Synthesis and Application of Chiral AraBOX ligands for Asymmetric Catalysis

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To Mom and Dad

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Abbreviations

µL	Microlitre
Ac	Acetyl group (CH_3CO)
ACN	1,1'-Azobis(cyclohexane-carbonitrile)
AIBN	Azobisisobutyronitrile
aq.	Aqueous
Ar	Aromatic
9-BBN	9-Borabicyclo[3.3.1]nonane
BHT	Butylhydroxytoluene
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl group ($C_6H_5CH_2$)
BOC	*Tert*-Butoxycarbonyl group [$(CH_3)_3COCO$]
BOX	Bisoxazoline
bp	Boiling point
br s	Broad singlet or broad/strong
BSA	*N*,*O*-Bis(trimethyl silyl)acetamide
Bu	Butyl
°C	Degree Celsius
c	Concentration (g/mL)
calcd	Calculated
Cbz	Carboxybenzyl group ($C_6H_5CH_2OCO$)
cm	Centimetre
COSY	Correlated spectroscopy
CSA	Camphorsulfonic acid
d	Doublet
DARC	Deprotection activation ring closure
DAST	Diethylaminosulfur trifluoride
DBU	1,8-Diazobicyclo[5.4.0]undec-7-ene
DCM	Dicyclohexylmethyl
dd	Double doublet
de	Diastereomeric excess
deg	Degree
DEPT	Distortionless enhancement by polarization transfer

DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMM	Dimethyl malonate
DOPA	3,4 Dihydroxy-1-phenylalanine
dm	Decimetre
dr	Diastereomeric ratio
E	Entgegen (*trans*)
ee	Enantiomeric excess
equiv.	Equivalent
ESI	Electrospray impact
Et	Ethyl
FID	Flame ionisation detector
FT	Fourier Transform
g	Gram
GC	Gas Chromatography
h	Hour
HMQC	Heteronuclear shift multiple quantum coherence
HOMO	Highest occupied molecular orbital
HPLC	High Performance Liquid Chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
IPA	Isopropyl alcohol
*i*Pr	Isopropyl
IR	Infra-Red
J	Coupling constant in NMR
L	Litre
lit.	Literature
LUMO	Lowest unoccupied molecular orbital
m	Multiplet or metre
M	Molar or Metal
m/z	Mass to charge ratio
Me	Methyl group (CH_3)

mg	Milligram
MHz	Mega Hertz
min	Minute
mL	Millilitre
mm	Millimetre
mmol	Millimole
mol	Mole
mol%	Mole percent
Mp	Melting point
Ms	Mesylate group (CH_3SO_2)
n/a	Non-applicable
nd	Non-determinable
nm	Nanometre
NMR	Nuclear Magnetic Resonance
Nu^-	Nucleophile
p	Para
Ph	Phenyl group (C_6H_5)
ppm	Parts per million
PYBOX	Pyridine bisoxazoline
q	Quartet
R	Rectus
RAMP	(*R*)-1-amino-2-methoxymethylpyrrolidine
R_f	Retention factor
rt	Room temperature
Rt	Retention time
s	Singlet or strong
S	Sinister
SAMP	(*S*)-1-amino-2-methoxymethylpyrrolidine
sat.	Saturated
t	Triplet
TADDOL	α,α,α,α-tetraaryl-1,3-dioxolane-4,5-dimethanol
TBAF	Tetra-*N*-butylammonium fluoride
TBDMS	*Tert*-butyldimethylsilyl group [$(CH_3)_3C(CH_3)_2Si$]

*t*Bu	*Tert*-butyl
TEA	Triethylamine
Temp	Temperature
Tf	Triflate group (CF_3SO_2)
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
Ts	Tosylate group ($CH_3C_6H_4SO_2$)
TS	Transition state
UV	Ultraviolet
vis	Visible
Z	Zusammen (*cis*)

Abstract

This thesis deals with the design, synthesis and reactivity of novel 4,4'-bisoxazoline ligands and their metal complexes; (*S*,*S*)-MePrAraBOX, (*S*,*S*)-PhPrAraBOX, (*S*,*R*)-MePrAraBOX, (*S*,*R*)-PhPrAraBOX, (*S*,*R*)-BnOAcAraBOX and (*S*,*R*)-BnOHAraBOX. Metal complexes of these ligands have been applied to transition metal catalysed asymmetric reactions, in particular asymmetric Diels Alder, cyclopropanation and allylic alkylation reactions.

A copper(II) complex of (*S*,*R*)-PhPrAraBOX catalysed a benchmark Diels Alder reaction in up to 57% *ee*, the highest enantioselectivity yet achieved for a 4,4'-BOX ligand in a Diels Alder reaction. An *ee* of 70% was achieved with a copper(I) complex of (*S*,*S*)-MePrAraBOX in a benchmark asymmetric cyclopropanation reaction, which is also the highest enantioselectivity yet achieved for a 4,4'-BOX ligand in these reactions. The ligands were also applied to the asymmetric allylic alkylation reaction. They were the first 4,4'-BOX ligands to generate enantiocontrol in the reaction, with a palladium complex of (*S*,*S*)-MePrAraBOX producing an *ee* of 72%. The rationalisation of these results, in particular the results relating to the cyclopropanation reaction, are supported by computational studies carried out by colleagues in Zaragoza.

The 4,4'-bisoxazoline ligands (*S*,*R*)-BnOAcAraBOX and (*S*,*R*)-BnOHAraBOX, which contain secondary binding sites, were applied to the Diels Alder and asymmetric allylic alkylation reactions with low activity and selectivity. Ligand (*S*,*R*)-BnOHAraBOX was also applied to an asymmetric alkylation of benzaldehyde, showing low conversion and no selectivity.

Chapter One deals with the introduction of the general concepts of asymmetric synthesis and asymmetric catalysis. **Chapter Two** discusses the synthesis of the 4,4'-bisoxazoline ligands and the application of the metal complexes of these ligands to the asymmetric reactions. **Chapter Three** contains the full experimental details for the project, including spectral and analytical data.

Chapter 1
Introduction

1.1 Asymmetric synthesis

A chiral compound is defined as a compound that that lacks an internal plane of symmetry, causing it to be non-superimposable on its mirror image **(Figure 1.1)**. The two mirror image stereoisomers are termed enantiomers and differ only in their three dimensional arrangement in space, with their physical and chemical properties being identical. However, in a chiral environment enantiomers may interact differently from one another. The absolute configuration of a stereocentre is determined using the Cahn Ingold Prelog system and labelled as (*R*) or (*S*).[1] A 1:1 mixture of enantiomers is called a racemate.

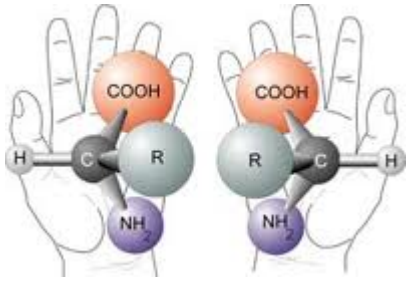


Figure 1.1

The importance of enantiopure drugs has led to significant research on the development of asymmetric methodologies. Legislation in both Europe and the US has driven this work. Over two decades ago, the U.S. Food & Drug Administration introduced guidelines on stereoisomeric drugs in an effort to encourage the synthesis of enantiomerically pure drugs.[2] Racemates could still be sold, but the individual enantiomers needed to be characterized pharmacologically and toxicologically. Since the cost of characterization can be very high and one of the enantiomers may be physiologically unsafe or merely inactive, industry has generally shifted away from racemates to making single enantiomer forms of chiral compounds, with more than half of the drugs approved worldwide sold in their chiral form. Six of the top ten drugs in 2006 were sold as single enantiomers, while two were achiral and two were racemates.[3]

Nowadays, it is known that many biological processes occur with a high degree of chiral recognition. As such, it is rare that both enantiomers show the same level of biological or therapeutic activity. Biological processes can be highly sensitive systems. Due to the importance of chirality in biological chemistry it is essential to establish the absolute configuration of these active forms. For example, Japonilure (the female-produced sex pheromone of a Japanese beetle) with a purity of 99% *ee*

was found to be only 2/3 as active as the pure bioactive pheromone.[4] In contrast, neither enantiomer of Sulcatol (the male produced aggregation pheromone of the ambrosia beetle) is bioactive. However, when combined into a racemic mixture the synthetically derived product was more active than the natural pheromone (which was a 35:65 mixture for the *R* and *S* forms). The various physiological effects of some common drugs are shown below **(Table 1.1)**.

Drug	Enantiomeric Form	Physiological Effects
Naproxen	(*R*)	Causes liver damage
	(*S*)	Analgesic effect
Dopa	(*R*)	Toxic
	(*S*)	Anti Parkinson
Thalidomide	(*R*)	Sedative
	(*S*)	Teratogen
Ibuprofen	(*R*)	Inactive
	(*S*)	Analgesic

Table 1.1

In an effort to move away from classical synthesis and the separation of racemic mixtures to obtain single enantiomers, great efforts have been made in the development of enantioselective synthesis, with numerous approaches now available to induce stereoselectivity in asymmetric reactions. However, in industry, due to the time constraints for the pharmacological testing of new drugs, manufacturers still regularly use resolution during the early development stages of new products, as it can be less expensive and time consuming than asymmetric synthesis.

1.1.1 Chiral pool synthesis

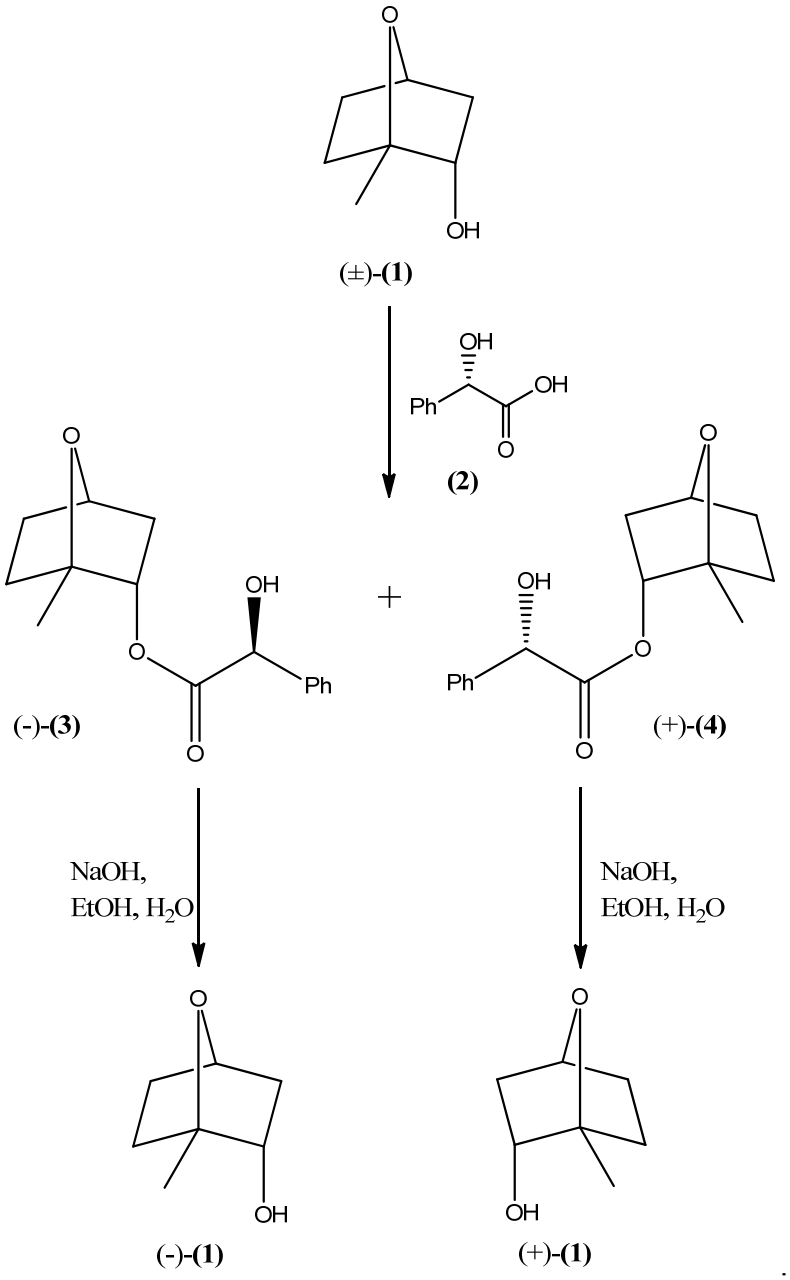
The chiral pool is a source of enantiomerically pure natural or synthetic products which are readily available to use as precursors in the synthesis of a desired chiral product. Derivatisation of these natural products can provide the desired molecule with the basic chiral structure in place. Any new chiral centre added on will do so diastereoselectively, under the control of the original stereocentre(s). There are numerous sources of these natural products available including terpenes, amino acids, sugars and alkaloids. They are usually inexpensive materials, but are commonly only available in one enantiomeric form. For example, naturally

occurring amino acids generally possess the L-configuration, while sugars are usually naturally sourced in the D-configuration. This can lead to problems in synthesising the other form of the desired product if necessary.

1.1.2 Resolution

One of the classical methods for preparing enantiomers involves synthesising the compound as its racemate and then separating it using resolution. Most resolution approaches are based on the concept of isolating the racemate and temporarily converting the two enantiomers into diastereomeric salts. The diastereomers are generated by reacting the racemate with an enantiomerically pure resolving agent such as tartaric acid, mandelic acid, α-methylbenzylamine, SAMP, menthol, etc., which can bind covalently to form neutral covalent diastereomers or form diastereomeric salts through ionic interactions with the two enantiomers. The diastereomers now possess different chemical properties and can be separated using recrystallisation, chromatography or some other separation technique. Once the compound has been separated, the resolving agent can be removed affording the desired enantiomer in its pure form.

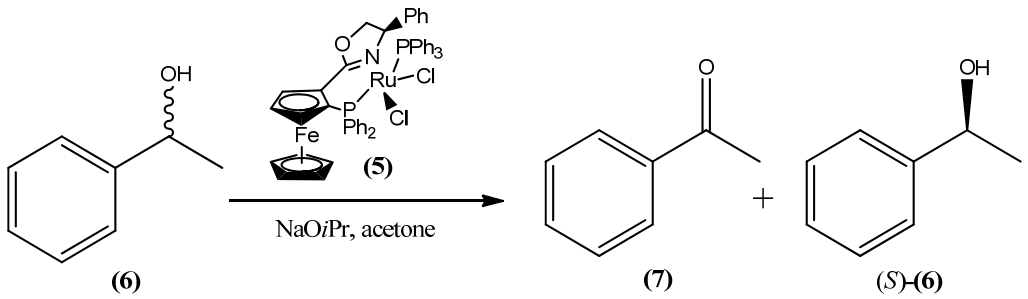
Li and Guan used mandelic acid as a resolving agent to separate the reduced alcohol of (±)-1-methyl-7-oxabicyclo[2.2.1]heptan-2-one (±)-**(1)**, which is a versatile precursor for the synthesis of terpenoids.[5] Alcohol **(1)** was reacted with (S)-(+)-mandelic acid **(2)** forming a diastereomeric mixture of esters **(3)** and **(4)** which were separated by flash chromatography. Saponification of the esters by NaOH yielded the optically pure alcohols (-)-**(1)** and (+)-**(1)** **(Scheme 1.1)**. Oxidation using Dess–Martin periodinane yielded the desired chiral building blocks.



Scheme 1.1

Other methods of isolating enantiomers from racemates include kinetic decomposition and kinetic resolution. Kinetic decomposition involves the breaking down of one of the enantiomers while the other remains essentially unaffected, due to a slower rate of decomposition. These reactions are generally carried out using enzymes to differentiate between the two enantiomers. In kinetic resolution the racemate is reacted with a chiral reagent which reacts with the two enantiomers at different rates. Unlike the decomposition technique, both enantiomers are available, as the reacted product can be easily reconverted to its original state. In order to

maximise yields the undesired enantiomer can undergo racemisation, followed by further resolution in order to isolate more of the desired product. Uemura *et al* have developed a ruthenium-ferrocenyloxazoline complex **(5)** which has resolved a wide range of secondary alcohols to high enantiopurity, using acetone as the hydrogen acceptor **(Scheme 1.2)**.[6]



Scheme 1.2

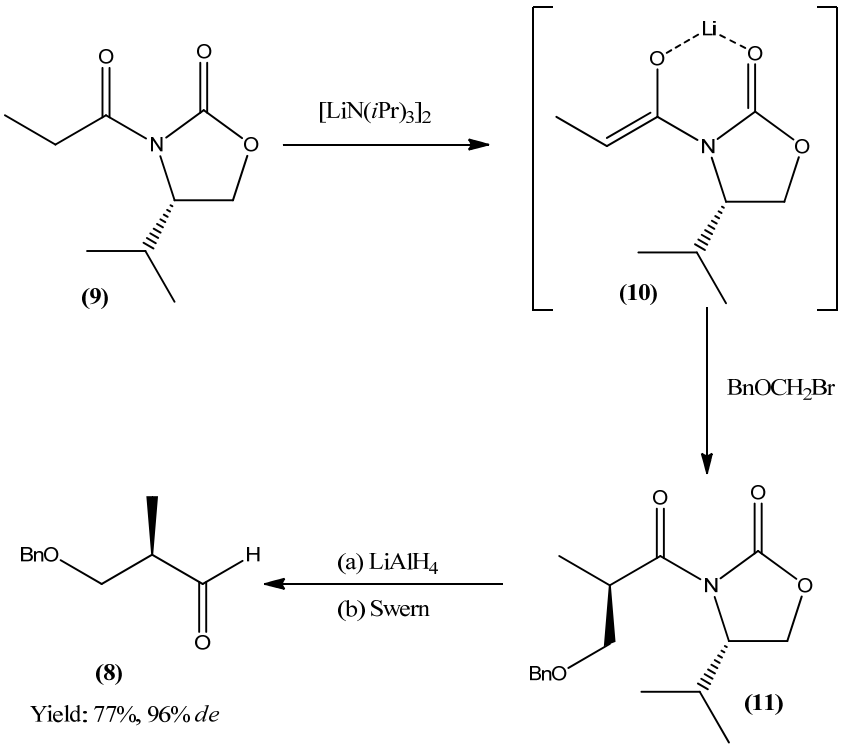
1.2 Chiral auxiliaries

Chiral auxiliaries are optically active compounds that are introduced temporarily into molecules to induce asymmetric control of new stereocentres formed in subsequent reactions. The best chiral auxiliaries should be able to undergo facile addition to the substrate, have a strong bias for high stereoselectivity, in subsequent reactions on the non-auxiliary part of the molecule, and allow for mild cleavage without racemisation of the desired product. If possible it should also be recyclable, to ensure maximum cost efficiency.

Many papers in this area have outlined the importance of chelation and rigidity when designing new more efficient chiral auxiliaries.[7,8] Numerous chiral auxiliaries are now available which fulfil the conditions outlined earlier. Among these the most popular include Evans' oxazolidinone and Enders' RAMP/SAMP hydrazones, with both acting as chelating agents.[8-11]

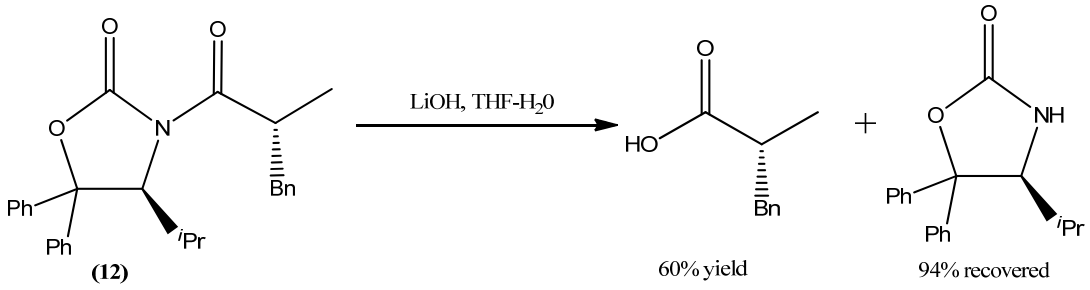
Chiral oxazolidinones and their derivatives have been employed as an auxiliary control in various reactions including asymmetric alkylations, aldol and Diels-Alder reactions.[9,12,13] Many structural variations of Evans' original oxazolidinone have been made. The variations cause the resulting molecules to display complimentary diastereoselective control depending on the asymmetric reaction taking place and the conditions.[8,13-15]

One example of the control given by chiral oxazolidinones was shown in the asymmetric synthesis of the calcium ionophore Ionomycin.[9] As part of the synthesis of the C_{17}-C_{22} subunit, Evans *et al* developed a practical asymmetric alkylation to prepare the "Roche aldehyde" **(8)**, which was seen as an important precursor. Treatment of the oxazolidinone **(9)** with the lithium base afforded the lithium enolate **(10)**. The *Z*-isomer is favoured due to co-ordination of the lithium cation forming a rigid structure, similar in nature to Meyers' oxazoline. Alkylation of **(10)** with bromomethyl benzyl ether occurred with good diastereoselectivity (96% *de*), due to steric hindrance on one face from the *iso*-propyl group, giving the desired product **(11)** in 77% yield. Reductive cleavage of the oxazolidinone followed by Swern oxidation provided the "Roche aldehyde" **(8)** which was used without further purification **(Scheme 1.3)**.



Scheme 1.3

The chiral oxazolidinone group can undergo non-destructive removal by employing various protocols.[16] An example of this was shown by Kennedy *et al* under mild conditions. Alkaline hydrolysis of the benzylated adduct **(12)** in aqueous THF gave the desired alkylated acid **(13)** in 60% yield and allowed recovery of the chiral oxazolidinone **(14)** in 94% yield **(Scheme 1.4)**.[17]

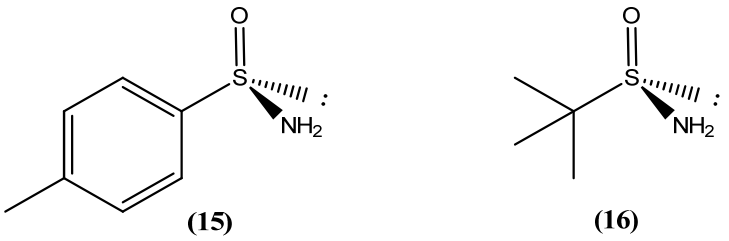


(12) (13) (14)

Scheme 1.4

1.2.1 *N-tert*-butylsulfinamide

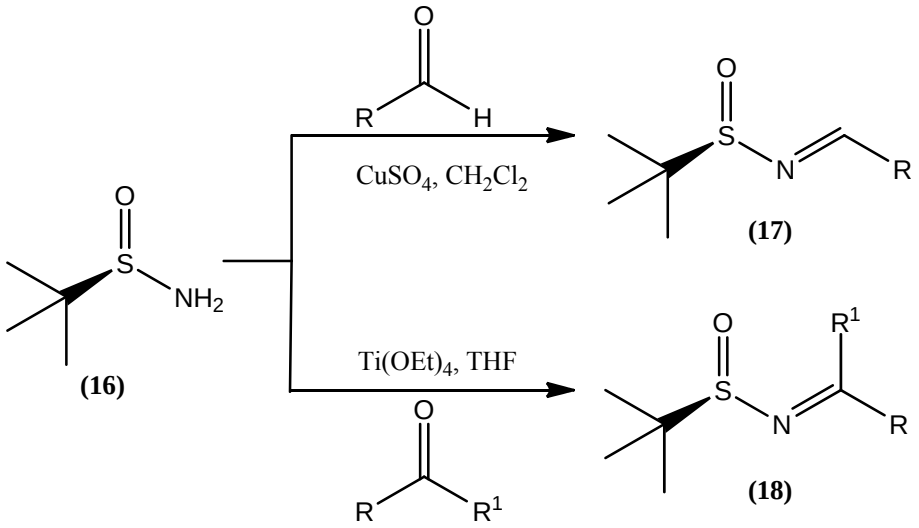
The application of chiral sulfinamides as chiral auxiliaries in the asymmetric synthesis of amines was first pioneered by Davis with his *p*-toluene-sulfinamide **(15)** **(Figure 1.2)**.[18] Sulfinimines, derived from chiral sulfinamides, offer numerous advantages in comparison to standard chiral imines. They undergo highly stereoselective additions under control of the *N*-sulfinyl chiral group. Furthermore, they are more stable, more electrophilic due to activation by the *N*-sulfinyl group, and can be easily cleaved by acid, without epimerisation of the product. Further work in this field by Ellman led to the development of enantiopure 2-methyl-2-propanesulfinamide (*N-tert*-butylsulfinamide) **(16)** **(Figure 1.2)**.[19,20] The *N-tert*-butylsulfinamide **(16)** offers the advantage of being less prone to unwanted nucleophilic attack at the sulfinyl group, due to the greater steric bulk of the *tert*-butyl group.



(15) (16)

Figure 1.2

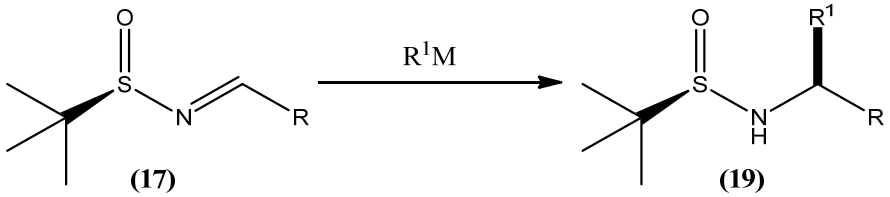
Condensation of **(16)** with aldehydes and ketones in the presence of a Lewis acid dehydrating agent, $CuSO_4$ for aldimines or $Ti(OEt)_4$ for ketimines or sterically hindered aldimines, provides the desired chiral sulfinimines, **(17)** and **(18)**, in moderate to high yields (63-96%) **(Scheme 1.5)**.[21] These sulfinimines provide asymmetric routes to a variety of building blocks including 1,2 and 1,3 amino alcohols,[22-24] α- and β-amino acids and esters,[25,26] diamines[27,28] and α- and α, α-branched amines.[20,21]



(17a): R = Et, R^1 = H; Yield = 96%
(17b): R = Ph, R^1 = H; Yield = 91%
(18a): R = *i*Pr, R^1 = Bu; Yield = 77%
(18b): R = Ph, R^1 = Bu; Yield = 77%

Scheme 1.5

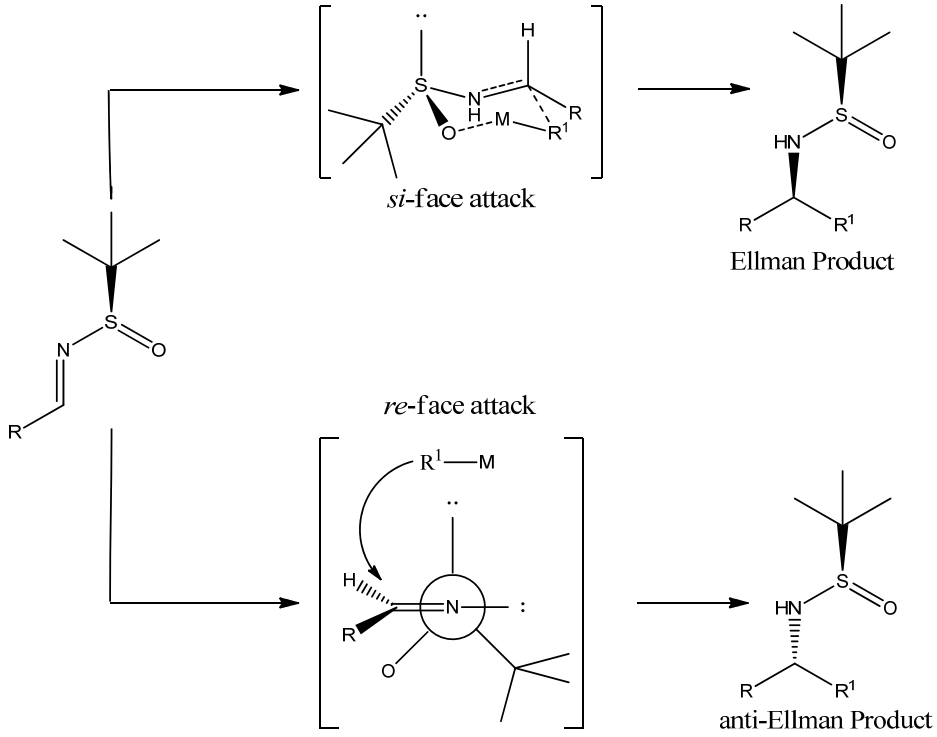
Cogan *et al* have shown that addition of Grignard reagents to *N*-sulfinyl aldimines **(17)** can be carried out with a wide range of substrates (aliphatic and aromatic imines), providing α-branched amines.[21] Reaction of MeMgBr with the aldimines of ethanal and benzaldehyde amongst others proceeded with high yields (89-97%) and high diastereoselectivities (86-96% *de*) **(Scheme 1.6)**. The Grignard reagent can also be varied with alkyl, aryl and vinyl derivatives all reacting successfully. While these reactions were carried out in Et_2O, use of THF as solvent led to lower diastereoselectivity. Acidic cleavage of the sulfinyl group by addition of 4M HCl afforded the product amine hydrochloride salts by recrystallisation.



(19a): R = Et, R^1M = MeMgBr: Yield = 96%, 93:7 *dr*
(19b): R = Ph, R^1M = MeMgBr: Yield = 100%, 97:3 *dr*
(19c): R = Et, R^1M = PhMgBr: Yield = 100%, 96:4 *dr*
(19d): R = *i*Pr, R^1M = vinylMgBr: Yield = 90%, 88:12 *dr*
(19e): R = Ph, R^1M = vinylMgBr: Yield = 79%, 91:9 *dr*

Scheme 1.6

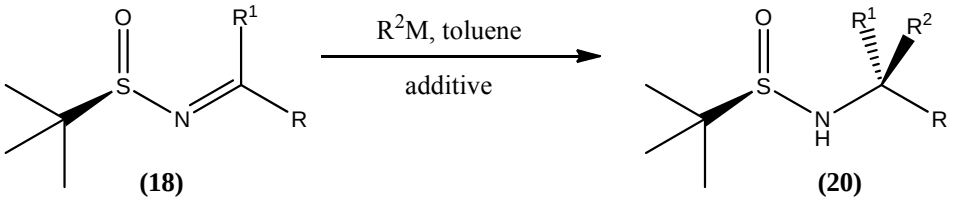
Either diastereomer can be obtained from a single enantiomer of *N-tert*-butylsulfinamide **(16)**, depending on the choice of conditions. The 6-membered transition state as shown below is most common for Grignard reagents and works best in non-coordinating solvents such as toluene and CH_2Cl_2. This allows for attack of the Grignard from the *si*-face of the imine, giving the so-called "Ellman" product **(Scheme 1.7)**. The open transition state is favoured for reactions carried out using organolithium reagents in coordinating solvents such as THF, with *re*-face addition giving the "anti-Ellman" product.



Scheme 1.7

Preparation of α-branched amines is also possible through reduction of *N*-sulfinyl ketimines **(18)**. Again, both diastereomers are available through variations in reaction conditions. Reduction of the ketimine using $NaBH_4$ proceeds through a chelated transition state with *si*-face attack, similar to a Grignard reagent for aldimines **(17)**. In contrast, use of L-Selectride as the reducing agent provides the opposite diastereomer, through the open transition state, with *re*-face attack.[29] Both DIBAL-H and 9-BBN have also been shown to offer the opposing stereoselectivity from that given by L-Selectride.[30]

In 1999, Ellman *et al* published a paper detailing the first reported method of asymmetric synthesis of tertiary carbinamines **(20)**, using a 1,2 addition of organometallics to *N*-sulfinyl ketimines **(18) (Scheme 1.8)**.[21] Once again, Grignard and organolithium reagents offered opposing diastereoselectivity. While additives had no great effect on the Grignard-mediated additions, organolithiums were found to require a Lewis acid additive such as $AlMe_3$ in order to achieve high yields and stereoselectivities.

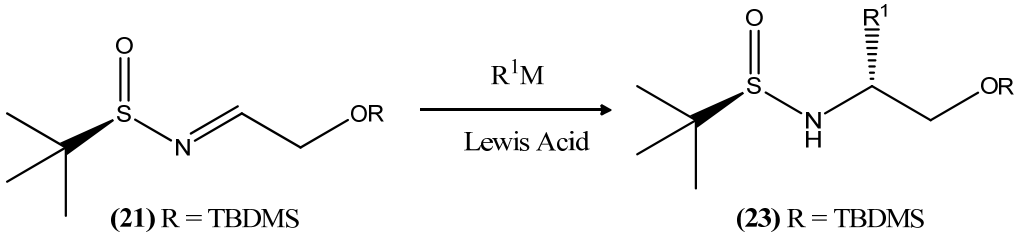


(18) **(20)**

(20a): R=Me, R^1=*i*Pr, R^2M=PhMgBr: 21%, 69:31 dr
(20b): R=Me, R^1=*i*Pr, R^2M=PhLi, no additive: 65%, 94:6 dr
(20c): R=Me, R^1=*i*Pr, R^2M=PhLi, Additive=$AlMe_3$: 93%, 97:3 dr

Scheme 1.8

Barrow *et al* have shown that 1,2 amino alcohols can be made from α-silyloxy sulfinimines **(21)** in modest to high yields (44-97%) and poor to moderate diastereoselectivities (1:1-4.4:1 *dr*) using Grignard reagents in non-coordinating solvents like CH_2Cl_2 **(Scheme 1.9)**.[22]



(21) R = TBDMS
(22) R = Bn

(23) R = TBDMS
(24) R = Bn

(23a): R = TBDMS, R^1M = PhMgBr: Yield = 96%, 3:1 *dr*
(23a): R = TBDMS, R^1M = PhLi: Yield = 81%, 2.7:1 *dr*
(24a): R = Bn, R^1M = PhMgBr: Yield = 90%, >10:1 *dr*
(24a): R = Bn, R^1M = PhLi: Yield = 70%, 2.4:1 *dr*
(23b): R = TBDMS, R^1M = vinylMgBr: Yield = 44%, 5.9:1 *dr*
(23c): R = TBDMS, R^1M = *n*BuMgBr: Yield = 100%, >10:1 *dr*

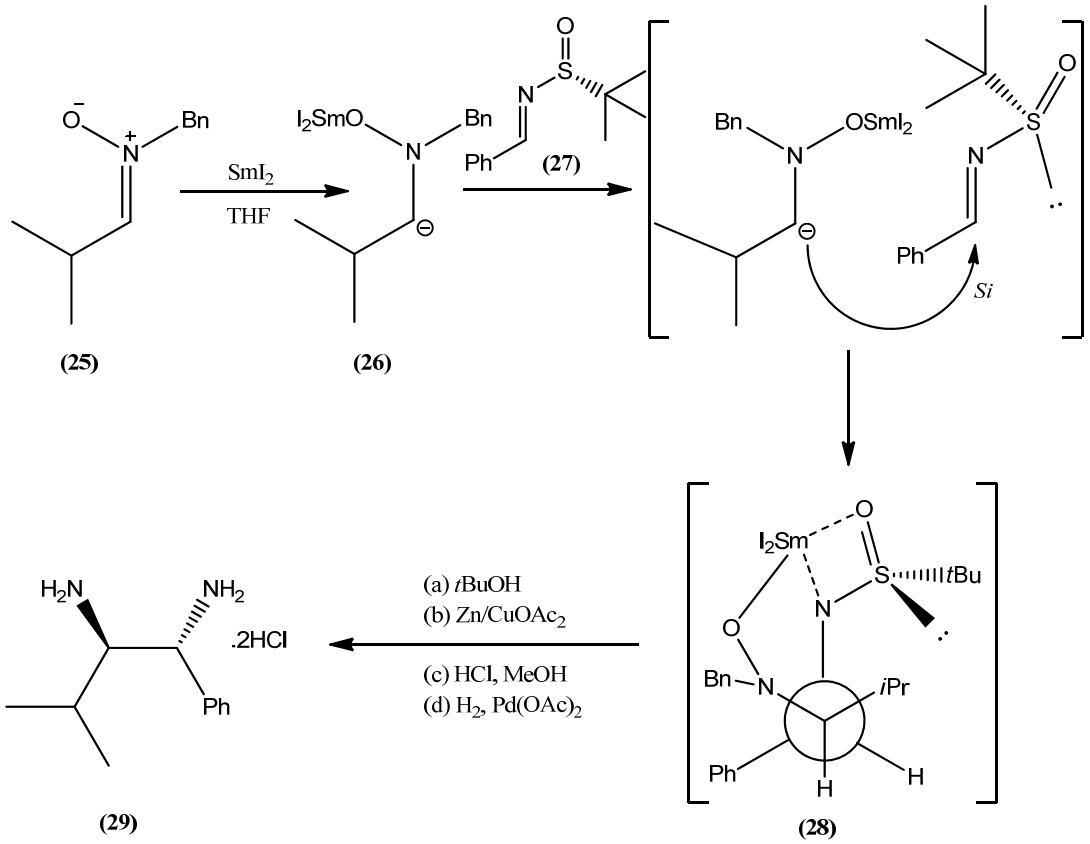
Scheme 1.9

Organometallic reagents also added in moderate to high yields (53-96%) with modest to good selectivities (2.4:1->10:1 *dr*) to α-benzyloxy sulfinimines **(22)**. The sense of induction, for both organolithiums and Grignard addition reagents, observed is in contrast to that observed for Grignard additions to sulfinimines lacking an α-coordinating group and leads to addition from the *re*-face or the so-called "anti-Ellman" product. This may possibly be due to metal chelation to the α-alkoxy group altering the proposed transition state to form the less stable *Z*-chelated isomer. This may occur due to coordination of the alkoxy group to the metal forcing it to take up an axial position in the transition state. However other transition states are also possible including Davis' open model.

Ellman *et al* also carried out solvent and additive screening experiments. This led them to conclude that toluene was the optimal solvent, while additives such as $AlMe_3$ had little effect on the Grignard additions.[31] Finally use of the benzyloxy imine **(22)** provided the desired products with slightly higher diastereoselectivities than the silyloxy derivatives **(23)**, in most cases. These results were all in agreement with Barrow's earlier work.

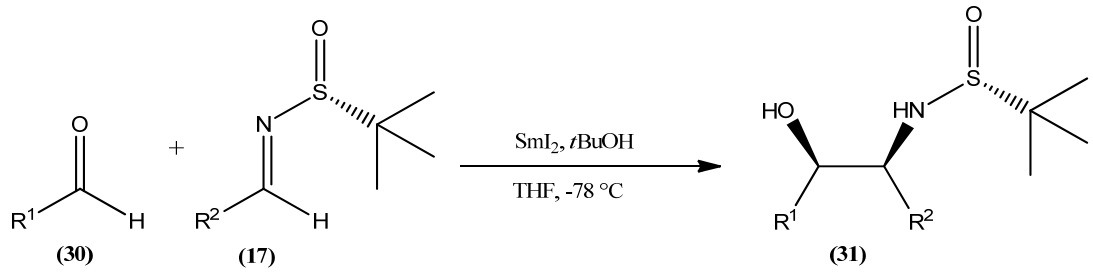
Xu *et al* have developed methods for preparing enantiomerically enriched C_2-symmetric vicinal diamines, unsymmetrical vicinal diamines and 1,2 amino alcohols as homo and cross-coupling products in the presence of SmI_2.[27,28,32] In order to generate the unsymmetrical diamines they carried out a SmI_2-mediated reductive cross-coupling reaction between nitrones and chiral *N*-*tert*-butylsulfinimines.[27] It was found that a slight excess of either reagent gave increased yields, while the absence of *t*BuOH also led to decreased yields. The diastereoselectivities were seen to fall as the nitrone substituent became more bulky.

The proposed mechanism involves a two-electron reduction of the nitrone **(25)** by the SmI_2 followed by addition to the sulfinimine **(27)**. The steric bulk of the sulfinimine **(27)** induces preferential approach from the *si*-face of the C=N bond. Deoxygenation by $Zn/Cu(OAc)_2$, followed by acidic cleavage of the sulfinyl group and hydrogenation of the benzyl group afforded the diamine hydrochloride product **(29)** in an 87% overall yield with >99% *ee* **(Scheme 1.10)**.



Scheme 1.10

Further research in these reductive cross coupling reactions showed that 1,2 amino alcohols were viable targets. Reaction of aliphatic aldehydes **(30)** (aromatic aldehydes led to pinacol formation) with *N-tert*-butylsulfinimines **(17)** proceeded smoothly to give the desired β-amino alcohols **(31)** in high yields and high diastereoselectivity **(Scheme 1.11)**.[32]



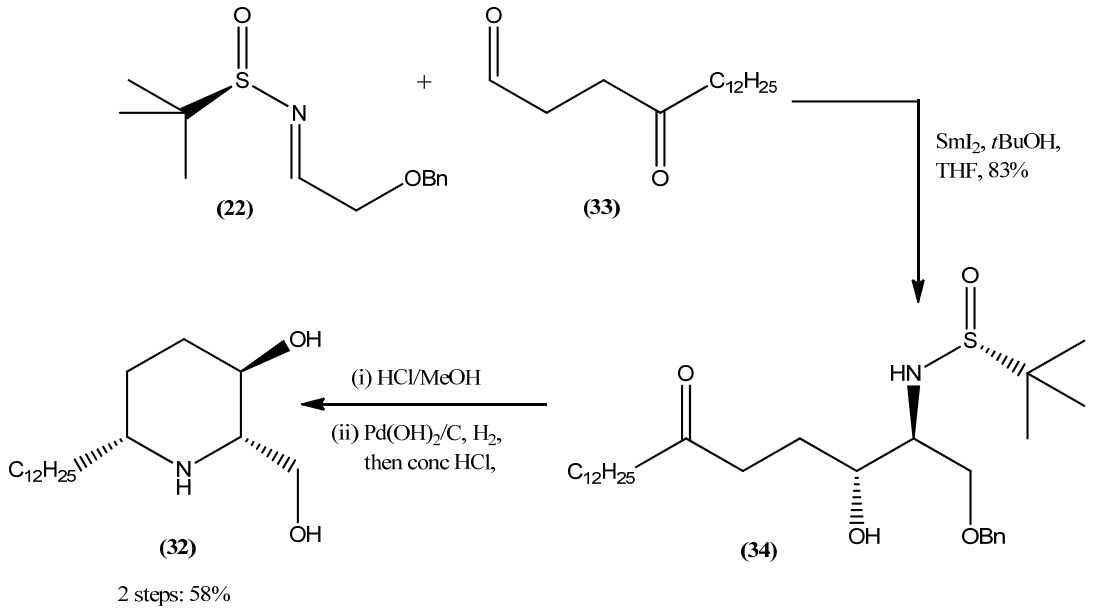
Scheme 1.11

Entry	R^1	R^2	Yield	*dr*	*ee*[a]
1	4-$CH_3C_6H_4$	*i*Pr	92	>99:1	98
2	4-$CH_3C_6H_4$	C_6H_{11}	90	99:1	>99
3	Ph	*i*Pr	86	99:1	97
4	*i*Pr	*i*Pr	88	>99:1	98
5	$PhCH_2CH_2$	*i*Pr	87	96:4	>99

[a] *ee* for the free β-amino-alcohol after acidic hydrolysis

Table 1.1

In 2008 Wei *et al* synthesised (-)-deoxoprosophylline **(32)**, a piperidine analog with potential analgesic, anesthetic and antibiotic biological properties.[33] The key step involved a SmI_2-mediated cross coupling reaction to produce a β-amino alcohol. Reaction of the aldehyde **(33)** with (*S*)-*N*-*tert*-butylsulfinamide **(22)** gave the desired benzyloxy-β-amino alcohol **(34)** in 83% yield with high diastereoselectivity (>99% *de*). Removal of the sulfinyl group, cyclization and reduction gave the final product **(32)** in an overall yield of 34% **(Scheme 1.12)**.



Scheme 1.12

1.3 Catalysis

A catalyst is a substance that alters the rate of a chemical reaction without itself being consumed in the same reaction. This definition covers a huge range of compounds, including biological molecules like enzymes to transition metals such as Pd and Cu. Catalysts are able to alter the rate of reaction by either lowering the activation energy of the reaction to speed it up or by raising the activation energy and slowing the reaction down. As such, catalysts can selectively control which products are predominately formed in a reaction, whether they are stereoisomers or completely different compounds.

Catalysts are used to ensure that reactions work more efficiently under relatively mild conditions, reducing waste streams. They are generally of two types, homogeneous (both reactant and catalyst are in the same phase) or heterogeneous (both are in different phases). The advantage of a heterogeneous system lies in the ease of recyclability of the catalysts, allowing for a greater total turnover number, reducing the quantity of catalyst required and its ease of removal from the product.

1.4 Asymmetric Catalysis

In asymmetric catalysis, the catalyst should be able to distinguish between the faces of prochiral molecules or enantiotopic groups. Since two enantiomers being generated will form *iso*-electronic transition states, the use of an achiral catalyst will have no effect on stereoselectivity. However, by introducing a chiral catalyst the new transition states formed will be diastereomeric with respect to one another and as such may have different activation energies. The degree of selectivity of the chiral reaction will be dependent upon the difference in the energies of the two states. A well designed chiral catalyst can induce high selectivity by increasing the energy difference between the two transition states.

Chiral catalysts can be separated into two groups, organocatalysts and transition metal catalysts. Organocatalysts are organic molecules such as proline and its derivatives, thioureas, amino acids and chiral primary amines.[34-36] They are generally used for the enantioselective functionalization of carbonyl containing compounds such as in aldol and Mannich reactions.[37,38] Transition metal catalysts are organometallic compounds with metal centres surrounded by chiral ligands. For well-known reactions, such as the Diels-Alder reaction, ene reaction and Michael reaction, the rational design of catalysts can be considered. However, generally

screening of various catalysts (ligands, metals, etc.) and the reaction conditions is necessary to produce superior catalysts.

1.4.1 Asymmetric transition metal catalysis

Transition metals, with organic ligands bound to them, can act as catalysts in many organic reactions. A chiral organic molecule bound to a transition metal can create a chiral pocket from the ligand-metal complex formed. Incoming reagents binding to the central metal, within the chiral pocket, come under its influence allowing for stereocontrol in the product. There are many factors which can influence how effective a newly designed catalyst will be. Consideration needs to be taken on the various coordination numbers a metal may have, as this will control the geometry of the chiral pocket being created. Metal geometries can range from linear to octahedral, to even more complex arrangements. For ligand design it is important to be aware of the possible denticities (mono-, bi- or poly-), the electronic properties, the ease of modification and the source of chirality amongst other factors. Ligands containing central chirality, axial chirality or planar chirality have all proven to be effective in asymmetric synthesis.[39-42]

Due to the high costs involved in synthesising chiral compounds, asymmetric catalysis has been viewed as possibly the most efficient and inexpensive method of generating optically active molecules. When a highly efficient chiral catalyst is used it can produce large volumes of enantiomerically pure material from a relatively small source. In some cases the catalysts can also be recycled, increasing its total turnover cost.

1.5 Bisoxazoline ligands

In the early 1990s, prompted by the success of by Pfaltz *et al* with C_2-symmetric *N*,*N*-ligands known as semicorrins **(35)**, many research groups began developing structurally related compounds for use in asymmetric transition metal catalysis **(Figure 1.3)**.[43] Of these, perhaps the most studied and successful was the bisoxazoline (BOX) class [e.g. **(36)**]. The bisoxazolines are amongst the most widely used ligands in asymmetric catalysis and have been employed in a wide range of enantioselective reactions including cyclopropanation reactions, allylic alkylation reactions, as well as oxidation and reductions.

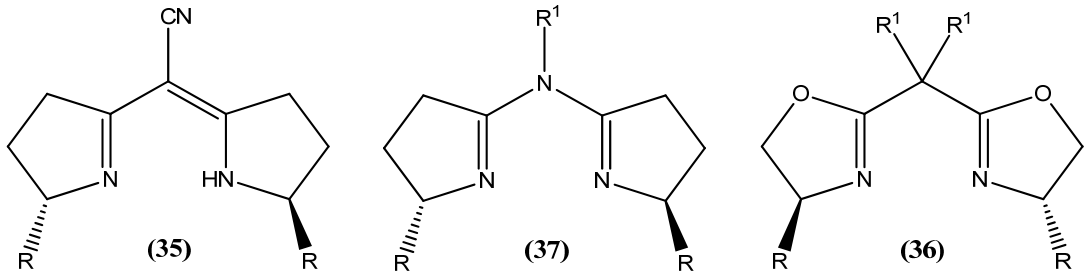


Figure 1.3

1.5.1 Structure

Many variations of C_2-symmetric bisoxazoline ligands exist. In general, bisoxazolines that contain a one carbon spacer between the two rings are the most commonly used. However, those which form a 5-membered chelate with no spacer between the two oxazoline moieties, as well as those which have 2 or more carbon spacers, forming 7-membered and larger chelate systems, have also been applied successfully to asymmetric reactions. Co-ordination of the two nitrogen atoms on the heterocyclic rings to the metal ion allows formation a six-membered metal chelate (**Figure 1.4**). The metal chelate is conformationally constrained due to the rigid nature of the ligand scaffold. The two substituents at the stereogenic centres are in close proximity to the donor nitrogen atoms and to the metal centre. This, therefore, should allow them to impose a strong directing effect on the stereochemical course of the metal-catalysed process.

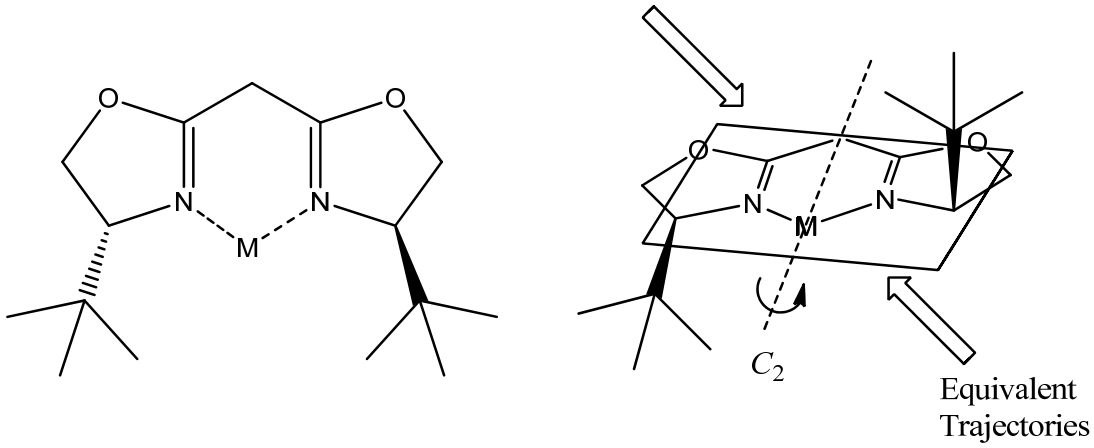


Figure 1.4

Due to the C_2-symmetric nature of the ligands the number of variables influencing the stereoselectivity (transition states, reaction pathways, etc.) is halved, due to the equivalency in the structure upon rotation by 180° **(Figure 1.4)**.

1.5.2 Naming of bisoxazolines

When naming a ring containing more than one heteroatom, the order of priority follows a simple pattern based on the Periodic Table. Group VII elements are given the highest priority, descending in order down the group to iodine. Next in priority comes Group VI, once again in descending order to tellurium, followed by Group V, Group IV, Group III (only boron) and lastly mercury. As such, sulphur is give higher priority than nitrogen, but lower priority than oxygen. The highest priority atom is labelled #1, with the numbering then proceeding in the direction that gives the lowest number for the next heteroatom.

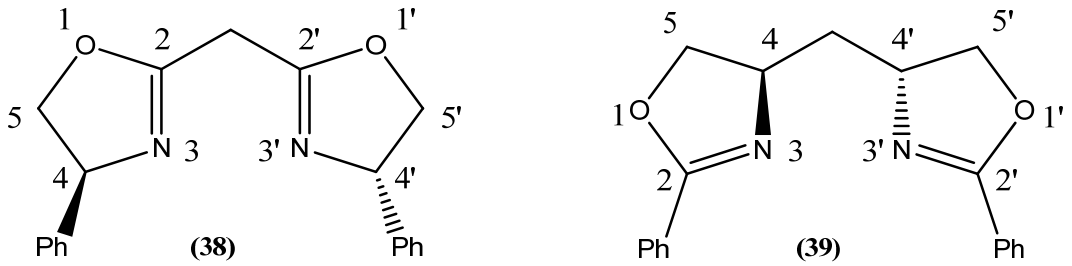


Figure 1.5

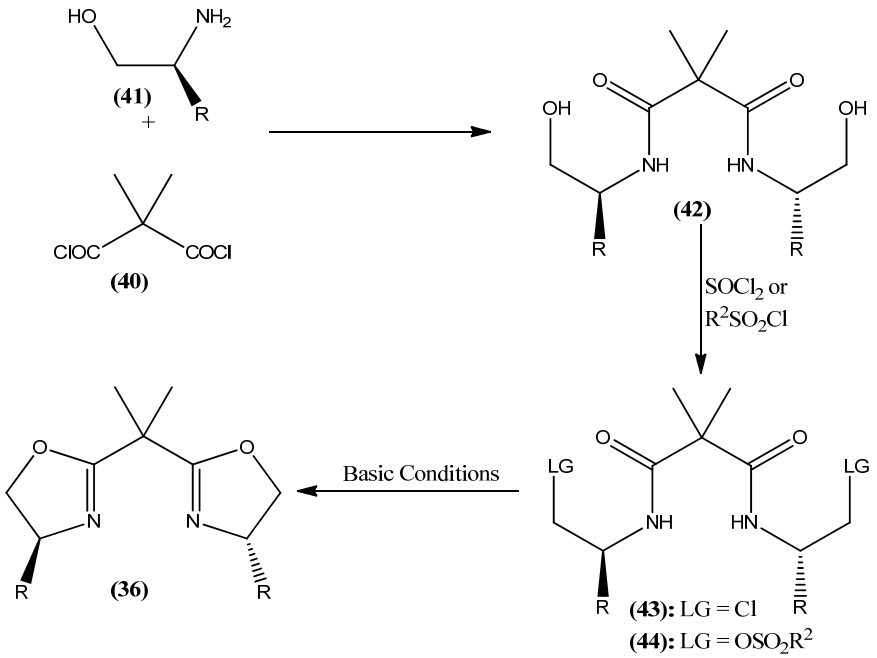
Standard bisoxazolines are described as 2,2'-bisoxazolines [e.g. **(38)**] due to the location of the carbon spacer, with the oxygen atom designated as the highest priority atom (#1), and the nitrogen then labelled #3 **(Figure 1.5)**. The 2,2' designates the two carbon atoms on each ring bonded to the carbon spacer. In 2009, O'Leary *et al* reported the synthesis of a new, regioisomeric class of bisoxazoline termed 4,4'-bisoxazolines [e.g. **(39)**], with the chiral centres now located on the ligand backbone.[44]

1.5.3 Synthesis of bisoxazolines

Chiral C_2-symmetric bisoxazoline ligands are seen as attractive ligands due to their ease in synthesis. They can be easily accessed using readily available, optically active β-amino alcohols or suitably protected amino acids. Since the chiral substituents on the rings are derived from the β-amino alcohol their structure can be easily altered by using different amino alcohols available. In this way the structure of the ligand can be adjusted, allowing for optimization for a particular reaction.

There are numerous reported methods for the synthesis of C_2-symmetric bisoxazoline ligands. Standard procedures involve the use of a symmetric malonic

acid derivative **(40)** coupled to two equivalents of β-amino alcohol **(41)**, providing the bis-β-hydroxyamide **(42)**. Activation of the alcohol as a leaving group, followed by cyclisation under basic conditions yields the desired bisoxazoline **(36) (Scheme 1.13)**.



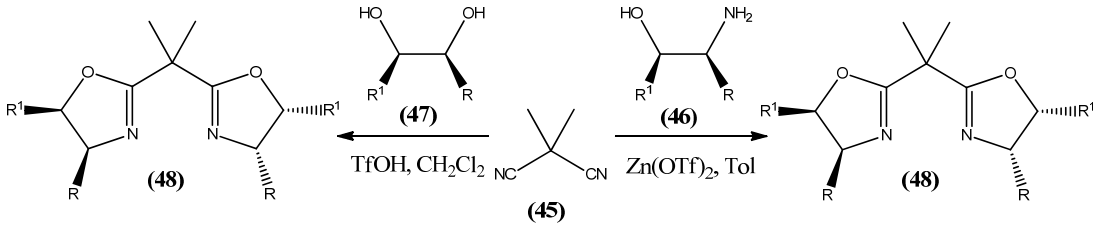
Scheme 1.13

Corey *et al*, in their original synthesis, treated the hydroxyamide **(42)** with thionyl chloride affording the bis-chloride **(43)**.[45] Other activating agents can also be employed. Procedures involving the conversion of the hydroxyl groups to give the corresponding bis-mesylate or tosylate **(44)** (R^2 = Me/4-MeC_6H_4) are also commonly used.[46,47]

Other protocols involve cyclisation in a single step from the hydroxyamide **(42)** using various dehydrating conditions. These include the use of Bu_2SnCl_2 in refluxing xylene (Masamune's conditions),[48] using $Ph_3P/CCl_4/Et_3N$,[49] with diethylaminosulfur trifluoride[50] or methyl *N*-(triethylammonium-sulfonyl)carbamate (Burgess reagent).[51]

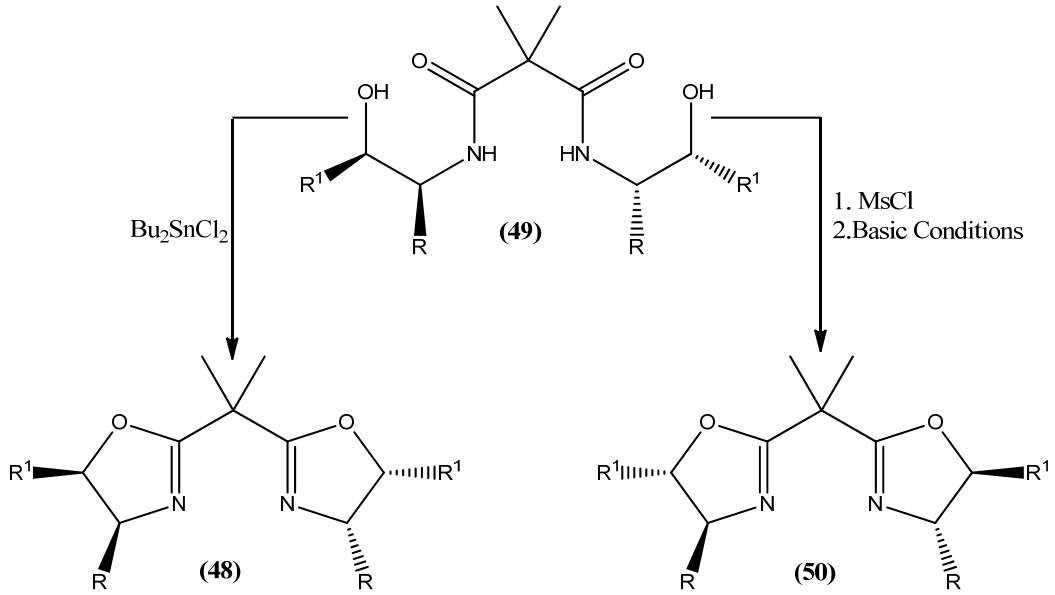
Malononitriles **(45)** or their imidate ester derivatives can also be used to generate the bisoxazoline moiety. Reaction with two equivalents of β-amino alcohol **(46)** or their related 1,2 diol counterpart **(47)** results in formation of the desired bisoxazoline **(48)**.[41,52] These reactions proceed in each case with retention of configuration, as can be seen in the synthesis of 4,5-disubstituted bisoxazolines **(48) (Scheme 1.14)**.

Garcia *et al* reported the synthesis of bisoxazolines by reacting (*S*)-(+)-2-phenylglycinol with dimethylmalononitrile to give the product bisoxazoline in 95% yield.[53] Stoichiometric amounts of the $Zn(OTf)_2$ catalyst were required, due to complexation upon formation of the bisoxazoline. PYBOX ligands (bisoxazolines where the spacer is a pyridyl group) could also be synthesised following this procedure, with only 5 mol% of catalyst required.



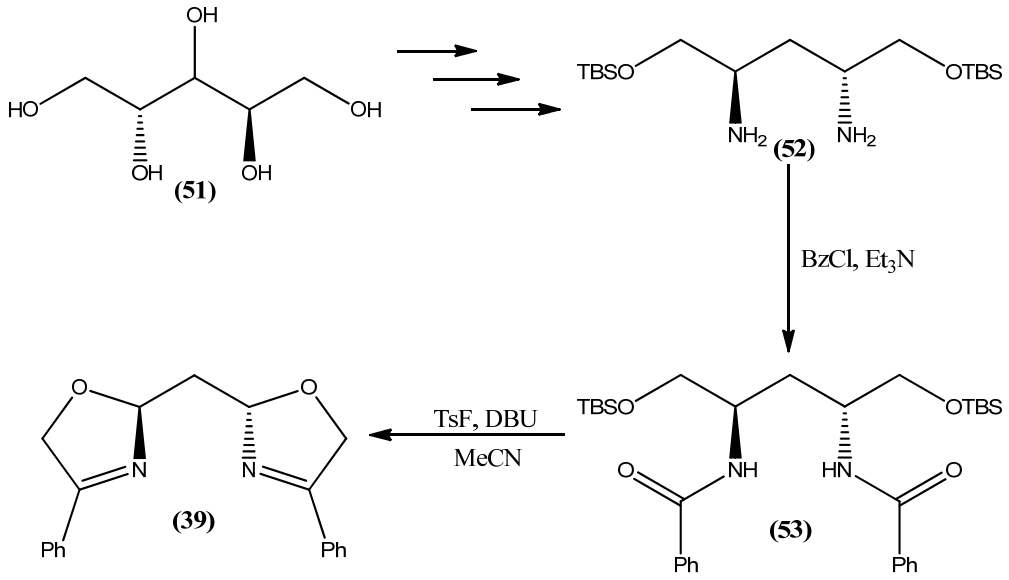
Scheme 1.14

4,5-disubstitued BOX ligands can also be diastereoselectively synthesised from the bis-hydroxyamide **(49)** by varying the conditions. Use of Masamune's conditions provides the *cis*-4,5-disubstitued bisoxazoline **(48)** with retention, in a similar fashion to that afforded by the diol or amino alcohol reactions above.[48,54] However, the use of methanesulfonyl chloride followed by basic conditions, as outlined earlier proceeds, with inversion of configuration affording the diastereomeric *trans*-4,5-disubstitued bisoxazoline **(50) (Scheme 1.15)**.[54]



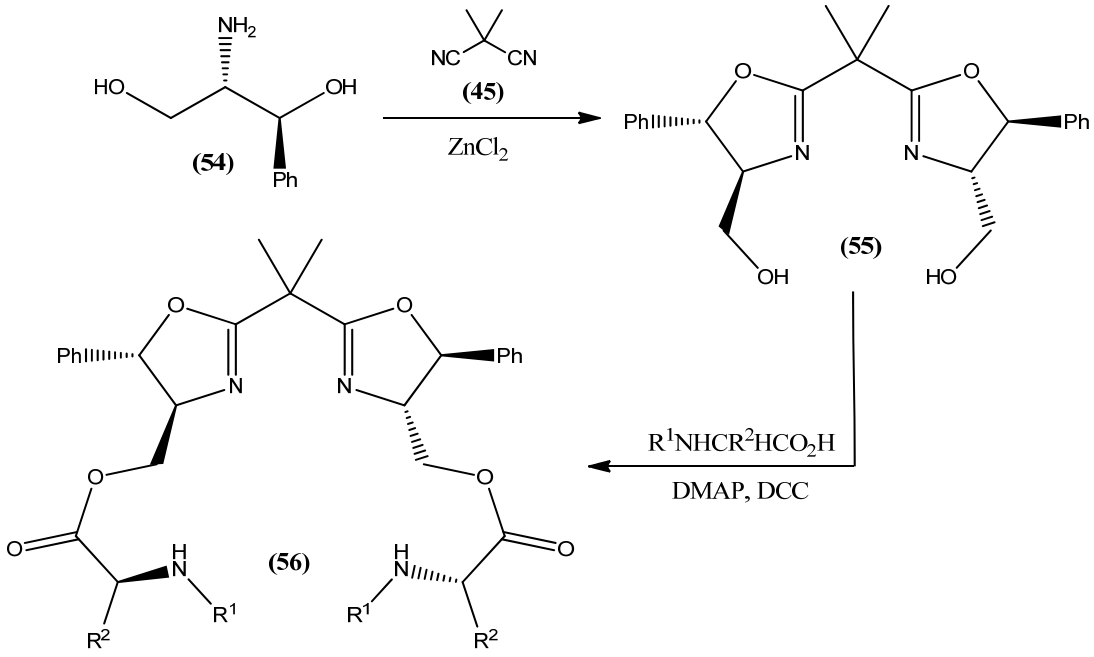
Scheme 1.15

In 2009 O'Leary *et al* reported the synthesis of a new class of BOX ligands with phenyl 4,4'-bis(oxazoline) [AraBOX] **(39)** from D-(+)-Arabitol **(51)**.[44] Synthesis of the key intermediate, a novel bis-β-amino alcohol **(52)**, was achieved in several steps. Conversion to the bis (*O*-silyl) benzamide **(53)** with benzoyl chloride, followed by reaction with TsF and DBU in refluxing acetonitrile afforded the novel bisoxazoline ligand **(39)** in 75% yield **(Scheme 1.16)**.



