Synthesis and application of novel chiral 4,4'-PheBOX ligands in asymmetric catalysis and Immobilisation study using 2,2'-PyBOX

Davina Flanagan, B.Sc. (Hons)

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School of Chemistry,
National University of Ireland, Galway
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Head of School: Professor Paul V. Murphy

Supervisor: Dr. Patrick O'Leary

To Daniel

and

my family

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Acknowledgments

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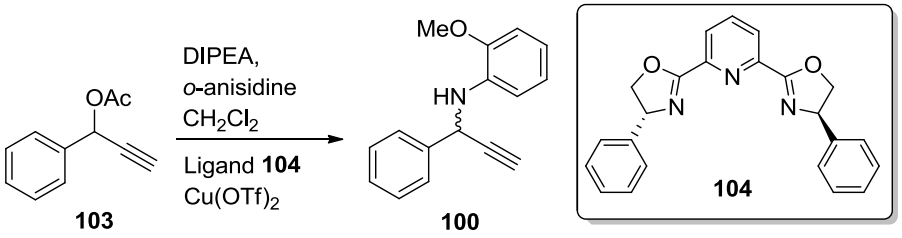
Abstract

A great deal is known about the reactivity of catalysts derived from 2,2'-PyBOX and 2,2'-PheBOX ligands in asymmetric reactions. The initial aim of this research was to investigate a new type of bisoxazoline ligand, where the chiral centres are adjacent to the aromatic core of the ligand, rather than just in the chiral side arms, as in the traditional ligands. This thesis documents the design and synthesis of novel 4,4'-PheBOX ligands (4,4'-phPHeBOX, 4,4'-MePhBOX and 4,4'-*n*-propylPheBOX) and attempted synthesis of 4,4'-PyBOX ligands. Metal complexes of the synthesised ligands were also tested in asymmetric reactions.

The second part of this study involved an immobilisation study using 2,2'-PyBOX ligands combined with metal salts, which were electrostatically immobilised on silica gel. These immobilised catalysts were then tested in asymmetric propargylic substitution reactions, asymmetric trimethylsilylation reactions and asymmetric ring opening of expoxides.



In the asymmetric propargylic substitution reaction, the heterogeneous reaction showed a lower enantiomeric excess (*ee*) of 40% compared to 50% *ee* achieved in the homogeneous reaction. However, when the catalyst was recycled and used again, an *ee* comparable to that obtained for the first use was observed. Unfortunately, when the catalyst was recycled and used for the third time, no conversion was seen and it was believed that the drop off in activity for the second and third heterogeneous runs were due to the *o*-anisidine displacing the catalyst from the silica gel due to the polar nature of the nucleophile. This and other immobilisation results are discussed herein.

Chapter 1:

Introduction

1.1 Asymmetric Synthesis

When a molecule is non-superimposable on its mirror image it is considered chiral. These chiral molecules lack all of the second order symmetry elements including mirror planes and centres of symmetry. Enantiomers are stereoisomers that are non-superimposable mirror images of each other. If the two enantiomers are present in equal quantities in a mixture, it is said to be a racemate. Racemic mixtures are very difficult to separate as enantiomers have the same chemical and almost all the same physical properties, except the rotation of plane polarised light

There are a number of different naming conventions for chiral molecules in use (**Figure 1.1**). One method uses Cahn-Ingold-Prelog priority rules to assign the labels *R* and *S* to enantiomers[1]. Other methods include naming by the direction in which it rotates the plane of polarized light, (+) and (-), and also by spatial configuration, D and L, a system most commonly used when describing amino acids and carbohydrates.

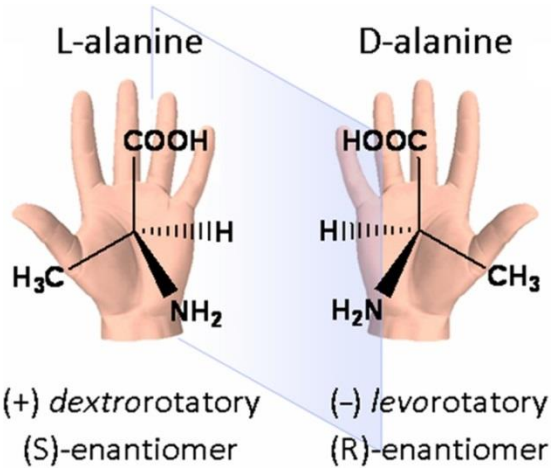


Figure 1.1

The world in which we live is chiral with a large number of organic compounds possessing this property. Carbohydrates, proteins and enzymes are all chiral and are built from chiral building blocks like amino acids and sugars. Likewise, all the biological receptors in the body are chiral, so when chiral molecules are placed in this chiral environment the difference between enantiomers becomes evident and

they often exhibit different biological activities within the body. For example, different enantiomers of drugs like Thalidomide[2], Naproxen[3] and Salbutamol[2] all have different biological activities (**Figure 1.2**).

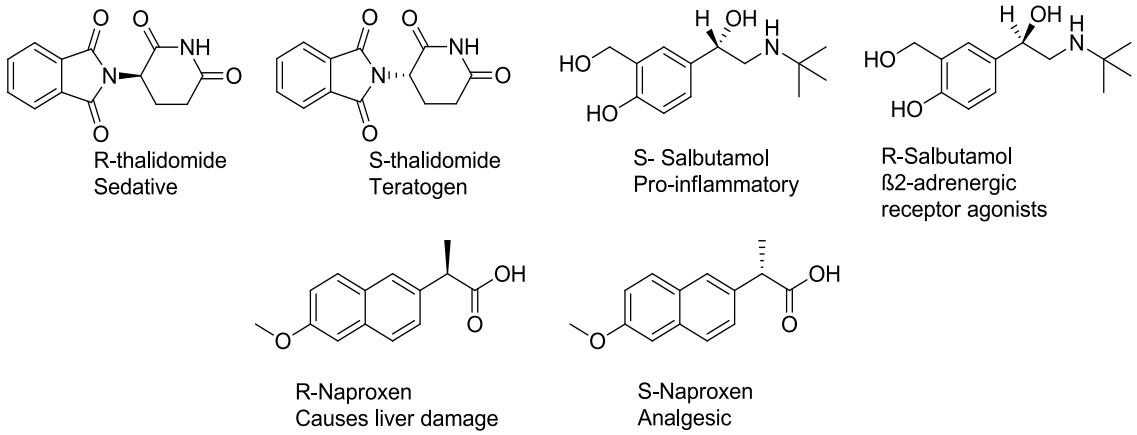


Figure 1.2

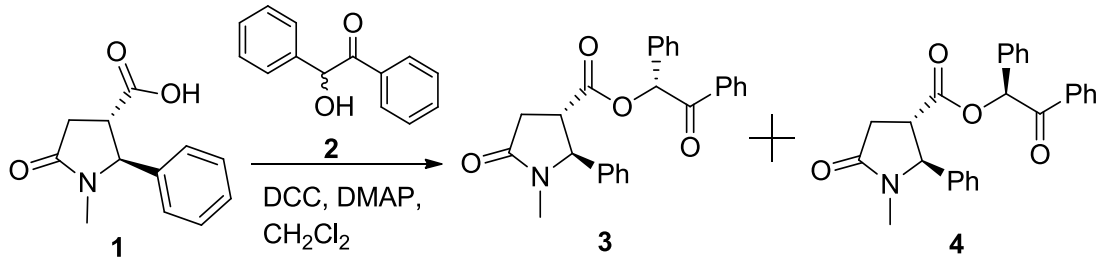
This difference in biological activity means that it is becoming increasingly important to synthesise only the required enantiomer. For this reason, it has become a vital part in drug design and development. The market share of single enantiomer dosage form drugs increased annually from 27 % (US $74.4 billion) in 1996, to 29 % in 1997, to 30 % in 1998, to 32 % in 1999, to 34 % in 2000, to 38 % in 2001 to 39 % (US $151.9 billion) in 2002[4]. Also the three top-selling drugs for 2008, Lipitor (atorvastatin calcium), Plavix (clopidogrel bisulfate) and Nexium (esomeprazole magnesium), with total sales of $30 billion, are all single enantiomer drugs[4-5]. It is obvious that asymmetric synthesis is an increasingly crucial tool in both the pharmaceutical and chemical industries alike.

Asymmetric synthesis or stereoselective synthesis involves chemical reactions, in which one or more new elements of chirality are formed in a substrate molecule, and which produce stereoisomeric products in an unequal amount[6-7]. Many different methods are available to induce the required stereochemistry however resolution of racemic mixtures is still used in industry as it may, in certain situations, be more cost effective than stereoselective routes.

1.2 Resolution of enantiomers

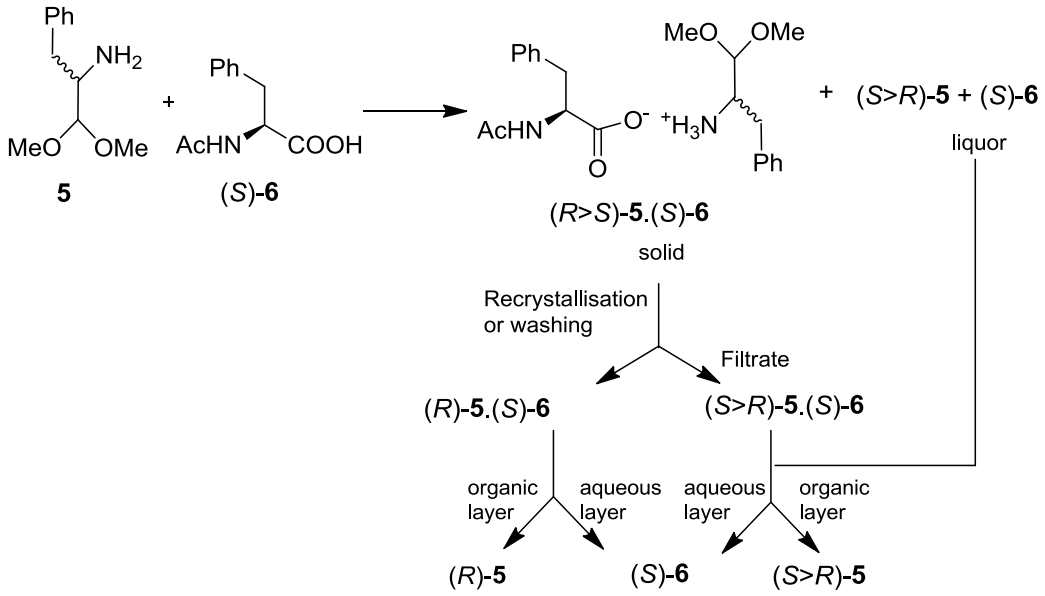
Access to enantiopure compounds is very important in synthesis and one method employed is resolution. If a racemate is separated into its two enantiomers, the maximum possible yield of each enantiomer is 50 %. There are many different methods available and include both physical and chemical processes.

Separation of enantiomers is possible through the use of chiral resolving agents which, via co-ordination or reaction, form diastereomeric systems from the racemate. The diastereomers can be separated by crystallisation, chromatography or other separation techniques. The resolving agent is then removed leaving behind the enantiomerically pure product. One disadvantage of this method is that the maximum yield of one enantiomer is only 50 %, so unless the undesired enantiomer can be recycled, these types of reactions can be wasteful. Piwowarczyk *et al* developed a novel chiral discriminating agent, 1, which was used to generate diastereomers from *rac*-benzoin, 2, using *N*,*N*-dicyclohexylocarbodiimide (DCC) in the presence of 4-*N*,*N*-dimethylaminopyridine (DMAP) through the formation of the ester from the carboxylic acid (**Scheme 1.1**). The reaction yielded 39 % of **3** and 37 % of **4** and mild ammonolysis of the esters afforded the separate enantiomers of benzoin in >95 % *ee*[8].



Scheme 1.1

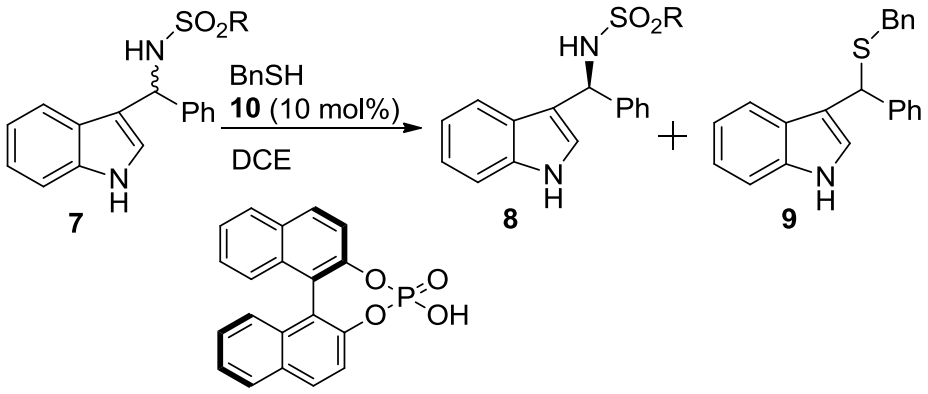
It is also possible to resolve enantiomers by forming diastereomeric salts. M. Albalat-Serradeil *et al* resolved racemic α-aminoacetals, **5**, via diastereoisomeric salt formation, (*R*>*S*)-**5.**(*S*)-**6**, using optically pure *N*-protected aminoacids, (*S*)-**6**[9] (**Scheme 1.2**).



Scheme 1.2

When the salt was synthesised it was recrystallised, which allowed (*R*)-**5**.(*S*)-**6** to be separated as a solid from (*S*>*R*)-**5**.(*S*)-**6**, which remained in the filtrate. This was then combined with the liquor from which salt (*R*>*S*)-**5.**(*S*)-**6** was first generated. Both salts, (*R*)-**5.**(*S*)-**6** and (*S*>*R*)-**5**.(*S*)-**6**, were then treated with different aqueous and organic solutions to give the free amines, (*R*)-**5** and (*S*>*R*)-**5** and amino acid, (*S*)-**6**. It can be seen that this can be quite a laborious and time consuming task.

Kinetic Resolution is another method employed to separate enantiomers and is possible due to a difference in the rate of reaction of two enantiomers in a racemate with a chiral reagent. The rate difference arises because of the difference in activation energy required to reach each transition state. The reaction results in the less reactive enantiomer being resolved. *N*-benzylic sulphonamides can be coupled with a range of nucleophiles, including aromatics, alkynes and thiols, which are often useful in organic synthesis. Wu and Tian used kinetic resolution to separate a variety of racemic *N*-benzylic sulphonamides with *N*-(3-indolyl)methyl groups using 10 mol % of a chiral phosphoric acid and half an equivalent of benzyl thiol[10] (**Table 1.1**).



Entry	R	Time/h	Yield (%)	*ee* (%)
1	4-MeC_6H_4	7.5	36	98
2	4-$MeOC_6H_4$	9	31	97
3	4-$O_2NC_6H_4$	120	28	94
4	1-Naphtyl	21	37	99
5	Me	36	28	99
6	2-MeC_6H_4	36	25	99

Table 1.1

Work previously carried out by the group found that thiols could be used to react with *N*-benzylic sulphonamides in the presence of TMSCl and $ZnCl_2$[11]. It was then discovered that when an *N*-(3-indolyl)methyl group was present in the *N*-benzylic sulphonamide, a weaker phosphoric acid could be employed as catalyst (10 mol%). This led the researchers to vary the sulfonyl group and investigate its effect on the reaction. From **Table 1.1**, it can be seen that varying this group had a major effect on reaction rate but had little effect on overall yields, which were moderate to good. Enantiomeric excesses (*ee*'s) for all variants were excellent. When a naphtyl group was introduced it produced the highest yield of 37 %, of a possible maximum 50 %, and an impressive enantiomeric excess of 99 %.

One method to overcome maximum yields of only 50 % is to use dynamic kinetic resolution. This method allows 100 % of a racemic starting material to be converted into one enantiopure product by the method shown in **Scheme 1.3**.

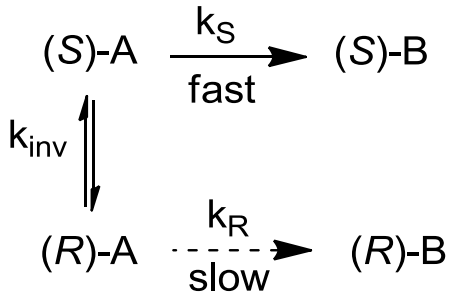


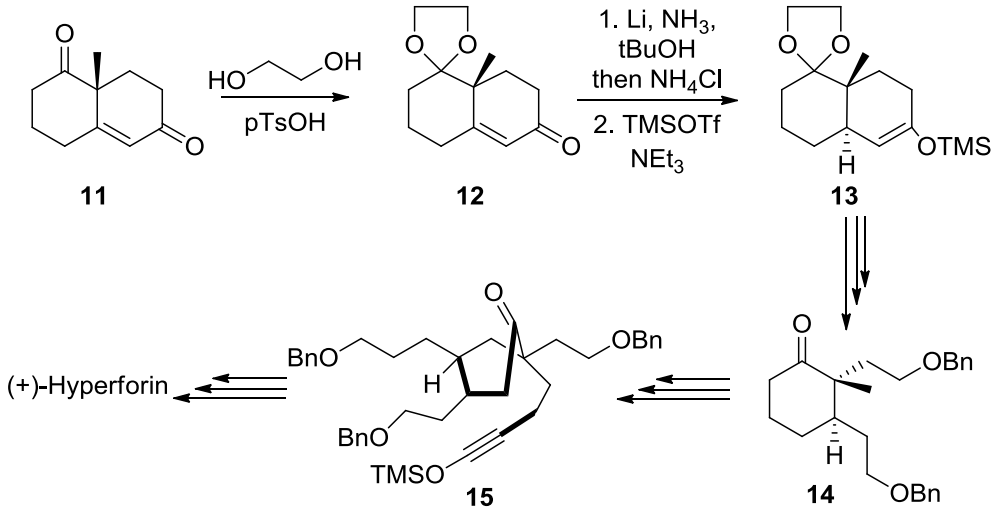
Figure 1.3

For this method to be useful, it is crucial that the rate of inversion (k_{inv}) is at least equal to, but preferably greater than, the rate of reaction of the faster forming enantiomer (k_S), so for complete conversion to only one enantiomer, i.e. 100 % yield, then it is necessary for $k_{inv} > k_S >>> k_R$. Dynamic kinetic resolution can be carried out in a number of different ways including use of a chiral catalyst[12], enzyme catalysed reactions[13] and can involve the formation of diastereomers[14-16].

1.3 Asymmetric Synthesis

1.3.1 Chiral pool synthesis

The sometimes wasteful nature of enantiomeric resolution has led to the development of asymmetric synthesis, where only the required enantiomer is synthesised. Chiral pool synthesis is one method that can be employed and involves using enantiomerically pure starting materials which incorporate chirality into the final product. The chiral pool is an assortment of inexpensive, accessible natural products, usually amino acids or sugars or sometimes synthetic products, from which the chiral centres can be incorporated into the desired product. Once the chiral centre from the starting material is in place, other chiral centres can be added using diastereocontrol. Richard and Chen used this kind of approach when synthesising (+)-Hyperforin[17] (**Scheme 1.3**). Utilising the (–)-Wieland–Miescher ketone, **11**, as a starting material it was possible to integrate its chirality into the product while also influencing selectivity at other chiral centres.



Scheme 1.3

The major disadvantage of using chiral pool synthesis is the limiting nature of the chiral pool. More often than not, natural products are only available in one enantiomeric form, so the required stereochemistry may not be available and also, the target molecule may be some synthetic distance from the available chiral pool molecule.

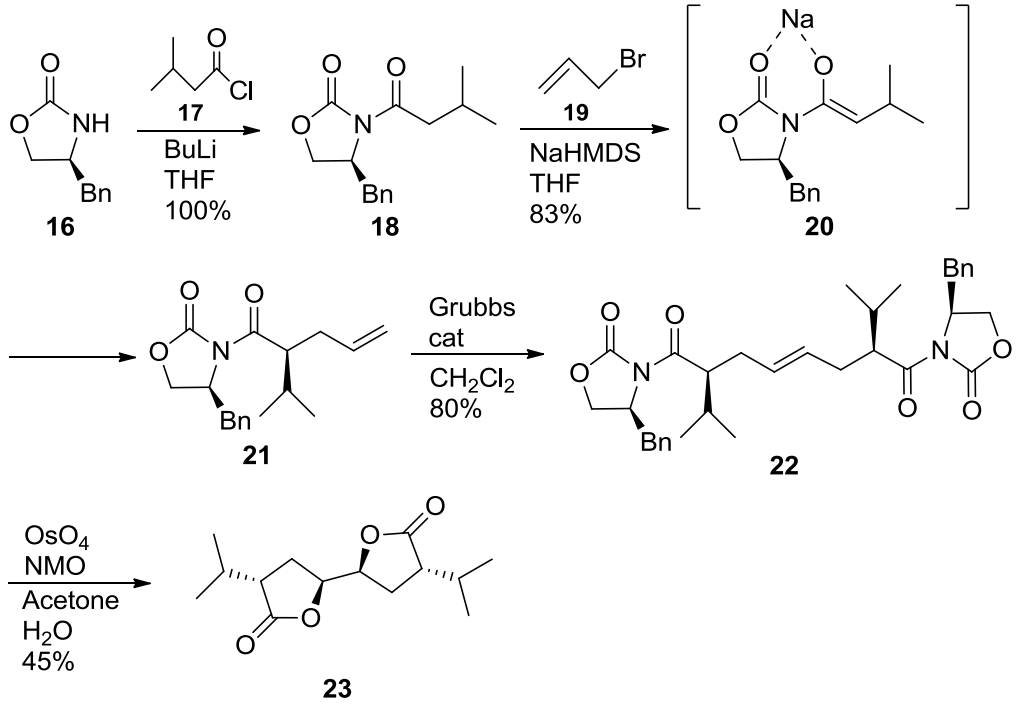
1.3.2 Chiral auxiliaries

Chiral auxiliaries are another useful tool which can be used in the synthesis of single enantiomers. A chiral auxiliary is an enantiopure substance that can be chemically bound to an achiral substrate forming a chiral intermediate. It will also go on to influence the stereoselectivity of any subsequent chiral centres that are formed, but at some stage in the synthesis it is removed, and so is not present in the final product. The most effective chiral auxiliaries are recyclable. The most commonly used chiral auxiliaries include oxazolidinones, sulfinamides and SAMP/RAMP hydrazones.

1.3.2.1 Oxazolidinones

Oxazolidinones, made popular by David Evans, can be used in a variety of asymmetric reactions including allylation[18], alkylations[19], and aldol reactions[20]. They can be easily and cheaply synthesised from amino acids, such as (*S*)-valine, making them one of the most commonly used chiral auxiliaries. Many variations of the structure of Evans original oxazolidinone have now been developed and this often allows one to choose between complimentary diastereoselective control by varying the auxiliary, depending on the reaction taking place, as well as conditions utilised[21-23].

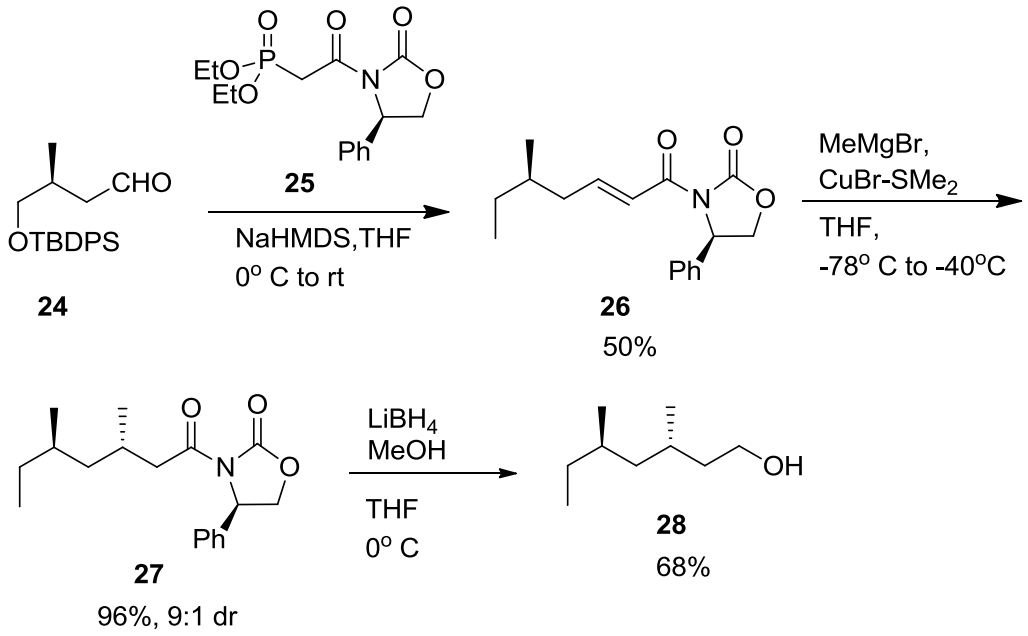
In the total synthesis of Aliskiren, an orally active renin inhibitor, by Nam and Ko, the *trans-cis*oid-*trans*-bis-lactone, **23**, was synthesised as a useful precursor to the building of Aliskiren[18] (**Scheme 1.4**).



Scheme 1.4

Several different pathways were used to prepare **23,** one of which involved the use of Evan's chiral auxiliary **16.** This was reacted with acid chloride, **17**, to give **18** which underwent allylation with allyl bromide, **19**, giving **21** in an 83 % yield with high diastereoselectivity. This was achieved through treatment of the oxazilidinone

17 with sodium hexamethyldisilazide giving the sodium enolate. The *Z*-isomer is favoured due to the co-ordination of the sodium to the two carbonyls giving a rigid structure, **20**. The enolate was alkylated stereoselectively under the influence of the chiral centre in the chiral auxiliary to give **21**. A Grubbs alkene metathesis reaction was then carried out to give the *trans*-alkene derivative, **22**, in an 80 % yield. Although the Sharpless dihydroxylation reaction was attempted, it was found that reaction times were too slow and the diastereoselectively was modest, even when twice the standard loading of catalyst was used. Instead NMO and OsO_4, were employed to give a 1:1 mixture of the *cis* and *trans* products which were separable by column chromatography giving a 45 % yield of *trans*-*cis*oid-*trans*-bis-lactone, **23**. The final reaction in the synthesis also resulted in the removal of the chiral auxiliary.



Scheme 1.5

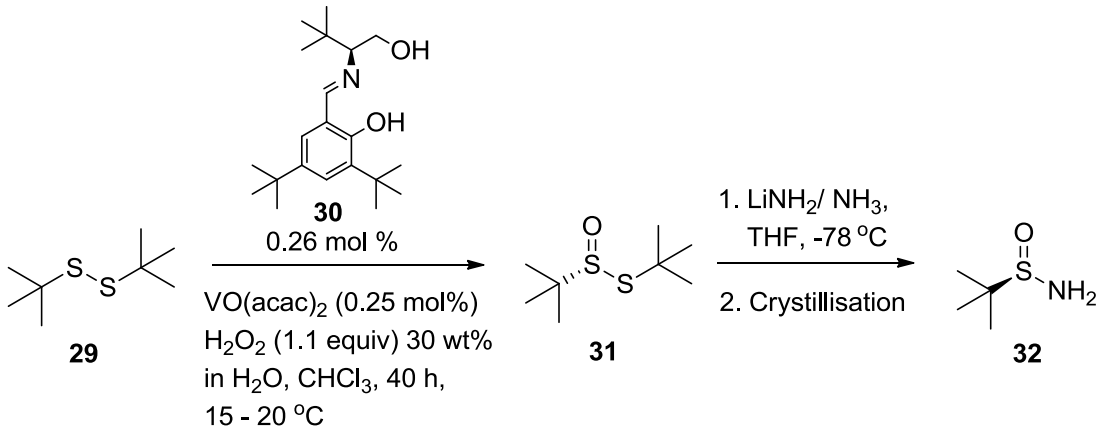
When Umezawa *et al* were attempting to synthesise Kalkitoxin, they utilized chiral oxazolidinone **25** and subjected it to a Horner−Wadsworth−Emmons reaction with ester **24** giving the α,β unsaturated acyloxazolidinone **26** in a 50 % yield[22] (**Scheme 1.5**). This was followed by a 1,4 addition of a methyl group to **26**. The methyl group was added using MeMgBr and CuBr-SMe_2 and gave the acyloxazolidinone **27** in a

96 % yield with a diastereomeric ratio of 9:1. The selectivity occurs through chelation of the copper. The predominant product was consistent with nucleophilic addition to the bis-chelated *syn*-*S*-*cis* enoyl system via *anti*-facial selectivity with respect to the 4-phenyl substituent[24]. Removal of the chiral auxiliary was carried out using $LiBH_4$ in methanol and THF leaving alcohol **28** in 68 % yield. This alcohol underwent numerous transformations in the synthesis of Kalkitoxin.

1.3.2.2 *N*-*tert*-butylsulfinamide

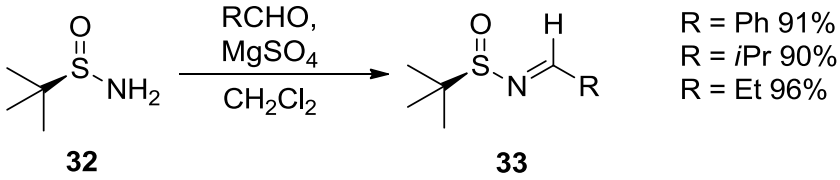
Another important family of chiral auxiliaries are the chiral sulfinamides. The sulfinamide can be condensed with aldehydes[25] or ketones, using titanium (IV) reagents[26], producing sulfinyl aldimines and sulfinyl ketimines respectively. This *N*-sulfinyl chiral group is a powerful chiral directing group during addition reactions which allows for high stereoselectivity in these reactions. When it is time to remove the chiral auxillary, a simple acid cleavage can be utilised often in nearly quantitative yields and without epimerisation[25]. The utilisation of these chiral sulfinimines has become popular as they are much less prone to tautomerization than most aryl- or alkyl- imines. They are also more electrophilic than their aryl- or alkyl- counterparts due to activation of the imine by the *N*-sulfinyl group. These sulfinimines offer asymmetric pathways to a variety of important chemical building blocks, including 1,2 and 1,3 amino alcohols[27-29], α- and β-amino acids and esters[30-32], diamines[33-34] and α- and α, α-branched amines[35-36].

One of the most commonly used sulfinamides is *tert*-butanesulfinamide, **32,** as the synthesis is relatively straightforward and robust making it inexpensive to synthesise either enantiomer on a large scale. The first synthesis of **32** was reported by Ellman and co. in 1997[37] with more details of the synthesis appearing in a subsequent paper[38] (**Scheme 1.6**). The disulphide, **29,** undergoes a catalytic asymmetric oxidation using the chiral Schiff base **30**, $VO(acac)_2$ and H_2O_2 as stoichiometric oxidant producing chiral thiosulfinate **31** in an 88 % yield and 91 % *ee***.** This then undergoes stereospecific nucleophilic displacement of the *tert*-butyl thiolate using $LiNH_2$ in liquid ammonia.



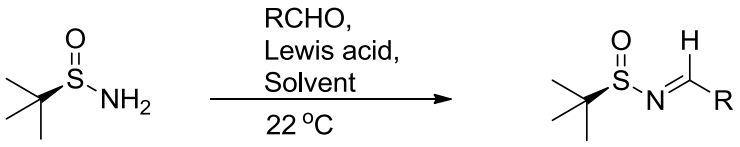
Scheme 1.6

A single recrystallization provides enantiomerically pure **32** in 77 % yield and >99 % *ee*. With only minor alterations to this original reaction, including a change of Schiff base and solvents used in the first step, as well as an optimised addition sequence of the H_2O_2, this process has been employed for the synthesis of the *N*-*tert*-butylsulfinamide on ton scale[25].



Scheme 1.7

N-*tert*-butyl imines are usually synthesised via a condensation reaction between *tert*-butylsulfinylamine and an aldehyde or a ketone. Many methods have been developed for the synthesis of the sulfinyl aldimines including, the first attempt by the Ellman group, condensation of **32** with 2-3 equivalents of aldehyde and excess $MgSO_4$ using catalytic amounts of pyridinium *p*-toluenesulfonate[37] (**Scheme 1.7**). Yields of 90-96 % were observed depending on the aldehyde used and no racemisation occurred.



32 **33**

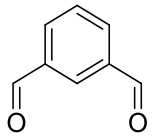
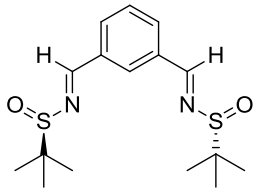
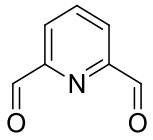
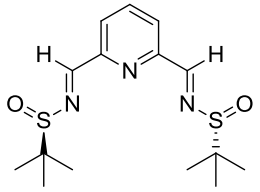
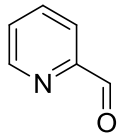
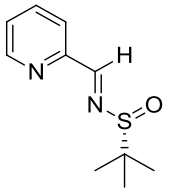
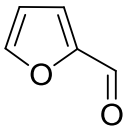
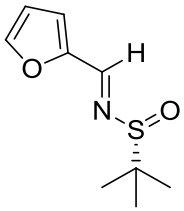
RCHO	Lewis acid	Solvent	Time h	Yield %	Product
	$CuSO_4$	$CHCl_3$	18	98	
	$CuSO_4$	$CHCl_3$	4	74	
	$CuSO_4$	$CHCl_3$	1	95	
	$Ti(OEt)_4$	THF	4	82	

Table 1.2

However, it was discovered that the Lewis acid $CuSO_4$ was a better reagent for this transformation and became the water scavenger of choice as it can be used with only 1.1 equivalents of aldehyde[39]. As seen in **Table 1.2**, it can be used with a wide variety of aldehydes, but for the preparation of sterically hindered or electronically deactivated imines, titanium ethoxide is often a preferred option. For this reason, $Ti(OEt)_4$ is often the catalyst of choice for the synthesis of ketimines.

The synthesis of α-branched amines is possible through the reaction of a *tert*-butanesulfinyl aldimines with organometallic reagents. Cogan *et al* investigated

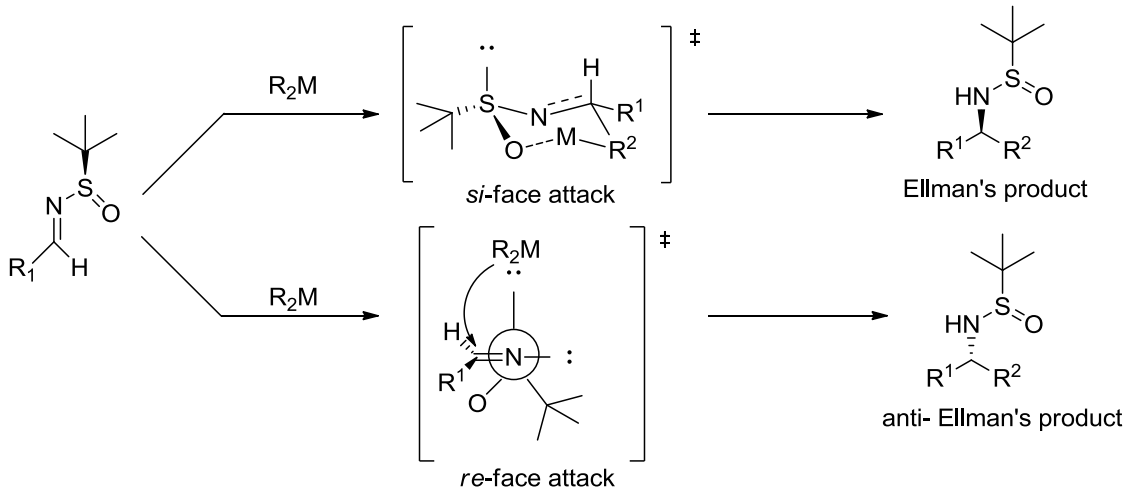
the use of organomagnesium, organolithium and organocerium reagents in the reaction with a variety of alkyl and aryl sulfinyl imines[40] (**Table 1.3**). It can be seen that reaction with Grignard organomagnesium reagents produced excellent yields and diastereomeric ratios with both alkyl and aryl substituents, while the organolithium and organolithium with a cerium additive gave more disappointing diastereoselectivities.

33 **34**

R^1	R^2M	solvent	yield	dr
Ph	EtMgBr	THF	91 %	50:50
Ph	EtMgBr	CH_2Cl_2	98 %	92:8
Et	MeMgBr	CH_2Cl_2	96 %	97:3
Ph	MeMgBr	THF	98 %	93:7
Et	MeLi	Et_2O	86 %	54:46
Et	$CeCl_3$/MeLi	THF	89 %	78:22

Table 1.3

Selection of solvent is paramount in these reactions as can be seen in the table above. Phenyl sulfinyl imine was reacted with EtMgBr in THF, a coordinating solvent, producing a *dr* of 50:50. However by changing the solvent to CH_2Cl_2, a non-coordinating solvent, the diastereomeric ratio (*dr*) was dramatically increased. This can be explained by considering the transition states when both coordinating and non-coordinating solvents are used in these reactions. In **Scheme 1.4**, it can be seen that there are two different possible transition states[41]. The first pathway leads to the Ellman's product and proceeds *via* the closed, 6-membered transition state. This is common in Grignard reactions where non-coordinating solvents like CH_2Cl_2 or toluene are used. This transition state allows for *si*-face attack by the Grignard reagent on the imine.



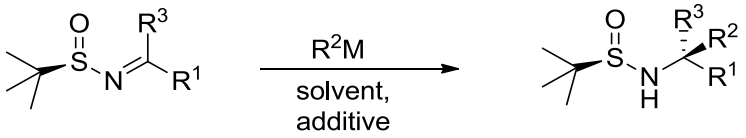
Scheme 1.4

The second route involves an open transition state where *re*-face attack produces the anti-Ellman's product. This transition state is commonly observed for reactions involving organolithium reagents where coordinating solvents like THF are used. It is because of these two possible transition states that either diastereomer of the addition product can be obtained from a single enantiomer of *N*-*tert*-butylsulfinamide.

The synthesis of α-branched amines has also been achieved using sulfinyl ketimines. A sulfinyl imine is generated through a one pot reaction of ketones with *N*-*tert*-butylsulfinamide in the presence of $Ti(OEt)_4$. This is then reacted *in situ* with $NaBH_4$ to afford the sulfinamides in good yields (66-86 %) and excellent *dr*s (90:10 to 97:3) for alkyl, aryl and dialkyl ketones[42]. The $Ti(OEt)_4$ in the reaction acts as both a dehydrating agent in the condensation step, and also as a Lewis acid in the reduction step of the reaction, improving overall yields and diastereomeric ratios in these reactions. In subsequent research by the Ellman group, it was discovered that L-Selectride could also be used as a reducing agent in this one pot synthesis[43]. However, it gave the opposite diastereomer when compared to reactions using $NaBH_4$. This difference was again attributed to the two possible transition states. The closed 6-membered transition state was proposed for the $NaBH_4$ mediated reactions, allowing for *si*-face attack, as in the Grignard aldimine reactions.

Conversely, the L-Selectride does not coordinate strongly, so these reactions progressed through the open form transition state and allowed for *re*-face attack.

To synthesise α, α-branched amines, 1,2 additions of organometallic reagents to sulfinyl ketimines can be utilized. Studies carried out by Cogan *et al* found that the reaction proceeded well (93 % yield, >95:5 dr) when allylmagnesium bromide was used. However, when PhMgBr was examined it was found that it gave poor results (21 % yield, 69:31 dr)[40] (**Table 1.4**).



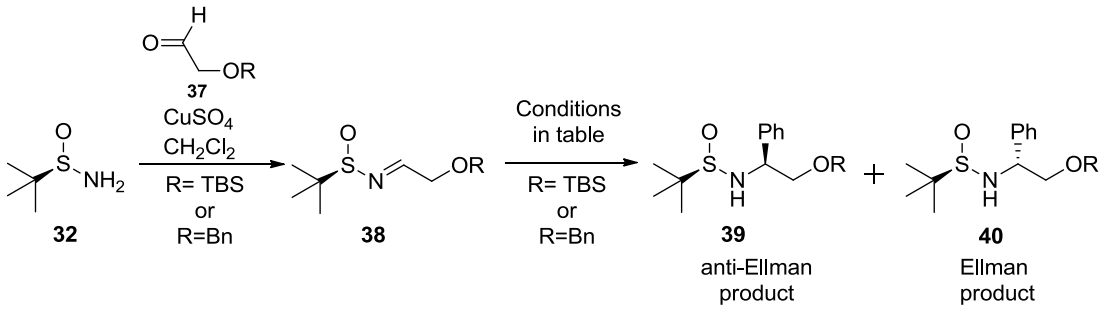
35 **36**

R^1	R^3	R^2M	solvent	additive	yield	dr
Me	*i*Pr	allylMgBr	CH_2Cl_2	N/A	93 %	>95:5
Me	*i*Pr	PhMgBr	CH_2Cl_2	N/A	21 %	69:31
Bu	*i*Pr	MeLi	toluene	N/A	54 %	82:18
Me	*i*Pr	PhLi	toluene	Me_3Al	93 %	97:3
Bu	Ph	MeLi	toluene	Me_3Al	Quant.	99:1

Table 1.4

Organolithium reagents looked more promising for a wider range of reactions. Further investigation by the group revealed that yields and selectivities could be improved by using a Lewis acid additive. Careful screening showed that Me_3Al was a useful, general Lewis acid.

Barrow *et al* were able to adapt the above methodology allowing for the direct synthesis of 1,2 amino alcohols through condensation of benzyloxyacetaldehyde or *tert*-butyldimethylsilyloxyacetaldehyde with *N*-*tert*-butylsulfinamide followed by reaction with an organometallic reagent under the conditions listed below (**Table 1.5**)[27].

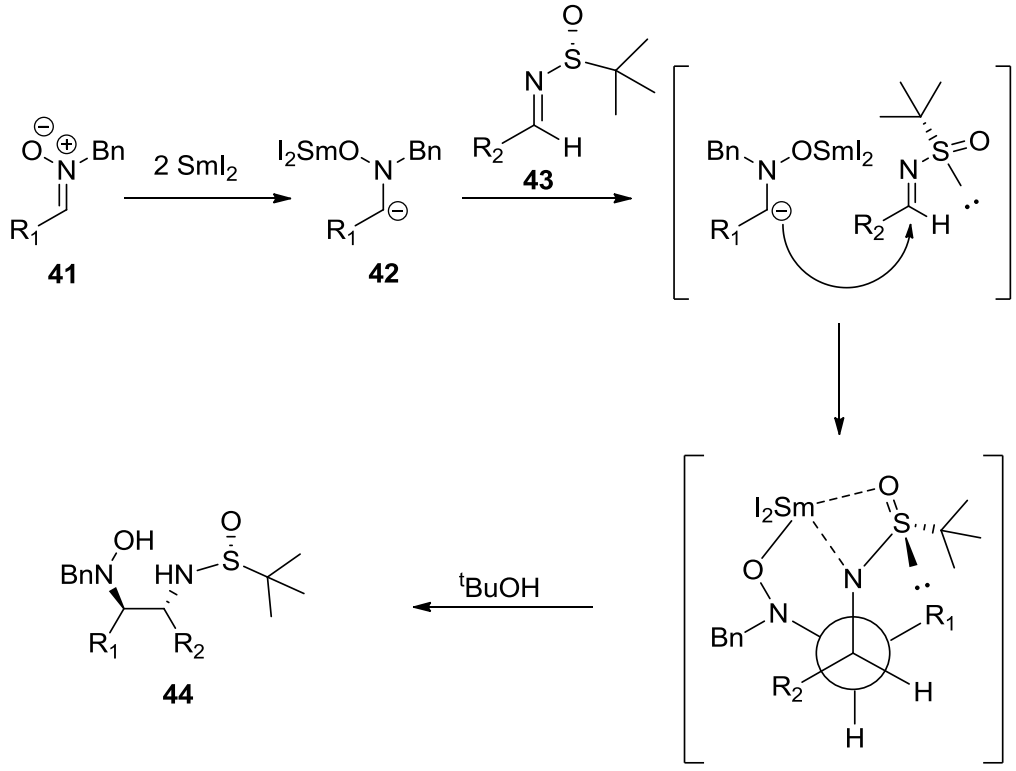


R	Solvent	Temp °C	RM	Solvent for RM	de	Yield %
Bn	CH_2Cl_2	-78	PhMgBr	Et_2O	>10:1	90
Bn	THF	-78	PhMgBr	Et_2O	9:1	96
Bn	Hexane	-78	PhLi	Et_2O/Pet	2:4.1	70
TMS	Et_2O	-78	PhMgBr	Et_2O	1:2.4	85
TMS	Et_2O	-78	PhLi	Et_2O/Pet	3.8:1	65
TMS	CH_2Cl_2	-50	PhMgBr	Et_2O	2.7:1	97
TMS	THF	-78	PhMgBr	Et_2O	1:3.5	89

Table 1.5

As can be seen from the table, under most conditions the yield of the desired adduct was high but the diastereoselectivity varied greatly (>10:1 to 2:4.1). Both, the Ellman and the anti-Ellman products were produced from this reaction and if conditions were varied it was possible to achieve preference for one diastereomer over the other. However, when α-silyloxy sulfinimines were reacted, in the presence of THF (used as either the reaction solvent or as the solvent for the Grignard reagent), there was modest selectivity for the Ellman product while reaction in non-coordinating solvents like CH_2Cl_2 with PhLi gave the anti-Ellman product. This selectivity was in contrast to that observed for additions to sulfinimines lacking an α-coordinating group[41]. Barrow explained this reversal through chelation of the α-alkoxy group to the metal forming a bicyclic transition state which would have required isomerization of the imine to the *Z* configuration, forcing the alkoxy group it into an axial position in the transition state. There are, however, other possible transition state models including Davis' open model.

Enantiomerically enriched unsymmetrical and C_2-symmetrical vicinal diamines have been synthesised by Zhong *et al* using homo coupling of chiral *N*-*tert*-butanesulfinyl imines and cross coupling of nitrones with *N*-*tert*-butanesulfinyl imines, respectively, both in the presence of samarium diiodide[33-34]. Reductive cross coupling of two imines or nitrones and N-*tert* butanesulfinyl imines, were used to synthesise the unsymmetrical vicinal diamines[34]. Studies of reaction conditions revealed that 2 equivalents of SmI_2, combined with a slight excess of either two imines or nitrones and N-*tert* butanesulfinyl imines as well as 2 equivalents of *t*BuOH produced the best yield (76 %). When the *t*BuOH was removed from the reaction the yield decreased dramatically to only 46 %. Also, diastereoselectivites were seen to decrease as the nitrone substituent became more bulky.

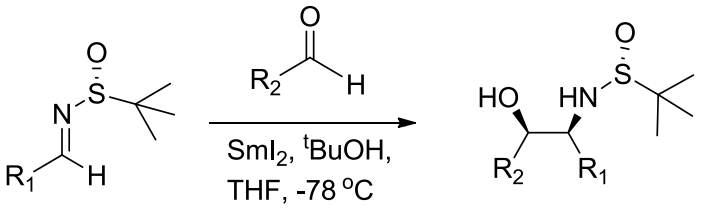


Scheme 1.5

The proposed mechanism for the reaction is shown in **Scheme 1.5.** Nitrone, **41**, underwent a two electron reduction using 2 equivalents of SmI_2, to give the anion **42,** which went on to react with the sulfinimine, **43**. The steric bulk of the *tert*-butyl group acts as a chiral directing group and the nitrone anion approaches

preferentially from the *si*-face of the C=N. Conversion of **44** to the corresponding free diamine could be achieved by deoxygenation of the hydroxylamino group using $Zn/Cu(OAc)_2$, followed by acidic removal of the sulfinyl group and hydrogenation to remove the benzyl group.

The synthesis of 1,2 amino alcohols has also been investigated by Zhong *et al* utilising a pinacol type cross-coupling between carbonyls and imines in the presence of samarium diiodide[44]. After the successful synthesis of unsymmetrical vicinal diamines[34] and also C_2-symmetrical vicinal diamines[33], the methodology was extended to the production of β-amino alcohols. Initial attempts, using aromatic aldehydes, lead to pinacol formation and not to the desired product. However, utilisations of aliphatic aldehydes gave both high yields (70-95 %) and high diastereoselectivities (88:12 - >99:1), with some examples shown in **Table 1.6**.



33 **45**

R_1	R_2	Time (h)	Yield (%)	dr	*ee*[*]
4-$CH_3C_6H_4$	*i*Pr	4	92	>99:1	98
$CH_3(CH_2)_4$	*i*Pr	6	95	98:2	97
3,4-$(MeO)_2C_6H_3$	*i*Pr	7	90	>99:1	>99
4-FC_6H_4	*i*Pr	4	89	99:1	>99
*i*Pr	*i*Pr	6	88	>99:1	>99
$PhCH_2CH_2$	*i*Pr	6	87	96:4	>99

[*]Enantiomeric excess for the free *β*-amino alcohols after acid hydrolysis

Table 1.6

The removal of a *N-tert*-butanesulfinyl group can, under most circumstances, be achieved by treatment with methanolic HCl to give amine hydrochloride products and *tert*-butylsulfinyl chloride.

N-*tert*-butylsulfinamide is considered a chiral auxiliary, which is defined as an enantiopure substance that is chemically bound to an achiral substrate forming a chiral intermediate. It will also go on to influence the stereoselectivity of any subsequent chiral centres that are formed but will not be present in the final product. However, the sulfinamides are not true chiral auxiliaries as the nitrogen will not be cleaved and will go on to form an amino group in the product. For this reason, sulfinamides can be considered pseudo-chiral auxiliaries.

While there are many advantages to using chiral auxiliaries, there are also disadvantages. For example, they must be chemically bound to the achiral starting material and then removed at a later stage. This means that two extra steps are added to any synthesis. Also, these auxiliaries are often very expensive and are required in stoichiometric amounts, so if they are not recyclable then this method of asymmetric synthesis may not be a viable option.

1.4 Asymmetric Catalysis

A catalyst, when added to a reaction, will alter the rate of the reaction without itself being consumed during that reaction. It works by either lowering the activation energy of the reaction, which will speed up the reaction, or it will increase the activation energy having the reverse effect. The influence of the catalyst may be increased by promoters in the reaction or its effect can be reduced by inhibitors or poisons. There are many different types of catalyst ranging from enzymes to acids or transition metals. The use of catalysts is considered “green chemistry” as it reduces the amount of waste produced during a chemical reaction and allows for the use of milder conditions, so it is kinder on the environment.

There are generally two different kinds of catalysts, homogeneous and heterogeneous. Homogeneous catalysts are in the same phase as the reactants i.e. they are dissolved in the reaction solvent with the other reagents. Heterogeneous catalysts are in a different phase to the reactants. Although homogeneous catalysis is generally better understood and shows better reactivity and selectivity,

heterogeneous catalysis is popular in industry, as the catalyst is easily removable from reaction products and can recycled. This allows for a greater total turnover number and reduces the amount of catalyst required for the reaction and also reduces cost.

Asymmetric catalysis is defined by IUPAC as a chemical reaction (or reaction sequence) in which one or more new elements of chirality are formed in a substrate molecule and which produces the stereoisomeric (enantiomeric or diastereoisomeric) products in unequal amounts[6]. In asymmetric catalysis, this is achieved by using a chiral catalyst that will result in a difference between the energy of the transition states for the pathways leading to different stereoisomers. It will favour the production of one stereoisomer (typically enantiomer) over the other.

Chiral catalysts can be separated into organocatalysts and transition metal catalysts. Organocatalysts are small chiral organic molecules predominantly composed of carbon, hydrogen, oxygen, nitrogen, sulphur or phosphorous. They are utilised in reactions as they are not water or air sensitive and are readily available at low costs and have low toxicity. Examples of organocatalysts include proline[45], secondary amines[46-47], cinchona alkaloids[48-49] and thioureas[49-50]. Transition metal catalysts are composed of a transition metal coordinated to chiral ligands. Most transition metal catalysts are effective at very low concentrations. However, to produce an efficient catalyst, it is often necessary to screen large numbers of metals, ligands and conditions to induce selectivity.

1.4.1 Transition metal catalysis

Typically these catalysts consist of a transition metal centre with organic chiral ligands attached. These metal centres can have between two and six coordination sites where ligands are connected by σ or π bonds and form chiral pockets. The metal acts as a catalytic centre in the pocket. Reagents entering the pocket bind to the metal in the chiral environment and react with one another under the control

of the chiral pocket, producing the stereoselectivity in the reaction. Small quantities of chiral catalyst can produce large amounts of optically active products if the correct combination of metal and ligand are used. The catalyst may even be recyclable, making this type of catalysis one of the most efficient and cost effective methods available.

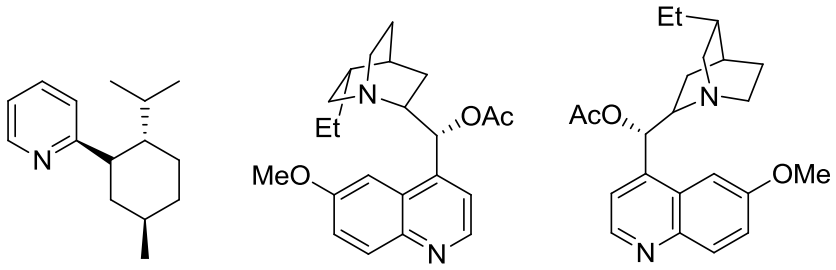
Design of new metal complexes is crucial with many factors influencing the performance of the catalyst. For example, geometry of the metal centre (square planar, octahedral, etc.) is controlled by the coordination numbers a metal may have, which in turn, is controlled by the electronic configuration of the metal. The metals co-ordination geometry will, of course, influence the geometry of the chiral pocket. Design and synthesis of the chiral ligand should consider factors like possible denticities, electronic properties and chirality, with potential ligands being screened using benchmark metals, reactions and conditions. Asymmetric catalysis using an optimised transition metal catalyst can give a product in high yields and stereoselectivities.

1.5 Cinchona alkaloid ligands

Cinchona alkaloid ligands have multiple uses in asymmetric synthesis including use as resolving agents[51] and use as organocatalysts in a number of different reactions including Mannich reactions[52], nitro- Mannich reactions[53] and additions of α-Nitro esters to azomethines[54]. They can also be used in combination with transition metals forming organometallic catalyst for use in reactions like the osmium catalysed Sharpless asymmetric dihydroxylation of alkenes[55], zinc catalysed desymmetrization of aziridines with phosphites[56], silver catalysed isocyanoacetate aldol reactions[57] and ruthenium catalysed heterogeneous hydrogenation of aromatic ketones[58].

While it was well understood that alkenes could be converted into *cis*-vicinal diols using stoichiometric amounts of osmium tetroxide[59], it was not until Sharpless *et al* investigated the use of chiral ligands in combination with OsO_4, that it was found

that asymmetric dihydroxylation, producing good yields and enantiomeric excesses, was possible[60]. The first chiral ligand considered was a chiral pyridine derivative **46** seen in **Figure 1.4**.

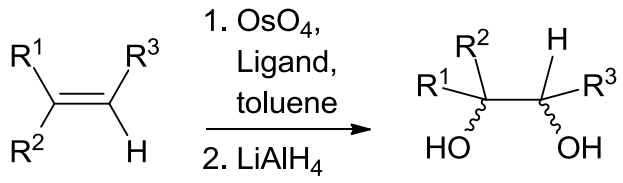


46 **47** **48**

Figure 1.4

However it was found that this chiral ligand gave poor enantiomeric excess (between 3-18 %). Research carried out by Griffith and co-workers revealed that the cinchona alkaloid quinuclidine, a tertiary alkyl bridgehead amine, formed a much more stable complex with OsO_4, than with the corresponding pyridine complex[61]. To explore the potential of chiral cinchona alkaloids as chiral inducing agents, Sharpless and co. synthesised dihydroquinine acetate, **47**, and dihydroquinidine acetate, **48**.

Test reactions were carried out using a number of alkenes including styrene, (*E*)-stilbene and 1-phenylcyclohexene and they were reacted with OsO_4 and either ligand **47** or **48** in toluene at room temperature, followed by reductive hydrolysis using $LiAlH_4$. The reaction produced vicinal diols of fair to high enantiomeric excess (*ee*) as seen in **Table 1.7**. It was discovered that carrying out the reaction at -78 °C improved selectivity.



Alkene	Ligand	Yield (%)	*Ee* (%)
Styrene	**47**	90	64.5
	48	62	61
(E)-stilbene	**47**	90	83
	48	85	82
1-phenylcyclohexene	**47**	88	68
	48	87	67

Table 1.7

However, there was major scope for improvement of the reaction, as stoichiometric amounts of both ligand and OsO_4 were required to react with the alkene. This was unappealing due to the cost and toxicity of OsO_4 and called for a catalytic solution. This was discovered several years later by the Sharpless research group, who found that addition of *N*-methylmorpholine-*N*-oxide allowed for the process to become catalytic, with the new additive acting as a co-oxidant[62]. Unfortunately, the enantiomeric excesses of diol products were found to be lower in the catalytic process when compared to reactions where stoichiometric amounts were employed. It was discovered that there was second catalytic cycle in operation for alkene to diol conversions (**Figure 1.4**)[63]. In this second cycle, there was little enantiomeric selectivity and the turnover frequency was reduced, which meant much longer reaction times. Wai deduced that addition of the alkene slowly *via* a syringe pump allowed for much improved yields and *ee*'s, when using catalytic amounts of OsO_4 in conjunction with dihydroquinidine-4-chlorobenzoate and NMO.

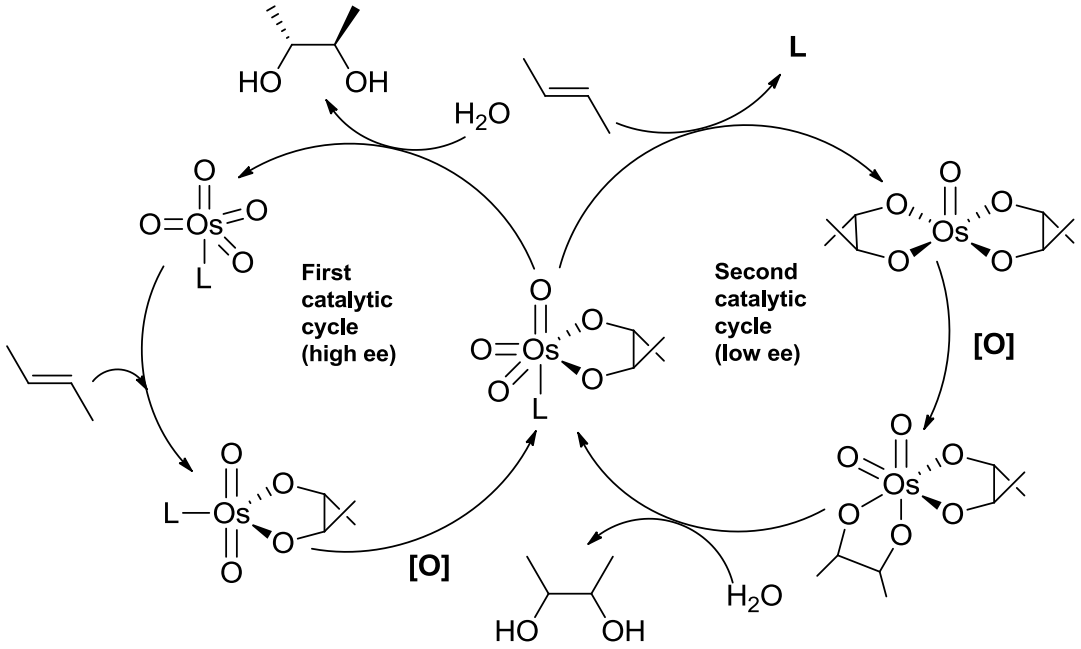
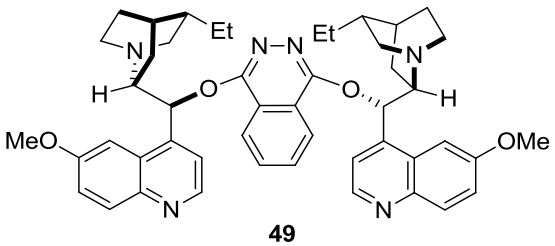


Figure 1.4

Sharpless *et al* continued research in this area and discovered that this second catalytic cycle could almost be eliminated by use of a two-phase system, where $K_3Fe(CN)_6$ was employed as a stoichiometric reoxidant[64]. In this newly discovered system, the organic layer contained only OsO_4 as oxidant, which allowed osmylation and hydrolysis to occur in this phase. The diol and the ligand remained in the organic layer, while the osmium(VI) had to enter the aqueous layer before re-oxidation could occur, which eliminated the possibility of the second cycle.

The next major development in asymmetric dihydroxylation came with the discovery that the phthalazine class of ligands could induce high enantioselectivity in the reaction[65].



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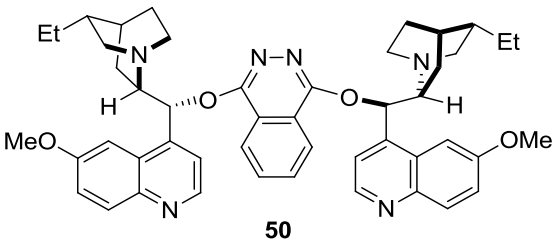
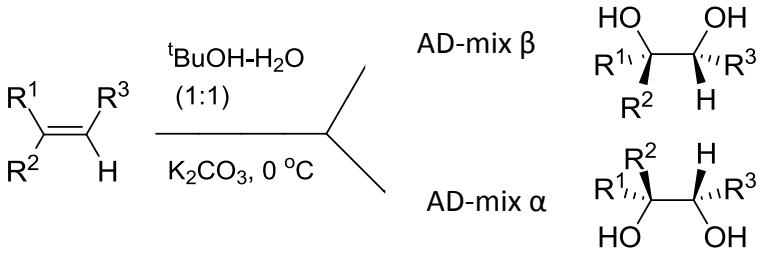


50

Figure 1.5

These ligands are derivatives of the cinchona alkaloids dihydroquinine and dihydroquinidine and are called $(DHQ)_2$-PHAL (**50**) and $(DHQD)_2$-PHAL (**49**) respectively**.** It was found that these ligands were superior to their predecessors and gave rise to the development of the 'AD-mix', which was a premix that contained $K_2OsO_2(OH)_4$ as a non-volatile osmium source, $K_3Fe(CN)_6$ as co-oxidant and either ligand, **49** or **50,** giving AD-mix β and AD-mix α respectively. By choosing either ligand, you can get opposite conformations so $(DHQD)_2$-PHAL will allow hydroxylation from one side and $(DHQ)_2$-PHAL will allow it from the other[66].

Reactions using 'AD-mix' were carried out in *t*BuOH:H_2O (1:1) at 0 °C. These new premixes gave high yields and enantiomeric excesses of above 90 % (**Table 1.8**).



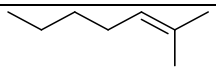
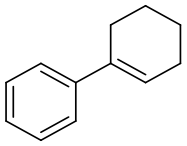
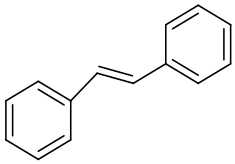
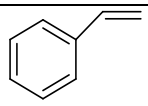
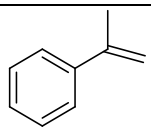
Alkene	$(DHQ)_2$-PHAL		$(DHQD)_2$-PHAL	
	% *ee*	Configuration	% *ee*	Configuration
	98	*R*	95	*S*
	99	*R,R*	97	*S,S*
	>99.5	*R,R*	>99.5	*S,S*
	97	*R*	97	*S*
	94	*R*	93	*S*

Table 1.8

Methanesulfonamide ($CH_3SO_2NH_2$) was added to the reaction for the first three examples in the table but was not added when terminal alkenes were hydroxylated. It was discovered that the addition of $CH_3SO_2NH_2$ dramatically accelerated the hydrolysis of the osmium (IV) glycolate product, with the increased reaction rate up to 50 times greater if no additive was present. It also allowed high catalytic turnovers with sterically hindered and tetrasubstituted substrates. However, this 'sulfonamide effect' did not work for terminal alkenes. In fact, it seemed to cause a slightly slower reaction when present.

1.6 Bisoxazoline ligands

Bisoxazoline or BOX ligands (**52**, **Figure 1.6**) have become a very important class of ligands in forming chiral metal complexes for use in asymmetric catalysis. Research carried out by Pfaltz *et al*, in the late 1980's, led to the synthesis of C_2-symmetric semicorrins (**51**, **Figure 1.6**), which were a class of bidentate nitrogen ligands, specifically designed for enantioselective catalysis[67]. The ligands were modelled on the biocatalysts corrinoid and porphinoid. This class of ligand proved useful in the copper catalysed enantioselective cyclopropanations and cobalt catalysed conjugate reduction of α,β-unsaturated carboxylic esters and amides.

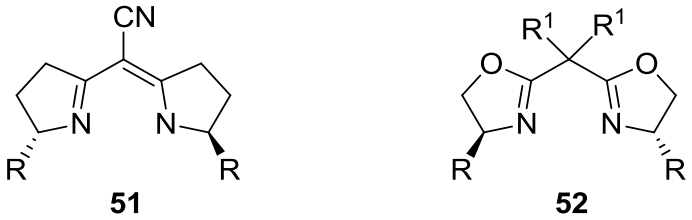


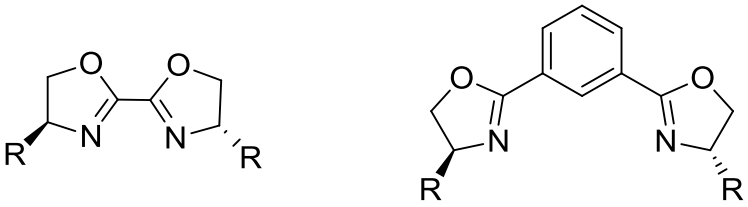
Figure 1.6

Due to the potential shown by the semicorrin ligand, investigations into related ligands, including the bisoxazolines, evolved. These ligands are now amongst the most widely used in asymmetric catalysis and have been employed in a wide range of enantioselective reactions including cyclopropanation reactions[68], asymmetric

alkylations[69], propargylic substitution reactions[70], trimethylsilycyanation reactions[71] and asymmetric ring opening of epoxides[72].

1.6.1 Structure

In the field of chiral Lewis acid catalysis, the catalyst may consist of a metal coordinated to an optically active ligand giving a chiral complex, which must have at least one vacant Lewis acid site suitable for coordination and activation of the reagent. The coordinated reagent should be suitably oriented to favour a selective attack to one specific face, thus inducing a good level of enantioselectivity.



53 **54**

Figure 1.7

Bisoxazoline ligands fulfil this requirement. They are C_2-symmetric and commonly consist of two oxazoline rings separated by a carbon bridgehead. However, this is not always the case. It is also possible to achieve good enantioselectivities using ligands consisting of two oxazoline moieties joined together with no spacer called BiOX (**53**) and also those that contain two or more carbon spacers in the bridgehead (**54**) as seen in **Figure 1.7**.

The nitrogen atoms of the oxazoline rings can coordinate to the metal centre forming an organometallic, chiral Lewis acid catalyst (**Figure 1.8**). For catalytic purposes, the ligand to metal ratio is generally 1:1 which means that two metal sites are occupied by the ligand leaving up to four vacant sites for substrate interaction. The metal chelate is conformationally constrained due to the rigid nature of the ligand scaffold and the chiral centres are located close to the coordination site. This produces a strong directing effect on the catalytic site, allowing for a level of control of approaching reactants during the reaction. When

the ligand is coordinated to the metal, there is a C_2-symmetric axis which minimises the number of possible transition states and so the number of variables influencing stereoselectivity is halved. This is due to equivalency in the structure upon rotation by 180°. Monodentate[73] and tridentate[70] BOX ligands have also been studied with the latter proving more useful for asymmetric catalysis.

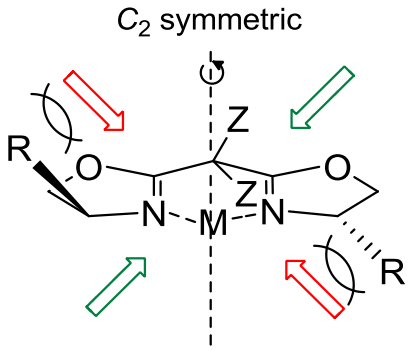


Figure 1.8

1.6.2 Naming bisoxazolines

When naming bisoxazoline ligands, it is important to remember that in ring structures that contain heteroatoms, oxygen will get the highest priority followed by sulphur and then nitrogen. The atom with the highest priority will be labelled 1 with the numbering continuing in the direction that gives the lowest number for the next heteroatom. In **Figure 1.9**, there are two bisoxazoline structures.

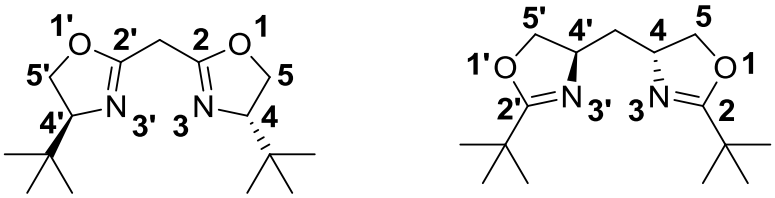


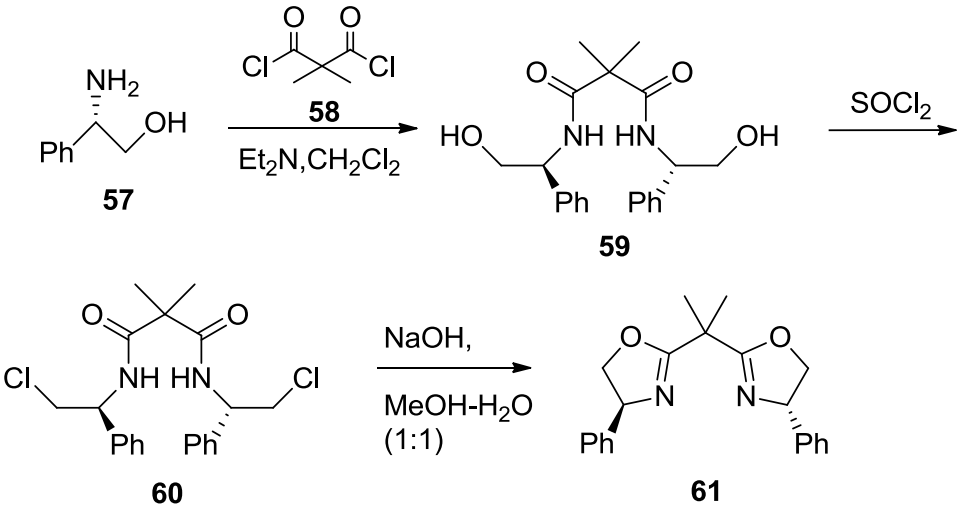
Figure 1.9

Structure **55** is a conventional 2,2'-BOX ligand, so called due to the position of the connection of the ring to the carbon backbone, while **56** is a 4,4'-BOX ligand first

synthesised by O'Leary *et al* and is a regioisomeric class of bisoxazoline where the chiral centres are now at the carbon which connects each oxazoline ring to the bridgehead[74].

