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Synthesis and Application of Novel Peptidic and Oxazoline Based Ligands for Asymmetric Catalysis

by

Paul Geoghegan

A thesis submitted to the faculty of
National University of Ireland, Galway
in partial fulfilment of the requirements for the degree of
Doctor of Philosophy

School of Chemistry
National University of Ireland, Galway
September 2012

Supervisor: Dr. P. F. O’Leary
Head of School of Chemistry: Prof. Paul V. Murphy
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Finally, I would like to express my sincere gratitude to my family for their endless patience, understanding and love over the years.
Abbreviations

AAS  Asymmetric allylic substitution
Ac   Acetyl (CH$_3$CO)
Alloc allyloxycarbonyl
ATH  Asymmetric transfer hydrogenation
BINOL 1,1’-Bi-2-naphthol
Boc  Tert-butoxycarbonyl [(CH$_3$)$_3$COCO]
bp   Boiling point
br s  Broad singlet or broad/strong
BSA  Bis(trimethylsilyl)acetamide
°C   Degrees Celsius
Cbz  Carboxybenzyl
CBS  Corey-Bakshi-Shibata
COSY Correlated spectroscopy
Cy   Cyclohexyl
d    Doublet
DAST Diethylaminosulfur trifluoride
DBU  1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC  Dicyclohexylcarbodiimide
DCM  Dichloromethane
DCU  Dicyclohexylurea
DEPT Distortion less Enhancement by Polarization Transfer
DFT  Density functional theory
DIAD Diisopropyl azodicarboxylate
DIOP [(2,2-dimethyl-1,3-dioxolane-4,5diyl)bis(methylene)]
bis(diphenylphosphane)
DIPEA Diisopropylethylamine
DMAP 4-Dimethylaminopyridine
DMF  Dimethylformamide
DMM  Dimethyl malonate
DNA  Deoxyribonucleic acid
L-DOPA L -3,4-dihydroxyphenylalanine
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
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<tbody>
<tr>
<td>$E^+$</td>
<td>Electrophile</td>
</tr>
<tr>
<td>$Ee$</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>Electron impact</td>
</tr>
<tr>
<td>equiv.</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Fmoc</td>
<td>9-Fluorenlyethyl carbamate</td>
</tr>
<tr>
<td>FID</td>
<td>Flame ionisation detector</td>
</tr>
<tr>
<td>G</td>
<td>Grams</td>
</tr>
<tr>
<td>GC</td>
<td>Gas Chromatography</td>
</tr>
<tr>
<td>GCMS</td>
<td>Gas chromatography/mass spectrometry</td>
</tr>
<tr>
<td>H</td>
<td>Hour</td>
</tr>
<tr>
<td>HETCOR</td>
<td>HETeronuclear COrrelation</td>
</tr>
<tr>
<td>HOBT</td>
<td>1-hydroxybenzotriazole</td>
</tr>
<tr>
<td>HOSU</td>
<td>Hydroxysuccinimide</td>
</tr>
<tr>
<td>HMQC</td>
<td>Heteronuclear shift multiple quantum coherence</td>
</tr>
<tr>
<td>HPLC</td>
<td>High Performance Liquid Chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>High-resolution mass spectrometry</td>
</tr>
<tr>
<td>HSAB</td>
<td>hard and soft (Lewis) acids and bases</td>
</tr>
<tr>
<td>IR</td>
<td>Infra-Red Spectroscopy</td>
</tr>
<tr>
<td>IPA</td>
<td>2-propanol, isopropyl alcohol</td>
</tr>
<tr>
<td>lit.</td>
<td>Literature</td>
</tr>
<tr>
<td>M</td>
<td>Multiplet or medium</td>
</tr>
<tr>
<td>M</td>
<td>Molar</td>
</tr>
<tr>
<td>$m/z$</td>
<td>Mass/charge</td>
</tr>
<tr>
<td>MeCN</td>
<td>Acetonitrile</td>
</tr>
<tr>
<td>Mg</td>
<td>Milligrams</td>
</tr>
<tr>
<td>MHz</td>
<td>Mega Hertz</td>
</tr>
<tr>
<td>Min</td>
<td>Minute</td>
</tr>
<tr>
<td>Ml</td>
<td>Millilitres</td>
</tr>
<tr>
<td>mm Hg</td>
<td>Millimetres of mercury</td>
</tr>
<tr>
<td>Mmol</td>
<td>Millimole (mole x $10^3$)</td>
</tr>
<tr>
<td>Mol</td>
<td>Mole</td>
</tr>
<tr>
<td>mol %</td>
<td>Mole percent</td>
</tr>
<tr>
<td>mp</td>
<td>Melting point</td>
</tr>
<tr>
<td>MS</td>
<td>Molecular sieves</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>MW</td>
<td>Microwave irradiation</td>
</tr>
<tr>
<td>n/a</td>
<td>Non-applicable</td>
</tr>
<tr>
<td>ND</td>
<td>Non-determinable</td>
</tr>
<tr>
<td>NHK</td>
<td>Nozaki-Hiyama-Kishi</td>
</tr>
<tr>
<td>NMM</td>
<td>N-methyl morpholine</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>Nu⁻</td>
<td>Nucleophile</td>
</tr>
<tr>
<td>Pyox</td>
<td>Pyridyl-2-oxazolines</td>
</tr>
<tr>
<td>PyrOx</td>
<td>2-(2’-pyrrolyl)oxazoline</td>
</tr>
<tr>
<td>Q</td>
<td>Quartet</td>
</tr>
<tr>
<td>R_f</td>
<td>Retention factor</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>Rt</td>
<td>Room temperature</td>
</tr>
<tr>
<td>Rt</td>
<td>Retention time</td>
</tr>
<tr>
<td>S</td>
<td>Singlet or Strong or Second</td>
</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
<tr>
<td>TBD</td>
<td>1,5,7-Triazabicyclo[4.4.0]dec-5-ene</td>
</tr>
<tr>
<td>TBSCN</td>
<td>Tert-butyl dimethylsilyl cyanide</td>
</tr>
<tr>
<td>TBTU</td>
<td>O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>TFAA</td>
<td>Trifluoroacetic anhydride</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Tetramethylsilane</td>
</tr>
<tr>
<td>TMSCl</td>
<td>Trimethylsilane chloride</td>
</tr>
<tr>
<td>TMSCN</td>
<td>Trimethylsilanecaronitrile</td>
</tr>
<tr>
<td>TMSI</td>
<td>Trimethylsulfonium iodide</td>
</tr>
<tr>
<td>Ts</td>
<td>Tosyl</td>
</tr>
<tr>
<td>TS</td>
<td>Transition state</td>
</tr>
<tr>
<td>W</td>
<td>Weak</td>
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Abstract

This thesis describes the synthesis and application of four novel chiral ligand classes. These were all hydroxyamide or oxazoline ligands with an L-pyroglutamic acid derived terminus. These ligands were applied as part of catalytic systems to the catalysis of three main asymmetric transformations, an alkylation reaction, an alkynylation reaction and transfer hydrogenation reaction.

Chapter one introduces the current state of the art with respect to chiral hydroxyamide ligands and oxazoline ligands. The comprehensive section on chiral hydroxyamide ligands has recently been published as a review paper in ACS Catalysis.

Chapter two outlines the synthesis of the four novel classes of ligand:

- hydroxyamide ligands based on a dipeptide framework, capped by a pyroglutamate at one terminus
- hydroxyamides based on a tripeptide framework, capped by a pyroglutamate at one terminus
- two different types of oxazoline ligands which had the pyroglutamate at one end of the carbon chain and the oxazoline at the other, which differed in the location of functionality on the carbon backbone.

A modular approach was used to synthesize chiral ligands, with the chirality originating from the chiral pool. The various synthetic methods employed are discussed, and where ligands were made by several methods, they are compared. The characterisation of all the ligands is discussed in detail. Electronic and steric properties of the ligand compounds were varied, and the electronic properties of the ligands were found to have a minor influence on the levels of enantioselectivity induced by the ligands. The influence of the steric properties was more important, especially where the ligands contained phenyl groups.

The application of the ligands to the three main reactions and several other minor reactions are discussed in detail. The dipeptide based ligands were used in a ruthenium-catalysed transfer hydrogenation reaction where one ligand gave the product in 72% ee though the conversion was poor. The ligands were also used in
two titanium-catalysed reactions, an alkylation where ees of up to 74% were achieved and a phenyl acetylene addition where more modest selectivities were observed. The tripeptide based ligands were used in a ruthenium-catalysed transfer hydrogenation reaction where they were far less selective than the dipeptides achieving ees of only 20%. The ligands were also used in the alkylation where ees of 21% were achieved and a phenyl acetylene addition where again modest selectivities were observed. The oxazoline ligands were used in the alkylations, where they gave very modest selectivities of ~20% ee, to the transfer hydrogenation where they gave selectivity of up to 27% ee and the alkylnylation where again they gave modest selectivity. This chapter also discusses the potential reasons for selectivity where it is observed. The sense of chiral induction looks to be determined by the absolute configuration of the pyroglutamate module of the ligands as the (R)-enantiomer of the chiral products was in excess in all cases, and the (S)-pyroglutamate was common to all the ligands.

Chapter 3 gives full experimental details for all of the reactions described in the thesis. The appendices contain the publications emanating from this research to date.
List of publications

This thesis is based on the following papers:


CHAPTER 1

INTRODUCTION

1.1 Chirality

The word chiral originates from the Greek word “χειρ”, meaning hand. The left and right human hands are non-superimposable forms that can be represented as mirror images. An object is “handed” if it has an identical mirror image counterpart, which cannot be superimposed on to itself. Analogously, a molecule is chiral if its identical mirror image counterpart cannot be superimposed onto itself. Fig. 1.1 shows two forms of mandelic acid. The two forms are not superimposable. They are known as enantiomers or optical isomers. A 1:1 mixture of the two enantiomers is called a racemic mixture.

![Figure 1.1 D-(-) and L-(+)-mandelic acid](image)

Enantiomers have identical physical and chemical properties, in an isotropic environment. Its chirality is only observed when the molecule is subjected to a chiral influence. A widely known example is the optical rotation of polarized light. Polarized light is rotated when passing through solutions containing chiral molecules (but not when passing through racemic mixtures). Optical isomers rotate the light in
an equal degree but in opposite direction. If the enantiomer rotates the light to the right, it will be indicated as dextrorotatory (Latin: dexter), “d” or “(+)”.

Optical isomers that rotate light to the left, on the other hand will be indicated as levorotatory (Latin: laevus), “l” or “(-)”. According to the Fischer convention\(^1\) the absolute configuration around a chiral centre can be noted as D- or L-. This notation, which is nowadays mainly used for amino acids and carbohydrates, correlates the configuration of a chiral centre to the configuration of D- and L- glyceraldehyde. The \(R/S\) notation (from Latin: rectus (right) and sinister (left)), which has largely replaced the D/L notation, is related to the Cahn-Ingold-Prelog convention,\(^2\) and can also be used for molecules containing more than one chiral centre.

### 1.1.1 History of Chiral Chemistry

Optically active compounds have been known since the early nineteenth century. In 1801, the French mineralogist Haüy noticed that quartz crystals exhibited hemihedral phenomena. In 1812 another French scientist, Biot, found that plates of quartz crystals cut at right angles to its symmetry axis rotated plane polarized light in opposite directions, depending on the original symmetry. Biot extended his investigations to solutions of organic compounds and found that many compounds of natural origin behaved in a similar manner.\(^3\)

At the time, the phenomenon was explained by the fact that the compounds were of natural origin, produced by living organisms. In 1848 Pasteur was able to separate the two enantiomorphous crystal forms of racemic sodium ammonium tartrate (Fig. 1.2) manually, with a pair of tweezers, by a simple assignment of the crystal shape through a lens.\(^4\)

![Figure 1.2 The two enantiomers of sodium ammonium tartrate](image-url)
He found that a solution of the enantimorphous crystals rotated the polarized light in equal intensity but in opposite directions. Pasteur then made an important statement that the rotation of polarized light caused by the different tartaric acid salt crystals was the property of chiral molecules. The two forms of optically active tartaric acid were related to each other as three-dimensional mirror images.

Enantiomers have identical physical and chemical properties when acting in a non-chiral environment. The differences only occur when interacting with another chiral object (molecule) or plane-polarized light. Biological systems are built up by chiral molecules (e.g. DNA, RNA, sugars and proteins). As an example, 19 out of the 20 naturally occurring amino acids that make up proteins in living organisms are chiral. As a consequence of this chirality has been extensively investigated. The major breakthrough in the synthesis of chiral compounds was made in the late 1960’s, when the synthetic and analytic tools of organic chemistry became more sophisticated, development of organometallic chemistry, chiral catalysis, NMR and mass spectrometry. Advances in chiral methodologies have resulted in industrial applications. Several asymmetric processes are operating in chemical plants around the world today. The first large-scale processes were based on enzymatic systems, but during the 1990’s several metal catalyzed asymmetric reactions were setup for pharmaceutical- and speciality-chemical production.\(^5\)

The use and demand for optically active substances is greater today than ever, since the recognition that enantiomers of a specific molecule can interact differently in biological systems and thereby cause different actions.

### 1.1.2 Enantiomerically Pure Compounds

Today we know that chiral compounds are fundamental for the existence of life. The majority of biological processes are consequences of the fact that different enantiomers react with receptors in different ways, depending on their absolute
configuration. As mentioned above, life itself is in many ways chiral. For example, the mechanism of smell is based on stereogenic interactions between the sensor, our nose, and a volatile compound, i.e. the enantiomers of carvone smell differently, the (S)-enantiomer having a caraway odour and the (R)-enantiomer smelling of spearmint. This is also the case in taste, i.e. the enantiomers of the α-amino acid aspargine taste bitter or sweet, depending on the absolute configuration (Fig. 1.3).

Figure 1.2 The two enantiomers of aspargine the (R)-enantiomer tastes bitter (left) whereas the (S)-enantiomer tastes sweet (right)

Another more drastic and tragic example of different biological activity of enantiomers is the drug thalidomide, where the (R)-enantiomer is a mild tranquilizer whereas the (S)-enantiomer is a teratogen, causing abnormalities in human embryos. This clearly indicates the value of the ability to prepare enantiomerically pure compounds in the pharmaceutical industry and the necessity of development of improved synthetic methods in this field. This is necessary not only from a safety reason but also from an economical perspective. Producing only the active enantiomer of a drug or other fine chemicals may reduce production costs, and from an environmental perspective, if less solvents or reagents are required the environmental stress can be diminished.

With this in mind it is clear that a change to single enantiomer pharmaceutical and agricultural chemicals will change the market, increase patient safety and decrease environmental impact. The market of single enantiomer compounds is growing fast. Out of the 60% of all drugs that contain a chiral centre, a percentage that has remained relatively unchanged over the last 20 years, racemates dominated in 1983 (60%) and the drug compounds that were marketed as single enantiomers at that time were mainly of natural origin. In 2002 only 10% of the drugs that contained a chiral
compound were racemates, with the rest sold as single enantiomers. Since 1992, new chemical pharma compounds possessing chirality must have each enantiomer individually screened and evaluated as different chemical entities during the drug approval process.  

![Image](image_url)

1.1.3 Methods to Obtain Enantiomerically Pure Compounds

There are several ways to obtain enantiomerically pure or enriched compounds. The basic strategies can be divided into the following three categories:

1. Resolution of racemates

2. The “Chiral pool”

3. Asymmetric synthesis

1.1.3.1 Resolution of Racemates

This classic way of obtaining enantiopure or enriched compounds relies on a racemate being temporarily converted into diastereomers; this is often obtained by formation of diastereomeric salts, using an enantiomerically pure compound. The obtained diastereomers possess different physiochemical properties making a separation possible. An example is the resolution by recrystallization of (S)-propranolol, a β-adrenergic receptor antagonist (Scheme 1.1).
Scheme 1.1 Resolution of (R, S)-propranolol. The (S)-enantiomer is a β-receptor antagonist while the (R)-enantiomer a contraceptive.

The reagents used to resolve a compound are often of natural origin i.e. tartaric acid, lactic acid, brucine, quinidine and other related alkaloids. Enzymatic methods, like lipase catalyzed reactions are also employed especially on large scale.

Resolution of racemates suffers from some drawbacks such as the need for stoichiometric amounts of the enantiopure compound and the maximum theoretical yield is only 50%. Recovery and racemization of the unwanted isomer can in some cases overcome this problem. A good method for this is a dynamic kinetic resolution, where the unwanted isomer is racemized in situ and then transformed again into the desired enantiomer via resolution.

1.1.3.2 The “Chiral Pool”

The fundamental of the naturally occurring “chiral pool” approach is that non-racemic compounds occurring in nature, can serve as chiral starting materials for a synthesis. Nature provides a vast diversity of chiral species in several types of compound classes of which amino acids, carbohydrates, terpenes, carboxylic acids and alkaloids play important roles (Fig. 1.4).
Many chiral compounds have been synthesized from the “chiral pool” approach. One example is oseltamivir phosphate, Tamiflu®. This compound is a potent antiviral agent and can be synthesized from the naturally occurring (−)-shikimic acid (Scheme 1.2), extracted from the Chinese star anise plant.

This way of producing chiral compounds is a very efficient methodology and it has become the most used strategy for obtaining chiral compounds. In order to produce an enantiomerically enriched product at least one part of the reacting system must be chiral itself. Hence, chiral substrates, chiral auxiliaries, chiral reagents or a chiral catalyst can be used to achieve an asymmetric synthesis:

1. In the substrate controlled asymmetric synthesis a chiral compound is used as a starting material, not necessarily a naturally occurring material. The formation of the new chiral centre is induced by the presence of a stereogenic fragment on the substrate.
2. In the auxiliary controlled asymmetric strategy an enantiomerically pure compound, chiral auxiliary, is temporarily attached to the starting material. After a diastereoselective reaction the auxiliary is removed, obtaining the product in an enantiomerically pure form.

3. In the reagent controlled asymmetric synthesis the enantioselectivity is induced by a chiral reagent e.g. base, reducing agent or hydroboration reagent.

4. In asymmetric catalysis the enantioselectivity is induced by a catalyst, present in sub stoichiometric amounts, the catalyst lowers the activation energy of one diastereomeric TS and thereby enhances the reaction rate and asymmetry in the product. Asymmetric catalysis is described in more detail below.

1.2 Asymmetric Catalysis

Ever since the first report of a catalytic reaction by Michael Faraday in 1834 the field of catalysis has grown tremendously and in 1904 Marckwald reported the first catalytic asymmetric synthesis, a decarboxylation of a prochiral, malonic acid 2-ethyl-2-methylmalonic acid, catalyzed by the naturally occurring alkaloid brucine.12

The first synthetically useful asymmetric catalysis was reported in the late 1950s. Izumi et al. reported the hydrogenation of methyl acetoacetate into chiral methyl 3-hydroxybutyrate with enantioselectivities up to 80%, using Raney nickel modified with tartaric acid.13

The first industrial application employing asymmetric catalysis was Monsanto's production of L-DOPA 4, an important anti-Parkinson’s drug. The process is an asymmetric hydrogenation of an acyl enamine 2 with a modified Wilkinson catalyst 1, developed by William Knowles (Scheme 1.3).14,15
A few years later, Ryoji Noyori introduced the binaphthalene based BINAP-ligand 5 (Scheme 1.4) that coordinated to Ru or Rh is especially successful in enantioselective hydrogenation of unsaturated carbon-carbon bonds and ketones$^{16-19}$. An example is the hydrogenation of 2-(6'-methoxynapthyl-2'-yl) acid 6 using [Ru -(S)-BINAP(OCOCH$_3$)$_2$] to give the anti-inflammatory drug (S)-Naproxen® 7.

After the introduction of a large number of ligands suitable for asymmetric hydrogenation reactions, enantioselective hydrogenation has become an established reaction. Catalytic asymmetric oxidations have also been studied and developed. Reactions such as epoxidations, dihydroxylations and aminohydroxylations have been
reported; Sharpless and Katsuki introduced the first practical useful asymmetric oxidation in 1980.\textsuperscript{20,21}

It involves epoxidation of allylic alcohols and is still one of the most popular oxidative asymmetric processes. Today there are also a variety of asymmetric reductions, addition reactions and other miscellaneous methods available, some of them highly useful. At present, asymmetric hydrogenation is the most used catalytic asymmetric transformation,\textsuperscript{22} with several companies offering asymmetric hydrogenation technology on a license basis.\textsuperscript{23}

### 1.3 The Design of Asymmetric Catalysts

The discovery of asymmetric catalysts which facilitate new and desirable reactions enantioselectively has become an important core process in organic chemistry over the past few decades.\textsuperscript{24} Most common of the asymmetric catalytic techniques involves the use of a ligand metal complex as the catalyst. Developments in this area involve to a great degree the development of new ligands, which support the central metal ions and govern their enantioselectivity in asymmetric reactions. Successful ligand design/synthesis/test cycles are greatly aided by the following guiding principles:

1. Proposed syntheses should be modular, i.e., it should be possible to generate many different members of a ligand family using the same reaction(s) simply by varying the combination of starting materials.

2. Ligands should be accessible in only a very few steps, and the diversification step(s) should be placed as close as possible to the end of the synthetic route.

3. Simple, high-yielding reactions should be used whenever possible.

4. In order to generate meaningful quantities of material and to avoid enantiomeric and/or diastereomeric separations, the reagents should be readily available and optically pure as both enantiomers. Moreover, the synthetic chemistry should be stereospecific and not affect any of these built-in stereocentres in an unpredictable way.
(5) It should be possible to install multiple stereocentres that are independently variable. This in turn should allow for trivial expansion of ligand families.

(6) Basic ligand frameworks should be easily modifiable.

The design and discovery of new catalyst structures finds inspiration from a variety of sources, including considerable insight from the ability of enzymes (composed of polypeptides) to catalyze reactions, by hydrogen bonding, nucleophilic and/or metal catalysis. Chemists have attempted to mimic these systems with the use of single or poly-amino acid catalysts.

There are a number of attractive properties of peptide-based catalyst systems: (1) optically pure building blocks in the form of amino acids and alcohols are either commercially available or easily synthesized, (2) procedures for the synthesis of polypeptides are well-established and high yielding, (3) synthesis in most cases can be accomplished upon solid support, which greatly increases the efficiency of catalyst synthesis as well as subsequent screening.

The O’Leary group has an interest in the use of peptide-based catalysts as tools to probe and understand how the manipulation of steric, electronic or stereochemical properties of our catalyst systems influence enantioselectivity in a given reaction. The goal is to use these observations to direct the development of new asymmetric catalyst systems.

There can be identified two main strategies for asymmetric catalyst development, namely discovery and design. The catalyst discovery strategy relies on the ability to generate and screen a large number of catalysts quickly and efficiently in an empirical manner in hopes of observing promising asymmetric catalysis. An initial lead is then further optimized in attempts to achieve a mature chiral catalyst. This method relies heavily from the capability to conduct experiments in a high throughput manner to quickly rule out poor catalyst structures/reaction conditions and allow researchers to focus on beneficial components of the catalyst system.

Both the discovery and design strategies contribute to modern methods for catalyst development. This section will focus on select cases demonstrating the development of polypeptide based catalysts directed by either discovery or design approaches.
1.3.1 Positional Scanning Approach to Catalyst Discovery

There are a number of combinatorial methods which can be used in the discovery of polyamino acid systems that exhibit high selectivity in an asymmetric reaction. One of these is the positional scanning approach, consisting of systematically and independently modifying one position of a ligand structure and evaluating the effects of these changes on catalyst rate and product enantiomeric ratio.\textsuperscript{32}

For example, in the evaluation of a three amino acid peptide system, the AA1 position of the peptide would first be derivatized with a range of amino acids while the other positions are not changed (Fig. 1.5). The resulting ligands would then be evaluated in a given reaction of interest. The ligand framework bearing the optimal substituent is then taken on to the next evaluation step where the second position is derivatized (AA2). Systematic manipulation of the remaining modules progresses in the same manner as above. This cycle can then be repeated to achieve a mature asymmetric catalyst.\textsuperscript{33} This section will highlight the use of positional scanning and how it has been used in the discovery of a number of catalytic asymmetric methodologies.
Figure 3.5 Illustration of catalyst discovery using a positional scanning approach

Inoue and co-workers were one of the first research groups to demonstrate the effective use of peptides as highly modular and convenient frameworks for asymmetric catalysts. They were able to access ligands similar to 8 by synthesizing an array of optically pure peptides and then capping the N-terminus of the peptides, with a variety of salicylaldehyde derivatives to form imines, which serve as metal binding motifs (Fig. 1.6). Employing ligands of this type in the titanium-catalyzed addition of hydrogen cyanide to aldehydes, they found that they performed well, furnishing the optically active cyanohydrins in high yield and good enantioselectivity (up to 78% ee).
Insight drawn from the work of Inoue and co-workers, as well as technological breakthroughs allowing for the synthesis of a large number of polypeptides in a facile manner upon solid support,\textsuperscript{36} led the Hoveyda research group to the application of peptide ligands to various organometallic reactions. The employment of ligand 9 in the Ti-promoted addition of TMSCN to meso-epoxides demonstrated that peptide ligands could be efficiently used to impart asymmetry in this catalytic system (scheme 1.5).\textsuperscript{37} Interestingly, moderately good selectivity ($ee = 40\%$) was observed in the reaction with little modification to the system previously reported by Inoue and co-workers. Following this initial lead, the ligand scaffold could be easily modified and screened using solid support and combinatorial techniques, allowing for the expedited synthesis of a large number of ligands (>20 ligands/day). Positional scanning was used to evaluate different amino acids at the AA1 and AA2 positions of ligand. Finally, the N-terminus was diversified with a variety of salicylaldehyde derivatives (positional scanning at the Ald site), chosen to cover a wide range of steric and electronic possibilities. The overall process involved the synthesis and screening of more than 30 ligands. The positional scanning approach in conjunction with the ability to synthesize and screen the catalysts upon solid support greatly reduced the time needed to achieve the mature catalyst system. Performing this task in the classical stepwise fashion, where purification would be obligatory after each step, would have required a considerable amount of additional labour. The catalytic reaction discussed can be performed either upon solid support or as a homogenous mixture by removal of the ligand from the polystyrene bead (Fig. 1.7). The latter is
favoured in some cases due to the possible interference of solid support linkers (6-amino caproic acid or glycine).\(^{38}\) The optimal ligand for the reaction was thus found to be ligand 10, which affords the product in 65% yield and an 87% ee, a notable increase from the initial 40% ee (Scheme 1.5).

The method of positional scanning proved to be very worthwhile and was further applied to the asymmetric addition of TMSCN to imines, utilizing ligands such as 11 and 12. A wide variety of aryl and \(\alpha,\beta\)-unsaturated imines were found to be excellent substrates for the transformation (Fig. 1.8).\(^{39,40}\)

\[\text{Scheme 1.5 The use of positional scanning in the discovery of an efficient catalyst for the addition of TMSCN to meso-cyclohexene oxide}\]
Figure 1.7 Example of solid support bound catalyst and catalyst removed from solid support
Figure 1.8 Enantioselective Strecker reaction employing Ti-peptide catalysts

One of many beneficial qualities of a positional scanning approach is the ability to tune a ligand system to a given substrate or set of reagents. The common method for catalyst optimization focuses on only a few substrates in the hopes of then transferring this selectivity to similar or specialized substrates. This assumption is often shortsighted when evaluating substrates which are more complex than the model substrate. Being able to overcome the shortfall in selectivity using the modular nature of peptide
based systems to tune selectivity is very valuable. For example, in the study of the asymmetric addition of TMSCN to meso epoxides (scheme 1.6), Hoveyda and co-workers illustrated that 13 the optimal ligand for addition to cyclopentene oxide, furnishing the product in an ee of 83% (Table 1.1).\textsuperscript{37} When evaluating substrates that contained larger ring structures, specialized ligands (10, 14 and 15) were required for each substrate. Minor differences in ligand structure allowed for optimal catalyst systems to be obtained, which speaks to the ability to fine tune a catalyst system through substituent manipulations.

Positional scanning can also allow for the development of ligands with interesting traits, which would be hard to predict from a design perspective. While conducting a systematic study of ligands for the asymmetric addition of TMSCN to meso epoxides (Table 1.1), differing the amino acids at the AA2 position of the peptide ligand framework (22 different protected amino acids), it was observed that all but one substitution resulted in a bias for the \((S, R)\) enantiomer of the desired product (Fig. 1.9).\textsuperscript{41} Interestingly, ligand 16 bearing a trityl protected asparagine furnished an ee of 58% for the \((R, S)\)-enantiomer. When comparing 16 to 17, which furnishes the \((S, R)\)-enantiomer of the product in an ee of 83%, it is hard to rationalize why a simple modification to ligand structure (trityl protected asparagine vs. \(t\)-butyl protected threonine) has such a dramatic effect on the observed enantioselectivity. The positional scanning approach to ligand discovery, illustrated above, can be seen as an efficient and productive method in furnishing new catalyst systems, but some caution must be taken when using this method. One concern with using an approach of this type is the possibility of overlooking a more selective ligand. This is a valid concern, and one that must be addressed in any attempt to design or discover a new asymmetric system. An alternative approach to catalyst discovery is the use of a parallel library, which evaluates all possible ligand structures for a given set of variables.\textsuperscript{42,43}

![Scheme 1.6 Asymmetric addition of TMSCN to meso epoxides](image-url)
Table 1.1 Substrate specific catalysts for the asymmetric addition of TMSCN to meso epoxides

<table>
<thead>
<tr>
<th>Product</th>
<th>Ligand</th>
<th>ee (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC&lt;sub&gt;C&lt;/sub&gt;OTMS</td>
<td><img src="image1.png" alt="Image" /></td>
<td>83</td>
<td>72</td>
</tr>
<tr>
<td>NC&lt;sub&gt;C&lt;/sub&gt;OTMS</td>
<td><img src="image2.png" alt="Image" /></td>
<td>87</td>
<td>65</td>
</tr>
<tr>
<td>NC&lt;sub&gt;C&lt;/sub&gt;OTMS</td>
<td><img src="image3.png" alt="Image" /></td>
<td>84</td>
<td>68</td>
</tr>
<tr>
<td>NC&lt;sub&gt;C&lt;/sub&gt;OTMS</td>
<td><img src="image4.png" alt="Image" /></td>
<td>78</td>
<td>69</td>
</tr>
</tbody>
</table>
Figure 1.9 An observed inversion in facial selectivity by simple manipulation of AA2 substituent in ligands 16 and 17.

For example, Jacobsen and Sigman reported the highly selective catalyst 18 for the asymmetric Strecker reaction (Fig. 1.10), which was discovered using a parallel library.\textsuperscript{44} The important point to note from this study is the comparison of catalysts 18 and 19.

Figure 1.10 The comparison of catalysts 18 and 19 upon solid support, which were screened in the catalytic asymmetric Strecker reaction.
Both the best and the worst catalysts for the reaction contain the tert-Leu amino acid residue in the peptide backbone. If this project had been approached using positional scanning, the key element of the eventual catalyst that resulted in the highest selectivity may not have been detected. Due to the vast number of amino acid/aldehyde combinations, as well as combinations of relative stereochemistry about the chiral centres, it would be ambitious to prevent this oversight in all circumstances, especially with peptide systems containing more than three modules.

The studies discussed above demonstrate how the application of positional scanning methods together with useful combinatorial techniques has led to the discovery of a number of interesting asymmetric methodologies. This pioneering work has illustrated how the ability to systematically and independently modify peptide ligand scaffolds allows researchers to modify the steric or electronic environment that impacts reaction rate, yield, and selectivity.

1.3.2 Conclusions and Outlook

The modular nature of peptide-based systems offers a unique framework for researchers interested in the design or discovery of asymmetric catalysts. The ability to independently manipulate a portion of the peptide structure lends itself well to positional scanning or mechanistic approaches. The use of such approaches has led to the development of a number of structurally interesting and selective catalysts for asymmetric methodologies. The ability to quickly synthesize and evaluate catalysts in a combinatorial approach allows for the discovery of suitable catalyst structures. Initial leads can then be manipulated and studied to further improve the system. Although the case studies in this chapter were separated into two extremes, discovery and design, it is quite obvious that research programs focused toward the development of peptide based catalysts can benefit from the overlap of both. The subsequent chapters of this thesis will illustrate our approach to catalyst development, incorporating both the design and discovery elements.
1.4 Chiral Hydroxyamide Ligands in Asymmetric Catalysis

1.4.1 Introduction

The asymmetric catalysis of organic reactions by metal complexes of amines and amino alcohols or indeed their use without metals in organocatalysis is a very active area of research. Many very successful catalytic systems have been reported for key organic reactions. More recently there has been growing interest in the use of amido alcohols as ligands in metal complexes which show good activity in asymmetric organic reactions.