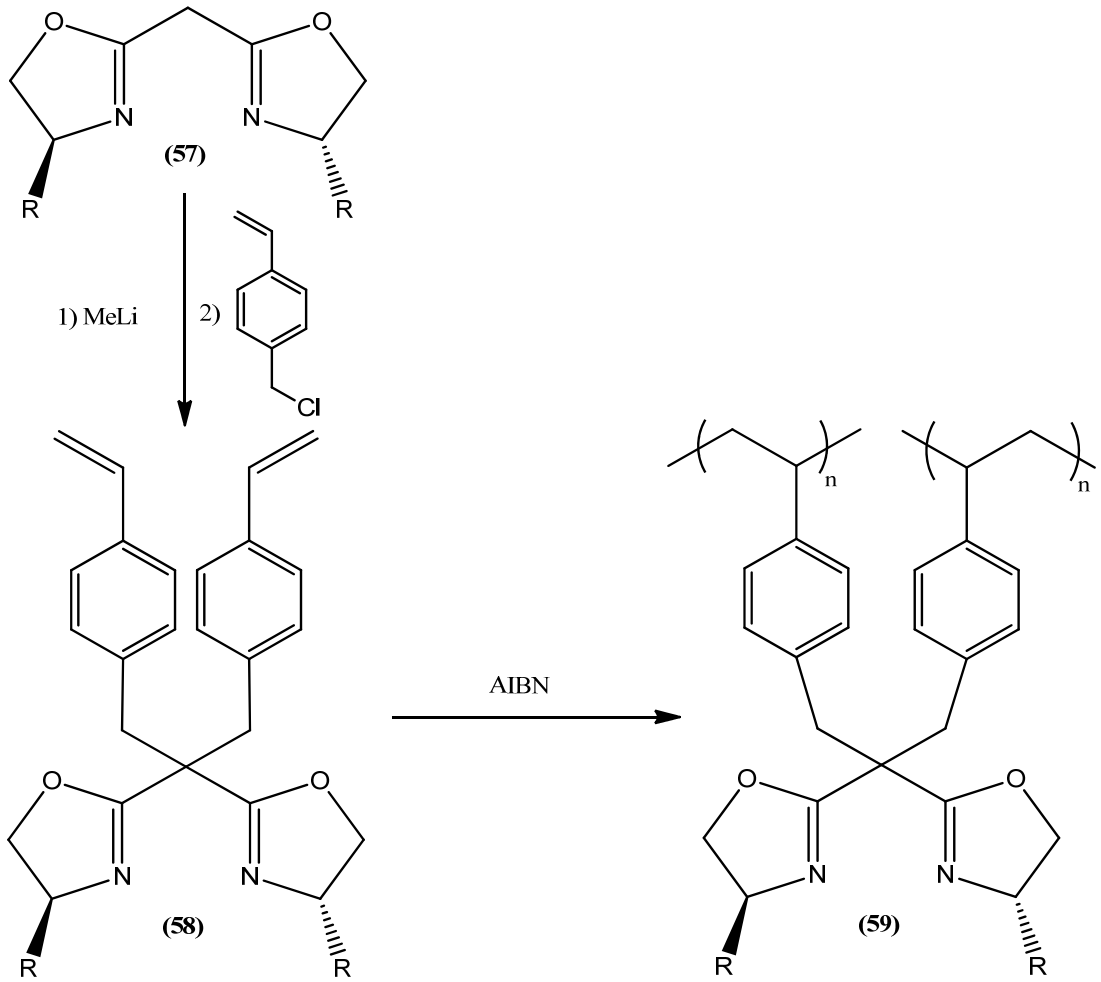
Scheme 1.16

Bisoxazoline ligands with secondary asymmetric binding sites on the side chains have also been synthesised. The heteroatoms located on the molecule can increase the ligand's denticity, which can enhance its stereoselectivity or allow it to be grafted onto solid surfaces for use as a recyclable, heterogeneous catalyst. Reiser *et al* have developed bisoxazolines with secondary binding sites.[55] The ligands were synthesised by reacting the amino alcohol **(54)** with dimethyl malononitrile **(45)** to give the desired bisoxazoline **(55)**. Further derivatisation of the side-chains gave a variety of α-amino ester ligands **(56)**. The dihydroxy bisoxazoline ligand **(55)** was converted to the corresponding amines **(56)** in good yields, 78-98% **(Scheme 1.17)**.



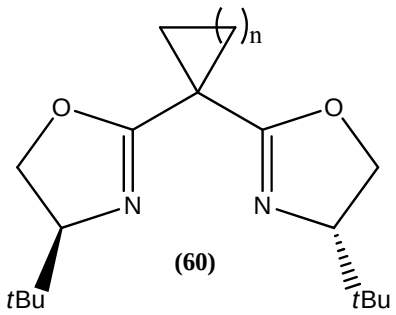
Scheme 1.17

Bisoxazolines containing a methylene bridgehead can also be altered and substituents added in place of the acidic hydrogens. 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. Garcia *et al* have reported the preparation of polymeric bisoxazoline catalysts using this technique.[56] Deprotonation of **(57)** using MeLi followed by alkylation with *p*-vinylbenzyl chloride led to the chiral monomer **(58)**. Polymerization in the presence of AIBN gave the desired products **(59)** in good yields, 75-95% **(Scheme 1.18)**.

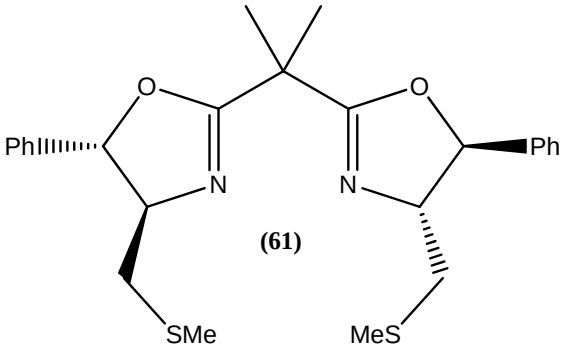


Scheme 1.18

Manipulations of the substituents on the oxazoline rings, as well as modifications of the spacer linking the two rings have produced a wide range of bisoxazoline ligands for use in asymmetric catalysis **(Figure 1.6)**.[57-59]



(60)



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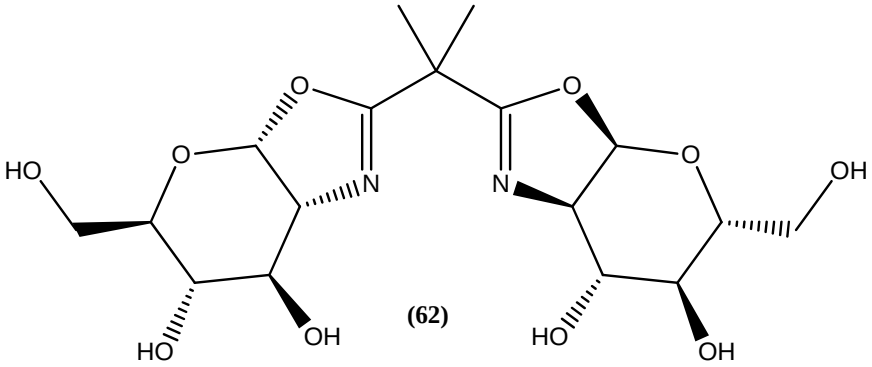


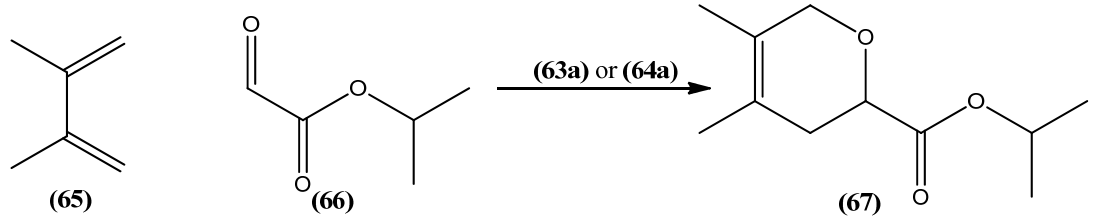
(62)

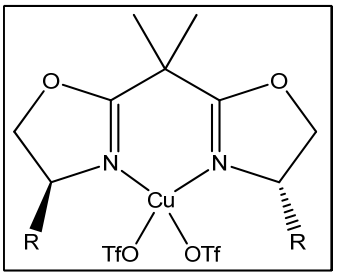
Figure 1.6

1.5.4 Metal bisoxazoline complexes

Chiral bisoxazolines have been used as ligands with a wide variety of transition metals including copper, zinc, ruthenium and palladium. Ligation to metals of differing oxidation states is also possible. Chiral bisoxazoline-metal complexes are usually formed in situ by mixing the bisoxazoline ligand and the corresponding metal salt in an organic solvent prior to their use. Standard procedure involves using a 1:1 mixture of the bisoxazoline ligand and the metal ion to form the chelated metal complex. Bisoxazoline ligands generally coordinate singly through their nitrogen atoms as bidentate ligands, with a few exceptions.

Generally the metals involved in forming the complexes with bisoxazolines have between four to six coordination sites. The importance of a complex's coordination geometry is illustrated by an interesting result reported by Jorgensen *et al* in 1995.[60] They observed analogous copper complexes derived from *tert*-butyl-bisoxazoline [Cu-(*S*,*S*)-*t*Bu-BOX)](OTf)$_2$ **(63a)** and phenyl bisoxazoline [Cu-(*S*,*S*)-Ph-BOX)](OTf)$_2$ **(64a)** giving opposing stereoselectivity in an asymmetric hetero-Diels Alder reaction **(Scheme 1.19)**.





(63a): R = *t*Bu: Yield = 12%, *ee* = 77 (*S*)
(64a): R = Ph : Yield = 31%, *ee* = 87 (*R*)

Scheme 1.19

Jorgensen's original hypothesis was that phenyl bisoxazoline complex was adopting a tetrahedral geometry, while the *tert*-butyl-bisoxazoline complex adopted a square planar geometry.[60] In these complexes two coordination sites are occupied by the nitrogens and two by the carbonyls of the reagent. These are the most common geometries seen in tetra-coordinated bisoxazoline complexes. Complexes adopting either of these two geometries will show opposite stereoselectivities. This occurs as

rotation of the coordinated substrate by 90° will bring the accessible face from the shielded to the unshielded region of the complex and vice versa **(Figure 1.7)**.

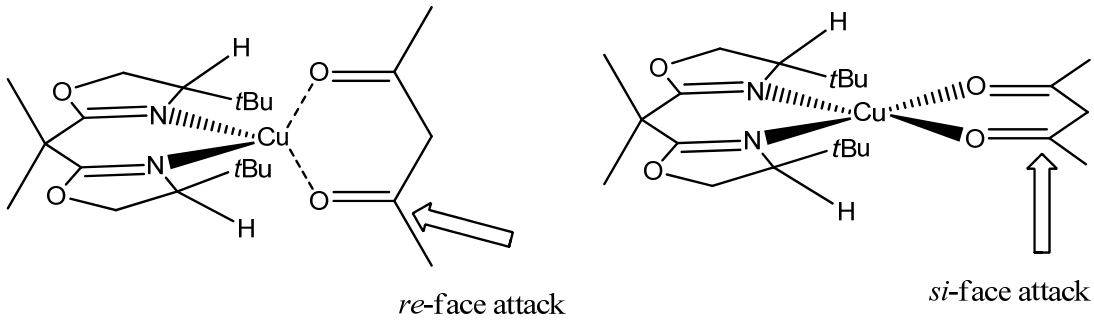


Figure 1.7

However, further studies by Evans found no evidence for the existence of a tetrahedral intermediate.[61] Copper(II) complexes with bisoxazolines are generally found to favour distorted square planar conformations. Complexation of bisoxazolines to Cu(II) halide salts have shown the anions to favour occupying quadrants free from the ligands substituents, in many cases (R = Ph, *t*Bu, *i*Pr).[42] This causes a large distortion in the complex away from the ideal square planar geometry. In some cases, X-ray crystal analysis of the hydrated analogues of the bisoxazoline-copper complexes show a change from this geometry.[62] The hydrated *tert*-butyl-bisoxazoline complex shows a large degree of distortion similar to that seen in the halide complexes. In contrast, the distortion in the phenyl bisoxazoline complex is small, and unusually, the distortion is in the other direction, with the coordinating water molecules actually occupying the same quadrant as the phenyl substituents **(Figure 1.8)**. X-ray analysis of complexes with α-dicarbonyl and related substrates bound show similar geometry to these hydrated crystal structures.

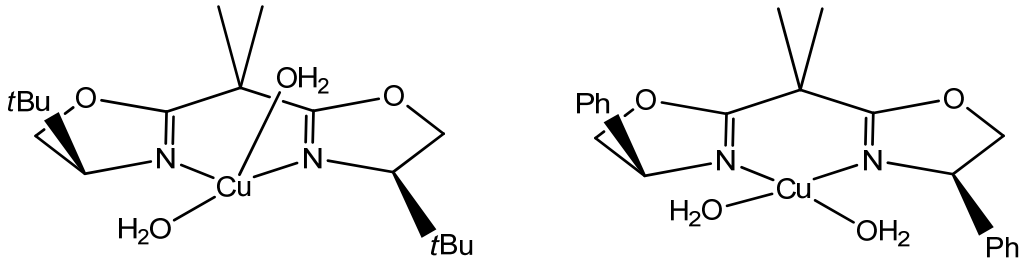
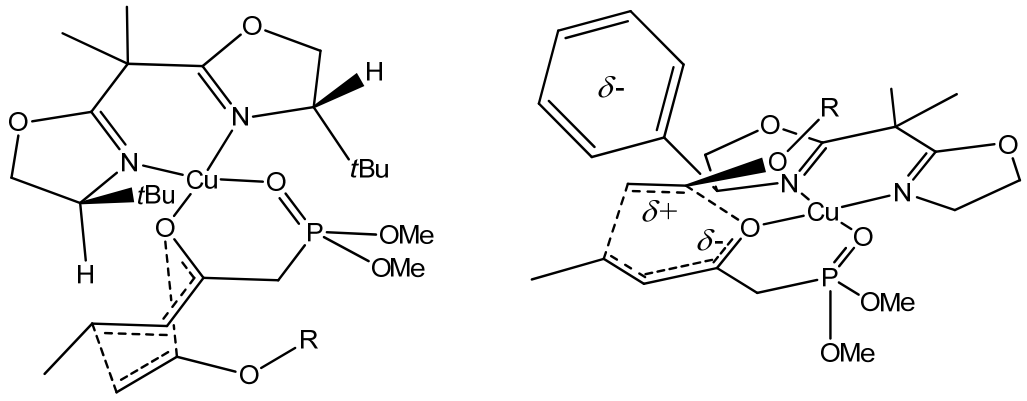


Figure 1.8

With this data in hand, Evans postulated that both complexes adopted a square planar structure.[61] In the case of the *tert*-butyl-bisoxazoline complex, the dienophile approaches the diene from the opposite face to the sterically hindering *tert*-butyl

substituent. However, for the phenyl bisoxazoline complex, the substrate's approach occurs *syn*, due to π-stabilisation of the transition state **(Figure 1.9)**.



re-face attack
Occurs on opposite to *tert*-butyl substituent

si-face attack
Syn addition due to π-stabilisation

Figure 1.9

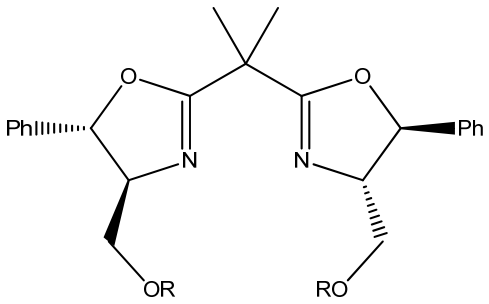
Jorgensen has since proposed a different hypothesis to the observed reversal in stereoselectivity. Experimental and theoretical evidence implies that the phenyl-bisoxazoline complex is much more flexible than the *tert*-butyl-bisoxazoline complex.[63] While the *tert*-butyl substituents appear to be locked into so-called pseudo-axial positions, the phenyl substituents are able to rock between pseudo-axial and pseudo-equatorial positions much more freely. These results show the danger involved in over-interpreting solid state data, with respect to solution state behaviours. The focus on isolated, static intermediates can sometimes provide over exaggerated information and should probably be avoided, with Jorgensen also reporting that differing solvents had a large effect on the selectivities seen in reactions involving the phenyl-bisoxazoline complex, but not the *tert*-butyl-bisoxazoline complex. Also, since a diminishing effect in the selectivity of these reactions can also be seen with the *iso*-propyl-bisoxazoline complex, Jorgensen postulated that the π-stabilisation proposed by Evans could not be the only factor controlling the reversal.

1.5.5 Bisoxazoline ligands with secondary binding sites

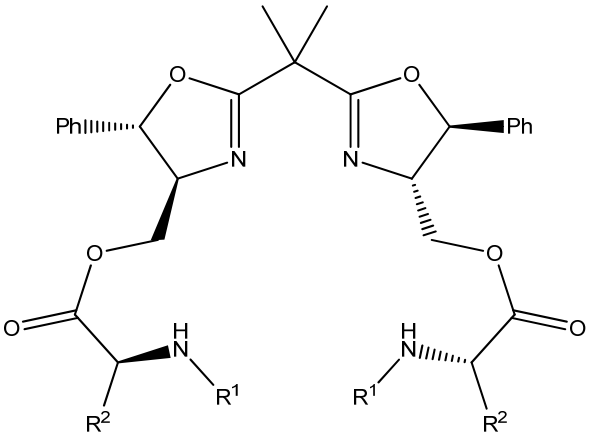
The design of bisoxazoline ligands containing heteroatoms on the substituents of the heterocyclic ring has been pursued in the hopes of generating secondary binding interactions between the ligand and one of the incoming substrates, which would offer improved selectivity. This could arise through secondary interactions with the

bound substrate or even the metal centre, creating a more rigid chemical environment within the reacting intermediate or through interactions with the incoming reagent, somehow promoting stereoselectivity. These multifunctional catalysts are widespread throughout nature, in the form of highly complex enzymes. However, the majority of these bisoxazolines have not met expectations and usually only participate through steric interactions.

Generally, the ligands designed incorporate a hydroxyl group or derivative as part of the sidechain, in the hope that hydrogen bonds may arise as the secondary interactions. Reiser *et al* synthesised a range of bisoxazoline ligands containing an α-amino ester sidechain **(Figure 1.10)**.[55] The synthesis of these ligands has been discussed in **Section 1.5.3**.



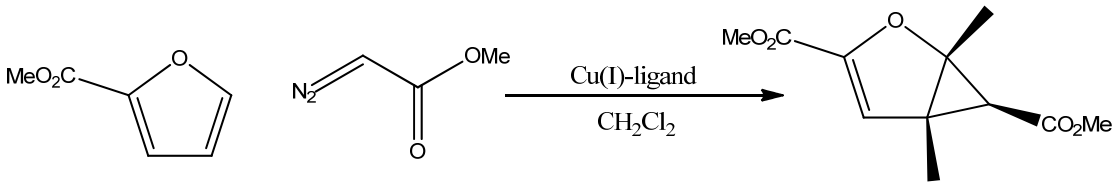
(55) R = H
(68) R = Ac



(56a): R^1 = Cbz, R^2 = *i*Pr
(56b): R^1 = Boc, R^2 = Me
(56c): R^1 = Ac, R^2 = Me
(56d): R^1 = Ts, R^2 = Me

Figure 1.10

The Cu(I) catalysts prepared from these ligands were used to catalyse the cyclopropanation reaction between furancarboxylate **(69)** and methyl diazoacetate **(70)**. In all cases the reaction took place at the lesser substituted double bond, providing the *exo*-adduct **(71)** exclusively, with yields of 39-46% and moderate to good enantioselectivity (45-88% *ee*) **(Scheme 1.20)**.



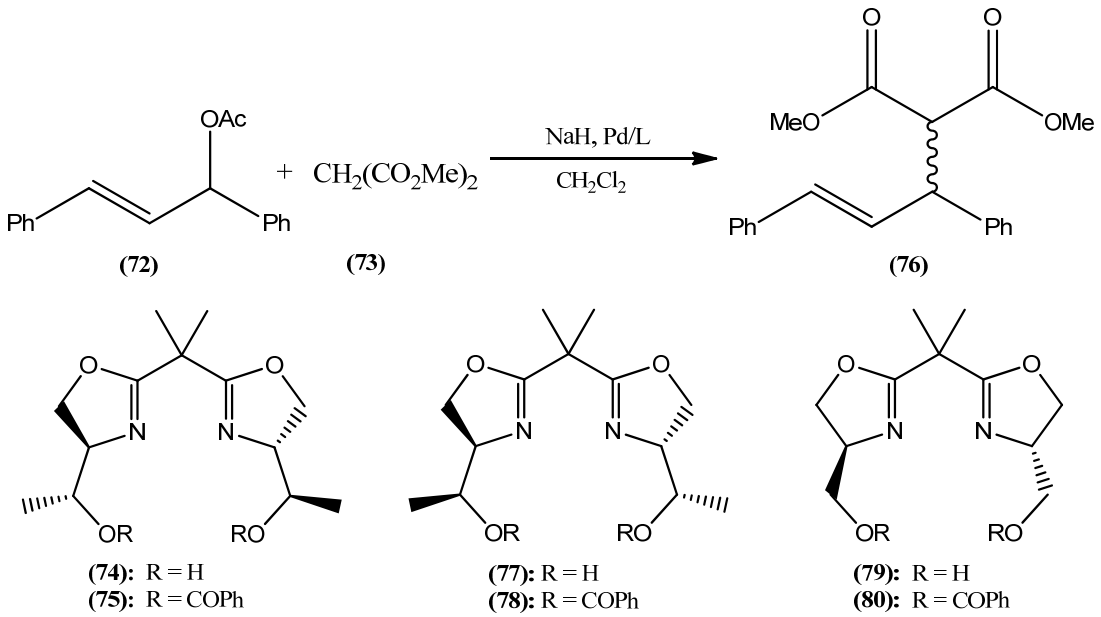
(69) **(70)** **(71)**

Scheme 1.20

In agreement with the assertion that hydrogen donation was occurring, switching from a free hydroxyl side-chain as in ligand **(55)** to the acetyl protected derivative **(68)** resulted in a drop in enantioselectivity from 69% *ee* with **(55)** to 45% *ee* with **(68)**. Selectivities were also shown to be highest with ligands possessing the strongest hydrogen donors, with the tosyl protected amino ester ligand **(56c)** providing **(71)** in 39% yield and 88% *ee*.

Ait-Haddou *et al* tested bisoxazoline ligands on the palladium catalysed allylic alkylation of (±)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene **(72)** with dimethyl malonate **(73)**, using sodium hydride as a base **(Scheme 1.21)**.[64] They reported that use of the free hydroxyalkyl ligand **(74)** provided the opposite enantiomer, in 90% yield and in 63% *ee*(*R*), to that afforded from the alkoxy-substituted ligand **(75)**, which afforded the desired product **(76)** in 90% yield and 68% *ee*(*S*). They proposed that hydrogen bonding between the hydroxyl group and the dimethyl malonate **(73)** brought about the observed reversal in selectivity.

Surprisingly, it would seem that the relative stereochemistry of the ligand is a key factor in determining the sense of chiral induction. When the two stereogenic centres have the same absolute configuration [as in ligands **(74)** and **(75)**], a reversal in sense of chiral induction occurs when switching between the free hydroxyl ligand and its alkoxy derivative. However, no reversal occurs when the two ligands have either differing absolute configurations [ligands **(77)** and **(78)**], with both the hydroxyl and alkoxy substituted ligands giving 72% *ee*(*S*) and 97% *ee*(*S*) respectively, or have no secondary stereocentre [ligands **(79)** and **(80)**] with both ligands providing the product **(76)** in 100% yield and 80% *ee*(*S*). As such, it is necessary to have a specific structure to induce a reversal in the enantioselectivity. The reasons for this are still not clearly understood.

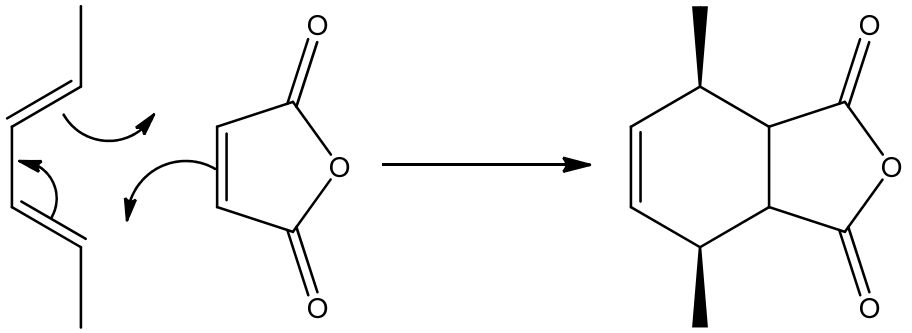


Scheme 1.21

1.6 Asymmetric reactions using bisoxazoline ligands

1.6.1 Diels Alder reactions

The Diels Alder reaction is a [4+2]-cycloaddition between a conjugated diene [e.g. *E*,*E*-2,4-hexadiene **(81)**] that can exist in the s-*cis* conformation and a dienophile [e.g. maleic anhydride **(82)**] to produce a six-membered ring **(83) (Scheme 1.22)**. The reaction proceeds by overlap of the highest occupied molecular orbital of the diene (HOMO) and the lowest unoccupied molecular orbital of the dienophile (LUMO) provided they are of similar energy. This occurs most effectively when the dienophile is conjugated to an electron-withdrawing, which lowers the energy of its LUMO, and the diene conjugated to an electron-donating group, raising its HOMO.



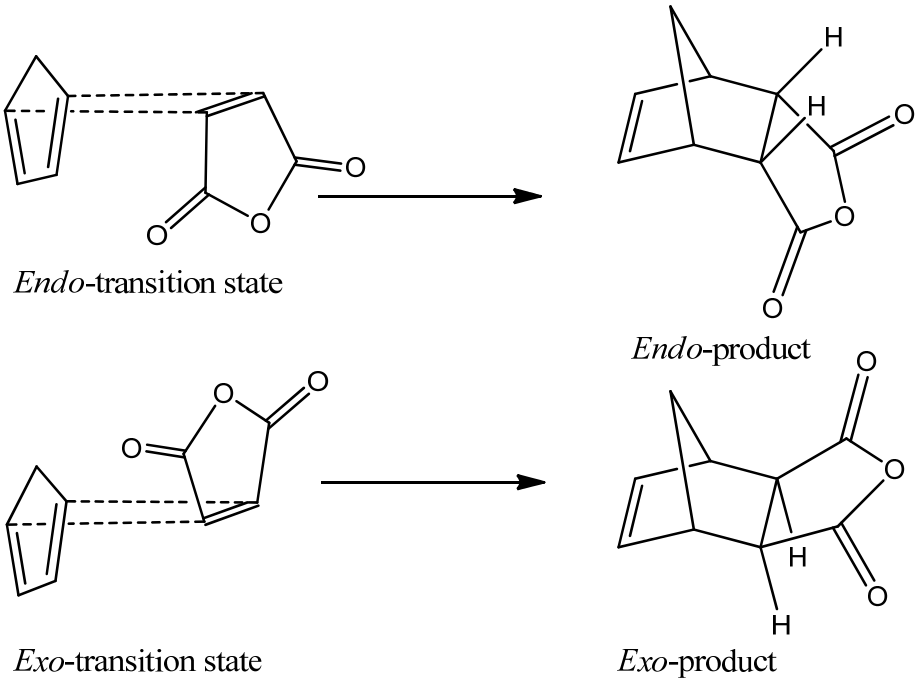
(81) **(82)** **(83)**

Scheme 1.22

The Diels Alder is a stereospecific reaction, with *syn* addition occurring with respect to both the diene and the dienophile. As such the *cis*-isomer of a dienophile will afford a product in which the substituents are *cis* to one another, while the *trans*-isomer will yield a product with substituents *trans* to one another. The diene substituents also maintain the relative configurations in the product. If the diene substituents possess the same stereochemistry (i.e. both are *cis* or both are *trans*) then both of the substituents will end up on the same face of the product. If they have the opposite stereochemistry (i.e. *cis* and *trans*) then the substituents will end up on opposite faces of the product.

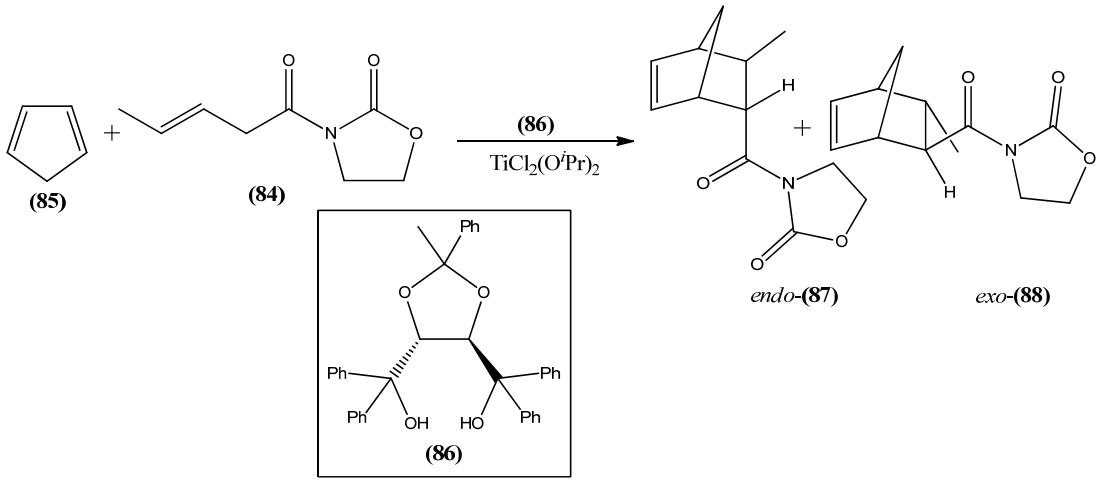
The Diels Alder reaction can also give stereoisomeric products, known as the *endo* and *exo*-adducts, depending on the approach of the diene **(Scheme 1.23)**. While the *exo* adduct is generally the thermodynamically favoured product, the *endo* product is usually the formed in higher yields. One rationalization for the preferential formation of the *endo* isomer is that secondary orbital overlap occurs between the diene and the carbonyl group of the dienophile in the transitions state.

It has long been known that Lewis acids are capable of catalysing Diels Alder reactions.[65-67] By binding to the electron withdrawing group of the dienophile, the Lewis acid can reduce the LUMO of the dienophile even further. Regio- and stereoselectivity have both been reported to increase in Lewis acid catalysed reactions with respect to uncatalysed reactions.[67] By introducing chiral Lewis acids as catalysts, researchers have hoped to generate further stereocontrol over the reaction.



Scheme 1.23

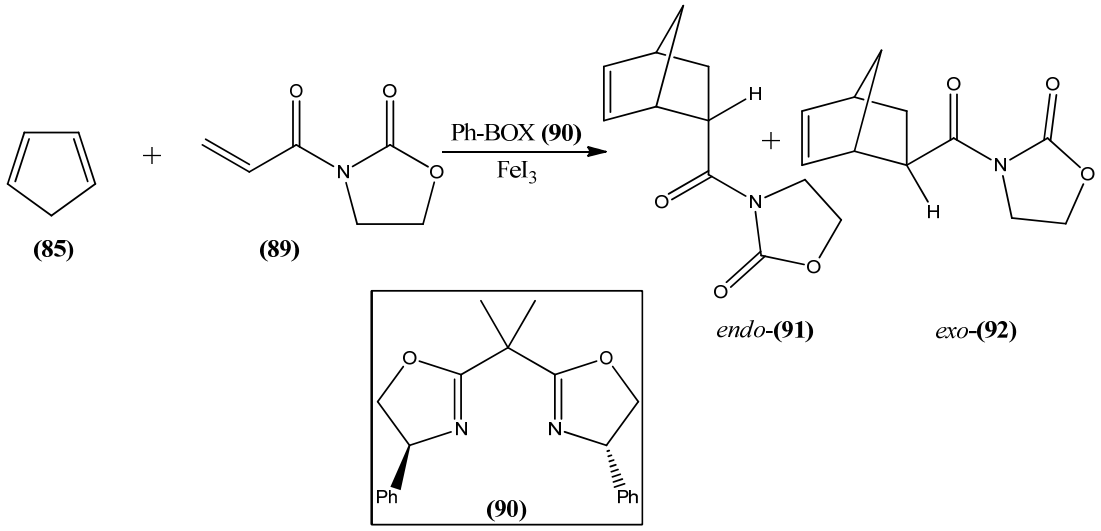
Naraska *et al* catalysed the asymmetric Diels Alder reaction of *trans*-(crotonyl)-2-oxazolidinone **(84)** and cyclopentadiene **(85)** using the titanium complex of the TADDOL ligand **(86)**.[68] They were able to achieve an 87% yield of the Diels Alder adduct with an *endo*:*exo* ratio of 92:8 and 91% *ee* of the *endo* product **(87) (Scheme 1.24)**. Transition metal complexes of salen and BINOL ligands, amongst others, have also shown highly impressive stereoselectivity in catalytic asymmetric Diels Alder reactions.[69,70]



Scheme 1.24

In 1991 Corey *et al* published a communication describing Diels Alder reaction of 3-acryloyl-2-oxazolidinone **(89)** and cyclopentadiene **(85)** catalysed by the complexes

formed between Fe(III) halides and phenyl bisoxazoline ligand **(90)**.[45] The reaction resulted in a 95% yield and was found to be highly stereoselective, with an *endo*:*exo* ratio of 96:4 and 82% *ee*(*R*) for the *endo* product **(91) (Scheme 1.25)**. Over time this reaction has become one of the benchmark reactions for testing the effectiveness of new metal-bis(oxazoline) complexes for asymmetric Diels Alder reactions.



Scheme 1.25

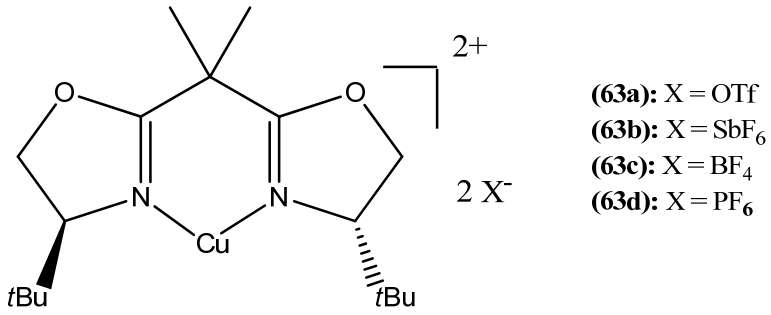
Following this, Evans *et al* carried out further asymmetric Diels Alder reactions using the Cu(II) complexes with various salts.[71] While the Fe(III) complex of the phenyl bisoxazoline ligand **(90)** was more efficient than its Cu(II) counterpart, Evan's was able to show that the Cu(II)-*tert*-butyl bisoxazoline complex **(63a)** was as active, resulting in a 86% yield, and more stereo- and enantioselective [*endo*:*exo* ratio of 98:2 and >98% *ee*(*R*) of the *endo* product **(91)**].

Engberts has shown that, in general, Cu(II) complexes outperform other metal complexes including Zn(II), Co(II) and Ni(II).[72] Follow up studies performed by Evans, using the metal triflate-*tert*-butyl bisoxazoline complexes, backed up these results.[73] The Cu(II) complex easily produced the highest *ee's* (>98%), with only the $Zn(OTf)_2$ complex showing comparable *endo*:*exo* diastereoselectivities **(Table 1.2)**.

Entry	Metal salt	Yield	*endo*:*exo*	*endo ee* (%)
1	$Cu(OTf)_2$	86%	98:2	>98
2	$Zn(OTf)_2$	85%	95:5	38
3	$Co(OTf)_2$	85%	90:10	50
4	$Mn(OTf)_2$	80%	85:15	50
5	$Li(OTf)_2$	89%	85:15	14
6	$Ni(OTf)_2$	75%	90:10	40

Reactions between cyclopentadiene **(85)** and imide **(89)** carried out with catalysts derived from $M(OTf)_2$ and *t*BuBOX ligand **(93)**

Table 1.2



(63a): X = OTf
(63b): X = SbF_6
(63c): X = BF_4
(63d): X = PF_6

Figure 1.11

Evans has also shown the importance of the counterions used with the metal salts. This was done by testing Cu(II) complexes **(63a)**, **(63b)**, **(63c)** and **(63d)**. While the various salts showed similar enantioselectivity, with an *endo ee* >98% in all cases, the activity of the SbF_6 complex **(63b)** was much higher than that of the others. After 1 h, the % conversion of the **(63b)** catalysed reaction was greater than that of the **(63a)** catalysed reaction by a factor of 20. **(63b)** was also the only catalyst to lead to complete conversion of the adduct **(91)** at -78 °C. However, the diastereoselectivity for the **(63b)** catalysed reactions was lower (*endo*:*exo* ratio of 91:9) than that of the other complexes (*endo*:*exo* ratio of 98:2 in all other cases), which may be due to its high reactivity.

The effect of catalyst loading on activity and enantioselectivity has also been tested using the Cu(II) complexes of SbF_6 **(63b)** and OTf **(63a)**.[73] Dropping from 10 mol% to 1 mol% has little impact on the efficiency of **(63b)**, even at -78 °C. However below a 5 mol% loading **(63a)** was no longer able to promote the reaction well, even on raising the temperature to -50 °C **(Table 1.3)**.

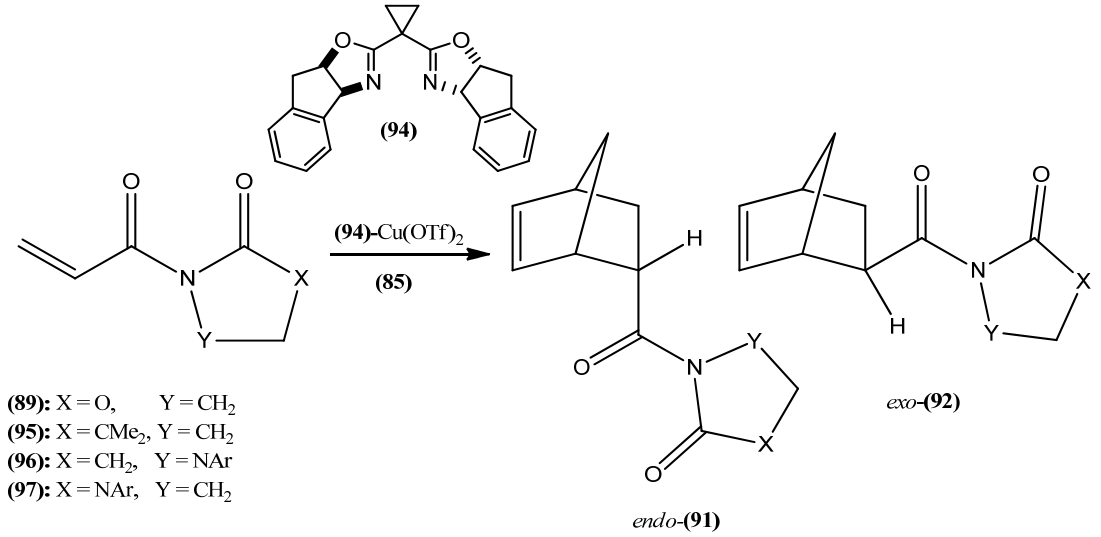
Entry	Catalyst	mol%	Temp (°C)	*endo*:*exo*	*endo ee* (%)
1	X =OTf	10	-78	98:2	>98
2	X = SbF_6	10	-78	96:4	>98
3	X = OTf	5	-50	97:3	96
4	X = SbF_6	5	-78	96:4	96
5	X = OTf	1	-50	-	-
6	X = SbF_6	1	-78	96:4	96

Effect of catalyst loadings in reactions between cyclopentadiene **(85)** and imide **(89)** with catalysts derived from $Cu(X)_2$ and *t*BuBOX **(93)**

Table 1.3

Sibi *et al* have investigated the effects on dienophile variation in Diels Alder reactions.[74] The amino indanol derived spirocyclic cyclopropyl bisoxazoline ligand **(94)** and copper triflate were combined to form a chiral complex. The dienophiles examined were all capable of forming 6-membered chelates with the chiral complex. Replacement of the oxygen in the oxazolidinone ring with a methylene group gave the pyrrolidinone template. Pyrrolidinone **(95)**, with a *gem*-dimethyl group in the 3-position, was shown to give the highest selectivity, as well as being the most reactive. Reactions with the pyrrolidinone resulted in complete conversion in 3 min at 0 °C, with an *endo*:*exo* ratio of 20:1 and 95% *ee*(*S*). Reducing the temperature to -78 °C lengthened the reaction time to 6 h, resulting in a 91% yield and higher stereoselectivity [*endo*:*exo* ratio of >100:1 and 99% *ee*(*S*)] **(Scheme 1.26)**.

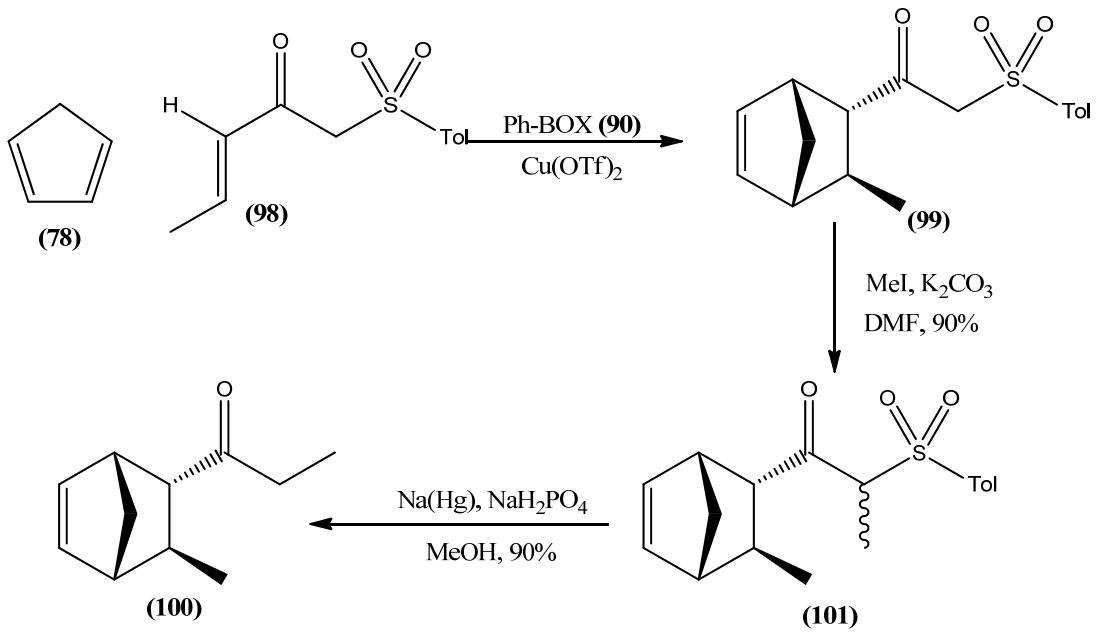
Imidazolidinones such as **(97)**, where the oxazolidinone oxygen has been converted to a nitrogen, maintained high yields (90-94%) and enantioselectivities [(80-94% *ee*(*S*)] **(Scheme 1.26)**. However, reaction times increased to 3-5 days at -78 °C and diastereoselectivities fell to <30:1. In general, they found the following reactivity trend was observed: pyrrolidinones > pyrazolidinones > oxazolidinones > imidazolidinones.



Scheme 1.26

Following the work of Wada with TADDOL-Ti(IV) complexes, Pedro *et al* have tested β-sulphonyl enones as bidentate dienophiles with copper bisoxazoline complexes.[75,76] Screening of various metal salts and bisoxazoline ligands showed the $Cu(OTf)_2$ complex of phenyl bisoxazoline ligand **(90)** significantly outperformed the other combinations. Testing on the β-sulphonyl enones showed that variations made on the aryl sulphonyl group (R^2 = Cl, Me or OMe) had little impact on results, with high yields and selectivity in all cases. Placing substituents at the α-carbon (R^1 = Me) while maintaining high enantioselectivity, removed any sense of diastereoselectivity, producing a 1:1 diastereomeric mixture. Finally, changes made to substituents at the β-carbon (R = Me, 4-$MeOC_6H_4$ or 4-$NO_2C_6H_4$) had no impact on stereoselectivity, while large bulky substituents (R = *t*Bu) impacted on diastereoselectivity, also producing a 1:1 diastereomeric mixture.

These β-sulphonyl enones have been used in place of monodentate enones, which have proven to be poor dienophiles in this catalytic system. Reaction of β-sulphonyl enone **(98)** and cyclopentadiene **(85)** proceeded to give a 93% yield, with an *endo*:*exo* ratio of 92:8 and an *ee* of 91% for the *endo* product **(99)**. Alkylation of **(99)** with methyl iodide in DMF, followed by cleavage of the sulphonyl group using a Na/Hg amalgam gave the alkylated enone product **(100)** in 74% yield over three steps **(Scheme 1.27)**.



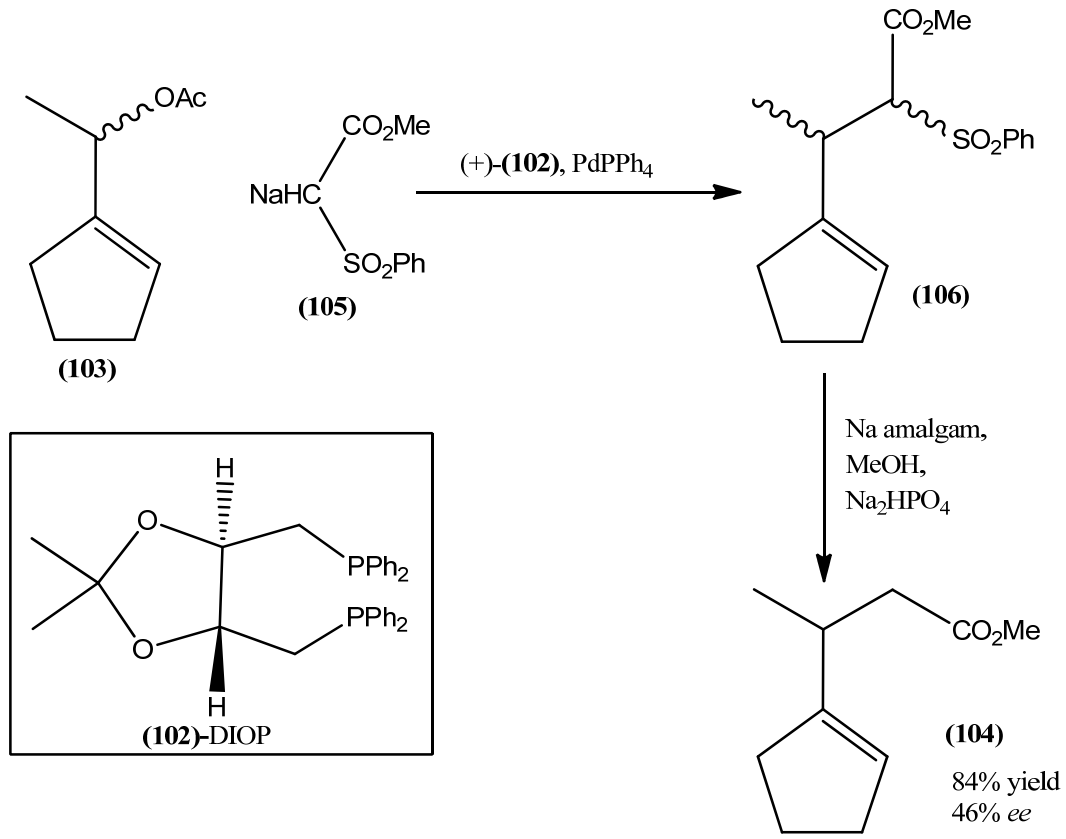
Scheme 1.27

1.6.2 Allylic Alkylation reactions

The transition metal catalysed allylic alkylation substitution reaction is important synthetic tool for the controlled introduction of functional groups to organic compounds **(Scheme 1.28)**. The reaction can be used for various transformations, affording high regio-, chemo- and stereoselectivity. A variety of transition metals have been used as catalysts for this process including palladium, iridium, molybdenum, iron and rhodium amongst others.

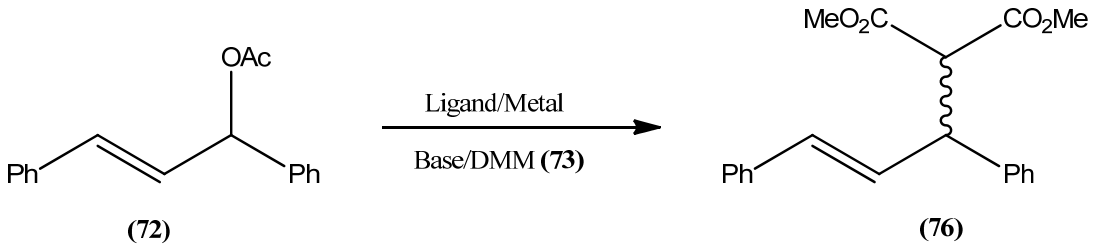
Scheme 1.28

In 1977, Trost *et al* carried out the first catalytic asymmetric allylic alkylation using a chiral palladium complex.[77] The chiral ligand involved was a C_2-symmetric diphosphine ligand by Kagan and Dang in the early 1970s, known as DIOP **(102)**. Using substrate **(103)** they obtained **(104)** in good yield (84%) with moderate enantioselectivity (46% *ee*) **(Scheme 1.29)**.



Scheme 1.29

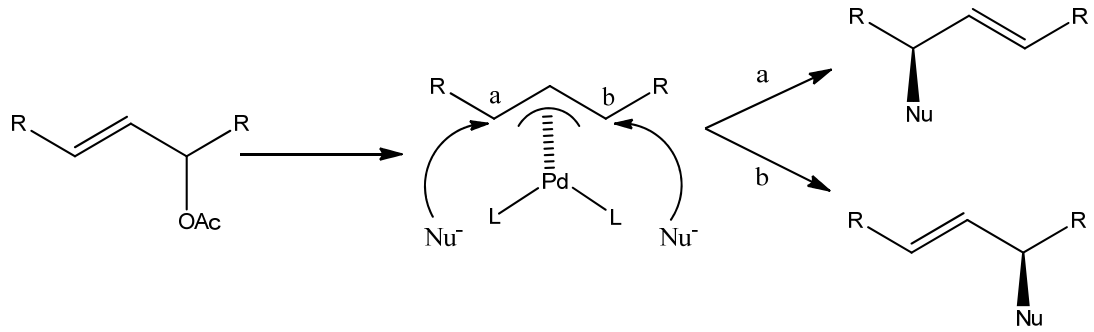
Optimization of allylic alkylation reactions has led to improvements in stereoselectivity with enantiopurities of >90% *ee* being routinely achieved with a variety of substrates. The reaction of the 1,3-diphenylallyl system has become one of the benchmark reactions in allylic substitutions since its introduction **(Scheme 1.30)**. Like all benchmark reactions, it has become commonplace to use it for the design and evaluation of novel ligands. The most common nucleophile employed in this reaction is dimethyl malonate **(73)**, with a base such as sodium hydride or *N*,*O*-bis(trimethylsilyl)acetamide (BSA) with catalytic amounts of KOAc.



Scheme 1.30

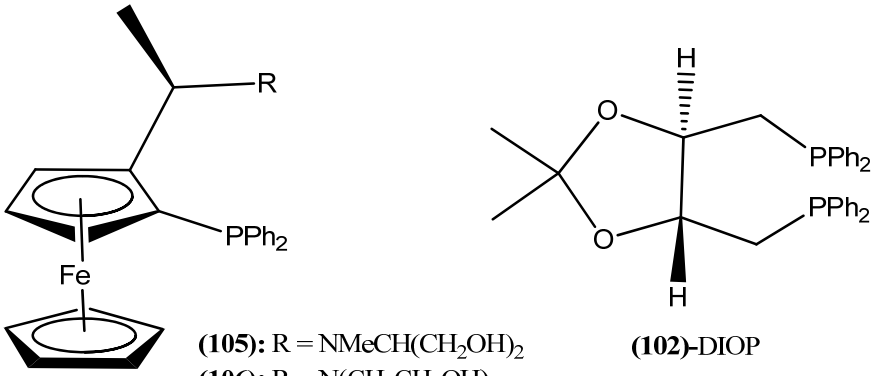
The success of symmetrical substrates like these lies in their ability to proceed *via* a *meso* intermediate complex. The two allylic termini of the *meso* intermediate are

enantiotopic. The allyl group to which the nucleophile adds will dictate the enantiomer of the product formed. As such, the problem of enantioselectivity becomes one of regioselectivity. Use of a chiral catalyst will perturb the symmetry of the intermediate causing the allylic termini to become diastereotopic **(Scheme 1.31)**.



Scheme 1.31

This can occur through steric interactions as demonstrated by Hayashi *et al* with their ferrocenyl phosphine ligands **(105)-(107)** among the first to achieve >90% *ee* **(Figure 1.12)**.[78] A palladium complex of **(105)** gave a 97% yield and 90 % *ee*, while the palladium complex of **(106)** gave an 86% yield and 81% *ee* of the desired product **(76)**. The high selectivity was attributed to the hydroxyl groups on the amino side-chain controlling the attack of the nucleophile on the π–allyl system. The use of ligands lacking these interactive functional groups, such as complexes derived from ligand **(107)** or DIOP, resulted in the formation of nearly racemic products, with the Pd-**(107)** complex providing product **(76)** in 92% yield, but only 10% *ee*, while the Pd-DIOP complex gave **(76)** in 88% yield with 0% *ee*.



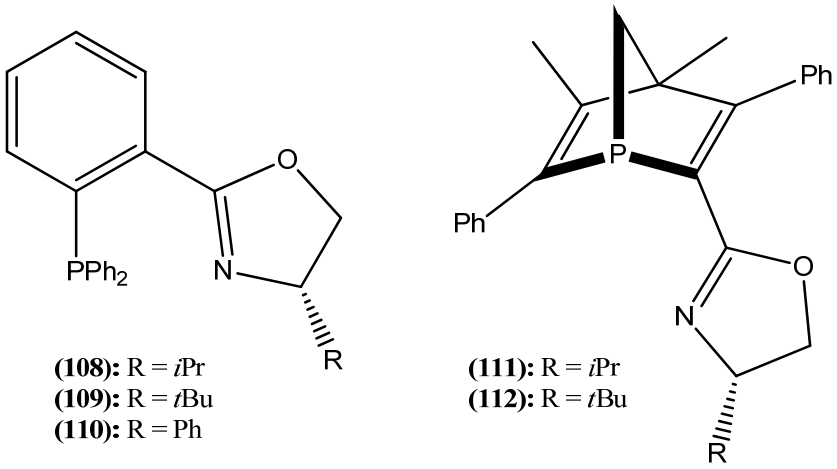
(105): R = $NMeCH(CH_2OH)_2$
(106): R = $N(CH_2CH_2OH)_2$
(107): R = Me

(102)-DIOP

Figure 1.12

Alternatively, electronic effects can be used to disrupt the geometry of the allyl palladium intermediate. This can be done by using non-C_2-symmetric ligands which

possess two different donor atoms, such as nitrogen and phosphorous. If one of the donor atoms is a better π-acceptor it may weaken metal-carbon bond *trans* to it. For example, it has been shown that in a (L*)Pd(II)(π-allyl) complex, with phosphorous and nitrogen chelation sites, the metal-carbon bond *trans* to the phosphorous atom is the weaker, longer bond than the bond *trans* to the nitrogen atom. As such, it is becomes more susceptible to attack from the nucleophile.



(108): R = *i*Pr
(109): R = *t*Bu
(110): R = Ph

(111): R = *i*Pr
(112): R = *t*Bu

Figure 1.13

This type of approach has been used by various groups including Helmchen, Williams and Pfaltz who each independently reported the synthesis of phosphinoxazoline ligands **(108)-(110)** for use in asymmetric allylic alkylation reactions (**Figure 1.13**).[79-81] Helmchen *et al* applied Pd-**(108)** complex to the reaction of 1,3-diphenyl-2-propenyl acetate **(72)** shown in **Scheme 1.30**.[79] The catalysed reaction gave **(76)** in 99% yield with excellent selectivity (98% *ee*). Gilbertson *et al* have also applied their rigid bicyclic ligands **(111)** and **(112)** to the symmetrical allylic substitution reaction achieving excellent yields (>99%) and high enantioselectivity (93-94% *ee*) **(Figure 1.13)**.[82]

Ait-Haddou *et al* have applied their bisoxazoline ligands [**(113)** and **(114)**] **(Figure 1.14)** to the allylic alkylation reaction **(Scheme 1.30)**.[64] Using the Pd-**(113)** complex and sodium hydride as base to generate the nucleophile gave product **(76)** in 98% yield and 92% *ee*(*S*). Interestingly, by switching the ligand to **(114)** the sense of chiral induction was reversed, with product **(76)** obtained in 90% *ee*(*R*). It was assumed that an interaction by one of the hydroxyl groups was governing the regioselective attack of the incoming nucleophile on the palladium π-allyl intermediate. Use of ligand **(114)** removed this effect reversing the sense of

asymmetric induction. In order to investigate the effect of the base on selectivity the reaction was carried out with BSA/KOAc, producing a softer anionic nucleophile. The results were surprising, with both ligand complexes giving the (*R*) enantiomer in 90% *ee*. The results indicated that a ketene silyl acetate maybe acting as the nucleophile in the reaction, preventing interaction between the nucleophile and the hydroxyl groups.

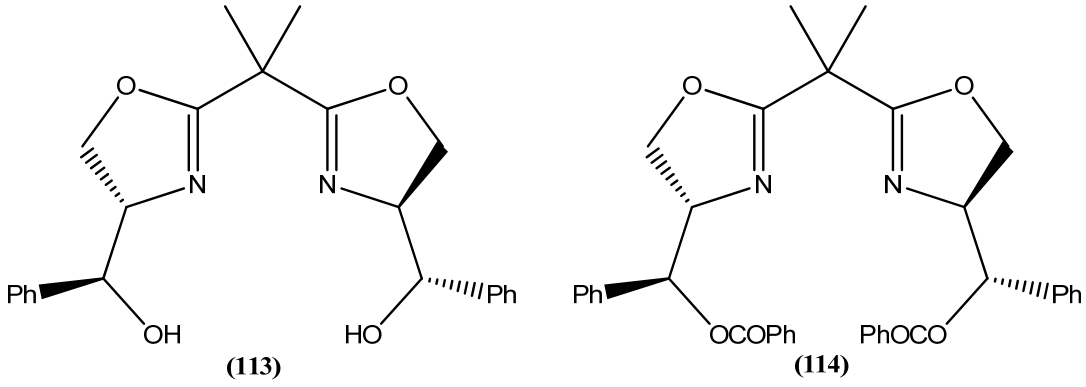
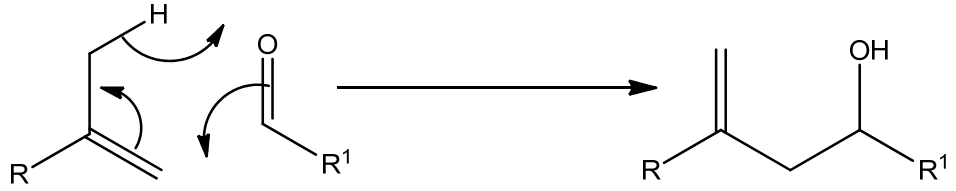


Figure 1.14

1.6.3 Ene reactions

An ene reaction can be generally classified as the reaction between the ene reagent, an alkene bearing an allylic hydrogen, and the enophile, a compound containing a multiple bond. The reaction involves formation of a new C-C bond, with migration of the ene double bond and a 1,5 hydrogen shift. The product is a substituted alkene with the double bond shifted to the allylic position. The class of reaction which involves using a carbonyl compound as the enophile is known as a carbonyl ene reaction. The products of these reactions are homo allylic alcohols **(Scheme 1.32)**.

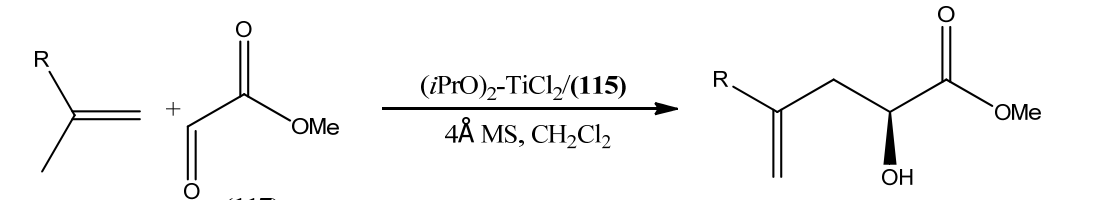


Scheme 1.32

The main orbital interaction occurs between the HOMO of the ene component, which can be thought of as similar to the diene in a Diels Alder reaction, and the LUMO of the enophile. As such, electron rich alkenes are generally more reactive

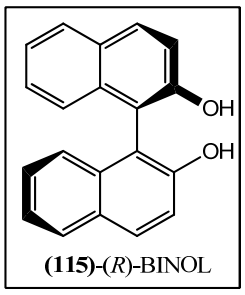
than their electron poor alternatives. Studies have found that 1,1-disubstituted alkenes are the preferred ene reagents, followed by trisubstituted alkenes. Both are significantly more reactive than the alternatives; tetrasubstituted, monosubstituted and 1,2 disubstituted alkenes.[83]

In the early 90s, Nakai *et al* developed chiral titanium-BINOL complexes for the asymmetric glyoxylate-ene reaction. The BINOL-$TiCl_2$ complex **(115)** catalysed the reaction of alkenes **(116a)** and **(116b)** with methyl glyoxylate **(117)** in the presence of 4Å molecular sieves, affording the corresponding α-hydroxyl esters **(118a)** and **(118b)** in good yields (72-100%) with high enantioselectivity (95-97% *ee*). The molecular sieves proved crucial to the reaction, with enantioselectivities falling drastically in their absence (7-10% *ee*), although the reaction did proceed smoothly with yields of 79-81% obtained.[84] Further work by Mikami showed that variation in the catalyst preparation allowed the use of only 0.2 mol% with *ee*'s of 98.7% achieved. While 1,1-disubstituted alkenes like those in **Scheme 1.33** have provided carbonyl ene products with extremely high enantiopurity, no product is obtained in reactions with mono- and 1,2-disubstituted alkenes using the titanium complex.[85]



(116a): R = Me
(116b): R = Ph
(117)

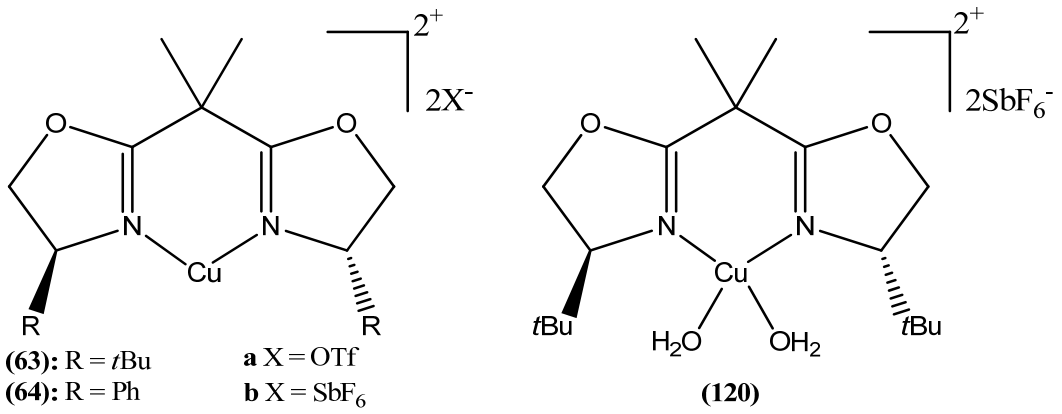
(118a): R = Me: 72% yield, 95% *ee*
(118b): R = Ph: 100% yield, 97% *ee*



(115)-(*R*)-BINOL

Scheme 1.33

Chiral Cu(II) complexes have also been used to catalyse the enantioselective carbonyl ene reactions. Studies carried out using copper complexes with chiral bisoxazoline ligands have shown impressive results. Evans *et al* have studied the reaction of ethyl glyoxylate **(119)** with a variety of olefins, using a number of different bisoxazoline-Cu(II) complexes **(Figure 1.15)**, reporting high levels of activity and stereoselectivity.



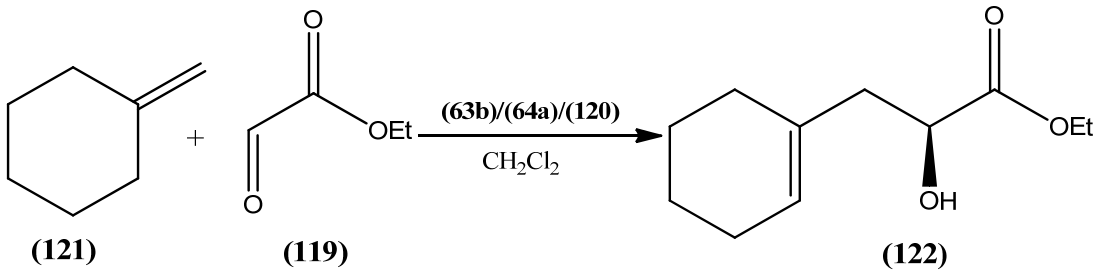
(63): R = *t*Bu
(64): R = Ph

a X = OTf
b X = SbF_6

(120)

Figure 1.15

Reaction of methylene cyclohexane **(121)** with ethyl glyoxylate **(119)** gave the desired product **(122)** in 97% yield and 97% *ee*(*S*) when catalysed by **(63b) (Scheme 1.34)**.[86] Use of the bisaquo complex **(120)** gave similar results for **(122)**, with the only noticeable difference being a slight decrease in reaction rate. The PhBOX-Cu(II) complex **(64a)** was also used to catalyse this system, with the ene product **(122)** formed in 99% yield and 87% *ee*(*R*).



(121) **(119)** **(122)**

Scheme 1.34

The reversal in the sense of asymmetric induction by two complexes derived from ligands of the same configuration has been previously mentioned in the Metal bisoxazoline complexes section **(Section 1.5.4)**. As discussed earlier, Evans has proposed a mechanism in which π-stabilisation in the transition state causes the reversal in geometry, while Jorgensen has attributed a greater flexibility in the PhBOX complex **(64a)** compared to the *t*BuBOX complex **(63b)** as being the possible cause.[61,63] The stereoselectivity observed for the *t*BuBOX complex **(63b)** is consistent with a square planar complex geometry, with approach of the ene from the *si*-face opposite the nearby *tert*-butyl substituent, which blocks off attack from the *re*-face causing it to be disfavoured **(Figure 1.16)**.

