Synthesis of novel pentacyclo-undecane chiral ligands for application in asymmetric catalysis

by

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B.Sc. Hons

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As the candidate's supervisors I have / have not approved this dissertation for submission

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Abstract

There is enormous interest in the design and development of efficient chiral ligands for asymmetric catalysis, as a result, this field has become one of the most popular areas of research in organic chemistry. This project involved the investigation of the novel chiral pentacyclo-undecane (PCU) diol **54a**, PCU bisimine **87** and PCU bis(oxazoline) **100** type ligands. The PCU diol ligand was synthesized, but proved to be difficult to obtain enantiomerically pure which hindered further investigation into this type of ligand. The PCU bisimine ligand **87** was synthesized. However due to its instability it was not further pursued. Synthesis of the PCU bis(oxazoline) ligand **100** was successful. This ligand was complexed to various metal salts and its efficiency as a chiral Lewis acid catalyst was evaluated on the asymmetric Diels-Alder reaction between 3-acryloyloxazolidin-2-one **52** and cyclopentadiene **33**. The anhydrous magnesium perchlorate ligand complex emerged as the best catalyst providing the *endo*-cycloadduct product **53** in 81 % enantiomeric excess at -40 ^{o}C. Optimizations of the possible conformations of the magnesium complex of ligand **100** with the substrate **52** were performed using Density Functional Theory (DFT) calculations. The more energetically favoured complex conformation was established. The *Re*-face of the dienophile which was less hindered produced the product consistent with the experimentally observed product **16.** Based on the calculated bond lengths from the computational model binding of the ether oxygen on the PCU moiety to magnesium was observed. All the novel compounds were fully characterized using NMR, IR and mass spectroscopy as the main tools.

List of publications

- Boyle, G. A.; Govender, T.; Kruger, H. G.; Maguire, G. E. M.; Naicker, T., NMR elucidation of some ligands derived from the pentacyclo-undecane skeleton. *Structural Chemistry* **2008,** *19*, 429-434.

- Boyle, G. A.; Govender, T.; Kruger, H. G.; Maguire, G. E. M.; Naicker, T., NMR elucidation of the novel (*S,S*)-pentacyclo-undecane bis(4-phenyloxazoline) ligand and related derivaitives. *Magnetic Resonance in Chemistry* **2008**, Accepted DOI 10.1002/mrc.2279.

- Arvidsson P.I; Govender, T.; Kruger, H. G.; Maguire, G. E. M.; Naicker, T., Application of (*S,S*)-pentacyclo-undecane bis(4-phenyloxazoline) as a novel chiral ligand for catalysis of the asymmetric Diels-Alder reaction of cyclopentadiene with 3-acryloyl-2-oxazolidinone. *South African Journal of Chemistry* **2008**, Submitted.

Declaration

The experimental work described in this dissertation was carried out at the School of Chemistry, University of KwaZulu-Natal, Durban from January 2007 to May 2008, under the supervision of Prof. Gert Kruger, Dr Glenn Maguire and Dr Thavendran Govender.

These studies represent original work by the author and have not otherwise been submitted in any form for any degree or diploma to any tertiary institution. Where use has been made of the work of others it is duly acknowledged in the text.

_____

Tricia Naicker

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Date

Acknowledgements

~Om Shree Ganeshaya Namaha~

My sincere gratitude to:

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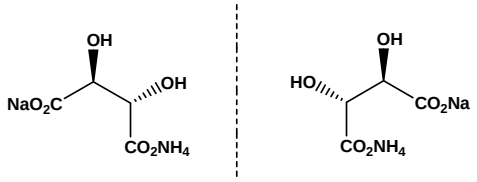
Chapter 1

1.1 Origin and Importance of Chirality

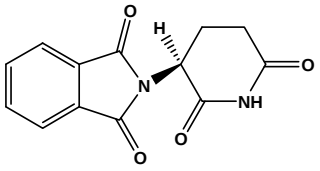
In 1848 Louis Pasteur was the first scientist to recognize that the optical activity of molecules is related to what we now refer to as chirality.[1,2] He stated that similar molecules which rotate plane-polarised light through equal angles but in opposite directions must be related to each other as an object and its non-superimposable mirror image. Pasteur came to this remarkable realization while working with crystals of sodium ammonium tartrate **1**.[2] He observed that the crystals were not identical, some of the crystals were 'right-handed' and some of them 'left-handed'. Pasteur was able to separate these two enantiomorphous crystal forms with the use of a magnifying glass and a pair of tweezers. He then found that plane-polarised light was reflected clockwise and anti-clockwise by solutions of the right-handed and left-handed crystals respectively. This phenomenon was attributed to a property possessed by chiral molecules and the two forms of the optically active tartaric acid were related to each other as three-dimensional non-superimposable mirror images (enantiomers).[1,2]



1

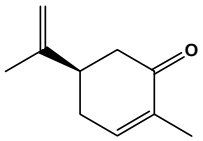
Enantiomers have identical chemical and physical properties[3] hence they exhibit similar physiochemical properties such as melting points, solubility, chromatographic retention time, infrared[4] (IR) and nuclear magnetic resonance (NMR) spectra. However, enantiomers differ in the way they rotate plane-polarised light as stated above and when interacting with another chiral molecule.[3,5] The majority of the vital building blocks which make up biological macromolecules (e.g. DNA, RNA, sugars and proteins) exist predominantly in one enantiomeric form. As a result, when a biologically active chiral compound such as a drug interacts with a chiral receptor site in biological systems the two enantiomers of the drug will interact differently and may lead to different biochemical effects.[3,5] In relation to biological activity their tastes, smells, toxicity, and other properties of enantiomers often differ vastly.[1] There are a variety of examples of the

different activities of enantiomers.[1-3,5] One of the most cited examples of this behavior was the fatal drug thalidomide which was used in the 1960's. Both enantiomers of the drug had the same sedative effect but only the (*S*)-(-)-enantiomer **2** caused death and deformities in foetuses when used by pregnant women.[6,7]



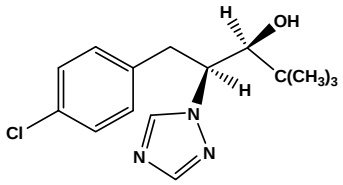
(*S*)-(-)-2

Another biological example displaying the sometimes dramatic different effects of enantiomers is the naturally occurring oil from seeds of the caraway plant called carvone. The (*S*)-(+)-carvone smells like caraway, a pungent anise like odour while the (*R*)-(-)-carvone **3** smells like spearmint.[8]



(*R*)-(-)-3

A further illustration of contrasting enantiomer characteristics comes from the agrochemical industry, namely (*R,R*)-paclobutrazol which serves as a fungicide while its enantiomer **4** acts as a plant growth regulator. [9]



(*S,S*)-4

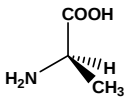
The synthesis of chiral molecules in optically pure form is not only imperative to the pharmaceutical industry but also in the generation of non-linear optical devices,[10] the control of polymer structure and properties,[11] the agrochemical industry,[12] flavours, fragrances,[13] the study of nearly all biochemical processes and the pursuit of understanding molecular recognition.[14] Therefore, chirality has been an important concept in various fields of chemistry and has been extensively studied. Today, the use and demand for optically active molecules is greater than ever, hence chiral methodologies in asymmetric synthesis plays a crucial role in science as it can provide materials and methods for various applications of chiral compounds.

1.2 Routes to Obtain Optically Pure Compounds

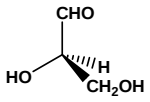
Amongst numerous routes to obtain optically pure or enriched compounds, the basic approaches can be divided into the following three classes:

1.2.1 The "Chiral Pool"

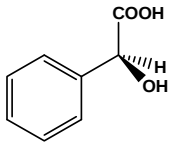
The chiral pool strategy involves the use of nature's 'limited' catalogue of enantiopure starting materials such as amino acids, carbohydrates, hydroxyl acids, terpenes **5-8** and related compounds.[15]



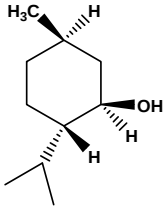
5, Amino acid, (*R*)-alanine



6, Carbohydrate, (*R*)-(+)-glyceraldehyde

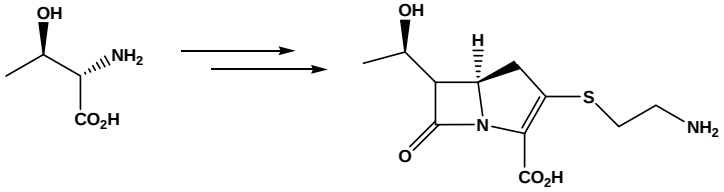


7, Hydroxy acid, (*S*)-mandelic acid



8, Terpene, (*1R,2R,5R*)-menthol

Achiral reagents were utilized to transform chiral starting materials to the desired target molecule during the development stages of asymmetric synthesis. An example making use of the chiral pool strategy is the synthesis of the potent β-lactam antibiotic thienamycin **10** which utilizes naturally occurring amino acid (*R*)-threonine **9** as one the chiral starting materials.[16]

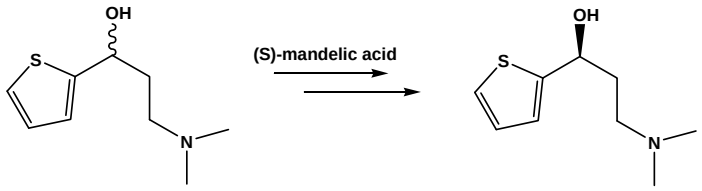


9 **10**

Several pharmacologically relevant compounds have been synthesized using this approach. Despite this fact it suffers severe potential drawbacks which include the cost and availability of the stoichiometric amounts of the suitable chiral precursors along with more challenging multi-step synthetic routes. For example, the synthesis of taxol, an effective anti-cancer agent, involves more than twenty synthetic steps.[16] Nevertheless, this method of asymmetric synthesis is still frequently utilized.

1.2.2 Resolution of Racemates

Chiral resolution is a process whereby racemic (equimolar) mixtures of the two enantiomers are separated.[17,18] These methods include enzymatic methods or more commonly diastereomer formation in which crystallization or chromatographic techniques are used to separate the diastereomers.[19,20] A chiral resolving agent (CSA) is used to convert enantiomers into diastereoisomers. A recent example making use of diastereomer formation using a CSA involves the synthesis of the drug duloxetine, which has been reported to treat psychiatric disorders. In a part of its synthetic route (*S*)-mandelic acid (CSA) is added to the racemic mixture **11** resulting in the (*S*)-alcohol complexed to the (*S*)-mandelic acid to crystallize out of solution. A basic workup liberates the free (*S*)-alcohol **12** in 93 % enantiomeric excess (ee).[21]



Racemic-11 **(S)-12**

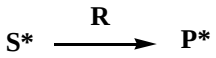
The major disadvantage of chiral resolution is that the theoretical yield is limited to 50 % unless alternative routes to convert the opposite enantiomer into the desired product is further carried out.[22] Some enzymatic techniques exist where complete resolution (100 % conversion) of the racemate is achieved under conditions where the "other" enantiomer is racemized.[23,24] One such example is the conversion of racemic hydantoins to a single amino acid enantiomer by means of the hydantionase enzyme.[23]

1.2.3 Asymmetric Synthesis

This approach involves the conversion of an achiral starting material into a single enantiomer induced by a chiral environment. At present it is the most powerful and common approach to obtaining optically active compounds. The basic strategies can be divided into four classes:[5,17,18,25]

Substrate-Controlled

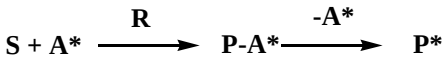
The starting chiral substrate **S*** is incorporated into the final product and it serves to direct the formation of new chiral center/s on the product **P***.



R = reagents and * denotes chirality

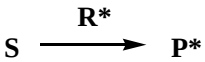
Auxiliary-Controlled

A chiral auxiliary **A*** is deliberately attached to an achiral substrate **S**. This serves to direct the enantioselective reaction after which the auxiliary is removed or recycled and the enantiomerically pure compound is obtained when reacting with the reagent **R**.



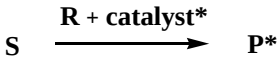
Reagent-Controlled

An achiral substrate is directly converted into a chiral product using a chiral reagent **R*** e.g. a reducing agent.



Catalyst-Controlled

A substiochiometric amount of a chiral catalyst promotes the conversion of an achiral substrate into a chiral product with preference for the formation of one of the enantiomers.[25]



Remarkable progress has been made in this field resulting in the vast majority of important asymmetric reactions primarily relying on this approach to generate chiral products.[17] The enormous practical potential of asymmetric catalysis makes it one the most widely explored areas of research in recent years.[5,17,18]

Asymmetric catalysis is described in more detail in the following section.

1.3 Asymmetric Catalysis

There are three main classes of asymmetric catalysts employed:

1.3.1 Biocatalysts

Biocatalysis makes use of enzymatic or microbial methods to effect stereoselective changes to unnatural substrates.[26] These methods include the use of hydrolases, lipases, lyases etc. The synthetic route of the antibiotic cefalexin has been shortened from ten to six steps using an enzymatic procedure.[27] There are problems with this methodology as biocatalysts cannot be applied to a wide range of asymmetric reactions but recently a steady increase in research output in this field has emerged.[20,26]

1.3.2 Organocatalyts

Chiral organocatalysis involves the use of organic molecules as catalysts to promote the conversion of achiral substrates into chiral products.[26] Due to the limited scope, these catalysts had not attracted much attention in asymmetric synthesis. However, in the past decade there has been a substantial increase in the number of studies in this field.[26,20] A recent example is the alkylation of crotonaldehyde with an organotrifluoroborate salt as the catalyst.[28]

1.3.3 Metal-Ligand complexes as catalysts

These catalysts consist of metal-ligand complexes derived from chiral ligands. From the 1950's metal-ligand catalysts have had a significant impact on asymmetric catalysis.[17] It has been extensively studied and provides flexible methods for many types of organic reactions leading to some spectacular practical applications.[5,17,18]

For the purpose of this project these types of catalysts will be discussed in further detail.

1.4 Metal-Ligand Complexes Derived From Chiral Ligands

The advances in asymmetric synthesis utilizing a molecular catalyst that consist of a metallic centre and a chiral organic ligand have lifted many of the restrictions on the classical approaches to the synthesis of optically pure compounds. Chiral ligands alter the reactivity and selectivity of the metal catalyst such that the transition leading to the product has preference for the formation of one enantiomer in an asymmetric reaction.[17,25] Figure 1.1 illustrates the general principle

behind an asymmetric catalytic reaction promoted by a chiral metal-ligand complex.[18] A substiochiometric amount of the chiral catalyst **1A** combines with the achiral reactant **A** and substrate **B** to form intermediate **1B**. The chiral environment induced by complex **1B** enables the asymmetric transformation into the chiral product **A-B*** [which is either (*R*) or (*S*)] *via* intermediate **1C**.[18]

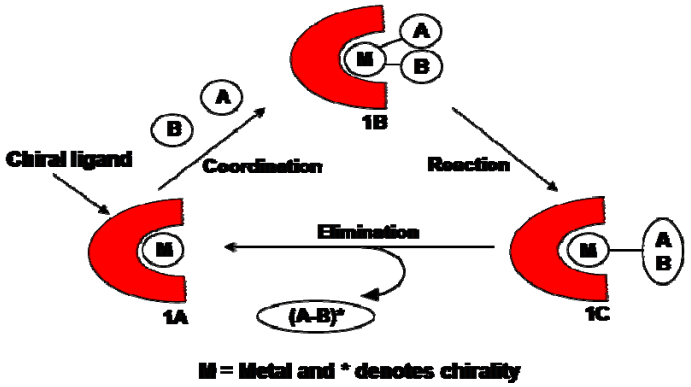
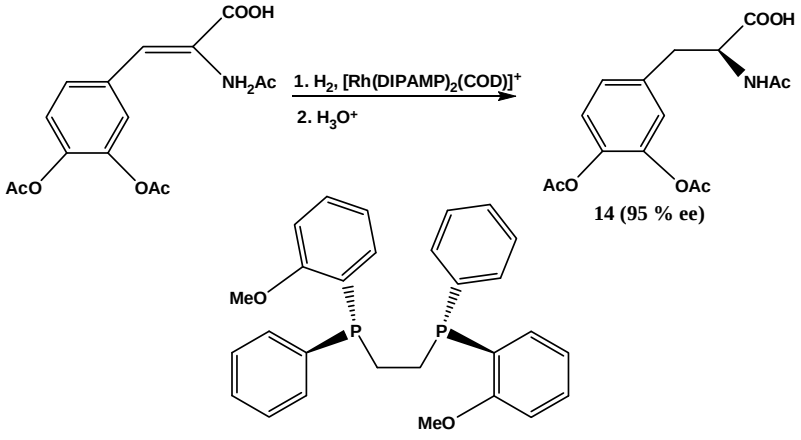


Figure 1.1 Principle of asymmetric catalysis by a metal-ligand complex.[18]

Based on this principle numerous metal-ligand complexes have been found to catalyze a range of reactions with impressive enantioselectivities.[17] Amongst many, a well-known example of an industrial application employing asymmetric catalysis using a metal-ligand complex is rhodium and (*R,R*)-1,2-ethanediyl-bis-[(2-methoxyphenyl)-phenylphosphine] or DIPAMP **13**. The resulting chiral ligand/metal complex is used in the production of (*S*)-2-amino-3-(3,4-dihydroxyphenyl)-propanoic acid **14** commonly known as L-DOPA[29], an important anti-Parkinson's drug.

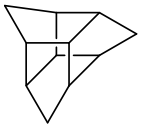


This project involves the synthesis of novel chiral ligands based on the pentacyclo-undecane (PCU) cage compound. The ligands will be complexed with various metals and the chiral metal-ligand complexes will be used as catalysts in a typical Diels-Alder reaction. More details on cage compounds and Diels-Alder type reactions follow.