Asymmetric ligands whose key functional component consists of an amide and a hydroxyl functional group, in the absence of other co-ordinating groups, are a relatively recent development in asymmetric catalysis. These ligands in complex with ruthenium, zinc, titanium and others have catalyzed a range of key organic reactions showing high activity and selectivity. The review looks at the ligands reported and their performance as catalysts.

The following is a comprehensive review that seeks to look at ligands of this type and their complexes’ use in key synthetic asymmetric transformations.

1.4.2 Diakylzinc Addition to Carbonyl Groups

The stereoselective creation of stereogenic centres is an important process in organic chemistry. Approaches based on C–C bond formation reactions provide a basic strategy for synthesizing these molecules. The catalytic asymmetric addition of organozinc reagents to carbonyl groups in the presence of chiral ligands (Scheme 1.7) has proved a very useful and versatile approach, synthesizing optically active secondary alcohols. Many ligands inducing high enantioselectivities have been reported. The organozinc reagents, due to their low reactivity, can tolerate the
presence of many reactive functional groups and are highly selective in nucleophilic addition reactions to carbonyl compounds.

Scheme 1.7 Enantioselective addition of organozinc reagents to carbon electrophiles

Although many types of ligands can catalyse this reaction, the derivatives of chiral amino alcohols are amongst the most studied ligand types due to the high stereoselectivities achieved.\textsuperscript{38,45} \textit{N,N}-dialkyl-substituted \textit{\beta}-amino alcohols such as Noyori’s \textit{(2S)-(-)-3-exo-(dimethylamino)isoborneol} (DAIB) 20 and Nugent’s \textit{(2S)-(-)-3-exo-(morpholino)isoborneol} (\textit{\textendash}MIB), are particularly noteworthy (Fig. 1.11).\textsuperscript{50,51}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{20.png}
\caption{\textit{N,N}-dialkyl-substituted \textit{\beta}-amino alcohols 20 and 21}
\end{figure}

The mechanism of diethylzinc addition to benzaldehyde is well known with \textit{\beta}-amino alcohols as ligands. The amino alcohol acts as a Lewis base which activates the zinc reagent and forms a Lewis acidic zinc species, which activates the aldehyde. Upon treatment of an amino alcohol with an alkylzinc reagent, the nitrogen and oxygen donor atoms of the amino alcohol coordinate to the zinc atom, yielding a complex which is capable of acting as an alkyl donor. The zinc atom in the five-membered chelate ring is a Lewis acid, which coordinates the aldehyde through the oxygen non-
bonding orbital, and hence the carbonyl carbon atom is activated for nucleophilic attack.\textsuperscript{52,53}

1.4.2.1 Asymmetric Dialkylzinc Addition to Carbonyl Groups Using Chiral $\beta$-Hydroxyamides as Ligands

Certain chiral $\beta$-hydroxyamides have proved to be efficient ligands in the addition of organozincs to carbonyl compounds also. These compounds are attractive as they have the advantage of being easily prepared by the reaction of simple and cheap starting materials (e.g. hydroxy acids and amines or acids and amino alcohols), which can be obtained in enantiopure form from the chiral pool. In many cases titanium (IV) isopropoxide is used as a Lewis acidic additive.

Katsuki and co-workers described the application of 1,1’-bi-2-naphthol-3,3’-dicarboxamides 22a-e as chiral ligands, in the enantioselective addition of diethylzinc to a variety of aldehydes (Fig. 1.12).\textsuperscript{54,55} Among the ligands they used, the ligand 22c gave high yields and excellent enantioselectivities in the reaction of aromatic aldehydes (Scheme 1.8). The alkylation of phenyl propargyl aldehyde was also studied (Scheme 1.9). Ligand 22d induced excellent enantioselectivities with moderate yields in the reaction. The yields could be improved somewhat by increasing the excess of alkylating agent.

![Figure 1.12 Katsuki ligands 22a-e](image-url)
Oppolzer et al first reported the use of ketopinic acid derived tertiary amido-alcohol 23a (Fig. 1.13) in the addition of diethylzinc to benzaldehyde (68% yield, 91% ee) in 1988.\(^{56}\) The use of tertiary amido-alcohols in this reaction remained largely unexplored until the group of Engel developed ligands 24a-28a (Fig. 1.13 & Fig. 1.15), analogues of 23a, to investigate the influence of the nitrogen’s alkyl substitution and the ligand’s symmetry on its catalytic activity in the same reaction. These experiments were repeated with the corresponding \(N,N\)-dialkyl-amino alcohol ligands, 23b-27b.\(^{57,58}\)

**Figure 1.13** Isoborneol-based hydroxyamides and amino alcohols studied
The collected data in Table 1.2 shows that all the ligands promote Re face attack of the prochiral benzaldehyde, giving the R- product. It also demonstrates that hydroxyamides can be more efficient than the analogous amino alcohols for certain ligand structures and reactions. A bis(hydroxyamide) C\textsubscript{2}-symmetric structure is more efficient and selective for these amido-isoborneols, whereas a C\textsubscript{1}-symmetric structure is better for amino-isoborneols.

The authors reasoned that the better catalytic results obtained with 27\textsubscript{a} in relation to the related amino alcohols 24\textsubscript{b} and 25\textsubscript{b} was due to the formation of a more enantioselective and reactive C\textsubscript{2}-symmetric zinc dialkoxide catalyst 29, instead of the C\textsubscript{1}-symmetric 30 (Fig. 1.14). The substitution of the methylamino group of 25\textsubscript{a} by the amide present in 26\textsubscript{a} must be enough to allow the extra coordination (by the closer carbonyl oxygen) giving rise to the efficient catalyst 29. It is proposed that the difference in performance between 27\textsubscript{a} and 27\textsubscript{b} can be explained by the loss of the usually advantageous C\textsubscript{2}-symmetry\textsuperscript{57,59} by the metallocatalyst formed in the case of 27\textsubscript{b}, which is similar in structure to 30 and gives similar results.

![Figure 1.14](image-url)
### Table 1.2 Enantioselective addition of diethylzinc to benzaldehyde in the presence of ligands 23a–28a and 23b–27b.\(^{57}\)

<table>
<thead>
<tr>
<th>Ligand Symmetry</th>
<th>Hydroxyamides</th>
<th></th>
<th></th>
<th>Amino Alcohols</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ligand</td>
<td>Yield (%)</td>
<td>ee (%)</td>
<td>Dominant Config</td>
<td>Ligand</td>
<td>Yield (%)</td>
<td>ee (%)</td>
</tr>
<tr>
<td>C&lt;sub&gt;1&lt;/sub&gt;</td>
<td>23a</td>
<td>68</td>
<td>91</td>
<td>(R)</td>
<td>23b</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>24a</td>
<td>96</td>
<td>48</td>
<td>(R)</td>
<td>24b</td>
<td>96</td>
</tr>
<tr>
<td>C&lt;sub&gt;2&lt;/sub&gt;</td>
<td>25a</td>
<td>93</td>
<td>50</td>
<td>(R)</td>
<td>25b</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>27a</td>
<td>97</td>
<td>90</td>
<td>(R)</td>
<td>27b</td>
<td>94</td>
</tr>
<tr>
<td>C&lt;sub&gt;3&lt;/sub&gt;</td>
<td>28a</td>
<td>92</td>
<td>73</td>
<td>(R)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>26a</td>
<td>70</td>
<td>39</td>
<td>(R)</td>
<td>26b</td>
<td>72</td>
</tr>
</tbody>
</table>

Reactions conducted at room temperature for 5h in hexane using Et<sub>2</sub>N 2mmol, Ligand 0.05 mmol, aldehyde 1 mmol. ee determined by GC.

It has been proposed, for a number of reasons, that transition metal complexes derived from C<sub>3</sub>-symmetric ligands have even greater potential for asymmetric catalysis than their C<sub>2</sub>-symmetric counterparts.\(^{60}\) Here the C<sub>3</sub>-symmetric ligands 26a and 26b promote the reaction poorly. The low enantioselectivity can be explained by the possible coexistence of different catalytic species due to multiple coordination sites in these ligands.

More recently a paper by the same author\(^{61}\) screened a selected library of ketopinic acid derived C<sub>2</sub>-symmetric bis(hydroxyamide) ligands in the enantioselective ethylation of benzaldehyde (Table 1.3). These ligands included previously reported 27a and 28a,\(^{57}\) and Uangs’s 31 and 32 (Fig. 1.15).\(^{62,63}\)
Figure 1.15

27a: X: C(O)
27b: X: CH₂

28a: X: C(O)
28b: X: CH₂

31

32

33

34

35

36

37
Table 1.3 Performance of ligands in the enantioselective diethylzinc addition to benzaldehyde.\textsuperscript{61}

<table>
<thead>
<tr>
<th>Ligand Configuration</th>
<th>Yield (%)</th>
<th>1-Phenylpropan-1-ol ee (%)</th>
<th>Dominant Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>27a</td>
<td>97</td>
<td>90</td>
<td>(R)</td>
</tr>
<tr>
<td>28a</td>
<td>92</td>
<td>73</td>
<td>(R)</td>
</tr>
<tr>
<td>31</td>
<td>43</td>
<td>24</td>
<td>(R)</td>
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<tr>
<td>32</td>
<td>45</td>
<td>24</td>
<td>(R)</td>
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<td>33</td>
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<td>(R)</td>
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<td>34</td>
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<td>(R)</td>
</tr>
<tr>
<td>37</td>
<td>65</td>
<td>10</td>
<td>(R)</td>
</tr>
</tbody>
</table>

Reactions conducted at room temperature for 5h in hexane using Et\textsubscript{2}N 2mmol, Ligand 0.05 mmol, aldehyde 1 mmol. ee determined by HPLC and yield by GC.

Of note, is the catalytic efficiency of aprotic over protic amide ligands and also that the bis(hydroxyamides) with shorter spacers (2-carbon length) between the amide Ns are superior to those with longer spacers. The ligands with longer spacers should form dimetallic, non-tetrahedral, C\textsubscript{1}-symmetric Zn catalysts similar to 30. It follows that their catalytic behaviour would be similar to less efficient C\textsubscript{1}-symmetric catalysts derived from C\textsubscript{1}-symmetric hydroxyamide ligands (24a-26a, Table 1.2). The catalytic behaviour of all the studied aprotic-amide based ligands demonstrates that both the length and the conformational flexibility of the diamine spacer are key structural factors controlling the catalytic activity. The effect of conformational flexibility is evident in the decreased selectivity of 28a.

The poor efficiency of the protic-amide ligands was explained by the formation of bimetallic zinc catalysts due to deprotonation of the amides and subsequent O/N zinc chelation which leads to competitive, undesired pro-(S) transition states in contrast to the zinc-centred catalyst 29.
The most efficient ligands 27a, 35 and 36 were tested in the ethylation of different benzaldehydes, bearing electron withdrawing or donating groups to influence their reactivity. Under the optimized conditions (0.02 mol% ligand) the reactions occurred with moderate to excellent yields and enantioselectivities (73–97% ee and 71–92% yield).

Velmathi et al. developed chiral β-hydroxyamide 38 (Fig. 1.16), synthesized from (1S,2R)-(+)-norephedrine and furoic acid, and applied it to catalyse the enantioselective ethylation of aromatic and heteroaromatic aldehydes to secondary alcohols.

![Figure 1.16 Velmathi's chiral β-hydroxyamide 38](image)

During initial optimization studies with the ligand in the asymmetric addition of diethylzinc to benzaldehyde, it was found that that the reaction temperature and ligand concentration had a significant influence on the efficacy of the catalyst. The results indicated that at 0 °C, 10 mol % of the 38 in toluene, and reaction times of 24 h were the best conditions to obtain the highest enantioselectivity. In order to study the effect of Ti(OiPr)₄ as a promoter in this catalytic system the diethylzinc addition to benzaldehyde was carried out, in the presence of Ti(OiPr)₄ and (R)-1-Phenyl propanol was formed in 99.8% ee with 90% yield. This performance is identical to the reaction without promoter the use of which does not seem to be beneficial in the case of this ligand.

The ligand’s performance was further studied in the asymmetric diethylzinc addition to other substituted benzaldehydes, salicylaldehydes, and heterocyclic aldehydes without the addition of Ti(OiPr)₄ (Table 1.4).
The performance of the catalytic system was good both in terms of yield and selectivity across a variety of aldehyde starting materials. The three final entries in Table 1.4 along with that for p-methoxy benzaldehyde show dramatically reduced selectivity. The authors speculate that this altered performance is due to coordination of the additional oxygens or nitrogens in the substrates to the zinc species.

The proposed catalytic cycle for the addition of diethylzinc to benzaldehyde catalysed by 38 is shown in Fig. 1.17. In the first step, 38 reacts with diethylzinc to yield monomeric alkylzinc complex. This alkoxide can subsequently form a mono-alkoxide diethylzinc complex by reaction with another equivalent of diethylzinc. Co-ordination of the reacting aldehyde followed by alkyl group transfer ultimately leads to the product.

To account for the preferential formation of the (R)-isomer in the addition of diethylzinc to the substrate aldehydes using 38 as catalyst, possible transition state assemblies were proposed by the authors as shown (Fig. 1.18). The phenyl group

Table 1.4 Diethylzinc additions to different aldehydes using 38 and no promoter$^{64}$

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Dominant Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzaldehyde</td>
<td>90</td>
<td>99.8</td>
<td>(R)</td>
</tr>
<tr>
<td>o-Nitro benzaldehyde</td>
<td>70</td>
<td>68</td>
<td>(R)</td>
</tr>
<tr>
<td>m-Nitro benzaldehyde</td>
<td>82</td>
<td>95</td>
<td>(R)</td>
</tr>
<tr>
<td>p-Nitro benzaldehyde</td>
<td>92</td>
<td>85</td>
<td>(R)</td>
</tr>
<tr>
<td>p-Methoxy benzaldehyde</td>
<td>90</td>
<td>30</td>
<td>(R)</td>
</tr>
<tr>
<td>p-Methyl benzaldehyde</td>
<td>90</td>
<td>76</td>
<td>(R)</td>
</tr>
<tr>
<td>p-Chloro benzaldehyde</td>
<td>95</td>
<td>99.8</td>
<td>(R)</td>
</tr>
<tr>
<td>Salicylaldehyde</td>
<td>23</td>
<td>99.8</td>
<td>(R)</td>
</tr>
<tr>
<td>5-Chloro salicylaldehyde</td>
<td>46</td>
<td>99</td>
<td>(R)</td>
</tr>
<tr>
<td>4-Hydroxy 3-methoxy benzaldehyde</td>
<td>20</td>
<td>20</td>
<td>(S)</td>
</tr>
<tr>
<td>Pyrrole-2-carboxaldehyde</td>
<td>99</td>
<td>53</td>
<td>(R)</td>
</tr>
<tr>
<td>Furfural</td>
<td>96</td>
<td>10</td>
<td>(R)</td>
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</tbody>
</table>

Reactions conducted at 0°C for 24h in toluene using Et$_2$N 2mmol, Ligand 0.1 mmol, aldehyde 1 mmol. ee determined by HPLC, yields are isolated yields.
present in the ligand exerts a steric effect with the phenyl group in benzaldehyde, thus favouring the transition state I over state II during the reaction. Due to the steric influence of the phenyl groups, the ethyl group of the second coordinating diethyl zinc molecule can only approach the Re-face of the aldehyde.

![Catalytic cycle for the addition of diethylzinc to benzaldehyde catalyzed by 38](Figure 1.17)

![Transition state models I and II for 38 as a catalyst](Figure 1.18)

Our group has published results where we applied new L-pyroglutamic acid derived chiral hydroxy amide ligands 39a-c and 40 (Fig. 1.19) in the enantioselective addition of diethylzinc to benzaldehyde (Table 1.5). The application of these ligands to a range of asymmetric catalytic transformations will be discussed in Chapter 2.
Testa and co-workers reported the synthesis of polydentate oxalamide-based ligands\textsuperscript{66} (Fig. 1.20) and their use as chiral catalysts for the enantioselective addition of diethylzinc to benzaldehyde. The results showed moderate induction of enantioselectivity (up to 67\% for \textit{42b}) and moderate to good yields (up to 85\% for \textit{41a}).

Table 1.5 Titanium-promoted ethylation using hydroxyamide ligands \textit{39a-c} and \textit{40}\textsuperscript{66}

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Dominant Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{41a}</td>
<td>85</td>
<td>60</td>
<td>(S)</td>
</tr>
<tr>
<td>\textit{41b}</td>
<td>82</td>
<td>23</td>
<td>(S)</td>
</tr>
<tr>
<td>\textit{42a}</td>
<td>64</td>
<td>40</td>
<td>(S)</td>
</tr>
<tr>
<td>\textit{42b}</td>
<td>75</td>
<td>67</td>
<td>(R)</td>
</tr>
<tr>
<td>\textit{42c}</td>
<td>57</td>
<td>15</td>
<td>(R)</td>
</tr>
</tbody>
</table>
Scheme 1.10 Pedro’s ligands applied to the enantioselective addition of diethylzinc to benzaldehyde

Pedro and co-workers had reported the synthesis of 41a-b prior to Testa along with other novel chiral tetradentate bis(amino alcohol) oxalamides with C₂-symmetry, 43, 44, 45a-b and 46 (Fig. 1.21). This group applied all of these ligands to the enantioselective addition of diethylzinc to benzaldehyde (Scheme 1.10). Pedro’s results were poorer than Testa’s, with enantioselectivities of 39% and 12% for 41a and 41b compared with 60% and 23% for Testa. The difference was probably due to the difference in amount of ligand used in the reaction (Pedro: 20 mol %, Testa 25 mol %) and also the solvents used. Testa performed the reactions in toluene as opposed to DCM. This is in accordance with previous results where toluene was found to be the most appropriate solvent for this reaction. Ligand 44 was found not to be very selective which was attributed to mismatching in the asymmetric induction caused by the two stereogenic centres in the molecule. Ligand 46 gave very poor reactivity and no selectivity which the authors point out is unexpected given the reported preference of titanium for co-ordinating groups with a 1,3 separation.

Ligand 45a was found to perform best in this reaction and was used in the diethylzinc addition to a range of different aldehydes, both with and without the addition of Ti(OiPr)₄ (Table 1.6).

Figure 1.21
Table 1.6 Diethylzinc addition to a range of different aldehydes using ligand 45a, both with and without the addition of Ti(OiPr)$_4$.

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>Yield$^a$</th>
<th>ee$^a$</th>
<th>Dominant$^a$ Configuration</th>
<th>yield$^b$</th>
<th>ee$^b$</th>
<th>Dominant$^b$ Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzaldehyde</td>
<td>81</td>
<td>58</td>
<td>(S)-(-)</td>
<td>92</td>
<td>61</td>
<td>(R)-(+</td>
</tr>
<tr>
<td>p-Methoxybenzaldehyde</td>
<td>60</td>
<td>36</td>
<td>(S)-(-)</td>
<td>26</td>
<td>38</td>
<td>(R)-(+</td>
</tr>
<tr>
<td>p-Chlorobenzaldehyde</td>
<td>74</td>
<td>60</td>
<td>(S)-(-)</td>
<td>21</td>
<td>30</td>
<td>(R)-(+</td>
</tr>
<tr>
<td>p-Bromobenzaldehyde</td>
<td>41</td>
<td>58</td>
<td>(S)-(-)</td>
<td>54</td>
<td>50</td>
<td>(R)-(+</td>
</tr>
<tr>
<td>p-Trifluoromethylbenzaldehyde</td>
<td>89</td>
<td>56</td>
<td>(S)-(-)</td>
<td>36</td>
<td>20</td>
<td>(R)-(+</td>
</tr>
<tr>
<td>p-Nitrobenzaldehyde</td>
<td>54</td>
<td>46</td>
<td>(S)-(-)</td>
<td>12</td>
<td>5</td>
<td>(R)-(+</td>
</tr>
<tr>
<td>p-Cyanobenzaldehyde</td>
<td>77</td>
<td>50</td>
<td>(S)-(-)</td>
<td>6</td>
<td>53</td>
<td>(R)-(+</td>
</tr>
<tr>
<td>o-Methylbenzaldehyde</td>
<td>19</td>
<td>31</td>
<td>(S)-(-)</td>
<td>10</td>
<td>10</td>
<td>(R)-(+</td>
</tr>
<tr>
<td>Decanal</td>
<td>82</td>
<td>66</td>
<td>(S)-(-)</td>
<td>50</td>
<td>41</td>
<td>(R)-(+</td>
</tr>
<tr>
<td>Dihydrocinnamaldehyde</td>
<td>79</td>
<td>74</td>
<td>(S)-(-)</td>
<td>-</td>
<td>-</td>
<td>(R)-(+</td>
</tr>
<tr>
<td>Cyclohexanecarboxyaldehyde</td>
<td>85</td>
<td>78</td>
<td>(S)-(-)</td>
<td>80</td>
<td>67</td>
<td>(R)-(+</td>
</tr>
<tr>
<td>2-Butylhexanal</td>
<td>35</td>
<td>42</td>
<td>(S)-(-)</td>
<td>-</td>
<td>-</td>
<td>(R)-(+</td>
</tr>
</tbody>
</table>

$^a$Reactions conducted at 0°C for 24h in CH$_2$Cl$_2$ using Et$_2$Zn 3mmol, Ti(OiPr)$_4$ 1.4 mmol, Ligand 0.2 mmol, aldehyde 1 mmol. ee determined by HPLC, yields determined by HPLC. $^b$ as $^a$ except no Ti(OiPr)$_4$.

With the exception of benzaldehyde, the presence of titanium isopropoxide increased both the yield and enantioselectivity of the reaction. In all cases opposite configurations of product were obtained depending on the presence or absence of Ti(IV). This shift in configuration of the product is thought to be due to a different reaction pathway, when titanium is present, involving dinuclear metal complexes of both titanium and zinc atoms as the active catalyst.

The same group described the enantioselective addition of dimethyl and diethylzinc to aromatic and aliphatic aldehydes using, easily prepared, mandelamide ligands 47a-f (Fig. 1.22), and titanium isopropoxide which was necessary for promotion of the reaction. Ligands 47a and 47e were the most effective for dimethylzinc addition (up to 85% yield and 78% ee), whereas ligand 47d performed best in diethylzinc addition (94%, 86% ee). In the case of dimethylzinc addition to aromatic aldehydes, electron withdrawing groups on the para position were found to decrease the enantioselectivity dramatically, while electron donating groups promoted it. The electronic character of ortho and meta substituents generally had no substantial effect on enantioselectivity.
Ortho substituents, regardless of electronic character, caused a dramatic decrease in enantioselectivity indicating the importance of steric hindrance near the reaction centre.

Figure 1.22

The (S) configuration was the dominant stereochemical outcome for both alkylzinc additions for each of the mandelamide ligands. Two bimetallic, Ti(IV) transition state structures, related to previously proposed structures for the addition of dialkylzinc to carbonyl compounds, were described to explain the observed stereochemistry (Fig. 1.23). In both the carbonyl of the aldehyde is coordinated to an octahedral Ti and its Si face is exposed to attack from an alkyl group on the second Ti atom. Stabilization for the structure should be provided by hydrogen bonding between the ligand O and the aldehyde H, similar to that described in previous studies,\textsuperscript{70-72} and by π-stacking between the aryl aldehyde and the phenyl group of the ligand. Where either aromatic group is missing, e.g., with an aliphatic aldehyde, the stereoselectivity of the reaction is reduced which supports this argument.

Figure 1.23 Bimetallic transition state structures proposed to explain the observed stereochemistry
Hydroxyamide ligands have also been used to catalyse the enantioselective addition of dimethylzinc to α-ketoesters. Pedro et al. have applied ligands 47a-f to this reaction without the need of an additional Lewis acid promoter (such as titanium isopropoxide). The additional problem with the reaction of dialkylzinc with α-ketoesters is the competing background addition. Unlike with aldehydes and ketones, the uncatalyzed reaction of Et$_2$Zn with α-ketoesters is fairly rapid. The chiral catalyst must thus have significant activity; otherwise, uncatalyzed background reaction will reduce overall selectivity. This study based its ligand design on the likelihood that in competition between the chiral ligand and the substrate to coordinate the zinc metal ion, the chiral ligand-Zn complex may be favoured by increasing the electron-donating ability of the ligand. This would favour the enantioselective reaction over the achiral background reaction.

They found their results supported this hypothesis. Under the optimized conditions the best performing ligand 47a catalyzed the addition of dimethylzinc to α-ketoesters having aromatic and heteroaromatic substituents with good yields and ees from moderate (62%) to high (90%) (Scheme 1.11). It was found that the presence of electron-donating groups on the aromatic ring increases the enantioselectivity of the reaction.

Wang and co-workers reported the use of γ-hydroxyamide, (1R,3S)-N-Benzyl-3-(hydroxymethyl)-2,2-dimethylcyclo-propanecarboxamide 48 (Fig. 1.24) in the same reaction. Under the optimized conditions, a series of α-ketoesters were examined for the enantioselective Me$_2$Zn additions in the presence of 48. The corresponding products were obtained in good yield (60–87%) and moderate enantioselectivities (41–81%).

Scheme 1.11
Du and co-workers developed a series of tris(β-hydroxy amide) Ligands 49a-k and 50a-c used in the asymmetric addition of diethylzinc to benzaldehyde in the presence of Ti(O\textsuperscript{i}Pr\textsubscript{4}) (Fig. 1.25).\textsuperscript{75} Ligand 49d was the most efficient for this reaction, giving (R)-1-Phenylpropan-1-ol in 99% yield and 47% ee.

As indicated in the initial introduction, historically, the ligands most commonly used in the catalysis of alkylation reactions of this type are amino alcohols, which have
been in used in this context since the early 1980’s. Their performance has been reviewed by Pu.\textsuperscript{76} Hundreds of such ligands have been reported and high selectivity and activity is observed in most cases outperforming the hydroxyamides discussed here. However given the relatively few reports of the use of hydroxyamide ligands and the excellent performance of some ligands such as 38 it is clear that hydroxyamide ligands are excellent prospects for these alkylation reactions.

1.4.3 Asymmetric Addition of Terminal Acetylenes to Aldehydes

The enantioselective alkynylation of aldehydes as a method for the synthesis of chiral non-racemic secondary propargylic alcohols is highly convenient leading to C-C bond formation and stereogenic centre formation in one step. Propargylic alcohols are synthetically versatile intermediates with a heteroatom and alkyne centre which has resulted in their use in the efficient synthesis of many natural products and pharmaceuticals.\textsuperscript{77-79} Among the catalytic methods developed for this reaction, the addition of terminal acetylene to aromatic aldehydes is currently considered to be the most practical. Very few chiral ligands have been reported that give good activity and selectivity in the catalytic asymmetric alkynylation of aliphatic and vinyl aldehydes. Carreira reported the use of Zn(OTf)\textsubscript{2} and catalytic amount (+)-N-methyl ephedrine with an amine base gave good activity and stereoselectivity in the addition of terminal acetylides to aliphatic aldehydes.\textsuperscript{80} A titanium based complex of BINOL has been used by Pu’s group with good success.\textsuperscript{81} An indium(iii) complex of BINOL also formed the basis of a successful system.\textsuperscript{82} A number of amido alcohol ligands have been used in these reactions with good success.

1.4.3.1 Tris(amido alcohol) Catalyzed Acetylene Addition
Du’s Ligands 49a, 49b, 49e and 49f were used in the catalytic asymmetric alkynylation of aldehydes. In initial screening of the enantioselective addition of phenylacetylene to benzaldehyde, it was found that the use of diethyl zinc, Ti(O\text{Pr})_4 as an additive and one of the ligands 49a, 49b or 49f gave the corresponding (R)-propargyl alcohol in <20% ee. Promisingly, ligand 49e gave the (S)-enantiomer in 85% yield and 78% ee. By fine-tuning the proportion of 49e:Ti(O\text{Pr})_4 to a ratio of 1:7, the result was improved, providing the (S)-propargyl alcohol in 84% yield and 87% ee. The application of these metal complexes to other substituted benzaldehydes demonstrated their toleration of both electron-withdrawing and electron-donating groups, to give products in high yields and enantioselectivities (Scheme 1.12).

\[
\begin{align*}
\text{R}= & \text{H, } \sigma\text{-OMe}, \rho\text{-OMe}, \\
& \sigma\text{-F, } \sigma\text{-Cl, } \rho\text{-Cl}
\end{align*}
\]

**Scheme 1.12** Enantioselective addition of phenylacetylene to aldehydes catalysed by 49e

The C_1-symmetric and C_2-symmetric ligands 51 and 52 (Fig. 1.26) were synthesized and their catalytic activity in the enantioselective addition of phenylacetylene to benzaldehyde was evaluated against tris(\beta-hydroxyamide) 49e. Under the same optimized conditions used for 49e, the catalysts formed from 51 and 52 resulted in yields of 86% and 82%, and ees of 51 % and 62 %, respectively. Increasing the catalytic amount of ligand had no appreciable effect on enantioselectivity, demonstrating the efficacy of C_3-symmetry for this particular ligand type and reaction.
Blay and Pedro have reported that (S, S)-mandelamide 47c (Fig. 1.22) could catalyse the asymmetric additions of aryl-, alkyl- and silyl- alkynylzinc reagents to aromatic and heteroaromatic aldehydes with good yields (up to 94%) and good enantioselectivities (up to 92% ee). It is noteworthy that in order to improve the enantioselectivity of the reaction, the authors pre-formed the alkynylzinc reagent in the presence of the ligand prior to the addition of aldehyde. It was necessary to heat phenylacetylene with dimethylzinc at 70°C in toluene in the presence of 47c and then to add the aldehyde at 0 °C, which is different from the procedure described by Pu in the initial work in this area, where the ligand is added into the system after the formation of alkynylzinc reagent. In this case the amount of dimethylzinc used also proved critical leading the authors to speculate that it must be involved in the deprotonation of the ligand at 70°C a process which is not achieved by the alkynylzinc reagent at the lower temperature used in Pu’s method. This study did not use Ti(O’Pr)₄ as an additive to avoid the side reaction where the aldehyde is alkylated.

Hui et al. reported the facile synthesis of β-hydroxyamide ligands 53a-c and 54 (Fig. 1.27) from chiral amino alcohols and the application of their titanium (IV) complexes to the enantioselective addition of phenylacetylene to aromatic and aliphatic aldehydes in the presence of diethyl zinc at room temperature. Ligand 53b proved to be by far the most efficient, consistently affording high yields (up to 96%) and ees (up to 97%). The ligand was used in relatively large amounts (20 mol%) and the ligand performance was found to be adversely affected by the introduction of less flexible aromatic groups α to the hydroxyl group and non-aromatic groups at R1. The titanium tetraisopropoxide:ligand ratio was also found to be critical to the enantioselectivity, 3:1 being the best ratio.

![Figure 1.27](image-url)
One such ligand was immobilized on amorphous silica gel using Seebach’s strategy, to afford silica-immobilized ligand 55 (Fig. 1.28). Ligand 55 was used in the asymmetric addition of phenylacetylene to aromatic aldehydes to afford the propargylic alcohols (Table 1.7).

![Figure 1.28](image_url)

**Table 1.7**

<table>
<thead>
<tr>
<th>Aldehydes</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzaldehyde</td>
<td>95</td>
<td>78</td>
</tr>
<tr>
<td>2-Chlorobenzaldehyde</td>
<td>87</td>
<td>69</td>
</tr>
<tr>
<td>3-Chlorobenzaldehyde</td>
<td>86</td>
<td>74</td>
</tr>
<tr>
<td>4-Chlorobenzaldehyde</td>
<td>84</td>
<td>72</td>
</tr>
<tr>
<td>4-Tolualdehyde</td>
<td>89</td>
<td>70</td>
</tr>
<tr>
<td>2-Naphthaldehyde</td>
<td>93</td>
<td>81</td>
</tr>
</tbody>
</table>

Reaction conducted in toluene at r.t. for 18 h. Ligand 0.2 mmol, Ti(OiPr)₄ 0.6 mmol, ZnEt₂, 3 mmol, phenylacetylene 3 mmol, ArCHO 1 mmol. Yields are isolated yields, ees determined using HPLC.