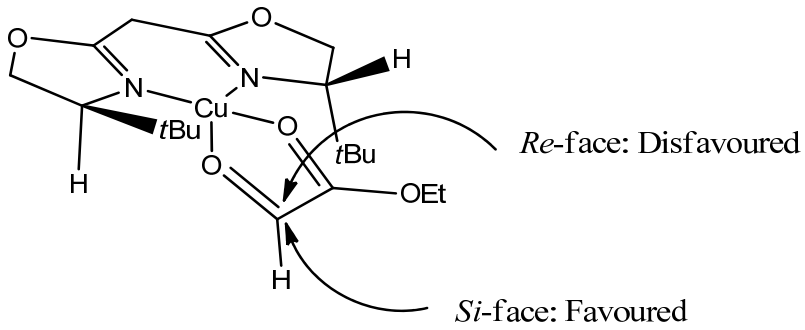
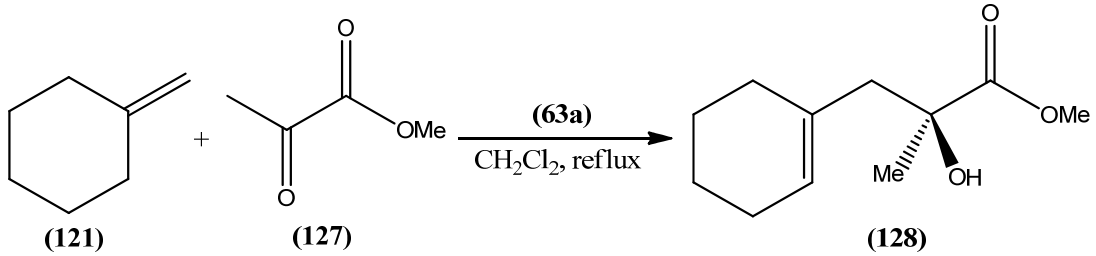


Figure 1.16

Evans' cationic Cu(II) complexes have also been shown to be more reactive than Mikami's Ti(IV) based catalysts. The Cu(II) bisaquo complex **(120)** has successfully catalysed reactions of less reactive enophiles such as mono and 1,2-disubstituted alkenes; reactions which the titanium complexes failed to promote. Use of complex **(120)** to promote the addition of cyclohexene **(123)** and ethyl glyoxylate **(119)** gave the product **(124)** in 95 % yield and 98% *ee*. For monosubstituted alkenes the use of 1-hexene **(125)** provided the desired product **(126)** in 96% yield and 92% *ee* in the presence of complex **(63b)**.[87]

Pyruvate esters have been shown to be less reactive than glyoxylate esters, with Mikami's titanium complexes also unable to promote carbonyl ene reactions using them as enophiles. However, Cu catalysed additions of 1,1 disubstituted alkenes to methyl pyruvate **(127)** have been reported by Evans. *t*BuBOX complex **(63a)** catalysed the addition of methylene cyclohexane **(121)** to methyl pyruvate **(127)** in 84% yield and 98% *ee* **(Scheme 1.35)**.[87]



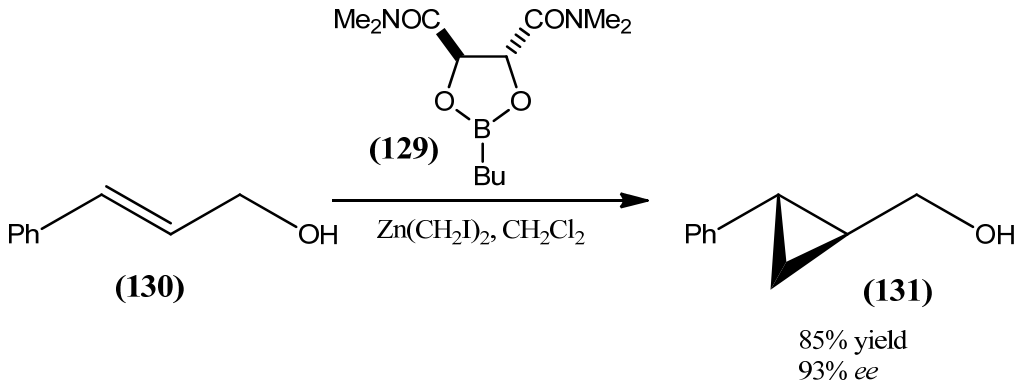
Scheme 1.35

1.6.4 Cyclopropanation reactions

Cyclopropane rings, despite being highly strained systems, are a common structural motif found in a nature.[88-90] The prevalence of the cyclopropyl ring in natural and synthetic compounds with biological activity has led to diverse approaches to their

synthesis. These include the Simmons-Smith reaction,[91-93] the Michael-initiated ring closure[94,95] and the use of metal-carbenoid mediated reactions.[43,48,49,55,90,96]

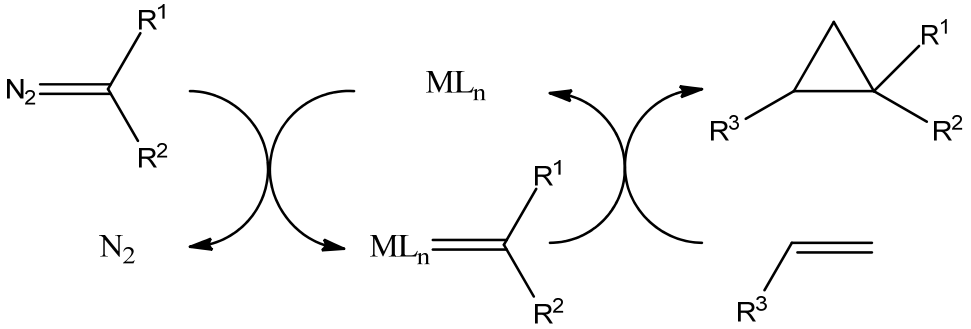
The reaction of alkenes with a diiodoalkane in the presence of activated zinc to afford cyclopropanes is known as the Simmons-Smith reaction.[91-93] In 1998, Charette *et al* reported the synthesis of a novel dioxaborolane ligand **(129)**. The chiral ligand was successfully employed in the enantioselective cyclopropanation of cinnamoyl alcohol **(130)**, giving the cyclopropane product **(131)** in 85% yield and 93% *ee* **(Scheme 1.36)**.[91] Other ligands such as BINOL and TADDOL derivatives have also been used in these systems.[92,93]



Scheme 1.36

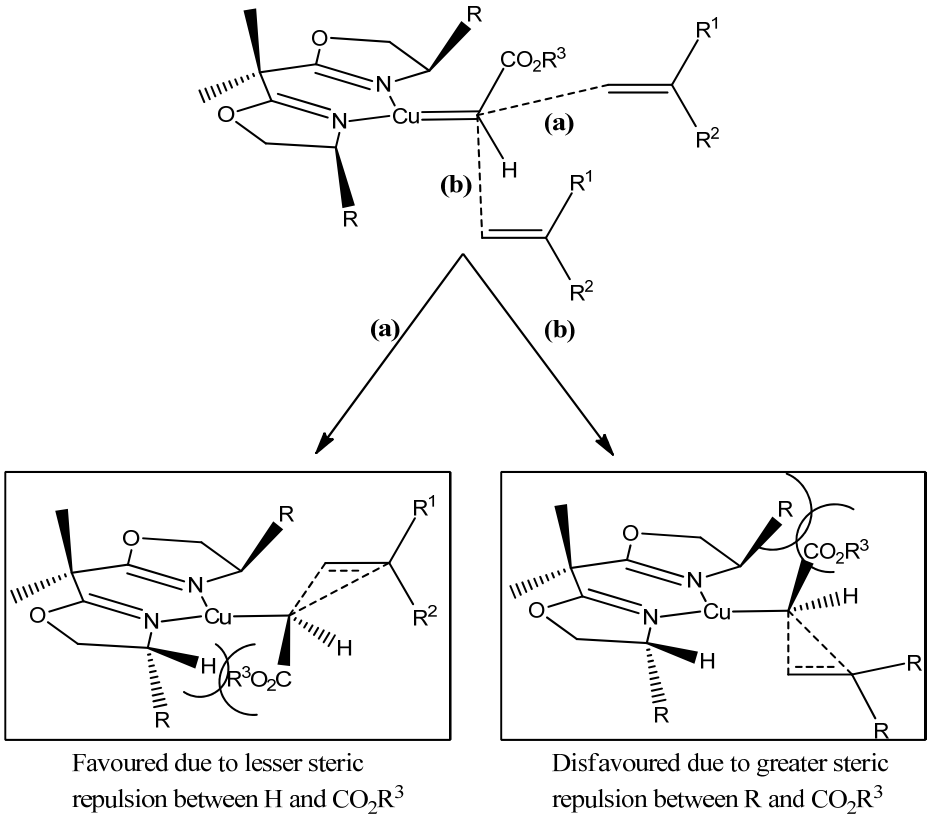
Of the methods available, the use of transition metal carbenoids in catalysing the cyclopropanation of olefins, are often the most utilized. Catalysts using copper, ruthenium and rhodium, amongst others, have all been reported. Some of the highest enantioselectivites have been achieved using Cu(I) complexes of chiral C_2-symmetric bisoxazoline ligands.[49,90]

The catalytic cycle of the carbenoid cyclopropanation reaction is outlined below **(Scheme 1.37)**. Transition metal catalysed decomposition of the diazo precursor affords the metallocarbene complex as the key intermediate, with concomitant release of nitrogen. Electrophilic addition of the carbene to an appropriate substrate such as an olefin follows, yielding the desired cyclopropane ring. Enantiocontrol in the carbene-transfer step can be generated by use of chiral transition metal catalysts.



Scheme 1.37

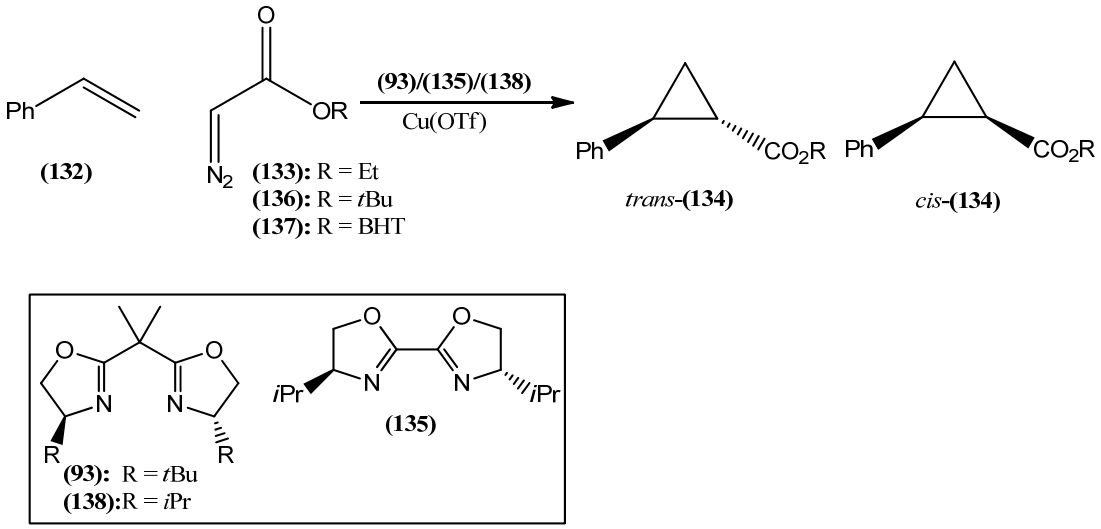
Pfaltz *et al* have attempted to rationalize the origin of the excellent enantioselectivities obtained with C_2-symmetric complexes of bidentate nitrogen ligands such as semicorrins and bisoxazolines.[43] Following formation of the metal carbene complex above **(Scheme 1.37)**, the reactive carbenoid species proceeds to attack the olefin. The carbenoid substituents occupy positions perpendicular to the plane of the metal oxazoline complex. Upon attack on the olefin the acyl moiety of the carbenoid can move either forward [pathway **(a)**] or backward [pathway **(b)**] relative to the perpendicular plane **(Scheme 1.38)**.



Scheme 1.38

Enantioselectivity is governed by the difference in the accessibility of the two enantiotopic faces of the metallocarbene bond. Moving the acyl group forward and away from the bulky R substituent, as in pathway **(a)**, is favoured over **(b)**, where large repulsive steric interaction occurs between the acyl group and the R substituent of the ligand.

In 1991, Evans *et al* reported the use of a Cu(OTf) complex derived from *t*Bu-bisoxazoline ligand **(93)** in the asymmetric cyclopropanation of styrene **(132)** and ethyl diazoacetate **(133)**.[49] The complex proved to be a highly effective catalyst with moderate diastereoselectivity (*trans*:*cis* ratio of 73:27) and excellent enantioselectivity, giving *trans*-**(134)** (99% *ee*) and *cis*-**(134)** (93% *ee*) in 75% combined yield (**Scheme 1.39**). This reaction has taken on significance as one of the benchmark reactions used for the testing and evaluation of new catalysts.

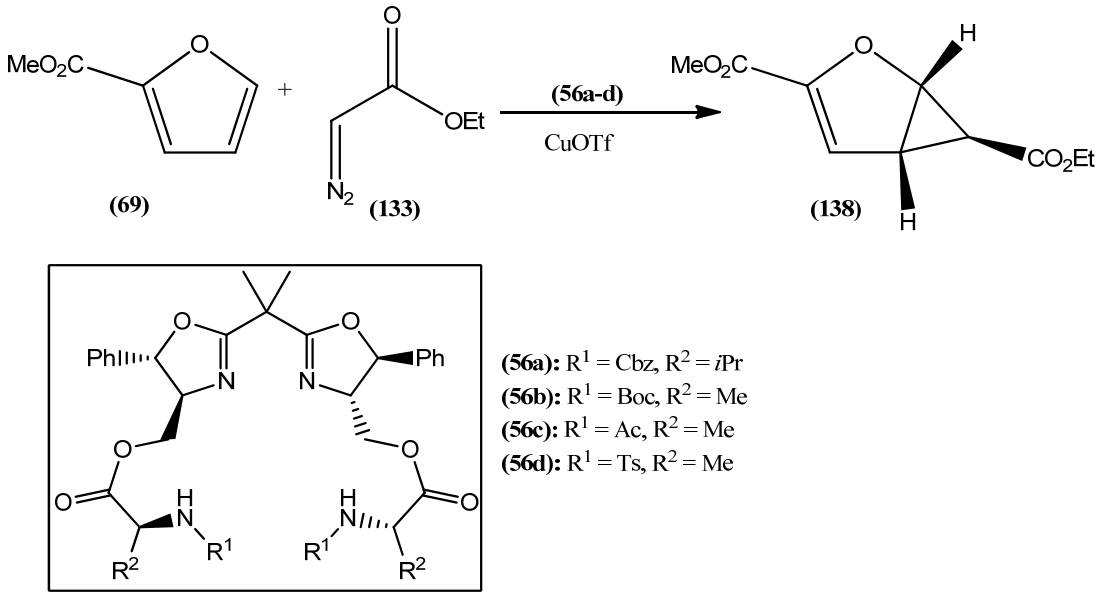


Scheme 1.39

Variation in ligand design showed the effect of the ligand substituents on the enantioselectivity of the cyclopropanation. The 5-membered chelate complex formed using Cu(OTf) and bisoxazoline **(135)** gave almost no enantiocontrol (*ee*'s of 3-8%). Replacement of the *t*Bu groups of **(93)** with the sterically less hindering *i*Pr group gave ligand **(138)**, whose Cu(I) complex yielded reduced enantioselectivities, with *ee*'s of 49% for the *trans* and 45% for the *cis*. Diastereocontrol however was less influenced by variation in the ligand and more so by the alkene/diazo ester combination. Transforming the ethyl ester of the diazo reagent **(133)** to the *t*Bu ester **(136)** increased the diastereoselectivity (*trans*:*cis* ratio of 81:19), while use of the

2,6-di-*tert*-butyl-*p*-tolyl (BHT) derived diazo ester **(137)** gave excellent selectivity (*trans*:*cis* ratio of 94:6).

Variations in the olefin structure have also been studied. As previously discussed, Reiser *et al* have designed novel bisoxazoline ligands **(56a-d)** with secondary binding sites in the form of α-amino esters.[55] These ligands have been successfully applied to the asymmetric cyclopropanation of furans. Reaction of methyl furan-2-carboxylate **(69)** with ethyl diazoacetate **(133)** afforded the corresponding cyclopropane **(138)** in 100% *de* in all cases and good enantioselectivites (83- 91% *ee*) **(Scheme 1.40)**.



Scheme 1.40

The degree of stereocontrol for the reaction was rationalised on secondary binding interactions between the ester group on the furan ring and the ligand substituents. Hydrogen donation from the amino groups on the side chain could limit the furan **(69)** ring's freedom when approaching the catalyst's metal centre **(Figure 1.17)**. In accordance with this proposal, moving the ester group out by one carbon led to significantly reduced selectivity (*ee*'s 40-68%), which is consistent with the theory that hydrogen bonding would be less efficient in those cases. Transformation of the furan ring in **(69)** to an *N*-Boc-pyrrole ring led to a reduction in enantioselectivity, with *ee*'s less than 50% obtained. The authors attributed this to being a consequence of steric hindrance from the bulky *N*-Boc impeding hydrogen bonding.

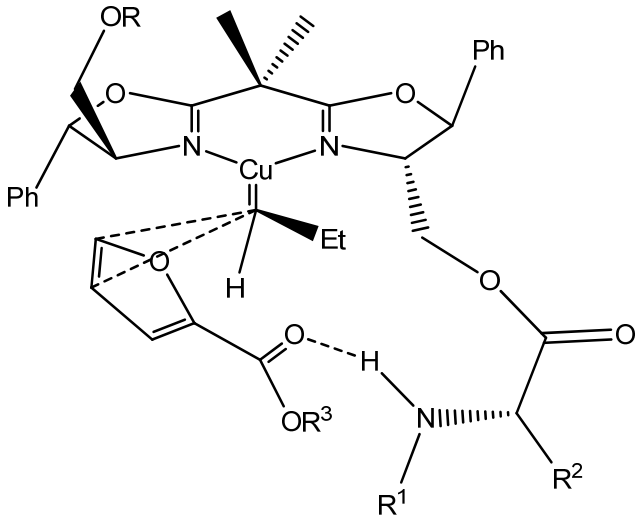
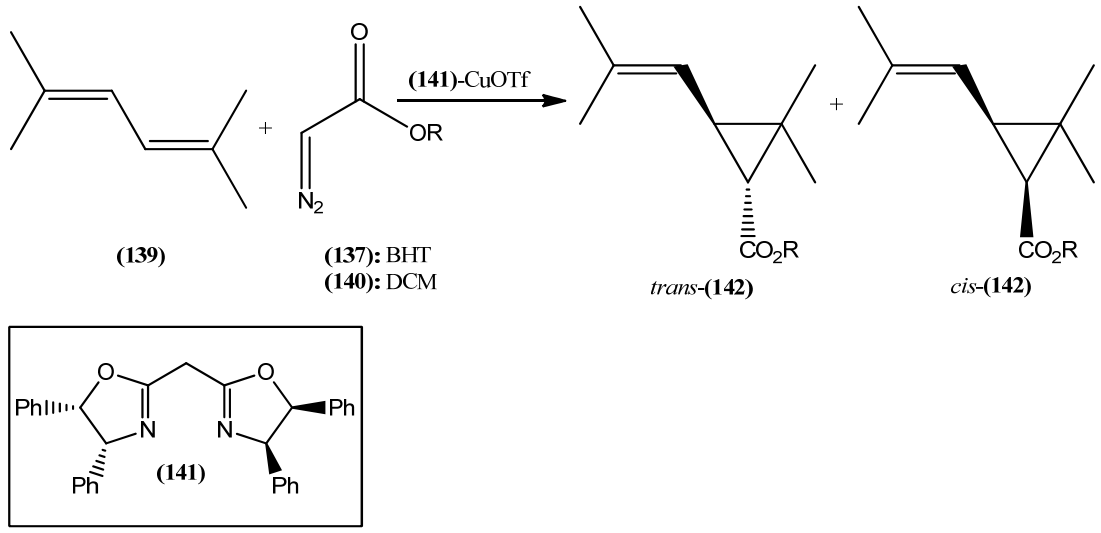


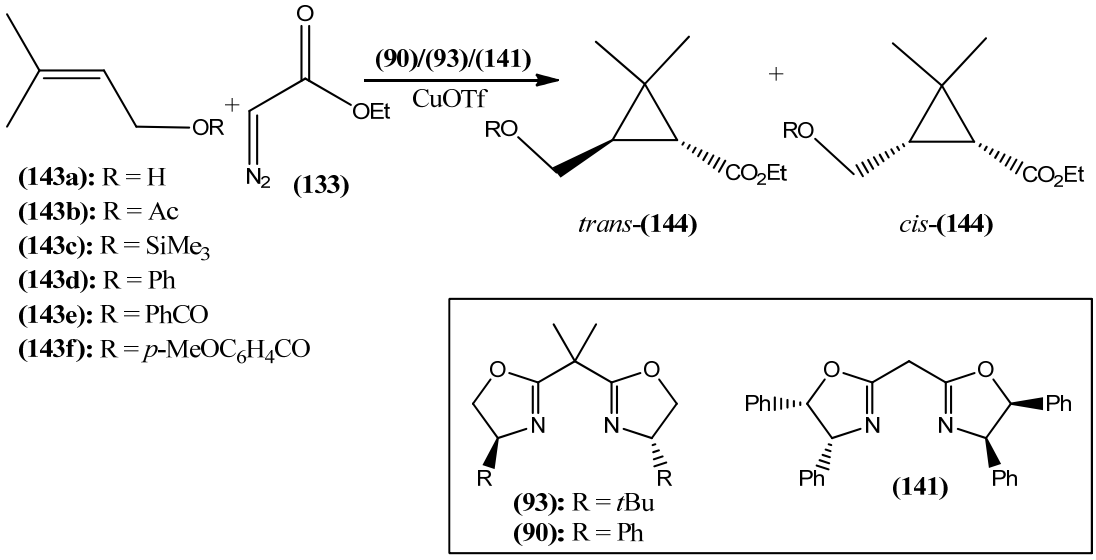
Figure 1.17

Masamune *et al* have also reported high diastereocontrol in the reaction of trisubstituted alkene **(139)**, with both BHT and dicyclohexylmethyl (DCM) derived diazo esters **(137)** and **(140)** giving excellent results of 94:6 and 95:5 *trans*:*cis* ratios respectively, using the Cu(I) complex of 4,5-*cis*-diphenyl bisoxazoline **(142)** **(Scheme 1.41)**.[90] Hydrolytic removal of the DCM ester **(141)** can also be effected under standard acidic or basic conditions, unlike the BHT ester **(137)**, offering DCM-**(141)** as a synthetically useful derivative of BHT-**(141)**. In comparison to reactions performed with styrene **(132)** and DCM ester **(140)**, which gave poor enantioselectivity (20-36% *ee*), high enantioselectivities were observed (*ee*'s of 93-99%) in all of the cyclopropanation reactions of alkene **(139)** with Cu(I) complex of **(142)**.



Scheme 1.41

Cu(I)-bisoxazoline complexes have also been successful in the cyclopropanation reaction of several other trisubstituted olefins. Tanner *et al* have reported results from tests carried out on derivatives of 3-methyl-2-buten-1-ol **(143a)** with chiral complexes of various bisoxazoline ligands **(Scheme 1.42)**.[96] Reaction of **(143b)** (R = Ac) with the Cu(I) complex of *t*Bu-bisoxazoline-**(93)** gave a *trans*:*cis* ratio of 62:38 and 67% *ee* for *trans*-**(144)** at room temperature. When the reaction was carried out at 0 °C, improved stereoselectivity was observed with a *trans*:*cis* ratio of 79:21 of and 93% *ee* for *trans*-**(144)**. Reactions using same complex at 0 °C, gave good *trans*:*cis* ratios in all cases [76:24 to 91:9 for **(143b-f)**], with excellent enantioselectivities also reported (87-93% *ee*). Finally, switching to the Cu(I) complexes of Ph-bisoxazoline-**(90)** or bisoxazoline-**(142)** gave reduced stereoselectivities in comparison to complexes of **(93)**.



Scheme 1.42

References

(1) Cahn, R. S.; Ingold, C. K.; Prelog, V. *Experientia* **1956**, *12*, 81.

(2) Stinson, S. C. *Chem. Eng. News* **1992**, *70*, 46.

(3) Van Arnum, P. *Pharmaceut. Technol.* **2006**, *30*, 58.

(4) Mori, K. *Chem. Commun.* **1997**, 1153.

(5) Guan, Y. K.; Li, Y. L. *Chirality* **2005**, *17*, 113.

(6) Nishibayashi, Y.; Takei, I.; Uemura, S.; Hidai, M. *Organometallics* **1999**, *18*, 2291.

(7) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567.

(8) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

(9) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290.

(10) Gnas, Y.; Glorius, F. *Synthesis-Stuttgart* **2006**, 1899.

(11) Enders, D.; Voith, M.; Lenzen, A. *Angew. Chem.-Int. Edit.* **2005**, *44*, 1304.

(12) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.

(13) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883.

(14) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894.

(15) Ghosh, A. K.; Duong, T. T.; McKee, S. P. *J. Chem. Soc.-Chem. Commun.* **1992**, 1673.

(16) Paquette, L. A. *Chiral Reagents for Asymmetric Syntheses*, 2003.

(17) Alexander, K.; Cook, S.; Gibson, C. L.; Kennedy, A. R. *J. Chem. Soc.-Perkin Trans. 1* **2001**, 1538.

(18) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy, G. V.; Portonovo, P. S.; Zhang, H. M.; Fanelli, D.; Reddy, R. T.; Zhou, P.; Carroll, P. J. *J. Org. Chem.* **1997**, *62*, 2555.

(19) Ruano, J. L. G.; Fernandez, I.; Catalina, M. D.; Cruz, A. A. *Tetrahedron: Asymmetry* **1996**, *7*, 3407.

(20) Liu, G. C.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913.

(21) Cogan, D. A.; Liu, G. C.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883.

(22) Barrow, J. C.; Ngo, P. L.; Pellicore, J. M.; Selnick, H. G.; Nantermet, P. G. *Tetrahedron Lett.* **2001**, *42*, 2051.

(23) Evans, J. W.; Ellman, J. A. *J. Org. Chem.* **2003**, *68*, 9948.

(24) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 6518.

(25) Naskar, D.; Roy, A.; Seibel, W. L.; Portlock, D. E. *Tetrahedron Lett.* **2003**, *44*, 8865.

(26) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12.

(27) Zhong, Y. W.; Xu, M. H.; Lin, G. Q. *Org. Lett.* **2004**, *6*, 3953.

(28) Zhong, Y. W.; Izumi, K.; Xu, M. H.; Lin, G. Q. *Org. Lett.* **2004**, *6*, 4747.

(29) Tanuwidjaja, J.; Peltier, H. M.; Ellman, J. A. *J. Org. Chem.* **2007**, *72*, 626.

(30) Chelucci, G.; Baldino, S.; Chessa, S.; Pinna, G. A.; Soccolini, F. *Tetrahedron: Asymmetry* **2006**, *17*, 3163.

(31) Tang, T. P.; Volkman, S. K.; Ellman, J. A. *J. Org. Chem.* **2001**, *66*, 8772.

(32) Zhong, Y. W.; Dong, Y. Z.; Fang, K.; Izumi, K.; Xu, M. H.; Lin, G. Q. *J. Am. Chem. Soc.* **2005**, *127*, 11956.

(33) Liu, R. C.; Wei, J. H.; Wei, B. G.; Lin, G. Q. *Tetrahedron: Asymmetry* **2008**, *19*, 2731.

(34) Notz, W.; Tanaka, F.; Barbas, C. F. *Accounts Chem. Res.* **2004**, *37*, 580.

(35) Wei, Q.; Gong, L. Z. *Org. Lett.* **2010**, *12*, 1008.

(36) Peng, F. Z.; Shao, Z. H. *J. Mol. Catal. A-Chem.* **2008**, *285*, 1.

(37) Wu, C. L.; Long, X. Q.; Li, S.; Fu, X. K. *Tetrahedron: Asymmetry* **2012**, *23*, 315.

(38) Kano, T.; Sakamoto, R.; Akakura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2012**, *134*, 7516.

(39) McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151.

(40) Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497.

(41) Desimoni, G.; Faita, G.; Jorgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561.

(42) Rasappan, R.; Laventine, D.; Reiser, O. *Coordination Chemistry Reviews* **2008**, *252*, 702.

(43) Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Helv. Chim. Acta* **1988**, *71*, 1553.

(44) Frain, D.; Kirby, F.; McArdle, P.; O'Leary, P. *Synlett* **2009**, 1261.

(45) Corey, E. J.; Imai, N.; Zhang, H. Y. *J. Am. Chem. Soc.* **1991**, *113*, 728.

(46) Denmark, S. E.; Nakajima, N.; Nicaise, O. J. C.; Faucher, A. M.; Edwards, J. P. *J. Org. Chem.* **1995**, *60*, 4884.

(47) Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541.

(48) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005.

(49) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726.

(50) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165.

(51) Wipf, P.; Venkatraman, S. *Tetrahedron Lett.* **1996**, *37*, 4659.

(52) Davies, I. W.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1996**, *37*, 813.

(53) Cornejo, A.; Fraile, J. M.; Garcia, J. I.; Gil, M. J.; Martinez-Merino, V.; Mayoral, J. A.; Pires, E.; Villalba, I. *Synlett* **2005**, 2321.

(54) Desimoni, G.; Faita, G.; Mella, M. *Tetrahedron* **1996**, *52*, 13649.

(55) Schinnerl, M.; Bohm, C.; Seitz, M.; Reiser, O. *Tetrahedron: Asymmetry* **2003**, *14*, 765.

(56) Diez-Barra, E.; Fraile, J. M.; Garcia, J. I.; Garcia-Verdugo, E.; Herrerias, C. I.; Luis, S. V.; Mayoral, J. A.; Sanchez-Verdu, P.; Tolosa, J. *Tetrahedron: Asymmetry* **2003**, *14*, 773.

(57) Denmark, S. E.; Stiff, C. M. *J. Org. Chem.* **2000**, *65*, 5875.

(58) Aggarwal, V. K.; Bell, L.; Coogan, M. P.; Jubault, P. *J. Chem. Soc.-Perkin Trans. 1* **1998**, 2037.

(59) Minuth, T.; Irmak, M.; Groschner, A.; Lehnert, T.; Boysen, M. M. K. *Eur. J. Org. Chem.* **2009**, 997.

(60) Johannsen, M.; Jorgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5757.

(61) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635.

(62) Evans, D. A.; Johnson, J. S.; Burgey, C. S.; Campos, K. R. *Tetrahedron Lett.* **1999**, 2879.

(63) Thorhauge, J.; Roberson, M.; Hazell, R. G.; Jorgensen, K. A. *Chemistry-A European Journal* **2002**, *8*, 1888.

(64) Ait-Haddou, H.; Hoarau, O.; Cramailere, D.; Pezet, F.; Daran, J.-C.; Balavoine, G. G. A. *Chemistry - A European Journal* **2004**, *10*, 699.

(65) Inukai, T.; Kojima, T. *J. Org. Chem.* **1967**, *32*, 869.

(66) Inukai, T.; Kojima, T. *J. Org. Chem.* **1967**, *32*, 872.

(67) Houk, K. N.; Strozier, R. W. *J. Am. Chem. Soc.* **1973**, *95*, 4094.

(68) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340.

(69) Evans, D. A.; Lectka, T.; Miller, S. J. *Tetrahedron Lett.* **1993**, *34*, 7027.

(70) Kobayashi, S.; Araki, M.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3758.

(71) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460.

(72) Otto, S.; Bertoncin, F.; Engberts, J. *J. Am. Chem. Soc.* **1996**, *118*, 7702.

(73) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559.

(74) Sibi, M. P.; Chen, J. X.; Stanley, L. *Synlett* **2007**, 298.

(75) Wada, E.; Pei, W.; Yasuoka, H.; Chin, U.; Kanemasa, S. *Tetrahedron* **1996**, *52*, 1205.

(76) Barroso, S.; Blay, G.; Al-Midfa, L.; MunÌ*f*oz, M. C.; Pedro, J. R. *J. Org. Chem.* **2008**, *73*, 6389.

(77) Trost, B. M.; Strege, P. E. *J. Am. Chem. Soc.* **1977**, *99*, 1649.

(78) Hayashi, T.; Yamamoto, A.; Hagihara, T.; Ito, Y. *Tetrahedron Lett.* **1986**, *27*, 191.

(79) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769.

(80) Dawson, G. J.; Frost, C. G.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 3149.

(81) Vonmatt, P.; Pfaltz, A. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 566.

(82) Gilbertson, S. R.; Genov, D. G.; Rheingold, A. L. *Org. Lett.* **2000**, *2*, 2885.

(83) Clarke, M. L.; France, M. B. *Tetrahedron* **2008**, *64*, 9003.

(84) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949.

(85) Terada, M.; Mikami, K. *J. Chem. Soc.-Chem. Commun.* **1994**, 833.

(86) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824.

(87) Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936.

(88) Pellissier, H. *Tetrahedron* **2008**, *64*, 7041.

(89) Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603.

(90) Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373.

(91) Charette, A. B.; Juteau, H.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc.* **1998**, *120*, 11943.

(92) Lacasse, M. C.; Poulard, C.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 12440.

(93) Voituriez, A.; Charette, A. B. *Adv. Synth. Catal.* **2006**, *348*, 2363.

(94) Huang, K.; Huang, Z. Z. *Synlett* **2005**, 1621.

(95) Lloyd-Jones, G. C.; Wall, P. D.; Slaughter, J. L.; Parker, A. J.; Laffan, D. P. *Tetrahedron* **2006**, *62*, 11402.

(96) Ostergaard, N.; Jensen, J. F.; Tanner, D. *Tetrahedron* **2001**, *57*, 6083.

Chapter 2
Results and Discussion

Results and Discussion

2.1 Introduction

A series of novel methylene 4,4'-bisoxazoline ligands were synthesised in this study. These 4,4'-bisoxazoline ligands were tested in the asymmetric Diels-Alder reaction, allylic alkylation reaction, ene reaction, cyclopropanation reaction and the 1,2 diethylzinc addition to aldehydes.

This study forms part of a larger research project on 4,4'-bisoxazoline ligands. In the discussion we will also report, for comparison purposes only, some of the significant results obtained by other researchers (David Frain and Dr. Fiona Kirby) working on this project.

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

2.2 Synthesis of 4,4'-bisoxazoline ligands

Frain *et al* first reported the synthesis of 4,4'-bisoxazoline ligands in 2009.[1] Here, they reported the synthesis of a novel 4,4'-bisoxazoline ligand (*R*)-PhAraBOX **(1)**. Subsequently, two new 4,4'-bisoxazoline ligands were synthesised, (*S*)-*t*BuAraBOX **(2)** and PhXyliBOX **(3)**. The ligands were given these names based on their original starting materials, with AraBOX ligands derived from the alcohol Arabitol and XyliBOX ligands from Xylitol **(Figure 2.1)**.

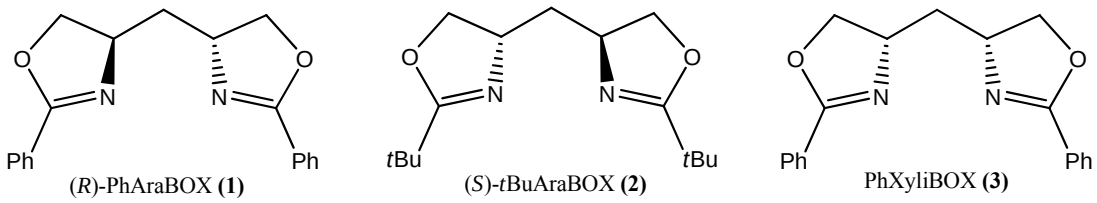


Figure 2.1

These first generation ligands were then applied to both the asymmetric Diels Alder and cyclopropanation reactions with limited success.[2,3] While the AraBOX ligands showed moderate enantioselectivity, the XyliBOX ligand showed none, due to its *meso*-structure. The next step in expanding the design of these ligands involved incorporating chiral moieties into the sidearms of the XyliBOX framework, giving it potential for use in asymmetric reactions **(Figure 2.2)**.[3] Copper complexes of the

chiral XyliBOX ligands were then applied to the asymmetric cyclopropanation reaction, amongst others, proving modest *ee*'s.

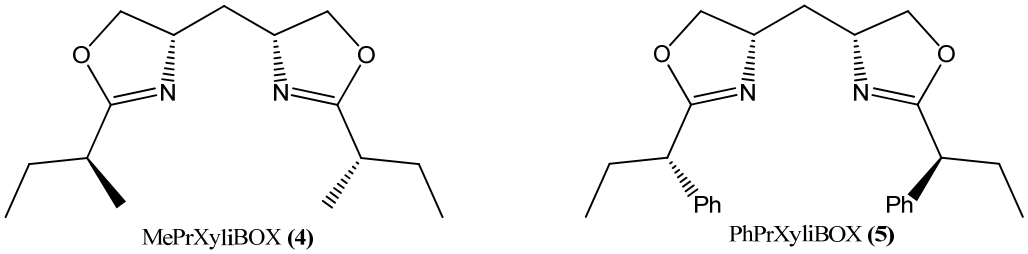
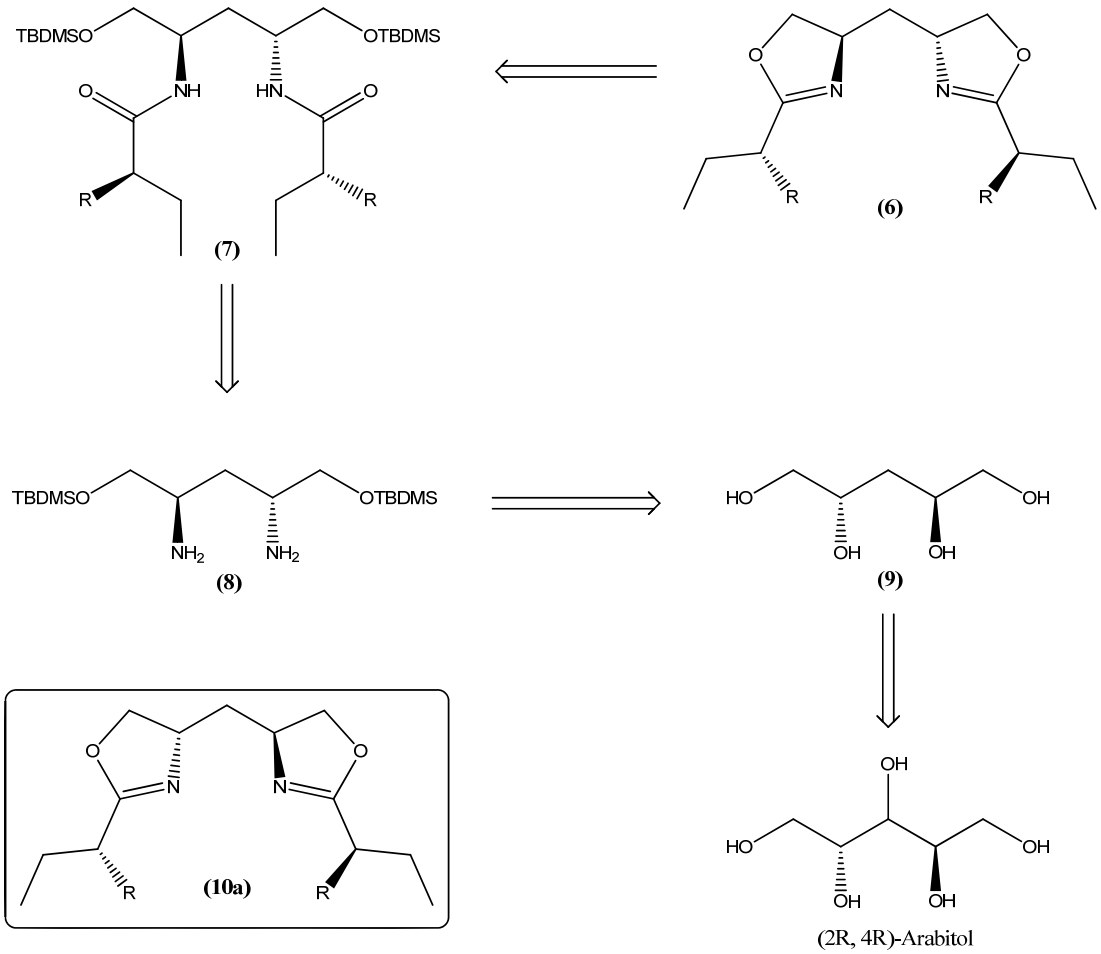


Figure 2.2

As such, following the work of Frain *et al* with AraBOX ligands and Kirby *et al* with chiral XyliBOX ligands, we envisaged synthesising the modified AraBOX ligands, incorporating additional chiral moieties on the bisoxazoline structure in a similar fashion to the chiral XyliBOX ligands **(4)** and **(5)**.

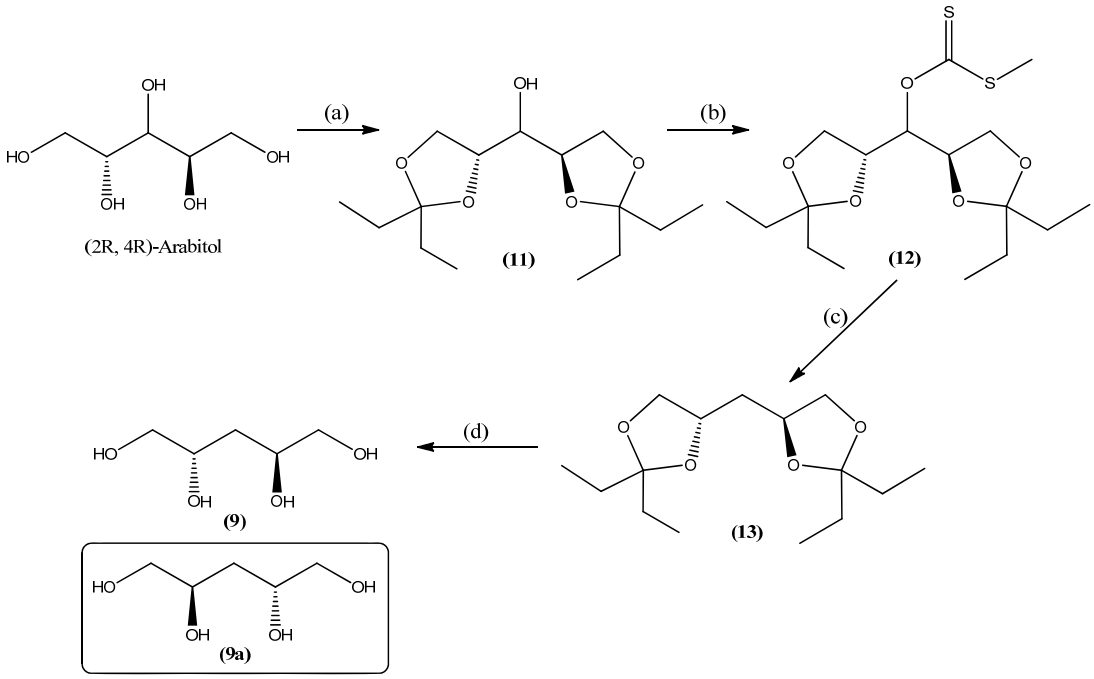


Scheme 2.1

While many synthetic approaches exist to form 2,2' bisoxazoline ligands, as discussed in **Chapter 1**, there has only been one reported approach to the synthesis of their regioisomeric counterparts, the 4,4' bisoxazoline ligands.[1] Our synthetic strategy consisted of following the same retrosynthetic pathway as those of previous group members **(Scheme 2.1)**.

As such, we concluded that the di-TBDMS protected bis-β-amido alcohol **(7)** would be the key intermediate in synthesising the desired 4,4' bisoxazoline ligands **(6)**. These amides could be prepared from the di-TBDMS protected bis-β-amino alcohol **(8)** which would provide a route to a variety of amides by varying the R sidechain. From work previously carried out by Frain *et al* it can be seen that (2*R*, 4*R*)-arabitol would be the ideal starting material in the synthesis of di-TBDMS protected bis-β-amino alcohol **(8)**. The synthesis of the diastereomeric ligands **(7)** would follow the same synthetic route, beginning instead with (2*S*, 4*S*)-arabitol as the starting material.

The key intermediate tetraol **(9)** was synthesised by following the same procedure adopted by Frain *et al*, a modified version of that performed by Linclau *et al*.[1,4]

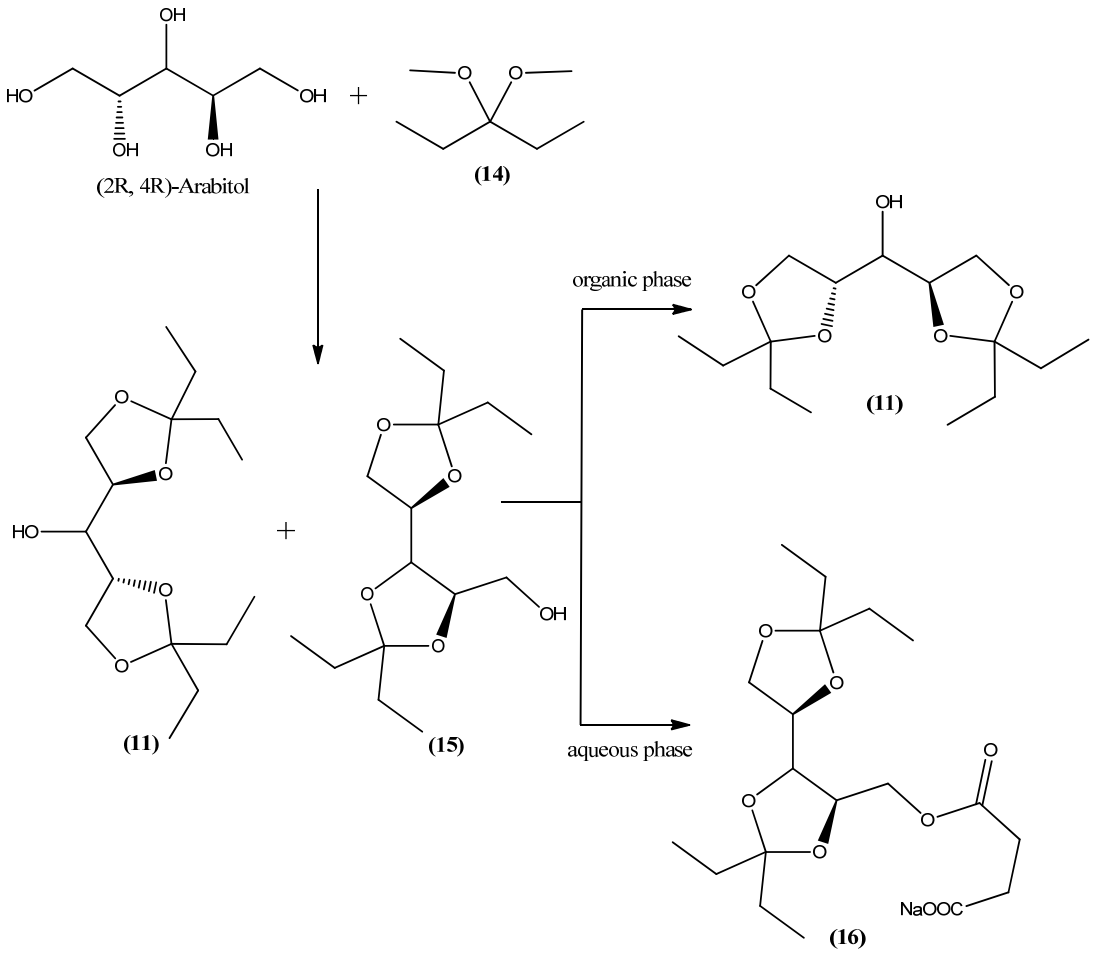


Scheme 2.2

Reagents and conditions: (a) (i) 3,3-dimethoxypentane **(14)**, camphorsulfonic acid, THF, reflux, 5 min (ii) Et_3N, succinic anhydride, CH_2Cl_2, reflux, 1 h, 67-74% **(b)** CS_2, NaH, THF, 0 °C-rt., 16 h, then MeI, 0 °C-rt., 6h, 95-99% **(c)** AIBN, Bu_3SnH, toluene, reflux, 4 h, 90-93% **(d)** 0.5 M H_2SO_4, EtOH, reflux, 4 h, 90-99%

The first step involved the preparation of 3,3-dimethoxypentane **(14)** from 3-pentanone. Treatment of 3-pentanone with trimethyl orthoformate and camphorsulfonic acid gave 3,3-dimethoxypentane **(14)** in 63% yield. Synthesis of the 3,3-dimethoxypentane **(14)** was performed on a large scale starting with 200 ml of 3-pentanone to give 140-155 g of product. The 3,3-dimethoxypentane **(14)** was purified by distillation and the structure was confirmed by comparison with the published data.[5]

The 3,3-dimethoxypentane **(14)** was then used to protect the starting material, either (2*R*, 4*R*)-arabitol or (2*S*, 4*S*)-arabitol. Since reactions involving either enantiomer were carried out using the exact same methodology, giving enantiomeric products, we will report the reaction as beginning with (2*R*, 4*R*)-arabitol. However, the results of these reactions also apply to the compounds which used (2*S*, 4*S*)-arabitol as the starting material. The corresponding methodology, yields and characterisation data are reported in the experimental section.



Scheme 2.3

10 g of (2*R*, 4*R*)-arabitol was protected by reacting it with 4 equivalents of 3,3-dimethoxypentane in the presence of camphorsulfonic acid in THF at 66 °C for 5 min. The reaction generally yielded a 4:1 mixture of the desired product [1,2:4,5 bisacetal **(11)**] and an isomeric by-product [1,2:3,4 bisacetal **(15)**]. This mixture was then treated with an excess of succinic anhydride which reacted with the more reactive primary alcohol of the 1,2:3,4 bisacetal **(15)**, as reported by Linclau **(Scheme 2.3)**.[6] The reaction was carried out in DCM and heated at reflux for 1 h. The resulting by-product **(16)** was easily separated from the desired product by a basic aqueous extraction. The crude product was purified by column chromatography on silica gel. The product separated with a gradient elution of petroleum ether:ethyl acetate 97:3 to 92:8. The desired bisacetal **(11)** was obtained in 67-74% yield. The structure of the product was confirmed by comparison with the published data.[6]

The protected bisacetal **(11)** was then treated with NaH at 0 °C in THF to generate the alkoxide at the free hydroxyl group in the 3-*O* position. Excess carbon disulphide was added and the mixture was allowed to stir at room temperature for 6 h. Subsequent cooling to 0 °C and followed by addition of methyl iodide provided the xanthate product after overnight stirring. The reaction was generally carried out using 10-14 g of bisacetal **(11)** as the starting material. The crude product was purified by column chromatography on silica gel. The product separated with a gradient elution of petroleum ether:ethyl acetate 96:4 to 9:1. The xanthate product **(12)** was obtained in 95-99% yield. The structure of the product was confirmed by comparison with the published data.[4]

Following this, radical deoxygenation of xanthate **(12)** was carried out with tributyltin hydride and 1,1-azobis(cyclohexane-carbonitrile) (ACN) as the radical initiator. 11-17 g of xanthate **(12)** in toluene was heated to reflux in the presence of 1.1 equivalents of tributyltin hydride and 0.25 equivalents of ACN. This step involved a modification of Linclau's procedure. Previous work, carried out within our group, had shown that using ACN as the radical initiator in place of AIBN, as per Linclau's procedure, led to an increase in yields being observed. The crude product was purified by column chromatography on silica gel. The product separated with a gradient elution of petroleum ether:ethyl acetate 97:3 to 96:4. The deoxygenated product **(13)** was obtained in 90-93% yield. The structure of the product was confirmed by comparison with the published data.[4]

The purified deoxygenated product **(13)** was then heated to reflux in a 1:1 solution of in 0.5 M sulphuric acid and ethanol, hydrolysing the acetal protecting groups. The reaction was then quenched with K_2CO_3, which involved a second modification of Linclau's procedure, in which $BaCO_3$ was used as the quenching reagent. It was found that K_2CO_3 could be more easily removed and so it was used instead. The reaction was generally carried out on a scale of 11-16 g of starting material **(13)**. The crude product was purified by column chromatography on silica gel. The product eluted with dichloromethane:methanol 7:3 providing tetraol **(9)** in 90-99% yield.

The structure of tetraol **(9)** was confirmed by ^{1}H and ^{13}C NMR. The characteristic signals of the backbone of the molecule were present in the ^{1}H NMR. The CHO hydrogens, of the two secondary alcoholic groups, appear as a multiplet at 3.78-3.72. Two of the hydrogens of the two CH_2O appear as a double doublet at 3.45 (J = 11.7, 3.9 Hz). The other two hydrogens of the two CH_2Os appear as a double doublet at 3.34 (J = 11.7, 6.8 Hz). The CH_2 of the $CHCH_2CH$ appears as a double doublet at 1.37 (J = 7.3, 5.7 Hz).

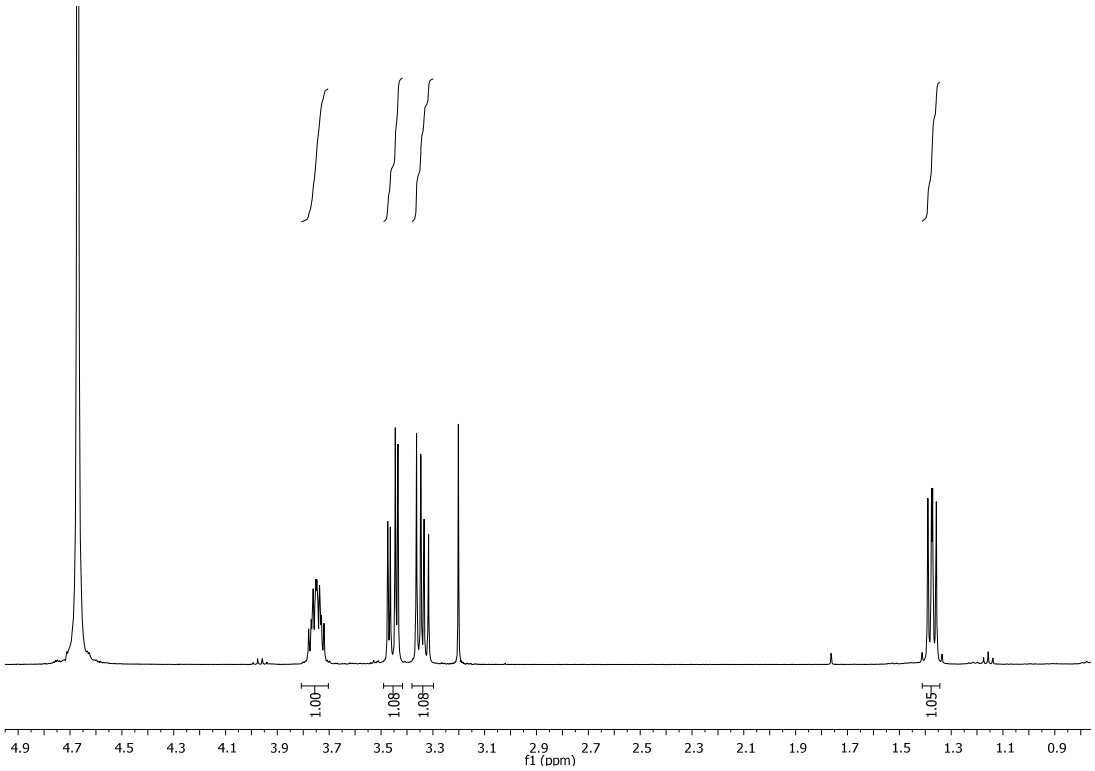
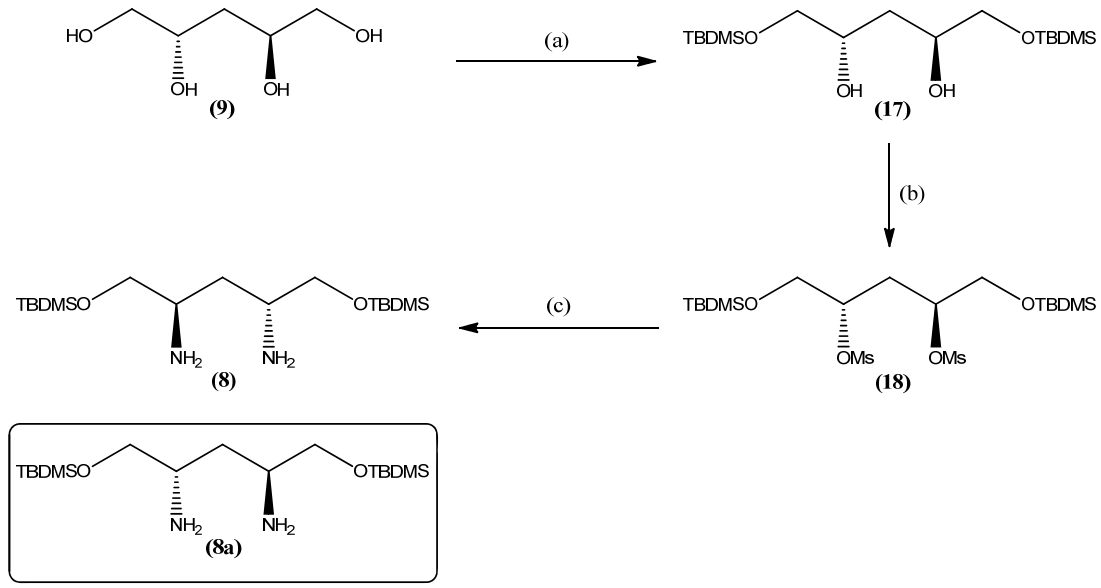


Figure 2.3: ^{1}H NMR spectrum of **(9)**

The lack of the acetal protecting groups and their signals in the ^{1}H and ^{13}C NMR spectra were key in identifying the product, as was the appearance of the broad signal identifying the hydroxyl groups at 3240 cm^{-1} in the IR spectrum. The structure of the product was confirmed by comparison with the published data **(Figure 2.3)**.[7] With the tetraol **(9)** in hand, the next step involved preparation of the di-TBDMS protected bis-β-amino alcohol **(8) (Scheme 2.4)**. Frain *et al* had shown this to be the key precursor in the synthesis of any novel 4,4' bisoxazoline ligand.[1] As such the focus now turned to the conversion of the secondary alcohols to amines.



Scheme 2.4

Reagents and conditions: (a) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, -15 °C-rt., 40 h, 42-55% **(b)** MsCl, Et_3N, CH_2Cl_2, 0 °C-rt., 4 h, 96-97% **(c)** (i) NaN_3, DMF, 85 °C, 16 h (ii) Pd/C, H_2 (7-8 atm.), MeOH, rt., 12 h, 57-65%

To allow for this, the primary hydroxyl groups of tetraol **(9)** underwent selective protection of using *tert*-butyldimethylsilyl chloride in the presence of triethylamine and dimethylaminopyridine in CH_2Cl_2. The crude product was purified by column chromatography on silica gel. The di-TBDMS protected product **(17)** separated with a gradient elution of petroleum ether:ethyl acetate 95:5 to 75:25. The protected product **(17)** was obtained in 42-55% yield. Generally, ~5.0 g of di-TBDMS protected product **(17)** was isolated from 3.5 g of tetraol **(9)**.

The structure of the di-TBDMS protected diol **(17)** was confirmed by ^{1}H and ^{13}C NMR. The characteristic signals of the backbone of the molecule were present in the ^{1}H NMR. The key signals identifying the product are the singlets appearing at 0.89 and 0.06, which integrate for 18H and 12H respectively. These signals correspond to the $C(CH_3)_3$ and the $Si(CH_3)_2$ of the two new TBDMS protecting groups.

The protected diol **(17)** underwent mesylation using methanesulfonyl chloride. 3-6 g of protected diol **(17)** was reacted with 2.2 equivalents of methanesulfonyl chloride and triethylamine in CH_2Cl_2 at 0 °C. The reaction mixture was left to stir at room temperature for 4 h. The crude product was purified by column chromatography on silica gel. The product separated with a gradient elution of petroleum ether:ethyl acetate 9:1 to 4:1, with the mesylated product **(18)** being obtained in 96-97% yield.

The structure of the di-TBDMS protected dimesylate **(18)** was confirmed by ^{1}H and ^{13}C NMR. The characteristic signals of the backbone of the molecule were all present in the ^{1}H NMR. The key signal identifying the product is the singlet appearing at 3.12, which integrates for 6H. This signal corresponds to the SCH_3 of the two new mesylate groups.

TBDMS-protected dimesylate **(18)** was then treated with sodium azide in *N*,*N*-dimethylformamide, with displacement of the mesylate groups by the azide in an S_N2 type reaction. The reaction was generally performed on a 2-4 g scale, using a large excess of sodium azide (30 equivalents). The reaction was carried out in toluene and heated to 85 °C for 16 h. Filtration of the sodium azide through celite afforded the crude diazido product, which was carried through to the next step without any further purification. The IR spectrum showed a signal at 2104 cm^{-1}, which is consistent with that of an azide group.

The crude diazido product underwent hydrogenation using 10% palladium on activated carbon in methanol to give the di-TBDMS protected bis-β-amino alcohol **(8)**. The reaction was carried out at 7 bar for 12 h with vigorous stirring to give the desired diamine product **(8)**. The palladium was removed by filtration through celite. The crude product was purified by column chromatography on silica gel. The product separated with a gradient elution of ethyl acetate:methanol 9:1 to 3:2. The diamine product **(8)** was obtained in 57-65% yield.

The structure of the di-TBDMS protected diamine **(8)** was confirmed by ^{1}H and ^{13}C NMR. The characteristic signals of the backbone of the molecule were present in the ^{1}H NMR. The key signal identifying the product is the broad singlet appearing at

1.70, which integrates for 4H. This signal corresponds to the four hydrogens of the two new primary amines **(Figure 2.4)**.

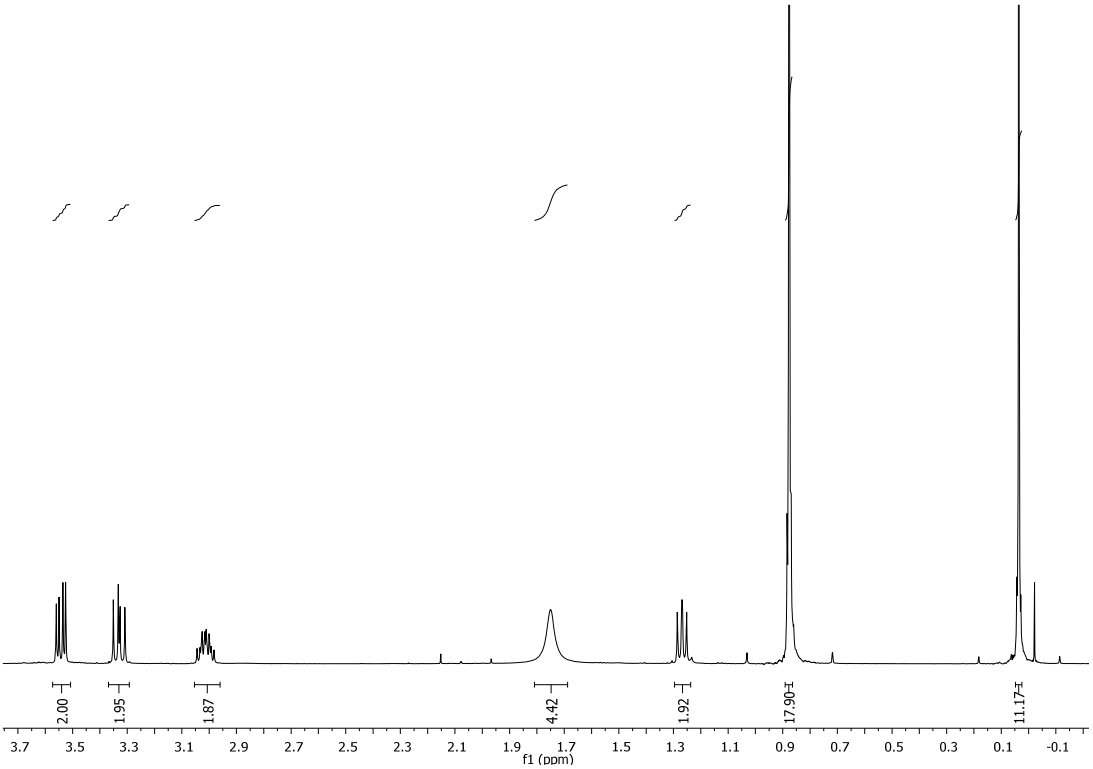


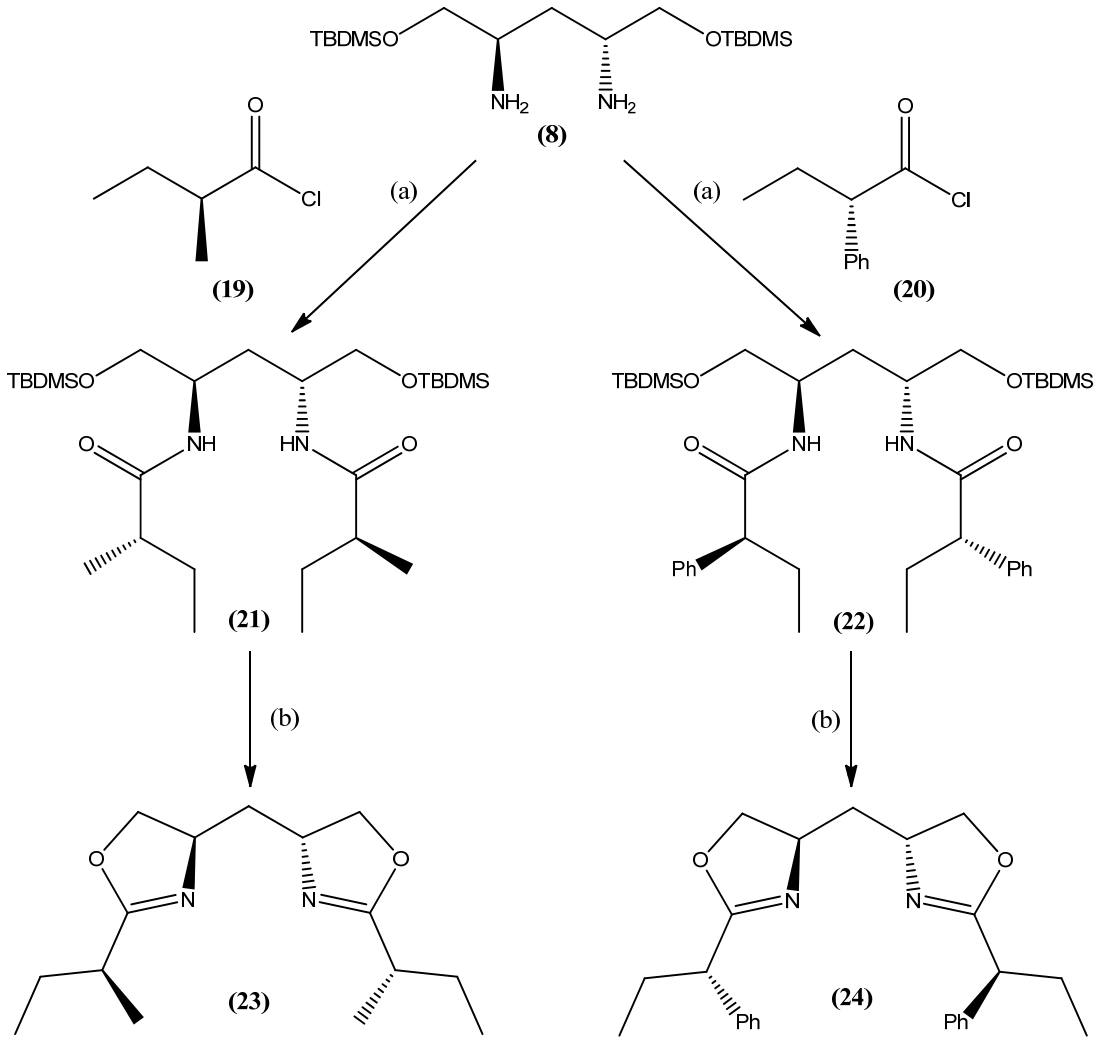
Figure 2.4: ^{1}H NMR spectrum of **(8)**

The synthesis of the novel chiral ligands involved the incorporation of chiral moieties on the sidechains of the AraBOX structure reported by Frain. Using the di-TBDMS protected diamine **(8)** as a common starting material a variety of amides could be synthesised. These chiral amides could then be cyclised using various ring closing techniques such as Frain's DARC methodology to provide the desired chiral 4,4' bisoxazoline ligands **(Scheme 2.5)**.