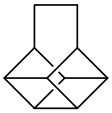
1.5 Cage Compounds

Organic chemists have explored the chemistry of polycyclic cage compounds for several years.[1,30-33] The effect of the unique cage geometry on chemical reactivity and behavior of the rest of the molecule has been extensively studied.[30-32] Examples of these cage compounds include **15-18.** Only trishomocubane **16** is chiral while the remaining cages illustrated below are *meso*-compounds (bearing a stereogenic center with a plane of symmetry).[1]

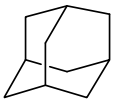
15, Pentacyclo-undecane (PCU)



16, Trishomocubane



17, Basketane

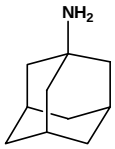


18, Adamantane

Cage compounds extend their applications into various important fields. A few examples of these applications include:

Pharmaceuticals

A well known example of a cage compound employed as a pharmaceutical drug is the anti-Parkinson's drug adamantan-1-amine **19**.[33]

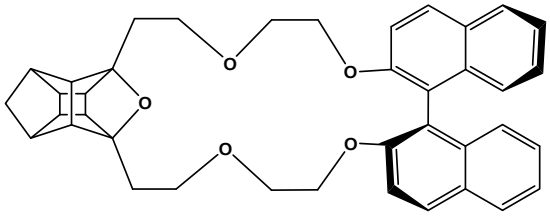


19

The cage structure is a useful scaffold to deliver drugs and can also be used to modify and improve the pharmacokinetic and pharmacodynamic properties of drugs.[30] However, to date not many enantiopure cage compounds with promising pharmaceutical characteristics have been reported.[33]

Chiral Recognition

Chiral molecular recognition is an important aspect in various fields of chemistry such as asymmetric catalysis,[34] enzyme mimics[35,36] and enantiomeric separation of racemates. Consequently, there is considerable interest in ligands that have potential in monitoring chiral host-guest recognition events.[37] Marchand *et al.* incorporated the PCU cage with the chiral binaphthol crown ether and this macrocycle **20** showed promising enantioselectivity towards recognition of chiral ammonium ions.[38]



20

Compounds of this type and related analogues form a new class of binaphthol host systems for the study of host-guest interactions.

Since then members of our research group* have been involved in the synthesis of a number of chiral PCU ligands.[4,39,40] A short summary of the chiral ligands from our group demonstrating the application of these compounds in asymmetric catalysis is presented below.

Asymmetric Catalysis

PCU cage compounds **21-23** have been incorporated into macrocycles and used as successful chiral catalysts in the alkylation of benzaldehyde with diethylzinc and Michael addition reactions.[4,39,40]

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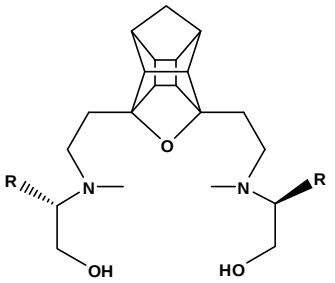
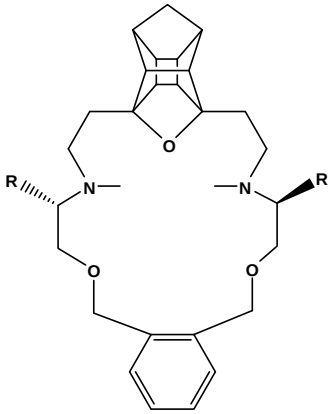
* See www.ukzn.ac.za/ggkm/ggkm.htm date accessed 1/10/08



21

a) R = CH_2CH_3
b) R = $CH(CH_3)_2$
c) R = $CH_2CH(CH_3)_2$
d) R = C_6H_5



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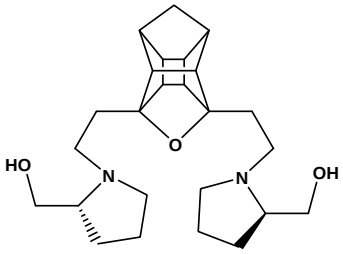


23

For the purpose of this project, a strategy was developed to synthesize novel PCU derived ligands for studying a typical asymmetric Diels-Alder reaction.

1.6 Scope of Investigation Pertaining to Asymmetric Catalysis

This project focused on the incorporation of the PCU cage as part of novel chiral ligands. Since this cage has two 'arms', it was an attractive option to combine the chemistry of the cage and chiral auxiliaries to act as a host to bind to metal ions serving as Lewis acid catalysts (molecules or ions capable of coordinating with unshared electron pairs).[2] The PCU cage renders the 'faces' of the ligand inherently diastereotopically non-equivalent, therefore it is expected to play a significant role in asymmetric induction when tested in an enantioselective reaction.

1.7 The Diels-Alder Reaction

Since the discovery of the Diels-Alder cycloadditon reaction in 1928[41] there have been more than 17 000 papers published up to 2002 on the synthetic, mechanistic and theoretical aspects of this reaction.[42] This reaction plays a prominent role in organic chemistry as it creates two new σ–carbon–carbon bonds forming a cyclic molecule in a regio- and stereo-controlled manner. In addition, this reaction can also form carbon-heteroatom and heteroatom-heteroatom bonds. As a

result the Diels-Alder reaction has become an essential tool for constructing simple and complex molecules.[42] It involves a reaction between a conjugated diene **24** and a dienophile **25** (a compound that has at least one π bond) to form a cyclic product **26** as illustrated in Figure 1.2.[2]

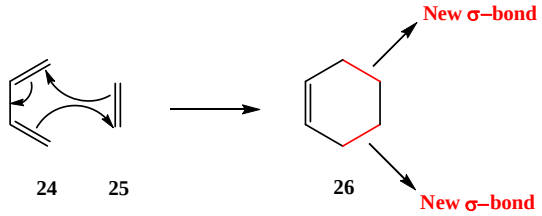
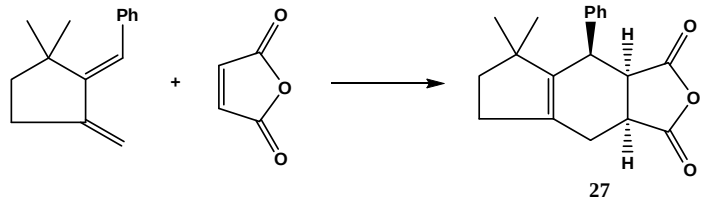
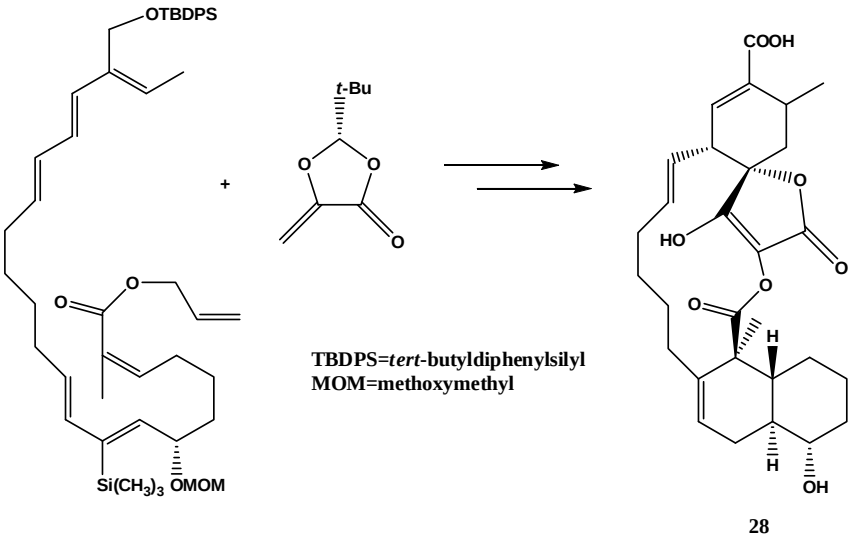


Figure 1.2 Typical Diels-Alder reaction mechanism.

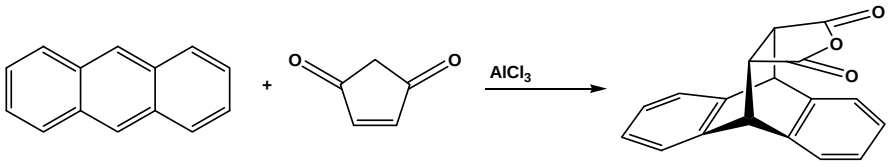
Diels-Alder reactions can be carried out under various experimental conditions encompassing a variety of different dienes and dienophiles and can take place *via* intramolecular or intermolecular additions.[42] An example of an intermolecular addition is the synthesis of the tricyclic compound **27**[43] while a combination of intermolecular and intramolecular additions take place in the synthesis of the more complicated molecule **28**[44], an anti-biotic agent.





The discovery that Lewis acids could promote Diels-Alder reactions sparked great interest and has become invaluable to synthetic organic chemists. In 1960 Yates *et al.*[45] reported the first

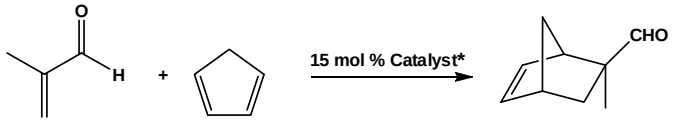
example of a Lewis acid catalyzed non-chiral Diels-Alder reaction of anthracene **29** and maleic anhydride **30** in the presence of aluminum chloride.[17,45]



29 **30** **31**

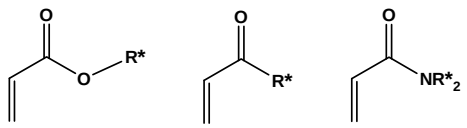
With Catalyst $t_{1/2}$ = < 1 min
Without Catalyst $t_{1/2}$ = 2400 hr

This breakthrough had important practical ramifications as it demonstrated that the Diels-Alder reaction could take place with the presence of an electropositive metal acting as a catalyst.[17] In 1979 Koga *et al.* reported the first practical example of a catalytic enantioselective Diels-Alder reaction of acrolein **32** and cyclopentadiene **33** in the presence of 'menthoxyaluminum dichloride' as the chiral* catalyst to yield the *exo*-cycloadduct **34**.[46]



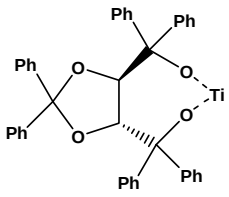
32 **33** **34 (74 % ee)**

This chiral catalyst was derived from menthol and ethylaluminum dichloride, but its structure remains undefined.[17] Subsequent studies found Lewis acid catalysts to not only increase the rate of the cycloadditon but allow the reaction to proceed under milder conditions; to enable regio- and stereoselectivity of the chiral products and permit reactions of unusual dienes and dienophiles that would not normally proceed.[17,42] Over the years a tremendous amount of Lewis-acid catalysts have been reported, including the common Lewis acids such as $AlCl_3$, $TiCl_4$, $SnCl_4$ etc., lanthanide complexes, most of which are metal-ligand complexes derived from chiral ligands. Asymmetric Diels-Alder reactions involving chiral dienophiles **35-37** form a major component in this class of organic reactions and metal-ligand complexes as catalysts for these reactions are rapidly developing, as it allows the control of enantioselectivity of the reaction product.[5,17,18,42]



35 **36** **37**

Several of these complexes have been evaluated, examples of a few that have had a profound impact on various asymmetric Diels-Alder reactions are illustrated below **38-42**. (Please note that all ligands on metal centre are not displayed).[47-50]



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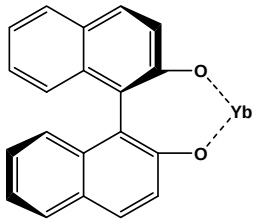

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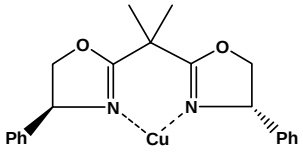

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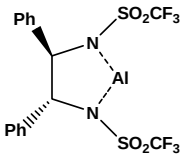

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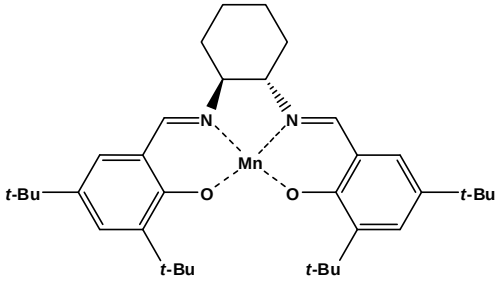


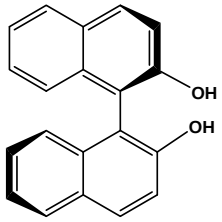
42

The following chapters describe in further detail the novel PCU based chiral ligands investigated for this project. Chapters 2 and 3 briefly discuss PCU-diol and PCU bisimine based ligands respectively. Unfortunately the synthesis of these ligands proved to be difficult and products were unstable, therefore catalytic evaluation was not carried out. Chapter 4 discusses the PCU-bis (oxazoline) derived ligand in depth since the synthesis of the ligand was successful and its potential in a Diels Alder type reaction was evaluated.

Chapter 2

2.1 Chiral Diol Ligands

From a variety of chiral auxiliaries/ligands, chiral diols have contributed a major part since many diols can be obtained from natural sources and are synthons for diamine and diphosphine compounds.[51] Thus numerous chiral 1,2-, 1,3- and 1,4-diols have been found to be efficient chiral ligands. Some popular chiral diol ligands **43-46** that have displayed excellent enantioselectivity in various asymmetric reactions are illustrated below.[17,51-55] These ligands are versatile as they can be applied to a range of asymmetric reactions. However, only their application in Diels-Alder reactions will be discussed here.



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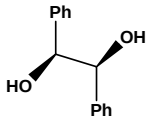

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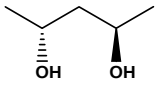
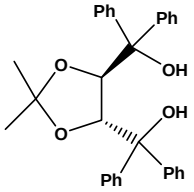
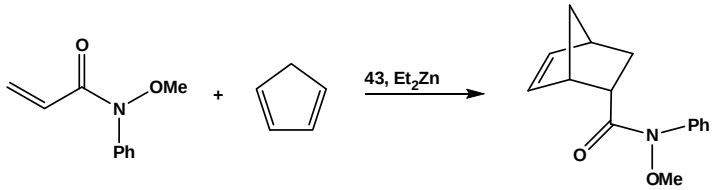


45



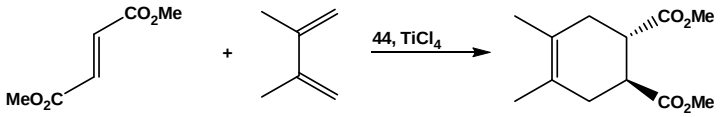
46

(*R*)-1,1'-Binaphthyl-2,2'-diol **43** commonly known as BINOL is one of the most widely used ligands for asymmetric catalysis.[5,17,47,56,57] Its use in a range of Diels-Alder reactions have been explored by several researchers.[47,58] An example is the reaction of an *N*-alkylacrylamide **47** with cyclopentadiene **33** catalyzed by (*R*)-BINOL **43** and diethylzinc to yield the *endo*-adduct **48**.[59]



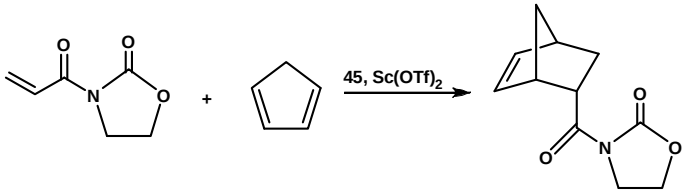
47 **33** **48 (96 % ee)**

Devine *et al.* showed that the titanium Lewis acid catalyst derived from (*R,R*)-hydrobenzoin **44** and titanium chloride showed promising enantioselectivity in the reaction with the less reactive carboxylic ester dienophile **49** and 1,3 diene **50** to furnish the cyclic adduct **51**.[60]



49 **50** **51 (92 % ee)**

The chiral diol (*R,R*)-2,4-pentanediol **45** has been used to promote the benchmark Diels-Alder reaction of 3-acryloyloxazolidin-2-one **52** and cyclopentadiene **33** to yield the *endo* product **53**.[61]

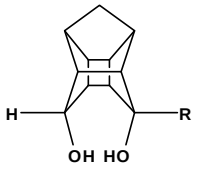


52 **33** **53 (83 % ee)**

Several other chiral diol ligand-metal complexes that have been used to catalyze Diels-Alder type reactions are reported in literature.[51,47,62,63]

2.2 PCU Diol Ligands

Inspired by the success of the above mentioned ligands in Diels-Alder type reactions it was decided to design PCU-diol type chiral ligands **54a-d** from the general PCU cage skeleton **15**.



