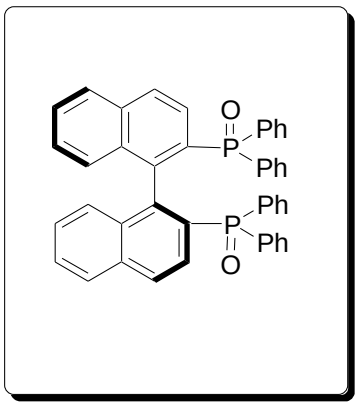
4,5-Bis-(diphenyl-phosphinoylmethyl)-2,2-dimethyl-[1,3]dioxolane 103

A 35% solution of H_2O_2 (690 mg, 20.46 mmol) was added to a solution of (+)-DIOP (150 mg, 0.30 mmol) in CH_2Cl_2 (10 mL) at 0 °C and the mixture was then left to stir for 4 h. Upon completion H_2O (10 mL) was added, the aqueous phase was extracted with CH_2Cl_2 (10 mL), and the organic extracts were combined and washed with a 20 % aqueous solution of sodium hydrogen sulphite. The organic layer was then dried over Na_2SO_4, and the solvent removed *in vacuo* to obtain **101** (137 mg, 86%) as a white powder: mp 147-149 °C; $[\alpha]_D$ + 84.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 6H), 2.57-2.63 (m, 2H), 2.57-2.63 (m, 2H), 2.80 (dt, *J* = 16.0, 4.0 Hz, 2H), 4.16-4.12 (m, 2H), 7.42-7.52 (m, 12H), 7.80-7.75 (m, 8H); ^{31}P NMR ($CDCl_3$) δ 30.56 in accordance with the literature;[84] IR (ATR, cm^{-1}) 1437 (P-Ph), 1120 (P=O); MS (FAB), *m/z* (%) 531 $(M+H)^+$(100), 473 (28), 338 (44); HRMS (FAB) 531.1854 ($C_{31}H_{33}O_4P_2$ requires 531.1857).



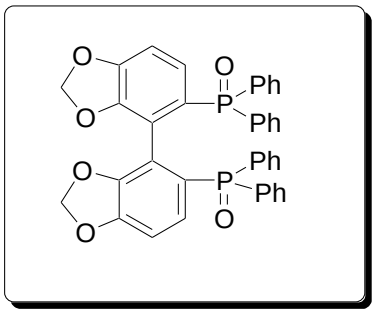
1,2-Bis[(2*R*,5*R*)-2,5-dimethylphospholano]benzene dioxide 103

A 35% aqueous solution of H_2O_2 (570 mg, 16.87 mmol) was added to a solution of mono-oxide (80 mg, 0.25 mmol) in CH_2Cl_2 (10 mL) at 0 °C and the mixture was left to stir for 4 hours. Upon completion, H_2O (20 mL) was added, the aqueous phase was extracted with CH_2Cl_2 (20 mL), the organic fractions were combined and washed with sodium hydrogen sulphite, dried over Na_2SO_4, and evaporated to obtain **103** (81.3 mg, 97%) as a white solid: mp 175-179 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, *J* = 8 Hz, 3H), 0.93 (d, *J* = 8 Hz, 3H), 1.27-1.22 (m, 6H), 1.40-1.28 (m, 2H), 1.93-1.81 (m, 2H), 1.93-1.81 (m, 2H), 2.45-2.31 (m, 4H), 2.75-2.62 (m, 2H), 7.67-7.56 (m, 4H); ^{31}P NMR ($CDCl_3$) δ 68.25; IR (ATR, cm^{-1}) 1126 (P=O); MS (EI), *m*/*z* (%) 338.1 (22), 295.0 (95), 253.9 (100) in accordance with the literature;[84] HRMS (EI) 338.1565 ($C_{18}H_{28}O_2P_2$ requires 338.1561).