The isolated yields were high (84–95%) and good enantioselectivities (69–81%) were achieved by using silica-immobilized chiral ligand 55. The best enantioselectivity (81% ee) was obtained in the alkynylation of 2-naphthaldehyde. The performance in terms of enantioselectivity and conversion, while good, does fall short of that obtained with the homogeneous system. The reusability of silica-immobilized ligand 55 was checked by using benzaldehyde as a representative substrate. After each catalytic cycle, 55 was recovered and dried for the next catalytic cycle. A small reduction in yields (95-86%) and enantioselectivities (78-75%) was observed over five runs. Hui and Xu reported the synthesis of new C₂-symmetric bis(hydroxyamide) ligands 56 and
Ligand 56 proved to be an effective ligand for the Ti(O\(^3\)Pr)_4 catalysed addition of phenylacetylene to a variety of aldehydes providing high yields (82-94\%) and enantioselectivities (87-98\%) for aromatic aldehydes and more moderate yields (83-87\%) and selectivities (52-67\% ee) for aliphatic aldehydes under the optimized reaction conditions. Ligand 57 was used to investigate whether each hydroxyamide moiety in the bis(hydroxyamide) 56 could act as an independent coordinating ligand in the alkynylzinc addition reaction. It was applied to the enantioselective addition of phenylacetylene to benzaldehyde, providing the desired propargylic alcohol in good yield and 78\% ee under the same conditions used for 56 and under slightly altered conditions enantioselectivities of up to 94\% were achieved. The authors assert that this means the hydroxyamide units can act as independent ligands which is supported by their previously reported similar result with the mono hydroxyamide ligands.

In an effort to develop new hydroxyamide ligands with greater efficiency in catalyzing the asymmetric alkynylzinc addition to aliphatic and vinyl aldehydes Xu reported novel L-tyrosine derived ligands 58a-c (Fig. 1.30). Ligand 58b proved to be the best in optimization studies where phenylacetylene was added to n-butyraldehyde.

**Figure 1.29**

**Figure 1.30**
The generality of the success of ligand \textbf{58b} in the asymmetric phenylacetylene addition to aliphatic and vinyl aldehydes was examined using Ti(OiPr)$_4$ as a promoter under the optimized reaction conditions and the results are summarized in Table 1.8. The chiral propargyl alcohols could be obtained in 88–96\% ee for aliphatic and vinyl aldehydes. Aliphatic aldehydes with bulky groups gave slightly lower enantioselectivities. The catalytic system was also tested with the typical aromatic aldehydes, e.g. benzaldehyde, which proceeded smoothly to give the product in 92\% ee.

**Table 1.8 Asymmetric phenylacetylene addition to aliphatic and vinyl aldehydes using ligand \textbf{58b} and Ti(OiPr)$_4$ as a promoter.**

<table>
<thead>
<tr>
<th>Aldehydes</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Dominant Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propioaldehyde</td>
<td>75</td>
<td>90</td>
<td>(R)</td>
</tr>
<tr>
<td>n-Butyraldehyde</td>
<td>85</td>
<td>91</td>
<td>(R)</td>
</tr>
<tr>
<td>Isobutyraldehyde</td>
<td>87</td>
<td>92</td>
<td>(R)</td>
</tr>
<tr>
<td>3-Methylbutanal</td>
<td>83</td>
<td>90</td>
<td>(R)</td>
</tr>
<tr>
<td>n-Heptanal</td>
<td>80</td>
<td>91</td>
<td>(R)</td>
</tr>
<tr>
<td>Pivaldehyde</td>
<td>81</td>
<td>88</td>
<td>(R)</td>
</tr>
<tr>
<td>Cyclohexanaldehyde</td>
<td>81</td>
<td>88</td>
<td>(R)</td>
</tr>
<tr>
<td>2-Phenylacetaldehyde</td>
<td>79</td>
<td>94</td>
<td>(R)</td>
</tr>
<tr>
<td>Trans-Cinnamaldehyde</td>
<td>83</td>
<td>96</td>
<td>(R)</td>
</tr>
<tr>
<td>Acrylaldehyde</td>
<td>71</td>
<td>90</td>
<td>(R)</td>
</tr>
<tr>
<td>(E)-but-2-enal</td>
<td>86</td>
<td>90</td>
<td>(R)</td>
</tr>
<tr>
<td>Benzaldehyde</td>
<td>85</td>
<td>92</td>
<td>(R)</td>
</tr>
</tbody>
</table>

Reaction conducted in toluene at r.t. for 18 h. Ligand 0.2 mmol, Ti(OiPr)$_4$ 0.6 mmol, ZnEt$_2$, 3 mmol, phenylacetylene 3 mmol, ArCHO 1 mmol. Yields are isolated yields, ees determined using HPLC.

In an effort to develop recyclable ligands Hui and Xu reported the synthesis of polymer supported chiral β-hydroxy amides and C$_2$-symmetric β-hydroxy amides (Fig. 1.31) and successfully used them for the titanium promoted enantioselective addition of phenylacetylene to aldehydes.

C$_1$-symmetric monomer \textbf{59} was chosen as a model ligand for the system and when applied to the asymmetric addition of phenylacetylene to benzaldehyde gave 1,3-
diphenylprop-2-yn-1-ol in 85% yield and 89% ee. A polymeric version of this monomer was obtained by copolymerisation with other styrene type monomers. When the polymer immobilised ligand **60a** was used (20% loading) the product was isolated in 80% yield and an ee of 88% using 30 mol% of the ligand and a 3.5:1 ratio of Ti(O'Pr)$_4$ to ligand. Polymer **60b**, with a lower ligand loading of 10 % and 20 mol% ligand gave the enantioenriched product in 87% ee with a yield of 85%. These results are comparable to that obtained with the non-immobilised ligand. The polymeric **60b** was also tested in the reaction of a variety of other aromatic and aliphatic aldehydes giving consistent reactivity and selectivity.

This group also immobilised the ligand on a Merrifield resin to give **61** however the titanium promoted reaction using 20 mol% of the ligand gave the propargyl alcohol in only 58% yield and 49% ee. The poorer performance in this case is attributed to interference between adjacent catalytic sites given the loading was 98%.

C$_2$-symmetric monomers and their polymer-supported analogues were also applied to the titanium promoted addition of phenylacetylene to benzaldehyde. Use of monomer **62** led to good catalytic activity with a yield of 93 % and an ee of 92%. The polymeric ligands **63a** and **63b** were also tested in the same reaction and found to have moderate activities, with yields of 66% and 83% and ees of 56% and 78%, respectively. The authors attributed the reduced reactivity with these ligands compared to **60b** to their higher mechanical robustness leading to reduced ability to swell. Polymer-supported ligand **64** also provided moderate results with a yield of 80% and an ee of 74%.

The reusability of the ligand **60b** was examined with benzaldehyde as the substrate. The resin was reused three times to afford 1,3-diphenylprop-2-yn-1-ol in high yields with enantioselectivities decreasing from 87% to 80%.
Figure 1.31
Wang reported the application of ligand \textbf{65a-f} (Fig. 1.32) derived from the L-Phe-based N-Cbz protected dipeptides in the asymmetric addition reaction of phenylacetylene to acetophenone (Table 1.9). The alkynylzinc reagents were generated \textit{in situ} from phenylacetylene with diethylzinc at room temperature. There were no additional metal promoters in the asymmetric addition reaction.

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{figure.png}
\caption{Figure 1.32}
\end{figure}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
Ligand & Yield (%) & ee (%) \\
\hline
\textbf{65a} & 85 & 10 \\
\textbf{65b} & 72 & 10 \\
\textbf{65c} & 66 & 6 \\
\textbf{65d} & 76 & 15 \\
\textbf{65e} & 43 & 5 \\
\textbf{65f} & 72 & 72 \\
\hline
\end{tabular}
\caption{Asymmetric addition reaction of phenylacetylene to acetophenone using Wang’s ligands \textbf{65a-f}}
\end{table}

Reaction conducted in CH$_2$Cl$_2$ at r.t. for 24-48 h. Et$_2$Zn:phenylacetylene:ketones:ligand ratio was 3.0:3.0:1.0:0.1

Yields are isolated yields, ees determined using HPLC.

Ligands \textbf{65a} and \textbf{65f} gave good yields of the desired product, but only \textbf{65f} gave a satisfactory ee of 72%. Under the optimized reaction conditions, ligand \textbf{65f} was employed to induce the enantioselective addition of phenylacetylene to various
aromatic ketones. The enantioselectivities were up to 91% ee while yields up to 90% were obtained. Under the same conditions, ligand 65f was used in the addition of phenylacetylene to the aliphatic ketone isopropyl methyl ketone. The enantioselectivity was found to be 54%ee with a yield of 80%.

As indicated earlier very few chiral ligands apart from these hydroxyamides have been reported that give good activity and selectivity in this reaction.\textsuperscript{80-82} The better ones that have been reported have tended to give the products in ees in or around 90% with some examples using BINOL reaching 99% ee. The activity of the reactions using these ligands has been poorer with yields typically between 70 and 80%. The hydroxyamides discussed herein compare very favourably in performance. Notably in all cases, hydroxyamide and other, catalyst loading is high, typically 20 mol%, with only one example where a hydroxyamide was used in 10 mol%. This catalyst loading is an impediment to their wider use and catalysts of greater activity are needed.

1.4.4 Asymmetric Transfer Hydrogenation Reaction

The asymmetric transfer hydrogenation reaction, using 2-propanol or formic acid as hydrogen source, is an extremely mild reduction method and has been the focus of much research.\textsuperscript{94-97} The use of Ru(II) complexes of chiral amino alcohols or diamines has been highly successful in this area. Adolfsson had studied a range of amido-oxazolines as ligands for ruthenium and used the resulting complexes with very limited success.\textsuperscript{98} However the precursor amido alcohols proved to be effective ligands and the resulting catalysts gave encouraging selectivity in the transfer hydrogenation reaction (Fig. 1.33). Where the R group was a phenyl group the reactivity was low but the selectivity was good. Other stereoisomers of 67 gave better activity but yields remained below 80%. The importance of both stereocentres was tested by using the glycine derivative 66 which was less selective than 67 and thus it was apparent that both centres had an influence of the stereochemistry of the outcome.
The Boc protection of the N terminus of the peptidic ligand proved crucial as the deprotected ligands showed no catalytic activity. They also determined that the ruthenium precursor with p-cymene gave catalysts of similar activity to the less hindered ruthenium benzene precursor however selectivity was superior when the former was used. Reduction of other acetophenones was also achieved with a notable increase in conversion when the aromatic group bore electron withdrawing groups with no decrease in selectivity.

This initial study was followed by a larger one where 45 dipeptide amido alcohol ligands (Fig. 1.34) were prepared. In addition the N-terminal protection was investigated using a variety of protecting groups and none. Ligands with two stereocentres gave lower activity. The most active ligands were those derived from phenylglycine and 2-aminoethanol, though these proved disappointing with regard to stereoselectivity. They also found that some diastereomeric ligands gave dramatically different activity indicating a matched mismatched situation.
The ligands gave almost universally high stereoselectivity (>85% ee). The amino alcohol was found to influence the stereoselectivity when no chiral centre was present on the amino acid portion. However, where there was a chiral centre on the amino acid residue this determined the absolute configuration of the product.

![Chemical structures](image)

**Figure 1.35** Adolfsson’s ligands 68 and 69

The protecting group on the nitrogen proved very important. They studied a number of ligands (Fig. 1.35) and discovered that the nitrogen did need to be protected or the catalyst became inactive and the only protecting groups which worked were the carbamate protecting groups (with the exception of Fmoc). The carbamate protecting groups Boc, Alloc and Cbz proved to give similar conversion and selectivity (78-81% and 93-95% ee). The free hydroxyl is also critical as O-methylation gave a very poor catalyst.

A second generation of the catalysts focused particularly on the use of chiral secondary alcohols leading to ligands such as 68. 36 similar ligands were studied and in the standard reduction of acetophenone a catalyst derived from 68 gave superior activity (90%) and selectivity (96% ee). A number of other ligands gave similarly good results. The selectivity is again largely controlled by the configuration of the amino acid residue but they also report a definite match-mismatch situation where the amino alcohol configuration is varied. This paper gives a number of experimental details which ultimately aided with the proposal of a mechanism. Three equivalents of base are required and the best results are achieved with a 1:1 ligand:Ru ratio.

Thioamide based ligands such as 69 when used in catalysis in combination with either ruthenium or rhodium sources gave opposite selectivity to the related amide ligands. Interestingly, though in both cases the reversal of selectivity was observed,
with ruthenium the amide was more selective whereas with rhodium the thioamide ligand gave the greater selectivity.

Where the ligands were generated from the 1,2 disubstituted amino alcohols they showed very poor activity \(^{100,102}\) and when a chiral tertiary alcohol was incorporated into the ligand the resulting complex was not an effective catalyst. \(^{103}\)

![Chemical reaction image]

**Figure 1.36**

In a 2005 communication Adolfsson reported the *in situ* formation of the hydroxyamide from N-Boc protected amino acid nitrophenylester and an amino alcohol (Fig. 1.36). \(^{104}\) The ligands ruthenium complex, formed in the same pot by addition of the base and ruthenium source, was then used in the transfer hydrogenation reaction giving results comparable to the catalysts generated by the conventional manner. The ligand shown in Fig. 1.36 was the most successful.

Over the years a number of closely related theories have been presented as to the mechanism of the asymmetric transfer hydrogenation catalysed by ruthenium complexes of these amido alcohols. Most of the early theories were based on the mechanism described by Noyori for amine type systems. \(^{105}\) More recently three comprehensive studies by Adolfsson have brought some clarity to the situation. \(^{106-108}\)

The proposed mechanism is supported by the observation that the alkali cation has an effect on the reaction selectivity, with lithium being the best cation. The reaction must involve a fairly tight catalytic complex because when the ion was enlarged by using sodium or potassium or using a crown ether in combination with lithium the selectivity dropped. With already selective ligands the ion effect on selectivity was small but using lithium as the anion with ligands which performed poorly with other
anions increased the ee by up to 40%. Where the second generation ligands are used in combination with lithium the alcohol configuration was found to have a greater influence on the stereochemical outcome of the reaction, which otherwise is dominated by the amino acid residue, indicating an interaction between the lithium and the alcohol during the reaction. The mechanism was then developed with support from DFT calculations and work on the kinetics including kinetic isotope effect experiments (Scheme 1.13).

Structure activity studies indicated all of the ligand functionalities interact with the ruthenium centre in the initially formed complex 70. As previously indicted 3 equivalents of base are optimum and < 2 equivalents results in virtually no activity. Adolfsson thus concluded that two of the sites (alcohol and amide) are deprotonated by the isopropoxide base present in the ATH reaction mixture. The carbamate binds in a neutral fashion. The third equivalent of base is involved in a different process because if the carbamate was also deprotonated an inactive anionic ruthenium complex would be formed.

As the reaction proceeds, an alkali metal alkoxide interacts with the catalyst. The release of the ligand alkoxide coordinating to ruthenium allows the alkali metal ion to be transferred to the oxygen of the ligand, while the hydride is transferred to the now vacant coordination site on the ruthenium leading to 71. The acetophenone enters the coordination sphere of the bimetallic catalyst through attraction by the Lewis acidic lithium ion, and once it coordinates, transfer of the hydride to the activated substrate can occur via the transition state shown and the cycle is completed by proton transfer from the 2-propanol to the lithium salt of the product. The structure of the postulated transition state particularly the CH-\pi interaction explains the high degree of stereoselectivity achieved as it stabilises the transition state for the transfer of the hydride. It also accounts somewhat for the better selectivity observed with these systems in the reduction of aromatic carbonyls.
Adolfsson has done extensive work on the kinetics of the reduction process. One interesting discovery during this study was the fact that the rate of the reaction when conducted in a solvent mixture (IPA and THF) was not directly dependant on the concentration of the hydrogen donor. Indeed the initial reaction rate in the reduction of acetophenone was found to be at a maximum in a mixed solvent with IPA at 6.4 M concentration. They speculated that one possible reason for this rate change was the altered polarity of the system which uses THF which may make key components taking part in the reaction more soluble. This discovery was then exploited in the reduction of a variety of acetophenones which were previously difficult substrates with catalyst 70. Some of the reported reductions are shown in Table 1.10. It is interesting to note that the catalysts loading in these cases has been reduced to 0.5 mol % from the previously used 1 mol % but still gives good activity and selectivity.
Table 1.10 Asymmetric transfer hydrogenation reaction of various acetophenones using [Ru-70] and propan-2-ol/THF

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Time (min)</th>
<th>Yield (%)\textsuperscript{[a]}</th>
<th>ee (%)\textsuperscript{[b]}</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Substrate1" /></td>
<td>60</td>
<td>45</td>
<td>&gt;99</td>
</tr>
<tr>
<td><img src="image2" alt="Substrate2" /></td>
<td>30</td>
<td>80</td>
<td>&gt;99</td>
</tr>
<tr>
<td><img src="image3" alt="Substrate3" /></td>
<td>45</td>
<td>79</td>
<td>98</td>
</tr>
<tr>
<td><img src="image4" alt="Substrate4" /></td>
<td>30</td>
<td>70</td>
<td>&gt;99</td>
</tr>
<tr>
<td><img src="image5" alt="Substrate5" /></td>
<td>45</td>
<td>75\textsuperscript{[b]}</td>
<td>&gt;99</td>
</tr>
<tr>
<td><img src="image6" alt="Substrate6" /></td>
<td>90</td>
<td>82</td>
<td>98</td>
</tr>
<tr>
<td><img src="image7" alt="Substrate7" /></td>
<td>120</td>
<td>18\textsuperscript{[b]}</td>
<td>&gt;99</td>
</tr>
<tr>
<td><img src="image8" alt="Substrate8" /></td>
<td>15</td>
<td>89</td>
<td>96</td>
</tr>
</tbody>
</table>

Reaction was carried out at 30°C with \{Ru (p-cymene)Cl\}_2 0.0125 mmol, LiCl (21.2 mg, 0.5 mmol), propan-2-ol (9.75 mL), Ligand 0.0275 mmol, THF (12.5 mL), the substrate 5 mmol and iPrONa 0.25 mmol. \textsuperscript{[a]} isolated yields, \textsuperscript{[b]} determined by GLC analysis

This area of asymmetric transfer hydrogenation reactions is a very active area of research as illustrated by the recent review.\textsuperscript{94} It is clear from that review there are very many good catalytic systems to effect these transformations based on ruthenium, iridium and rhodium along with ligands with amine, sulfonylamide, amino alcohol, oxazoline and various type of phosphorous based functional groups. It is also clear that these hydroxyamide based catalytic systems perform very well in comparison with the other reported systems. The yields are still in need of improvement but the selectivity, particularly with the more challenging acetophenones shown in Table 1.10, compares very well with other catalytic systems.
1.4.5 Asymmetric Borane Reduction

Du et al. reported the use of $C_3$-symmetric, tripodal ligands in the asymmetric borane reduction of prochiral ketones.\textsuperscript{109} Under the optimized reaction conditions, ligand 49\textit{k} was found to be the best ligand and it was applied to the asymmetric borane reduction of a variety of aromatic and aliphatic ketones.

\textbf{Table 1.11} Asymmetric borane reduction of ketones using ligand 49\textit{k}.\textsuperscript{109}

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R$</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Dominant Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>96</td>
<td>94</td>
<td>(R)</td>
</tr>
<tr>
<td>2</td>
<td>$p$-FC\textsubscript{6}H\textsubscript{4}</td>
<td>94</td>
<td>97</td>
<td>(R)</td>
</tr>
<tr>
<td>3</td>
<td>$p$-Cl\textsubscript{6}H\textsubscript{4}</td>
<td>91</td>
<td>97</td>
<td>(R)</td>
</tr>
<tr>
<td>4</td>
<td>$p$-Br\textsubscript{6}H\textsubscript{4}</td>
<td>93</td>
<td>96</td>
<td>(R)</td>
</tr>
<tr>
<td>5</td>
<td>$p$-MeOC\textsubscript{6}H\textsubscript{4}</td>
<td>90</td>
<td>91</td>
<td>(R)</td>
</tr>
<tr>
<td>6</td>
<td>$p$-NO\textsubscript{2}\textsubscript{6}H\textsubscript{4}</td>
<td>94</td>
<td>97</td>
<td>(R)</td>
</tr>
<tr>
<td>7</td>
<td>o-MeOC\textsubscript{6}H\textsubscript{4}</td>
<td>91</td>
<td>87</td>
<td>(R)</td>
</tr>
<tr>
<td>8</td>
<td>2-naphthyl</td>
<td>94</td>
<td>95</td>
<td>(R)</td>
</tr>
<tr>
<td>9</td>
<td>tert-butyl</td>
<td>99</td>
<td>89</td>
<td>(R)</td>
</tr>
<tr>
<td>10</td>
<td>3,5-NO\textsubscript{2}\textsubscript{6}H\textsubscript{4}</td>
<td>94</td>
<td>74</td>
<td>(R)</td>
</tr>
</tbody>
</table>

Reaction was carried out on a 0.5-mmol scale in 2 mL of THF for 1 h, molar ratio of acetophenone–BH\textsubscript{3} = 1:1.2. Yields are isolated yields, ees were determined by HPLC.

As the results, summarized in Table 1.11 show, high yields and enantioselectivities (up to 97%) were obtained for prochiral ketones containing electron-donating or electron-withdrawing groups except 3,5-dinitro acetophenone (Table 1.11, entries 1–9). A slightly decreased ee was obtained with a substituent at the ortho position probably due to the steric effect (entry 7). Reduction of the aliphatic ketone 3,3-dimethylbutan-2-one was also achieved in high enantioselectivity.
In contrast, much lower enantioselectivity (11%) was obtained in the reduction of acetophenone in the presence of the amino alcohol analogue of 49\textsuperscript{k} namely 72 (Fig. 1.37). This result indicates that the amido group is important for the catalyst enantioselectivity and indeed that reduction of the amide of the ligand is not key to the reaction.

Du later studied the catalytic activity of a series of bis-hydroxyamides 73\textsuperscript{a-c} and 74 synthesized from diphenylamine-2,2-dicarboxylic acid and chiral amino alcohols (Fig. 1.38).\textsuperscript{110}

The ligands were applied to the enantioselective borane reduction of 1-acetyl-naphthalene using 1.2 equivalents of BH\textsubscript{3}-THF complex at 50°C. The activity of the
catalytic systems were good (87-93% yield) however ligands 73a-c gave poor selectivities (23-52% ee). Ligand 74 proved the most stereoselective in the reaction (91% ee) and was applied to a range of aromatic prochiral ketones under optimized catalytic conditions (Table 1.12).

Table 1.12 Borane reduction of aromatic ketones using ligand 74.111

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Dominant configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Naphthyl</td>
<td>Me</td>
<td>94</td>
<td>97</td>
<td>(R)</td>
</tr>
<tr>
<td>C₆H₅</td>
<td>Me</td>
<td>87</td>
<td>96</td>
<td>(R)</td>
</tr>
<tr>
<td>4-MeC₆H₄</td>
<td>Me</td>
<td>93</td>
<td>90</td>
<td>(R)</td>
</tr>
<tr>
<td>4-MeOC₆H₄</td>
<td>Me</td>
<td>93</td>
<td>93</td>
<td>(R)</td>
</tr>
<tr>
<td>3-MeOC₆H₄</td>
<td>Me</td>
<td>95</td>
<td>95</td>
<td>(R)</td>
</tr>
<tr>
<td>2-MeOC₆H₄</td>
<td>Me</td>
<td>95</td>
<td>90</td>
<td>(R)</td>
</tr>
<tr>
<td>4-FC₆H₄</td>
<td>Me</td>
<td>85</td>
<td>97</td>
<td>(R)</td>
</tr>
<tr>
<td>4-ClC₆H₄</td>
<td>Me</td>
<td>90</td>
<td>95</td>
<td>(R)</td>
</tr>
<tr>
<td>4-BrC₆H₄</td>
<td>Me</td>
<td>84</td>
<td>97</td>
<td>(R)</td>
</tr>
<tr>
<td>2-BrC₆H₄</td>
<td>Me</td>
<td>96</td>
<td>90</td>
<td>(R)</td>
</tr>
<tr>
<td>4-NO₂C₆H₄</td>
<td>Me</td>
<td>99</td>
<td>91</td>
<td>(R)</td>
</tr>
<tr>
<td>C₆H₅</td>
<td>Et</td>
<td>85</td>
<td>90</td>
<td>(R)</td>
</tr>
<tr>
<td>1-Naphthyl</td>
<td>C₆H₅</td>
<td>86</td>
<td>81</td>
<td>(S)</td>
</tr>
<tr>
<td>c-C₆H₁₁</td>
<td>Me</td>
<td>55</td>
<td>79</td>
<td>(R)</td>
</tr>
</tbody>
</table>

Reactions were conducted on a 0.5 mmol scale at 50°C in c-hexane under the catalysis of 10 mol % 55. Yields are isolated yields, ees were determined by HPLC.

Excellent yields and enantioselectivities were achieved in the cases of both electron-donating groups and electron-withdrawing groups substituted onto the aromatic ketones. Generally, electron-deficient ketones gave better results than electron-rich ketones. The dominant configuration of the product was determined to be R- except in
the case where $R^1=1$-naphthyl and $R^2$=phenyl. Here $\pi-\pi$ stacking was proposed to influence the stereochemical outcome more than steric hindrance and give predominantly the $(S)$ enantiomer.

C$_1$-symmetric ligand 75 was synthesized to further study the catalyst system. Its catalytic performance was compared to 74 in the enantioselective reduction of 1-acetylnaphthalene under the same conditions. The enantioselectivity decreased from 97% to 92% ee, indicating a certain synergy between the two pyrrolidine-amide units in the catalytic complex. The nature of the catalytic species and a transition state for the reduction reaction was postulated by the authors to account for the stereochemical outcome. The catalytic species when ligand 74 is used involves one boron atom and the ligand with the boron being co-ordinated to one NH and bonded to the two oxygen ligand alcohols. The transition state involves the ketone co-ordinating to the boron through the carbonyl oxygen thus bringing the reaction centre into the chiral pocket where it is reduced by another borane (Fig. 1.39).

![Figure 1.39 Transition state of borane reduction using ligand 74](image)

Many catalytic systems have been investigated for this type of reaction. Among them, the CBS system developed by Corey attracts the most attention, as it is highly enantioselective. In addition to CBS system, other active catalysts derived from amino alcohols, such as chiral phosphinamido alcohols, phosphoramido alcohols, and sulphonamide alcohols, have also been developed. The hydroxyamide ligands described here are very competitive with the previously reported catalytic systems.
given their consistently high activity combined with high enantioselectivity across a wide variety of substrates with acceptable catalyst loading (5-10mol%).

Figure 1.40 Uang’s ligands used in enantioselective addition of trimethylsilylcyanide to aldehydes catalysed by chiral titanium complexes

Uang et al. described a highly enantioselective addition of trimethylsilylcyanide to aldehydes catalysed by chiral titanium complexes of hydroxyamide ligands (Fig. 1.40). In the case of addition to benzaldehyde, optimum results were obtained when the reaction was carried out at -78 °C in dichloromethane using the complex prepared from 16.5 mol% of ligand 31 and 15 mol% of titanium tetraisopropoxide in the presence of 4 Å molecular sieves. In the absence of molecular sieves, the reaction was extremely slow and no sign of reaction was observed after 24 h at -30 °C. The asymmetric induction achieved by 31 was high for a range of aromatic (> 94% ee) and aliphatic (> 87% ee) aldehydes (Table 1.13). Ligand 32, a stereoisomer of 31, gave very poor selectivity in this reaction (4% ee)

Ligand 76, with vicinal phenyl groups replacing the cyclohexane moiety in 31, was synthesized and its catalytic performance examined with the same aldehydes. The enantioselectivities were again excellent and indeed better than with 31 (Table 1.13).
It was proposed that the bulkier phenyl group increased the energy difference between the two diastereomeric transition structure orientations, thereby giving better enantioselectivity. Ligand 77 was synthesized to study the effect of the chirality of the diamide moiety in 76, in the enantioselective addition of trimethylsilylcyanide to benzaldehyde. The enantioselectivity under the optimum conditions was decreased to 61% ee, demonstrating the importance of the chirality of the diamide backbone on the selectivity in the reaction.

**Table 1.13** Silylcyanation of aromatic aldehydes with ligands 31 and 76

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>Yielda (%)</th>
<th>eea (%)</th>
<th>Dominanta Configuration</th>
<th>Yieldb (%)</th>
<th>eeb (%)</th>
<th>Dominantb Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzaldehyde</td>
<td>79</td>
<td>94</td>
<td>(S)</td>
<td>87</td>
<td>93</td>
<td>(S)</td>
</tr>
<tr>
<td>3-Phenoxybenzaldehyde</td>
<td>57</td>
<td>97</td>
<td>(S)</td>
<td>54</td>
<td>95</td>
<td>(S)</td>
</tr>
<tr>
<td>4-Methoxybenzaldehyde</td>
<td>53</td>
<td>97</td>
<td>(S)</td>
<td>47</td>
<td>99</td>
<td>(S)</td>
</tr>
<tr>
<td>2-Naphthaldehyde</td>
<td>76</td>
<td>96</td>
<td>(S)</td>
<td>67</td>
<td>99</td>
<td>(S)</td>
</tr>
<tr>
<td>(E)-Cinnamaldehyde</td>
<td>51</td>
<td>95</td>
<td>(S)</td>
<td>49</td>
<td>97</td>
<td>(S)</td>
</tr>
<tr>
<td>3-Phenylpropionaldehyde</td>
<td>62</td>
<td>98</td>
<td>(S)</td>
<td>61</td>
<td>97</td>
<td>(S)</td>
</tr>
<tr>
<td>2-Methylbenzaldehyde</td>
<td>68</td>
<td>97</td>
<td>(S)</td>
<td>56</td>
<td>94</td>
<td>(S)</td>
</tr>
<tr>
<td>Cyclohexanecarboxaldehyde</td>
<td>94</td>
<td>87</td>
<td>(S)</td>
<td>90</td>
<td>&gt;99</td>
<td>(S)</td>
</tr>
<tr>
<td>Valeraldehyde</td>
<td>96</td>
<td>89</td>
<td>(S)</td>
<td>92</td>
<td>97</td>
<td>(S)</td>
</tr>
</tbody>
</table>

Reactions were conducted in CH₂Cl₂ at -78°C and monitored by TLC. Ligand 0.33 mmol, 4 Å molecular sieves 130 mg, Ti(OiPr)₄ 0.3 mmol, TMSCN 3.5 mmol, aldehyde 2 mmol. Yields are isolated yields and ees were determined by HPLC.

Ketoamide 78 was found to give no enantioselectivity in the silylcyanation of benzaldehyde, as was the case with cyclohexanamides 79-81, suggesting that the hydroxyl groups in the ligand structure of 31 and 76 have a privileged effect on the formation of efficient chiral catalysts for this reaction. α-hydroxyamides 82 and 83, gave low enantioselectivities (up to 13%), in contrast to 31, probably resulting from the less hindered phenyl groups when compared to the isoborneol structure.
A wide range of catalysts are available for the preparation of cyanohydrins which include the use of enzymes, synthetic peptides, chiral Lewis bases and chiral transition metal complexes. A recent review of chemical methods for the enantioselective synthesis of cyanohydrins discusses catalytic systems based on Salen, BINOL, phosphine and amino alcohol ligands using ruthenium, titanium, aluminium and other metals. The performance of the hydroxyamide ligands discussed here compare very well with the large number of previously reported systems in terms of the stereoselectivity which is achieved. The yields achieved do fall somewhat short of some other systems and the reported results do not refer to the synthetically more challenging ketone starting materials which should be the focus of further developments.

1.4.6 Enantioselective Epoxidation of Olefins

In 1978 Schurig et al. reported the preparation of an optically active Mo(VI)-oxodiperoxo complex 84 (Fig. 1.41) and its application in the enantioselective epoxidation of trans-but-2-ene. The olefin could be transformed into the trans-(1R,2R)-but-2-ene oxide with a yield of 70% and an ee of up to 34%. Shortly afterwards, Kagan et al. reported a catalytic version of this reaction, in which they showed that a range of olefins could be epoxidized enantioselectively, using only 10mol% of the ligand. The highest ee obtained was only 35%, again for the epoxidation of trans-but-2-ene. The authors worried that kinetic resolution of a racemic epoxide could have led to the enantioenriched product but by careful monitoring of the enantiomeric composition of the epoxides during the reaction they confirmed that the enantioselection occurs during the epoxidation itself.  