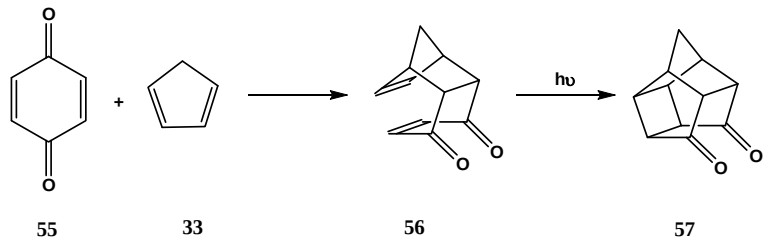
a) R = C_6H_5
b) R = $(C_6H_5)_2$
c) R = $CH(CH_3)_2$
d) R = $CH_2CH(CH_3)_2$

54a-d

However, classical synthesis of these compounds **54a-d** will produce racemic mixtures. In order to synthesize the above PCU-diol ligands in optical pure form, the *meso* nature of the PCU cage **15** had to be altered at some stage as only one enantiomer of the ligands **54a-d** was required. Naemura *et al.* reported a procedure to obtain optically pure PCU derivatives by carrying out an enzyme-catalyzed reduction on the PCU dione which is the starting material for the above ligands.[64] As mentioned in chapter 1, enzymatic catalysts are commonly used to influence changes on unnatural substrates stereoselectively.[26]

2.3 Synthesis of PCU-Diol Ligands

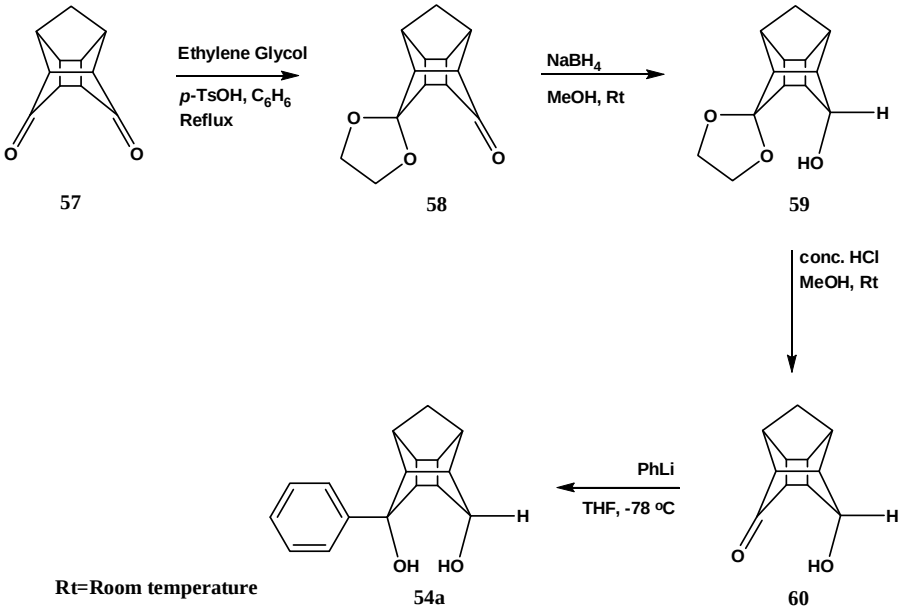
For all PCU ligands discussed in this project the overall starting material was the PCU dione **57**.[65,66] Coincidently, the synthesis of the PCU dione involves the Diels-Alder reaction of *p*-benzoquinone **55** and cyclopentadiene **33** to afford the adduct **56** which then undergoes a photochemical reaction resulting in the PCU dione **57** as shown in Scheme 2.1.[65,66]



55 **33** **56** **57**

Scheme 2.1 Synthesis of the PCU dione 57

Initially it was decided to synthesize the PCU-diol ligand **54a** as a racemate for two reasons. Firstly the high cost of the enzyme which was required to induce asymmetry onto the cage and secondly a literature survey revealed that these ligands were the first example in which lithiation techniques were going to be employed to attach aromatic moieties directly to the PCU cage (Scheme 2.2). Once proof of concept was established, one could revert to chiral synthesis of the desired product(s). Note that all the intermediates below were obtained as racemates.

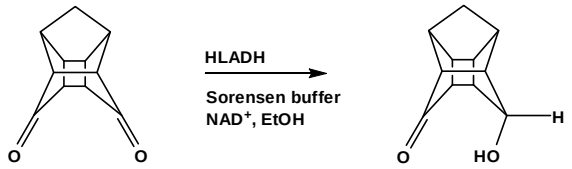


57 **58** **59** **60** **54a**

Scheme 2.2 Synthesis of novel PCU-diol ligand 54a

The synthetic route from the PCU dione **57** to the hydroxyl ketone **60** was carried out from established procedures.[67-70] The PCU dione **57** was treated with ethylene glycol under Dean-

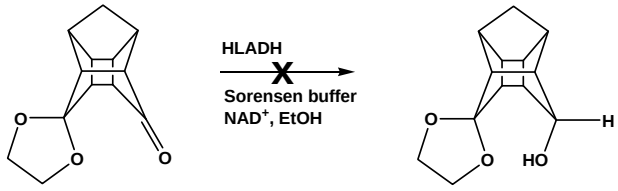
Stark conditions to yield the racemic mono-protected ketal **58**. The ketal **58** was then reduced using sodium borohydride to the *endo*-hydroxy acetal **59**. Thereafter the ketal group was removed by treatment of **59** with hydrochloric acid to yield the hydroxyl ketone **60**. The hydroxyl ketone **60** was then reacted with excess phenyllithium at -78 ^{O}C to furnish the novel racemic ligand **54a**. The structure of this ligand was confirmed by ^{1}H and ^{13}C NMR spectra and the full 2D NMR elucidation was recently published.[71] Once the synthetic route to the ligand was established, the enzyme horse liver alcohol dehydrogenase (HLADH) was applied to the PCU dione **57** to obtain the optically pure hydroxyl ketone **60** as outlined by Naemura *et al.* (Scheme 2.3).[64]



57 **60**

Scheme 2.3 Enzyme-catalyzed reduction of PCU dione 57

The PCU dione **57** was incubated at room temperature in a Sorensen phosphate buffer containing the HLADH for 72 hours (until which time no staring material was observed on thin layer chromatography [TLC] plates). Analysis of the product obtained from the enzyme-catalyzed reduction using high pressure liquid chromatography (HPLC) with a chiral column indicated that this product **60** was racemic. According to literature only one other group[72] has been able to reproduce the results obtained by Naemura *et al.*[73] It was decided that perhaps the enzyme was not fresh enough, therefore the reaction was carried out again with a new batch of HLADH but the product **60** was still obtained as a racemate. It was also decided to carry out the enzyme-catalyzed reduction on the mono-protected ketal **58** with the fresh batch of HLADH since the protecting group could assist in the stereochemical recognition (Scheme 2.4).

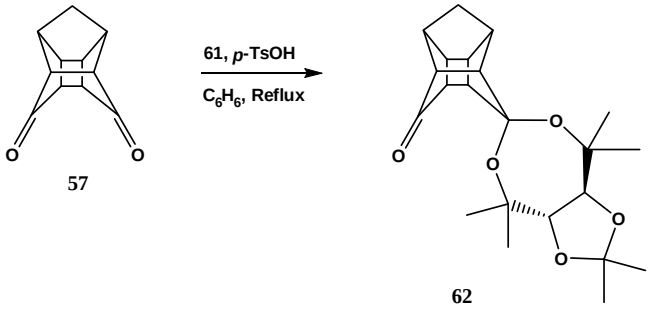


58 **59**

Scheme 2.4 Attempted enzyme-catalyzed reduction of PCU mono-protected ketal 58

Tracking this reaction for several days indicated that only starting material was present on TLC and no reaction had occurred. Another approach was required to obtain the hydroxyl ketone **60** in

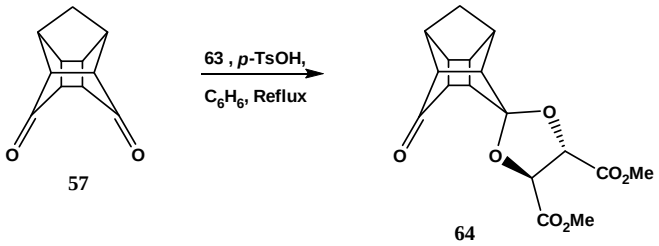
its optically pure form. The PCU dione **57** was treated with (4*S*,5*S*)-4,5-bis([1-hydroxy-1-methyl]ethyl)-2,2-dimethyl-1,3-dioxolane **61** under Dean-Stark conditions (Scheme 2.5) in the hope that this bulky protecting group would form the novel pair of diastereomers **62** that could be separated using column chromatography.



57 62

Scheme 2.5 Protection of the PCU dione 57

However, separation of these diastereomers **62** proved to be challenging. Based on the same principle another protecting group, (2*S*,3*S*)-dimethyl tartrate **63** was employed (Scheme 2.6) but unfortunately these novel diastereomers **64** also could not be separated by column chromatography.



57 64

Scheme 2.6 Protection of PCU dione 57

Several recrystallization attempts were carried out on the mixtures of **62** and **64** with the expectation that one of the diastereomers could possibly precipitate out of solution but none of these attempts proved to be successful.

2.4 Conclusion

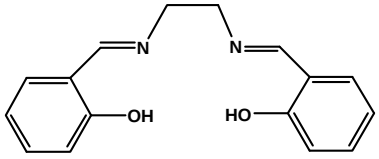
An NMR elucidation of the novel racemic ligand **54a** and related compounds was recently published.[71] The fact that these ligands can be easily obtained *via* lithiation techniques makes further investigation into methods to obtain optically pure PCU precursors a worthwhile study. A possible start could be by applying other types of enzymes on the PCU dione. A second option is to reduce **62** with sodium borohydride and then try to achieve separation of the resulting diastereomeric alcohols. Once symmetry of the PCU cage is broken by reacting one of the ketone

groups in a stereo-controlled manner it has the potential to open up an exciting new field of PCU ligands that will not be limited to diol type ligands but various other types of chiral ligands.

Chapter 3

3.1 Chiral Salen Ligands

'Salen' is an acronym that refers to a family of bisimine compounds with a *N,N'*-bis(salicylidine)ethylenediamine **65** framework.[74] The salen ligand **66** was commercialized in 1994. It is commonly referred to as 'Jacobsen's ligand' and is well known for its breakthrough in asymmetric epoxidation[75] reactions although it has shown to be highly effective in numerous other asymmetric reactions when complexed to different metals.[48,57,75,74,76-78] Following the lead of Jacobsen, several other research groups expanded the scope of chiral salen ligands **66-69**. As a result a wide variety of chiral salen-metal complexes have been developed and serve as efficient chiral catalysts in many different asymmetric reactions.[57,79-82]



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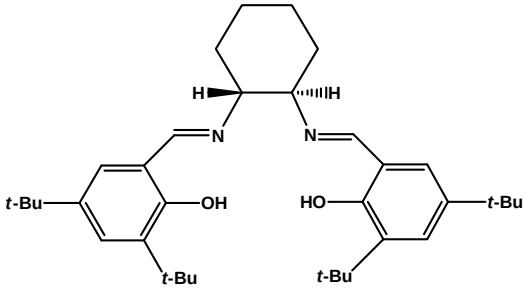
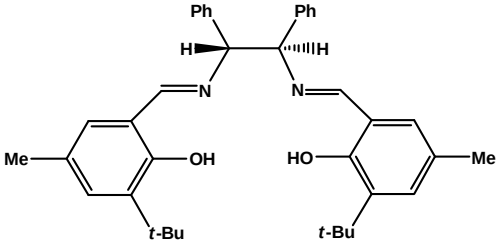


66



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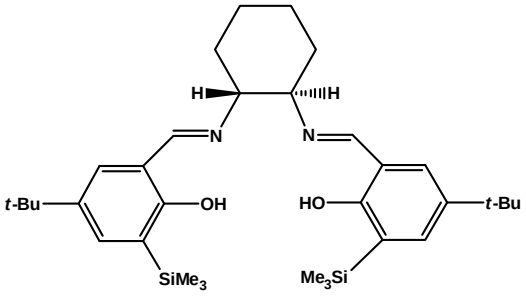

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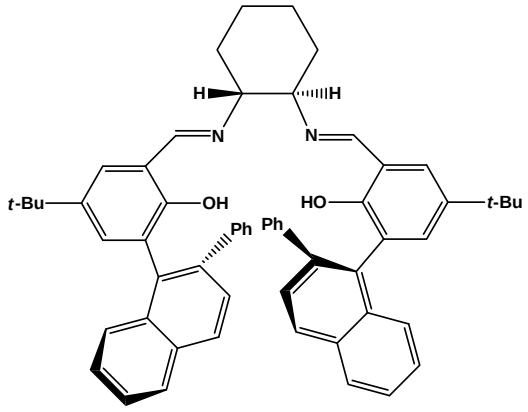
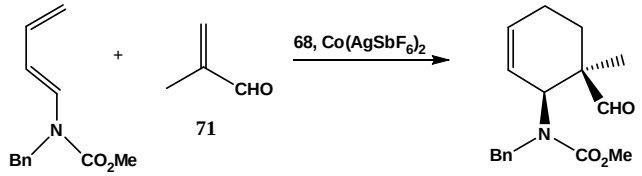


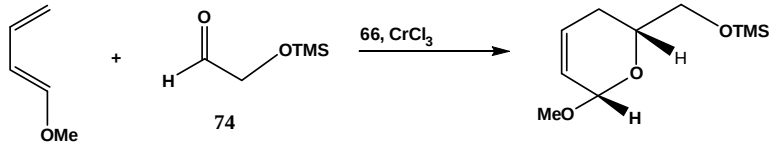
69

Amongst several salen analogue catalysts developed, mainly ligand **66** has been investigated for its application in asymmetric Diels-Alder reactions. Rawal *et al.* documented the enantioselectivity of the Diels-Alder reaction between 1-amino-1,3-butadiene and substituted acroleins catalyzed by **66**-chromium (III) complexes to be generally greater than 90 %.[78,83-85] They extended their studies to include the trialkylsilyl substituted salen ligand **68** with cobalt (II) in the reaction between the carbamate-substituted diene **70** and methacrolein **71** to afford the cycloadduct **72**.[78]



70 **71** **72 (95 % ee)**

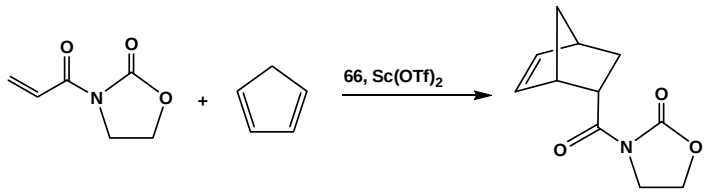
Jurczak *et al.* investigated the Hetero-Diels-Alder reaction between 1-methoxybuta-1,3-diene **73** and *tert*-butyldimethylsilyoxyacetaldehyde **74** catalyzed by a **66**-chromium (III) complex yielding product **75**.[86]



73 **74** **75 (94 % ee)**

TMS = trimethylsilyl

The potential of ligand **66** with scandium in another Diels-Alder reaction was demonstrated by Fukuza *et al.* between 3-acryloyloxazolidin-2-one **52** and cyclopentadiene **33** to yield *endo*-**53** as the major product.[61]

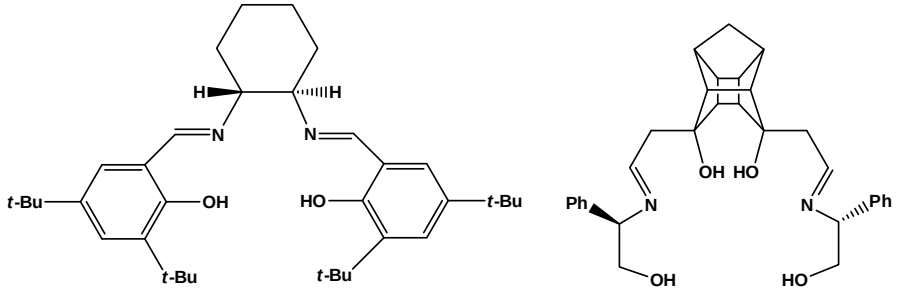


52 33 53 (85 % ee)

A literature survey revealed that amongst many salen analogues, ligand **66** has been most often investigated for Diels-Alder reactions.

3.2 PCU Bisimine Ligand

Due to the success of the salen backbone (such as for **66**), it was decided to design the PCU bisimine type ligand **80**. This ligand differs from the typical salen framework as it possesses four aliphatic hydroxyl groups. Despite this difference, the presence of the imine functionality which is known to be well suited to form complexes with metal ions[87] and the close proximity of the PCU hydroxyl groups it was anticipated that ligand **80** could perhaps act as a Lewis acid catalyst when complexed to a metal ion. In addition, it would be interesting to determine (if possible) whether there would be a competition between the pairs of hydroxyl groups to complex with the metal ion.



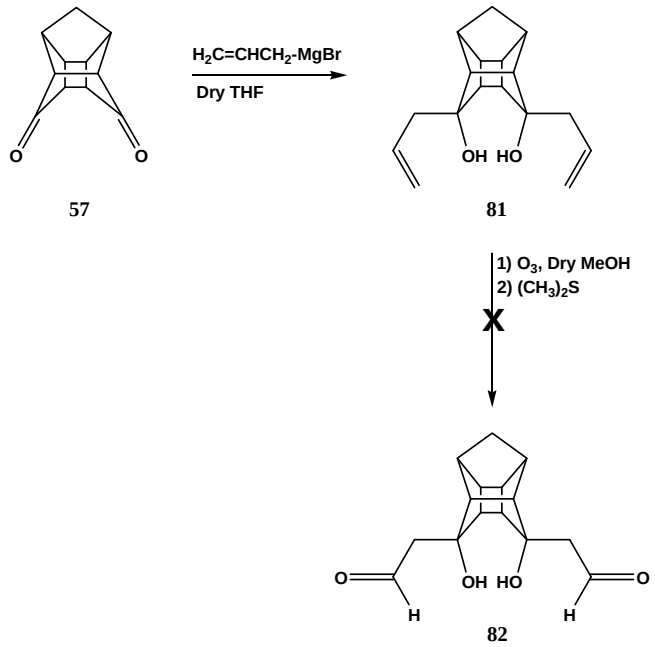
66 80

Another attractive feature of this ligand was the envisaged final step of the synthesis which involves a simple Schiff base condensation[2] reaction between the PCU dihydroxy dialdehyde and an amino alcohol.[74]

3.3 Synthesis of PCU Bisimine Ligand

The starting material for the synthesis was the PCU dione **57**. The dione **57** underwent a Grignard reaction with allylmagnesium bromide to yield the *endo*-3,5-diallyl-4-oxahexacyclo [5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$] dodecane **81** as described from established procedures.[39,40,88] This PCU diol-diene **81** then underwent ozonolysis followed by a reductive workup using dimethyl

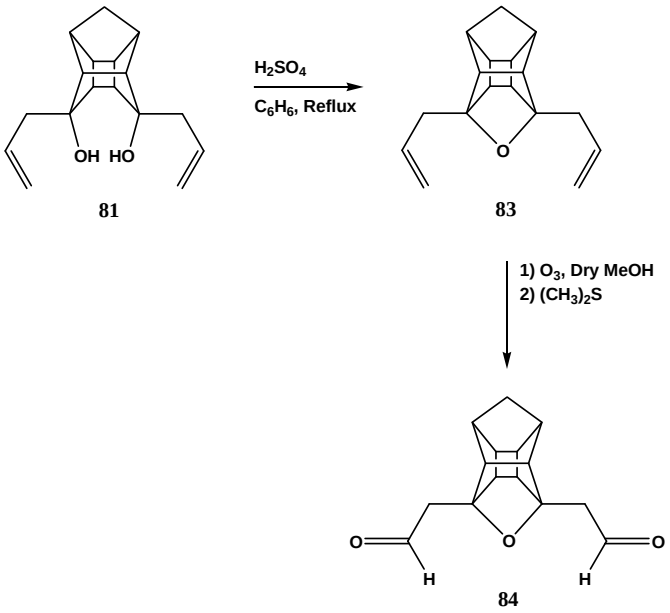
sulphide (a mild reducing agent) in attempt to yield the novel PCU dialdehyde **82** as outline in Scheme 3.1**.** The crude ^{1}H spectrum of this compound **82** indicated the presence of the aldehyde peak but unfortunately it could not be purified using chromatographic or recrystallization techniques.