(*S*)-BINAPO 102

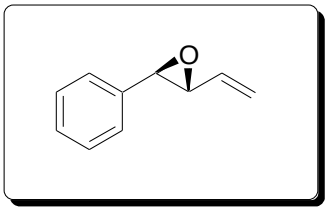
H_2O_2 (30% aq, 0.1 mL, 3.09 mmol) was added to a suspension of (*S*)-BINAP (380 mg, 0.62 mmol) in acetone (25 mL) and the mixture was stirred at room temperature for 5 h. The reaction was quenched with the addition of MnO_2 (100 mg), the mixture was then filtered through celite (50 g) and the filtrate was evaporated *in vacuo*. The crude product was purified by crystallization, using a toluene-hexane mixture (3:1), to give (*S*)-BINAPO **102** (355 mg, 88%) as white crystals: mp 230-232 °C, $[\alpha]_D$ -393.9 (*c* 0.5, benzene); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (d, *J* = 3.8 Hz, 4H), 7.22-7.45 (m, 20H), 7.65-7.70 (m, 4H), 7.80-7.85 (m, 4H); ^{31}P NMR ($CDCl_3$) δ 28.27 in accordance with the literature.[69,85]



(*S*)-SEGPHOS Dioxide 153

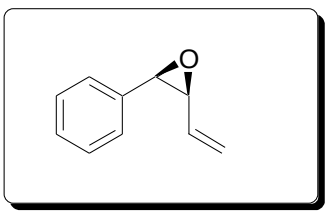
H_2O_2 (76 mg, 2.23 mmol) was added to a solution of *(S)*-SEGPHOS (20 mg, 3.28×10^{-2} mmol) in CH_2Cl_2 (2 mL) at 0 °C and the mixture was then left to stir for 4 h. Upon completion, H_2O (5 mL) was added, the aqueous phase was extracted with CH_2Cl_2 (5 mL), the organic fractions were combined and washed with sodium hydrogen sulphite, dried over Na_2SO_4, and evaporated to obtain **153**

(13.8 mg, 66%) as a white solid: mp 223-230 °C, $[\alpha]_D$ -196.3 (*c* 0.5, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) δ 5.27 (d, *J* = 1.2 Hz, 2H), 5.68 (d, *J* = 1.2 Hz, 2H), 6.58-6.60 (d, *J* = 8 Hz, 2H), 6.68-6.73 (m, 2H), 7.22-7.67 (m, 30H); ^{31}P NMR ($CDCl_3$) δ 29.50; MS (FAB), *m/z* (%) 643.1 $(M+H)^+$(100), 441.1 (35), 201.5 (70); HRMS (FAB) 643.1439 ($C_{38}H_{29}O_6P_2$ requires 643.1422).



2-Phenyl-3-vinyloxirane 156

A stirred suspension of NaH (5 mg, 0.24 mmol) in dry CH_2Cl_2 (2 mL) was cooled in an ice bath under argon. A solution of 2-bromo-1-phenylbut-3-en-1-ol **98-f** (37 mg, 0.12 mmol) in dry CH_2Cl_2 (0.5 mL) was added and the mixture was stirred at 0 °C for 2 h. The reaction was quenched by adding cold water dropwise and the layers were separated. The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure to leave pure **156** (22 mg, 82 %) as a pale yellow oil, which did not require further purification: ^1H NMR (400 MHz, CDCl3) δ 3.59 (dd, *J* = 8.0, 4.3 Hz, 1H), 4.16 (d, *J* = 4.3 Hz, 1H), 5.21 (dd, *J* = 10.0, 1.5 Hz, 1H), 5.35 (dd, *J* = 17.1, 10.0 Hz, 1H), 5.49 (dd, *J* = 17.1, 1.5 Hz, 1H), 6.76-6.92 (m, 5H) in accordance with the literature data.[75,79,86]



2-Phenyl-3-vinyloxirane 157

A stirred suspension of NaH (2 mg, 6.78×10^{-2} mmol) in dry CH_2Cl_2 (2 mL) was cooled in an ice bath under argon. A solution of 2-bromo-1-phenylbut-3-en-1-ol

98-a (10 mg, 0.039 mmol) in dry CH_2Cl_2 (0.5 mL) was added and the mixture was stirred at 0 ^oC for 2 h. The reaction was quenched by adding cold water dropwise and the layers were separated. The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. No product was observed, only starting material was recovered.

References

[1] Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673.

[2] Mendez, F.; Del Romero, M.; Gazquez, J. L. *J. Chem. Sci.* **2005**, *117*, 525.

[3] Rendler, S.;Oestreich, M. *Synthesis*. **2005**, *11*, 1727.

[4] (a) Colvin, E. *Silicon in Organic Synthesis*, Butterworths, 1980, (b) Brook, M. A. *Silicon in Organic, Organometallic and Polymer Chemistry*; Wiley: NewYork, 2000.