1.6.3 Synthesis of bisoxazolines

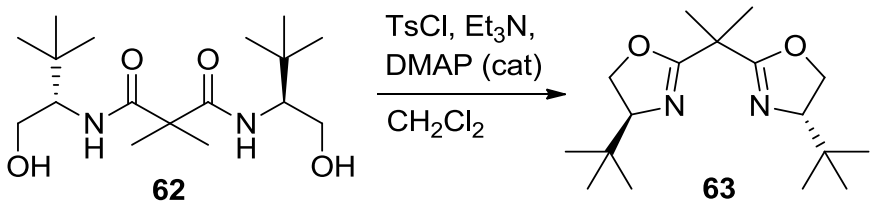
There are many methods available to synthesise chiral C_2-symmetric BOX ligands ranging from modification of preformed BOX ligands, to construction of the oxazoline rings from a symmetrically disubstituted malonic acid derivatives combined with an optically active β-amino alcohols. This latter method was pioneered by Evans and Corey, and has become a widely used and widely modified method of bisoxazoline synthesis.



Scheme 1.9

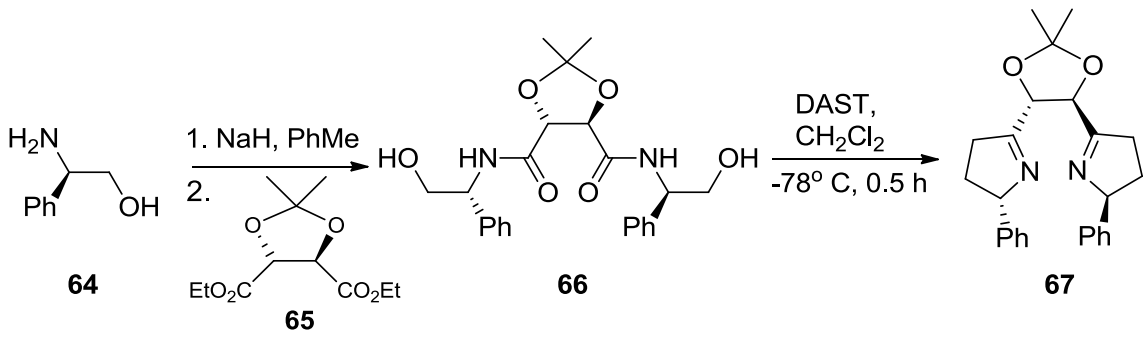
Corey *et al* synthesised **61** from two equivalents of (*S*)-(+)-Phenylglycinol, **57**, (**Scheme 1.9**), which was reacted with one equivalent of dimethylmalonyl chloride, **58** to give bis-β-hydroxylamide, **59**[75]. The alcohol was then reacted to give the chloride leaving group using thionyl chloride, yielding **60**. This was then cyclised under basic conditions to give 2,2'-bis[2-[4(*S*)-phenyl-1,3-oxazolinyl]] propane (**61**) in 78 % yield from **57.** It is also possible to transform the alcohol into other leaving groups like mesylates or tosylates. For example, Evans *et al* investigated several

methods for ring closure[76]. It was found that the most effective method for large scale synthesis involved the synthesis of the bis-tosylate in situ, using toluenesulfonyl chloride, triethylamine and catalytic amounts of DMAP, followed by ring closure under the same conditions (**Scheme 1.10**).



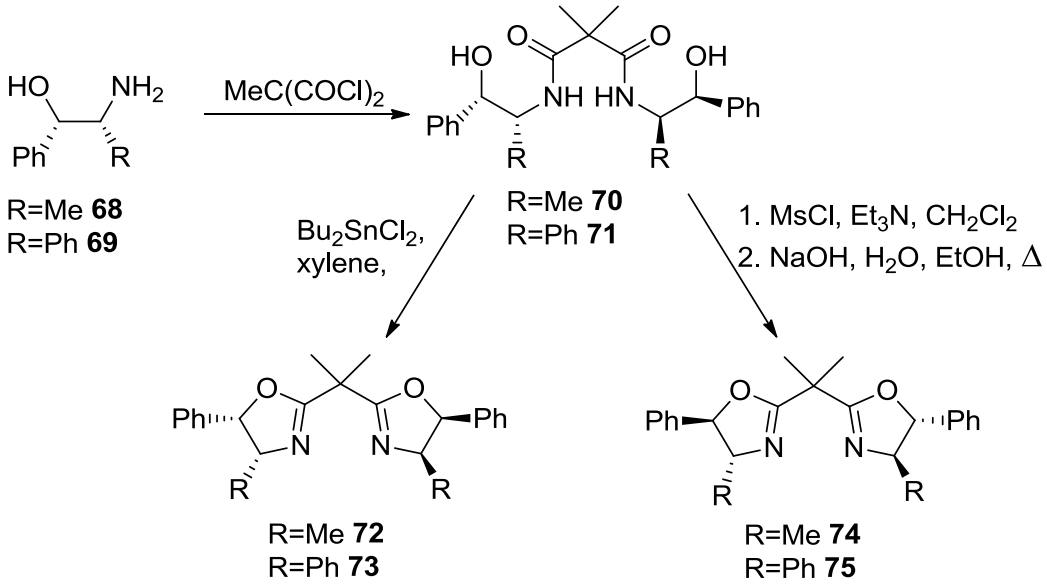
Scheme 1.10

Some methods for bisoxazoline synthesis involve cyclisation of the bis-amide without isolation of an activated intermediate. This can be achieved in a number of ways including the use of Masamune protocol[77]. The route involved reflux of the bis-amide in xylene with dibutyl tin chloride to afford the ring closed BOX ligand. Another method for ring closure, utilised by Evans *et al*, is reaction of triphenylphosphine and triethylamine with the bis-amide in chloroform[78]. The activating agent diethylamino-sulfurtrifluoride (DAST) can also ring close from the bis-amide and was utilised by the Knight research group[79]. They synthesised bis-amido alcohol, **66**, by deprotination of (*R*)-phenylglycinol, **64**, with sodium hydride followed by treatment with isopropylidene diethyl L-tartrate, **65**. The bis-amido alcohol, **66**, was then ring closed using DAST at -78^{o} C for 0.5 h producing the bisoxazoline **67** in 52 % yield (**Scheme 1.11**).



Scheme 1.11

Synthesis of 4,5 disubstituted bisoxazolines is also possible. Desimoni *et al* developed a stereodivergent synthesis, in 1996, which gave access to the commonly accessible *cis* configuration, and also to the rarer *trans* configuration, by reacting two equivalents of an optically active β-amino alcohol with a suitable malonyl dichloride[80] (**Scheme 1.12**).

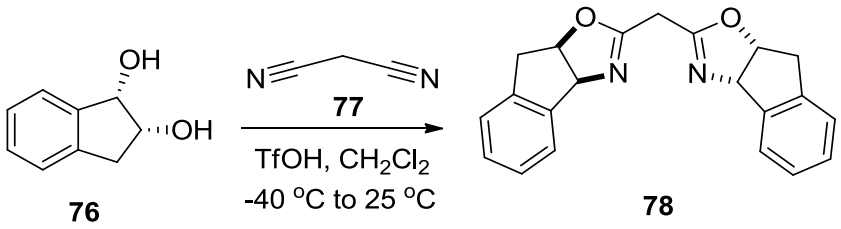


Scheme 1.12

To synthesise the bis-hydroxylamides, (1*S*,2*R*)-norephedrine, **68**, or (1*S*,2*R*)-diphenylaminoethanol, **69** were reacted to with dimethyl malonyl dichloride to yield the corresponding diamide in an 87 % (**70**) and 98 % (**71**) yield. Then by using two different methods to ring close, both the *cis* and the *trans* product were available. By using the Masamune protocol of refluxing in xylene with dibutyl tin dichloride, the *cis* products **72** and **73** could be isolated, or alternatively methanesulfonyl chloride could be used to convert the amides into their bis-mesylate derivatives. Ring closure, with inversion of configuration, could be achieved by heating the bis-mesylate derivatives in aqueous ethanoic NaOH, giving **74** and **75** or the *trans* products. Both the *cis* and *trans* products were synthesised in good yields.

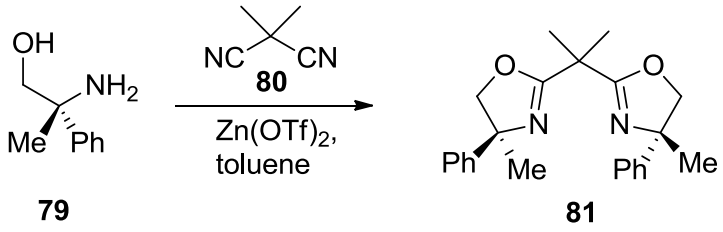
It is also possible to synthesise BOX ligands using disubstituted malononitrile. It can be reacted with two equivalents of an optically active β-amino alcohol or a 1,2-diol.

This method of synthesis retains the configuration of the chiral amino alcohol or diol. During research into the synthesis of the HIV protease inhibitor, Indinavir, Davies *et al* discovered that when trifluoromethanesulfonic acid was reacted with a mixture of malononitrile, **77**, and 1*S*,2*R*-indandiol, **76**, in dichloromethane, bisoxazoline **78** was formed in an 80 % yield (**Scheme 1.13**)[81]. When dimethylmalononitrile was tested in the reaction, the required bisoxazoline product only formed in a 30 % yield.



Scheme 1.13

Cornejo *et al* developed a one pot condensation reaction of chiral β-amino alcohols with a dinitrile using zinc triflate to synthesise the BOX ligand[82]. They succeeded in synthesising a range of mono- and di-substituted bisoxazolines as well as ligands containing a pyridine ring spacer, PyBOX, in high or quantitative yields, with no need for product purification. **Scheme 1.14** shows the previously unreported synthesis of **81.**

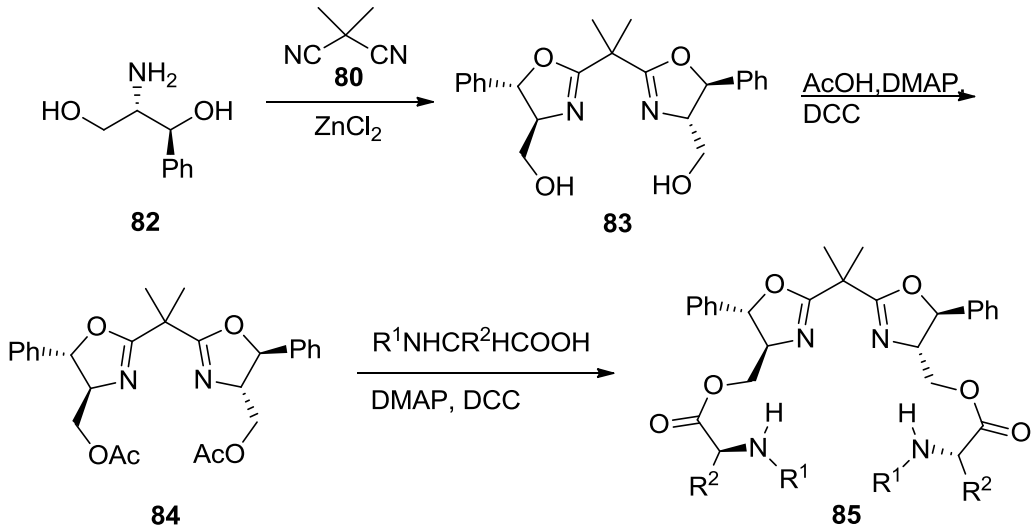


Scheme 1.14

Two equivalents of (*S*)-2-methylphenylglycinol, **79**, were reacted with dimethylmalononitrile, **80**, in the presence of $Zn(OTf)_2$ in toluene. It was necessary to use the zinc catalyst in stoichiometric amounts because, as the bisoxazoline formed, it coordinated to the $Zn(OTf)_2$. Ligand **81** was formed in an 85 % yield. The

mono substituted BOX ligands containing benzyl and indanyl moieties were both synthesised in quantitative yields using this method. When the research group began studying the reaction to make the PyBOX ligand, it was found that 5 mol% of the catalyst was sufficient to produce excellent yields.

Another development in the synthesis of 2,2'-BOX ligands, is the use of heteroatoms in the chiral asymmetric side chains, to add other possible binding sites. This increases the denticity of the ligand, which may improve stereoselectivity in reactions, or these secondary binding sites can also be used to immobilise catalysts on solid supports for recycling purposes. Schinnerl *et al* developed ligand, **85**, (**Scheme 1.15**) for use in a number of different cyclopropanation reactions as they hoped that the secondary binding sites would allow molecules to interact with substrates in reactions by means of secondary interactions[83].

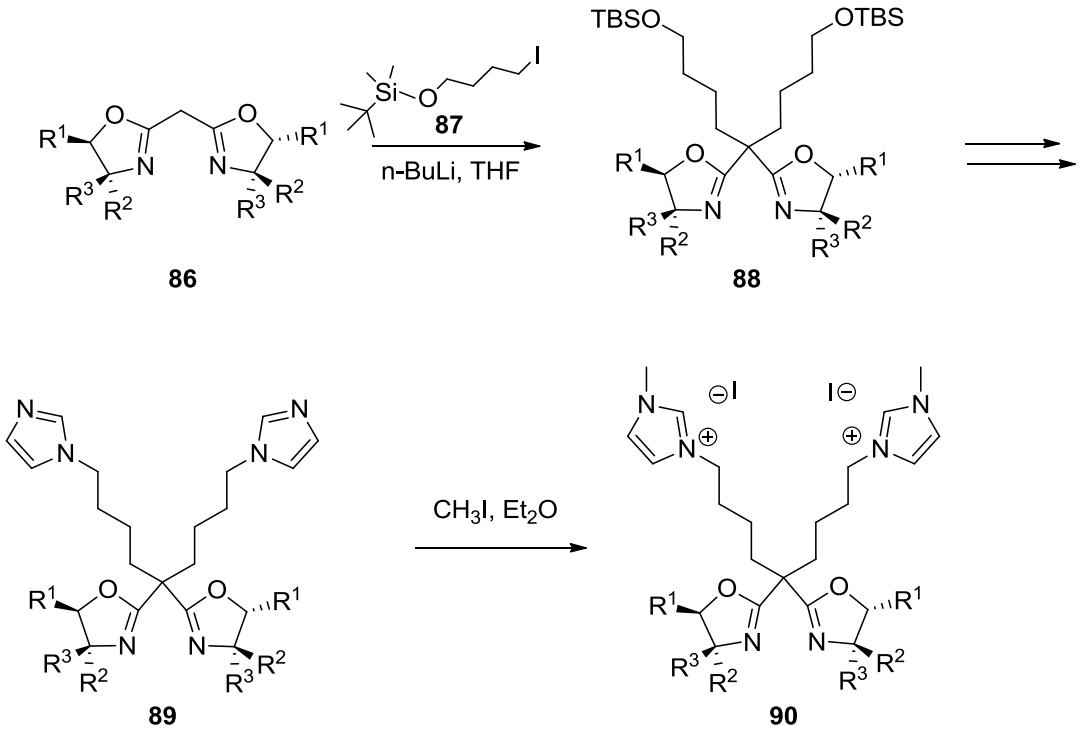


Scheme 1.15

To synthesise the ligand amino alcohol, **82**, was reacted with dimethylmalononitrile, **80**, in the presence of $ZnCl_2$ to give bisoxazoline **83** as seen in **Scheme 1.15**. Further derivatisation of the side chain was carried out by reacting **83** with acetic acid, DMAP and *N,N'*-Dicyclohexylcarbodiimide (DCC) to give the acetylate bisoxazoline, **84**, in the hope that the more extensive side chain would exert better secondary interactions with the substrates involved in the

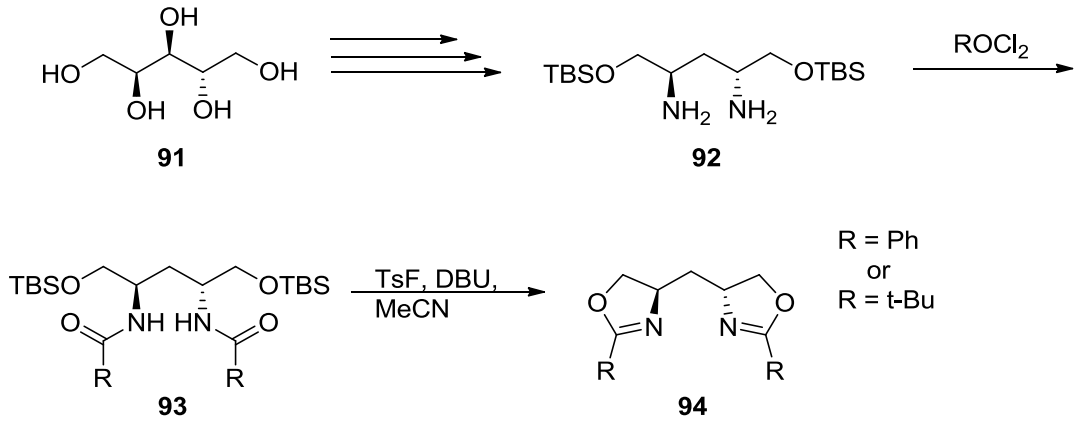
cyclopropanation reactions. Finally, **84** was converted into ligand **85** in good yields (78-98 %).

It is also possible to alter BOX ligands that contain a methylene bridge head as substituents can be added in place of the acidic protons. Deprotonation can be carried out with two equivalents of base followed by nucleophilic substitution with two equivalents of alkyl halide or one equivalent of an alkyl dihalide to generate a ring on the bridgehead. Zhou *et al* were interested in developing ionic liquids for use as recyclable catalysts[84]. As seen in **Scheme 1.16** bisoxazoline **86** was the starting material of choice. It was reacted with 4-iodobutoxy-(*tert*-butyl) dimethylsilane, **87**, and n-butyllithium in THF to afford the desired (*tert*-butyl)dimethylsilane-butyl-substituted bis(oxazoline), **88**. This was then converted into the tosyl-substituted BOX followed by the introduction of the imidazolium tag producing **89**. Finally, reaction with methyl iodide in diethyl ether produced the ionic liquid, **90**.



Scheme 1.16

Synthesis of the novel 4,4'-BOX ligands by the O'Leary research group can be seen in **Scheme 1.17**, and was achieved over a number of steps using Arabitol, **91**, as the starting material[74]. The key intermediate in the synthesis is the C_2-symmetric O-silyl bis-β-amino alcohol, **92.** This TBS protected amino alcohol was then treated with the required acid chloride, in this case either benzoyl or trimethylacetyl chloride, to give the bis-amide, **93**. This was then followed by a one-pot tandem deprotection/activation/ring-closure (DARC) reaction to give the corresponding AraBOX ligand, **94**.



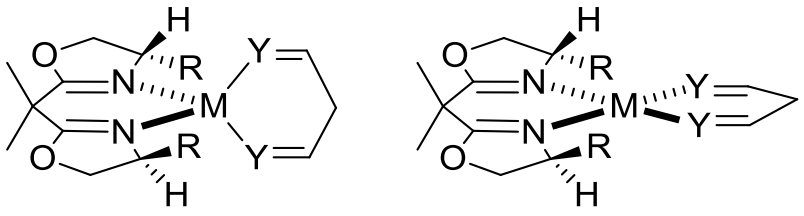
Scheme 1.17

1.6.4 Metal Bisoxazoline Complexes

Chiral bisoxazoline ligand–metal complexes are efficient catalysts in numerous asymmetric reactions. Metals like zinc[85], copper[70], palladium[69], ruthenium[86], rhodium[71] and ytterbium[72] are just some of the transition metals known to form complexes with BOX ligands and its derivatives. When a chiral BOX ligand and a metal salt are mixed together in an organic solvent a metal-bisoxazoline complex is usually formed. These catalysts usually contain a 1:1 ratio of metal to ligand and the metals used to form the complex usually have four to six coordination sites. The ligand coordinates to the metal *via* the donor nitrogen atoms, so a metal-ligand complex involving a BOX ligand with carbon spacers will generally be bidentate leaving two to four coordination sites available to substrates, solvent molecules or counter ions.

X-ray crystallography has been used to study the structure of solid crystalline BOX-metal complexes. These chiral complexes are the precursors of the reacting intermediate involved in the catalytic cycle. Any information concerning their structure is important to try to understand how the molecules involved in the reaction are arranged at the metal centre, as this is the source of the stereoselectivity in the reaction. X-ray crystal structure analysis gives an immediate view of the arrangement of the chiral ligand at the metal centre, the anions and any actor ligands that can be replaced by at least one of the reagents that give rise to the reacting intermediate. It can reveal the structure of the chiral pocket and gives information about the coordination number, so it is a vital tool in the development of reasonable models for the reacting intermediate and also the reaction mechanism.

Although BOX ligands can act as monodentate ligands[87], it is far more common in asymmetric catalysis to see them utilised as bidentate ligands. Tetracoordinated complexes of BOX ligands are common intermediates in asymmetric catalysis reactions. The two principle geometries possible for these tetracoordinated bisoxazoline complexes are tetrahedral, **95**, and square-planar, **96**, as seen in **Figure 1.10**.



95 **96**

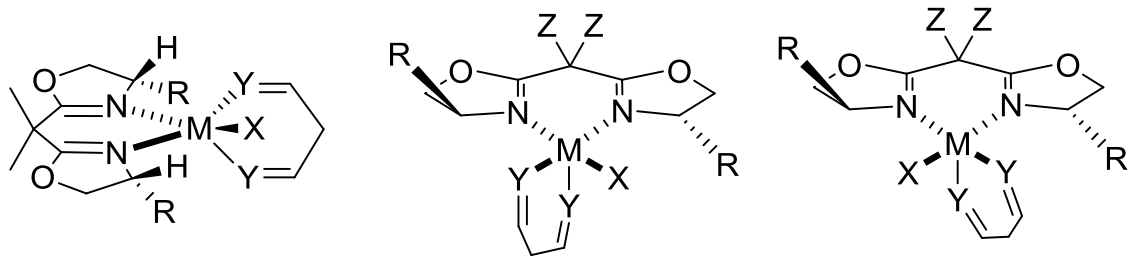
Figure 1.10

Complexes that form either of these two geometries show opposing selectivity because by turning the coordinated substrate by 90°, the accessible face is moved from the shielded into the unshielded area of the ligand. This means that it is

possible to use the same chiral BOX ligand to produce both enantiomers of a product through suitable selection of a metal[87].

It is common for zinc(II), nickel(II) and iron(II) chloride to form tetrahedral complexes, with little distortion, when combined with BOX ligands **63** and **61** while copper(II) halide-BOX complexes have distorted geometries and are moving from tetrahedral towards square planar orientations. With these salts, it cannot always be assumed that increasing steric bulk of the chiral side arms will enhance stereoselectivity. In fact, larger R groups may cause distortion from tetrahedral to square planar geometries. On the other hand copper(II) complexes with hydroxyl, as well as, carbonyl ligands exhibit a marked preference for square planar geometries when coordinated to BOX ligands[87]. From this, it can be seen that it is very important to have an understanding of the complex geometry when selecting bisoxazoline ligands and metal salts to form catalysts in asymmetric transformations.

Pentacoordinated BOX-metal complexes are also possible with trigonal-bipyramidal, **97**, and square pyramidal geometries, **98** and **99** (**Figure 1.11**).

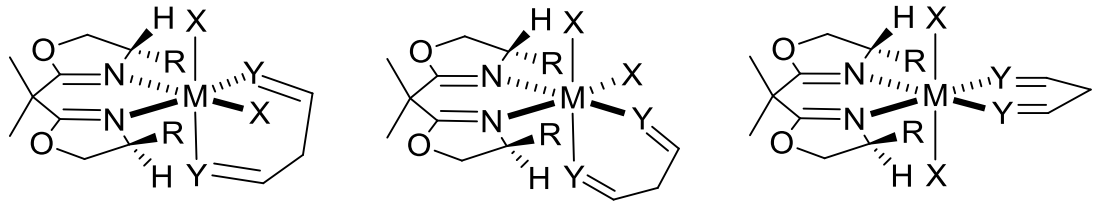


97 **98** **99**

Figure 1.11

It is worth noting that it is possible for solvent ligands to coordinate to a tetrahedral complex creating a trigonal bipyrimidal geometry and this may alter the stereochemical outcome of a given reaction. While there are few known examples of trigonal-bipyramidal complexes with bisoxazoline ligands, square-pyramidal metal complexes play an important role as intermediates in catalysis with pyridine-bisoxazoline ligands.

Hexacoordinated BOX-metal complexes are also possible and employ octahedral geometries as seen in **Figure 1.12**.



100 **111** **112**

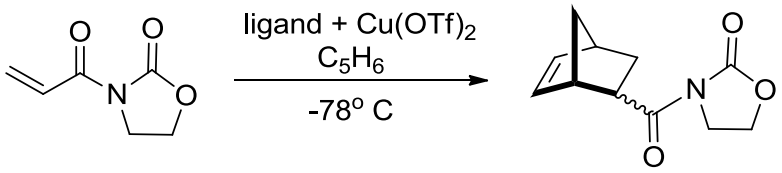
Figure 1.12

Octahedral complexes with bisoxazoline ligands of copper, tungsten and ruthenium have been characterized with only the last two having found applications as catalysts[87].

1.6.5 Example of BOX reaction

Metal-BOX complexes can catalyse numerous organic reactions and their application has been aided by easy access to a large number of BOX ligands and many transition metals sources. Diels-Alder reactions are one of the most broadly investigated reactions and Evans *et al*, for example, reported on the use of chiral BOX-Cu(II) complexes in enantioselective Diels-Alder reactions[88]. This research investigated the reaction of acrylate imide **113**, with cyclopentadiene in the presence of a series of catalysts derived from a selection of BOX ligands and $Cu(OTf)_2$ to give **114** (**Table 1.9**). When the catalyst derived from BOX ligand **60** was used in the reaction for one hour at -78 °C, it produced **114** in 92 % yield and an endo/exo ratio of 95:5. The enantiomeric excess of the endo product was 30 %. Due to the poor *ee* achieved, it was decided to try alkyl groups in place of the phenyl group in the BOX ligand. When the reaction was carried out using *iso*-propyl-BOX, **63**, under the same reaction conditions, **114** was produced in a 93 % yield and an endo/exo ratio of 96:4 while the *ee* of the endo product was 58 %. Finally by changing from *iso*-propyl R groups, **63**, to *tert*-butyl, **115**, the reaction gave an 86 % yield with an endo/exo ratio of 98:2 but the enantiomeric excess of the endo

product was >98 %, albeit the reaction the reaction took 10 hours before it reached completion at -78^{o} C.



113 **114**

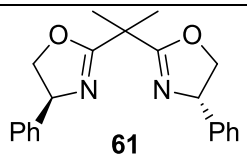
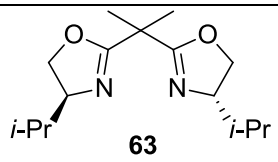
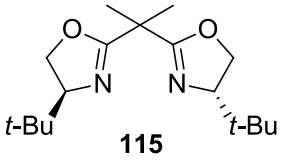
Ligand	Time , h	Endo/Exo	Endo *ee*, %	Yield , %
 **61**	1	95:5	30	92
 **63**	1	96:4	58	93
 **115**	10	98:2	>98	86

Table 1.9

For the above ligand-metal complexes, it was reported that a square planar geometry or slightly distorted square planar geometry was adopted by the catalyst-dieneophile intermediate. The diene, **113**, preferentially approaches from the *re* face. The difference in the enantiomeric excess between the phenyl-BOX and the *tert*-butyl-BOX can be attributed to, the *tert*-butyl substituent being more sterically bulky than the *iso*-propyl substituent or the phenyl group and so produced better *ee*'s.

Other research carried out by Evans *et al* into the reversal of enantioselectivity of *tert*-butyl versus phenyl substituted BOX copper(II) catalysed hetero Diels-Alder and ene reactions implied that in the case of *t*-Bu, the coordination seems to lean more

towards a tetrahedral geometry, while the phenyl complex produced a square planar geometry when solid state structures were investigated[89]. This resulted in the same enantiomer of the two ligands producing the opposite enantiomer of the product in the test reactions. So the reaction in **Table 1.9** could also be effected by these differences in geometry and it could have led to the difference in enantioselectivity between the phenyl-BOX and the *tert*-butyl-BOX as well as a switch in overall configuration of the dominant stereoisomer.

1.7 PyBOX and PheBOX

PyBOX and PheBOX are two other types of bisoxazoline ligands that can be utilised as organometallic catalysts when used in conjunction with metals. The PyBOX ligand contains a pyridine ring spacer between the two oxazoline rings, while the PheBOX contains a phenyl ring spacer. Both the PyBOX and the PheBOX can interact with a metal in a tridentate fashion, with coordination through the three nitrogens in the former[90] and through the two nitrogens of the oxazolines and via a carbon-metal bond with the phenyl ring in the latter[91] (**Figure 1.13**).

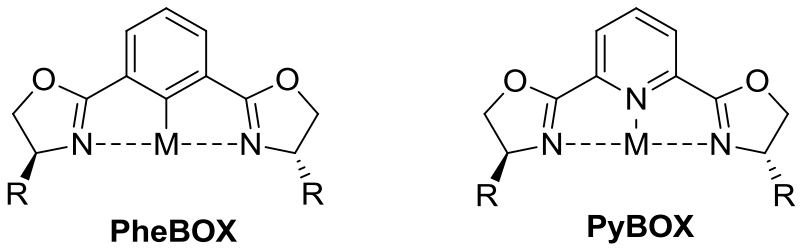
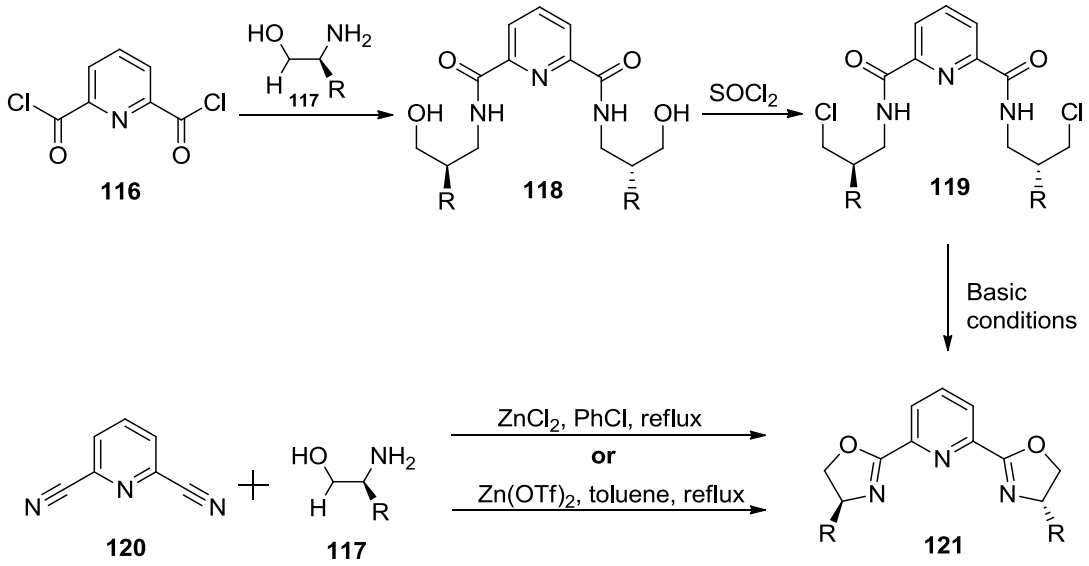


Figure 1.13

1.7.1 PyBOX

Pyridine-2,6-bisoxazolines were first synthesised by Nishiyama in 1989[92] and the development of this type of chiral ligand meant that a choice between a bidentate ligand, a BOX, or a tridentate ligand, a PyBOX was possible, when designing chiral catalysts for asymmetric catalysis. Most synthetic routes to these compounds employ either pyridine-2,6-dicarbonyl dichloride, **116**, or 2,6-dicyanopyridine, **120**,

as starting materials[82, 93-95]. In **Scheme 1.18**, the two most common routes to PyBOX **121** can be seen. The first method, as used by Nishiyama, utilised pyridine-2,6-dicarbonyl dichloride, **116**, and reacted it with chiral amino alcohol, **117**, to produce the bis-hydroxylamide, **118**. This was converted to the bis-chloroamide, **119**, followed by ring closure under basic conditions to give **121**.



Scheme 1.18

The other approach employed 2,6-dicyanopyridine, **120**, which was refluxed with a chiral amino alcohol, **117**, in the presence of zinc chloride[96] or triflate[82] producing **121**. This process is a modification of one of the major methods of BOX synthesis. In many cases the one pot approach gives superior yields when compared to the multi-step synthesis[96].

When PyBOX ligands are mixed with metal salts, ligand-metal complexes form, as they do with BOX ligands. Complexes with a 1:1 or 1:2 metal to ligand ratio can form, with the ligand being bidentate or tridentate depending on the metal salt used. Salts of rhenium, platinum, molybdenum and tungsten involving a bidentate PyBOX ligand, where the nitrogen of the pyridine and one other nitrogen is coordinated, have been investigated[97-98]. However, the most common mode of coordination is via a tridentate PyBOX ligand, where all three nitrogens coordinate to the metal[92, 99-101]. As with the BOX ligands, complexes formed between the

metal and PYBOX ligand have three coordination sites that can be occupied by substrates, solvent molecules or counter ions.

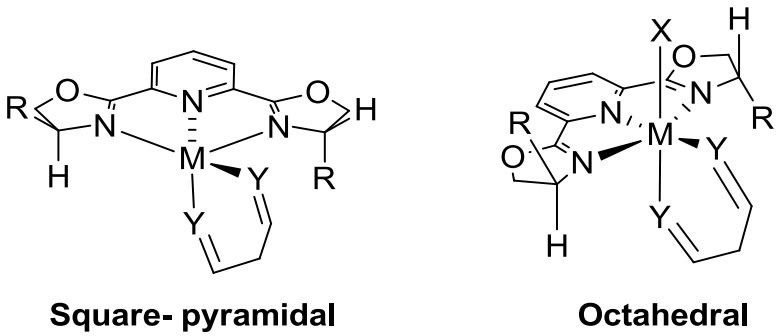


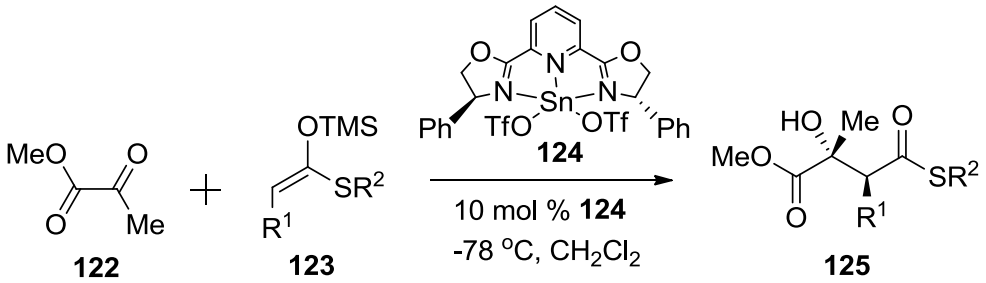
Figure 1.14

There are two major types of coordination geometries possible for PyBOX complexes, square-pyramidal and octahedral as shown in **Figure 1.14**. Pentacoordinated complexes have a square-pyramidal geometry while hexacoordinated complexes have octahedral geometry. In both cases, the most active substrate site is equatorial. The axial site is less active as it is shielded by the chiral substituent of the PYBOX ligand. Bidentate ligands also assume an octahedral geometry with only two nitrogens (one from the pyridine ring and one from one oxazoline ring) coordinated to the metal, leaving space for four substrates, solvent molecules or counter ions rather than three when the PyBOX acts as a tridentate ligand.

Pyridine-2,6-bisoxazolines can be combined with metal salts, in the same manner as BOX ligands, to form catalytically active complexes that can be used in a wide number of organic reactions including aldol addition reactions[102], asymmetric hydrosilylation of ketones[103], enantioselective addition of TMSCN to aldehydes[71], cyclopropanation reactions[104], aziridination reactions[105], epoxide ring opening reactions[72] and propargylic substitutions[70].

Evans *et al* carried out extensive research examining BOX and PyBOX ligands for use in organic synthesis. In the aldol reaction shown in **Table 1.10**, the research group studied the reaction of a number of different silylketene acetals, with methyl

pyruvate, **122,** in the presence of 10 mol% of {Sn[(*S,S*)-Ph-PyBOX]}$(OTf)_2$, **124**[106]. Results from the experiment showed that at -78 °C yields between 76-94 % of *R*-**125** were obtained while enantiomeric excesses were between 96-99 %.



R^2	R^1	% *ee*	% yield
^{t}Bu	Me	99	94
^{t}Bu	Et	97	84
^{t}Bu	^{i}Bu	99	81
Et	Et	97	94
Et	^{i}Bu	97	76

Table 1.10

Further investigation into the reaction revealed that the catalyst-pyruvate intermediate had an octahedral geometry, while approach of the silylketene acetals was preferentially from the *re* face of the ester carbonyl, as the *si* face is blocked by the phenyl group, leading to a high degree of enantiocontrol (**Figure 1.15**).

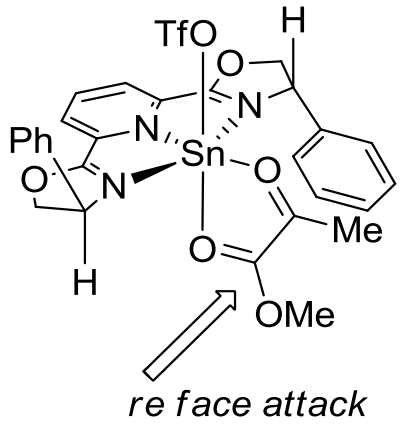
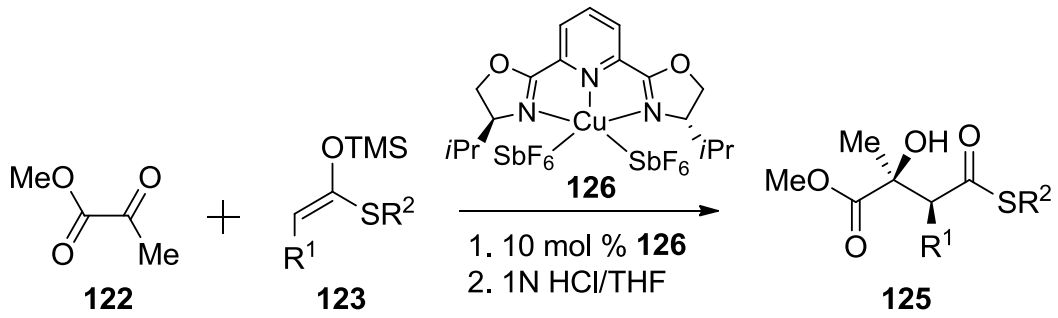


Figure 1.15

Research carried out by the same group investigated using [Cu(*S,S*)-*i*-propyl-PyBOX)]$(SbF_6)_2$, **126**, as the catalyst in the reaction outlined in **Table 1.11**[107]. In this case, yields reported were 87 % and 92 % of product *S*-**125** and *ee*'s were between 74-95 %.



R^1	R^2	% *ee*	% yield
^{t}Bu	H	95	92
Et	H	82	87
Et	Me	74	No Data

Table 1.11

Interestingly in this case, the catalyst-pyruvate intermediate had a square-pyramidal geometry with approach of the silylketene acetals from the *si* face of the ester carbonyl, as the *re* face is blocked by the *iso*-propyl group, as seen in **Figure 1.16**. This produces the opposite enantiomer to the reaction shown in **Figure 1.15**.

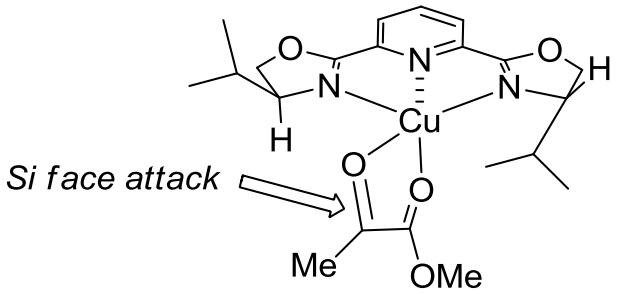
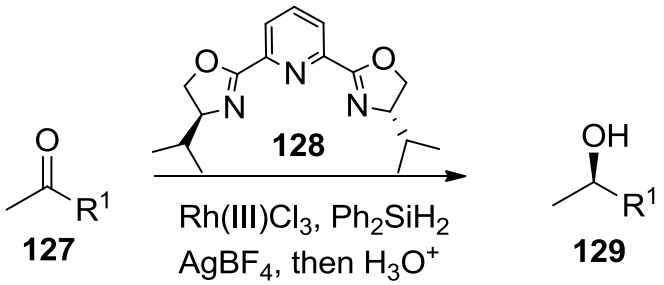


Figure 1.16

Another common asymmetric reaction involving PyBOX ligands is the hydrosilylation of ketones. Nishiyama and co-workers investigated the reaction of a

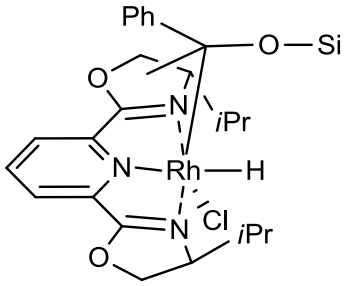
number of ketones shown in **Table 1.12**[108] using the rhodium complex of a PYBOX ligand.



R^2	Temp °C	Time, h	% yield	% *ee*
Ph	0	2	91	94
B-naphtyl	-5	6	93	93
$(CH_2)_2COOEt$	0	7	91	95

Table 1.12

The hydrosilylation of the ketones listed above was catalysed using (*S,S*)-*i*-Pr-PyBOX (**128**)-rhodium(III)chloride complex and gave *S*-**129** in yields between 91-93 % with enantiomeric excesses between 93-95 %.



re face attack

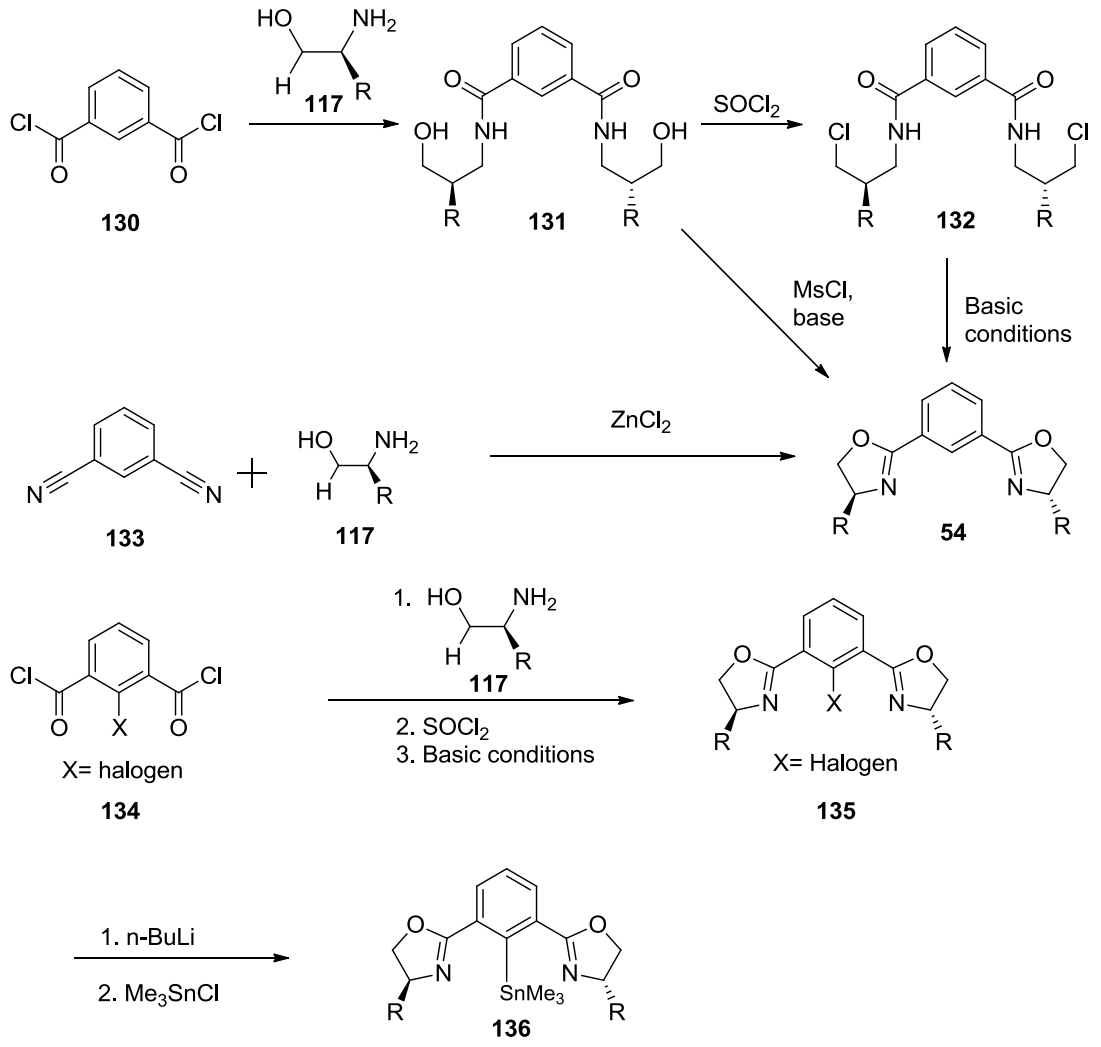
Figure 1.17

Research showed that the catalyst-diphenylsilane intermediate had an octahedral geometry and approach of the ketone derivative from the *re* face lead to the formation of the *S* product with a high level of enantioselectivity (**Figure 1.17**)[92].

1.7.2 PheBOX

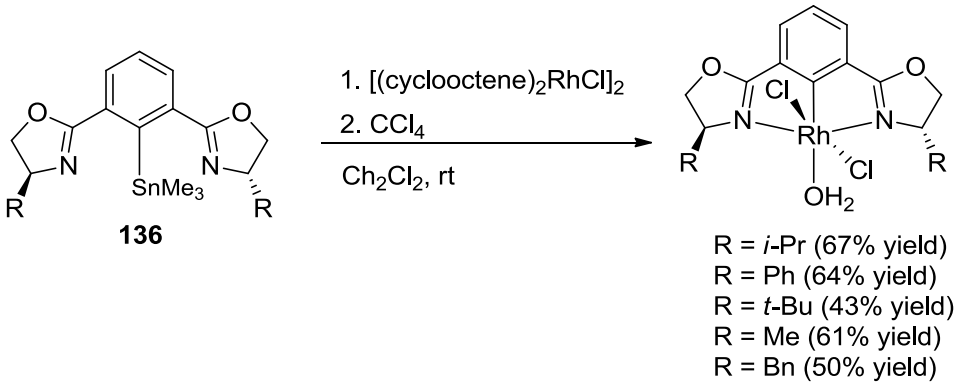
1,3-bis(oxazolinyl)benzene is a tridentate pincer type ligand. It is related to the PyBOX ligand but had an N,C,N coordination pattern which has a central covalent carbon-metal bond while the metal also coordinates to the two oxazoline nitrogens. PheBOX was also developed by Nishiyama and co-workers as they found that there was some dissociation of the PyBOX ligand from the metal during some reactions, meaning that extra ligand was required. It was hoped that the strength of the central sigma bond would stop this occurring.

The synthesis of PheBOX ligands can be achieved from a number of starting materials including isophthalic acid[109], 2-haloisophthalic acid[110], and 1,3 dicyanobenzene[111]. The isophthalic acid can be converted to the corresponding acid chloride **130** and then reacted with a chiral amino alcohol **117** to give bis-amidoalcohol **131** (**Scheme 1.19**)[109, 112-113]. This can then undergo one of two reactions. Amidoalcohol **131** can be reacted with thionyl chloride to form the bis-amido chloride **132** which under basic conditions is converted into PheBOX **54**[113]. Amidoalcohol **131** could also be ring closed using methanesulfonyl chloride in the presence of a base to produce the same PheBOX[112]. Another method used to synthesise PheBOX ligands utilized 1,3 dicyanobenzene, **133**, as a starting material (**Scheme 1.19**)[111]. Reaction of **133** with chiral amino acid, **117**, using zinc dichloride as a catalyst also produces PheBOX **54**. It is also possible to synthesise PheBOX-Br in the same manner as PheBOX **54** (**Scheme1.19**)[110]. Starting material **134** was reacted with a chiral amino alcohol followed by thionyl chloride after which, ring closure was achieved using basic conditions, producing PheBOX-Br **135**. It is also possible to produce the stannyl derivative **136** by lithiation of the bromide of **135** using n-butyl lithium followed by reaction with trimethyltin chloride to give **136**[114].



Scheme 1.19

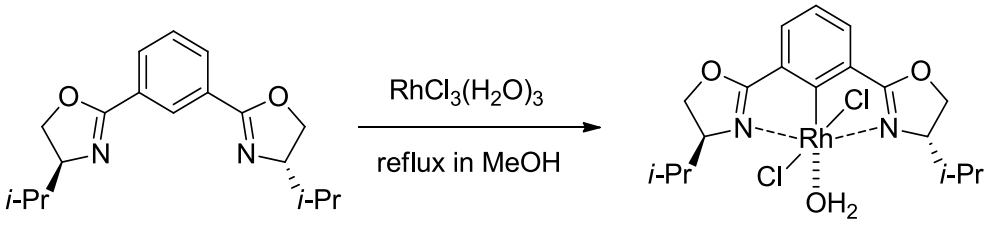
Making PheBOX-metal complexes is slightly different when compared to complexes involving PyBOX or BOX ligands, due to the demand for a carbon-metal covalent bond. For the synthesis of rhodium-PheBOX complexes the most common methods used are transmetalation[114] and cyclometalation[115]. Transmetalation of stannyl derivatives using $[(cyclooctene)_2\text{-}RhCl)_2$ in dichloromethane followed by carbon tetrachloride was carried out by Nishiyama *et al*, who optimised the reaction and produced good yields for a range of PheBOX ligands (**Scheme 1.20**)[114]. When all the above metal-PheBOX complexes were subjected to X-ray analysis results showed a distorted-octahedral geometry.



136

Scheme 1.20

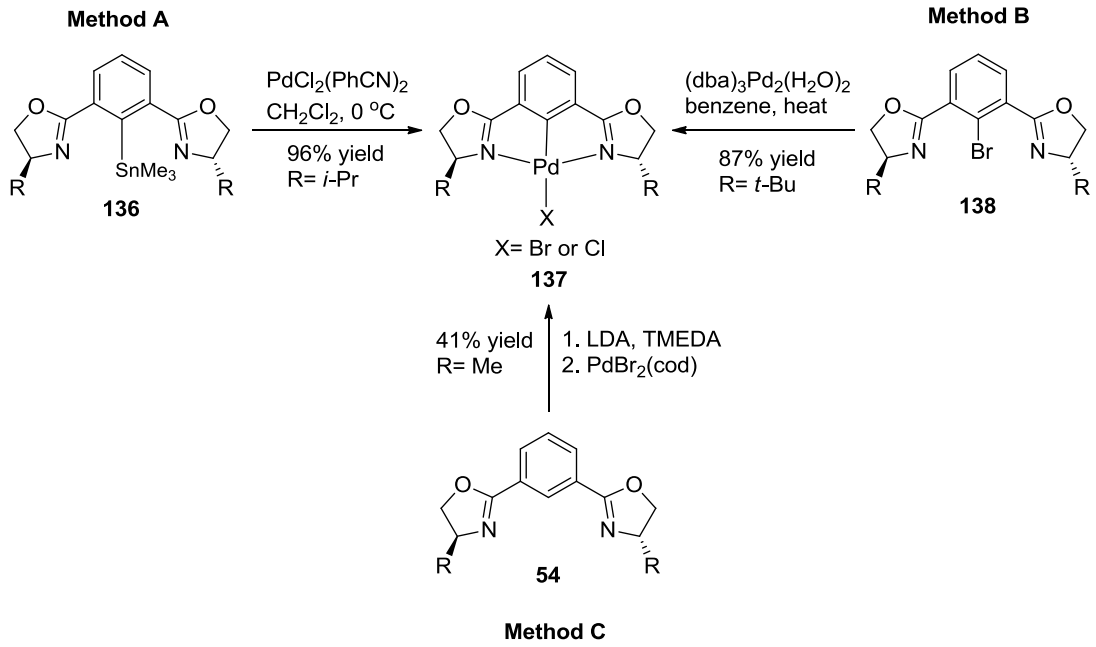
It is also reported that it is possible to create a carbon-metal bond in PheBOX **137** by refluxing the ligand with rhodium chloride in methanol to give complex **138** in 56 % yield (**Scheme 1.21**)[113].



137 **138**

Scheme 1.21

Palladium-PheBOX complexes can also be generated using transmetalation of stannyl derivatives[116]. Research by Nishiyama *et al* showed that reaction of **136** with $PdCl_2(PhCN)_2$ in dichloromethane at 0 °C produced the *iso*-propyl complex **137** in 96 % yield (Method A, **Scheme 1.22**). In Method B, Denmark reported the first synthesis of PheBOX-Pd bromide complexes by oxidative addition[110]. PheBOX **138** was reacted with $(dba)_3Pd_2(H_2O)_2$ in benzene and heated. The *t*-Bu complex was produced in an 87 % yield. Finally Stark and co-workers succeeded in synthesising the methyl complex in 41 % yield by *ortho*-lithiation of PheBOX **54** using LDA and TMEDA followed by transmetalation using $PdBr_2(cod)$[117] (Method C **Scheme 1.22**).



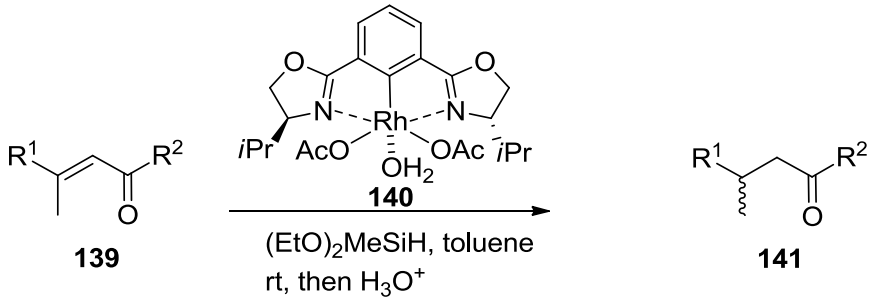
Scheme 1.22

For metals like platinum[118], nickel[119] and titanium[120], transmetalation can be used to produce the metal-PheBOX complexes. Oxidative addition can also be utilised when using nickel[121], iron[122] or platinum[123] salts to make complexes while cyclometalation is also possible when salts of platinum[124] and ruthenium[125] are used to make the complex.

PheBOX can be reacted with a number of different metal salts and the resulting complexes used to catalyse reactions like asymmetric allylations[114], hetero-Diels-Alder reactions[126], Michael additions[127], hydrosilylation of alkenes and conjugate reductions[112]. Research carried out by Nishiyama *et al* into the asymmetric conjugate reduction of α,β-unsaturated ketones and esters used chiral rhodium(2,6-bisoxazolinylpenyl) catalysts, achieved high yields and enantiomeric excesses[112]. The Rh-PheBOX complexes were synthesised by heating $RhCl_3(H_2O)_3$, the required PheBOX and $NaHCO_3$ in methanol and water giving a moderate yield of 50 % of the required complex. Reaction of this complex with silver acetate then produced the corresponding acetate complexes.

The research group then examined the reduction of α,β-unsaturated ketones, **139**, using Rh-(*S,S*)-PheBOX-(*i*Pr), **140**, as a catalyst (**Table 1.13**). When PheBOX-Ph or

PheBOX-Bn were used to make the catalyst complex, it resulted in lower enantioselectivities[112]. The selection of a hydrosilane as a hydride donor was crucial to achieving 1,4 reduction rather than 1,2 reduction. Examination of the reaction using a number of different hydrosilane candidates found that diethoxymethylsilane gave the best results and after hydrolysis, **141** was produced. In **Table 1.13**, it can be seen that increasing the size of the ketone substituent from ethyl to *iso*-propyl to phenyl caused a decrease in enantioselectivity from 95 % to 82 % *ee* (entries 2-4).



Entry no	R^1	R^2	E/Z	Product *R/S*	Yield (%)	*Ee* (%)
1	Ph	Me	E	R	96	91
2	Ph	Et	E	R	98	95
3	Ph	*i*Pr	E	R	97	92
4	Ph	Ph	E	R	99	82
5	(CH_2)Ph	Me	E	S	97	95
6	Ph	Me	Z	S	90	51
7	(CH_2)Ph	Me	Z	R	96	91

Table 1.13

When entry 1, the (*E*)-isomer, and entry 6, the (*Z*)- isomer, are compared it can be seen that the *trans* isomer gave a better yield and *ee* of the *R*-product (96 %, 91 %) while the *cis* isomer gave a yield of 90 % with a poorer *ee* of 51 % of the *S*-product. The same reversal of absolute configuration was present in the reactions of the *trans* isomer, entry 5, and the *cis* isomer, entry 7. Nishyama *et al* then presented a proposed mechanism for the reactions shown in **Table 1.13**. It was proposed that the starting Rh(III) complex was reduced to Rh(I) species by excess hydrosilane

present in the reaction. It is then thought that the hydrosilane reacts with the Rh(I) species which gives a Rh(III) species with a hydrogen and silicon ligand.

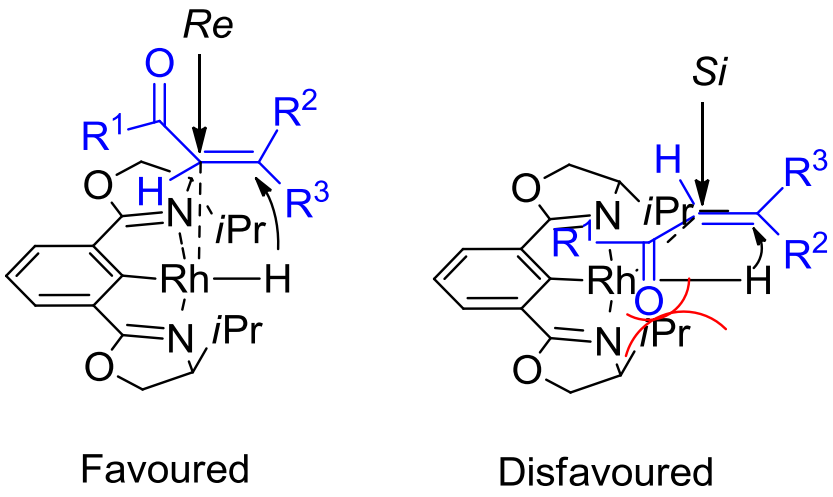


Figure 1.18

In **Figure 1.18**, the hydrogen attached to the rhodium can be seen but the silicon has been left out for clarity. Next, the α,β-unsaturated ketone approaches the Rh-H, which is the active species and *si* coordination of the Rh to the α-carbon of the alkene (closest to the carbonyl). The hydride then attacks the β-carbon and gives the product with an *R* absolute configuration. The absolute *S* configuration seen when (*Z*)-alkenes were investigated can also be explain *via* the favoured mechanism. *Re*-face coordination is disfavoured because of the steric repulsion between the carbonyl of the α,β-unsaturated ketone and the *iso*-propyl group on the PheBOX ligand.

1.8 Immobilisation of homogeneous catalysts

Asymmetric catalysis is a very important tool in organic synthesis. However, very often, the chiral catalyst employed is expensive as the synthesis of the ligands used can involve multi-step procedures utilising chiral building blocks to introduce chirality. For this reason, recovery and recycling of these catalysts could make these

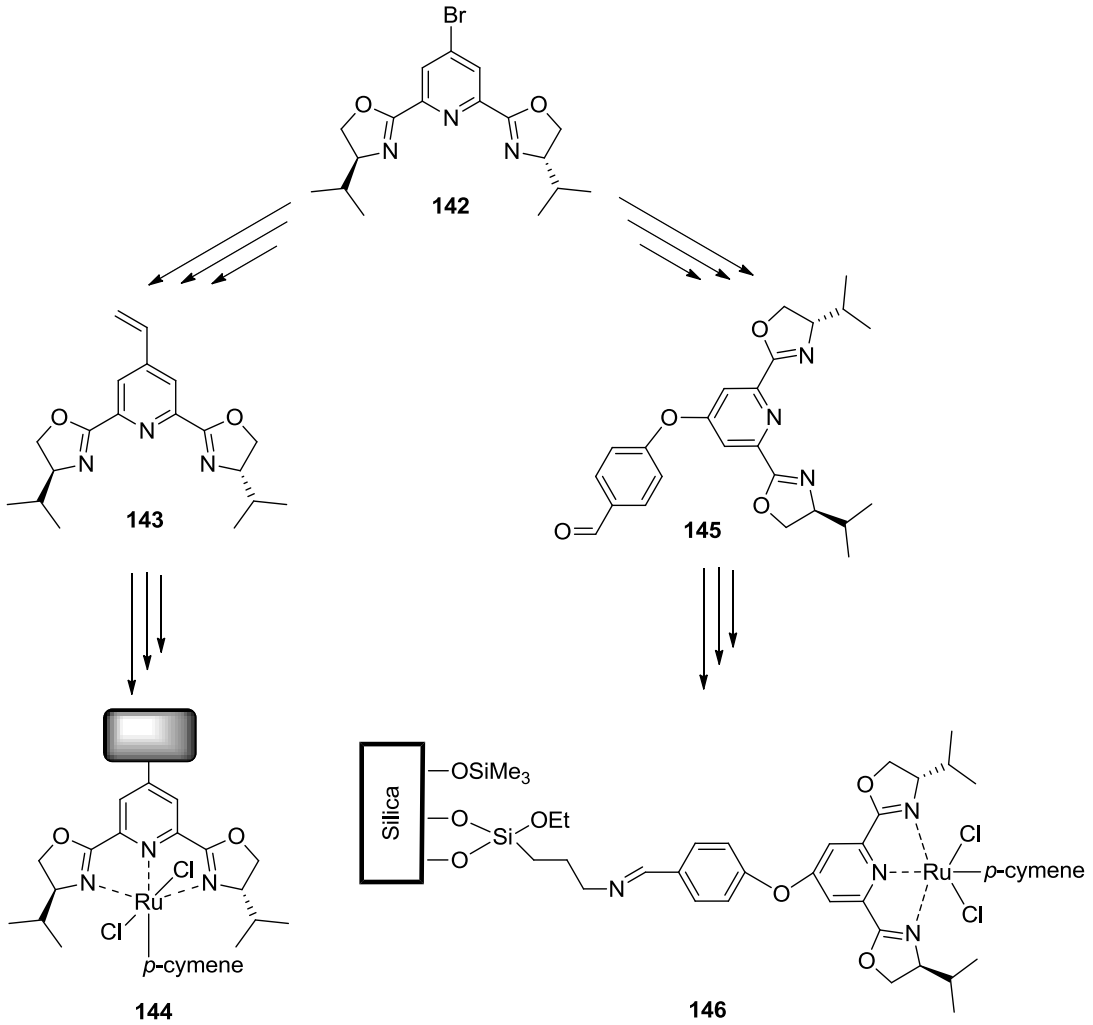
asymmetric reactions a more viable option on large scales where the expense of the catalyst becomes important.

One method that can be used to improve the recyclability of a chiral catalyst is to immobilise the homogeneous catalyst on a non-soluble support. This creates a chiral heterogeneous catalyst that will remain in a different phase to the reactants and products, allowing for easy separation at the end of the reaction[128]. It also permits efficient recovery of the catalyst and would, theoretically, allow for the adaptation of immobilised catalysts for use in continuous flow type processes, provided the catalyst has not become deactivated during the course of the reaction. Four distinct methodologies have been developed for the creation of heterogeneous catalysts and they are encapsulation[129], covalent tethering[130], adsorption[131] and electrostatic interactions[132].

Encapsulation involves assembling the catalyst within the pores of the support or assembling the support around the catalyst. It is the only immobilisation process that does not involve any interaction between the catalyst and the support. To allow for encapsulation, the catalyst must be larger than the pores of the support material, as this will prevent leaching of the catalyst into solution during reactions. There are some limitations to this kind of immobilisation. For example, the solid support must be stable under reaction conditions if the catalyst is built within the pores of the support. Also, synthesis of the catalyst should involve no side reactions and multistep synthesis should be high yielding all the way through. Sabater and co-workers encapsulated chiral salen manganese complex within zeolite Y and used it as a heterogeneous catalyst in the asymmetric epoxidation of alkenes and achieved results in line with a similar homogeneous catalyst [129].

Adsorption of catalysts involves the adhesion of atoms, ions or molecules onto a support. The support involved can vary from a metal surface[133] to a silica surface[131] to porous glass beads[134]. Catalysts immobilised in this manner usually only rely on weak attractions between the catalyst and the support, such as Van der Waals interactions. This can cause the catalyst to leach from the support. It may be possible to improve the stability of the catalyst by modifying the catalyst to allow

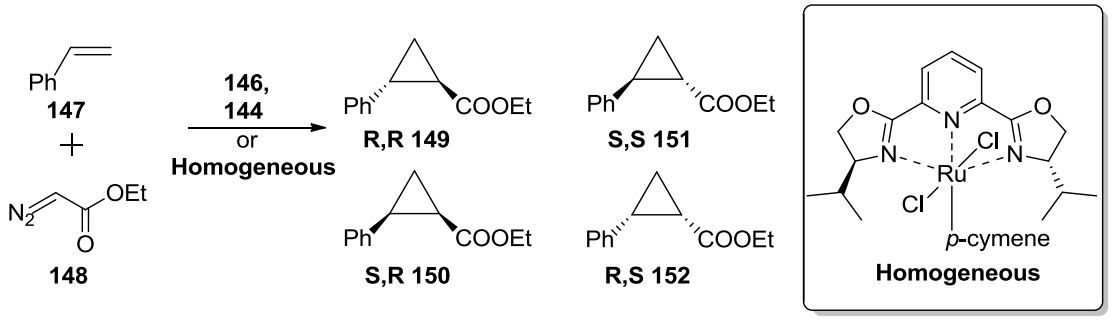
hydrogen bonding to occur. Research carried out by Bianchini *et al* involved the immobilisation of chiral rhodium phosphine catalysts on silica[135]. To improve on methods previously utilized to immobilise Rh-phosphine complexes, the research involved modification of the phosphine ligand to incorporate sulfonic acid groups that could hydrogen bond to the silica via the silanols present on the surface. Investigation of the activity of the free and anchored catalyst in asymmetric hydrogenation of olefins showed that yields and enantiomeric excesses were similar in both homogeneous and heterogeneous reactions.



Scheme 1.23

Covalent tethering involves using covalent molecular attachments to hold the catalyst and the support together. It is the most favoured method to create stable heterogeneous catalysts. Many different techniques exist to achieve covalent

tethering. Cornejo *et al* reported the immobilisation of ruthenium-PYBOX catalyst by grafting onto silica gel[130]. Copolymerisation of the catalyst with styrene and divinylbenzene was also investigated. **Scheme 1.23** shows the immobilised PyBOX ligands. The PyBOX derivative, **143**, was synthesised from 4-bromoPyBOX, **142**, and was copolymerised with styrene and divinylbenzene, using porogen and AIBN, producing monolithic resins. Three different polymers were produced by varying the degree of cross-linking and the porogen, all of which incorporated the PyBOX ligand into the polymer in a high yield. The immobilised ligand was then treated with dichloro(*p*-cymene) ruthenium to give the active catalyst. The research group also used another PyBOX derivative, **145**, and immobilised it on silica gel (**146, Scheme 1.23**). This required six extra synthetic steps from the initial PyBOX ligand, **142**, which was modified at the 4-position of the pyridine ring in 2 steps to insert a benzyl spacer. Preparation of the silica gel, using sequential treatments of hexamethyldisilazane and 3-aminopropyltriethoxysilane, allowed for the modified PyBOX ligand, **145**, to be grafted onto the prepared silica by heating in toluene. The silica gel grafted PYBOX ligand was complexed with dichloro(*p*-cymene) ruthenium to give the immobilised catalyst **146**.



	% Yield	*Trans:Cis*	% *ee* (*trans*)	% *ee* (*cis*)
Homogeneous	34	90:10	88	70
144	31	85:15	85	41
146	15	82:18	64	34

Table 1.14

The asymmetric cyclopropanation of styrene, **147**, with ethyl diazoacetate, **148**, was used to test the reactivity of the immobilised catalysts as seen in **Table 1.14**. As can be seen the homogeneous catalyst gave the best results with the polymerised PYBOX complex, **144**, showing similar results in the *trans:cis* selectivity and *trans* enantioselectivity. The PyBOX complex, **146**, immobilised on silica showed poorer selectivity and the enantioselectivities were also lower when compared to the homogeneous reaction.

Immobilisation using covalent tethers has some disadvantages. Firstly, it is often necessary to modify ligands in order to introduce the tether required to immobilise the catalyst. This usually requires extra synthetic steps when compared to the homogeneous catalyst as seen above. Another major disadvantage of this technique is a potential reduction in activity or selectivity in the heterogeneous system. This can be frequently attributed to the modifications made to the homogeneous catalyst in order to immobilise the catalyst on the solid support.

In order to combat the possible reduction in activity and selectivity, another more attractive immobilisation technique was developed. Electrostatic interactions do not need a covalent tether to hold the catalyst and the support together, so hopefully will allow for more correlation between the homogeneous and heterogeneous system. Another advantage is less synthetic steps to the immobilised catalyst when compared to the use of tethers as seen above in **Scheme 1.23**[130]. Complexes of Cu(II)BOX[136] and Cu(I) and Cu(II)PyBOX[132] ligands have been electrostatically immobilised on silica through the use of a triflate counterion. McDonagh *et al* reported on the electrostatic immobilisation of copper(I) and copper(II) PyBOX trifluoromethane sulfonates on silica[132] for use in the synthesis of propargylamines. To generate the immobilised catalyst, the PhPyBOX was stirred with Cu(I)OTf in dichloromethane. This solution was then added to dried silica and stirred until the colour of the complex disappeared from the solution and the silica became coloured. A graphical representation is shown in **Figure 1.19**. The ease of synthesis of the immobilised catalysed is one of the main benefits of this technique.