![Figure 1.41](image-url) Hydroxyamide ligands and complexes used by Schurig et al.
Schurig et al. prepared a number of other chiral Mo(VI)-oxodiperoxo complexes based on a series of enantiomerically pure hydroxyamides like (S)-piperidine lactamide (PLA) 84 (Fig. 1.41) and evaluated them in a series of stoichiometric epoxidations of olefins. Prochiral, chiral racemic and chiral non-racemic olefins were used in this study. The best results were obtained using trans-but-2-ene with the complex derived from 84, [MoO(O₂)₂·PLA, (49% ee)], and (S)-3-methylpent-1-ene with either MoO(O₂)₂·PLA (51% ee for the 2S,3S diastereomer and 49% for the 2R,3S diastereomer) or with MoO(O₂)₂·DMLA 85 (51% for the 2S,3S diastereomer and 49% for the 2R,3S diastereomer).

In 2000, Yoon reported the preparation of the W(VI) and Mo(VI)-oxodiperoxo complexes based on (R)-piperidinyl phenylacetamide 86 and (R)-piperidinylmandelamide 87 and the first report of a catalytic epoxidation using this type of complex when both (E)- and (Z)-β-methylstyrene were transformed to the corresponding epoxides. Using only 10 mol% of the isolated Mo(VI)-oxodiperoxo complexes of 86 and 87 in concert with tert-butyldihydroperoxide (TBHP) which was used as the terminal oxidant, they were able to achieve moderate to good ees (26–81%). The highest ee (81%) (Scheme 1.14) was obtained using (E)-β-methylstyrene and complex 85b, with moderate yields.

![Scheme 1.14](image)

The use of hydroxyamides as ligands in the epoxidation reaction has been reported rarely and those reports to date do not bear comparison with the large number of highly successful and well established asymmetric epoxidation systems available.125,126
1.4.7 Nozaki-Hiyama-Kishi Reaction

Kibayashi et al. applied tertiary β-hydroxyamides 88a-b (Fig. 1.42) in the chromium mediated allylation of aromatic aldehydes in an early example of the Nozaki-Hiyama-Kishi reaction. The reaction consists of the initial formation of a chromium(III) complex 89 from chromium(II) chloride and the lithium alkoxide derived from the chiral hydroxyamide and butyl lithium. The addition of allyl bromide gives the chromium(III) species which reacts with the added aldehyde to yield the homoallylic alcohol 90 with induced stereoselectivity (Scheme 1.15).

![Figure 1.42 Kibayashi’s ligands 88a and 88b](image)

**Scheme 1.15**

The chromium complex is considered to constitute preferential coordination between chromium and the nitrogen atom rather than the oxygen atom of the amide group to form a five-membered chelate ring in a trans planar structure which is quite rigid which helps to differentiate the enantiotopic faces during the NHK coupling. The allyl coupling to benzaldehyde was undertaken using allylchromium complexes 91 derived from N-benzyol-L-prolinol derivatives 88a-b (Table 1.14). 88b proved to be the most efficacious in chiral induction, affording predominantly the R- enantiomer with an enantiomeric excess of 82%.
Table 1.14 Nozaki-Hiyama-Kishi Reaction\textsuperscript{127}

<table>
<thead>
<tr>
<th>β-hydroxyamide</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>88a</td>
<td>72</td>
<td>30</td>
</tr>
<tr>
<td>88b</td>
<td>62</td>
<td>82</td>
</tr>
</tbody>
</table>

Reactions were conducted in THF at -30°C for 1-12 h using CrCl\textsubscript{2} 2.0 mmol, lithium alkoxide 2mmol, allyl bromide 1.0 mmol, aldehyde 0.5 mmol.

The enantioselective NHK reaction has been developed substantially since the initial Kibayashi report discussed here. Many successful ligands have been reported for these reactions since that early report including salen, amino oxazoline and amido oxazoline ligands and it is the last two which have proved the most successful with enantioselectivities and yields in excess of 90% becoming commonplace.\textsuperscript{128}

1.4.8 Hydrosilylation of Imines

Onomura reported the use of $N$-picolinoylpyrrolidine hydroxyamide derivative derivative 92 to activate trichlorosilane in the hydrosilylation of aromatic imines to amines.\textsuperscript{129} The catalytic activity of 92 was investigated with a range of aromatic imines and enamines with similar stereoselectivities in each case (Table 1.15) (67-80% ee for imine substrates derive from methyl ketones).
Table 1.15 Hydrosilylation of aromatic Imines

![Chemical Structure]

<table>
<thead>
<tr>
<th>Aromatic imines</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Dominant Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Imine Structure] (N = NMe, R = CH₃)</td>
<td>86</td>
<td>73</td>
<td>S</td>
</tr>
<tr>
<td>![Imine Structure] (N = NMe, R = Me)</td>
<td>90</td>
<td>75</td>
<td>S</td>
</tr>
<tr>
<td>![Imine Structure] (N = NMe, R = Ph)</td>
<td>90</td>
<td>71</td>
<td>S</td>
</tr>
<tr>
<td>![Imine Structure] (N = Cl, R = Me)</td>
<td>73</td>
<td>71</td>
<td>S</td>
</tr>
<tr>
<td>![Imine Structure] (N = OMe, R = Ph)</td>
<td>84</td>
<td>73</td>
<td>S</td>
</tr>
<tr>
<td>![Imine Structure] (N = OMe, R = Mn)</td>
<td>67</td>
<td>80</td>
<td>S</td>
</tr>
<tr>
<td>![Imine Structure] (N = Me, R = Ac)</td>
<td>24</td>
<td>67</td>
<td>ND</td>
</tr>
<tr>
<td>![Imine Structure] (N = Me, R = CO₂Me)</td>
<td>80</td>
<td>45</td>
<td>R</td>
</tr>
<tr>
<td>![Imine Structure] (N = Me, R = CO₂Et)</td>
<td>65</td>
<td>41</td>
<td>S</td>
</tr>
</tbody>
</table>

Reactions were conducted in CH₂Cl₂ at room temperature over 4h using Cl₃SiH 0.45 mmol, imine (0.3 mmol) and ligand 0.03 mmol. Yields are isolated yields and ees were determined by HPLC.
The authors proposed a working hypothesis for the transition state of the reduction of aromatic imines with 92 in which the silane co-ordinates to the pyridine nitrogen and the carbonyl oxygen of the amide. The approach of the imine is controlled by the hydrogen bonding of the imine nitrogen with the alcohol and it is steric factors which influence which face of the imine reacts (Fig. 1.43). Though, in general, in this review ligands with amines or other ligating groups have been excluded in this case the pyridine based ligand is included because of the clear indication that the amide and alcohol are both involved in the key step of the reaction mechanism.

![Chemical structure diagram](image)

**Figure 1.43** Transition states of the reduction of aromatic imines with 92

Though the reduction of imines is possible in many ways the lack of any metal involvement in this organocatalytic process give the reactions some advantage in terms of usability. Several peptidic organocatalysts have been reported for this reaction.\textsuperscript{130,131} The performance of the hydroxyamide catalysts discussed here is competitive with those peptidic catalysts albeit that the enantioselectivity is in need of some improvement.
1.4.9 Simmons –Smith Cyclopropanation

Katsuki and co-workers reported the synthesis of BINOL derivatives, 1,1’-bi-2-naphthol-3,3’-dicarboxamides, and their application as chiral ligands in the asymmetric Simmons Smith cyclopropanation of (E)-allylic alcohols.\textsuperscript{55}

Ligand 22b, with the diethylamide group, exhibited the highest enantioselectivity of 94\% ee. The reaction of both conjugated and non-conjugated (E)-allylic alcohols, catalysed by 22b, showed good enantioselectivity (87 - 94\% ee) in moderate yields (50 - 78\%) (Scheme 1.16). However, in the case of (Z)-allylic alcohol, a lower chemical yield and enantioselectivity were observed, although only two examples were reported.

\[
\begin{align*}
\text{R}^1\text{O}H & \quad + \quad 22b \\
\text{CH}_2\text{H}_2 (3 \text{ eq}) & \quad \text{ZnEt}_2 (6 \text{ eq}) \\
0^\circ\text{C-rt}, 15\text{h} & \quad \text{DCM/Hexane}
\end{align*}
\]

\[
\begin{align*}
\text{R}^1=\text{Ph} & \quad 55\% \quad (94\% \text{ ee}) \\
\text{R}^1=\text{CH}_3\text{Bn} & \quad 65\% \quad (89\% \text{ ee}) \\
\text{R}^1=\text{CH}_2\text{OCPh}_3 & \quad 64\% \quad (88\% \text{ ee})
\end{align*}
\]

\[
\begin{align*}
\text{R}^2\text{O}H & \quad - \quad 22b \\
\text{CH}_2\text{H}_2 (3 \text{ eq}) & \quad \text{ZnEt}_2 (6 \text{ eq}) \\
0^\circ\text{C-rt}, 15\text{h} & \quad \text{DCM/Hexane}
\end{align*}
\]

\[
\begin{align*}
\text{R}^2=\text{Ph} & \quad 44\% \quad (92\% \text{ ee}) \\
\text{R}^2=\text{CH}_2\text{OCPh}_3 & \quad 34\% \quad (65\% \text{ ee})
\end{align*}
\]
The Simons-Smith reaction is a well-known cyclopropanation method and many ligands have been reported which give good enantioselection including amino alcohols, amides, BINOL derived phosphorus based ligands and others. The results for the hydroxyamides are limited but the initial reports do seems to indicate potential for good enantioselectivity but the yields reported are somewhat short of the established catalysts.

1.4.10. Michael Addition

Scheme 1.17 Katsuki’s asymmetric Michael addition reaction using 22b

Figure 1.44 Ligand 22b in its proposed Sc(III) complex

Katsuki also reported the use of the optically active N,N,N′,N′-tetraalkyl-BINOL-3,3′-dicarboxamides such as 22b as chiral auxiliaries for asymmetric Michael addition reactions (Scheme 1.17). As an intramolecular hydrogen bond between phenolic hydrogen and carbonyl oxygen was considered to fix the conformation of the amide moiety in 22b, it was expected that the Sc(OTf)3 complex (Fig. 1.44) would serve as a chiral catalyst for the Michael addition reaction. Although anti-selectivity was high (>50: 1), both the chemical yield (48%) and enantioselectivity (18%) were only modest.
The authors reasoned that the amide alkyl groups of ligand 22b directing away from the reaction site could not induce asymmetry in the product effectively.

1.4.11 Enantioselective Conjugate Addition of Nucleophilic Radicals to Enoates

Sibi and Manyem have reported that lanthanide triflate along with proline-derived ligand 93 is a catalyst for the enantioselective conjugate addition of nucleophilic radicals to enoates (Scheme 1.18).\textsuperscript{135}

\[
\begin{align*}
\text{Scheme 1.18} & \quad \text{The addition of nucleophilic isopropyl radical to an } \alpha, \beta-\text{unsaturated enoate} \\
\end{align*}
\]

The enantioselectivity obtained in the reaction (23\%) was much lower than that obtained by related carbamate analogues (>80\%) and the reaction completion was also significantly slower and yields were moderate.

1.4.12 Conclusions and Outlook

Asymmetric ligands whose key functional component consists of amide and hydroxyl functional groups, in the absence of other co-ordinating groups, are showing real promise as part of catalytic systems for a wide range of reactions. For ligands that have largely only been researched for the last 12 years they have found application to a large number of synthetically key reactions. In many cases the activity and selectivity has been optimised somewhat through a number of generations of ligand. That being said, there is undoubtedly more progress yet to come. One feature which is striking in reviewing the literature in this area is the lack of characterisation of the
metal complexes involved and should this change it will surely give insights which will help the development of the next generations of the ligands.

1.5 Oxazoline Based Ligands in Asymmetric Catalysis

Oxazolines are five-membered cyclic iminoesters. Originally they found use in chemistry as masked or protected carboxylic acids.\textsuperscript{136} Pioneering work by Evans in the 1980s introduced the oxazoline (4,5-dihydrooxazole) ring 94 into prominence, leading to its use as the chiral framework of a wide variety of ligands that have been used to great effect in a diverse range of asymmetric catalytic transformations.\textsuperscript{137} Its position of privilege among chiral ligands has its origins in a convenient synthesis (Scheme 1.19) from readily available enantiopure amino alcohols (e.g., norephedrine and related compounds, and those derived from reduction of naturally occurring amino acids). Many oxazolines have a stereogenic centre at the carbon atom adjacent to the co-ordinating nitrogen. As a result, the active metal site is in close proximity to the chiral centre, which can directly influence the stereochemistry of the reaction.

A large number of methods for the synthesis of 2-substituted-2-oxazolines are known to date. The most widely applied procedures involve the coupling of carboxylic acids with amino alcohols followed by ring closure (path a)\textsuperscript{138} and the direct condensation of nitriles with amino alcohols, in the presence of a Lewis acid such as zinc chloride (path b).\textsuperscript{139} Alternatively, oxazolines can be prepared from the amide in the presence of a triethylxonium salt (path c)\textsuperscript{140} or by treatment of the acid chloride with the appropriate amino alcohol followed by cyclization with thionyl chloride (path d) (scheme 1.19)\textsuperscript{141}
Given the almost ubiquitous use of these rings in catalysts systems there will not be a comprehensive review of the area, but just give a flavour of the breadth of ligand designs in which they are seen, and the vast array of reactions in which they have found application. Mono oxazoline $N,N$ ligands are a well-represented class of chiral compounds. In 1984 Brunner et al started the development of nitrogen containing ligands because phosphine ligands tended to fail in enantioselective hydrosilylations, which was the focus of many research groups.\textsuperscript{142} This study described a nitrogen-nitrogen bidentate ligand with a pyridine group fused to a thiazolidine group. The results included many examples of high yields and enantioselectivities (scheme 1.20). Ligand 95 gave an ee of 97\% in hydrosilylation of acetophenone.
Scheme 1.20 Use of thiazolidine ligands in the enantioselective hydrosilylations of acetophenone with diphenylsilane as H donor

Brunner and co-workers developed the first series of pyridyloxazoline ligands for asymmetric catalysis replacing the thiazolidine, with which they had difficulty controlling the stereochemistry, with an oxazoline group. These pyridyl-2-oxazolines (PyOX) were first used as ligands in the asymmetric Cu-catalyzed monophenylation of meso-diols by triphenylbismuth diacetate (scheme 1.21), with 96 affording a moderate yield of 54% and an ee of 45%.

Scheme 1.21 Cu-catalyzed monophenylation of meso-diols by triphenylbismuth diacetate

Metal complexes bearing mono-oxazoline N,O ligands such as those (97-100) in fig. 1.45 have been applied in a variety of asymmetric reactions. For ligand 97, it was shown that the stereogenic centre at the carbon atom bearing the hydroxyl group was crucial to achieve high enantioselectivities in certain asymmetric reactions, such as the addition of diethylzinc to imines. Some mono(oxazoline) N,O ligands
containing a ferrocenyl moiety were also employed in catalysis (fig. 1 , compound 98).\textsuperscript{148,149} An analogue bound to a soluble polymer gave good results in catalysis and could be recycled efficiently (fig.1, 99).\textsuperscript{150} Hiroi also investigated the use of oxazoline sulfoxides of type 100.

Figure 1.45

Guiry has reported the preparation of ligand class 101 (Fig. 1.46) and its application in the NHK allylation of benzaldehyde.\textsuperscript{151} The highest enantioselectivity of 57% was obtained with complete conversion and high isolated yield using the ligand derived from the phenyl-substituted oxazoline.

Figure 1.46 Guiry's ligand 101 used in the Nozaki-Hiyama-Kishi allylation of benzaldehyde

Guiry et al. have also reported the straightforward synthesis of tridentate bis(oxazoline)-based ligands 102 and 103, proline-oxazoline ligands 104 and pyridine containing oxazoline 105 from the readily available 2-(o-aminophenyl)oxazoline
The ligands 102, 103 and 104 were applied to the enantioselective Nozaki–Hiyama–Kishi (NHK) allylation, crotylation and methallylation of a series of aromatic and aliphatic aldehydes, providing the products in both high yields and high enantioselectivities.

![Figure 1.47](image)

The optimum enantioselectivity obtained using 102 in all three NHK processes was from the non C\textsubscript{2}-symmetric ligand with \textsuperscript{t}Bu/Bn-substituted oxazolines, affording excellent enantioselectivities, for example 99.5\% in the methallylation of benzaldehyde. 104 gave its highest ee of 57\% in the allylation of benzaldehyde and the best result of 103 was 73\% ee for the allylation of benzaldehyde. Ligand 105 was applied to the asymmetric addition of diethylzinc to various aldehydes, with the highest enantioselectivity of 68\% achieved in the case of 1-naphthaldehyde.\textsuperscript{154}

A vast number of bis(oxazoline) ligands 107, referred to as “box” ligands, were first applied in catalysis in 1991 by Evans, who reported the asymmetric cyclopropanation of alkenes,\textsuperscript{155} and Corey, who performed enantioselective Diels-Alder reactions.\textsuperscript{156}
Some examples of bis(oxazoline ligands synthesized later are shown in Fig 1.48. The ferrocenyl substituted box 108 was prepared by Moyano and co-workers. It afforded good enantioselectivities in Pd-catalyzed alkylations but yields were generally low. 109a-c, bearing respectively, a hydroxyl, alkyl or acetyl group at the stereogenic 4-position of the oxazoline rings, were used by Ait-Haddou in Pd-catalyzed alkylations. Moderate to high yields were obtained. It was observed that 109a gave the opposite configuration of the product compared to 109b-c. This phenomenon was explained by the authors as being due to hydrogen bonding of the hydroxyl group of 109a to the substrate.

Figure 1.48

In 1989, Nishiyama introduced a pyridine ring as the spacer between the two oxazoline rings giving a tridentate pyridine oxazoline ligand. Since then many of these Pybox ligands have been synthesized and used in asymmetric catalysis. Due to their modular synthesis from readily available starting materials (amino alcohols and pyridines), they are a very attractive ligand type. Ligands 110a-e (Fig. 1.49) were the first of this type to be synthesized and provided good results in a variety of reactions such as Diels Alder, cyclopropanations, aziridinations, hydrosilylations, silylcyanations, oxidations of allylic and benzylic compounds and 1,3 dipolar cycloadditions.
Some other types of bis(oxazoline) $N,N,N$ ligands used in catalysis to varying degrees of success are shown in Fig. 1.50. These compounds have been used as ligands in a wide variety of asymmetric transformations. These include: alkylation (111, 113)$^{68,161,162}$, allylation (113)$^{163}$ and crotylation (113)$^{163}$ of aldehydes, transfer hydrogenations (112)$^{164}$, asymmetric Henry reactions (113)$^{165}$ and Michael additions (113).$^{166}$
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CHAPTER 2

RESULTS and DISCUSSION

2.1 Aims of this thesis

Note that a numbering scheme independent of that used in Chapter One is used from this point forward.

2.1.1 Novel Pyroglutamate Derived Modular Oxazoline Ligands

The initial aim of the work described in this thesis was the synthesis of two new modular ligand classes, amido-oxazolines 3 and 5 from L-pyroglutamic acid 1 (Scheme 2.1). Furthermore we aimed to make multiple versions of each ligand type varying both the stereochemistry and substitution of the ligands. We hoped that utilizing the modular nature of our ligand classes, the effects of ligand modification on enantioselectivity could be studied over a wide variety of reactions. The ultimate aim was obviously to maximise the product enantiomeric ratio in the test reactions, and provide the basis for elucidating structure-selectivity relationships.\(^1\) We made significant progress, but as in any project, some goals proved elusive.

\[ \text{Scheme 2.1 Retrosynthetic analysis for the tripeptide oxazoline ligands in this study} \]
During the course of the syntheses of these ligands we read Adolfsson’s publication on modular dipeptide-analogue amido alcohol ligands and their use in efficient asymmetric transfer hydrogenation of ketones. This prompted us to apply the tripeptide amido alcohols, intermediates in the synthesis of our target ligands, to a range of catalytic asymmetric transformations. We also decided to synthesize dipeptide hydroxyamide ligands from 1 and a range of α-amino alcohols and apply them to the same reactions (Scheme 2.2).

![Image of chemical reactions](scheme22.png)

**Scheme 2.2** Retrosynthesis of Dipeptide amido alcohol ligands 6

To begin there will be a discussion of the syntheses of these ligands, before discussing the types of reactions to which they were applied.

### 2.1.2 Approach to the Synthesis of Ligands

The concept of positional scanning was introduced in section 1 of the present study. The philosophy of this "positional scanning approach" for identifying a chiral catalyst consisting of three modular subunits, for example, is to optimize each of the three modular subunits while keeping the other two subunits constant. This approach, especially when coupled with automated screening not only offers unique opportunities for the identification of substrate-specific catalysts (fine tuning), but also permits the discovery of ligands that possess unusual properties, and which might otherwise elude detection.

Enantioselective catalysts are often discovered by such an iterative, stepwise process wherein the structure of an initial catalyst candidate is modified, and the new catalyst is evaluated in the reaction of choice. These two steps are repeated until an optimal catalyst is obtained.
The approach to the syntheses of the ligands in this study was an adapted positional scanning method. There were economic and practical limitations preventing us from using implementing a thorough positional scanning system in finding suitable ligands. We were limited to cheaply available chiral α-amino acids and amino acid derivatives as starting materials, and homogenous solution peptide synthesis methods rather than solid phase combinatorial methods were used to form the peptidic intermediates, due to the associated costs. This meant a longer synthetic timeline. During the ligand optimization process two of the three chiral sub-units of the ligand structure (2, scheme 2.1) were varied. All the ligands produced in this study were derived from the chiral acid, L-pyroglutamic acid 1.

2.2 Syntheses of Novel Oxazoline and β-hydroxyamide Ligands

A key element of our catalyst designs is the ability to expand the diversity of accessible structures while incorporating recognized metal binding motifs used in reported asymmetric catalysts.3 We sought to use synthetically robust methods to allow for the preparation of diverse ligands. Additionally the catalysts were synthesized from readily available chiral building blocks in order to make systematic changes more facile.

The ligands synthesized in this study were of the types 2, 3, 5 and 6 as shown in Fig. 2.1.
This section will start with a discussion of dipeptide ligands then move on to the tripeptide and the oxazoline based ligands. Having discussed the synthesis of the ligands, the discussion will turn towards the use of each ligand class in asymmetric catalytic systems. The catalytic reactions studied will be introduced briefly, before the first set of results generated using that reaction are outlined.

### 2.2.1 Pyroglutamate Derived β-hydroxyamide Ligands D1-D4

In the last ten years, amides derived from α-amino acids were reported as efficient chiral ligands in combination with Ru(II)(η⁶-arene) complexes for the asymmetric reduction of aldehydes and ketones.⁴⁻⁶ In this context Adolfsson investigated the effect of a novel class of amido-oxazolines ⁷ (Fig. 2.2) for the ruthenium catalyzed asymmetric reduction of ketones under transfer hydrogenation conditions (2-propanol). These ligands had previously been employed in titanium-catalyzed enantioselective addition of diethylzinc to aldehydes.⁷ In the transfer hydrogenation reaction in particular they performed poorly, giving the secondary alcohol in poor yield and low enantioselectivity.
Of particular interest to us was Adolfsson’s discovery that a precursor to an oxazoline ligand, amido alcohol 8, gave much better selectivity than the parent ligand structure in the asymmetric transfer hydrogenation of acetophenone (Scheme 2.3). This result has been discussed in detail in Chapter 1. In essence Adolfsson discovered that both chiral centres influence the stereochemical outcome of the reaction and the Boc protection of the N-terminus of the peptidic ligand proved crucial as the deprotected ligands showed no catalytic activity.

With Adolfsson’s reports in mind we decided to synthesize the class 6 β-hydroxyamide ligands, which will be labelled D1-D4 from now on (Fig. 2.3), and class 3 β-hydroxyamide ligands, which will be labelled L1-L7 (Fig. 2.4). These will be applied to a range of ‘benchmark’ catalytic reactions. These were the asymmetric transfer
hydrogenation of acetophenone with 2-propanol, the asymmetric addition of diethylzinc to benzaldehyde and the asymmetric addition of phenylacetylene to benzaldehyde. We would use L-pyroglutamic acid as a source of chirality. The method for synthesizing the ligands is outlined in the following section.

![Dipeptide Ligands D1-D4](image_url)

**Figure 2.3** Dipeptide Ligands D1-D4 synthesized in this study
2.2.1.1 Synthesis of Pyroglutamate Derived β-hydroxyamide Ligands D1-D4

We have synthesized four modular hydroxyamide ligands, D1-D4, in a facile one-step from the methyl ester of L-pyroglutamic acid and four different amino alcohols (Scheme 2.4). The target ligands were produced in reasonable yields of up to 78%.
Scheme 2.4 Synthesis of the four dipeptide ligands D1-D4 used in this study

Ligand D1 was formed from the aminolysis of methyl-(S)-2-pyrrolidine-5-carboxylate 10 with (R)-phenylglycinol 11a (scheme 2.4), which had previously been made by the NaBH₄-I₂ reduction of D-phenylglycine in 74% yield, according to a published procedure.⁸ The reaction was catalyzed by 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD)⁹ and the product was isolated in 70% yield.

Ester 10 was produced by a previously reported esterification of 1 (scheme 2.5), by gently refluxing and stirring the chiral acid in methanol in the presence of Amberlyst 15 resin, a strongly acidic cation exchange resin for heterogeneous acid catalysis. The reaction was continued overnight to form 10.¹⁰ Removal of the resin by filtration and concentration in vacuo afforded the methyl ester, which required no further purification, in 94% yield. The spectral analysis agreed with published data.¹⁰

Scheme 2.5 Synthesis of ester 10
Ligands D2, D3, and D4 were synthesized by the same method used for D1, substituting the amino alcohols (S)-valinol 11b, (S)-phenylalaninol 11c and (S)-leucinol 11d. Yields of 74%, 67% and 78% were obtained for the respective ligands. The last dipeptide D4, incorporates an L-leucine derived module. It was synthesized to investigate whether it would afford different enantioselectivities in the catalytic reactions than the valine-derived analogue due to its altered steric effects. The structures of the ligands were confirmed by NMR spectroscopy, IR spectroscopy and mass spectrometry.

**Characterization of Ligands D1-D4**

As might be expected given the similarities between compounds D1-D4, albeit there is a marked stereochemical difference in compound D1, the characteristic signals for the compounds in the 1H NMR spectra are very similar. Fig. 2.5 shows the 1H NMR spectrum of D3 which will be used as a guide to these characteristic signals. The lactam ring CH2s appear as multiplets between 1.7 and 2.05 ppm and integration indicates that the first signal is due to one proton and the latter due to three. It is likely the diastereotopic Hs of the ring CH2 adjacent to the CHNH give rise to two different signals one of which overlaps with the signal due to the other CH2 at ~2.05 ppm. Signals similar to these are seen for D1 and D4. In the case of D3 they are also present but the upfield signal integrates for two Hs as it also contains the signal due to the CH of the iPr group.

The multiplet at ~3.3 ppm is due to the CH2 adjacent to the OH group. A similar signal appears in the spectra of D2 and D4. The equivalent signal in the 1H NMR spectrum of D1 appears as a triplet at 3.53 ppm. This difference could be influenced by the different stereochemistry present in the D1 ligand but obviously the R group will also have an influence. Quite why the signal appears as a triplet in the case of D1 is difficult to see given the Hs of the CH2 are diastereotopic and can also couple to the OH and adjacent CH.
Figure 2.5 $^1$H NMR spectrum of ligand D3
The multiplet at ~3.85 ppm is due to both the CHs in the molecule. Again similar signals appear in the $^1$H NMR spectra for D1 and D2. The position of the CH adjacent to the CH$_2$OH is very much dependant on the R group and in these three ligands this signal is distinct from the lactam CH moving upfield in the case of R = iPr and downfield when R = Ph. The CH of the lactam remains at ~4 ppm for all three ligands. In the case of D4 two distinct multiplets are observed at ~3.8 ppm and though the more downfield is likely to be the lactam CH the peaks are too close to be certain.

The OH signal appears between 4.6 and 4.9 ppm in the four ligands either as a triplet or broad singlet.

The amide N-Hs appear at ~7.7 and 7.8 ppm in the $^1$H NMR spectrum of D3 and this is typical of this ligand class. The only exception to this is D1 which has signals for the amide NHs in the $^1$H NMR spectrum at 7.9 and 8.3ppm.

![Figure 2.6](image_url)  
**Figure 2.6** Position of key signals in $^{13}$C NMR spectrum of D3 (expressed as whole numbers in ppm)

The key signals observed in the $^{13}$C NMR spectrum of D3 are shown in Fig. 2.6. These signals were again characteristic of the ligand class as a whole. The CH carbons could not be absolutely assigned in this case but in the cases of D1 and D2 assignment was possible with the aid of HETCOR experiments Reassuringly the NMR spectra of the ligands D1-D4 either crude or purified gave any indication of diastereomeric compounds being present. This makes it highly unlikely that any racemization at the chiral centres took place. Each of the ligands gave substantial optical rotation of plane polarised light.
The IR spectrum showed NH and OH peak at 3372 cm\(^{-1}\), two amide peaks at 1655 and 1638 cm\(^{-1}\), which was typical of this class of compound.

### 2.2.1.2 Synthesis of β-hydroxyamide Ligands L1-L7

Synthetically, the ligand structures can be broken down into three amino acid derived modules, as can be seen in scheme 2.6 below. This scheme outlines the synthetic pathway to ligand L1 and is representative of the methods used to produce dipeptide esters E1-E5 and hydroxyamides L1-L7 with some noted exceptions.

**Scheme 2.6** Synthetic pathway to ligand L1
Dipeptide esters E1-E5

Figure 2.7 Dipeptide esters synthesized

Synthesizing the amido-oxazoline ligands would require the peptide coupling of the $\alpha$-amino acid ester hydrochlorides of glycine, L-valine, L-phenylalanine, L-alanine and D-phenylglycine to L-pyroglutamic acid 1, to give dipeptide esters E1-E5. The reaction leading to E2 using glycine ethyl ester hydrochloride 12, is shown in scheme 2.6. The synthetic method employed used 1.1 equiv. of 1,3 dicyclohexylcarbodiimide (DCC) as a coupling reagent along with 1.1 equiv. of hydroxysuccinimide (HOSu), a racemization suppressant and reaction rate enhancer. Originally, the coupling reaction was carried out at 0°C-RT in DCM for 20 h in the presence of N-methylmorpholine as the base. An important optimization of the reaction was using 50:50 DCM/MeCN as the reaction solvent rather than DCM only for the peptide coupling. This improved our yields from the reaction by up to 30%, as the dicyclohexyl urea (DCU) side product is much less soluble in this solvent system than in DCM. This facilitated the work-up, as we could filter off most of the insoluble DCU precipitate and then dissolve the product in ethyl acetate and cool to remove the remaining DCU. The reaction also proceeded faster in the more polar DCM/MeCN solvent system. The crude solids were purified by column chromatography on silica gel using EtOAc/MeOH (gradient elution) as eluent. The dipeptide esters synthesized in this study are shown in Fig. 2.7 along with the yields obtained.
Figure 2.8 $^1$H NMR spectrum of ligand E2
Characterization of dipeptide esters E1-E5

The structures of the ester compounds were confirmed by NMR, IR spectroscopy and mass spectrometry. The carbon signals were assigned with the aid of a DEPT spectrum for each compound.

As was the case with the ligands D1-D4, given the similarities between compounds E1-E5, albeit there is a stereochemical difference in compound E5, the characteristic signals for the compounds in the \(^1\)H NMR spectra are very similar. Fig. 2.8 shows the \(^1\)H NMR spectrum of E2 which is representative of these characteristic signals. The characterization spectra of all the dipeptide esters E1-E5 will be compared with the spectra of E2. The lactam CH\(_2\)s appear as multiplets from ~ 2.10-2.57 ppm and integration indicates that the signal is due to five protons. The extra proton signal is the signal due to the CH of the \(^i\)Pr group. Signals similar to these are seen for E1, E3, E4 and E5, but they integrate for 4 Hs in the absence of the CH of the \(^i\)Pr group.