[5] Denmark, S.; Fu, J. *Chem. Comm.* **2003**,167.

[6] Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976**, 941.

[7] Hosomi, A.; Sakuri, H.*Tetrahedron Lett.* **1976**, 1295.

[8] Trost, B.M.; Theil, O.R.; Tsui, H. *J. Am. Chem. Soc.* **2003**, *125*, 13155.

[9] Kobayashi, S.; Nishio, K. *Tetrahedron Lett.* **1993**, *34*, 3453.

[10] Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620.

[11] Massa, A.; Malkov, A. V.; Kocovsky, P.; Scettri, A. *Tetrahedron Lett.* **2003**, *44*, 7179.

[12] Iseki, K.; Mizuno, S., Kuroki, Y., Kobayashi, Y.; *Tetrahedron Lett.* **1998**, *39*, 2767.

[13] Denmark, S.; Coe, D.; Pratt, N.; Griedel, B. *J. Org. Chem.* **1994**, *59*, 6161.

[14] Smyth, C. P. *J. Am. Chem. Soc.* **1938**, *60*, 183.

[15] Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.*, **2000**, *122*, 12021.

[16] Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.*, **2001**, *123*, 9488.

[17] Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.*, **2003**, *125*, 2208.

[18] Denmark, S. E.; Fu, *J. Org. Lett.* **2002**, *4*, 1951.

[19] Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998**, *120*, 6419.

[20] Shimada, T.; Kina, A.; Ikeda, S.; Hayashi, T. *Org. Lett.* **2002**, *16*, 2799.

[21] Shimada, T.; Kina, A.; Hayashi, T. *J. Org. Chem.* **2003**, *68*, 6329.

[22] Traverse, J.F. ; Zhao, Y. ; Hoveyda, A.H. ; Snapper, M.L. *Org. Lett.* **2005**, *7*, 3151.

[23] Malkov, A., V.; Orsini, M.; Pernazza, D.; Muir, K., W.; Langer, V.; Meghani, P.; Kocovsky, P. *Org. Lett.*, **2002**, *4*, 1047.

[24] Malkov, A.; Orsini, M.; Pernazza, D.; Bell, M.; Massa, A.; Herrmann, P.; Meghani, P.; Kocovsky, P. *J. Org. Chem.* **2003**, *68*, 9659.

[25] Malkov, A.V.; Bell, M.; Castelluzzo, F.; Kocovsky, P. *Org. Lett.* **2005**. *7*, 3219.

[26] Dalko, P. I., Ed. Enantioselective Organocatalysis: Reactions and Experimental Procedures; John Wiley and Sons, **2007**, p260.

[27] Malkov, A., V.; Ramirez-Lopez, P.; Biedermannova, L.; Rulisek, L.; Dufkova, L.;Kotora, M.; Zhu, F.; Kocovsky, P. *J. Am. Chem. Soc.*, **2008**, *130*, 5341 – 5348.

[28] Malkov, A. V.; Dufkova, L.; Farrugia, L.; Kocovsky, P. *Angew. Chem. Int. Ed.*, **2003**, *42*, 3674-7.

[29] Wong, W.; Lee, C.; Leung, H.; Kwong, H. *Org. Biomol. Chem.* **2004**, *2*. 1967.

[30] Denmark, S. E.; Fu, J.; Lawler, M. J. *J. Org. Chem.* **2006**, *71*, 1523.

[31]Iseki, K.; Mizuno, S., Kuroki, Y., Kobayashi, Y.; *Tetrahedron Lett.* **1998**, *39*, 2767.

[32] Iseki, K.; Mizuno, S., Kuroki, Y., Kobayashi, Y.; *Tetrahedron.* **1999**, *55*, 977.

[33] Furuya, N.; Sukawa, T. *J.Organomet.Chem.* **1975**, *96*, C1-C3.

[34] Seyferth, D.; Mammarella, R. *J.Organomet.Chem.* **1978**, *156*, 299.

[35] Carter, M.J.; Fleming, I.; Percival, A. *Perkin Trans. 1*, **1981**, 2415.

[36] Jung, M. E.; Gaede, B. *Tetrahedron*, **1979**, *35*, 621.

[37] Grant, B.; Djerassi, C. *J. Org. Chem.* **1974**, *39*, 968.