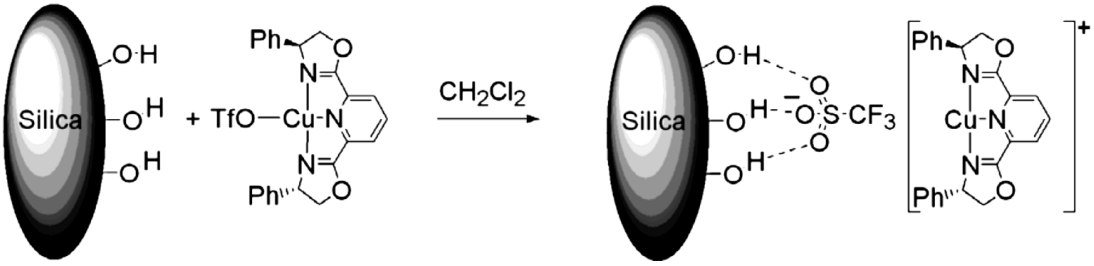
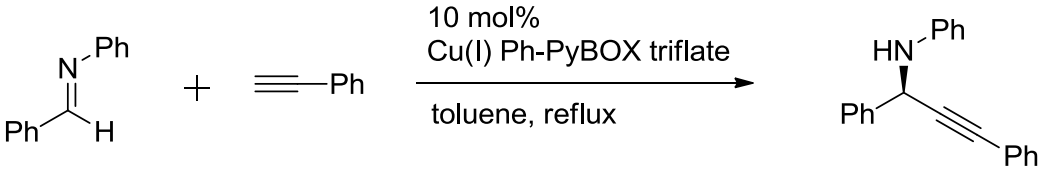


Figure 1.19

The electrostatically immobilised catalyst was then tested in the reaction shown in **Table 1.15**. Imine **153** was firstly synthesised by reacting benzaldehyde with aniline for 2h at 60 °C. This was then added to phenylacetylene, **154**, the immobilised catalyst and toluene and heated to reflux. Upon reaction completion, the crude reaction mixture was decanted from the solid catalyst, which allowed the recyclability of the catalyst to be investigated. From **Table 1.15**, it can be seen that the first heterogeneous reaction produced **155** and gave very similar conversion and enantiomeric excess values, 97 % conversion, 47.5 % *ee* when compared to 100 % conversion and 51 % *ee* of the homogeneous reaction. When the immobilised catalyst was used the second time conversion and *ee* values were similar to the first heterogeneous reaction. On the third use, the values fell only slightly. A relatively small amount of leaching of the complex was detected accounting for the changing activity.



153 **154** **155**

Catalyst type	Cycle	Conversion (%)	*Ee* (%)
Homo	N/A	100	51
Hetero	1	97	47.5
Hetero	2	98	44.5
Hetero	3	91	33.5

Table 1.15

Electrostatic immobilisation is not limited to using silica as a support. Clays[137], zeolites[138] and alumina[139] are just a number of solids that can be utilized.

1.9 Asymmetric reactions using PyBOX ligands

PyBOX ligands are very versatile ligands and can used, in conjunction with metals salts, in numerous asymmetric reactions.

1.9.1 Propargylic substitution

The propargylic functional group is very useful in organic synthesis, as the electron-rich triple bond along with the relatively acidic hydrogen of the terminal alkene means that it is commonly used in chemical transformations e.g. click chemistry[140] or the Sonogashira reaction[141]. During the course of research carried out by van Maarseveen *et al* in the total synthesis of (+)-Anisomycin and (-)-Cytoxazone, studies were carried out on the enantioselective copper-catalysed propargylic substitution[70]. A variety of different propargylic esters were converted into their amine counterparts using amine nucleophiles and copper-PyBOX catalysts with, in some cases, good to excellent *ee*'s. The research group were then able to use these propargylic amines as building blocks in the synthesis of (+)-Anisomycin and (-)-Cytoxazone.

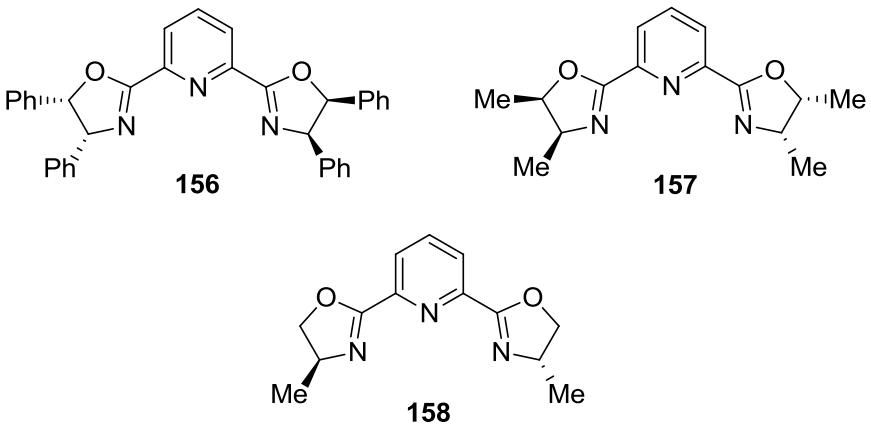
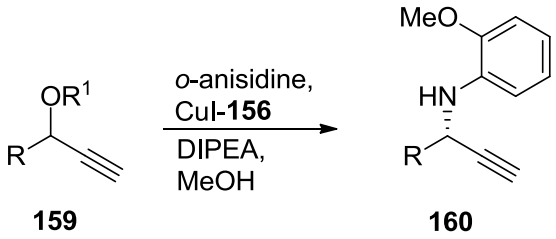


Figure 1.20

The researchers began the investigation by screening PyBOX ligands for use in the reaction. The ligands shown in **Figure 1.20** produced the best enantiomeric excesses in a number of test reactions.



159 **160**

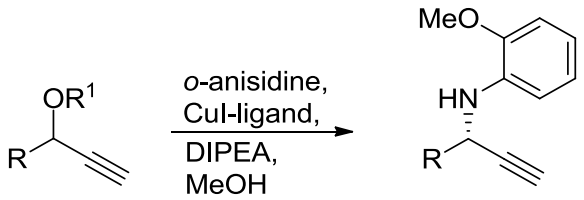
R	R^1	*Ee* (%)
Aromatic side chain	Ac	Up to 88 %
n-pentyl	Ac	13 %

Table 1.16

It was discovered that diPh-PyBOX, **156**, was the optimal ligand for use in reactions where the propargylic substrate contained an aromatic side chain. Unfortunately when the propargylic substrate contained an *n*-pentyl group, the *ee* using **156** was only 13 % (**Table 1.16**). After examination of a number of other ligands, it was ascertained that diMe-PyBOX, **157** and Me-PyBOX, **158**, gave *ee*'s of 64 % and 66 % respectively, in the reaction, when an alkyl group was present in the propargylic substrate.

The next investigation looked at the scope of the reaction using substrates with more hindered side chains. As seen in **Table 1.17**, a number of different substrates were used, both aromatic and aliphatic. When acetate ester **161** was reacted using ligand **158** in the catalyst, a yield of 84 % was achieved with an enantiomeric excess of 67 %. Yields of 60-96 % and *ee*'s 67-89 % were achieved when the acetate ester was used as starting material and either ligand **157** or **158,** with the later proving to be the most useful. In some cases, the benzoate or pivalate esters were investigated (**163** and **166** respectively). These more sterically demanding esters produced increased yields without any loss of enantioselectivity. Ligands **158** and **157** in combination with CuI can also be used for the amination of certain

quaternary propargylic acetates which is of considerable use as there are only a few methods known to synthesis these α,α-dibranched propargylic amines.



159 **160**

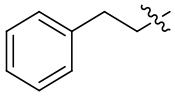
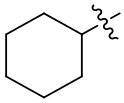
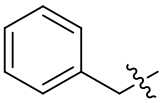
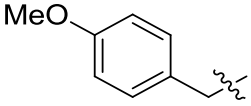
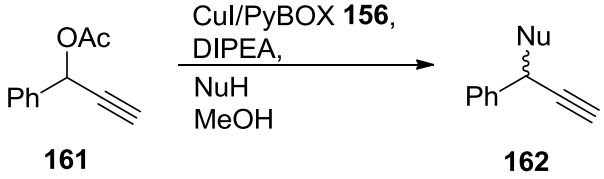
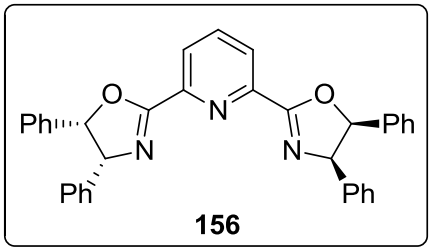
R	No.	R^1	Ligand	Yield (%)	*Ee* (%)
	**161**	Ac	**158**	84	67
	**162**	Ac	**158**	77	82
	163	Bz	**158**	89	79
	**164**	Ac	**158**	96	85
			157	63	86
	**165**	Ac	**158**	66	88
			157	60	89
	**166**	Piv	**158**	59	90

Table 1.17

Finally, the last aspect of the enantioselective propargylic substitution they investigated was the nucleophile used in the reaction. Both nitrogen and carbon nucleophiles were examined, as can be seen in **Table 1.18**.



161 162



156

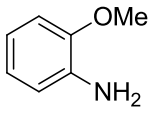
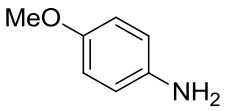
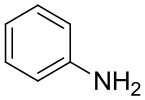
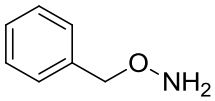
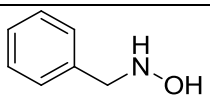
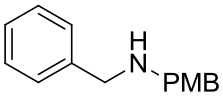
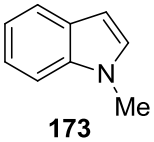
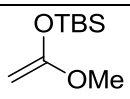
NuH	Temp (°C)	Yield (%)	*Ee* (%)
 167	-20	97	85
 168	-20	93	78
 169	-20	94	87
 170	0	74	36
 171	0	77	No data
 172	-20	94	68
 173	-20	91	98
 174	RT	>10	No data

Table 1.18

After the investigation of the propargylic acetates in **Table 1.17**, 1-phenylprop-2-ynyl acetate **161** was selected as the most suitable for investigation of possible nucleophiles, while PyBOX **156 -** CuI complex was used as the catalyst, with *N*,*N*-diisopropylethylamine as the base and the reaction was carried out in methanol. The first nitrogen nucleophile tested was *o*-anisidine, **167**, giving an excellent yield of 97 % and an enantiomeric excess of 85 %, when the reaction was carried out at -20 °C. However when *p*-anisidine, **168**, was used, the yield and the *ee* was lower, 93 % and 78 % respectively. Aniline, **169**, gave similar results to those obtained with *o*-anisidine at -20 °C. *O*-benzylhydroxylamine, **170**, gave product in good yield (74 %) but the *ee* values were substantially lower (36 %) while *N*-benzylhydroxylamine, **171**, showed similar yields, 77 %. It was not possible to separate the enantiomers by chiral HPLC and so no *ee* value could be determined. Next the research group decided to investigate *N*-benzyl-*N*-methoxybenzylamine, **172**, which gave product in an excellent yield of 94 % but and moderate selectivity with an *ee* of 68 %.

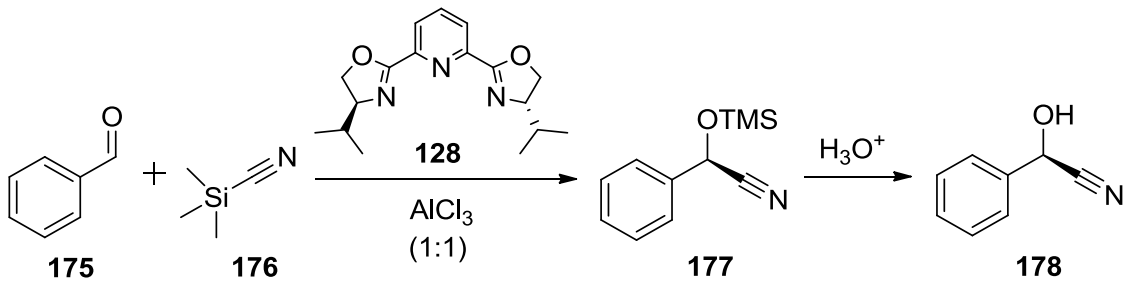
Carbon nucleophiles were also examined using the same reaction conditions used to test the nitrogen nucleophiles. The best results obtained were from *N*-methylindole, **173**, producing a yield of 91 % and an *ee* of 98 %. However, most of the tested nucleophiles gave disappointing results, with little or no desired product produced or poor enantioselectivities, for example, **174** only produced ≈10 % yield and no data for any enantioselectivity.

1.9.2 Trimethylsilylcyanation of aromatic aldehydes

The synthesis of aromatic cyanohydrins and cyanohydrin derivatives is an important step in the synthesis of several natural and biologically active products[142-143].They can be easily prepared by the addition of a cyanide to a carbonyl compound in the presence of a chiral catalyst or an enzyme giving access to a versatile intermediate that can be utilised in the synthesis of compounds such as α-hydroxyacids [144], α-amino acids [145] and α-hydroxyaldehydes [146] to name but a few.

Several Lewis acids are known to catalyse the trimethylsilylcyanation reaction of aldehydes including boron-based Lewis acids reported by Reetz[147] and Corey[148], while Ti(IV) complexes composed from titanium alkoxides with optically active ligands like Schiff's bases[149] and sulfoximines[150] can also be used. Iovel *et al* investigated the use of PyBOX-$AlCl_3$ complexes as catalysts of TMSCN addition to aldehydes[71].

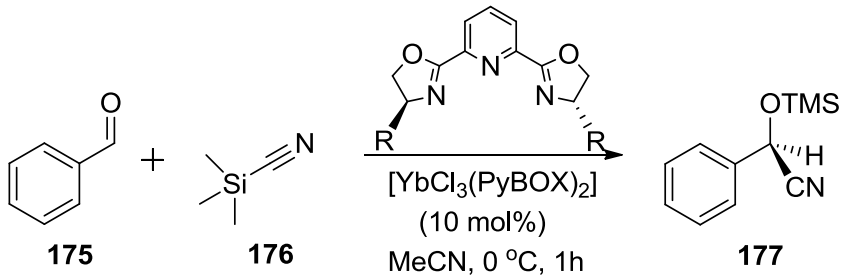
Benzaldehyde, **175**, was reacted with trimethylsilyl cyanide, **176**, in the presence of 20 mol% of the PyBOX-$AlCl_3$ complex, which was generated *in situ*, producing the corresponding siloxy nitrile, **177**, after four hours. This was followed by hydrolysis to give mandelonitrile, **178** (**Scheme 1.24**). Initially the addition reaction was carried out at room temperature in dichloromethane which produced mandelonitrile, **178**, in 90 % yield and an enantiomeric excess of 44 %. In order to increase the enantioselectivity, the addition of the TMSCN to the benzaldehyde was carried out in a reaction where the temperature slowly increased from 0 °C to 10 °C over 16 hours producing **178** in 92 % yield, while the *ee* was increased to 90 %.



Scheme 1.24

The research group also carried out ^1H NMR studies and quantum-chemical calculations of the PyBOX-$AlCl_3$ complex. The ^1H NMR studies revealed that there were two unidentical oxazoline rings in the complex formed by the PyBOX and $AlCl_3$ as the C_2-symmetrical structure of the PyBOX was no longer visible in the proton NMR. The quantum-chemical calculations carried out were consistent with the findings of the ^1H NMR study[71] and revealed that only one oxazoline ring was coordinated to the metal centre in the PyBOX-$AlCl_3$ complex.

Aspinall *et al* also investigated the enantioselective silylcyanation of aldehydes, however they used lanthanide-PyBOX complexes as catalysts[151]. They examined the formation of complexes using lanthanide metal chlorides e.g. ytterbium chloride, samarium chloride and europium chloride, in combination with *S*-PyBOX ligands. It was found that a metal-ligand ratio of 1:2 produced the highest enantioselectivity while $YbCl_3$(S-*i*Pr-PyBOX)$_2$ was the optimum catalyst for the reaction of benzaldehyde with TMSCN producing a yield of 87 % and an *ee* of 67 %. *S*-Ph-PyBOX also yielded 77 % of the product and an 80 % *ee*. The research group chose *i*Pr-PyBOX ligand due to its higher activity and it's somewhat easier synthesis when compared to the Ph-PyBOX (**Table 1.19**). Surprisingly the *t*Bu-PyBOX gave very poor enantioselectivity (13 % *ee*) but still showed good activity with a yield of 88 % which suggested that the poor *ee* was not due to poor accessibility of the substrate to the active site of the catalyst.

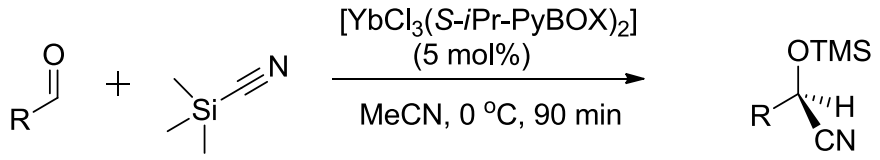


175 **176** **177**

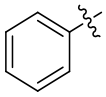
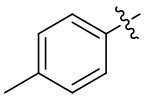
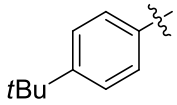
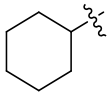
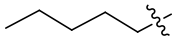
R	Yield (%)	*Ee* (%)
*i*Pr	87	67
Ph	77	80
CH_2Ph	>99	60
*t*Bu	88	13

Table 1.19

They also investigated the use of hydrated $YbCl_3$ and also anhydrous $YbCl_3$ using a number of different aldehydes. As the results show in **Table 1.20** better yields and *ee*'s were achieved in most cases when anhydrous $YbCl_3$ was used in the reaction and although the hydrated $YbCl_3$ was easier to work with, the conversions and *ee*'s were far less reproducible.



178 **176** **179**

R	Hydrated $YbCl_3$		Anhydrous $YbCl_3$	
	Yield, %	***Ee*, %**	**Yield, %**	***Ee*, %**
	96 %	71 %	86 %	91 %
	22 %	64 %	89 %	80 %
	56 %	0 %	88 %	88 %
	NR	NR	86 %	60 %
	NR	NR	88 %	56 %

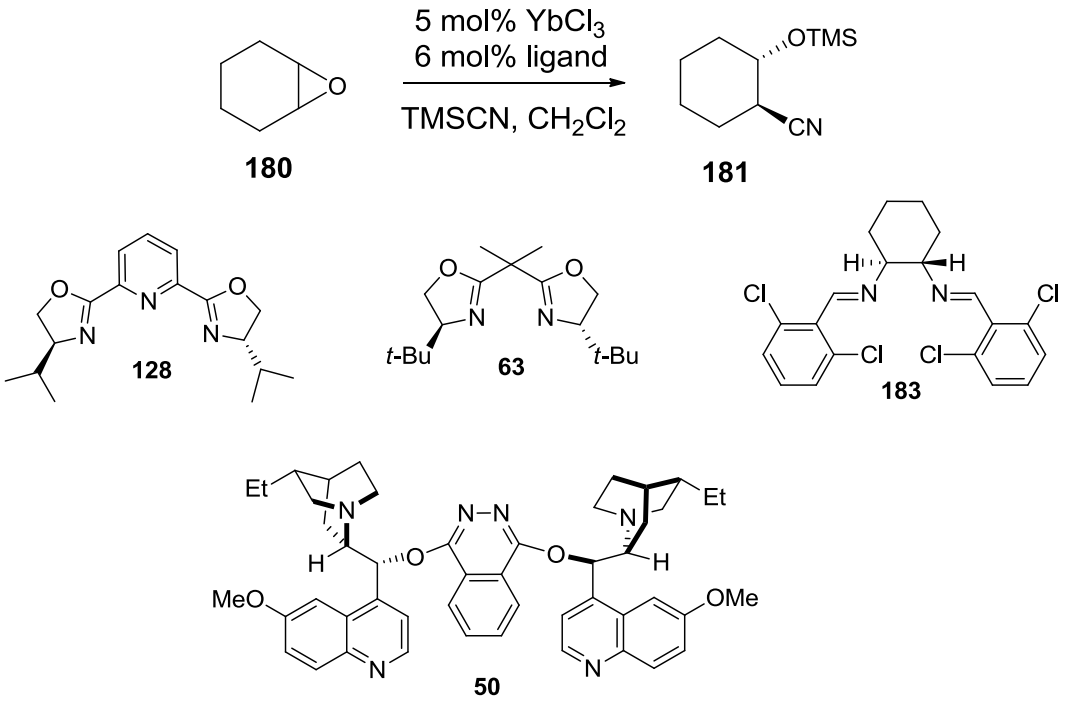
Scheme 1.20

1.9.3 Asymmetric Ring Opening of Meso Epoxides

Epoxides are very important intermediates in organic synthesis, as they are easily prepared. They will also react with numerous different nucleophiles, due to their ring strain, producing ring opened products in high regioselectivity. The use of *meso* epoxides offers a cost effective and straightforward pathway to enantio-enriched products. The majority of nucleophiles used are hetroatom based and can give access to chiral products like 1,2-azido alcohols[152], 1,2-halohydrins[153], 1,2-hydroxy sulphides[154] and 1,2 benzoyloxy alcohols[155].

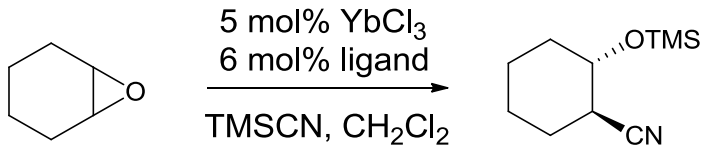
Asymmetric ring opening, also known as ARO, using carbon based nucleophiles remains challenging but offers the advantage of simple and stereoselective carbon-carbon bond formation. Cyanide and trimethylsilyl cyanide have become important carbon nucleophiles because of their low cost and the nitrile,

ring-opened, products produced from the reaction are synthetically valuable. Research carried out by Kagan *et al* into the effective use of lanthanide chlorides to promote the ring opening of propylene oxides using TMSCN[156] and later work carried out by Utimoto *et al* using ytterbium salts in similar reactions[157], caused Jacobsen *et al* to investigate the possibility of using chiral ligands in combination with the lanthanide salts to asymmetrically catalyse these reactions[72].



Scheme 1.25

A number of different ligands were tested in the reaction, as can be seen in **Scheme 1.25** to find the optimum ligand. Initially the metal-ligand catalyst was generated in THF, with the solvent being removed after the dissolution of the usually insoluble salt, and re-dissolved in CH_2Cl_2 for the reaction. After 4 hours at room temperature only ligand **128** produced the product, **181**, in 47 % *ee*. The other ligands produced the racemic product. Armed with this information, a series of PYBOX ligands were reacted with 5 mol% $YbCl_3$ at room temperature for 4 hours, to identify the most enantioselective system for the asymmetric ring opening of cyclohexene oxide with TMSCN.



180 **181**

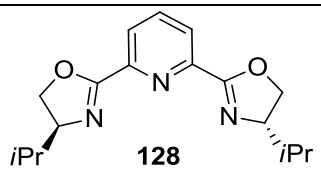
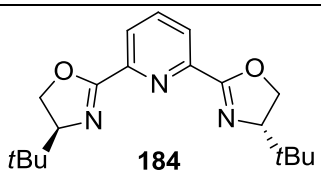
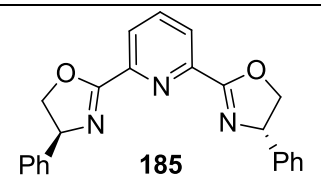
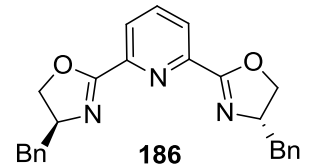
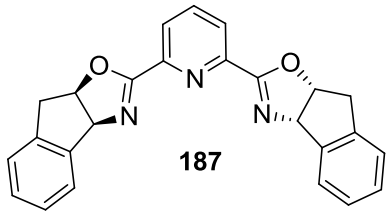
Ligand	Yield (%)	*Ee* (%)	Configuration of **181**
 **128**	95	47	1*S*,2*R*
 **184**	93	57	1*S*,2*R*
 **185**	96	67	1*R*,2*S*
 **186**	96	28	1*S*,2*R*
 **187**	93	28	1*S*,2*R*

Table 1.21

The *iso*-propyl, **128**, *tert*-butyl, **184**, phenyl, **185**, and benzyl, **186**, PyBOX ligands were evaluated, as well as, **187**, with (*S*,*S*)-phenyl-PyBOX, **185**, producing the highest enantioselectivity, yielding the product, **181**, in 67 % *ee* (**Table 1.21**). Further optimisation of the reaction using ligand **185,** led to the reaction being

carried out at -40 °C, with 10 mol% of $YbCl_3$ as catalyst in chloroform and produced **181** in 90 % yield and 91 % *ee* after four days.

The reaction also proved successful for a number of other *meso* epoxides including cyclopentene oxide (83 % yield, 92 % *ee* using **184** at -10 °C for 7 days), *cis*-2,3 epoxybutane (80 % yield, 90 % *ee* using **185** at -40^{o} C for 7 days) and *trans*-ethyl-3,4-epoxy-ethyl-1-cyclopentanecarboxylate (86 % yield, 83 % *ee* using **184** at 0 °C for 7 days). These results showed that the optimum ligand and reaction temperatures were highly substrate dependant. It was also noted that ligands **184** and **185** consistently gave product in the opposite absolute configuration.

Mechanistic studies of the reaction deduced that a cyano - ytterbium species is the active catalyst in the reaction. A plot of product *ee* versus catalyst *ee* for the ARO of cyclohexene oxide with TMSCN using 5 mol% of catalyst **184** - $YbCl_3$ produced a graph that was non-linear indicating that perhaps a bimetallic mechanism was involved. A nonlinear effect is symptomatic of catalyst aggregation at some point in the catalytic cycle and is consistent with the catalyst playing the dual role of cyanide - delivery agent and Lewis acid[72] as shown in **Figure 1.21**. Kinetic studies involving measurements being carried out at five different catalyst loadings over an 8-fold concentration range. The rate constants obtained correlated in a linear manner with the square of catalyst concentration showing a second-order dependence on the catalyst, which is also consistent with a bimetallic rate-limiting ring-opening reaction.

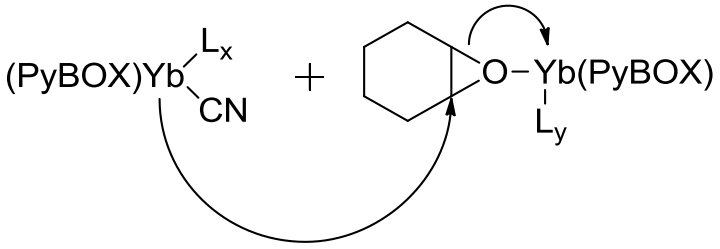


Figure 1.21

References

[1] R. S. Cahn, C. Ingold, V. Prelog, *Angewandte Chemie International Edition in English* **1966**, *5*, 385-415.

[2] S. W. Smith, *Toxicological Sciences* **2009**, *110*, 4-30.

[3] A. N. C. A. N. G. N. S. J. Crosby, Chichester : Wiley **1992**.

[4] H. Caner, E. Groner, L. Levy, I. Agranat, *Drug Discovery Today* **2004**, *9*, 105-110.

[5] I. Agranat, S. R. Wainschtein, *Drug Discovery Today* **2010**, *15*, 163-170.

[6] A. D. McNaught, A. Wilkinson, *IUPAC. Compendium of Chemical Terminology*, 2.3.2. ed., Blackwell Scientific Publications, Oxford, **1997**.

[7] V. T. Nguyen, I. Y. H. Chan, R. Bishop, D. C. Craig, M. L. Scudder, *New Journal of Chemistry* **2009**, *33*, 1736-1741.

[8] K. Piwowarczyk, A. Zawadzka, P. Roszkowski, J. Szawkało, A. Leniewski, J. K. Maurin, D. Kranz, Z. Czarnocki, *Tetrahedron: Asymmetry* **2008**, *19*, 309-317.

[9] M. Albalat-Serradeil, G. Primazot, D. Wilhelm, J.-C. Vallejos, N. Vanthuyne, C. Roussel, *Amino Acids* **2012**, *43*, 687-696.

[10] X.-S. Wu, S.-K. Tian, *Chemical Communications* **2012**, *48*, 898-900.

[11] C.-R. Liu, M.-B. Li, C.-F. Yang, S.-K. Tian, *Chemistry – A European Journal* **2009**, *15*, 793-797.

[12] A. Orue, E. Reyes, J. L. Vicario, L. Carrillo, U. Uria, *Organic Letters* **2012**, *14*, 3740-3743.

[13] Y. Sato, Y. Kayaki, T. Ikariya, *Chemical Communications* **2012**, *48*, 3635-3637.

[14] P. Liu, X. Yang, V. B. Birman, K. N. Houk, *Organic Letters* **2012**, *14*, 3288-3291.

[15] A. Ros, M. Alcarazo, D. Monge, E. Álvarez, R. Fernández, J. M. Lassaletta, *Tetrahedron: Asymmetry* **2010**, *21*, 1557-1562.

[16] C. Kobler, F. Effenberger, *Tetrahedron: Asymmetry* **2004**, *15*, 3731-3742.

[17] J.-A. Richard, D. Y. K. Chen, *European Journal of Organic Chemistry* **2012**, *2012*, 484-487.

[18] G. Nam, S. Y. Ko, *Helvetica Chimica Acta* **2012**, *95*, 1937-1945.

[19] M. Dickman, J. B. Jones, *Bioorganic & Medicinal Chemistry* **2000**, *8*, 1957-1968.

[20] J. Murga, J. García-Fortanet, M. Carda, J. A. Marco, *Tetrahedron Letters* **2004**, *45*, 7499-7501.

[21] G. Symkenberg, M. Kalesse, *Organic Letters* **2012**, *14*, 1608-1611.

[22] T. Umezawa, M. Sueda, T. Kamura, T. Kawahara, X. Han, T. Okino, F. Matsuda, *The Journal of Organic Chemistry* **2011**, *77*, 357-370.

[23] C. G. Nelson, T. R. Burke, *The Journal of Organic Chemistry* **2011**, *77*, 733-738.

[24] D. R. Williams, W. S. Kissel, J. J. Li, R. J. Mullins, *Tetrahedron Letters* **2002**, *43*, 3723-3727.

[25] M. T. Robak, M. A. Herbage, J. A. Ellman, *Chemical Reviews* **2010**, *110*, 3600-3740.

[26] D. A. Cogan, J. A. Ellman, *Journal of the American Chemical Society* **1998**, *121*, 268-269.

[27] J. C. Barrow, P. L. Ngo, J. M. Pellicore, H. G. Selnick, P. G. Nantermet, *Tetrahedron Letters* **2001**, *42*, 2051-2054.
[28] T. P. Tang, S. K. Volkman, J. A. Ellman, *The Journal of Organic Chemistry* **2001**, *66*, 8772-8778.
[29] T. Kochi, T. P. Tang, J. A. Ellman, *Journal of the American Chemical Society* **2002**, *124*, 6518-6519.
[30] F. A. Davis, N. Theddu, *The Journal of Organic Chemistry* **2010**, *75*, 3814-3820.
[31] F. A. Davis, W. McCoull, *The Journal of Organic Chemistry* **1999**, *64*, 3396-3397.
[32] T. Hjelmgaard, S. Faure, P. Lemoine, B. Viossat, D. J. Aitken, *Organic Letters* **2008**, *10*, 841-844.
[33] Y.-W. Zhong, K. Izumi, M.-H. Xu, G.-Q. Lin, *Organic Letters* **2004**, *6*, 4747-4750.
[34] Y.-W. Zhong, M.-H. Xu, G.-Q. Lin, *Organic Letters* **2004**, *6*, 3953-3956.
[35] J. Zhang, Y. Yang, M. Wang, L. Lin, R. Wang, *Tetrahedron Letters* **2012**, *53*, 6893-6896.
[36] B.-L. Chen, B. Wang, G.-Q. Lin, *The Journal of Organic Chemistry* **2009**, *75*, 941-944.
[37] G. Liu, D. A. Cogan, J. A. Ellman, *Journal of the American Chemical Society* **1997**, *119*, 9913-9914.
[38] D. A. Cogan, G. Liu, K. Kim, B. J. Backes, J. A. Ellman, *Journal of the American Chemical Society* **1998**, *120*, 8011-8019.
[39] T. D. Owens, A. J. Souers, J. A. Ellman, *The Journal of Organic Chemistry* **2002**, *68*, 3-10.
[40] D. A. Cogan, G. Liu, J. Ellman, *Tetrahedron* **1999**, *55*, 8883-8904.
[41] N. Plobeck, D. Powell, *Tetrahedron: Asymmetry* **2002**, *13*, 303-310.
[42] G. Borg, D. A. Cogan, J. A. Ellman, *Tetrahedron Letters* **1999**, *40*, 6709-6712.
[43] J. Tanuwidjaja, H. M. Peltier, J. A. Ellman, *The Journal of Organic Chemistry* **2006**, *72*, 626-629.
[44] Y.-W. Zhong, Y.-Z. Dong, K. Fang, K. Izumi, M.-H. Xu, G.-Q. Lin, *Journal of the American Chemical Society* **2005**, *127*, 11956-11957.
[45] J. G. Hernández, V. García-López, E. Juaristi, *Tetrahedron* **2012**, *68*, 92-97.
[46] J. Xiao, Y.-P. Lu, Y.-L. Liu, P.-S. Wong, T.-P. Loh, *Organic Letters* **2011**, *13*, 876-879.
[47] C. Garzon, M. Attolini, M. Maffei, *Tetrahedron Letters* **2010**, *51*, 3772-3774.
[48] C. Quigley, Z. Rodriguez-Docampo, S. J. Connon, *Chemical Communications* **2012**, *48*, 1443-1445.
[49] C. G. Kokotos, *The Journal of Organic Chemistry* **2011**, *77*, 1131-1135.
[50] Q. Guo, J. C.-G. Zhao, *Organic Letters* **2013**, *15*, 508-511.
[51] L. Marzorati, J. L. Fejfar, C. F. Tormena, C. D. Vitta, *Tetrahedron: Asymmetry* **2012**, *23*, 748-753.
[52] D. Uraguchi, K. Koshimoto, T. Ooi, *Journal of the American Chemical Society* **2008**, *130*, 10878-10879.
[53] Y. Wei, W. He, Y. Liu, P. Liu, S. Zhang, *Organic Letters* **2012**, *14*, 704-707.

[54] A. Singh, J. N. Johnston, *Journal of the American Chemical Society* **2008**, *130*, 5866-5867.
[55] A. B. Zaitsev, H. Adolfsson, *Synthesis* **2006**, 1725-1756.
[56] M. Hayashi, N. Shiomi, Y. Funahashi, S. Nakamura, *Journal of the American Chemical Society* **2012**, *134*, 19366-19369.
[57] F. Sladojevich, A. Trabocchi, A. Guarna, D. J. Dixon, *Journal of the American Chemical Society* **2011**, *133*, 1710-1713.
[58] H.-y. Jiang, H. Chen, R.-x. Li, *Catalysis Communications* **2010**, *11*, 584-587.
[59] N. A. Milas, S. Sussman, *Journal of the American Chemical Society* **1936**, *58*, 1302-1304.
[60] S. G. Hentges, K. B. Sharpless, *Journal of the American Chemical Society* **1980**, *102*, 4263-4265.
[61] M. J. Cleare, P. C. Hydes, W. P. Griffith, M. J. Wright, *Journal of the Chemical Society, Dalton Transactions* **1977**, *0*, 941-944.
[62] E. N. Jacobsen, I. Marko, W. S. Mungall, G. Schroeder, K. B. Sharpless, *Journal of the American Chemical Society* **1988**, *110*, 1968-1970.
[63] J. S. M. Wai, I. Marko, J. S. Svendsen, M. G. Finn, E. N. Jacobsen, K. B. Sharpless, *Journal of the American Chemical Society* **1989**, *111*, 1123-1125.
[64] H.-L. Kwong, C. Sorato, Y. Ogino, H. Chen, K. B. Sharpless, *Tetrahedron Letters* **1990**, *31*, 2999.
[65] K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K. S. Jeong, H. L. Kwong, K. Morikawa, Z. M. Wang, *The Journal of Organic Chemistry* **1992**, *57*, 2768-2771.
[66] P.-O. Norrby, H. C. Kolb, K. B. Sharpless, *Journal of the American Chemical Society* **1994**, *116*, 8470.
[67] A. Pfaltz, *Accounts of Chemical Research* **1993**, *26*, 339-345.
[68] A. J. Burke, E. d. Palma Carreiro, S. Chercheja, N. M. M. Moura, J. P. Prates Ramalho, A. I. Rodrigues, C. I. M. dos Santos, *Journal of Organometallic Chemistry* **2007**, *692*, 4863-4874.
[69] J. Bayardon, D. Sinou, *Tetrahedron: Asymmetry* **2005**, *16*, 2965-2972.
[70] R. J. Detz, Z. Abiri, R. le Griel, H. Hiemstra, J. H. van Maarseveen, *Chemistry – A European Journal* **2011**, *17*, 5921-5930.
[71] I. Iovel, Y. Popelis, M. Fleisher, E. Lukevics, *Tetrahedron: Asymmetry* **1997**, *8*, 1279-1285.
[72] S. E. Schaus, E. N. Jacobsen, *Organic Letters* **2000**, *2*, 1001-1004.
[73] S. Ma, S. Wu, *New Journal of Chemistry* **2001**, *25*, 1337-1341.
[74] D. Frain, F. Kirby, P. McArdle, P. O'Leary, *Tetrahedron Letters* **2010**, *51*, 4103-4106.
[75] E. J. Corey, N. Imai, H. Y. Zhang, *Journal of the American Chemical Society* **1991**, *113*, 728-729.
[76] D. A. Evans, G. S. Peterson, J. S. Johnson, D. M. Barnes, K. R. Campos, K. A. Woerpel, *The Journal of Organic Chemistry* **1998**, *63*, 4541-4544.
[77] R. E. Lowenthal, A. Abiko, S. Masamune, *Tetrahedron Letters* **1990**, *31*, 6005-6008.
[78] D. A. Evans, K. A. Woerpel, M. M. Hinman, M. M. Faul, *Journal of the American Chemical Society* **1991**, *113*, 726-728.

[79] A. M. Harm, J. G. Knight, G. Stemp, *Synlett* **1996**, *1996*, 677-678.
[80] G. Desimoni, G. Faita, M. Mella, *Tetrahedron* **1996**, *52*, 13649-13654.
[81] I. W. Davies, C. H. Senanayake, R. D. Larsen, T. R. Verhoeven, P. J. Reider, *Tetrahedron Letters* **1996**, *37*, 813-814.
[82] A. Cornejo, J. M. Fraile, J. I. García, M. J. Gil, V. Martínez-Merino, l. J. A. Mayora, E. Pires, I. Villalbaa, *Synlett* **2005**, 2321.
[83] M. Schinnerl, C. Böhm, M. Seitz, O. Reiser, *Tetrahedron: Asymmetry* **2003**, *14*, 765-771.
[84] Z.-M. Zhou, Z.-H. Li, X.-Y. Hao, X. Dong, X. Li, L. Dai, Y.-Q. Liu, J. Zhang, H.-f. Huang, X. Li, J.-l. Wang, *Green Chemistry* **2011**, *13*, 2963-2971.
[85] K. Takeuchi, T. Takeda, T. Fujimoto, I. Yamamoto, *Tetrahedron* **2007**, *63*, 5319-5322.
[86] M. K. Tse, H. Jiao, G. Anilkumar, B. Bitterlich, F. G. Gelalcha, M. Beller, *Journal of Organometallic Chemistry* **2006**, *691*, 4419-4433.
[87] R. Rasappan, D. Laventine, O. Reiser, *Coordination Chemistry Reviews* **2008**, *252*, 702-714.
[88] D. A. Evans, S. J. Miller, T. Lectka, P. von Matt, *Journal of the American Chemical Society* **1999**, *121*, 7559-7573.
[89] D. A. Evans, J. S. Johnson, C. S. Burgey, K. R. Campos, *Tetrahedron Letters* **1999**, *40*, 2879-2882.
[90] A. El Hatimi, M. Gomez, S. Jansat, G. Muller, M. Font-Bardia, X. Solans, *Journal of the Chemical Society, Dalton Transactions* **1998**, *0*, 4229-4236.
[91] J.-i. Ito, R. Asai, H. Nishiyama, *Organic Letters* **2010**, *12*, 3860-3862.
[92] H. Nishiyama, H. Sakaguchi, T. Nakamura, M. Horihata, M. Kondo, K. Itoh, *Organometallics* **1989**, *8*, 846-848.
[93] I. W. Davies, L. Gerena, N. Lu, R. D. Larsen, P. J. Reider, *The Journal of Organic Chemistry* **1996**, *61*, 9629-9630.
[94] R. Nesper, P. Pregosin, K. Püntener, M. Wörle, A. Albinati, *Journal of Organometallic Chemistry* **1996**, *507*, 85-101.
[95] G. Chelucci, S. Deriu, G. A. Pinna, A. Saba, R. Valenti, *Tetrahedron: Asymmetry* **1999**, *10*, 3803-3809.
[96] G. Desimoni, G. Faita, P. Quadrelli, *Chemical Reviews* **2003**, *103*, 3119-3154.
[97] P. J. Heard, C. Jones, *Journal of the Chemical Society, Dalton Transactions* **1997**, *0*, 1083-1092.
[98] P. J. Heard, D. A. Tocher, *Journal of the Chemical Society, Dalton Transactions* **1998**, *0*, 2169-2176.
[99] D. A. Evans, Z. K. Sweeney, T. Rovis, J. S. Tedrow, *Journal of the American Chemical Society* **2001**, *123*, 12095-12096.
[100] G. Faita, M. Mella, M. Toscanini, G. Desimoni, *Tetrahedron* **2010**, *66*, 3024-3029.
[101] D. Cuervo, M. P. Gamasa, J. Gimeno, *Journal of Molecular Catalysis A: Chemical* **2006**, *249*, 60-64.
[102] D. A. Evans, M. C. Kozlowski, J. S. Tedrow, *Tetrahedron Letters* **1996**, *37*, 7481-7484.
[103] K. Junge, K. Möller, B. Wendt, S. Das, D. Gördes, K. Thurow, M. Beller, *Chemistry – An Asian Journal* **2012**, *7*, 314-320.

[104] H. Nishiyama, Y. Itoh, H. Matsumoto, S.-B. Park, K. Itoh, *Journal of the American Chemical Society* **1994**, *116*, 2223-2224.
[105] C. Langham, P. Piaggio, P. McMorn, D. J. Willock, G. J. Hutchings, D. Bethell, D. F. Lee, P. C. Bulman Page, C. Sly, F. E. Hancock, F. King, *Chemical Communications* **1998**, *0*, 1601-1602.
[106] D. A. Evans, D. W. C. MacMillan, K. R. Campos, *Journal of the American Chemical Society* **1997**, *119*, 10859-10860.
[107] D. A. Evans, C. S. Burgey, M. C. Kozlowski, S. W. Tregay, *Journal of the American Chemical Society* **1999**, *121*, 686-699.
[108] H. Nishiyama, M. Kondo, T. Nakamura, K. Itoh, *Organometallics* **1991**, *10*, 500-508.
[109] W. J. Li, S. X. Qiu, *Journal of Heterocyclic Chemistry* **2010**, *47*, 1340-1343.
[110] S. E. Denmark, R. A. Stavenger, A.-M. Faucher, J. P. Edwards, *The Journal of Organic Chemistry* **1997**, *62*, 3375-3389.
[111] M. Peer, J. C. de Jong, M. Kiefer, T. Langer, H. Rieck, H. Schell, P. Sennhenn, J. Sprinz, H. Steinhagen, B. Wiese, G. Helmchen, *Tetrahedron* **1996**, *52*, 7547-7583.
[112] Y. Kanazawa, Y. Tsuchiya, K. Kobayashi, T. Shiomi, J.-i. Itoh, M. Kikuchi, Y. Yamamoto, H. Nishiyama, *Chemistry – A European Journal* **2006**, *12*, 63-71.
[113] H. Nishiyama, *Chemical Society Reviews* **2007**, *36*, 1133-1141.
[114] Y. Motoyama, M. Okano, H. Narusawa, N. Makihara, K. Aoki, H. Nishiyama, *Organometallics* **2001**, *20*, 1580-1591.
[115] A. A. H. Van der Zeijden, G. Van Koten, R. A. Nordemann, B. Kojic-Prodic, A. L. Spek, *Organometallics* **1988**, *7*, 1957-1966.
[116] Y. Motoyama, H. Kawakami, K. Shimozono, K. Aoki, H. Nishiyama, *Organometallics* **2002**, *21*, 3408-3416.
[117] M. A. Stark, C. J. Richards, *Tetrahedron Letters* **1997**, *38*, 5881-5884.
[118] Y. Motoyama, Y. Mikami, H. Kawakami, K. Aoki, H. Nishiyama, *Organometallics* **1999**, *18*, 3584-3588.
[119] M. Stol, D. J. M. Snelders, M. D. Godbole, R. W. A. Havenith, D. Haddleton, G. Clarkson, M. Lutz, A. L. Spek, G. P. M. van Klink, G. van Koten, *Organometallics* **2007**, *26*, 3985-3994.
[120] M. Stol, D. J. M. Snelders, J. J. M. de Pater, G. P. M. van Klink, H. Kooijman, A. L. Spek, G. van Koten, *Organometallics* **2005**, *24*, 743-749.
[121] J. S. Fossey, C. J. Richards, *Journal of Organometallic Chemistry* **2004**, *689*, 3056-3059.
[122] S. Hosokawa, J.-i. Ito, H. Nishiyama, *Organometallics* **2010**, *29*, 5773-5775.
[123] J. Terheijden, G. Van Koten, J. L. De Booys, H. J. C. Ubbels, C. H. Stam, *Organometallics* **1983**, *2*, 1882-1883.
[124] J. S. Fossey, C. J. Richards, *Organometallics* **2004**, *23*, 367-373.
[125] J.-i. Ito, S. Ujiie, H. Nishiyama, *Organometallics* **2008**, *28*, 630-638.
[126] Y. Motoyama, Y. Koga, H. Nishiyama, *Tetrahedron* **2001**, *57*, 853-860.
[127] Y. Motoyama, Y. Koga, K. Kobayashi, K. Aoki, H. Nishiyama, *Chemistry – A European Journal* **2002**, *8*, 2968-2975.
[128] P. McMorn, G. J. Hutchings, *Chemical Society Reviews* **2004**, *33*, 108-122.

[129] M. J. Sabater, A. Corma, A. Domenech, V. Fornes, H. Garcia, *Chemical Communications* **1997**, *0*, 1285-1286.
[130] A. Cornejo, J. M. Fraile, J. I. García, M. J. Gil, S. V. Luis, V. Martínez-Merino, J. A. Mayoral, *Comptes Rendus Chimie* **2004**, *7*, 161-167.
[131] J. Jamis, J. R. Anderson, R. S. Dickson, E. M. Campi, W. R. Jackson, *Journal of Organometallic Chemistry* **2001**, *627*, 37-43.
[132] C. McDonagh, P. O'Conghaile, R. J. M. Klein Gebbink, P. O'Leary, *Tetrahedron Letters* **2007**, *48*, 4387-4390.
[133] A. Baiker, *Journal of Molecular Catalysis A: Chemical* **1997**, *115*, 473-493.
[134] K. T. Wan, M. E. Davis, *Journal of Catalysis* **1995**, *152*, 25-30.
[135] C. Bianchini, P. Barbaro, V. Dal Santo, R. Gobetto, A. Meli, W. Oberhauser, R. Psaro, F. Vizza, *Advanced Synthesis & Catalysis* **2001**, *343*, 41-45.
[136] P. O'Leary, N. P. Krosveld, K. P. De Jong, G. van Koten, R. J. M. Klein Gebbink, *Tetrahedron Letters* **2004**, *45*, 3177-3180.
[137] M. Mazzel, W. Marconi, M. Riocci, *Journal of Molecular Catalysis* **1980**, *9*, 381-387.
[138] S. Taylor, J. Gullick, P. McMorn, D. Bethell, P. C. Bulman Page, F. E. Hancock, F. King, G. J. Hutchings, *Journal of the Chemical Society, Perkin Transactions 2* **2001**, *0*, 1714-1723.
[139] C. Simons, U. Hanefeld, I. W. C. E. Arends, T. Maschmeyer, R. A. Sheldon, *Journal of Catalysis* **2006**, *239*, 212-219.
[140] V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angewandte Chemie International Edition* **2002**, *41*, 2596-2599.
[141] R. Chinchilla, C. Nájera, *Chemical Reviews* **2007**, *107*, 874-922.
[142] F. Effenberger, *Angewandte Chemie International Edition in English* **1994**, *33*, 1555-1564.
[143] N.-u. H. Khan, R. I. Kureshy, S. H. R. Abdi, S. Agrawal, R. V. Jasra, *Coordination Chemistry Reviews* **2008**, *252*, 593-623.
[144] M. A. Schwindt, D. T. Belmont, M. Carlson, L. C. Franklin, V. S. Hendrickson, G. L. Karrick, R. W. Poe, D. M. Sobieray, J. Van De Vusse, *The Journal of Organic Chemistry* **1996**, *61*, 9564-9568.
[145] J.-M. Brunel, I. P. Holmes, *Angewandte Chemie International Edition* **2004**, *43*, 2752-2778.
[146] M. C. Pirrung, S. W. Shuey, *The Journal of Organic Chemistry* **1994**, *59*, 3890-3897.
[147] M. T. Reetz, F. Kunisch, P. Heitmann, *Tetrahedron Letters* **1986**, *27*, 4721-4724.
[148] D. H. Ryu, E. J. Corey, *Journal of the American Chemical Society* **2004**, *126*, 8106-8107.
[149] Y. Belokon, N. Ikonnikov, M. Moscalenko, M. North, S. Orlova, V. Tararov, L. Yashkina, *Tetrahedron: Asymmetry* **1996**, *7*, 851-855.
[150] C. Bolm, P. Müller, *Tetrahedron Letters* **1995**, *36*, 1625-1628.
[151] H. C. Aspinall, J. F. Bickley, N. Greeves, R. V. Kelly, P. M. Smith, *Organometallics* **2005**, *24*, 3458-3467.
[152] S. E. Schaus, J. F. Larrow, E. N. Jacobsen, *The Journal of Organic Chemistry* **1997**, *62*, 4197-4199.

[153] S. E. Denmark, P. A. Barsanti, K.-T. Wong, R. A. Stavenger, *The Journal of Organic Chemistry* **1998**, *63*, 2428-2429.
[154] M. H. Wu, E. N. Jacobsen, *The Journal of Organic Chemistry* **1998**, *63*, 5252-5254.
[155] E. N. Jacobsen, F. Kakiuchi, R. G. Konsler, J. F. Larrow, M. Tokunaga, *Tetrahedron Letters* **1997**, *38*, 773-776.
[156] A. E. Vougioukas, H. B. Kagan, *Tetrahedron Letters* **1987**, *28*, 5513-5516.
[157] S. Matsubara, H. Onishi, K. Utimoto, *Tetrahedron Letters* **1990**, *31*, 6209-6212.

Chapter 2:

Results and

Discussion

2.1 Introduction

Asymmetric catalysis is a vital part of chemical synthesis. Bisoxazoline (BOX), pyridine bisoxazoline (PyBOX) and phenyl bisoxazoline ligands (PheBOX), complexed with metal salts, have been used to catalyse of a wide variety of reactions, as discussed in chapter 1[1-3]. There are two parts to the research described in this thesis. The first part of the study consists of the attempts to synthesise novel ligands, which were used in combination with metal salts, and tested in a number of asymmetric catalytic reactions, including asymmetric cyclopropanation[4] and asymmetric transfer hydrogenation reactions[5]. These novel 4,4'-phenyl-bisoxazoline (PheBOX) ligands are a redesign of the traditional 2,2'-PheBOX ligands, where the chiral centres are now adjacent to the aromatic core of the ligand, rather than just in the chiral side arms, as found in the traditional ligands. This means that when the metal is co-ordinated, the chirality is now internal to the metalocycle and this gives potential for better stereoselectivity (**Figure 2.1**).

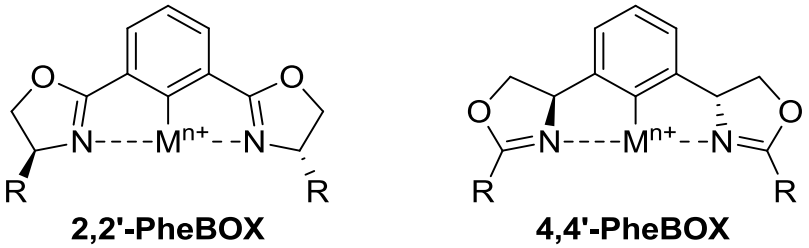


Figure 2.1

In asymmetric catalysis, very often, the chiral catalyst employed is expensive, as the synthesis of the ligands used can involve multi-step procedures utilising chiral building block to introduce chirality. For this reason, recovery and recycling of these catalysts could make these asymmetric reactions a more viable option on large scales where the expense of the catalyst becomes important. The second part of this study involves the complexing of commercially available 2,2'-pyridine-bisoxazoline (PyBOX) ligands with metal salts and electrostatically

immobilising these catalysts on silica. A graphical representation is shown in **Figure 2.2**[6].

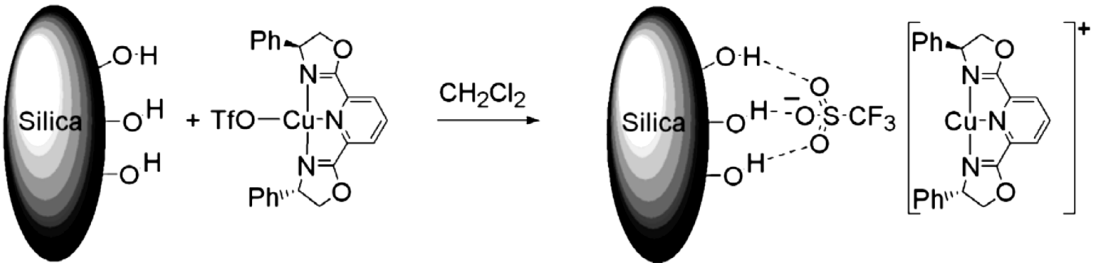


Figure 2.2

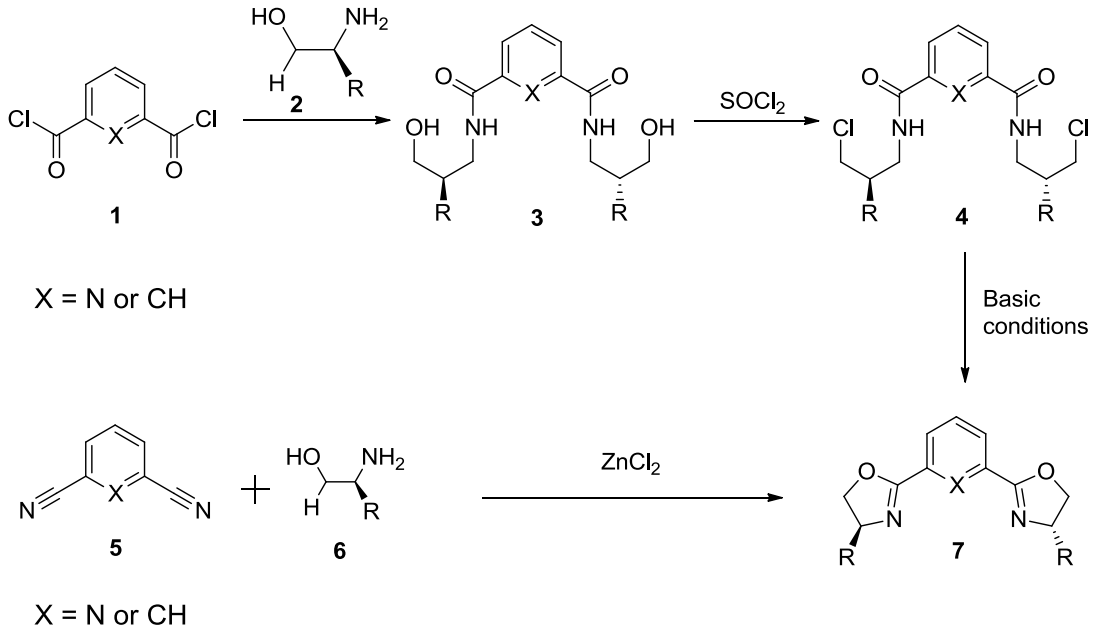
These immobilised catalysts were tested in asymmetric propargylic substitution reactions[7], asymmetric trimethylsilylcyanation reactions[8] and asymmetric ring opening reactions[9]. These reactions were chosen as the equivalent unimmobilised catalysts had shown some activity and stereoselectivity in these reactions.

A numbering scheme, independent of the in **Chapter 1**, is used from this point onwards.

2.2 Synthesis of 4,4'-PheBOX ligands

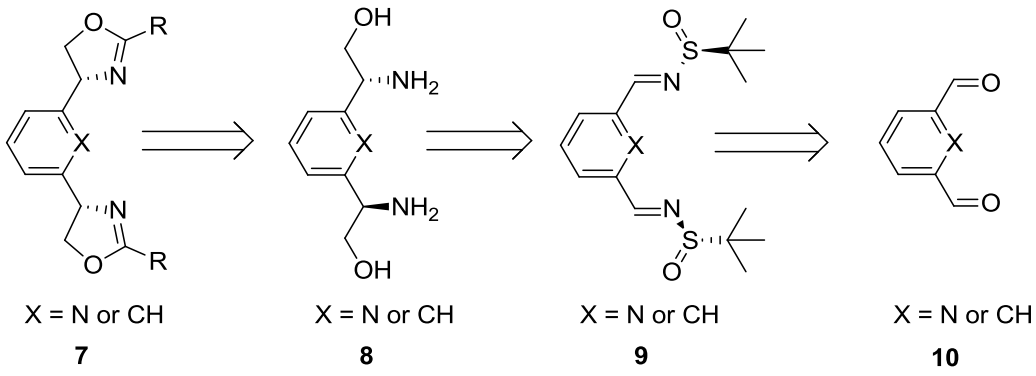
2.2.1 Attempted synthesis *via* sulfinimine

While there are several methods used for the synthesis of 2,2'-PheBOX ligands, **Scheme 2.1** shows two of the most common methods. The first option involves the reaction of acid chloride, **1**, with a chiral amino alcohol **2**, to give bis-amidoalcohol **3**. This can then be reacted with thionyl chloride to form the bis-amido chloride **4** which under basic conditions, is converted into bisoxazoline **6**. The other option uses dinitrile **5**, as a starting material, which is reacted with chiral amino acid, **2**, using zinc dichloride as a catalyst, to produce bisoxazoline **6**.



Scheme 2.1

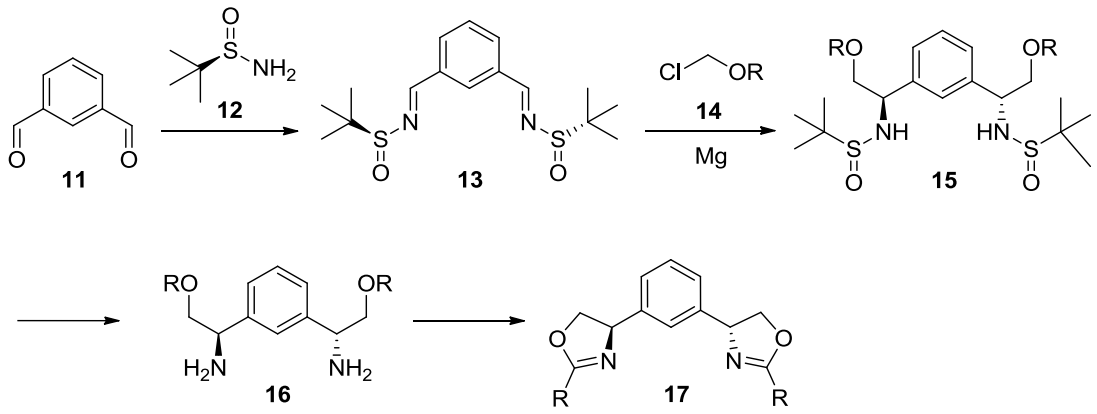
Both 2,2'-PheBOX and 2,2'-PyBOX can by synthesised using these strategies, however these approaches would not allow for the chiral centres to be moved adjacent to the aromatic core of the ligand, so a new synthetic approach was required. A retrosynthetic scheme for the proposed ligands was developed (**Scheme 2.2**). It can be seen that it could be possible to prepare **7** from the corresponding diamino-dialcohol, **8**. That in turn could be formed from reactions involving the sulfinimine **9**. It was conceived that the reaction of the di-aldehyde, **10**, with *N-tert*-butylsulfinamide could be used to synthesise sulfinimine **9**.



Scheme 2.2

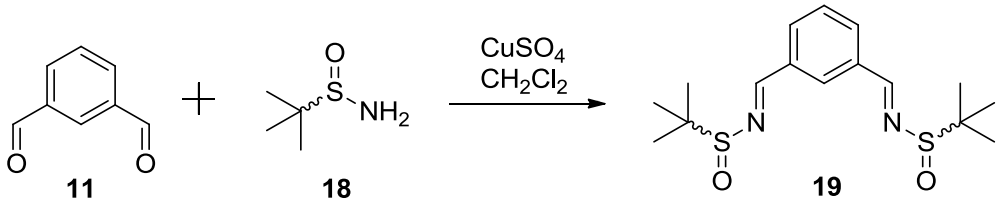
While the aim of the project was to synthesise both the novel PheBOX and novel PyBOX, it was decided to start by using isophthalaldehyde (X = CH in **10**) as financial constraints meant that using 2,6-Pyridinedicarboxaldehyde (X = N in **10**) for method development was not an option.

Our initial plan for the synthesis of **17** (**Scheme 2.3**) would start by reacting isophthalaldehyde, **11**, with *N*-*tert*-butylsulfinamide, **12,** to give the corresponding sulfinimine, **13**. It was thought that the bis-sulfinamide, **15**, could be generated *via* Gringard addition to the sulfinimine, using **14**. Subsequent cleavage of the sulfinyl groups would give the amino alcohol, **16**. This amino alcohol could then undergo a ring closing reaction to give the required ligand **17**.



Scheme 2.3

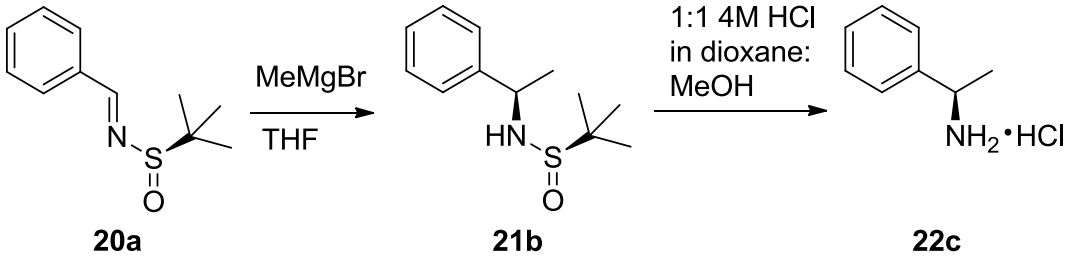
The first step of the synthesis involved the synthesis of sulfinimine, **13**. Owens *et al* previously generated **13** by the Lewis acid-catalysed, condensation of isophthalaldehyde, **11**, and *N*-*tert*-butylsulfinamide, **12**, in the presence of $CuSO_4$[10]. In this reaction the $CuSO_4$ fulfilled a dual role of both a Lewis acid and a dehydrating/drying agent. Again, due to the cost of chiral *N*-*tert*-butylsulfinamide, the racemic reagent, was used initially to investigate the viability of the reaction (**Scheme 2.4**).



Scheme 2.4

Isophthalaldehyde, **11**, was added to an excess of $CuSO_4$ dissolved in CH_2Cl_2 followed by (±)*N*-*tert*-butylsulfinamide, **18**. Owens *et al* stirred the reaction for 4 hours at room temperature and produced bis-*tert*-butanesulfinyl imine, **19** in a 74 % yield. Following the same experimental procedure, but stirring for 48 hours, **19** was successfully synthesised in 69 % yield.

The next step of the synthesis involved the generation of **15** *via* a Grignard reaction. Research carried out by Cogan *et al* showed that it was possible to synthesis α-branched amines using Grignard reactions[11].

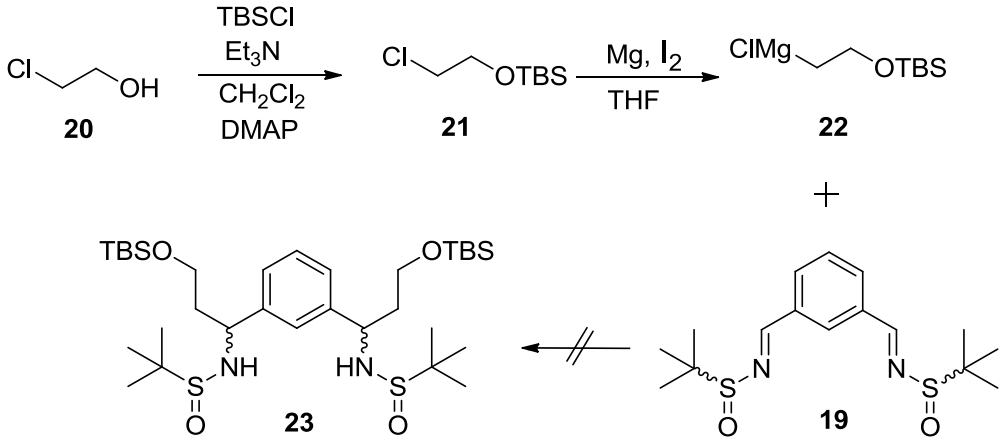


Scheme 2.5

Sulfinimine, **20a**, was reacted with MeMgBr in THF (**Scheme 2.5**) and gave **21b** in 98 % yield with a diastereomeric ratio of 93:7. To remove the *tert*-butanesulfinyl group, **21b** was stirred in 1:1 4M HCl in dioxane:MeOH at room temperature, to produce **22c** in 88 % yield.

It was hoped this method could be exploited in the attempted synthesis of **23** (**Scheme 2.6**). Protected alcohol **21** was generated using a method utilised by Jiang *et al*[12]. Alcohol **20** was reacted with triethylamine (Et_3N), dimethylaminopyridine (DMAP), *tert*-butyldimethylsilyl chloride (TBSCl) in CH_2Cl_2 at -15 °C and gradually

allowed to warm to room temperature over 40 hours, to produce **21**, in 88 % yield. Magnesium turnings, iodine and THF were stirred for 10 minutes at which point **21** was added. The reaction was refluxed for 4 hours, in an attempt to complete the formation of Grignard reagent, **22**, and then cooled to 0 °C, at which point **19** dissolved in THF was added slowly. This reaction was quenched with saturated NH_4Cl after stirring for 2 hours. Analysis of the crude reaction mixture showed that **19** still remained and there was no indication of formation of **23**.

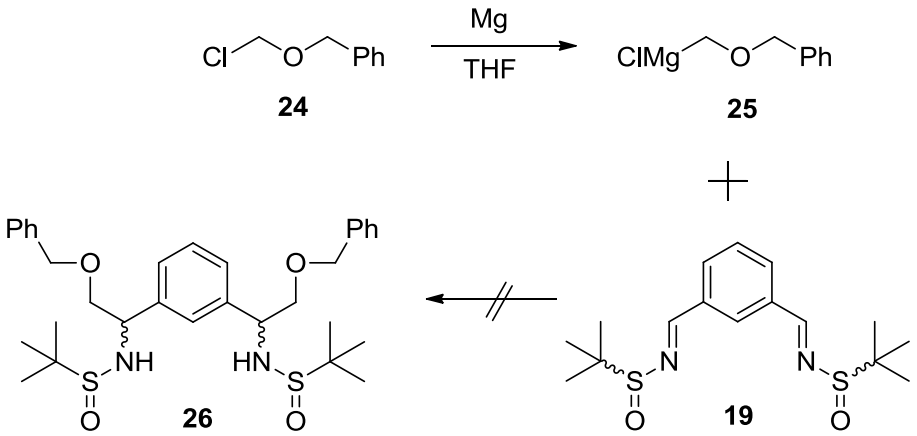


Scheme 2.6

The same reaction was attempted using magnesium powder in the hope that the greater surface area would allow for the initiation of the reaction which formed **22**. Again, only **19** was present at the end of the reaction. Another variation of the reaction involved the use of LiCl to catalyse the Mg/halogen exchange[13]. Unfortunately this also proved to be fruitless. It was hypothesised that the difficulties lay in generating the Grignard reagent **22**, as the grey cloudy colour commonly seen in Grignard reagent generation was not observed. It was conceived that perhaps the protection of alcohol **20**, may be the step that was causing difficulties as **21** may not have been as pure and dry as required for Grignard reactions.

It was decided to attempt the same type of reaction using benzyl chloromethyl ether, **24**, a reagent that was available commercially. Magnesium turnings and THF

were stirred and benzyl chloromethyl ether, **24**, in THF, was added to produce Grignard reagent **25** as seen in **Scheme 2.7**. Bis-sulfinyl imine, **19**, dissolved in THF was then added and the reaction was refluxed overnight.

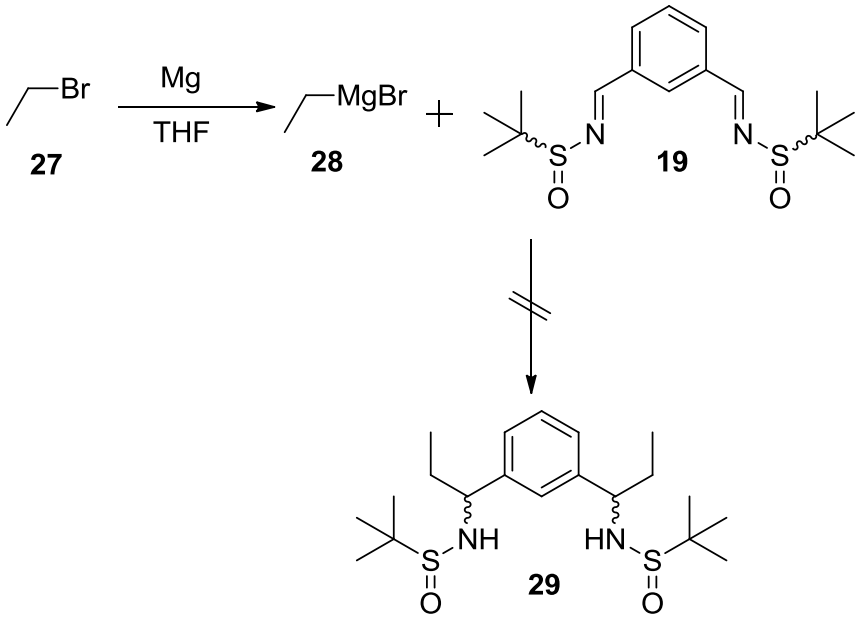


Scheme 2.7

Certain ^{1}H NMR signals would have been expected to show that **26** had been formed including a signal between 6 – 7 ppm, integrating for two protons, representing the N*H* protons. The C*H*NH proton signals should be seen between 4 - 5 ppm, integrating for two protons, and two more signals between 3 – 4 ppm, integrating for four protons, corresponding to the two CHCH_2O groups. However, ^{1}H NMR and ^{13}C NMR spectral analysis of the crude reaction mixture showed that **19** was still present and no reaction had occurred. This reaction was also attempted using magnesium powder rather than magnesium turnings, however again no reaction took place.