57 81 82

Scheme 3.1 Attempted synthesis of PCU dihydroxy dialdehyde 82

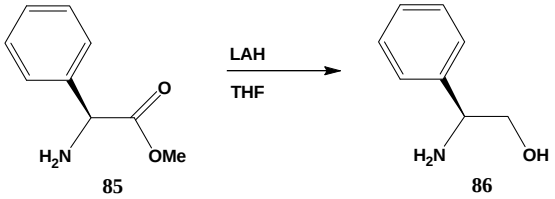
Due to keen interest in PCU bisimine type ligands, further thought was necessary to design the initial ligand **80**. It was decided to replace the hydroxyl groups in **82** with an ether bridge since the absence of the polar hydroxyl groups would make purification *via* chromatography easier and also previous work on the PCU ether derivatives have been reported.[4,40] The *endo* diol-diene **81** was dehydrated with a catalytic amount of sulphuric acid in a Dean-Stark apparatus to produce the PCU ether diene **83**.[4,89] Ozonolysis of **83** followed by a reductive workup using dimethyl sulphide, afforded the novel PCU ether dialdehyde **84** as illustrated in Scheme 3.2 which was purified using column chromatography. The aldehyde **84** proved to be stable for only 24 hours. Nevertheless, it was decided that this was sufficient time for further derivatisation of this compound **84**.



81 83 84

Scheme 3.2 Synthesis of PCU ether dialdehyde 84

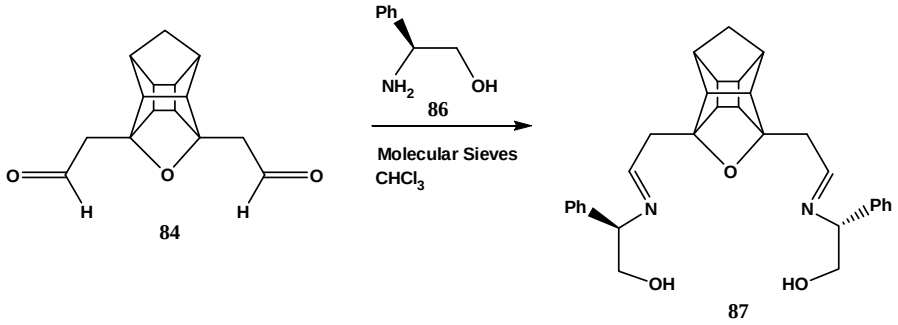
Commercially available (*S*)-phenylglycine methyl ester **85** was reduced to the corresponding amino alcohol **86** using lithium aluminum hydride (Scheme 3.3).[90] The amino ester was preferred over the amino acid as the ester proved to produce higher yields upon reduction.



85 86

Scheme 3.3 Reduction of (*S*)-phenylglycinol 86

A Schiff base condensation reaction of **84** with **86** in the presence of molecular sieves afforded the novel PCU ether bisimine ligand **87** as shown in Scheme 3.4.[74]



Scheme 3.4 Synthesis of PCU ether bisimine ligand 87

Ligand **87** was stable for an hour, therefore only the ^{1}H and ^{13}C spectra were obtained. Due to the instability of ligand **87** and its precursor **84** it was decided that *in situ* complexation and testing of this ligand would be very difficult.

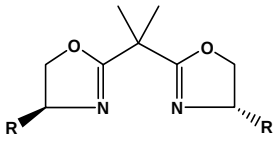
3.4 Conclusion

The full NMR elucidation of the novel PCU ether dialdehyde **84** and other PCU derivatives was recently published.[91] Due to the difficulty in the purification of the precursor **82,** instability of **84** and PCU ether bisimine ligand **87** further investigations into these types of ligands was not pursued.

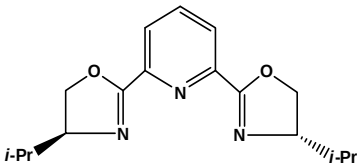
Chapter 4

4.1 Chiral Bis(oxazoline) Ligands

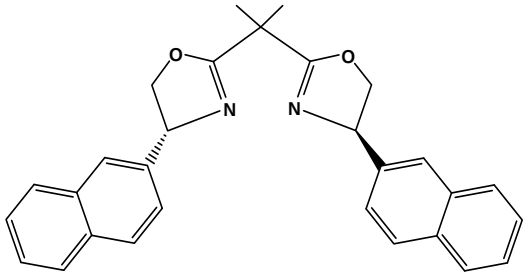
C_2-symmetric bis(oxazoline) ligand-metal complexes have become one of the most versatile and commonly used classes of chiral catalysts.[50,92-96] Interest in these type of ligands for asymmetric catalysis was initiated in 1991 by two successive communications. First by Evans *et al.* and then by Corey *et al.* for work on asymmetric cyclopropanation of alkenes[97] with ligand **89** and Diels-Alder reactions[98] with ligand **90** respectively. Subsequently, bis(oxazoline) type molecules quickly became widely accepted and popular as bidentate ligands due to its facile synthesis and remarkable enantioselectivities achieved for the above types of reactions. A large majority of these ligands are derived from readily available chiral amino alcohols. The enantiocontrolling stereocenter lies adjacent to the coordinating nitrogen of the oxazoline ring bringing the active metal in close proximity to the stereogenic centers.[95,99] Over the years, bis(oxazoline) type ligands have developed further by incorporation of two or more oxazoline rings, a range of heteroatoms, additional chiral elements and other structural motifs as demonstrated with structures **91-99**.[50,95,100]



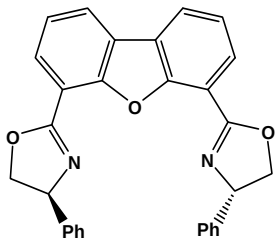
89 (R = *t*-Bu)
90 (R = Ph)



91



92



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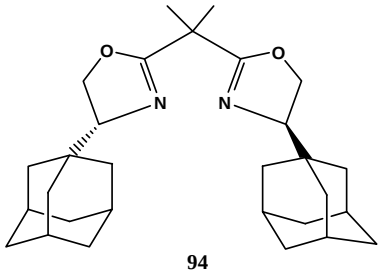

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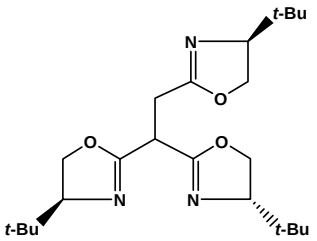

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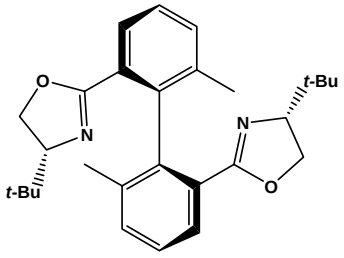

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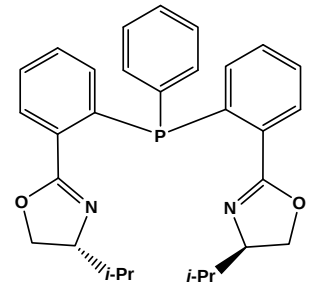

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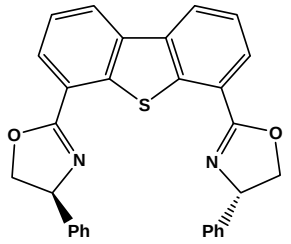

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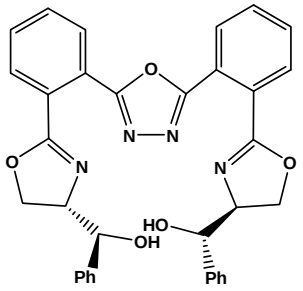
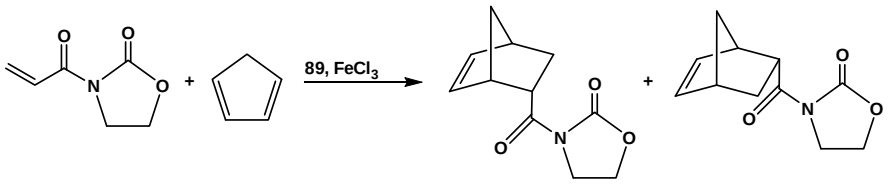


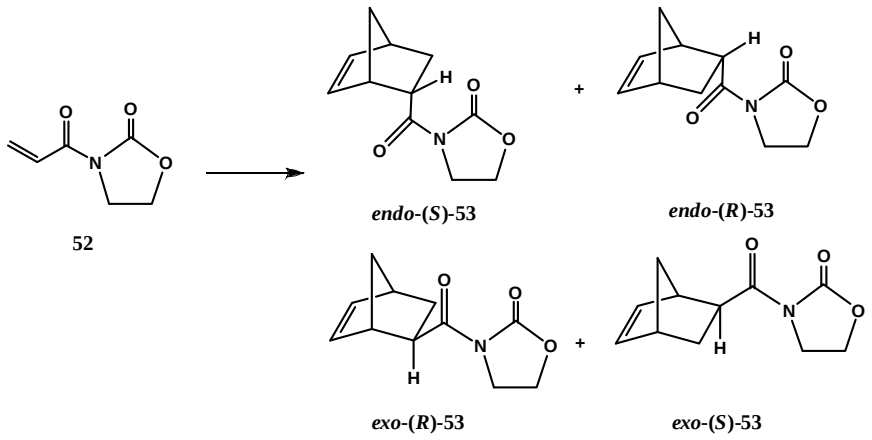
99

The diverse range of these ligands when complexed to different metals have found widespread applications as successful chiral catalysts in a variety of asymmetric reactions such as, Friedel-Crafts,[101] Heck,[102] pinacol coupling,[103] epoxidation of olefins,[104] allylic oxidation,[105] Michael addition,[106] Hetero-Diels-Alder[107] and Mukaiyama aldol[94] reactions etc. However, only their application in Diels-Alder reactions will be discussed for the purpose of this study. Corey *et al.* first described the use of the chiral bis(oxazoline) ligand **90** in the enantioselective Diels-Alder reaction between 3-acryloyloxazolidin-2-one **52** and cyclopentadiene **33** catalyzed by the complex of **89** with iron (III). The reaction product **53** was found to be *endo*-selective with an *endo:exo* ratio of 96:4.[98]



52 **33** **(*S*)-53 (82 % ee)** **(*R*)-53**

There are four different ways the diene **33** can approach the dienophile **52**. Firstly, the dienophile **52** can either attack from above the plane of the paper and secondly from below the plane of the paper. (*R*)-**53** is formed *via* attack of the diene **33** from above the plane of the paper and (*S*)-**53** is the result of the diene attacking from below the plane of the paper. The chiral catalyst is supposed to limit the formation of one enantiomer over the other.[50] During the reaction of the substrates (**52** and **33**) in the presence of the chiral catalyst **89**, the top side of attack is blocked or hindered to such an extent that *endo*-(*S*)-**53** is almost exclusively observed. Note that in both these cases the diene **33** approaches the dienophile **52** with the CH_2-group pointing away from the carbonyl oxygen of **52**. This is the more kinetically preferred approach and leads to what is called the *endo*-product.



The last two possibilities are both the result of the diene **33** attacking the dienophile **52** with the CH_2-group pointing towards the carbonyl carbon of **52**. Again, two products are possible (i.e attack of the diene from either above or below the plane of the paper). *Exo*-(*S*)-**53** forms when attack is from below the plane of the paper and *exo*-(*R*)-**53** forms when attack occurs from above the plane of the paper. This approach is the less kinetically preferred and leads to what is called the *exo*-product.[2]

There are various other examples of asymmetric Diels-Alder reactions between several different dienophiles and dienes that have been tested under different conditions with bis(oxazoline) derived catalysts, but the reaction between 3-acryloyloxazolidin-2-one **52** and cyclopentadiene **33** is the most extensively studied.[108-111] This reaction is accepted as the 'standard' test for the efficiency of bis(oxazoline) derived catalysts since the *endo:exo* ratio of the product can be easily determined by ^{1}H NMR and the enantioselectivity by chiral HPLC analysis.[100] Therefore only this particular Diels-Alder reaction with a few important examples of bis(oxazoline) derived ligands will be discussed here (Table 4.1).

Complexes of ligands **89-90** have been thoroughly investigated for its role as a catalyst in the above mentioned reaction by changing the metal, counterion, solvent, temperature and the effects of different additives. The best metal for ligand **89** appears to be Cu(II) and the best counterions are OTf^{-1} and SbF_6^{-1} (Table 4.1, entries 1-2). The ideal combination for ligand **90** was reported with $Zn(SbF_6)_2$ as the metal salt (Table 4.1, entry 3).

Table 4.1 Summary of the best results obtained for the reaction between 3-acryloyloxazolidin-2-one 52 and cyclopentadiene 33 catalyzed by ligands 89-94 with CH_2Cl_2 as the solvent.

Entry	Ligand	Metal salt	Temp. (°C)	Yield (%)	Endo:exo	Time (hours)	Endo ee (%)	Ref.
1	(*S*)-**89**	$Cu(OTf)_2$	-78	86	98:2	1	>98 (*S*)	112-115
2	(*S*)-**89**	$Cu(SbF_6)_2$	-78	>95	96:4	4	>98 (*S*)	112,116
3	(*S*)-**90**	$Zn(SbF_6)_2$[a]	-78	>90	98:2	8	92 (*R*)	112,116
4	(*S*)-**91**	$Sc(OTf)_3$	-78	63	98:2	2	82 (*S*)	117
5	(*R*)-**91**	$La(OTf)_3$	-20	>99	69:31	16	>99 (*R*)	118
6	(*R*)-**92**	$Mg(OTf)_2$	-50	>99	89:11	16	94 (*R*)	119
7	(*R*)-**93**	$Ni(ClO_4)_2$[b]	-40	96	97:3	14	>99 (*S*)	120
8	(*R*)-**94**	$Cu(SbF_6)_2$	-84	66	92:8	[c]	98 (*R*)	121

[a]Addition of molecular sieves, [b]The hexahydrate was salt used, [c]Not reported.

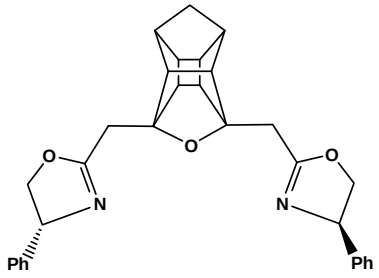
Studies on ligands **89-90** with respect to its coordination geometry and electronic properties aided by single crystal X-ray data and NMR analysis have also been carried out to understand their function in asymmetric reactions.[122,123] An interesting analysis of the above reaction occurred with (*R*)-**90** and $Mg(ClO_4)_2$.[50,122] When the counterion is perchlorate the product of the reaction is (*S*)-**53**, but if two equivalents of water are added to the reaction the product obtained is (*R*)-**53**. If the counterion is changed to triflate the reaction product is (*R*)-**53** and no change occurs to the enantioselectivity of the reaction product even if water is added. This result was rationalized by establishing that water acts as an auxiliary ligand that expands the coordination number from four (tetrahedral) to six (octahedral) when the counterion is perchlorate. The ligand-metal complex with the more nucleophilic triflate counterion already has an octahedral geometry and therefore does not change upon the addition of water.[50] This change in coordination is supported by NMR

spectroscopy experiments; the position of the water ligands was determined by replacing water with ethylene glycol.[122,124,125]

The best results for ligand type **91** were obtained with lanthanide complexes (Table 4.1, entry 4-5). Desimoni *et al.*[118] investigated the catalysts derived from **92** with different metal salts. The optimum results emerged with $Mg(OTf)_2$ (Table 4.1, entry 6). The cationic *aqua* complexes prepared from ligand **93** with various metal perchlorates were studied by Kanemasa *et al.*[120] with Ni(II) appearing to yield excellent enantioselectivity (Table 4.1, entry 7). Morena *et al.*[121] synthesized ligand **94** and tested the Cu(II) complexes of this ligand in several reactions including the above Diels Alder reaction (Table 4.1, entry 8). A trend displayed by all the catalysts mentioned above and in related literature is that an increase in enantiomeric excess results from a decrease in temperature since better kinetic resolution is obtained at lower temperatures. These low temperatures however, result in longer reaction times which sometimes becomes impractical. This literature review prompted the design of a novel PCU based bis(oxazoline) type ligand.

4.2 PCU Bis(oxazoline) Ligand

Motivated by the success of the bis(oxazoline) type ligands **89-99** and its application in Diels-Alder type reactions it was decided to design the novel PCU bis(oxazoline) derived ligand **100**.