The singlet at ~3.7 ppm is due to the CH\(_3\) of the ester group. A similar signal appears in the spectra of E3-E5. The equivalent OCH\(_2\) signal in the \(^1\)H NMR spectrum of the ethyl ester E1 appears as a quartet at 4.15 ppm, with the adjacent CH\(_3\) appearing as a triplet at 1.28 ppm.

The CH of the lactam remains at ~4.2 ppm for all the dipeptide esters. The multiplet at ~4.55 ppm is due to the CH at the chiral centre in the molecule. Again similar signals appear in the \(^1\)H NMR spectra for E3 and E4. The position of the CH adjacent to the carbonyl of the ester group is dependent on the R group and in these three ligands this signal is downfield from the lactam CH. The signal in E5 is further downfield at 5.56 ppm when R=Ph. In the glycine derived compound E1 the CH\(_2\) at this position appears as a multiplet at 4.26 ppm. The signal in the L-alanine derived E4 appears as an apparent quintuplet at 4.59 ppm. The amide N-Hs appear at ~6.53 and 6.91 ppm in the \(^1\)H NMR spectrum of E2, and this is typical of these molecules. An exception to this is E4 which has more downfield signals for the amide NHs in the \(^1\)H NMR spectrum between 7.08 and 7.15 ppm.
Figure 2.9 Position of key signals in $^{13}$C NMR spectrum of E2 (expressed as whole numbers in ppm)

The key signals observed in the $^{13}$C NMR spectrum of E2 are shown in Fig. 2.9. These signals were again characteristic of the ligand class as a whole. The CH carbons could be absolutely assigned in this case, and for the analogous esters with the aid of HETCOR experiments.

Again the NMR spectra of the ligands E1-E5 either crude or purified gave any indication of diastereomeric compounds being present. This makes it highly unlikely that any racemization at the chiral centres took place. Each of the ligands gave substantial optical rotation of plane polarised light. The IR spectrum showed NH and OH peaks at 3346 and 3275 cm$^{-1}$, two amide peaks at 1655 and 1638 cm$^{-1}$ and an ester carbonyl peak at 1735 cm$^{-1}$ which was typical of this class of compound.

**TBD-mediated aminolysis of Esters E1-E5 to form Ligands L1-L7**

The aminolysis of the free esters E1-E5, outlined in schemes 2.7, 2.8 and 2.9, by various amino alcohols gave the oxazoline precursor $\beta$-hydroxyamides L1-L7. The amino alcohols were all synthesized from the parent amino acids using Meyers’ NaBH$_4$-I$_2$ reduction method in good yields (74-83%).$^8$ These acyl transfer reactions, in most cases, were catalyzed by 1,5,7 triazabicyclo[4.4.0]dec-5-ene (TBD) (20 mol%).$^{12}$ The use of TBD was vital in improving the yields of the reactions from the direct non-catalyzed ester aminolysis reactions.
The various novel ‘tripeptide’ \( \beta \)-hydroxyamides synthesized by the TBD-mediated reaction are represented in scheme 2.7. The reaction is solvent free and carried out at 85°C for 12 h. The structures of the ligands were confirmed by NMR spectroscopy, IR spectroscopy and mass spectrometry.

Scheme 2.7 Representative synthetic pathway to the novel ‘tripeptide’ amido-alcohols \( \text{L1-L4} \) and \( \text{L6} \)

**DBU/1,2,4 triazole-mediated aminolysis**

Ligand \( \text{L5} \) was derived from ester \( \text{E2} \) and glycinol \( \text{14} \) in an 80% yield. A 20 mol % DBU/1, 2, 4 triazole catalyst system was used to promote the aminolysis reaction to afford the \( \beta \)-hydroxyamide product as we did not have TBD at hand at the time this compound was synthesized. The yield was of \( \text{L1} \) was also further improved by catalyzing the aminolysis of \( \text{E1} \) by \( \text{L-valinol \ 13} \) with DBU/1,2,4 triazole\(^{12} \) (20 mol%) at 85°C, giving the product in 67% yield. The spectroscopic data was in agreement with that found using the TBD-mediated coupling. The reaction scheme for the synthesis of \( \text{L1} \) and \( \text{L5} \) using the DBU/1,2,4 triazole promoted system is outlined in scheme 2.8.
Scheme 2.8 DBU/1,2,4 triazole-mediated aminolysis of dipeptide esters to form L1 and L5

Direct Coupling Aminolysis

Hydroxyamide L7 was afforded from the direct coupling of ester E5 with glycinol 14 in a 59% yield (scheme 2.9). The reaction was carried out in a closed pressure tube in a 150°C oil bath. No organocatalyst was used to promote the condensation.

Scheme 2.9 Direct coupling of ester E5 to glycinol 14 to give L7
Table 2.1

<table>
<thead>
<tr>
<th>β-hydroxyamide</th>
<th>Promoters</th>
<th>Yield (%)</th>
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</thead>
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</tr>
<tr>
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<td>TBD</td>
<td>55</td>
</tr>
<tr>
<td>L7</td>
<td>-</td>
<td>59</td>
</tr>
</tbody>
</table>

Characterization of ligands L1-L7

Fig. 2.10 shows the $^1$H NMR spectrum of L2 which will be used as a representative guide of the characteristic signals of the tripeptide amido alcohol ligands L1-L7. The methyl protons of the $^1$Pr group appear ~0.7 ppm. There are similar signals in the 1 H spectra of L3 and L4 where there are R groups on the adjacent amino acid ester derived or amino alcohol derived part of the molecules. These R groups influence appears to move the methyl signals upfield. In the cases where the adjacent part of the molecule to the valine derived part does not have an alkyl branch, i.e. derived from glycine, the methyl protons appear ~0.9-1.0 ppm. This is the case with L1 and L5.

The lactam CH$_2$s appear as multiplets at ~1.7 and between 1.8-2.15 ppm and integration indicates that the first signal is due to one proton and the latter due to three. As was the case with D1-D3 and E1-E5 it is likely the diastereotopic Hs of the lactam CH$_2$ adjacent to the CHNH give rise to two different signals one of which overlaps with the signal due to the other CH$_2$ at ~2.1 ppm. Signals similar to these are seen for all the other tripeptide ligands. The integration of the spectra of L1 and L5 show an extra proton among the lactam peaks. These are due to the CH of the $^1$Pr groups.
Figure 2.10 $^1$H NMR spectrum of ligand L2 less the aromatic region
The signals of the diastereotopic CH₂s on the benzyl chain of L₂ appear as doublet of doublets at 2.49 and 2.75 ppm. There are similar signals for L₃ and L₆. The multiplet at ~3.2 ppm is due to the CH₂ adjacent to the OH group. A similar signal appears in the spectra of all the other L ligands. The spectra of L₁ and L₆ have NHCH₂ multiplet signals at ~3.7 ppm, while L₇ has an NHCH₂ signal at 3.1, moved upfield due to the absence of an adjacent carbonyl group.

The multiplet at ~3.50 ppm is due to the CH near the iPr group in the molecule. Again similar signals appear in the ¹H NMR spectra for L₁, and L₃-L₅. The position of the CHs adjacent to the CH₂OH is very much dependant on the R group and in these ligands this signal is distinct from the lactam CH moving upfield in the case of R=iPr and downfield when R=Ph. In the case of L₂ the CH is next to a CH₂Ph group and the signal appears at 3.80 ppm. Similar signals are present for L₆. The signal for L₃ is shifted further downfield due to the influence of the adjacent carbonyl. For L₇, the CH is next to a Ph group and is moved downfield to 5.46 ppm.

The CH of the lactam remains at ~4.0 ppm for all the ligands. The OH signal appears between 4.6 and 4.9 ppm in all ligands either as a triplet or broad singlet. The amide NHs appear between from ~7.7 to 8.0 ppm in the ¹H NMR spectrum of L₂ and this is typical of this ligand class. The only exception to this is L₇ which has signals for the amide NHs in the ¹H NMR spectrum at 7.9 and 8.3-8.5 ppm.

![Figure 2.11](image.png)

**Figure 2.11** Position of key signals in ¹³C NMR spectrum of L₃ (expressed as whole numbers in ppm)

The key signals observed in the ¹³C NMR spectrum of L₂ are shown in Fig. 2.11. These signals were again characteristic of the ligand class as a whole. The CH carbons
could not be absolutely assigned. The NMR spectra of the ligands L1-L7 show no indication of diastereomeric compounds being present.

The IR spectrum of L2 showed NH and OH peaks at 3293 cm\(^{-1}\), two amide peaks at 1675 and 1633 cm\(^{-1}\) which was typical of this class of compound.

### 2.2.2 Synthesis of Pyroglutamate derived amido-oxazoline ligands

#### 2.2.2.1 Synthesis of oxazoline ligands OX1 and OX2

The preparation of OX1, from the chiral acid L-pyroglutamic acid 1, is outlined below (Scheme 2.10). These ligands were of the ligand class 5. The ligand forming reactions are the coupling of chiral pyroglutamine 18 with oxazoline esters 19 and 20.

![Scheme 2.10 Reaction pathways to form Ligand OX1](image-url)
A previously reported esterification of 1 was performed initially, by gently refluxing and stirring the chiral acid in methanol in the presence of Amberlyst 15 resin, a strongly acidic cation exchange resin for heterogeneous acid catalysis. The reaction was continued overnight to form the ester 10. Removal of the resin by filtration and concentration in vacuo afforded the methyl ester, which required no further purification, in 94% yield. The spectral analysis agreed with published data.

Ester 10 was reduced to the corresponding alcohol by sodium borohydride in ethanol overnight, affording 15 as a colourless gum in 87% yield. Spectral analysis of the product obtained was again in agreement with published data. In order to form azide 17, alcohol 15 was first transformed to the mesylate 16, using triethylamine and methanesulfonyl chloride in 83% yield. This compound was dissolved in water and charged to a 10 ml Ace pressure tube and reacted with excess sodium azide under temperature controlled (120 °C) microwave irradiation for 30 min, giving the azide 17 in a yield of 95%. This procedure was a slight variation on Varma’s method, which he applied to the syntheses of azides, thiocyanates and sulfones from substrates with halide and tosylate leaving groups. This method reduced the reaction time from 36 h, which was the case in Bateman’s method. The azide was sufficiently pure to use in further reactions. Within a very short period of time, microwave synthesis has developed into a tool to be taken seriously. The short reaction times and improved yields offered by this methodology have piqued the interest of industry, particularly in the area of drug development. Particularly, microwave conditions have proved excellent for S_N2 reactions, as in this example.

The corresponding amine 18 was obtained by hydrogenation of 17 with 10% palladium on carbon in ethanol in a hydrogenation apparatus at 40 psi of H_2 for 15 h. The crude product was purified by column chromatography to give 18 as viscous yellow oil in 94% yield.
Scheme 2.11 Synthesis of oxazoline ester intermediates 19 and 20

The oxazoline ester 19 was synthesised by the condensation of ethyl benzimidate HCl 21 and L-serine methyl ester HCl 22 in a 71% yield (Scheme 2.11). Oxazoline ester 20 was obtained in an 80% yield by the reaction of the ethyl ester of L-threonine hydrochloride 23 with ethyl benzimidate hydrochloride 21, as presented in scheme 2.11. The spectroscopic data for the compound agreed with the published data.

The final step in the synthesis of novel ligand OX1 was the aminolysis of L-serine derived ester 19 with amine 18. The crude product was purified by recrystallization affording the pure ligand OX1 in 53% yield as an off-white powder.

Ligand OX2, was synthesized using the same method as for ligand OX1 (scheme 2.12), with 20 in place of 19, reacted with amine 18 to give OX2 in a 45% yield. The structure was confirmed with the aid of $^1$H, $^{13}$C, COSY and HETCOR NMR spectroscopy.

Scheme 2.12 Synthesis of ligand OX2
These one-pot direct aminolysis of the oxazoline esters to the amines, using 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as an organocatalyst (Scheme 2.12)\(^9\) represented a more facile synthesis, in terms of reaction protocol, than converting the ester to the corresponding carboxylic acid by hydrolysis with NaOH, and subsequently coupling with the amine by means of standard amide formation procedures using O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) and pyrox 1-hydroxybenzotriazole (HOBT). The peptide coupling reagents TBTU and HOBT are also considerably more expensive. This method was previously applied by Pfaltz and co-workers for their related bis[dihydrooxazole] ligand 25 (Scheme 2.13)\(^{17}\) and is a common approach in these type of reactions. These peptide coupling reagents were used in stoichiometric amounts and gave a yield of 72%.

Scheme 2.13 Pfaltz method for synthesis of bis[dihydrooxazole] ligand

Characterization of Oxazoline ligands OX1 and OX2

The \(^1\)H NMR spectrum of OX1 is shown in Fig. 2.12. The \(^1\)H NMR spectrum of OX2 is, as expected, very similar. The characteristic oxazoline protons of OX1 showed up at \(~4.60\) for the CH adjacent to the C=N and as two doublet of doublets at 4.71 and 4.87 ppm for the O\(\text{CH}_2\) group. In the case of OX2 the oxazoline protons appeared at 4.31 for the CH adjacent to the C=N and as a multiplet at 4.88 ppm for the O\(\text{CHCH}_3\) signal.
The $\text{CH}_2\text{NH}$ group of $\text{OX1}$ appeared as a multiplet at 3.2-3.43 ppm, while the same group in $\text{OX2}$ appeared as two multiplets at 3.22-3.30 ppm and 3.38-3.45 ppm. The two $\text{CH}_2$s of the 2-pyrrolidone gave peaks from 1.75-2.36 ppm and 1.72-2.31 ppm for $\text{OX1}$ and $\text{OX2}$ respectively. The lactam and amide $\text{NH}$ peaks of $\text{OX1}$ were at 5.82 and 6.99 ppm, while the $^1\text{H}$ NMR spectrum of $\text{OX2}$ showed the equivalent peaks at 7.16 and 7.41 ppm. These signals could not be assigned. The methyl group present in $\text{OX2}$, adjacent to the stereogenic carbon, appeared as a doublet at 1.57 ppm.

![Figure 2.13](image)

*Figure 2.13* Position of key signals in $^{13}\text{C}$ NMR spectrum of $\text{OX1}$ (expressed as whole numbers in ppm)

In the $^{13}\text{C}$ NMR spectrum of $\text{OX1}$ (Fig. 2.13) the lactam carbonyl signal was at 178.1 ppm, while the signals for the other amide and the N=C-O appears at 172.5 and 166.8 ppm respectively. The assignment of the specific signals will be addressed in section 2.3. A DEPT spectrum confirmed the presence of the oxazoline carbons, with the OCH$_2$ appearing at 68.8 ppm and the C=N-CH appearing at 69.2 ppm. The $^{13}\text{C}$ NMR spectrum of $\text{OX2}$ had an additional peak at 21.9 ppm confirmed by DEPT experiment to be the methyl group on the oxazoline ring. IR spectroscopy showed the presence of the NH band at 3337 cm$^{-1}$ and the amide carbonyl stretch at 1642 cm$^{-1}$. These peaks were similar to those present in the IR spectrum of $\text{OX2}$. 

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Figure 2.12 $^1H$ NMR spectrum of OX1
2.2.2.2 Synthesis of Oxazolines OX3-OX5

Sigman et al. reported the use of tridentate oxazoline amide ligands in the Cr-catalyzed addition of allyl bromide to acetophenone with some success (Fig 2.14). These ligands featured a Boc-protected proline module linked to an amide module, which was linked to an oxazoline module. Synthesis of these ligands involves the intramolecular cyclization of tripeptide amido alcohols to oxazolines under Mitsunobu conditions (Scheme 2.14).

\[
\text{HO-CH}_2-N\text{amide alcohols} \xrightarrow{\text{PPh}_3, \text{DIAD, DCM}} \text{oxazolines}
\]

Scheme 2.14

<table>
<thead>
<tr>
<th>Ligand</th>
<th>ee (%)</th>
<th>Yield (%)</th>
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</tr>
<tr>
<td>32</td>
<td>27</td>
<td>56</td>
<td>R</td>
</tr>
</tbody>
</table>
Figure 2.14 Evaluation of Boc-proline amido oxazoline ligand diastereomers in the enantioselective allylation of acetophenone by Sigman and Miller. This prompted us to explore the use of our similar tripeptide amido alcohol ligands as oxazoline precursors (Fig. 2.15) and we were successful in synthesizing ligands OX3-OX5.

![Figure 2.14](image1)

In our initial efforts to synthesize OX3, DAST was evaluated in the dehydration/cyclization reaction of tripeptide amido alcohol L1, and was found to successfully yield the desired oxazoline. However, the yield was poor at 13%, and purification required multiple recrystallizations to remove the impurities. When L1 was subjected to Mitsunobu cyclization conditions (PPh₃/DIAD) (scheme 2.15), the reaction progressed cleanly to the cyclized oxazoline OX3 in 55% isolated yield, following purification by column chromatography.

![Scheme 2.15](image2)

In our initial efforts to synthesize OX3, DAST was evaluated in the dehydration/cyclization reaction of tripeptide amido alcohol L1, and was found to successfully yield the desired oxazoline. However, the yield was poor at 13%, and purification required multiple recrystallizations to remove the impurities. When L1 was subjected to Mitsunobu cyclization conditions (PPh₃/DIAD) (scheme 2.15), the reaction progressed cleanly to the cyclized oxazoline OX3 in 55% isolated yield, following purification by column chromatography.

Ligand OX5 was formed by the intramolecular cyclization reaction, as used for OX3, of hydroxyamide L2 under Mitsunobu reaction conditions in 49% yield (scheme 2.16). The compound was purified by column chromatography. ¹H NMR spectroscopy confirmed the structure of the ligand.
OX4 was synthesized by Wipf's method, utilizing DAST as the cyclization reagent. A freshly opened bottle of DAST was used and afforded the desired oxazoline product in 78% yield after purification, in contrast to the results for OX3 where the bottle of DAST had been opened for around a month. We found it essential that the DAST reagent was required to be as pure as possible in order for the reaction to progress smoothly. The reaction pathway is outlined in scheme 2.17. $^1$H and $^{13}$C NMR spectroscopy confirmed the structure of the ligand.

Characterization of oxazolines OX3-OX5

The characteristic signals for the compounds in the $^1$H NMR spectra for compounds OX3-OX5 are very similar. Fig. 2.16 shows the $^1$H NMR spectrum of OX3 which will be used as a guide to these characteristic signals.
The lactam CH$_2$s appear as multiplets between 1.75-1.90 ppm and between ~2.25-2.40 ppm. Integration indicates that the first signal is due to two protons and the latter due to three. Again, as with other our other pyroglutamide compounds, it is likely the diastereotopic Hs of the ring CH$_2$ adjacent to the CHNH give rise to two different signals one of which overlaps with the signal due to the other CH$_2$ at ~2.25 ppm. Signals similar to these are seen for OX4 and OX5. For each compound, the upfield signal integrates for two Hs as it also contains the signal due to the CH of the 3Pr group.

The multiplet at ~3.4 ppm is due to the CH$_2$ adjacent to the NH of the amide group. The equivalent signal in the $^1$H NMR spectrum of OX4 and OX5 appears as a multiplet at ~4.25 ppm. This difference could be influenced by the different stereochemistry present in the OX4 ligand but obviously the 3Pr group will also have an influence. Quite why the signal appears as a triplet in the case of OX5 is difficult to see. The multiplet at ~3.95 ppm is due to lactam CH in the molecule. Again similar signals appear in the $^1$H NMR spectra for OX4 and OX5.

The position of the oxazoline OCH$_2$ is very much dependant on the R groups adjacent to it. For OX3 the signals appear as triplets at 4.17 and 4.48 ppm, with the diastereotopic Hs giving rise to two different signals. OX4 has no chiral group on the oxazoline so the OCH$_2$signal appears as a multiplet at ~3.80 ppm. OX5 is similar to OX3 with two peaks, a triplet at 4.54 ppm and a signal at ~4.35 ppm overlapping with the signal for adjacent CHBn group in the ring as a multiplet. In OX3 the equivalent oxazoline CH appears as a multiplet between 4.02 and 4.09 ppm. All of these signals were assigned with the aid of COSY experiments.

The amide N-Hs appear at ~6.80 and 7.81 ppm in the $^1$H NMR spectrum of OX3 and this is typical of this ligand class.
Figure 2.16 $^1$H NMR spectrum of OX3
The key signals observed in the $^{13}$C NMR spectrum of OX3 are shown in Fig. 2.17. These signals were characteristic of this ligand class as a whole. The CH carbons were absolutely assigned with the aid of HETCOR experiments. The assignment of the quaternary C and the amide and lactam Cs will be dealt with in a later section.

The NMR spectra of the ligands OX3-OX5 both crude and purified gave no indication of diastereomeric compounds being present, and each of the ligands gave substantial optical rotation of plane polarised light.

The IR spectrum of OX3 showed NH and OH peaks at 3219 cm$^{-1}$, two amide peaks at 1681 and 1640 cm$^{-1}$ which was typical of this class of compound.
2.2.2.3 Synthesis of pyrrolidone-oxazoline ligands

The first series of pyridyloxazoline ligands for asymmetric catalysis were introduced by Brunner and co-workers.\textsuperscript{21-23} These ligands are easily and modularly made by ZnCl\textsubscript{2}-catalyzed condensation of 2-cyanopyrrole (or 2-cyanopyridine) with different amino alcohols, to give a library of ligands with different absolute configurations of the stereocentres and of the ligand’s steric bulk. These pyridyl-2-oxazolines (PyOX) were first used as ligands in the asymmetric Cu-catalyzed monophenylation of meso-diols, e.g. \textit{36}, by triphenylbismuth diatetate (scheme 2.18). The best result was achieved by the (S)-valinol derived ligand, \textit{35} which gave the monophenyl ether \textit{37} in 50% \textit{ee}.

\textbf{Scheme 2.18} Brunner’s Ligand \textit{35} used in the Cu-catalyzed monophenylation of meso-diols by triphenylbismuth diatetate

Chiral pyridyl oxazolines have been used extensively as ligands in palladium catalyzed allylic substitution reactions. Moberg’s Ligand \textit{38}, achieved an \textit{ee} of >99\% in the asymmetric alkylation of 1,3-diphenyl-2-propenyl acetate \textit{39} with dimethyl malonate (scheme 2.19).\textsuperscript{24} Many other PyOX ligands have been applied to a large range of key asymmetric transformations including other palladium-catalysed allylic substitutions, the Diels-Alder reaction\textsuperscript{25-27} and in asymmetric Rh-catalyzed hydrosilylations\textsuperscript{28,29} of aromatic prochiral ketones.
Scheme 2.19 Asymmetric alkylation of chalconol acetate 39 using PyOX-ligands

2-(2’-pyrrolyl)oxazolines (PyrOX) were first reported in 1977. They differ from PyOX-ligands mostly by the relatively acidic pyrrolidine proton, which affects the chemistry of this ligand family compared to the PyOX. The first chiral PyrOX-ligands (41) was introduced by Brunner in 1998. These ligands were tested in an asymmetric cyclopropanation reaction using ethyl diazoacetate 42 and alkene compounds (Scheme 2.20), yielding enantioselectivities of below 15% ee. This discovery, however, gave indications of the asymmetric catalysis possibilities of this kind of ligand.

Scheme 2.20 Asymmetric cyclopropanation reaction by Brunner

Guiry used pyrrolidine oxazolines ligands of type 47 in the asymmetric transfer hydrogenation of acetophenone 33 (scheme 2.21). After optimization, their best results arose from catalysts generated in situ from 1: 2 mixtures of [IrCl(η⁴cod)]₂ (0.25 mol%) and the ligands bearing either iPr or Ph substitutes at the C4 positions of the oxazoline ring, giving 79–91% conversion to the alcohol 48 after 15 h, and 32–38% ee. Use of
[Ru(p-cymene)Cl$_2$]$_2$ as pre-catalyst at a 2.5 mol% loading gave improved ee’s of up to 61% at the expense of yield (only 73% conversion).

Scheme 2.21 Asymmetric Transfer Hydrogenation of acetophenone using ligand 47

These studies prompted us to synthesize novel 2-pyrrolidone oxazolines with a view towards investigating their use as chiral ligands in a variety of asymmetric catalytic reactions.

2.2.2.3.1 Synthesis of oxazolines OX6 and OX7

The oxazolines OX6 and OX7 were synthesized by the cyclization of our dipeptide hydroxyamides D3 and D4 to OX6 and OX7 in 41% and 58% yield respectively using DAST. The method involved adding DAST dropwise to a solution of the hydroxyamide in DCM at -78°C with stirring for 2 hr. The reaction was quenched by the addition of potassium carbonate, and allowed to warm to room temperature (scheme 2.22).

Scheme 2.22 Synthesis of oxazoline ligands OX6 and OX7
The structure and purity of the novel chiral ligands OX6 and OX7 were confirmed by NMR, IR and MS analysis. The $^{1}$HNMR spectrum for OX6 showed a multiplet integrating for 6 Hs from 0.86-0.98 ppm representing the two methyl groups. The two CH$_{2}$s of the lactam ring were present in a multiplet from 2.22-2.49 ppm. The CH of the oxazoline appeared as a triplet peak at 3.86 ppm in the proton spectrum with the peaks of the oxazolines CH$_{2}$ showing up as multiplet integrating for 1 H from 4.07 to 4.18 and as a multiplet from 4.31-4.42 integrating for 2 Hs. This multiplet also included the signal for the CH of the lactam. These signals were confirmed by HETCOR. The $^{13}$C spectrum showed the CH of the oxazoline at 64.7 ppm and the OCH$_{2}$ at 73.9 ppm. The signal for the iminoester carbon (N=C-O) was at 166.0 ppm.
Figure 2.18 $^1$H NMR spectrum of OX6
Characterization of OX6 and OX7

Fig. 2.18 shows the $^1$H NMR spectrum of OX6 which will be used as a representative guide of the characteristic signals of the tripeptide amido alcohol ligands OX6 and OX7. The methyl protons of the 'Bu group appear as two doublets at ~0.9 ppm and 1.0 ppm. The diastereotopic CH$_2$ protons of the isobutyl group appear as two multiplet peaks between 1.23-1.33 ppm and 1.51-1.60 ppm. The CH of the 'Bu group gives a multiplet between 1.67-1.79 ppm.

The lactam CH$_2$s appear as a multiplet from 2.22-2.49. The $^1$H NMR spectrum for OX7 shows a similar peak. The CH of the oxazoline ring gave a triplet peak at ~3.86 ppm, with the peaks of the OCH$_2$ of the oxazoline showing up as a multiplet, integrating for 1 H from 4.07-4.18 ppm and as another multiplet, integrating for 2 H, from 4.31-4.42. This signal overlapped with the signal due to the CH of the lactam ring. In the $^1$H NMR spectrum for OX7 the diastereotopic OCH$_2$ gives two signals, a double doublet at 4.05 ppm and a triplet at 4.25 ppm. The peak of the lactam CH is at 4.28-4.34. The CH of the oxazoline is more downfield than the corresponding peak for OX6, due to the stereogenic and electronic influence of the Bn group.

The signals of the diastereotopic CH$_2$s on the benzyl chain of OX7 appear as doublet of doublets at 2.70 and 3.04 ppm. The lactam N-Hs typically appear ~6.80 ppm in the $^1$H NMR spectrum of OX6 and OX7, however as can be seen in Fig. 2.18, this signal did move, presumably due to H-bonding and other effects at different concentrations. These signals were assigned with the aid of a HETCOR experiment.

Figure 1.19 Positions of key signals in $^{13}$C NMR spectrum of OX6 (expressed as whole numbers in ppm)
The key signals observed in the $^{13}$C NMR spectrum of OX6 are shown in Fig. 2.19. These signals were characteristic of ligand OX7 also. The NMR spectra of the ligands OX6 and OX7 showed no indication of diastereomeric compounds being present.

The IR spectrum of OX6 showed NH peaks at 3077 cm$^{-1}$, an amide carbonyl peak at 1683 and a C=N peak at 1666 cm$^{-1}$, which was typical of this class of compound.

2.3 Assignment of $^{13}$C NMR Carbonyl Signals of 2-pyrrolidone Compounds

Assignment of the $^{13}$C carbonyl signals was based on the array of related structures synthesized during the project, and on published data for comparable structures. Most of the ligands applied to the asymmetric reactions in this project contain a lactam and an amide carbonyl group.

The NMR data was compared to Bateman’s two ligands, UNIFIDE and CROSIDE (Table 2.2). In the case of UNIFIDE there are two carbonyl signals at 179.6 ppm and 172.1 ppm, whereas, CROSIDE shows two carbonyl signals at 165.0 ppm and 178.6 ppm. Bateman assigned the signals based on the position of the pyridylamide carbonyl given in the Trost ligand data. The carbonyl is in a similar environment and is found at 164.6 ppm. It was deduced from this information that the lactam carbonyl would appear around 179 ppm in a $^{13}$C NMR spectrum. This was supported by data from the UNIFIDE ligand, whose lactam C=O is at 179.5 ppm and also by the starting materials that were prepared for the synthesis of the ligands in the present study. In particular, pyroglutamine 18 agreed well with the postulation, since the carbonyl appears at 179.0 ppm. The amide and lactam carbonyls of the dipeptide esters E1-E5, $\beta$-hydroxyamides L1-L7 and oxazolines OX1-OX7 were assigned by comparison. The table of $^{13}$C NMR spectral assignments for relevant and related structures in this study is shown below.
Table 2.2 $^{13}$C NMR spectrum carbonyl signals for compounds synthesized in this study and related structures

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>Lactam C=O</th>
<th>Amide/Ester C=O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trost Ligand</td>
<td></td>
<td></td>
<td>164.6</td>
</tr>
<tr>
<td>18</td>
<td></td>
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<tr>
<td>10</td>
<td></td>
<td>178.5</td>
<td>172.6</td>
</tr>
<tr>
<td>UNIFIDE</td>
<td></td>
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<td>172.1</td>
</tr>
<tr>
<td>CROSIDE</td>
<td></td>
<td>178.6</td>
<td>165.0</td>
</tr>
<tr>
<td>L2</td>
<td></td>
<td>178.0</td>
<td>171.7/170.8</td>
</tr>
<tr>
<td>L3</td>
<td></td>
<td>177.4</td>
<td>170.8/172.3</td>
</tr>
<tr>
<td>L4</td>
<td></td>
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<td>171.8/172.0</td>
</tr>
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<tr>
<td>L5</td>
<td></td>
<td>177.4</td>
<td>168.0/172.6</td>
</tr>
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<td></td>
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<td>170.4/172.5</td>
</tr>
<tr>
<td>L7</td>
<td></td>
<td>178.0</td>
<td>170.2/172.4</td>
</tr>
<tr>
<td>Compound</td>
<td>Structure</td>
<td>Lactam C=O</td>
<td>Amide/C=N</td>
</tr>
<tr>
<td>----------</td>
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<td>172.7/167.4</td>
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<td>----------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----</td>
</tr>
<tr>
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<tr>
<td>20</td>
<td><img src="image2.png" alt="Structure 20" /></td>
<td>171.3</td>
<td>165.2</td>
</tr>
</tbody>
</table>

With the four $\beta$-hydroxyamide ligands D1-D4, two 2-pyrrolidone oxazolines OX6 and OX7, seven tripeptide $\beta$-hydroxyamide ligands L1-L7 and oxazoline amide ligands OX1-OX5 produced, it was decided to investigate their catalytic efficiency in a range of catalytic asymmetric transformations.

2.4 Asymmetric Transformations

2.4.1 Asymmetric alkylations of benzoaldehyde

The novel ligands D1-D4, L1-L7 and OX3-OX7 were applied to two asymmetric alkylation reactions. These were the titanium-promoted diethylzinc addition to benzaldehyde and the titanium-promoted addition of phenylacetylene to benzaldehyde. Both reactions will be introduced in a brief overview and then the results of the reactions are discussed.