Since the Grignard reaction using the TBS protected chloroethanol, **21**, and benzyl chloromethyl ether, **24**, was proving difficult, it was decided to investigate the reaction using a simpler reagent, ethyl bromide, **27** (**Scheme 2.8**). In this reaction, **27** in THF was slowly added to a stirring solution of magnesium turnings in THF. After 4 hours, the solution was cloudy grey which indicated that the Grignard reagent, **28**, had formed, so the solution was cooled to 0 °C. Then **19** in THF was slowly added and the reaction was stirred overnight and allowed to gradually warm

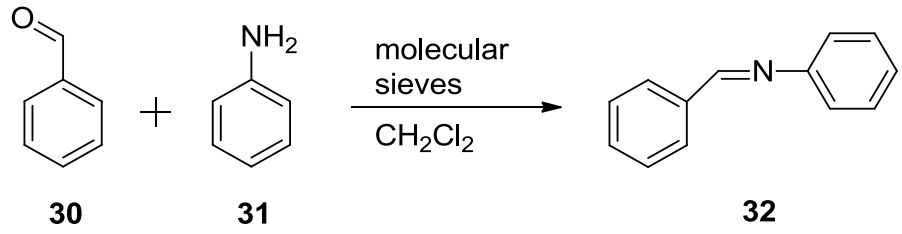
to room temperature. The reaction was monitored by TLC and when it was complete it was quenched and worked up to give a brown oil crude product.



Scheme 2.8

This crude product was analysed by ^{1}H NMR, which revealed some interesting signals including 7.30 – 7.17 ppm (4H, m), 4.27 - 4.25 ppm (1H, m), 3.38 ppm (1H, dd), 2.08 – 2.01 ppm (2H, m) and several signals between 1.85 ppm and 0.72 ppm, however, these did not correspond to what would be expected for the required product, **29**.

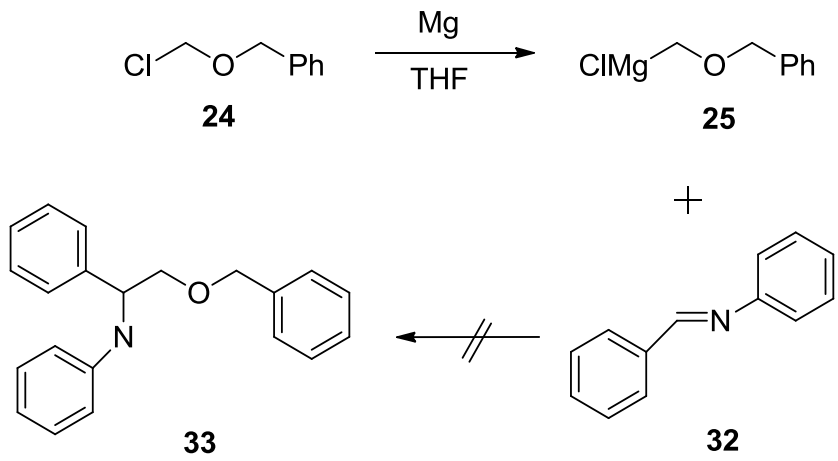
Finally, to investigate whether the problem with the reactions lay in the sulfinyl imine, **19**, it was decided to investigate the Grignard reaction using a simpler imine, **30** (**Scheme 2.9**).



Scheme 2.9

N-(phenylmethylene)benzenamine, **32**, was synthesised using a method reported by Derdau *et al* [14]. Benzaldehyde, **30** was reacted with aniline, **31**, in anhydrous CH_2Cl_2 in the presence of oven dried 4Å molecular sieves. The reaction was stirred at room temperature for 40 hours and the crude product was purified by recrystalisation, giving a 62 % yield of yellow crystalline solid, **32.** This imine, **32**, was then subjected to a Grignard reaction.

Benzyl chloromethyl ether, **24**, dissolved in THF was added to a stirring solution of magnesium turnings in THF (**Scheme 2.10**). The solution was stirred for 2 hours at room temperature, to generate the Grignard reagent, **25**, and then a solution of imine **32** dissolved in THF was slowly added. The reaction was refluxed for 15 hours and quenched with saturated NH_4Cl.

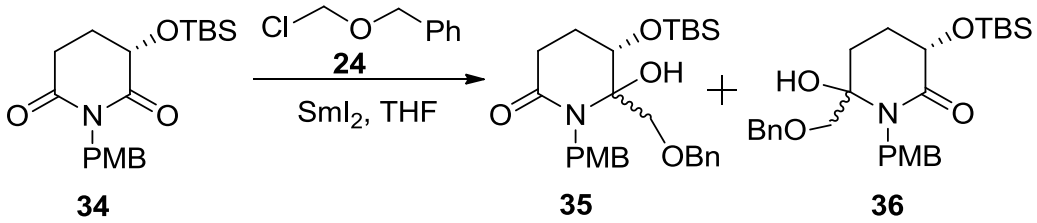


Scheme 2.10

Certain ^{1}H NMR signals would have been expected to show that **33** had been formed, including a signal between 4.5 – 5.5 ppm, integrating for one proton, representing the N*H* proton. The C*H*NH proton signals should be seen between 4 - 5 ppm, integrating for one proton and two more signals between 3 – 5 ppm, integrating for four protons, corresponding to the two CH_2O groups. ^{1}H NMR and TLC analysis of the crude product showed that the starting products still remained.

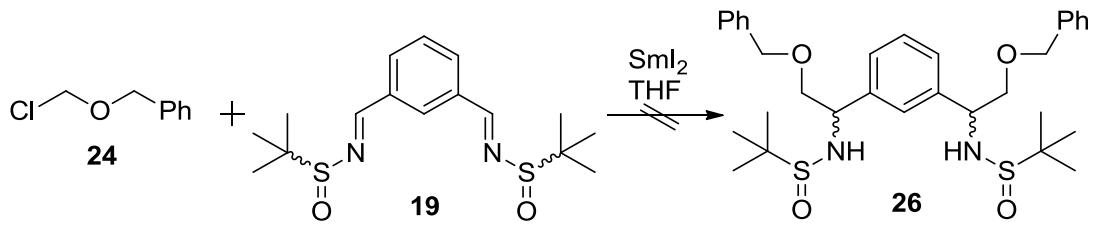
From all of these results, it became clear that the Grignard reaction was not a viable option for the generation of a bis-sulfinyl amide. It seems generation of the required Gringard reagents is synthetically difficult and also, even if formed, addition to the sulfimine appears challenging. From this, it became apparent that it was necessary to do some more research to find other possible methods of generating **23** or **26**.

Wei et al synthesised 2-epi-deoxoprosopinine and aza-sugar derivatives by utilising using SmI_2 mediated coupling of (S)-3-silyloxyglutarimide, **34**, with benzyl chloromethyl ether, **24**, in the presence of samarium diiodide[15]. The reaction was carried out at room temperature and was stirred for 10 minutes producing **35** and **36** in a combined yield of 84 % with a ratio of 81:19 **35**:**36** as seen in **Scheme 2.11**.



Scheme 2.11

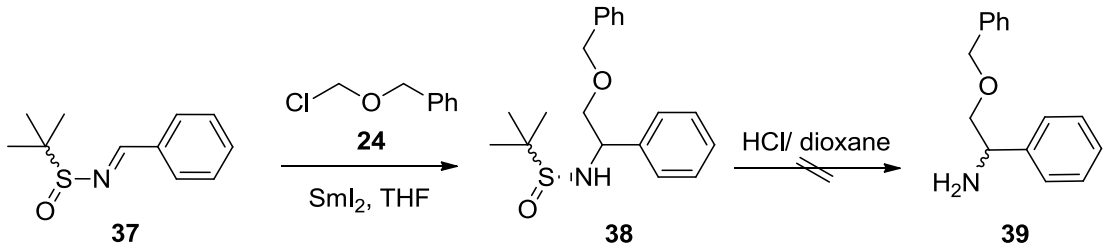
Utilising this information, the synthesis of **26** was attempted using a modified method. Benzyl chloromethyl ether, **24** and bis-sulfinyl imine, **19** were dissolved in THF and samarium diiodide in THF (1M in THF) was added quickly under N_2. The reaction was stirred overnight at room temperature as seen in **Scheme 2.12**.



Scheme 2.12

After the reaction was worked up a yellowish brown liquid remained. While ^{1}H NMR and ^{13}C NMR spectral analysis of the crude reaction mixture showed that the starting materials were no longer present, it proved impossible to separate the products formed and unfortunately, the identifying signals listed above corresponding to the required product **26**, were not visible.

After the failed attempted synthesis of **26**, it was possible that the difficulty lay in the double reaction of the benzyl chloromethyl ether, **24**, with the bis-sulfinyl imine. To test this hypothesis the reaction was carried out on the mono substituted **37** as seen in **Scheme 2.13**.



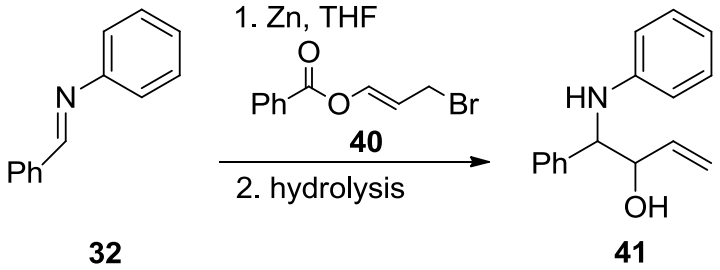
Scheme 2.13

In this reaction, **37** was dissolved in THF and **24** and 0.1 M SmI_2 in THF were added under an inert atmosphere. The reaction was stirred for 16 hours at room temperature. After the reaction was quenched, the crude product was purified by column chromatography (9:1 to 6:4 Pet ether:EtOAc). ^{1}H and ^{13}C NMR and MS analysis proved inconclusive as to whether **38** had formed. It was hoped that a cleared picture could be obtained if the sulfinyl group was removed, so 1 mL of HCl/1,4 dioxane (4:8.5) was added to the crude product and the mixture was stirred at room temperature for 5 hours. When ^{1}H and ^{13}C NMR spectral analysis of the crude reaction mixture was carried out, it showed many interesting peaks, however, none of them corresponded to the desired product **39**.

Without fully characterising what is happening in the reaction, it was decided that the synthesis of **26** should be attempted *via* a different method, as not only did we

need to get the reaction to work, but also work in good yield on a reasonable scale, so we would have sufficient material to continue with the synthesis.

The final attempt at synthesising **26** employed a Barbier type reaction, as unlike the Grignard reaction, the Barbier reaction is a one pot synthesis and does not require the generation of a Grignard type reagent. Keinicke *et al* developed a protocol for the synthesis of vicinal amino alcohols[16]. The method employed a Barbier-type reaction between an imine and 3-benzoyloxyallyl bromide in the presence of zinc metal. The addition products are debenzoylated to afford amino alcohols in good yields and with high diastereomeric ratios (**Scheme 2.14**)

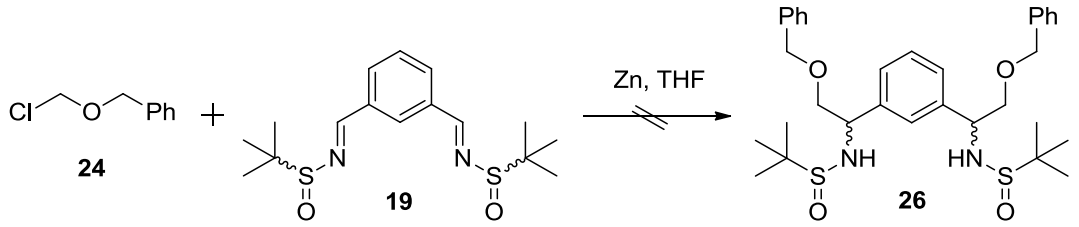


Scheme 2.14

For example, imine, **32**, and **40** were dissolved in THF and activated zinc was added. The zinc was activated by stirring in 1M HCl followed by washing with water, acetone and ether and then dried under vacuum. When the reaction was complete, (determined by TLC that no starting material remained) the crude reaction mixture was worked up and hydrolysis was carried out to remove the benzoyl group, leaving **41** in 90:10 diastereomeric ratio.

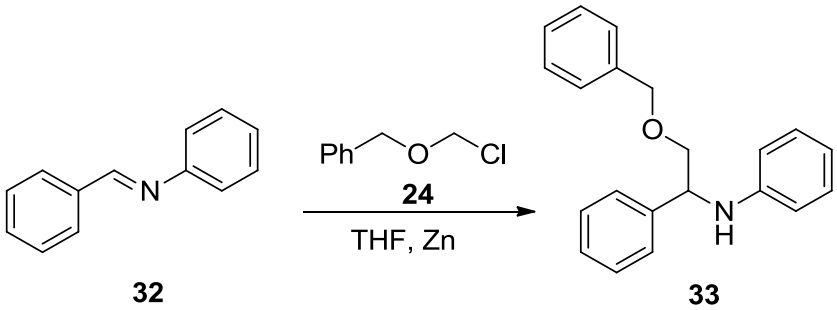
Using this method, the synthesis of **26** was attempted. Benzyl chloromethyl ether, **24** and bis-sulfinyl imine, **19** were dissolved in THF and activated zinc was added under N_2 (**Scheme 2.15**). The zinc was activated in the same manner as previously described. The reaction was stirred for 3 hours at room temperature and followed by TLC. When the reaction was complete, the reaction mixture was filtered through

a celite pad, which was then thoroughly washed with THF. The organic phases were combined and reduced *in vacuo*.



Scheme 2.15

This produced an inseparable mixture of products. ^{1}H NMR and ^{13}C NMR spectral analysis showed it contained none of the required identifying signals listed above for **26**. Again it was queried whether the difficulty of this type of reaction lay in the double reaction of sulfinyl imine, **19**. It was decided to investigate the reaction using the same simpler imine, **32** that was used for testing the Grignard reaction (**Scheme 2.16)**



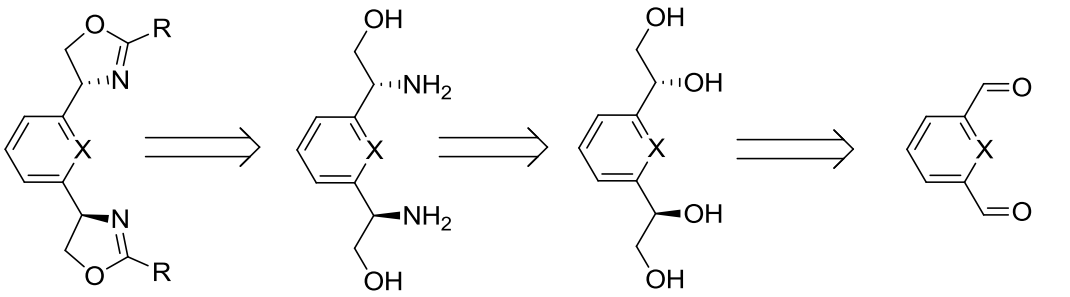
Scheme 2.16

Imine **32** was reacted with benzyl chloromethyl ether, **24**, and activated zinc. The zinc was activated in the same manner as previously described. The reaction was stirred for 1.5 hours at room temperature and followed by TLC. When the reaction was complete, the reaction mixture was filtered through a celite pad, and then thoroughly washed with THF. ^{1}H NMR spectral analysis of the crude product showed some interesting signals like 8.84 ppm (s), 7.37 - 7.28 ppm (m),

5.74 - 5.72 ppm (m), 5.66 ppm (dd), 5.59 ppm (dd), 4.89 ppm (s), 4.84 ppm (s), 4.64 ppm (d), 4.34 ppm (t), 4.00 – 3.93 ppm (m) and several signals between 2.50 ppm and 1.70 ppm. Analysis of integration led to no clear picture of what had formed, however it seems unlikely that **33** was generated.

2.2.2 Synthesis *via* tetrol 45

From all these unsuccessful attempts, it became clear that it was necessary to find a new reaction pathway for the synthesis of these novel 4,4'-PheBOX ligands that did not involve the use of Grignard or Barbier type reactions. From the retrosynthetic analysis in **Scheme 2.17**, the amino alcohol, **8**, was identified as an important intermediate.

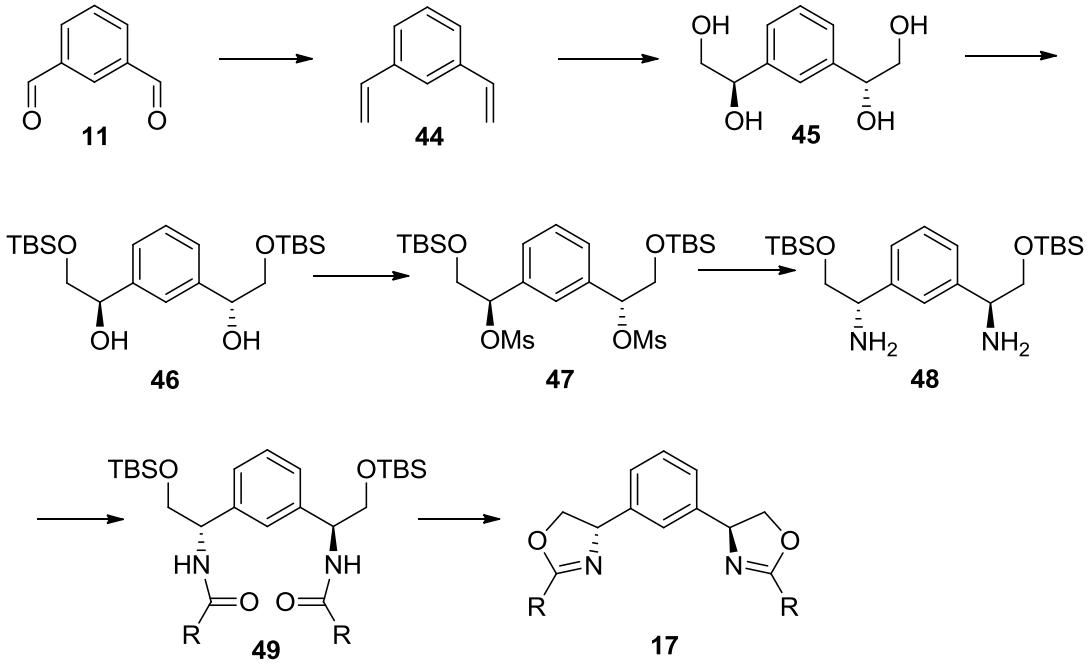


Scheme 2.17

As the sulfinyl imine reactions proved very difficult, it was identified that **7** could be synthesised from the amino alcohol (**Scheme 2.17**). That in turn could be generated in a number of steps from the tetrol **43**, which could be produced from the same starting material used in the previous reactions, **10**.

Again, our planned synthesis began with isophthalaldehyde, **11**, which could be converted into divinylstyrene, **44** (**Scheme 2.18**). This in turn could undergo a Sharpless asymmetric dihydroxylation reaction to produce tetrol **45**. It was then conceived that the primary alcohols could be selectively protected over the

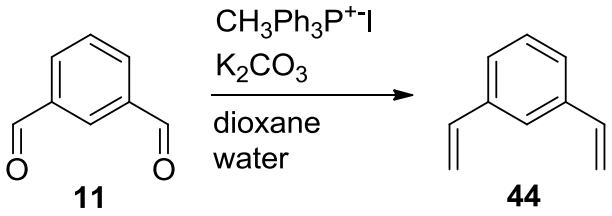
secondary alcohols using *tert*-Butyldimethylsilyl chloride to generate **46**. After the primary alcohols were protected, it was hoped to react methanesulfonyl chloride with the secondary alcohols giving **47**. It was thought that **48** could be synthesised through substitution of the methanesulfonates with azides followed by reduction to give amines. Then **48** could be reacted with numerous different acid chlorides to produce various versions of **49**, each of which could undergo a ring closing reaction to produce various versions of **17**.



Scheme 2.18

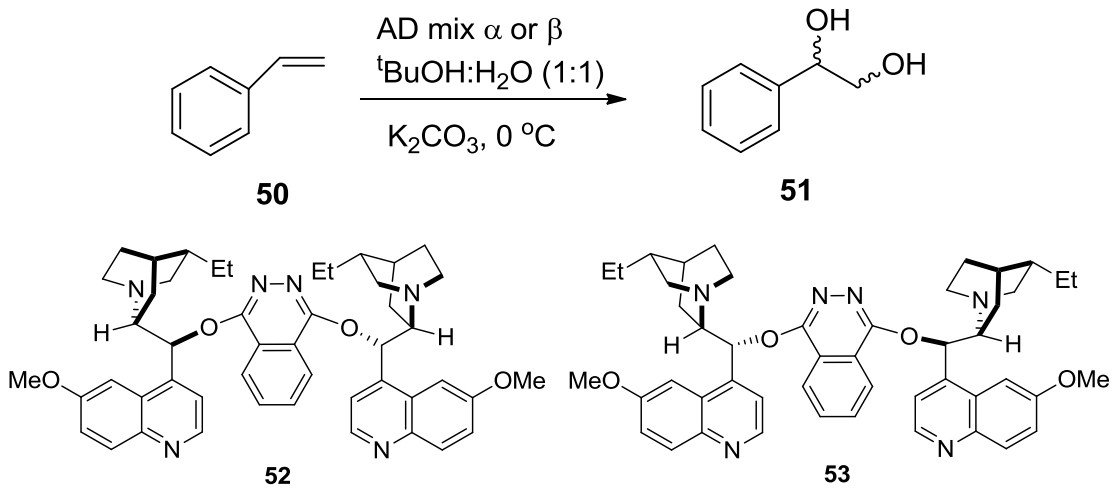
The first step of the synthesis involved the generation of 1,3 divinylbenzene, **44**, using isophthalaldehyde, **11** by Wittig reaction and a method developed by Gauler *et al*[17]. Firstly, methyltriphenylphosphonium iodide was generated by the addition of MeI to a stirring solution of PPh_3 in toluene at 0 °C. The solution was allowed to warm to room temperature and stirred for 3 hours. The solution was concentrated *in vacuo* to give Ph_3PMeI in 100 % yield as a white solid. It was then dissolved in dioxide with 1.5 % water and K_2CO_3 and isophthalaldehyde, **11** was added (**Scheme 2.19**). The reaction mixture was heated to reflux for 16 hours under an inert atmosphere. After the work, up the crude product was purified using flash

chromatography on silica gel (gradient elution 100:0 - 95:5 Pet ether:EtOAc) to give 3.86 g (54 % yield) of a colourless liquid, **44**. The ^{1}H and ^{13}C NMR data corresponded to those reported by Gauler *et al*.



Scheme 2.19

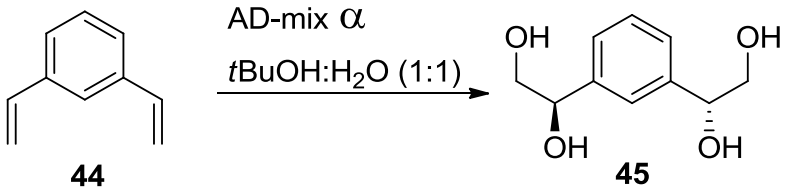
The next step of the synthesis was to introduce chirality and alcohol groups into the molecule. From a publication search carried out, it was identified that the easiest method involved using a catalytic Sharpless asymmetric dihydroxylation. Research carried out by Sharpless *et al* showed that osmium-catalyzed asymmetric dihydroxylation was easily applicable to a wide range of olefins. For example, styrene, **50** was reacted with AD mix α or β and potassium carbonate in a 1:1 mix of ^{t}BuOH:water at 0 °C to give either the *R* or the *S* derivative of **51**, in a 97 % *ee*, depending on whether AD mix α or β was utilised (**Scheme 2.20**).



Scheme 2.20

The 'AD mix', developed by Sharpless *et al,* is a premix containing $K_2OsO_2(OH)_4$ as a non-volatile osmium source, $K_3Fe(CN)_6$ as co-oxidant and either ligand, **52** or **53,** giving AD-mix β and AD-mix α respectively. For all the examples that were reported 1 mmol of mono-substituted olefin was reacted with 1.4 g of AD mix α or β.

Encouraged by these results, it was decided to attempt the reaction using divinylbenzene, **44** (**Scheme 2.21**). However, it appears that there is no report, to date, of a dihydroxylation of such a divinyl aromatic system in the literature.



Scheme 2.21

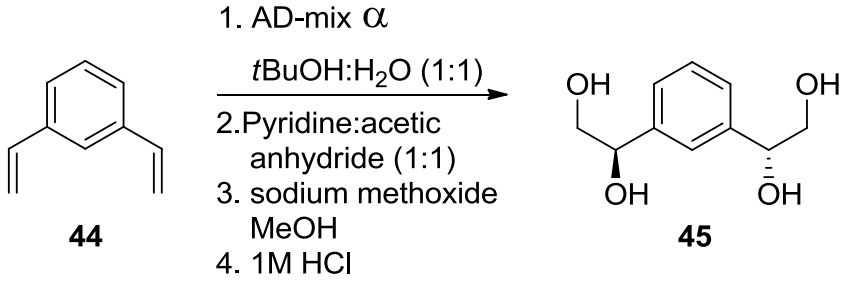
There were many elements to consider when determining the optimum reaction conditions. Initially the reaction was successfully carried out at 0 °C for 2 hours using one mmol of **44**. Due to the demand for large amounts of tetrol in this multi-step synthesis, the reaction was next attempted using 10.8 mmol of **44** which was reacted with 31.9 g of AD mix α and was stirred at 0 °C for 2.25 hours, but this only generated 30 mg of the required product, **45**. When the amount of divinylstyrene was decreased to 5.4 mmol and the reaction was carried out under the same conditions, the only product produced was 480 mg of mono-diol mono-styrene.

In an attempt to improve the yield of the required product, **45**, it was decided to increase the reaction time. This in itself created problems, as keeping the reaction at 0 °C for prolonged periods of time was difficult. After testing a number of different methods, a methanol cooling bath became the method of choice. The reaction was then attempted using 3.84 mmol of **44** (500 mg) with 11.2g of AD mix α and was stirred at 0 °C for 41 h which produced **45** in 37 % yield of white

crystalline solid. This became the optimum temperature and stirring time for the reaction.

Another problem that was encountered was the solubility of the tetrol **45**. The diol **51** produced by Sharpless *et al* was extracted using either ethyl acetate or CH_2Cl_2. That was not an option for tetrol **45** due to the increased polarity of the molecule. Initial work up methods involved quenching the reaction using sodium sulphate, filtration through a celite pad and a separation of the organic and aqueous layers, however when the aqueous layer was concentrated *in vacuo* and sonicated in ethyl acetate more tetrol **45** was found. For this reason, it was decided that an acetylation reaction should be carried out on the crude reaction mixture after it had been quenched, to allow for the easy removal of all the synthesised tetrol, followed by deacetylation, producing **45**.

Finally the last problem encountered was carrying out the reaction on a large scale. When the reactions were carried out on gram scales, the volume of AD mix required caused problems. It was also found that there were dramatically lower yields of tetrol **45** produced when the reaction was carried out on these larger scales. From all the research into the reaction, the optimum reaction conditions and method were uncovered (**Scheme 2.22**). To begin with, 11.4g of AD mix α was stirred in 1:1 *t*BuOH:water at room temperature for one hour. The reaction was then cooled to 0 °C and **44** (3.84 mmol, 500mg) was added. This was stirred for 41 hours. The reaction was quenched by the addition of sodium sulphite (5.7g) and the solvent was removed under vacuum.



44 **45**

Scheme 2.22

The crude reaction mixture was then cooled to 0 °C and acetylated using 1:1 acetic anhydride:pyridine. This was stirred overnight and the crude acetylated product was extracted using EtOAc. The acetylated product was then dissolved in MeOH and 1M sodium methoxide in MeOH was added. This was again stirred overnight. The solution was acidified using 1M HCl or Dowex (H^+) or Amberlyst (H^+) and evaporated under reduced pressure. The product was then purified using flash chromatography to give 474 mg (62 % yield) of a white crystalline solid **45**. The reaction to prepare tetrol **45** was carried out repeatedly until sufficient quantities were produced to continue with the synthesis.

The structure of **45** was confirmed by ^{1}H NMR (**Figure 2.3**) and ^{13}C NMR analysis. The multiplet from 7.33 - 7.19 ppm represents the four aromatic hydrogens in the molecule, while C*H*OH appears as the multiplet at 4.68 - 4.63ppm. Finally, a doublet at 3.61 ppm corresponded to the four CH_2OH protons which displays vicinal coupling to C*H*OH (J = 5.8 Hz). As the NMR's were carried out in D_2O the OH signals are not seen.

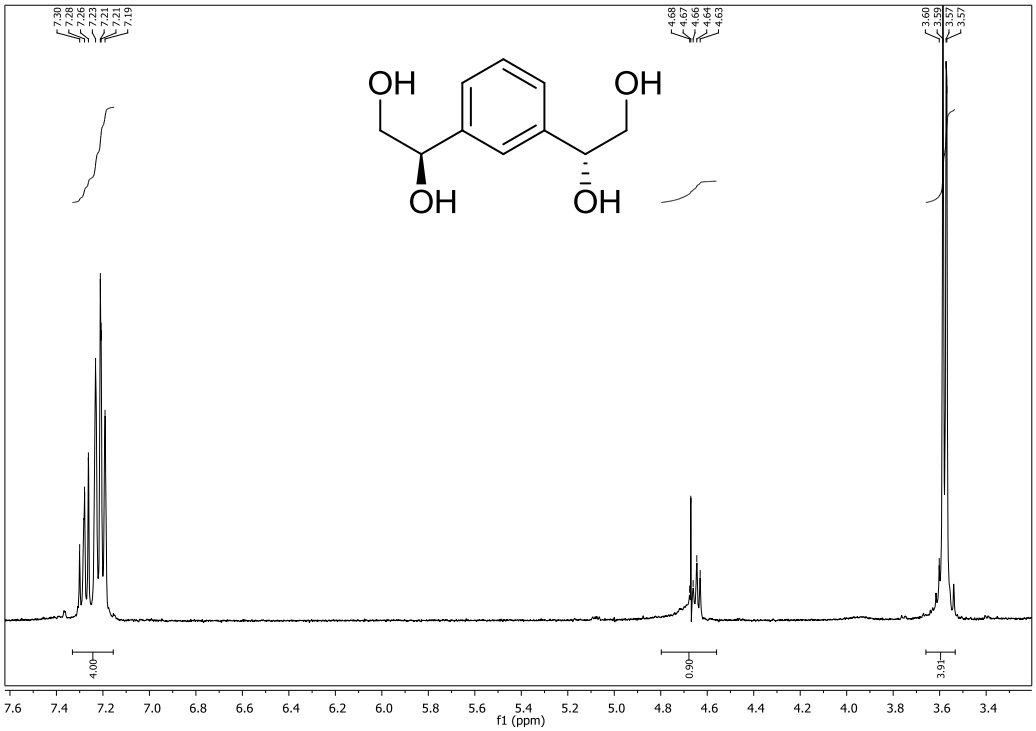
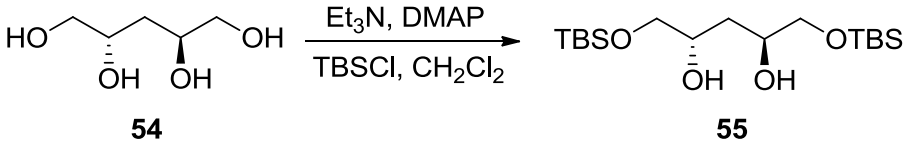


Figure 2.3

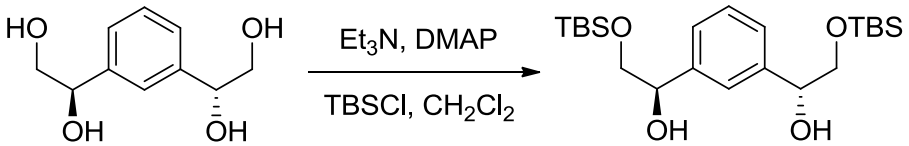
The next step of the synthesis involved the selective protection of the primary alcohols using *tert*-butyldimethylsilyl chloride. Frain *et al* achieved this during the synthesis of a novel 4,4'-BOX ligand, AraBOX[18] (**Scheme 2.23**).



54 **55**

Scheme 2.23

Tetrol **54** was reacted with triethylamine, dimethylaminopyridine, *tert*-butyldimethylsilyl chloride in CH_2Cl_2 at -15 °C – r.t. for 40 hours, to produce **55** in a 65 % yield. The same method was employed for the protection of the primary alcohols of tetrol **45** (**Scheme 2.24**).



45 **46**

Scheme 2.24

A stirring solution of **45** in CH_2Cl_2 was cooled to -15 °C and triethylamine was added. It was allowed to stir for 15 minutes. Then dimethylaminopyridine and *tert*-butyldimethylsilyl chloride were added and the reaction was allowed to gradually warm to room temperature and stirred for 42 hours. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography producing a 46 % yield of a colourless crystalline solid **46**. The structure of **46** was confirmed by reference to the ^{1}H NMR (**Figure 2.4**) and ^{13}C NMR spectra.

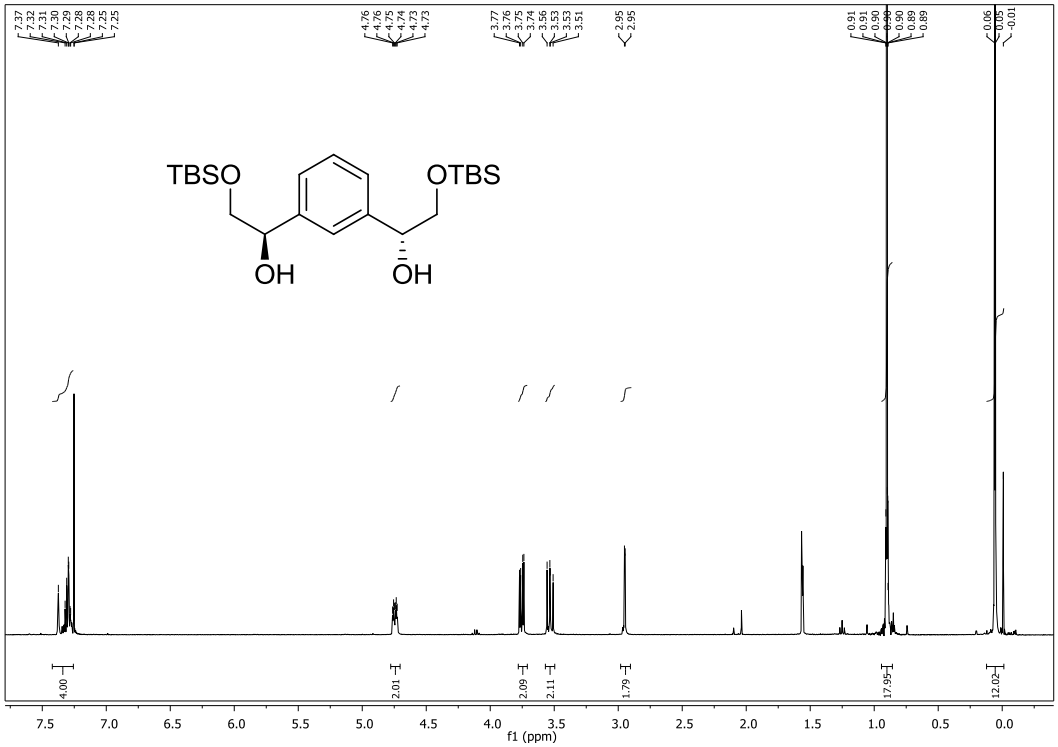
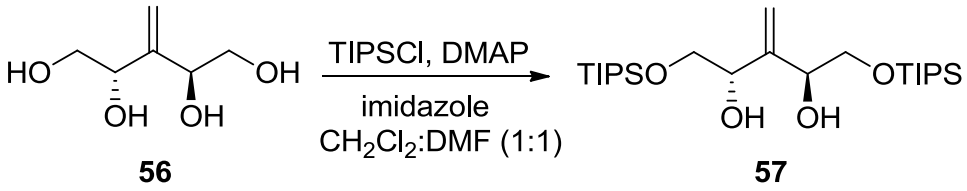


Figure 2.4

The ^{1}H NMR spectrum of **46** was more complicated than that of tetrol. The four aromatic protons are still represented by a multiplet at 7.37 - 7.28 ppm. Next, there is a double triplet signal at 4.72 ppm representing the two C*H*OH protons in the molecule, with vicinal coupling to CH_2OH (J = 8.6 Hz) and long range coupling to the aromatic proton (J = 3 Hz). This is followed by two double doublet signals at 3.75 ppm and 3.52 ppm that correspond to the four protons of the CH_2OH's. These signals show vicinal coupling to C*H*OH (J = 3.6 Hz and 8.7 Hz) and geminal coupling (J = 10.1 Hz and 10.1 Hz) respectively. At 2.95 ppm a doublet, corresponding to the two protons of the alcohol groups is seen, which exhibits vicinal coupling to C*H*O (J = 2.3 Hz). This was followed by a singlet at 0.89 ppm, which represents the eighteen protons in the *tert*-butyl (CCH_3) of the silyl protecting group, and a doublet at 0.05 ppm that is due to the 12 protons of the di-methyl (SiCH_3) of the protecting groups. These last two signals are central to identifying that **46** has formed. Even after an extended period on the vac-line, a small amount of ethyl acetate and water still remained in the product.

The relatively low yield in this reaction is due to the generation of tri-TBS and tetra-TBS products as well as the di-product. These by-products were easily desilylated by stirring them with 1 % HCl in methanol for 24 h. When the reaction was complete, the organic solvent was evaporated under reduced pressure and the crude product was then purified using flash chromatography. Due to the relatively low yield of the reaction at an early point in the multi-step synthesis, other reagents were investigated for the protection of the primary alcohols.

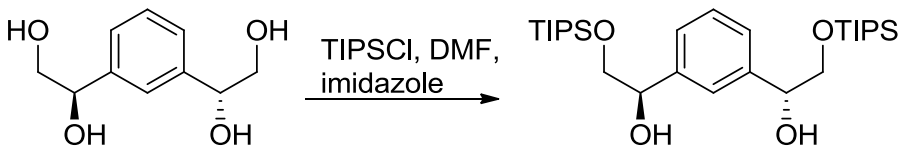


56 **57**

Scheme 2.25

Triisoproplysilyl chloride was identified as a more sterically hindered protecting group and so this could impede the formation of the unwanted by-products. Maleczka *et al* successfully protected the primary alcohols over the secondary alcohols using TIPS chloride[19] (**Scheme 2.25**). Tetrol **56** was reacted with triisoproplysilyl chloride, dimethylaminopyridine and imidazole in a 1:1 mixture of CH_2Cl_2 and DMF. The reaction was stirred at room temperature for 12 hours to give a 97 % yield of **57.**

Encouraged by these results, tetrol **45** was dissolved in dimethylformamide (DMF) and cooled to 0 °C. Imidazole was added and it was allowed to stir for 10 minutes. Then, triisoproplysilyl chloride was added and the reaction was allowed to gradually warm to room temperature and stirred for 24 hours.



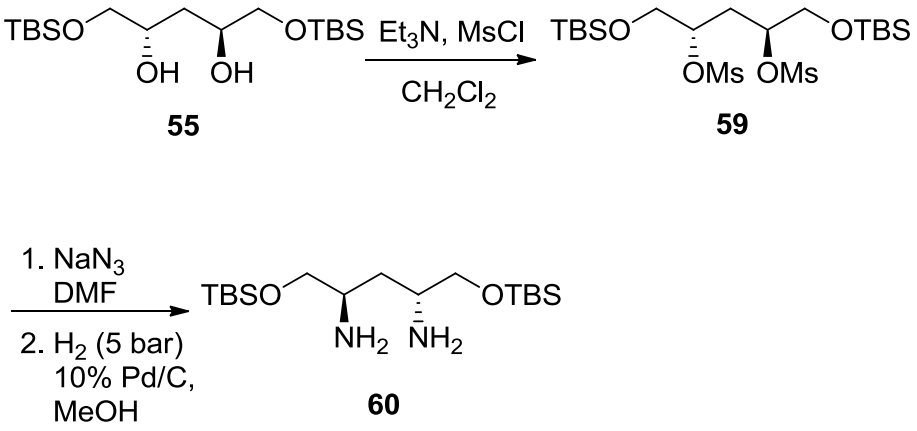
45 **58**

Scheme 2.26

The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography using silica gel (gradient elution 99:1 - 60:40 Pet ether:EtOAc) to give a 33 % yield of a colourless crystalline solid, **58**.

The structure of **58** was confirmed by analysis of its ^{1}H NMR spectrum, which shows signals due to the backbone signals similar to **45**. In this case, the aromatic protons are seen as a singlet integrating for one proton at 7.38 ppm and a multiplet, integrating for three protons, between 7.34 - 7.28 ppm. Next, there is a double doublet signal at 4.77 ppm representing the two C*H*OH protons in the molecule with vicinal coupling to CH_2OH (J = 8.7 Hz) and long range coupling to the aromatic proton (J = 3.5 Hz). This is followed by a double doublet signal at 3.75 ppm and a multiplet signal from 3.63 – 3.58 ppm that corresponds to the four protons in CH_2OH. The former signal shows vicinal coupling to C*H*OH (J = 3.6 Hz) and geminal coupling (J = 9.9 Hz). At 3.08 ppm a broad singlet, corresponding to the two protons of the alcohol groups, was seen followed by a multiplet from 1.07 - 1.05 ppm, integrating for 42 protons, which represents six C*H*$(CH_3)_2$ and twelve CHCH_3. While the poor yield of the reaction was disappointing, it was decided to investigate the use of the TIPS diol, **58**, in the next step of the synthesis before its use was completely ruled out.

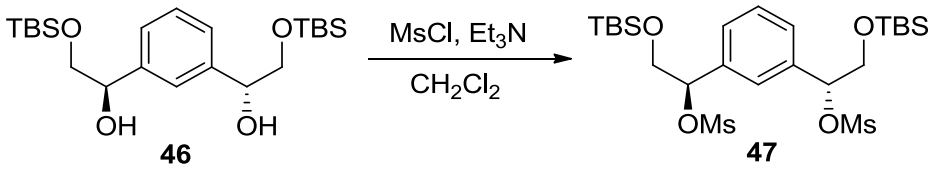
The next step of the synthesis required the conversion of the alcohol groups to leaving groups so that they can be converted to azides and then reduced to amines. Again, a similar technique to this was used by Frain *et al* in the synthesis of AraBOX[18]. Tetrol **55** was reacted with triethylamine and methanesulfonyl chloride in CH_2Cl_2 for 4 hours with the temperature initially at 0 °C and allowed to rise to room temperature producing **59** in 99 % yield (**Scheme 2.27**). The next step involved conversion of **59**, initially to the di-azide, and then to the di-amine. So, **59** was reacted with sodium azide in dimethylformamide for 16 hours at 85 °C. The reaction mixture was filtered through a celite pad and the solution was concentrated under reduced pressure. The diazido compound, **59** was not purified any further but was hydrogenated using 10 % Pd/C, H_2 (5 bar) in MeOH. This was stirred for 4 days at room temperature and produced **60** in 76 % yield.



55 **59** **60**

Scheme 2.27

This method was utilised for the synthesis of **47** and then **48**. Firstly a solution of **46** was dissolved in CH_2Cl_2 and was cooled to 0 °C (**Scheme 2.28**). Triethylamine and methanesulfonyl chloride were then added and the reaction was allowed to gradually warm to room temperature and stirred for 18 hours. The reaction was quenched using saturated sodium bicarbonate solution and extracted using EtOAc. The combined organic layers were dried over $MgSO_4$ and filtered.



46 **47**

Scheme 2.28

Initially, when the reaction was carried out on smaller scales (0.3 to 0.6 mmol of **46**), the crude reaction mixture was successfully purified using column chromatography. However when the reaction was carried out using 3.5 mmol of **46** and the crude reaction mixture was purified using a silica column, none of the required product **47** was found. ^{1}H NMR analysis of the material that came off the column showed many signals between 5.5-5.0 ppm, which indicated that perhaps some kind of polymer had formed. This could have been due to a reaction of the compound on the silica used in the column. As a result of this loss of product, **47**

was no longer isolated and the crude reaction mixture was used without further purification. In this case, **47** was produced in 105 % yield of a colourless liquid.

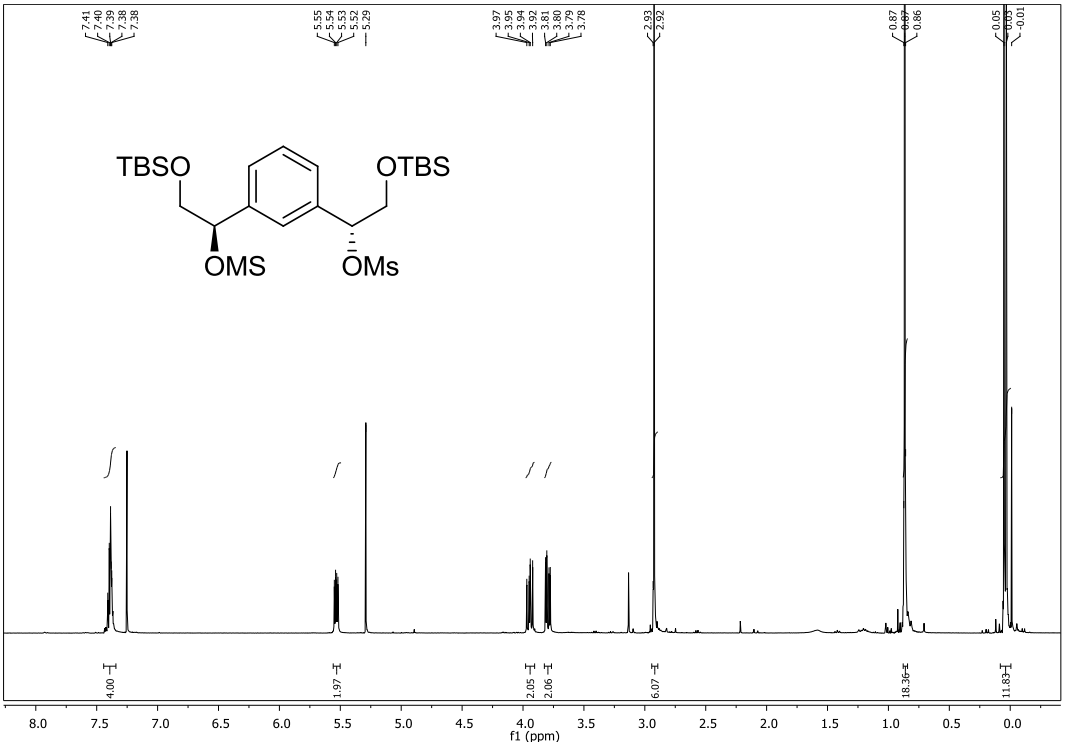
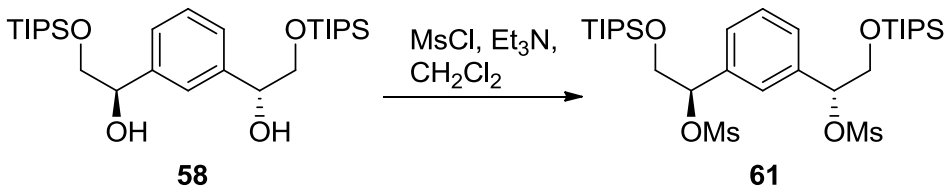


Figure 2.5

The structure of **47** was verified using ^{1}H NMR and ^{13}C NMR analysis. Again, the backbone ^{1}H NMR signals are similar to those seen in the ^{1}H NMR of **46**. The four aromatic protons correspond to the multiplet at 7.44 - 7.36 ppm (**Figure 2.5**). The double doublet at 5.54 ppm is due to the two C*H*OMs protons which display vicinal coupling to the CH_2O protons (J = 7.8 Hz and 4.0 Hz). There are also two double doublet signals at 3.94 ppm and 3.80 ppm that are due to the four protons in CH_2OH. These signal show vicinal coupling to C*H*OH (J = 7.9 Hz and 4.1 Hz) and geminal coupling (J = 11.3 Hz and 11.4 Hz) respectively. A singlet at 2.92 ppm integrating for six protons corresponds to the two SCH_3 groups in the mesylate and this is a central signal for confirming that **47** was formed. Finally, a singlet at 0.87 ppm integrating for eighteen protons and a doublet at 0.04 ppm integrating for twelve protons correspond to the six CCH_3 and four SiCH_3 of the silyl protecting

groups respectively. A CH_2Cl_2 solvent signal can also be seen in the spectrum at 5.29 ppm.

This same reaction was attempted on TIPS protected diol, **58** (**Scheme 2.29**). Again, a solution of **61** was dissolved in CH_2Cl_2 and was cooled to 0 °C.

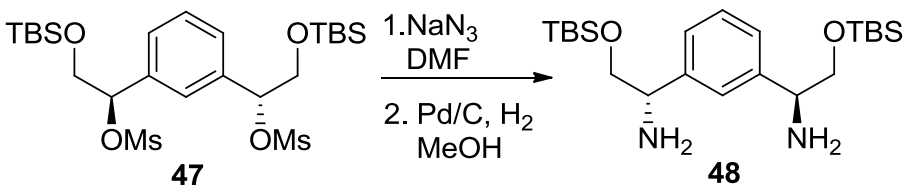


58 **61**

Scheme 2.29

Triethylamine and methanesulfonyl chloride were then added and the reaction was allowed to gradually warm to room temperature and stirred for 6 hours. In this case, the crude product was purified by column chromatography using silica gel (99:1 - 60:40 Pet ether:EtOAc) to give a 60 % yield of white solid **61**. The structure of **61** was confirmed by ^{1}H NMR analysis. Due to the initial poor yield of the TIPS protection of the primary alcohols coupled with the relatively poor yield of the mesylate reaction (60 %), it was decided to cease the investigation into the use and optimisation of the reactions involving TIPS protecting groups instead of the TBS protecting groups.

The next step in the synthesis of the novel PheBOX involved the displacement of the methanesulfonyl groups using sodium azide, followed by hydrogenation to produce di-amine, **48** (**Scheme 2.30**)



47 **48**

Scheme 2.30

A solution of **47** and sodium azide in *N,N*-dimethylformamide was heated to 85 °C for 16 hours, then filtered through a celite pad and concentrated under reduced pressure, giving a 92 % yield of crude azide. 2 g of this azide was then dissolved in CH_3OH and transferred to a Parr apparatus. Palladium on activated carbon was added and the suspension was stirred under hydrogen. Initial attempts followed the procedure described by Frain *et al* (5 bar for 4 days), however ^{1}H NMR spectral analysis of the crude reaction mixture showed little or no product formed. In the reactions where no product was formed, there were a lot of new signals in the ^{1}H NMR spectrum and the aromatic protons were not present indicating that the hydrogenation process had continued and may have had an effect on the aromatic ring. To combat this, the pressure was increased and the reaction was monitored by TLC. The optimum conditions were found to be 6.5 bar pressure for 6 hours. The solution was then filtered, washed through celite and concentrated under reduced pressure giving 84 % yield of **48** as a yellow liquid which was used without any further purification.

The structure of **48** was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy. In **Figure 2.6** the ^{1}H NMR spectrum can be seen.

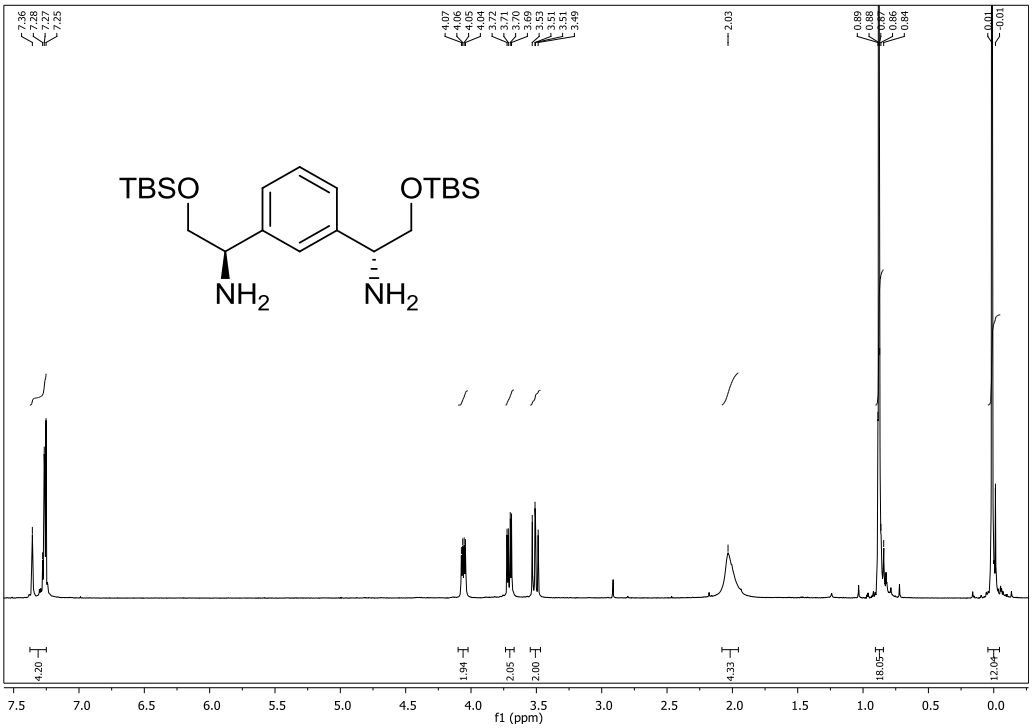
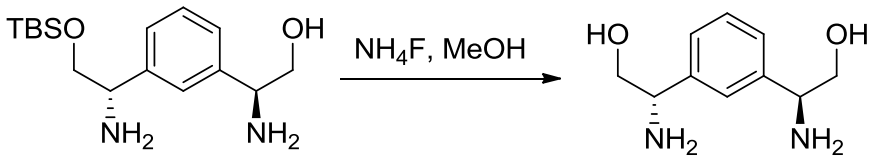


Figure 2.6

The multiplet from 7.37 - 7.25 ppm integrates for four protons and corresponds to the aromatic hydrogens. The double doublet at 4.06 ppm is due to the two C*H*N protons and exhibits vicinal coupling to the two CH_2O protons (J = 8.4 Hz and 3.9 Hz). Upfield of this signal are two double doublet signals at 3.71 ppm and 3.51 ppm that correspond to the four protons in CH_2OH. These signal show vicinal coupling to C*H*OH (J = 4.0 Hz and 8.4 Hz) and geminal coupling (J = 9.8 Hz and 9.8 Hz) respectively. A broad singlet at 2.01 ppm, integrating for four protons, corresponds to the two NH_2 groups and this is the key signal for confirmation that **48** was formed. Finally, a singlet at 0.88 ppm integrating for 18 protons and a singlet at 0.01 ppm integrating for twelve protons correspond to the six CCH_3 and four SiCH_3 groups of the silyl protecting groups respectively.

One some occasions the reaction shown in **Scheme 2.30** produced **62**, as it is possible for hydrogenation to remove *tert*-butyldimethylsily protecting groups. In these cases it was necessary to remove the remaining alcohol protecting group as seen in **Scheme 2.31**. Monoalcohol **62** was dissolved in CH_3OH and it was then reacted with ammonium fluoride in methanol and stirred at reflux for 24 hours.



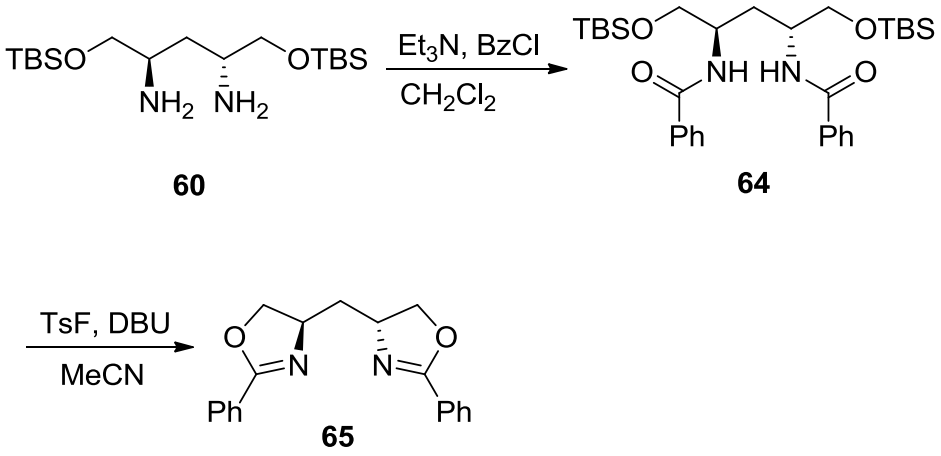
62 **63**

Scheme 2.31

^{1}H NMR spectral analysis, in D_2O, of the product showed signals 7.29 – 7.18 ppm (4H, m) and 3.97 ppm (2H, t). There also looked like there was a signal hidden by the residual water signal in the D_2O. This information suggested that **63** was not formed and in fact the HF salt of **63** was present, as a ^{1}H NMR in $CDCl_3$ showed no product signals. Conventional oxazoline synthesis involves a reaction between an acid chloride and an amino alcohol to yield a hydroxyamide, followed by activation with tosyl chloride, and subsequent base-promoted cyclisation. In order to access

the free amino alcohol, an ion exchange resin could be used to exchange the $^{-}$F ions for $^{-}$OH ions. However, incorrect preparation of the ion exchange resin led to the loss of the material.

With **48** in hand, we turned our attention to conversion of this di-amine to the oxazoline. We based our method on that described by Frain *et al*[18]. In that study di-amine, **60**, was converted to the di-amide, **64**, using triethylamine and benzoyl chloride in dichloromethane as seen in **Scheme 2.32.**

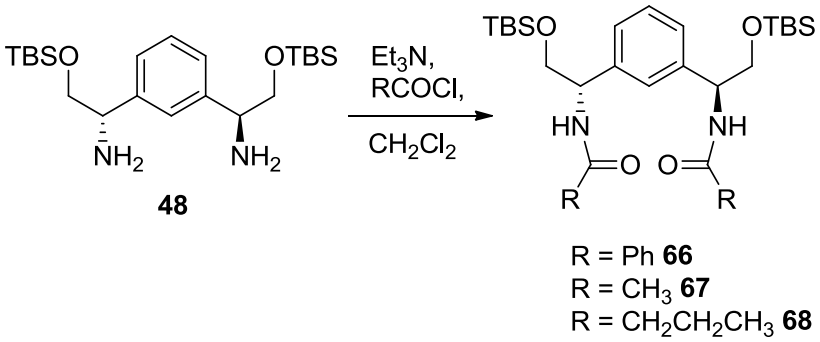


60 **64** **65**

Scheme 2.32

The reaction was stirred at 0 °C for 4 hours and produced **64** in 76 % yield. Then **64** underwent a one-pot tandem deprotection/activation/ring-closure (DARC) reaction, to form phenyl AraBOX, **65** using 2.2 equivalents of *p*-toluenesulfonyl fluoride and 1,8-diazabicycloundec-7-ene (DBU) in dry acetonitrile. The reaction was refluxed for 16 hours and produced **65** in 75 % yield.

A similar method was utilised in the synthesis of di-amides **66**, **67** and **68** as seen in **Scheme 2.33**. Di-amine, **48** was dissolved in CH_2Cl_2 and triethylamine was added. The reaction was stirred at 0 °C for 10 minutes. Then the appropriate acid chloride in CH_2Cl_2 was added slowly over an hour and the reaction mixture was allowed to stir for 18 hours. The resultant crude product was then purified using column chromatography on SiO_2.



Scheme 2.33

Benzoyl chloride was used to produce **66** which was columned using a gradient elution of a silica column (90:10 – 70:30 Pet ether:EtOAc) giving the product as a colourless foam (70 % yield), while acetyl chloride was used to produce **67** which was columned using 99:1 - 90:10 CH_2Cl_2:MeOH giving the product as a colourless foam in an 88 % yield. Finally, butyryl chloride was used to form **68** which was columned using 90:10 – 70:30 Pet ether:EtOAc giving the product as a colourless foam in a 32 % yield.

Each di-amide structure was assigned using ^{1}H NMR and ^{13}C NMR spectroscopy. For example, the ^{1}H NMR spectrum of **66** is seen in **Figure 2.7**. In this case, the aromatic region of the ^{1}H NMR is more complicated due to the presence of the two phenyl rings in the amide portion of the molecule. The fourteen aromatic protons are seen as a multiplet at 7.81 – 7.73 ppm, integrating for four protons, a triplet at 7.49 ppm (J = 7.3 Hz) integrating for two protons, another triplet at 7.41 ppm (J = 7.5 Hz), integrating for five protons, and a singlet at 7.29 ppm, integrating for three protons. A doublet at 6.92 ppm corresponds to the two N*H* protons and displays vicinal coupling to C*H*N (J = 7.5 Hz). The signal at 5.22 ppm is a double triplet and represents the two C*H*N protons. It shows vicinal coupling to N*H* and CH_2O (J = 8.0 Hz and 4.2 Hz). Two double doublets at 4.02 ppm and 3.89 ppm correspond to the four protons in CH_2OH. These signal show vicinal coupling to C*H*OH (J = 4.4 Hz and 8.2 Hz) and geminal coupling (J = 10.2 Hz and 10.2 Hz) respectively. Finally, a singlet at 0.84 ppm, integrating for 18 protons, and a doublet at -0.05 ppm

(J = 16 Hz), integrating for twelve protons, correspond to the six CCH_3 and four SiCH_3 groups of the silyl protecting groups respectively.

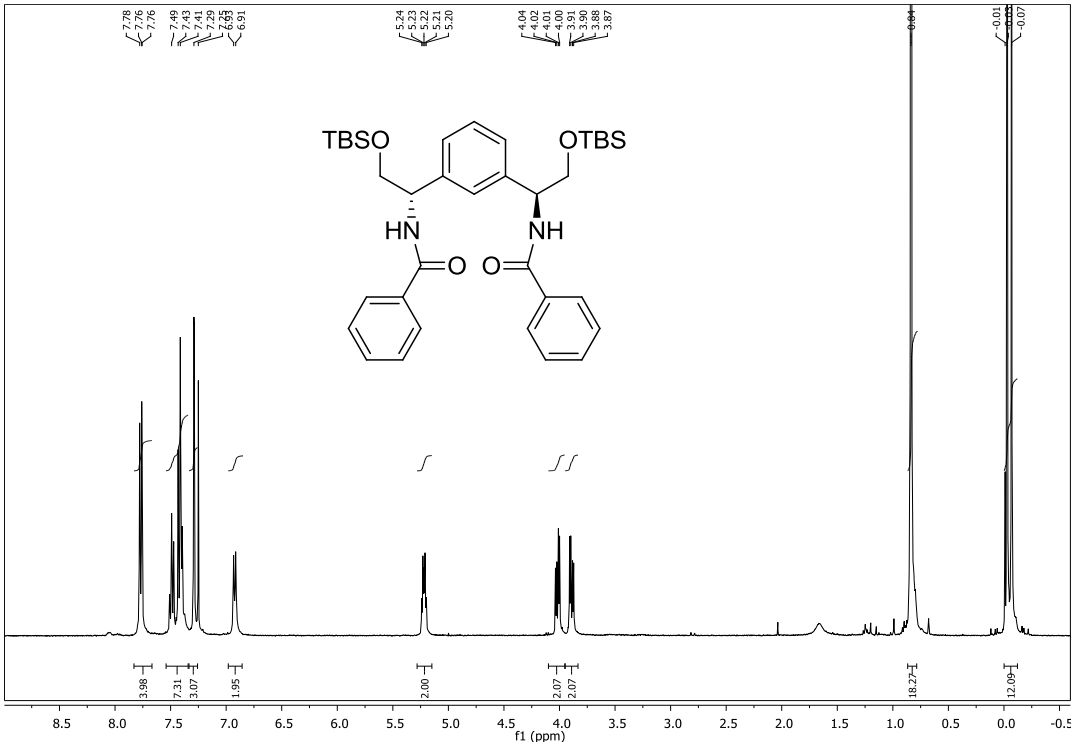


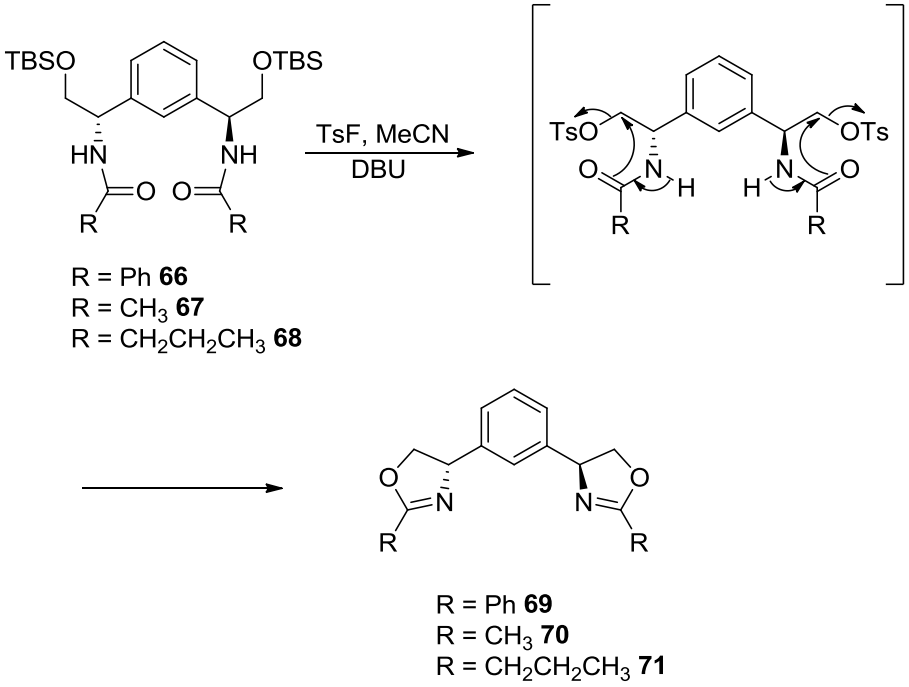
Figure 2.7

The ^{1}H NMR spectral data for **67** was similar to **66** but had a simpler aromatic region with a multiplet corresponding to the four aromatic protons from 7.37 - 7.05 ppm. The rest of the signals are in similar positions except for the doublet at 2.04 ppm (J = 1.8 Hz) which represents the six protons in the two CH_3 groups and is the central signal used to identify that **67** has been synthesised.

Again ^{1}H NMR spectral data for **68** was similar to both **66** and **67**. The signals are in similar places to **67**, except for the signals that identify **68**. The first distinctive signal is a triplet at 2.20 ppm, integrating for four protons, and corresponds to the two COCH_2 groups. This signal displays vicinal coupling to CH_2CH_2 (J = 7.6 Hz). The next distinguishing signal is a double triplet at 1.66 ppm corresponding to the two CH_2CH_2 and shows coupling to COCH_2 and CH_2CH_3 (J = 14.7 Hz and 7.3 Hz). Finally,

the last signal is a triplet at 0.95 ppm representing CH_2CH_3 and this exhibits vicinal coupling to CH_2CH_2 (J = 7.4 Hz).

The last step in the synthesis of the novel 4,4'-PheBOX ligands is the one-pot tandem deprotection/activation/ring-closure also known as the DARC reaction (**Scheme 2.34**) developed by Frain *et al*. The *p*-toluenesulfonyl fluoride (TsF) doubly deprotects the silyl-protected alcohols and activates them as tosylates. The DBU plays a dual role by catalysing the deprotection step and then it acts as a base in the *in situ* ring closure.



Scheme 2.34

In our synthesis, to a stirring solution of the selected di-amide and Tsf in dry acetonitrile was added 1,8-diazabicycloundec-7-ene. The mixture was stirred at reflux overnight, cooled and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 to yield the desired ligand. The reaction that generated **69** used Pet ether:EtOAc, 2:1 to purify the crude product by column chromotography and yielded 51 % of **69** as a very viscous liquid. The reaction that generated **70** used 99:1 - 95:5 EtOAc:MeOH to purify the crude product by column

chromatography and yielded 20 % of **70** as a white solid. Finally the reaction that generated **71** used Pet ether:EtOAc, 2:1 to purify the crude product by column chromatography and yielded 60 % of **71** as a white solid.

Each ligand structure was assigned using ^{1}H NMR and ^{13}C NMR spectroscopy. For example, the ^{1}H NMR spectrum of **69** is seen in **Figure 2.8**.