[38] Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595.

[39] Gawley, R. *Synthesis.* **1976**, 777.

[40] Stock, G.; Jung, M.; Colvin, E.; Noel, Y. *J. Am. Chem. Soc.* **1974**, *96*, 3684.

[41] Denmark, S.; Coe, D.; Pratt, N.; Griedel, B. *J. Org. Chem.* **1994**, *59*, 6161.

[42] Wei, X.; Taylor, R. J. *J. Org. Chem,* **2000**, *65*, 616.

[43] Just, G; Ouellet, R. *Can. J. Chem* **1976**, *54*, 2925.

[44] Ma, S; Lu, X. *Chem. Comm.* **1990**, 1643; *Org. Synth.* **1993**, *72*, 112.

[45] Ireland, R. E.; Norbeck, D. W.; Mandel, G. S.; Mandel, N.S. *J.Am.Chem.Soc,***1985**, *107*, 3285.

[46] Magid, R.M.; Fruchey, O.S.; Johnson, Q.L.; Allen, T.G.; *J. Org. Chem.*. **1979**,*44*, 359.

[47] Wender, P. A.; Wisniewski Grissom, J.; Hoffmann, U.; Mah, R. *Tetrahedron Lett.* **1990**, *31*, 6605.

[48] Cookson, R. C.; Crumbie, R. L. *Tetrahedron Lett.* **1985**, *26*, 3377.

[49] Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J.Am.Chem.Soc.* **1998**, *120*, 6419.

[50] Malkov, A.; Bell, M.; Castelluzzo, F.; Kocovsky, P. *Org Lett.* **2005**, *7*, 3219.

[51] Mihelich, E.; Eickhoff, D. *J. Org. Chem*. **1983**, *48*, 4135.

[52] Kwong, H.; Wong, W.; Lee, W.; Cheng, L.; Wong, W.T. *Tetrahedron: Asymmetry*. **2001**, *12*, 2683.

[53] Kuwata, T. *J. Am. Chem. Soc*. **1937**, 2509.

[54] Malkov, A. V.; Westwater, M, Gutnov, A.; Ramirez-Lopez, P.; Friscourt, F.; Kadlcikova, A.; Hodacova, J.; Rankovic, Z.; Kotora, M.; Kocovsky, P. *Tetrahedron*, **2008**, *64*, 11335.

[55] Nakajima, M.; Sasaki, Y.; Shiro, M.; Hashimoto, S. *Tetrahedron: Asymmetry*.**1997**, *8*, 341.

[56] Nystrom, R. F.; Brown.W. G. *J. Am. Chem. Soc*. **1947**, *69*, 1197.

[57] Goswami, S.; Jana, S.; Dey, S.; Adak, A. *Chem. Lett*. **2005**, *34*, 194.

[58] Vázquez, M.; Bermejo, M. R.; Licchelli, M.; González-Noya, A.; Pedrido, R. M.; Sangregorio, C.; Sorace, L.; García-Deibe, A.; Sanmartín, J. *Eur. J. Inorg. Chem*. **2005**, *17*, 3479.

[59] Thummel, R. P.; Lefoulon, F. *J. Org. Chem*. **1985**, *50*, 666.

[60] Simonini, V.; Benaglia, M.; Benincori, T. *Adv. Synth. Catal*. **2008**, *350*, 561.

[61] Phillips, D. L.; Ko, C.; Kwok, W.; Yam, V. W. *Chem. Eur. J*. **2006**, *12*, 5840.

[62] Liu, Z.; Yasseri, A. A,; Loewe, R. S.; Lysenko, A. B.; Malinovskii, V. L.; Zhao, Q.; Surthi, S.; Li, Q.; Misra, V.; Lindsey, J. S.; Bocian, D. F. *J. Org. Chem*. **2004**, *69*, 5568.

[63] Nikitidis, G.; Gronowitz, S.; Hallberg, A.; Stalhandske, C. J. Org. Chem. 1991, 56, 4064.

[64] Krayushkin, M. M.; Stoyanovich, F. M.; Shorinov, S. V. *Russ. Chem. Bull*. **2004**, *53*, 2338.

[65] Bilge, A.; Zen, A.; Forster, M.; Li, H.; Galbrecht, F.; Nehls, B. S.; Farrell, T.; Neher, D.; Scherf, U. *J. Mater. Chem.*, **2006**, *31*, 3177.