2.4.1.1 Overview of the asymmetric diethylzinc addition reaction

The catalytic asymmetric alkylation of a prochiral aldehyde using an organometallic reagent is one of the most useful methods to synthesize chiral secondary alcohols. A
stereogenic centre is generated in the reaction and, at the same time, a new carbon-carbon bond is formed. This is one advantage of the enantioselective alkylation of aldehydes compared with the enantioselective reduction of ketones, in which the carbon skeleton is left unchanged throughout the reaction. The addition of diethylzinc to aldehydes,$^{34,35}$ is a frequently studied carbon-carbon bond forming reaction system, and it serves well as a model for evaluating how ligand structure affects the enantioselectivity of the product. Typical experimental conditions used are outlined in Scheme 2.23. The typical reaction setup employs zinc catalysts coordinated to amino alcohol ligands, but the use of titanium based catalysts tends to be more efficient and selective.$^{36-39}$

![Scheme 2.23 Asymmetric addition of diethylzinc to aldehydes](image)

Titanium tetraisopropoxide, Ti(OiPr)$_4$, is an additive that is commonly employed to help facilitate the asymmetric addition of diorganozinc reagents to carbonyl substrates. This reagent has become almost ubiquitous in its application in this process, as it has been proven to be a particularly efficient promoter of the dialkylzinc addition reaction.$^{40}$ Walsh et al. demonstrated that there is a reaction between the Ti(OiPr)$_4$ and diethylzinc to give a reactive intermediate EtTi(OiPr)$_3$ that is likely to be the alkylating agent.$^{41}$

Early enantioselective alkylation of aldehydes were achieved with alkylolithiums and dialkylmagnesium reagents.$^{42,43}$ However, a stoichiometric amount (sometimes more) of the chiral ligand, with respect to the organometallic reagent, was needed due to the high tendency of these reagents to add to the aldehyde, even at low temperatures. The first catalytic enantioselective alkylation of benzaldehyde by the use of diethylzinc was reported by Oguni and Omi in 1984.$^{44}$ They showed that a catalytic amount of optically
active β-amino alcohols promoted the reaction. When (S)-leucinol was employed, (R)-1-phenyl-1-propanol was formed in 49% ee. The advantage of using diethylzinc instead of other organometallic reagents was that it did not add to the aldehyde in the absence of the chiral inducer. Consequently, the non-selective background reaction was no longer a problem.

Shortly after the successful application of (S)-leucinol as a ligand in the catalytic enantioselective alkylation of benzaldehyde, Noyori and co-workers showed that the β-amino alcohol DAIB 49 (Fig. 2.22) promoted the addition of diethylzinc to aromatic aldehydes with high levels of enantioselectivity (up to 99% ee). It was also shown that an equimolar mixture of diethylzinc and 49 was unable to alkylate benzaldehyde, and that an excess of diethylzinc relative to 49 was necessary for the reaction to take place, indicating the presence of a binuclear zinc complex in the catalytic cycle.

When DAIB of 15% ee was used, (S)-1-phenyl-1-propanol was produced in 95% ee. Soai et al. used the β-amino alcohol (-) N,N-dibutylnorephedrine (DBNE) 50 (Fig. 2.20) obtained from norephedrine, in the enantioselective alkylation of aliphatic aldehydes with excellent levels of enantioselectivity. Since these early reports of highly enantioselective alkylations of aldehydes a large number of successful ligands have been reported some examples are also shown in Fig. 2.20.
2.4.1.2 Asymmetric addition of diethylzinc to benzaldehyde

The first of our ligands tested in the asymmetric addition of diethylzinc to benzaldehyde were the $\beta$-hydroxyamides D1-D4.\(^{48}\)

![Scheme 2.24 Asymmetric addition of diethylzinc to benzaldehyde](image)

The reactions were carried out using 10 mol% of the ligand and 20 mol% of titanium isopropoxide, with anhydrous toluene as solvent (scheme 2.24). After stirring for 1 h at room temperature, 2 equivalents of diethylzinc solution was added by syringe in one portion. The reaction vessel was then immersed in an ice-bath and benzaldehyde was added. The reaction was continued at 0°C until all the benzaldehyde was consumed or the progress of the reaction had ceased. Generally, the reaction was ceased after 16 h. The product was isolated from the reaction mixture, purified by column chromatography and the enantiomeric excess was measured by HPLC (Chiralcel OD, hexane:iso-propyl alcohol, 98:2, 0.5 ml/min). The absolute configuration was assigned by comparison of the sign of the specific rotation to the literature data.\(^{49}\) The (S) product was eluted at around 31.8 min and the (R)-product was eluted at around 24.4 min. The results are shown in Table 2.3.

Significant enantioselectivity was only achieved in the case of (R)-phenylglycinol derived ligand D1 where an ee of 74% was achieved. The stereoselectivity of the other ligands were poor in comparison, with the next best performance achieved by ligand D3, giving 24% ee. The activity of the ligands was good, with conversion of around 80% and higher achieved for each of the ligands. In all cases where asymmetric induction was achieved the (R)-enantiomer was the dominant configuration.
Table 2.3 Ligands D1-D4 used in the addition of diethylzinc to benzaldehyde

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Time (h)</th>
<th>Temperature (° C)</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
<th>R/S</th>
</tr>
</thead>
<tbody>
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<td>R</td>
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</tr>
<tr>
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<td>rt</td>
<td>82</td>
<td>24</td>
<td>R</td>
</tr>
<tr>
<td>D4</td>
<td>16</td>
<td>rt</td>
<td>79</td>
<td>6</td>
<td>R</td>
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</tbody>
</table>

The β-hydroxyamides L1-L7 were then applied to the same reaction under the same reaction conditions. The results are outlined in Table 2.5.

Table 2.4 Ligands L1-L7 used in the addition of diethylzinc to benzaldehyde

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Time (h)</th>
<th>Temperature (° C)</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
<th>R/S</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>16</td>
<td>rt</td>
<td>89</td>
<td>20</td>
<td>R</td>
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</tr>
<tr>
<td>L3</td>
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<td>rt</td>
<td>80</td>
<td>11</td>
<td>R</td>
</tr>
<tr>
<td>L4</td>
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<td>83</td>
<td>18</td>
<td>R</td>
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<td>90</td>
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</table>

The conversion was over 77% in all cases and each ligand gave the (R)-enantiomer in excess. The ligands which had slightly higher enantioselectivity, L1, L5 and L7, all had a glycine derived module. This could indicate a minimal steric influence on stereoselectivity, where the ligands with less bulky R groups giving higher ees.

The oxazoline ligands OX3-OX7 were also applied to the diethylzinc addition to benzaldehyde, giving good conversion in most cases, but the stereoselectivity was poor. The results are shown in Table 2.5.
Table 2.5 Ligands OX3-OX7 used in the addition of diethylzinc to benzaldehyde

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Time (h)</th>
<th>Temperature (° C)</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
<th>R/S</th>
</tr>
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<tbody>
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<td>OX4</td>
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<td>R</td>
</tr>
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</tr>
</tbody>
</table>

Figure 2.21 Bimetallic Ti(IV) transition state structures including D1, described to explain the observed stereochemistry

The (R)-configuration was the dominant stereochemical outcome for both alkylzinc additions for each of the hydroxyamide ligands. Two bimetallic, Ti(IV) transition state structures 56 and 57, related to previously proposed structures for the addition of dialkylzinc to carbonyl compounds, are postulated to explain the observed stereochemistry (Fig. 2.21).50-53 In both the carbonyl of the aldehyde is coordinated to an octahedral Ti and its Si face is exposed to attack from an alkyl group on the second Ti atom. Stabilization for the structure should be provided by hydrogen bonding between the ligand O and the aldehyde H, similar to that described in previous studies, and by π-stacking between benzaldehyde and the phenyl group of the ligand. When the aromatic group is not present on the ligand, the stereoselectivity of the reaction is greatly reduced to less than 10% ee, which supports this argument. When a benzyl
group is present as in \textbf{D3}, a possible TS \textbf{58} can be postulated (Fig 2.22). The orientation of ligand co-ordination to the titanium would have to be the reverse of that postulated for ligand \textbf{D1} as the opposite chirality of ligand gives the same product. Thus in \textbf{58} the alcohol is shown co-ordinating at the front and the amine at the rear as drawn. There is still possibly a small amount of $\pi$-stacking, but not as efficient as there is for the phenyl group (Fig. 2.22).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.22}
\caption{Bimetallic Ti(IV) transition state structures including \textbf{D3}, described to explain the observed stereochemistry}
\end{figure}

\section*{2.4.2 Asymmetric addition of phenylacetylene to benzaldehyde}

\subsection*{2.4.2.1 Overview of the asymmetric addition of terminal alkynes to aldehydes}

Optically active propargylic alcohols are versatile precursors for the synthesis of many natural products and pharmaceuticals. The asymmetric alkynylzinc addition to carbonyl compounds can simultaneously form a new C-C bond and a stereogenic centre in one step and among the many organometallic nucleophiles, organozinc reagents tolerate the presence of many functional groups that are reactive toward organolithium and Grignard reagents. This property renders the organozinc species attractive alternatives to these other highly active reagents. The development of various chiral ligands as catalysts for the enantioselective alkynylation has thus been the focus of much research in recent years. Efficient catalytic systems for the asymmetric addition of terminal alkynes to aldehydes have been achieved only in the past several years and remain less developed than the analogous asymmetric addition of organozinc reagents.
to aldehydes. Among the examples in alkylzinc mediated asymmetric alkynylation reactions of aldehydes, chiral N, O-ligands have been amongst the most attractive, in terms of their performance in asymmetric catalysis.

A significant early study involved the addition reactions of dialkynylzinc reagents reported by Niwa and Soai (scheme 2.25). The metalated acetylene is prepared by allowing the terminal acetylenes to react with Et$_2$Zn. In the presence of ligand 60 the dialkynylnzinc reagents add to aldehydes to afford propargyl alcohol products 61 with modest enantioselectivities (up to 43% ee)

![Scheme 2.25](image)

The proline-derived bimetallic catalyst system developed by Trost and co-workers has proved a universal and efficient catalyst for many enantioselective transformations, showing excellent chemical activities and enantioselectivities (up to 99% ee.) for the asymmetric alkynylation of unsaturated aldehydes (scheme 2.26).

![Scheme 2.26](image)

Scheme 2.26 Asymmetric alkynylation of unsaturated aldehydes using Trost’s ligand 62
Titanium isopropoxide is also commonly used to promote acetylene additions to carbonyl compounds. An example of a Ti(OPr)₄-promoted alkynylation of aldehydes using alkylzincs is shown in scheme 2.27, in which a modular C₁-symmetric oxazolidine ligand 64 synthesized by Mao from readily available (1R, 2S)-cis-1-amino-2-indanol, was applied to the addition of phenylacetylene 63 to various aromatic aldehydes. High enantioselectivities and yields (up to 95% ee, 98% yield) were obtained.⁵⁹

![Scheme 2.27](image)

**Scheme 2.27** Enantioselective addition of phenylacetylene to various aldehydes with ligand 64

Recently, Dogan and co-workers prepared the optically active ferrocenyl-substituted aziridinylmethanol (Fam) 65 and studied its use in asymmetric alkynylation of a range of aldehydes, affording the corresponding propargylic alcohols in up to 96% yield and 96% ee (Scheme 2.28).⁶⁰

![Scheme 2.28](image)

**Scheme 2.28**
2.4.2.2 Asymmetric Addition of Phenylacetylene to Benzaldehyde

β-hydroxyamide ligands D1-D7 were applied in the asymmetric addition of phenylacetylene 63 to benzaldehyde 53.

The method involved mixing the ligand and titanium tetraisopropoxide in DCM at room temperature. Then diethylzinc was added. After stirring at room temperature for 2 h, phenylacetylene was added and the mixture was stirred for 1 h. Then the solution was treated with benzaldehyde. The crude product was purified by flash column chromatography to give 1,3-diphenyl-prop-2-yn-1-ol. The enantioselectivity was determined by HPLC analysis using a Daicel Chiralcel OD column and hexane/2-propanol 90.0: 10.0, 1.0 mL/min as mobile phase. The retention times were t (R) = 10.0 min and t(S) = 17.8 min. The predominant configuration of the products was given by the sign of the optical rotation compared with the literature data. The ligands showed poor to moderate activities and enantioselectivities. The results are shown in Table 2.6.

![Chemical reaction](image)

**Table 2.6** Ligands D1-D4 used in the addition of phenylacetylene to benzaldehyde

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Time (h)</th>
<th>Temperature (°C)</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
<th>R/S</th>
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<tr>
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<tr>
<td>D4</td>
<td>24</td>
<td>Rt</td>
<td>78</td>
<td>16</td>
<td>R</td>
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</table>

Dipeptide hydroxyamide D3 and D2 gave the best results with conversions of 89 and 88% and ees of 34 and 20% respectively. In each case where the ligands afforded
asymmetric induction to the products, the (R)-enantiomer was in excess. In the case of ligand D3, a similar transition state structure to the one for the diethylzinc addition reaction, TS-D3, can be proposed for this reaction (Fig. 2.23). However in the case of the phenylacetylene addition, the enantioselectivity for the phenyl substituted ligand D1 are poor in comparison to the results it gave in the diethylzinc addition. D1 only gave 11% ee, as opposed to 74% ee for the diethylzinc addition. The activity for all the ligands was good with conversion over 78% for all four ligands.

![Diagram of D3 and TS-D3](image)

**Figure 2.23**

Tripeptide β-hydroxyamide ligands L1-L7 were applied to the same reaction under the same experimental conditions. The results for these catalytic reactions are shown in Table 2.7.

**Table 1.7** Ligands L1-L7 used in the addition of phenylacetylene to benzaldehyde

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Time (h)</th>
<th>Temperature (°C)</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
<th>R/S</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>18</td>
<td>Rt</td>
<td>73</td>
<td>19</td>
<td>R</td>
</tr>
<tr>
<td>L2</td>
<td>18</td>
<td>Rt</td>
<td>67</td>
<td>11</td>
<td>R</td>
</tr>
<tr>
<td>L3</td>
<td>18</td>
<td>Rt</td>
<td>60</td>
<td>16</td>
<td>R</td>
</tr>
<tr>
<td>L4</td>
<td>16</td>
<td>Rt</td>
<td>63</td>
<td>18</td>
<td>R</td>
</tr>
<tr>
<td>L5</td>
<td>16</td>
<td>Rt</td>
<td>70</td>
<td>32</td>
<td>R</td>
</tr>
<tr>
<td>L6</td>
<td>20</td>
<td>Rt</td>
<td>69</td>
<td>19</td>
<td>R</td>
</tr>
<tr>
<td>L7</td>
<td>20</td>
<td>Rt</td>
<td>77</td>
<td>28</td>
<td>R</td>
</tr>
</tbody>
</table>
All the tripeptide ligands showed good activity, giving conversions over 60% in all cases. The highest ees were produce from ligands L5 and L7, with 32% and 28% ee. These ligands were derived from glycinol, which have no chiral centres on the amino alcohol module. This module is likely to be the co-ordinating part of the ligand. It appears, with these tripeptide ligands, steric bulk on the amino alcohol which gives free alcohol terminus has a dramatic negative effect on the stereoselectivity of the reaction. This is puzzling given steric bulk on the same residue in the dipeptide derived ligand has a positive influence on the stereoselectivity of the reaction in the alkylation of benzaldehyde. C1-symmetric amido-oxazoline ligands OX3-OX7 were also applied to the phenylacetylene addition to benzaldehyde, giving moderate conversion in most cases, and the stereoselectivity was poor. The results are shown in Table 2.8.

Table 2.8 Ligands OX3-OX7 used in the addition of phenylacetylene to benzaldehyde

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Time (h)</th>
<th>Temperature (° C)</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
<th>R/S</th>
</tr>
</thead>
<tbody>
<tr>
<td>OX3</td>
<td>19</td>
<td>Rt</td>
<td>54</td>
<td>15</td>
<td>R</td>
</tr>
<tr>
<td>OX4</td>
<td>16</td>
<td>Rt</td>
<td>59</td>
<td>18</td>
<td>R</td>
</tr>
<tr>
<td>OX5</td>
<td>20</td>
<td>Rt</td>
<td>65</td>
<td>21</td>
<td>R</td>
</tr>
<tr>
<td>OX6</td>
<td>16</td>
<td>Rt</td>
<td>38</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>OX7</td>
<td>16</td>
<td>Rt</td>
<td>40</td>
<td>0</td>
<td>---</td>
</tr>
</tbody>
</table>

Again ligands OX6 and OX7 showed no stereoselectivity in this reaction. OX3-OX5 showed moderate activity, with conversions over 54%. The % ees achieved were similar to the ees delivered by the tripeptide hydroxyamide ligands L1-L7.

In both the alkylation and alkynylation reactions the (R)-enantiomer was the dominant configuration for every reaction studied. Whereas we can present potential transition states which might explain the outcome and particularly the fact that the opposite stereochemistry in the case of the phenyl ligand D1 gives the same stereochemical outcome as the other ligands the exact nature of the stereochemical induction is still somewhat speculative. One could also imagine that given the same enantiomer of pyroglutamic acid was used in each case it might suggest that the pyroglutamic acid derived module of the ligand is the chiral centre responsible for inducing chirality in the
products, since it is the common to all of the ligands used in this study. This however would contradict the outcomes for previously reported ligands. Though beyond the scope of this study it would be useful to compare the outcome of these reactions with those using the diastereomeric ligands where the opposite enantiomer of the pyroglutamic acid is used. This would determine the influence of the pyroglutamic acid residue on the stereochemical induction during the reaction.

2.4.3 Asymmetric Transfer Hydrogenation

The novel \( C_1 \)-symmetric amido oxazolines OX3-OX5 and \( \beta \)-hydroxyamide ligands L1-L7 and D1-D7 were applied in the ruthenium(II)-catalyzed transfer hydrogenation of acetophenone. The methodology of the reaction is outlined in section 2.3.3.2.

2.4.3.1 Overview of the asymmetric transfer hydrogenation reaction

Catalytic reduction of polar functional groups, such as ketones and imines mediated by transition metal complexes has attracted remarkable interest in both the academic and industrial world.\(^{62-64}\) Among the catalytic methods available for reduction, the transfer hydrogenation has advantages over other processes in operational simplicity and because of the use of non-hazardous hydrogen donors, such as 2-propanol and formic acid. The general reaction is depicted in Scheme 2.29.

![Scheme 2.29 General transfer hydrogenation of a ketone](image_url)
Hydrogen transfer reactions in which formally two hydrogen atoms are transferred from an alcohol to a ketone have been known since 1925. At that time, aluminium isopropoxide was used to promote transfer of hydrogen from 2-propanol to a ketone. This reduction is referred to as the Meerwein-Ponndorf-Verley (MPV) reduction after its discoverers.\textsuperscript{65} The reaction can also be run in the opposite direction, a reaction studied by Oppenauer in the mid-1930s. The hydrogen transfer reactions are equilibrium reactions that can be shifted to a certain side by the use of an excess of either alcohol or ketone as starting materials.

Catalytic transfer hydrogenations have been carried out most commonly using iridium,\textsuperscript{66-68} ruthenium\textsuperscript{69,70} or rhodium\textsuperscript{71,72} as metal precursors. However, ruthenium complexes have been found to be the best catalysts in transfer hydrogenations.

Asymmetric transfer hydrogenation (ATH) can be defined as “the reduction of prochiral compounds with a hydrogen donor other than hydrogen gas in the presence of a chiral catalyst”\textsuperscript{73}. The chiral catalysts used in this reaction most often consist of a transition metal ion in combination with chiral ligands.\textsuperscript{74,75} However, in recent years, simple organic chiral catalysts have also been used for this particular transformation.\textsuperscript{76}

Among the most active and selective catalyst types reported so far are those containing pyridine derivatives, such as 67, amino alcohols, 68, and aza-norbornyl alcohols, 69 (Fig. 2.24), as well as complexes 70 and 71 (Fig. 2.25), which are based on mono-tosylated diamine ligands.

![Figure 2.24 Examples of ligands applied to asymmetric transfer hydrogenation of aryl ketones](image)

The pyridine derived ligand binds in a pincer type fashion when coordinated to \([\text{RuCl}_2(\text{PPh}_3)_3]\). When this complex is combined with a chiral diphosphine ligand,
the catalyst formed shows astonishingly high turnover frequencies at loadings as low as 0.005 mol%.\textsuperscript{77}

Amino alcohols and mono-tosylated diamine ligands are normally used together with Ru, Rh or Ir half-sandwich complexes to form bifunctional catalysts.\textsuperscript{78} Besides inducing enantioselectivity, the chiral ligand accepts and donates a proton with its basic nitrogen, whereas the hydride is received and delivered by the transition metal, as illustrated in Scheme 2.30.\textsuperscript{79,80}

\begin{scheme}
\centering
\includegraphics[width=0.9\textwidth]{rutsdpen_bifunctional_catalyst}
\caption{Scheme 2.30 Ru-TsDPEN as an example of bifunctional catalyst}
\end{scheme}

\begin{figure}
\centering
\includegraphics[width=0.9\textwidth]{noyori_catalysts}
\caption{Figure 2.25 Noyori’s catalyst Ru-TsDPEN 70 and the tethered analogue catalyst 71}
\end{figure}

Complex 70 (Ru-TsDPEN, where DPEN = 1,2 diphenylethylenediamine), developed and thoroughly studied by Noyori, is perhaps the most well-known and successful catalyst for asymmetric transfer hydrogenation.\textsuperscript{81} A tethered version of this catalyst, 71, shows enhanced activity and selectivity in several cases over the untethered diamine due to the locked conformation of the arene.\textsuperscript{82-84}

The class of substrates that can be highly selectively reduced by catalysts containing Ru, Rh or Ir half-sandwich complexes is limited to aryl alkyl ketones. The high selectivity associated with these reactions is ascribed to a stabilizing dipolar
interaction between the arene CH of the catalyst (e.g., \( p \)-cymene) and the \( \pi \)-system of the substrate.\textsuperscript{85,86}

Noyori et al. have proposed in their studies that the active species in the ruthenium(II)-catalyzed transfer hydrogenation is a 16-electron ruthenium(II) complex which contains a diphenylethylene diamine ligand and an arene moiety (Scheme 2.30). In the presence of 2-propanol, an 18-electron ruthenium hydride species is formed and this species catalyzes the reduction of various ketones. It was also proposed that an N-H moiety in the ligand framework might be very important to obtain the product in high enantioselectivities (99 % ee). In addition, Noyori et al. suggested a six-membered cyclic transition structure as a possible way in which a hydride can be transferred from the metal to the substrate.\textsuperscript{87}

This mechanism outlines the general process of a Ru-catalyzed ATH reaction.

\textbf{Scheme 2.31} Noyori’s mechanism of transfer hydrogenation
2.4.3.2 Asymmetric Transfer Hydrogenation of Acetophenone

The reduction of acetophenone was catalysed by 1 mol% of a homogenous complex derived from the ligand and \([\text{RuCl}_2(\text{p-cymene})]_2\). The catalyst was added to \(^1\text{PrOH}, 10\) mol\% NaOH (or KOH) and acetophenone. The reaction was carried out at rt for 16 h. This led to the formation of 1-phenylethanol. A \(^1\text{H}\) NMR spectrum was recorded of the crude product to determine the % conversion. The % conversion was calculated by comparing the amount of unreacted acetophenone [signal at 2.60 (3 H)] to the amount of product formed [signal at 1.48 (3 H)] in the \(^1\text{H}\) NMR spectrum. The crude product was then purified by column chromatography on silica gel, affording the product 1-phenylethanol. The enantiomeric purity was determined by HPLC. The \((R)\)- and \((S)\)-enantiomers eluted at 11.3 min and 13.6 min. The configurations were assigned by comparison with the sign of specific rotation of the known compounds.\(^{88}\)

The ligands showed poor to moderate activities and enantioselectivities. Dipeptide hydroxyamides D1 and D3 gave the best results with conversions of 30 and 28% and \(e\)es of 50 and 72% respectively. Both of these ligands contain a phenyl group indicating that a bulkier R group gives better enantioselectivity. This was in agreement with results from Adolfsson, who had studied similar ligands. Adolfsson et al had previously applied a range of amido-oxazolines as ligands in ruthenium catalyzed transfer hydrogenations (scheme 2.33).\(^2\) Where the R group was a phenyl group the reactivity was low but the selectivity was good.

The importance of both stereocentres was tested by using the glycine derivative 66 which was less selective than 67 and thus it was apparent that both centres had an influence of the stereochemistry of the outcome. The Boc protection of the N terminus

![Scheme 2.32 Ruthenium(II)-catalyzed transfer hydrogenation of acetophenone](image-url)
of the peptidic ligand proved crucial as the deprotected ligands showed no catalytic activity. In our ligands the Boc group was replaced by the pyroglutamate and retained the activity, but with lower selectivities.

Scheme 2.33 Adolfsson’s amido-alcohol ligands applied to ATH reaction

In all cases where asymmetric induction was achieved the \((R)\)-enantiomer was the dominant configuration. This could indicate that the constant portion of all the ligands, the 2-pyrrolidone from L-pyroglutamic acid, was the main influence of enantioselectivity in the ligands. The results obtained for the dipeptide hydroxyamide ligands are outlined below in Table 2.9.

Table 2.9 Ligands D1-D4 used in the Ru-catalyzed transfer hydrogenation of acetophenone

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Time (h)</th>
<th>Temperature (°C)</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
<th>R/S</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>24</td>
<td>Rt</td>
<td>30</td>
<td>50</td>
<td>R</td>
</tr>
<tr>
<td>D2</td>
<td>24</td>
<td>Rt</td>
<td>28</td>
<td>27</td>
<td>R</td>
</tr>
<tr>
<td>D3</td>
<td>24</td>
<td>Rt</td>
<td>35</td>
<td>72</td>
<td>R</td>
</tr>
<tr>
<td>D4</td>
<td>24</td>
<td>Rt</td>
<td>27</td>
<td>18</td>
<td>R</td>
</tr>
</tbody>
</table>

The \(\beta\)-hydroxyamides L1-L7 were then applied to the same reaction under the same reaction conditions as D1-D4. The results are outlined in Table 2.10.
Table 2.10 Ligands L1-L7 used in the Ru-catalyzed transfer hydrogenation of acetophenone

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Time (h)</th>
<th>Temperature (° C)</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
<th>R/S</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>21</td>
<td>rt</td>
<td>35</td>
<td>19</td>
<td>R</td>
</tr>
<tr>
<td>L2</td>
<td>23</td>
<td>rt</td>
<td>28</td>
<td>21</td>
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<tr>
<td>L3</td>
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<td>rt</td>
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<tr>
<td>L4</td>
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<td>18</td>
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<tr>
<td>L7</td>
<td>20</td>
<td>rt</td>
<td>29</td>
<td>21</td>
<td>R</td>
</tr>
</tbody>
</table>

Again the activity of all the ligands was around 30% conversion. The highest enantioselectivity achieved was 21% for L2 and L7 and the lowest was 15% for L3. There was no significant influence from the presence or absence of R groups at the stereocentres of the amino acid and amino alcohol portions of the ligands on the activities and selectivities of the ligands.

Table 2.11 Ligands OX3-OX5 used in the Ru-catalyzed transfer hydrogenation of acetophenone

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Time (h)</th>
<th>Temperature (° C)</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
<th>R/S</th>
</tr>
</thead>
<tbody>
<tr>
<td>OX3</td>
<td>24</td>
<td>Rt</td>
<td>24</td>
<td>25</td>
<td>R</td>
</tr>
<tr>
<td>OX4</td>
<td>24</td>
<td>Rt</td>
<td>29</td>
<td>19</td>
<td>R</td>
</tr>
<tr>
<td>OX5</td>
<td>23</td>
<td>Rt</td>
<td>32</td>
<td>27</td>
<td>R</td>
</tr>
</tbody>
</table>

Ligands OX3-OX5 were applied to the same transfer hydrogenation reaction. The results are shown in Table 2.11. The conversions achieved by the oxazoline ligands OX3-OX5 were again around 30%. The enantioselectivities were slightly higher than the tripeptide ligands L1-L7. The highest ee was 27% given by OX5.
Adolfsson proposed a mechanism for the reaction for his similar ligands. We can argue that the mechanism of reaction for our ligands would be similar. In our reaction mechanism scheme (Fig 2.26) we propose that two of the sites (alcohol and amide) are deprotonated by the isopropoxide base present in the ATH reaction mixture. The lactam NH binds in a neutral fashion. If the lactam NH was also deprotonated an inactive anionic ruthenium complex would be formed.

As the reaction proceeds, an alkali metal alkoxide interacts with the catalyst. The release of the ligand alkoxide coordinating to ruthenium allows the alkali metal ion to be transferred to the oxygen of the ligand, while the hydride is transferred to the now vacant coordination site on the ruthenium leading to 69. The acetophenone enters the coordination sphere of the bimetallic catalyst through attraction by the Lewis acidic sodium ion, and once it coordinates, transfer of the hydride to the activated substrate can occur via the transition state shown and the cycle is completed by proton transfer from the 2-propanol to the sodium salt of the product. The structure of the postulated transition state particularly the CH-π interaction explains the stereoselectivity achieved as it stabilises the transition state for the transfer of the hydride.89
Figure 2.26
2.4.4 Asymmetric Allylic Substitution Reactions

With the desired ligands in hand, we turned our attention to the task of probing the performance of the ligands in benchmark reactions for AAS and NHK reactions.

The prepared ligands were initially applied to a variety of asymmetric allylic substitutions namely Pd and Mo catalyzed allylic alkylations and Nozaki-Hiyama-Kishi allylations, in order to investigate the level of stereocontrol that they could induce in those reactions.

2.4.4.1 Overview of Asymmetric Allylic Substitution reactions

Transition-metal-catalyzed asymmetric allylic substitution (AAS) is one of the most efficient and most versatile methods for enantioselective C-C and C-heteroatom bond formation. The search for new chiral ligands and catalyst systems which afford high enantiomeric excesses (ee) in this reaction is a continuing area of research. The specific name of the transformation in question is denoted according to the type of nucleophile used in the reaction, i.e., alkylation or amination.

The Tsuji-Trost reaction is the name given to the alkylation of allylic substrates by stabilized carbanions, such as malonates. The reaction was first reported by Tsuji et al. in 1965 using pre-formed (η3-allyl)Pd complexes. Thereafter, the reaction was further developed by Trost et al. using additional phosphine ligands, and later the asymmetric version of the reaction was reported. Trost and Strege developed the first catalytic AAS reaction in 1977 with the DIOP ligand achieving good enantioselectivity. Since then, this transformation has been further developed achieving high enantioselectivities (>90% ee) with a large range of substrates. A wide range of transition metals have been used to form the active catalytic complexes in these reactions, palladium being the most common, followed closely by molybdenum. Typically, acetates and carbonates are used as the leaving groups (X) (Scheme 2.34).
Scheme 2.34 General outline of the allylic alkylation reaction

**Mechanism**

The following briefly describes the catalytic cycle for the palladium-catalyzed reaction. Palladium(0) is generated *in situ* from palladium(II) and a ligand. The metal coordinates to an alkene, giving the \( \eta^2 - \pi \)-allyl-Pd(II)-L\(_2\) complex. Oxidative addition occurs, expelling the leaving group, and a \( \eta^3 - \pi \)-allyl-Pd(II)-L\(_2\) complex is formed. The nucleophile adds to the proximal carbon of the allyl group regenerating the \( \eta^2 - \pi \)-allyl-Pd(II)-L\(_2\) complex. The product alkene dissociates from the palladium complex, resulting in completion of the reaction and the catalytic cycle can begin again (Fig. 2.27).  