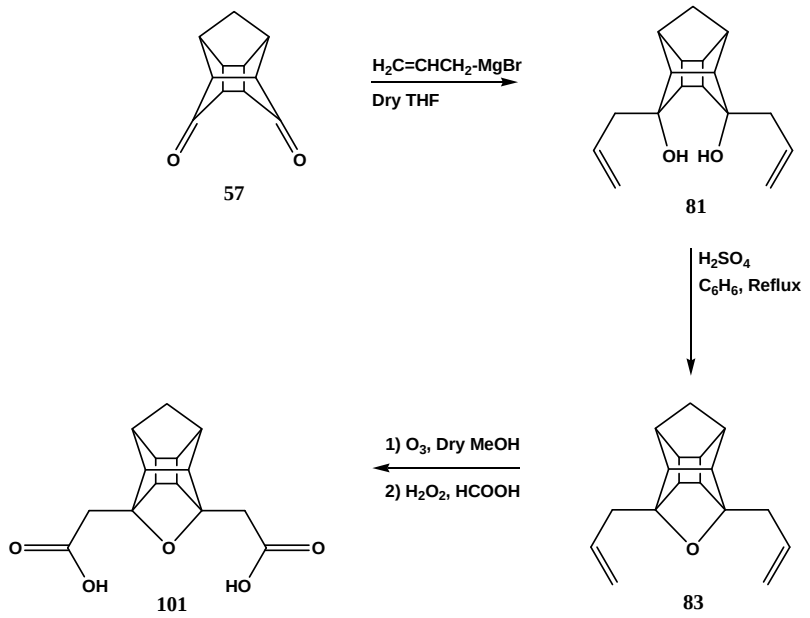


100

Since the PCU cage has two 'arms' it seemed promising to combine the chemistry of the cage with that of two oxazoline moieties to act as a chiral ligand for asymmetric catalysis. The PCU cage renders the 'faces' of the ligand inherent diastereotropically non-equivalent therefore it was expected to play a significant role in asymmetric induction when coupled with oxazoline moieties. It also offers a central ether type oxygen which could potentially participate in the binding of the metal, thus leading to a tridentate complex. Bis(oxazoline) catalysts complexes with this arrangement have not been pursued to any large extent for examples see references 120,126,127.

4.3 Synthesis of PCU Bis(oxazoline) Ligand

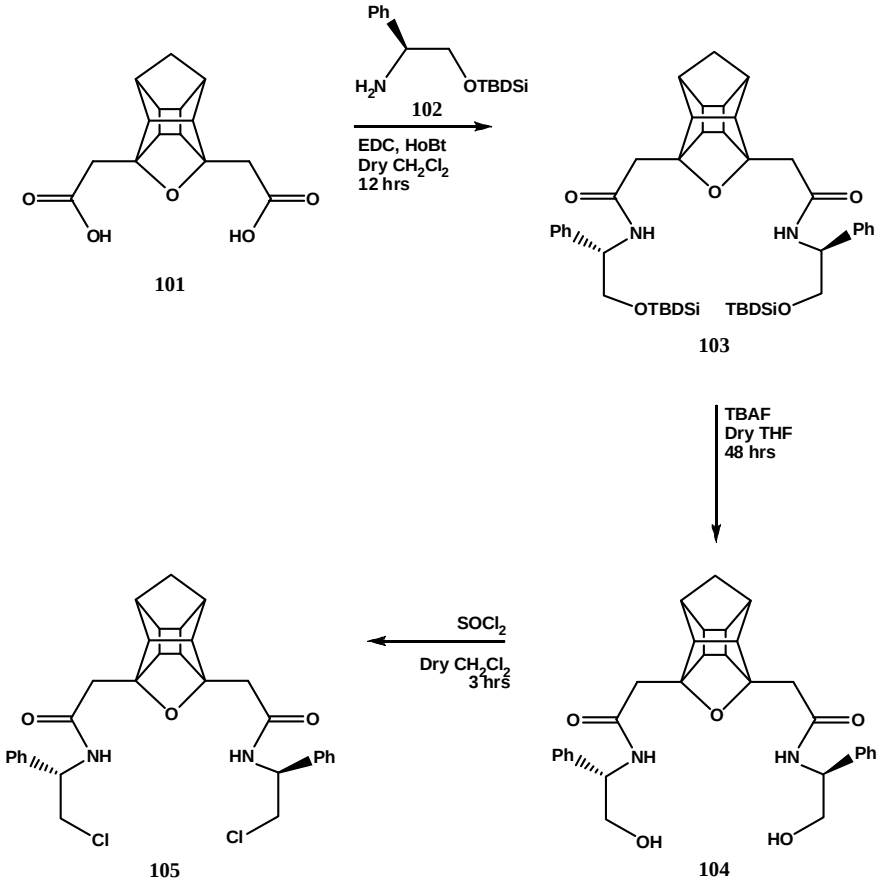
Synthesis of the novel PCU bis (4-phenyloxazoline) ligand **100** followed the classical route involving the reaction of a diacid derivative (in this case the PCU diacid) with an amino alcohol to give the bis-amide intermediate that is converted to the bis(oxazoline).[50,95] The PCU dione **57** was converted to the 3,5-diallyl-4-oxahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecane **83** as described in chapter 3.[40,88] Ozonolysis of **83** followed by an oxidative workup using formic acid and hydrogen peroxide afforded the PCU diacid **101** which was carried out from an established procedure as outlined in Scheme 4.1.[40]



Scheme 4.1 Synthesis of PCU diacid 101

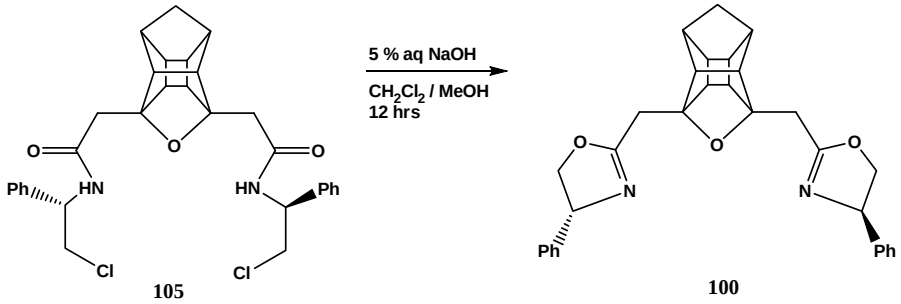
To avoid competing reactions due to the hydroxyl group on the amino alcohol **86** (Scheme 3.3) it was decided to protect the alcohol by using tertiary butyl dimethyl silyl chloride (TBDSi) to give *(S)-tert*-butyldimethylsilyl-2-amino-3-phenylpronoate **102.**[128] This protecting group is known to be selective towards hydroxyl groups in the presence of a primary amine. A *N,N*-dicyclohexylcarbodiimide (DDC) promoted condensation of the PCU diacid **101** with **102** afforded the novel protected PCU bis-amide **103** which was purified using column chromatography as adapted from literature.[129] The novel PCU bis-amino alcohol **104** was obtained by deprotection of **103** with tetra-*N*-butylammonium fluoride (TBAF) and purification was again achieved using column chromatography based on the related report.[128] Cyclization was achieved by the chlorination of **104** using thionyl chloride to give the PCU bis-chloride **105**

as shown in Scheme 4.2. Note that the source of chirality is (*S*)-**102** with the stereogenic center being unchanged in the remainder of the synthesis. The elucidation of these ligands with the use of conventional analytical techniques will be discussed later in this chapter.



Scheme 4.2 Synthesis of PCU bis-chloride 105

The PCU bis-chloride **105** was not isolated due to instability. The crude ^{1}H NMR spectrum for **105** displayed a downfield shift of the -CH_2Cl (5.02 ppm) in comparison with -CH_2OH (3.73 ppm) in **104**, which confirmed the synthesis of **105**. Hence, without further purification the PCU bis-chloride **105** was treated with aqueous sodium hydroxide[50,120] to yield the novel ligand PCU bis(4-phenyloxazoline) **100** as outlined in Scheme 4.3 The novel ligand **100** was isolated by column chromatography in 80 % yield from the PCU bis-amino alcohol **104**.



Scheme 4.3 Synthesis of the novel PCU bis(4-phenyloxazoline) 100

The full characterization of the novel compounds **100**, **103** and **104** will be discussed in section 4.5.2

4.4 Results

The efficiency of ligand **100** was tested with the benchmark enantioselective Diels-Alder reaction between 3-acryloyloxazolidin-2-one **52** and cyclopentadiene **33**. Various alkali earth and transition metals that are known to complex to bis(oxazoline) derived ligands were screened for the *in situ* formation of the catalyst complex with the ligand (*S*,*S*)-**100**. The enantioselectivities of the various metals are reported in Table 4.2. The complexation procedure involved the addition of an equimolar amount of the metal salt to a solution of the ligand in dichloromethane and the details are reported in the experimental section.[97]

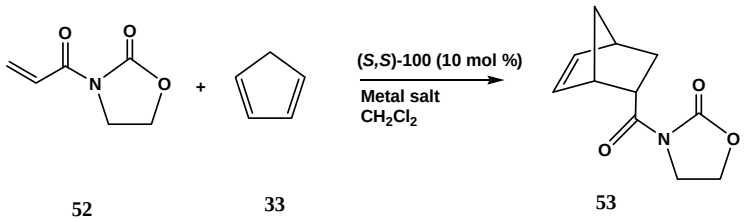


Table 4.2 Results obtained for the reaction between 3-acryloyloxazolidin-2-one 52 and cyclopentadiene 33 catalyzed by ligand (*S,S*)-100 complexed to various metal salts with CH_2Cl_2 as the solvent at room temperature.

Entry	Metal Salt	Time (min)	Yield (%)	Endo:exo[a]	Endo ee (%)[b]	Configuration (53)
1	Blank	240	80	96:4	0	-
2	$Ca(ClO_4)_2$	45	77	84:16	33	*R*
3	$Cu(ClO_4)_2$	30	71	86:14	25	*R*
4	$Zn(ClO_4)_2$	15	75	88:12	40	*R*
5	$Ni(ClO_4)_2$	120	60	83:17	25	*S*
6	$Mg(ClO_4)_2$	15	85	90:10	72	*S*
7	$Ba(ClO_4)_2$	150	17	80:20	0	-
8	$Al(ClO_4)_2$	20	86	83:17	0	-
9	$Co(ClO_4)_2$	45	86	86:14	28	*S*
10	$Fe(ClO_4)_2$	15	62	86:14	30	*S*
11	$Mn(ClO_4)_2$	60	78	89:11	36	*S*
12	$Cu(OTf)_2$	75	55	81:19	7	*S*
13	$Sc(OTf)_2$	15	62	85:15	5	*S*
14	$Ca(ClO_4)_2 \cdot 4H_2O$	45	80	86:14	43	*R*
15	$Zn(ClO_4)_2 \cdot 6H_2O$	15	71	88:12	56	*R*
16	$Ni(ClO_4)_2 \cdot 6H_2O$	30	73	88:11	20	*S*
17	$Mg(ClO_4)_2 \cdot 6H_2O$	30	82	90:10	70	*S*
18	$Co(ClO_4)_2 \cdot 6H_2O$	15	82	83:17	15	*S*
19	$Mn(ClO_4)_2 \cdot 6H_2O$	45	75	86:14	28	*S*

[a] Determined by ^{1}H NMR, [b] Determined by HPLC (Chiralpak IB).

Since anhydrous magnesium perchlorate gave the highest enantiomeric excess it was decided to optimize the solvent for this reaction.

Table 4.3 Effect of different solvents on the reaction between 3-acryloyloxazolidin-2-one 52 and cyclopentadiene 33 catalyzed by ligand (*S*,*S*)-100 complexed to $Mg(ClO_4)_2$ at room temperature.

Solvent	Time (min)	Yield (%)	Endo:exo	Endo ee (%)
DCM	15	85	90:10	72 (*S*)
THF	150	87	89:11	2 (*S*)
CH_3CN	240	80	92:8	14 (*S*)

Once it was established that dichloromethane (DCM) was the best solvent it was decided to optimize the counterion of the metal-ligand complex.

Table 4.4 Effect of different counterion on reaction between 3-acryloyloxazolidin-2-one 52 and cyclopentadiene 33 catalyzed by ligand (*S*,*S*)-100 and Mg with CH_2Cl_2 as the solvent at room temperature.

Metal salt	Time (min)	Yield (%)	Endo:exo	Endo ee (%)
$Mg(ClO_4)_2$	15	85	90:10	72 (*S*)
$MgBr_2$	240	60	90:10	2 (*S*)
$MgCl_2$	150	48	92:8	8 (*S*)
$Mg(OTf)_2$	120	73	91:9	17 (*S*)
$Mg(SbF_6)_2$	30	95	92:8	23 (*S*)

Thereafter the effect of catalytic loading, addition of additives and temperature on this reaction, was investigated.

Table 4.5 Effect of different catalytic loading, additives and temperature on reaction between 3-acryloyloxazolidin-2-one 52 and cyclopentadiene 33 catalyzed by ligand (*S*,*S*)-100 complexed to $Mg(ClO_4)_2$ with CH_2Cl_2 as the solvent.

Entry	Ligand (mol %)	Temperature (^oC)	Time (min)	Yield (%)	Endo:exo[a]	Endo ee (%)[b]
1	1	rt	60	80	87:13	25 (*S*)
2	5	rt	45	79	89:11	30 (*S*)
3	10[c]	rt	15	86	90:10	71 (*S*)
4	10	rt	10	87	90:10	72 (*S*)
5	10[d]	rt	10	86	90:10	72 (*S*)
6	10	0	30	84	90:10	74 (*S*)
7	10	-40	[e]	-	98:2	81 (*S*)

rt = Room temperature, [a] Determined by ^1H NMR, [b] Determined by HPLC (Chiralpak IB), [c] 4 Å Molecular sieves added, [d] slow addition of cyclopentadiene over 1hr, [e] Reaction was too slow and stopped after 24 hrs, it did not go to completion.

In the next section the observed results and efforts to explain the enantioselectivity will be discussed.

4.5 Discussion

The first part of this discussion will cover the evaluation of the ligand **100** in the Diels-Alder reaction between 3-acryloyloxazolidin-2-one **52** and cyclopentadiene **33** and the second part will cover the elucidation of the novel compounds **103, 104** and **100.**

4.5.1 Evaluation of the novel ligand 100 in the Diels-Alder reaction

From the various metals salts evaluated, anhydrous $Mg(ClO_4)_2$ emerged as the best Lewis acid in terms of enantioselectivity (Table 4.2, entry 6) of the *endo*-cycloadduct product **53**. Other bis(oxazoline) magnesium complexes previously reported also display reasonable catalytic activity in this Diels-Alder reaction.[120,124,130] Although the $Mg(ClO_4)_2.6H_2O$ demonstrated a comparable enantiotiomeric excess to its anhydrous counterpart (Table 4.2, entries 6 and 7), this result was not pursued as the reaction mixture upon complexation of the hexahydrate metal salt was not homogenous.

Substitution of the solvent dichloromethane (DCM) with tetrahydrofuran (THF) or acetonitrile (CH_3CN) led to lower yields and enantioselectivities (Table 4.3). Different magnesium salts were

investigated to determine the effect of the different counterion on the catalyst in the reaction (Table 4.4). These results indicated that the enantiomeric excess improved with increasing Lewis acidity of the metal [$Mg(OTf)_2$< $Mg(SbF_6)_2$< $Mg(ClO_4)_2$].

Once the optimum solvent and counterion was found, different catalytic loadings were investigated and 10 mol % yielded the best result (Table 4.5, entries 1-2 and 4). Also the addition of molecular sieves to ensure strictly anhydrous conditions did not significantly affect the enantiomeric excess or yield of the reaction (Table 4.5, entry 3). In order to evaluate the reaction temperature-enantioselectivity profile, experiments at room temperature, 0 ^{o}C and -40 ^{o}C were carried out (Table 4.5, entries 5-7). As expected for this reaction, the enantiomeric excess increased with decreasing temperature.[98,112,120] Experiments at lower temperatures were impossible due to extremely low reaction rates, therefore the reaction at -40 ^{o}C was the best result obtained with an enantiomeric excess of 81 % (Table 4.5, entry 7).

It was important to note that the blank reaction (Table 4.2, entry 1) proceeded (i.e. without any catalyst) much slower. In order to investigate to what extent the enantioselectivity was influenced by the non-catalyzed (racemic products form) reaction, the experiment was performed with slow addition of cyclopentadiene (Table 4.1, entry 5). From the data, it was clear that the enantioselectivity was not influenced by the concurrent non-catalyzed racemic reaction.

From the metals screened (Table 4.2, entries 2-4) namely, calcium, zinc and copper products resulted in excess of the (*R*)-enantiomer whilst the other metals gave rise to excess of the (*S*)-enantiomer. According to literature bis(oxazoline) ligands are known to sometimes reverse the chirality of **53** when zinc or copper are used.[100,112,113,116,119] There are no other reports in literature on bis(oxazoline) calcium complexes tested on Diels-Alder type reactions, therefore a comparison to the calcium result could not be made.