The di-TBDMS protected bis-β-amino alcohol **(8)** was prepared from (2*R*, 4*R*)-arabitol, as described earlier. Two different chiral butyric acids were chosen to generate the secondary chiral centres on the oxazoline sidechains. The two butyric acids chosen were (*S*)-(+)-2-methylbutyric acid and (*S*)-(+)-2-phenylbutyric acid. It should be noted that while both these acids possess the same named configuration (*S*), the methyl and phenyl sidechains are actually directed in opposite directions. This is due to a change in priority rankings when the R sidechain is changed from a methyl group to a phenyl group.

The two chiral acids were converted to their acid chloride derivatives **(19)** and **(20)** by heating them separately at reflux in thionyl chloride for 3 h. The thionyl chloride

was removed and the acid chlorides were used without any further purification. Separately, 2.2 equivalents of chiral acid chlorides **(19)** and **(20)** and triethylamine were reacted with **(8)**, in CH_2Cl_2 at 0 °C. Both reactions were left to stir overnight at room temperature. Both amides were purified by column chromatography on silica gel.



Scheme 2.5

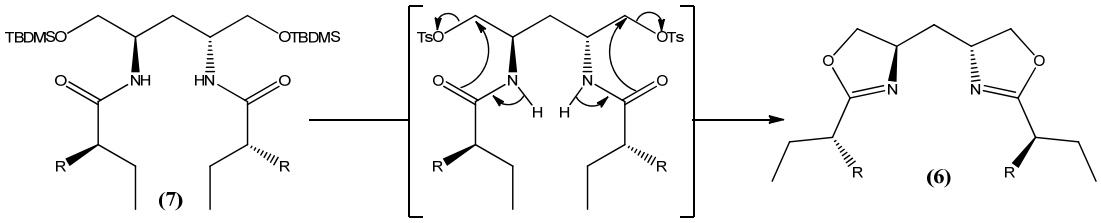
Reagents and conditions: (a) (19)/(20), Et_3N, CH_2Cl_2, 0 °C-rt., 16 h, 67-74% **(b)** TsF, DBU, MeCN, reflux, 16 h, 63-66%

The methyl propyl amide **(21)** separated with a gradient elution of petroleum ether:ethyl acetate 9:1 to 7:3, while phenyl propyl amide **(22)** separated with a gradient elution of petroleum ether:ethyl acetate 9:1 to 4:1. The amides **(21)** and **(22)** were isolated 67% and 74% yields respectively.

The structures of the chiral amides **(21)** and **(22)** were confirmed by ^{1}H and ^{13}C NMR. For the amide **(21)**, the characteristic signals of the backbone of the molecule were present in the ^{1}H NMR. The ^{1}H NMR spectrum was more complicated than usual due to the product existing as a mixture of amide rotamers. One of the key signals identifying the presence of the product is the CH_3 of the CH_3CH group, appearing as a series of doublets in a 2:1:1 ratio at 1.13-1.09 (J = 6.8 Hz). This signal and the $Si(CH_3)_2$ of the TBDMS protecting groups both appear as a series of signals due to the mixture of amide rotamers. The $Si(CH_3)_2$ of the TBDMS groups appear as a series of singlets in a 2:1:1 ratio at 0.05-0.03. Another key signal is the multiplet at 6.23-6.14. The signal integrates for 2H, representing the two NHs of the amide. The ^{13}C NMR spectrum shows the presence of multiple quaternary centres at 176.66, 176.63, 176.59 and 176.55. The presence of the amide rotamers is responsible for these extra signals. The IR spectrum shows a peak at 1641 cm^{-1}. This is strong evidence for the presence of an amide carbonyl.

For the amide **(22)**, the characteristic signals of the backbone of the molecule were present in the ^{1}H NMR. Once again, the ^{1}H NMR spectrum was more complicated than usual, due to the product existing as a mixture of amide rotamers. One of the key signals is the multiplet at 7.31-7.21 identifying the presence of the two aromatic phenyl groups. The other key signal is a series of (three) doublets, in a 4:1:1 ratio, appearing at 6.19 (J = 7.9 Hz). The signal integrates for 2H, representing the two NHs of the amide. The $Si(CH_3)_2$ of the TBDMS protecting groups also appear as six singlets in a 1:1:5:5:1:1 ratio at 0.05- -0.11, again due to the presence of rotamers. The ^{13}C NMR spectrum shows the presence of multiple quaternary centres at 173.68, 173.64 and 173.58. Again, the presence of rotamers is responsible for the extra signals. The IR spectrum shows a peak at 1647 cm^{-1}. This is strong evidence for the presence of an amide carbonyl.

The amides **(21)** and **(22)** were both cyclised in a tandem DARC reaction. The reaction works with the tosyl fluoride used to deprotect the alcohols and then activate them as tosylates, thus facilitating the ring closure. The DBU plays a catalytic role in the deprotection reaction, but is required in excess in the cyclisation step **(Scheme 2.6)**.



Scheme 2.6

Separately, 2.2 equivalents of tosyl fluoride and DBU were reacted with amides **(21)** and **(22)** in MeCN. Both reactions were heated to reflux and stirred overnight. The crude products were purified by column chromatography on silica gel. The methyl propyl bisoxazoline **(23)** separated with a gradient elution of petroleum ether:ethyl acetate 7:3 to 3:7, while phenyl propyl bisoxazoline **(24)** separated with a gradient elution of petroleum ether:ethyl acetate 9:1 to 4:1.

The new chiral ligands (4*R*,4'*R*)-4,4'-methylenebis{2-[(1*S*)-1-methylpropyl]-4,5-dihydro-1,3-oxazole} **(23)** and (4*R*,4'*R*)-4,4'-methylenebis{2-[(1*S*)-1-phenylpropyl]-4,5-dihydro-1,3-oxazole} **(24)** were isolated 63% and 66% yields respectively. The ligands **(23)** and **(24)** were given abbreviations (*S*,*R*)-MePrAraBOX and (*S*,*R*)-PhPrAraBOX respectively, because of the methyl propyl and phenyl propyl groups attached at the 2 and 2' positions of the bisoxazoline rings. AraBOX was the root of the name, as the ligands are bisoxazolines derived from arabitol. The (*S*,*R*) designation indicates that the ligands are derived from (*S*)-methyl or (*S*)-phenyl butyric acids and the (2*R*, 4*R*)-arabitol enantiomer.

The structures of the chiral bisoxazolines **(23)** and **(24)** were confirmed by ^{1}H and ^{13}C NMR. In the ^{1}H NMR spectrum of the (*S*,*R*)-MePrAraBOX **(23)**, the characteristic signals of the backbone were present. The lack of the TBDMS protecting group and its signals in the ^{1}H and ^{13}C NMR spectra were key in identifying the product, as was the disappearance of the NH hydrogens of the amide groups at 6.23-6.14. The ^{13}C NMR spectrum shows the presence of quaternary centres at 171.2 and 171.1, corresponding to the C=N of the bisoxazoline rings. The IR spectrum shows a signal at 1651 cm^{-1} representing the C=N of the bisoxazoline rings.

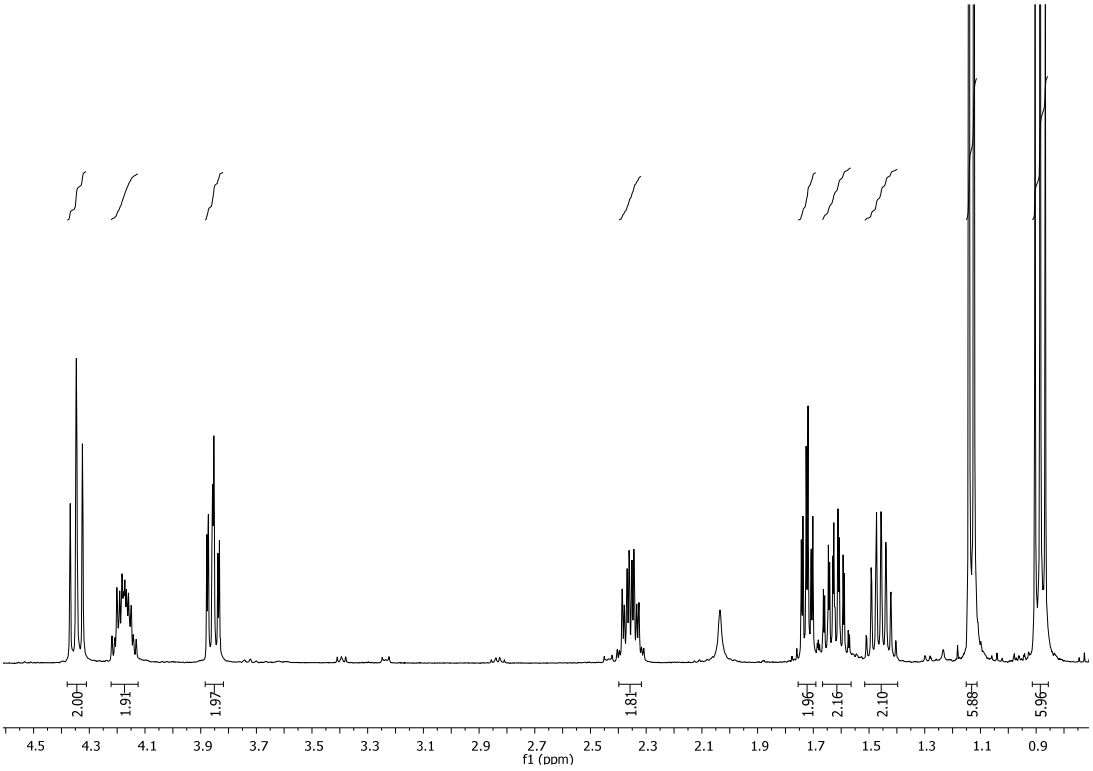


Figure 2.5: ^{1}H NMR spectrum of **(23)**

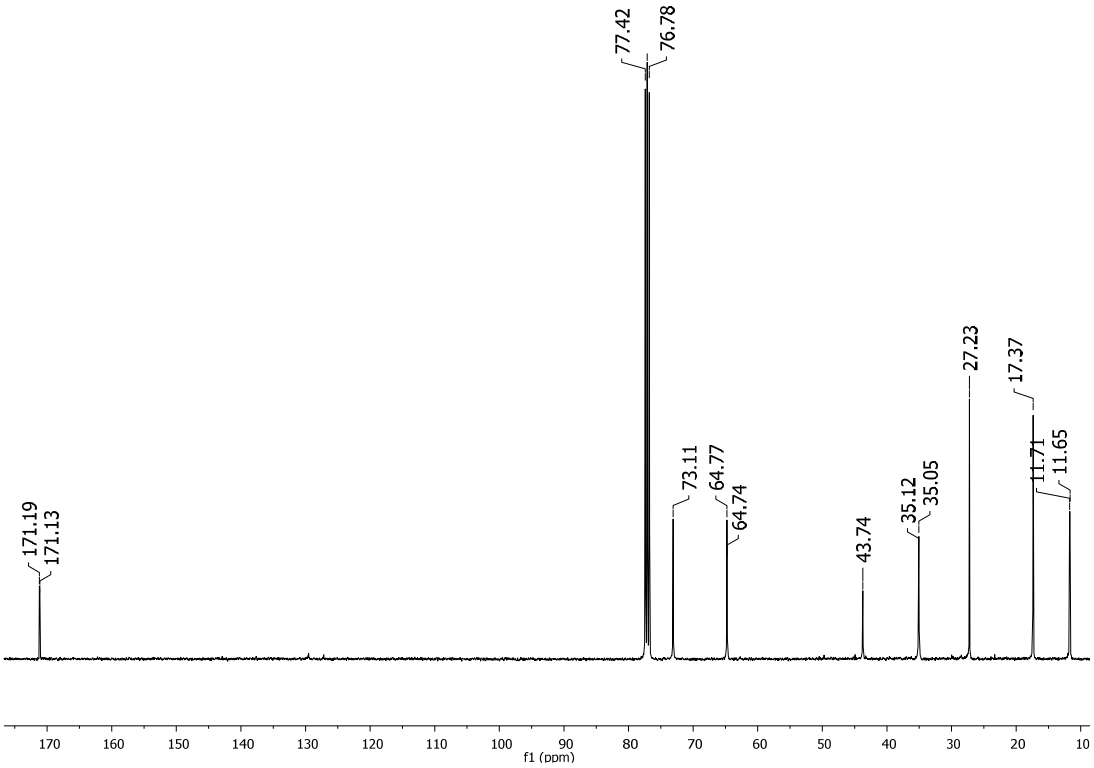


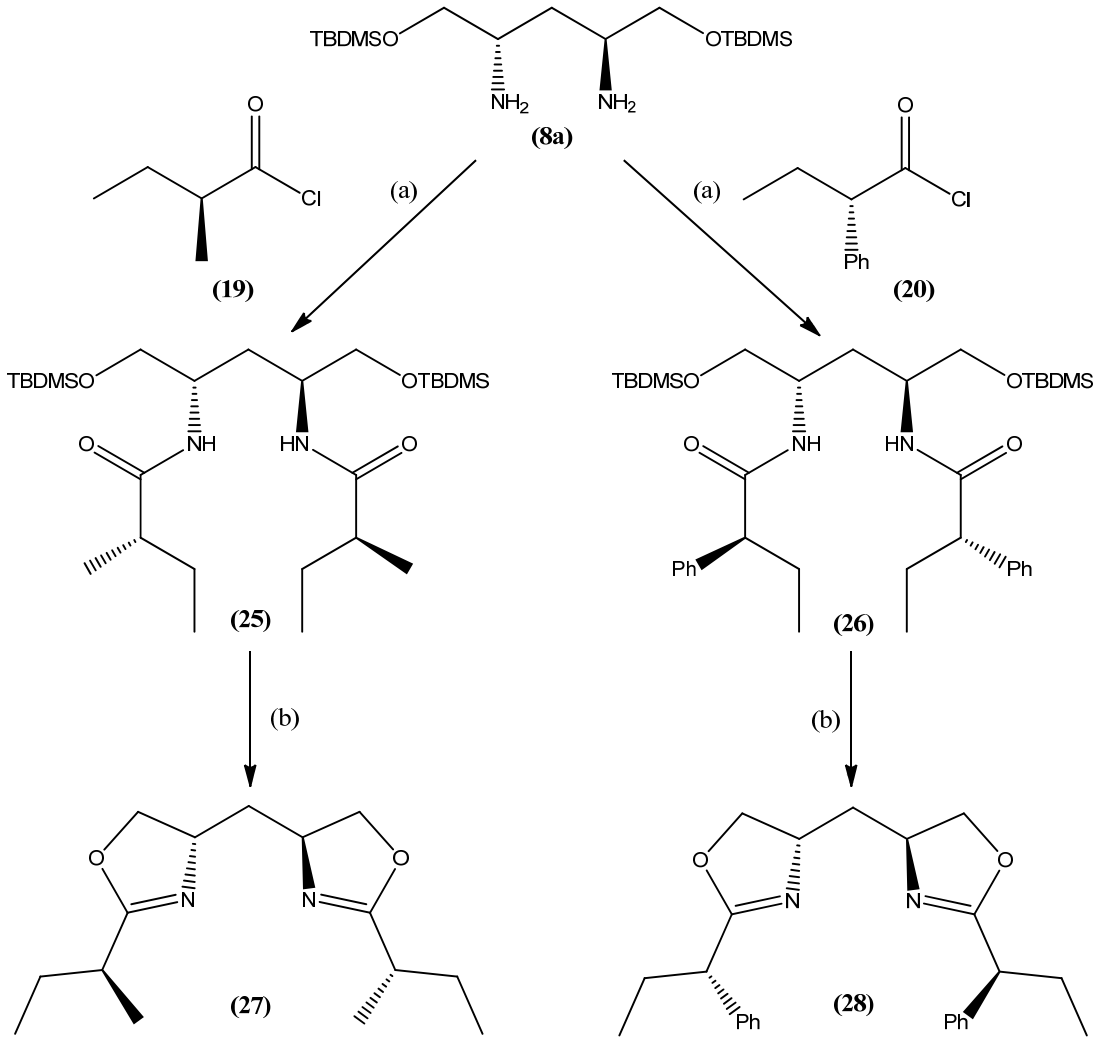
Figure 2.6: ^{13}C NMR spectrum of **(23)**

For bisoxazoline **(24)**, the characteristic signals of the backbone of the molecule were present in the ^{1}H NMR. Again, the lack of the TBDMS protecting group and its

signals in the ^{1}H and ^{13}C NMR spectra and the disappearance of the NH hydrogens of the amide groups at 6.19 were key to identifying the product bisoxazoline **(24)**. The ^{13}C NMR spectrum shows the presence of a quaternary carbon at 168.8. This signal corresponds to the C=N of the bisoxazoline rings. The IR spectrum shows a signal at 1657 cm^{-1} representing the C=N of the bisoxazoline rings.

In order to efficiently assess the relative importance of the differing stereocentres (i.e. the chiral centres on the backbone against those on the sidechains), it became necessary to synthesise diastereomeric ligands of **(23)** and **(24) (Scheme 2.7)**. The diastereomers were prepared following the same procedures as that used for ligands **(23)** and **(24)**, using the di-TBDMS protected bis-β-amino alcohol **(8a)**, which was prepared from (2*S*, 4*S*)-arabitol, as described earlier.

The same two chiral butyric acids were chosen to generate the secondary chiral centres on the sidechains, (*S*)-(+)-2-methylbutyric acid and (*S*)-(+)-2-phenylbutyric acid. These chiral acids were again converted to their acid chloride derivatives **(19)** and **(20)** by heating them at reflux in thionyl chloride for 3 h. The thionyl chloride was removed and the acid chlorides were used without any further purification. Separately, 2.2 equivalents of chiral acid chlorides **(19)** and **(20)** and triethylamine were reacted with **(8a)**, in CH_2Cl_2 at 0 °C. Both reactions were left to stir overnight at room temperature. Both amides were purified by column chromatography on silica gel. The methyl propyl amide **(25)** separated with a gradient elution of petroleum ether:ethyl acetate 9:1 to 3:7, while phenyl propyl amide **(26)** separated with a gradient elution of petroleum ether:ethyl acetate 9:1 to 4:1. The amides **(25)** and **(26)** were isolated 35% and 60% yields respectively.



Scheme 2.7

Reagents and conditions: (a) (19)/(20), Et_3N, CH_2Cl_2, 0 °C-rt., 16 h, 35-60% **(b)** TsF, DBU, MeCN, reflux, 16 h, 37-55%

The structures of the chiral amides **(25)** and **(26)** were confirmed by ^{1}H and ^{13}C NMR. For the amide **(25)**, the characteristic signals of the backbone of the molecule were present in the ^{1}H NMR. As with its diastereomeric counterpart **(21)**, one of the key signals identifying the presence of the product is the CH_3 of the CH_3CH group, which appears as three doublets in a 1:1:2 ratio at 1.12-1.10 (J = 6.8 Hz). This signal and the $Si(CH_3)_2$ of the TBDMS protecting groups again both appear as a series of signals due to the product being a mixture of amide rotamers. The $Si(CH_3)_2$ of the TBDMS groups appear as a three singlets in a 2:1:1 ratio at 0.05-0.04. The other key signal is the multiplet at 6.23-6.13, integrating for 2H and representing the two NHs of the amide. The ^{13}C NMR spectrum shows the presence of multiple quaternary centres at 176.61, 176.57 and 176.52. These extra signals are all caused by the

presence of the amide rotamers. The IR spectrum shows a peak at 1642 cm^{-1}, showing strong evidence for the presence of an amide carbonyl.

For the amide **(26)**, the characteristic signals of the backbone of the molecule were present in the ^{1}H NMR. Again, as with its diastereomer **(22)**, one of the key signals is the multiplet at 7.30-7.25 identifying the presence of the two aromatic phenyl groups. Another key signal is the appearance of three doublets, in a 1:1:8 ratio, at 6.17-6.03 (J = 8.2 Hz). The signal integrates for 2H, representing the two NHs of the amide. The $C(CH_3)_3$ and the $Si(CH_3)_2$ of the TBDMS protecting groups also appear as three singlets in a 1:8:1 ratio at 0.78-0.77 and in a 8:1:1:1:8:1:8:1 ratio at 0.01- -0.12 respectively, due to the presence of rotamers. The ^{13}C NMR spectrum shows the presence of a quaternary centre at 173.6 and the IR spectrum shows a peak at 1649 cm^{-1}. This is strong evidence for the presence of an amide carbonyl. The only indication of rotamers in the ^{13}C NMR spectrum is the appearance of two signals at -5.49 and -5.59 for the two $Si(CH_3)_2$.

The amides **(25)** and **(26)** were cyclised in a tandem DARC reaction, as described before for amides **(21)** and **(22)**. Separately, amides **(25)** and **(26)** were reacted with tosyl fluoride and DBU, heated to reflux and stirred overnight in MeCN. The crude products were purified by column chromatography on silica gel. The methyl propyl bisoxazoline **(27)** separated with a gradient elution of petroleum ether:ethyl acetate 9:1 to 3:7, while phenyl propyl bisoxazoline **(28)** separated with a gradient elution of petroleum ether:ethyl acetate 9:1 to 1:4.

The new chiral ligands (4*S*,4'*S*)-4,4'-methylenebis{2-[(1*S*)-1-methylpropyl]-4,5-dihydro-1,3-oxazole} **(27)** and (4*S*,4'*S*)-4,4'-methylenebis{2-[(1*S*)-1-phenylpropyl]-4,5-dihydro-1,3-oxazole} **(28)** were isolated 55% and 37% yields respectively. The ligands **(27)** and **(28)** were given abbreviations (*S*,*S*)-MePrAraBOX and (*S*,*S*)-PhPrAraBOX respectively, because of the methyl propyl and phenyl propyl groups attached at the 2 and 2' positions of the bisoxazoline rings. AraBOX was the root of the name, as the ligands are bisoxazolines derived from arabitol. The (*S*,*S*) designation indicates that the ligands are derived from (*S*)-methyl or (*S*)-phenyl butyric acids and the (2*S*, 4*S*)-arabitol enantiomer.

The structures of the chiral bisoxazolines **(27)** and **(28)** were confirmed by ^{1}H and ^{13}C NMR. In the ^{1}H NMR spectrum of the (*S*,*S*)-MePrAraBOX **(27)**, the characteristic signals of the backbone were present. The lack of the TBDMS protecting group and its signals in the ^{1}H and ^{13}C NMR spectra were again key in

identifying the product, as was the disappearance of the NH hydrogens of the amide groups at 6.23-6.13. The ^{13}C NMR spectrum shows the presence of a quaternary centre at 171.2, corresponding to the C=N of the bisoxazoline rings. The IR spectrum shows a signal at 1669 cm^{-1} representing the C=N of the bisoxazoline rings.

For bisoxazoline **(28)**, the characteristic signals of the backbone of the molecule were present in the ^{1}H NMR. Again, the lack of the TBDMS protecting group and its signals in the ^{1}H and ^{13}C NMR spectra and the disappearance of the NH hydrogens of the amide groups at 6.17-6.03 were key to identifying the product bisoxazoline **XAPX**. The ^{13}C NMR spectrum shows the presence of a quaternary carbon at 168.7. This signal corresponds to the C=N of the bisoxazoline rings. The IR spectrum shows a signal at 1656 cm^{-1} representing the C=N of the bisoxazoline rings.

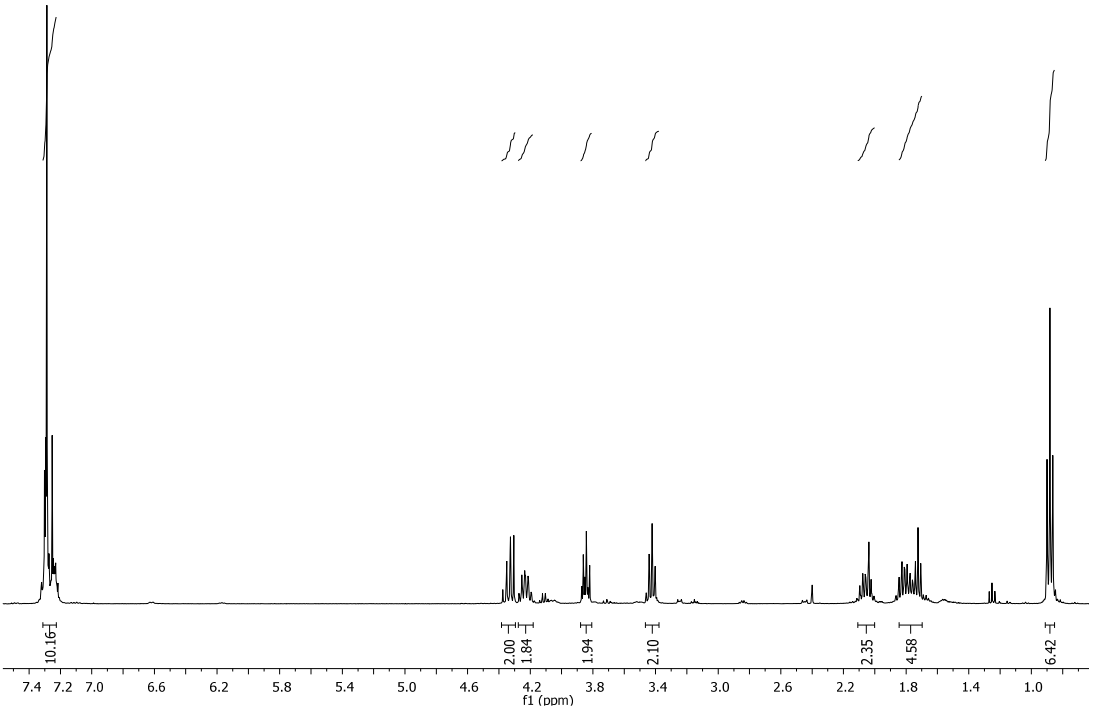


Figure 2.7: ^{1}H NMR spectrum of **(28)**

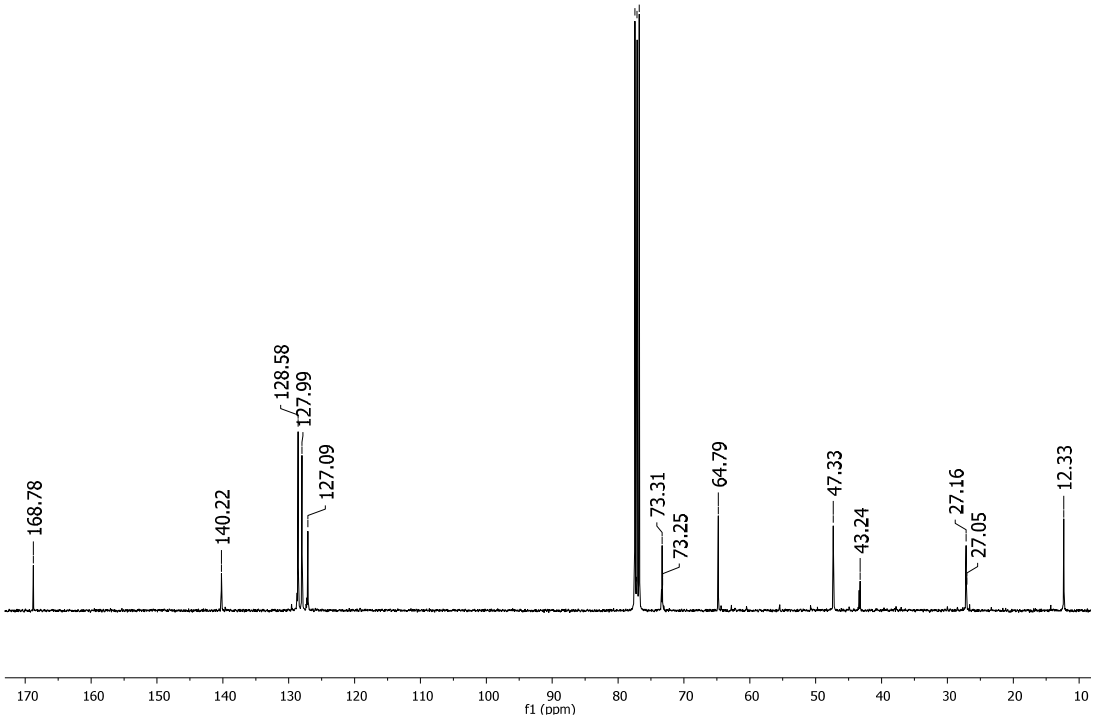
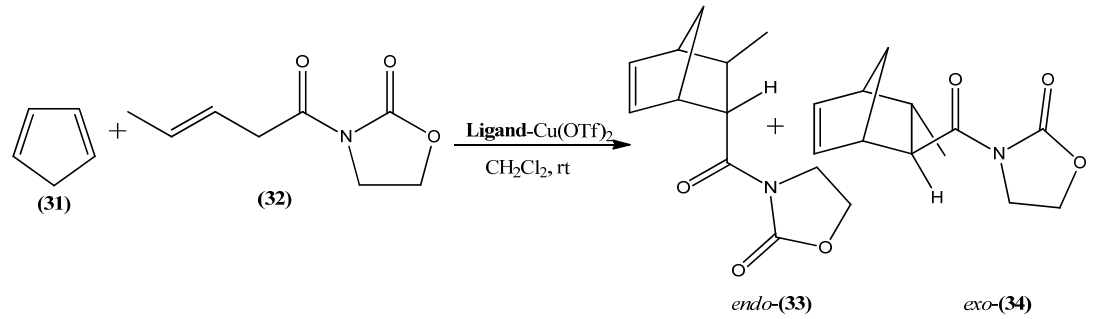


Figure 2.8: ^{13}C NMR spectrum of **(28)**

2.2.1 Diels Alder reaction

Corey *et al* were the first group to use BOX ligands to investigate the Diels Alder reaction, using Fe(III) complexes of 2,2' PhBOX **(29)**, as discussed in **Chapter 1**.[8] Evans *et al* applied Cu(II) complexes of *t*BuBOX **(30)**, catalysing the reaction between cyclopentadiene **(31)** and *trans*-(crotonoyl)-2-oxazolidinone **(32)**, yielding an *endo*:*exo* ratio of 94:4 and 97% *ee* of the *endo* product **(33)**.[9] Cu(II) complexes of 4,4'-BOX ligands have also been applied to this reaction, achieving *ee*'s an *endo*:*exo* ratio of 70:30 and 44% *ee* of the *endo* product **(33)**.[2]

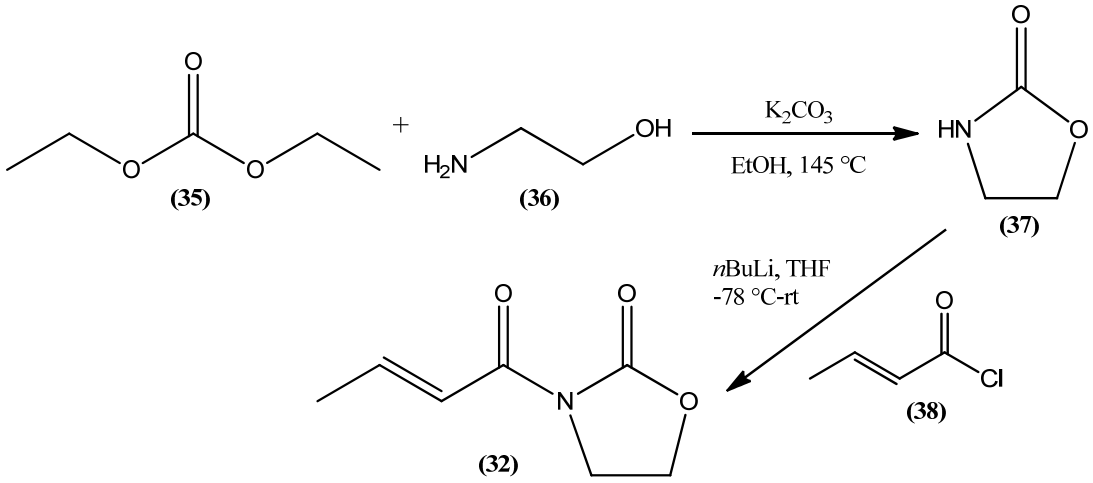
The asymmetric Diels Alder reaction was the first reaction used to test the applicability of the novel 4,4' bisoxazoline ligands. The reaction carried out was the benchmark reaction between cyclopentadiene **(31)** and *trans*-(crotonoyl)-2-oxazolidinone **(32)**, catalysed using complexes derived from our novel 4,4'-BOX ligands and copper(II)triflate **(Scheme 2.8)**.



Scheme 2.8

2.2.1.1 Synthesis of substrate for Diels Alder reaction

The dienophile **(32)** was synthesised according to literature procedure **(Scheme 2.9)**.



Scheme 2.9

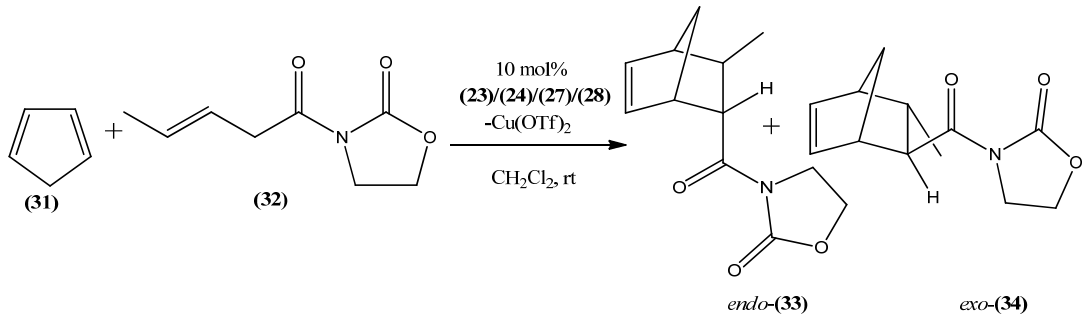
The substrate was synthesised in two steps from ethanolamine **(36)**. Ethanolamine **(36)** and potassium carbonate were heated at 145 °C for 2 h in the presence of diethyl carbonate **(35)**. The resulting crude oil was then dissolved in CH_2Cl_2 and the resulting suspension was filtered and concentrated *in vacuo*. The crude product was then recrystallized from ethyl acetate to give oxazolidinone **(37)** in 42% yield. The structure of the product was confirmed by comparison with the published data.[10]

Oxazolidinone **(37)** was then lithiated using *n*-butyllithium in THF at -78 °C and treated with *trans*-crotonyl chloride **(38)**. The reaction was left to stir overnight allowing it to warm to room temperature. The reaction was then quenched and isolated following several washes. The crude product was purified by column chromatography on silica gel affording *trans*-crotonyl-2-oxazolidinone **(32)** in 31%

yield. The structure of the product was confirmed by comparison with the published data.[11]

Cyclopentadiene **(31)** was prepared by cracking dicyclopentadiene at 160-180 °C for 2 h. Cyclopentadiene **(31)** was then distilled at 40 °C. Cyclopentadiene **(31)** was cracked and distilled freshly prior to use.

2.2.1.2 Diels Alder reaction: Methodology



Scheme 2.10

The reaction of cyclopentadiene **(31)** and *trans*-(crotonoyl)-2-oxazolidinone **(32)** was catalysed by 10 mol% of a homogenous complex derived from **(23)**, **(24)**, **(27)** or **(28)** and copper(II) triflate. The reaction led to the formation of {3-(3-methylbicyclo[2.2.1]hept-5-ene-2-carbonyl)-2-oxazolidinone} **(33)** and **(34)**. The reaction was carried out at room temperature in CH_2Cl_2 for 20 h. A ^1H NMR spectrum of the crude mixture was recorded to determine the % conversion and the *endo*:*exo* ratio. The % conversion was determined by comparing the amount of unreacted *trans*-crotonyl-2-oxazolidinone **(32)** [signal at 1.96 (3H)] compared to the sum of the product signals **(33)** and **(34)** [*endo* at 1.13 (3H) and *exo* at 0.85 (3H)]. The *endo*:*exo* ratio was calculated by comparing the *endo* peak [signal at 1.13 (3H)] and *exo* peak [signal at 0.85 (3H)] in the ^1H NMR spectrum.

The crude mixture was purified by column chromatography on silica gel, affording a mixture of *endo*-**(33)** and *exo*-**(34)**. The enantiomeric excess (*ee*) of the *endo* diastereomer **(33)** was then measured using chiral HPLC (CHIRACEL OD, 254 nm, hexane:*iso*-propyl alcohol, 98:2, 1.0 mL/min). The (*S*) product was eluted at ~42.0 min and the (*R*) product was eluted at ~45.0 min.

The results of the reactions carried out using Cu(II) complexes of 4,4' bisoxazoline ligands **(27)**, **(28)**, **(23)** and **(24)** in CH_2Cl_2 at room temperature **(Scheme 2.10)** are shown in **Table 2.1**.

Ligand	Time (h)	Metal Salt	Conversion %	*endo*:*exo* ratio	%*ee* *R*/*S*
(*S*,*S*)-MePrAraBOX **(27)**	24	$Cu(OTf)_2$	100	82:18	1 *R*
(*S*,*S*)-PhPrAraBOX **(28)**	24	$Cu(OTf)_2$	97	70:30	45 *R*
(*S*,*R*)-MePrAraBOX **(23)**	20	$Cu(OTf)_2$	91	75:25	11 *S*
(*S*,*R*)-PhPrAraBOX **(24)**	20	$Cu(OTf)_2$	85	64:36	57 *S*
MePrXyliBOX **(4)**[5]	18	$Cu(OTf)_2$	86	45:55	12 *R*
PhPrXyliBOX **(5)**[5]	16	$Cu(OTf)_2$	37	48:52	26 *S*
(*R*)-PhAraBOX **(1)**[2]	16	$Cu(OTf)_2$	60	70:30	44 *S*
*t*BuBOX **(30)**[9]	8	$Cu(OTf)_2$	95	87:13	94 *S*

Table 2.1

We found that the Cu(II) complexes of (*S*,*S*)-MePrAraBOX **(27)** and (*S*,*S*)-PhPrAraBOX **(28)** [derived from (2*S*, 4*S*)-arabitol] showed excellent activity with conversions of 100% and 97% respectively. Cu(II) complexes of (*S*,*R*)-MePrAraBOX **(23)** and (*S*,*R*)-PhPrAraBOX **(24)** [derived from (2*R*, 4*R*)-arabitol] also showed good activity with conversions of 91% and 85% respectively. The conversions achieved for all four of the novel Cu(II)-ligand complexes compare favourably to those of both the Cu(II) complexes of the traditional 2,2' *t*BuBOX **(30)** and the 4,4' MePrXyliBOX **(4)**, and outperform those of the first generation (*R*)-PhAraBOX **(1)**.

All four ligand-metal complexes showed the typical *endo*:*exo* diastereoselectivity seen for standard 2,2' BOX ligand-metal complexes and first generation Cu(II)-AraBOX complexes. The (*S*,*S*)-MePrAraBOX **(27)** showed an *endo*:*exo* ratio of 82:18 outperforming it phenyl counterpart (*S*,*S*)-PhPrAraBOX **(28)** which gave an *endo*:*exo* ratio of 70:30. Similarly, in reactions catalysed by the diastereomers of both ligands, (*S*,*R*)-MePrAraBOX **(23)** and (*S*,*R*)-PhPrAraBOX **(28)**, the methyl derivative gave a more favourable *endo*:*exo* ratio of 75:25 and 64:36 respectively. These diastereoselectivities are all comparable to those produced using the (*R*)-PhAraBOX **(1)**, while only the [Cu(II)-(*S*,*S*)-MePrAraBOX](OTf)$_2$ showed selectivity akin to that obtained using the traditional 2,2' *t*BuBOX **(30)**.

As discussed earlier, while the two butyric acids chosen, (*S*)-(+)-2-methylbutyric acid and (*S*)-(+)-2-phenylbutyric acid, possess the same named configuration, (S), the methyl and phenyl sidechains are actually directed in opposite directions. The results of this can be seen in the products of the Diels Alder reactions carried out using chiral XyliBOX ligands **(4)** and **(5)**, which give the opposite enantiomers as the major products. The [Cu(II)-(*S*,*S*)-MePrXyliBOX](OTf)$_2$ complex achieved an *ee* of 12% for the (*R*) enantiomer of the *endo*-**(33)** product, while the [Cu(II)-PhPrXyliBOX](OTf)$_2$ complex produced an *ee* of 26% for the (*S*) enantiomer of the *endo*-**(33)** product. A second point to note is that we will use the (*R*)-PhAraBOX **(1)**, which achieved an *ee* of 44% for the (*S*) enantiomer, as a *pseudo*-reference point for ligands lacking chiral sidearms. With this in mind we began testing the novel ligands on the aforementioned Diels Alder reaction.

Unfortunately the (*S*,*S*)-MePrAraBOX **(27)** showed almost no enantioselectivity, producing a 1% (*R*)*ee* for the *endo*-**(33)** product. In comparison, its diastereomeric counterpart, (*S*,*R*)-MePrAraBOX **(23)**, showed a 11% (*S*)*ee* for the *endo*-**(33)** product. Unusually, both these ligands show a subtractive effect on the enantioselectivities achieved by the *pseudo*-reference ligand (*R*)-PhAraBOX **(1)**. While the subtractive effect showed in the *ee* obtained for the (*S*,*R*)-MePrAraBOX **(23)** was expected, the MePr sidechain would have been expected to enhance the enantioselectivity of the chiral AraBOX backbone in the (*S*,*S*)-MePrAraBOX **(27)** ligand complex. However, surprisingly, the [Cu(II)-(*S*,*S*)-MePrAraBOX](OTf)$_2$ complex produced a near racemic mixture of products.

The (*S*,*S*)-PhPrAraBOX **(28)** gave higher enantioselectivity with a 45% (*R*)*ee* for the *endo*-**(33)** product. However, the highest *ee* was achieved using the (*S*,*R*)-

PhPrAraBOX ligand, 57% (*S*)*ee* for the *endo*-**(33)** product. This is the highest *ee* yet achieved by any complex derived from 4,4'-BOX ligands in an asymmetric Diels Alder reaction. Both phenyl propyl diastereomers showed enhanced enantioselectivites compared to the *pseudo*-reference ligand (*R*)-PhAraBOX **(1)**. Again, while the enhanced *ee* was expected for the (*S*,*R*)-PhPrAraBOX ligand, results obtained using the PhPrXyliBOX **(5)**, led us to expect a drop in *ee* when the (*S*,*S*)-PhPrAraBOX **(28)** ligand was employed.

In all cases, the phenyl propyl ligands complexes outperformed their methyl propyl derivatives, with respect to the enantioselectivities. It maybe that the enhanced steric bulk of the phenyl group is causing an additive effect in enantioselectivity, while the reduced steric bulk of the methyl substituents is the cause behind the reduced *ee*'s seen in the MePr ligands **(27)** and **(23)**. Both [Cu(II)-(*S*,*S*)-PhPrAraBOX]$(OTf)_2$ and [Cu(II)-(*S*,*R*)-PhPrAraBOX]$(OTf)_2$ showed comparable enantioselectivity to that achieved using the first generation (*R*)-PhAraBOX **(1)**. However, the *ee*'s achieved in all cases were modest in comparison to those achieved with Cu(II) complexes of the traditional 2,2' *t*BuBOX.

Variation in counterion study

Work carried out by Evans *et al* has shown that the reaction rate for asymmetric Diels-Alder reactions can be strongly dependant on the counterion used. Initial investigations used $Cu(OTf)_2$ as their source of Cu(II), but further work showed that 2,2' BOX-$Cu(SbF_6)_2$ catalysts are up to 20 times more reactive.[9] The reaction shown in **Scheme 2.10** was carried out as discussed above, except $Cu(SbF_6)_2$ was used in place of $Cu(OTf)_2$ as the source of Cu(II).

Table 2.2 shows the results of the reactions carried out using Cu(II) complexes of 4,4' bisoxazoline ligands **(27)**, **(28)**, **(23)** and **(24)** in CH_2Cl_2 at room temperature.

When SbF_6^- was used as the counterion at room temperature, the [Cu(II)-(*S*,*S*)-PhPrAraBOX]$(SbF_6)_2$ complex showed decreased activity. The reaction resulted in a 56% conversion compared to 97% conversion with the triflate as the counterion. The diastereoselectivity of the reaction increased however, from an *endo*:*exo* ratio of 70:30 with the triflate counterion to 78:12 using SbF_6^- as the counterion. The *ee* for the *endo* product was lower at 20% (*R*).

Ligand	Time (h)	Metal Salt	Conversion %	*endo*:*exo* ratio	%*ee* *R*/*S*
(*S*,*S*)-PhPrAraBOX **(28)**	22	$Cu(SbF_6)_2$	56	78:22	20 *R*
(*S*,*R*)-MePrAraBOX **(23)**	20	$Cu(SbF_6)_2$	74	78:22	9 *S*
(*S*,*R*)-PhPrAraBOX **(24)**	20	$Cu(SbF_6)_2$	87	80:20	31 *S*
MePrXyliBOX **(4)**[5]	16	$Cu(SbF_6)_2$	100	52:48	8 *R*
(*R*)-PhAraBOX **(1)**[2]	16	$Cu(SbF_6)_2$	52	70:30	-
*t*BuBOX **(30)**[9]	8	$Cu(SbF_6)_2$	98	82:18	96 *S*

Table 2.2

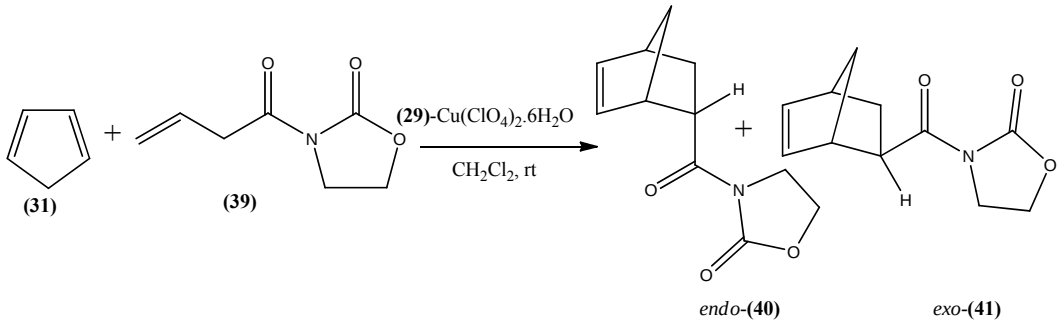
Similar results were also reported for the [Cu(II)-(*S*,*R*)-MePrAraBOX]$(SbF_6)_2$ and [Cu(II)-(*S*,*R*)-PhPrAraBOX]$(SbF_6)_2$ complexes. Decreased activity was observed for [Cu(II)-(*S*,*R*)-MePrAraBOX]$(SbF_6)_2$ complex with respect to reactions carried out using triflate as the counterion, 74% conversion compared to 91% conversion respectively. Use of the [Cu(II)-(*S*,*R*)-PhPrAraBOX]$(SbF_6)_2$ complex in place of its triflate counterpart had little to no effect on activity, giving conversions of 87% and 86% respectively. These results are in contrast to those observed for traditional 2,2' *t*BuBOX **(30)** and the 4,4' MePrXyliBOX **(4)**, which both showed increased activity when SbF_6^- was employed as the counterion. However, the 4,4' (*R*)-PhAraBOX **(1)** showed similar results, with decreased activity observed when employing SbF_6^- as the counterion in place of a triflate.

An increase in the diastereoselectivity was also observed for both the [Cu(II)-(*S*,*R*)-MePrAraBOX]$(SbF_6)_2$ and [Cu(II)-(*S*,*R*)-PhPrAraBOX]$(SbF_6)_2$ complexes. Use of the [Cu(II)-(*S*,*R*)-MePrAraBOX]$(SbF_6)_2$ complex resulted in an *endo*:*exo* ratio of 78:22, a very slight increase from the 75:25 *endo*:*exo* ratio obtained using the triflate complex. However, when the [Cu(II)-(*S*,*R*)-PhPrAraBOX]$(SbF_6)_2$ complex was employed as the catalyst, an *endo*:*exo* ratio of 80:20 was achieved, a marked increase from that achieved using the triflate as a counterion (*endo*:*exo* ratio of 64:36).

Finally, enantioselectivities also dropped when the triflate was replaced by SbF_6^- as the counterion. The (*S*,*R*)-MePrAraBOX **(23)** showed a slight decrease to 9% (*S*)*ee* for the *endo*-**(33)** product, down from 11% (*S*)*ee* with the triflate. Once again, the highest *ee* of the novel ligands tested was achieved with the (*S*,*R*)-PhPrAraBOX ligand **(24)**, 31% (*S*)*ee* for the *endo*-**(33)** product, dropping from 57% (*S*)*ee* when the triflate counterion was employed. Its diastereomeric counterpart (*S*,*S*)-PhPrAraBOX ligand **(28)** produced a 20% (*R*)*ee* for the *endo*-**(33)** product, also showing a decrease, from 45% (*R*)*ee* when the triflate counterion was employed. Again, both phenyl propyl ligands showed superior enantioselectivity in these reactions when compared to those obtained using the methyl propyl ligand (*S*,*R*)-MePrAraBOX **(23)**. Unfortunately, the (*S*,*S*)-MePrAraBOX ligand **(27)** could not be tested due to there being only a limited amount of material synthesised.

Other researchers have also investigated the influence of variations of the counterion on these reactions.

Ghosh *et al* reported the use of the cationic aqua complexes of inexpensive $Cu(ClO_4)_2.6H_2O$ and *t*BuBOX **(30)** and PhBOX **(29)**. They were able to achieve a conversion of 84% with excellent *endo*:*exo* ratio of 97:3, and a moderate *ee* of 41% (*S*) in the reaction of 3-acryloyl-2-oxazolidinone **(39)** and cyclopentadiene **(31)** using the PhBOX **(29)**, while use of the *t*BuBOX **(30)** resulted in a similar yields and diastereoselectivity, but with an extremely poor *ee* of 6% (*S*) **(Scheme 2.11)**.[12]



Scheme 2.11

Frain *et al* have also reported the use of this counterion in reactions for the 4,4' (*R*)-PhAraBOX **(1)**. They reported an increase in both activity and enantioselectivity in comparison to reactions performed with triflate as the counterion **(**

Scheme 2.10).[2] The reaction shown in **Scheme 2.10** was carried as discussed above, except that $Cu(ClO_4)_2.6H_2O$ was used as the source of Cu(II). **Table 2.3** shows the results of these reactions.

Ligand	Time (h)	Metal Salt	Conversion %	*endo*:*exo* ratio	%*ee* *R*/*S*
(*S*,*S*)-PhPrAraBOX **(28)**	16	$Cu(ClO_4)_2.6H_2O$	2	84:16	-
(*S*,*R*)-MePrAraBOX **(23)**	20	$Cu(ClO_4)_2.6H_2O$	18	71:29	39 *S*
(*S*,*R*)-PhPrAraBOX **(24)**	20	$Cu(ClO_4)_2.6H_2O$	18	72:28	49 *S*
MePrXyliBOX **(4)**[5]	16	$Cu(ClO_4)_2.6H_2O$	18	57:43	4 *R*
PhPrXyliBOX **(5)**[5]	16	$Cu(ClO_4)_2.6H_2O$	84	50:50	16 *S*
(*R*)-PhAraBOX **(1)**[2]	16	$Cu(ClO_4)_2.6H_2O$	90	70:30	53 *S*
*t*BuBOX **(30)**[12]	1, 0 °C	$Cu(ClO_4)_2.6H_2O$	84	97:3	6 *S*

Table 2.3

The [Cu(II)-(*S*,*S*)-PhPrAraBOX]$(ClO_4)_2.6H_2O$ complex showed a very poor conversion of 2%, with the %*ee* not determined. However, the complex also showed high diastereoselectivity, giving an *endo*:*exo* ratio of 84:16. The [Cu(II)-(*S*,*R*)-MePrAraBOX]$(ClO_4)_2.6H_2O$ and the [Cu(II)-(*S*,*R*)-PhPrAraBOX]$(ClO_4)_2.6H_2O$ complexes also showed a significant drop in activity with an 18% conversion for both. Both complexes also gave good diastereoselectivities achieving *endo*:*exo* ratios of 71:29 and 72:28 respectively.

Frain *et al* had seen enhanced enantioselectivity when testing the singly chiral (*R*)-PhAraBOX ligand **(1)**. The [Cu(II)-(*R*)-PhAraBOX]$(ClO_4)_2.6H_2O$ complex showed an increased *ee* to 53% (*S*) from that obtained using the SbF_6^- and triflate counterions, 0% and 44% (*S*) respectively. Similarly, the [Cu(II)-(*S*,*R*)-MePrAraBOX]$(ClO_4)_2.6H_2O$ complex showed a large increase in the enantioselectivity of the reaction, with 39% (*S*) achieved, when compared to the *ee*'s of 9% (*S*) and 11% (*S*) obtained when using SbF_6^- or triflate as the counterion. The [Cu(II)-(*S*,*R*)-PhPrAraBOX]$(ClO_4)_2.6H_2O$ complex also resulted in an improved *ee* of 49% (*S*) from the 31% (*S*) obtained with the SbF_6^- counterion. However, it was

still a reduced result when compared to the *ee* of 57% (*S*) produced using a triflate counterion. Unfortunately, no enantioselectivities were obtained for the diastereomeric ligands with the (*S*,*S*)-Arabitol backbone, due to poor conversions for the (*S*,*S*)-PhPrAraBOX ligand **(28)** and lack of ligand to test in the case of the (*S*,*S*)-MePrAraBOX ligand **(27)**. Once again, the phenyl propyl ligand showed superior enantioselectivity in comparison to its methyl propyl derivative.

Variation in cation study

Desimoni *et al* have investigated the use of magnesium(II)-2,2'-BOX complexes in the asymmetric Diels Alder reaction. They were able to achieve a conversion of 100% with an *endo*:*exo* ratio of 92:8, and a moderate *ee* of 72% (*S*) in the reaction of 3-acryloyl-2-oxazolidinone **(39)** and cyclopentadiene **(31)**, using Mg(II) complexes of 2,2' PhBOX **(29)**.[13] They found that changing the counterion from ClO_4^- to OTf^- caused a reversal in the sense of asymmetric reversal, similar to that seen by Jorgensen *et al* with their Cu(II)-BOX complexes, as discussed in **Section 1.5.4**.

The reaction shown in **Scheme 2.10** was carried as discussed above, except that $Mg(ClO_4)_2$ and $Mg(OTf)_2$ were used as the source of Mg(II). **Table 2.4** shows the results of the reactions.

All of the complexes formed between the novel ligands and magnesium salts gave poor results in the Diels Alder reaction. Only one of the novel ligands was complexed with $Mg(ClO_4)_2$. The resulting complex, [Mg(II)-(*S*,*S*)-PhPrAraBOX]$(ClO_4)_2$, gave a 5% conversion and an *endo*:*exo* ratio of 66:34. The conversion was lower than that obtained using the chiral XyliBOX ligands, while the diastereoselectivity was very similar. The *ee* of the reactions could not be determined due to a lack of product material.

When $Mg(OTf)_2$ was used as the magnesium salt the results were also very poor with [Mg(II)-(*S*,*S*)-PhPrAraBOX]$(OTf)_2$, [Mg(II)-(*S*,*R*)-MePrAraBOX]$(OTf)_2$ and [Mg(II)-(*S*,*R*)-PhPrAraBOX]$(OTf)_2$ giving conversions of 4%, 6% and 2% respectively. The *endo*:*exo* ratio for the reactions was similar to those obtained using $Mg(ClO_4)_2$ as the metal salt. Once again, the poor conversions meant that the *ee* of the reactions could not be determined due to a lack of product material.

Ligand	Time (h)	Metal Salt	Conversion %	*endo*:*exo* ratio	%*ee* *R*/*S*
(*S*,*S*)-PhPrAraBOX **(28)**	16	$Mg(ClO_4)_2$	5	66:34	-
MePrXyliBOX **(4)**[5]	16	$Mg(ClO_4)_2$	13	65:35	-
PhPrXyliBOX **(5)**[5]	16	$Mg(ClO_4)_2$	14	69:31	4 *R*
(*S*,*S*)-PhPrAraBOX **(28)**	16	$Mg(OTf)_2$	4	66:34	-
(*S*,*R*)-MePrAraBOX **(23)**	20	$Mg(OTf)_2$	6	66:34	-
(*S*,*R*)-PhPrAraBOX **(24)**	20	$Mg(OTf)_2$	2	-	-
PhPrXyliBOX **(5)**[5]	16	$Mg(OTf)_2$	4	69:31	-

Table 2.4

Evans *et al* have tested the suitability of various metal triflates in asymmetric Diels Alder reactions. They found that the 2,2' *t*BuBOX **(30)** complex of $Zn(OTf)_2$ achieved a conversion of 85% with an *endo*:*exo* ratio of 95:5, and a moderate *ee* of 38% (*R*) in the reaction of 3-acryloyl-2-oxazolidinone and cyclopentadiene.[9] Subsequent studies showed the 2,2' PhBOX ligand **(29)** to be optimal ligand for $Zn(OTf)_2$ in these reactions. The resulting complex catalysed the above reaction resulting in conversion of 90% with an *endo*:*exo* ratio of 98:2, and a moderate *ee* of 92% (*R*). The reaction shown in **Scheme 2.10** was carried as discussed above, except that $Zn(OTf)_2$ was used as the source of Zn(II). **Table 2.5** shows the results of the reactions.

Ligand	Time (h)	Metal Salt	Conversion %	*endo*:*exo* ratio	%*ee* *R*/*S*
(*S*,*S*)-PhPrAraBOX **(28)**	20	$Zn(OTf)_2$	32	80:20	20 *S*
(*S*,*R*)-MePrAraBOX **(23)**	20	$Zn(OTf)_2$	5	77:23	-
(*S*,*R*)-PhPrAraBOX **(24)**	20	$Zn(OTf)_2$	10	73:27	-

Table 2.5

All of the complexes formed between the novel ligands and $Zn(OTf)_2$ gave poor conversions in the Diels Alder reaction. The resulting complex, [Zn(II)-(*S*,*S*)-PhPrAraBOX]$(OTf)_2$, gave a 32% conversion. The *endo*:*exo* ratio also rose from 70:30 to 80:20 when the cation was changed from Cu(II) to Zn(II). Interestingly, the [Cu(II)-(*S*,*S*)-PhPrAraBOX]$(OTf)_2$ complex produced a 45% (*R*)*ee*, while the [Zn(II)-(*S*,*S*)-PhPrAraBOX]$(OTf)_2$ complex produced a 20% (*S*)*ee* for the same reaction. This behaviour has previously been seen in metal-2,2'-bisoxazoline catalysis of Diels Alder and ene reactions. Previous work on variation of the metal source in the testing of 4,4'-bisoxazoline ligands has also shown a similar type of behaviour, with Mg(II) complexes producing the opposite enantiomer to that favoured by Cu(II) complexes. This reversal in selectivity is believed to arise from a change in the metal's geometry. While, Zn(II) complexes generally favour a tetrahedral geometry, square planar geometries are favoured by Cu(II) complexes. This change in geometry around the metal centre results in the opposite face of the dienophile being exposed, resulting in a reversal in stereoselectivity between the two complexes.

The other complexes formed, [Zn(II)-(*S*,*R*)-MePrAraBOX]$(OTf)_2$ and [Zn(II)-(*S*,*R*)-PhPrAraBOX]$(OTf)_2$, gave very poor conversions of 5% and 10% respectively. Again, it was found that the *endo*:*exo* ratios improved when switching the cation source from Cu(II) to Zn(II). When the [Zn(II)-(*S*,*R*)-MePrAraBOX]$(OTf)_2$ complex was used in place of the [Cu(II)-(*S*,*R*)-MePrAraBOX]$(OTf)_2$ complex, the *endo*:*exo* ratio was raised to 77:23 from 75:25. While switching from the [Cu(II)-(*S*,*R*)-MePrAraBOX]$(OTf)_2$ complex to the [Zn(II)-(*S*,*R*)-MePrAraBOX]$(OTf)_2$ complex,

the *endo*:*exo* ratio was raised from 64:36 to 73:27. Unfortunately, the *ee* of the two reactions could not be determined due to a lack of product material.