![General mechanism of a Pd catalyzed AAS reaction](image)

During the catalytic cycle, Pd(II) prefers square planar geometry and Pd(0) can either be trigonal or tetrahedral. Since two coordination sites are used by the allyl moiety, there remain two available sites for the ligand. The ligands employed may be bidendate or monodentate. If a non-symmetrical oxidative addition product is involved, Pd
favours nucleophilic attack at the least sterically hindered allyl terminal. This least sterically hindered terminal is often unsubstituted which results in an achiral, linear product.\(^9\)

The molybdenum-catalyzed allylic substitution is similar to that of the palladium-catalyzed version. One major difference between them is apparent when non-symmetrical allyl substrates are used, e.g. \(70\), where palladium prefers nucleophilic attack at the least sterically hindered allyl terminal, forming a linear product \(71\). On the other hand, molybdenum shows the opposite regioselectivity, affording the branched chiral product \(72\) (Scheme 2.35).

\[
\text{Scheme 3.35 The molybdenum-catalyzed allylic substitution}
\]

The bis(picolinamide) ligand \(73\) reported by Trost (Fig. 2.28) has been employed successfully as part of a catalytic molybdenum complexes used in asymmetric allylic substitution reactions (Scheme 2.36).\(^8,9\) Numerous derivatives have been synthesised to probe its structure–behaviour relationship, and it has been shown that only one pyridine ring or picolinamide unit is required for the formation of an active catalytic complex.\(^10\)

Kocovshy et al. demonstrated that “one chiral centre in the (ligand) scaffold is sufficient to determine the sense of chiral environment at the metal”\(^1\).\(^1\)

\[
\text{Figure 2.28 Trost Ligand used as part of catalytic molybdenum complexes used in asymmetric allylic substitutions}
\]
Inspired by the success of bis(picolinamide) ligand 73 in molybdenum-catalysed asymmetric allylic substitution reactions, a former researcher in our group, Dr. Lorraine Bateman, developed a novel set of structurally related chiral diamide ligands 77 and 78 (Fig. 2.29), and successfully applied them to an asymmetric allylic substitution reaction. A palladium complex of one of the diamide ligands achieved enantioselectivities of up to 93% in the allylic alkylation of (rac)-1,3-diphenyl-3-acetoxyprop-1-ene (Scheme 2.37).\(^\text{10}\)

![Scheme 2.36](image)

**Figure 2.29**

**Scheme 2.37**

\[79\] to \[80\] with up to 93% ee, 72% yield
The most widely used, and indeed the most successful, substrates used in allylic substitutions have been 1, 3-symmetrical allylic acetates. The reaction of dimethyl malonate with substrate 79 has been widely used as a ‘benchmark’ reaction, in order to evaluate novel ligand transition metal complexes for asymmetric substitution reactions (Scheme 2.38). In this reaction an identical, symmetrical π-allyl intermediate forms, from both enantiomers of the substrate. The metal binds in a η³-fashion to the allyl group and the nucleophilic addition step is the enantio-discriminating step.

![Scheme 2.38](image)

Unsymmetrical allylic substrates are more demanding in terms of enantioselectivity and regioselectivity than substrates that form π-allyl complexes, and so offer a more difficult challenge in terms of evaluating novel ligand complexes. Molybdenum is typically the metal of choice for such systems as Pd complexes favour substitution at the least substituted terminal resulting in an achiral product. Molybdenum complexes afford branched products in high yields, enantio- and regioselectivity from either linear or branched substrates. Following the excellent results which the Trost ligand 73 achieved in substitution reactions of the type shown in Scheme 2.36, and the results achieved by Bateman, we decided to apply our C₁-symmetric amido-oxazoline ligands to reactions of the type shown above. To that end we began by synthesizing the substrates for the Pd- and Mo-catalyzed allylic alkylation test reactions.
2.4.4.2 Synthesis of Substrates for Allylic Substitution Reactions

Synthesis of \((\text{rac})-(E)-1,3\text{-diphenyl-3-acetoxyprop-1-ene}\)

![Chemical structure](image)

Substrate 79 was synthesized in two steps from trans-chalcone 81. Trans-chalcone 81 was reduced by sodium borohydride, in the presence of cerium(III) trichloride heptahydrate, by a Luche reduction reaction. The reaction reduces an enone to an allyl alcohol, in a 1,2 addition, with competing 1,4 addition being suppressed. The selectivity can be explained in terms of HSAB theory or Pearson Acid Base Concept. Carbonyl groups require hard nucleophiles for 1,2-addition. The hardness of the borohydride is increased by replacing hydride groups with alkoxide groups, a reaction catalyzed by the cerium salt, by increasing the electrophilicity of the carbonyl group. This is selective for ketones because it is more Lewis basic. The reaction was stirred at room temperature for 16 h. An acidic work-up afforded the crude alcohol 82 (Scheme 2.39). The crude product was purified by column chromatography on silica gel, to give 82 in...
64% yield. The structure of 82 was confirmed by comparison with published spectroscopic data.\textsuperscript{102}

Alcohol 82 was acetylated using acetic anhydride in pyridine, and a catalytic amount of DMAP. The reaction was stirred at room temperature for 16 h. The crude product was purified by column chromatography on silica gel, to give the required substrate (rac)-(E)-1,3-diphenyl-3-acetoxyprop-1-ene 79 in 87% yield. The structure of the product was confirmed by comparison with published spectroscopic data.\textsuperscript{10}

**Phenyl-prop-2-enyl methyl carbonate**

![Scheme 2.40](image)

Methyl carbonate 74 was synthesized by stirring a mixture of cinnamyl alcohol 83, potassium carbonate and methyl chloroformate in DCM overnight followed by reflux for 4 h (Scheme 2.40). The reaction was quenched with water and the organic layer extracted with DCM and the volatiles removed in vacuo. The crude product obtained from the reaction was purified by column chromatography, affording 74 as clear oil in 36% yield. The purity and structure of the compound were confirmed by comparison with spectral data in the literature.\textsuperscript{103,104}
2.4.4.3 Pd Catalyzed Allylic Alkylation Reactions

The first reaction studied was the allylic alkylation of diphenyl acetoxy propene with the anion derived from dimethyl malonate.

![Chemical structure](image)

Under Schlenk conditions 15 mol% of ligand and 10 mol% of Pd$_2$(dba)$_3$ were heated in solvent for 2 h. Separately, the nucleophile was prepared from dimethyl malonate and sodium hydride in toluene at 85 °C. The mineral oil in the sodium hydride was removed beforehand by washing with dry hexane. To the nucleophile, the substrate 79 and the active catalyst were added by a gas tight syringe. The reaction was stirred for 48 h, at 40 °C when the reaction took place in CH$_2$Cl$_2$, and at 85 °C when the reaction took place in toluene. This led to the formation of the substitution product 80. A $^1$H NMR spectrum was recorded of the crude product to determine the % conversion. The % conversion was calculated by comparing the amount of unreacted starting material 79 [signal at 2.14 (3H)] to the amount of product 80 formed [signal at 4.27 (1H)] in the $^1$H NMR spectrum. In the case where there was conversion to the desired product achieved the enantiomeric excess of the product from these reactions was determined by chiral HPLC analysis (Daicel Chiralcel OD). The product was purified by column chromatography using ethyl acetate: petrol (95:5). The product could be isolated for the reaction using ligand OX3, with a conversion of 12% was achieved. There was no enantiomeric induction for this ligand however. The results of the catalytic reactions shown in scheme 2.41 are in table 2.12 below.
Table 2.12 Palladium catalyzed allylic alkylation using ligands OX1-OX3

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Solvent</th>
<th>Temperature (° C)</th>
<th>Conversion (%)</th>
<th>ee (%) R/S</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Ligand 1" /></td>
<td>Toluene</td>
<td>85</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><img src="image2.png" alt="Ligand 2" /></td>
<td>Toluene</td>
<td>85</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><img src="image3.png" alt="Ligand 3" /></td>
<td>Toluene</td>
<td>85</td>
<td>12</td>
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2.4.4.4 Molybdenum Complex Catalyzed Asymmetric Allylic Alkylation of 3-phenyl-prop-2-enyl methyl carbonate

Ligands OX1-OX3 were also applied to the molybdenum catalyzed asymmetric allylic alkylation of 3-phenyl-prop-2-enyl methyl carbonate with the anion of dimethyl malonate.

![Scheme 2.42](image4.png)

Scheme 2.42

The Mo complex catalyzed asymmetric allylic alkylation of 3-phenyl-prop-2-enyl methyl carbonate 74, with sodiodimethyl malonate nucleophile was conducted
according to the general procedure F. The active catalyst was formed from the reaction of 15 mol% ligand and 10 mol% Mo(CO)$_6$ in toluene at 85°C for 2 h. During this time the solution changed to a bright orange colour. Separately the nucleophile was formed by deprotonation of dimethyl malonate with sodium hydride affording sodiodimethyl malonate. The mineral oil in the sodium hydride was removed beforehand by washing with dry hexane. The substrate 74 was added to the mixture containing the nucleophile, before addition of the active catalyst via a gastight syringe. The catalyst and malonate anion mixture was only partially soluble in toluene and formed a gel, which made it impossible to form a homogenous solution on addition of the substrate and catalyst mixture.

In the case of ligand OX1, no conversion to the products was achieved. A number of steps were taken to optimize the reaction procedure for evaluating the amido-oxazoline ligand complexes in the alkylation of 74. To improve the solubility of the sodiodimethyl malonate nucleophile, the toluene mixture was sonicated before transfer to the reaction vessel. This proved unsuccessful, as the solids remained only partially soluble.

Sodium hydride was suspended in THF before addition of dimethyl malonate (1.1 eq.), and the resulting gelatinous mixture was stirred at room temperature overnight before heating to reflux for 6 h. This preformed salt was applied to substitutions of 74 catalyzed by Mo(CO)$_6$-ligand complexes formed from 10 mol% Mo(CO)$_6$ and 15 mol% ligand. The reaction was then carried out by suspending the pre-formed nucleophile in toluene, and sonicating for 30 mins at rt. It was then heated to 85°C before addition of substrate, followed by the catalyst complex. The reactions were carried out for 48 h at 85°C.

Unfortunately, there was negligible conversion to the desired products despite the efforts made to improve the reaction procedure. The same experiment was repeated three times with no conversion each time. Ligands OX2 and OX3 were also applied to the reaction, and again gave no conversion. The other novel ligands synthesized in this project were not applied to the reaction due to the poor results of these oxazoline ligands in this reaction.
2.4.4.5 Overview of the Nozaki-Hiyama-Kishi Allylation Reaction

The asymmetric allylation of carbonyl substrates has proven to be a powerful method for the synthesis of enantiomerically enriched homoallylic alcohols. There are a number of very efficient methods for this transformation, employing various transition metals and allyl sources such as allyl tins, boranes, and silanes.

In the late 1970s, Nozaki and Hiyama demonstrated that Cr(II) salts could mediate the addition of allylic halides to aldehyde and ketone substrates (Scheme 2.43). Further modifications were made by Kishi and co-workers during their synthesis of palytoxin in 1986, warranting the addition of Kishi's name to what is now coined the Nozaki-Hiyama-Kishi (NHK) reaction. At its inception, this transformation was performed with super-stoichiometric amounts of toxic Cr salts. This factor made the application of this methodology impractical from an asymmetric aspect, where large amounts of a chiral ligand would be required.

Scheme 2.43 Addition of allylic halides to aldehydes and ketones

A renaissance of the reaction was sparked in 1996 when Fürstner and Shi disclosed a method to render the process catalytic in Cr through the addition of Mn(0) as a sacrificial reductant and trimethylsilyl chloride (TMSCl) as a turnover reagent (Fig. 2.30). The accepted catalytic cycle shown in Fig. 2.30 begins with two equivalents of a Cr(II) salt (A) which undergo two single electron transfer reactions with the allylic halide (B). One equivalent of Cr(III)-halide (C) and an equivalent of a Cr(III)-allyl (D) is formed in this step. The allyl species D then coordinates and delivers the allyl fragment to the carbonyl to form Cr-alkoxide E. Under the original NHK conditions (stoichiometric Cr) both C and E were final resting states of the Cr metal. The addition of TMSCl to the reaction mixture allows for the substitution of a weaker Cr-O bond (102 kcal/mol) for a stronger Si-O bond (191 kcal/mol), delivering the silyl protected product F and an 61-94% yield.
additional equivalent of Cr-halide (C). In order to render the reaction catalytic, Mn(0) is added, and an equivalent of Mn reduces two equivalents of Cr salt C to regenerate the active Cr(II) species.

**Figure 2.30** Fürstner’s modification made to the NHK allylation of aldehydes render the reaction catalytic in Cr

Fürstner’s modifications facilitated the development of a number of catalytic asymmetric Cr(II) processes employing various asymmetric ligands, which were used primarily in the allylation of aldehydes. Shown in Fig. 2.31 are a number of chiral ligands that have been used in asymmetric NHK reactions over the past fifteen years.\textsuperscript{116-121} Of particular interest to our group was the application of amino-oxazoline based ligands to the asymmetric addition of allyl halides to aldehydes under NHK conditions.\textsuperscript{122} Kishi and Nakada independently demonstrated that their amino-oxazoline systems could furnish good yield and enantioselectivity in the asymmetric allylation of aldehydes under NHK conditions (Fig. 2.31).\textsuperscript{118,123}
Figure 2.31 Ligands that have been used in asymmetric NHK reactions over the past fifteen years.116-121
Sigman et al. applied all four diastereoisomers of the modular proline-oxazoline ligand 84a-d (Fig. 2.32) in the Nozaki-Hiyama-Kishi (NHK) allylation of benzaldehyde with allyl bromide, with ligand 84d affording the highest enantiomeric excess of 94% (R). This ligand was then applied in the allylation of a range of aldehydes (Scheme 2.44), with excellent yields and enantioselectivities reported, particularly for aryl aldehydes (Table 2.13).124

![Image of ligands 84a-d](image)

**Figure 2.32** Sigman’s oxazoline ligands used in NHK allylation of aldehydes

**Scheme 2.44** The Nozaki–Hiyama allylation of aldehydes as described by Sigman and co-workers

**Table 2.13** Nozaki–Hiyama allylation of aldehydes

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<tr>
<td>C₆H₅</td>
<td>89</td>
<td>94</td>
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<tr>
<td>4-BrC₆H₄</td>
<td>73</td>
<td>90</td>
</tr>
<tr>
<td>4-MeOC₆H₄</td>
<td>98</td>
<td>89</td>
</tr>
<tr>
<td>2-Furyl</td>
<td>61</td>
<td>92</td>
</tr>
<tr>
<td>PhCH₂CH₂</td>
<td>98</td>
<td>48</td>
</tr>
<tr>
<td>C₆H₁₁</td>
<td>64</td>
<td>87</td>
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</tbody>
</table>
The reaction was conducted according to General Procedure D. Three ligands, OX1, OX2 and OX3 were applied to the reaction. Unfortunately no conversion was achieved with any of the three ligands used. The reaction was run without a ligand present to determine the retention times of the enantiomers of the product. There was a conversion of 73% and the retention times of the racemic product were found to be 25.1 min and 27.3 mins for the enantiomers using a Daicel Chiralcel OD HPLC column. The specific retention times for the R- and S- enantiomers were not determined. The results are outlined in table 2.14. The reaction methodology is outlined below.

The reaction was carried out by first adding anhydrous chromium (III) chloride and manganese were added simultaneously to the solvent mixture. The resulting suspension was allowed to stand at room temperature for approximately 30 minutes. The mixture was stirred vigorously under an atmosphere of nitrogen for 1 h resulting in a green reaction mixture. DIPEA was added, followed by the ligand (12 mol %). This was stirred at room temperature for 1 hour prior to the addition of allyl bromide with the resulting Cr(III) allyl solution being stirred for a further 1 hour. The reaction was initiated by the addition of benzaldehyde and chlorotrimethylsilane and stirred under an atmosphere of nitrogen at room temperature for 16 hours. After work-up the % conversion of the reaction was determined from the $^1$H NMR spectrum of the crude product by measuring the ratio of aldehyde to product and assuming that all aldehyde consumed went to product.
As was the case with the Pd-catalyzed allylic substitution reactions, there was no conversion to the desired products despite the efforts made to improve the reaction procedure. The same experiment was repeated three times with each of the oxazoline ligands OX1-OX3. The other novel ligands synthesized in this project were not applied to the reaction due to the poor results of these oxazoline ligands in this reaction. The reaction was tested in the absence of a ligand and resulted in a conversion of 61% to the allyl product 85 (scheme 2.45), indicating that these oxazoline amide ligands are unsuitable for this reaction type. This was unexpected due to the structural similarity between our ligands and Sigman’s ligands.\textsuperscript{124}

Table 2.14

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Solvent</th>
<th>Temperature (° C)</th>
<th>Conversion (%)</th>
<th>ee (%) R/S</th>
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<tr>
<td>---</td>
<td>THF/MeCN</td>
<td>Rt</td>
<td>61</td>
<td>ND</td>
</tr>
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<td>![Ligand Image]</td>
<td>THF/MeCN</td>
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<td>THF/MeCN</td>
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<td>![Ligand Image]</td>
<td>THF/MeCN</td>
<td>rt</td>
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Chapter 3

Experimental

3.1 General experimental conditions

Unless otherwise stated, all procedures were carried out under an atmosphere of nitrogen. All solvents were distilled prior to use as follows: dichloromethane and acetonitrile were distilled from calcium hydride; toluene and tetrahydrofuran were distilled from sodium benzophenone ketyl.

Organic phases were dried using anhydrous magnesium sulphate. All chemicals were purchased from Aldrich Chemical Company or Acros Organics and were used without further purification. All asymmetric reactions were carried out using standard Schlenk line techniques and all Schlenk tubes were heat dried under vacuum to remove moisture prior to use.

Melting points were measured on a Stuart Scientific SMP3 apparatus and are uncorrected. IR spectra were measured on a Perkin Elmer Spectrum One FT-IR, where liquid samples were measured as thin films and solids were measured directly. Optical rotations were measured on a Unipol L1000 polarimeter at 589 nm (Na) in a 10 cm cell; concentrations (c) are expressed in g/1000 ml. \([\alpha]_D\) is the specific optical rotation of a compound and is measured in units of \(10^{-1}\text{deg cm}^2\text{g}^{-1}\). Thin layer chromatography (TLC) was carried out on pre-coated silica gel plates (Merck 60 F254); column chromatography was carried out using Apollo Scientific silica gel 40-63 micron. Visualisation was achieved by UV (254 nm) light detection, vanillin stain or ninhydrin stain. Elemental analysis was performed on a Perkin Elmer 2400 analyser.

High resolution mass spectra were carried out using electron spray ionisation (ESI) on a Walters LCT Premier XE spectrometer by manual peak matching. \(^1\)H NMR (400 MHz) and \(^{13}\)C NMR (100 MHz) were recorded on a JEOL ECX-400 NMR spectrometer. All spectra were recorded at probe temperatures (~20 °C) in deuterated chloroform (CDCl\(_3\)) unless otherwise stated, using tetramethylsilane (TMS) as an
internal standard. Chemical shifts are expressed in parts per million (ppm) and coupling constants in Hertz (Hz), unless indicated all coupling constants represent 3 bond couplings.

$^{13}$C NMR spectra were assigned with the aid of DEPT experiments. Compounds which were assigned with the aid of DEPT experiments were assigned by identifying both the carbon, (CH$_3$, CH$_2$, CH or C), and also the atom position of the carbon, for example, (CH, CH$_2$CHOH). For compounds where DEPT spectra were not recorded; the carbon spectra were assigned by comparison to analogous compounds. HMQC (Heteronuclear Shift Multiple Quantum Coherence) establishes links between protons and attached carbons. COSY (Correlated Spectroscopy) established links between protons and attached carbons.

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

*R*-Phenylglycinol 11a

![Chemical Structure of R-Phenylglycinol](image)

A solution of iodine (12.61 g, 49.7 mmol) in THF (100 ml) was added slowly over 1 h to a stirring suspension of sodium borohydride (4.51 g, 0.119 mol) in THF (50 ml) at 0 °C in a 500 ml round bottomed flask fitted with a condenser and under a stream of nitrogen gas. When the addition of iodine was complete (*D*-phenylglycine (7.51 g, 49.7 mmol) was added in one portion and the reaction mixture was allowed to warm to room temperature under \(N_2\) and then refluxed for 20 h. The reaction mixture was then cooled in an ice-salt bath and water (40 ml) was added cautiously (evolution of \(H_2\) gas) until the mixture changed from a milky suspension to a homogeneous solution. The volatiles were removed *in vacuo* to leave a white paste, which was dissolved in KOH solution (20 %, 200ml), and stirred at 80 °C for 1h. The solution was then cooled and extracted with EtOAc (3 x 200 ml). The organic layers were combined, dried, filtered and concentrated *in vacuo*, affording 11 as a white solid (6.81 g, 74%) which was sufficiently pure to use in subsequent reactions; mp 72-76 °C (lit.\(^1\), 75-77 °C); \([\alpha]_D\) -32.5 (c 0.76, 1 N HCl, 20 °C) [lit.\(^1\), \([\alpha]_D\) -32.0 (c 0.76, 1 N HCl, 20 °C)]; IR (solid) \(\nu_{\text{max}}/\text{cm}^{-1}\) 3328 br, 2910, 2835; \(\delta_H\) (400 MHz, CDCl\(_3\)) 2.05 (3H, br s, \(NH_2\) and \(OH\)), 3.50 (1 H, dd, \(J_{11}, J_8\), one of \(\text{CH}_2\text{OH}\)), 3.68 (1 H, dd, \(J_{11.0}, J_4.0\), one of \(\text{CH}_2\text{OH}\)), 4.0 (1 H, dd, \(J_{8.3}, J_{4.6}\), \(\text{CHNH}_2\)), 7.17-7.32 (5 H, m, ArCH); \(\delta_C\) (100 MHz, CDCl\(_3\)) 57.4 (\(\text{CHNH}_2\)), 68.0 (\(\text{CH}_2\text{OH}\)), 126.5 (2 x ArCH), 127.5 (1 x ArCH), 128.7 (2 x ArCH), 142.7 (ArC)
An oven-dried, 1-L, three-necked flask equipped with a magnetic stirrer, a condenser and a nitrogen bubbler was flushed with nitrogen, and then charged with lithium aluminium hydride (8.55 g, 0.225 mol) in THF (300 ml). The mixture was cooled (0 °C, ice-water bath) and L-valine (17.64 g, 0.151 mol) was added portion wise (under gentle flow of nitrogen) over a 10-min period so as not to produce too vigorous an evolution of hydrogen. After the addition is complete, the ice bath was removed, and the reaction mixture was warmed to room temperature and then refluxed for 16 hr. The reaction mixture was then cooled again (0 °C, ice-water bath) and diluted with diethyl ether (200 ml). The reaction was quenched by sequential addition of water (10 ml, over 30 min), aqueous 15% NaOH (10 ml, over 20 min), and water (30 ml, over 30 min). The solution was stirred for 30 min and the white precipitate was filtered. The filter cake was washed with diethyl ether (3 × 30 ml) and the organic filtrates were combined, dried with anhydrous magnesium sulfate, and concentrated *in vacuo*. Bulb to bulb distillation of the residue under vacuum (0.15 mm Hg, 90 °C) afforded 11b (13.1 g, 83.4%) as a clear viscous liquid. \([\alpha]_D + 18.5 \ (c 2.0 \ \text{EtOH}, 20 ^\circ \text{C}) \ [\text{lit.}^2, [\alpha]_D +14.6 \ (c 1.455, \text{neat}, 20 ^\circ \text{C})]; \ \text{IR} \ \nu_{\text{max}}/\text{cm}^{-1} \ 3378 \ \text{br}, 2962; \ \delta_H(400 \ \text{MHz, CDCl}_3); 0.91 \ [3 \ H, d, \ J 5.5, \text{one of CH(CH}_3)_2], 0.94 \ [3 \ H, d, \ J 5.5, \text{one of CH(CH}_3)_2], 1.55 \ [1 \ H, \text{octet, } J 6.9, \ CHCH(CH}_3)_2], 1.80 \ (3 \ H \ \text{br s, NH}_2 \ \text{and OH}); 2.52-2.59 \ (1 \ H, \text{m, CH(NH}_2)_2], 3.28 \ (1 \ H,\text{dd, } J -10.3 \ J 8.7, \text{one of CH}_2\text{OH}), 3.64 \ (1 \ H, \text{dd, } J 10.5 \ J 4.1, \text{one of CH}_2\text{OH}); \ \delta_C (100 \ \text{MHz, CDCl}_3); 18.5[\text{one of CH(CH}_3)_2], 19.4 \ [\text{one of CH(CH}_3)_2], 31.6 \ [\text{CH(CH}_3)_2], 58.6 \ \text{CH(NH}_2)_2], 68.1 \ \text{CH}_2\text{OH}).
S-Phenylalaninol 11c

S-Phenylalaninol was prepared from L-phenylalanine (10.0 g, 60.5 mmol), sodium borohydride (5.5 g, 0.145 mmol) and iodine (15.4 g, 60.5 mmol) by the same procedure used for R-phenylglycinol.1 S-phenylalaninol was isolated as a white solid 11c (7.41 g, 81%); mp 89-92 °C (lit.1, 90-93 °C); [α]D -22.3 (c 1.2, 1 M HCl, 20 °C) [lit.1, [α]D -22.0 (c 1.2, 1 M HCl, 20 °C)]; IR (solid) υmax/cm⁻¹ 3356, 3297, 1642, 697; δH (400 MHz, CDCl₃); 1.92 (3 H, br s, NH₂ and OH), 2.52 (1 H, dd, J 13.5, J 8.7, one of ArCH₂CH), 2.79 (1 H, dd, J 13.5, J 5.3, one of ArCH₂CH), 3.08-3.15 (1 H, m, CH₂CHCH₂); 3.38 (1 H, dd, J 10.6, J 7.1, one of CHH₂OH), 3.63 (1 H, dd, J 10.6, J 3.9, one of CHH₂OH), 7.14-7.35 (5 H, m, ArCH); δC (100 MHz, CDCl₃); 40.7 (PhCH₂), 54.3 (CHNH₂), 66.2 (CH₂OH), 126.5 (1 x ArCH), 128.7 (2 x ArCH), 129.3 (2 x ArC).

(S)-Leucinol 11d

The compound was prepared from L-leucine (10.0 g, 60.5 mmol), sodium borohydride (5.5 g, 145 mmol) and iodine (15.4 g, 60.5 mmol) by the same procedure used for 11a¹ and isolated as a colourless oil 11d (7.41 g, 81%); [α]D + 4.3° (c 1.2, MeOH, 20 °C) [lit.3, [α]D + 4.1 (c 0.3, MeOH, 20 °C)]; IR (solid) υmax/cm⁻¹ 3278 br s, 2955, 2912, 1588; δH (400 MHz, CDCl₃); 0.88 [3 H, d, J 6.4, one of CH(CH₃)₂], 0.91 [3 H, d, J 6.6, one of CH(CH₃)₂], 1.15-1.20 [2 H, m, CH₂ CH(CH₃)₂], 1.64-1.74 [1 H, m, CH(CH₃)₂], 2.85-2.93 (1 H, m, NH₂CHCH₂); 3.21 (1 H, dd, J 10.6, J 8.0, 1 H of CHH₂OH), 3.63 (1 H, dd, J 10.5, J 3.9, 1 H of CHH₂OH); δC (100 MHz, CDCl₃)
22.2 [one of CH(CH$_3$)$_2$], 23.4 [one of CH(CH$_3$)$_2$], 24.7 [CH(CH$_3$)$_2$], 43.9 [CH$_2$CH(CH$_3$)$_2$], 50.6 (NH$_2$CH), 67.2 (CH$_2$OH).

Methyl-(S)-2-pyrrolidinone-5-carboxylate 10$^4$

![Methyl-(S)-2-pyrrolidinone-5-carboxylate 10$^4$](image)

Amberlyst 15 resin (wet) (5.0 g) was added to a solution of L-pyroglutamic acid (12.92 g, 0.1 mol) in methanol (50 ml). The mixture was refluxed for 24 h, cooled in an ice-water bath, filtered and concentrated in vacuo, affording the product as yellow oil which was sufficiently pure to be used in future reactions. (13.50 g, 94%), [α]$_D$ -8.5 (c 1, DCM, 20 ºC) [lit.$^4$ [α]$_D$ – 8.4 (c 1, DCM, 20 ºC)]; IR $\nu_{max}$/cm$^{-1}$ 3369, 1748, 1699, 1220, $\delta$ $H$ (400 MHz, CDCl$_3$) 2.18-2.48 (4 H, m, CH$_2$CH$_2$), 3.74 (3 H, s, OCH$_3$), 4.23 [1 H, m, CH$_2$CH(O)], 7.25 (1H, br s, NH); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 24.8 [C(O)CH$_2$CH$_2$], 29.4 [C(O)CH$_2$CH$_2$], 52.7 (CHNH), 55.6 (OCH$_3$), 172.6 [C(O)OCH$_3$], 178.5 [NHC(O)].

(S)-5-(Hydroxymethyl)-2-pyrrolidone 28$^4$

![Sodium borohydride (3.83 g, 0.10 mol) was added in portions, over 15 min, to a](image)

Sodium borohydride (3.83 g, 0.10 mol) was added in portions, over 15 min, to a solution of methyl-(S)-2-pyrrolidinone-5-carboxylate (13.81 g, 0.96 mol) in ethanol (130 ml) and the mixture stirred for 16 h. The reaction was quenched with dilute HCl (10 %, 25 ml) and the solvents were removed in vacuo. The crude product was purified by column chromatography (ethyl acetate: methanol; 90:10) affording 28 as a
colourless gum (9.42 g, 87 %); [α]D + 29.3 (c 5, EtOH, 20 ºC) [lit.4, [α]D + 29.2 (c 5, EtOH, 20 ºC); IR νmax/cm⁻¹ 3325 br , 1670 , 1423 w; δH (400 MHz, CDCl₃) 1.74-1.85 [1 H, m, one of C(O)CH₂CH₂], 2.12-2.22 [1 H, m, one of C(O)CH₂CH₂], 2.29-2.41 [1 H, m, one of C(O)CH₂CH₂], 3.46 (1 H, dd, J 11.2, J 7.3, one of CHCH₂OH), 3.69 (1 H, dd, J 11.2, J 3.2, one of CHCH₂OH), 7.10 (1 H, br s, NH); δC (100 MHz, CDCl₃) 22.6 [C(O)CH₂CH₂], 29.7 [C(O)CH₂CH₂], 37.6 [S(O)₂CH₃], 53.5 (CH₂OMs), 71.1 (CH), 179.7 [C(O)NH].

(2S)-5-Oxopyrrolidin-2-yl methyl methanesulfonate 29⁴

Methanesulfonyl chloride (6.60 ml, 85.4 mmol) and triethylamine (15.7 ml, 112 mmol) were added to a suspension of (S)-5-(hydroxymethyl)-2-pyrrolidone (6.47 g, 56.3 mmol) in DCM (40 ml) at 0 ºC. The reaction mixture was allowed to reach room temperature over 4 h, at which stage water (2 ml) was added and the reaction mixture concentrated in vacuo. The crude product was purified by column chromatography (ethyl acetate-methanol, 92:8) affording the desired product 29 as a colourless solid (9.01 g, 83 %); m.p. 74-77 ºC (lit.⁴ 75-77 ºC); [α]D + 15.2 (c 1, EtOH, 20 ºC) [lit.⁴, [α]D + 15.7 (c 1, EtOH, 20 ºC)]; IR νmax/cm⁻¹ 3321, 2928, 1668, 1307, 1192; δH (400 MHz, CDCl₃) 1.81-1.91 [1 H, m, one of C(O)CH₂CH₂], 2.24-2.32 [1 H, m, one of C(O)CH₂CH₂], 2.33-2.43 [2 H, m, C(O) CH₂CH₂], 3.06 [3 H, s, OS(O)₂CH₃], 3.96-4.02 (1 H, m, NHCH), 4.08 (1 H, dd, J 10.1, J 6.8, one of CHCH₂OMs), 4.24 (1 H, dd, J 10.3, J 3.9, one of CHCH₂OMs), 6.91 [1 H, br s, C(O)NH]; δC (100 MHz, CDCl₃) 22.6 [C(O)CH₂CH₂], 29.7 [C(O)CH₂CH₂], 37.6 [S(O)₂CH₃], 53.5 (CH₂OMs), 71.1 (CH), 178.9 [C(O)NH].
(S)-5-(Azidomethyl)-2-pyrolidone 30

(2S)-5-Oxopyrrolidin-2-yl methyl methanesulfonate (0.94 g, 4.9 mmol) and sodium azide (0.87 g, 13.5 mmol) were dissolved in water (8.5 ml) in a 10 ml Ace pressure tube, which was then flushed with nitrogen gas and tightly sealed. The reaction was carried out under temperature controlled (130 °C) microwave irradiation for 30 min. The solution was then cooled to room temperature and extracted with EtOAc (3 x 10 ml). The organic solution was dried with MgSO₄ and concentrated in vacuo, affording the desired product 30 as a yellow oil (0.65 g, 95%) which was sufficiently pure to use in further reactions. \([\alpha]_D^\circ + 72.1\ (c\ 5,\ \text{EtOH},\ 20\ ^\circ\text{C});\ \{\text{lit.}^4,\ [\alpha]_D^\circ + 72.8\ (c\ 1,\ \text{EtOH},\ 20\ ^\circ\text{C})\};\ \text{IR}\ \nu_{\text{max}}/\text{cm}^{-1}\ 3222,\ 2934,\ 2095,\ 1684;\ \delta_{\text{n}}(400\ \text{MHz, CDCl}_3)\ 1.77-1.86\ [1\ \text{H, m, one of C(O)CH}_2\text{C}(\text{CH}_2)_2],\ 2.21-2.45\ [3\ \text{H, m, C(O)CH}_2\text{CH}_2\text{ and one of C(O)CH}_2\text{CH}_2],\ 3.29\ (1\ \text{H, dd, J12.4, J7.6, one of CHCH}_2\text{N}_3),\ 3.47\ (1\ \text{H, dd, J12.4, J4.6, one of CHCH}_2\text{N}_3),\ 3.77-3.84\ (1\ \text{H, m, CHCH}_2\text{N}_3),\ 6.11\ [1\ \text{H, br s, C(O)NH}];\ \delta_{\text{C}}\ (100\ \text{MHz, CDCl}_3)\ 23.9\ [\text{C(O)CH}_2\text{CH}_2],\ 29.8\ [\text{C(O)CH}_2\text{CH}_2],\ 53.6\ (\text{CH, CHCH}_2\text{N}_3),\ 55.8\ (\text{CH},\ \text{CHCH}_2\text{N}_3),\ 178.6\ [\text{C(O)}].