[66] Hankansson, R. *Acta. Chem. Scand*. **1971**, *25*, 1313.

[67] Benincori, T.; Cesarotti, E.; Piccolo, O.; Sannicolo, F. *J. Org. Chem*. **2000**, *65*, 2043.

[68] Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron*, **1984**, *40*, 1245.

[69] Nakajima, M.; Kotani, S.; Hashimoto, S. *Tetrahedron*. **2007**, *63*, 3122.

[70] Shimada, T.; Kina, A.; Ikeda, S.; Hayashi, T. *J. Org. Chem*. **2001**, *66*, 8854.

[71] Thummel, R. P.; Lefoulon, F. *J. Org. Chem*. **2004**, *69*, 5518.

[72] Nakajima, M.; Kotani, S.; Ishizuka, T.; Hashimoto, S. *Tetrahedron Lett*. **2005**, *46*, 157.

[73] (a) Lindstrom, U. M.; Olofsson, B.; Somfati, P. *Tetrahedron Lett*, **1999**, *40*, 9276. (b) Solladie-Cavallo, A.; Bouerat, L.; Roje, M. *Tetrahedron Lett*. **2000**, *41*, 9276.

[74] Masuyama, Y.; Ita, A.; Kurusu, Y. *Chem. Comm*. **1998**, 315.

[75] Bandini, M.; Cozzi, P.; Melcgiorre, P.; Morganti, S.; Umani-Ronchi, A. *Org. Lett*. **2001**, *3*, 1153.

[76] (a) Ochiai, M.; Fujita, E. *Tetrahedron Lett*. **1980**, *21*, 4369, (b) Hosomi, A.; Kohra, S.; Tominaga, Y.; Ando, M.; Sakurai, H. Chem. Pharm. Bull. **1987**, *7*, 3058.

[77] (a) Hu, S.; Jayaraman, S.; Oehlschlager, A. *J. Org. Chem*. **1996**, *61*, 7513. (b) Hu, S.; Jayaraman, S.; Oehlschlager, A. *Tettrahedron Lett*. **1995**, *36*, 4765.

[78] Champeil, E.; Pradhan, P.; Lakshman, M.K. *J. Org. Chem*. **2007**, *72*, 5035.

[79] Benfatti, F.; Cardillo, G.; Gentilucci, L.; Perciaccants, R.; Tolomeli, A.; Catapano, A. *J. Org. Chem*. **2006**, *71*, 9229.

[80] (a) Auge, J.; David, S. *Tetrahedron Lett.*,**1983**, *24*, 4009. (b) Auge, J. *Tetrahedron Lett.*,**1988**, *29*, 6107.

[81] (a) Hatch, L.F.; Harwell, K. E. *J. Org.Chem*. **1953**, *75*, 6002, (b) Hatch, L.F.; Harwell, K. E. *J. Am. Chem. Soc*.. 1955, 77, 1682.

[82] (a) Cho, W.; Kim, E.; Park, I.; Jeong, E.; Kim, T.; Le, T.; Kim, D. *Bioorg. Med. Chem*. **2002**, *10*, 2953, (b) Usifoh, C. O. *J. Heterocyclic. Chem*. **2001**, *38*, 597.

[83] (a) Yoshida, K.; Saeki, T.; Fueno, T. *J. Org. Chem*. **1971**, *36*, 3673. (b) Lim, S.; An, B.; Park, S. *Macromolecules*, **2005**, *38*, 6236.

[84] (a) Berthod, M.; Saluzzo, C.; Mignani, G.; Lemaire, M. *Tetrahedron Asymmetry*. **2004**, *15*, 639. (b) Nakajima, M.; Sugiura, M.; Kotani, S.; Tando, T.; Shimoda, Y. *Tetrahedron Asymmetry*, **2009**, *20*,1369.

[85] Gladiali, S.; Pulacchini, S.; Fabbri, D.; Manassero, M.; Sansoni, M. *Tetrahedron Asymmetry* **1998**, *9*, 391.

[86] (a) Okazaki, Y.; Ando, F.; Koketsu, J. *Bull. Chem. Soc. Jpn*. **2004**, *9*, 1687, (b) Mallaiah, K.; Satyanarayana, J.; Ila, I.; Junjappa, H. *Tetrahedron Lett*. **1993**, *34*, 3145.