2.2.1.3 Comparison of the structure and performance of 2,2' and 4,4' BOX complexes

Since their introduction as ligands in asymmetric catalysis over 20 years ago, there has been much written about the structure and performance of the 2,2'BOX ligands as their copper(II) complexes in the Diels-Alder reaction. One of the most interesting discussions on this topic is centred on the reversal of selectivity seen when the same enantiomer of the phenyl and *tert*-butyl BOX ligands, **(29)** and **(30)**, are used. Jorgensen and Evans have each discussed the merits of square planar *versus* tetrahedral geometry about the metal centre, as well as the distorted versions of each geometry. While numerous calculations have been carried out on the subject, only a small number of X-Ray crystal structures have been reported, which help in considering the nature of the complex formed when the reacting dieneophile is complexed through its two carbonyl groups. Of particular interest is the X-Ray structure reported by Evans *et al* of a Cu(II) complex of the *t*BuBOX ligand **(30)** with a malonate based reagent **(Figure 2.9)**.[14]

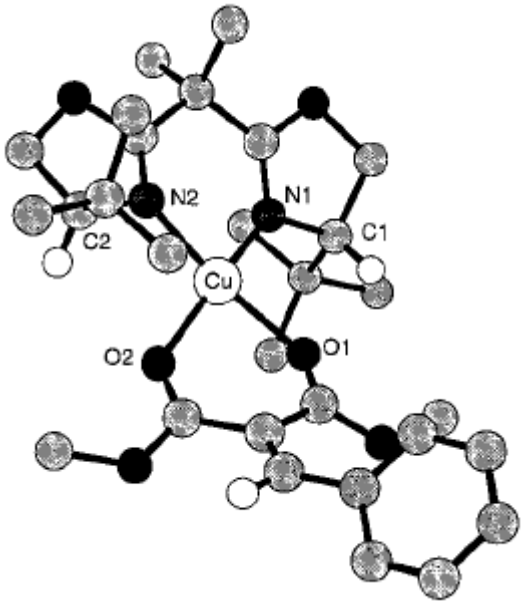


Figure 2.9

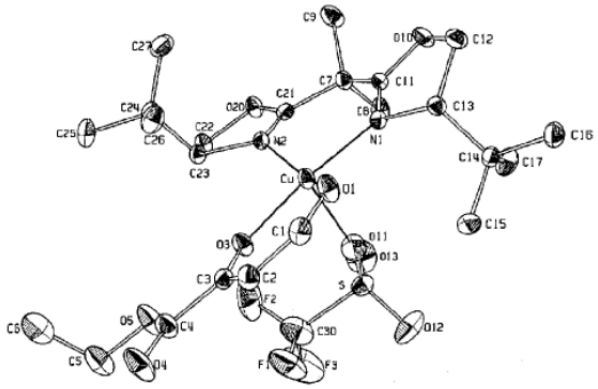


Figure 2.10

Jorgensen *et al* have also reported the structure of a complex in which a hydrolysed enone is bound to a Cu(II)-*t*BuBOX system **(Figure 2.10)**.[15]

In both of these structures the geometry around the copper centre may be described as distorted square planar and does not deviate dramatically from the geometry seen in the simple bis aqua complexes, of which a number of which have been reported. Evans *et al* for instance have also reported the structure of the Cu(II)-*t*BuBOX hexafluoroantimonate aqua complex **(Figure 2.11)**.[16]

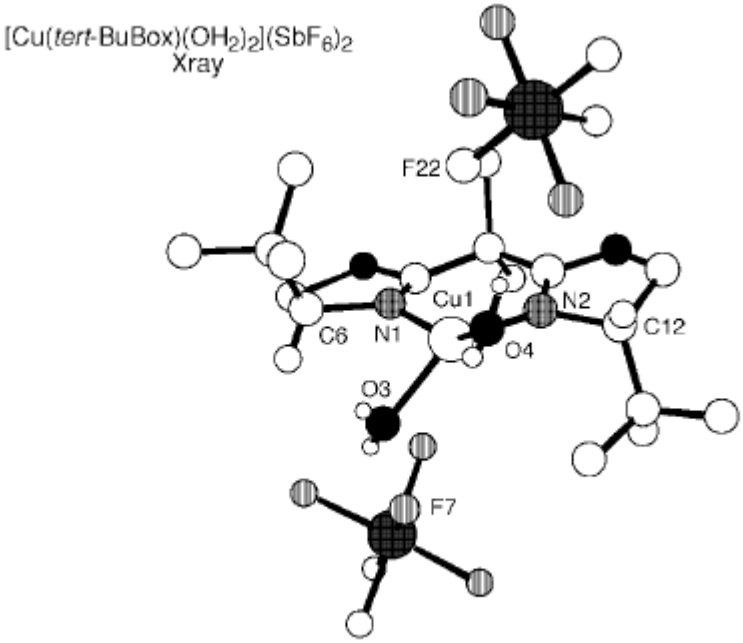


Figure 2.11

Generally in the bis aquo complexes, the X-Ray crystal structures shows a distorted square planar geometry around the copper centre. In fact the dihedral angle for the O(H_2O)-Cu-N-C (chiral carbon atom in ligand) lies in the range from +33.3° for

*t*BuBOX-Cu$(OH_2)_2^{2+}$ to -9.3° for PhBOX-Cu$(OH_2)_2^{2+}$.[15] This, in turn, is not too dissimilar to the structures reported for the simple dichloride salts. In one example of this, Rutjes *et al* reported the structure of the Cu(II) napthyl complex, which again shows a distorted square planar geometry **(Figure 2.12)**.[17]

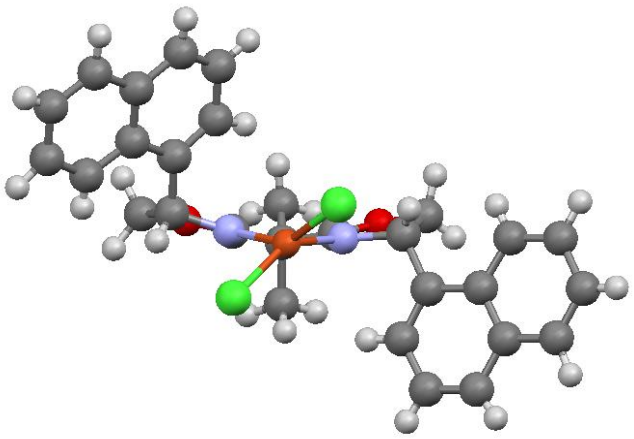


Figure 2.12

In all of these 2,2'-BOX complexes it should be noted that the ligand portion remains planar, as one would expect, regardless of any variations in the geometry about the copper. The groups on the chiral carbon of the ligand point largely up and down from that plane, blocking approach by incoming reagents from those quadrants they occupy. The complex is also likely to be quite rigid with reduced flexibility, due to the Thorpe-Ingold effect generated by the gem-dimethyl group on the bridgehead.

While our group has, as of yet, not managed to get a crystal structure of a 4,4'-BOX copper complex, where the copper is also complexed to oxygen containing groups (be they aqua or dicarbonyl), Frain has obtained a crystal structure of the phenyl 4,4'-BOX ligand copper(II) complex showing a dihedral angle for the Cl-Cu-N-C (sp^2 carbon atom in ligand) of +23.9° **(Figure 2.13)**.[2]

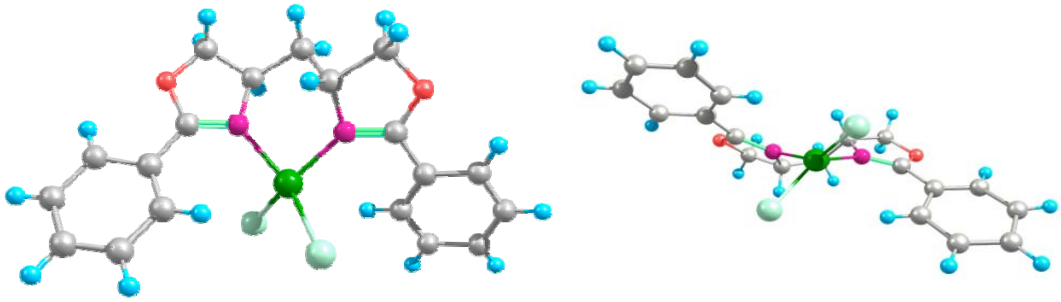


Figure 2.13

We have used this X-Ray structure as the basis for a DFT calculation with Spartan 10 on the equilibrium geometry of a complex with the carbonyl's of a dieneophile co-ordinated. Three views of the calculated structure are shown in **Figure 2.14**.

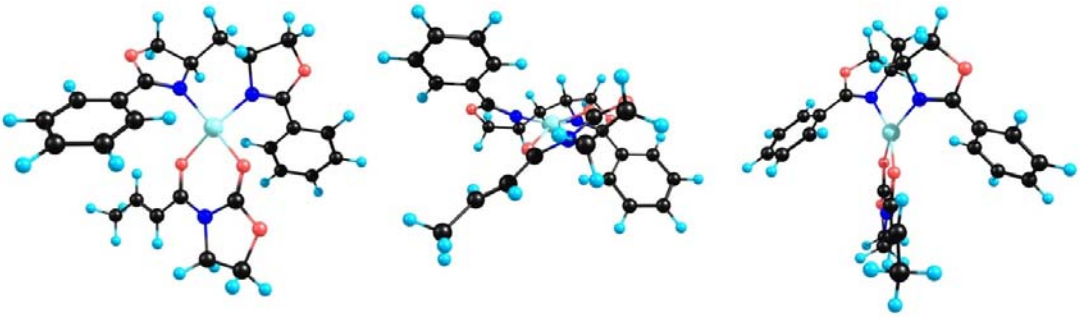


Figure 2.14

It is clear from these structures (both X-Ray and calculated) that the geometry around the metal remains distorted square planar. It is also clear that by putting chirality in the backbone of the ligand, that the ligand portion of the complex is no longer planar and in some ways is more reminiscent of the salen ligand with a bent backbone. Though the work described in this thesis does not contain an X-Ray crystal structure we can infer something about these ligands from what is known from their simpler analogues, the first generation 4,4'-bisoxazoline ligands. The blocking of quadrants in this ligand is much less obvious and apparently from the Diels-Alder reaction results to date has been less effective than that achieved in the 2,2'-BOX reactions. Particularly the enantioselectivities reported with our 4,4'-bisoxazoline ligands are not as high as those seen with the 2,2'-bisoxazoline ligands. One factor which may be mitigating against the performance of the 4,4'-bisoxazoline ligands, with regard to selectivity, is the flexibility of the metallocycle formed on co-ordination of the copper. This flexibility was also evident in the work done in

conjunction with Prof. García in Zaragoza, on the cyclopropanation transition states which is discussed elsewhere in this chapter **(Section 2.2.4.1)**.

The introduction of gemdimethyl substituents at the bridgehead position, in a similar manner to that seen with the 2,2'-bisoxazoline ligands shown in the earlier X-Ray crystal structures, may reduce this proposed flexibility. Unfortunately, the introduction of such a group is hard to achieve given our current synthetic method. Another option would be to convert the methylene bridgehead position to an sp^2 carbon, giving an alkene (effectively replacing the 2H's with a $=CH_2$). This would reduce the flexibility in the metallocycle severely, which may have the desired effect. Work on this project is currently ongoing in the group.

Another issue could be the hydrogen on the chiral centre which is not very sterically demanding, allowing the metallocycle to be flexible. Replacing these H's with methyl or larger groups may also increase the stereoselectivity. This work is at an early stage in the group and presents an interesting issue. The group which replaces the H's could effectively block off approach to the metal from the two available quadrants opposite those already occupied, and thus it may present a very fine balancing act to achieve the greatest possible selectivity.

The results reported in this thesis make it apparent that chiral centres on the sidearms of the AraBOX ligands also have a substantial effect on the stereochemical performance of the catalysts derived from these ligands. As discussed above, introduction of the chiral phenyl propyl sidearms resulted in increased enantioselectity, in comparison to that achieved using the first generation ligands lacking them. While, the addition of chiral methyl propyl sidearms to the bisoxazoline framework also affected the enantioselectivites, all be it by yielding reduced *ee*'s.

Conclusion

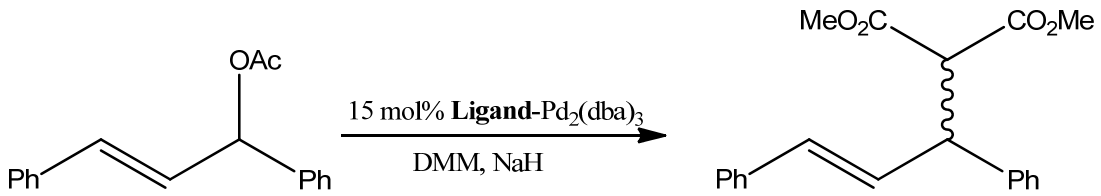
All $Cu(OTf)_2$ complexes showed excellent activities with conversions of 85-100% achieved. The [Cu(II)-(*S*,*S*)-MePrAraBOX]$(OTf)_2$ achieved the highest conversion and diastereoselectivity of 100% and 82:18 of the $Cu(OTf)_2$ complexes of the four ligands, but only produced a 1% (*R*)*ee* for the *endo*-**(33)** product.. The highest *ee* was achieved with the [Cu(II)-(*S*,*R*)-PhPrAraBOX]$(OTf)_2$ complex, producing a 57% (*S*)*ee* for the *endo*-**(33)** product. This is the highest *ee* yet achieved by any complex derived from 4,4'-BOX ligands in an asymmetric Diels Alder reaction.

Changing the counterion from triflate to SbF_6^- resulted in decreased conversions and enantioselectivity and increased diastereoselectivity in all cases. Use of $Cu(ClO_4)_2.6H_2O$ as the metal source, resulted in very poor conversions of 2-18% and decreased enantioselectivity.

Changes in the cation source also resulted in poor conversions with Mg(II) complexes giving poor conversions of 2-6% and Zn(II) complexes producing conversions of 5-32%. With the Mg(II) conversions being so poor, no enantioselectivities could be determined. However, the [Zn(II)-(*S*,*S*)-PhPrAraBOX](OTf)$_2$ complex produced a modest conversion of 32% allowing for an *ee* of 20%(*S*) to be determined. Interestingly, its Cu(II) analog, [Cu(II)-(*S*,*S*)-PhPrAraBOX](OTf)$_2$, produced a 45% (*R*)*ee*, showing a reversal of selectivity. This type of effect has been seen in other systems involving both 2,2' bisoxazoline ligands and 4,4' bisoxazoline ligands.

2.2.2 Allylic Alkylation reaction

The allylic alkylation reaction can be used in the formation of either carbon-carbon or carbon-herteroatom bonds. The reaction of the 1,3-diphenylallyl system has become one of the benchmark reactions in allylic substitutions, used to evaluate novel ligands. Palladium complexes are favoured over other metal complexes in these reactions, as they show greater reactivity and selectivity. The use of C_1-symmetric ligands bearing different donor atoms has been shown to give high selectivity, with only a few examples of C_2-symmetric bisoxazoline complexes present in the literature.[18,19]

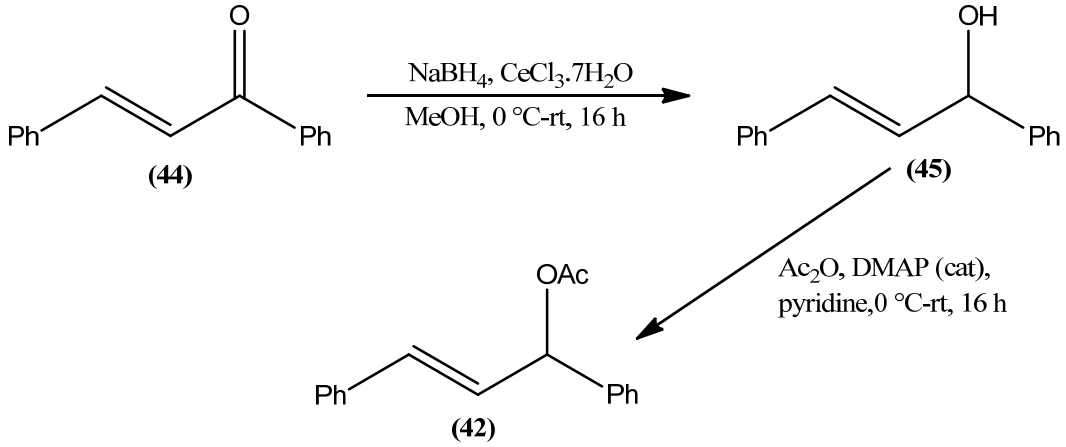


(42) **(43)**

Scheme 2.12

We decided to investigate the allylic alkylation reaction of dimethyl malonate and (±)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene **(42)**, employing sodium hydride as the base, using complexes derived from our novel 4,4'-BOX ligands and tris(dibenzylideneacetone)dipalladium **(Scheme 2.12)**.

2.2.2.1 Synthesis of substrates for Allylic Alkylation reaction

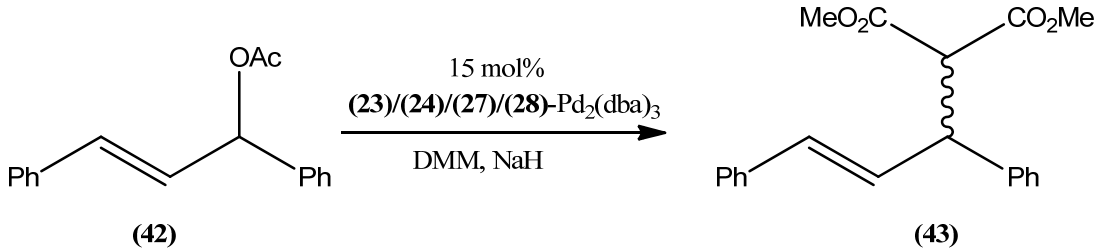


Scheme 2.13

The substrate (±)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene **(42)** was synthesised in two steps from *trans*-chalcone **(44)**. *Trans*-chalcone **(44)** was reduced using sodium borohydride in the presence of cerium(III) trichloride heptahydrate at 0 °C. The reaction was left to stir overnight, allowing it to warm to room temperature. Following an acidic workup, the crude product was isolated and purified by column chromatography on silica gel giving **(45)** in 57% yield **(Scheme 2.13)**. The structure of the product was confirmed by comparison with the published data.[20]

Alcohol **(45)** was then acetylated using acetic anhydride and a catalytic amount of 4-dimehtylaminopyridine at 0 °C. The reaction was left to stir overnight, allowing it to warm to room temperature. The crude product was isolated following several washings. The crude product was purified by column chromatography on silica gel affording acetate **(42)** in 44% yield. The structure of the product was confirmed by comparison with the published data.[20]

2.2.2.2 Allylic Alkylation reaction: Methodology



Scheme 2.14

10 mol% of tris(dibenzylideneacetone)dipalladium and 15 mol% of **(23)**, **(24)**, **(27)** or **(28)** were heated in toluene at 80 °C for 2 h. In a separate flask, the nucleophile

was prepared by heating a mixture of dimethyl malonate and sodium hydride to 80 °C for 15 min. The substrate, (±)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene **(42)**, and the active catalyst were then added to the nucleophile flask. This reaction mixture was heated in toluene at 80 °C for 60 h, leading to the formation of product **(43)** A ^{1}H NMR spectrum of the crude mixture was recorded to determine the % conversion [unreacted (±)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene **(42)** signal at 2.14 (3H) compared to the product **(43)** signal at 4.27 (1H)].

The crude mixture was purified by column chromatography on silica gel, affording **(43)**. The enantiomeric excess (*ee*) of the product was then measured using chiral HPLC (CHIRACEL OD, 254 nm, hexane (0.1% diethylamine):*iso*-propyl alcohol, 98:2, 0.5 mL/min). The (*R*) product was eluted at ~25.0 min and the (*S*) product was eluted at ~27.0 min.

The results of the reactions carried out using palladium complexes of 4,4' bisoxazoline ligands **(28)**, **(27)**, **(24)** and **(23)** in toluene at 80 °C for 60 h are shown in **Table 2.6**.

Ligand	**Metal Salt**	**Conversion %**	**%*ee* *R*/*S***
(*S*,*S*)-PhPrAraBOX **(28)**	$Pd_2(dba)_3$	16	6 *R*
(*S*,*S*)-MePrAraBOX **(27)**	$Pd_2(dba)_3$	99	72 *R*
(*S*,*R*)-PhPrAraBOX **(24)**	$Pd_2(dba)_3$	90	68 *S*
(*S*,*R*)-MePrAraBOX **(23)**	$Pd_2(dba)_3$	71	62 *S*

Table 2.6

Since neither first generation AraBOX ligands nor chiral propyl XyliBOX ligands had previously been applied to this reaction, we had no indication of how our novel ligands would perform. The palladium complex of (*S*,*S*)-PhPrAraBOX **(28)** showed very little activity for this reaction, giving only 16% conversion. However, fortunately, the three other ligands, (*S*,*S*)-MePrAraBOX **(27)**, (*S*,*R*)-PhPrAraBOX **(24)** and (*S*,*R*)-MePrAraBOX **(23)**, all showed excellent activity, giving conversions of 99%, 90% and 71% respectively.

The (*S*,*S*)-PhPrAraBOX **(28)** also produced the lowest enantioselectivity, with an *ee* of only 6% (*R*) obtained. In contrast, the palladium complex of its diastereomer, (*S*,*R*)-PhPrAraBOX **(24)**, achieved a good *ee* of 68% (*S*). The palladium complex of its methyl derivative, (*S*,*S*)-MePrAraBOX **(27)**, achieved an *ee* of 72% (*R*), the highest *ee* yet achieved of any complex derived from 4,4'-BOX ligands in an asymmetric allylic alkylation reaction. The diastereomeric counterpart, (*S*,*R*)-MePrAraBOX **(23)**, also produced a good enantioselectivity 62% (*S*). Without any previous results from their earlier analogues, it is difficult to determine the influence that the sidearms of the ligands are having on these reactions. However, it does seem that the phenyl propyl sidearms are having a large effect on the enantioselectivities being produced. While the (*S*,*R*)-PhPrAraBOX **(24)** produced an *ee* of 68% (*S*), its diastereomer could only produce a poor *ee* of 6% (*R*). This may indicate that the phenyl propyl sidearm favours the (*S*) enantiomer of the desired product, working with the backbone of the (*S*,*R*)-PhPrAraBOX ligand **(24)** and against the backbone of the (*S*,*S*)-PhPrAraBOX ligand **(28)**.

Both methyl propyl ligands, (*S*,*S*)-MePrAraBOX **(27)** and (*S*,*R*)-MePrAraBOX **(23)**, gave good *ee*'s which may indicate that these sidearms are having a lesser effect on the selectivity of the resulting complexes. In this case the (*S*) methyl propyl sidearm appears to favour the (*R*) product, whereas in the PhPr case, the (*S*) sidearm appears to favour the (*S*) product.

Conclusion

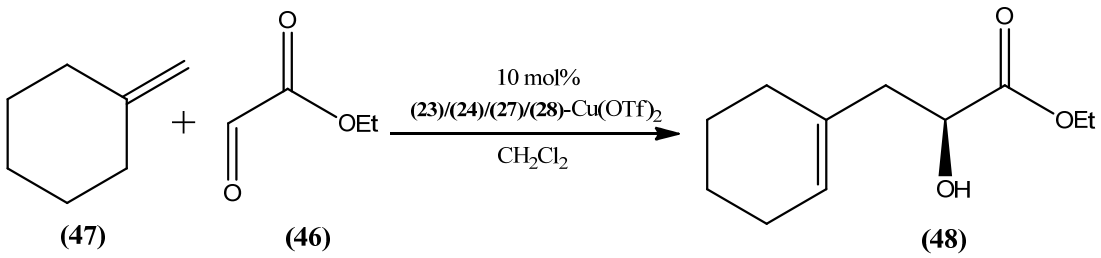
Three of the four ligands produced excellent conversions in the test reactions performed. All three also gave good enantioselectivities for palladium catalysed reactions. Since the ligands all but one of the novel metal-ligand complexes showed high activities, further studies could focus on reducing the temperature of the reactions to facilitate greater enantioselectivity.

2.2.3 Ene reaction

The ene reaction, as discussed in **Chapter 1**, is an important atom-efficient, carbon-carbon bond forming reaction.[21] As mentioned earlier, Evans *et al* have investigated the reaction of ethyl glyoxylate **(46)** with a wide range of olefins, using a variety of 2,2'-BOX ligands with copper(II)triflate and copper(II)hexafluoroantimonate. These complexes catalysed the reaction of ethyl glyoxylate **(46)** and methylene

cyclohexane **(47)** to yield the ene product in high yields (97-99%) and enantioselectivities (87-97% *ee*).[22]

We decided to employ complexes derived from our novel 4,4'-BOX ligands and copper(II)triflate to investigate the ene reaction of ethyl glyoxylate **(46)** and methylene cyclohexane **(47) (Scheme 2.15)**.



(47) **(46)** **(48)**

Scheme 2.15

2.2.3.1 Ene reaction: Methodology

The reaction of ethyl glyoxylate **(46)** and methylene cyclohexane **(47)** was catalysed by 10 mol% of a homogenous complex derived from **(23)**, **(27)**, **(28)** or **(24)** and copper(II)triflate. The reaction led to the formation of ethyl-3-(1-cyclohexenyl)-2-hydoxy-propionate **(48)**. The reactions were performed in CH_2Cl_2, heated to reflux and left stirring for 16 h. A ^1H NMR spectrum was recorded of the crude product to determine the % conversion. The % conversion was calculated by comparing the amount of unreacted methylene cyclohexane **(47)** [signal at 4.58 (2H)] to the amount of product **(48)** [signal at 5.53 (1H)] in the ^1H NMR. The crude product was purified by column chromatography on silica gel. The product eluted with petroleum ether:diethyl ether 7:3.

The enantiomeric excess (*ee*) of the purified product was then measured using chiral GC (Cyclodex-β-30 m x 0.252 mm 0.25 μm, conditions; 110 ^oC hold 10 mins, ramp 1 ^oC/min to 130 ^oC hold 20 min, ramp 2 ^oC/min to 150 ^oC). The (*R*) product was eluted at ~45.0 min and the (*S*) product was eluted at ~47.0 min.

The results of the reactions carried out using Cu(II) complexes of 4,4' bisoxazoline ligands **(23)**, **(27)**, **(28)** and **(24)** in CH_2Cl_2, heated to reflux for 16 h are shown in **Table 2.7**.

We found that the Cu(II) complexes of all four ligands showed excellent activity with conversions of 100% in all cases. However all four complexes also gave low *ee*'s. Both methyl propyl complexes, [Cu(II)-(*S*,*S*)-MePrAraBOX](OTf)$_2$ and

[Cu(II)-*(S,R)*-MePrAraBOX](OTf)$_2$, showed almost no enantioselectivity, giving *ee*'s of 1% (*R*) and 2% (*R*) respectively.

Ligand	**Time (h), Temp (^{o}C)**	**Metal Salt**	**Conversion %**	**%*ee* *R*/*S***
(*S,S*)-PhPrAraBOX **(28)**	16, 50	Cu(OTf)$_2$	100	9 *S*
(*S,S*)-MePrAraBOX **(27)**	16, 50	Cu(OTf)$_2$	100	1 *R*
(*S,R*)-PhPrAraBOX **(24)**	16, 50	Cu(OTf)$_2$	100	4 *S*
(*S,R*)-MePrAraBOX **(23)**	16, 50	Cu(OTf)$_2$	100	2 *R*
*t*BuBOX **(30)**[22]	n/a, 0	Cu(OTf)$_2$	99	87 *R*

Table 2.7

The phenyl propyl complexes, [Cu(II)-*(S,S)*-PhPrAraBOX](OTf)$_2$ and [Cu(II)-*(S,R)*-PhPrAraBOX](OTf)$_2$, showed very slight improvements, giving *ee*'s of 9% (*S*) and 4% (*S*) respectively. Interestingly, both methyl propyl ligands **(27)** and **(23)** gave the (*R*) enantiomer of the product **(48)**, while the phenyl propyl ligands **(28)** and **(24)** gave the (*S*) enantiomer of the product **(48)** indicating that the stereocentres on the sidechains were having a larger influence on the stereochemical outcome of the reaction than the stereocentres on the backbone of the ligands. Again it appears that the two sidearms have had the opposite effect to each other.

The poor enantioselectivities seen in these reactions maybe a result of the flexibility of these ligands, discussed in **Section 2.2.1.3**. In a similar manner to the Diels Alder reactions, the complex catalysing the ene reaction forms by co-ordination of the two carbonyl groups of the reagent. However, in contrast to the Diels Alder reaction, the ene reaction occurs at one of these co-ordinated carbonyl groups. It maybe that, by bringing the reaction centre in, closer to the complex's metal centre (as in the case of the ene reaction), that the need for rigidity in the complex increases. As such, these ligands [**(23)**, **(27)**, **(28)** and **(24)**], which lack a gemdimethyl bridgehead or any

other substituent capable of reducing flexibility in the ligand portion of the complex, cannot govern the selectivity of this reaction to any significant degree.

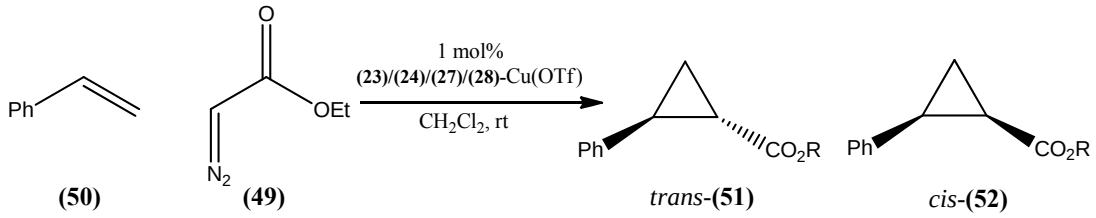
Conclusion

The four ligands all produced excellent conversions in each of the test reactions performed. However, all four showed almost no enantioselectivity for those reactions. Since the ligands all showed high activities, further studies would focus on reducing the temperature of the reactions to facilitate greater enantioselectivity.

2.2.4 Cyclopropanation Reaction

Evans *et al*, amongst others, have investigated the asymmetric cyclopropanation reaction using 2,2'-BOX ligands with copper(I)triflate, as discussed in **Chapter 1**.[23-26] The Cu(I) complex of *t*BuBOX **(30)** catalysed the reaction of ethyl diazoacetate **(49)** and styrene **(50)**, producing an *ee* of 99% for both the *cis* and *trans* diastereomers and a *dr* of 73:27.[23] Cu(I) complexes of 4,4'-BOX ligands have also been applied to this reaction with the Cu(I) complex of (*R*)-PhAraBOX **(1)** achieving *ee*'s of 32% and 16% for the *cis* and *trans* products respectively, and a *dr* of 60:40.[3]

Our novel 4,4' bisoxazoline ligands were next applied to the asymmetric cyclopropanation reaction. The reaction carried out was the benchmark reaction between styrene **(50)** and ethyl diazoacetate **(49)**, catalysed using complexes derived from our novel 4,4'-BOX ligands and copper(I)triflate.



(50) **(49)** *trans*-**(51)** *cis*-**(52)**

Scheme 2.16

2.2.4.1 Cyclopropanation Reaction: Methodology

The reaction of styrene **(50)** and ethyl diazoacetate **(49)** was catalysed by 1 mol% of a homogenous complex derived from **(27)**, **(28)**, **(23)** or **(24)** and copper(I)triflate. The reaction led to the formation of *trans*-**(51)** and *cis*-**(52)** ethyl-2-phenylcyclopropane-1-carboxylate. The ethyl diazoacetate **(49)** was added to the styrene **(50)** over *ca*. 6 h *via* a syringe pump. The reaction was carried out at room

temperature in CH_2Cl_2 for 20 h. A ^1H NMR spectrum was recorded to determine the % conversion and the *cis*:*trans* ratio. The % conversion was determined by comparing the amount of unreacted ethyl diazoacetate **(49)** [signal at 4.72 (1H)] to the sum of the product peaks [*cis*-**(52)** at 3.87 (2H) and *trans*-**(51)** at 4.17 (2H)] minus the sum of the by-product peaks [diethyl fumarate at 6.84 (2H) and diethyl maleate at 6.22 (2H)]. The *cis*:*trans* ratio was calculated by comparing the *cis* product [signal at 3.87 (2H)] to the *trans* product [signal at 4.17 (2H)] in the ^1H NMR spectrum.

The crude mixture was purified by column chromatography on silica gel, affording a mixture of products *trans*-**(51)** and *cis*-**(52)**. The enantiomeric excess (*ee*) of the *trans*-**(51)** and the *cis*-**(52)** diastereomers were then measured using chiral GC (Cyclodex-β-30 m x 0.252 mm 0.25 μm, conditions; 100 ^oC hold 5 min, ramp 1 ^oC/min to 165 ^oC hold 5 min). The (1*S*, 2*R*) product was eluted at around 39.0 min and the (1*S*, 2*S*) product was eluted at around 42.0 min.

The results of the reactions carried out using Cu(I) complexes of 4,4' bisoxazoline ligands **(27)**, **(28)**, **(23)** and **(24)** in CH_2Cl_2 at room temperature for 20 h **(Scheme 2.16)** are shown in **Table 2.8**.

We found that the Cu(I) complexes of (*S*,*S*)-MePrAraBOX **(27)** and (*S*,*R*)-MePrAraBOX **(23)** showed good activity with conversions of 93% and 91% respectively. Cu(I) complexes of (*S*,*S*)-PhPrAraBOX **(28)** and (*S*,*R*)-PhPrAraBOX **(24)** also showed excellent activity with conversions of 86% and 85% respectively. The conversions achieved for all four of the novel Cu(I)-ligand complexes compare favourably to those of both the Cu(I) complexes of the traditional 2,2' *t*BuBOX **(30)** and the MePrXyliBOX **(4)**. However, both the PhPrXyliBOX **(5)** and the first generation (*R*)-PhAraBOX **(1)** have shown greater activity, with both achieving conversions of 99%.

Both methyl propyl ligands showed similar diastereoselectivity with the [Cu(I)-(*S*,*S*)-MePrAraBOX](OTf) achieving a *trans*:*cis* ratio of 40:60, while its diastereomeric counterpart [Cu(I)-(*S*,*R*)-MePrAraBOX](OTf) achieved a similar *trans*:*cis* ratio of 39:61 ratio.

Ligand	Conversion %	*trans*:*cis*	% *ee* (*cis*)	% *ee* (*trans*)
(*S*,*S*)-MePrAraBOX **(27)**	93	40:60	70-(1*S*, 2*R*)	69-(1*S*, 2*S*)
(*S*,*S*)-PhPrAraBOX **(28)**	86	37:63	64-(1*S*, 2*R*)	61-(1*S*, 2*S*)
(*S*,*R*)-MePrAraBOX **(23)**	91	39:61	46-(1*R*, 2*S*)	27-(1*R*, 2*R*)
(*S*,*R*)-PhPrAraBOX **(24)**	85	59:41	20-(1*R*, 2*S*)	8-(1*R*, 2*R*)
MePrXyliBOX **(4)**[3]	80	53:47	24-(1*S*, 2*R*)	24-(1*S*, 2*S*)
PhPrXyliBOX **(5)**[3]	99	59:41	6-(1*S*, 2*R*)	4-(1*S*, 2*S*)
(*R*)-PhAraBOX **(1)**[3]	99	60:40	32-(1*R*, 2*S*)	16-(1*R*, 2*R*)
*t*BuBOX **(30)**[24]	77	77:23	99	99

Table 2.8

formation of the *trans* product [with the PhPrXyliBOX ligand **(5)** giving a *trans*:*cis* ratio of 59:41]. The diastereoselectivity was slightly better with the [Cu(I)-(*S*,*S*)-PhPrAraBOX](OTf), which gave a *trans*:*cis* ratio of 37:63. Interestingly, the only complex to favour the *trans* isomer of the product was the [Cu(I)-(*S*,*R*)-PhPrAraBOX](OTf), showing a reversal in diastereoselectivity, giving a *trans*:*cis* ratio of 59:41.

The highest enantioselectivity seen using 4,4'-bisoxazoline ligands in asymmetric cyclopropanation reactions had been achieved using the (*R*)-PhAraBOX **(1)** ligand, which achieved *ee*'s of 32% (1*R*, 2*S*) and 16% (1*R*, 2*R*) for the *cis* and *trans* products respectively. Work carried out on the XyliBOX ligands **(4)** and **(5)** had shown that both favoured formation of the opposite enantiomers of the product, (1*S*, 2*R*) for the *cis* and (1*S*, 2*S*) for the *trans*. The MePrXyliBOX **(4)** ligand also showed greater selectivity in these reactions, giving *ee*'s of 24% (1*S*, 2*R*) for the *cis* and 24% (1*S*, 2*S*) for the *trans* product, than its phenyl propyl counterpart PhPrXyliBOX **(5)**,

which only produced *ee*'s of 6% (1*S*, 2*R*) for the *cis* and 4% (1*S*, 2*S*) for the *trans* product. With these results in mind, we expected the (*S*)-AraBOX ligands to show enhanced enantioselectivity, due to the additive effect of the chiral sidearms, while the (*R*)-AraBOX ligands would suffer reduced selectivity due to a clash with the effects of the chiral sidearms.

Following completion of the reactions, the highest *ee*'s were achieved with the (*S*,*S*)-MePrAraBOX **(27)**, 70% for the *cis* diastereomer and 69% for the *trans* diastereomer. The (*S*,*S*)-PhPrAraBOX **(28)** also gave good enantioselectivity with 64% for the *cis* cyclopropane and 61% for the *trans* cyclopropane, as expected due to the co-operative effect of the chiral sidearms. The (*S*,*R*)-MePrAraBOX **(23)** gave moderate *ee*'s of 46% and 27% for the *cis* and *trans* products respectively, while the (*S*,*R*)-PhPrAraBOX **(24)** produced the lowest *ee*'s, 20% for the *cis* diastereomer and 8% for the *trans* diastereomer.

In all cases, the methyl propyl ligands complexes outperformed their phenyl propyl derivatives with respect to the enantioselectivities. These results are in agreement with earlier work carry out with the chiral XyliBOX ligands, which also showed superior enantioselectivities for the MePrXyliBOX **(4)** ligand over its PhPrXyliBOX **(5)** counterpart. Three of the novel ligand-metal complexes, [Cu(I)-(*S*,*S*)-PhPrAraBOX](OTf), [Cu(I)-(*S*,*S*)-PhPrAraBOX](OTf) and [Cu(I)-(*S*,*R*)-MePrAraBOX](OTf), also showed superior enantioselectivity to that achieved using the first generation (*R*)-PhAraBOX **(1)**. However, the *ee*'s achieved for all of the novel complexes were modest in comparison to those achieved with Cu(I) complexes of the traditional 2,2' *t*BuBOX **(30)**, which gave an *ee* of 99% for both the *cis* and *trans* diastereomers.

In order to get some insights on the origin of the enantiodifferentiation leading to the enantioselectivities and absolute configurations of the major enantiomers found, a computational study was undertaken in conjunction with our synthetic project by our colleagues Prof. García and Antonio Rodríguez-García in Zaragoza. This study was based on the previously successful results obtained with 2,2'-bisoxazolines.[27-31]

First of all, they calculated the structure of the cationic **(1)**-Cu(I)-carbene intermediate, whose optimized geometry was similar to that of the **(1)**-$CuCl_2$ complex, determined by X-ray diffraction.[3] Once the adequacy of the theoretical level used to reproduce molecular geometries was tested, they started the modelling the cyclopropanation reaction using ethylene as the alkene. Although the resulting

cyclopropane is not chiral, the corresponding transition state (TS) of the approaches of ethylene through the *Re* and *Si* faces of the carbene carbon atom of the chiral bisoxazoline-copper complexes are diastereomeric, and hence different in energy. Previous studies have shown that the main steric interactions responsible for the enantioselection are retained in this simplified model, leading to good estimations of the enantioselectivity of real systems, and, consequently, they adopted the same approach in this study.[27-29] As already mentioned, ethylene can approach to the carbene carbon atom through its *Re* or *Si* faces. Furthermore, there are two conformations of the ester group for each approach. This leads to at least four possible reaction channels. Whereas the *Re* TS displays a chelate structure almost identical to that of the carbene intermediate, the *Si* TS is much more deformed, and the six-membered copper chelate ring changes its conformation from the initial half-chair to a boat-like disposition. **Figure 2.15** highlights these structural differences by superimposing the **(1)**-Cu(I)-carbene intermediate with the minimum energy *Re* and *Si* TS, respectively. However, by inspecting the relative energies of the four possible TS, one realizes that the geometric deformation observed has a rather low energy cost, since three of the four TS have almost the same energy.

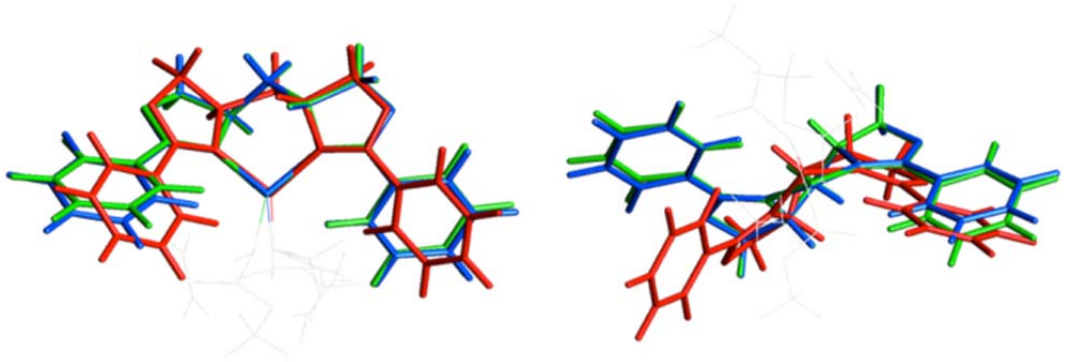


Figure 2.15: Superimposition of the calculated **(1)**-Cu-carbene geometry (green) with those of the *Re* (blue) and *Si* (red) transition structures. Left, zenithal view, right, front view.

The modest enantioselectivity observed seems to have its origin in the slight preference for one of the reaction channels over the other three **(Figure 2.15)**. The calculated enantioselectivity (39% *ee* in the 1*R* enantiomer) is in excellent agreement with the experimental values obtained **[Table 2.8**, ligand **(1)]**.

They next considered the case of XyliBOX ligands, namely that of MePrXyliBOX **(4)**. The situation turns to be much more complex, due to two main reasons. First, due to the different absolute configuration at the oxazoline carbon atoms, the ligand is no longer C_2-symmetric, so the number of possible alkene approaches to the corresponding carbene intermediate doubles, as we must consider the approach of the alkene through the *S* and *R* sides, both when the ester group is up and down, which are now sterically inequivalent. Secondly, we must take into account the possible conformations, not only of the six-membered chelate ring, but also of the 1-methyl propyl substituent. To this end, they carried out an exploratory conformational analysis, and concluded that, as far as the methyl propyl substituent is concerned, there are three main conformational dispositions gathering most of the conformational population, schematized in **Figure 2.16**. This means that, if we consider again ethylene as the alkene, we have at least 2 x 2 x 2 x 3 = 24 possible reaction channels for the reaction (*Re/Si* approaches with the ester up/down by two possible rotamers for the ester by three possible conformations for the methyl propyl substituents).

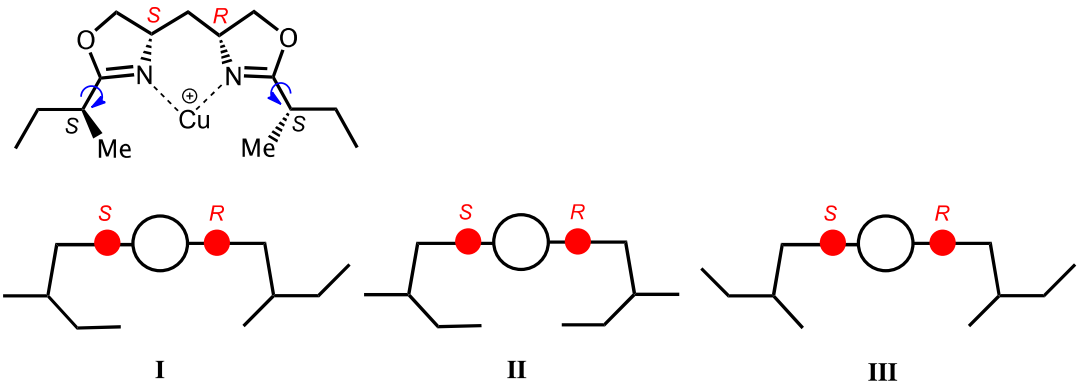


Figure 2.16: Most populated conformations of the methyl propyl substituents in MePrXyliBOX **(4)**

Table 2.9 shows the summary of the calculated energies. As can be seen, the lowest energy TS corresponds to a *Si* approach and, overall, the 1*S*-cyclopropane product is favoured. Furthermore, only the reaction channels through conformation **I** of the methyl propyl substituent contribute significantly to determine the enantioselectivity **(Figure 2.16)**. Again, there is a fairly good agreement between the calculated (29% *ee* in 1*S*-cyclopropane) and the experimental results (24% *ee* in both 1*S*,2*R*—*cis*— and 1*S*,2*S*—*trans*—cyclopropanes). The minimum energy TS, contributing the most to the final enantioselectivity are shown in **Figure 2.17**.

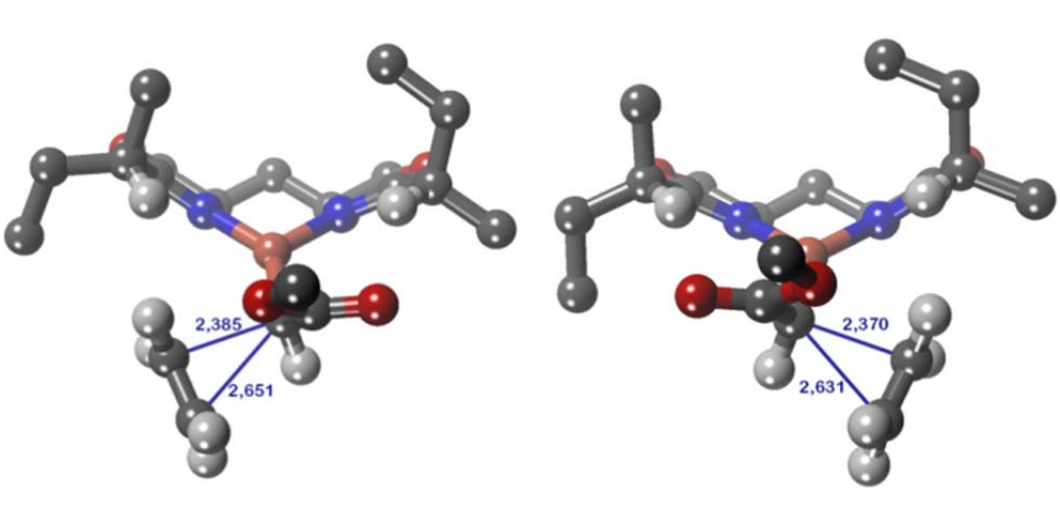


Figure 2.17: Minimum energy TS for the *Re* (left) and *Si* (right) alkene approaches to the **(4)**-Cu-carbene intermediate

Finally, they considered the case of the analogous (*S*,*S*)-MePrAraBOX ligand **(27)**. It must be noted that the only difference with ligand **(4)** lies in the absolute configuration of one of the carbon atoms at the 4 position, but this difference results in a noticeable improvement of enantioselectivity. Ligand **(27)** is again C_2-symmetric, which reduces the number of possible reaction channels to 12.

TS				$\Delta\Delta G^{\ddagger}$[a]
Re/Si	**Ester up/down**	**MePr rotam.**	**Ester rotam.**	
Re	up	I	1	0,7
Re	down	I	1	0,3
Re	up	II	1	5,2
Re	down	II	1	3,0
Re	up	III	1	2,3
Re	down	III	1	5,9
Re	up	I	2	1,3
Re	down	I	2	1,1
Re	up	II	2	3,3
Re	down	II	2	4,0
Re	up	III	2	2,9
Re	down	III	2	5,8
Si	up	I	1	0,4
Si	down	I	1	0,0
Si	up	II	1	2,6
SI	down	II	1	3,5
Si	up	III	1	2,6
Si	down	III	1	2,8
Si	up	I	2	1,5
Si	down	I	2	0,3
Si	up	II	2	2,9
Si	down	II	2	2,9
Si	up	III	2	3,9
Si	down	III	2	3,8

[a] Measured in kcal mol^{-1}

Table 2.9: Calculated enantioselectivity in the reaction of ethylene with methyl diazoacetate, catalysed by the **(4)**-Cu complex.

Table 2.10 gathers the calculated relative energies of the corresponding TS, and the minimum energy TS, contributing the most to the final enantioselectivity are shown in **Figure 2.18**. As in the case of XyliBOX **(4)**, only the reaction channels through

conformation **I** of the methyl propyl substituent contribute significantly to the reaction. However, unlike XyliBOX **(4)**, the AraBOX ligand **(27)** display a clear preference for the *Si* reaction channels, leading to a calculated enantioselectivity of 75% *ee* in 1*S*-cyclopropane, again in excellent agreement with the experimental observations (ca. 70% *ee* in both 1*S*,2*R*—*cis*— and 1*S*,2*S*—*trans*—cyclopropanes). If we compare the minimum energy TS for *Re* and *Si* approaches **(Figure 2.18b)**, we realize that there are only very minor changes in the global geometry of the ligand, associated to the spatial disposition of the carbonyl group. These minor changes in the position of one of the methyl propyl substituents seem to be in the origin of the small energy differences leading to the enantiodiscrimination.

TS			$\Delta\Delta G^{\ddagger}$[a]
Re/Si	**MePr rotam.**	**Ester rotam.**	
Re	I	1	1.2
Re	I	2	1.8
Re	II	1	2.3
Re	II	2	4.3
Re	III	1	4.6
Re	III	2	4.0
Si	I	1	**0.0**
Si	I	2	0.5
Si	II	1	4.6
Si	II	2	5.0
Si	III	1	2.1
Si	III	2	5.7

[a] Measured in kcal mol^{-1}

Table 2.10: Calculated enantioselectivity in the reaction of ethylene with methyl diazoacetate, catalysed by the **(27)**-Cu complex.

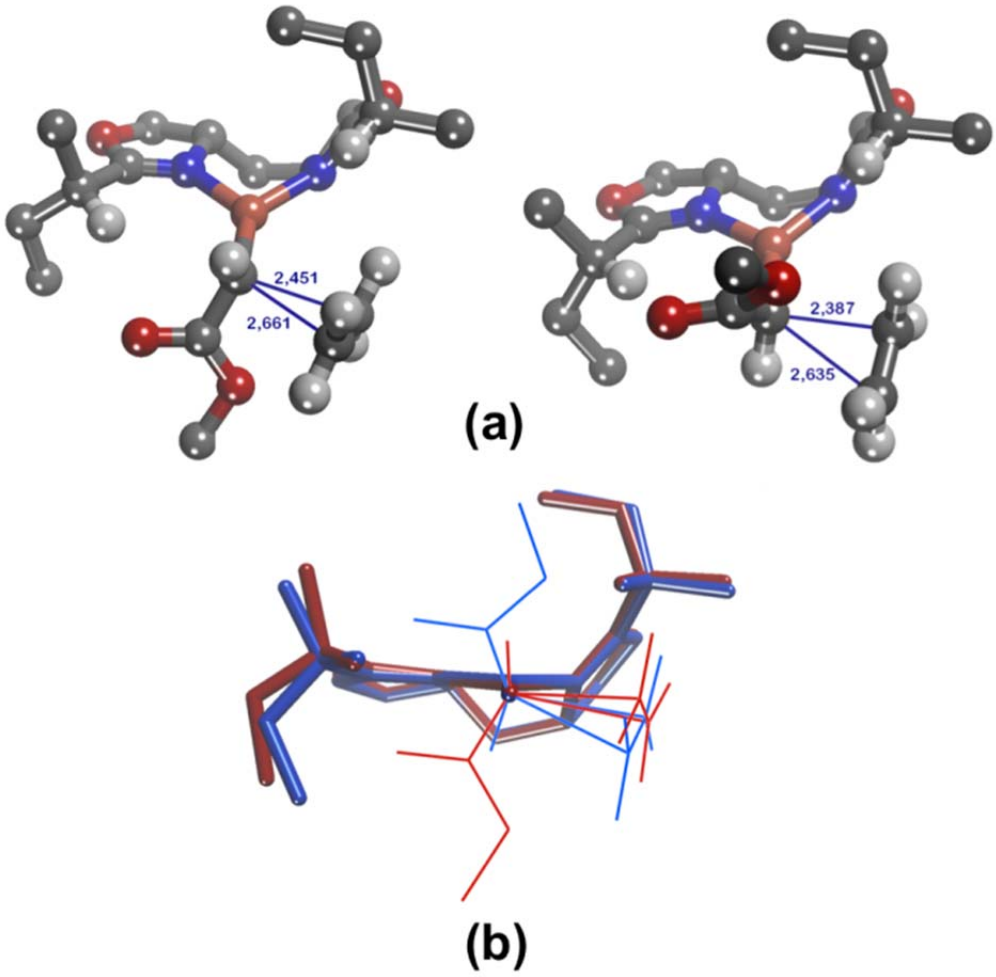


Figure 2.18: (a) Minimum energy TS for the *Re* (left) and *Si* (right) alkene approaches to the **(27)**-Cu-carbene intermediate. **(b)** Superimposition of both TS (red, *Re* TS; blue, *Si* TS).

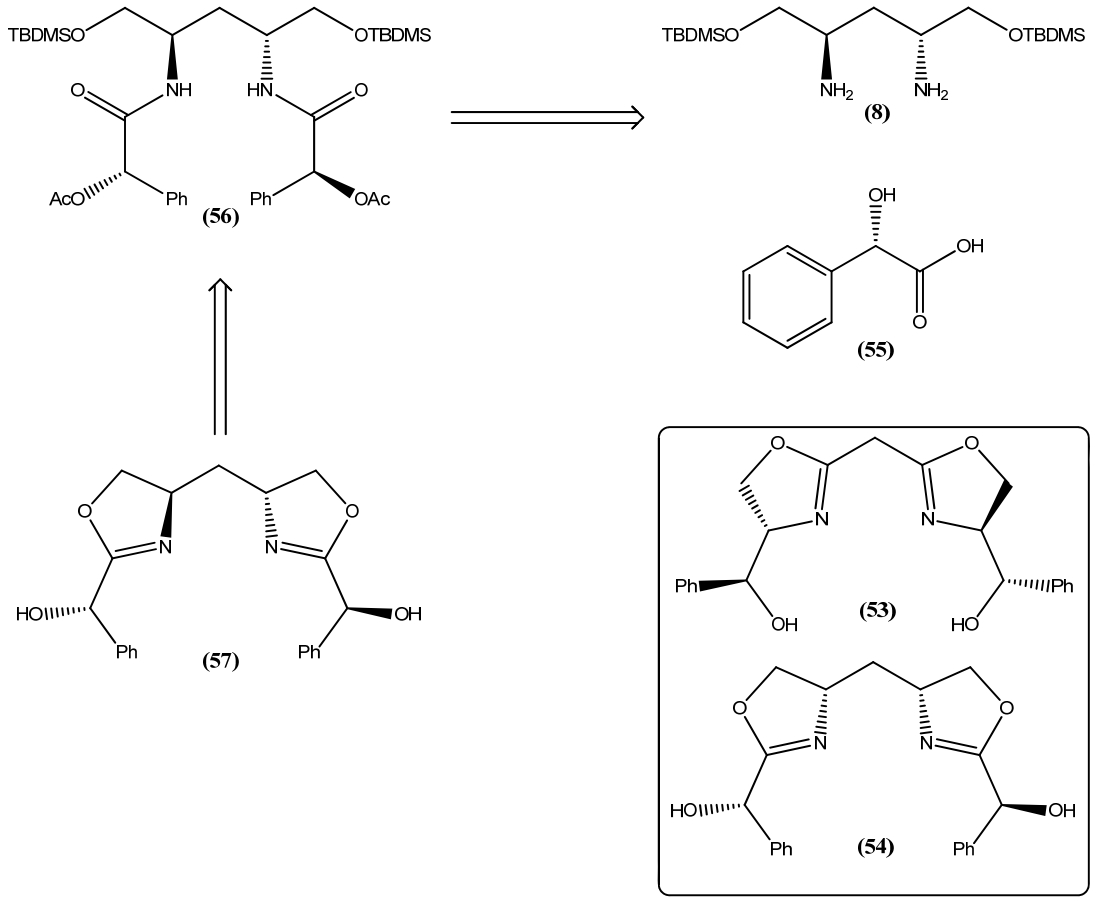
Conclusion

The [Cu(I)-(*S*,*S*)-MePrAraBOX](OTf) complex proved to be the most successful of the complexes tested for the asymmetric cyclopropanation reaction between ethyl diazoacetate and styrene. At room temperature the complex produced a *trans*:*cis* ratio of 40:60 and achieved 70% *ee* for the *cis* diastereomer and 69% *ee* for the *trans* diastereomer. These *ee*'s are the highest yet achieved for any complex derived from 4,4'-BOX ligands in an asymmetric cyclopropanation reaction. Two other novel complexes, [Cu(I)-(*S*,*S*)-PhPrAraBOX](OTf) and Cu(I)-(*S*,*R*)-MePrAraBOX](OTf), also produced enantioselectivities higher than the first generation 4,4'-BOX ligands. Unusually, all but one of the novel ligands also favoured the *cis* isomer. The only

other first generation 4,4'-BOX ligand to favour the *cis* product was the *meso*-XyliBOX **(3)**.

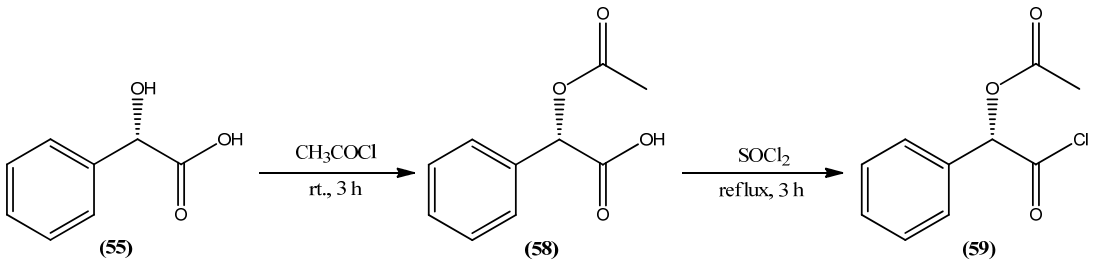
2.3 Synthesis of 4,4'-bisoxazoline ligands with secondary binding sites

The focus of the study now turned to the synthesis of 4,4'-bisoxazoline ligands with secondary binding sites. As discussed in **Section 1.6.2**, Aït-Haddou *et al* synthesised a series of 2,2'-bisoxazoline ligands such as ligand **(53)** containing chiral hydroxyalkyl pendent arms **(Scheme 2.17)**.[32] Subsequently, from within our group, Fiona Kirby was able to synthesise the 4,4'-bisoxazoline ligand **(54)** which contained a XyliBOX backbone with chiral hydroxyalkyl pendent arms **(Scheme 2.17)**.[5] This chiral XyliBOX **(53)** was made by following in the work of Bolm *et al*, who had used mandelic acid **(55)** in the synthesis of their chiral-α-hydroxy-2-oxazoline ligands.[33] As such, we envisaged the synthesis of a similar 4,4'-bisoxazoline ligands using an AraBOX backbone, which would hopefully offer improved selectivity on the ligand synthesised by Kirby. We thought di-TBDMS protected bis-β-amino alcohol **(8)** and mandelic acid **(55)** could be used as the starting material to synthesise the bisamide **(56)**. The bisamide **(56)** could then be carried through giving the desired 4,4'-bisoxazoline **(57) (Scheme 2.17)**.



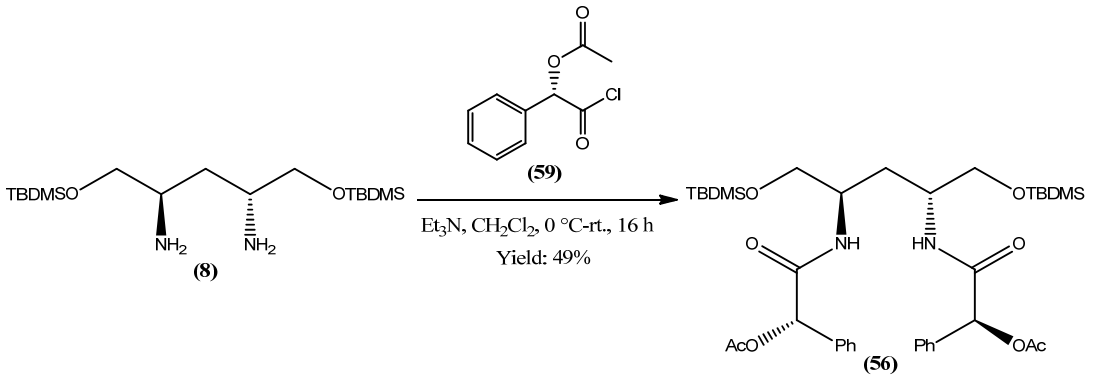
Scheme 2.17

The di-TBDMS protected bis-β-amino alcohol **(8)** was prepared from (2*R*, 4*R*)-arabitol, as described earlier. (*S*)-(+)-Mandelic acid **(55)** was stirred in excess acetyl chloride at room temperature for 2 h. The acetyl chloride was removed and the crude acetyl-protected mandelic acid **(58)** was then heated at reflux in excess thionyl chloride for 3 h. The thionyl chloride was removed and the crude product was purified by Kugelrohr distillation the yield pure (*S*)-*O*-acetylmandelic acid chloride **(59)** in 67% yield **(Scheme 2.18)**. The structure of the product was confirmed by comparison with the published data.[33]



Scheme 2.18

Following this, 2.2 equivalents of the purified (*S*)-*O*-acetylmandelic acid chloride **(59)** and triethylamine were reacted with **(8)**, in CH_2Cl_2 at 0 °C. The reaction was left to stir overnight at room temperature. The crude product was purified by column chromatography on silica gel. The product **(56)** separated with a gradient elution of petroleum ether:ethyl acetate 9:1 to 1:1. The amide **(56)** was isolated in 49% yield **(Scheme 2.19)**.

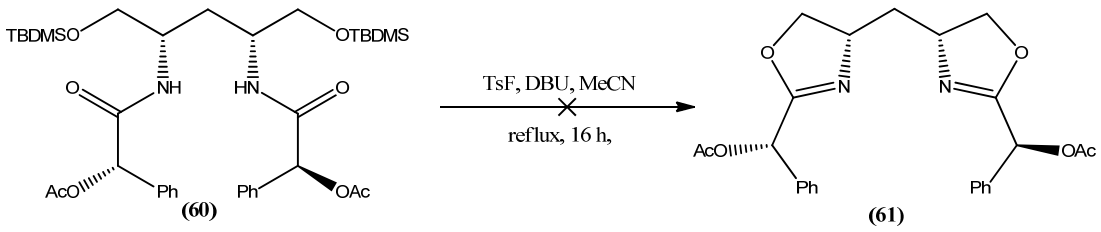


Scheme 2.19

The structure of the chiral di-TBDMS protected bisamide **(56)** was confirmed by ^{1}H and ^{13}C NMR. The characteristic signals of the backbone of the molecule were

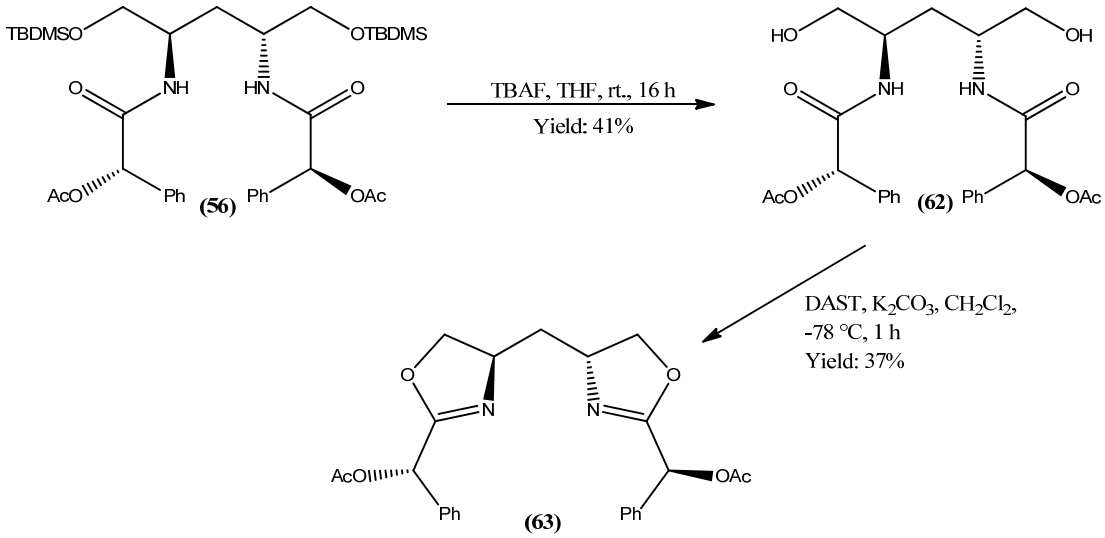
present in the ^{1}H NMR. The CHN hydrogens appear as a multiplet overlapping with the four hydrogens of the two CH_2O at 3.72-3.64. The CH_2 of the $CHCH_2CH$ appears as a triplet at 1.84 (J = 6.3 Hz). The two NHs of the amide appear as a multiplet at 6.99-6.84. The product exists as a mixture of amide rotamers. The CH_3CO hydrogens appear as a series of singles (three) in a ratio of 2:1:1. The The $C(CH_3)_3$ and the $Si(CH_3)_2$ of the TBDMS protecting groups also appear as a series of singlets due to the mixture of amide rotamers. The $C(CH_3)_3$ appear as three singlets in a 2:1:1 ratio and the $Si(CH_3)_2$ appear as six singlets in a 1:2:2:2:1:1 ratio. The ^{13}C NMR spectrum shows the presence of quaternary carbons at 169.3, 169.2, 168.6 and 168.5. The signals at ~169 represent the C=O of the acetate and the signals at ~168 represent the C=O of the amide carbonyl. The IR spectrum shows a signal at 1744 cm^{-1} representing the carbonyl of the acetate and a signal at 1670 cm^{-1} representing the carbonyl of the amide group.

Previous work carried out by Fiona Kirby, on the synthesis of chiral XyliBOX **(54)** had shown that the di-TBDMS protected bisamide **(60)** would not cyclise to the desired bisoxazoline **(61)** under the same DARC conditions that had previously worked when synthesising the butyric acid derived bisoxazoline ligands described in **Section 2.2 (Scheme 2.20)**.[5]



Scheme 2.20

It was found that the desired 4,4'-bisoxazoline ligands could be accessed *via* the bishydroxyamide **(62)**, following the same protocol used by Bolm *et al*.[33] This involved first deprotecting the TBDMS groups, followed by cyclisation of the bishydroxyamide **(62)** using diethylaminosulfur trifluoride (DAST).



Scheme 2.21

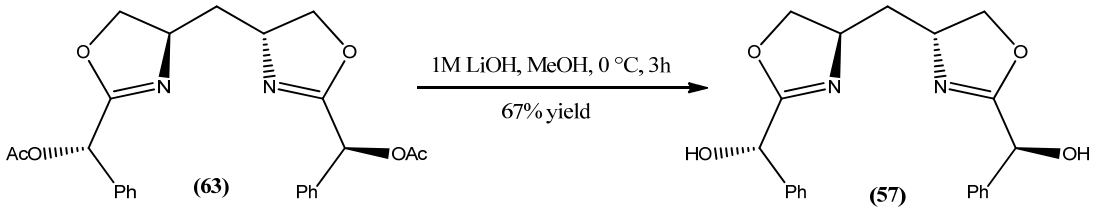
The di-TBDMS protected bisamide **(56)** was first deprotected by treatment with TBAF in THF. The reaction was stirred at room temperature for 16 h. The crude product was purified by column chromatography on silica gel. The product **(62)** separated with a gradient elution of petroleum ether:ethyl acetate 9:1 to 1:4. The bishydroxyamide **(62)** was isolated in 41% yield **(Scheme 2.21)**.

The structure of the chiral bishydroxyamide **(62)** was confirmed by ^{1}H and ^{13}C NMR. The characteristic signals of the backbone of the molecule were present in the ^{1}H NMR. The CHN hydrogens appear as a multiplet at 4.45-4.36. Two of the hydrogens of the two CH_2Os appear as a double doublet at 4.04 (J = 11.2 and 4.3 Hz). The other two hydrogens of the two CH_2Os appear as a double doublet at 4.04 (J = 11.3 and 7.2 Hz). The CH_2 of the $CHCH_2CH$ appears as a double doublet at 1.79 (J = 9.0 and 7.3 Hz). The lack of the TBDMS protecting group and its signals in the ^{1}H and ^{13}C NMR spectra were key in identifying the product. The ^{13}C NMR spectrum shows the presence of quaternary carbons at 174.4, representing the C=O of the acetate, and at 170.9, representing the C=O of the amide carbonyl. The IR spectrum shows a signal at 1714 cm^{-1} representing the carbonyl of the acetate and a signal at 1647 cm^{-1} representing the carbonyl of the amide group.