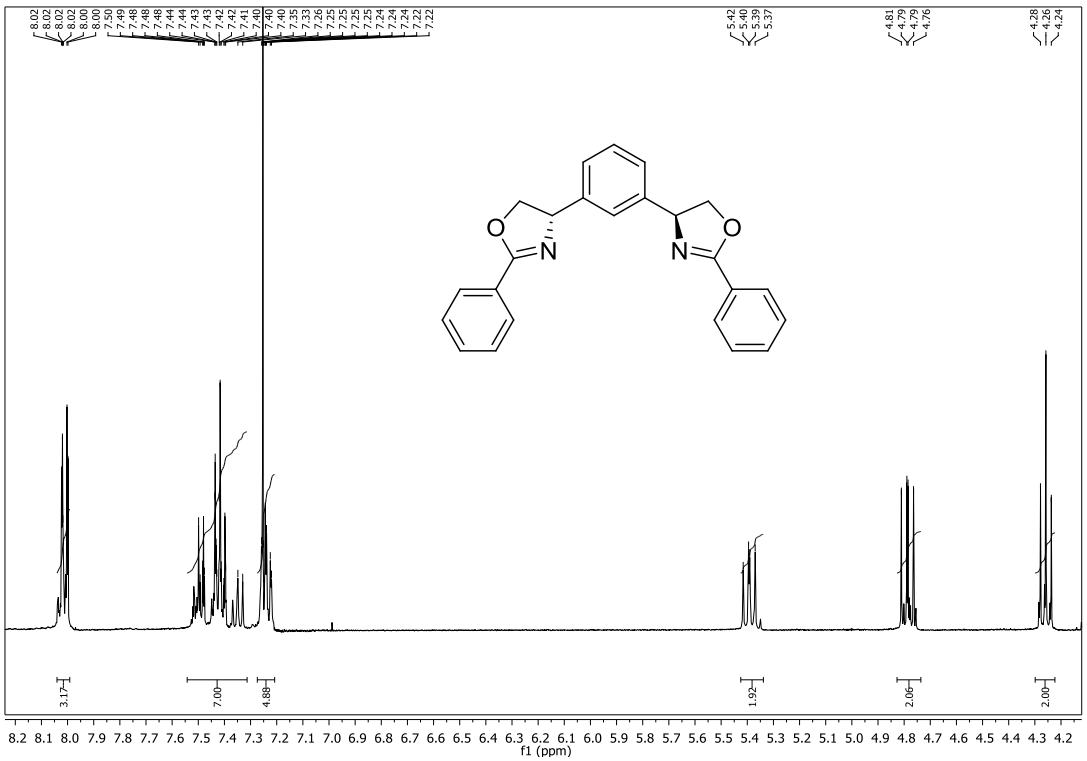


Figure 2.8

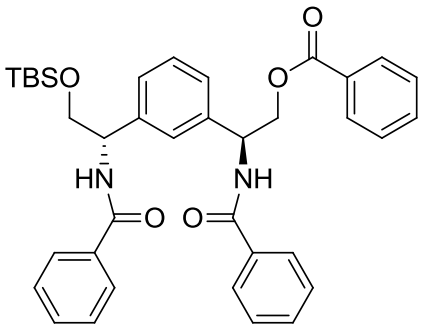
In this case, the aromatic region of the spectrum is quite complicated due to the phenyl rings in the side arms of this ligand. In total, there are fourteen aromatic protons and they appear as a multiplet from 8.04 – 7.97 ppm which integrates for three hydrogens, a multiplet from 7.53 – 7.33 ppm which integrates for seven protons and finally a multiplet from 7.26 – 7.22 ppm which represents the last three protons. This peak integrates for almost five protons due to the presence of the residual chloroform solvent peak. The next signal is a double doublet at 5.39 ppm which corresponds to the two C*H*N protons and shows coupling to the four CH_2O protons (J = 10.1, 8.3 Hz). The double doublet at 4.79 ppm and triplet at 4.26 ppm correspond to the four CH_2O protons. The signal at 4.79 ppm shows coupling to

C*H*N and C*H*$_2$O (J = 10.1, 8.4 Hz) while the triplet signal is caused by coupling to C*H*$_2$O (J = 8.3 Hz).

The ^{1}H NMR spectral data for **70** has similar backbone signals to that seen for **69**. The aromatic region of the spectra is less complicated for ligand **70** with a multiplet from 7.40 – 7.26 ppm integrating for one proton and a second multiplet from 7.21 - 7.05 ppm integrating for three protons. A triplet at 5.16 ppm represents the two C*H*N protons and shows vicinal coupling to C*H*$_2$O (J = 9.2 Hz). Two multiplets from 4.62 - 4.56 ppm and 4.11 - 3.95 ppm correspond to the four C*H*$_2$O protons while the doublet at 2.08 ppm integrating for six protons represents the two C*H*$_3$ groups which show long range coupling to C*H*N through the C=N (J = 1.3 Hz).

Finally, the ^{1}H NMR spectral data for **71** has similar backbone signals to that seen for **69** and **70**. Again, the aromatic region is not as complicated as **69** with two multiplets, one from 7.32 – 7.28 ppm, integrating for one proton, and the second from 7.14 – 7.11 ppm, integrating for three protons. A triplet at 5.16 ppm corresponds to the two C*H*N protons and shows coupling to C*H*$_2$O (J = 9.1 Hz). A double doublet at 4.57 ppm and a triplet at 4.03 ppm correspond to the four C*H*$_2$O protons with the double doublet showing vicinal coupling to C*H*N (J = 8.4 Hz) and geminal coupling to C*H*$_2$O (J = 10.2 Hz), while the triplet displays vicinal coupling to C*H*N (J = 8.3 Hz). The next signals represent the protons in the propyl groups. A multiplet from 2.43 – 2.25 ppm integrates for four protons and corresponds to the two CC*H*$_2$ groups. Another multiplet from 1.77 – 1.67 ppm represents the four protons in the two CCH$_2$C*H*$_2$ groups. Finally, a triplet at 1.01 ppm corresponds to the six protons in the two CH$_2$C*H*$_3$ groups.

Due to the relative ease of removal of the TBS protecting groups, it was found that the reaction shown in **Scheme 2.33** also produced **72** when benzoyl chloride was used as shown in **Figure 2.9**.



72

Figure 2.9

Again, the structure for **72** was assigned using ^{1}H NMR and ^{13}C NMR spectroscopy with the ^{1}H NMR spectrum seen in **Figure 2.10**. Due to the loss of symmetry in the molecule, the whole spectrum becomes more complicated and so it was also necessary to use a HMQC to assign the structure. The aromatic region of the spectrum is quite complicated, due to the loss of symmetry in the molecule, as well as having the phenyl rings on the side arms.

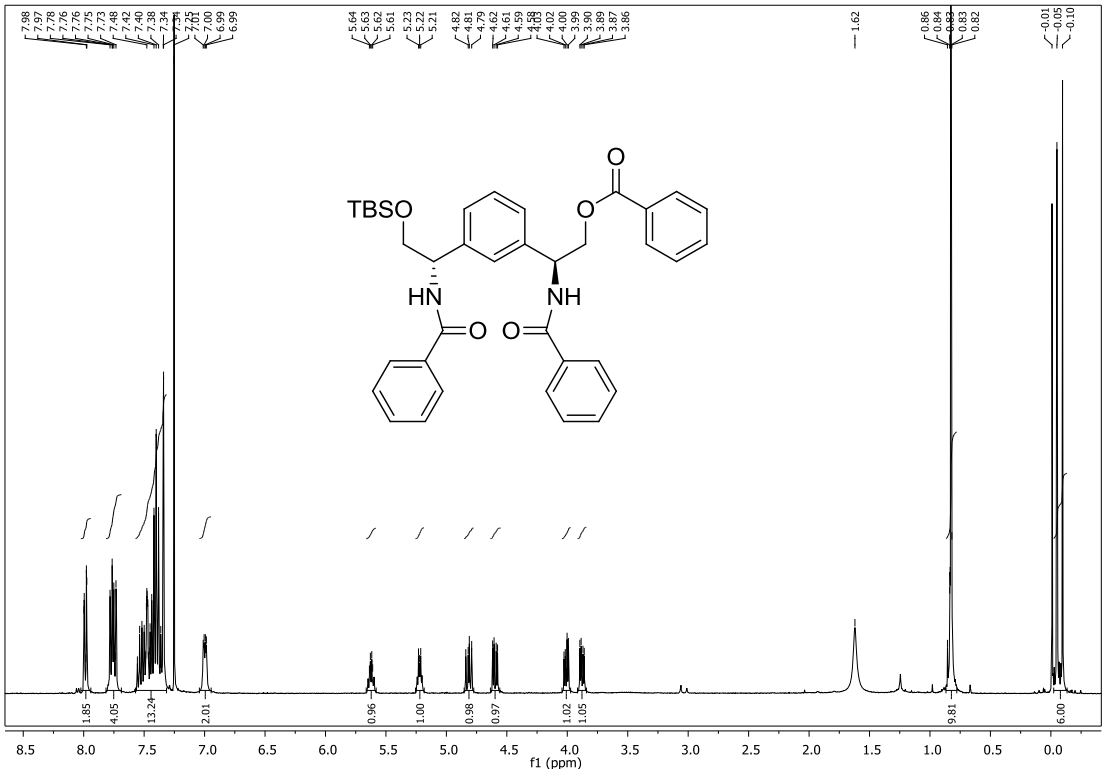
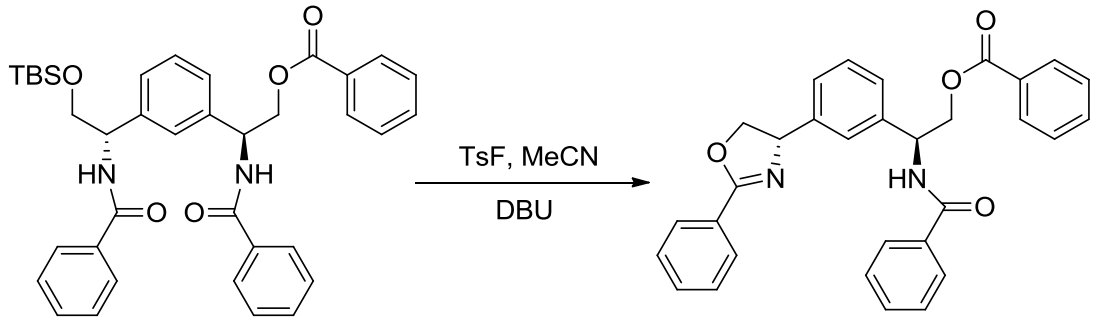


Figure 2.10

The first signal seen is a double doublet at 7.99 ppm, which integrates for two protons, followed by two multiplets from 7.78 – 7.73 ppm and 7.56 - 7.34 ppm, which integrate for four and thirteen protons respectively. This accounts for all nineteen aromatic protons. This is followed by a double doublet at 7.00 ppm which is due to the two N*H* hydrogens and shows vicinal coupling to C*H*NH (J = 7.0 Hz) and long range coupling to an aromatic proton (J = 2.3 Hz). A double triplet at 5.62 ppm corresponds to one C*H*N proton and shows vicinal coupling to CH_2O and N*H* (J = 7.7 Hz and 4.7 Hz) followed by another double triplet at 5.22 ppm corresponding to the other C*H*N. Again it exhibits vicinal coupling to CH_2O and N*H* (J = 7.8 Hz and 4.2 Hz). Two double doublets at 4.81 ppm and 4.60 ppm, both integrate for one proton each, and represent one of the CH_2O protons each. Both signals show vicinal coupling to C*H*N (J = 7.9Hz and 4.6 Hz) and geminal coupling (J = 11.6 Hz and 11.6 Hz) respectively. Another set of double doublets at 4.01 ppm and 3.88 ppm correspond to the other two protons in CH_2O and again show vicinal coupling to C*H*N (J = 4.3 Hz and 4.1 Hz) and geminal coupling (J = 10.3 Hz and 10.3 Hz) respectively. Finally, the last two signals correspond to the *tert*-butyldimethylsilyl protecting groups, with a singlet at 0.83 ppm, integrating for the nine protons in the three CCH_3 groups and another singlet at -0.06 ppm, integrating for the six protons in the two SiCH_3 groups.



72 **73**

Scheme 2.35

It was decided to attempt the ring closing reaction on **72** as the product **73** could possibly be utilised as an asymmetric catalyst, when combined with a metal salt.

1.1 equivalents of *p*-toluenesulfonyl fluoride and DBU in dry acetonitrile were added to a stirring solution of **72** (**Scheme 2.35**). The reaction was refluxed overnight and purified by flash chromatography on SiO_2 (Pet ether:EtOAc 7:3) to yield a white crystalline solid, **73,** in 49 % yield.

Again the ^{1}H NMR spectrum for **73** is more complicated when compared to the spectra of other ligands synthesised, due to the loss of symmetry in the molecule (**Figure 2.11**).

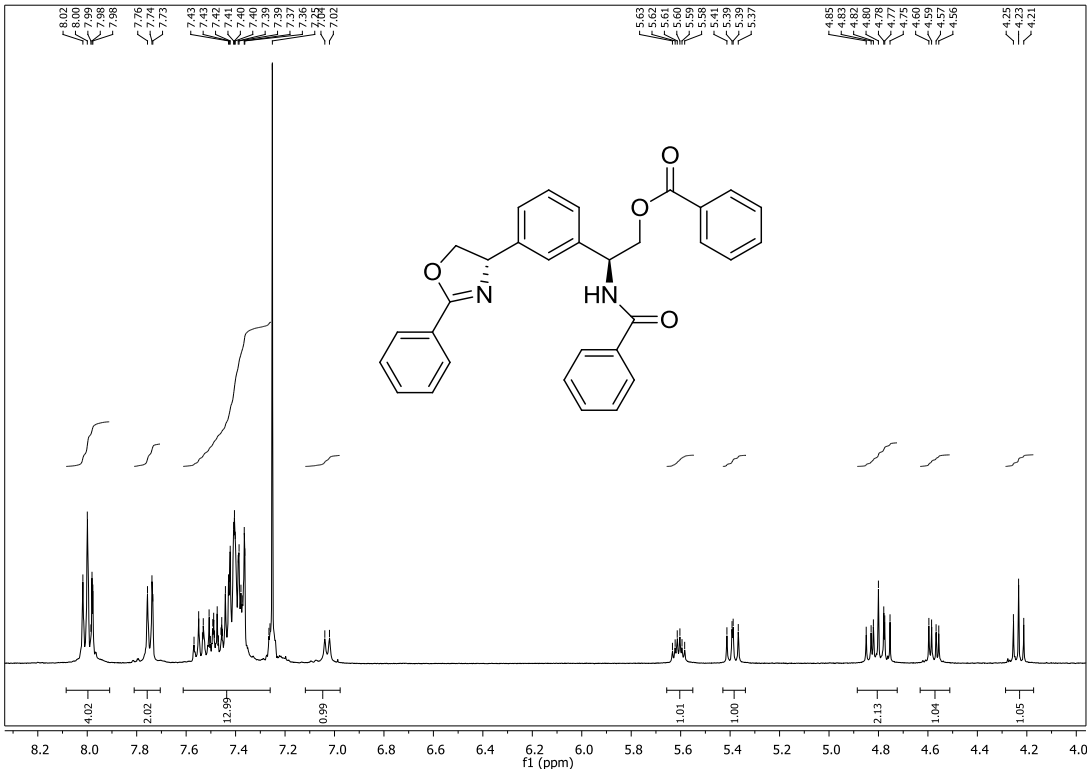


Figure 2.11

The nineteen aromatic protons are represented by a three multiplets from 8.02 - 7.98 ppm, 7.76 - 7.73 ppm and 7.55 - 7.25 ppm, integrating for four, two and thirteen protons respectively. A doublet a 7.03 ppm corresponds to the N*H* proton and shows coupling to C*H*N (J = 7.5 Hz). This is followed by a double triplet at 5.60 ppm and a double doublet at 5.39 ppm which represent the two C*H*N protons and both these signals show vicinal coupling to N*H* and C*H*N (J = 7.7, 3.9 Hz and 10.1, 8.3 Hz). Finally the four CH_2O hydrogens are represented by a multiplet from 4.85 - 4.75 ppm, integrating for two protons, a double doublet at 4.58 ppm and a

triplet at 4.23 ppm both integrating for one proton each. The signal at 4.58 ppm shows geminal coupling (J = 11.7 Hz) and vicinal coupling to C*H*N (J = 4.4 Hz), while the signal at 4.23 ppm shows identical coupling to two adjacent protons (J = 8.4) however, it was not possible to determine which protons are responsible for the splitting pattern seen.

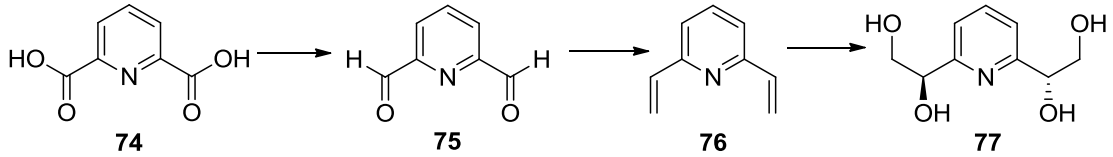
2.2.3 Conclusions

The synthesis of novel 4,4'-PheBOX ligands proved to be quite challenging. The first attempted synthesis involved reacting isophthalaldehyde with *N*-*tert*-butylsulfinamide to give the corresponding bis-sulfinimine. It was then planned to carry out a Grignard addition to the sulfinimine with subsequent cleavage of the sulfinyl groups to give the amino alcohol. This could then be followed by ring closure to produce the required ligand. While the bis-sulfinimine was easily generated, the Grignard addition proved extremely difficult. Further attempts to synthesise the bis-sulfinamide using samarium diiodide and Barbier type reactions were also proved unsuccessful in our hands.

Undeterred by these results, the novel ligands were generated *via* a multi-step synthesis that utilised isophthalaldehyde as a starting material. Generation of a tetrol by Sharpless asymmetric dihydroxylation proved to be a trying step but was imperative to the synthesis, so after extensive investigation of the reaction, the optimum conditions were identified, allowing for access to this important chiral molecule. Another step that proved difficult was the mesylation step when it was carried out on a large scale. Loss of the material on the column was a major setback in the synthesis. However, in the end, three novel PheBOX ligands were generated, 4,4'-phPheBOX, 4,4' -MePheBOX and 4,4'-*n*-propylPheBOX, with a possible fourth mono-oxazoline ligand.

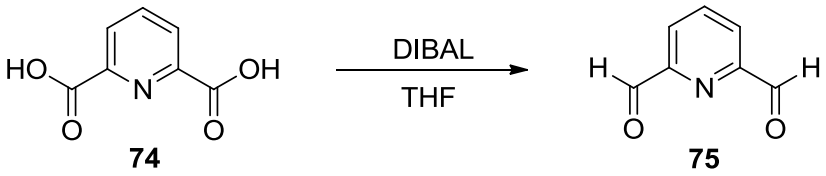
2.3 Attempted synthesis of novel 4,4'-PyBOX

After these ligands were synthesised, an attempt was made to generate novel 4,4'-PyBOX ligands. Following a similar path to the synthesis of the novel PheBOX ligands, the starting material, 2,6-pyridinedicarboxylic acid, **74**, was utilised due to the cost of 2,6-pyridinedicarboxaldehyde, **75**. It was envisaged that 2,6-pyridinedicarboxylic acid, **74** could be reduced to the dialdehyde, **75**, which in turn could undergo a Wittig reaction to form the divinylpyridine, **76**. It was hypothesised that this molecule could then undergo a Sharpless asymmetric dihydroxylation producing, **77** as seen in **Scheme 2.36**.



Scheme 2.36

The first attempt at the reduction of **74** involved the use of diisobutylaluminium hydride or DIBAL (**Scheme 2.37**)**.**

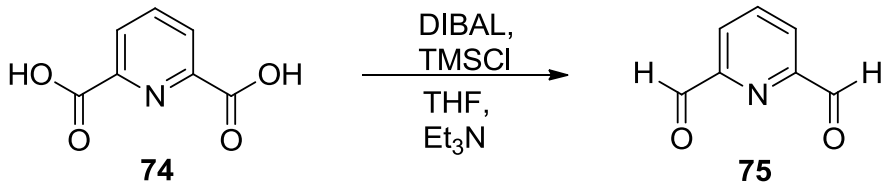


Scheme 2.37

To a stirring solution of **74**, in anhydrous THF, was added DIBAL (1M in THF) at -78 °C, under N_2. The reaction stirred for 3 hours, then MeOH was added and it was allowed to warm to room temperature. The reaction was quenched using saturated NH_4Cl solution and was stirred for 1 hour. After the reaction was worked

up, ^{1}H NMR spectral and TLC analysis of the crude reaction mixture revealed an inseparable mixture of products and spectral evidence for **75** was not found.

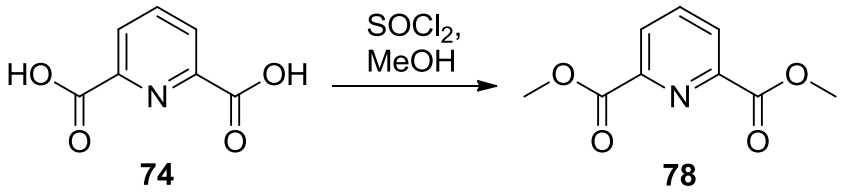
Following this failed attempt, a similar reaction was carried out with slightly altered conditions, whereby **74** was dissolved in CH_2Cl_2 under N_2 and Et_3N was added. Then the reaction mixture was cooled to -78 °C and stirred for 10 min (**Scheme 2.38**).



Scheme 2.38

TMSCl was added and the solution was stirred for a further 1 hour. Then DIBAL (1M in THF) was added and the reaction mixture was allowed to stir for 3 hours at -78 °C. Methanol was added and the reaction was allowed to warm to room temperature. Saturated NH_4Cl solution was added to quench the reaction and it was stirred for a further hour. After the reaction was worked up, ^{1}H NMR spectral and TLC analysis of the crude product revealed an inseparable mixture of products and again, **75** had not been formed.

The reduction of the dicarboxylic acid, **74**, to the dialdehyde, **75** using DIBAL proved difficult, so it was envisaged that instead, **74** could be firstly converted into the dicarboxylate ester, **78** (**Scheme 2.39**)[20], and then that could be reduced using DIBAL to form diol **79** (**Scheme 2.40**). One equivalent of dicarboxylic acid **74** was dissolved in MeOH and two equivalents of $SOCl_2$ were added. The reaction was refluxed for 16 hours and quenched using saturated $NaHCO_3$. The resultant crude product was purified by flash chromatography using silica gel (gradient elution 99:1 - 60:40 Pet ether:EtOAc) to give 104 mg (54 % yield) of white solid **78**.

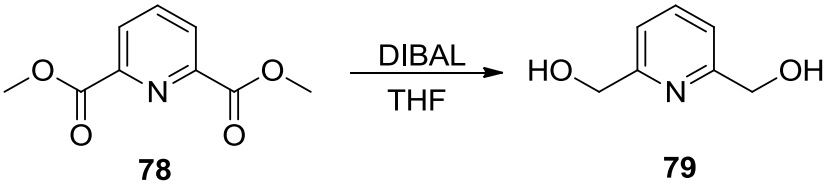


74 **78**

Scheme 2.39

^{1}H NMR spectral analysis showed a doublet at 8.32 ppm corresponding to two aromatic protons and showed vicinal coupling to the other aromatic proton (J = 7.8 Hz). A triplet at 8.03 ppm corresponded to the hydrogen *para* to the nitrogen and showed coupling to the other two aromatic protons (J = 7.8 Hz). Finally a singlet at 4.03 ppm represented the six C*H*$_3$ protons in the two methyl groups. This data corresponded to that found by Jew *et al*[20].

The next step involved reduction of the dicarboxylate ester, **78** to the diol **79** (**Scheme 2.40**). A stirring solution of **78** in anhydrous THF was cooled to -78 °C and DIBAL (1 M in THF) was added under N_2. The reaction mixture was stirred for 3 hours, MeOH was added and the reaction was allowed to warm to room temperature. Saturated NH_4Cl solution was added and the reaction mixture was stirred for 1 hour and then worked up.

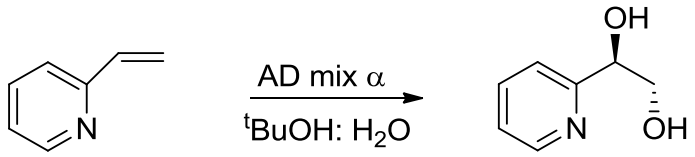


78 **79**

Scheme 2.40

The crude product was analysed by ^{1}H NMR and TLC and revealed a mixture of products that proved inseparable, none of which corresponded with expected signals for **79**.

Considering the difficulties encountered when working with the di-substituted molecules, it was decided to investigate the viability of the asymmetric dihydroxylation on molecules containing a pyridine ring before any more time was spent trying to obtain the divinylpyridine. A basic test reaction using one mole of 2 – vinylpyridine, **80,** was carried out as seen in **Scheme 2.41**. 1.4g of AD mix α was stirred in 1:1 *t*BuOH:water at room temperature for one hour. The reaction was cooled to 0 °C and **80** was added. This was stirred for 24 hours. The reaction was quenched by the addition of sodium sulphite and the solvent was removed under vacuum. ^{1}H NMR spectral analysis of the isolated reaction mixture showed that only starting material remained and there were no signals that would correspond to the formation of the required product **81**.



80 **81**

Scheme 2.41

As a result of the disappointing outcome of the attempted asymmetric dihydroxylation of 2 - vinylpyridine and the time constrains of this research project, it was decided to no longer continue with the attempted synthesis of the novel 4,4'-PyBOX ligands.

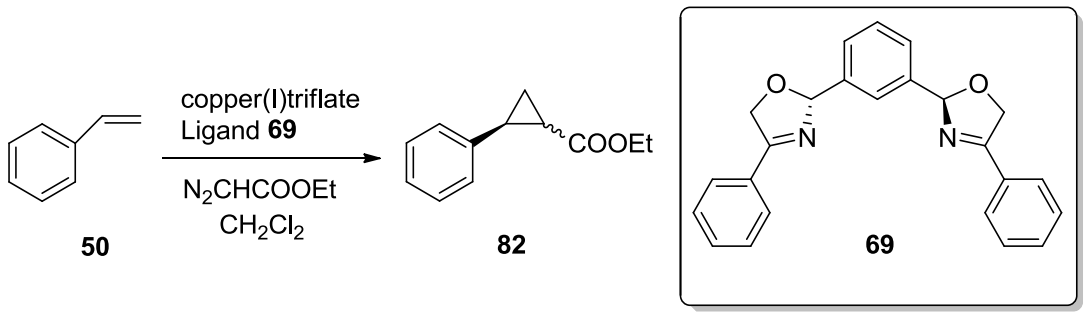
2.3.1 Conclusions

It was hoped that this research project would generate novel 4,4'-PyBOX ligands and this work began by the attempted synthesis of 2,6-pyridinedicarboxaldehyde *via* reduction of the corresponding di-carboxylic acid. After several failed attempts, it was decided to instead generate the dicarboxylate ester which could then be reduced to the corresponding diol and oxidised to the corresponding dialdehyde.

Again the reduction of the dicarboxylate ester proved challenging and when the attempted asymmetric dihydroxylation on 2 – vinylpyridine yielded none of the expected products, it was decided to no longer continue the attempted synthesis of the novel 4,4'-PyBOX ligands.

2.4 Generation of ligand-metal complexes

Following the successful synthesis of three novel PheBOX ligands, **69**, **70** and **71**, and a fourth possible ligand, **73**, the next step was to form chiral metal complexes which could act as catalysts. When a chiral PheBOX ligand and a metal salt are mixed together, in an organic solvent, a metal-bisoxazoline complex is usually formed which, in turn, can be used as an asymmetric catalyst in numerous reactions. The first reactions tested were simple asymmetric cyclopropanation reactions. Atodiresei *et al* tested numerous chiral bisoxazoline ligands in asymmetric cyclopropanations[4]. Following the method reported by them, [copper(I)triflate]$_2$·C_6H_6 (1 mol%) was added to a flame-dried, N_2 filled, Schlenk. PheBOX ligand **69** (1.2 mol%) was weighed into a second flame-dried, N_2 filled, Schlenk and dissolved in CH_2Cl_2 (**Scheme 2.42**).



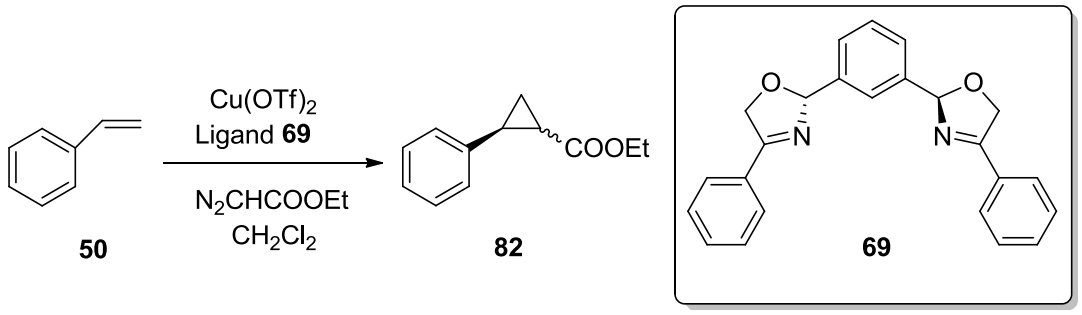
50 **82** **69**

Scheme 2.42

The ligand solution was then transferred under N_2, into the Schlenk containing the metal triflate. The resulting mixture was then stirred for 90 minutes at room temperature. To this stirring catalyst, was added styrene, **50**, (5 equiv.) in CH_2Cl_2 and a solution of ethyl diazoacetate (1 equiv.) in CH_2Cl_2, which was added over 6

hours *via* a syringe pump. This reaction mixture was stirred at room temperature for 12 hours. After the reaction was worked up, the ^{1}H NMR spectrum was analysed and found that the starting material, **50**, and the ethyl diazoacetate still remained and there were no signals corresponding to the required product **82**.

The reaction was then attempted using copper(II)triflate (1 mol%) and carried out according to procedure described above, using ligand **69**, styrene, **50**, and ethyl diazoacetate (**Scheme 2.43**). The reaction was carried out at room temperature for 18 hours. ^{1}H NMR analysis of the crude reaction mixture showed that the starting materials, styrene **50** and ethyl diazoacetate were still present and **82** had not formed.

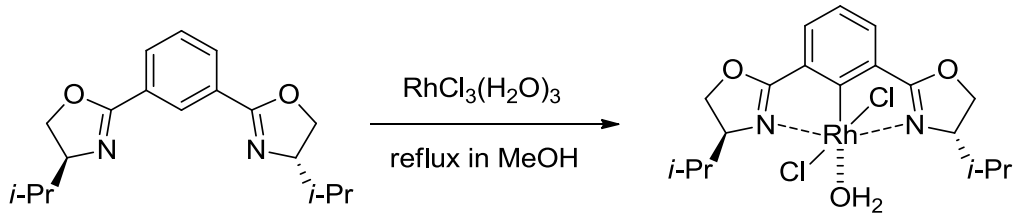


Scheme 2.43

Previous PheBOX ligands, combined with copper metal sources, were also not catalytically active in these types of reactions, as complexes failed to form. It was felt that it was still worthwhile to test our ligands in these types of catalysts, as they are structurally very different. However, it is apparent from the results that the C-H bond of the aromatic group blocks complexation of the metal to the oxazoline nitrogens.

Due to the lack of results from the asymmetric cyclopropanation reactions, it was decided to investigate the possible methods for complexing PheBOX ligands, particularly those that involve the formation of a carbon-metal bond. From research carried out, a number of methods of introducing this carbon-metal bond were available. C–H bond activation was an easy way to prepare the complexes, by

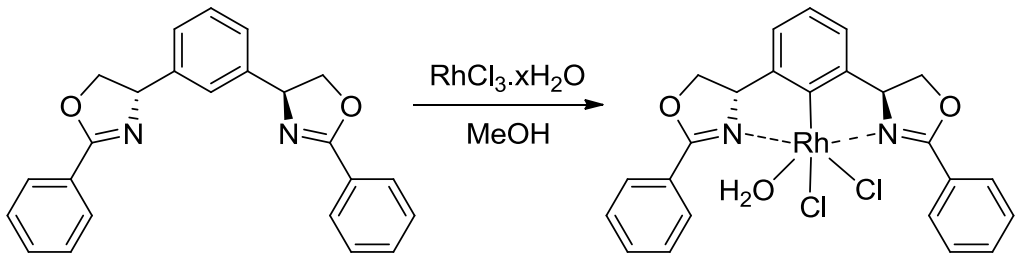
simply heating the ligands with rhodium chloride. Nishiyama *et al* successfully generated **84** by refluxing the ligand with rhodium chloride in methanol to give complex **84** in 56 % yield (**Scheme 2.44**) [21].



83 **84**

Scheme 2.44

This same method was utilised on our novel 4,4'-PheBOX **84**. A stirring solution of **69** in MeOH was heated to reflux and $RhCl_3.xH_2O$ was added (**Scheme 2.45**). The mixture was allowed to reflux for 45 minutes and then filtered through a celite pad. The pad was washed thoroughly with MeOH.



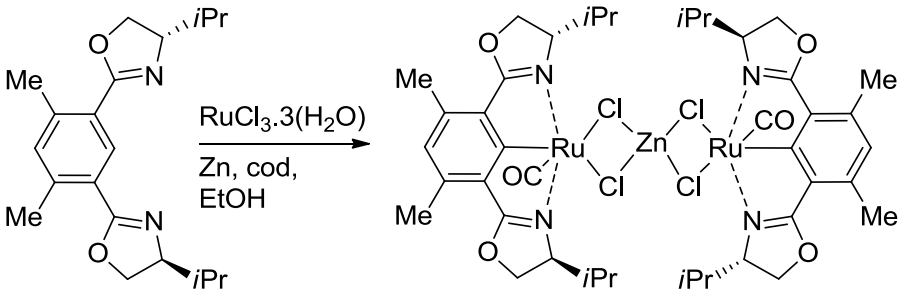
69 **85**

Scheme 2.45

The organic layers were combined and the solvent was removed under reduced pressure leaving an orange solid. The solid was dissolved in a small volume of EtOAc and washed through a small plug of silica using 1:1 Pet Ether:Ethyl Acetate followed by 9:1 Ethyl Acetate:Methanol and the combined organic layers were concentrated *in vacuo.* This produced a non-homogeneous mixture of both an orange solid and a white solid from the reaction solution. While ^1H NMR analysis showed free ligand (the white solid), there were also other interesting signals including 5.81 - 5.75 ppm

(1H, m), 5.24 - 5.19 ppm (1H, m), 4.55 ppm (1H, dd) and several phenyl signals over 7 ppm. However it proved impossible to isolate the molecule responsible for these signals.

Another method for the generation of the carbon-metal bond was reported by Ito *et al* through the reaction of selected 2,2'-PheBOX ligands with $RuCl_3.3(H_2O)$ in the presence of zinc and 1,5-cyclooctadiene (cod) which afforded a $ZnCl_4$-bridged (Phebox)Ru dimer through C – H bond activation[22]. Treatment of **86** with $RuCl_3.3(H_2O)$ in the presence of Zn and 1,5 cyclooctadiene in ethanol under reflux for 24 hours produced $ZnCl_4$-bridged (Phebox)Ru dimer **87** in a 73 % yield. The complex was found to have an unexpected CO ligand on the Ru metal, which the research group thought could have come from the oxidation of the ethanol to the aldehyde followed by decarbonylation[22]. Complex **87** was found to exhibit catalytic activity in the transfer hydrogenation of ketones.

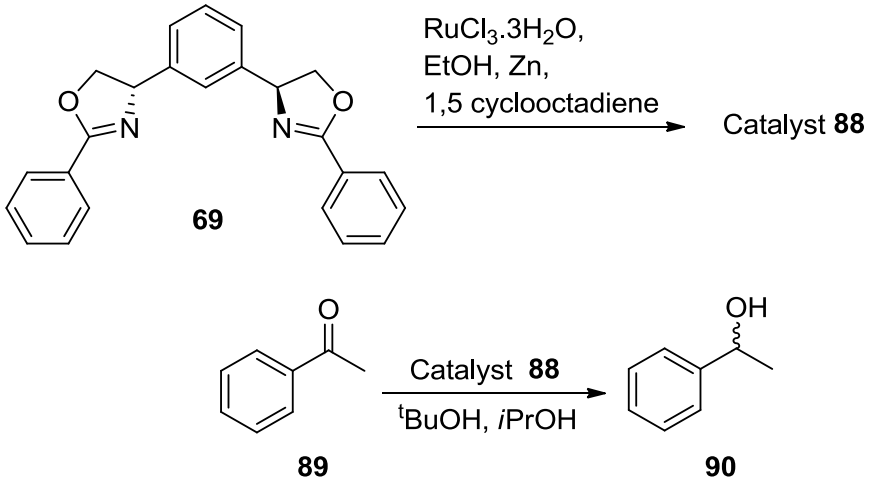


86 **87**

Scheme 2.46

It was decided to attempt to generate a similar complex using ligand **69** and test the newly generated complex in a transfer hydrogenation reaction using acetophenone. The asymmetric transfer hydrogenation of ketones is a facile method for obtaining optically active secondary alcohols (**Scheme 2.47**). Two equivalents of $RuCl_3.3H_2O$ were added to a flame-dried, N_2 filled, Schlenk. One equivalent of PheBOX ligand, **69**, was weighed into a second flame-dried, N_2 filled, Schlenk and dissolved in EtOH. The ligand solution was then transferred under N_2, into the Schlenk containing the

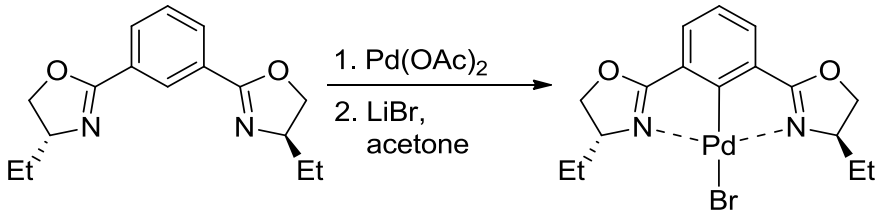
ruthenium salt, followed by five equiv. of both zinc and 1,5-cyclooctadiene. The reaction was then refluxed for 24 hours.



Scheme 2.47

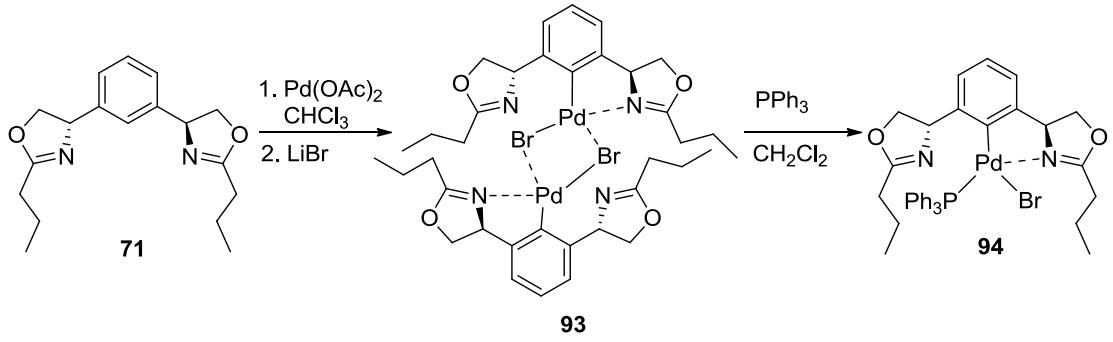
At that point, the reaction mixture was diluted with toluene and water was added. The aqueous layer was extracted with toluene, the organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo* to yield an orange solid that was hoped to be catalyst **88**, however no colour change, from orange, was observed. 10 mol% of the catalyst was added to dry *i*PrOH and acetophenone, **89** (1 equiv) and then *t*BuOK (15 mol%) was added. The reaction mixture was stirred at 50 °C for 16 hours. When the reaction was complete, it was worked up. ^{1}H NMR spectral analysis of the crude reaction mixture showed that the starting material, acetophenone, **89**, was still present and **90** had not formed. It was believed that this was due to the fact that catalyst **88** had not been generated.

The final attempt to generate the carbon-metal bond using the novel 4,4'-PheBOX ligands utilised a method developed by El Hatimi *et al*[23] where palladium complexes were generated (**Scheme 2.48**). According to a report by El Hatimi *et al*, **91** was reacted with $Pd(OAc)_2$ in chloroform and refluxed for three days. Then lithium bromide was added and the reaction was refluxed for a further 2 hours and worked up, producing **92** in 45 % yield.



Scheme 2.48

Utilising the same method, **71** (1 equiv) was dissolved in chloroform and $Pd(OAc)_2$ (2 equiv) was added (**Scheme 2.49**). The reaction was refluxed for 3 days, at which stage, lithium bromide was added and the reaction was refluxed for a further 2 hours. The reaction mixture was then filtered through a celite pad and washed with ether. The combined organic layers were concentrated *in vacuo* giving a yellowish black solid.



Scheme 2.49

^{1}H NMR and ^{13}C NMR spectral analysis of the reaction product did not confirm the presence of the expected product that was seen in **Scheme 2.48**. The ^{13}C NMR spectrum showed signals at 167.86 ppm, 145.56 ppm, 128.89 ppm, 125.83 ppm, 119.17 ppm, 72.65 ppm, 72.36 ppm, 38.80 ppm, 30.44 ppm, 29.80 ppm, 23.82 ppm, 23.08 ppm, 20.12 ppm, 14.25 ppm, 13.83 ppm and 11.05 ppm. The ^{1}H NMR spectrum showed signals including 7.21 ppm, 7.07 ppm, 6.70 ppm (1H, dd), 5.63 ppm (1H, d), 5.50 - 5.40 ppm (1H, m), 4.91 - 4.84 ppm (1H, m), 4.66 ppm

(1H, dd), 4.21 ppm (1H, ddd), 3.82 ppm (1H, dd) and several signals between 2 ppm and 0.8 ppm (**Figure 1.12**). The ^{1}H NMR signals at 5.63 ppm, 5.50 - 5.40 ppm, 4.91 - 4.84 ppm, 4.66 ppm, 4.21 ppm and 3.82 ppm, all integrating for one proton, could be correlated to the three backbone signals seen in ligand **71** at 5.15(t), 4.56(dd), 4.03(t) which represent C*H*N and CH_2O. Also, when the metal salt forms the complex, it is common to see a movement of these signals.

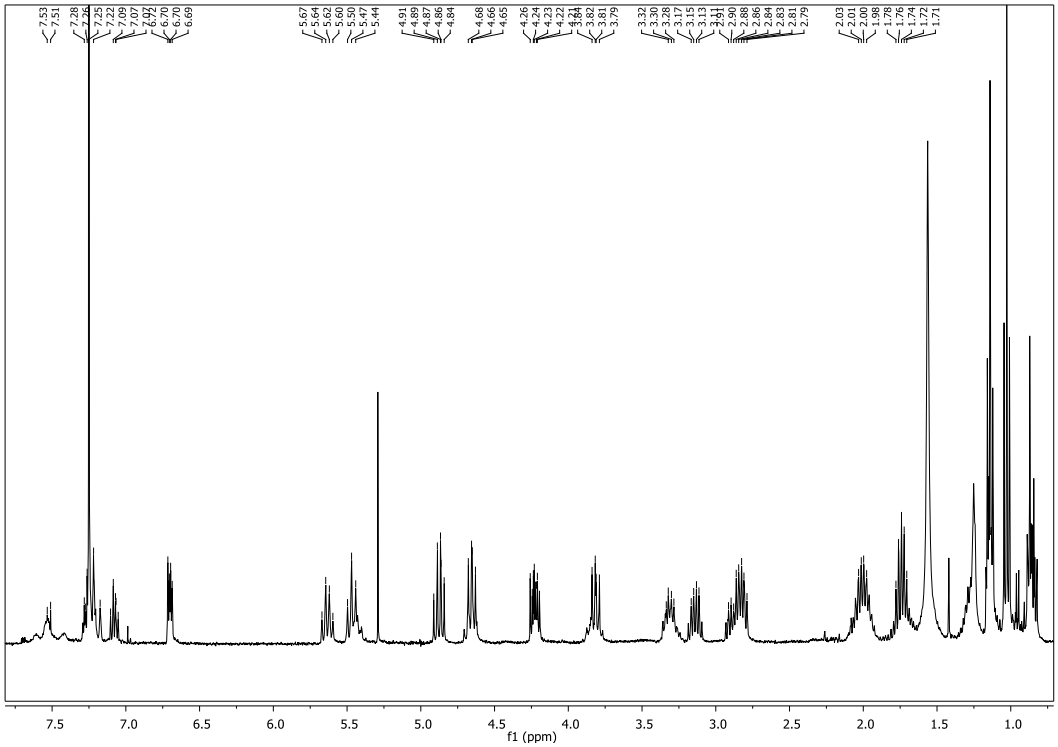


Figure 1.12

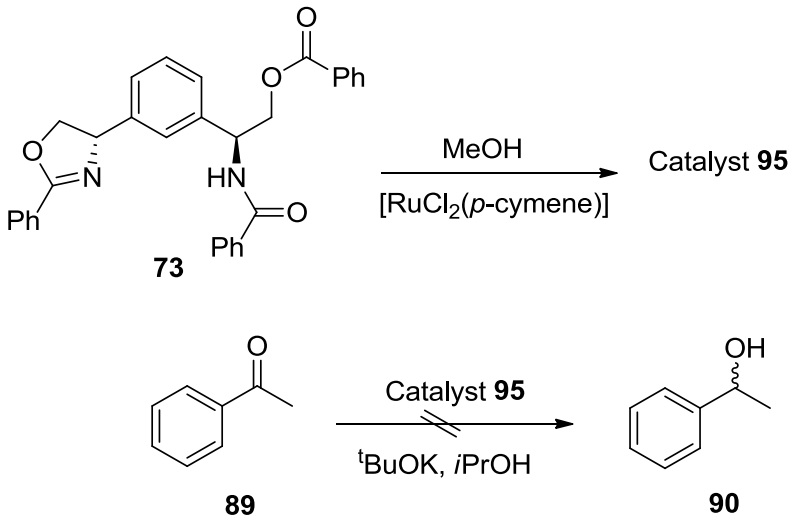
From this information it was believed that *trans* or *cis* - **93** was present. It seems clear from the spectral results that the symmetry in the ligand is gone which would be consistent with this conclusion. Attempts were made to purify the product in attempt to get more conclusive proof of the formation of **93**. A small quantity of the crude product was washed through a small silica plug, however, it moved very slowly through the silica plug and ^{1}H NMR spectral analysis of the purified product showed many new peaks indicating the product had decomposed on the column. Another attempt to purify the crude product involved using a more tightly packed

celite pad. However, this did not improve the purity of the product. Recrystllisation was also attempted but, unfortunately, was also successful.

With **93** in hand, it was decided to try and generate a ligand with a 1:1 metal:ligand ratio from **93**. Again, from research reported by El Hatimi *et al*, **93** was dissolved in dichloromethane and triphenylphosphine was added. The reaction was refluxed for 16 hours. It was then filtered through a celite pad and rinsed with CH_2Cl_2 and the combined washes were concentrated under reduced pressure. This produced a brown crystalline solid. ^{1}H NMR spectral analysis of the reaction mixture showed many interesting signals including several signals from 7.75 - 7.25 ppm, 6.70 ppm (1H, dd), 5.67 - 5.60 ppm (1H, m), 5.19 - 5.14 ppm (1H, m), 4.91 - 4.84 ppm (1H, m), 4.57 ppm (1H, dd), 4.26 - 4.20 ppm (1H, m), 4.03 ppm (1H, t), 2.35 ppm, 1.72 ppm and 1.02 ppm. ^{13}C NMR spectral analysis showed several signals between 135.25 - 127.96 ppm, 127.96 ppm, 74.50 ppm, 69.58 ppm, 30.05 ppm, 29.34 ppm, 19.65 ppm and 13.92 ppm. Again, when the ^{1}H NMR of the free ligand **71** is compared to **94**, it can be seen that the backbone signals of 5.19 - 5.14 ppm, 4.57 ppm and 4.03 ppm could correspond to an oxazoline ring that is not coordinated to the Pd. The signals 5.67 - 5.60 ppm, 4.91 - 4.84 ppm and 4.26 - 4.20 ppm could then represent the oxazoline protons in a coordinated ring. From this information it was felt that the mono-coordinated **94** was formed, but due to the difficulty in removing all the triphenylphosphine from the reaction, attempted recrystallization and crystal growth, of the brown solid above, was unsuccessful.

Ruthenium complexes of Boc protected hydroxyamides and pyroglutamic derived hydroxyamides have shown good activity and high selectively for the transfer hydrogenation of ketones[24-25]. With this in mind, it was decided to investigate the possible use of ligand **73** in the asymmetric transfer hydrogenation reaction (**Scheme 2.50**). Following the method described by Debono *et al*[5] $[RuCl_2(p\text{-cymene})]_2$ (0.5 mol%) was added to a flame-dried, N_2 filled, Schlenk. PheBOX ligand **73** (1.0 mol%) was weighed into a second flame dried, N_2 filled, Schlenk and dissolved in MeOH. The ligand solution was transferred under N_2, into

the Schlenk containing the $[RuCl_2(p\text{-cymene})]_2$ which changed immediately from an orange colour solution to brown. The resulting mixture was stirred for 3 hours at room temperature.



Scheme 2.50

The solvent was then evaporated and the white solid obtained, which indicated that catalyst **95** may not formed, was dried under vacuum. To the dry catalyst, was added dry *i*PrOH, acetophenone, **89**, (1 equiv.) and *t*BuOK. This reaction mixture was then stirred at 50 °C for 16 hours. At that point, the reaction mixture was diluted with CH_2Cl_2 and washed with 1M HCl. The aqueous layer was extracted using CH_2Cl_2, the organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. As expected, ^{1}H NMR analysis of this crude reaction mixture showed that the starting material, acetophenone **89**, was still present and **90** had not formed.

2.4.1 Conclusions

With the novel PheBOX ligands in hand, the generation of ligand-metal complexes was attempted. In some cases, the complexes were tested in asymmetric reactions. After the asymmetric cyclopropanation reactions using Copper(I)triflate and

$Cu(OTf)_2$ produced none of the desired cyclopropane products, it was believed that copper coordination with the PheBOX type ligand was not possible. This was due to the C-H bond from the aromatic ring, which is in the plane where the cooper would need to coordinate. As a result, it was believed that a carbon-metal bond should be generated for the novel ligands to be utilised as chiral catalysts.

Armed with this information, the simple heating of the ligands and rhodium chloride should produce the required complex. Even though ^{1}H NMR spectral analysis showed many interesting signals, it proved impossible to isolate the molecule responsible for these signals. Another attempt was made using $RuCl_3.3H_2O$, 1,5-cyclooctadiene and zinc to generated the complex, which was subsequently tested in an asymmetric transfer hydrogenation reaction. Unfortunately, ^{1}H NMR spectral analysis of the crude reaction mixture showed that the starting material, acetophenone was still present and the desired product had not formed. In reality, it is unlikely the metal complex formed in this reaction. The final attempt to generate the ligand-metal complex involved the use of $Pd(OAc)_2$ in chloroform followed by reaction with lithium bromide. ^{1}H NMR and ^{13}C NMR spectral analysis of the product, again, showed many interesting signals but did not correspond to what was expected. Instead it was believed that the *trans* or *cis* - dimer was present. In an attempt to generate the monopalladated product, the dimer was reacted with triphenylphosphine. Again, ^{1}H NMR spectral analysis of the reaction mixture showed many interesting signals, which could have corresponded to the monopalladated product, but attempted recrystallization and crystal growth, was unsuccessful and a single compound could not be isolated.

The last attempt described, involved the use of the mono-oxazoline ligand complexed with $[RuCl_2(p\text{-cymene})]_2$ in an asymmetric transfer hydrogenation. Again, it was felt that the catalyst did not form, so it was not surprising that ^{1}H NMR analysis of this crude reaction mixture showed that the starting material, acetophenone, was still present and the desired product had not formed. All of these results were very disappointing after all the difficulties that were overcome in the synthesis of the novel PheBOX ligands.

2.5 Immobilisation of ligands and asymmetric test reactions

Asymmetric catalysis is a very important tool in organic synthesis. However, very often, the chiral catalyst employed is expensive. For this reason, recovery and recycling of these catalysts could make these asymmetric reactions a more viable option on large scales, where the expense of the catalyst becomes important. One method that can be used to improve the recyclability of a chiral catalyst is to immobilise a homogeneous catalyst on a non-soluble support. This creates a chiral heterogeneous catalyst that will remain in a different phase to the reactants and products, allowing for easy separation at the end of the reaction[26] and it also permits efficient recovery of the catalyst. As described in **Chapter 1**, there are numerous methods for the immobilisation of catalysts on solid supports including encapsulation[27], covalent tethering[28], adsorption[29] and electrostatic interactions[6].

Electrostatic interaction is the chosen method of immobilisation in this research project, as it is hoped for more correlation between the homogeneous and heterogeneous system, when compared to covalent tethering, which needs a covalent tether to hold the catalyst and the support together. Another advantage of electrostatic interactions is the ease at which the immobilisation can be achieved, reducing the number of steps in a given synthesis. Complexes of Cu(II)BOX[30] and Cu(I) and Cu(II)PyBOX[6] ligands have been electrostatically immobilised on silica through the use of a triflate counterion. McDonagh et al reported on the electrostatic immobilisation of copper(I) and copper(II)PyBOX trifluoromethane sulfonates on silica[6] for use in the synthesis of propargylamines. To genetrate the immobilised catalyst, the PhPyBOX was stirred with Cu(I)OTf in dichloromethane. This solution was then added to dried silica and stirred until the colour of the complex disappeared from the solution and the silica became coloured. A graphical representation is shown in **Figure 2.2**. The ease of synthesis of the immobilised catalysed is one of the main benefits of this technique.

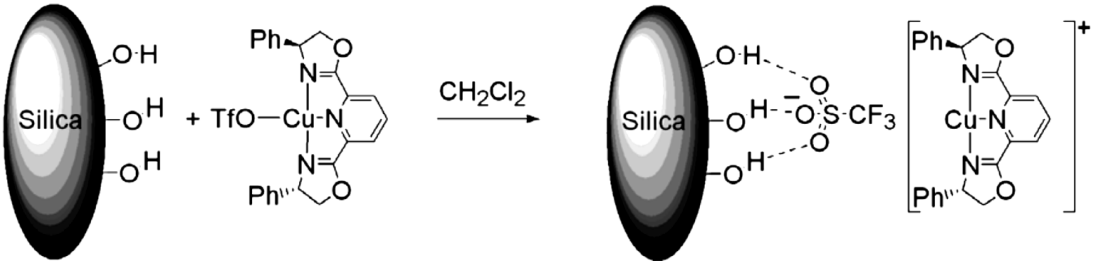
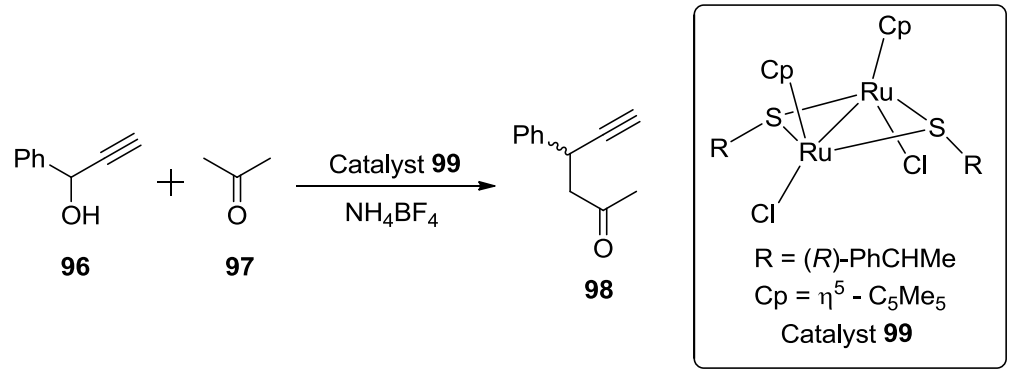


Figure 2.2

In all the reactions tested, it is important to note that the ligands used are not necessarily the most enantioselective ones reported. They are however commercially available. There is an advantage to using ligands, which are not the most selective, in the homogeneous reactions, in studies like this. It allows one to determine if there is an improvement in performance on immobilisation. This is not possible if the homogeneous ligand already gives >98 % *ee*. The purpose of this study is to establish that these reactions can be conducted with immobilised catalysts and that performance is maintained. It thus opens up the possibility of a wider study with better ligands which are more expensive or difficult to synthesise.

2.5.1 Propargylic substitution

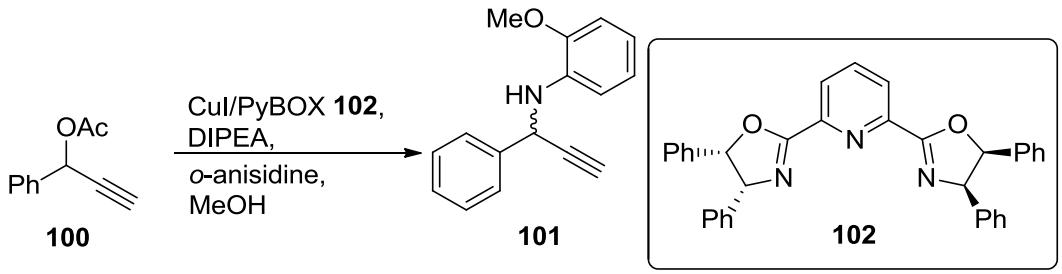
The propargylic functional group is very useful in organic synthesis, as the electron-rich triple bond along with the relatively acidic hydrogen of the terminal alkene means that it is commonly used in chemical transformations e.g. click chemistry[31] or the Sonogashira reaction[32]. The first example of an enantioselective propargylic substitution reaction was developed in the group of Uemura, Hidai and Nishibayashi, using a chiral diruthenium complex. It induced asymmetry in the C-C bond formation during the propargylation of aromatic compounds or acetone with propargylic alcohols (**Scheme 2.51**)[33]. However, propargylic substitution reactions with heteroatom-centred nucleophiles, such as alcohols, amines and thiols did not proceed enantioselectively in the presence of this diruthenium complex[34].



Scheme 2.51

It was during research carried out by van Maarseveen *et al* in to total synthesis of (+)-Anisomycin and (-)-Cytoxazone, that studies were carried out on enantioselective copper-catalysed propargylic substitutions[7]. A variety of different propargylic esters were converted into their amine counterparts using amine nucleophiles and copper-PyBOX catalysts producing, in some cases, good to excellent *ee*'s. The research group were then able to use these propargylic amines as building blocks in the synthesis of (+)-Anisomycin and (-)-Cytoxazone.

After extensive investigation into the reaction the optimum reaction conditions were established as discussed in **Chapter 1**.



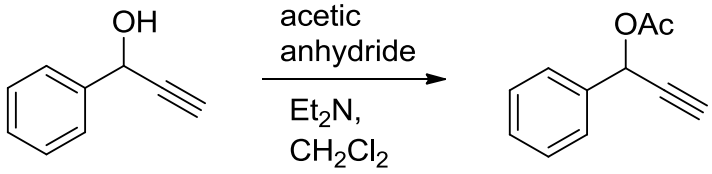
Scheme 2.52

For example, the CuI/PyBOX **102** complex, was generated and propargylic acetate, **100**, was reacted with DIPEA, and *o*-anisidine in the presence of this complex (**Scheme 2.52**). The reaction was stirred for 24 hours at -20 °C and produced **101** in 97 % yield with an 85 % *ee*. This reaction had never been studied using catalysts immobilised as described earlier so it was decided to use this reaction in

combination with the commercially available 2,2'-PyBOX and 2,2'-BOX ligands in the investigation of the effectiveness of the immobilised of catalysts.

2.5.1.1 Synthesis of substrate for propargylic substitution reaction

The substrate **100** was generated by the method described by van Maarseveen *et al*[7]. 1-phenylprop-2-ynyl alcohol, **103**, was dissolved in CH_2Cl_2 and acetic anhydride and triethylamine were added under N_2 (**Scheme 2.53**). The reaction was stirred at room temperature for 21 hours and then concentrated under vacuum.



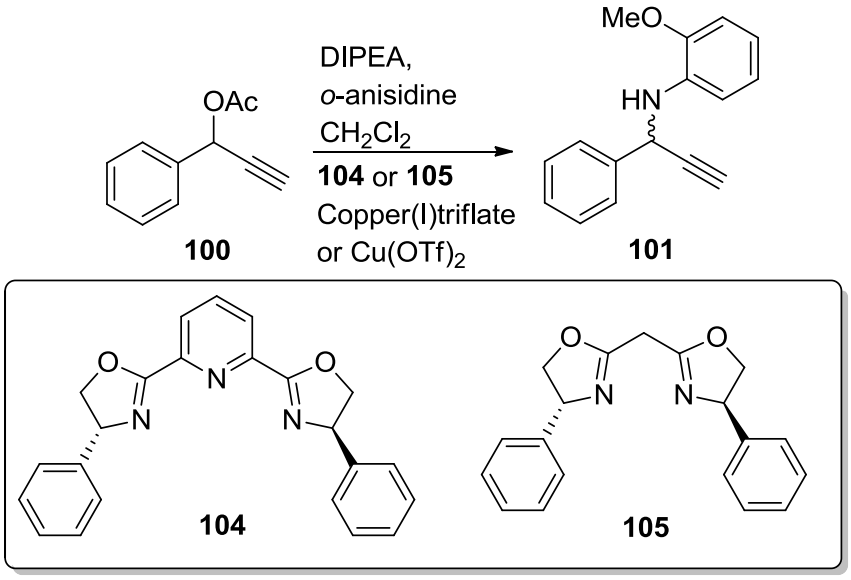
103 **100**

Scheme 2.53

The crude reaction mixture was purified by column chromatography and the product, **100**, was isolated as a colourless liquid in an 85 % yield. ^{1}H NMR spectral analysis of the product was compared to that reported by van Maarseveen *et al* and confirmed that the acetylated product had been synthesised.

2.5.1.2 Propargylic substitution: Methodology

The reaction of 1-phenylprop-2-yn-1-yl acetate, **100**, with DIPEA and *o*-anisidine was catalysed by 10 mol% of a homogeneous complex derived from ligand **104** or ligand **105** and [copper(I)triflate]$_2$·C_6H_6 or $Cu(OTf)_2$, depending on ligand used, as shown in **Scheme 2.54**. The reaction led to the formation of (*R*) and (*S*) 2-methoxy-(1-phenylprop-2-yn-1-yl) aniline, **101**. The reaction was carried out in CH_2Cl_2 at room temperature for 16 hours. For the heterogeneous reactions, the catalysts were immobilised onto silica with a loading of ~0.1 mmol g^{-1} (200mg silica). The reactions using the immobilised complex were carried out according to the conditions outlined above.

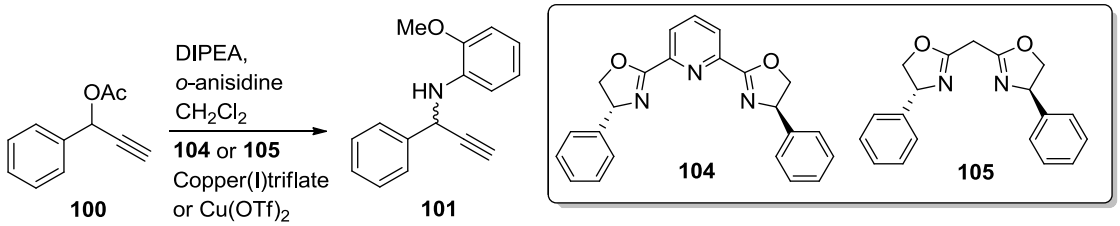


Scheme 2.54

A ^{1}H NMR spectrum was recorded to determine the percentage conversion by comparing the integration of the signal due to the starting material **100** at 6.45, which corresponded to CH_3OCH, and the signal at 5.29 due to the product **101**, which corresponded to C*H*N. The crude mixture was purified by column chromatography on silica gel with the enantiomeric excess (*ee*) measured using chiral HPLC. Spectral characterisation of **101** was consistent with that reported previously[7].

The results of the reactions can be seen in **Table 2.1**. Firstly ligand **104** was complexed with [copper(I)triflate]$_2$·C_6H_6 and in the homogeneous reaction a 100 % conversion to **101** was observed with a 20 % isolated yield and 53 % *ee*. When the same catalyst was immobilised on silica gel, the first reaction showed 98 % conversion to **101**, with 16 % isolated yield with 36 % *ee*. The catalyst was recycled and tested again in the same reaction giving a 33 % conversion to **101** with only 5 % isolated yield and 35 % *ee*. The third time the catalyst was used in the same reaction, no product was detected and only the starting material remained. It was quite clear that there was a large difference between percentage conversion values and isolated yields. It was felt that this could have been due to either some

decomposition of the product, **101**, or strong co-ordination of **101** to the silica, which prevented complete elution from the column.



Ligand	Metal triflate	Homogeneous/ Heterogeneous catalyst	% conversion to 101	Yield (%)	% *ee*
104	Copper(I)triflate	Homogeneous	100	20	53
104	Copper(I)triflate	Hetero 1	98	16	36
104	Copper(I)triflate	Hetero 2	33	5	35
104	Copper(I)triflate	Hetero 3	0	0	0
104	$Cu(OTf)_2$	Homogeneous	100	18	50
104	$Cu(OTf)_2$	Hetero 1	100	15	40
104	$Cu(OTf)_2$	Hetero 2	40	2	39
104	$Cu(OTf)_2$	Hetero 3	0	0	0
105	Copper(I)triflate	Homogeneous	No reaction	No reaction	No reaction

Table 2.1

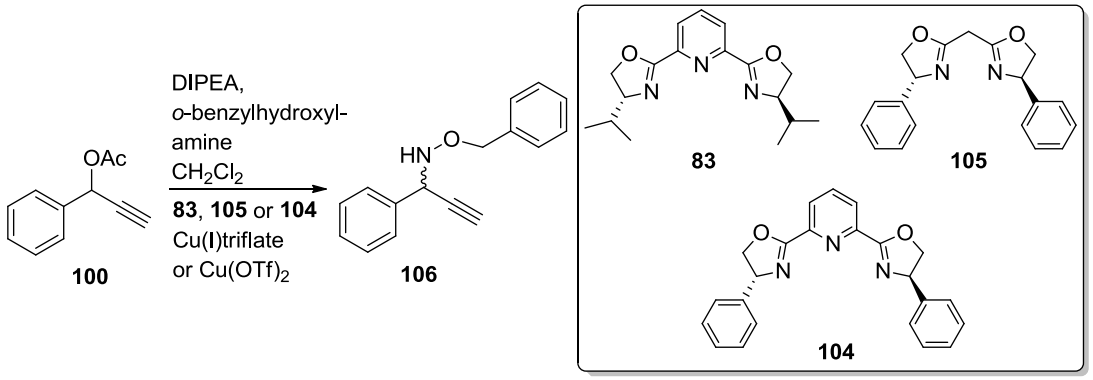
The next catalyst investigated was the ligand **104**-$Cu(OTf)_2$ complex. When the reaction was carried out using the homogeneous catalyst, 100 % conversion to **101** was observed, with an isolated yield of 18 % and an *ee* of 50 %. Subsequently the reaction was carried out using immobilised catalyst on silica gel and produced 100 % conversion to **101**, an isolated yield of 15 % and an *ee* of 40 %. The catalyst was recycled and then tested again in the reaction giving 40 % conversion to **101**, with a 2 % isolated yield and an *ee* of 39 %. When the reaction was carried out for a

third time, using the same immobilised catalyst, no product was detected and only the starting material remained. Again, the same issues arose with the large difference between percentage conversion and yields obtained as described above. Finally BOX ligand **105** was complexed with [copper(I)triflate]$_2$·C_6H_6 and when the reaction was carried out homogeneously, no reaction was observed.

From the above results in **Table 2.1**, it can be clearly seen that the *ee* values for the reactions using the homogeneous catalysts [ligand **104** and either copper(I)triflate or copper(II)triflate] are better than the results seen for the heterogeneous catalyst. However, it was possible to use the immobilised catalyst in two consecutive reactions and achieve similar enantioselectivity. It was believed that the drop off in activity for the second and third heterogeneous runs were due to the *o*-anisidine displacing the catalyst from the silica gel due to the polar nature of the nucleophile. Led by this information, it was decided to attempt the same reaction using *o*-benzylhydroxylamine as a nucleophile instead of *o*-anisidine.

The attempted reaction of 1-phenylprop-2-yn-1-yl acetate, **100**, with DIPEA and *o*-benzylhydroxylamine was catalysed by 10 mol% of a homogeneous complex derived from ligand **83** or ligand **105** or ligand **104** and [copper(I)triflate]$_2$·C_6H_6 or Cu(OTf)$_2$, depending on ligand used, as shown in **Table 2.2**. It was hoped that the reaction would lead to the formation of (*R*) and (*S*) *N*-(benzyloxy)-1-phenylprop-2-yn-1-amine, **106**. The reaction was carried out in CH_2Cl_2 at room temperature for 16 hours. For the heterogeneous reactions, the catalysts were immobilised onto silica with a loading of ~0.1 mmol g^{-1} (200mg silica). The reactions using the immobilised complex were carried out according to the conditions outlined above. Again, a ^{1}H NMR spectrum was recorded to determine the percentage conversion by comparing the integration of the signal at 6.45 due to the CH_3OCH, in the starting material, **100**, and the signal at 5.29 due to the C*H*N in the product **106**. Disappointingly, all combinations tested yielded none of the desired product, **106**, as can be seen in **Table 2.2**. Firstly, ligand **83** was complexed with [copper(I)triflate]$_2$·C_6H_6 and used as a homogeneous catalyst in the reaction but

only starting material remained. When the same catalyst was immobilised on silica gel and tested as a heterogeneous catalyst, the same results were observed.



Ligand	Metal triflate	Homogeneous/ Heterogeneous Catalyst	% conversion to 101
83	Copper(I)triflate	Homogeneous	No reaction
83	Copper(I)triflate	Heterogeneous	No reaction
105	Copper(I)triflate	Homogeneous	No reaction
104	$Cu(OTf)_2$	Homogeneous	No reaction

Table 2.2

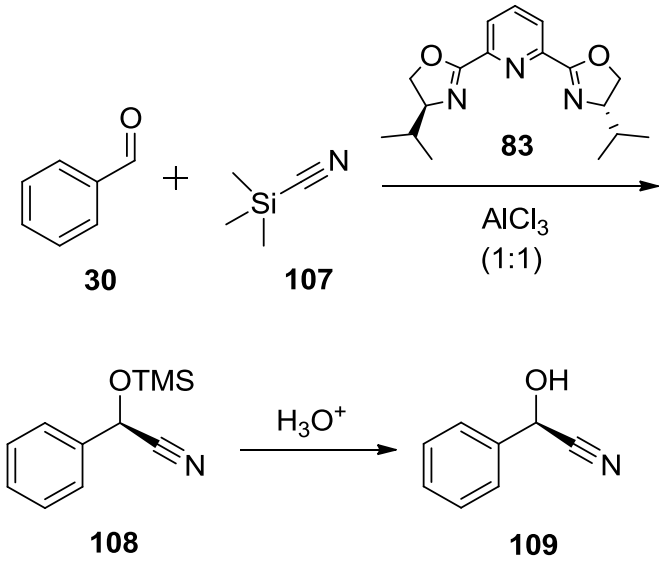
Next, ligand **105** was complexed with [copper(I)triflate]$_2$·C_6H_6 and again used in the reaction as a homogeneous catalyst. Once more, no reaction was seen and only the starting material, **100**, was detected. Finally, ligand **104** was complexed with $Cu(OTf)_2$ and used homogeneously in the reaction. Yet again, no product was generated.