The inversion of chirality on the products when zinc or copper are used was attributed to the different transition states experienced by the complex as a result of changing the metal cation or substituents on the ligand.[114] Corey *et al.*[130] observed, when magnesium complexes of (*R*)-**90** (R=Ph) were tested for the reaction, that the predominant product was the (*S*)-configuration. They proposed a tetrahedral magnesium-bis(oxazoline) dienophile complex to account for the observed asymmetric induction. Evans *et al.*[113] proposed a square planar coordination for the copper complex of (*R*)-**89** (R=*t*-Bu) in which the product was the (*R*)-configuration for the same Diels-Alder reaction. An interesting observation occurred when both Evan's and Corey's ligands with the (*R*)-configuration were complexed to magnesium. When the counterion is perchlorate the product of the reaction is (*S*)-**53**, but if two equivalents of water is added to the reaction the

product obtained is (*R*)-**53**.[125] This stereochemical outcome was explained by Desimoni *et al.* by establishing that water acts as an auxiliary ligand which will expand the coordination number from four (tetrahedral) to six (octahedral) when the counterion is perchlorate.[50,124,131]

Since our best result was from $Mg(ClO_4)_2$ it was decided to do a theoretical investigation to determine if the tetrahedral complex form proposed in literature is applicable in the reaction investigated by us. Optimizations of the two possible conformations of the magnesium complex of ligand **100** with the substrate **52** were performed using Density Functional Theory (DFT) calculations. The first complex A has the unsaturated bond of the dienophile **52** facing upwards while the second structure (complex B) has it facing downwards.

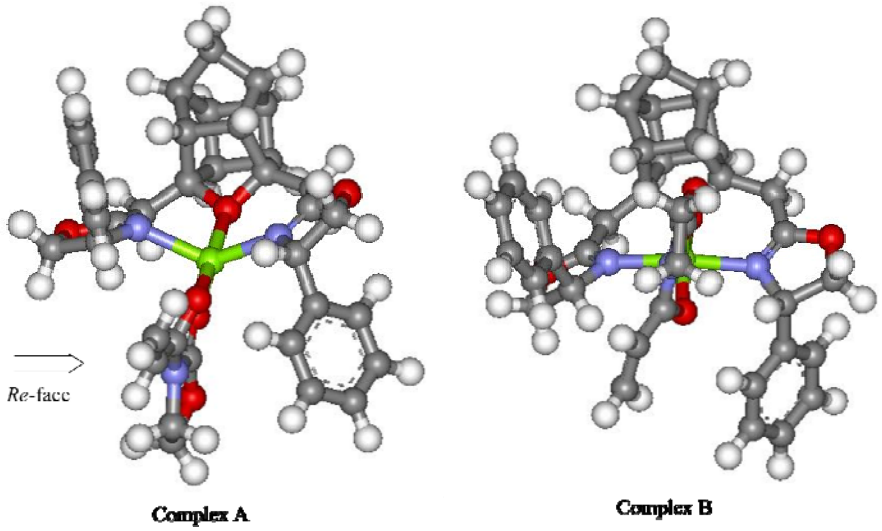


Figure 4.1 Optimized structures of the ligand-Mg-dienophile complexes [B3LYP/6-31+G(d)].[†]

The geometry of both complexes was penta-coordinate. The calculations revealed the distance between the magnesium ion and imine nitrogens to be 2.18 Å and 2.11 Å. The distance between the magnesium ion and carbonyl oxygen of the dienophile was 2.01 Å. The ether oxygen on the PCU moiety also participated in binding to the magnesium ion since the calculated metal to oxygen distance was 2.21 Å. It was then sensible to propose that the reacting catalyst complex between ligand **100** and dienophile **52** was a penta-coordinated system (Figure 4.1) and behaves similarly to the octahedral complex suggested by Desimoni *et al.* This could possible explain the observation of no inversion occurring on the chirality of the reaction product. This implied that ligand **100** is one of very few tridentate *N,O,N*-bis(oxazoline) type ligands reported.[120,132,133]

[†] The Cartesian coordinates of these structures are available on a CD that accompanies this thesis.

In addition, the calculated energies of these possible complex structures show that complex A is more energetically favoured than complex B by 5 kcal mol^{-1}. Upon inspection of the low energy complex structure it was quite clear that the *Re* face of the unsaturated bond of the dienophile **52** is much less hindered than the *Si* face (Figure 4.1). This will lead to the (*S*)-*endo* product **53**. This theoretical result was consistent with the experimentally observed absolute configuration and enantiomeric purity of the (*S*)-*endo* product **53** determined by chiral HPLC analysis.

Further more, inspection of the HOMO[‡] of the computational complex structure also revealed that the dienophile (oxazolidinone **52**) experienced a high level of delocalization (Figure 4.2).

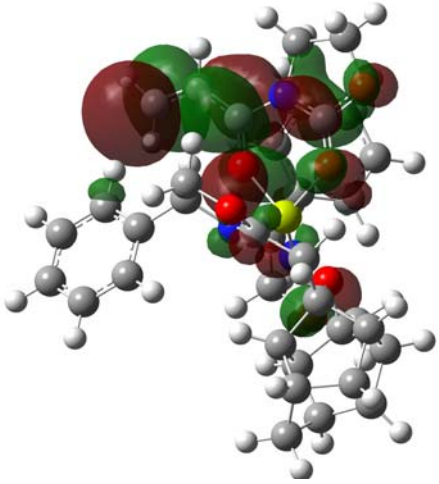
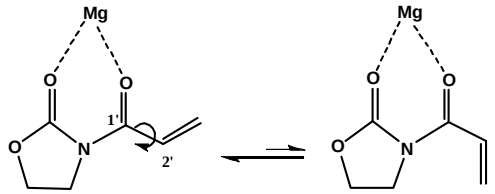


Figure 4.2 Illustration of the calculated HOMO orbitals of the ligand-Mg-dienophile complex.

This delocalization will explain the rigidity of the dienophile which prevents rotation around the C-1'-C-2' bond as indicated in Figure 4.3.

[‡] The cube file of the calculated complex HOMO is available on a CD that accompanies this thesis.



52a **52b**

Figure 4.3 Extraction of dienophile 52 from the complexed structure.

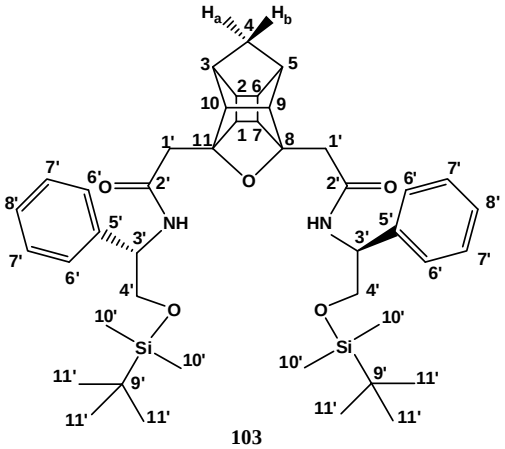
Oxazolidinone in form **52a** will yield the correct product for pro-*S* attack whilst **52b** will give the opposite enantiomer. Note that cyclopentadiene attacks the alkene with the CH_2 group furthest away from the carbonyl oxygen as explained earlier in this chapter.

Finally, the NMR elucidation of the novel chiral ligands will be discussed below.

4.5.2 Elucidation of the novel compounds 103, 104 and 100.

The following results was recently published.[91] For the purpose of this discussion, a basic knowledge of NMR techniques (including 2D experiments) and terms is assumed. If additional reading is required, the reader is referred to numerous excellent NMR textbooks.[134-136]

Two dimensional NMR proved to be a powerful technique in overcoming the difficulties associated with the elucidation of PCU cage compounds when only one dimensional NMR data is utilized. Since a chiral substituent was attached to the PCU derivatives **103**, **104** and **100**, the cage therefore displayed C_1 symmetry which resulted in all its atoms being non-equivalent. Note that the left half of the PCU skeleton is the mirror image of the right half, with the result that the chiral side arms induce a diastereomeric character to the cage skeleton. Due to overlapping in the ^1H spectra, identification of the non-equivalent protons was challenging. However, the ^{13}C spectra gave rise to clear splitting of the carbon atoms (C-1 to C-11) and (C1' to C-8') on the cage and 'side arms' of **103** respectively.



103

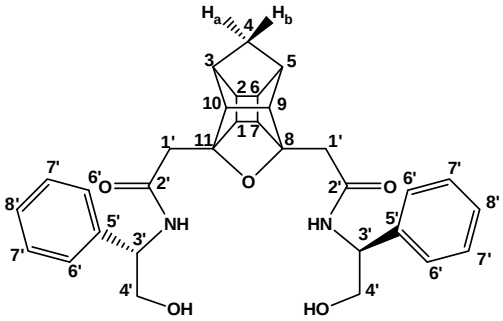
The splitting of all side chain carbons (C-1 to C-8') is unprecedented compared to analogous PCU derivatives previously reported.[137-141] The nature of this effect was investigated and is herein discussed. From the ^{1}H spectrum of **103**, the characteristic methylene protons (H-4) register as doublets at 1.65 ppm (H-4a) and 1.98 ppm (H-4b) with a coupling constant of 10.5 Hz which corresponds to analogous PCU ligands.[137-141] Due to major overlapping of protons, only the coupling constant of H-4 could be calculated. Also from the ^{1}H spectrum, protons H-3' and H-4' at 5.21 ppm and 4.05 ppm were assigned respectively by integration of the signals.[128,142] In addition the silyl protons was assigned based on integration, 0.0 ppm (H-10' = 12 H's) and 0.9 ppm (H-11' = 18 H's). Recording the ^{13}C spectra in attach proton test (APT) mode assisted in distinguishing the quaternary and methylene carbons from the methine and methyl carbons. Based on the HSQC spectrum of **103** the corresponding carbons to H-4' and H-4 were identified. By way of elimination the methylene signal at 3.0 ppm was assigned to C-1' (later confirmed by HMBC correlation to the cage) and its HSQC correlation to the doublet at 2.56 ppm led to the assignment of H-1'. H-1' also displayed a COSY and NOESY interaction with the overlapping cage methine signals at 2.87 ppm. The quaternary carbons were assigned as follows: C-9' was assigned to 18.2 ppm due its correlation to the silyl protons in the HMBC spectrum; C-5' was assigned to 140 ppm based on its correlations to H-3' and H-4' and C-2' to 169 ppm which is characteristic of a carbonyl carbon. C-2' also has HMBC correlations to H-3', H-1' and the aromatic protons (7.36-7.52 ppm). Through elimination the quaternary carbon at 94.1 ppm was assigned to the diastereomeric C-8 and C-11 carbons. All the cage carbon signals display splitting as a result of the diastereomeric effect (induced by the chiral side arm). The nature of this effect is confirmed due to the absence of any splitting of the non-chiral (non-diastereomeric) methylene signal of H-4. In addition, high temperature NMR experiments of **103** at 60 ^{o}C, 120 ^{o}C and 150 ^{o}C revealed that the cage carbon signals of C-1/7, C-9/10 and C-8/11 remained split

throughout the temperature ramp. This confirmed the diastereomeric effect experienced by these carbon atoms.

This is the first report where splitting of all the cage carbon atoms was observed. Previous reports of similar PCU diasteromeric ligands observed splitting only of the cage atoms closest to the source of chirality.[137-141] The proton signal appearing at 2.56 ppm displayed a HMBC correlation to a cage carbon signal at 44.1 ppm and a COSY and NOESY correlation to H-4; therefore it could either be assigned to H-2/6 or H-3/5. However this signal (44.1 ppm) also shows HMBC with H-1', thus eliminating H-2/6. Therefore the signal at 44.1 ppm was assigned to H-3/5. Signals at 58.0 ppm share HMBC correlations to H-4, H-1', H-3/5 and the overlapping cage protons. The possibility of this signal being C-1/7 was ruled out as it cannot correlate to H-4; these carbon signals were therefore assigned to C-9/10. The remaining cage carbon signals at 47.0 ppm and 41.4 ppm were assigned to C-1/7 and C-2/6 respectively based on the HMBC and NOESY interactions.

In view of the above stated assignments the overlapping cage methine protons at 2.87 ppm results from H1/7, H2/6 and H9/10. Interestingly, the aromatic protons (7.36-7.52 ppm) show NOESY interactions with H-1', H1/7, H2/6, H9/10 and H-3/5. The silyl protons H-10' and H-11' display NOESY interactions with H-1', H1/7, H2/6 and H9/10. This observation suggests a conformation of **103** in which one of the 'arms' is perhaps positioned in front and the other at the back of the cage moiety. From the high temperature experiments, the split carbon signals on the side arm (C-1'to C-8') at room temperature gradually became a single peak as the temperature was increased indicating these carbon atoms experienced splitting due to a conformational effect. When the hetero-atoms on the side arms are positioned in close proximity to the cage it induces a through space deshielding effect resulting in non-equivalence of atoms on the cage and that of the 'arm' similar to a previous report of a related chiral PCU ligand.[139,141]

The IR spectrum of **103** displayed a sharp N-H absorption at 3312 cm^{-1}, methyl absorptions at 2949 cm^{-1} and 2929 cm^{-1} and the absorption at 1646 cm^{-1} confirmed the presence of the amide bond. The mass spectrum of **103** exhibited the correct molecular ion peak at *m/*z 743.4146 ($M + H^+$). The same methodology was used to elucidate the structure of **104**. All the carbon signals of **104** display splitting except C-8/11, C-2' and C-4'.

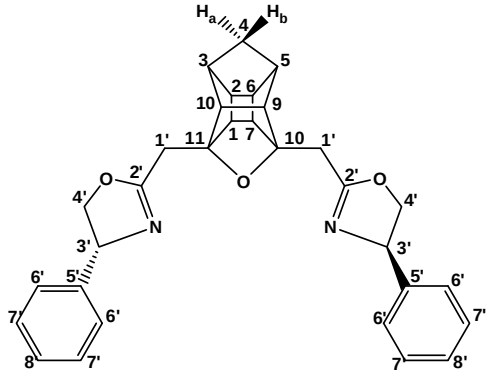


104

A possible explanation could be the absence of the bulky *t*-butyl dimethyl silyl group in **104** hence the conformational effect in which one of the 'arms' is closer to a different part of the cage moiety is less pronounced.

From the IR spectrum the presence of the alcohol group was confirmed by the broad band at 3292 cm^{-1} and as with **103** the presence of the amide bond absorption was recorded at 1641 cm^{-1}. Presence of the expected molecular ion peak of *m/*z 515.2418 ($M + H^+$) in the mass spectrum confirmed the formation of compound **104.**

The elucidation of the PCU bis(4-phenyloxazoline) ligand **100** followed a similar approach as presented above. The ^1H spectrum of **100** differs from its precursors in that all the cage protons appear as clear signals and H-4' is split into two separate doublet of doublets.



100

From the ^{13}C spectrum, the absence of the carbonyl carbon signal at 170 ppm and the presence of the characteristic imine carbon signal at 165 ppm was indicative that cyclization was achieved. Also, C-3' displays a distinct downfield shift as a result of the adjacent imine bond. HMBC correlations of C-2' with protons H-3' and H-4' confirms the formation of the oxazoline ring. The aromatic protons (7.21-7.38 ppm) show a NOESY interaction with H-2/6. Similar to **103** this observation indicates the different conformations of **100** in which the 'arms' exists as different conformations with respect to the cage moiety.

A weak but observable COSY correlation between H-3' and H-1' is observed which is unusual as these protons are more than three bonds apart. This was attributed to a rare long range 'through space' coupling which has been reported in systems with proton correlations that are five-six bonds apart.[143-145] These couplings are known to occur when an intervening atom is sp^2 hybridized[146] or when an oxygen[147] or sulphur[148] atom is involved. In this case an oxygen atom and sp^2 nitrogen are present between protons H-3' and H-1' which appears to result in this long range interaction.

The IR spectrum of **100** displays the characteristic imine absorption band at 1663 cm^{-1} and an aromatic ether absorption band at 1217 cm^{-1}. Also, as expected the disappearance of the amide bond absorptions was observed. The mass spectrum of **100** displays the correct molecular ion peak at *m/*z 479.2350 ($M + H^+$). The detailed NMR assignments for **103**, **104** and **100** are presented in Table 4.6

Table 4.6 NMR data for PCU derivatives 103, 104 and 100[a].

	Derivative 103		Derivative 104		Derivative 100	
Atom no.	**^{1}H ppm[b]**	**^{13}C ppm**	**^{1}H ppm[b]**	**^{13}C ppm**	**^{1}H ppm[b]**	**^{13}C ppm**
1/7	2.87	48.83/47.82	2.73	48.63/48.01	2.82	48.67/48.58
2/6	2.87	41.50/41.44	2.73	41.54/41.39	2.64	41.86/41.84
3/5	2.56	44.28/44.19	2.45	44.12/44.00	2.41	44.64/44.61
4a	1.65	43.35	1.55	43.48	1.51	43.55
4b	1.98	43.35	1.90	43.48	1.90	43.55
8/11	-	94.21/94.16	-	94.14	-	93.71/93.69
9/10	2.87	59.11/58.06	2.73	59.05/58.40	2.75	59.26/59.16
1’	3.06	39.91/39.89	2.82	39.49/39.47	2.98	32.11/32.96
2’	-	169.2/169.1	-	170.1	-	165.9/165.8
3’	5.21	54.64/54.60	5.02	55.23/55.17	5.18	69.66/69.61
4’	4.05	66.60/66.11	3.73	65.90	4.61/4.08	74.76/74.69
5’	-	140.36/140.30	-	139.33/139.32	-	142.3
6’	7.52	126.92/126.91	7.43	126.6	7.34	126.5
7’	7.43	128.52/128.32	7.29	128.6	7.28	128.8
8’	7.36	127.24/127.27	7.23	127.6	7.24	126.5
9’	-	18.26				
10’	0.984	-5.600				
11’	0.003	25.83				

[a] Solvent $CDCl_3$, [b.] 400 MHz for ^{1}H and 100 MHz for ^{13}C.