The bishydroxyamide **(62)** was next treated with 2.2 equivalents of DAST. The reaction was stirred at -78 °C for 1 h, then treated with K_2CO_3 and allowed to warm to room temperature. The crude product was purified by column chromatography on

silica gel. The product **(63)** separated with a gradient elution of petroleum ether:ethyl acetate 9:1 to 1:1, in 37% yield.

The structure of bisoxazoline **(63)** was confirmed by ^{1}H and ^{13}C NMR. The characteristic signals of the backbone of the molecule were present in the ^{1}H NMR. The CHN hydrogens appear as a multiplet overlapping with the four hydrogens of the two CH_2O at 4.27-4.07. The CH_2 of the $CHCH_2CH$ appears as a multiplet at 1.90-1.79. The product exists as a mixture of rotamers. The CHOAc hydrogens appear as a series of singles (eight) in a ratio of 1:1:2:1:1:1:2:1 at 5.85-5.61. The CH_3CO hydrogens appear as a series of singles (four) in a ratio of 1:2:1:1 at 2.07-1.96. The ^{13}C NMR spectrum shows the presence of quaternary carbons at 171.0, 169.2, 169.1, 168.9 and 168.8. The signal at 171.0 represents the C=O of the acetate and the signals at ~169 represent the C=N of the bisoxazoline rings. The IR spectrum shows a signal at 1732 cm^{-1} representing the carbonyl of the acetate and a signal at 1656 cm^{-1} the C=N of the bisoxazoline rings.



Scheme 2.22

The bisoxazoline **(63)** was the treated with 1.0M LiOH in methanol at 0 °C, to hydrolyse the acetates. After stirring for 3 h, the reaction was allowed to warm to room temperature and extracted with CH_2Cl_2. The solvent was removed to yield the hydroxy-bisoxazoline **(57)** in 67% yield **(Scheme 2.22)**.

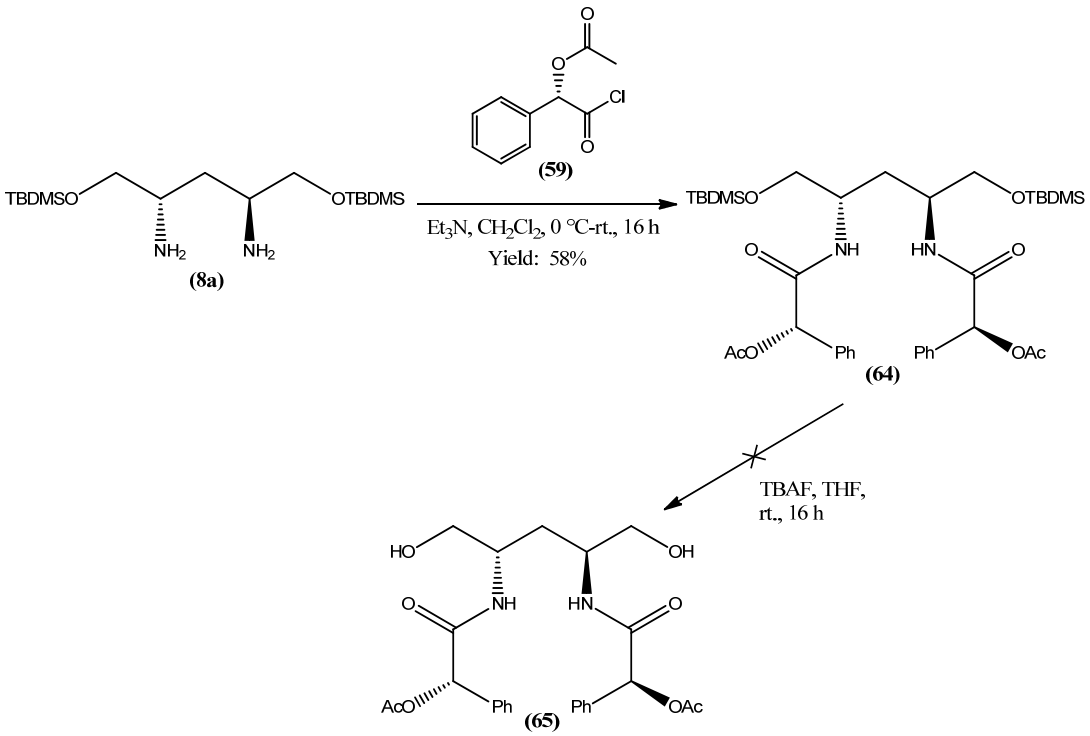
The structure of bisoxazoline **(57)** was confirmed by ^{1}H and ^{13}C NMR. The characteristic signals of the backbone of the molecule were present in the ^{1}H NMR. The two OH hydrogens appear as a broad singlet at 4.36-3.96. The CHN hydrogens appear as a multiplet overlapping with the four hydrogens of the two CH_2O at 3.81-3.58. The CH_2 of the $CHCH_2CH$ appears as a multiplet at 1.83-1.78. The lack of the acetate protecting group and its signals in the ^{1}H and ^{13}C NMR spectra, as well as in the IR spectrum, were key in identifying the product. The product also exists as a mixture of rotamers. The C*H*OH hydrogens appear as a series of eight singlets in a ratio of 1:1:2:1:1:1:2:1 at 5.79-5.61.

The ^{13}C NMR spectrum shows the presence of quaternary carbons at 169.8 and 169.6 representing the C=N of the bisoxazoline rings. The IR spectrum shows a signal at 1658 cm^{-1} the C=N of the bisoxazoline rings.

The bisoxazolines **(63)** and **(57)** were given the abbreviations (*S*,*R*)-BnOAcAraBOX and (*S*,*R*)-BnOHAraBOX respectively.

2.2 equivalents of (S)-*O*-acetylmandelic acid chloride and triethylamine were reacted with **(8a)**, in CH_2Cl_2 at 0 °C, with the reaction then left to stir overnight at room temperature. The crude product was purified by column chromatography on silica gel. The product **(64)** separated with a gradient elution of petroleum ether:ethyl acetate 9:1 to 4:1. The amide **(64)** was isolated in 58% yield **(Scheme 2.23)**.

The structure of the chiral amide **(64)** was confirmed by ^{1}H and ^{13}C NMR. The characteristic signals of the backbone of the molecule were present in the ^{1}H NMR. The CHN hydrogens appear as a multiplet at 4.00-3.91. Two of the hydrogens of the two CH_2O appear as a multiplet at 3.74-3.63. The other two hydrogens of the two CH_2Os appear as a doublet at 3.46 (J = 9.9, 7.2 Hz). The CH_2 of the $CHCH_2CH$ appears as a triplet at 1.93 (J = 5.9 Hz). The product exists as a mixture of amide rotamers, with the two NHs of the amide appearing as three doublets in a 3:1:1 ratio at 7.06-6.86 (J = 8.5 Hz). The CHOAc hydrogens also appear as a series of singlets (three) in a ratio of 1:1:3 at 6.01-5.88, while the CH_3CO hydrogens appear as three singlets in a ratio of 3:1:1 at 2.23-2.12.The The $C(CH_3)_3$ and the $Si(CH_3)_2$ of the TBDMS protecting groups also appear as a series of singlets due to the mixture of amide rotamers. The $C(CH_3)_3$ appear as three singlets in a 1:1:3 ratio at 0.89-0.81 and the $Si(CH_3)_2$ appear as six singlets in a 1:1:1:1:3:3 ratio at 0.06- -0.08. The ^{13}C NMR spectrum shows the presence of quaternary carbons at 171.5, 171.3, 168.6 and 168.1. The signals at ~171 represent the C=O of the acetate and the signals at ~168 represent the C=O of the amide carbonyl. The IR spectrum shows a signal at 1741 cm^{-1} representing the carbonyl of the acetate and a signal at 1671 cm^{-1} representing the carbonyl of the amide group.

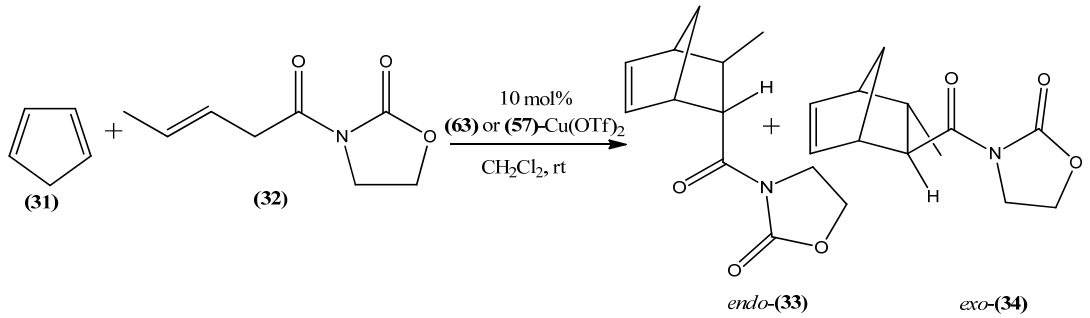


Scheme 2.23

The next step involved deprotecting the TBDMS amide **(64)** to give the bis(hydroxyamide) **(65)**. The amide was stirred in THF and treated with TBAF. The reaction was stirred at room temperature for 16 h. However, the ^{1}H and ^{13}C NMR spectral analysis showed an unidentifiable mixture of compounds.

2.3.1 Diels Alder reaction

The Diels Alder reaction was the first test used to evaluate the 4,4' bisoxazoline ligands **(63)** and **(57)**. The Diels Alder reaction investigated was the reaction of cyclopentadiene **(31)** and *trans*-(crotonoyl)-2-oxazolidinone **(32)** **(Scheme 2.24)**. The reaction was catalysed by a 10 mol% homogeneous complex derived from (*S*,*R*)-BnOAcAraBOX **(63)** or (*S*,*R*)-BnOHAraBOX **(57)** and copper(II)triflate.



Scheme 2.24

Table 2.11 shows the results of the reactions carried out in CH_2Cl_2, at room temperature **(Scheme 2.24)**.

Ligand	Time (h), Temp	Metal Salt	Conversion %	*endo*:*exo* ratio	%*ee* *R*/*S*
(*S*,*R*)-BnOAcAraBOX **(63)**	20, rt	$Cu(OTf)_2$	44	82:18	15 *S*
(*S*,*R*)-BnOHAraBOX **(57)**	20, rt	$Cu(OTf)_2$	15	80:20	5 *S*
BnOAcXyliBOX **(61)**[5]	16, rt	$Cu(OTf)_2$	86	84:16	-
BnOHXyliBOX **(66)**[5]	16, rt	$Cu(OTf)_2$	0	-	-

Table 2.11

The [Cu(II)-(*S*,*R*)-BnOAcAraBOX]$(OTf)_2$ complex gave a modest conversion of 44% and an excellent *endo*:*exo* ratio of 82:18 which compares favourably with that achieved by BnOAcXyliBOX **(61)**, which achieved the highest *endo*:*exo* ratio of any 4,4' bisoxazoline ligand so far. However, the [Cu(II)-(*S*,*R*)-BnOAcAraBOX]$(OTf)_2$ complex showed a disappointing 15% (*S*)*ee* for the *endo*-**(33)** product.

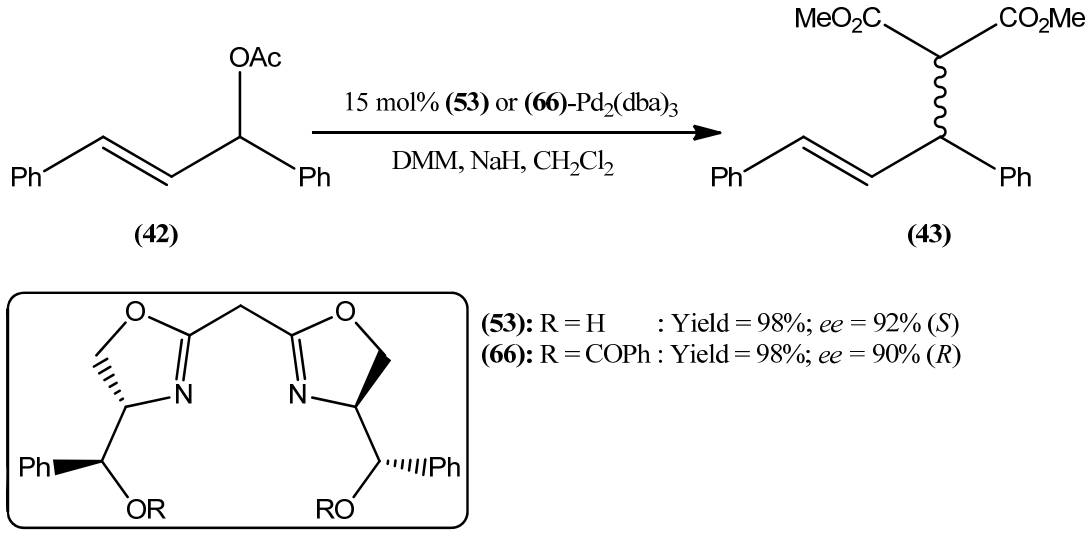
The [Cu(II)-(*S*,*R*)-BnOHAraBOX]$(OTf)_2$ complex gave a poor conversion of 15%. However, it gave excellent *endo*:*exo* ratio of 80:20 similar to that achieved by its acetate derivative. The [Cu(II)-(*S*,*R*)-BnOHAraBOX]$(OTf)_2$ complex showed a 5% (*S*)*ee* for the *endo*-**(33)** product. For both the AraBOX and the XyliBOX derived ligands, the acetoxy-ligand showed superior activity and selectivity to its hydroxyl counterpart in the Diels Alder reaction.

Conclusion

Both the (*S*,*R*)-BnOAcAraBOX **(63)** and (*S*,*R*)-BnOHAraBOX **(57)** gave poor results for the test reactions performed, showing modest catalytic activity, with low conversions and good diastereoselectivity. However, both complexes produced poor *ee*'s. Unfortunately, further studies could not be carried out on these reactions with these ligands due to a limited amount of material.

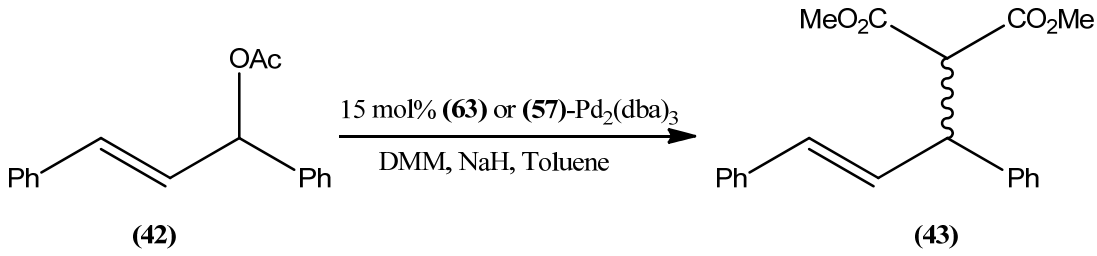
2.3.2 Allylic Alkylation reaction

The palladium catalysed allylic alkylation was the next reaction to be used to test bisoxazolines **(63)** and **(57)**. As mentioned earlier, Aït-Haddou *et al* have developed novel 2,2'-BOX ligands possessing secondary binding sites. They applied these ligands to the palladium catalysed allylic alkylation of (±)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene **(42)** with dimethyl malonate. They used the Pd-**(53)** complex and sodium hydride as base to generate the nucleophile, giving the product in 98% yield and 92% *ee*(*S*). Use of the Pd-**(66)** complex resulted in a 98% yield and 90% *ee*(*R*) **(Scheme 2.25)**.[32]



Scheme 2.25

The reaction shown in **Scheme 2.26** was catalysed by a 15 mol% homogenous complex derived from (*S*,*R*)-BnOAcAraBOX **(63)** or (*S*,*R*)-BnOHAraBOX **(57)** and tris(dibenzylideneacetone)dipalladium. The reaction was carried out as described in **Section 2.2.2.2.**



Scheme 2.26

The results of the reactions from **Scheme 2.26**, carried out in toluene at 80 °C for 60 h, are shown in **Table 2.12**.

Ligand	Metal Salt	Conversion %	%*ee R/S*
(*S*,*R*)-BnOAcAraBOX **(63)**	$Pd_2(dba)_3$	0	-
(*S*,*R*)-BnOHAraBOX **(57)**	$Pd_2(dba)_3$	0	-
PhXyliBOX **(3)**[5]	$Pd_2(dba)_3$	53	-
BnOAcXyliBOX **(61)**[5]	$Pd_2(dba)_3$	0	-
BnOHXyliBOX **(66)**[5]	$Pd_2(dba)_3$	0	-

Table 2.12

Neither (*S*,*R*)-BnOAcAraBOX **(63)** nor (*S*,*R*)-BnOHAraBOX **(57)** showed any catalytic activity for this reaction. These results parallel those seen with the XyliBOX derivatives which also showed no activity. So far, the PhXyliBOX **(3)** has been the only ligand of its class to produce a conversion in this reaction.

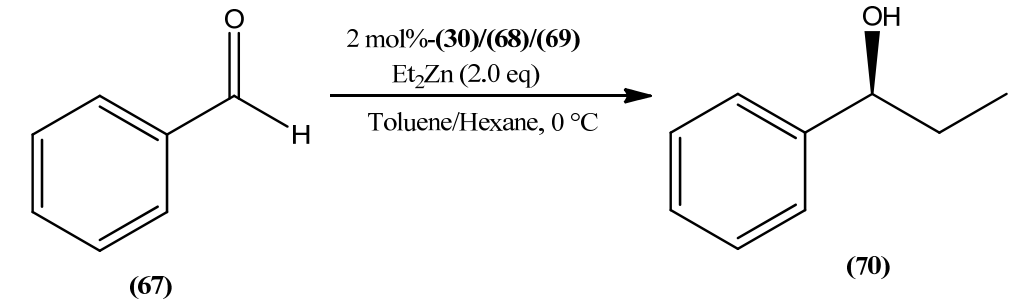
Conclusion

Both the (*S*,*R*)-BnOAcAraBOX **(63)** and (*S*,*R*)-BnOHAraBOX **(57)** gave poor results for the test reactions performed, showing zero catalytic activity. Further studies could not be carried out on these reactions with these ligands due to a limited amount of material.

2.3.3 Alkylation of benzaldehyde

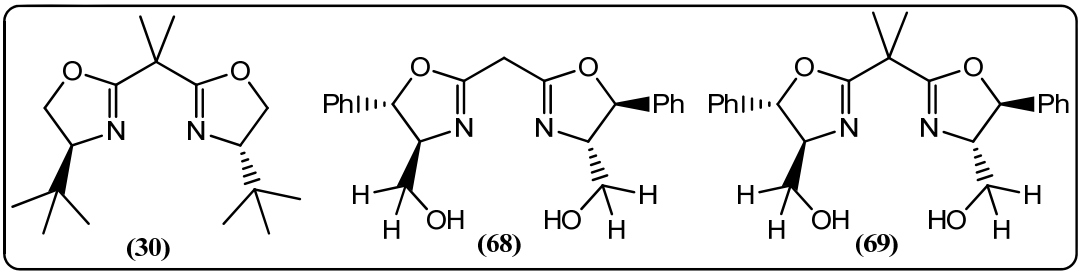
The asymmetric 1,2 addition of organozinc reagents to carbonyl groups is a facile method for synthesising optically active secondary alcohols. There are very few examples of the reaction being catalysed by bisoxazoline complexes, with amino alcohols and amido alcohols being the preferred ligand choice. However, Reiser *et al* have reported using *t*BuBOX **(30)** to catalyse the 1,2 addition of diethylzinc to benzaldehyde **(67)**, producing a 60% yield and a modest 20% *ee*.[34] Bisoxazoline ligands bearing secondary binding sites (hydroxymethylene sidechains) were also applied to the reaction. While bisoxazoline **(68)** failed to catalyse the reaction, the gem-dimethyl substituted ligand **(69)** was able to catalyse the reaction giving a 96%

yield and a 93% *ee* **(Scheme 2.27)**. Due to its anionic nature, ligand **(68)** was unable to promote the reaction. As such, we hoped that our ligand **(57)**, which would not undergo deprotonation as easily due to the redesign of the bisoxazoline structure, would be able to catalyse the 1,2 addition successfully and decided to apply it to same reaction **(Scheme 2.27)**.



(67) **(70)**

(30): Yield = 60%; *ee* = 20% (*S*)
(68): Yield = 0%
(69): Yield = 96%; *ee* = 93% (*S*)



(30) **(68)** **(69)**

Scheme 2.27

2.2.3.1 Alkylation of benzaldehyde: methodology

The reduction of benzaldehyde **(67)** was catalysed by 2 mol% of **(57)** in toluene. Benzaldehyde **(67)** was added to the catalyst mixture and stirred at room temperature for 20 min. After cooling to -78 °C, 2.0 equivalents of Et_2Zn was added and the mixture was allowed to stir at 0 °C for 40 h. This led to the formation of 1-phenylpropanol **(70)**. A ^1H NMR spectrum was recorded of the crude product to determine the % conversion. The % conversion was calculated by comparing the amount of unreacted benzaldehyde **(67)** [signal at 9.94 (1H)] to the amount of product **(70)** [signal at 4.60 (1H)] in the ^1H NMR. The crude product was purified by column chromatography on silica gel. The product eluted with petroleum ether:ethyl acetate 4:1.

The enantiomeric purity was determined using chiral HPLC (CHIRACEL OD, 254 nm, hexane:*iso*-propyl alcohol, 98:2, 0.5 mL/min). The (*R*) product was eluted at ~28.0 min and the (*S*) product was eluted at ~33.0 min.

The (*S*,*R*)-BnOHAraBOX **(57)** was the only ligand used to investigate this reaction, producing a poor conversion of 20%. The (*S*,*R*)-BnOHAraBOX **(57)** produced a poor *ee* of 1% (*R*).

Conclusion

The (*S*,*R*)-BnOHAraBOX **(57)** gave poor results for the test reaction performed, showing poor activity and giving almost no selectivity. Further studies could not be carried out on this reaction with the ligand due to a limited amount of material.

2.4 Attempted synthesis of 4,4'-PYBOX ligands

The second project carried out during the course of this thesis involved research into the synthesis of 4,4'-PYBOX ligands **(71)**, analogous to the 4,4'-BOX ligands [e.g. **(1)**] synthesised by Frain *et al* **(Figure 2.19)**.[1]

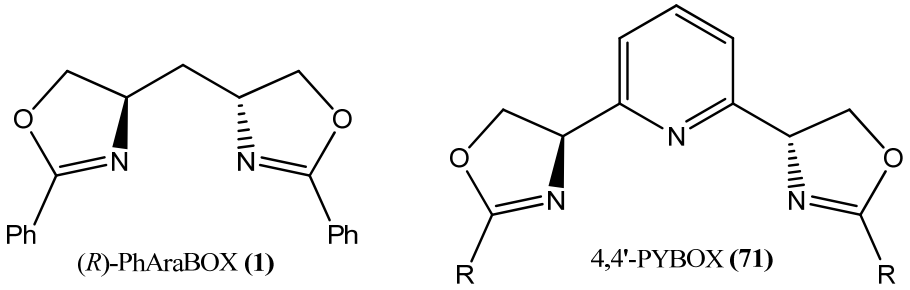
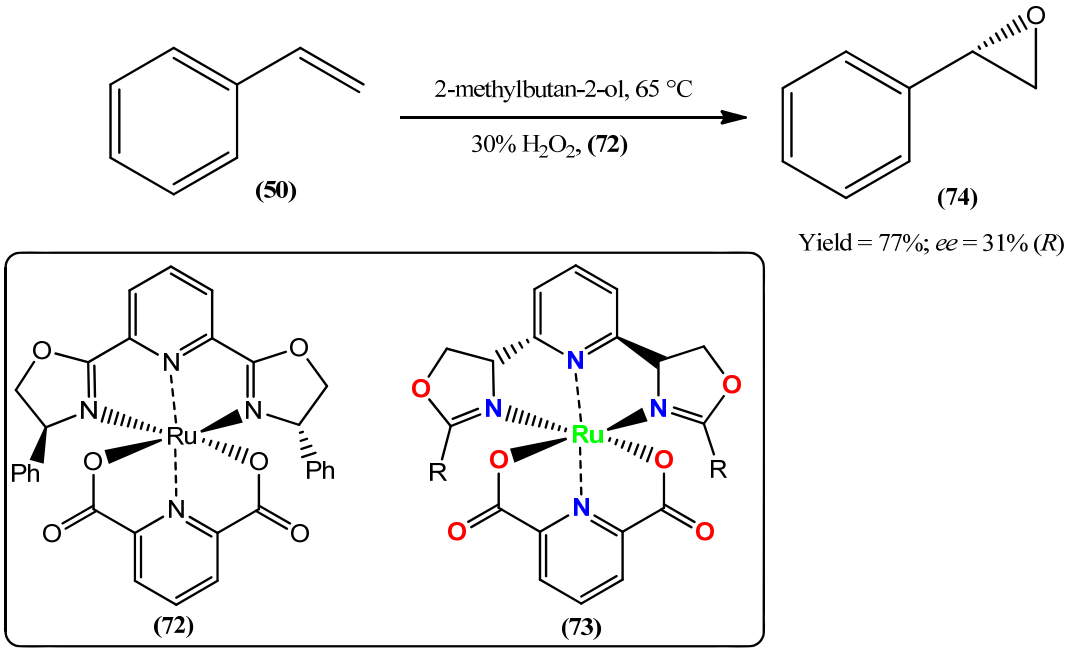


Figure 2.19

Beller had previously reported ruthenium bisoxazoline catalysts which were active in epoxidation reactions, using hydrogen peroxide as the oxidant and which generated some degree of enantiocontrol.[35] Catalyst **(72)** catalysed the epoxidation of styrene and achieved a 70% yield of the styrene oxide in 31% *ee*, while a related catalyst achieved 59% *ee* **(Scheme 2.28)**. Having studied a range of related catalysts, Beller correlated the enantioselectivity achieved with the closeness of the chiral centres to the metal. A similar correlation has also been made with the structure and enantioselectivity of manganese salen catalysts in epoxidation and cyclopropanation reactions.[36] Our project sought to develop ruthenium epoxidation catalysts **(73)** modelled on those of Beller, but with the added advantage of the chiral centres in the molecule being moved closer to the ruthenium, dramatically altering the geometry around the metal in the new ligand **(Scheme 2.28)**.



Scheme 2.28

An initial molecular modelling study of the two catalysts showed that moving the attachment point of the oxazolines to the 4 position resulted in the introduction of a twist in the 4,4'-PYBOX metal complex **(73)** **(Figure 2.20)**. This would hopefully prove to be effective in the shielding of some of the approaches to the metal centre, resulting in enantioselection during reaction. The limited enantioselection of Beller's complex is not surprising given the large quadrants around the metal which are not affected by the phenyl groups on the chiral centres. The twist present in **(73)** while a less obvious effect than the facial blocking in **(72)** is very significant. This twist is very similar to the structure around the metal in the manganese salen epoxidation complexes.[36] The manganese salen complexes routinely give enantioselections of >90% across a range of substrates, though they typically use less benign oxidant systems than Beller's catalyst. Our hope was to combine the environmentally benign oxidant H_2O_2 and the enantio-discrimination of the salen catalysts to produce a versatile selective catalyst system.

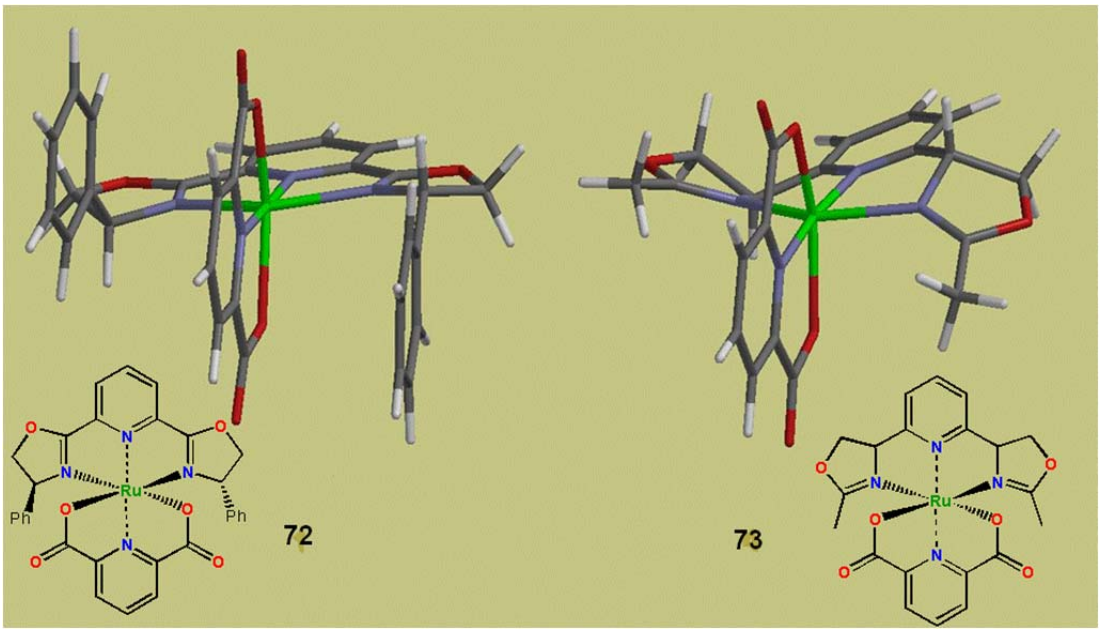
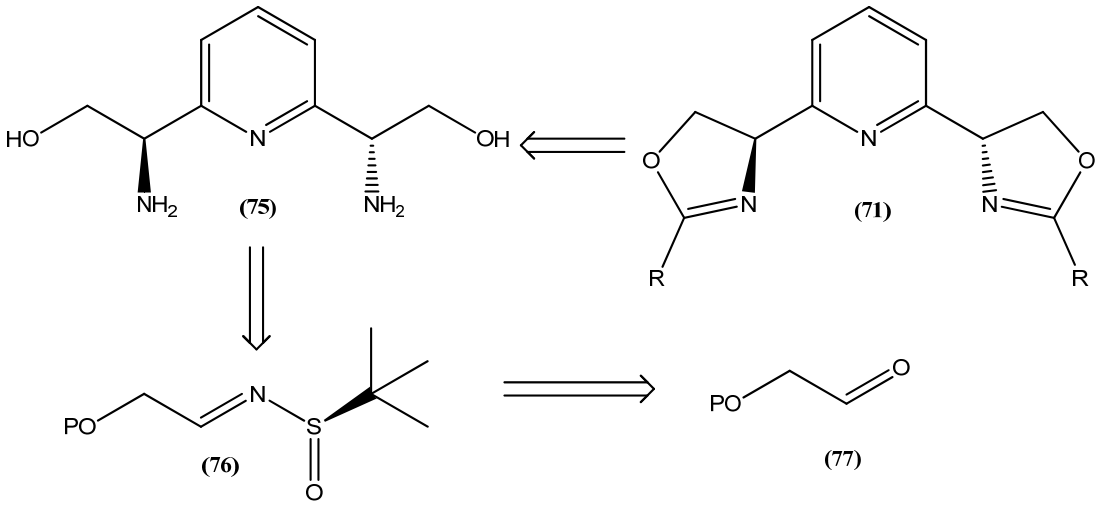


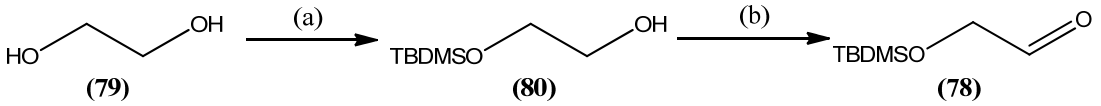
Figure 2.20

To date the synthesis of 4,4'-BOX ligands has centred on the use of either Arabitol or Xylitol as the starting material, providing a suitable backbone of the desired ligands. Unfortunately, no such starting material exists, as far as we are aware, to synthesise potential 4,4'-PYBOX ligands **(71)**. Therefore, we began the project by researching alternative routes to synthesise the regioisomeric 4,4'-PYBOX ligands **(71)**. Retrosynthetic analysis of the target 4,4'-PYBOX ligands **(71)**, led us to conclude that the pyridyl bis-β-amino alcohol **(75)** could be a key intermediate in the potential synthesis **(Scheme 2.28)**. This bis-β-amino alcohol **(75)** could be accessed by Grignard or organometallic addition to chiral *N-tert*-butylsulfinimines **(76)**, an area of research which has been studied and developed by Ellman. The chiral *N-tert*-butylsulfinimines **(76)** in turn could themselves be prepared from protected aldehydes **(77)** by simple condensation reactions, using a dehydrating agent.



Scheme 2.29

The first step in our synthesis involved the preparation of the required protected aldehydes **(77)**. The first aldehyde to be used was the TBDMS protected aldehyde **(78)**. This could be easily synthesised from ethylene glycol **(79)** by protecting one of the two hydroxyl groups and then oxidising the remaining alcohol using a Swern oxidation **(Scheme 2.30)**.



Scheme 2.30

Reagents and conditions: (a) NaH, TBDMSCl, THF, rt., 2 h, 90% **(b)** DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C-0 °C, 50 min, 73%

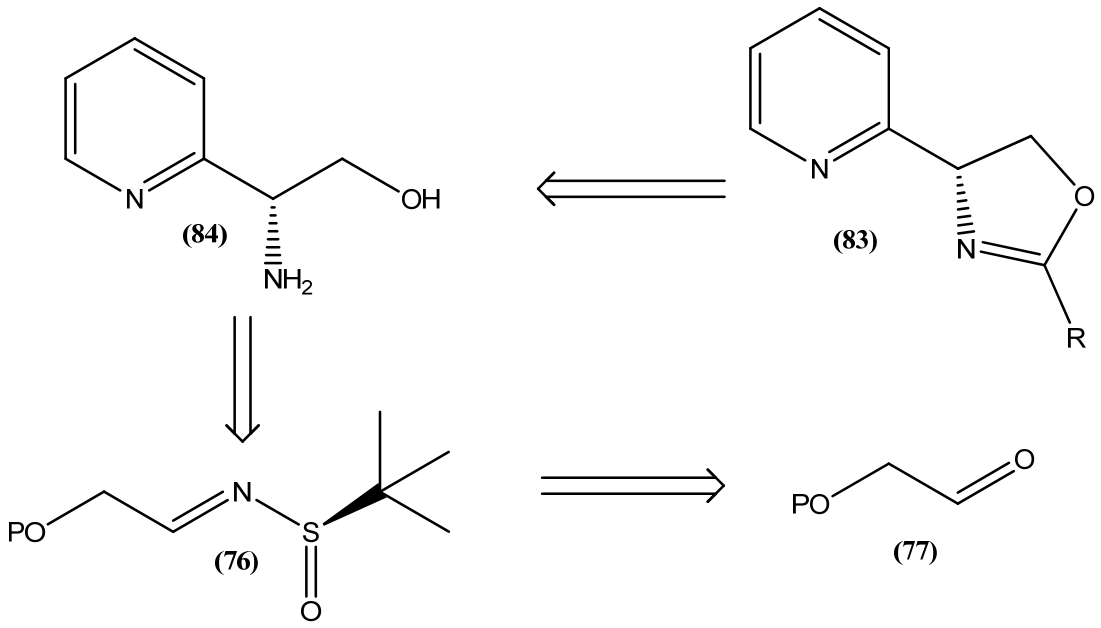
Starting with a mixture of sodium hydride in THF, an excess of ethylene glycol **(79)** was added. This stirring solution was then treated with *tert*-butyldimethylsilyl chloride and stirred for 1 h. Following workup, the organics were concentrated *in vacuo* providing the protected product **(80)** in 90% yield. The reaction was carried out on a ~1.0 g scale, providing ~3.0 g of the mono-protected product **(80)**. The structure of the product was confirmed by comparison with the published data.[37]

The mono-protected diol **(80)** was the subjected to a Swern oxidation. The primary alcohol was oxidised using DMSO, oxalyl chloride and triethylamine in CH_2Cl_2 at -78 °C. The reaction mixture was left to stir for ~30 min and then allowed to warm to 10 °C and stirred for a further 20 mins. Following workup, the crude product was purified by column chromatography on silica gel. The product separated with a

gradient elution of petroleum ether:dichloromethane 3:2. The oxidised product **(78)** was obtained in 73% yield. The structure of the product was confirmed by comparison with the published data.[38]

With the protected aldehyde **(78)** in hand, the next step involved preparation of the *N*-*tert*-butylsulfinimine **(81)**. Aldehyde **(78)** was treated with 1.0 equivalent of (R_S)-2-methyl-2-propanesulfinamide **(82)** and 2.0 equivalents of anhydrous $CuSO_4$ in CH_2Cl_2. The solution was left to stir at room temperature for 2 h and then filtered through celite. The crude product was purified by column chromatography on silica gel. The product **(81)** separated with a gradient elution of petroleum ether:ethyl acetate 95:5 to 1:1. The *N*-*tert*-butylsulfinimine **(81)** was obtained in 68% yield. Generally, ~150 mg of product **(81)** was isolated from ~150 mg of aldehyde **(78)**. The structure of the product was confirmed by comparison with the published data.[39]

The next step involved the addition of the *N*-*tert*-butylsulfinimine **(81)** to the pyridyl bridgehead to form the precursor to the bis-β-amino alcohol **(75)**. Before attempting the difficult bis addition we felt that it would be prudent to first carry out a simpler test reaction. Therefore we decided that mono addition of *N*-*tert*-butylsulfinimine **(81)** to a suitable pyridine analogue would suffice. In addition, these test reactions would provide us with novel pyridyl mono-oxazoline ligands **(83)**, which could also be tested as catalysts in asymmetric reactions. The retrosynthetic analysis was the same as that previously described, with the exception of only a single oxazoline group being attached to the pyridyl ring. As before, we saw the pyridyl β-amino alcohol **(84)** as a key intermediate in the synthesis of **(83)** **(Scheme 2.31)**. The β-amino alcohol **(84)** would itself by derived from the chiral *N*-*tert*-butylsulfinimines **(76)** and the chiral *N*-*tert*-butylsulfinimines **(76)** in turn accessed *via* protected aldehydes **(77)**.

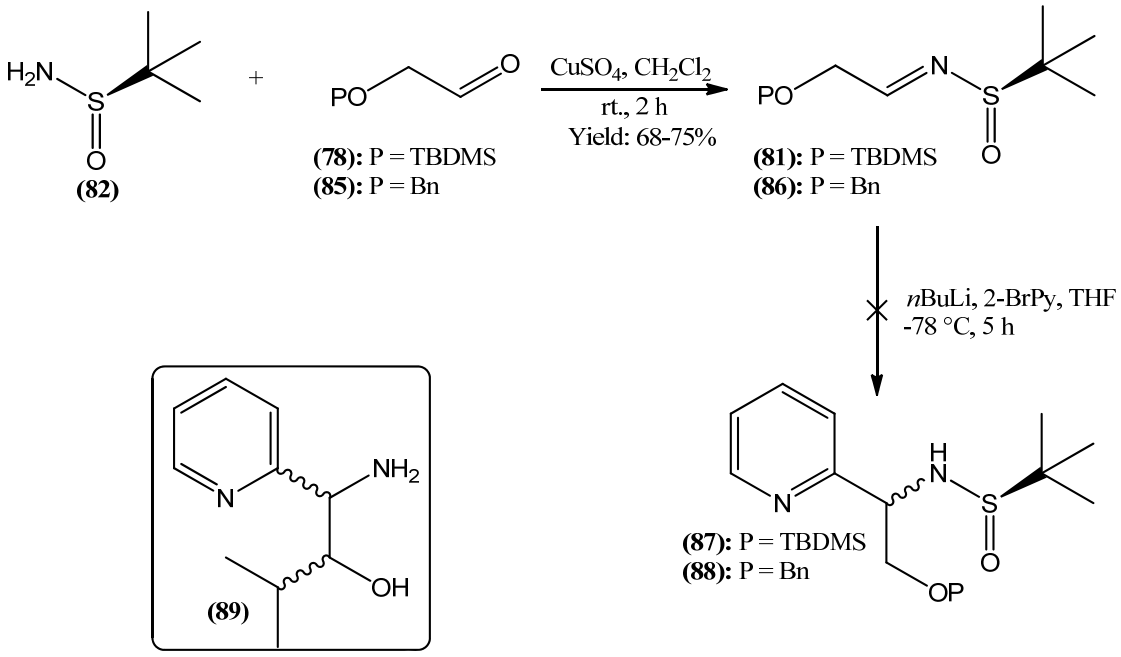


Scheme 2.31

We decided to generate the organolithium derivative, in place of the potential Grignard reagent, and use it as the attacking nucleophile. Treatment of 2-bromopyridine with an excess of *n*-butyllithium in THF at -78 °C for 1 h generated the lithiated nucleophile. To this solution was added *N-tert*-butylsulfinimine **(81)**, with the reaction then left to stir for 5 h. Following workup of the reaction, the ^{1}H and ^{13}C NMR spectral analysis showed that no reaction had taken place **(Scheme 2.32)**.

With *N-tert*-butylsulfinimine **(81)** unable to produce the desired amide, and the requirement to synthesise the aldehyde, we decided to attempt the synthesis using a different protecting group. ~300 mg benzyloxyacetaldehyde **(85)** was reacted with 1.0 equivalent of (R_S)-2-methyl-2-propanesulfinamide **(82)** and 2.0 equivalents of anhydrous $CuSO_4$ in CH_2Cl_2. As before, the solution was left to stir at room temperature for 2 h and then filtered through celite. The crude product was purified by column chromatography on silica gel. The product separated with a gradient elution of petroleum ether:ethyl acetate 95:5 to 1:1, yielding ~380 mg of the *N-tert*-butylsulfinimine product **(86)**, resulting in a 75% yield **(Scheme 2.32)**. The structure of the product was confirmed by comparison with the published data.[39]

Next, we attempted the addition of the pyridyl group to the *N-tert*-butylsulfinimine **(81)**. 2-bromopyridine was treated with an excess of *n*-butyllithium in THF at -78 °C for 1 h generating the lithiated nucleophile.

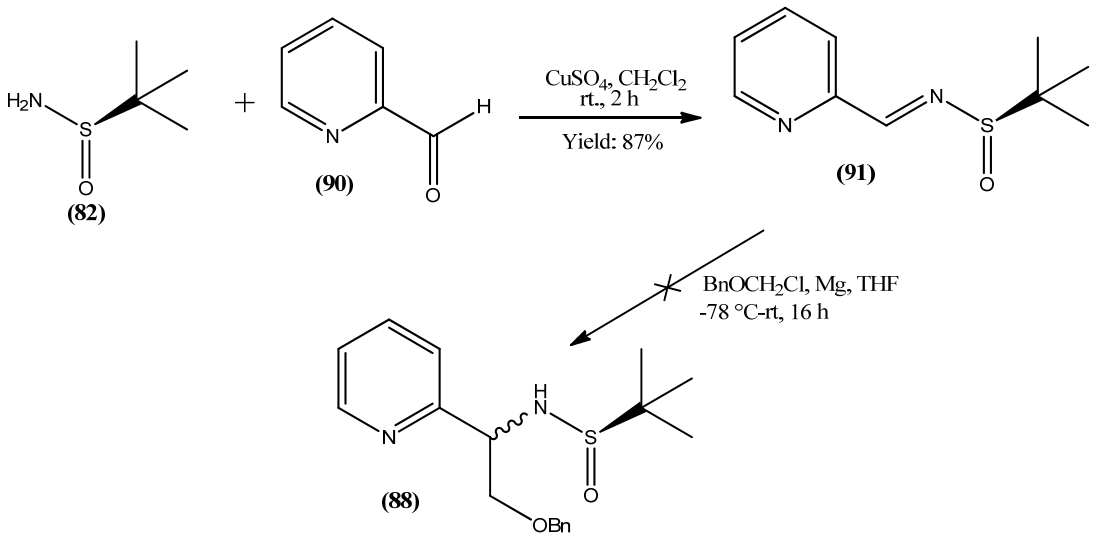


Scheme 2.32

To this solution was added the benzyl protected *N-tert*-butylsulfinimine **(86)**, with the reaction then left to stir for 5 h. Following workup of the reaction, the ^{1}H and ^{13}C NMR spectral analysis showed a mixture of compounds, with the major signals belonging to the starting material **(86)**. We attributed the appearance of new signals at ~8.6 to the formation of our desired product. These signals were reminiscent of signals which had appeared in a similar compound [β-amino alcohol **(89) (Scheme 2.32)**] described later in the chapter. The two signals, a double double doublet at 8.56 (J = 4.8, 1.8, 1.0 Hz) and a multiplet at 8.61-8.59 with a similar pattern, appear in a ~45:55 ratio. The ^{1}H NMR spectrum of β-amino alcohol **(89)**, which shows two diastereomeric signals with similar splitting patterns to our desired product, a double double doublet at 8.72 (J = 5.9, 1.6, 0.6 Hz) and a double double doublet at 8.68 (J = 5.9, 1.6, 0.6 Hz) for the hydrogen of the C(5) carbon on the pyridyl ring. The low conversion of the reaction meant that any other possible signals relating to the product were unidentifiable due to nearby overlap with similar signals. Due to the poor conversion of the reaction, we were unable to isolate either of these compounds to confirm the structure of these compounds and they were not characterised.

With the addition of the pyridyl group to the *N-tert*-butylsulfinimine **(86)** resulting in poor conversions and showing no diastereoselectivity we decided to revise our synthetic route. Instead, we decided to incorporate the pyridyl moiety into the

sulfinimine structure and attempt to add the hydroxyl substituent to it using a Grignard addition **(Scheme 2.33)**.



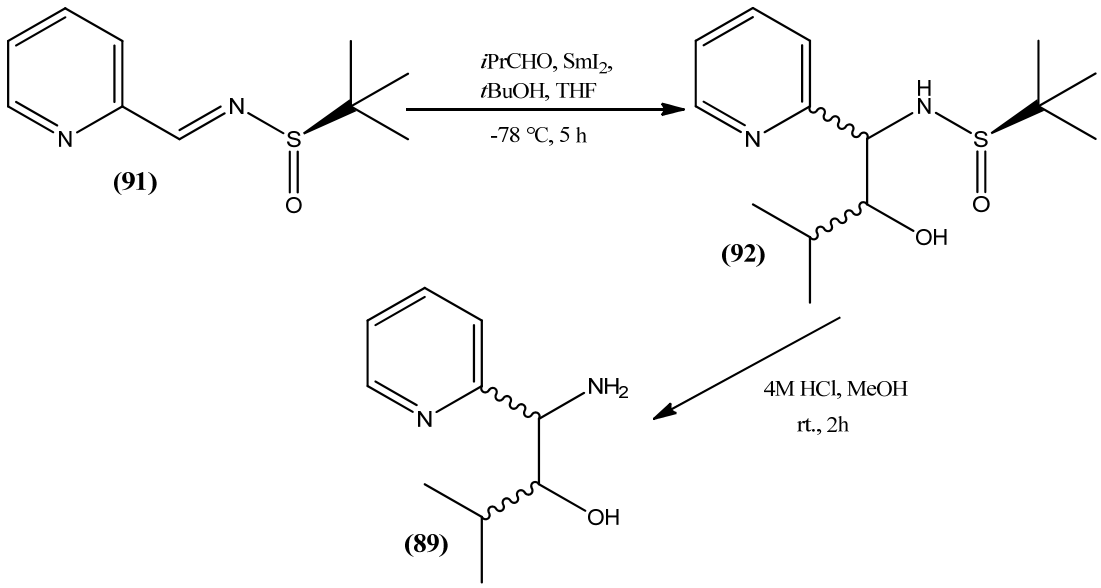
Scheme 2.33

The first step in our revised synthesis involved the preparation of the pyridyl *N-tert*-butylsulfinimine **(91)**. 2-pyridinecarboxaldehyde **(90)** was reacted with 1.0 equivalent of (R_S)-2-methyl-2-propanesulfinamide **(82)** and 2.0 equivalents of anhydrous $CuSO_4$ in CH_2Cl_2. As before, the solution was left to stir at room temperature for 2 h and then filtered through celite. The crude product was purified by column chromatography on silica gel. The product separated with a gradient elution of petroleum ether:ethyl acetate 98:2 to 7:3. The *N-tert*-butylsulfinimine **(91)** was obtained in 87% yield **(Scheme 2.33)**. Generally, ~180 mg of product **(91)** was isolated from ~110 mg of 2-pyridinecarboxaldehyde **(90)**. The structure of the product was confirmed by comparison with the published data.[40]

We then attempted the addition of the benzyloxymethyl group to the *N-tert*-butylsulfinimine **(91)**. Benzyloxymethyl chloride was added to a mixture of excess of magnesium turnings, in the presence of a catalytic amount of freshly sublimed mercuric chloride, in THF at -10 °C and stirred for 2 h to generate the Grignard reagent. The mixture was then cooled to -78 °C, with the pyridyl *N-tert*-butylsulfinimine **(91)** then added. The reaction was then left to stir overnight allowing it to gradually warm to room temperature. Following workup of the reaction, the ^{1}H and ^{13}C NMR spectral analysis showed that no reaction had taken place.

As discussed in **Section 1.2.1**, work has been carried out by Xu *et al* on the reductive cross coupling reactions of aliphatic with *N-tert*-butylsulfinimines, providing the desired optically active 1,2 amino alcohols with high diastereo- and enantiocontrol.[41] This also offered a wider scope of potential substituents which could be varied depending on the choice of aldehyde. Using this methodology we hoped to synthesise a library of optically active 1,2 amino alcohols and 4,4'-PYBOX ligands using a range of aldehydes.

With **(91)** in hand, our attention turned to the synthesis of **(92)**. *N-tert*-butylsulfinimine **(91)** underwent a SmI_2 mediated reductive cross coupling reaction **(Scheme 2.34)**. ~100 mg of *N-tert*-butylsulfinimine **(91)** was reacted with 1.5 equivalents of *iso*-butyraldehyde and 2.0 equivalents of SmI_2 and *tert*-butyl alcohol in THF at -78 °C. The reaction mixture was monitored by TLC and then quenched with a saturated $Na_2S_2O_3$ solution. After workup, the crude product was purified by column chromatography on silica gel. The product separated with a gradient elution of petroleum ether:ethyl acetate 98:2 to 4:1. The desired product **(92)** was obtained in 54% yield, as an inseparable mixture of what appeared to be two separate diastereomers (3:2).



Scheme 2.34

The characteristic signals of the pyridyl groups were present in the ^1H NMR spectrum of **(92)**. The hydrogen of the C(5) carbon on the pyridyl ring appears as a double double doublet at 8.48 (J = 4.9, 1.8, 0.9 Hz) and a double doublet at 8.45 (J =

4.8, 1.8 Hz) in a ratio of 2:3. The hydrogens of the CHN appeared also appeared as doublets at 4.65 (J = 7.5 Hz) and at 4.48 (J = 7.5 Hz) in a ratio of 3:2. The *tert*-butyl signal accounting for the sulfinyl group key appeared at 0.94 and 1.07 as singlets. The lack of the CH=N signal at 8.73 was key in identifying that the starting material **(91)** had reacted. Since we were unable to separate the diastereomers as *N-tert*-butylsulfinamides, we decided to proceed with our synthesis and attempt to separate the diastereomers at a later stage.

The next stage of the synthesis involved the cleavage of the sulfinyl group. To achieve this, *N-tert*-butylsulfinamide **(92)** was treated with a 4M HCl in 1,4 dioxane and stirred in methanol for 2 h. After removing the solvent, the product was dissolved in ethyl acetate, placed under a NH_3 atmosphere and left to stir for 1 h. The solution was filtered and concentrated in *vacuo* to afford the product **(89)** in 77% yield as a mixture of diastereomers. The characteristic signals of the pyridyl groups were present in the ^{1}H NMR spectrum. The hydrogen of the C(2) carbon in the diastereomers appeared as a doublet at 8.11 (J = 8.0 Hz) and at 7.99 (J = 8.0 Hz) in a ratio of 2:3. The hydrogens of the CHN appeared also appeared as doublets at 4.84 (J = 3.9 Hz) and at 4.74 (J = 5.6 Hz) in a ratio of 2:3. The lack of the *tert*-butyl signal accounting for the sulfinyl group in the ^{1}H NMR spectrum was key in identifying the product. However, sufficient quantities of the β-amino alcohol **(89)** could not be isolated, so the compound was not fully characterised and no further reactions could be carried out.

While the reductive cross coupling reactions produced moderate yields, our diastereomeric ratio was much lower than expected (60:40). In addition to this, the reducing reagent SmI_2 had a very short shelve life and proved to be difficult to maintain, with the majority of reactions failing to show any conversion. This meant that we were unable to generate sufficient amount of the β-amino alcohol **(89)** to proceed further with our synthetic plan. It was suggested in a communication from Prof. Xu that this problem could be overcome by preparing the reagent in situ, but in light of the hazardous nature of the reagents, it was decided to revise our synthetic plan.

2.5 Conclusions

We have synthesised six novel 4,4'-bisoxazoline ligands. The novel ligands **(23)**, **(24)**, **(57)** and **(63)** are all prepared from a common compound, di-TBDMS protected

bis-β-amino alcohol **(8)**, which is synthesised in 8 steps from (2*R*, 4*R*)-arabitol. Similarly, the novel ligands **(27)** and **(28)**, which are diastereomers of ligands **(23)** and **(24)**, were both prepared from an enantiomeric starting material (2*S*, 4*S*)-arabitol, *via* the enantiomeric di-TBDMS protected bis-β-amino alcohol **(8a)**. The transformation of the ligands from enantiomeric derivatives to diastereomeric was achieved by the introduction of secondary stereocentres, at a late stage in the ligand synthesis from commercially available chiral acids. The ligands **(23)**, **(24)**, **(27)** and **(28)** were formed from the amides **(21)**, **(22)**, **(25)** and **(26)** in a highly efficient manner using a one-pot deprotection-activation-ring-closure (DARC) reaction; a method which was developed in our research group.

Copper complexes of the 4,4'-bisoxazoline ligands **(23)**, **(24)**, **(27)** and **(28)** were successfully applied to the asymmetric Diels Alder, cyclopropanation and ene reactions. In the Diels Alder reaction *ee*'s of up to 57% were achieved with the 4,4'-BOX ligand **(24)**, the highest enantioselectivity yet achieved for a 4,4'-BOX ligand in a Diels Alder reaction. The 4,4'-BOX ligand **(27)** produced an *ee* of 70% in the cyclopropanation of ethyl diazoacetate **(49)** and styrene **(50)**, which was also the highest *ee* yet achieved for a 4,4'-BOX ligand in a cyclopropanation reaction. The same ligand **(27)** also produced an *ee* of 72% in the allylic alkylation reaction of (±)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene **(42)** with the sodiodimethyl malonate nucleophile.

These second generation 4,4'-BOX ligands have clearly shown that the added chirality of the pendent sidearms can have a drastic effect on the enantioselectivity of a reaction. The *ee*'s achieved show an improvement from those achieved by first generation 4,4'-BOX ligands in nearly all reactions. While these results are encouraging there is still room to improve and further develop this class of ligand. Development of 4,4'-BOX ligands is on-going in our research group.

References

(1) Frain, D.; Kirby, F.; McArdle, P.; O'Leary, P. *Synlett* **2009**, 1261.

(2) Frain, D.; Kirby, F.; McArdle, P.; O'Leary, P. *Tetrahedron Lett.* **2010**, *51*, 4103.

(3) Kirby, F.; Frain, D.; McArdle, P.; O'Leary, P. *Catalysis Communications* **2010**, *11*, 1012.

(4) Boydell, A. J.; Jeffery, M. J.; Burkstummer, E.; Linclau, B. *J. Org. Chem.* **2003**, *68*, 8252.

(5) Kirby, F., National University of Ireland, Galway, 2011.

(6) Linclau, B.; Boydell, A. J.; Clarke, P. J.; Horan, R.; Jacquet, C. *J. Org. Chem.* **2003**, *68*, 1821.

(7) Attwood, S. V.; Barrett, A. G. M. *J. Chem. Soc.-Perkin Trans. 1* **1984**, 1315.

(8) Corey, E. J.; Imai, N.; Zhang, H. Y. *J. Am. Chem. Soc.* **1991**, *113*, 728.

(9) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559.

(10) Le Gall, E.; Hurvois, J. P.; Sinbandbit, S. *Eur. J. Org. Chem.* **1999**, 2645.

(11) Soloshonok, V. A.; Cai, C. Z.; Hruby, V. J.; Van Meervelt, L.; Yamazaki, T. *J. Org. Chem.* **2000**, *65*, 6688.

(12) Ghosh, A. K.; Cho, H.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 3687.

(13) Carbone, P.; Desimoni, G.; Faita, G.; Filippone, S.; Righetti, P. *Tetrahedron* **1998**, *54*, 6099.

(14) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994.

(15) Audrain, H.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2000**, *65*, 4487.

(16) Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541.

(17) Lingen, H. L. v.; Zhuang, W.; Hansen, T.; Rutjes, F. P. J. T.; Jørgensen, K. A. *Organic and Biomolecular Chemistry* **2003**, 1953.

(18) Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497.

(19) Desimoni, G.; Faita, G.; Jorgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561.

(20) Leung, W.; Cosway, S.; Jones, R. H. V.; Mc Cann, H.; Wills, M. *Journal of the Chemical Society; Perkin Transactions I* **2001**, *1*, 2588.

(21) Clarke, M. L.; France, M. B. *Tetrahedron* **2008**, *64*, 9003.

(22) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824.

(23) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726.

(24) Knight, J. G.; Belcher, P. E. *Tetrahedron: Asymmetry* **2005**, *16*, 1415.

(25) Portada, T.; Roje, M.; Hamersak, Z.; Zinic, M. *Tetrahedron Lett.* **2005**, *46*, 5957.

(26) Pellissier, H. *Tetrahedron* **2008**, *64*, 7041.

(27) Garcia, J. I.; Jimenez-Oses, G.; Martinez-Merino, V.; Mayoral, J. A.; Pires, E.; Villalba, I. *Chemistry - A European Journal* **2007**, *13*, 4064

(28) Fraile, J. M.; Garcia, J. I.; Martinez-Merino, V.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **2001**, *123*, 7616.

(29) Fraile, J. M.; García, J. I.; Gil, M. J.; Martínez-Merino, V.; Mayoral, J. A.; Salvatella, L. *Chemistry - A European Journal* **2004**, *10*, 758.

(30) Fraile, José M.; García, José I.; Gissibl, A.; Mayoral, José A.; Pires, E.; Reiser, O.; Roldán, M.; Villalba, I. *Chemistry - A European Journal* **2007**, *13*, 8830.

(31) Garcia, J. I.; Jimenez-Oses, G.; Mayoral, J. A. *Chemistry-a European Journal* **2011**, *17*, 529.

(32) Aït-Haddou, H.; Hoarau, O.; Cramailére, D.; Pezet, F.; Daran, J.-C.; Balavoine, G. G. A. *Chemistry - A European Journal* **2004**, *10*, 699.

(33) Bolm, C.; Zani, L.; Schiffers, I. *Synthesis-Stuttgart* **2004**, *2004*, 2173.

(34) Schinnerl, M.; Seitz, M.; Kaiser, A.; Reiser, O. *Org. Lett.* **2001**, *3*, 4259.

(35) Tse, M. K.; Dobler, C.; Bhor, S.; Klawonn, M.; Magerlein, W.; Hugl, H.; Beller, M. *Angew. Chem.-Int. Edit.* **2004**, *43*, 5255.

(36) Katsuki, T. *Adv. Synth. Catal.* **2002**, *344*, 131.

(37) Brown, J. M.; Leppard, S. J.; Thornthwaite, D. *Chirality* **2000**, *12*, 496.

(38) Aszodi, J.; Bonnet, A.; Teutsch, G. *Tetrahedron* **1990**, *46*, 1579.

(39) Barrow, J. C.; Ngo, P. L.; Pellicore, J. M.; Selnick, H. G.; Nantermet, P. G. *Tetrahedron Lett.* **2001**, *42*, 2051.

(40) Owens, T. D.; Souers, A. J.; Ellman, J. A. *J. Org. Chem.* **2003**, *68*, 3.

(41) Zhong, Y. W.; Dong, Y. Z.; Fang, K.; Izumi, K.; Xu, M. H.; Lin, G. Q. *J. Am. Chem. Soc.* **2005**, *127*, 11956.

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 were distilled from calcium hydride, toluene and tetrahydrofuran were distilled from sodium benzophenone ketyl or dried through an Innovative Technology Pure Solv PS-MD-5 Purification System.[1] Organic phases were dried using anhydrous magnesium sulphate or sodium sulphate. All chemicals were purchased from Aldrich Chemical Company, Fisher Scientific or Acros Organics 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. Cyclopentadiene was cracked and distilled freshly prior to use. Dicyclopentadiene was cracked at 160-170 °C and cyclopentadiene distilled at ~40 °C. Ethyl glyoxylate was distilled according to a literature procedure.[2]

Melting points were measured on a Stuart Scientific SMP3 or SMP11 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 589 nm (Na) in a 1 dm cell; concentrations (*c*) are expressed in g/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, vanillin stain, permanganate stain or ninhydrin stain.

High resolution mass spectra were carried out using electrospray ionisation (ESI) on a Walters LCT Premier XE spectrometer by manual peak matching.

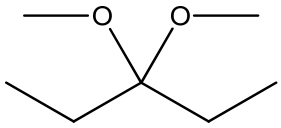
^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a JEOL ECX-400 NMR spectrometer. All spectra were recorded at probe temperatures (~20 ºC) in deuterated chloroform ($CDCl_3$) unless otherwise stated, using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in parts per million (ppm) and coupling constants in Hertz (Hz), unless indicated all coupling constants represent 3 bond couplings. ^{13}C NMR spectra were assigned with the aid of DEPT experiments. Compounds which were assigned with the aid of DEPT experiments 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, $CH_2C\mathit{H}OH$). In order to distinguish the characterisation of these compounds from non-DEPT aided assignments, compounds for which DEPT spectra were not recorded, were identified using a combination of both atom numbering and signal identification, for example, [*C*-2]. HMQC (Heteronuclear Shift Multiple Quantum Coherence) establishes links between protons and attached carbons. COSY (Correlated Spectroscopy) established links between protons 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 4,4'-BOX ligands

3,3-Dimethoxypentane (14)[3,4]

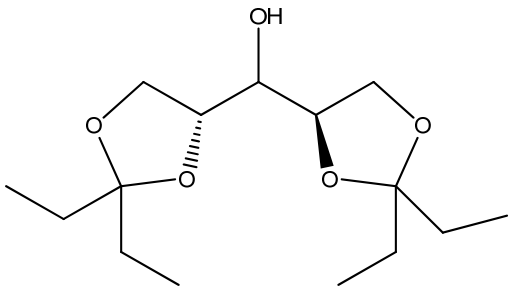


(14)

Pentanone (200 mL, 1.88 mol), trimethyl orthoformate (254 mL, 2.32 mol) and camphorsulfonic acid (13 g, 56 mmol) were added to MeOH (1.2 L) and the mixture was stirred overnight. Methyl formate was removed by distillation. The solution was then neutralized with sodium methoxide, poured onto water (1.2 L) and extracted with Et_2O (3 x 1 L). The combined extracts were then washed with brine (500 mL) and dried over K_2CO_3. Ether was removed under reduced pressure to leave a cloudy solution, which was then extracted with Et_2O (2 x 100 mL), dried over K_2CO_3, filtered and concentrated *in vacuo* to yield the product **(14)** (155.07 g, 63%) as a clear oil.

IR 2972, 2946, 1049, 901 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ = 3.13 (6H, s, 2 x OCH_3), 1.56 (4H, q, J=7.5 Hz, 2 x CH_2CH_3), 0.79 (6H, t, J=7.5 Hz, 2 x CH_2CH_3) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 104.2 [*C*, $C(OCH_3)_2$], 47.7 (CH_3, 2 x OCH_3), 24.3 (CH_2, 2 x CH_2), 7.9 (CH_3, 2 x CH_3).

(2*R*,4*R*)-1,2:4,5-Di-*O*-(3,3-pentylidene)-arabitol (11)[3,5]



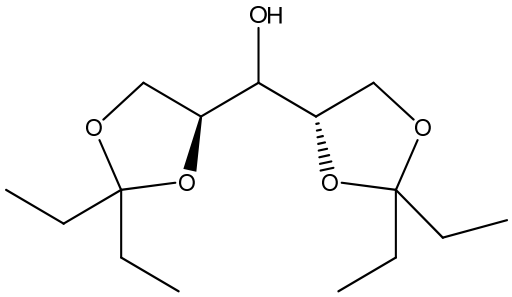
(11)

(2*R*, 4*R*)-arabitol (10 g, 65.7 mmol) and **(14)** (38.25 g, 0.29 mol) were added to THF (100 mL). The solution was heated to reflux and stirred for 15 min. Camphorsulfonic acid (4.58 g, 19.72 mmol) was added and reflux was continued for 5 min. The solution was then cooled to room temperature at which point NaOH (20 mL, 2.0 M) was added to quench the reaction. The THF was removed under reduced pressure, after which, the solution was taken up in Et_2O (50 mL) and water (10 mL). The organic layer was the separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*, to give the crude product, a mixture of **(11)** and 1,2:3,4 bis-acetal by-product [4:1, estimated by ^{1}H-NMR signals: by-product signal at 2.46 (1H) compared to the product signal formed at 2.39 (1H)]. This crude mixture was dissolved in CH_2Cl_2 (200 mL) and Et_3N (10 mL) was added. The solution was heated to reflux and succinic anhydride (1.71 g, 17.09 mmol) was added. After an hour of stirring, the solution was allowed to cool to room temperature and $NaHCO_3$ (5% aq., 100 mL) was used to quench the reaction. The layers were then separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 100 mL) and the combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (gradient elution, Petrol:EtOAc, 97:3 to 92:8) yielded the product **(11)** (12.75 g, 67%) as a clear oil.