2.5.2 Asymmetric Trimethylsilylcyanation

The addition of a cyanide to a carbonyl compound, in the presence of a chiral catalyst, gives easy access to a versatile intermediate that can be utilised in the synthesis of many compounds such as α-hydroxyacids[35] and α-amino acids[36]. Many different Lewis acids are known to catalyse the trimethylsilylcyanation reaction of aldehydes, including boron-based Lewis acids[37] and Ti(IV) complexes prepared from titanium alkoxides with optically active ligands like Schiff's bases[38]

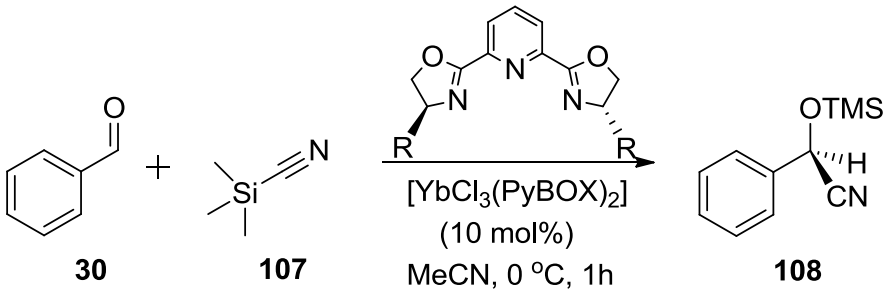
and sulfoximines[39]. Iovel *et al* investigated the use of PyBOX-$AlCl_3$ complexes as catalysts of the asymmetric TMSCN addition to aldehydes[8].

In this reaction, benzaldehyde, **30**, and trimethylsilyl cyanide, **107**, were reacted together in the presence of 20 mol% of the PyBOX-$AlCl_3$ complex (1:1), which was generated *in situ*. This produced the corresponding siloxy nitrile, **108**, after four hours at room temperature (**Scheme 2.55**). This was followed by hydrolysis to give mandelonitrile, **109**, in 90 % yield and an enantiomeric excess of 44 %. Further studies into the addition reaction revealed that by slowly increasing the reaction temperature from 0 °C to 10 °C and stirring for 16 hours the yield of **109** increased to 92 %, while the *ee* was increased to 90 %.



Scheme 2.55

Interestingly, further research carried out Aspinall *et al* into the same reaction showed that lanthanide-PyBOX complexes could also be used to catalyse the reaction[40]. They examined the formation of complexes using lanthanide metal chlorides e.g. ytterbium chloride, samarium chloride and europium chloride, in combination with *S*-PyBOX ligands. The study found that when benzaldehyde, **30**, was reacted with trimethylsilyl cyanide, **107**, a metal-ligand ratio of 1:2 produced the highest enantioselectivity, with $YbCl_3$(S-*i*Pr-PyBOX)$_2$ producing the best yield of **108** (87 %) and *ee* (67 %) (**Scheme 2.56**).

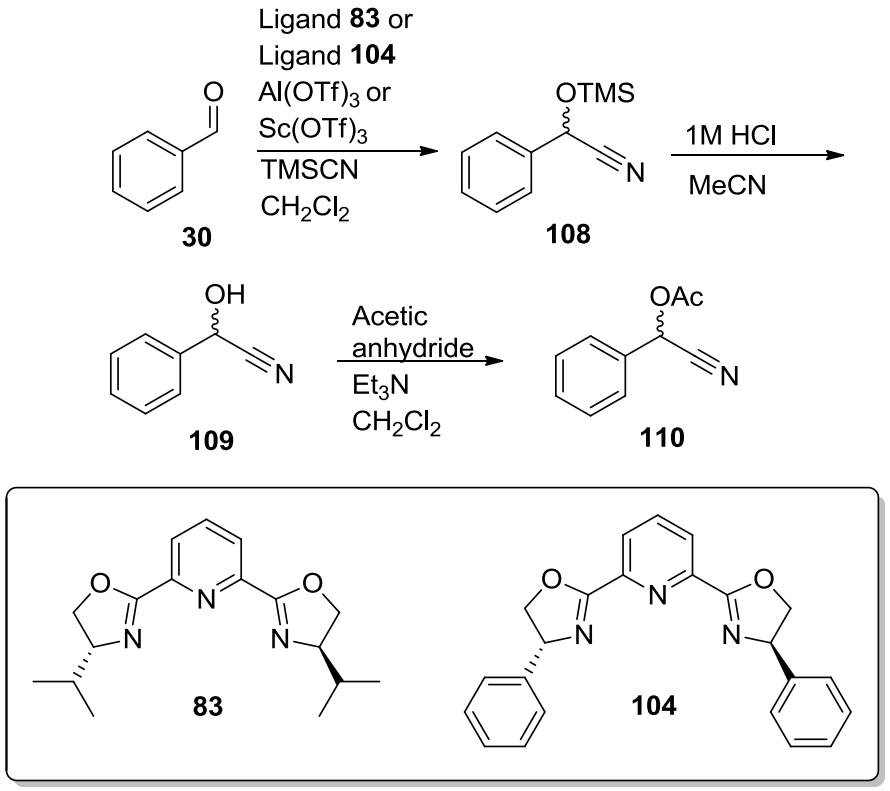


Scheme 2.56

When *S*-Ph-PyBOX was used in the same reaction it yielded 77 % of the desired product, **108**, and an 80 % *ee*. The research group chose *i*Pr-PyBOX ligand due to its higher activity and it's somewhat easier synthesis when compared to the Ph-PyBOX. Encouraged by these results, it was decided that this research project would investigate these reactions using catalysts electrostatically immobilised on silica gel.

2.5.2.1 Asymmetric Trimethylsilylcyanation methodology

The reaction of benzaldehyde, **30**, with trimethylsilylcyanide in dichloromethane was catalysed by 10 mol% of a homogeneous complex derived from ligand **83** or ligand **104** and $Al(OTf)_3$ or $Sc(OTf)_3$, depending on ligand used, formed **108** as shown in **Scheme 2.57**. The reaction was carried out at either room temperature or slowly increasing from 0 °C to 10 °C with the reaction taking 18 - 24 hours. For the heterogeneous reactions, the catalysts were immobilised on silica with a loading of ~0.11 mmol g^{-1} (400mg silica). The reactions using the immobilised complex were carried out according to the conditions outlined above. A ^{1}H NMR spectrum was recorded to determine the percentage conversion using starting material, benzaldehyde, **30**, signal at 10.02, due to C*H*O and product, **108**, signal at 5.49, due to C*H*O.

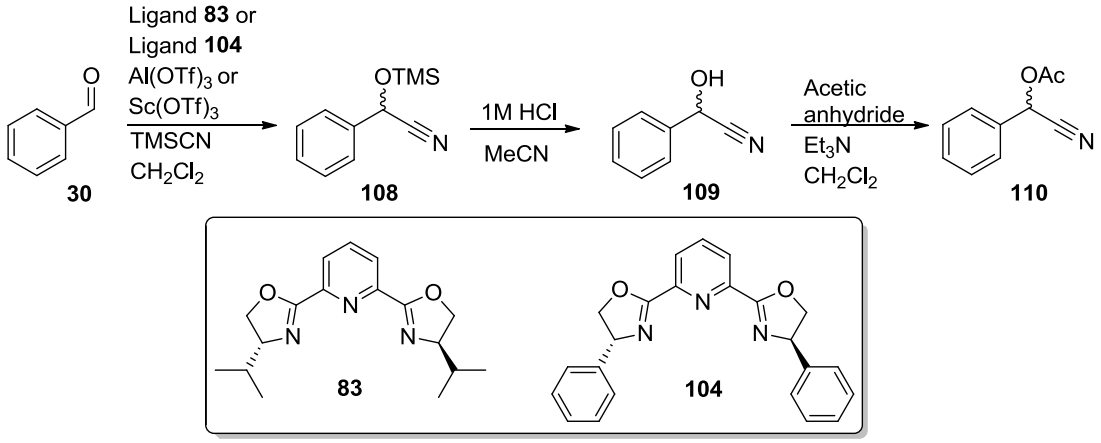


Scheme 2.57

The purified product was then dissolved in MeCN and 1M HCl was added and the reaction was stirred at room temperature overnight producing **109**. The crude alcohol was then acetylated using acetic anhydride. The reaction led to the formation of (*R*) and (*S*) cyano(phenyl)methyl acetate, **110**. The enantiomeric excess (*ee*) of the purified product was measured using chiral GC (CYCLODEX-β 0.25 mmΦ x 30 m column, conditions 125 °C hold 3 min, ramp 3 °C/min to 180 °C hold 3 min), *t*(*R*) 13.5 min and *t*(*S*) 13.7 min. Spectral characterisation of **109** was consistent with that reported[8]. All isolated yields reported were of **109**.

The results for the reaction can be seen in **Table 2.3**. Initially the reaction described by Iovel *et al* was investigated. Ligand **83** was combined with $Al(OTf)_3$ to form the catalyst and was used homogeneously in the reaction. The reaction was stirred at room temperature for 24 hours. This led to 54 % conversion to **108** and an isolated yield of 25 % of **109**. After acetylation an enantiomeric excess of 6 % was recorded.

When the catalyst was immobilised on silica gel and used in the reaction, unfortunately, none of the desired product **108** was formed.



Ligand	Metal triflate	Homogeneous/ Heterogeneous catalyst	Temp (°C)	Time (h)	% conversion to 108	Yield* (%)	*Ee*** (%)
83	$Al(OTf)_3$	Homogeneous	rt	24	54	25	6
83	$Al(OTf)_3$	Hetero 1	rt	24	No product	N/A	N/A
83	$Sc(OTf)_3$	Homogeneous	rt	18	100	76	14
83	$Sc(OTf)_3$	Homogeneous	0 →10	18	64	51	12
83	$Sc(OTf)_3$	Hetero 1	rt	18	82	46	20
83	$Sc(OTf)_3$	Hetero 2	rt	18	77	40	12
83	$Sc(OTf)_3$	Hetero 3	rt	18	73	12	12
104	$Sc(OTf)_3$	Homogeneous	rt	20	100	31	18
104	$Sc(OTf)_3$	Hetero 1	rt	20	100	29	16
104	$Sc(OTf)_3$	Hetero 2	rt	20	100	17	14
104	$Sc(OTf)_3$	Hetero 3	rt	20	75	5	14

Table 2.3

* measured after **109** had been generated ** measured after **110** had been generated

In this case, it was believed that the difference between the percentage conversion and the yields could have been due to the slightly acidic nature of the silica gel surface, used during the column chromatography, and it may have removed the trimethylsilyl protecting group leaving the alcohol.

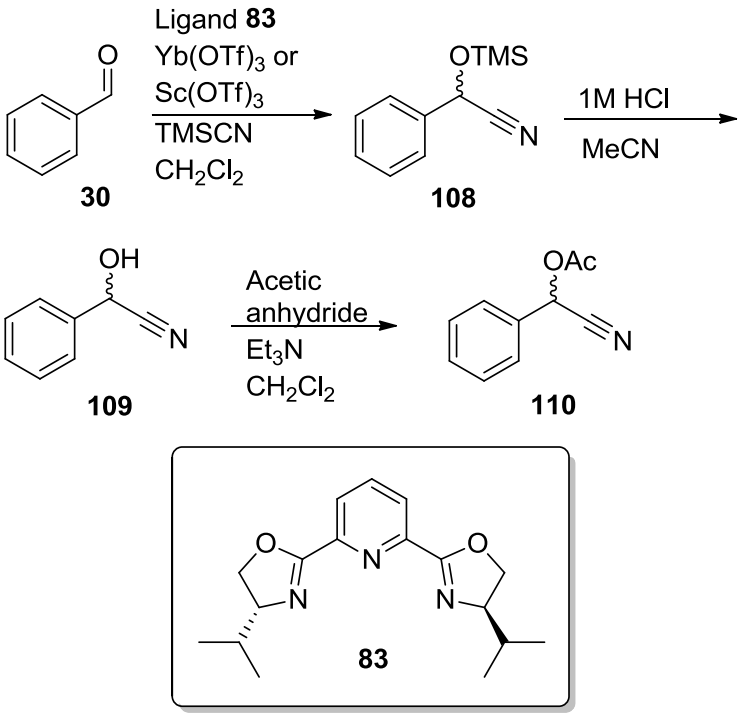
It was then decided to test the reaction using $Sc(OTf)_3$ with the same ligand, **83**. To begin with the reaction was carried out using a homogeneous catalyst, at room temperature for 18 hours. This produced 100 % conversion to **108** with 76 % isolated yield of **109**, an *ee* of 14 % was observed. In order to try and improve the enantiomeric excess, it was decided to carry out the reaction at 0 °C, which was slowly increased to 10 °C over the course of the reaction. Unfortunately, this only gave 68 % conversion to **108** and 51 % isolated yield of **109** with only 12 % *ee*. From this, it was decided to carry out the remaining reactions at room temperature for 18 hours. Subsequently, the same catalyst was immobilised on silica and used as a heterogeneous catalyst in the same reaction. The first time the immobilised catalyst was used, an 82 % conversion was observed with 46 % isolated yield and 20 % *ee*. Even though the percentage conversion and isolated yield were lower for the heterogeneous catalyst when compared to the reaction involving the homogeneous catalyst under the same conditions, the heterogeneous catalyst produced a higher *ee*. Encouraged by this result, the recycled heterogeneous catalyst was tested in the same reaction for a second time and produced 77 % conversion to **108** with an isolated yield of 40 % and an *ee* of 12 %. When the catalyst was recycled for the third time the reaction produced **108** in 12 % isolated yield (73 % conversion) and 12 % *ee*.

Following these encouraging results, ligand **83** was stirred with $Sc(OTf)_3$ and used as a homogeneous catalyst in the reaction seen in **Scheme 2.57**. This produced 100 % conversion to **108,** with an isolated yield of only 31 % and an *ee* of 18 %. The same catalyst was immobilised on silica and used as a heterogeneous catalyst in the same reaction. Again this gave 100 % conversion to **108**, but the isolated yield was reduced to 29 % and the *ee* to 16 %. When the recycled catalyst was used for the second time it produced 100 % conversion with only 17 % isolated yield and 14 %

ee. Disappointingly, on the third use only a 5 % isolated yield (75 % conversion) was seen with an *ee* of 14 %.

From the results above, it was seen that $Al(OTf)_3$ was not a compatible metal for use as an electrostatically immobilised catalyst in this reaction. When scandium(III)triflate was combined with both ligands **83** and **104**, the optimum reaction conditions were found to be at room temperature for 18 – 20 hours. Enantiomeric excess values for reactions that used homogeneous catalysts, again, produced higher values than those reactions that used heterogeneous catalysts, however the difference was minimal. When the heterogeneous catalyst was used for the second and third time, *ee*'s were the same but a small drop in enantioselectivity was seen compared to the first use of the catalyst. A higher *ee* was observed when ligand **83** and $Sc(OTf)_3$ were complexed and immobilised on silica, compared to the reaction using the homogeneous catalyst. While this higher *ee* was encouraging, overall the recycled catalyst results were disappointing. It was decided to investigate the reaction using different ligand to metal triflate ratio and also a different metal triflate.

The reaction of benzaldehyde, **30**, with trimethylsilyl cyanide in dichloromethane was catalysed by a homogeneous complex derived from 2 equiv. of ligand **83** and 1 equiv. of either $Yb(OTf)_3$ or $Sc(OTf)_3$, forming **108** as shown in **Scheme 2.58**. The reaction was carried out at either room temperature or slowly increasing from 0 °C to 10 °C for 20 - 26 hours. For the heterogeneous reactions, the catalysts were immobilised onto silica with a loading of ~0.17 mmol g^{-1} (400mg silica). The reactions using the immobilised complex were carried out according to the conditions outlined above. A ^1H NMR spectrum was recorded to determine the percentage conversion using the starting material, benzaldehyde **30**, signal at 10.02, due to CO*H* and the product, **108**, signal at 5.49, due to C*H*O. The crude product was then dissolved in MeCN and 1M HCl was added and the reaction was stirred at room temperature overnight producing **109**. The purified product was then acetylated using acetic anhydride. The reaction led to the formation of (*R*) and (*S*) cyano(phenyl)methyl acetate, **110**.

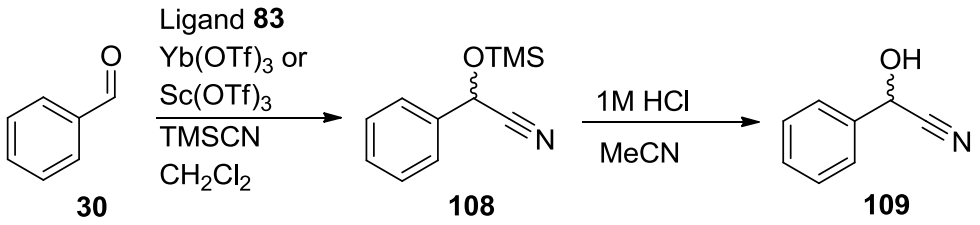


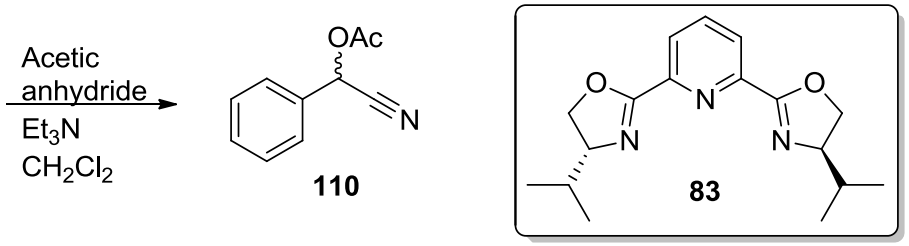
Scheme 2.58

The results for the reaction can be seen in **Table 2.4**. Initially, ligand **83** and $Sc(OTf)_3$ were mixed together in a 2:1 ratio to form the catalyst. The homogeneous catalyst was then stirred with the reactants at 0 °C, which was slowly increased to 10 °C over the course of the reaction which took 26 hours. The reaction produced 77 % conversion to **108**, with a 46 % isolated yield and 12 % enantiomeric excess. As this reaction produced a poorer isolated yield and *ee* than the reaction when a 1:1 ratio of ligand and metal salt was used, it was not tested heterogeneously.

Next the reaction was carried out using $Yb(OTf)_3$ and ligand **83**. When the reaction was carried out using the homogeneous catalyst, at room temperature for 20 hours, an isolated yield of 84 % was obtained, with a conversion of 90 %, and an *ee* of 8 %. Then, the catalyst was electrostatically immobilised on silica and used in the first heterogeneous reaction, stirring at room temperature for 20 hours. On this occasion, a poor conversion of 16 % and isolated yield of only 6 % was recorded. The enantiomeric excess was 6 %. When the reaction was carried out for a second

and subsequent third time using the recycled catalyst, **108** was not produced and only starting material remained.





Metal triflate	Homogeneous/ Heterogeneous catalyst	Temp (°C)	Time (h)	% conversion to 108	Yield* (%)	*Ee*** (%)
$Sc(OTf)_3$	Homogeneous	0 → 10	26	77	46	12
$Yb(OTf)_3$	Homogeneous	rt	20	90	84	8
$Yb(OTf)_3$	Hetero 1	rt	20	16	6	6
$Yb(OTf)_3$	Hetero 2	rt	20	No product	N/A	N/A
$Yb(OTf)_3$	Hetero 3	rt	20	No product	N/A	N/A

Table 2.4

*measured after **109** had been generated **measured after **110** had been generated

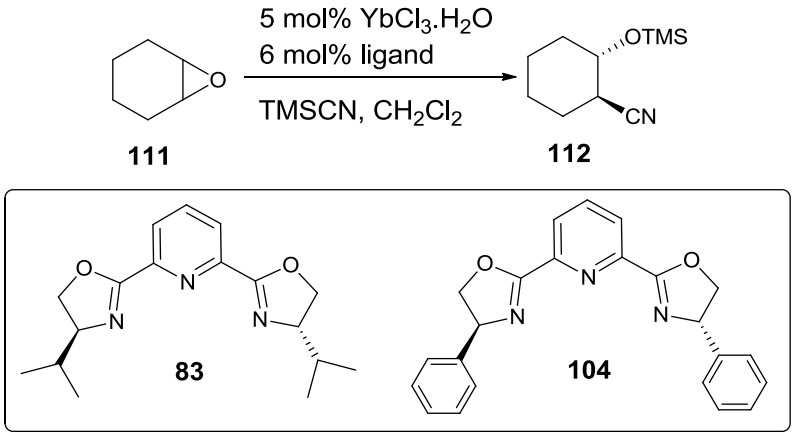
So when using 2:1 ligand:metal ratio in the reaction involving scandium(III)triflate complexed with ligand **83**, the homogeneous reaction produced a poor isolated yield and the same *ee* compared to the same reaction using a 1:1 ligand:metal ratio. When $Yb(OTf)_3$ was combined with the same ligand, **83**, in a 2:1 ligand:metal ratio, the homogeneous reaction produced a good yield but the *ee* was very low. When the catalyst was immobilised on silica, the isolated yields dramatically dropped but it produced a similar *ee*. When the catalyst was reused for a second and third time, none of the required product was produced. The very low reactivity of the

heterogeneous catalyst could be down to over-crowding around the metal centre blocking the reaction sites, due to the catalyst being immobilised on silica.

2.5.3 Asymmetric Ring Opening of epoxides

Again, epoxides are important intermediates in synthetic chemistry as they are synthetically useful and easily prepared. They can also react with numerous different nucleophiles, due to their ring strain, and can produce ring opened products with high regioselectivity. The use of *meso* epoxides offers a cost effective and straightforward pathway to enantioenriched products. The majority of nucleophiles used are heteroatom based and can offer synthetic pathways to important chiral molecules like 1,2-azido alcohols[41] and 1,2 benzoyloxy alcohols[42]. The use of carbon based nucleophiles remains challenging, but offers the advantage of simple and stereoselective carbon-carbon bond formation. Research carried out by Jacobenson *et al* investigated the possibility of using chiral ligands, in combination with the lanthanide salts, to asymmetrically catalyse reactions between trimethylsilyl cyanide and meso epoxides[9].

In the reaction shown in **Scheme 2.59**, a series of PYBOX ligands were reacted with 5 mol% $YbCl_3$ hydrate at room temperature for 4 hours, to identify the most enantioselective system for the asymmetric ring opening of cyclohexene oxide, **111**, with TMSCN.

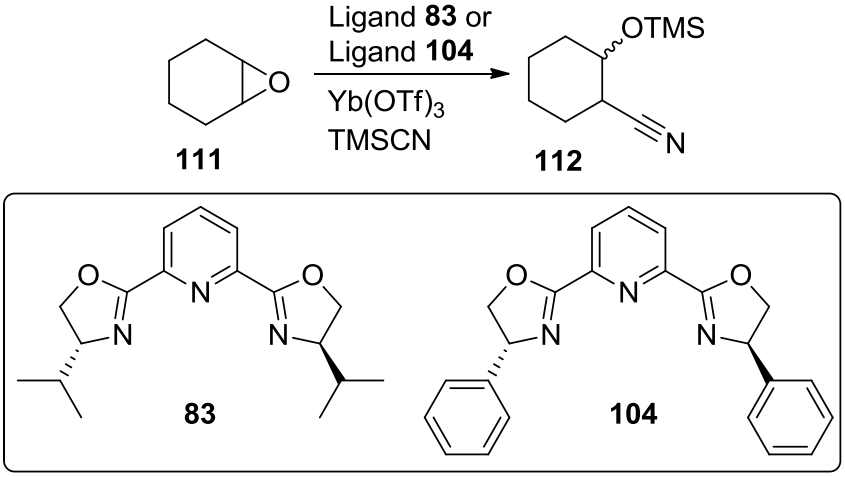


Scheme 2.59

When the asymmetric catalyst, derived from **83,** was used to catalyse the reaction, a yield of 95 % of **112** was produced with and enantiomeric excess of 47 %. When ligand **104** was utilized, a yield of 96 % of **112** was formed with an *ee* of 67 %. Further optimisation led to the reaction being carried out using the catalyst derived from ligand **83** and 10 mol% of metal salt**,** at -40 °C, in chloroform and produced **112** in 90 % yield and 91 % *ee* after four days. The research group also tested a number of different meso epoxides in the reaction, including cyclopentene oxide, *cis*-2,3 epoxybutane and *trans*-ethyl-3,4-epoxy-ethyl-1-cyclopentanecarboxylate which all produced high yields and *ee*'s. We decided to apply our immobilised catalysts to this reaction, to compare the performance of the immobilised and homogeneous catalysts.

2.5.3.1 Asymmetric Ring Opening of epoxides methodology

The reaction of cyclohexene oxide, **111**, with trimethylsilyl cyanide was catalysed by 10 mol% of a homogeneous complex derived from ligand **83** or ligand **104** and $Yb(OTf)_3$, forming **112** as shown in **Scheme 2.60**.



Scheme 2.60

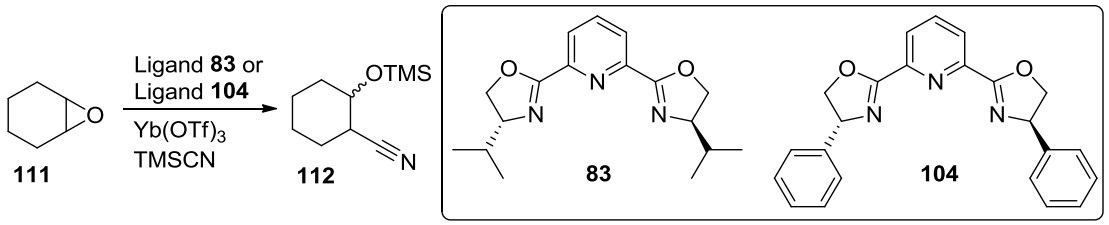
The reaction was carried out at -40 °C, -20 °C, -15 °C or room temperature for 17 - 96 hours, depending on the reaction temperature, with the end point of the reaction being determined by ^{1}H NMR spectroscopy. For the heterogeneous

reactions, the catalysts were immobilised onto silica with a loading of ~0.36 mmol g^{-1} (300mg silica). The reactions using the immobilised complex were carried out according to the conditions outlined above. In both the homogeneous and heterogeneous reactions, a ^{1}H NMR spectrum was recorded to determine the percentage conversion using starting material, cyclohexene oxide, **111**, signal at 3.12, due to the two *H*CO and product, **112**, signal at 3.69 – 3.64, due to C*H*. The crude product was then purified by column chromatography (95:5 Pet ether:EtOAc). The enantiomeric excess was measured using chiral GC, *t* = 30.9 min and 32.2 min. Spectral characterisation for **112**, was consistent with that reported in the literature[9].

The results of the reaction are shown in **Table 2.5**. Initially, the reaction was carried out using chloroform as the reaction solvent, and homogeneous catalyst and was stirred at -40 °C for 96 hours. The crude ^{1}H NMR showed that none of the desired product, **112** had been generated and only the starting material remained. With this information in hand, the reaction was attempted again using a homogeneous catalyst in chloroform and was stirred at -15 °C for 96 hours. The % conversion to **112** was recorded as 78 % with a 22 % isolated yield and 20 % *ee*.

Encouraged by these results, the catalyst was electrostatically immobilised on silica gel and was tested in the same reaction using chloroform as solvent. The reaction was carried out at -20 °C for 48 hours. Unfortunately, this did not produce the required product, **112**, and the starting materials remained. The same result was obtained when the catalyst was recycled and used a second time in the reaction, which was stirred at room temperature for 48 hours.

At this point, it was decided to carry out the reaction using dichloromethane as the reaction solvent because chloroform had not produced very good results and this solvent made using the immobilised catalyst quite difficult. It was found that the silica gel became translucent and very difficult to see when using chloroform and this made decanting off the solvent very trying. The first reaction, using CH_2Cl_2 as a reaction solvent, was carried out with a homogeneous catalyst which was stirred at room temperature for 48 hours.



Homogeneous/ heterogeneous	Ligand	Solvent	Temp (°C)	Time (h)	% conversion to 112	Yield (%)	*Ee* (%)
Homogeneous	**83**	$CHCl_3$	-40	96	No product	N/A	N/A
Homogeneous	**83**	$CHCl_3$	-15	96	78	22	20
Hetero 1	**83**	$CHCl_3$	-20	48	No product	N/A	N/A
Hetero 2	**83**	$CHCl_3$	rt	48	No product	N/A	N/A
Homogeneous	**83**	CH_2Cl_2	rt	48	100	36	8
Hetero 1	**83**	CH_2Cl_2	rt	17	76	29	2
Hetero 2	**83**	CH_2Cl_2	rt	18	70	23	0
Homogeneous	**83**	CH_2Cl_2	-20	96	68	20	20
Hetero 1	**83**	CH_2Cl_2	-20	21	62	13	16
Hetero 2	**83**	CH_2Cl_2	-20	21	58	5	16
Hetero 3	**83**	CH_2Cl_2	-20	21	41	2	12
Homogeneous	**104**	CH_2Cl_2	-20	21	100	17	24
Hetero 1	**104**	CH_2Cl_2	-20	21	47	18	20
Hetero 2	**104**	CH_2Cl_2	-20	21	21	2	20
Hetero 3	**104**	CH_2Cl_2	-20	21	52	30	14

Table 2.5

This time, a 100 % conversion to **112** was observed with an isolated yield of 36 % and an *ee* of 8 %. The reaction was then carried out using the immobilised catalyst at room temperature for 17 hours. This gave 76 % conversion to **112**, 29 % isolated yield and 2 % *ee*. This same catalyst was recycled and used in the reaction for a second time giving **112** in 23 % isolated yield (70 % conversion) but gave a 50:50 ratio of each enantiomer. Due to the lack of enantioselectivity, the reaction was not attempted for a third time. Again, a large difference between percentage conversion values and isolated yields was observed. It was felt that this could have been because of the slightly acidic nature of the silica gel surface, used during the column chromatography, and it may have removed the trimethylsilyl protecting group leaving the alcohol.

Finally, with optimised reaction conditions, the homogeneous catalyst, ligand **83** and $Yb(OTf)_3$, was used in the reaction and was stirred at -20 °C for 96 hours. A 68 % conversion to **112** was observed with a 20 % isolated yield and 20 % *ee*. Following this, the catalyst was immobilised on silica and was used in the reaction as a heterogeneous catalyst at -20 °C for 21 hours. This produced a 62 % conversion to **112**, an isolated yield of 13 % and an *ee* of 16 %. The catalyst was recycled and used in the reaction for a second time giving **112** in 5 % isolated yield (58 % conversion) and 16 % *ee*. Lastly the catalyst was reused for a third time in the reaction and a 41 % conversion was recorded with a 2 % isolated yield and 12 % *ee*.

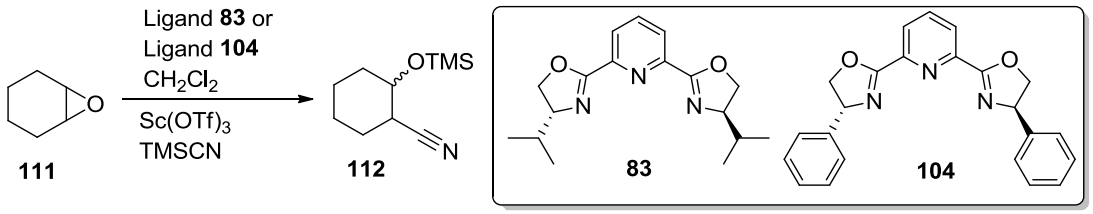
Subsequently, the ligand was changed and ph-PyBOX, **104**, was complexed with $Yb(OTf)_3$ and used as a homogeneous catalyst in the reaction. This was stirred at -20 °C for 21 hours. It produced 100 % conversion to **112**, 17 % isolated yield and 24 % *ee*. The catalyst was immobilised on silica gel and used in the same reaction, under the same conditions. A 47 % conversion to **112** was observed with an 18 % isolated yield and 20 % enantiomeric excess. The catalyst was recycled and used for a second time in the same reaction. On this occasion, a 21 % conversion rate was seen, with a poor isolated yield of 2 % and an *ee* of 20 %. On the third use, the reused catalyst produced a 52 % conversion to **112**, 30 % isolated yield and 14 % *ee*.

From the results above using $Yb(OTf)_3$ complexed with **83** as the catalyst, the optimised reaction conditions were found to be -20 °C for 21 hours. When the reaction was carried out at room temperature, *ee*'s were very poor, but by lowering the reaction temperature, *ee*'s were improved. Again, the reactions using the homogeneous catalysts produced the best *ee*'s. When the reaction was carried out at optimum conditions, the heterogeneous catalyst first and second use showed the same enantioselectivity, however, there was a small drop on the third use. Also, the relatively good percentage conversions were not reflected by the isolated yields. $Yb(OTf)_3$ was also combined with ligand **104**, and when it was used as a homogeneous catalyst the best *ee*'s were seen. The first and second use of the heterogeneous catalyst produced the same enantiomeric excess values with a small drop in enantioselectivity seen on the third use. Again, the poor isolated yields, compared to the percentage conversion values could be attributed to the possible loss of the trimethylsilyl protecting group during the purification of the crude reaction mixture on silica gel. It was believed that the slightly acidic nature of the silica gel surface, used during the column chromatography, may have removed the trimethylsilyl protecting group.

The next step of the investigation involved testing $Sc(OTf)_3$ in the reaction of cyclohexene oxide, **111**, with trimethylsilylcyanide, in dichloromethane and was catalysed by 10 mol% of a homogeneous complex derived from ligand **83** or ligand **104** and $Sc(OTf)_3$, forming **112** as shown in **Table 2.5**. The reaction was carried out at -20 °C, or room temperature for 24 - 68 hours, depending on the reaction temperature. For the heterogeneous reactions, the catalysts were immobilised onto silica with a loading of ~0.36 mmol g^{-1} (300mg silica). The reactions using the immobilised complex were carried out according to the conditions outlined above. Spectral characterisation for **111**, reported below was consistent with that reported in the literature[9].

The results of the reaction are shown in **Table 2.6**. The first reaction that was attempted used ligand **83** and $Sc(OTf)_3$, to form the homogeneous catalyst which was reacted with cyclohexene oxide, **111**, and TMSCN. The reaction was stirred at

room temperature for 68 hours and produced 100 % conversion to **112**, with an isolated yield of 32 % and an enantiomeric excess of 2 %. The same catalyst was electrostatically immobilised on silica gel and used as a heterogeneous catalyst in the same reaction which was also stirred at room temperature for 68 hours. In this case, none of the required product, **112** was produced.



Ligand	Metal triflate	Homogeneous/ Heterogeneous	Temp (°C)	Time (h)	% conversion to 112	Yield (%)	*Ee* (%)
83	$Sc(OTf)_3$	Homogeneous	rt	68	100	32	2
83	$Sc(OTf)_3$	Hetero 1	rt	68	No product	N/A	N/A
104	$Sc(OTf)_3$	Homogeneous	-20	24	100	11	2
104	$Sc(OTf)_3$	Hetero 1	-20	24	100	43	0
104	$Sc(OTf)_3$	Hetero 2	-20	24	62	16	0

Table 2.6

Finally, ligand **104** was stirred with $Sc(OTf)_3$, to form the homogeneous catalyst used in the reaction. In this case, the reaction was stirred at -20 °C for 24 h and produced 100 % conversion to **112**, with an isolated yield of 11 % and an *ee* of only 2 %. The same catalyst was immobilised on silica and used as a heterogeneous catalyst in the same reaction, under the same conditions. On this occasion, a 100 % conversion to **112** was achieved with an isolated yield of 43 %, however there was no enantioselectivity observed. When the catalyst was reused in the same reaction, under the same conditions, a 62 % conversion to **112** was seen, with an isolated yield of 16 % and again no enantioselectivity.

When $Sc(OTf)_3$ was complexed with ligand **83** the homogeneous catalyst produced very poor *ee*'s, at room temperature, with the heterogeneous catalyst producing none of the required product. When the $Sc(OTf)_3$ was complexed with ligand **104**, no enantioselectivity was observed.

2.5.4 Conclusions

For all three reactions tested, the isolated yields and enantiomeric excess values were similar when the homogeneous catalyst and the heterogeneous catalyst were used for the first time. In almost all the reactions, a drop in isolated yields and enantiomeric excess was seen when the heterogeneous catalyst was reused.

In the asymmetric propargylic substitution, 1-phenylprop-2-yn-1-yl acetate, **100**, was reacted with DIPEA and *o*-anisidine. It was found that when ligand **104** was complexed with copper(I)triflate and $Cu(OTf)_2$ similar percentage conversions, isolated yields and *ee*'s were obtained for homogeneous and heterogeneous reactions, including the reactions using the recycled catalyst. When BOX ligand **105** was combined with copper(I)triflate, the reaction produced none of the required product, **101**. When the nucleophile was changed from *o*-anisidine to *o*-benzylhydroxylamine, all reactions tested failed to produce any of the required product, **106**. The poor recycalability and activity observed in the heterogeneous reactions, compared to the homogeneous, were thought to be due to the polar nature of the nucleophiles displacing the catalyst from the silica gel or possibly displacing the ligand from the metal. The large difference between the percentage conversions and isolated yields of all the reactions could possibly be attributed to some decomposition of the product **101** or strong co-ordination of **101** to the silica, which prevented complete elution from the column.

In the asymmetric trimethylsilyl cyanation reactions, benzaldehyde, **30**, was reacted with trimethylsilyl cyanide in dichloromethane. It was catalysed by 1:1 complexes of ligand **83** and $Al(OTf)_3$, ligand **83** and $Sc(OTf)_3$ and finally ligand **104** and $Sc(OTf)_3$. The complex of ligand **83** and $Al(OTf)_3$ proved unsuccessful as a heterogeneous catalyst when tested in the reaction with the homogeneous catalyst achieving a

poor conversion, isolated yield and *ee*. Better results were achieved when ligand **83** and $Sc(OTf)_3$ was used. After testing, the optimum reaction temperature was found to be room temperature and, interestingly, the first use of the heterogeneous catalyst produced a higher *ee* compared to the homogeneous catalyst, however the percentage conversion and yield were higher for the homogeneous catalyst. When the immobilised catalyst was used in subsequent second and third reactions, percentage conversions remained similar. The isolated yield of the second use reaction produced a similar yield to the first use of the catalyst but the third reaction yield was poor at only 12 %. The enantiomeric excess for the second and third reactions, using heterogeneous catalysts, were the same but less than that achieved for the first heterogeneous reaction. When ligand **104** and $Sc(OTf)_3$ were used as a catalyst, high percentage conversions were achieved but the isolated yields were substantially lower. Interestingly the enantiomeric excess values were all similar ranging from 18 % - 14 %. Again, in the third reaction using the heterogeneous catalyst, a substantial drop in the isolated yield was observed.

Finally, the ratio of ligand to metal triflate was changed to 2:1, with ligand **83** and $Sc(OTf)_3$ tested first. The reaction was carried out using a homogeneous catalyst and produced lower percentage conversion, yield and *ee* when compared to the reaction using a 1:1 ratio of ligand to metal triflate. Then ligand **83** was complexed with $Yb(OTf)_3$ and the homogeneous reaction produced a good conversion and isolated yield but the *ee* was very low. When the reaction was attempted using an immobilised catalyst, unfortunately, the first reaction produced low isolated yields and *ee* and subsequent reactions failed to produce any of the required product **108**. In this reaction, the percentage conversion values and the yields showed quite a disparity. It was felt that this could have been due to the loss of the TMS group, during column chromatography, giving the alcohol.

The final reaction that was tested, using electrostatically immobilised catalysts, was asymmetric ring opening of epoxides. Cyclohexene oxide, **111**, was reacted with trimethylsilyl cyanide, and was catalysed by ligand **83** and $Yb(OTf)_3$. Initially the reaction used chloroform as a reaction solvent but results were poor with none of

the required product, **112**, formed. When dichloromethane was used, the required product was formed.

Following this, the effect of the reaction temperature was explored. It was found that percentage conversion values and yields were lower but enantiomeric excess values were higher when the reaction was carried out at -20 °C compared to room temperature. In almost all cases, the homogeneous catalyst provided better conversions, isolated yields and *ee*'s. However, in the reaction at -20 °C, the three reactions using the recycled heterogeneous catalyst produced similar conversions (62 – 41 %) and *ee*'s (16 – 12 %). When ligand **83** was complexed with $Sc(OTf)_3$ and used as a homogeneous catalyst, at room temperature, it showed very poor enantioselectivity and when the catalyst was immobilised, none of the required product, **112**, was produced. Then, ligand **104** and $Sc(OTf)_3$ were used to form a catalyst, which was tested at -20 °C. The homogeneous and recycled heterogeneous catalyst produced good to excellent percentage conversions, but poor yields and little or no enantioselectivity. Lastly, ligand **104** and $Yb(OTf)_3$ were complexed. This reaction, at -20 °C, showed the best enantiomeric excess values but the heterogeneous catalyst conversions and isolated yields were poor.

Again, it is important to note that the ligands used are not necessarily the most enantioselective ones reported. This allows for improvements in performance to be observed between homogenous and heterogeneous reactions. This is not possible if the homogeneous ligand already produces excellent *ee*'s. The purpose of this study was to establish that these reactions can be conducted with immobilised catalysts and that performance was maintained. Unfortunately, the poor recyclability we have seen does present an issue which will have to be tackled.

References

[1] F. A. Davis, W. McCoull, *The Journal of Organic Chemistry* 1999, *64*, 3396-3397.

[2] Y. Motoyama, Y. Koga, H. Nishiyama, *Tetrahedron* 2001, *57*, 853-860.

[3] D. A. Evans, M. C. Kozlowski, J. S. Tedrow, *Tetrahedron Letters* 1996, *37*, 7481-7484.

[4] I. Atodiresei, I. Schiffers, C. Bolm, *Tetrahedron: Asymmetry* 2006, *17*, 620-633.

[5] N. Debono, C. Pinel, R. Jahjah, A. Alaaeddine, P. Delichère, F. Lefebvre, L. Djakovitch, *Journal of Molecular Catalysis A: Chemical* 2008, *287*, 142-150.

[6] C. McDonagh, P. O'Conghaile, R. J. M. Klein Gebbink, P. O'Leary, *Tetrahedron Letters* 2007, *48*, 4387-4390.

[7] R. J. Detz, Z. Abiri, R. le Griel, H. Hiemstra, J. H. van Maarseveen, *Chemistry – A European Journal* 2011, *17*, 5921-5930.

[8] I. Iovel, Y. Popelis, M. Fleisher, E. Lukevics, *Tetrahedron: Asymmetry* 1997, *8*, 1279-1285.

[9] S. E. Schaus, E. N. Jacobsen, *Organic Letters* 2000, *2*, 1001-1004.

[10] T. D. Owens, A. J. Souers, J. A. Ellman, *The Journal of Organic Chemistry* 2002, *68*, 3-10.

[11] D. A. Cogan, G. Liu, J. Ellman, *Tetrahedron* 1999, *55*, 8883-8904.

[12] C.-S. Jiang, R. Zhou, J.-X. Gong, L.-L. Chen, T. Kurtán, X. Shen, Y.-W. Guo, *Bioorganic & Medicinal Chemistry Letters* 2011, *21*, 1171-1175.

[13] A. Krasovskiy, P. Knochel, *Angewandte Chemie International Edition* 2004, *43*, 3333-3336.

[14] V. Derdau, V. Snieckus, *The Journal of Organic Chemistry* 2001, *66*, 1992-1998.

[15] B.-G. Wei, J. Chen, P.-Q. Huang, *Tetrahedron* 2006, *62*, 190-198.

[16] L. Keinicke, P. Fristrup, P.-O. Norrby, R. Madsen, *Journal of the American Chemical Society* 2005, *127*, 15756-15761.

[17] R. Gauler, N. Risch, *European Journal of Organic Chemistry* 1998, *1998*, 1193-1200.

[18] D. Frain, F. Kirby, P. McArdle, P. O'Leary, *Synlett* 2009, *2009*, 1261-1264.

[19] R. E. Maleczka, L. R. Terrell, F. Geng, J. S. Ward, *Organic Letters* 2002, *4*, 2841-2844.

[20] S.-s. Jew, B.-s. Park, D.-y. Lim, M. G. Kim, I. K. Chung, J. H. Kim, C. I. Hong, J.-K. Kim, H.-J. Park, J.-H. Lee, H.-g. Park, *Bioorganic & Medicinal Chemistry Letters* 2003, *13*, 609-612.

[21] H. Nishiyama, *Chemical Society Reviews* 2007, *36*, 1133-1141.

[22] J.-i. Ito, S. Ujiie, H. Nishiyama, *Organometallics* 2008, *28*, 630-638.

[23] A. El Hatimi, M. Gomez, S. Jansat, G. Muller, M. Font-Bardia, X. Solans, *Journal of the Chemical Society, Dalton Transactions* 1998, *0*, 4229-4236.

[24] P. Geoghegan, P. O'Leary, *Tetrahedron: Asymmetry* 2010, *21*, 867-870.

[25] I. M. Pastor, P. Vastila, H. Adolfsson, *Chemical Communications* 2002, 2046-2047.

[26] P. McMorn, G. J. Hutchings, *Chemical Society Reviews* 2004, *33*, 108-122.

[27] M. J. Sabater, A. Corma, A. Domenech, V. Fornes, H. Garcia, *Chemical Communications* 1997, *0*, 1285-1286.

[28] A. Cornejo, J. M. Fraile, J. I. García, M. J. Gil, S. V. Luis, V. Martínez-Merino, J. A. Mayoral, *Comptes Rendus Chimie* 2004, *7*, 161-167.

[29] J. Jamis, J. R. Anderson, R. S. Dickson, E. M. Campi, W. R. Jackson, *Journal of Organometallic Chemistry* 2001, *627*, 37-43.

[30] P. O'Leary, N. P. Krosveld, K. P. De Jong, G. van Koten, R. J. M. Klein Gebbink, *Tetrahedron Letters* 2004, *45*, 3177-3180.

[31] V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angewandte Chemie International Edition* 2002, *41*, 2596-2599.

[32] R. Chinchilla, C. Nájera, *Chemical Reviews* 2007, *107*, 874-922.

[33] Y. Nishibayashi, G. Onodera, Y. Inada, M. Hidai, S. Uemura, *Organometallics* 2003, *22*, 873-876.

[34] H. Matsuzawa, Y. Miyake, Y. Nishibayashi, *Angewandte Chemie International Edition* 2007, *46*, 6488-6491.

[35] M. A. Schwindt, D. T. Belmont, M. Carlson, L. C. Franklin, V. S. Hendrickson, G. L. Karrick, R. W. Poe, D. M. Sobieray, J. Van De Vusse, *The Journal of Organic Chemistry* 1996, *61*, 9564-9568.

[36] J.-M. Brunel, I. P. Holmes, *Angewandte Chemie International Edition* 2004, *43*, 2752-2778.

[37] M. T. Reetz, F. Kunisch, P. Heitmann, *Tetrahedron Letters* 1986, *27*, 4721-4724.

[38] Y. Belokon, N. Ikonnikov, M. Moscalenko, M. North, S. Orlova, V. Tararov, L. Yashkina, *Tetrahedron: Asymmetry* 1996, *7*, 851-855.

[39] C. Bolm, P. Müller, *Tetrahedron Letters* 1995, *36*, 1625-1628.

[40] H. C. Aspinall, J. F. Bickley, N. Greeves, R. V. Kelly, P. M. Smith, *Organometallics* 2005, *24*, 3458-3467.

[41] S. E. Schaus, J. F. Larrow, E. N. Jacobsen, *The Journal of Organic Chemistry* 1997, *62*, 4197-4199.

[42] E. N. Jacobsen, F. Kakiuchi, R. G. Konsler, J. F. Larrow, M. Tokunaga, *Tetrahedron Letters* 1997, *38*, 773-776.

Chapter 3:

Experimental

3.1 General experimental conditions

Unless otherwise stated, all procedures were carried out under an atmosphere of nitrogen. All solvents were distilled prior to use as follows: dichloromethane and acetonitrile from calcium hydride, toluene and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl or dried through an Innovative Technology Pure Solv PS-MD-5 Purification System. Organic phases were dried using anhydrous magnesium sulphate or sodium sulphate. All chemicals were purchased from Aldrich Chemical Company, Acros Organics, Fisher Scientific or Alfa Aesar and were used without further purification. All asymmetric reactions were carried out using standard Schlenk line techniques and all Schlenk tubes were heat dried under vacuum to remove moisture prior to use. Heterogeneous catalysis used Apollo Scientific silica gel 40-63 micron as the solid support.

Melting points were measured on a Stuart Scientific SMP3 or a Stuart Scientific SMP1 apparatus. IR spectra were measured on a Perkin Elmer Spectrum One FT-IR, where liquid samples were measured as thin films and solids were measured directly. Optical rotations were measured on a Uniplol L1000 polarimeter at 589nm (Na) in a 10 cm cell; concentrations (c) are expressed in g/1 mL. $[\alpha]_D$ is the specific optical rotation of a compound and is measured in units of deg cm^2 g^{-1}.

Thin layer chromatography (TLC) was carried out on pre-coated silica gel plates (Merck 60 F_{254}). Column chromatography was carried out using Apollo Scientific silica gel 40-63 micron. Visualisation was achieved by UV (254 nm) light detection, iodine vapour, vanillin stain or ninhydrin stain. Elemental analysis was performed on a Perkin Elmer 2400 analyser. High resolution mass spectra were carried out using electron spray ionisation (ESI) on a Waters LCT Premier XE spectrometer by manual peak matching.

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a JOEL ECX-400 NMR spectrometer. All spectra were recorded at probe temperatures (~20 °C) in deuterated chloroform ($CDCl_3$) unless otherwise stated, using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in parts per million

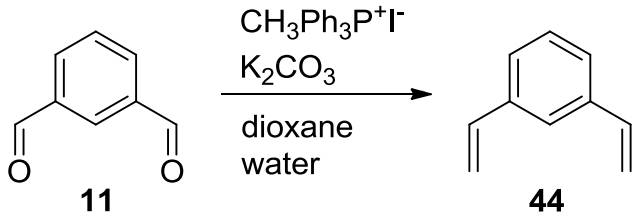
(ppm) and coupling constants in Hertz (Hz). Unless indicated all coupling constants represent three bond couplings. ^{13}C NMR spectra were assigned with the aid of DEPT experiments or comparison to spectra of similar compounds. Compounds were assigned by identifying both the carbon (CH_3, CH_2, CH or C), and also the atom position of the carbon, for example (CH, $CH_2C\mathit{H}OH$). HMQC (Heteronuclear Shift Multiple Quantum Coherence) established links between protons and attached carbons. COSY (Correlated Spectroscopy) established links between proton and attached carbons.

All chiral HPLC analysis was carried out on a Varian Prostar instrument, with a UV/Vis detector at the specified wavelength, with a CHIRACEL OD 0.46 cmΦ x 25 cm column under conditions described for each experiment.

All chiral GC analysis was carried out on a Varian 3900 instrument, using helium as the mobile phase and a FID (Flame Ionisation Detector), with a CYCLODEX-β 0.25 mmΦ x 30 m column under conditions described for each experiment.

3.2 Synthesis of novel 4,4'-PheBOX ligands

1,3- divinylbenzene[1], 44



Scheme 3.1

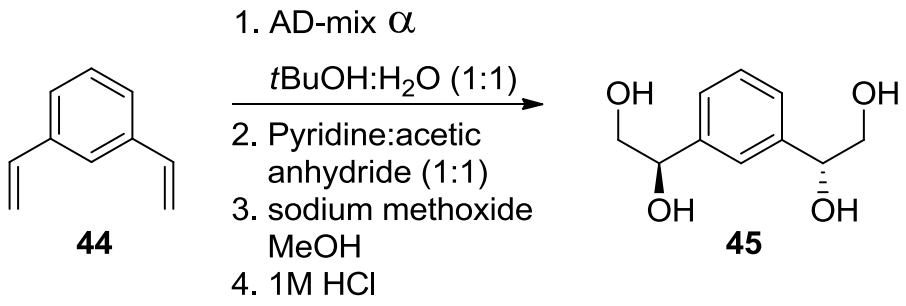
Preparation of Methyltriphenylphosphonium iodide (Ph_3PMeI)

MeI (90 mmol, 5.62 mL) was added to a stirring solution of PPh_3 (90 mmol, 23.615 g) in toluene (75 mL) at 0 °C. The reaction mixture was allowed to return to room temperature and stirred for 3 hours. The solution was concentrated *in vacuo* to yield Ph_3PMeI (39.61 g, 100 %) as a white solid.

Ph_3PMeI (132 mmol, 53.35 g), K_2CO_3 (74.55 mmol, 19.00 g), water (1.65 mL) and dioxane (110 mL) were added to isophthalaldehyde, **11**, (55 mmol, 7.38 g) as seen in **Scheme 3.1**. The reaction mixture was heated to reflux for 16 h under an inert atmosphere (N_2). Upon cooling to room temperature, CH_2Cl_2 (220 mL) was added and the organic layer was extracted with water (3 x 200 mL), dried, filtered and evaporated under reduced pressure. The crude product was purified using flash chromatography on silica gel (gradient elution 100:0 - 95:5 Pet ether:EtOAc) to give 3.86 g (54 % yield) of a colourless liquid, **44**.

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.47 – 7.38 (1H, m, 1 x C***H***$_{aryl}$), 7.35 – 7.26 (3H, m, 3 x C***H***$_{aryl}$), 6.72 (2H, dd, J = 17.6, 10.9 Hz, 2 x C***H***), 5.77 (2H, dd, J = 17.6, 0.9 Hz, 2 x one of C***H***$_2$), 5.26 (2H, dd, J = 10.9, 0.9 Hz, 2 x one of C***H***$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.86 (C, 2 x ***C***$_{aryl}$), 136.79 (CH, 2 x ***C***HCH_2), 128.76 (CH, 1 x ***C***H_{aryl}), 125.68 (CH, 2 x ***C***H_{aryl}), 124.31 (CH, 1 x ***C***H_{aryl}), 114.16 (CH_2, 2 x ***C***H_2).

(1S, 1S')- 1, 1'- (1,3- phenylene)diethane- 1,2 diol, 45

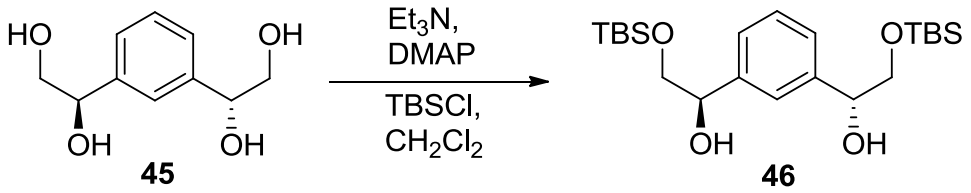


Scheme 3.2

11.40 g of AD mix α was stirred in 1:1 *t*BuOH:water (50 mL) at room temperature for one hour. The reaction was then cooled to 0 °C and **44** (3.84 mmol, 500 mg) was added (**Scheme 3.2**). This was stirred for 41 hours. The reaction was quenched by the addition of sodium sulphite (5.70 g) and the solvent was removed under vacuum. The crude reaction mixture was then cooled to 0 °C and acetylated using 1:1 acetic anhydride:pyridine (60 mL). This was stirred overnight and the crude acetylated product was extracted using EtOAc (3 x 60 mL). The organic layer was then washed with 1M HCl (3 x 60 mL) and brine (3 x 60 mL) and then it was dried over $MgSO_4$, filtered and the solvent was removed under vacuum. The acetylated product was then dissolved in MeOH (4 mL) and 1M sodium methoxide in MeOH (10 mL) was added. This was stirred overnight. The solution was acidified using 1M HCl and evaporated under reduced pressure. The crude product was then purified using flash chromatography on silica gel (gradient elution 99:1 - 70:30 EtOAc:MeOH) to give 474 mg (62 % yield) of a white crystalline solid **45**.

^{1}H NMR (400 MHz, D_2O): δ = 7.33 - 7.19 (4H, m, 4 x C***H***$_{aryl}$), 4.74 (m, 2H, 2 x C***H***), 3.61 (4H, d, J = 5.8 Hz, 2 x C***H***$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.92 (C, 2 x ***C***$_{aryl}$), 128.93 (CH, ***C***$_{aryl}$), 126.12 (CH, 2 x ***C***$_{aryl}$), 124.37 (CH, ***C***$_{aryl}$), 74.01 (CH, 2 x ***C***HO), 66.21 (CH_2, 2 x ***C***H_2OH). IR 3335, 2967, 2875, 1458 cm^{-1}. MP 128-131 °C. $[\alpha]_D$ +55.2, (*c* 0.01, MeOH, 20 °C).

(1S)-2-{[tert-butyl(dimethyl)silyl]oxy}-1-(3-{(1S)-2-{[dimethyl (trimethyl-λ⁴-sulfanyl)silyl]oxy}-1-[(methylsulfonyl)oxy]ethyl}phenyl) ethyl methanesulfonates, 46



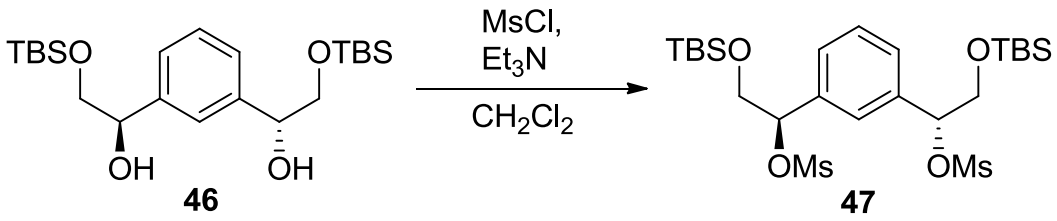
Scheme 3.3

The reaction to prepare tetrol **45** was carried out repeatedly until sufficient quantities were produced, then a stirring solution of **45** (14.025 mmol, 2.78 g) in CH_2Cl_2 was cooled to -15 °C and triethylamine (30.86 mmol, 4.3 mL) was added (**Scheme 3.3**). It was allowed to stir for 15 minutes. Dimethylaminopyridine (4.628 mmol, 565.4 mg) and *tert*-butyldimethylsilyl chloride (28.75 mmol, 4.33 g) were then added and the solution was allowed to gradually warm to room temperature and stirred for 42 hours. The solution was evaporated under reduced pressure and the crude product was purified by column chromatography using silica gel (gradient elution 99:1 - 60:40 Pet ether:EtOAc) to give 5.6 g (46 % yield) of a colourless crystalline solid **46**.

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.37 - 7.28 (4H, m, C***H***$_{aryl}$), 4.74 (2H, dt, J = 8.6, 3.0 Hz, 2 x C***H***OH), 3.75 (2H, dd, J = 10.1, 3.6 Hz, 2 x one of C***H***$_2$O), 3.52 (2H, dd, J = 10.1, 8.7 Hz, 2 x one of C***H***$_2$O), 2.95 (2H, d, J = 2.3 Hz, 2 x O***H***), 0.89 (18H, s, 6 x CC***H***$_3$), 0.05 (12H, d, J = 2.2 Hz, 4 x SiC***H***$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.46 (C, 2 x ***C***$_{aryl}$), 128.38 (CH, ***C***H$_{aryl}$), 125.76 (CH, 2 x ***C***H$_{aryl}$), 124.07 (CH, ***C***H$_{aryl}$), 74.41 (CH, 2 x ***C***HOH), 68.96 (CH_2, 2 x ***C***H_2O), 25.96 (CH_3, 6 x C***C***H_3), 18.39 (C, 2 x ***C***CH_3), -5.27 (CH_3, 4 x Si***C***H_3). IR 3322, 2950, 2883, 1470, 1461 cm $^{-1}$. Anal. Calcd. for

$C_{22}H_{42}O_4Si_2$: C, 61.92; H, 9.92. Found: C, 61.75; H, 10.12. MP 59 - 61 °C. $[\alpha]_D$ +20.3 (*c* 0.01, EtOAc, 20 °C).

TBS protected (2R)-2-{m-[(1R)-2-hydroxy-1(methylsulfonyloxy)ethyl] phenyl}-2-(methylsulfonyloxy)ethanol, 47

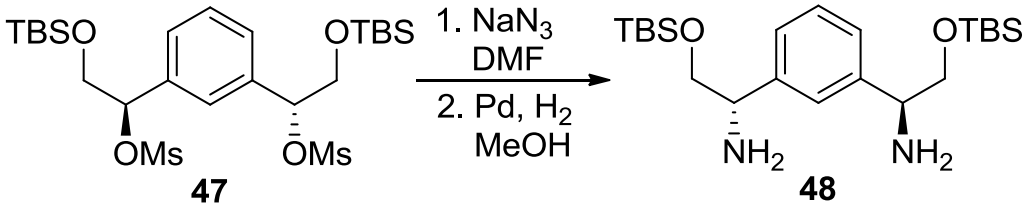


Scheme 3.4

A solution of **46** (13.31 mmol, 5.68 g) in CH_2Cl_2 was cooled to 0 °C and Et_3N (37.6 mmol, 5.24 mL) and methanesulfonyl chloride (37.6 mmol, 2.91 mL) were then added (**Scheme 3.4**). The reaction was allowed to gradually warm to room temperature and stirred for 18 hours. The reaction was quenched using saturated sodium bicarbonate solution (20 mL) and extracted using EtOAc (3 x 100 mL), dried over $MgSO_4$ and filtered. The organic layer was then evaporated under reduced pressure to give 8.17 g (105 % yield), of **47** as a colourless liquid which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.44 - 7.36 (4H, m, C***H***$_{aryl}$), 5.54 (2H, dd, J = 7.8, 4.0 Hz, 2 x C***H***OMs), 3.94 (2H, dd, J = 11.3, 7.9 Hz, 2 x one of C***H***$_2$O), 3.80 (2H, dd, J = 11.4, 4.1 Hz, 2 x one of C***H***$_2$O), 2.92 (6H, s, 2 x SC***H***$_3$), 0.87 (18H, s, 6 x CC***H***$_3$), 0.04 (12H, d, J = 7.5 Hz, 4 x SiC***H***$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.57 (C, 2 x ***C***$_{aryl}$), 129.30 (CH, ***C***H$_{aryl}$), 127.62 (CH, 2 x ***C***H$_{aryl}$), 125.50 (CH, ***C***H$_{aryl}$), 84.27 (CH, 2 x ***C***HOMs), 66.25 (CH_2, 2 x ***C***H_2O), 38.89 (CH_3, 4 x Si***C***H_3), 25.78 (CH_3, 6 x C***C***H_3), 18.28 (C, 2 x ***C***CH_3), -5.30 (CH_3, 2 x Si***C***H_3), -5.40 (CH_3, 2 x Si***C***H_3). IR 2954, 2886, 1472 cm^{-1}. $[\alpha]_D$ +69.2 (*c* 0.01, EtOAc, 20 °C).

(1S)-1-[3-((1S)-1-amino-2-{[tert-butyl(dimethyl)silyl]oxy}ethyl)phenyl-2- {[dimethyl(trimethyl-λ⁴-sulfanyl)silyl]oxy}ethanamine, 48



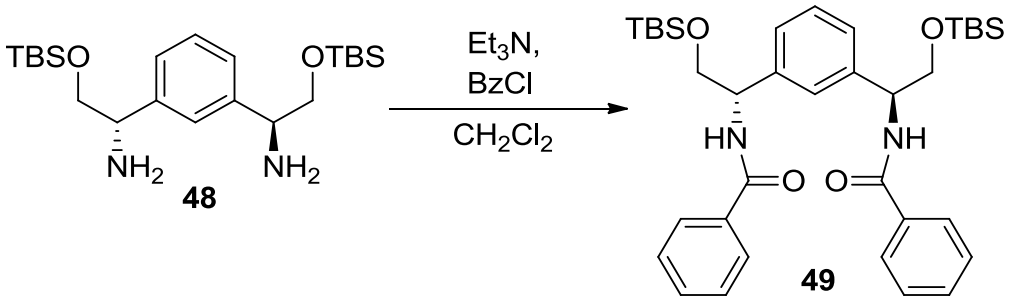
47 **48**

Scheme 3.5

To a solution a of **47** (14.02 mmol, 8.17 g) in *N,N*-dimethylformamide (DMF) (200 mL) was added sodium azide (245.27 mmol, 15.95 g) as seen in **Scheme 3.5**. The mixture was heated to 85 °C for 16 hours, then filtered through a celite pad and concentrated under reduced pressure giving 6.14 g (92 % yield) of crude azide. 2 g of this azide was then dissolved in CH_3OH (90 mL) and transferred to a Parr apparatus. Palladium on activated carbon (10 %, 150 mg) was added and the suspension was stirred under hydrogen (6.5 bar), for 6 hours. The solution was then filtered through celite and concentrated under reduced pressure giving 1.5 g (84 % yield) of **48** as a yellow liquid and was used without any further purification.

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.37 - 7.25 (4H, m, C***H***$_{aryl}$), 4.06 (2H, dd, J = 8.4, 3.9 Hz, 2 x C***H***N), 3.71 (2H, dd, J = 9.8, 4.0 Hz, 2 x one of C***H***$_2$O), 3.51 (2H, dd, J = 9.8, 8.4 Hz, 2 x one of C***H***$_2$O), 2.01 (4H, br s, N***H***$_2$), 0.88 (18H, s, 6 x CC***H***$_3$), 0.01 (12H, s, 4 x Si***CH***$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.63 (C, 2 x ***C***$_{aryl}$), 128.41 (CH, ***C***H$_{aryl}$), 126.04 (CH, 2 x ***C***H$_{aryl}$), 125.60 (CH, ***C***H$_{aryl}$), 69.50 (CH_2, 2 x ***C***H_2O), 57.72 (CH, 2 x ***C***HNH_2), 25.99 (CH_3, 6 x C***C***H_3), 18.38 (C, 2 x ***C***CH_3), -5.30 (CH_3, 4 x Si***C***H_3). IR 3377, 2953, 2856, 1607, 1471 cm^{-1}. ESI-HRMS calcd. for $C_{22}H_{44}N_2O_2Si_2$: 425.3016 $(M+H)^+$, Found *m/z* 425.3020. $[\alpha]_D$ -25.6 (*c* 0.005, MeCN, 20 °C).

N,N'-[1,3-phenylenebis((1S)-2-{[tert-butyl(dimethyl)silyl]oxy}ethane-1,1-diyl)]dibutanamide, 49



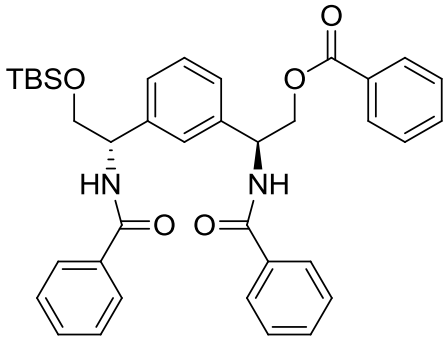
Scheme 3.6

To a stirring solution of **48** (0.47 mmol, 200 mg) in CH_2Cl_2 (5 mL) was added triethylamine (1.79 mmol, 0.25 mL) at 0 °C for 10 minutes (**Scheme 3.6**). Benzoyl chloride (1.59 mmol, 0.185 mL) in CH_2Cl_2 (2 mL) was added slowly over an hour and the mixture was allowed to stir for 18 hours. The reaction was then quenched using saturated $NaHCO_3$ (5 mL) and the aqueous layer was extracted using CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resultant crude product was then purified using column chromatography (gradient elution 90:10 – 70:30 Pet ether:EtOAc) to yield **49** (197 mg, 70 % yield) as a colourless foam.

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.81 – 7.73 (4H, m, C***H***$_{aryl}$), 7.45 (7H, dt, J = 31.1, 7.2 Hz, C***H***$_{aryl}$), 7.29 (3H, s, C***H***$_{aryl}$), 6.92 (2H, d, J = 7.5 Hz, 2 x N***H***), 5.22 (2H, dt, J = 8.0, 4.2 Hz, 2 x C***H***N), 4.02 (2H, dd, J = 10.2, 4.4 Hz, 2 x one of C***H***$_2$O), 3.89 (2H, dd, J = 10.2, 4.2 Hz, 2 x one of C***H***$_2$O), 0.84 (18H, s, 6 x CC***H***$_3$), -0.05 (12H, d, J = 16.0 Hz, 4 x Si***CH***$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.73 (C, 2 x ***C***=O), 140.39 (C, 2 x ***C***$_{aryl}$), 134.47 (C, 2 x ***C***$_{aryl}$), 131. 46 (CH, 2 x ***C***H$_{aryl}$), 128.56 (CH, 4 x ***C***H$_{aryl}$), 128.44 (CH, 4 x ***C***H$_{aryl}$), 126.88 (CH, 2 x ***C***H$_{aryl}$), 126.11 (CH, ***C***H$_{aryl}$), 125.82 (CH, ***C***H$_{aryl}$), 65.94 (CH_2, 2 x ***C***H_2O), 54.74 (CH, 2 x ***C***HNH), 25.78 (CH_3, 6 x C***C***H_3), 18.15 (C, 2 x ***C***CH_3), -5.48 (CH_3, 4 x Si***C***H_3). IR 3300, 3061, 2929, 1636, 1630 cm^{-1}. Anal. Calcd. for $C_{36}H_{52}N_2O_4Si_2$: C; 68.31, H; 8.28, N; 4.43, Found: C; 68.04, H; 8.57, N; 4.36.

ESI-HRMS calcd. for $C_{36}H_{52}N_2O_4Si_2$: 633.3541 $(M+H)^+$, Found *m/z* 633.3544. MP 55 - 61 °C. $[\alpha]_D$ +27.2 (*c* 0.005, MeCN, 20 °C).

TBS protected (2S)-2-{m-[(1S)-1-(benzoylamino)-2-hydroxyethyl] phenyl}-2-(benzoylamino)ethyl benzoate, 72



72

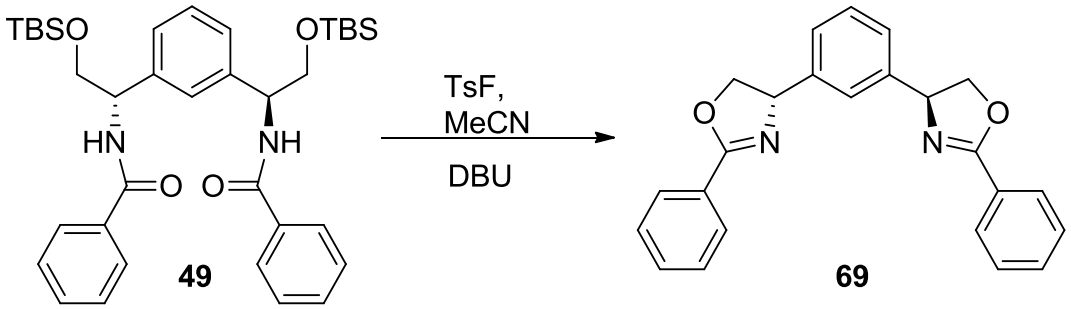
Figure 3.1

The reaction shown in **Scheme 3.6** on some occasions also produced **72** (**Figure 3.1**) as a white solid with typical yields of 7 – 9 %.