4.6 Conclusion

The novel PCU bis(4-phenyloxazoline) ligand **100** was synthesized and tested on the asymmetric Diels-Alder reaction between 3-acryloyloxazolidin-2-one **52** and cyclopentadiene **33.** The anhydrous magnesium perchlorate complex emerged as the best catalyst providing the *endo*-cycloadduct product **53** of the above mentioned reaction in 81 % enantiomeric excess with an *endo:exo* ratio of 98:2. From the molecular modeling of this magnesium complex with substrate **52**, the more energetically favoured conformation was established which had the *Re*-face of the dienophile in a less hindered position. Diels-Alder cycloaddition of cyclopentadiene to the *Re*-face leads to a product consistent with the experimentally observed *endo* product **53**. A penta-coordinated complex system is observed in the computational complex. The calculated bond

length revealed that the ether oxygen of the PCU moiety acts as at donor atom to the magnesium ion in the complex. The computational model also suggests that further modifications on the PCU skeleton will not influence asymmetric induction and therefore further study will focus on the derivatisation on the R-group of the oxazoline moiety and testing of ligand **100** and its analogues on additional asymmetric catalytic reactions.

The NMR elucidation of the novel ligand (*S*)-pentacyclo-undecane bis-(4-phenyloxazoline) **100** and two of its precursors **103-104** was successfully achieved. 2D NMR techniques were required to identify the NMR signals for the PCU derivatives which display C_1 symmetry with all the cage atoms being non-equivalent. The ^{13}C spectra of these derivatives gave rise to clear splitting of the non-equivalent carbons with exception to C-9', C-10', C-11' in **103**, C-8/11, C-2', C-4', C-6', C-7', C-8' in **104** and C-6', C-7', C-8' in **100**. NOESY correlations of derivatives indicated conformational differences with respect to the side arms. The hetero-atoms on the side arm induced a through space deshielding effect resulting in non-equivalence of atoms on the cage skeleton and that of the 'arm'. Even though the cage carbons become diastereomeric with respect to the chiral side arms, the same level of non-equivalence by related chiral cage ligands have not yet been reported.

Chapter 5

5.1 Summary

Incorporation of the PCU cage as part of a novel chiral ligand was investigated, this included PCU diol **54a**, PCU bisimine **87** and PCU bis(oxazoline) **100**. The PCU diol ligand was synthesized, however various methods (enzymatic methods, diastereomer formation and recrystallization) that were utilized to obtain the compound enantiomerically pure proved to be unsuccessful. This hindered further investigation into this type of ligand. The PCU bisimine ligand was synthesized, but due to its instability it was not further pursued. Synthesis of the PCU bis(oxazoline) ligand **100** was successful and it was complexed to various metal salts and tested on the benchmark asymmetric Diels-Alder reaction between 3-acryloyloxazolidin-2-one **52** and cyclopentadiene **33**. The anhydrous magnesium perchlorate complex emerged as the best catalyst providing the *endo*-cycloadduct product **53** in 81 % enantiomeric excess at -40 ^{o}C. Optimizations of the possible conformations of the magnesium complex of ligand **100** with the substrate **52** were performed using Density Functional Theory (DFT) calculations. The more energetically favoured complex conformation was established. The *Re*-face of the dienophile is less hindered which should produce a product consistent with the experimentally observed product **16.** Based on the calculated bond lengths from the computational model binding of the ether oxygen on the PCU moiety to magnesium was observed. This implied that ligand **100** is one of very few tridentate *N,O,N*-bis(oxazoline) type ligands reported so far. In addition, the complete NMR elucidation of the novel PCU diol **54a**, PCU ether dialdehyde **84**, PCU bis-amide **103**, PCU bis-amino alcohol **104** and (*S*)-pentacyclo-undecane bis(4-phenyloxazoline) **100** was successfully achieved.

Chapter 6

6.1 Experimental

General

All solvents were distilled from the appropriate desiccant. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 instrument with an Attenuated Total Reflectance (ATR) attachment. Optical rotations were carried out on a Perkin Elmer 341 polarimeter. All melting points are uncorrected. Column chromatography was carried out using silica gel 60. Electron spray mass spectra were carried out on a Waters LCT Premier Time of Flight (TOF) mass spectrometer. HPLC analysis was carried out with a Shimadzu Prominence fitted with a LC-2AD pump, SIL-20A auto sampler and SPD-M2OA diode array detector. The type of column and conditions are described within the appropriate experiment below. NMR spectra were recorded on a Bruker AVANCE III 400 MHz instrument.

Parameters for the NMR experiments ran in $CDCl_3$ were as follows: The ^{1}H NMR spectrum was recorded at 400.222 MHz (spectral width, 8223.685 Hz; acquisition time, 1.992 s; pulse width, 9μs; scans, 16; relaxation delay, 1.0 s). The ^{13}C NMR spectrum was recorded at 100.635 MHz (spectral width, 24038.461 Hz; acquisition time, 1.363 s; pulse width, 13.801 μs; scans, 2400; relaxation delay, 2.00 s).

The 2D experimental data parameters were as follows: 90^{o} pulse width, 9 μs for all spectra; spectral width for ^{1} H, 822.68 **103, 104, 100**; spectral width for ^{13}C, 24038.46 for **103, 104, 100**; number of data points per spectrum, 2048, (COSY) for **103, 104, 100**, 2048, (NOESY) for **103, 104, 100**, 4096, (HMBC) for **103, 104, 100**, 1024 (HSQC) for **103, 104, 100** ; number of time-incremented spectra, 128 (COSY) for **103, 104, 100**, 256, (NOESY) for **103, 104, 100**, 128, (HMBC) for **103, 104, 100**, 256 (HSQC) for **103, 104, 100**; relaxation delay, 1.38 s (COSY) for **104** and **100**, 1.39 s (COSY) for **103**, 1.98 s (NOESY) for **104** and **100**, 1.96 s (NOESY) for **103**, 1.31s, 1.25 s, 1.30 s (HMBC) for **103, 104, 100** respectively, 1.45 s, 1.43 s, 1.45 s, (HSQC) for **103, 104, 100** respectively; spectra acquired in phase-sensitive mode, **103, 104, 100** (NOESY and HSQC); spectra acquired in absolute value mode, **103, 104, 100** (COSY and HMBC); gradients used for **103, 104, 100** (COSY, HSQC and HMBC).

Synthesis of Pentacyclo-[5.4.0.0^{2,6}.0^{3,10}.0$^{5.,9}$]-undecane-8,11-dione-mono-ethylene ketal 58.[69]

A mixture of the dione **57**[65] (183 g, 1.05 mol), ethylene glycol (89.9 g, 1.45 mol), *p*-toluenesulfonic acid (6.11 g, 32.1mmol) in dry benzene (800 ml) was gently refluxed with stirring

in a Dean-Stark trap for four days thereby ensuring azeotropical removal of water. The reaction mixture was left to cool and poured slowly into an ice-cold saturated aqueous sodium carbonate solution. The aqueous mixture was extracted with 4 x 250 ml portions of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4. The mixture was filtered and the solvent evaporated *in vacuo*. The resulting brown residue was recrystallised from hexane to give **58** as a white solid (135g, 74 %). Melting point = 73.0-74.0 ^oC. ^1H NMR ($CDCl_3$): δ = 1.55 (d), 1.8 7(d), 2.47 (m), 2.6 (m), 2.81 (m), 2.91 (m). ^{13}C NMR ($CDCl_3$): δ = 36.3 (d), 38.7 (t), 41.3 (d), 41.4 (d), 42.3 (d), 42.8 (d), 45.8 (d), 50.7 (d), 53.0 (d), 64.5 (t), 65.7 (t), 113.9 (s) and 215.3 (s).

Synthesis of 11-Hydroxypentacyclo-[5.4.0.0^{2,6}.0^{3,10}.0^{5,,9}]-undecane-8-one--ethylene ketal 59.[69]

The mono-ketal **58** (10.0 g, 45.9 mmol) was dissolved in methanol (100 ml) and placed in an ice-bath to cool. A solution of sodium borohydride (3.50 g in 50 ml methanol) was added, while stirring over 15 minutes. The mixture was left to stir for two hours in an ice-bath and an additional two hours at ambient temperature. A small amount (2 ml) of the mixture was withdrawn from the flask and extracted with CH_2Cl_2 to confirm complete reduction of the keto functional group using IR spectroscopy. The solvent was removed *in vacuo*, and the residue extracted using 100 ml of CH_2Cl_2. Compound **59** was obtained (7.80 g, 78 %) as a clear oil. ^1H NMR ($CDCl_3$): δ= 1.16 (d), 1.65 (d), 2.34 (m), 2.55(m), 2.72 (m). ^{13}C NMR ($CDCl_3$): δ = 35.0 (d), 38.8 (d), 39.0 (d), 39.2 (d), 39.9 (d), 43.6 (d), 44.6 (d), 46.7 (d), 47.2 (d), 72.35 (d), 62.9 (t), 65.5 (t) and 115.8 (s).

Synthesis of 11-Hydroxypentacyclo-[5.4.0.0^{2,6}.0^{3,10}.0^{5,,9}]-undecane-8-one.[69]

The hydroxy-ketal **59** (10.0 g, 45.4 mmol) was dissolved in methanol (100 ml) and placed in an ice-bath to cool. Concentrated hydrochloric acid (100 ml) was added and the solution was stirred for 1 hour. The ice bath was removed and the mixture stirred overnight. The solvent was removed *in vacuo*, and the residue extracted using 100 ml of CH_2Cl_2. A white solid **60** was obtained (8.5 g, 85 %). Melting point = 254-255 ^oC. ^1H NMR ($CDCl_3$): δ = 1.51(d), 1.87 (d), 2.55 (m), 2.83(m), 4.05 (m), 4.60 (m) and 5.72 (s). ^{13}C NMR ($CDCl_3$): δ = 36.8 (d), 38.4 (t), 40.5 (d), 41.5 (d), 43.2 (d), 44.7 (d), 45.2 (d), 45.6 (d), 71.8 (d), 81.4 (d) and 119.2 (s).

Synthesis of the novel Ligand 54a.

A solution of bromobenzene in dry THF (5 mol equivalents relative to **60**) was cooled under nitrogen atmosphere to -78 ^oC using a dry-ice-acetone bath. Butyllithium solution (15 % in hexane, 1.2 mole equivalents relative to bromobenzene) was added and the solution stirred for 10 minutes. A solution of the hydroxy-ketal **60** (1 mol equivalent) in dry THF was added and the

solution stirred at -78 ^{o}C for 1 hour and then at room temperature overnight. The reaction was quenched by the dropwise addition of water. The white precipitated product was filtered off and the solvent was removed *in vacuo*. The unprecipitated product was isolated using column chromatography (EtOAc/Hexane = 50:50, R_f = 0.5) to yield the ligand as a white solid (1.05g, 73 %). Melting point = 126-130 °C. IR: ν_{max}: 3068(m), 2967(m), 1484(m), 1104(s), 1070(s), 700(vs) cm^{-1}., HRMS calculated for $C_{17}H_{18}O_2$ ($M + H^+$) 254.1344, found 254.1345. ^{1}H NMR ($CDCl_3$) δ = 0.99 (H-4a), 1.51 (H-4s), 1.79 (H-5), 2.35 (H-3), 2.55 (H-9), 2.56 (H-2), 2.58 (H-6), 2.59 (H-10), 2.86 (H-1), 3.12 (H-7), and 7.33 (H-2'). ^{13}C NMR δ = 34.11 (C-4), 38.90 (C-1), 39.01 (C-20), 41.50 (C-7), 41.52 (C-6), 44.30 (C-3), 46.10 (C-10), 46.69 (C-5), 71.92 (C-11), 79.40 (C-8), 81.31 (C-9), 125.45 (C-2'), 127.19 (C-4'), 128.38 (C-3'), 146.29 (C-1').

Enzyme catalyzed reduction on PCU dione 57.[64]

To one liter of Sorensen buffer (pH 7.0) a mixture of 0.05 g of NAD^+, 0.11g HLADH and 2.0 g of PCU dione dissolved in 5 ml of ethanol was added. The reaction vessel was sealed and left to stir for 72 hours until which time no more starting material was present on TLC plate (EtOH/Hexane = 50:50). The reaction mixture was extracted with 4 x 250 ml portions of CH_2Cl_2. The combined organic phases were dried with anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The resulting residue was purified by column chromatography (EtOAc/Hexane = 50:50, R_f = 0.3) to afford product **60** (4.5 g, 83 %) as white solid. The enantiomeric excess determined by HPLC with a Daicel IB column (hexane-*i*-PrOH = 90/10) flow rate = 1 L/min, Racemic mixture with retention times 17.0 min and 19.3min. The HPLC chromatograph appears in Appendix A.

Enzyme catalyzed reduction on PCU mono-protected ketal 58.

To 500 ml of Sorensen buffer (pH 7.0) a mixture of 0.01g of NAD^+, 0.05g HLADH and 0.53 g of PCU **57** was dissolved in 1 ml of ethanol was added. The reaction vessel was sealed and left to stir until which time no more starting material was present on the TLC plate. This reaction did not proceed even after several days only starting material was observed on the TLC plate.

Protection of PCU dione 57 with 61.

A mixture of the dione **57** (1.00 g, 57.5 mmol), (4*S*,5*S*)-4,5-bis([1-hydroxy-1-methyl]ethyl)-2,2-dimethyl-1,3-dioxolane **61** (3.22 g, 6.99 mmol), *p*-toluenesulfonic acid (1.00 g, 5.80 mmol) in dry benzene (100 ml) was gently refluxed with stirring in a Dean and Stark trap for two days. The reaction mixture was left to cool to room temperature and then poured slowly into an ice-cold saturated aqueous sodium carbonate solution. The aqueous mixture was extracted with 100 ml of CH_2Cl_2. The combined organic phases were dried with anhydrous Na_2SO_4 and the solvent was

removed *in vacuo*. The resulting residue was attempted to be purified by column chromatography using (EtOH/Hexane = 50:50) but the desired product was not obtained.

Protection of PCU dione 57 with 63.

A mixture of the dione **57** (1.00 g, 57.5 mmol), (2*S*,3*S*)-dimethyl D-tartrate **63** (1.50 g, 6.99 mmol), *p*-toluenesulfonic acid (1.00 g, 5.80 mmol in dry benzene (100 ml) was gently refluxed with stirring in a Dean and Stark trap for two days. The reaction mixture was left to cool to room temperature and then poured slowly into an ice-cold saturated aqueous sodium carbonate solution. The aqueous mixture was extracted with CH_2Cl_2 (100 ml). The combined organic phases were dried with anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The resulting residue was attempted to be purified by column chromatography using (EtOH/Hexane = 50:50) but the desired product was not obtained.

Synthesis of *exo*-8-*exo*-11-Diallylpentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-*endo*-8-*endo*-11-diol 81.[39,40]

A solution of dione **57** (3.0 g, 17.3 mmol) in dry THF (200 ml) was added dropwise over 1.5 hours to a stirred mixture of freshly prepared allylmagnesium bromide under nitrogen at 0 ^{o}C. After the addition had been completed, the external ice-water bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring under nitrogen during 24 hours. The reaction was quenched by the addition of saturated aqueous NH_4Cl (until pH was 6~7), the layers were separated, and the aqueous layer was extracted with EtOAc (2 x 100 ml). The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered, and the filtrate was concentrated *in vacuo*. The residue resulting residue was purified by column chromatography (Hexane/EtOAc = 80:20, R_f = 0.35) to afford **81** (3.54 g, 78 %) as viscous colourless liquid. ^{1}H NMR ($CDCl_3$): δ = 1.05 (*A*B, J_{AB} = 10.8 Hz, 1 H), 1.49 (A*B*, J_{AB} = 10.8 Hz, 1 H), 1.97-2.24 (m, 6 H), 2.30-2.61 (m, 6 H), 5.01 (dd, *J* = 8.0 & 2.6 Hz, 2 H), 5.04 (dd, *J* = 16.85 and 2.6 Hz, 2 H), 5.90 (m, 2 H), 6.52 (br s, 2 H); ^{13}C NMR ($CDCl_3$): δ_C 33.9 (t), 40.0 (d), 42.8 (d), 44.0 (d), 44.1 (t), 49.1 (d), 77.2 (s), 117.5 (t), 133.8 (d).

Synthesis of PCU dihydroxy dialdehyde 82.[39]

A solution of the diene **7** (5.0 g, 20.3 mmol) in dry methanol (150 ml) was cooled to -78°C *via* application of an external dry ice–acetone bath and then was purged with nitrogen for 20 minutes. Ozone was bubbled into the mixture until a blue-purple color persisted, thereby indicating the presence of excess ozone and completion of reaction. Excess ozone was flushed from the reaction vessel with a stream of nitrogen. The reaction mixture was then transferred to a round bottom flask and $(CH_3)_2S$ (6.4 ml, 83.2 mmol) was added and stirred for 12 hours at ambient

temperature. The solvents were evapourated *in vacuo* and the residue was extracted with CH_2Cl_2 (150 ml). The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvents were removed *in vacuo*. The resulting residue was attempted to be purified by column chromatography (Hexane/EtOAc = 70:30) to afford the PCU dialdehyde **82** but unfortunately it was not obtained.

Synthesis of 3,5-Diallyl-4-oxahexacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]dodecane 83.[40]

A solution of **81** (3.5 g, 0.014 mol) and *p*-toluenesulphonic acid (0.5 g, 2.9 mmol) in benzene (~250 ml) was refluxed using a Dean-Stark apparatus. After every 12 hours, additional *p*-toluenesulphonic acid (0.25 g) was added. When TLC indicated the absence of **81** (72 hours), the reaction mixture was allowed to cool to ambient temperature and washed sequentially with 10 % aqueous $NaHCO_3$ (100 ml), water (100 ml) and brine (100 ml). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified *via* column chromatography (Hexane/EtOAc = 80:20, R_f = 0.7,) to yield **83** as a brown oil, (2.50 g, 70 %). ^{1}H NMR ($CDCl_3$): δ = 1.46 (*A*B, J_{AB} = 10.2 Hz, 1 H), 1.82 (A*B*, J_{AB} = 10.2 Hz, 1 H), 2.35 (br s, 2 H), 2.45-2.65 (m, 10 H), 5.01 (dd, *J* = 9.8 & 2.2 Hz, 2 H), 5.07 (dd, *J* = 15.4 and 1.4 Hz, 2 H), 5.78 (m, 2 H); ^{13}C NMR ($CDCl_3$): δ =37.5 (t), 41.7 (d), 43.3 (t), 44.5 (d), 47.8 (d), 58.6 (d), 95.1 (s), 116.8 (t), 134.4 (d).