R_f = 0.32 (Petrol:EtOAc, 9:1); $[\alpha]_D$ +3.1 (*c* 0.005, $CHCl_3$, 20 °C); IR 3485, 2972, 2940, 2883, 1463, 1076, 913 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400MHz) δ = 4.22-4.16 (1H, m, one of C*H*O), 4.12 (1H, dd, *J*=7.7, 5.7 Hz, one of CH_2O), 4.07 (1H, dd, *J*=8.2, 6.6 Hz, one of CH_2O), 4.00-3.89 (2H, m, one of C*H*O, one of CH_2O), 3.84 (1H, app. t,

J=8.0 Hz, one of C*H*$_2$O), 3.47-3.41 (1H, m, C*H*OH), 2.38 (1H, d, *J*=5.8 Hz, O*H*), 1.72-1.56 (8H, m, 4 x C*H*$_2$CH$_3$), 0.93-0.84 (12H, m, 4 x CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 113.4, 113.0 (2 x *C*, 2 x *C*), 76.9, 76.5 (2 x *C*H, 2 x CH$_2$*C*HO), 73.1 (*C*H, *C*HOH), 68.0, 66.6 (2 x *C*H$_2$, 2 x *C*H$_2$O), 29.7, 29.6, 29.1, 29.0 (4 x *C*H$_2$, 4 x *C*H$_2$CH$_3$), 8.4, 8.3, 8.2, 8.1 (4 x *C*H$_3$, 4 x CH$_2$*C*H$_3$).

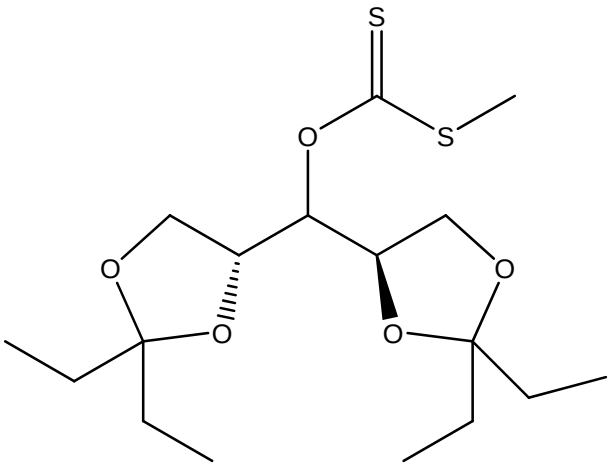
(2*S*,4*S*)-1,2:4,5-Di-*O*-(3,3-pentylidene)-arabitol (11a)



(11a)

(11a) was synthesised in the same manner from 10g of (2*S*, 4*S*)-arabitol and the reaction gave 13.92 g of **(11a)** (74%); [α]$_D$ -3.9 (*c* 0.008, CHCl$_3$, 20 °C); the R$_f$, IR, ^{1}H and ^{13}C NMR correspond to those of **(11)**.

(2*R*,4*R*)-Di-*O*-(3,3-pentylidene)-3-*O*[(methylthio)thiocarbonyl]-arabitol (12)



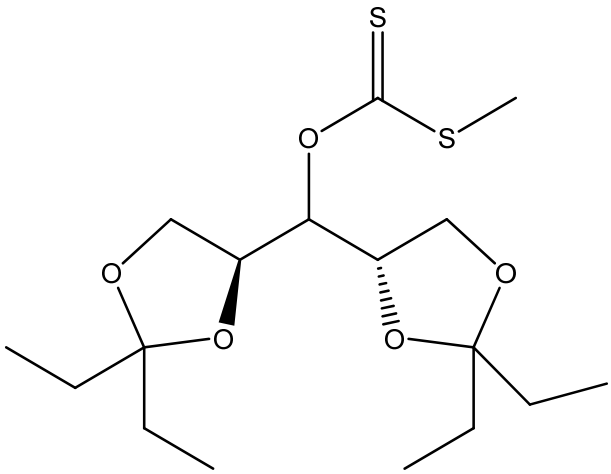
(12)

CS_2 (34 mL, 0.56 mol) was added to a stirring solution of **(11)** (12.75 g, 44.21 mmol) in THF (150 mL) at 0 °C. NaH (2.14 g, 60% dispersion in mineral oil, 53.1 mmol) was then added. The solution was allowed to gradually warm to room temperature and stirred for 6 h. The reaction was cooled to 0 °C and MeI (3.59 mL, 57.5 mmol) was added. After stirring overnight at room temperature, the reaction was again cooled to 0 °C and quenched with slow addition of saturated aqueous NH_4Cl (100 mL). The mixture was the concentrated *in vacuo* removing the organics. Et_2O (100 mL) was added and the layers were separated. The aqueous phase was extracted with Et_2O (2 x 100 mL), and the combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (gradient elution, Petrol:EtOAc, 96:4 to 90:10) yielded the product **(12)** (16.72 g, 99%) as a yellow oil.

R_f = 0.63 (Petrol:EtOAc, 9:1); $[\alpha]_D$ +30.8 (*c* 0.007, $CHCl_3$, 20 °C); IR 2972, 2939, 2882, 1462, 1197, 1078, 914 $cm^{-}1$; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.13 (1H, dd, *J*=5.7, 2.6 Hz, C*H*OCS), 4.45-4.36 (2H, m, 2 x CH_2CHO), 4.09 (1H, dd, J=8.8, 6.4 Hz, one of CH_2O) 4.05-3.96 (2H, m, 2 x one of CH_2O), 3.71 (1H, t, *J*=8.2 Hz, one of CH_2O), 2.60 (3H, s, SCH_3), 1.69-1.58 (8H, m, 4 x CH_2CH_3), 0.97-0.72 (12H, m, 4 x CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 217.3 (*C*, *C*S), 113.4, 113.3 (2 x *C*, 2 x

CCH_2), 79.5 (*C*H, *C*HOCS), 75.7, 75.5 (2 x *C*H, 2 x CH_2*C*HO), 66.5, 65.7 (2 x *C*H_2, 2 x *C*H_2O), 29.7, 29.4, 29.1, 29.0 (4 x *C*H_2, 4 x *C*H_2CH_3), 19.4 (*C*H_3, S*C*H_3), 8.2, 8.1 (4 x *C*H_3, 4 x CH_2*C*H_3).

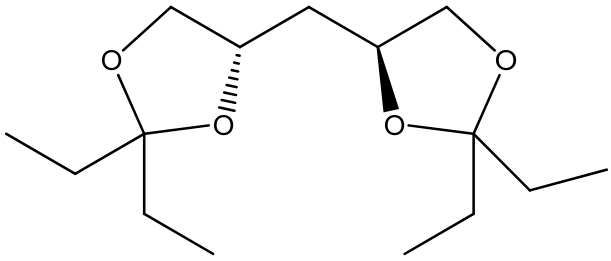
(2*S*,4*S*)-Di-*O*-(3,3-pentylidene)-3-*O*[(methylthio)thiocarbonyl]-arabitol (12a)



(12a)

(12a) was synthesised in the same manner from 9.80 g of **(11a)** and the reaction gave 12.85 g of **(12a)** (99%); $[\alpha]_D$ -25.9 (*c* 0.008, $CHCl_3$, 20 °C); the R_f, IR, ^1H and ^{13}C NMR correspond to those of **(12)**.

(2*S*,4*S*)-Di-*O*-(3,3-pentylidene)-3-deoxyarabitol (13)



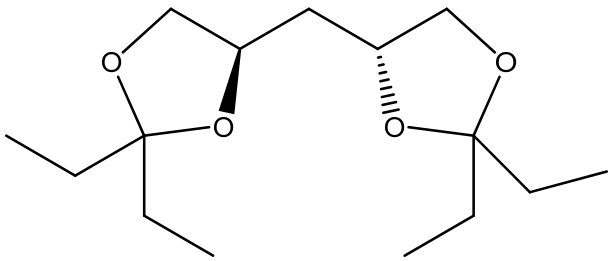
(13)

A solution of **(12)** (16.96 g, 44.8 mmol), 1,1'-azobis(cyclohexanecarbonitrile) (440 mg, 1.8 mmol) and tributyltin hydride (13.3 mL, 49.3 mmol) in toluene (150 mL)

was heated to reflux and stirred overnight. The solution was then allowed to cool to room temperature and concentrated *in vacuo*. Purification by column chromatography (gradient elution, Petrol:EtOAc, 97:3 to 92:8) yielded the product **(13)** (11.0 g, 90%) as a clear oil.

R_f = 0.61 (Petrol:EtOAc, 9:1); $[\alpha]_D$ +4.5 (*c* 0.004, $CHCl_3$, 20 °C); IR 2972 , 2940, 2881, 1464, 1172, 1056, 921 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ = 4.21-4.08 (4H, m, 2 x CH_2CHO, 2 x one of CH_2O), 3.55-3.47 (2H, m, 2 x one of CH_2O), 1.80 (2H, t, J=6.4 Hz, $CHCH_2CH$), 1.68-1.57 (8H, m, 4 x CH_2CH_3), 0.92-0.86 (12H, m, 4 x CH_3CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 112.7 (*C*, 2 x *C*), 74.1 (*C*H, 2 x *C*HO), 70.6 (CH_2, 2 x CH_2O), 37.7 (CH_2, $CHCH_2CH$), 30.0, 29.8 (2 x CH_2, 4 x CH_2CH_3), 8.3, 8.1 (2 x CH_3, 4 x CH_3CH_2).

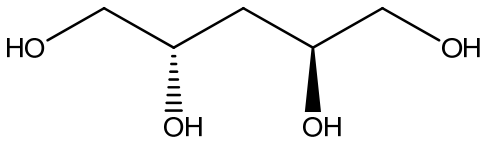
(2*R*,4*R*)-Di-*O*-(3,3-pentylidene)-3-deoxyarabitol (13a)



(13a)

(13a) was synthesised in the same manner from 18.64 g of **(12a)** and the reaction gave 12.44 g of **(13a)** (93%); $[\alpha]_D$ -3.9 (*c* 0.008, $CHCl_3$, 20 °C); the R_f, IR, ^1H and ^{13}C NMR correspond to those of **(13)**.

(2*S*,4*S*)-3-deoxyarabitol (9)

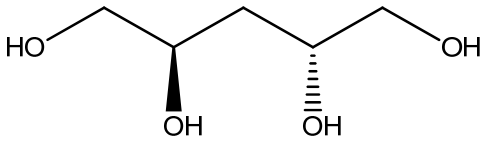


(9)

A solution of **(13)** (11.0 g, 40.4 mmol) in 0.5 M H_2SO_4 (40 mL) and EtOH (40 mL) was heated to reflux and stirred for 4 h. The reaction was quenched by addition of K_2CO_3 until neutral. After stirring at reflux for another 10 min the reaction mixture was allowed to cool to room temperature, filtered and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2:MeOH, 7:3) yielded **(9)** (5.46 g, 99%) as a white solid.

R_f = 0.50 (CH_2Cl_2:MeOH, 7:3); Mp 101-104 °C (lit.,[6] Mp 106-107 °C); $[\alpha]_D$ -18.7 (*c* 0.015, MeOH, 20 °C); IR; 3240 (br), 2931, 2908, 1083, 1019 cm^{-1}; ^1H NMR (D_2O, 400MHz) δ = 3.78-3.72 (m, 2H, 2 x C*H*OH); 3.45 (2H, dd, *J* = 11.7, 3.9 Hz, 2 x one of CH_2OH); 3.34 (2H, dd, *J* = 11.7, 6.8 Hz, 2 x one of CH_2OH); 1.37 (2H, dd, *J* = 7.3, 5.7 Hz, CHCH_2CH); ^{13}C NMR (100 MHz, D_2O) δ = 68.33 (*C*H, 2 x *C*HOH), 65.97 (*C*H_2, 2 x *C*H_2OH), 35.69 (*C*H_2, CH*C*H_2CH).

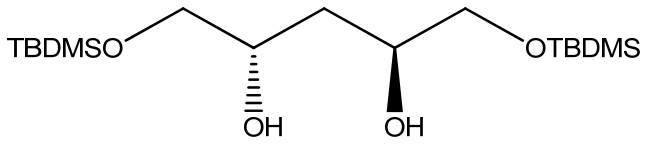
(2*R*,4*R*)-3-deoxyarabitol (9a)



(9a)

(9a) was synthesised in the same manner from 16.03 g of **(13a)** and the reaction gave 7.2 g of **(9a)** (90%); Mp 98-102 °C (lit.,[6] Mp 106-107 °C); $[\alpha]_D$ +15.1 (*c* 0.010, MeOH, 20 °C); the R_f, IR, ^1H and ^{13}C NMR correspond to those of **(9)**.

(2*S*,4*S*)-1,5-bis-*O*-[*tert*-butyl(dimethyl)silyl]-3-deoxyarabitol (17)

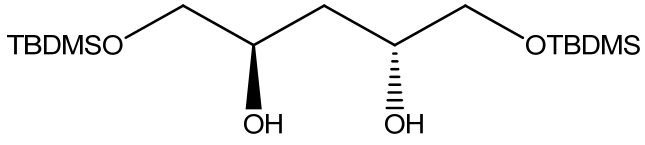


(17)

A stirring suspension of **(9)** (5.17 g, 38.0 mmol) in CH_2Cl_2 (120 mL) was cooled to -15 °C using an ice-water/salt bath. Triethylamine (11.7 mL, 83.6 mmol), 4-dimethylaminopyridine (1.53 g, 12.5 mmol) and *tert*-butyldimethylsilyl chloride (12.03 g, 79.8 mmol) were then added. The reaction mixture was allowed to gradually warm to room temperature and was stirred for 40 h. The solution was concentrated *in vacuo* and the resultant solid was purified by column chromatography (gradient elution, Petrol:EtOAc, 95:5 to 75:25) to give as a **(17)** (5.84 g, 42%) white solid.

R_f = 0.50 (Petrol:EtOAc, 4:1); Mp 33-34 °C; $[\alpha]_D$ -3.9 (*c* 0.0036, $CHCl_3$, 20 °C); IR 3291, 2929, 2858, 1250, 1065, 832, 773 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ = 3.99-3.90 (2H, m, 2 x C*H*OH), 3.65 (2H, dd, *J* = 9.9, 4.1 Hz, 2 x one of CH_2OSi), 3.46 (2H, dd, *J* = 9.9, 7.2 Hz, 2 x one of CH_2OSi), 1.52 (2H, t, *J* = 6.1 Hz, CHCH_2CH), 0.89 [18H, s, 2 x C(CH_3)$_3$], 0.06 [12H, s, 2 x Si(CH_3)$_2$]; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 69.3 (*C*H, 2 x *C*HOH), 67.4 (*C*H_2, 2 x *C*H_2OSi), 35.5 (*C*H_2, CHCH_2CH), 25.9 [*C*H_3, 2 x C(*C*H_3)$_3$], 18.4 (*C*, 2 x *C*), -5.3 [*C*H_3, 2 x Si(*C*H_3)$_2$].

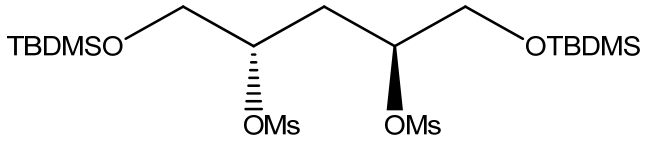
(2*R*,4*R*)-1,5-bis-*O*-[*tert*-butyl(dimethyl)silyl]-3-deoxyarabitol (17a)



(17a)

(17a) was synthesised in the same manner from 3.65 g of **(9a)** and the reaction gave 5.37 g of **(17a)** (55%); Mp 30-33 °C; $[\alpha]_D$ +2.3 (*c* 0.0031, $CHCl_3$, 20 °C); the R_f, IR, ^1H and ^{13}C NMR correspond to those of **(17)**.

(2*S*,4*S*)-1,5-bis-*O*-[*tert*-butyl(dimethyl)silyl]-3-deoxy-2,4-bis-*O*-(methylsulfonyl)-arabitol (18)

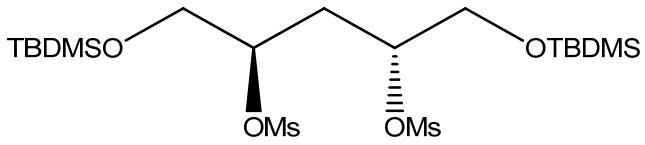


(18)

A solution of **(17)** (5.35 g, 14.66 mmol) in CH_2Cl_2 (70 mL) was stirred at 0 °C for 5 min. Triethylamine (5.7 mL, 41.1 mmol) was then added and the mixture was stirred for a further 5 min. MsCl (2.5 mL, 32.3 mmol) was then added and the solution was stirred at room temperature for 4 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (50 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (gradient elution, Petrol:EtOAc, 9:1 to 4:1) yielded the product **(18)** (7.31 g, 96%) as a white solid.

R_f = 0.42 (Petrol:EtOAc, 4:1); Mp 84-85 °C; $[\alpha]_D$ -13.2 (*c* 0.003, MeCN, 20 °C); IR 3485, 3443, 2945, 2931, 1320, 1158, 881 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ 4.85-4.78 (2H, m, 2 x C*H*OS), 3.87-3.79 (4H, m, 2 x CH_2OSi), 3.12 (6H, s, 2 x SCH_3), 2.07 (2H, dd, *J* = 6.8, 5.7 Hz, CHCH_2CH), 0.90 [18H, s, 2 x C(CH_3)$_3$], 0.09 [12H, s, 2 x Si(CH_3)$_2$]; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 79.3 (*C*H, 2 x *C*HOS), 65.0 (*C*H_2, 2 x *C*H_2OSi), 38.8 (*C*H_3, 2 x S*C*H_3), 37.8 (*C*H_2, CH*C*H_2CH), 25.9 [*C*H_3, 2 x C(*C*H_3)$_3$], 18.4 (*C*, 2 x *C*), -5,4 [*C*H_3, 2 x Si(*C*H_3)$_2$].

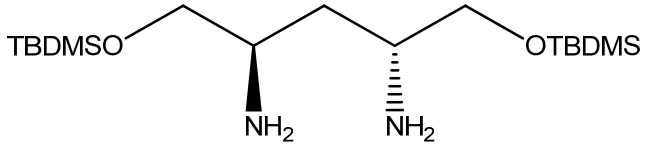
(2*R*,4*R*)-1,5-bis-*O*-[*tert*-butyl(dimethyl)silyl]-3-deoxy-2,4-bis-*O*-(methylsulfonyl)-arabitol (18a)



(18a)

(18a) was synthesised in the same manner from 5.28 g of **(17a)** and the reaction gave 7.34 g of **(18a)** (97%); Mp 84-85 °C; $[\alpha]_D$ +13.9 (*c* 0.0031, $CHCl_3$, 20 °C); the R_f, IR, ^1H and ^{13}C NMR correspond to those of **(18)**.

(2*R*,4*R*)-1,5-bis-*O*-[*tert*-butyl(dimethyl)silyl]-2,4-diaminopentane (8)



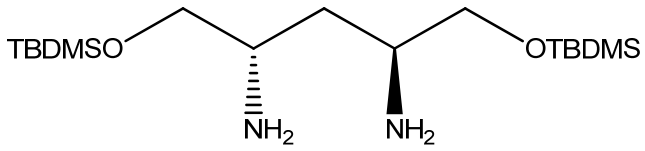
(8)

To a solution of **(18)** (7.31 g, 14.03 mmol) in *N*, *N*-dimethylformamide (150 mL) was added NaN_3 (15.96 g, 245.53 mmol). The mixture was heated to 85 °C for 16 h. The mixture was then concentrated *in vacuo*, dissolved in EtOAc, filtered through celite and concentrated *in vacuo* again. The intermediate bis-azide was reduced without further purification. After dissolving in MeOH (50 mL) the solution was transferred to a Parr apparatus, palladium on activated carbon (10% Pd on C, 100 mg) was added, and the suspension was vigorously stirred under an atmosphere of hydrogen (7 bar) for 12 h at room temperature, until the azide had disappeared by TLC. The mixture was filtered through celite, concentrated *in vacuo* and purified by column chromatography (gradient elution, EtOAc:MeOH, 99:1 to 60:40) to yield **(8)** (2.90 g, 57%) as a clear oil.

R_f = 0.24 (EtOAc:MeOH:NH_4OH, 85:15:10); $[\alpha]_D$ +2.5 (*c* 0.005, MeCN, 20 °C); IR 2929, 2856, 1251, 1093, 832, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ =3.53 (2H, dd, *J* = 9.7, 4.2 Hz, 2 x one of C*H*$_2$OSi), 3.32 (2H, dd, *J* = 9.7, 7.2 Hz, 2 x one of

C*H*$_2$OSi), 3.05-2.98 (2H, m, 2 x C*H*N), 1.70 (4H, br s, 2 x CHN*H*$_2$), 1.26 (2H, dd, *J* = 7.0, 6.4 Hz, CHC*H*$_2$CH), 0.90 [18H, s, 2 x C(C*H*$_3$)$_3$], 0.06 [12H, s, 2 x Si(C*H*$_3$)$_2$]; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 69.1 (*C*H$_2$, 2 x *C*H$_2$O), 50.0 (*C*H, 2 x *C*HN), 37.0 (*C*H$_2$, CH*C*H$_2$CH), 26.0 [*C*H$_3$, 2 x C(*C*H$_3$)$_3$], 18.4 (*C*, 2 x *C*), -5.3 [*C*H$_3$, 2 x Si(*C*H$_3$)$_2$].

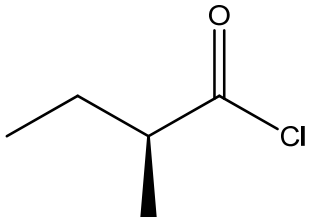
(2*S*,4*S*)-1,5-bis-*O*-[*tert*-butyl(dimethyl)silyl]-2,4-diaminopentane (8a)



(8a)

(8a) was synthesised in the same manner from 7.34 g of **(18a)** and the reaction gave 3.17 g of **(8a)** (62%); $[\alpha]_D$ -3.2 (*c* 0.009, $CHCl_3$, 20 °C); the R_f, IR, ^{1}H and ^{13}C NMR correspond to those of **(8)**.

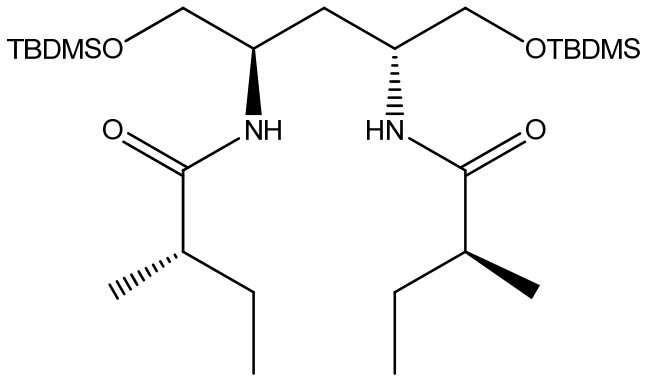
(*S*)-(+)-2-Methylbutyric acid chloride (19)[7]



(19)

Thionyl chloride (0.50 mL, 6.91 mmol) was added to a flask containing (S)-(+)-2-Methylbutyric acid (0.49 mL, 4.61 mmol). The solution was heated to reflux and stirred for 1 h and then concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 and concentrated *in vacuo* once more, yielding **(19)** (556 mg, 100%) as a yellow oil, which was used without purification.

(2*S*)-*N*-(1*R*,3*R*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3-{[(2*S*)-2-methylbutanoyl]amino}butyl-2-methyl butanamide (21)[8,9]



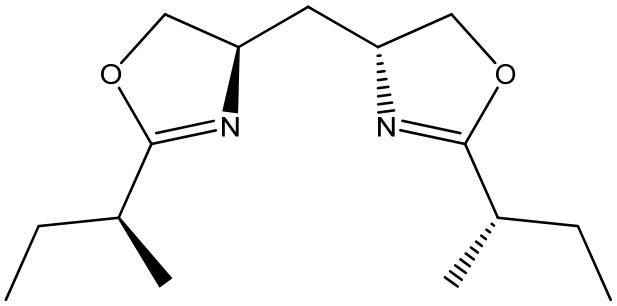
(21)

To a stirring solution of **(8)** (0.7 g, 1.93 mmol) and triethylamine (0.6 mL, 4.25 mmol) in CH_2Cl_2 (20 mL) at 0 °C, was added **(19)** (510 mg, 4.25 mmol). This solution was left to stir for 14 h, warming to room temperature. The solution was then concentrated *in vacuo*, dissolved in EtOAc, filtered and concentrated *in vacuo* again. Purification by column chromatography (gradient elution, Petrol:EtOAc, 9:1 to 7:3) yielded **(21)** (684 mg, 67%) as a white solid.

R_f=0.38 (Petrol:EtOAc, 7:3); Mp 62-63 °C; $[\alpha]_D$ +23.6 (*c* 0.004, MeCN, 20 °C); IR 3287, 2960, 2928, 2857, 1641, 1538, 1109, 836 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.23-6.14 (2H, m, 2 x N*H*), 3.89-3.77 (2H, m, 2 x C*H*N), 3.69-3.66 (4H, m, 2 x CH_2OSi), 2.16-2.05 (2H, m, 2 x C*H*CH_3), 1.81 (2H, dt, *J* = 5.6, 1.2 Hz, CHCH_2CH), 1.65-1.54 (2H, m, 2 x one of C$H_2$$CH_3$), 1.45-1.35 (2H, m, 2 x one of C$H_2$$CH_3$), 1.13-1.09 (6H, series of doublets (3) due to rotamers, 2:1:1, *J* = 6.8 Hz, 2 x CH_3CH), 0.91-0.85 [24H, m, 2 x C(CH_3)$_3$, 2 x C$H_3$$CH_2$], 0.05-0.03 [12H, series of singlets (3) due to rotamers, 2:1:1, 2 x Si(CH_3)$_2$]; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 176.66, 176.63, 176.59, 176.55 (*C*, 2 x *C*=O, 4 x signals due to rotamers, 1:1:1:1), 64.96, 64.92, 64.83, 64.80 (*C*H_2, 2 x *C*H_2O, 4 x signals due to rotamers, 1:1:1:1), 48.51, 48.39, 48.37, 48.23 (*C*H, 2 x *C*HN, 4 x signals due to rotamers, 2:2:2:1), 43.4 (*C*H, 2 x *C*HCH_3), 33.79, 33.67, 33.52 (*C*H_2, CH*C*H_2CH, 3 x signals due to rotamers, 1:2:1), 27.48, 27.33 (*C*H_2, 2 x *C*$H_2$$CH_3$, 2 x signals due to rotamers, 1:1), 25.9 [*C*H_3, 2 x C(*C*H_3)$_3$], 18.3 [*C*, 2 x *C*(CH_3)$_3$], 17.63, 17.55 (*C*H_3, 2 x *C*H_3CH, 2 x signals due to rotamers, 1:1), 12.03, 12.02 (*C*H_3, 2 x *C*$H_3$$CH_2$, 2 x signals due to rotamers, 1:1), -

5.33, -5.40 [CH_3, 2 x Si(CH_3)$_2$, 2 x signals due to rotamers, 1:1]; ESI-HRMS calcd for $C_{27}H_{58}N_2O_4Si_2$ 529.3857 [M-H^+], found *m/z* 529.3873.

(4*R*,4'*R*)-4,4'-methylenebis{2-[(1*S*)-1-methylpropyl]-4,5-dihydro-1,3-oxazole} (23)[5,9]

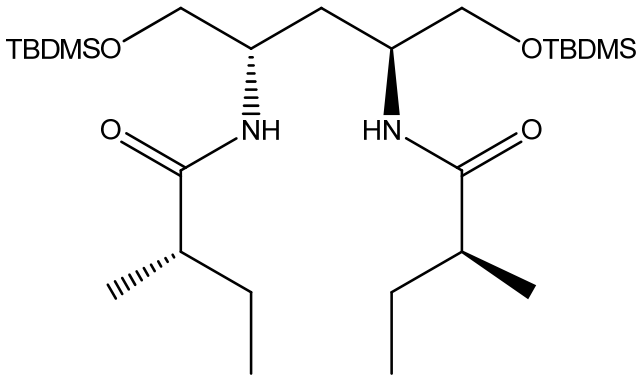


(23)

To a solution of **(21)** (615 mg, 1.16 mmol) and *p*-toluenesulfonyl fluoride (452 mg, 2.60 mmol) in dry acetonitrile (30 mL) was added DBU (390 µL, 2.60 mmol). The mixture was heated to reflux and stirred overnight. It was then allowed to cool to room temperature and concentrated *in vacuo*. Purification by column chromatography (gradient elution, Petrol:EtOAc, 7:3 to 3:7) yielded **(23)** (207.8 mg, 63%) as a colourless oil.

R_f=0.45 (Petrol:EtOAc, 3:7); $[\alpha]_D$ +44.7 (*c* 0.004, MeCN, 20 °C); IR 2966, 2934, 1651, 1461, 974 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 4.35 (2H, t, *J* = 8.9 Hz, *2* x one of CH_2O), 4.22-4.13 (2H, m, 2 x C*H*N), 3.85 (2H, td, *J* = 8.0, 2.1 Hz, 2 x one of CH_2O), 2.42-2.33 (2H, m, 2 x C*H*CH$_3$), 1.72 (2H, td, *J* = 7.0, 2.3 Hz, CHCH_2CH), 1.66-1.56 (2H, m, 2 x one of CH_2CH$_3$), 1.52-1.41 (2H, m, 2 x one of CH_2CH$_3$), 1.13 (6H, dd, *J* = 6.9, 0.8 Hz, 2 x CH_3CH), 0.90 (6H, t, *J* = 7.3 Hz, 2 x CH_3CH$_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 171.20, 171.13 (*C*, 2 x *C*=N), 73.11 (*C*H$_2$, 2 x *C*H$_2$O), 64.77, 64.73 (*C*H, 2 x *C*HN), 43.78, 43.74, 43.70 (*C*H$_2$, CH*C*H$_2$CH), 35.12, 35.05 (*C*H, 2 x *C*HCH$_3$), 27.2 (*C*H$_2$, 2 x *C*H$_2$CH$_3$), 17.4 (*C*H$_3$, 2 x *C*H$_3$CH), 11.71, 11.65 (*C*H$_3$, 2 x *C*H$_3$CH$_2$); ESI-HRMS calcd for $C_{15}H_{26}N_2O_2$ 267.2072 [M+H^+], found *m/z* 267.2078.

(2*S*)-*N*-(1*S*,3*S*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3-{[(2*S*)-2-methylbutanoyl]amino}butyl-2-methyl butanamide (25)[8,9]



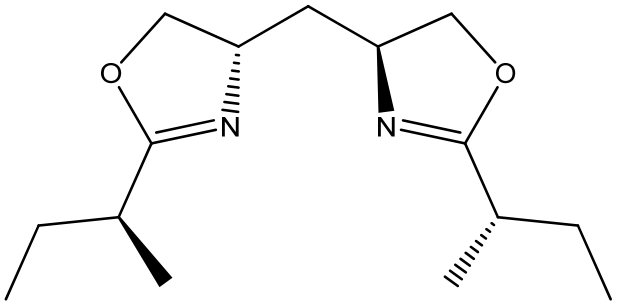
(25)

To a stirring solution of **(8a)** (0.4 g, 1.1 mmol) and triethylamine (0.34 ml, 2.5 mmol) in CH_2Cl_2 (20 mL) at 0 °C, was added **(19)** (300 mg, 2.5 mmol).This solution was left to stir for 14 h, warming to room temperature. The solution was then concentrated *in vacuo*. Purification by column chromatography (gradient elution, Petrol:EtOAc, 9:1 to 3:7) yielded **(25)** (203 mg, 35%) as a colourless oil.

R_f=0.30 (Petrol:EtOAc, 4:1); $[\alpha]_D$ -15.2 (*c* 0.003, MeCN, 20 °C); IR 3294, 2957, 2932, 2862, 1642 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.23-6.13 (2H, m, 2 x N*H*), 3.89-3.78 (2H, m, 2 x C*H*N), 3.69-3.64 (4H, m, 2 x CH_2OSi), 2.13-2.05 (2H, m, 2 x C*H*CH_3), 1.81 (2H, t, *J* = 6.4 Hz, CHCH_2CH), 1.69-1.56 (2H, m, 2 x one of C$H_2$$CH_3$), 1.46-1.35 (2H, m, 2 x one of C$H_2$$CH_3$), 1.12-1.10 (6H, series of doublets (3) due to rotamers, 1:1:2, *J* = 6.8 Hz, 2 x CH_3CH), 0.91-0.87 [24H, m, 2 x C(CH_3)$_3$, 2 x C$H_3$$CH_2$], 0.05-0.04 [12H, series of singlets (3) due to rotamers, 2:1:1, 2 x Si(CH_3)$_2$]; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 176.61, 176.57, 176.52 (*C*, 2 x *C*=O, 3 x signals due to rotamers, 1:1:2), 64.96, 64.91, 64.82 (*C*H_2, 2 x *C*H_2O, 3 x signals due to rotamers, 2:1:1), 48.40, 48.38, 48.24 (*C*H, 2 x *C*HN, 3 x signals due to rotamers, 1:1:2), 43.4 (*C*H, 2 x *C*HCH_3), 33.68, 33.54 (*C*H_2, CH*C*H_2CH, 2 x signals due to rotamers, 1:1), 27.5 (*C*H_2, 2 x *C*$H_2$$CH_3$), 25.9 [*C*$H_3$, 2 x C(*C*$H_3$)$_3$], 18.28 [*C*, 2 x *C*(C$H_3$)$_3$], 17.64, 17.55 (*C*$H_3$, 2 x *C*$H_3$CH, 2 x signals due to rotamers, 1:1), 12.0

(CH_3, 2 x CH_3CH_2), -5.33, -5.41 [CH_3, 2 x Si(CH_3)$_2$, 2 x signals due to rotamers, 1:1]; ESI-HRMS calcd for $C_{27}H_{58}N_2O_4Si_2$ 529.3857 [M-H$^+$], found *m/z* 529.3880.

(4*S*,4'*S*)-4,4'-methylenebis{2-[(1*S*)-1-methylpropyl]-4,5-dihydro-1,3-oxazole} (27)[5,9]

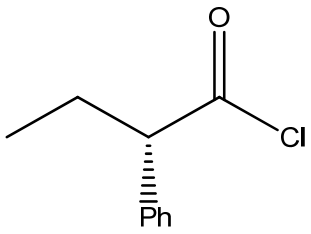


(27)

To a solution of **(25)** (190 mg, 0.36 mmol) and *p*-toluenesulfonyl fluoride (138 mg, 0.79 mmol) in dry acetonitrile (10 ml) was added DBU (118 µL, 0.79 mmol). The mixture was stirred at reflux overnight, cooled and concentrated *in vacuo.* Purification by column chromatography (gradient elution, Petrol:EtOAc, 9:1 to 3:7) yielded **(27)** (52.6 mg, 55%) as a colourless oil.

R_f=0.06 (Petrol:EtOAc, 4:1); $[\alpha]_D$ +17.58 (*c* 0.003, MeCN, 20 °C); IR 2971, 2946, 1669, 1470, 979 cm^{-1} ; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 4.36 (2H, t, *J* = 8.9 Hz, 2 x one of CH_2O), 4.25-4.14 (2H, m, 2 x C*H*N), 3.85 (2H, t, *J* = 8.1 Hz, 2 x one of CH_2O), 2.42-2.33 (2H, m, 2 x C*H*CH_3), 1.76-1.71 (2H, m, CHCH_2CH), 1.68-1.58 (2H, m, 2 x one of C$H_2$$CH_3$), 1.52-1.41 (2H, m, 2 x one of C$H_2$$CH_3$), 1.14 (6H, m, C$H_3$CH), 0.90 (6H, t, *J* = 7.3 Hz, 2 x C$H_3$$CH_2$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 171.2 (*C*, 2 x *C*=N), 73.1 (*C*H_2, 2 x *C*H_2O), 64.8 (*C*H, 2 x *C*HN), 47.3 (*C*H_2, CH*C*H_2CH), 35.1 (*C*H, 2 x *C*HCH_3), 27.2 (*C*H_2, 2 x *C*$H_2$$CH_3$), 17.4 (*C*$H_3$, 2 x *C*$H_3$CH), 11.7 (*C*$H_3$, 2 x *C*$H_3$$CH_2$); ESI-HRMS calcd for $C_{15}H_{26}N_2O_2$ 267.2072 [M+H$^+$], found *m/z* 267.2078.

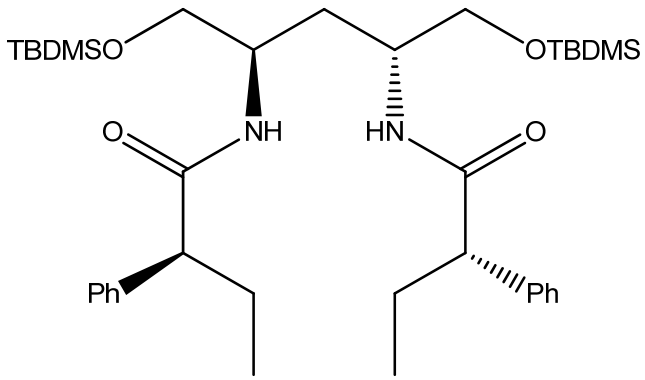
(*S*)-(+)-2-Phenylbutyric acid chloride (20)[10]



(20)

Thionyl chloride (0.83 g, 7.0 mmol) was added to a flask containing (*S*)-(+)-2-Phenylbutyric acid (0.77 g, 4.67 mmol). The solution was heated to reflux for 3 h and then concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 and concentrated *in vacuo* once more, yielding **(20)** (853 mg, 100%) as a yellow oil, which was used without purification.

(2*S*)-*N*-(1*R*,3*R*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3-{[(2*S*)-2-phenylbutanoyl]amino}butyl-2-phenyl butanamide (22)[8,9]

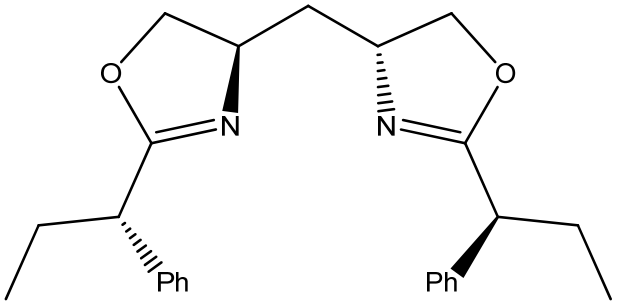


(22)

To a stirring solution of **(8)** (678 mg, 1.87 mmol) and triethylamine (0.57 mL, 4.11 mmol) in CH_2Cl_2 (20 mL) at 0 °C, was added **(20)** (751 mg, 4.11 mmol). This solution was left to stir for 14 h, warming to room temperature. The solution was then concentrated *in vacuo*. Purification by column chromatography (gradient elution, Petrol:EtOAc, 9:1 to 4:1) yielded **(22)** (910 mg, 74%) as a colourless oil.

R_f=0.60 (Petrol:EtOAc, 4:1); $[\alpha]_D$ +18.3 (*c* 0.0035, MeCN, 20 °C); IR 3312, 2957, 2929, 2857, 1647, 1253, 1097, 832 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.31-7.21 (10H, m, 10 x Ar*H*), 6.21-6.08 (2H, series of doublets (3) due to rotamers, 4:1:1, *J* = 7.9 Hz, 2 x N*H*), 3.74-3.64 (2H, m, 2 x C*H*N), 3.54-3.49 (2H, series of doublets (3) due to rotamers, 4:1:1, *J* = 4.6 Hz, 2 x CH_2OSi), 3.26-3.12 (2H, m, 2 x C*H*Ar), 2.20-2.08 (2H, m, one of C$H_2$$CH_3$), 1.83-1.69 (2H, m, one of C$H_2$$CH_3$), 1.61 (2H, t, *J* = 6.2 Hz, CHCH_2CH), 0.85-0.75 [24H, m, 2 x C(CH_3)$_3$, 2 x C$H_3$$CH_2$], 0.05- -0.11 [12H, series of singlets (6) due to rotamers, 1:1:5:5:1:1, 2 x Si(CH_3)$_2$]; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 173.68, 173.64, 173.58 (*C*, 2 x *C*=O, 3 x signals due to rotamers, 1:3:1), 140.0 (*C*, 2 x Ar*C*), 128.8 (*C*H, 4 x Ar*C*H), 128.21, 128.15, 128.08 (*C*H, 4 x Ar*C*H, 3 x signals due to rotamers, 1:3:1), 127.1 (*C*H, 2 x Ar*C*H), 64.70, 64.52, 64.40 (*C*H_2, 2 x *C*H_2O, 3 x signals due to rotamers, 1:1:3), 55.40, 55.36, 55.23 (*C*H, 2 x *C*HAr, 3 x signals due to rotamers, 1:3:1), 48.61, 48.50, 48.46 (*C*H, 2 x *C*HN, 3 x signals due to rotamers, 3:1:1), 33.43, 33.36 (*C*H_2, CH*C*H_2CH, 2 x signals due to rotamers, 1:2), 26.55, 26.47 (*C*H_2, 2 x *C*$H_2$$CH_3$, 2 x signals due to rotamers, 1:3), 25.8 [*C*H_3, 2 x C(*C*H_3)$_3$], 18.2 [*C*, 2 x *C*(CH_3)$_3$], 12.5 (*C*H_3, 2 x *C*$H_3$$CH_2$), -5.43, -5.50, -5.60 [*C*H_3, 2 x Si(*C*H_3)$_2$, 3 x signals due to rotamers, 4:4:1]; ESI-HRMS calcd for $C_{37}H_{62}N_2O_4Si_2$ 653.4170 [M-H^+], found *m/z* 653.4175.

(4*R*,4'*R*)-4,4'-methylenebis{2-[(1*S*)-1-phenylpropyl]-4,5-dihydro-1,3-oxazole} (24)[5,9]

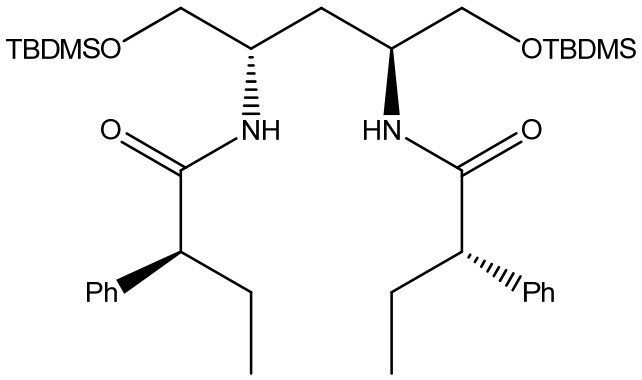


(24)

To a solution of **(22)** (800 mg, 1.22 mmol) and *p*-toluenesulfonyl fluoride (469 mg, 2.68 mmol) in dry acetonitrile (30 mL) was added DBU (400 µL, 2.68 mmol). The mixture was heated to reflux and stirred overnight. It was then allowed to cool to room temperature and concentrated *in vacuo*. Purification by column chromatography (gradient elution, Petrol:EtOAc, 9:1 to 1:4) yielded **(24)** (315 mg, 66%) as a yellow oil.

R_f=0.50 (Petrol:EtOAc, 1:4); $[\alpha]_D$ +57.4 (*c* 0.0042, MeCN, 20 °C); IR 2964, 2932, 1657, 977, 696 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.31-7.20 (10H, m, 10 x Ar*H*), 4.40-4.35 (2H, m, 2 x one of CH_2O), 4.28-4.17 (2H, m, 2 x C*H*N), 3.88-3.81 (2H, m, 2 x one of CH_2O), 3.47-3.40 (2H, m, 2 x C*H*Ar), 2.12-2.00 (2H, m, 2 x one of CH_3CH_2), 1.88-1.67 (4H, m, 2 x one of CH_3CH_2, $CHCH_2CH$), 0.88 (6H, t, *J* = 7.5 Hz, 2 x CH_3CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 168.7 (*C*, 2 x *C*=N), 140.1 (*C*, 2 x Ar*C*), 128.5 (*C*H, 4 x Ar*C*H), 127.8 (*C*H, 4 x Ar*C*H), 127.0 (*C*H, 2 x Ar*C*H), 73.3 (CH_2, 2 x CH_2O), 64.6 (*C*H, 2 x *C*HN), 47.2 (*C*H, 2 x *C*HAr), 43.4 (CH_2, $CHCH_2CH$), 27.0 (CH_2, 2 x CH_2CH_3), 12.2 (CH_3, 2 x CH_3CH_2); ESI-HRMS calcd for $C_{25}H_{30}N_2O_2$ 389.2229 [M-H$^+$], found *m/z* 389.2238.

(2*S*)-*N*-(1*S*,3*S*)-4-{[*tert*-butyl(dimethyl)silyl]oxy}-1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-3-{[(2*S*)-2-phenylbutanoyl]amino}butyl-2-phenyl butanamide (26)[8,9]

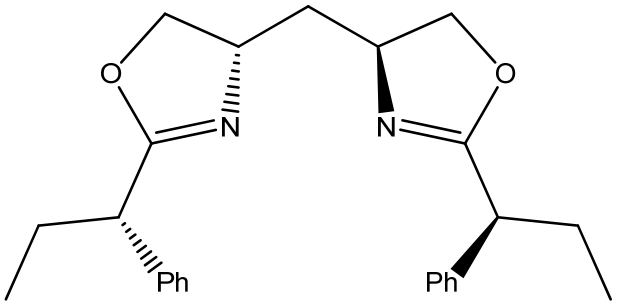


(26)

To a stirring solution of **(8a)** (1.6 g, 2.76 mmol) and triethylamine (1.45 ml, 6.1 mmol) in CH_2Cl_2 (20 mL) at 0 °C, was added **(20)** (1.12 g, 4.11 mmol). This solution was left to stir for 14 h, warming to room temperature. The solution was then concentrated *in vacuo*. Purification by column chromatography (gradient elution, Petrol:EtOAc, 9:1 to 4:1) yielded **(26)** (1.08 g, 60%) as a colourless oil.

R_f=0.64 (Petrol:EtOAc, 4:1); $[\alpha]_D$ -13.6 (*c* 0.004, MeCN, 20 °C); IR 3314, 2957, 2930, 2857, 1649 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.30-7.25 (10H, m, 10 x Ar*H*), 6.17-6.03 (2H, series of doublets (3) due to rotamers, 1:1:8, *J* = 8.2 Hz, 2 x N*H*), 3.74-3.64 (2H, m, 2 x C*H*N), 3.53-3.44 (4H, m, 2 x CH_2OSi), 3.23-3.12 (2H, m, 2 x C*H*Ar), 2.21-2.09 (2H, m, 2 x one of CH_2CH$_3$), 1.84-1.73 (2H, m, 2 x one of CH_2CH$_3$), 1.64 (2H, t, *J* = 6.4 Hz, CHCH_2CH), 0.87 (6H, t, *J* = 7.4 Hz, 2 x CH_3CH$_2$), 0.78-0.77 [18H, series of singlets (3) due to rotamers, 1:8:1, 2 x C(CH_3)$_3$,], -0.01- -0.12 [12H, series of singlets (7) due to rotamers, 8:1:1:1:8:1:8:1, 2 x Si(CH_3)$_2$]; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 173.6 (*C*, 2 x *C*=O), 140.2 (*C*, 2 x Ar*C*), 128.8 (*C*H, 4 x Ar*C*H), 128.1 (*C*H, 4 x Ar*C*H), 127.2 (*C*H, 2 x Ar*C*H), 64.7 (*C*H$_2$, 2 x *C*H$_2$O), 55.3 (*C*H, 2 x *C*HAr), 48.5 (*C*H, 2 x *C*HN), 33.4 (*C*H$_2$, CHCH_2CH), 26.2 (*C*H$_2$, 2 x *C*H$_2$CH$_3$), 25.9 [*C*H$_3$, 2 x C(*C*H$_3$)$_3$], 18.2 [*C*, 2 x *C*(CH$_3$)$_3$], 12.4 (*C*H$_3$, 2 x *C*H$_3$CH$_2$), -5.49, -5.59 [*C*H$_3$, 2 x Si(*C*H$_3$)$_2$, 2 x signals due to rotamers, 1:1]; ESI-HRMS calcd for $C_{37}H_{62}N_2O_4Si_2$ 653.4170 [M-H$^+$], found *m/z* 653.4168.

(4*S*,4'*S*)-4,4'-methylenebis{2-[(1*S*)-1-phenylpropyl]-4,5-dihydro-1,3-oxazole} (28)[5,9]

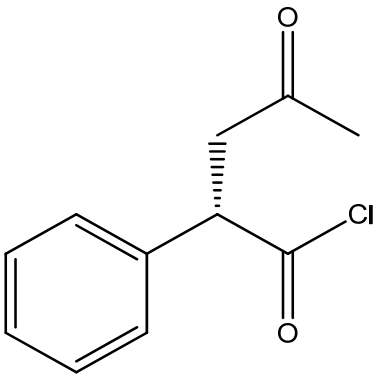


(28)

To a solution of **(26)** (1.00 g, 2.2 mmol) and *p*-toluenesulfonyl fluoride (843 mg, 4.84 mmol) in dry acetonitrile (30 mL) was added DBU (724 µL, 4.84 mmol). The mixture was stirred at reflux overnight, cooled and concentrated *in vacuo*. Purification by column chromatography (gradient elution, Petrol:EtOAc, 9:1 to 1:4) yielded **(28)** (316.8 mg, 37%) as a colourless oil.

R_f=0.56 (Petrol:EtOAc, 3:7); $[\alpha]_D$ -18.7 (*c* 0.003, MeCN, 20 °C); IR 2964, 2932, 1656 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.33-7.20 (10H, m, 10 x Ar*H*), 4.38-4.30 (2H, m, 2 x one of CH_2O), 4.27-4.19 (2H, m, 2 x C*H*N), 3.88-3.82 (2H, m, 2 x one of CH_2O), 3.46-3.40 (2H, m, 2 x C*H*Ar), 2.10-2.01 (2H, m, 2 x one of CH_3CH_2), 1.87-1.67 (4H, m, 2 x one of CH_3CH_2, $CHCH_2CH$), 0.89 (6H, t, *J*=7.3 Hz, 2 x CH_3CH_2); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 168.8 (*C*, 2 x *C*=N), 140.2 (*C*, 2 x Ar*C*), 128.6 (*C*H, 4 x Ar*C*H), 128.0 (*C*H, 4 x Ar*C*H), 127.1 (*C*H, 2 x Ar*C*H), 73.41, 73.32, 73.25 (CH_2, 2 x CH_2O), 64.76, 64.72 (*C*H, 2 x *C*HN), 47.3 (*C*H, 2 x *C*HAr), 43.52, 43.38 (CH_2, $CHCH_2CH$), 27.16, 27.05 (CH_2, 2 x CH_2CH_3), 12.3 (CH_3, 2 x CH_3CH_2); ESI-HRMS calcd for $C_{25}H_{30}N_2O_2$ 389.2229 [M-H^+], found *m/z* 389.2240.

(*S*)-(+)-*O*-Acetylmandelic acid chloride (59)[8]

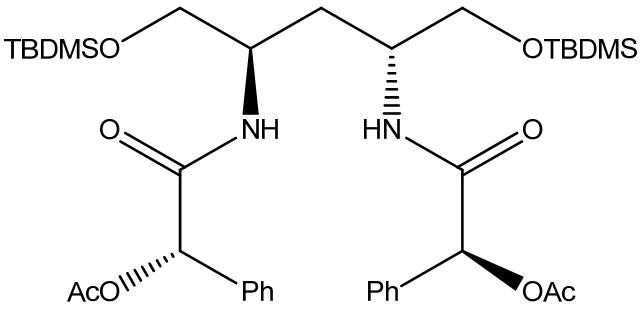


(59)

(*S*)-(+)-Mandelic acid **(55)** (1.521g, 10.0 mmol) was dissolved in acetyl chloride (11.7 mL, 103.5 mmol). The solution was stirred at room temperature for 2 h. The excess acetyl chloride was removed under high vacuum. Thionyl chloride (6.7 mL, 92.6 mmol) was added to the residue. The resulting solution was heated to reflux and left to stir for 3 h. The reaction mixture was cooled to room temperature and the excess thionyl chloride was removed under high vacuum. The crude product was purified by Kugelrohr distillation to yield pure (*S*)-(+)-*O*-acetylmandelic acid chloride **(59)** (1.34 g, 63%) as a pink oil.

IR 1786, 1747, 1216, 972 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.52-7.43 (5H, m, 5 x Ar*H*), 6.08 (1H, s, C*H*), 2.21 (3H, s, CH_3).

(1*S*)-2-{[(1*R*,3*R*)-3-{[(2*S*)-2-(acetyloxy)-2-phenylacetyl]amino}-4-{[*tert*-butyl(dimethyl)silyl]oxy}-1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)butyl]amino}-2-oxo-1-phenylethyl acetate (56)[8]



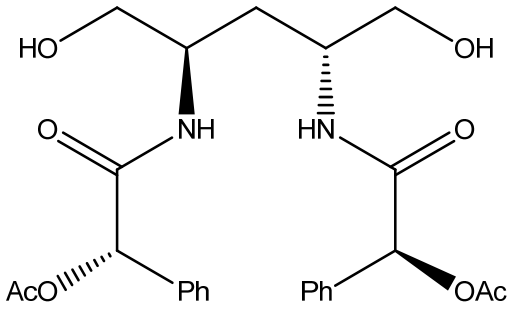
(56)

To a stirring solution of **(8)** (1.24 g, 3.42 mmol) and triethylamine (0.95 mL, 6.91 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added (*S*)-*O*-acetylmandelic acid chloride (1.48 g, 6.90 mmol). The mixture was stirred at room temperature overnight, concentrated *in vacuo* and the resultant brown oil purified by column chromatography (gradient elution, Petrol:EtOAc, 9:1 to 1:1) to yield **(56)** (1.20 g, 49%) as a yellow oil.

R_f=0.19 (Petrol:EtOAc; 4:1); $[\alpha]_D$ +31.3 (*c* 0.0083, MeCN, 20 °C); IR 3320, 2953, 2930, 2857, 1744, 1670, 1218, 833 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.44-7.32 (10H, m, 10 x Ar*H*), 6.99-6.85 (2H, m, 2 x N*H*), 6.01 (2H, s, 2 x C*H*OAc), 3.72-3.64 (6H, m, 2 x C*H*N, 2 x CH_2OSi), 2.15-2.12 (6H, series of singlets (3) due to rotamers, 2:1:1, 2 x CH_3CO), 1.84 (2H, t, *J*=6.3 Hz, CHCH_2CH), 0.88-0.86 [18H, series of singlets (3) due to rotamers, 1:2:1, 2 x C(CH_3)$_3$], 0.03--0.02 [12H, series of singlets (6) due to rotamers, 1:2:2:2:1:1, 2 x Si(CH_3)$_2$]; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 169.3, 169.2 (*C*, 2 x O*C*=O, 2 x signals due to rotamers, 3:1), 168.6, 168.5 (*C*, 2 x N*C*=O, 2 x signals due to rotamers, 3:1), 135.9, 135.7 (*C*, 2 x Ar*C*, 2 x signals due to rotamers, 3:1), 129.1, 129.0 (*C*H, 2 x Ar*C*H, 2 x signals due to rotamers, 1:2), 128.8 (*C*H, 4 x Ar*C*H), 127.6, 127.5 (*C*H, 4 x Ar*C*H, 2 x signals due to rotamers, 3:1), 75.8, 75.7, 75.6 (*C*H, 2 x *C*HOAc, 3 x signals due to rotamers, 1:2:1), 64.3 64.3, 64.1 (*C*H_2, 2 x *C*H_2O, 3 x signals due to rotamers, 1:2:1), 49.6, 49.1, 48.9 (*C*H, 2 x *C*HN, 3 x signals due to rotamers, 1:2:1), 33.3, 33.0 (*C*H_2, CH*C*H_2CH, 2 x signals due to rotamers, 1:1), 25.9 [*C*H_3, 2 x C(*C*H_3)$_3$], 21.2, 21.1, 21.0 (*C*H_3, 2 x *C*H_3CO, 3 x

signals due to rotamers, 1:3:3), 18.2 [*C*, 2 x *C*$(CH_3)_3$], -5.3, -5.4, -5.5, -5.6 [*C*H_3, 2 x Si(*C*$H_3)_2$, 4 x signals due to rotamers, 3:1:3:1]; ESI-HRMS calcd for $C_{37}H_{58}N_2O_8Si_2$ 713.3653 [M-H^+], found *m/z* 713.3687.

(1*S*)-2-{(1*R*,3*R*)-3-{[(2*S*)-2-(acetyloxy)-2-phenylacetyl]amino}-4-hydroxy-1-(hydroxymethyl)butyl] amino}-2-oxo-1phenylethylacetate (62)[11]

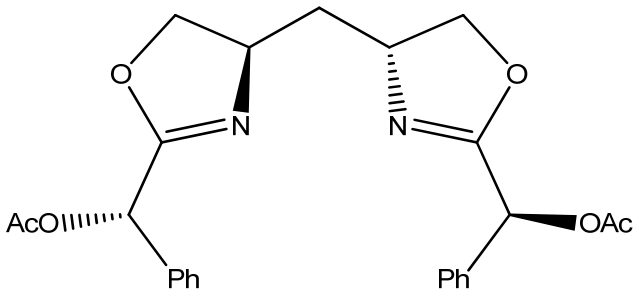


(62)

To a solution of **(56)** (1.34 g, 1.87 mmol) in 30 mL THF was added a solution of TBAF (8 mL, 8 mmol, 1.0 M in THF). The solution was stirred at room temperature for 16 h, concentrated *in vacuo* and the residue purified by column chromatography (gradient elution, Petrol:EtOAc, 9:1 to 1:4) to yield **(62)** (0.37 g, 41%) as a white solid.

R_f=0.63 (Petrol:EtOAc; 1:4); Mp 67-68 °C; $[\alpha]_D$ +16.7 (*c* 0.003, MeOH, 20 °C); IR 3621, 3279, 2944, 1714, 1647, 1537, 1247, 1226, 1038 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.46-7.29 (10H, m, ArC*H*), 5.12 (2H, s, 2 x C*H*OAc), 4.45-4.36 (2H, m, 2 x C*H*N), 4.04 (2H, dd, *J*=11.2, 4.3 Hz, 2 x one of CH_2OH), 3.92 (2H, dd, *J*=11.3, 7.2 Hz, 2 x one of CH_2OH), 1.86 (6H, s, 2 x COCH_3), 1.79 (2H, dd, *J*=9.0, 7.3 Hz, CHCH_2CH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 174.4 (*C*, 2 x *C*OCH_3), 170.9 (*C*, 2 x N*C*=O), 138.5 (*C*, 2 x Ar*C*), 128.6 (*C*H, 4 x Ar*C*H), 128.4 (*C*H, 2 x Ar*C*H), 126.4 (*C*H, 4 x Ar*C*H), 74.7 (*C*H, 2 x *C*HOAc), 65.9 (*C*H_2, 2 x *C*H_2OH), 44.3 (*C*H, 2 x *C*HN), 31.1 (*C*H_2, CH*C*H_2CH), 20.6 (*C*H_3, 2 x *C*H_3CO); ESI-HRMS calcd for $C_{25}H_{30}N_2O_8$ 485.1924 [M-H^+], found *m/z* 485.1941.

(*S*)-[(4*R*)-4-({(4*R'*)-2-[(*S*)-acetyloxy(phenyl)methyl]-4,5-dihydro-1,3-oxazol-4-yl}methyl)-4,5-dihydro-1,3-oxazol-4-yl}methyl)-4,5-dihydro-1,3-oxazol-2-yl](phenyl)methyl acetate (63)[8]



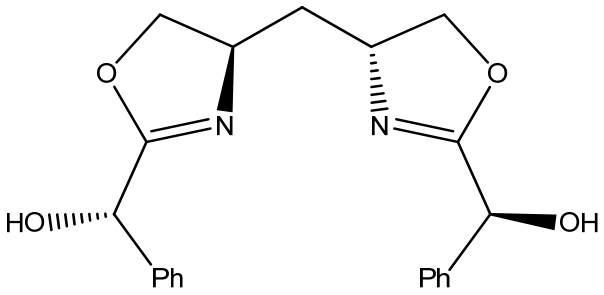
(63)

A solution of **(62)** (612 mg, 1.26 mmol) in CH_2Cl_2 (15 mL) was cooled to -78 °C. Diethylaminosulphur triflouride (DAST) (0.35 mL, 2.52 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 1 h. K_2CO_3 (0.58 g, 3.61 mmol) was added in one portion and the reaction mixture was allowed to warm to room temperature. A solution of sat. aq $NaHCO_3$ (15 mL) was used to added to the reaction and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 15 mL) and the combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (gradient elution, Petrol:EtOAc, 9:1 to 1:1) yielded the product **(63)** (208 mg, 37%) as a white solid.

R_f=0.44 (Petrol:EtOAc, 1:1); Mp 141-144 °C; $[\alpha]_D$ +14.4 (*c* 0.0035, MeCN, 20 °C); IR 2926, 1732, 1656, 1547, 1223, 694 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.47-7.31 (10H, m, 10 x Ar*H*), 6.93-6.71 (2H, m, 2 x N*H*), 5.85-5.61 (2H, series of singlets (8) due to rotamers, 1:1:2:1:1:1:2:1, 2 x C*H*OAc), 4.27-4.07 (6H, m, 2 x C*H*N, 2 x CH_2O), 2.07-1.96 (6H, series of singlets (4) due to rotamers, 1:2:1:1, 2 x CH_3CO), 1.90-1.79 (2H, m, CHCH_2CH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 171.0 (*C*, 2 x O*C*=O), 169.15, 169.08, 168.93, 168.86 (*C*, 2 x *C*=N, 4 x signals due to rotamers, 1:1:1:1), 134.58, 13.349 (*C*, 2 x Ar*C*, 2 x signals due to rotamers, 1:1), 129.66, 129.60 (*C*H, 2 x Ar*C*H, 2 x signals due to rotamers, 1:1), 128.88, 128.84, 128.80 (*C*H, 4 x Ar*C*H, 3 x signals due to rotamers, 1:3:2), 126.97, 126.91 (*C*H, 4 x Ar*C*H, 2 x signals due to rotamers, 1:1), 92.82, 90.95 (*C*H, 2 x *C*HOAc, 2 x signals

due to rotamers, 1:1), 65.76, 65.54, 65.34, 65.24 (*C*H_2, 2 x *C*H_2O, 4 x signals due to rotamers, 1:1:2:1), 46.56, 46.48, 46.19, 45.32 (*C*H, 2 x *C*HN, 4 x signals due to rotamers, 2:1:1:1), 32.80, 32.72 (*C*H_2, CH*C*H_2CH, 2 x signals due to rotamers, 1:1), 20.86, 20.75 (*C*H_3, 2 x *C*H_3CO, 2 x signals due to rotamers, 2:1); ESI-HRMS calcd for $C_{25}H_{26}N_2O_6$ [M+H^+], 451.1869 found *m/z* 451.1877.

(*S*)-[(4*R*)-4-({(4*R'*)-2-[(*S*)-hydroxy(phenyl)methyl]-4,5-dihydro-1,3-oxazol-4-yl}methyl)-4,5-dihydro-1,3-oxazol-4-yl}methyl)-4,5-dihydro-1,3-oxazol-2-yl](phenyl)methanol (57)[8]



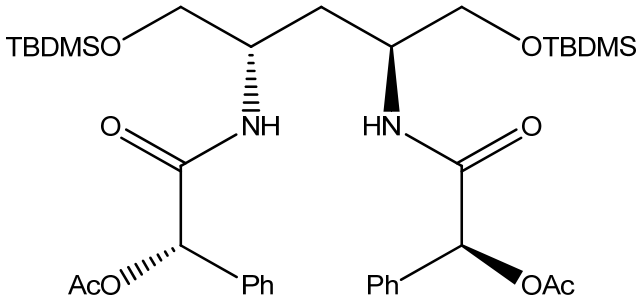
(57)

A solution of **(63)** (117 mg, 0.26 mmol) in MeOH was cooled to 0 °C. An aqueous LiOH solution (1.60 mL, 1.6 mmol, 1.0 M) was added dropwise. The mixture was stirred at 0 °C for 3 h and allowed to warm to room temperature. The mixture was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organic phases were washed with saturated aqueous NaCl solution (2 x 10 mL). The organics were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to yield **(57)** (64 mg, 67%) as a white solid.

$[\alpha]_D$ +19.5 (*c* 0.0025, MeCN, 20 °C); IR 3281, 2924, 1658, 1548, 1044, 696 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.51-7.30 (10H, m, 10 x Ar*H*), 5.79-5.61 (2H, series of singlets (8) due to rotamers, 1:1:2:1:1:1:2:1, 2 x C*H*OH), 4.36-3.96 (2H, br s, 2 x CHO*H*), 3.81-3.58 (6H, m, 2 x C*H*N, 2 x C*H*$_2$O), 1.83-1.78 (2H, m, CHC*H*$_2$CH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 169.84, 169.62 (*C*, 2 x *C*=N, 2 x signals due to rotamers, 3:2), 134.6 (*C*, 2 x Ar*C*), 129.7 (*C*H, 2 x Ar*C*H), 128.9 (*C*H, 4 x Ar*C*H), 126.91, 126.84 (*C*H, 4 x Ar*C*H, 2 x signals due to rotamers, 1:1), 92.68, 90.78 (*C*H, 2 x *C*HOH, 2 x signals due to rotamers, 1:1), 63.5 (*C*H_2, 2 x *C*H_2O),

49.31, 49.18 (*C*H, 2 x *C*HN, 2 x signals due to rotamers, 2:1), 32.2 (CH_2, CH*C*H_2CH); ESI-HRMS calcd for $C_{21}H_{22}N_2O_4$ 365.1501[M-H^+], found *m/z* 365.1510.