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.99 (2H, dd, J = 8.2, 1.3 Hz, C***H***$_{aryl}$), 7.78 – 7.73 (4H, m, C***H***$_{aryl}$), 7.56 – 7.34 (13H, m, C***H***$_{aryl}$), 7.00 (2H, dd, J = 7.0, 2.3 Hz, 2 x N***H***), 5.62 (1H, td, J = 7.7, 4.7 Hz, C***H*N**), 5.22 (1H, dt, J = 7.8, 4.2 Hz, C***H*N**), 4.81 (1H, dd, J = 11.6, 7.9 Hz, 1 x C***H***$_2$**O**), 4.60 (1H, dd, J = 11.6, 4.6 Hz, 1 x C***H***$_2$**O**), 4.01 (1H, dd, J = 10.3, 4.3 Hz, 1 x C***H***$_2$**O**), 3.88 (1H, dd, J = 10.3, 4.1 Hz, 1 x C***H***$_2$**O**), 0.83 (9H, s, 3 x CC***H***$_3$), -0.06 (6H, s, 2 x SiC***H***$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.29 (C, ***C***=O), 167.09 (C, N***C***=OPh), 166.91 (C, N***C***=OPh), 141.17 (C, ***C***$_{aryl}$), 138.34 (C, ***C***$_{aryl}$), 134.43 (C, ***C***$_{aryl}$), 134.12 (C, ***C***$_{aryl}$), 133.44 (CH, ***C***H$_{aryl}$), 131.72 (CH, ***C***H$_{aryl}$), 131.67 (CH, ***C***H$_{aryl}$), 129.84 (CH, 2 x ***C***H$_{aryl}$), 129.58 (C, ***C***$_{aryl}$), 128.74 (CH, 2 x ***C***H$_{aryl}$), 128.68 (CH, 2 x ***C***H$_{aryl}$), 128.57 (CH, 2 x ***C***H$_{aryl}$), 127.10 (CH, 2 x ***C***H$_{aryl}$), 127.01 (CH, 2 x ***C***H$_{aryl}$), 126.85 (CH, 2 x ***C***H$_{aryl}$), 126.08 (CH, ***C***H$_{aryl}$), 125.65 (CH, ***C***H$_{aryl}$), 66.58 (CH_2, ***C***H_2O), 66.12 (CH_2, ***C***H_2O), 54.87 (CH, ***C***HNH), 53.64 (CH, ***C***HNH), 25.88 (CH_3, 3 x C***C***H_3),

18.26 (C, ***C***CH_3), -5.49 (CH_3, 2 x Si***C***H_3). IR 3298, 3062, 1717, 1636, 1603 cm^{-1}. Anal. Calcd. for $C_{37}H_{42}N_2O_5Si$: C; 71.35, H; 6.80, N; 4.50, Found: C; 71.25, H; 6.44, N; 4.73. ESI-HRMS calcd. for $C_{37}H_{42}N_2O_5Si$: 623.2909 $(M+H)^+$, Found *m/z* 623.2941. MP 136 - 140 °C. $[\alpha]_D$ +21.2 (*c* 0.005, MeCN, 20 °C).

(4R,4'S)-4,4'-(1,3-phenylene)bis(2-phenyl-4,5-dihydro-1,3-oxazole), 69

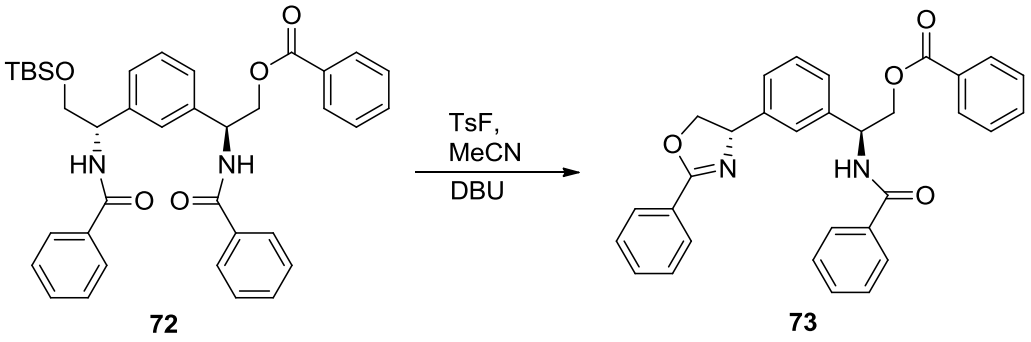


Scheme 3.7

To a stirring solution of **49** (0.26 mmol, 157 mg) and *p*-toluenesulfonyl fluoride (0.575 mmol, 100 mg) in dry acetonitrile (MeCN) (5 mL) was added 1,8-diazabicycloundec-7-ene (DBU) (0.575 mmol, 86 µL) as seen in **Scheme 3.7**. The mixture was stirred at reflux overnight, cooled and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (Pet ether:EtOAc, 2:1) to yield desired **69** in 51 % yield (50 mg) as a viscous colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.04 - 7.97 (4H, m, C***H***$_{aryl}$), 7.53 - 7.33 (7H, m, C***H***$_{aryl}$), 7.26 - 7.22 (3H, m, C***H***$_{aryl}$), 5.39 (2H, dd, J = 10.1, 8.3 Hz, 2 x C***H***N), 4.79 (2H, dd, J = 10.1, 8.4 Hz, 2 x one of C***H***$_2$O), 4.26 (2H, t, J = 8.3 Hz, 2 x one of C***H***$_2$O). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.94 (C, 2 x ***C***=N), 142.97 (C, 2 x ***C***$_{aryl}$), 131.64 (CH, 2 x ***C***H$_{aryl}$), 129.46 (CH, 2 x ***C***H$_{aryl}$), 128.57 (CH, 4 x ***C***H$_{aryl}$), 128.47 (CH, 4 x ***C***H$_{aryl}$), 127.62 (C, 2 x ***C***$_{aryl}$), 126.05 (CH, ***C***H$_{aryl}$), 125.38 (CH, ***C***H$_{aryl}$), 74.89 (CH_2, 2 x ***C***H_2O), 70.12 (CH, 2 x ***C***HN). IR 2962, 1642, 1602, 1579, cm^{-1}. $[\alpha]_D$ +34 (*c* 0.005, MeCN, 20 °C).

(2S)-2-(benzoylamino)-2-{3-[(4S)-2-phenyl-4,5-dihydro-1,3-oxazol -4-yl]phenyl}ethylbenzoate, 73



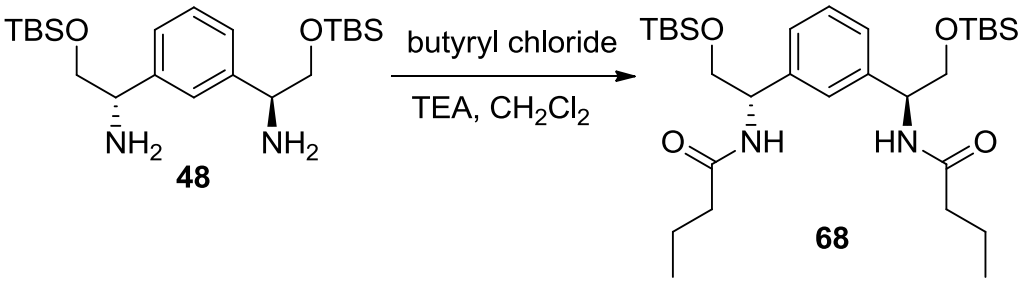
72 73

Scheme 3.8

To a stirring solution of **72** (0.372 mmol, 232 mg) and *p*-toluenesulfonyl fluoride (0.41 mmol, 71.37 mg) in dry MeCN (5 mL) was added DBU (0.41 mmol, 61 µL) as seen in **Scheme 3.8**. The mixture was stirred at reflux overnight, cooled and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (Pet ether:EtOAc, 7:3) to yield a white crystalline solid **73** in 49 % yield (240 mg).

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.02 – 7.98 (4H, m, C***H***$_{aryl}$), 7.76 – 7.73 (2H, m, C***H***$_{aryl}$), 7.55 - 7.25 (13H, m, C***H***$_{aryl}$), 7.03 (1H, d, J = 7.5 Hz, 1 x N***H***), 5.60 (1H, dt, J = 7.7, 3.9 Hz, C***H***N), 5.39 (1H, dd, J = 10.1, 8.3 Hz, C***H***N), 4.85 – 4.75 (2H, m, 2 x one of C***H***$_2$O), 4.58 (1H, dd, J = 11.7, 4.4 Hz, 1 x C***H***$_2$O), 4.23 (1H, t, J = 8.4 Hz, 1 x C***H***$_2$O). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.38 (C, ***C***=O), 167.12 (C, HN***C***=O), 165.06, (C, ***C***=N), 143.23 (C, 2 x ***C***$_{aryl}$), 138.85 (C, ***C***$_{aryl}$), 134.11 (C, ***C***$_{aryl}$), 133.50 (CH, ***C***H$_{aryl}$), 131.76 (CH, ***C***H$_{aryl}$), 131.71 (CH, ***C***H$_{aryl}$), 129.84 (CH, 2 x ***C***H$_{aryl}$), 129.60 (CH, ***C***H$_{aryl}$), 129.53 (CH, ***C***H$_{aryl}$), 128.71 (CH, 2 x ***C***H$_{aryl}$), 128.59 (CH, 2 x ***C***H$_{aryl}$), 128.50 (CH, 2 x ***C***H$_{aryl}$), 127.50 (C, ***C***$_{aryl}$), 127.08 (CH, 2 x ***C***H$_{aryl}$), 126.18 (CH, 2 x ***C***H$_{aryl}$), 126.10 (CH, ***C***H$_{aryl}$), 125.55 (CH, ***C***H$_{aryl}$), 74.88 (CH_2, ***C***H_2O), 70.11 (CH, ***C***HN), 66.78 (CH_2, ***C***H_2O), 53.87 (CH, ***C***HN). IR 3297, 2959, 1718, 1639, 1602, 1580 cm^{-1}. ESI-HRMS calcd. for $C_{31}H_{26}N_2O_5$: 491.1971 $(M+H)^+$, Found *m/z* 491.1971. MP 61 - 63 °C. $[\alpha]_D$ +28.6 (*c* 0.0025, MeCN, 20 °C).

N,N'-[1,3-phenylenebis((1S)-2-{[tert-butyl(dimethyl)silyl]oxy}ethane-1,1-diyl)]dibutanamide, 68



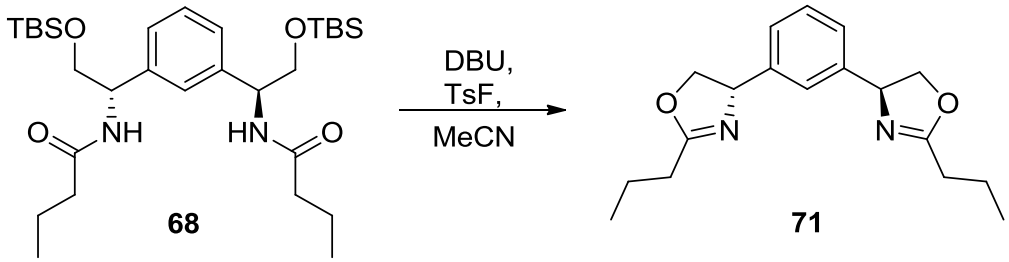
Scheme 3.9

To a stirring solution of **48** (1.86 mmol, 790 mg) in CH_2Cl_2 (15 mL) was added triethylamine (7.07 mmol, 0.99 mL) at 0 °C (**Scheme 3.9**). This was allowed to stir for 10 minutes. Butyryl chloride (6.324 mmol, 0.65 mL) in CH_2Cl_2 (5 mL) was added slowly over an hour and allowed to stir for 18 hours. The reaction was then quenched using saturated $NaHCO_3$ (15 mL) and the aqueous layer was extracted using CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The resultant crude product was then purified using column chromatography on SiO_2 (gradient elution 90:10 – 70:30 Pet ether:EtOAc) to yield **68** (330 mg, 32 % yield) as a colourless foam.

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.32 – 7.15 (4H, m, 4 x C***H***$_{aryl}$), 6.14 (2H, d, J = 7.6 Hz, 2 x N***H***), 5.02 (2H, dt, J = 8.0, 4.3 Hz, 2 x C***H***NH), 3.88 (2H, dd, J = 10.2, 4.5 Hz, 2 x one of C***H***$_2$O), 3.76 (2H, dd, J = 10.2, 4.4 Hz, 2 x one of C***H***$_2$O), 2.20 (4H, t, J = 7.6 Hz, 2 x COC***H***$_2$), 1.66 (4H, dt, J = 14.7, 7.3 Hz, 2 x CH$_2$C***H***$_2$), 0.95 (6H, t, J = 7.4 Hz, 2 x CH$_2$C***H***$_3$), 0.84 (18H, s, 6 x CC***H***$_3$), -0.07 (s, 12H, 4 x SiC***H***$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.39 (C, 2 x ***C***=O), 140.52 (CH, 2 x ***C***$_{aryl}$), 128.40 (CH, 1 x ***C***H$_{aryl}$), 126.11 (CH, 2 x ***C***H$_{aryl}$), 123.60 (CH, 1 x ***C***H$_{aryl}$), 66.04 (CH$_2$, 2 x ***C***H$_2$O), 54.36 (CH, 2 x ***C***HNH), 38.88 (CH$_2$, 2 x ***C***H$_2$CO), 25.91 (CH$_3$, 6 x C***C***H$_3$), 19.24 (CH$_2$, 2 x ***C***H$_2$CH$_3$), 18.31 (C, 2 x ***C***CH$_3$), 13.90 (CH$_3$, 2 x CH$_2$***C***H$_3$), -5.43 (CH$_3$, 2 x Si***C***H$_3$), -5.53 (CH$_3$, 2 x Si***C***H$_3$). IR 3290, 2958, 2857, 1641, 1542 cm^{-1}. ESI-HRMS calcd. for

$C_{30}H_{56}N_2O_4Si_2$: 565.3865 $(M+H)^+$, Found *m/z* 565.3857. $[\alpha]_D$ -45.1 (*c* 0.0035, $CHCl_3$, 20 °C).

(4R,4'S)-4,4'-(1,3-phenylene)bis(2-propyl-4,5-dihydro-1,3-oxazole), 71

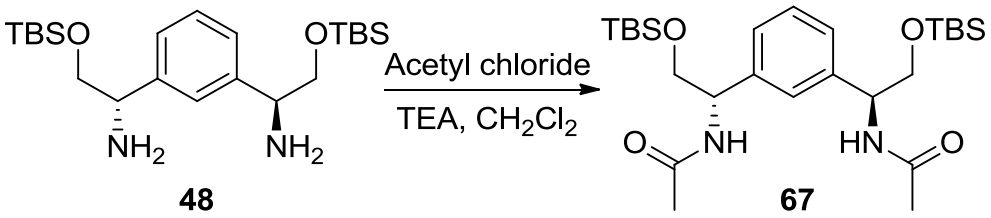


Scheme 3.10

To a stirring solution of **68** (0.53 mmol, 330 mg) and *p*-toluenesulfonyl fluoride (1.168 mmol, 203.5 mg) in dry MeCN (5 mL) was added DBU (1.168 mmol, 0.175 mL) as seen in **Scheme 3.10**. The mixture was stirred at reflux overnight, cooled and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (Pet ether:EtOAc, 2:1) to yield desired **71** in 60 % yield (95 mg) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.32 – 7.28 (1H, m, 1 x C***H***$_{aryl}$), 7.14 – 7.11 (3H, m, 3 x C***H***$_{aryl}$), 5.16 (2H, t, J = 9.1 Hz, 2 x C***H***N), 4.57 (2H, dd, J = 10.2, 8.4 Hz, 2 x one of C***H***$_2$O), 4.03 (2H, t, J = 8.3 Hz, 2 x one of C***H***$_2$O), 2.43 – 2.25 (4H, m, 2 x CC***H***$_2$), 1.77 - 1.67 (4H, m, 2 x CH_2C***H***$_2$), 1.01 (6H, t, J = 7.4 Hz, 2 x CH_2C***H***$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.02 (C, 2 x ***C***=N), 143.16 (C, 2 x ***C***$_{aryl}$), 129.11 (CH, 1 x ***C***H$_{aryl}$), 125.79 (CH, 2 x ***C***H$_{aryl}$), 124.68 (CH, 1 x ***C***H$_{aryl}$), 74.49 (CH_2, 2 x ***C***H_2O), 69.57 (CH, 2 x ***C***HN), 30.05 (CH_2, 2 x CO***C***H_2), 19.65 (CH_2, 2 x ***C***H_2CH_3), 13.92 (CH_3, 2 x CH_2***C***H_3). IR 2964, 2934, 2875, 1661 cm^{-1}. ESI-HRMS calcd. for $C_{18}H_{24}N_2O_2$: 301.1928 $(M+H)^+$, Found *m/z* 301.1916. $[\alpha]_D$ +66.4 (*c* 0.005, $CHCl_3$, 20 °C).

N,N'-[1,3-phenylenebis((1S)-2-{[tert-butyl(dimethyl)silyl]oxy}ethane-1,1-diyl)]diacetamide, 67

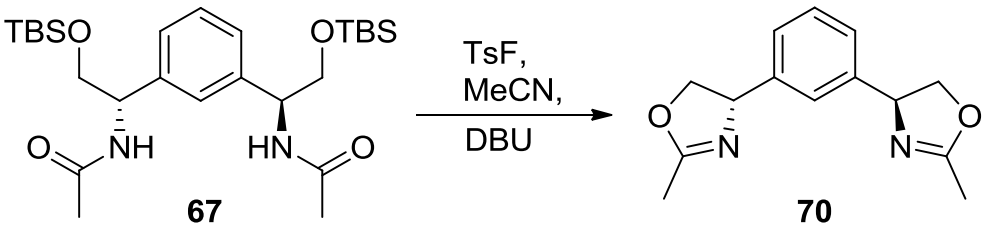


Scheme 3.11

To a stirring solution of **48** (1.18 mmol, 500 mg) in CH_2Cl_2 (10 mL) was added triethylamine (4.47 mmol, 0.623 mL) at 0 °C (**Scheme 3.11**). This was allowed to stir for 10 minutes. Acyl chloride (4 mmol, 0.285 mL) in CH_2Cl_2 (3 mL) was added slowly over an hour and allowed to stir for 18 hours. The reaction was then quenched using saturated $NaHCO_3$ (10 mL) and the aqueous layer was extracted using CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and reduced *in vacuo*. The resultant crude was then purified using column chromatography on SiO_2 (gradient elution 99:1 - 90:10 CH_2Cl_2:MeOH) to yield **67** as a colourless foam (492 mg, 88 % yield).

H^1 NMR (400 MHz, $CDCl_3$, TMS): δ = 7.37 – 7.05 (4H, m, 4 x C***H***$_{aryl}$), 6.15 (2H, d, J = 7.7 Hz, 2 x N***H***), 5.01 (2H, dt, J = 8.1, 4.2 Hz, 2 x C***H***NH), 3.89 (2H, dd, J = 10.2, 4.4 Hz, 2 x one CHC***H***$_2$), 3.77 (2H, dd, J = 10.2, 4.2 Hz, 2 x one CHC***H***$_2$), 2.04 (6H, d, J = 1.8 Hz, 2 x COC***H***$_3$), 0.83 (18H, d, J = 4.8 Hz, 6 x CC***H***$_3$), -0.06 (12H, d, J = 7.7 Hz, 4 x SiC***H***$_3$). IR 3290, 2930, 2857, 1641, 1542 cm^{-1}. Anal. ESI-HRMS calcd. for $C_{30}H_{56}N_2O_4Si_2$: 565.3857 $(M+H)^+$, Found *m/z* 565.3865. $[\alpha]_D$ -45.1 (*c* 0.0035, $CHCl_3$, 20 °C).

(4R,4'S)-4,4'-(1,3-phenylene)bis(2-methyl-4,5-dihydro-1,3-oxazole), 70

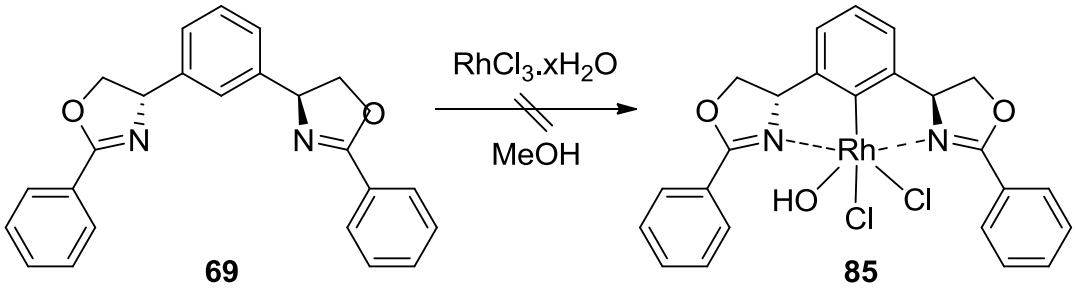


Scheme 3.12

To a stirring solution of **67** (1.032 mmol, 492 mg) and *p*-toluenesulfonyl fluoride (2.27 mmol, 395.4 mg) in dry MeCN (10 mL) was added DBU (2.27 mmol, 0.33 mL) as seen in **Scheme 3.12**. The mixture was stirred at reflux overnight, cooled and concentrated *in vacuo*. The residue was purified by flash chromatography on SiO_2 (gradient elution 99:1 - 95:5 EtOAc:MeOH) to yield desired **70** in 20 % yield (50 mg).

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.40 – 7.26 (1H, m, 1 x C***H***$_{aryl}$), 7.21 - 7.05 (3H, m, 3 x C***H***$_{aryl}$), 5.16 (2H, t, J = 9.2 Hz, 2 x C***H***N), 4.62 - 4.56 (2H, m, 2 x one of C***H***$_2$O), 4.11 – 3.95 (2H, m, 2 x one of C***H***$_2$O), 2.08 (6H, d, J = 1.3 Hz, 2 x C***H***$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.11 (C, 2 x ***C***=N), 142.90 (C, 2 x ***C***$_{aryl}$), 129.23 (CH, 1 x ***C***H$_{aryl}$), 125.76 (CH, 2 x ***C***H$_{aryl}$), 124.70 (CH, 1 x ***C***H$_{aryl}$), 74.67 (CH_2, 2 x ***C***H_2), 69.71 (CH, 2 x ***C***H), 14.05 (CH_3, 2 x ***C***H_3). IR 3290, 2958, 2857, 1641, 1542 cm^{-1}. ESI-HRMS calcd. for $C_{30}H_{56}N_2O_4Si_2$: 565.3857 $(M+H)^+$, Found *m/z* 565.3865. $[\alpha]_D$ -45.1 (*c* 0.0035, $CHCl_3$, 20 °C).

Attempted synthesis of a rhodium complex of phenyl-PheBOX, 85

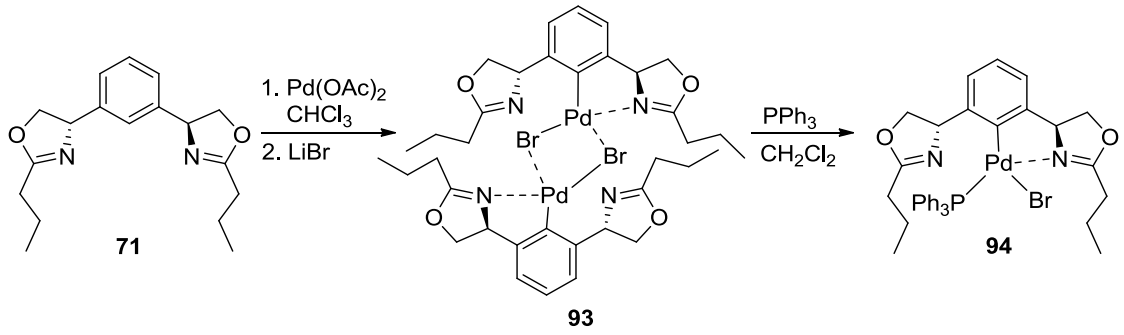


69 **85**

Scheme 3.13

A stirring solution of **69** (0.33 mmol, 120 mg) in MeOH (5 mL) was heated to reflux and then $RhCl_3.xH_2O$ (0.25 mmol, 63 mg) was added (**Scheme 3.13**). The solution was heated to reflux and allowed to react for 45 minutes and then filtered through a celite pad and washed through the pad with MeOH (3 x 5 mL). The organic layers were combined and the solvent was removed under reduced pressure leaving an orange solid. The solid was dissolved in a small volume of EtOAc was then washed through a small plug of silica using 1:1 Pet Ether:Ethyl Acetate followed by 9:1 Ethyl Acetate:Methanol and the combined organic layers were concentrated *in vacuo.* This produced a non-homogeneous mixture of both an orange solid and a white solid from the reaction solution. While ^{1}H NMR analysis showed free ligand (the white solid), there was also other interesting signals including 5.81 - 5.75 ppm (1H, m), 5.24 - 5.19 ppm (1H, m), 4.55 ppm (1H, dd) and several phenyl signals over 7 ppm. However, it proved impossible to isolate the molecule responsible for these signals.

Attempted synthesis of a palladium complex of propyl-PheBOX, 94



Scheme 3.14

To a stirring solution of **71** (0.27 mmol, 80 mg) in chloroform (5 mL) was added $Pd(OAc)_2$ (0.53 mmol, 122.5 mg) as seen in **Scheme 3.14**. The solution was heated to reflux and allowed to react for 3 days. Lithium bromide (0.53 mmol, 48 mg) was then added and the reaction solution was heated to reflux for a further 2 hours, filtered through a celite pad and washed with ether (3 x 10 mL). The combined organic layers were concentrated *in vacuo* giving a yellowish black solid. ^{1}H NMR analysis of the reaction mixture showed signals including 7.21 ppm, 7.07 ppm, 6.70 ppm (1H, dd), 5.63 ppm (1H, d), 5.50 - 5.40 ppm (1H, m), 4.91 - 4.84 ppm (1H, m), 4.66 ppm (1H, dd), 4.21 ppm (1H, ddd), 3.82 ppm (1H, dd) and several signals between 2 and 0.8 ppm. ^{13}C NMR (100 MHz, $CDCl_3$) analysis showed signals at 167.86 ppm, 145.56 ppm, 128.89 ppm, 125.83 ppm, 119.17 ppm, 72.65 ppm, 72.36 ppm, 38.80 ppm, 30.44 ppm, 29.80 ppm, 23.82 ppm, 23.08 ppm, 20.12 ppm, 14.25 ppm, 13.83 ppm and 11.05 ppm. From this information it was believed that *trans* or *cis* - **93** was present. To a stirring solution of **93** (0.026 mmol, 25 mg) in CH_2Cl_2 (2 mL) was added triphenylphosphine (0.1 mmol, 27 mg) and the reaction was refluxed for 16 hours. The solution was then filtered through a celite pad and rinsed with CH_2Cl_2 (3 x 5 mL) and the combined washes were concentrated under reduced pressure. This produced a brown crystalline solid. ^{1}H NMR spectral analysis of the reaction mixture showed signals including several signals from

7.75 - 7.25 ppm, 6.70 ppm (1H, dd), 5.67 – 5.60 ppm (1H, m), 5.19 – 5.14 ppm (1H, m), 4.91 – 4.84 ppm (1H, m), 4.57 ppm (1H, dd), 4.26 – 4.20 ppm (1H, m), 4.03 ppm (1H, t), 2.35 ppm, 1.72 ppm and 1.02 ppm. ^{13}C NMR spectral analysis showed several signals between 135.25 – 127.96 ppm, 127.96 ppm, 74.50 ppm, 69.58 ppm, 30.05 ppm, 29.34 ppm, 19.65 ppm and 13.92 ppm. This information pointed to **94** being formed, however attempted recrystallization and crystal growth of the brown solid above, were unsuccessful.

Other attempts made during the synthesis of 4,4'-PheBOX

TIPS diol, 58

45 **58**

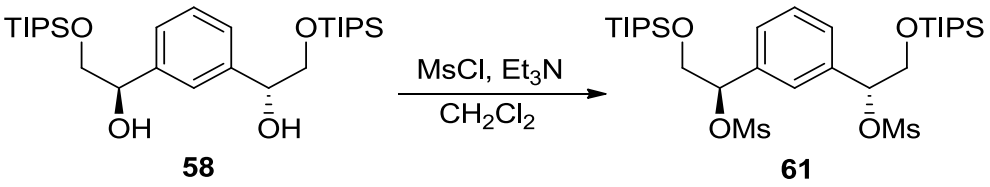
Scheme 3.15

A stirring solution of **45** (0.757 mmol, 150 mg) in dimethylformamide, was cooled to 0 °C and imidazole (3.785 mmol, 257.68 mg) was added (**Scheme 3.15**). It was allowed to stir for 10 minutes. Then triisopropylsilyl chloride (1.59 mmol, 0.34 mL) was added and the reaction was allowed to gradually warm to room temperature and stirred for 24 hours. When the reaction was complete, it was evaporated under reduced pressure and the crude product was purified by column chromatography using silica gel (gradient elution 99:1 - 60:40 Pet ether:EtOAc) to give 170 mg (33 % yield) of a colourless crystalline solid **58**.

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.38 (1H, s, 1 x C***H***$_{aryl}$), 7.34 - 7.28 (3H, m, 3 x C***H***$_{aryl}$), 4.77 (2H, dd, J = 8.7, 3.5 Hz, 2 x C***H***OH), 3.84 (2H, dd, J = 9.9, 3.6 Hz, 2 x one of C***H***$_2$O), 3.63 - 3.58 (2H, m, 2 x one of C***H***$_2$O), 3.08 (2H, br s, 2 x O***H***),

1.07 - 1.05 (42H, m, 6 x C***H***$(CH_3)_2$ and 12 x CHC***H***$_3$). IR 3434, 2942, 2892, 1734, 1463 cm^{-1}.

TIPS protected mesylate, 61



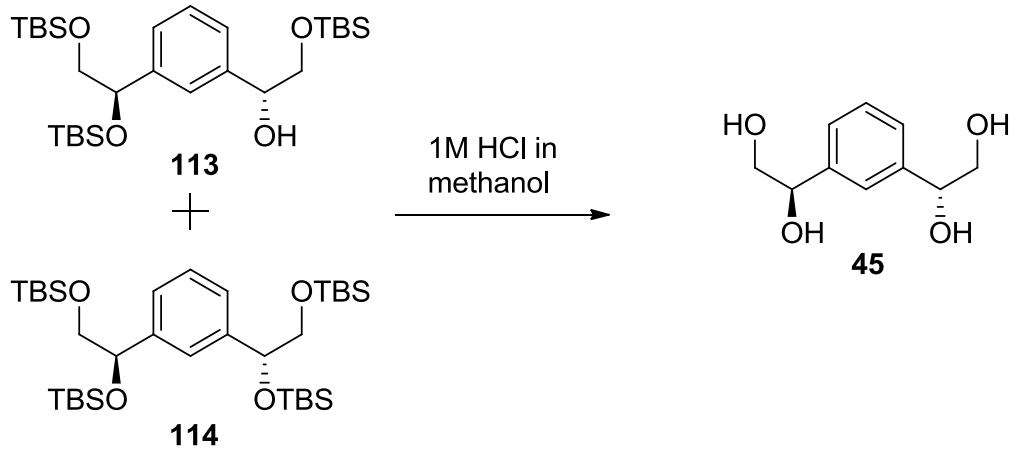
58 **61**

Scheme 3.16

A solution of **58** (0.33 mmol, 170 mg) was dissolved in CH_2Cl_2 and was cooled to 0 °C. Et_3N (0.94 mmol, 0.131 mL) and methanesulfonyl chloride (0.7326 mmol, 57 µL) were then added and the reaction was allowed to gradually warm to room temperature and stirred for 6 hours (**Scheme 3.16**). The reaction was quenched using saturated sodium bicarbonate solution (5 mL) and extracted using EtOAc (3 x 20 mL), dried over $MgSO_4$ and filtered. The organic layer was then evaporated under reduced pressure and the crude product was purified by column chromatography using silica gel (gradient elution 99:1 - 60:40 Pet ether:EtOAc) to give 207 mg (60 % yield) of white solid **61**.

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.41 - 7.36 (4H, s, 4 x C***H***$_{aryl}$), 5.56 (2H, dd, J = 7.6, 4.2 Hz, 2 x C***H***OMs), 4.04 (2H, dd, J = 11.1, 7.7 Hz, 2 x one of C***H***$_2$O), 3.87 (2H, dd, J = 11.1, 4.2 Hz, 2 x one of C***H***$_2$O), 2.91 (6H, s, 2 x SC***H***$_3$), 1.15 - 0.99 (42H, m, 6 x C***H***$(CH_3)_2$ and 12 x CHC***H***$_3$).

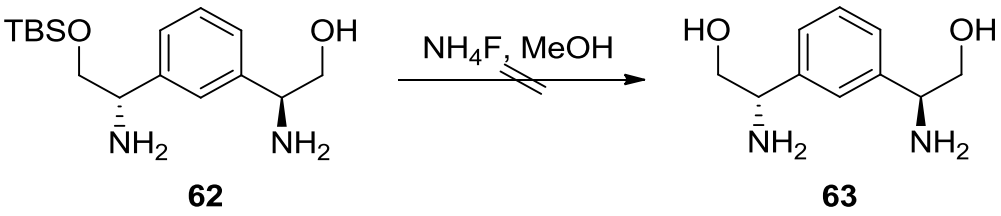
Synthesis of *(1S, 1S')- 1, 1'- (1,3- phenylene)diethane- 1,2 diol from tri- and tetra-TBS protection, 45*



Scheme 3.17

To a stirring solution of **113** and **114** (400 mg) in methanol was added 1.716 mL of concentrated (conc.) HCl (37 %) in 20 mL of methanol and the reaction mixture was stirred for 24 h at room temperature (**Scheme 3.17**). The organic solvent was evaporated under reduced pressure and the crude product was then purified using flash chromatography on silica gel (gradient elution 99:1 - 70:30 EtOAc:MeOH) to give a white solid **45**. The ^{1}H NMR and ^{13}C NMR spectra were consistent with that reported above.

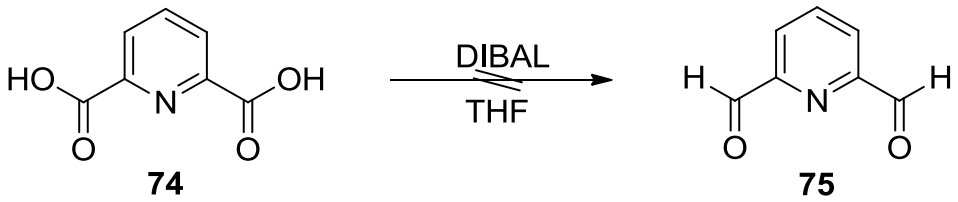
Attempted synthesis of mono-TBS protected - mono-alcohol di amine, 63



Scheme 3.18

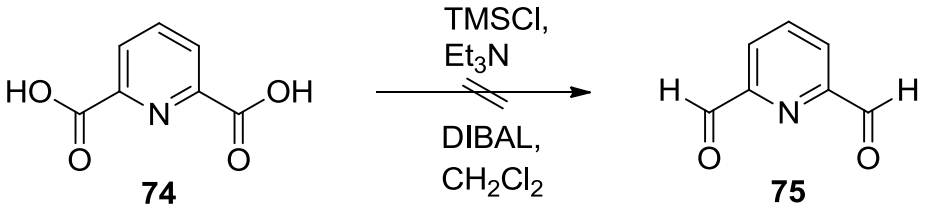
On one occasion the reaction shown in **Scheme 3.5** produced **62** instead of the desired product so mono-alcohol **62** (1.63 mmol, 550 mg) was dissolved in CH_3OH (20 mL) and it was then reacted with ammonium fluoride (0.7 mmol, 25.93 mg) in methanol (5 mL) and stirred at reflux for 24 hours (**Scheme 3.18**). ^{1}H NMR (D_2O) analysis of the product showed signals 7.29 – 7.18 ppm (4H, m) and 3.97 ppm (2H, t). There also appeared to be a signal hidden by the D_2O signal which showed that **63** was not formed and in fact the HF salt of **63** was present. As discussed in **Chapter 2**, the attempted recovery of the ligand from the salt was attempted using an ion exchange resin, however it proved unsuccessful.

Attempted synthesis of 2,6-Pyridinedicarbaldehyde, 75



Scheme 3.19

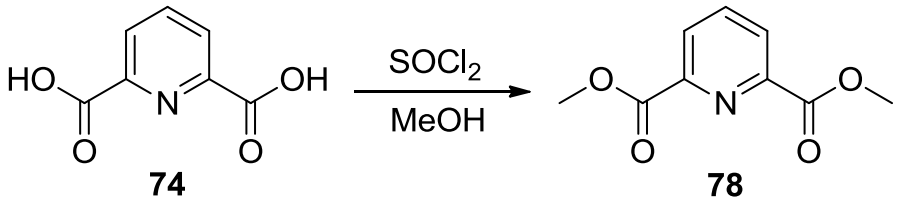
To a stirring solution of **74** (0.6 mmol, 100 mg) in anhydrous THF (5 mL) was added DIBAL (1M in THF, 1.2 mmol, 1.2 mL) at -78 °C, under N_2 (**Scheme 3.19**). The solution was stirred for 3 hours, then MeOH (10 mL) was added and the reaction was allowed to warm to room temperature. Saturated NH_4Cl solution was added and the mixture was stirred for 1 hour. The reaction mixture was extracted using EtOAc (3 x 10 mL) and the combined organic layers were dried over $MgSO_4$ and filtered. The organic layer was then evaporated under reduced pressure and ^{1}H NMR spectral and TLC analyses of the crude product revealed an inseparable mixture of products.



Scheme 3.20

To a stirring solution of **74** (0.6 mmol, 100 mg) under N_2 in CH_2Cl_2 (5 mL) was added Et_3N (1.2 mmol, 0.17 mL) as seen in **Scheme 3.20**. The solution was cooled to -78 °C and stirred for 10 minutes and then TMSCl (1.2 mmol, 0.15 mL) was added. The mixture was stirred for 1 hour when DIBAL (1M in THF, 1.2 mmol, 1.2 mL) was added. It was allowed to stir for 3 hours at -78 °C, then MeOH (10 mL) was added and the reaction was allowed to warm to room temperature. Saturated NH_4Cl solution was added and the reaction was stirred for 1 hour. The crude product was extracted using EtOAc (3 x 10 mL) and the combined organic layers were dried over $MgSO_4$ and filtered. The organic layer was then evaporated under reduced pressure and ^1H NMR and TLC analyses of the crude product revealed an inseparable mixture of products.

Dimethyl 2,6-pyridinedicarboxylate[2], 78

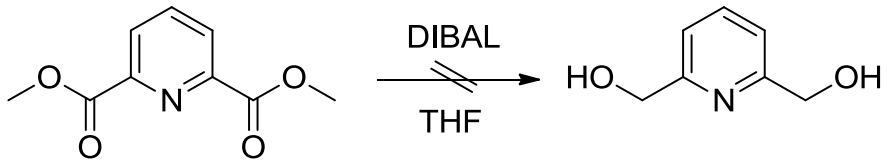


Scheme 3.21

To a stirring solution of **74** (0.6 mmol, 100 mg) in MeOH (5 mL) was added $SOCl_2$ (1.2 mmol, 0.1 mL) as seen in **Scheme 3.21**. The reaction was refluxed for 16 hours and quenched using saturated $NaHCO_3$ (5 mL) and the aqueous layer was extracted using CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and reduced *in vacuo*. The resultant crude product was purified using flash chromatography using silica gel (gradient elution 99:1 - 60:40 Pet ether:EtOAc) to give 104 mg (54 % yield) of white solid **78**.

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.32 (2H, d, J = 7.8 Hz, 2 x C***H***$_{aryl}$), 8.03 (1H, t, J = 7.8 Hz, C***H***$_{aryl}$), 4.03 (6H, s, 2 x C***H***$_3$).

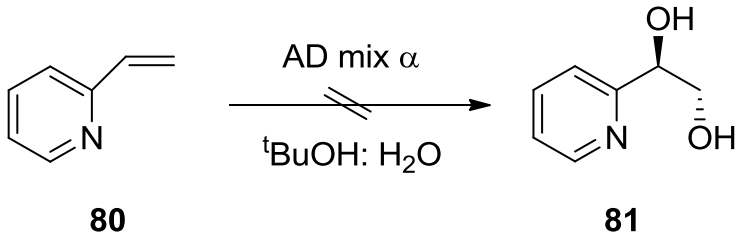
Attempted synthesis of benzene-1,3-diyldimethanol, 79



Scheme 3.22

A stirring solution of **78** (0.53 mmol, 104 mg) in anhydrous THF (10 mL) was cooled to -78 °C and DIBAL (1 M in THF, 1.76 mmol, 1.76 mL) was added under N_2 (**Scheme 3.22**). The reaction mixture was stirred for 3 hours, then MeOH (10 mL) was added and the reaction was allowed to warm to room temperature. Saturated NH_4Cl solution was added and the reaction mixture was stirred for 1 hour. The crude product was extracted using EtOAc (3 x 10 mL) and the combined organic layers were dried over $MgSO_4$ and filtered. The organic layer was then evaporated under reduced pressure and the crude product was analysed by NMR spectroscopy and TLC, revealing a mixture of products that proved inseparable and did not look as though **79** was present.

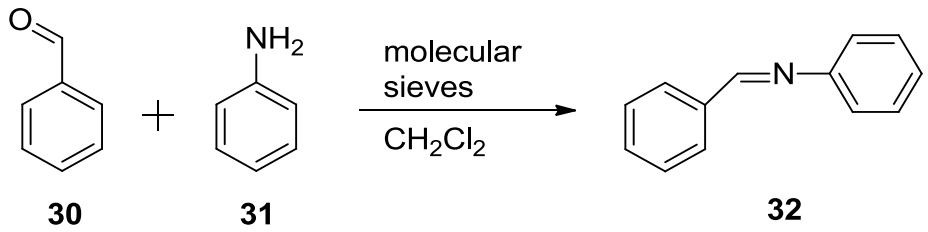
Attempted synthesis of (1R)-1-(pyridin-3-yl)ethane-1,2-diol, 81



Scheme 3.23

1.4 g of AD mix α was stirred in 1:1 *t*BuOH:water (10 mL) at room temperature for 1 hour. The reaction was then cooled to 0 °C and **80** (1 mmol, 0.11 mL) was added (**Scheme 3.23**). This solution was stirred for 24 hours. The reaction was quenched by the addition of sodium sulphite (5.7 g) and the solvent was removed under vacuum. ^{1}H and ^{13}C NMR spectral analyses of the isolated reaction mixture showed that **81** had not formed and only starting material remained.

N-(phenylmethylene)benzenamine[3], 32

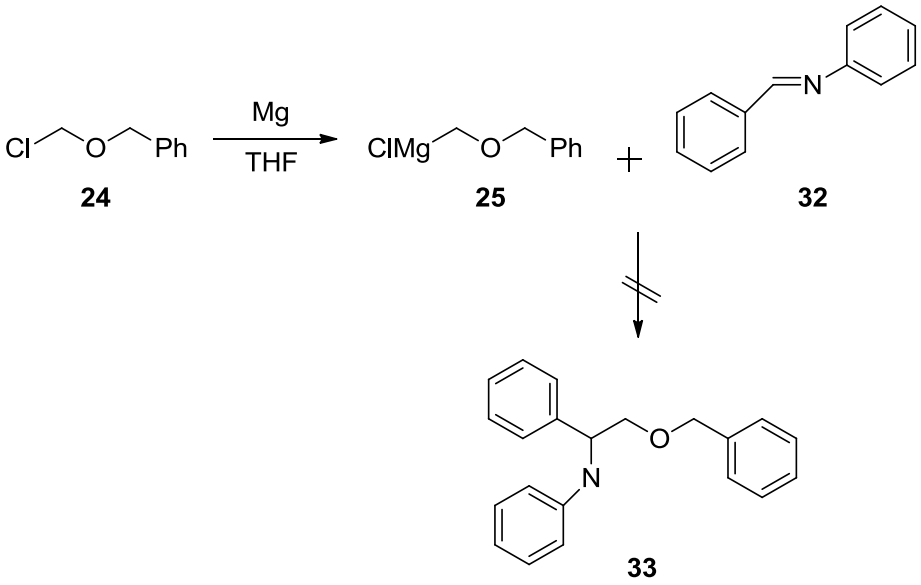


Scheme 3.24

To a stirring solution of benzaldehyde, **32**, (10 mmol, 1.6 g) in anhydrous CH_2Cl_2 (10 mL) was added aniline, **31**, (10 mmol, 0.912 mL) and oven dried 4Å molecular sieves (1.25 g) as seen in **Scheme 3.24**. The reaction was stirred at room temperature for 40 hours, concentrated *in vacuo* and the resulting crude product was purified by recrystalisation (9:1 hexane/chloroform) giving 1.2 g (62 % yield) of yellow crystalline solid, **32.**

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.46 (1H, s, C***H***=N), 7.92 - 7.89 (2H, m, C***H***$_{aryl}$), 7.50 - 7.46 (3H, m, C***H***$_{aryl}$), 7.42 - 7.36 (2H, m, C***H***$_{aryl}$), 7.26 - 7.20 (2H, m, C***H***$_{aryl}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.54 (C, ***C***=N), 152.18 (C, ***C***$_{aryl}$), 136.29 (C, ***C***$_{aryl}$), 131.49 (CH, ***C***H$_{aryl}$), 129.25 (CH, 2 x ***C***H$_{aryl}$), 128.90 (CH, 2 x ***C***H$_{aryl}$), 128.86 (CH, 2 x ***C***H$_{aryl}$), 126.03 (CH, ***C***H$_{aryl}$), 120.96 (CH, 2 x ***C***H$_{aryl}$).

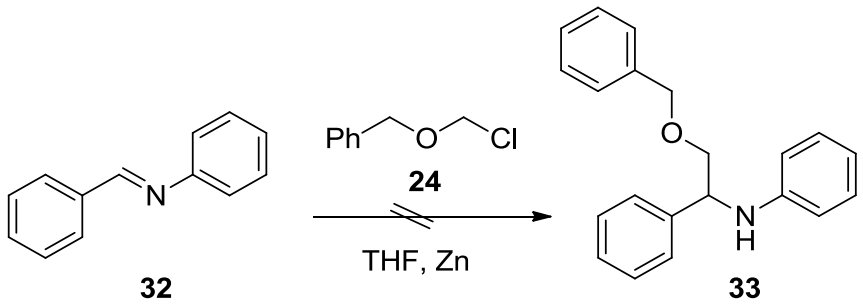
Attempted synthesis of [2-(Benzyloxy)-1-phenylethyl]aniline, 33



Scheme 3.25

Benzyl chloromethyl ether, **24**, (1 mmol, 0.14 mL) in THF (3 mL) was slowly added to a stirring solution of magnesium turnings (1 mmol, 24.31 mg) in THF (2 mL). The solution was stirred for 2 hours (**Scheme 3.25**). A solution of imine **32** (1 mmol, 181.23 mg), dissolved in THF (2 mL), was added slowly and the reaction was refluxed for 15 hours. It was quenched using saturated NH_4Cl (5 mL). The THF was removed under vacuum and CH_2Cl_2 (5 mL) was added. The organic layer was washed using water (3 x 5 mL) and brine (3 x 5 mL). The organic layer was then dried over $MgSO_4$ and reduced *in vacuo*. ^{1}H NMR spectral and TLC analyses of the

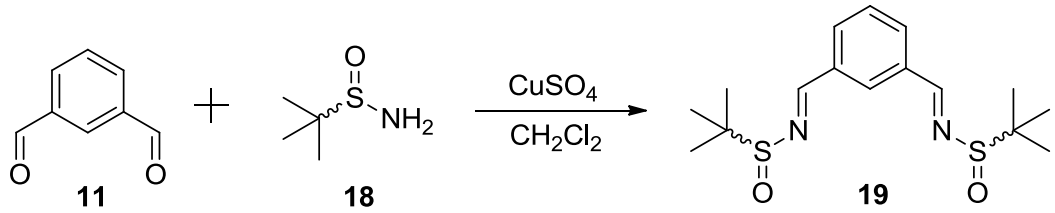
crude product showed that the starting material still remained and **33** had not formed.



Scheme 3.26

To a stirring solution of imine **32** (1.9 mmol, 345 mg) in THF (5 mL) was added benzyl chloromethyl ether (3.2 mmol, 0.45 mL) and activated zinc (2.8 mmol, 182 mg) as seen in **Scheme 3.26**. The zinc was activated by stirring in 1 M HCl followed by washing with water (20 mL), acetone (20 mL) and ether (20 mL) and then dried under vacuum. The reaction mixture was stirred for 1.5 hours at room temperature and followed by TLC. The reaction mixture was filtered through a celite pad and thoroughly washed with THF (3 x 10 mL). The combined organic phases reduced *in vacuo*. ^{1}H NMR spectral analysis of the crude product showed some interesting signals with 8.84 ppm (s), 7.37 – 7.28 ppm (m), 5.74 – 5.72 ppm (m), 5.66 ppm (dd), 5.59 ppm (dd), 4.89 ppm (s), 4.84 ppm (s), 4.64 ppm (d), 4.34 ppm (t), 4.00 – 3.93 ppm (m) and several signals between 2.50 ppm and 1.70 ppm but indicated that **33** was not formed.

(tert-Butylsulfinylimino){m-[(tert-butylsulfinylimino)methyl]phenyl} methane[4], 19

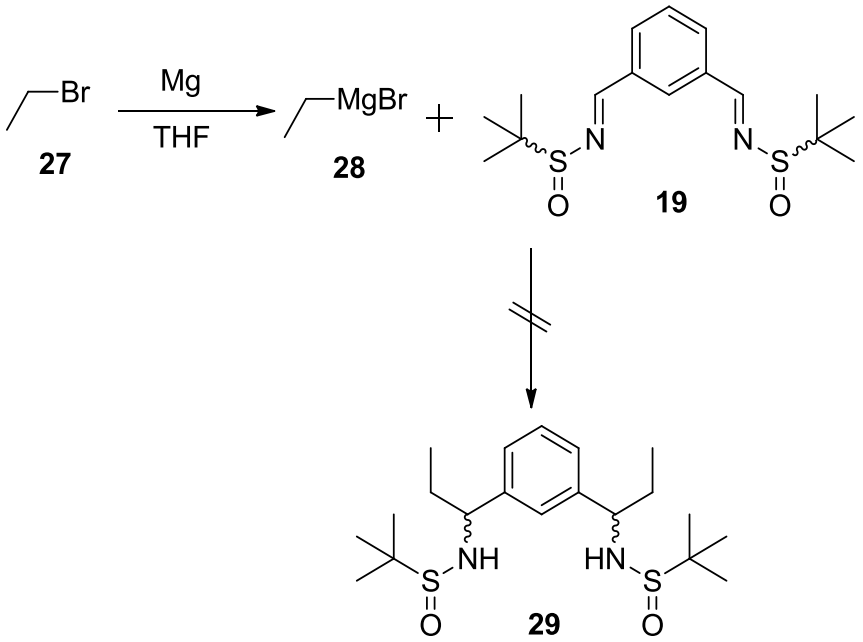


Scheme 3.27

To a stirring solution of isophthaldehyde, **11**, (4.125 mmol, 553 mg) in dry CH_2Cl_2 (20 mL) was added (±)2-methylpropane-2-sulfinamide, **18**, (8.25 mmol, 1 g) and $CuSO_4$ (16.5 mmol, 2.63 mg) as seen in **Scheme 3.27**. The reaction was stirred for 48 hours at room temperature, after which it was filtered through a celite pad. The filter cake was washed with CH_2Cl_2 (3 x 20 mL) and the solvent was removed under vaccum. The crude product was then purified by column chromatography (gradient elution 7:3 - 1:1 Pet ether:EtOAc) to afford **19** (1.41 g, 69 % yield) as a colourless foam.

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.64 (2H, s, NC***H***), 8.30 (1H, dt, J = 3.5, 1.5 Hz, C***H***$_{aryl}$), 8.00 (2H, ddd, J = 7.7, 3.1, 1.7 Hz, 2 x C***H***$_{aryl}$), 7.60 (1H, t, J = 7.7 Hz, C***H***$_{aryl}$), 1.28 (18H, d, J = 1.7 Hz, 6 x C***H***$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.91 (CH, 2 x N***C***H), 134.92 (C, 2 x ***C***$_{aryl}$), 132.82 (CH, 1 x ***C***H$_{aryl}$), 132.69 (CH, 1 x ***C***H$_{aryl}$), 130.34 (CH, 1 x ***C***H$_{aryl}$), 130.14 (CH, 1 x ***C***H$_{aryl}$), 58.13 (C, 2 x ***C***CH_3), 22.73 (CH_3, 6 x C***C***H_3). IR 2960, 2868, 1737, 1604 cm^{-1}.

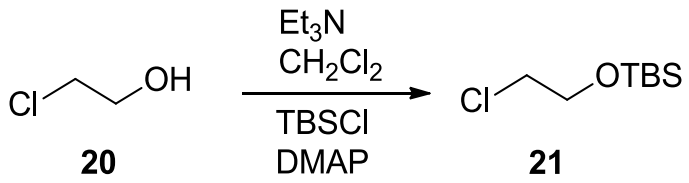
Attempted synthesis of N,N'-(1,3-phenylenedipropane-1,1-diyl)bis(2-methylpropane-2-sulfinamide), 29



Scheme 3.28

Bromoethane, **27**, (28.798 mmol, 3.14 g) in THF (15 mL) was slowly added to a stirring solution of magnesium turnings (20.57 mmol, 500 mg) in THF (15 mL) as seen in **Scheme 3.28**. After 4 hours, the solution was cloudy grey, and cooled to 0 °C. A solution of **19** (0.1 mmol, 30 mg) in THF (3 mL) was added slowly and the reaction was stirred overnight and allowed to warm gradually to room temperature. When the reaction was complete, it was quenched with saturated NH_4Cl (5 mL). The THF was removed under reduced pressure and CH_2Cl_2 (10 mL) was added. The organic layer was washed using water (3 x 10 mL), saturated $NaHCO_3$ (2 x 10 mL) and brine (10 mL). The organic layer was then dried over $MgSO_4$ and reduced *in vacuo* revealing a brown oil as the crude product. This crude product was analysed by ^1H NMR spectroscopy which revealed some interesting signals including 7.30 – 7.17 ppm (4H, m), 4.27 - 4.25 ppm (1H, m), 3.38 ppm (1H, dd), 2.08 – 2.01 ppm (2H, m) and several signals between 1.85 ppm and 0.72 ppm but these were not consistent with **29**.

TBS protected chloroethanol, 21

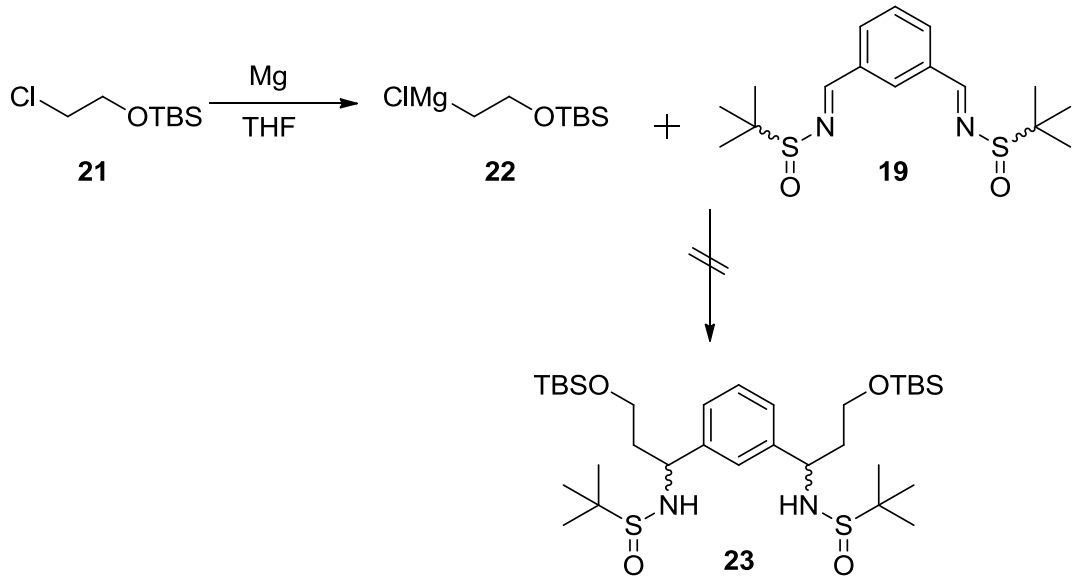


Scheme 3.29

A stirring solution of 2-chloroethanol, **20** (11.7 mmol, 0.785 mL) in CH_2Cl_2 (35 mL) was cooled to -15 °C and triethylamine (11.7 mmol, 1.63 mL) was added (**Scheme 3.29**). The solution was allowed to stir for 15 minutes. Dimethylaminopyridine (DMAP) (3.77 mmol, 460.76 mg) and *tert*-butyldimethylsilyl chloride (13.2 mmol, 2.00 g) were then added and the reaction was allowed to gradually warm to room temperature and stirred for 22 hours. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography using silica gel (Pet ether:EtOAc, 95:5) to give 2.01 g (88 % yield) of a colourless liquid **21**.

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 3.84 (2H, t, J = 6.2 Hz, C***H***$_2$), 3.54 (2H, t, J = 6.2 Hz, ClC***H***$_2$), 0.89 (9H, s, 3 x CC***H***$_3$), 0.08 (6H, s, 2 x SiC***H***$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 64.4 (CH_2, ***C***H_2), 45.7 (CH_2, Cl***C***H_2), 26.4 (CH_3, 3 x C***C***H_3), 18.7 (C, ***C***CH_3), -5.1 (CH_3, 2 x Si***C***H_3).

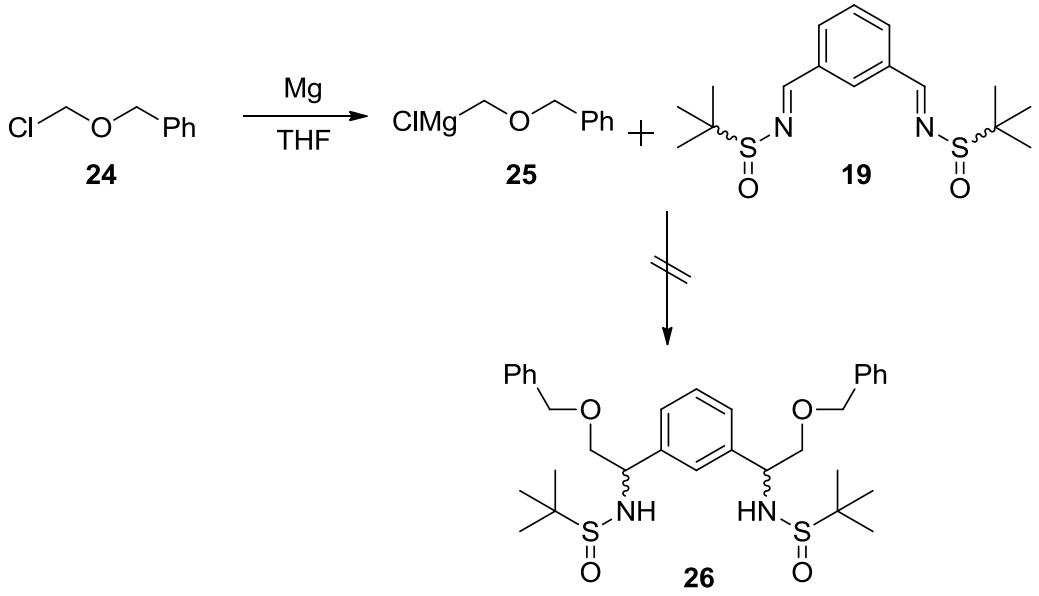
Attempted synthesis of TBS protected 3-{m-[3-hydroxy-1-(tert-butylsulfinylamino)propyl] phenyl}-3-(tertbutylsulfinylamino) propanol, 23



Scheme 3.30

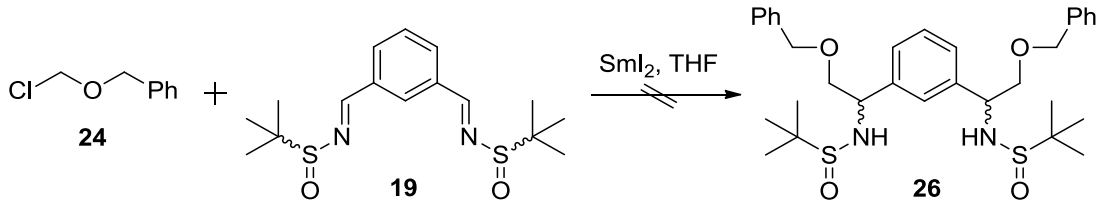
Magnesium turnings (20.57 mmol, 500 mg), iodine (0.079 mmol, 10 mg) and THF (15 mL) were stirred for 10 minutes when **21** (1.54 mmol, 300 mg) in THF (10 mL) was added (**Scheme 3.30**). The solution was refluxed for 4 hours and then cooled to 0 °C. A solution of **19** (0.325 mmol, 100 mg) in THF (3 mL) was slowly added and the reaction was stirred for 2 hours and quenched with saturated NH_4Cl (5 mL). The THF was removed and CH_2Cl_2 (10 mL) was added. The organic layer was washed using water (3 x 10 mL), $NaHCO_3$ (2 x 10 mL) and brine (10 mL). The organic layer was then dried over $MgSO_4$ and reduced *in vacuo*. Analysis of the crude reaction mixture showed that only the starting materials remained and **23** had not formed.

Attempted synthesis of 2-(benzyloxy)-1-{m-[2-(benzyloxy)-1-(tert-butylsulfinylamino)ethyl] phenyl}-1-(tert-butylsulfinylamino) ethane, 26



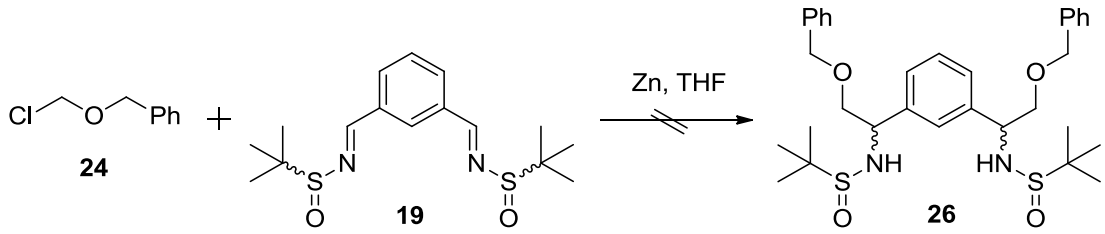
Scheme 3.31

Magnesium turnings (0.81 mmol, 19.75 mg) in THF (3 mL) were stirred and benzyl chloromethyl ether, **24**, (0.81 mmol, 0.11 mL) in THF (2 mL) was added (**Scheme 3.31**). The solution was stirred for 2 hours. A solution of **19** (0.33 mmol, 100 mg) in THF (3 mL) was slowly added and the mixture was heated to reflux and stirred overnight. The reaction was quenched with saturated NH_4Cl (5 mL). The THF was removed under vacuum and CH_2Cl_2 (10 mL) was added. The organic layer was washed using water (3 x 10 mL), $NaHCO_3$ (2 x 10 mL) and brine (10 mL). The organic layer was then dried over $MgSO_4$ and reduced *in vacuo*. Analysis of the crude product showed no reaction had taken place and **19** remained.



Scheme 3.32

To a stirring solution of **19** (0.234 mmol, 80 mg) in THF (1 mL) was added benzyl chloromethyl ether, **24**, (0.71 mmol, 98 µL) as seen in **Scheme 3.32**. Under an inert atmosphere, SmI_2 (0.71 mmol, 7.1 mL of 0.1 M in THF) was added quickly and the reaction was stirred at room temperature for 16 hours. The reaction was quenched using saturated NH_4Cl (5 mL) then ether (30 mL) was added and the organic layer was extracted. The aqueous layer was then washed with ether (3 x 5 mL). The combined organic layers were washed with saturated aqueous NH_4Cl (3 x 5 mL) and brine (3 x 5 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The reaction produced an inseparable mixture of products and NMR analysis revealed that the required product, **26**, had not formed.

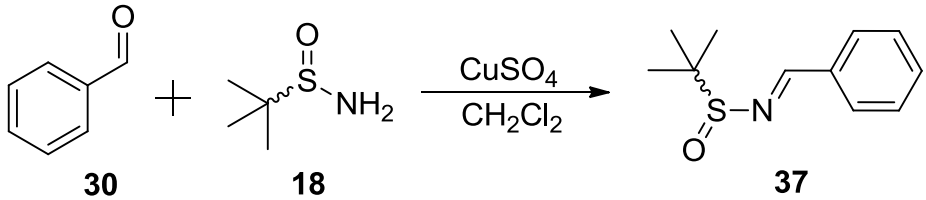


Scheme 3.33

To a stirring solution of imine, **19**, (0.49 mmol, 150 mg) in THF (10 mL) was added benzyl chloromethyl ether, **24**, (1.65 mmol, 0.23 mL) and activated zinc (1.46 mmol, 96 mg) under N_2 (**Scheme 3.33**). The zinc was activated by stirring in 1M HCl followed by washing with water (20 mL), acetone (20 mL) and ether (20 mL)

and then dried under vacuum. The reaction was stirred for 3 h at room temperature and followed by TLC. The reaction mixture was filtered through a celite pad and the filter cake was thoroughly washed with THF (3 x 20 mL). The organic phases were combined and reduced *in vacuo*. This produced an inseparable mixture of products and NMR spectral analysis revealed that the required product, **26**, had not formed.

(R)-(-)-N-(benzylidene)-2-methylpropanesulfinamide[5], 37



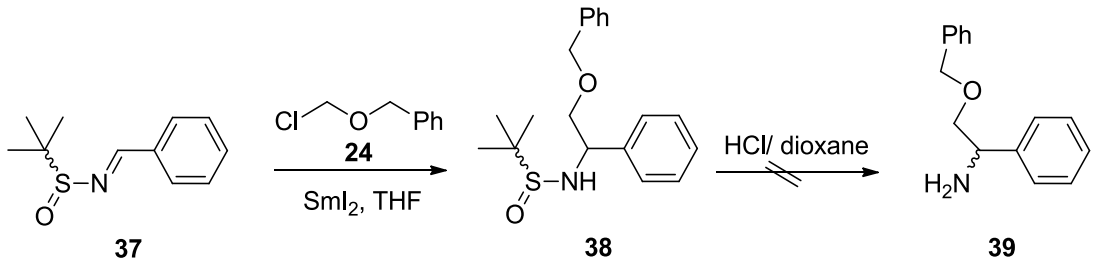
30 **18** **37**

Scheme 3.34

To a stirring solution of benzaldehyde, **30**, (2.0 mmol, 212.24 mg) in dry CH_2Cl_2 (5 mL) was added (±)2-methylpropane-2-sulfinamide, **18**, (2.0 mmol, 242.4 mg) and $CuSO_4$ (4.0 mmol, 638.4 mg) as seen in **Scheme 3.34**. The reaction was stirred for 1 hour at room temperature after which it was filtered through a celite pad. The filter cake was washed with CH_2Cl_2 (3 x 20 mL) and then the solvent was removed under vacuum. The crude product was purified by column chromatography (Pet ether:EtOAc, 9:1) to afford **37** (418.6 mg, 95 % yield) as a colourless foam.

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.59 (1H, s, ***H***CN), 7.85 (2H, dd, J = 8.1, 1.5 Hz, 2 x C***H***$_{aryl}$), 7.52 – 7.47 (3H, m, 3 x C***H***$_{aryl}$), 1.26 (9H, s, 3 x C***H***$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.89 (CH, 1 x H***C***N), 134.18 (C, 1 x ***C***$_{aryl}$), 132.54 (CH, 1 x ***C***H$_{aryl}$), 129.5 (CH, 2 x ***C***H$_{aryl}$), 129.05 (CH, 2 x ***C***H$_{aryl}$), 57.89 (C, 1 x ***C***CH$_3$), 22.74 (CH$_3$, 3 x C***C***H$_3$). IR 3306, 2926, 1706, 1606, 1572 cm^{-1}.

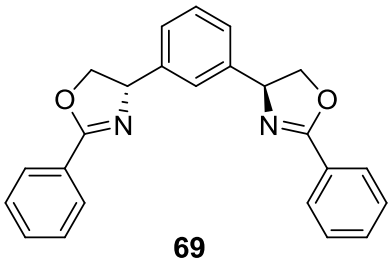
Attempted synthesis of (tert-butylsulfinyl)[2-(benzyloxy)-1-phenylethyl]amine, 39



Scheme 3.35

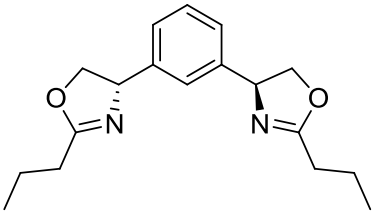
To a stirring solution of **37** (0.382 mmol, 80 mg) in THF (1 mL) was added benzyl chloromethyl ether, **24**, (1.53 mmol, 213 µL). Under an inert atmosphere, SmI_2 (1.53 mmol, 15.3 mL of 0.1 M in THF) was added quickly and the reaction was stirred at room temperature for 16 hours. The reaction was quenched using saturated NH_4Cl (5 mL) then ether (30 mL) was added and the organic layer was extracted. The aqueous layer was then washed with ether (3 x 5 mL). The combined organic layers were washed with saturated aqueous NH_4Cl (3 x 5 mL) and brine (3 x 5 mL), dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was then purified by column chromatography (gradient elution 9:1 - 6:4 Pet ether:EtOAc). ^{1}H NMR, ^{13}C NMR and MS analyses proved inconclusive as to whether **38** was formed so 1 mL of HCl:1,4 dioxane (4:8.5) was added to the crude product and the mixture was stirred at room temperature for 5 hours. It was then washed with 1,4 dioxane (3 x 2 mL) and the solvent was removed from the combined organic layers under reduced pressure. ^{1}H NMR spectral analysis of the crude reaction mixture showed many peaks but none of which corresponded to the desired product, **39**.