Synthesis of the novel PCU ether dialdehyde 84.[40]

A solution of the diene **83** (5.0 g, 20.3 mmol) in dry methanol (150 ml) was cooled to -78 °C *via* application of an external dry ice–acetone bath and then was purged with nitrogen for 20 minutes. Ozone was bubbled into the mixture until a blue-purple color persisted, thereby indicating the presence of excess ozone and completion of reaction. Excess ozone was flushed from the reaction vessel with a stream of nitrogen. The reaction mixture was then transferred to a round bottom flask and $(CH_3)_2S$ (6.4 ml, 83.2 mmol) was added and stirred for 12 hours at ambient temperature. The solvents were evapourated *in vacuo* and the residue was extracted with CH_2Cl_2 (150 ml). The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvents were removed *in vacuo*. The resulting residue was purified by column chromatography (Hexane/EtOAc = 70:30, R_f = 0.6) to afford the PCU dialdehyde **84** (0.49 g, 49 %) as a yellow oil. IR ν_{max}: 2958 cm $^{-1}$ (s) 1719 cm $^{-1}$ (vs), 1075 (s) and 527 cm $^{-1}$ (w). HRMS calculated for $C_{15}H_{16}O_3$ (M + H^+) 245.1133, found 244.1099. The NMR elucidation of this compound was recently published.[91] ^{1}H NMR ($CDCl_3$) δ = 1.59 (H-4a), 1.93 (H-4s), 2.50 (H-3/5), 2.64 (H-

9/10), 2.68 (H-1/7), 2.71 (H-2/6), 2.85 (H-1') and 9.77 (H-2'). ^{13}C NMR δ = 48.57 (C-1/7), 41.62 (C-2/6), 44.16 (C-3/5), 43.45 (C-4), 92.77 (C-8/11), 59.21 (C9/10), 45.99 (C-1'), 200.5 (C-2').

Reduction of (*S*)-phenylglycinol 86.[90]

(*S*) Phenylglycine methyl ester (1.0 g, 4.9 mmol) was added to a stirred solution of lithium aluminum hydride (0.4 g, 9.8 mmol) in dry THF (150 ml) at ambient temperature. Thereafter the solution was refluxed for 1.5 hr. The reaction mixture was then removed from heat and allowed to cool after which an equal volume of diethyl ether was added. The reaction was quenched with saturated aqueous Na_2SO_4 solution. It was filtered and the solvent removed *in vacuo* to yield pure amino alcohol as yellow crystals (0.6 g, 88 %). ^{1}H NMR ($CDCl_3$) δ = 2.80 (O-H, H-4), 3.5-.7 (2H, m, H-3), 4.0 (1H, m, H-2), 7.2-7.4 (1H, dd, H-3') and 7.50 (5H, m, aromatic H-5 to H-10). ^{13}C NMR δ = 58.9 (C-2), 70.0 (C-3), 126-128 (aromatic, C-6 to C-10), 142.0 (C-5).

Synthesis of PCU diimine 87.

PCU dialdehyde **84** (0.05 g, 0.20 mmol) was dissolved in 5 ml dry $CHCl_3$ and **86** (0.10 g, 0.40 mmol) was added along with 4A molecular sieves. The reaction mixture was left to stand without stirring for 1.5 hours. The reaction mixture was filtered and the solvent removed *in vacuo* to afford the PCU diimine **87** (0.14 g, 100 %) as a brown oil. ^{1}H NMR ($CDCl_3$) δ = 1.01 (AB, J_{AB} = 10 Hz, 1H), 1.52 (AB, J_{AB} = 10 Hz, 1H), 2.13–2.62 (m), 3.3-3.8(m); 4.15 (H-3'), 4.05 (H-4') and 7.2-7.4 (aromatic). ^{13}C NMR δ = 48.1 (C-1/7), 41.5 (C-2/6), 44.1 (C-3/5), 43.5 (C-4), 94.1 (C-8/11), 59.1 (C9/10), 38.4 (C-1'), 162.5 (C-2'), 58.5 (C-3'), 68.0 (C-4'), 140.1 (C-5'), 126-130 (C-6', C-7', C-8'), 18.1 (C-9'), -4.2 (C-10') and 26.0 (C-11').

Synthesis of 5,5-Dicarboxymethyl-4-oxahexacyclo[5.4.1.0^{2,6}.0^{5,10}.0^{5,9}.0^{8,11}]dodecane 101.[40]

A solution of the diene **83** (5.0 g, 20.3 mmol) in dry methanol (150 ml) was cooled to -78 °C *via* application of an external dry ice–acetone bath and then was purged with nitrogen for 20 minutes. Ozone was bubbled into the mixture until a blue-purple color persisted, thereby indicating the presence of excess ozone and completion of the reaction. Excess ozone was flushed from the reaction vessel with a stream of nitrogen, and the reaction mixture was concentrated *in vacuo* to yield the ozonide. Hydrogen peroxide (50 ml, 30 %) was added dropwise to a stirred, ice bath cooled mixture of the ozonide and formic acid (50 ml, 80 %). The resulting mixture was stirred at ambient temperature for 1 hour and then gently refluxed for 12 hours. The reaction mixture was allowed to cool gradually to ambient temperature during which time the product precipitated out of solution. Pure **101** (4.7 g, 82 %) was thereby obtained as a white microcrystalline solid. Melting point = 175-175.5 ^{O}C, ^{1}H NMR (DMSO) δ = 1.45 (AB, J_{AB}=10 Hz, 1H),1.83 (AB,

J_{AB}=10 Hz, 1H), 2.36–2.80 (m, 12H), 12.15(br s, 2H); ^{13}C NMR δ = 37.94 (t), 41.27 (d), 42.81 (t), 44.04 (d), 47.91(d), 58.55 (d), 92.56 (s) and 171.40 (s).

Synthesis of (*S*)-*tert*-Butyldimethylsilyl 2-amino-3-phenylpronoate 102.[128,142]

(*S*)-Phenylglycine methyl ester (1.0 g, 4.9 mmol) was added to a stirred solution of lithium aluminum hydride (0.4 g, 9.8 mmol) in dry THF (150 ml) at ambient temperature. Thereafter the solution was refluxed for 1.5 hr. The reaction mixture was then removed from heat and allowed to cool after which an equal volume of diethyl ether was added. The reaction was quenched with saturated aqueous Na_2SO_4 solution. It was filtered and the solvent removed *in vacuo* to yield pure amino alcohol as yellow crystals (0.6g, 88 %). To a solution of the amino alcohol **(**3.0 g, 21.7 mmol) in dry CH_2Cl_2 (150 ml) were added at room temperature Et_3N (6.3 ml, 44.5 mmol) and DMAP (0.5 g, 4.09 mmol). The solution was cooled to 0 °C and TBDMSiCl (3.4 g, 27.7 mmol) in CH_2Cl_2 (20 ml) was added. The solution was stirred for further 48 h at room temperature and then H_2O (30 ml) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (150 ml). The combined organic phases were dried with anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The resulting residue was purified by column chromatography (CH_2Cl_2/MeOH = 95:5) to afford product **102** (4.5 g, 83 %) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ = 0.04 (6H, s), 0.91 (9H, s), 1.85 (NH, br s), 3.50 (1H, dd CH_2O), 3.72 (1H, dd, CH_2O), 4.07 (1H,dd, C*H*Ph), 7.40-7.23 (5H, m); ^{13}C NMR ($CDCl_3$) δ =-5.41 (CH_3), 18.3 (CH_3), 25.9($C(CH_3)_3$), 57.6 (*C*HPh), 69.5 (CH_2O), 126.9, 127.2, 128.2, 142.6 (aromatic).

Synthesis of the novel PCU bis -amide 103.

To a stirred solution of **101** (2.0 g, 7.25 mmol) in dry CH_2Cl_2 (150 ml), hydroxybenzotriazole (2.0 g, 14.6 mmol) and DCC (3.0 g, 14.6 mmol) were added respectively. This mixture was allowed to stir for 15 minutes until a clear homogenous solution was obtained. Thereafter a mixture of **102** (4.5 g, 18.0 mmol) and Et_3N (4.0 ml, 28.9 mmol) in dry CH_2Cl_2 (50 ml) was added and the resulting mixture was stirred at ambient temperature for a further 12 hours. The reaction mixture was then filtered and H_2O added to the filtrate. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The resulting residue was purified by column chromatography (Hexane/EtOAc = 50:50, R_f = 0.7) to afford compound **103** (4.8 g, 90 %) as a yellow solid. $[\alpha]^{20}_D$-11.35 (c = 1 g/100 ml, CH_2Cl_2). IR ν_{max}: 3312 cm $^{-1}$ (s), 1646 cm $^{-1}$ (vs), 1112 cm $^{-1}$ (vs) and 776 cm $^{-1}$ (vs). Melting point = 126-130 ^{o}C. HRMS calculated for $C_{43}H_{62}N_2O_5Si_2$ ($M + H^+$) 743.4231, found 743.4146. The NMR elucidation of this compound was recently published[91] and appears in Table 4.6

Synthesis of the novel PCU bis-amino alcohol 104.

The PCU bis-amide **103** (5.5 g, 7.41 mmol) was dissolved in dry THF (200 ml) and tetra-*N*-butylammonium fluoride (29.6 ml, 1 M in THF) was added. The mixture was stirred for 48 hours at ambient temperature. Brine was added and the layers were separated. The aqueous layer was extracted with EtOAc (150 ml). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvents were removed *in vacuo*. The resulting residue was purified by column chromatography (EtOAc/MeOH = 95:5, R_f = 0.5) to afford the deprotected alcohol **104** (3.0 g, 76 %) as a pale yellow solid. $[\alpha]^{20}_D$+32.45 (c = 1 g/100 ml, CH_2Cl_2). IR ν_{max}: 3288 cm $^{-1}$ (br), 1641 cm $^{-1}$ (vs), 1039 cm $^{-1}$ (s) and 706 (vs). Melting point 50-52 ^{o}C. HRMS calculated for $C_{31}H_{34}N_2O_5$ (M + H^+) 515.2501, found 515.2418. The NMR elucidation of this compound was recently published[91] and appears in Table 4.6

Synthesis of the novel PCU bis(4-phenyloxazoline) 100.[120]

To a stirred solution of **104** (1.0 g, 1.88 mmol) in dry CH_2Cl_2 (100 ml), $SOCl_2$ (2.7 ml, 37.5 mmol) was added. The solution was stirred at ambient temperature for 3 hours. The resulting mixture was poured into H_2O and extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and the solvent removed *in vacuo* to yield a brown residue of the PCU bis-chloride **105** (100% EtOAc, R_f = 0.8) which was used without further purification. The residue was treated with NaOH (1 g in 20 ml H_2O) in a MeOH (50 ml)/CH_2Cl_2 (30 ml) solution at ambient temperature for 12 hours. The organic solvents were evapourated *in vacuo* and the residue was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvents were removed *in vacuo*. The resulting residue was purified by column chromatography (100 % EtOAc, R_f = 0.6) to afford the PCU bis (4-phenyloxazoline) **100** (0.72 g, 80 %) as a yellow oil. $[\alpha]^{20}_D$-57.24[c = 0.85 g/100ml, $(CH_3)_2CHOH$]. IR ν_{max}: 2964 cm $^{-1}$ (w) 1663 cm $^{-1}$ (s), 984 cm $^{-1}$ (s) and 700 cm $^{-1}$ (vs). HRMS calculated for $C_{31}H_{30}N_2O_3$ (M + H^+) 479.2290, found 479.2350. The NMR elucidation of this compound was recently published[91] and appears in Table 4.6 NMR data for PCU derivatives 103, 104 and 100a..

Synthesis of 3-(2-Propenoyl)-2-oxazolidinone 52.[112]

To a solution of freshly vacuum distilled acrylic acid (0.98 ml, 14.3 mmol) in EtOAc (80 ml) at 0 ^{o}C was added Et_3N (2.5 ml, 14.3 mmol), followed by acyolyl chloride (1.16 ml, 14.3 ml) *via* a syringe. An immediate white precipitate formed and the reaction mixture was stirred at ambient temperature for 30 minutes. The reaction mixture was then filtered through paper, and the filter cake washed with EtOAc. The resultant cloudy filtrate was concentrated *in vacuo*. The residue

was dissolved in dry hexane (100 ml), then filtered and concentrated *in vacuo* again. The anhydride was dissolved in 50 ml dry THF and immediately used in the following step. To a suspension of 2-oxazolidinone (1.0 g, 11.5 mmol) and LiCl (0.61 g, 14.3 mmol) in dry THF (100 ml), Et_3N (2.5 ml, 14.3 mmol) was added *via* a syringe followed by the anhydride solution *via* a cannula, followed by a 20 ml wash. The resulting slurry was stirred at ambient temperature for 12 hours. The solvent was removed *in vacuo.* To the residue 1N HCl (50 ml) solution was added and extracted with CH_2Cl_2 (50 ml). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ followed by brine and dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo.* The resulting yellow oil was purified by column chromatography (Hexane/EtOAc = 50:50, R_f = 0.55) to afford the pure 3-(2-Propenoyl)-2-oxazolidinone **52** (1.3 g, 81 %) as white crystalline solid. Melting point = 80-81 ^oC. ^1H NMR ($CDCl_3$) δ = 4.0-4.2 (2H, m, H-4), 4.4-4.5 (2H, m, H-5), 5.91 (1H, dd, H-3'), 6.56 (1H, dd, H-3') and 7.50 (1H, dd, H-2'). ^{13}C NMR δ = 42.63 (C-4), 62.17 (C-5), 126.99 (C-2'), 131.82 (C-3'), 153.41 (C-2) and 165.08 (C-1').

General Procedure for the Diels-Alder Reactions catalyzed by the PCU bis (4-phenyloxazoline) complexes.[120]

Preparation of the anhydrous Magnesium (II) complex.

A mixture of PCU bis(4-phenyloxazoline) **100** ligand (17 mg, 0.04 mmol), anhydrous $MgBr_2$ (6.5 mg, 0.04 mmol), and anhydrous $AgClO_4$ (14.7 mg, 0.08 mmol) in dry CH_2Cl_2 (5 ml) was stirred under dry nitrogen at ambient temperature for 6 h, during which time a gray precipitate of silver bromide appeared. The resulting suspension was used without filtration for the Diels-Alder reactions as follows: 3-acryloyl-2-oxazolidinone **52** (50 mg, 0.4 mmol) and freshly distilled cyclopentadiene **33** (0.3 ml, 4.0 mmol) were added to this suspension. The reaction was performed at room temperature and monitored by TLC. After the completion of reaction, saturated aqueous ammonium chloride (20 ml) was added and the mixture was extracted with CH_2Cl_2 (20 ml). The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvents were removed *in vacuo*. The resulting residue was purified by flash column chromatography (Hexane/EtOAc = 50:50, R_f = 0.7) to give a mixture of *endo* and *exo* isomers of cycloadduct **53** (60 mg, 85 %). The *endo:exo* ratio was evaluated on the basis of the ^1H NMR spectrum and the enantiomeric excess determined by HPLC with a Daicel Chiralpak IB column (Hexane/*i*-PrOH = 95/5) flow rate = 1 L/min, *t*(*R*) 22.0 min, *t*(*S*) 20.2 min. Other anhydrous PCU bis(4-phenyloxazoline) complexes were prepared according to a similar procedure by using anhydrous metal halides such as $NiBr_2$, $CaBr_2$, $MnBr_2$, $FeCl_2$, $CoBr_2$, $CuCl_2$, and ZnI_2.

Preparation of the hydrated complexes.

The hexahydrated complexes of the ligand **100** with Mg, Mn, Co, Ni, Zn and Ca (II) perchlorates was carried out according to a similar procedure as stated above without adding the silver perchlorate. Isolation and analysis of the product was exactly the same as outlined above.

3-(Bicyclo[2.2.1]hept-5-en-2-ylcarbonyl)-2-oxazolidinone 53.[112,120]

Colorless solid; enantiomeric purity was estimated on the basis of HPLC using a chiral column as described above and the *endo:exo* ratio was evaluated on the basis of the ^{1}H NMR spectrum. Melting point = 86-87 ^{O}C. ^{1}H NMR ($CDCl_3$) δ = 1.3-1.7 (3H, m, H-3 and one of H-7), 1.9-2.1 (1H, m, the other of H-7), 2.94 (1H, m, H-1 or H-4), 3.31 (1H, m, H-4 or H-1), 3.8-4.1(3H, m, H-2 and H-4'), 4.40 (2H, t, H-5'), 5.88 (1H, dd, H-5), and 6.25 (1H, dd, H-6); ^{13}C NMR ($CDCl_3$) δ = 29.56 (C-3), 42.89, 42.95, 43.21, 46.39 (C-1, C-2, C-4, and C-4'), 50.18 (C-7), 61.97 (C-5'), 131.63, 138.11 (C-5 and C-6), 153.41 (C-2'), and 174.75 (CO). The HPLC chromatograph appears in Appendix A.

Computational details

Complexes A and B were optimized using GAUSSIAN 03[149] utilizing density functional theory (DFT) in the gas phase at the B3LYP level of theory with the 6-31+*(G)d* basis set. Diffuse functions are typically used for a more accurate description where lone pair electrons are involved, while polarization functions remove some limitations of the basis set by expansion of the virtual space. Solvation effects were not considered in order to simplify the model. Cartesian coordinates of the optimized structures are available as on a CD that accompanies this thesis. Various variations of the starting geometry were explored, but it was quite clear that the rigid nature of the complex reverts to the same low energy structures.

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Appendix A

- **NMR spectra**
- **IR spectra**
- **HPLC chromatographs**