(1*S*)-2-{[(1*S*,3*S*)-3-{[(2*S*)-2-(acetyloxy)-2-phenylacetyl]amino}-4-{[*tert*-butyl(dimethyl)silyl]oxy}-1-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)butyl]amino}-2-oxo-1-phenylethyl acetate (64)[8]



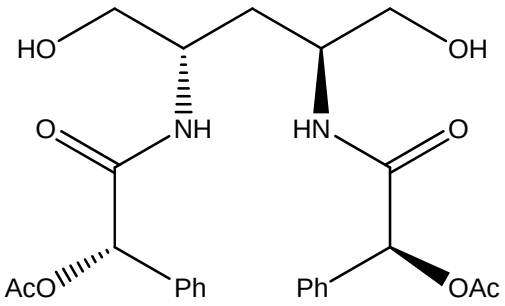
(64)

To a stirring solution of **(8a)** (1.01 g, 2.78 mmol) and triethylamine (0.78 mL, 5.62 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added (*S*)-*O*-acetylmandelic acid chloride (1.22 g, 5.60 mmol). The mixture was stirred at room temperature overnight, concentrated *in vacuo* and the resultant brown oil purified by column chromatography (gradient elution, Petrol:EtOAc, 9:1 to 4:1) to yield **(64)** (1.51 g, 58%) as a yellow oil.

R_f=0.69 (Petrol:EtOAc, 4:1); $[\alpha]_D$ -2.1 (*c* 0.0053, MeCN, 20 °C); IR 3383, 2954, 2929, 2856, 1741, 1671, 1229, 834 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.50-7.33 (10H, m, 10 x Ar*H*), 7.06-6.86 (2H, series of doublets (3) due to rotamers, 3:1:1, *J* = 8.5 Hz, 2 x N*H*), 6.01-5.88 (2H, series of singlets (3) due to rotamers, 1:1:3, 2 x C*H*OAc), 4.00-3.91 (2H, m, 2 x C*H*N), 3.74-3.63 (2H, m, 2 x one of CH_2O), 3.52 (2H, d, *J* = 5.5 Hz, 2 x one of CH_2O), 2.23-2.12 (6H, series of singlets (3) due to rotamers, 3:1:1, 2 x COCH_3), 1.93 (2H, t, *J* = 5.9 Hz, CHCH_2CH), 0.89-0.81 [18H, series of singlets (3) due to rotamers, 1:1:3, 2 x C(CH_3)$_3$], 0.06- -0.08 [12H, series of singlets (6) due to rotamers, 1:1:1:1:3:3, Si(CH_3)$_2$]; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 171.5, 171.3 (*C*, 2 x O*C*=O, 2 x signals due to rotamers, 2:1), 168.6, 168.1 (*C*, 2 x N*C*=O, 2 x signals due to rotamers, 1:2), 134.9 (*C*, 2 x Ar*C*), 129.0 (*C*H, 2 x Ar*C*H),

128.8, 128.7 (*C*H, 4 x Ar*C*H, 2 x signals due to rotamers, 1:2), 127.6, 127.5 (*C*H, 4 x Ar*C*H, 2 x signals due to rotamers, 1:3), 76.6 (*C*H, 2 x *C*HCO), 64.2, 64.1 (CH_2, 2 x CH_2O, 2 x signals due to rotamers, 3:1), 48.5 (*C*H, 2 x *C*HN), 31.1 (CH_2, $CHCH_2CH$), 25.9, 25.8 [CH_3, 2 x $C(CH_3)_3$, 2 x signals due to rotamers, 1:1], 21.2, 21.1 (CH_3, 2 x $COCH_3$, 2 x signals due to rotamers, 3:1), 18.1 [*C*, 2 x $C(CH_3)_3$], -5.3, -5.4, -5.5, -5.6 [CH_3, 2 x $Si(CH_3)_2$, 4 x signals due to rotamers, 1:1:2:2]; ESI-HRMS calcd for $C_{37}H_{58}N_2O_8Si_2$ 713.3653 [M-H^+], found *m/z* 713.3681.

(1*S*)-2-{(1*S*,3*S*)-3-{[(2*S*)-2-(acetyloxy)-2-phenylacetyl]amino}-4-hydroxy-1-(hydroxymethyl)butyl] amino}-2-oxo-1phenylethylacetate (65)[11]

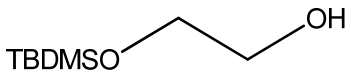


(65)

To a solution of **(64)** (0.55 g, 0.75 mmol) in THF (5 mL) was added a solution of TBAF (3.0 mL, 3.0 mmol, 1.0 M in THF). The solution was stirred at room temperature for 16 h, concentrated *in vacuo* ^{1}H NMR spectral analysis showed an unidentifiable mixture of compounds,

3.3 Attempted synthesis of 4,4'-PYBOX ligands

2-{[*tert*-butyl(dimethyl)silyl]oxy}ethanol (80)[12]

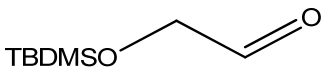


(80)

To a solution of sodium hydride (1.03 g, 60% dispersion in mineral oil, 25.4 mmol) suspended in THF (10 mL) was added ethylene glycol (1.65 mL, 30 mmol) at room temperature. The resulting suspension was left to stir for 45 min. *Tert*-butyldimethylsilyl chloride (3.00 g, 19.9 mmol) in THF (5 mL) was then added and the mixture stirred vigorously for 1 h. Water (5 mL) was carefully added to quench the reaction and then poured into diethyl ether (25 mL). The organics were washed with 10% K_2CO_3 (15 mL), brine (25 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield **(80)** as a clear oil (3.15 g, 90%).

IR 3370, 2931, 1474, 1061 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 3.70-3.66 (2H, m, C*H*$_2$OH), 3.64-3.58 (2H, m, C*H*$_2$OSi), 2.31 (1H, t, *J* = 6.0 Hz, O*H*), 0.88 [9H, s, C(C*H*$_3$)$_3$], 0.06 [6H, s, Si(C*H*$_3$)$_2$]; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 64.2 (*C*H$_2$, *C*H$_2$OH), 63.7 (*C*H$_2$, *C*H$_2$OSi), 26.0 [*C*H$_3$, C(*C*H$_3$)$_3$], 18.4 [*C*, *C*(CH$_3$)$_3$], -5.3 [*C*H$_3$, Si(*C*H$_3$)$_2$].

2-{[*tert*-butyl(dimethyl)silyl]oxy}acetaldehyde (78)[13]



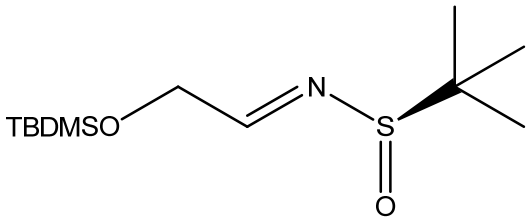
(78)

To a solution of DMSO (0.65 mL, 9.15 mmol) in CH_2Cl_2 (25 mL) was added dropwise, under N_2 at -78 °C, a solution of oxalyl chloride (0.45 mL, 5.24 mmol) in CH_2Cl_2 (2 mL) over 3 min. The reaction mixture was stirred for 10 min and a solution of **(80)** (0.815 g, 4.63 mmol) and pyridine (7.5 mL, 9.31 mmol) in CH_2Cl_2 (3 mL) was then added dropwise over 5 min at the same temperature. The stirring

was maintained for a 15 min. Triethylamine (0.72 mL, 5.16 mmol) was added over 5 min at -78 °C. After the addition, the mixture was warmed to 10 °C over 5 min and maintained at the temperature for an additional 20 min. The reaction was quenched by addition of 1N HCl solution until the solution reached a pH of 4. The organic phase was washed with distilled water (20 mL), saturated copper(II)sulphate solution (20 mL), distilled water (2 x 20 mL), and brine (20 mL). The organics were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (Petrol:CH_2Cl_2, 6:4) yielded the product **(78)** (0.59 g, 73%) as a clear oil.

IR 2823, 2715, 1737, 1262, 842 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 9.67 (1H, s, C*H*O), 4.19 (2H, s, CH_2), 0.90 [9H, s, C(CH_3)$_3$], 0.08 [6H, s, Si(CH_3)$_2$]; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.4 (*C*HO), 69.7 (*C*H_2OSi), 25.8 [C(*C*H_3)$_3$], 18.2 [*C*(CH$_3$)$_3$], -5.3 [Si(*C*H$_3$)$_2$].

(R_S)-*N*-((1*E*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}ethylidene)-2-methylpropane-2-sulfinamide (81)[14]



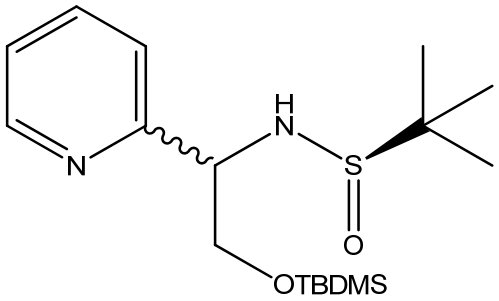
(81)

To a solution of (R_S)-2-methyl-2-propanesulfinamide **(82)** (103 mg, 0.85 mmol) and anhydrous $CuSO_4$ (272 mg, 1.7 mmol) in CH_2Cl_2 (10 mL) was added **(78)** (148 mg, 0.85 mmol). The solution was left to stir at room temperature for 2 h. It was then filtered through celite and washed through with CH_2Cl_2. The filtrate was concentrated *in vacuo*. Purification by column chromatography (gradient elution, Petrol:EtOAc, 95:5 to 1:1) yielded the product **(81)** (153 mg, 68%) as a yellow oil.

R_f = 0.42 (Petrol:EtOAc, 1:1); IR 2167, 1625, 1252, 832, 774 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ = 8.04 (1H, t, *J* = 2.9 Hz, C*H*N), 4.53 (2H, d, *J* = 2.9 Hz, CH_2O), 1.19 [9H, s, SC(CH_3)$_3$], 0.90 [9H, s, SiC(CH_3)$_3$], 0.08 [6H, s, Si(CH_3)$_2$]; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.8 (*C*H, *C*HN), 65.6 (*C*H_2, *C*H_2O), 56.9 [*C*,

S*C*$(CH_3)_3$], 26.0 [*C*H_3, SiC(*C*$H_3)_3$], 22.4 [*C*H_3, SC(*C*$H_3)_3$], 18.4 [*C*, Si*C*$(CH_3)_3$], -5.3 [*C*H_3, Si(*C*$H_3)_2$].

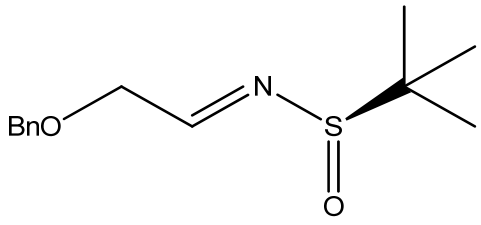
(R_S,1*R*)-*N*-((1*E*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}ethylidene)-2-methylpropane-2-sulfinamide, (R_S,1*S*)-*N*-((1*E*)-2-{[*tert*-butyl(dimethyl)silyl]oxy}ethylidene)-2-methylpropane-2-sulfinamide (87)[15]



(87)

To a solution of *n*-butyllithium (0.17 mL, 0.26 mmol, 1.6 M in hexane) in THF (5 mL) at -78 °C was added 2-bromopyridine (38 mg, 0.24 mmol) in THF (5 mL) dropwise. The solution was left to stir for 1 h. **(81)** (30 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) was added dropwise and the reaction mixture was left to stir for 5 h at -78 °C. The reaction was allowed to warm to room temperature, then quenched by the addition saturated NH_4Cl solution (5 mL) and extracted with EtOAc (3 x 5 mL). The organics were washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. ^{1}H NMR spectral analysis showed no reaction had occurred and starting materials were recovered.

(R_S)-*N*-[(1*E*)-2-(benzyloxy)ethylidene]-2-methylpropane-2-sulfinamide (86)[14]



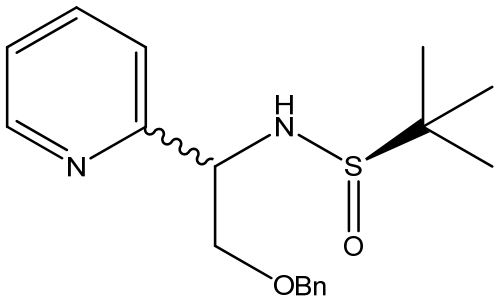
(86)

To a solution of (R_S)-2-methyl-2-propanesulfinamide **(82)** (242 mg, 2.0 mmol) and anhydrous $CuSO_4$ (640 mg, 4.0 mmol) in CH_2Cl_2 (10 mL) was added benzyloxyacetaldehyde **(85)** (300.4 mg, 2.0 mmol). The solution was left to stir at

room temperature for 2 h. It was then filtered through celite and washed through with CH_2Cl_2. The filtrate was concentrated *in vacuo*. Purification by column chromatography (gradient elution, Petrol:EtOAc, 95:5 to 3:1) yielded the product **(86)** (380 mg, 75%) as a yellow oil.

R_f = 0.55 (Petrol:EtOAc, 7:3); IR 2947, 1613, 1247, 1079, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ = 8.12 (1H, t, *J* = 3.2Hz, C*H*N), 7.35-7.25 (5H, m, 5 x Ar*H*), 4.63 (2H, s, PhCH_2), 4.40 (2H, dd, J = 3.2, 1.8 Hz, CH_2CHN), 1.21 [9H, s, C(CH_3)$_3$]; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.8 (*C*H, *C*HN), 137.3 (*C*, Ar*C*), 128.6 (*C*H, 2 x Ar*C*H), 128.1 (*C*H, Ar*C*H), 128.0 (*C*H, 2 x Ar*C*H), 73.4 (*C*H_2, *C*H_2Ph), 71.4 (*C*H_2, *C*H_2CHN), 57.0 [*C*, *C*(CH$_3$)$_3$], 22.5 [*C*H$_3$, C(*C*H$_3$)$_3$].

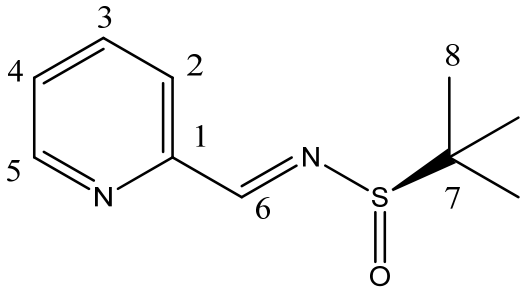
(*R*$_S$,1*R*)-*N*-[2-(benzyloxy)-1-pyridin-2-ylethyl]-2-methylpropane-2-sulfinamide, (*R*$_S$,1*S*)-*N*-[2-(benzyloxy)-1-pyridin-2-ylethyl]-2-methylpropane-2-sulfinamide (87)[15]



(87)

To a solution of *n*-butyllithium (0.9 mL, 1.44 mmol, 1.6 M in hexane) in THF (5 mL) at -78 °C was added 2-bromopyridine (210 mg, 1.33 mmol) in THF (5 mL) dropwise. The solution was left to stir for 1 h. **(86)** (154 mg, 0.61 mmol) in CH_2Cl_2 (2 mL) was added dropwise and the reaction mixture was left to stir for 5 h at -78 °C. The reaction was allowed to warm to room temperature, then quenched by the addition saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 x 10 mL). The organics were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. ^1H NMR spectral analysis showed a non-isolable mixture of products.

(*R*$_S$)-2-methyl-*N*-[(1*E*)-pyridin-2-ylmethylene]propane-2-sulfinamide (91)[16]

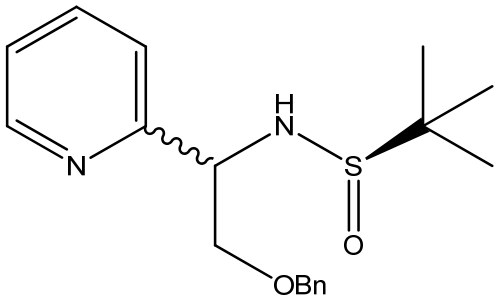


(91)

To a solution of (R_S)-2-methyl-2-propanesulfinamide **(82)** (121 mg, 1.0 mmol) and anhydrous $CuSO_4$ (360 mg, 2.0 mmol) in CH_2Cl_2 (5 mL) was added 2-pyridinecarboxaldehyde **(90)** (107 mg, 1.0 mmol). The solution was left to stir at room temperature for 2 h. It was then filtered through celite and washed through with CH_2Cl_2. The filtrate was concentrated *in vacuo*. Purification by column chromatography (gradient elution, Petrol:EtOAc, 98:2 to 7:3) yielded the product **(91)** (183 mg, 87%) as a yellow oil.

R_f = 0.26 (Petrol:EtOAc, 3:1); IR 2983, 1607, 1087 cm^{-1}; ^1H NMR ($CDCl_3$, 400MHz) δ = 8.75 [1H, dd, *J* = 4.8, 1.7 Hz, C(5)*H*], 8.73 [1H, s, C(6)*H*], 8.01 [1H, dt, *J* = 7.9, 1.1 Hz, C(3)*H*], 7.81 [1H, td, *J* = 7.7, 1.7 Hz, C(2)*H*], 7.40 [ddd, 1H, *J* = 7.5, 4.8, 1.2 Hz, C(4)*H*], 1.27 [9H, s, C(8)H_3]; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.8 (*C*-6), 152.6 (*C*-1), 150.3 (*C*-5), 136.9 (*C*-3), 126.0 (*C*-2 or *C*-4), 123.2 (*C*-2 or *C*-4), 58.2 (*C*-7), 22.8 (*C*-8).

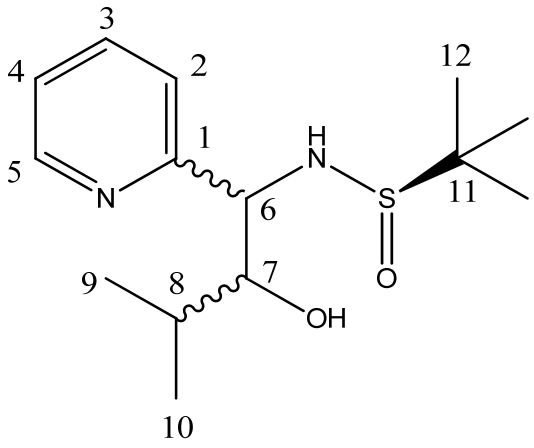
(R_S,1*R*)-*N*-[2-(benzyloxy)-1-pyridin-2-ylethyl]-2-methylpropane-2-sulfinamide, (R_S,1*S*)-*N*-[2-(benzyloxy)-1-pyridin-2-ylethyl]-2-methylpropane-2-sulfinamide (87)[15]



(87)

A mixture of magnesium turnings (19.2 mg, 0.48 mmol) and a spatula tip of freshly sublimed mercuric chloride in THF (3 mL) was cooled to -5 °C and benzyloxymethyl chloride (66 μL, 0.48 mmol) was added. The reaction mixture was left to stir for 2 h at -10 °C. The mixture was then cooled to -78 °C and of pyridyl *N*-*tert*-butylsulfinimine **(91)** (53.5 mg, 0.24 mmol) in THF (3 mL) was added dropwise. The reaction left to stir for 2 h at -78 °C and then allowed to warm to room temperature and left stirring for 16 h. The reaction quenched by the addition saturated NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organics were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. ^{1}H NMR spectral analysis showed a non-isolable mixture of products.

(R_S)-*N*-(2-hydroxy-3-methyl-1-pyridin-2-ylbutyl)-2-methylpropane-2-sulfinamide (92)[17]



(92)

Under nitrogen, SmI_2 (10 mL, 1.00 mmol, 0.1 M in THF) was cooled to -78 °C. A mixture of *tert*-butyl alcohol (76 mg, 1.00 mmol), *iso*-butyraldehyde (54 mg, 0.75 mmol), and **(91)** (105 mg, 0.50 mmol) in THF (6 mL) was added dropwise. The reaction was monitored by TLC and quenched with saturated $Na_2S_2O_3$ solution (5 mL) when the reaction reached completion. The layers were separated and the aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* yielding a mixture of diastereomers (3:2). Purification by column chromatography (gradient elution, Petrol:EtOAc, 98:2 to 4:1) yielded the product **(92)** (142 mg, 54%) as a brown oil.

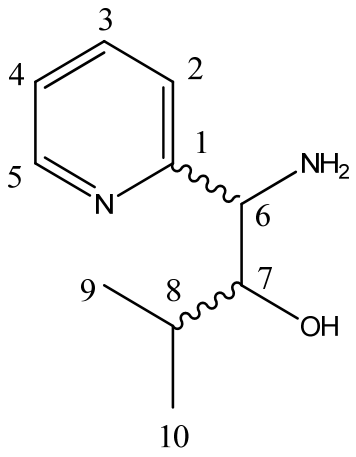
1st Isomer:

^{1}H NMR ($CDCl_3$, 400MHz) δ = 8.48 [1H, ddd, *J* = 4.9, 1.8, 0.9 Hz, C(5)*H*], 7.65-7.60 [1H, m, C(3)*H*], 7.22-7.14 [(2H, m, C(2)*H* and C(4)*H*], 4.48 [1H, d, *J* = 7.5 Hz, C(6)*H*], 4.42 [1H, dd, *J* = 7.4, 4.7 Hz, C(7)*H*], 1.68-1.59 [1H, m, C(8)*H*], 1.10 [9H, s, C(12)H_3], 0.94 [6H, d, *J* = 6.6 Hz, C(9)H_3 and C(10)H_3]; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.6 (*C*-1), 149.4 (*C*-5), 137.0 (*C*-3), 122.9 (*C*-2 or *C*-4), 122.8 (*C*-2 or *C*-4), 79.1 (*C*-7), 63.0 (*C*-6), 56.1 (*C*-11), 29.6 (*C*-8), 22.7 (*C*-12), 19.9 (*C*-9 or *C*-10), 16.9 (*C*-9 or *C*-10).

2nd Isomer:

^{1}H NMR ($CDCl_3$, 400MHz) δ = 8.45 [1H, dd, *J* = 4.8, 1.8 Hz, C(5)*H*], 7.65-7.60 [1H, m, C(3)*H*], 7.22-7.14 [2H, m, C(2)*H* and C(4)*H*], 4.65 [1H, d, *J* = 7.5 Hz, C(6)*H*], 4.52 [1H, dd, *J* = 7.7, 3.5 Hz, C(7)*H*], 1.29-1.20 [1H, m, C(8)*H*], 1.07 [9H, s, C(12)H_3], 0.83 [6H, d, *J* = 6.2 Hz, C(9)H_3 and C(10)H_3]; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.8 (*C*-1), 148.8 (*C*-5), 137.2 (*C*-3), 123.8 (*C*-2 or *C*-4), 122.9 (*C*-2 or *C*-4), 81.2 (*C*-7), 61.1 (*C*-6), 56.2 (*C*-11), 32.0 (*C*-8), 22.6 (*C*-12), 19.3 (*C*-9 or *C*-10), 19.2 (*C*-9 or *C*-10).

1-amino-3-methyl-1-pyridin-2-ylbutan-2-ol (89)[14]



(89)

To a solution of the sulfinyl amide **12** (16 mg, 0.055 mmol) in MeOH (2 mL) was added a 4N solution of HCl in 1,4-dioxane (55.5 μL). After 2 h at room temperature, the reaction mixture was concentrated in vacuo. It was then dissolved in EtOAc (5 mL) and placed under a NH_3 atmosphere and left to stir for 1 h. The solution was filtered and concentrated in vacuo to afford the product **(89)** (7.6 mg, 77%) as a yellow oil and as a mixture of diastereomeric (2:3).

1st Isomer:

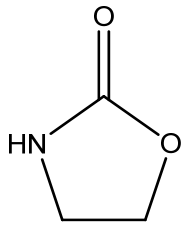
^{1}H NMR (D_2O, 400MHz) δ = 8.68 [1H, ddd, *J* = 5.9, 1.6, 0.6 Hz, C(5)*H*], 8.46 [1H, td, *J* = 8.0, 1.6 Hz, C(3)*H*], 7.99 [1H, d, *J* = 8.1, C(2)*H*], 7.98 [1H, m, C(4)*H*], 4.74 [1H, d, *J* = 5.6 Hz, C(6)*H*], 3.71 [1H, m, C(7)*H*], 1.51-1.42 [1H, m, C(8)*H*], 0.81 [3H, d, *J* = 6.8 Hz, C(9)H_3 or C(10)H_3], 0.78 [3H, d, *J* = 6.7 Hz, C(9)H_3 or C(10)H_3].

2nd Isomer:

^{1}H NMR (D_2O, 400MHz) δ = 8.72 [1H, ddd, *J* = 5.9, 1.6, 0.6 Hz, C(5)*H*], 8.52 [1H, td, *J* = 8.0, 1.6 Hz, C(3)*H*], 8.11 [1H, d, *J* = 8.0, C(2)*H*], 7.91 [1H, ddd, *J* = 7.9, 5.8, 1.2 Hz, C(4)*H*], 4.84 [1H, d, *J* = 3.9 Hz, C(6)*H*], 3.71 [1H, m, C(7)*H*], 1.25-1.15 [1H, m, C(8)*H*], 0.78 [3H, d, *J* = 6.7 Hz, C(9)H_3 or C(10)H_3], 0.74 [3H, d, *J* = 6.6 Hz, C(9)H_3 or C(10)H_3].

3.4 Synthesis of substrates

2-Oxazolidinone (37)[18]

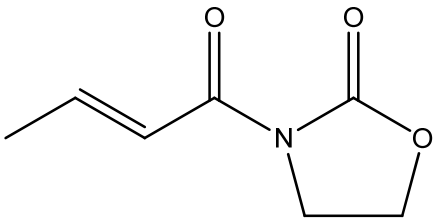


(37)

Ethanolamine **(36)** (10.0 mL, 0.17 mol) and potassium carbonate (2.30 g, 0.17 mol) were heated at 145 °C for 2 h in the presence of diethyl carbonate **(35)** (41.0 mL, 3.4 mol). Ethanol was distilled off. After cooling to room temperature, the soluble portion of the crude oil was dissolved in CH_2Cl_2 (3 x 30 mL) and the resulting suspension was filtered using a Buchner funnel to remove the potassium carbonate. The filtrate was dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield as a pale yellow solid. The crude product was recrystallized from ethyl acetate to yield **(37)** (5.16 g, 42%) as colourless crystals.

Mp 81-85 °C (lit.,[18] Mp 86 °C); IR 3257, 1770, 1251 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.08 (1H, br s, N*H*), 4.44 (2H, dd, *J* = 8.6, 7.3 Hz, CH_2O), 3.63 (2H, t, *J* = 8.0 Hz, CH_2N); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 160.8 (*C*=O), 65.1 (*C*H_2O), 40.8 (*C*H_2N).

***Trans*-(crotonyl)-2-oxazolidinone (32)[19]**

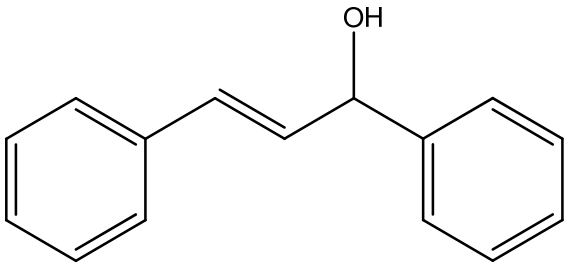


(32)

To a stirring solution of 2-oxazolidinone **(37)** (2.00 g, 23.0 mmol) in THF (80 mL) at -78 °C was added *n*-butyllithium (14.4 mL, 1.6 M in hexane, 23.0 mmol) *via* syringe. After 15 min *trans*-crotonyl chloride **(38)** (2.4 mL, 25.4 mmol) was added and stirring was continued at -78 °C for 2 h. The reaction was then allowed to warm to room temperature and stirring was continued overnight. The reaction was quenched with excess saturated aqueous NH_4Cl (20 mL) and the resulting white slurry was concentrated *in vacuo*. The residue was dissolved in ethyl acetate (100 mL) and the resulting organics were washed with saturated aqueous $NaHCO_3$ (60 mL) and brine (60 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield **(32)** as a yellow oil. The crude product was purified by column chromatography (Pet. Ether: Ethyl Acetate, 7:3) to yield (1.09 g, 31%) **(32)** as a colourless solid.

Mp 30-36 °C (lit.,[19] Mp 42-43 °C); IR 1770, 1682, 1637 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.26-7.13 (2H, m, 2 x C*H*=CH), 4.41 (2H, dd, *J* = 8.6, 7.6 Hz, CH_2O), 4.05 (2H, dd, *J* = 8.5, 7.5 Hz, CH_2N), 1.95 (3H, dd, *J* = 6.4, 1.2 Hz, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 165.3 (O*C*=O), 153.5 (CH*C*=ON), 147.0 (CH_3*C*H=CH), 121.5 (CH=*C*HC=O), 62.1 (*C*H_2O), 42.7 (*C*H_2N), 18.6 (*C*H_3).

(±)-(*E*)-1,3-diphenyl-3-hydroxyprop-1-ene (45)[20]

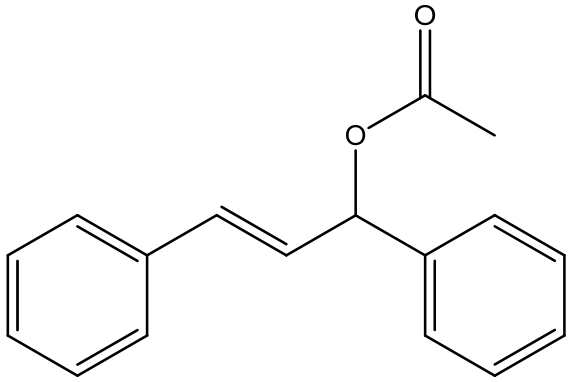


(45)

Cerium (III) trichloride heptahydrate (9.0 g, 24.0 mmol) was added to a solution of *trans*-chalcone **(44)** (5.0 g, 24.0 mmol) in methanol (60 mL). After cooling the solution to 0 °C, sodium borohydride (1.2 g, 31.2 mmol) was added. When effervescence had ceased the solution was allowed to warm to room temperature and left to stir overnight. The pH was then adjusted to 7 with 10% aq. hydrochloric acid. Water (30 mL) was added and the product was extracted with diethyl ether (3 x 30 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (gradient elution, Petrol:EtOAc, 9:1 to 1:1) yielded the product **(45)** (2.85 g, 57%) as a white solid.

Mp 53-56 °C (lit.,[21] Mp 55-57 °C); IR 3264, 3058, 1493, 1449 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.45-7.22 (10H, 10 x ArC*H*), 6.69 (1H, d, *J* = 16.0 Hz, C*H*CHCHOH), 6.39 (1H, dd, *J* = 15.8, 6.6Hz, CHC*H*CHOH), 5.39 (1H, d, *J* = 6.6 Hz, C*H*OH), 2.09 (1H, s, O*H*); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 142.9 (Ar*C*CHOH), 136.6 (Ar*C*CHCH), 131.6 (CH*C*HCHOH), 130.7 (C*H*CHCHOH), 128.8 (2 x Ar*C*H), 128.7 (2 x Ar*C*H), 127.9 (2 x Ar*C*H), 126.7 (2 x Ar*C*H), 126.5 (2 x Ar*C*H), 75.3 (*C*HOH).

(±)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene (42) [20]

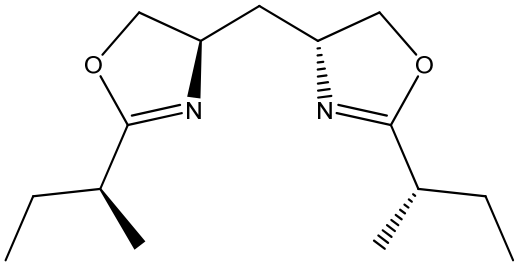


(42)

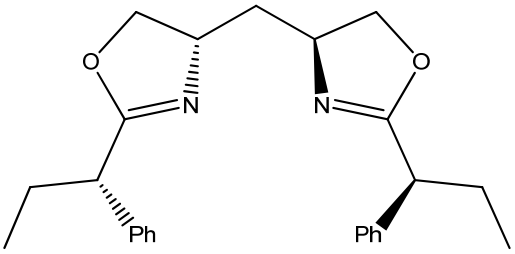
A crystal of 4-dimethylaminopyridine was added to a solution of **(45)** (2.6 g, 12.4 mmol) in pyridine (10 mL) at 0 °C. Acetic anhydride (3.5 mL, 37.8 mmol) was added dropwise and the mixture was allowed to warm to room temperature and left to stir overnight. Diethyl ether (150 mL) was added and the mixture was successively washed with aqueous copper sulphate solution (5 x 40 mL), saturated $NaHCO_3$ (3 x 40 mL) and water (2 x 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (gradient elution, Petrol:EtOAc, 96:4 to 90:10) yielded the product **(42)** (1.31 g, 44%) as a yellow oil.

IR 3063, 3030, 1735, 1226, 962 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.44-7.23 (10H, m, 10 x ArC*H*), 6.64 (1H, d, *J* = 15.6 Hz, C*H*CHCHO), 6.45 (1H, d, *J* = 6.9 Hz, CHCHC*H*OAc), 6.36 (1H, dd, *J* = 16.0, 6.9 Hz, CHC*H*CHO), 2.14 (3H, s, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 170.2 (*C*=O), 139.3 (Ar*C*CHO), 136.3 (Ar*C*CHCH), 132.7 (*C*HCHCHOAc), 128.7 (2 x Ar*C*H) , 128.3 (2 x Ar*C*H), 128.2 (2 x Ar*C*H), 127.6 (CH*C*HCHOAc), 127.1 (2 x Ar*C*H), 126.8 (2 x Ar*C*H), 76.3 (CHCH*C*HOAc), 21.5 (*C*H_3).

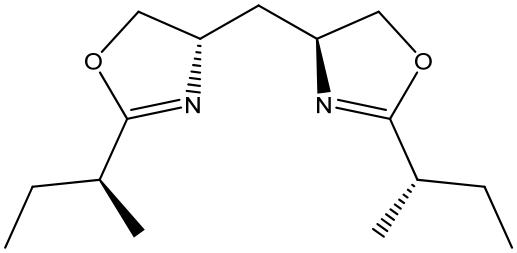
3.5 Asymmetric reactions using 4,4'-BOX ligands



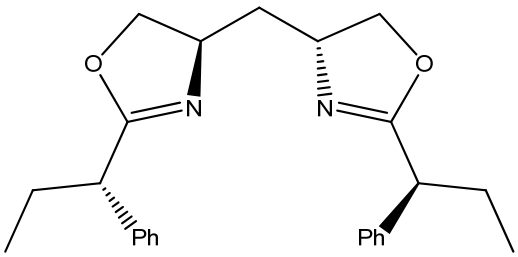
(*S*,*R*)-MePrAraBOX **(23)**



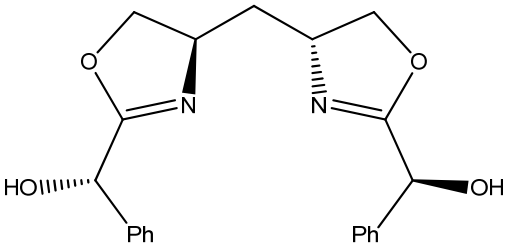
(*S*,*R*)-PhPrAraBOX **(24)**



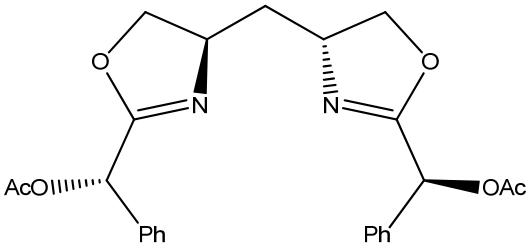
(*S*,*S*)-MePrAraBOX **(27)**



(*S*,*S*)-PhPrAraBOX **(28)**



(*S*,*R*)-BnOHAraBOX **(57)**



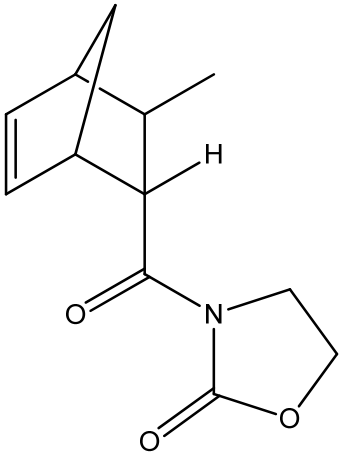
(*S*,*R*)-BnOAcAraBOX **(63)**

3.5.1 Asymmetric Diels Alder reactions[4,22]

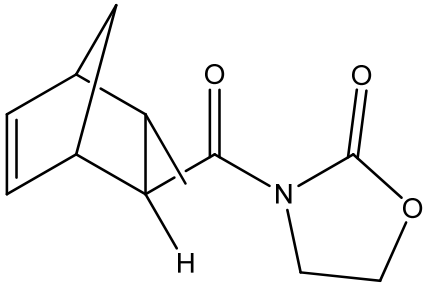
General Procedure A[23]

Metal triflate (10 mol%) was added to a flame dried N_2 filled schlenk. BOX ligand (11 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 coloured mixture was then stirred for 1 h at room temperature. Where necessary, the resulting mixture was filtered through a cotton plug, to remove any undissolved metal triflate, into a third flame dried N_2 filled schlenk. To this stirring catalyst was added *trans*-crotonyl-2-oxazolidinone **(32)** (1 equiv) in CH_2Cl_2 (1 mL) and freshly distilled cyclopentadiene **(31)** (3.5 equiv) *via* syringe. This reaction mixture was then stirred at room temperature for the time indicated. At this point the reaction was, where necessary, filtered through a silica gel (40-63 μm) plug into a round bottomed flask. The reaction flask was rinsed with CH_2Cl_2 (2 x 5 mL) and the CH_2Cl_2 rinse was filtered through the same silica 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 % conversion [unreacted *trans*-crotonyl-2-oxazolidinone **(32)** signal at 1.96 (3H) compared to the sum of the product signals, *endo* at 1.13 (3H) and *exo* at 0.85 (3H)] and the *endo*:*exo* ratio of the crude product formed [*endo* at 1.13 (3H) compared to *exo* at 0.85 (3H)]. The crude product was then purified by column chromatography (Pet. Ether: Ethyl Acetate, 9:1). The enantiomeric excess (*ee*) of the *endo* product was then measured using chiral HPLC (CHIRACEL OD, 254 nm, hexane:*iso*-propyl alcohol, 98:2, 1.0 mL/min), *t*(S) 41.8, *t*(R) 44.5.

Specific Example 1



***endo*-(33)**



***exo*-(34)**

The reaction was carried out according to **General Procedure A**, using copper(II)triflate (10.8 mg, 0.03 mmol), BOX ligand **(28)** (12.9 mg, 0.033 mmol), *trans*-crotonyl-2-oxazolidinone **(32)** (47 mg, 0.30 mmol) and cyclopentadiene **(31)** (0.10 mL, 1.21 mmol). The reaction was carried out at room temperature for 20 h. A mixture of products **(33)** and **(34)** were isolated as a green oil. The reaction resulted in 97% conversion to **(33)** and **(34)** with and *endo*:*exo* ratio of 70:30. The crude product was then purified by column chromatography (Pet. Ether: Ethyl Acetate, 9:1) yielding the purified product with an *endo*:*exo* ratio of 69:31. The enantiomeric excess (*ee*) of the *endo* diastereomer **(33)** was 45% *ee*(*R*), while the enantiomeric excess (*ee*) of the *exo* diastereomer **(34)** was not determined, on the purified product using chiral HPLC. The spectral results are consistent with those reported in the literature for **(33)** and **(34)**;[23] The *endo* product **(33)** was observed at δ_H (400 MHz, $CDCl_3$) = 6.36 (1H, dd, *J* = 5.7, 3.2 Hz, one of C*H*=CH), 5.78 (1H, dd, *J* = 5.7, 2.8 Hz, one of C*H*=CH), 4.39 (2H, t, *J* = 8.2 Hz, CH_2O), 4.06-3.89 (2H, m, CH_2N), 3.53 (1H, dd, *J* = 4.4, 3.4 Hz, $CH_2CHCHCO$ or $CHCO$), 3.27 (1H, br s, $CH_2CHCHCO$ or $CHCO$), 2.52 (1H, br s, $CH_2CHCHCH_3$), 2.12-2.05 (1H, m, $CHCH_3$), 1.70 (1H, d, *J* = 8.7 Hz, one of $CHCH_2CH$), 1.47-1.43 (1H, m, one of $CHCH_2CH$), 1.12 (3H, d, *J* = 7.1 Hz, $CHCH_3$); The *exo* product **(34)** w was observed at δ_H (400 MHz, $CDCl_3$) = 6.31 (1H, dd, *J* = 5.7, 3.1 Hz, one of C*H*=CH), 6.15 (1H, dd, *J* = 5.7, 3.0 Hz, one of CH=C*H*), 4.39 (2H, t, *J* = 8.2 Hz, CH_2O), 4.06-3.89 (2H, m, CH_2N), 2.89 (1H, br s, $CH_2CHCHCO$ or $CHCO$), 2.86 (1H, dd, *J* = 4.8, 1.1 Hz, $CH_2CHCHCO$ or $CHCO$), 2.73 (1H, br s, $CH_2CHCHCH_3$), 2.71-2.65 (1H, m, $CHCH_3$), 1.65 (1H, d, *J* = 8.5 Hz,

one of CHC*H*$_2$CH), 1.39-1.35 (1H, m, one of CHC*H*$_2$CH), 0.85 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$).

3.5.1.1 Reactions using copper(II)triflate and BOX ligands (28), (27), (23), (24), (63) and (57)

The reaction was carried out according to **General Procedure A**. Results and variations to the general procedure are shown in **Table 3.1** below. ^{1}H NMR spectra of the products were consistent with the full characterisation results reported above.

Ligand	Time (h), Temp (°C)	Conversion %	*endo*:*exo* ratio	%*ee endo R*/S
(28)	24, rt	97	70:30	45 *R*
(27)	24, rt	100	82:18	1 *R*
(23)	20, rt	91	75:25	11 *S*
(24)	20, rt	85	64:36	57 *S*
(63)	20, rt	44	82:18	15 *S*
(57)	20, rt	15	80:20	5 *S*

Table 3.1

3.5.1.2 General Procedure A exception: Variation in counterion (SbF_6)[23]

$CuCl_2$ (10 mol%) and $AgSbF_6$ (20 mol%) were added to a flame dried N_2 filled schlenk. BOX ligand (11 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 $CuCl_2$ and $AgSbF_6$, and the flask was wrapped in alumina foil to protect the reaction mixture from light. The resulting mixture was then stirred for 8 h at room temperature in the dark. To this stirring catalyst was added *trans*-crotonyl-2-oxazolidinone **(32)** (1 equiv) in CH_2Cl_2 (1 mL) and freshly distilled cyclopentadiene **(31)** (3.5 equiv) *via* syringe. This reaction mixture was then stirred at room for the time indicated. At this point the reaction was, where necessary, filtered through a silica gel (40-63 μm) plug into a round bottomed flask. The reaction flask was rinsed with CH_2Cl_2 (2 x 5 mL) and the CH_2Cl_2 rinse was filtered through the same silica plug into the round bottomed flask. The combined solution was then concentrated *in vacuo* to yield the crude product.

Variation to the general procedure is show in **Table 2** below. ^{1}H NMR spectra of the products were consistent with the full characterisation results reported above.

3.5.1.3 Variation in counterion (ClO_4)

The reaction was carried out according to **General Procedure A**. $Cu(ClO_4)_2.6H_20$ was used in place of copper(II)triflate. Results and variation to the general procedure are shown in **Table 3.2** below. ^{1}H NMR spectra of the products were consistent with the full characterisation results reported above.

Ligand	**Time (h), Temp (^{o}C)**	**Metal Salt**	**Conversion %**	***endo*:*exo* ratio**	**%*ee* *endo* *R*/S**
(28)	16, rt	$Cu(ClO_4)_2.6H_2O$	2	84:16	-
(28)	22, rt	$CuCl_2$+$AgSbF_6$	3	79:21	-
(28)	22, rt	$CuCl_2$+$AgSbF_6$	56	78:22	20 *R*
(23)	20, rt	$Cu(ClO_4)_2.6H_2O$	18	71:29	39 *S*
(24)	20, rt	$Cu(ClO_4)_2.6H_2O$	18	72:28	49 *S*
(23)	20, rt	$CuCl_2$+$AgSbF_6$	74	78:22	9 *S*
(24)	20, rt	$CuCl_2$+$AgSbF_6$	87	80:20	31 *S*

Table 3.2

3.5.1.4 Variation in cation

The reaction was carried out according to **General Procedure A**. $Mg(OTf)_2$ or $Zn(OTf)_2$ were used in place of $Cu(OTf)_2$. Results and variation to the general procedure are shown in **Table 3.3** below. ^{1}H NMR spectra of the products were consistent with the full characterisation results reported above.

Ligand	Time (h), Temp (^{o}C)	Metal Salt	Conversion %	*endo*:*exo* ratio	%*ee endo* *R*/S
(28)	16, rt	$Mg(ClO_4)_2$	5	66:34	-
(28)	16, rt	$Mg(OTf)_2$	4	66:34	-
(28)	20, rt	$Zn(OTf)_2$	12	80:20	-
(28) [a]	20, rt	$Zn(OTf)_2$	32	80:20	20 *S*
(23)	20, rt	$Mg(OTf)_2$	6	66:34	-
(24)	20, rt	$Mg(OTf)_2$	2	n/d	-
(23)	20, rt	$Zn(OTf)_2$	4	76:24	-
(24)	20, rt	$Zn(OTf)_2$	7	n/d	-
(23) [a]	20, rt	$Zn(OTf)_2$	5	77:23	-
(24) [a]	20, rt	$Zn(OTf)_2$	10	73:27	-

Table 3.3

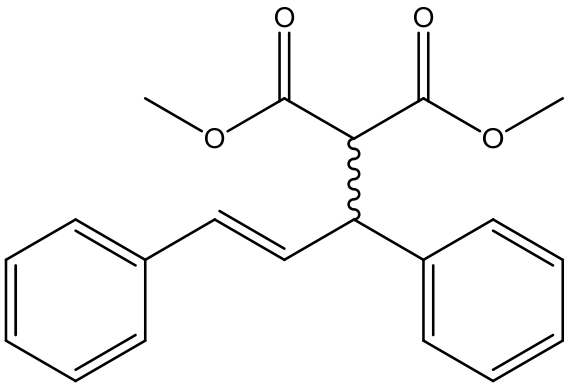
[a] Complex was generated in acetonitrile, reaction was carried out in dichloromethane.

3.5.2 Asymmetric Allylic Alkylation reactions[20,24]

General Procedure B

Tris(dibenzylideneacetone)dipalladium (10 mol%) was added to a flame dried N_2 filled schlenk. BOX ligand (15 mol%) was weighed into a second flame dried N_2 filled schlenk and dissolved in toluene (1 mL). The ligand solution was then transferred under N_2, into the schlenk containing the metal. The resulting mixture was then stirred for 2 h at 80 °C. NaH (2.2 equiv), dimethyl malonate (2.0 equiv) and toluene (8 mL), were weighed into a third flame dried N_2 filled schlenk. The resulting solution was stirred at 80 °C for 15 min, before the addition of (±)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene **(42)** (1 equiv) in toluene (1 mL), and was stirred for a further 15 min. The catalyst was transferred to the substrate-nucleophile mixture *via* a gas-tight syringe, along with a toluene rinse (1 mL). The reaction mixture was then stirred at 80 °C for 60 h. At that point saturated NH_4Cl solution (10 mL) was added, the organic layer was separated and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to yield the crude product. A ^1H NMR spectrum was recorded to determine the % conversion [unreacted (±)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene **(42)** signal at 2.14 (3H) compared to the product signal at 4.27 (1H)]. The crude product was then purified by column chromatography (Pet. Ether: Ethyl Acetate, 25:1). The enantiomeric excess (*ee*) of the product was then measured using chiral HPLC (CHIRACEL OD, 254 nm, hexane (0.1% diethylamine):*iso*-propyl alcohol, 98:2, 0.5 mL/min), *t*(*R*) 25.2, *t*(*S*) 26.9.[24]

Specific example 1



(43)

The reaction was carried out according to **General Procedure B**, using tris(dibenzylideneacetone)dipalladium (9.2 mg, 0.01 mmol), BOX ligand **(27)** (8.8 mg, 0.033mmol), NaH (60% dispersion in mineral oil, 17.0 mg, 0.48 mmol), dimethyl malonate (0.06 mL, 0.44 mmol) and (±)-(*E*)-1,3-diphenyl-3-acetoxyprop-1-ene **(42)** (55.5 mg, 0.22 mmol). The reaction was carried at 80 °C for 60 h in toluene. Saturated NH_4Cl solution (10 mL) was added, the organic layers was separated and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to yield the crude product **(43)** as a yellow oil. The reaction resulted in 99% conversion to the desired product. The crude product was then purified by column chromatography (Pet. Ether: Ethyl Acetate, 9:1). The enantiomeric excess (*ee*) was 72% *ee*(*R*), measured on the purified product **(43)** using chiral HPLC. The spectral results are consistent with those reported in the literature for **(43)**;[20] The product was observed at δ_H (400 MHz, $CDCl_3$) = 7.34-7.20 (10H, m, 10 x Ar*H*), 6.47 (1H, d , *J* = 15.7 Hz, PhC*H*=CH), 6.32 (1H, dd, *J* = 15.7, 8.6 Hz, PhCH=C*H*), 4.26 (1H, dd, *J* = 10.8, 8.6 Hz, CH=CHC*H*), 3.95 [1H, d, *J* = 10.9 Hz, C*H*$(COCH_3)_2$], 3.70 (3H, s, OCH_3), 3.51 (3H, s, OCH_3).

3.5.2.1 Reactions using tris(dibenzylideneacetone)dipalladium and BOX ligands (28), (27), (23) and (24).

The reaction was carried out according to **General Procedure B**. Results and variations to the general procedure are shown in **Table 3.4** below. ^{1}H NMR spectra of the products were consistent with the full characterisation results reported above.

Ligand	Time (h), Temp (^{o}C)	Metal Salt	Conversion %	%*ee R/S*
(28)	60, 80	$Pd_2(dba)_3$	16	6 *R*
(27)	60, 80	$Pd_2(dba)_3$	99	72 *R*
(24)	60, 80	$Pd_2(dba)_3$	90	68 *S*
(23)	60, 80	$Pd_2(dba)_3$	71	62 *S*
(63)	60, 80	$Pd_2(dba)_3$	0	-
(57)	60, 80	$Pd_2(dba)_3$	0	-

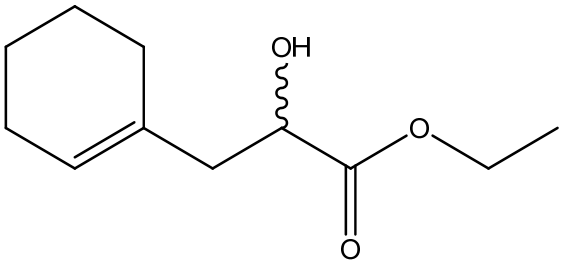
Table 3.4

3.5.3 Asymmetric Ene reactions[22,25]

General Procedure C

Metal triflate (10 mol%) was added to a flame dried N_2 filled schlenk. BOX ligand (11 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 coloured mixture was then stirred for 1 h at room temperature. Where necessary, the resulting mixture was filtered to a cotton plug, to remove any undissolved metal triflate, into a third flame dried N_2 filled schlenk. To this stirring catalyst was added methylene cyclohexane **(47)** (1 equiv) followed by ethyl glyoxylate **(46)** (4 equiv, toluene solution) *via* syringe. The reaction mixture was then stirred at 50 °C for 16 h. At that point the reaction mixture was filtered through a silica gel (40-63 μm) plug into a round bottomed flask. The reaction flask was rinsed with CH_2Cl_2 (2 x 5 mL) and the CH_2Cl_2 rinse was filtered through the same silica 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 % conversion [unreacted methylene cyclohexane **(47)** signal at 4.58 (2H) compared to the product **(48)** signal at 5.53 (1H)]. The crude product was then purified by column chromatography (Pet. Ether: Diethyl Ether, 7:3). The enantiomeric excess (*ee*) of the purified product **(48)** was then measured using chiral GC (Cyclodex-β-30 m x 0.252 mm 0.25 μm). (Cyclodex-β-30 m x 0.252 mm 0.25 μm, conditions; 110 ^{o}C hold 10 min, ramp 1 ^{o}C/min to 130 ^{o}C hold 20 min, ramp 2 ^{o}C/min to 150 ^{o}C), *t*(*R*) 45.0, *t*(*S*) 46.5.[25]

Specific reaction 1



(48)

The reaction was carried out according to **General Procedure C**, using copper(II)triflate (10.0 mg, 0.025 mmol), BOX ligand **(28)** (10.8 mg, 0.025 mmol), methylene cyclohexane **(47)** (30 μL, 0.25 mmol), and ethyl glyoxylate **(46)** (0.10 mL, ~1.0 mmol, toluene solution). The reaction was carried out at reflux for 20 h. The reaction product was isolated as a yellow oil. The reaction resulted in a % conversion to **(48)**. The crude product was then purified by column chromatography (Pet. Ether: Diethyl Ether, 7:3), affording **(48)** as a colourless oil which had a 9% *ee*(S). The enantiomeric excess (*ee*) of the purified product was measured using chiral GC. The spectral results are consistent with those reported in the literature for **(48)**;[25] The product **(48)** was observed at δ_H (400 MHz, $CDCl_3$) = 5.53 (1H, br s, C*H*=C), 4.29-4.24 (1H, m, C*H*OH), 4.22 (2H, q, *J* = 7.1 Hz, OCH_2), 2.65 (1H, d, *J* = 6.1 Hz, O*H*), 2.44 (1H, dd, $^2J_{HCH}$ = 14.1, 3.5 Hz, one of CH_2CHOH), 2.28 (1H, dd, $^2J_{HCH}$ = 13.8, 8.0 Hz, CH_2CHOH), 2.03-1.94 (4H, m, C=CHCH_2 and CH=CCH_2), 1.63-1.52 (4H, m, CHCH$_2$CH_2 and CCH$_2$CH_2), 1.29 (3H, t, *J* = 7.1 Hz, CH_3).

3.5.3.1 Reactions using copper(II)triflate and BOX ligands (28), (27), (23) and (24).

The reaction was carried out according to **General Procedure C**. Results and variations to the general procedure are shown in **Table 3.5** below. ^{1}H NMR spectra of the products were consistent with the full characterisation results reported above.

Ligand	**Time (h), Temp (^{o}C)**	**Metal Salt**	**Solvent**	**Conversion %**	**%*ee* *R*/*S***
(28)	16, 50	$Cu(OTf)_2$	CH_2Cl_2	100	9 *S*
(27)	16, 50	$Cu(OTf)_2$	CH_2Cl_2	100	1 *R*
(24)	16, 50	$Cu(OTf)_2$	CH_2Cl_2	100	4 *S*
(23)	16, 50	$Cu(OTf)_2$	CH_2Cl_2	100	2 *R*

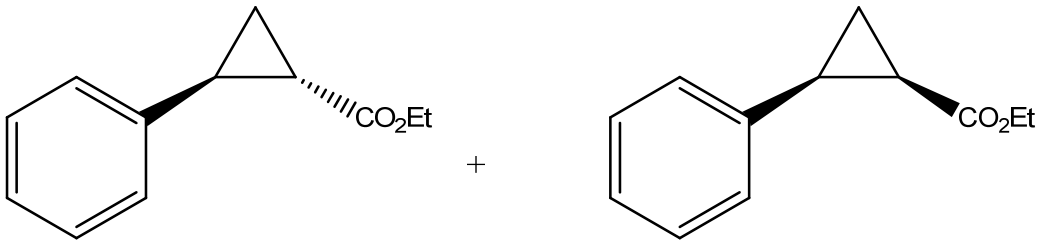
Table 3.5

3.5.4 Asymmetric Cyclopropanation reactions[4,9]

General Procedure D

Metal triflate (1 mol%) was added to a flame dried N_2 filled schlenk. BOX 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 coloured mixture was then stirred for 1 h at room temperature. Where necessary, the resulting mixture was filtered to a cotton plug, to remove any undissolved metal triflate, into a third flame dried N_2 filled schlenk. To this stirring catalyst was added styrene **(50)** (5 equiv) in CH_2Cl_2 (1 mL). A solution of ethyl diazoacetate **(49)** (1 equiv) in CH_2Cl_2 (4 mL) was added over *ca*. 6 h *via* syringe pump. The reaction mixture was then stirred at room temperature for 24 h. The reaction mixture was then filtered through a silica gel (40-63 μm) plug into a round bottomed flask. The reaction flask was rinsed with CH_2Cl_2 (2 x 5 mL) and the CH_2Cl_2 rinse was filtered through the same silica 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 % conversion [unreacted ethyl diazoacetate **(49)** signal (1H) at 4.72 compared to the sum of the product peaks, *cis* at 3.87 (2H) and *trans* at 4.17 (2H), minus the sum of the by-product peaks, diethyl fumarate 6.84 (2H) and diethyl maleate 6.22 (2H)] and *cis*:*trans* ratio of the product [*cis* product signal at 3.87 (2H) compared to *trans* product signal at 4.17 (2H)]. The crude product was then purified by column chromatography (Pet. Ether: Ethyl Acetate, 25:1). The enantiomeric excess (*ee*) of the purified product was then measured using chiral GC (Cyclodex-β-30 m x 0.252 mm 0.25 μm, conditions; 100 ^{o}C hold 5 min, ramp 1 ^{o}C/min to 165 ^{o}C hold 5 min), *t*(1*S*, 2*R*) 38.5, *t*(1*S*, 2*S*) 42.4.[26]

Specific example 1



***trans*-(51)** ***cis*-(52)**

The reaction was carried out according to **General Procedure D**, using [copper(I)triflate]$_2$·C_6H_6 (3.0 mg, 0.006 mmol), BOX ligand **(27)** (3.5 mg, 0.013 mmol), styrene **(50)** (0.69 mL, 6.0 mmol) and ethyl diazoacetate **(49)** (0.14 mL, 1.2 mmol). The reaction was carried out at room temperature for 16 h. A mixture of products **(51)** and **(52)** were isolated as a yellow oil. The reaction resulted in 93% conversion to **(51)** and **(52)** with a *cis*:*trans* ratio of 60:40. The crude product was then purified by column chromatography (Pet. Ether: Ethyl Acetate, 25:1) yielding the purified product with a *cis*:*trans* ratio of 39:61. The enantiomeric excess (*ee*) of the *trans* diastereomer **(51)** was 69% *ee* (1S, 2S), and the enantiomeric excess (*ee*) of the *cis* diastereomer **(52)** was 70% *ee* (1S, 2R), measured on the purified product using chiral GC. The spectral results are consistent with those reported in the literature for **(51)** and **(52)**;[27] The *trans* product **(51)** was observed at δ_H (400 MHz, $CDCl_3$) = 7.28-7.08 (5H, m, 5 x Ar*H*), 4.17 (2H, q, *J* = 7.1 Hz, C*H*$_2$CH$_3$), 2.55-2.49 (1H, m, one of C*H*), 1.90 (1H, ddd, *J* = 8.4, 5.3, 4.2 Hz, one of C*H*), 1.62 – 1.56 (1H, m, one of C*H*$_2$), 1.33-1.29 (1H, m, one of C*H*$_2$) 1.27 (3H, t, *J* = 7.1 Hz, C*H*$_3$CH$_2$). The *cis* product **(52)** was observed at δ_H (400 MHz, $CDCl_3$) = 7.28-7.08 (5H, m, 5 x Ar*H*), 3.87 (2H, q, *J* = 7.1 Hz, C*H*$_2$CH$_3$), 2.58 (1H, q, *J* = 8.6 Hz, one of C*H*), 2.07 (1H, ddd, *J* = 9.3, 7.8, 5.6 Hz, one of C*H*), 1.71 (1H, ddd, *J* = 7.5, 5.6, 5.1 Hz, one of C*H*$_2$), 1.33-1.29 (1H, m, one of C*H*$_2$), 0.97 (3H, t, *J* = 7.1 Hz, C*H*$_3$CH$_2$).

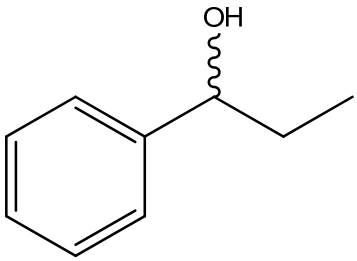
3.5.4.1 Reactions using copper(1)triflate and BOX ligands (28), (27), (23) and **(24).**

The reaction was carried out according to **General Procedure D**. Results and variations to the general procedure are shown in **Table 3.6** below. ^{1}H NMR spectra of the products were consistent with the full characterisation results reported above.

Ligand	**Metal Salt**	**Conversion %**	***trans*:*cis***	**% *ee* (*cis*)**	**% *ee* (*trans*)**
(28)	CuOTf	86	37:63	64-(1*S*, 2*R*)	61-(1*S*, 2*S*)
(27)	CuOTf	93	40:60	70-(1*S*, 2*R*)	69-(1*S*, 2*S*)
(24)	CuOTf	85	59:41	20-(1*R*, 2*S*)	8-(1*R*, 2*R*)
(23)	CuOTf	91	39:61	46-(1*R*, 2*S*)	27-(1*R*, 2*R*)

Table 3.6

3.5.5 Asymmetric Alkylation of Benzaldehyde using diethylzinc[28]



(70)

BOX ligand **(57)** (7.3 mg, 0.02 mmol) was weighed into a flame dried N_2 filled schlenk and dissolved in toluene (5 mL). To this stirring solution was added benzaldehyde **(67)** (102 μL, 1.00 mmol). The reaction mixture was then stirred at room temperature for 20 min. At that point the reaction mixture was cooled to -78 °C. At this temperature Et_2Zn (2.0 mL, 2.00 mmol, 1.0 M in hexane) was added dropwise. The mixture was allowed to stir at 0 °C for 40 h. At that point saturated NH_4Cl solution (10 mL) was added, the organic layer was separated and the aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic layers were washed with distilled water (25 mL) and brine (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to yield the crude product. The reaction resulted in 20% conversion [unreacted benzaldehyde **(67)** signal at 9.94 (1H) compared to the product **(70)** signal at 4.60 (1H)] to the desired product. The crude product was then purified by column chromatography (Pet. Ether: Ethyl Acetate, 4:1). The enantiomeric excess (*ee*) was 1% *ee*(R), measured on the purified product **(70)** using chiral HPLC (CHIRACEL OD, 254 nm, hexane:*iso*-propyl alcohol, 98:2, 0.5 mL/min), *t*(R) 27.6, *t*(S) 33.0.[28] The spectral results are consistent with those reported in the literature for **(70)**;[28] The product was observed at δ_H (400 MHz, $CDCl_3$) = 7.36-7.26 (5H, m, 5 x Ar*H*), 4.60 (1H, t, *J* = 6.6 Hz, C*H*OH), 1.86-1.70 (3H, m, CHO*H*, CH_2CH$_3$), 0.92 (3H, t, *J* = 7.4 Hz, CH_3CH$_2$).

References

(1) W.L.F., A. *Purification of Laboratory Chemicals*; Fourth Ed. ed.; Elsevier, 1998.

(2) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824.

(3) Linclau, B.; Boydell, A. J.; Clarke, P. J.; Horan, R.; Jacquet, C. *J. Org. Chem.* **2003**, *68*, 1821.

(4) Kirby, F., National University of Ireland, Galway, 2011.

(5) Frain, D.; Kirby, F.; McArdle, P.; O'Leary, P. *Synlett* **2009**, 1261.

(6) Attwood, S. V.; Barrett, A. G. M. *J. Chem. Soc.-Perkin Trans. 1* **1984**, 1315.

(7) Yuasa, Y. *J. Sulfur Chem.* **2008**, *29*, 139.

(8) Bolm, C.; Zani, L.; Rudolph, J.; Schiffers, I. *Synthesis-Stuttgart* **2004**, *2004*, 2173.

(9) Kirby, F.; Frain, D.; McArdle, P.; O'Leary, P. *Catalysis Communications* **2010**, *11*, 1012.

(10) Cardellina, J. H.; Barnekow, D. E. *J. Org. Chem.* **1988**, *53*, 882.

(11) Kaburagi, Y.; Kishi, Y. *Org. Lett.* **2007**, *9*, 723.

(12) Brown, J. M.; Leppard, S. J.; Oakes, J.; Thornthwaite, D. *Chirality* **2000**, *12*, 496.

(13) Aszodi, J.; Bonnet, A.; Teutsch, G. *Tetrahedron* **1990**, *46*, 1579.

(14) Barrow, J. C.; Ngo, P. L.; Pellicore, J. M.; Selnick, H. G.; Nantermet, P. G. *Tetrahedron Lett.* **2001**, *42*, 2051.

(15) Bowen, R. J.; Garner, A. C.; Berners-Price, S. J.; Jenkins, I. D.; Sue, R. E. *J. Organomet. Chem.* **1998**, *554*, 181.

(16) Owens, T. D.; Souers, A. J.; Ellman, J. A. *J. Org. Chem.* **2003**, *68*, 3.

(17) Zhong, Y. W.; Dong, Y. Z.; Fang, K.; Izumi, K.; Xu, M. H.; Lin, G. Q. *J. Am. Chem. Soc.* **2005**, *127*, 11956.

(18) Le Gall, E.; Hurvois, J. P.; Sinbandbit, S. *Eur. J. Org. Chem.* **1999**, 2645.

(19) Soloshonok, V. A.; Cai, C. Z.; Hruby, V. J.; Van Meervelt, L.; Yamazaki, T. *J. Org. Chem.* **2000**, *65*, 6688.

(20) Leung, W.; Cosway, S.; Jones, R. H. V.; Mc Cann, H.; Wills, M. *Journal of the Chemical Society; Perkin Transactions I* **2001**, *1*, 2588.

(21) Wasserman, H. H.; Aubrey, N. E. *J. Am. Chem. Soc.* **1955**, *77*, 590.

(22) McDonagh, C., National Univeristy of Ireland, Galway, 2008.

(23) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559.

(24) Bateman, L. PhD Thesis, National University of Ireland, 2006.

(25) Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936.

(26) Portada, T.; Roje, M.; Raza, Z.; Caplar, V.; Zinic, M.; Sunjic, V. *Eur. J. Org. Chem.* **2007**, 838.

(27) Lou, Y.; Horikawa, M.; Kloster, R. A.; Hawryluk, N. A.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8916.

(28) Schinnerl, M.; Seitz, M.; Kaiser, A.; Reiser, O. *Org. Lett.* **2001**, *3*, 4259.