3. 3 Asymmetric reactions using PheBOX and PyBOX ligands



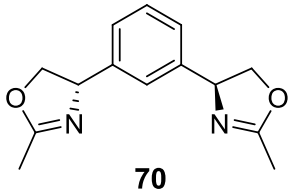
69

(4R,4'S)-4,4'-(1,3-phenylene)bis (2-phenyl-4,5-dihydro-1,3-oxazole)



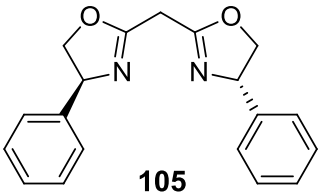
71

(4R,4'S)-4,4'-(1,3-phenylene)bis (2-propyl-4,5-dihydro-1,3-oxazole)



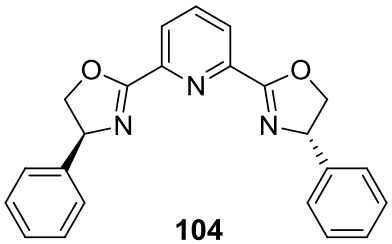
70

(4R,4'S)-4,4'-(1,3-phenylene)bis (2-methyl-4,5-dihydro-1,3-oxazole)



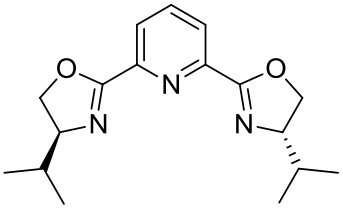
105

(4S,4'S)-2,2'-methanediylbis (4-phenyl-4,5-dihydro-1,3-oxazole)



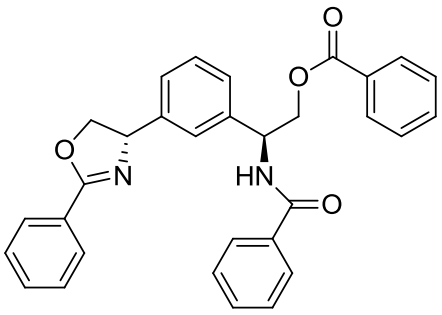
104

2,6-bis[(4S)-4-phenyl-2-oxazolinyl]pyridine



83

2,6-bis[(4S)-(-)-iso-propyl-2-oxazolin-2-yl]pyridine



73

(2S)-2-(benzoylamino)-2-{3-[(4S)-2-phenyl-4,5-dihydro-1,3-oxazol-4-yl]phenyl}ethyl benzoate

3.3.1 Asymmetric transfer hydrogenation

GENERAL PROCEDURE A (homogeneous catalysis)[6]

$[RuCl_2(p\text{-cymene})]_2$ (0.5 mol%) was added to a flame-dried, N_2 filled, Schlenk. PheBOX ligand (1.0 mol%) was weighed into a second flame dried, N_2 filled, Schlenk and dissolved in MeOH (10 mL). The ligand solution was then transferred, under N_2, into the Schlenk containing the $[RuCl_2(p\text{-cymene})]_2$. The resulting mixture was stirred for 3 hours at room temperature. The solvent was evaporated and the solid obtained was dried under vacuum. To this catalyst, was added dry *i*PrOH (10 mL), the appropriate ketone (1 equiv.) and *t*BuOK (15 mol%). This reaction mixture was then stirred at 50 °C for 16 hours. At that point, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with 1M HCl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL), the organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo* to yield the appropriate crude product. A ^1H NMR spectrum was recorded to determine the percentage conversion of the product formed using the unreacted acetophenone, **89**, signal at 2.60 ppm (3H) compared to product, **90**, signal at 1.48 ppm (3H). The crude product was then purified by column chromatography (Pet.ether:Ethyl acetate, 95:5). The enantiomeric excess (*ee*) of the purified product was measured using chiral GC (Cyclodex OD 0.46 cmΦ x 30 m column).

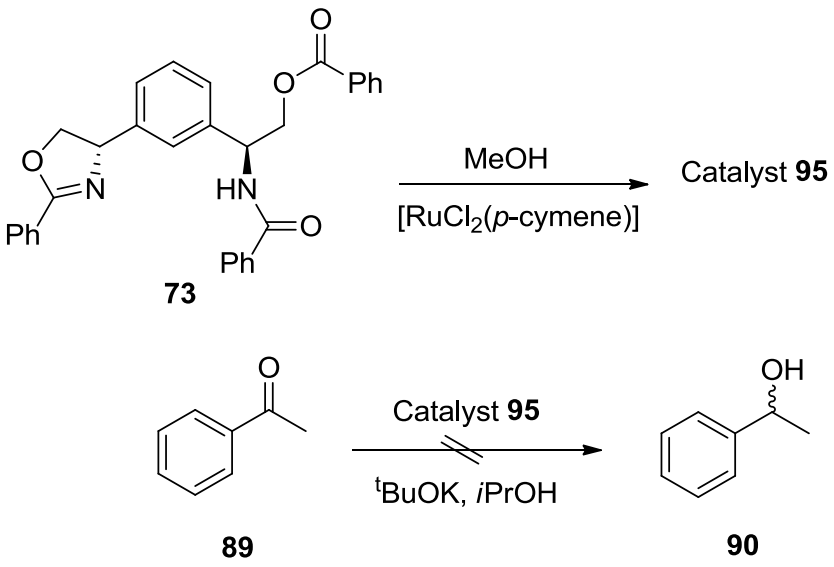
GENERAL PROCEDURE B (homogeneous catalysis)[6-7]

$RuCl_3.H_2O$ (2 equiv.) was added to a flame-dried, N_2 filled, Schlenk. PheBOX ligand (1 equiv.) was weighed into a second flame-dried, N_2 filled, Schlenk dissolved in EtOH (5 mL). The ligand solution was then transferred, under N_2, into the Schlenk containing the metal. Zinc (5 equiv.) and 1,5-cyclooctadiene (5 equiv.) were added and the reaction mixture was refluxed for 24 hours. At that point, the reaction mixture was diluted with toluene (10 mL). The aqueous layer was extracted with toluene (2 x 10 mL), the organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo* to yield the appropriate catalyst. To 10 mol% of catalyst, was

added dry *i*PrOH (10 mL), the appropriate ketone (1 equiv.) and *t*BuOK (15 mol%). This reaction mixture was stirred at 50 °C for 16 hours. At that point, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with 1M HCl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL), the organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo* to yield the appropriate crude product. A ^{1}H NMR spectrum was recorded to determine the percentage conversion of the product formed using the unreacted acetophenone, **89**, signal at 2.60 ppm (3H) compared to product, **90**, signal at 1.48 ppm (3H). The crude product was then purified by column chromatography (Pet.ether:Ethyl acetate, 95:5). The enantiomeric excess (*ee*) of the purified product was measured using chiral GC (Cyclodex OD 0.46 cmΦ x 30 m column).

Attempted synthesis of 1-Phenyl-1-ethanol, 90

Specific example 1

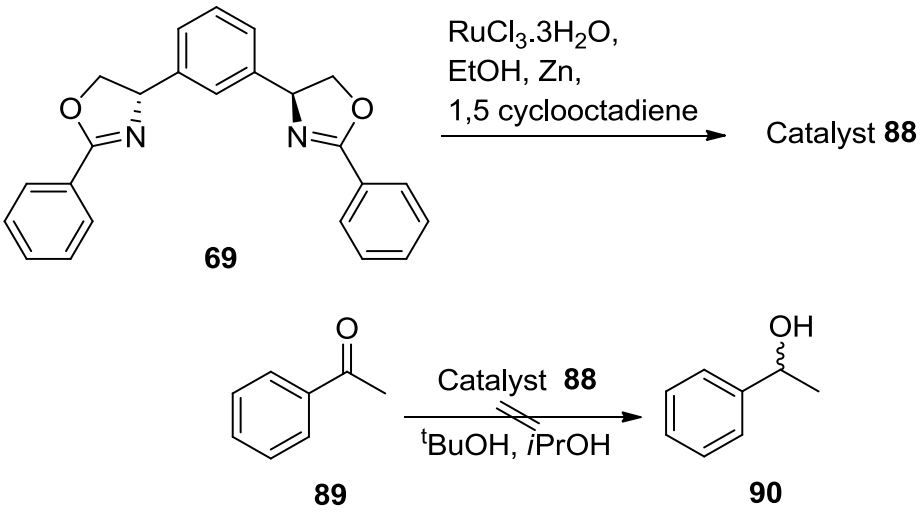


Scheme 3.36

The reaction was carried out according to general procedure A using $[RuCl_2(pcymene)]_2$ (0.011 mmol, 6.8 mg), ligand **73** (0.022 mmol, 10.7 mg),

acetophenone, **89**, (2.25 mmol, 270.0 mg) and *t*BuOK (0.34 mmol, 38.0 mg) as seen in **Scheme 3.36**. The reaction was carried out at 50 °C for 16 hours. The reaction was quenched and worked up as per the procedure. ^{1}H NMR spectral analysis of the crude reaction mixture showed that the starting material, acetophenone, **89**, was still present and that **90** had not formed.

Specific example 2



Scheme 3.37

The reaction was carried out according to general procedure B using $RuCl_3.H_2O$, (0.364 mmol, 95.5 mg), ligand **69** (0.182 mmol, 67 mg), zinc (1.82 mmol, 119 mg) and 1,5-cyclooctadiene (1.82 mmol, 0.22 mL) as seen in **Scheme 3.37**. To 10 mol% of catalyst **88** (0.011 mmol, 7 mg) was added acetophenone, **89**, (2.25 mmol, 270.0 mg) and *t*BuOK (0.34 mmol, 38.0 mg). The reaction was carried out at 50 °C for 16 hours. The reaction was quenched and worked up as per the procedure. ^{1}H NMR spectral analysis of the crude reaction mixture showed that the starting material, acetophenone, **89**, was still present and that **90** had not formed.

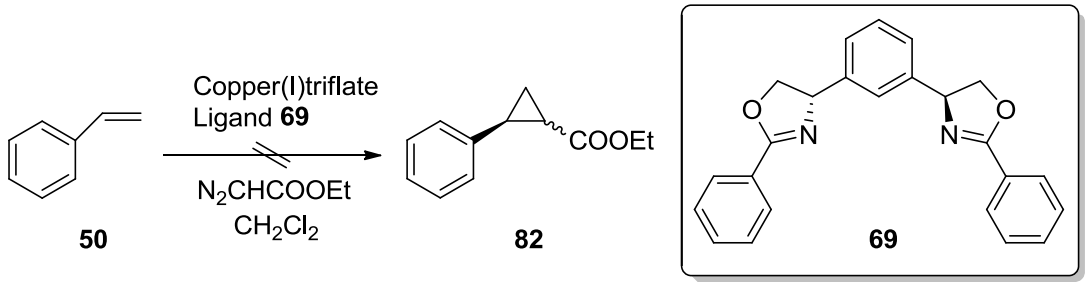
3.3.2 Asymmetric Cyclopropanation[8]

GENERAL PROCEDURE C (homogeneous catalysis)

Metal triflate (1 mol%) was added to a flame-dried, N_2 filled, Schlenk. PheBOX ligand (1.2 mol%) was weighed into a second, flame-dried, N_2 filled, Schlenk and dissolved in CH_2Cl_2 (1 mL). The ligand solution was then transferred, under N_2, into the Schlenk containing the metal triflate. The resulting mixture was then stirred for 90 minutes at room temperature. To this stirring catalyst, was added styrene (5 equiv.) in CH_2Cl_2 (1 mL). A solution of ethyl diazoacetate (1 equiv.) in CH_2Cl_2 (4 mL) was added over *ca*. 6 hours *via* a syringe pump. This reaction mixture was then stirred at room temperature for 12 hours. At that point the reaction mixture was filtered through a silica gel (40-63 μm) plug into a round bottomed flask. The reaction Schlenk was rinsed with CH_2Cl_2 (2 x 5 mL) and the CH_2Cl_2 rinse was filtered through the same silica gel plug into the round bottomed flask. The combined solution was then concentrated *in vacuo* to yield the crude product. A ^{1}H NMR spectrum was recorded to determine the percentage conversion, using the unreacted ethyl diazoacetate signal (1H) at 4.72 ppm compared to the sum of the product peaks, *cis* at 3.87 ppm (2H) and *trans* at 4.17 ppm (2H), minus the fumarate and maleate by-product signal at 4.26 ppm (4H). The *cis*:*trans* ratio of the product formed was determined using the *cis* product signal at 3.87 ppm (2H) compared to *trans* product signal at 4.17 ppm (2H). The crude product was then purified by column chromatography (Pet.ether:Ethyl acetate, 95:5). The enantiomeric excess (*ee*) of the purified product was measured using chiral GC (Cyclodex-OD 0.46 cmΦ x 30 m column).

Ethyl(2S)-2-phenylcyclopropanecarboxylate, 82

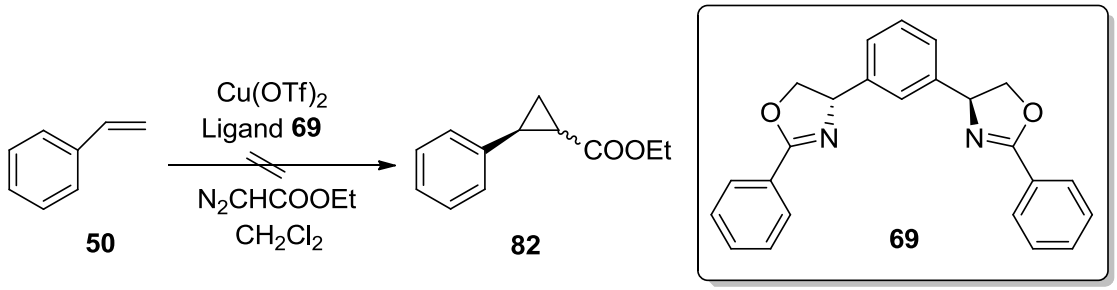
Specific example 1



Scheme 3.38

The reaction was carried out according to general procedure D using [copper(I)triflate]$_2$·C_6H_6 (0.006 mmol, 4 mg), ligand **69** (0.013 mmol, 4.79 mg), styrene, **50**, (6.0 mmol, 0.69 mL) and ethyl diazoacetate (1.2 mmol, 0.14 mL) as seen in **Scheme 3.38**. The reaction was carried out at room temperature for 18 hours. ^{1}H NMR spectral analysis of the crude reaction mixture showed that the starting materials, styrene, **50**, and ethyl diazoacetate were still present and **82** had not formed.

Specific example 2



Scheme 3.39

The reaction was carried out according to general procedure D using copper(II)triflate (0.006 mmol, 2 mg), ligand **69** (0.013 mmol, 4.79 mg), styrene, **50**, (6.0 mmol, 0.69 mL) and ethyl diazoacetate (1.2 mmol, 0.14 mL) as seen in **Scheme 3.39**. The reaction was carried out at room temperature for 18 hours. ^{1}H NMR spectral analysis of the crude reaction mixture showed that the starting materials, styrene, **50**, and ethyl diazoacetate were still present and **82** had not formed.

3.3.3 Asymmetric Propargylic Substitution[9]

GENERAL PROCEDURE D (homogeneous catalysis)

Metal triflate (10 mol%) was weighed into a flame-dried, N_2 filled, Schlenk. PyBOX or BOX ligand (12 mol%) was weighed into a second flame-dried, N_2 filled, Schlenk and dissolved in CH_2Cl_2 (1 mL). The ligand solution was then transferred, under N_2, into the Schlenk containing the metal triflate. The resulting mixture was stirred for 2 hours at room temperature. The catalyst mixture was then filtered through a cotton plug, to remove any undissolved metal triflate, into a third flame-dried, N_2 filled, Schlenk. This Schlenk, containing the reaction catalyst under N_2, was then brought to the appropriate reaction temperature. To this stirring catalyst was added the appropriate solution of propargylic acetate (1 equiv.), the appropriate nucleophile (2 equiv.) and the appropriate base (4 equiv.). This reaction mixture was then stirred at the appropriate reaction temperature and time. At that point, the reaction mixture was allowed warm to room temperature, where necessary, and then filtered through a silica gel plug (40-63 µm) into a round bottomed flask. The reaction Schlenk was then rinsed with CH_2Cl_2 (5 mL) and the CH_2Cl_2 rinse filtered through the same silica gel plug into the round bottomed flask. This silica gel (40-63 µm) plug was then washed with ethyl acetate (5 mL) and the ethyl acetate wash added to the round bottomed flask. The combined solution was then concentrated *in vacuo* to yield the appropriate crude product. A ^{1}H NMR spectrum was recorded to determine the percentage conversion using starting material, **100**, signal at 6.45 (1H) due to CH_3OCH, and product, **101**, signal at 5.29 (1H) due to C*H*N.

The crude product was then purified by column chromatography using the conditions reported below. The enantiomeric excess (*ee*) of the purified product was measured using chiral HPLC (CHIRACEL OD 0.46 cmΦ x 30 m column) according to the conditions reported below.

GENERAL PROCEDURE E (heterogeneous catalysis 1st use)

Metal triflate (10 mol%) was weighed into a flame-dried, N_2 filled, Schlenk. PyBOX or BOX ligand (12 mol%) was weighed into a second flame-dried, N_2 filled, Schlenk and dissolved in CH_2Cl_2 (1 mL). The ligand solution was then transferred under N_2, into the Schlenk containing the metal triflate. The resulting mixture was then stirred for 2 hours. The catalyst mixture was filtered through a cotton plug, to remove any undissolved metal triflate, onto 200 mg of pre-dried silica gel (40-63 μm, heated under vacuum at 70 °C for 2 hours) in a N_2 filled, wide bottomed Schlenk/round bottomed flask. The solution was stirred for 1 minute, then after the stirring was stopped the silica gel became coloured (where a copper salt was used and colourless otherwise) and settled to the bottom of the wide bottomed Schlenk/round bottomed flask. The clear supernatant liquid on top of the coloured silica gel was removed under N_2 *via* Pasteur pipette. The silica gel catalyst was washed twice with CH_2Cl_2 (5 mL) and the clear supernatant liquid on top of the coloured silica gel was removed. The silica gel catalyst was left under CH_2Cl_2 (~1 mL). This wide bottomed Schlenk/round bottomed flask, containing the stirring catalyst under N_2, was then brought to the appropriate reaction temperature. To this stirring catalyst was added the appropriate solution of propargylic acetate (1 equiv.), the appropriate nucleophile (2 equiv.) and the appropriate base (4 equiv.). This reaction mixture was then stirred at the appropriate reaction temperature and time. At that point, stirring was stopped and the reaction mixture was allowed warm to room temperature, where necessary. The silica gel catalyst settled and the supernatant liquid was filtered through a celite plug into a round bottomed flask. The catalyst was washed twice with CH_2Cl_2 (5 mL), and the CH_2Cl_2 washings filtered through the same celite plug into the round bottomed flask. The

silica gel catalyst was then stored in CH_2Cl_2 (~1mL) and under N_2 for subsequent use. The combined solution was then concentrated *in vacuo* to yield the appropriate crude product. A ^1H NMR spectrum was recorded to determine the percentage conversion using the starting material, **100**, signal at 6.45 ppm (1H) due to CH_3OCH, and product, **101**, signal at 5.29 ppm (1H) due to C*H*N. The crude product was then purified by column chromatography using the conditions reported below. The enantiomeric excess (*ee*) of the purified product was measured using chiral HPLC (CHIRACEL OD 0.46 cmΦ x 30 m column), according to the conditions reported below.

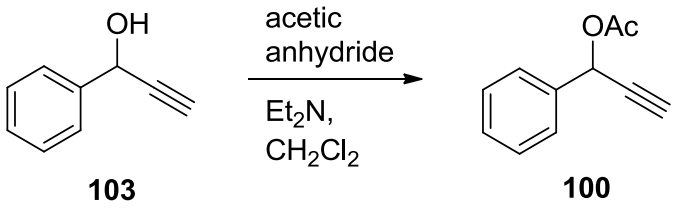
GENERAL PROCEDURE F (heterogeneous catalysis, 2nd and 3rd use)

The silica gel catalyst in CH_2Cl_2 (~1mL) under N_2 in a wide bottomed Schlenk/round bottomed flask recovered from a previous run was stirred under N_2 and was brought to the appropriate reaction temperature. To this stirring catalyst, was added the appropriate solution of propargylic acetate (1 equiv.), the appropriate nucleophile (2 equiv.) and the appropriate base (4 equiv.). This reaction mixture was then stirred at the appropriate reaction temperature and time. At that point, stirring was stopped and the reaction mixture was allowed warm to room temperature, where necessary. The silica gel catalyst settled and the supernatant liquid was filtered through a celite plug into a round bottomed flask. The catalyst was washed twice with CH_2Cl_2 (5 mL), and the CH_2Cl_2 washings were filtered through the same celite plug into the round bottomed flask. The silica gel catalyst was then stored in CH_2Cl_2 (~1mL) under N_2, if required for subsequent use. The combined solution was then concentrated *in vacuo* to yield the appropriate crude product. A ^1H NMR spectrum was recorded to determine the percentage conversion using the starting material, **100**, signal at 6.45 ppm (1H) due to CH_3OCH, and product, **101**, signal at 5.29 ppm (1H) due to C*H*N. The crude product was then purified by column chromatography using the conditions reported below. The enantiomeric excess (*ee*) of the purified product was measured using chiral HPLC

(CHIRACEL OD 0.46 cmΦ x 30 m column), according to the conditions reported below.

Synthesis of substrate

1-phenylprop-2-yn-1-yl acetate[9], 100



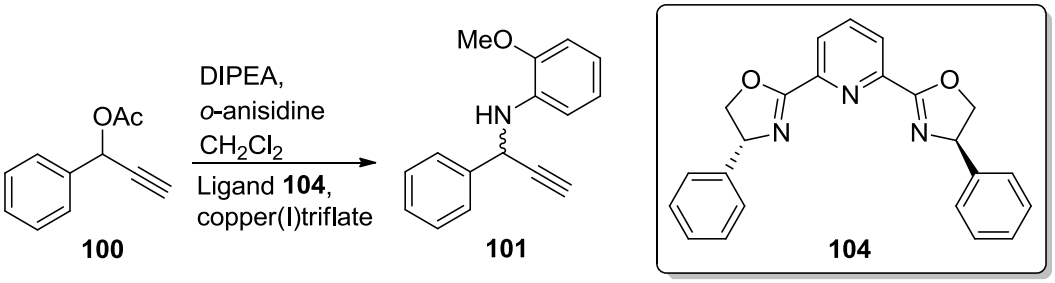
Scheme 3.40

To a stirring solution of 1-phenylprop-2-ynyl alcohol, **103**, (4.1 mmol, 0.5 mL) in CH_2Cl_2 (10 ml) was added acetic anhydride (5.5 mmol, 0.5 mL) and triethylamine (5.5 mmol, 0.75 mmol) under N_2 (**Scheme 3.40**) . The reaction was stirred at room temperature for 21 hours and then concentrated under vacuum. The crude reaction mixture was purified by column chromatography (CH_2Cl_2:Pet Ether, 5:1) and produced **100** as a colourless oil (1.2 g, 85 % yield).

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.55 – 7.52 (2H, m, 2 x C***H***$_{aryl}$), 7.41 – 7.37 (3H, m, 3 x C***H***$_{aryl}$), 6.44 (1H, d, J = 2.3 Hz, C***H***), 2.66 (1H, d, J = 2.3 Hz, CC***H***), 2.12 (3H, s, OC***C***H_3).

2-Methoxy-(1-phenylprop-2-yn-1-yl)aniline, 101

Specific Example 1 (Homogenous catalysis)

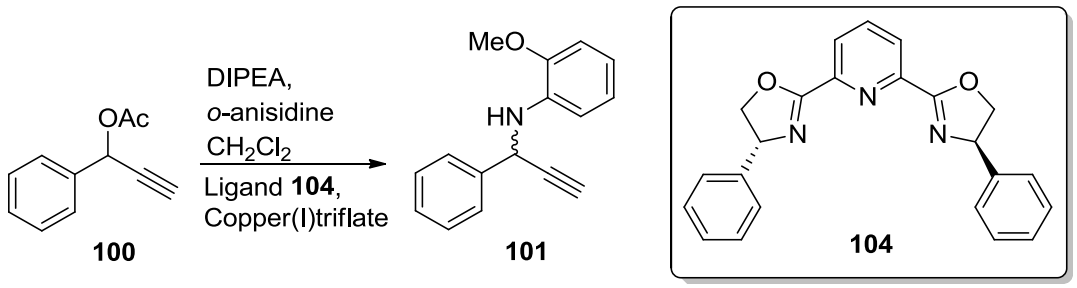


Scheme 3.41

The reaction was carried out according to general procedure D using [copper(I)triflate]$_2$·C_6H_6 (0.02 mmol, 10.1 mg), ligand **104** (0.024 mmol, 8.9 mg), **100** (0.2 mmol, 34.8 mg), DIPEA (0.35 mmol, 50 mg) and *o*-anisidine (0.4 mmol, 45 µL) as seen in **Scheme 3.41**. The reaction mixture was stirred for 16 hours at room temperature. The reaction product, **101**, was isolated as a yellow oil. The reaction resulted in 100 % conversion to **101**. The crude product was then purified by column chromatography (petrol:ethyl acetate, 4:1) affording the product **101** as a yellow oil (20 % yield) which had a 53 % *ee*. The enantiomeric excess was measured using chiral HPLC, CHIRACEL OD (4.6 x 300 mm), 98:2 hexane:*i*PrOH, 1.0 mL/min, λ = 254 nm, t = 15.1 min and 23.5 min. Spectral characterisation of **101** below was consistent with that reported[9].

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.62 – 7.60 (2H, m, 2 x C***H***$_{aryl}$), 7.41 – 7.31 (3H, m, 3 x C***H***$_{aryl}$), 6.89 – 6.72 (4H, m, 4 x C***H***$_{aryl}$), 5.29 (1H, dd, J = 7.1, 2.0 Hz, C***H***N), 4.67 (1 H, d, J = 7.0 Hz, N***H***), 3.82 (3H, s, C***H***$_3$), 2.46 (1H, d, J = 2.3 Hz, CC***H***). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.29 (C, ***C***$_{aryl}$), 139.31 (C, ***C***$_{aryl}$), 136.30 (C, ***C***$_{aryl}$), 128.94 (CH, 2 x ***C***H$_{aryl}$), 128.25 (CH, ***C***H$_{aryl}$), 127.41 (CH, 2 x ***C***H$_{aryl}$), 121.75 (CH, ***C***H$_{aryl}$), 118.03 (CH, ***C***H$_{aryl}$), 111.62 (CH, ***C***H$_{aryl}$), 109.72 (CH, ***C***H$_{aryl}$), 83.25 (CH, C***C***H), 73.04 (C, ***C***CH), 55.55 (CH, H***C***NH), 49.60 (CH_3, ***C***H_3).

Specific Example (Heterogeneous catalysis first use)



Scheme 3.42

The reaction was carried out according to general procedure E using [copper(I)triflate]$_2$·C_6H_6 (0.02 mmol, 10.1 mg), ligand **104** (0.024 mmol, 8.9 mg), **100** (0.2 mmol, 34.8 mg), DIPEA (0.35 mmol, 50 mg) and *o*-anisidine (0.4 mmol, 45 µL,) as seen in **Scheme 3.42**. The reaction mixture was stirred for 16 hours at room temperature. The reaction product **101** was isolated as a yellow oil. The reaction resulted in 100 % conversion to **101**. The crude product was then purified by column chromatography (Pet ether:Ethyl acetate, 4:1) affording the product **101** as a yellow oil (16 % yield) which had a 36 % *ee*. The enantiomeric excess was measured using chiral HPLC, CHIRACEL OD (4.6 x 300 mm), 98:2 hexane:*i*PrOH, 1.0 mL/min, λ = 254 nm, t = 15.1 min and 23.5 min. Spectral characterisation was consistent with that reported above for **101.**

Specific Example (Heterogeneous catalysis second use)

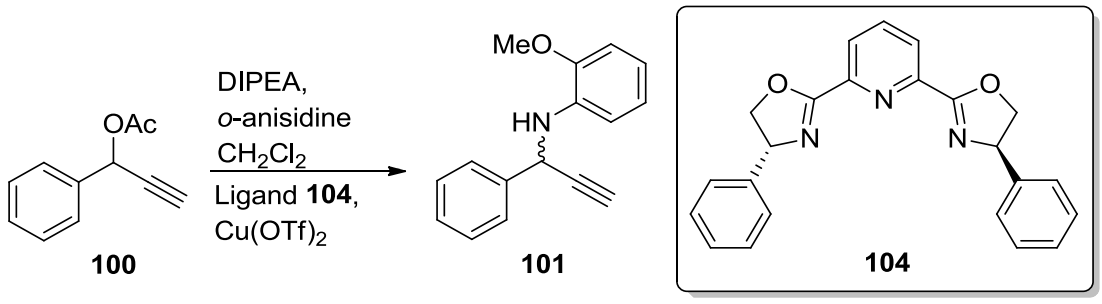
The reaction was carried out according to general procedure F using [copper(I)triflate]$_2$·C_6H_6 (0.02 mmol, 10.1 mg), ligand **104** (0.024 mmol, 8.9 mg), **100** (0.2 mmol, 34.8 mg), DIPEA (0.35 mmol, 50 mg) and *o*-anisidine (0.4 mmol, 45 µL,) as seen in **Scheme 3.42**. The reaction mixture was stirred for 16 hours at room temperature. The reaction product **101** was isolated as a yellow oil. The reaction resulted in 36 % conversion to **101**. The crude product was then purified by column chromatography (Pet ether:Ethyl acetate, 4:1) affording the product **101** as a yellow oil (5 % yield) which had a 35 % *ee*. The enantiomeric excess was measured using

chiral HPLC, CHIRACEL OD (4.6 x 300 mm), 98:2 hexane:*i*PrOH, 1.0 mL/min, λ = 254 nm, t = 15.1 min and 23.5 min. Spectral characterisation was consistent with that reported above for **101.**

Specific Example (Heterogeneous catalysis third use)

The reaction was carried out according to general procedure F using [copper(I)triflate]$_2$·C_6H_6 (0.02 mmol, 10.1 mg), ligand **104** (0.024 mmol, 8.9 mg), **100** (0.2 mmol, 34.8 mg), DIPEA (0.35 mmol, 50 mg) and *o*-anisidine (0.4 mmol, 45 µL,) as seen in **Scheme 3.42**. The reaction mixture was stirred for 16 hours at room temperature. Analysis of the crude product showed 0 % conversion to **101**.

Specific Example - Copper(II)triflate



Scheme 3.43

All reactions were carried out using Cu(OTf)$_2$ (0.02 mmol, 7.23 mg), ligand **104** (0.024 mmol, 8.9 mg), **100** (0.2 mmol, 34.8 mg), DIPEA (0.35 mmol, 50 mg) and *o*-anisidine (0.4 mmol, 45 µL) as seen in **Scheme 3.43**. The homogeneous reaction was carried out according to general procedure D. The first heterogeneous reaction was carried out according to general procedure E and the second and third heterogeneous reactions were carried out according to general procedure F. The reactions were stirred for 16 hours at room temperature. ^{1}H NMR spectra of the

products were consistent with the full product characterisation results reported above (see **Table 3.1** for results).

Catalyst	% conversion to 101	Yield (%)	% *ee*
Homogeneous	100	18	50
Heterogeneous 1	100	15	40
Heterogeneous 2	44	2	39
Heterogeneous 3	N/A	N/A	No products

Table 3.1

3.3.4 Asymmetric Trimethylsilylcyanation[10]

GENERAL PROCEDURE G (homogeneous catalysis)

Metal triflate (10 mol%) was weighed into a flame-dried, N_2 filled, Schlenk. PyBOX ligand (10 or 20 mol%) was weighed into a second flame-dried, N_2 filled, Schlenk and dissolved in CH_2Cl_2 (2 mL). The ligand solution was then transferred under N_2, into the Schlenk containing the metal triflate. The resulting mixture was then stirred for 2 hours at room temperature. The catalyst mixture was then filtered through a cotton plug, to remove any undissolved metal triflate, into a third flame-dried, N_2 filled, Schlenk. This Schlenk containing the reaction catalyst, under N_2, was then brought to the appropriate reaction temperature. To this stirring catalyst was added the benzaldehyde (1 equiv.) and trimethylsilyl cyanide (1.1 equiv.). This reaction mixture was then stirred at the appropriate reaction temperature and time. At that point, the reaction mixture was allowed warm to room temperature, where necessary, and then filtered through a silica gel plug (40-63 µm) into a round bottomed flask. The reaction Schlenk was then rinsed with CH_2Cl_2 (5 mL) and the CH_2Cl_2 rinse filtered through the same silica gel plug into the round bottomed flask. This silica gel (40-63 µm) plug was then washed with ethyl acetate (5 mL) and the ethyl acetate wash added to the round bottomed flask. The combined solution was then concentrated *in vacuo* to yield the crude product. A ^{1}H NMR spectrum was

recorded to determine the percentage conversion using starting material, benzaldehyde, **30**, signal at 10.02 ppm (1H) due to CO*H* and product, **108**, signal at 5.49 ppm (1H) due to *H*CO. The crude product was then dissolved in MeCN (2 mL) and 1M HCl (5 mL) was added and the reaction was stirred at room temperature overnight. The reaction mixture was extracted using ether (3 x 5 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The purified product was purified by column chromatography using the conditions reported below and then dissolved in CH_2Cl_2 (2 mL) and acetic anhydride (1 mL) was added and the reaction was allowed to stir overnight. When the reaction was complete, it was then extracted using EtOAc (3 x 5 mL), dried over $MgSO_4$, filtered and reduced *in vacuo*. The enantiomeric excess (*ee*) of the purified product was measured using chiral GC (CYCLODEX-β 0.25 mmΦ x 30 m column), according to the conditions reported below.

GENERAL PROCEDURE H (heterogeneous catalysis 1st use)

Metal triflate (10 mol%) was weighed into a flame-dried, N_2 filled, Schlenk. PyBOX ligand (10 or 20 mol%) was weighed into a second flame-dried, N_2 filled, Schlenk and dissolved in CH_2Cl_2 (5 mL). The ligand solution was then transferred, under N_2, into the Schlenk containing the metal triflate. The resulting mixture was then stirred for 2 hours. The catalyst mixture was then filtered through a cotton plug, to remove any undissolved metal triflate, onto 400 mg of pre-dried silica gel (40-63 μm, heated under vacuum at 70 °C for 2 hours) in a N_2 filled, wide bottomed Schlenk/round bottomed flask. The solution was stirred for 1 minute, then after stirring was stopped the silica gel became coloured (where a copper salt was used and colourless otherwise) and settled to the bottom of the wide bottomed Schlenk/round bottomed flask. The clear supernatant liquid on top of the silica gel was removed under N_2 *via* Pasteur pipette. The silica gel catalyst was washed twice with CH_2Cl_2 (5 mL) and the clear supernatant liquid on top of the silica gel was removed. The silica gel catalyst was left under CH_2Cl_2 (~1 mL). This wide bottomed Schlenk/round bottomed flask containing the stirring catalyst under N_2 was then

brought to the appropriate reaction temperature. To this stirring catalyst was added benzaldehyde (1 equiv.) and trimethylsilyl cyanide (1.1 equiv.). This reaction mixture was then stirred at the appropriate reaction temperature and time. At that point, stirring was stopped and the reaction mixture was allowed warm to room temperature, where necessary. The silica gel catalyst settled and the supernatant liquid was filtered through a celite plug into a round bottomed flask. The catalyst was washed twice with CH_2Cl_2 (5 mL), and the CH_2Cl_2 washings filtered through the same celite plug into the round bottomed flask. The silica gel catalyst was then stored under CH_2Cl_2 (~1 mL) and N_2 for subsequent use. The combined solution was then concentrated *in vacuo* to yield the crude product. A ^1H NMR spectrum was recorded to determine the percentage conversion using starting material, benzaldehyde, **30**, signal at 10.02 ppm (1H) due to CO*H* and product, **108**, signal at 5.49 ppm (1H) due to *H*CO. The crude product was then dissolved in MeCN (2 mL) and 1M HCl (5 mL) was added and the reaction was stirred at room temperature overnight. The reaction mixture was extracted using ether (3 x 5 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was then purified by column chromatography using the conditions reported below and then dissolved in CH_2Cl_2 (2 mL) and acetic anhydride (1 mL) was added and the reaction was allowed to stir overnight. The product was then extracted using EtOAc (3 x 5 mL), dried over $MgSO_4$, filtered and reduced *in vacuo*. The enantiomeric excess (*ee*) of the purified product was measured using chiral GC (CYCLODEX-β 0.25 mmΦ x 30 m column), according to the conditions reported below.

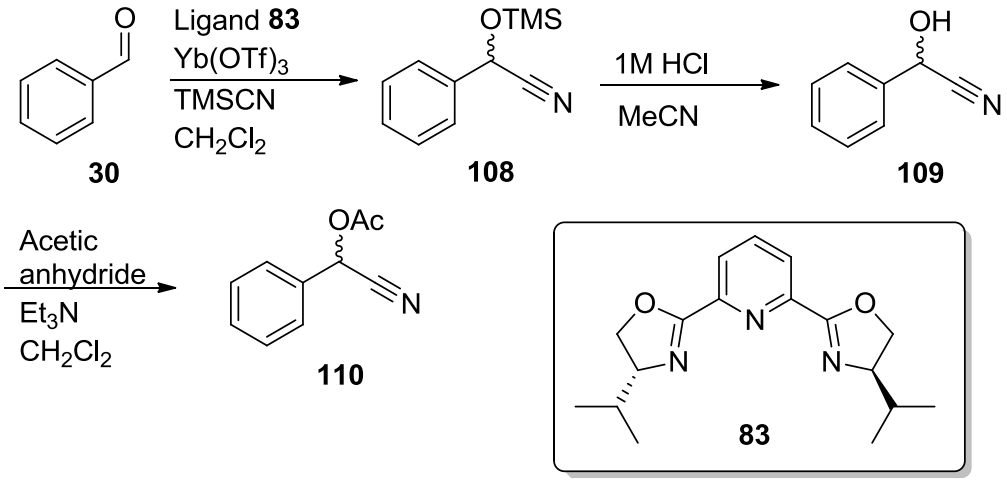
GENERAL PROCEDURE I (heterogeneous catalysis, 2nd and 3rd use)

The silica gel catalyst under CH_2Cl_2 (~1mL) and N_2 in a wide bottomed Schlenk/round bottomed flask recovered from a previous run was stirred under N_2 and was brought to the appropriate reaction temperature. To this stirring catalyst was added benzaldehyde (1 equiv.) and trimethylsilyl cyanide (1.1 equiv.). This reaction mixture was then stirred at the appropriate reaction temperature and

time. At that point, stirring was stopped and the reaction mixture was allowed warm to room temperature, where necessary. The silica gel catalyst settled and the supernatant liquid was filtered through a celite plug into a round bottomed flask. The catalyst was washed twice with CH_2Cl_2 (5 mL), and the CH_2Cl_2 washings filtered through the same celite plug into the round bottomed flask. The silica gel catalyst was then stored under CH_2Cl_2 (~1mL) and N_2, if required for subsequent use. The combined solution was then concentrated *in vacuo* to yield the appropriate crude product. A ^{1}H NMR spectrum was recorded to determine the percentage conversion using starting material, benzaldehyde, **30**, signal at 10.02 ppm (1H) due to CO*H* and product, **108**, signal at 5.49 ppm (1H) due to *H*CO. The crude product was then dissolved in MeCN (2 mL) and 1M HCl (5 mL) was added. The reaction was stirred at room temperature overnight. The crude product was extracted using ether (3 x 5 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using the conditions reported below and then dissolved in CH_2Cl_2 (2 mL) and acetic anhydride (1 mL) was added and the reaction was allowed to stir overnight. The product was then extracted using EtOAc (3 x 5 mL), dried over $MgSO_4$, filtered and reduced *in vacuo*. The enantiomeric excess (*ee*) of the purified product was measured using chiral GC (CYCLODEX-β 0.25 mmΦ x 30 m column), according to the conditions reported below.

Cyano(phenyl)methyl acetate, 110

Specific example (homogeneous catalysis)

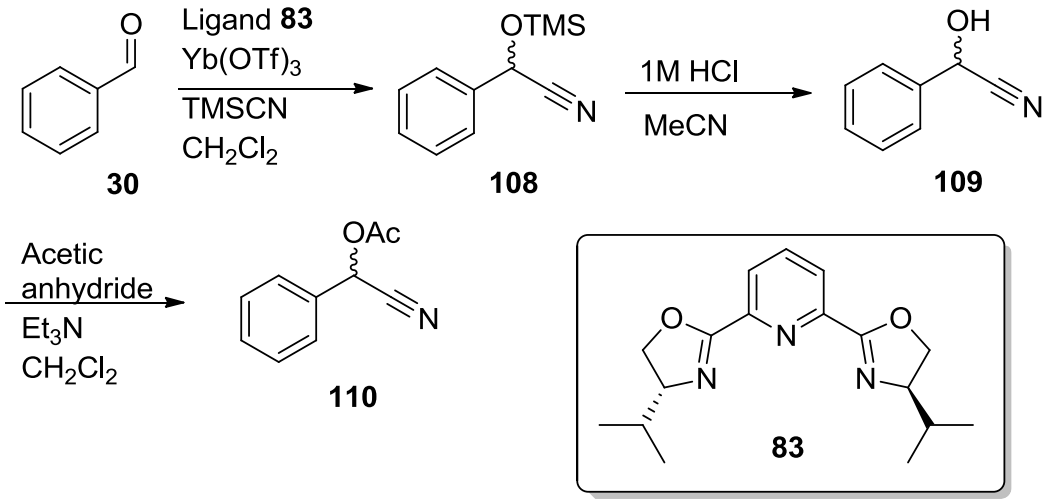


Scheme 3.44

The reaction was carried out according to general procedure G using ytterbium(III)triflate (0.05 mmol, 33.54 mg), ligand **83** (0.108 mmol, 32.6 mg), benzaldehyde, **30**, (0.54 mmol, 0.055 mL) and TMSCN (0.65 mmol, 0.08 mL) as seen in **Scheme 3.44**. The reaction mixture was stirred for 20 hours at room temperature. The reaction resulted in 90 % conversion to **108**. Hydrolysis of **108** was carried out producing **109**. The crude product was then purified by column chromatography (Pet ether:Chloroform, 5:1) affording the product **109** (84 % yield) as a clear oil which had a 8 % *ee* (measured after **110** had been generated by acetylation of **109**). The enantiomeric excess was measured using chiral GC (CYCLODEX-β 0.25 mmΦ x 30 m column, conditions 125 °C, hold 3 min, ramp 3 °C/min to 180 °C, hold 3 min), *t*(*R*) 13.5, *t*(*S*) 13.7. Spectral characterisation for **109** detailed below was consistent with data reported[10].

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.12 – 8.10 (2H, m, 2 x C***H***$_{aryl}$), 7.63 – 7.59 (1H, m, C***H***$_{aryl}$), 7.54 – 7.44 (2H, m, 2 x C***H***$_{aryl}$), 5.56 (1H, s, C***H***OH), 3.85 (1H, br s, O***H***). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.05 (C, ***C***$_{aryl}$), 129.63 (CH, 2 x ***C***H$_{aryl}$), 129.11 (CH, 2 x ***C***H$_{aryl}$), 126.65 (CH, ***C***H$_{aryl}$), 119.09 (C, ***C***N), 63.20 (CH, ***C***HOH).

Specific Example (Heterogeneous catalysis first use)



Scheme 3.45

The reaction was carried out according to general procedure H using ytterbium(III)triflate (0.05 mmol, 33.54 mg), ligand **83** (0.108 mmol, 32.6 mg), benzaldehyde, **30**, (0.54 mmol, 0.055 mL) and TMSCN (0.65 mmol, 0.08 mL) as seen in **Scheme 3.45**. The reaction mixture was stirred for 20 hours at room temperature. The reaction resulted in 16 % conversion to **108**. Hydrolysis of **108** was carried out producing **109**. The crude product was then purified by column chromatography (Pet ether:Chloroform, 5:1) affording the product **109** as a colourless oil (6 % yield) which had a 6 % *ee* (measured after **110** had been generated by acetylation of **109**). The enantiomeric excess was measured using chiral GC (CYCLODEX-β 0.25 mmΦ x 30 m column, conditions 125 °C, hold 3 min, ramp 3 °C/min to 180 °C, hold 3 min), *t*(*R*) 13.5, *t*(*S*) 13.7. Spectral characterisation was consistent with that reported above for **109**[10].

Specific Example (Heterogeneous catalysis second use)

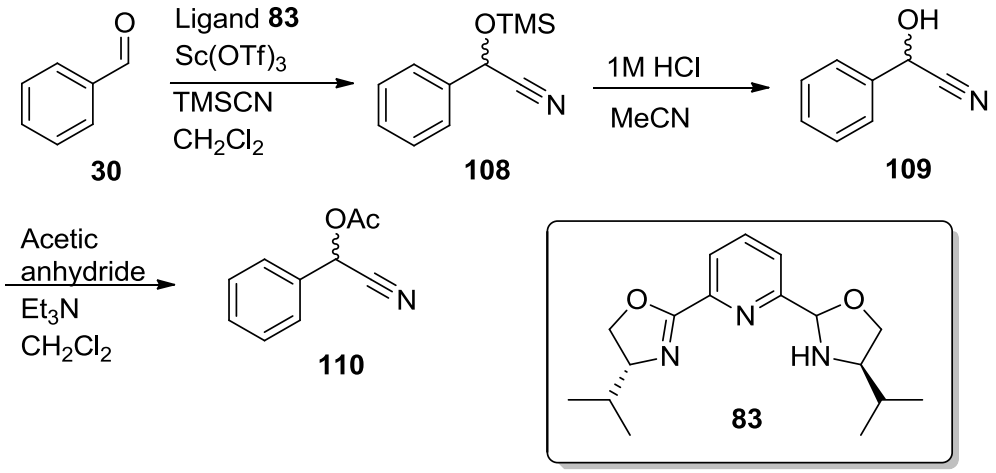
The reaction was carried out according to general procedure I using ytterbium(III)triflate (0.05 mmol, 33.54 mg), ligand **83** (0.108 mmol, 32.6 mg), benzaldehyde, **30**, (0.54 mmol, 0.055 mL) and TMSCN (0.65 mmol, 0.08 mL) as seen

in **Scheme 3.45**. The reaction was stirred for 20 hours at room temperature. Analysis of the crude product showed that **108** was not formed.

Specific Example (Heterogeneous catalysis third use)

The reaction was carried out according to general procedure I using ytterbium(III)triflate (0.05 mmol, 33.54 mg), ligand **83** (0.108 mmol, 32.6 mg), benzaldehyde, **30**, (0.54 mmol, 0.055 mL) and TMSCN (0.65 mmol, 0.08 mL) as seen in **Scheme 3.45**. The reaction was stirred for 20 hours at room temperature. Analysis of the crude product showed that **108** was not formed.

Specific example – Scandium(III)triflate



Scheme 3.46

All reactions were carried out using $Sc(OTf)_3$ (0.05 mmol, 24.61 mg), ligand **83** (0.05 mmol, 15.07 mg), benzaldehyde, **30**, (0.5 mmol, 0.055 mL) and TMSCN (0.65 mmol, 0.08 mL) as seen in **Scheme 3.46**. The homogeneous reaction was carried out according to general procedure G. The first heterogeneous reaction was carried out according to general procedure H, and the second and third heterogeneous reactions were carried out according to general procedure I. The

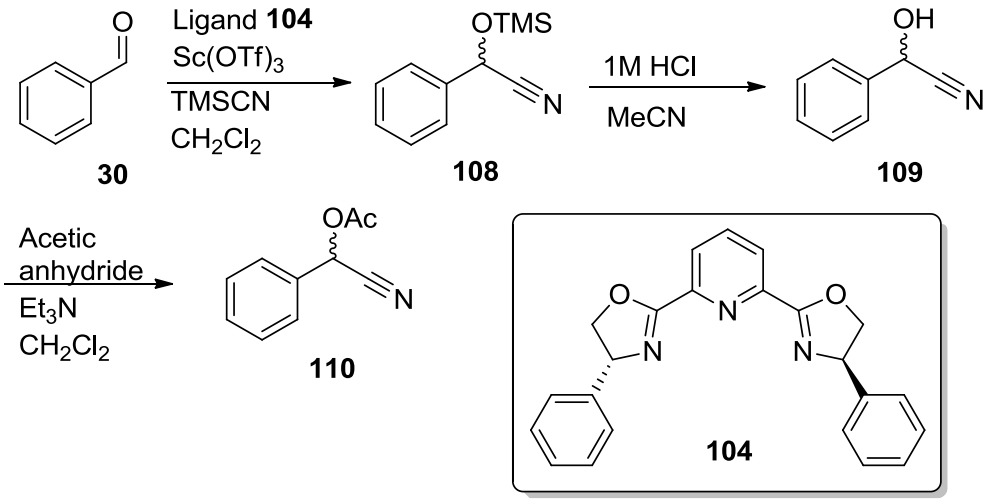
reactions were stirred for 18 hours at temperature reported in **Table 3.2**. ^{1}H NMR spectra of the products were consistent with the full product characterisation results reported above (see **Table 3.2** for results).

Catalyst	Temperature (°C)	% conversion to 108	Yield* (%)	% *ee***
Homogeneous	rt	100	76	14
Homogeneous	0 to 10	64	51	12
Heterogeneous 1	rt	82	46	20
Heterogeneous 2	rt	77	40	12
Heterogeneous 3	rt	73	12	12

Table 3.2

*measured after **109** had been generated **measured after **110** had been generated

Specific example – PhPyBOX , 104



Scheme 3.47

All reactions were carried out using $Sc(OTf)_3$ (0.05 mmol, 24.61 mg), ligand **104** (0.05 mmol, 18.47 mg), benzaldehyde, **30**, (0.5 mmol, 0.055 mL) and TMSCN (0.65 mmol, 0.08 mL) as seen in **Scheme 3.47**. The homogeneous reaction was carried out according to general procedure G. The first heterogeneous reaction was

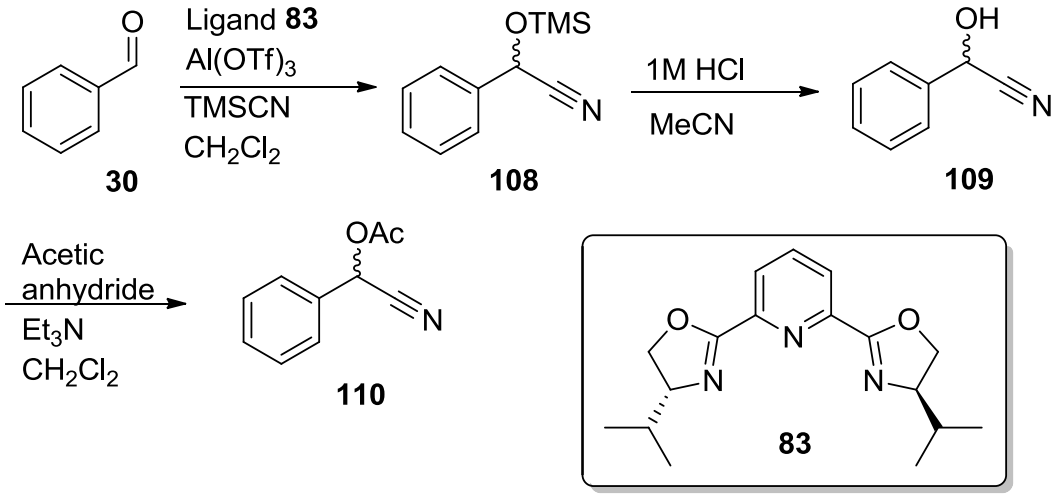
carried out according to general procedure H and the second and third heterogeneous reactions were carried out according to general procedure I. The reactions were stirred for 20 hours at room temperature. ^{1}H NMR spectra of the products were consistent with the full product characterisation results reported above (see **Table 3.3** for results).

Catalyst	**% conversion to 109**	**Yield*** **(%)**	**% *ee*** **
Homogeneous	100	31	18
Heterogeneous 1	100	29	16
Heterogeneous 2	100	17	14
Heterogeneous 3	75	5	14

Table 3.3

* measured after **109** had been generated ** measured after **110** had been generated

Specific example - Aluminium(III)triflate



Scheme 3.48

All reactions were carried out using $Al(OTf)_3$ (0.05 mmol, 24.61 mg), ligand **83** (0.05 mmol, 18.47 mg), benzaldehyde, **30**, (0.5 mmol, 0.055 mL) and TMSCN

(0.65 mmol, 0.08 mL) as seen in **Scheme 3.48**. The homogeneous reaction was carried out according to general procedure G. The first heterogeneous reaction was carried out according to general procedure H. The reactions were stirred for 24 hours at room temperature. ^{1}H NMR spectra of the products were consistent with the full product characterisation results reported above (see **Table 3.4** for results).

Catalyst	**% conversion to 108**	**Yield*** **(%)**	**% *ee*** **
Homogeneous	54	25	6
Heterogeneous 1	N/A	N/A	No product

Table 3.4

* measured after **109** had been generated ** measured after **110** had been generated

3.3.5 Asymmetric Ring Opening[11]

GENERAL PROCEDURE J (homogeneous catalysis)

Metal triflate (10 mol%) was weighed into a flame-dried, N_2 filled, Schlenk. PyBOX ligand (12 mol%) was weighed into a second flame-dried, N_2 filled, Schlenk and dissolved in THF (6 mL). The ligand solution was then transferred under N_2, into the Schlenk containing the metal triflate. The resulting mixture was then stirred for 1 hour at room temperature. The catalyst mixture was then filtered through a cotton plug, to remove any undissolved metal triflate, into a third flame-dried N_2 filled Schlenk. The solvent was then removed under reduced pressure. To this Schlenk containing the reaction catalyst under N_2, was added CH_2Cl_2 (1 mL) and the mixture was then brought to the appropriate reaction temperature. To this stirring catalyst was added the trimethylsilyl cyanide (1.2 equiv.) and cyclohexene oxide (1 equiv.). This reaction mixture was then stirred at the appropriate reaction temperature for the appropriate time. At that point, the reaction mixture was allowed warm to room temperature, where necessary, diluted with CH_2Cl_2 (20 mL) and then filtered through a silica gel plug (40-63 µm) into a round bottomed flask. The reaction

Schlenk was then rinsed with CH_2Cl_2 (10 mL) and the CH_2Cl_2 rinse filtered through the same silica gel plug into the round bottomed flask. This silica gel (40-63 μm) plug was then washed with CH_2Cl_2 (10 mL) and the wash added to the round bottomed flask. The combined solution was then concentrated *in vacuo* to yield the appropriate crude product. A ^1H NMR spectrum was recorded to determine the percentage conversion using starting material, cyclohexene oxide, **111**, signal at 3.12 ppm (2H) due to OC*H* and product, **112**, signal at 3.69 – 3.64 ppm (1H) due to C*H*. The crude product was then purified by column chromatography using the conditions reported below. The enantiomeric excess (*ee*) of the purified product was measured using chiral GC (CYCLODEX-β 0.25 mmΦ x 30 m column), according to the conditions reported below.

GENERAL PROCEDURE K (heterogeneous catalysis 1st use)

Metal triflate (10 mol%) was weighed into a flame-dried, N_2 filled, Schlenk. PyBOX ligand (12 mol%) was weighed into a second flame-dried, N_2 filled, Schlenk and dissolved in THF (6 mL). The ligand solution was then transferred under N_2, into the Schlenk containing the metal triflate. The resulting mixture was then stirred for 1 hour. The catalyst mixture was filtered through a cotton plug, to remove any undissolved metal triflate, and the solvent was then removed under reduced pressure. CH_2Cl_2 (1 mL) was added to the catalyst and it was transferred into a Schlenk containing of pre-dried silica gel (300 mg, 40-63 μm, heated under vacuum at 70 °C for 2 hours) in a N_2 filled, wide bottomed Schlenk/round bottomed flask. The solution was stirred for 1 minute, then after stirring was stopped the silica gel became coloured (where a copper salt was used, and colourless otherwise) and settled to the bottom of the wide bottomed Schlenk/round bottomed flask. The clear supernatant liquid on top of the silica gel was removed under N_2 *via* Pasteur pipette. The silica gel catalyst was washed twice with CH_2Cl_2 (5 mL) and the clear supernatant liquid on top of the silica gel was removed. The silica gel catalyst was left under CH_2Cl_2 (~1 mL). This wide bottomed Schlenk/round bottomed flask containing the stirring catalyst, under N_2, was brought to the appropriate reaction

temperature. To this stirring catalyst was added trimethylsilyl cyanide (1.2 equiv.) and cyclohexene oxide (1 equiv.). This reaction mixture was stirred at the appropriate reaction temperature and time. At that point, stirring was stopped and the reaction mixture was allowed warm to room temperature, where necessary, and diluted with CH_2Cl_2 (20 mL). The silica gel catalyst settled and the supernatant liquid was filtered through a celite plug into a round bottomed flask. The catalyst was washed twice with CH_2Cl_2 (10 mL), and the CH_2Cl_2 washings filtered through the same celite plug into the round bottomed flask. The silica gel catalyst was then stored under CH_2Cl_2 (~1 mL) and N_2 for subsequent use. The combined solution was then concentrated *in vacuo* to yield the appropriate crude product. A ^{1}H NMR spectrum was recorded to determine the percentage conversion using starting material, cyclohexene oxide, **111**, signal at 3.12 ppm (2H) due to OC*H* and product, **112**, signal at 3.69 – 3.64 ppm (1H) due to C*H*. The crude product was then purified by column chromatography using the conditions reported below. The enantiomeric excess (*ee*) of the purified product was measured using chiral GC (CYCLODEX-β 0.25 mmΦ x 30 m column), according to the conditions reported below.

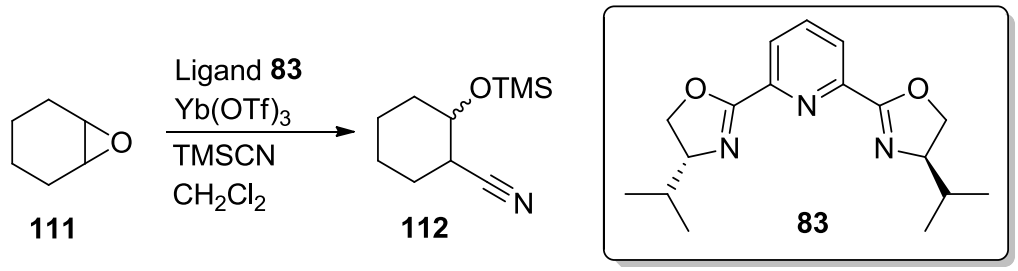
GENERAL PROCEDURE L (heterogeneous catalysis, 2nd and 3rd use)

The silica gel catalyst under CH_2Cl_2 (~1 mL) and N_2 in a wide bottomed Schlenk/round bottomed flask recovered from a previous run was stirred under N_2 and brought to the appropriate reaction temperature. To this stirring catalyst was added trimethylsilyl cyanide (1.2 equiv.) and cyclohexene oxide (1 equiv.). This reaction mixture was then stirred at the appropriate reaction temperature and time. At that point, stirring was stopped and the reaction mixture was allowed warm to room temperature, where necessary, and diluted with CH_2Cl_2 (20 mL). The silica gel catalyst settled and the supernatant liquid was filtered through a celite plug into a round bottomed flask. The catalyst was washed twice with CH_2Cl_2 (10 mL), and the CH_2Cl_2 washings filtered through the same celite plug into the round bottomed flask. The silica gel catalyst was then stored under CH_2Cl_2 (~1mL) and N_2 if required for subsequent use. The combined solution was then

concentrated *in vacuo* to yield the appropriate crude product. A ^{1}H NMR spectrum was recorded to determine the percentage conversion using starting material, cyclohexene oxide, **111**, signal at 3.12 ppm (2H) due to OC*H* and product, **112**, signal at 3.69 – 3.64 ppm (1H) due to C*H*. The crude product was then purified by column chromatography using the conditions reported below. The enantiomeric excess (*ee*) of the purified product was measured using chiral GC (CYCLODEX-β 0.25 mmΦ x 30 m column), according to the conditions reported below.

2-Trimethylsilyloxy-cyclohexane-1-carbonitrile, 112

Specific example (homogeneous catalysis)

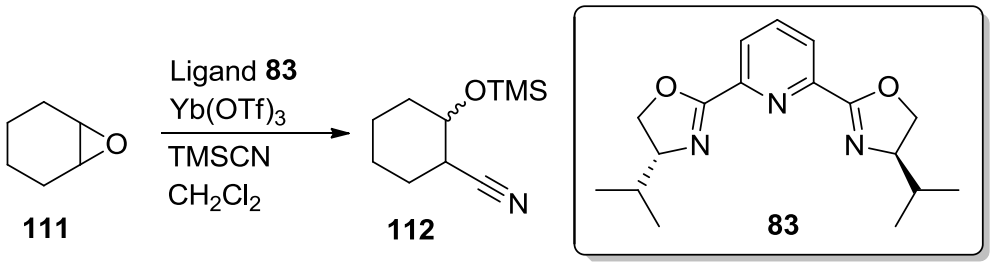


Scheme 3.49

The reaction was carried out according to general procedure J using ytterbium(III)triflate (0.1 mmol, 62 mg), ligand **83** (0.12 mmol, 45 mg), TMSCN (1.2 mmol, 160 µL) and cyclohexene oxide, **111**, (1 mmol, 100 µL) as seen in **Scheme 3.49**. The reaction mixture was stirred for 4 days at -20 °C. The reaction resulted in 40 % conversion to **112**. The crude product was purified by column chromatography (Pet ether:EtOAc, 95:5) affording **112** in a yield of 22 % and 20 % *ee*. The enantiomeric excess was measured using chiral GC (CYCLODEX-β 0.25 mmΦ x 30 m column, conditions 110 °C, hold 20 min, ramp 0.5 °C/min to 150 °C, hold 1 min, ramp 10 °C/min to 170 °C, hold 1 min), t = 30.9 min and 32.2 min. Spectral characterisation for **112**, reported below was consistent with that reported[11].

^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 3.69 – 3.64 (1H, m, C***H***), 2.43 - 2.37 (1H, m, C***H***), 2.11 - 2.07 (1H, m, C$\boldsymbol{H_{cyclo}}$), 1.92 - 1.89 (1H, m, C$\boldsymbol{H_{cyclo}}$), 1.73 - 1.52 (3H, m, C$\boldsymbol{H_{cyclo}}$), 1.32 - 1.18 (3H, m, C$\boldsymbol{H_{cyclo}}$), 0.16 (9H, s, 3 x C$\boldsymbol{H}_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 121.72 (C, ***C***N), 71.25 (CH, H***C***CN), 37.82 (CH, H***C***O), 34.80 (CH_2, ***C***H_2), 28.29 (CH_2, ***C***H_2), 24.06 (CH_2, ***C***H_2), 23.42 (CH_2, ***C***H_2), 0.29 (CH_3 3 x Si***C***H_3).

Specific Example (Heterogeneous catalysis first use)



Scheme 3.50

The reaction was carried out according to general procedure K using ytterbium(III)triflate (0.1 mmol, 62 mg), ligand **83** (0.12 mmol, 45 mg), TMSCN (1.2 mmol, 160 µL) and cyclohexene oxide, **111**, (1 mmol, 100 µL) as seen in **Scheme 3.50**. The reaction mixture was stirred for 21 hours at -20 °C. The reaction product **112** was isolated as a colourless oil. The reaction resulted in 62 % conversion to **112.** The crude product was purified by column chromatography (Pet ether:EtOAc, 95:5) affording **112** in a yield of 13 % and 16 % *ee*. The enantiomeric excess was measured using chiral GC (CYCLODEX-β 0.25 mmΦ x 30 m column conditions 110 °C, hold 20 min, ramp 0.5 °C/min to 150 °C, hold 1 min, ramp 10 °C/min to 170 °C, hold 1 min), t = 30.9 min and 32.2 min. Spectral characterisation was consistent with that reported above for **112.**

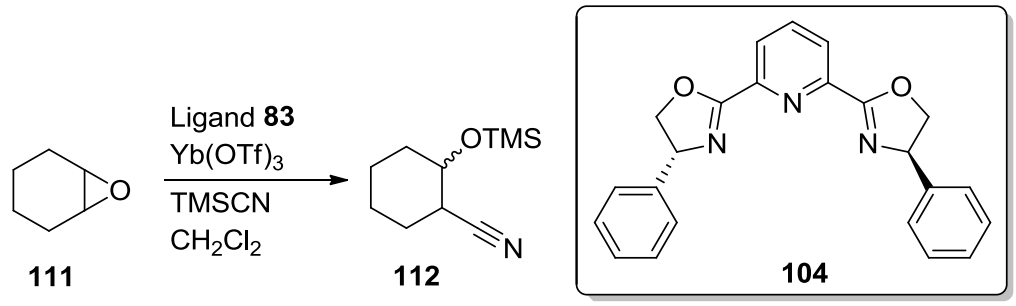
Specific Example (Heterogeneous catalysis second use)

The reaction was carried out according to general procedure L using ytterbium(III)triflate (0.1 mmol, 62 mg), ligand **83** (0.12 mmol, 45 mg), TMSCN (1.2 mmol, 160 µL) and cyclohexene oxide, **111**, (1 mmol, 100 µL) as seen in **Scheme 3.50**. The reaction mixture was stirred for 21 hours at -20 °C. The reaction product **112** was isolated as a colourless oil. The reaction resulted in 58 % conversion to **112**. The crude product was purified by column chromatography (Pet ether:EtOAc, 95:5) affording **112** in a yield of 5 % and 16 % *ee*. The enantiomeric excess was measured using chiral GC (CYCLODEX-β 0.25 mmΦ x 30 m column conditions 110 °C, hold 20 min, ramp 0.5 °C/min to 150 °C, hold 1 min, ramp 10 °C/min to 170 °C, hold 1 min), t = 30.9 min and 32.2 min. Spectral characterisation was consistent with that reported above for **112.**

Specific Example (Heterogeneous catalysis third use)

The reaction was carried out according to general procedure L using ytterbium(III)triflate (0.1 mmol, 62 mg), ligand **83** (0.12 mmol, 45 mg), TMSCN (1.2 mmol, 160 µL) and cyclohexene oxide, **111**, (1 mmol, 100 µL) as seen in **Scheme 3.50**. The reaction mixture was stirred for 21 hours at -20 °C. The reaction product **112** was isolated as a colourless oil. The reaction resulted in 41 % conversion to **112.** The crude product was purified by column chromatography (Pet ether:EtOAc, 95:5) affording **112** in a yield of 2 % and 12 % *ee*. The enantiomeric excess was measured using chiral GC (CYCLODEX-β 0.25 mmΦ x 30 m column conditions 110 °C, hold 20 min, ramp 0.5 °C/min to 150 °C, hold 1 min, ramp 10 °C/min to 170 °C, hold 1 min), t = 30.9 min and 32.2 min. Spectral characterisation was consistent with that reported above for **112.**

Specific Example – PhPyBOX, 104



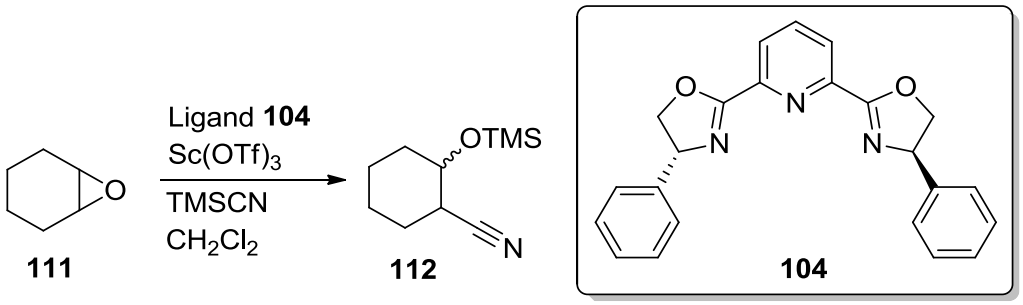
Scheme 3.51

All reactions were carried out using $Yb(OTf)_3$ (0.05 mmol, 31 mg), ligand **104** (0.05 mmol, 15.07 mg), TMSCN (0.6 mmol, 80 µL) and cyclohexene oxide, **111**, (0.5 mmol, 50 µL) as seen in **Scheme 3.51**. The homogeneous reaction was carried out according to general procedure J. The first heterogeneous reaction was carried out according to general procedure K and the second and third heterogeneous reactions were carried out according to general procedure L. The reactions were stirred for 21 hours at -20 °C. ^{1}H NMR spectra of the products were consistent with the full product characterisation results reported above (see **Table 3.5** for results).

Catalyst	**% conversion to 112**	**Yield (%)**	**% *ee***
Homogeneous	100	17	24
Heterogeneous 1	47	18	20
Heterogeneous 2	21	2	20
Heterogeneous 3	52	30	14

Table 3.5

Specific Example – Scandium(III)triflate



Scheme 3.52

All reactions were carried out using $Sc(OTf)_3$ (0.05 mmol, 25 mg), ligand **104** (0.05 mmol, 18.47 mg), TMSCN (0.6 mmol, 80 µL) and cyclohexene oxide, **111**, (0.5 mmol, 50 µL) as seen in **Scheme 3.52**. The homogeneous reaction was carried out according to general procedure J. The first heterogeneous reaction was carried out according to general procedure K and the second heterogeneous reaction was carried out according to general procedure L. The reactions were stirred for 24 hours at -20 °C. ^{1}H NMR spectra of the products were consistent with the full product characterisation results reported above (see **Table 3.6** for results).

Catalyst	**% conversion to 112**	**Yield (%)**	**% *ee***
Homogeneous	100	11	2
Heterogeneous 1	100	43	0
Heterogeneous 2	62	16	0

Table 3.6

References

[1] R. Gauler, N. Risch, *European Journal of Organic Chemistry* 1998, *1998*, 1193-1200.

[2] S.-s. Jew, B.-s. Park, D.-y. Lim, M. G. Kim, I. K. Chung, J. H. Kim, C. I. Hong, J.-K. Kim, H.-J. Park, J.-H. Lee, H.-g. Park, *Bioorganic & Medicinal Chemistry Letters* 2003, *13*, 609-612.

[3] V. Derdau, V. Snieckus, *The Journal of Organic Chemistry* 2001, *66*, 1992-1998.

[4] T. D. Owens, A. J. Souers, J. A. Ellman, *The Journal of Organic Chemistry* 2002, *68*, 3-10.

[5] G. Liu, D. A. Cogan, T. D. Owens, T. P. Tang, J. A. Ellman, *The Journal of Organic Chemistry* 1999, *64*, 1278-1284.

[6] N. Debono, C. Pinel, R. Jahjah, A. Alaaeddine, P. Delichère, F. Lefebvre, L. Djakovitch, *Journal of Molecular Catalysis A: Chemical* 2008, *287*, 142-150.

[7] J.-i. Ito, S. Ujiie, H. Nishiyama, *Organometallics* 2008, *28*, 630-638.

[8] I. Atodiresei, I. Schiffers, C. Bolm, *Tetrahedron: Asymmetry* 2006, *17*, 620-633.

[9] R. J. Detz, Z. Abiri, R. le Griel, H. Hiemstra, J. H. van Maarseveen, *Chemistry – A European Journal* 2011, *17*, 5921-5930.

[10] I. Iovel, Y. Popelis, M. Fleisher, E. Lukevics, *Tetrahedron: Asymmetry* 1997, *8*, 1279-1285.

[11] S. E. Schaus, E. N. Jacobsen, *Organic Letters* 2000, *2*, 1001-1004.