(5S)-5-(aminomethyl)pyrrolidin-2-one 31

(S)-5-(Azidomethyl)-2-pyrolidone (5.13 g, 35.6 mmol) was dissolved in ethanol (100 ml) in a hydrogenator. 10 % Palladium on carbon (850 mg) was added to the solution.
The hydrogenator was flushed with nitrogen three times to remove oxygen before finally charging the vessel with a H₂ atmosphere (40 psi). The reaction was stirred at room temperature for 15 h and the mixture was then filtered through a plug of celite. The plug was washed with EtOAc (2 x 15 ml) (care taken to not let the catalyst go dry due to danger of fire) and the volatiles were removed in vacuo. The product was purified by column chromatography on silica gel using chloroform-methanol (90:10) as eluant, affording the product **31** as a yellow oil. (3.81 g, 93.8%); [\(\alpha\)]D \(+ 33.0\) \((c 2, \text{EtOH}, 20 ^\circ \text{C})\); IR \(\nu_{\text{max}}/\text{cm}^{-1} 3241, 2925, 1669; \delta_\text{H}(400\ \text{MHz, CDCl}_3) 1.62\ (2\ \text{H, br s, N}_2\text{H}) , 1.68-1.78\ [1\ \text{H, m, one of C(O)CH}_2\text{C}_2\text{H}], 2.14-2.37\ [2\ \text{H, m, one of C(O)CH}_2\text{CH}_2, \text{one of C(O)CH}_2\text{CH}_2], 2.63\ (1\ \text{H, dd, J 12.8, J 7.6, one of CHCH}_2\text{NH}_2), 2.83\ (1\ \text{H, dd, J 12.8, J 4.6, one of CHCH}_2\text{NH}_2), 3.60-3.69\ (1\ \text{H, m, CHCH}_2\text{NH}_2), 6.91\ [1\ \text{H, br s, C(O)NH}]; \delta_\text{C} (100\ \text{MHz, CDCl}_3) 24.3\ [\text{C(O)CH}_2\text{CH}_2], 30.2\ [\text{C(O)CH}_2\text{CH}_2], 47.4\ (\text{CHCH}_2\text{NH}_2), 56.9\ (\text{CHCH}_2\text{NH}_2), 178.7\ (\text{C=O}).

(\text{S})-\text{methyl 2-(5-oxopyrrolidine-2-carboxamido)acetate E1}

To a stirred suspension of L-pyroglutamic acid (7.05 g, 54.61 mmol) in DCM (100 ml) at 0 °C was added 1,3 dicyclohexylcarbodiimide (11.26 g, 54.61 mmol). After 30 min \(N\)-hydroxysuccinimide (6.28 g, 54.61 mmol) was added followed by a solution of glycine ethyl ester HCl (7.62 g, 54.61 mmol) and triethylamine (7.7 ml, 55.0 mmol) in acetonitrile (100 ml). The reaction was continued for 3 h and then the solvents were removed in vacuo. The residue was stirred in EtOAc (100 ml) and cooled at 0 °C for 30 mins. The precipitates were removed by filtration and then the solution was concentrated in vacuo. The product was purified by column chromatography on silica gel using EtOAc/Methanol as eluent (gradient elution), yielding the product **E1** as a white powder. (8.66 g, 74 %); mp: 120.0-121.3 °C; [\(\alpha\)]D -21.5° \((c = 1,\text{MeOH}, 20 ^\circ \text{C})\); IR (solid) \(\nu_{\text{max}}/\text{cm}^{-1} 3276, 3223, 1748, 1686, 1657; \delta_\text{H}(400\ \text{MHz, CDCl}_3) 1.28\ (3\ \text{H, t, J 7.1, OCH}_2\text{CH}_3), 2.18-2.60\ [4\text{H, m, C(O)CH}_2\text{CH}_2], 3.99\ [2\ \text{H, m, , NHCH}_2], 4.15\ (2
H, q, J 7.1, OCH$_2$CH$_3$), 4.26 (1H, m, CH$_2$CH$_2$CH), 6.68 [1 H, br s, one of C(O)NH], 6.88 [1H, br s, one of C(O)NH]; δ$_C$ (100 MHz, CDCl$_3$); 14.2 (CH$_3$, CH$_2$CH$_3$), 26 (CH$_2$, CH$_2$CH$_2$CH), 29.2 [CH$_2$, C(O)CH$_2$CH$_3$], 41.2 [CH$_2$NHCH$_2$C(O)], 57.0 (CH, CH$_2$CH$_2$CH), 61.8 [one of CH$_2$CH$_2$CH$_3$], 169.8 [one of CH$_2$CHC(O)NH or C(O)OCH$_2$CH$_3$], 172.6 [one of CH$_2$CHC(O)NH or C(O)OCH$_2$CH$_3$] 179.4 [NHC(O)CH$_2$CH$_2$CH]; HRMS (ES$^+$): found [M-H]$^-$ C$_9$H$_{13}$N$_2$O$_4$ 213.0878, requires 213.0880.

(S)-methyl-3-methyl-2-[(S)-5-oxopyrrolidine-2-carboxamido]butanoate E2

![Chemical structure](image)

To a stirred suspension of L-pyroglutamic acid (1.78 g, 13.77 mmol) in DCM (20 ml) at 0 ºC was added 1, 3 dicyclohexylcarbodiimide (3.0 g, 14.46 mmol). After 30 min $N$-hydroxybenzotriazole hydrate (2.32 g, 15.15 mmol) was added followed by a solution of L-valine methyl ester HCl (2.31 g, 13.77 mmol) and triethylamine (2.1 ml, 15 mmol) in acetonitrile (15 ml). The reaction was continued for 3 h and then the solvents were removed in vacuo. The residue was stirred in EtOAc (100 ml) and cooled at 0 ºC for 30 mins. The precipitates were removed by filtration and then the solution was concentrated in vacuo. The product was purified by column chromatography on silica gel using EtOAc / Methanol as eluent (gradient elution), yielding the product E2 as a white solid. (2.94 g, 88%); m.p.119.8-121.5 ºC; [α]$_D$ -55.3 ºc (c = 1, MeOH, 20 ºC); IR $\nu_{\text{max}}$/cm$^{-1}$ 3346, 3275, 2968, 1735, 1685, 1663; δ$_H$(400 MHz, CDCl$_3$) 0.90 [6 H, t, J 7.1, CH(CH$_3$)$_2$], 2.10-2.57 (5 H, m, CH$_2$CH$_2$ and CH(CH$_3$)$_2$), 3.71 (3H, OCH$_3$), 4.21 (1H, m, CH$_2$CH$_2$CH), 4.55-4.59 [1H, m, NHCHCH(CH$_3$)$_2$], 6.53 (1H, br s, NH), 6.91 (1H, br d, J 8.4, NH); δ$_C$ (100 MHz, CDCl$_3$) 18.2 [CH$_3$, one of CH(CH$_3$)$_2$], 19.1 [CH$_3$, one of CH(CH$_3$)$_2$], 25.9 [CH$_3$, C(O)CH$_2$CH$_2$], 29.5 [CH$_2$, C(O)CH$_2$CH$_2$], 31.2 [CH, CH(CH$_3$)$_2$], 32.4 (CH$_3$, OCH$_3$), 57.2 (CH, CH$_2$CH$_2$CH), 57.6 [CH, NHCHCH(CH$_3$)$_2$C(O)], 172.7 [NHC(O)CH$_3$], 172.9 [C(O)OCH$_3$], 179.6 [C(O)CH$_2$CH$_2$]; HRMS (ES$^+$): found [M-H]$^-$ C$_{11}$H$_{17}$N$_2$O$_4$ 241.1191, requires 241.1193.
(S)-methyl 2-[(S)-5-oxopyrrolidine-2-carboxamido]propanoate E4

To a stirred suspension of L-pyroglutamic acid (4.52 g, 35 mmol) in DCM (50 ml) at 0 °C was added 1, 3 dicyclohexylcarbodiimide (7.22 g, 35 mmol). After 30 min N-hydroxysuccinimide (4.03 g, 35 mmol) was added followed by a solution of L-alanine methyl ester HCl (4.89 g, 35 mmol) and N-methylmorpholine (3.9 ml, 35 mmol) in acetonitrile (50 ml). The reaction was continued for 3 h and then the solvents were removed in vacuo. The residue was stirred in EtOAc (50 ml) and cooled at 0 °C for 30 mins. The precipitates were removed by filtration and then the solution was concentrated in vacuo. The product was purified by column chromatography on silica gel using EtOAc / Methanol as eluent (gradient elution), yielding the product E4 as a white solid. (5.85 g, 78%) ; m.p.120.9-121.8 °C; [α]D -57.6° (c = 1, MeOH, 20 °C); IR (solid) νmax/cm⁻¹ 3374, 3223, 1744, 1697, 1670; δH (400 MHz, CDCl₃) 1.42 [3 H, d, J 7.4, C(O)NHCHC₃H₃], 2.15-2.24 (1 H, m, one of CH₂C₃H₂CH), 2.30-2.59 (3 H, m, CH₂CH₃CH and one of CH₂C₃H₂CH), 3.73 (3 H, s, OCH₃), 4.22 (1 H, m, CH₂CH₂CH), 4.59 [1H, quint, J 7.6, CH₃CH(C(O))], 7.08-7.15 (2 H, m, 2 x NH); δC (100 MHz, CDCl₃) 17.9 (CH₃, NHCHCH₃), 25.8 [CH₂, C(O)CH₂CH₂], 29.3 [CH₂, C(O)CH₂CH₂], 47.9 [CH, NHCH(CH₃)C(O)], 52.6 (CH₃, OCH₃), 57.2 [CH, CH₂CH₂CHC(O)], 172.1,173.7 [C(O)OCH₃] and [CHC(O)NH], 179.4 [C(O)CH₂CH₂]; HRMS (ES⁺): found [M-H]⁻ C₉H₁₅N₂O₄ 213.0877, requires 213.0880.
To a stirred suspension of L-pyroglutamic acid (2.58 g, 20 mmol) in acetonitrile (50 ml) at 0 ºC was added 1, 3 dicyclohexylcarbodiimide (4.13 g, 20 mmol). After 30 min N-hydroxysuccinimide (2.30 g, 20 mmol) was added followed by a solution of D-phenylglycine methyl ester HCl (4.89 g, 20 mmol) and N-methylmorpholine (2.2 ml, 20 mmol) in acetonitrile (50 ml). The reaction was continued for 3 h and then the solvents were removed in vacuo. The residue was stirred in EtOAc (50 ml) and cooled at 0 ºC for 30 mins. The precipitates were removed by filtration and then the solution was concentrated in vacuo. The product was purified by column chromatography on silica gel using EtOAc / Methanol as eluent (gradient elution), yielding the product E5 as a white solid. (5.85 g, 78%); m.p. (159.4-161.1 ºC); [α]D -61.4° (c 1, MeOH, 20 ºC); IR νmax/cm⁻¹ 3283 br, 3086, 1686, 1661, 1637; δH (400 MHz, CDCl₃) 2.17-2.57 (4 H, m, CH₂CH₂), 3.71 (3 H, s, OC₃H), 4.20 (1 H, m, CH₂CH₂CHNH), 5.56 (1 H, d, J 7.3, NHCHPh), 6.80 (1 H, br s, one of NH), 7.18 (1 H, d, J 7.3, one of NH), 7.32-7.39 (5 H, m, ArCH); δC (100 MHz, CDCl₃); 25.7 [CH₂, CH₂CH₂CH], 29.2 [CH₂, CH₂CH₂CH], 52.9 (CH₃, OCH₃), 56.4 [CH, NHCH(Ph)(C)(O)], 56.8 [CH, CH₂CH₂CH], 127.4 (CH, 2 x ArCH), 128.8 (CH, 1 x ArCH), 129.1 (CH, 2 x ArCH), 135.8 (ArC), 171.1, 171.5 , [C(O)OCH₃ and CHC(O)NH], 179.3 [C(O)CH₂CH₂]; HRMS (ES⁺): found [M-H]⁻ C₁₄H₁₅N₂O₄ 275.1036, requires 275.1037.
(S)-methyl 2-[(S)-5-oxypyrroolidine-2-carboxamido]-3-phenylpropanoate E3

To a stirred suspension of L-pyroglutamic acid (1.29 g, 10 mmol) in acetonitrile (30 ml) at 0 °C was added 1, 3 dicyclohexylcarbodiimide (2.07 g, 10 mmol). After 30 min N-hydroxysuccinimide (1.15 g, 10 mmol) was added followed by a solution of L-phenylalanine methyl ester HCl (2.45 g, 10 mmol) and N-methylmorpholine (1.1 ml, 10 mmol) in acetonitrile (25 ml). The reaction was continued for 3 h and then the solvents were removed in vacuo. The reaction was continued for 3 h and then the solvents were removed in vacuo. The residue was stirred in EtOAc (30 ml) and cooled at 0 °C for 30 mins. The precipitates were removed by filtration and then the solution was concentrated in vacuo. The product was purified by column chromatography on silica gel using EtOAc /Methanol as eluent (gradient elution), yielding the product E3 as a white solid. (1.76 g, 61%); m.p. (161.1-161.9 °C); [α]_D -15.9°C (c = 1, MeOH, 20 °C); IR (solid) ν_max/cm⁻¹ 3291 br, 3094, 1732; δ H (400 MHz, CDCl₃) 2.16-2.54 (4 H, m, CH₂CH₂CH and CH₂CH₂CH), 3.01 (1 H, dd, J 14.0, J 8.4, one of CHCH₂Ph), 3.22 (1 H, dd, J 13.6, J 5.4, one of CHCH₂Ph), 3.74 (3 H, s, OCH₃), 4.08 (1 H, m, CH₂CH₂CH₂NH), 4.51-4.60 (1 H, m, NHCH₂CH₂Ph), 6.65 (1 H, m, one of NH), 7.11 (1 H, d, J 8.8, one of NH), 7.12-7.31 (5 H, m, ArCH); δC (100 MHz, CDCl₃) 25.7 [CH₂, C(O)CH₂CH₂], 29.2 [CH₂, C(O)CH₂CH₂], 38.1 (CH₂, CH₂Ph), 52.9 (CH₃, OCH₃), 56.4 [CH, NHCH₂CH₂Ph], 56.8 [CH, CH₂CH₂CH], 127.4 (CH, 2 x ArCH), 128.8 (CH, 1 x ArCH), 129.1 (CH, 2 x ArCH), 135.8 (ArC), 171.1, 171.5, [C(O)OCH₃] and [CH(C(O)NH], 179.3 [C(O)CH₂CH₂]; HRMS (ES): found [M-H]⁻ C₁₅H₁₇N₂O₄ 289.1265, requires 289.1267.
(S)-N-(S)-1-[(S)-1-hydroxy-3-phenylpropan-2-ylamino]-3-methyl-1-oxobut-2-yl-5-oxopyrrolidine-2-carboxamide L2

To a stirred solution of (S)-methyl 3-methyl-2-[(S)-5-oxopyrrolidine-2-carboxamido]butanoate (1.11 g, 5.18 mmol) and 1, 5, 7-triazabicyclo [4.4.0] dec-5-ene (TBD) (144 mg, 1.04 mmol) at 50 °C was added L-phenylalaninol (0.86 g, 5.7 mmol) under nitrogen atmosphere. The reaction mixture was warmed to 75 °C and stirred for 12 h, allowed to cool to ambient temperature and concentrated in vacuo. The residue obtained was chromatographed on silica gel using 8% methanol/ ethyl acetate as eluent to afford the product as a solid which was then triturated with cold acetonitrile to give the pure product as a white solid L2. (1.40 g, 75%) m.p. 183.4-184.9 ºC; [α]D -57.9° (c = 1 , DMF, 20 ºC); IR νmax /cm⁻¹ 3293, 3096, 2960, 1675, 1633, 744, 701; δH (400 MHz, DMSO-D6) 0.66 [3 H, d, J 6.7, one of CHCH(C₃H₃)₂], 0.68 [3 H, d, J 7.0 , one of CHCH(CH₃)₂], 1.53-1.68 [1 H, m, CHCH(CH₃)₂], 1.69-1.82 [1 H, m, one of CH₂CH₂CH₂CH(O)], 1.87-2.12 [3 H, m, CH₂CH₂CH and one of CH₂CH₂CH₂CH(O)], 2.49 (1 H, dd, J 13.6, 4.8, one of CHCH₂Ph), 2.75 (1 H, dd, J 13.6, 3.6, one of CHCH₂Ph), 3.11-3.26 (2 H, m, CH₂OH ), 3.44-3.55 [1 H, m, C(O)NHCHCH(CH₃)₂], 3.73-3.85 [1 H, m, C(O)NHCHCH₂Ph], 3.96 [1 H, m, CH₂CH₂CH₂CH(O)], 4.64-4.70 (1 H, m, OH), 7.11-7.27 (5 H, ArCH), 7.73 (1 H, br d, J 8.8, C(O)NHCHCH₂Ph), 8.03 (1 H, br s, C(O)NH lactam), [8.10, d, J 8.7, C(O)NHCHCH(CH₃)₂], δC (100 MHz, DMSO-D6) 18.8 [CH₃, one of CHCH(CH₃)₂], 19.7 [CH₃, one of CHCH(CH₃)₂], 25.9 (CH₂, CH₂CH₂CH₂CH), 29.7 (CH₂, CH₂CH₂CH₂CH), 31.2 [CH, CHCH(CH₃)₂], 36.9 (CH₂, CH₂Ph), 55.8 {[CH, CHCH(CH₃)₂] or (CH, CH₂CH₂CH₂CH)}, 58.4 {[CH, CHCH(CH₃)₂] or (CH, CH₂CH₂CH₂CH)}, 60.3 (CH, CHCH₂Ph), 63.1 (CH₂, CH₂OH), 126.4 (CH, 1 x ArCH), 128.5 (CH, 2 x ArCH), 129.6 (CH, 2 x ArCH), 139.6 (1 x ArC), 170.8 [one of C(O)NH], 171.7 [one of C(O)NH], 178.0 [one of C(O)NH]; HRMS (ES⁺): found [M-H] C₁₉H₂₇N₃O₄ 360.1926, requires 360.1929.

COSY experiments confirmed ¹H NMR assignments
(S)-N-[(S)-2-[(S)-1-hydroxy-3-methylbutan-2-ylamino]-2-oxo-1-phenylethyl]-5-oxopyrroolidine-2-carboxamide L3

To a stirred solution of (S)-methyl 2-[(S)-5-oxopyrroolidine-2-carboxamido]-3-phenylpropanoate (1.73 g, 5.95 mmol) and 1, 5, 7-triazabicyclo [4.4.0] dec-5-ene (TBD) (0.20 g, 1.79 mmol) at 50 °C was added L-valinol (0.706 g, 6.84 mmol) under nitrogen atmosphere. The reaction mixture was warmed to 75 °C and stirred for 12 h, allowed to cool to ambient temperature and concentrated in vacuo. The residue obtained was chromatographed on silica gel using 8% methanol/ethyl acetate as eluent to afford the product as a solid which was then triturated with cold acetone to give the pure product L3 (1.10 g, 71%); m.p. 185.3-187.2 °C; [α]D -13.89° (c 0.5, MeOH, 20 °C); IR vmax/cm-1 3372, 3267, 1707, 1679, 1635, 1550; δH (400 MHz, DMSO-D6) 0.77 [3 H, d, J 6.9, one of CHCH(CH3)_2], 0.80 [3 H, d, J 6.9, one of CHCH(CH3)_2], 1.61-1.71 [1 H, m, CHCH(CH3)_2], 1.74-1.83 [1 H, m, one of CH2CH2CHC(O)], 1.94-2.01 [2 H, m, one of CH2CH2CHC(O), one of CH2CH2CHC(O)], 2.10-2.21 [1 H, m, one of CH2CH2CHC(O)], 2.78 (1 H, dd, J 13.8, J 9.6, one of CHCH2Ph), 2.96 (1 H, dd, J 13.8, J 5.0, one of CHCH2Ph), 3.24-3.32 (2 H, m, CH2OH ), 3.49-3.58 [1 H, m, NHCHCH(CH3)_2], 3.93 [1 H, m, CH2CH2CH], 4.47-4.56 (2 H, m, NHCHCH2Ph, CH2OH), 7.11-7.27 (5 H, ArCH), 7.58 [br d, J 9.2, NHCHCH(CH3)_2], 7.73 [1 H, br s, NH lactam], 8.05 (1 H, br d, J 8.7, NHCHCH2Ph); δC (100 MHz, DMSO-D6) 18.5 [CH3, one of CHCH(CH3)_2], 20.1 [CH3, one of CHCHCH(CH3)_2], 25.8 (CH2, CH2CH2CH), 28.7 [CH, CHCH(CH3)_2], 29.5 (CH2, CH2CH2CH), 38.1 (CH2, CH2Ph), 55.9 [CH, CH2CH2CH or CHCH(CH3)_2], 56.1 [CH, CH2CH2CH or CHCH(CH3)_2], 60.5 (CH, CHCH2Ph), 61.7 (CH2, CH2OH), 126.2 (CH, ArCH), 128.0 (CH, 2 x ArCH), 129.3 (CH, 2 x ArCH), 137.8 (ArC), 170.8 [one of C(O)NH], 172.3 [one of C(O)NH], 177.4 [one of C(O)NH]; HRMS (ES') found [M-H]- C19H27N3O4 360.1930, requires 360.1929.

COSY experiments confirmed 1H NMR assignments
(2S)-N-[(1S)-2-[(1S)-1-(hydroxymethyl)-2-methylpropyl]amino]-1-methyl-2-oxoethyl]-5-oxopyrrolidine-2-carboxamide L4

To a stirred solution of (S)-methyl 2-[(S)-5-oxopyrrolidine-2-carboxamido]propanoate ester (1.79g, 8.35 mmol) and 1, 5, 7-triazabicyclo [4.4.0] dec-5-ene (TBD) (0.29g, 2.09 mmol) at 50 °C was added L-valinol (1.03 g, 10.0 mmol) under nitrogen atmosphere. The reaction mixture was warmed to 75 °C and stirred for 12 h, allowed to cool to ambient temperature and concentrated *in vacuo*. The residue obtained was chromatographed on silica gel using 8% methanol/ ethyl acetate as eluent to afford the product as a solid which was then triturated with cold acetonitrile to give the pure product L4. (1.64 g, 64%) as a yellow powder; mp 170.5-171.9°C ; $[\alpha]_D + 2.1^\circ$ (c 1 , DMF, 20 °C); IR $\nu_{\text{max}}$/cm$^{-1}$ 3468, 3268, 3083, 2962, 1691, 1635, 1549; $\delta$ H (400 MHz, DMSO-D6) 0.76 [3 H, d, $J$ 6.6, one of CH(CH$_3$)$_2$], 0.79 [3 H, d, $J$ 6.9, one of CH(CH$_3$)$_3$], 1.17 [3 H, d, $J$ 7.1, NHCH(CH$_3$)], 1.71-1.86 [2 H, m, NHCHCH(CH$_3$)$_2$ and one of CH$_2$CH$_2$CH], 1.98-2.23 (3 H, m, CH$_2$CH$_2$CH and one of CH$_2$CH$_2$CH), 3.26-3.37 (2 H, m, CH$_3$OH), 3.46-3.54 [1 H, m, NHCHCH(CH$_3$)], 4.01 (1 H, m, CH$_2$CH$_2$CH), 4.28 [1 H, app quint, $J$ 7.1, NHCH(CH$_3$)], 4.51 (1 H, t, $J$ 5.2, OH), 7.43 (1 H, d, $J$ 9.2, one of NH), 7.77 (1 H, br s, one of NH), 8.06 (1 H, d, $J$ 7.8 , NH lactam); $\delta$ C (100 MHz, DMSO-D6) 18.0 [CH$_3$, one of CHCH(CH$_3$)$_2$], 18.3 [CH$_3$, one of CHCH(CH$_3$)$_2$], 19.6 [CH$_3$, C(O)CH(CH$_3$)], 25.2 (CH$_2$, CH$_2$CH$_2$CH), 28.2 [CH, CHCH(CH$_3$)$_2$], 29.3 (CH$_2$, CH$_2$CH$_2$CH), 48.2 [CH, C(O)CH(CH$_3$)], 55.5 [CH, one of CHCH(CH$_3$)$_2$ or CH$_2$CH$_2$CH], 55.5 [CH, one of CHCH(CH$_3$)$_2$ or CH$_2$CH$_2$CH], 61.2 [CH$_2$, CH$_2$OH]), 171.8 [one of C(O)NH], 172.0 [one of C(O)NH], 177.5 [one of C(O)NH]; HRMS (ES$^-$): found [M-H] $^{13}$C$_{13}$H$_{23}$N$_3$O$_5$ 284.1656, requires 284.1658.

COSY experiments confirmed $^1$H NMR assignments
(S)-N-[(S)-1-(2-hydroxyethylamino)-3-methyl-1-oxobutan-2-yl]-5-oxopyrrolidine-2-carboxamide L5

(S)-methyl 3-methyl-2-[(S)-5-oxopyrrolidine-2-carboxamido]butanoate (0.68 g, 2.80 mmol) and glycinol (0.15 g, 3.1 mmol) were stirred with DBU (84 µL, 0.56 mmol) and 1, 2, 4 triazole (39.2 mg, 0.56 mmol), and the mixture was heated to 85°C in an oil bath. After 3 hrs the mixture had solidified completely. The reaction was heated for 24 hr and the solid mixture was broken up and suspended in 25 mL of hot ethanol. After cooling to rt, the suspension was filtered and the white powdery precipitate was rinsed with cold ethanol and dried under high vaccuum to give the product L5 (0.60 g, 79.5% yield), m.p. 168.2-170.4 °C; [α]D -27.2° (c 1, H2O, 20 °C); IR νmax/cm⁻¹ 3273, 2957, 1681, 1638, 1554; δ H (400 MHz, DMSO-D6) 0.92 [3 H, d, J 6.4, one of CH(CH3)2], 1.05 [3 H, d, J 6.4, one of CH(CH3)2], 1.74-2.26 [5 H, m, CHCH(CH3)2, CH2CH2CH(CH3)2 and CH2CH2CH], 3.01-3.17 (2 H, m, CH2NH), 3.35 (2 H, t, J 6.4, CH2OH), 4.06-4.12 [2 H, m, NHCHCH and CH2CH2CH], 4.66 (1 H, s, OH), 7.82 [1 H, s, one of C(O)NH], 7.91 [1 H, d, J 8.8, one of C(O)NH], 8.00 [1 H, t, J 5.6, one of C(O)NH]; δ C (100 MHz, DMSO-D6) 18.8 [CH3, one of CHCH(CH3)2], 19.8 [CH3, one of CHCH(CH3)2], 25.8 (CH2, CH2CH2CH), 29.7 (CH2, CH2CH2CH), 31.2 [CH, CHCH(CH3)2], 41.9 (CH2, NHCH2), 55.9 [CH, CH2CHNH or NHCHCH(CH3)2], 58.3 [CH, CH2CHNH or NHCHCH(CH3)2], 60.3 (CH2, CH2OH), 171.3 [one of C(O)NH], 172.8 [one of C(O)NH], 178.0 [one of C(O)NH]; HRMS (ES⁺): found [M-H]- C12H20N3O4 270.1461, requires 270.1459.
(S)-N-[2-[(S)-1-hydroxy-3-phenylpropan-2-ylamino]-2-oxoethyl]-5-oxopyrrolidine-2-carboxamide L6

To a stirred solution of (S)-methyl 2-(5-oxopyrrolidine-2-carboxamido)acetate (1.79g, 5.85 mmol) and 1, 5, 7-triazabicyclo [4.4.0] dec-5-ene (TBD) (0.16g, 1.17 mmol) at 50 °C was added L-phenylalaninol (0.72 g, 7.0 mmol) under nitrogen atmosphere. The reaction mixture was warmed to 75 °C and stirred for 12 h, allowed to cool to ambient temperature and concentrated in vacuo. The residue obtained was chromatographed on silica gel using 8% methanol/ethyl acetate as eluent to afford the product as a solid which was then triturated with cold acetonitrile to give the pure product L6 (1.03 g, 55%) as a white powder; m.p. 176.2-178.4 °C; [α]D -8.9° (c = 1, H2O, 20 °C); IR νmax /cm⁻¹ 3369, 3249, 3096, 2962, 1692, 1669, 1643; δ H (400 MHz, DMSO-D6) 1.83-1.91 (1 H, m, one of CH₂C₆H₂), 2.03-2.30 (3 H, m, CH₂C₆H₂ and one of CH₂CH₂CH), 2.62 (1 H, dd, J 14.0, J 8.4, one of CHCH₂Ph), 2.83 (1 H, dd, J 13.2, J 6.0, one of CHCH₂Ph), 3.27-3.39 (2 H, m, CH₂OH), 3.61-71 (2 H, m, NHCH₂), 3.86-3.94 (1 H, m, NHCHCH₂Ph), 4.04 (1 H, m, CH₂CH₂CH), 4.82 (1 H, t, J 5.2, OH), 7.15-7.29 (5 H, m, ArCH), 7.77 [1 H, d, J 8.4, one of C(O)NH], 7.84 [1 H, s, one of C(O)NH, 8.09 [1 H, t, J 5.6, one of C(O)NH]; δ C (100 MHz, DMSO-D6) 25.3 (CH₂, CH₂CH₂CH), 29.7 (CH₂, CH₂CH₂CH), 36.5 (CH₂, CH₂Ph), 41.8 [CH₂, NHCH₂C(O)], 52.5 (CH, one of CH₂CH₂CH or CHCH₂Ph), 55.6 (CH, one of CH₂CH₂CH or CHCH₂Ph), 62.3 (CH₂, CH₂OH), 126.0 (CH, ArCH), 128.1 (CH, 2 x ArCH), 129.1 (CH, 2 x ArCH), 139.0 (ArC), 168.0 [one of C(O)NH], 172.6 [one of C(O)NH], 177.4 [C(O)NH]; HRMS (ES⁺): found [M-H]⁻ C₁₆H₂₀N₃O₄ 318.1458, requires 318.1459.
(S)-N-2-[(S)-1-(hydroxymethyl)-3-methylbutan-2-ylamino]-2-oxoethyl]-5-oxopyrrolidine-2-carboxamide L1

(S)-methyl 2-(5-oxopyrrolidine-2-carboxamido)acetate (0.60 g, 2.80 mmol) and L-valinol (0.35 g, 3.1 mmol) were stirred with DBU (84 µL, 0.56 mmol) and 1, 2, 4 triazole (39.2 mg, 0.56 mmol), and the mixture was heated to 85°C in an oil bath. After 3 hrs the mixture had solidified completely. The reaction was heated for 24 hr, then the solid mixture was broken up and suspended in 25 mL of hot ethanol. After cooling to rt, the suspension was filtered and the white powdery precipitate was rinsed with cold ethanol to give the product L1 (0.510 g, 67.1%): mp 179.8-181.3 ºC; [α]D -23.1° (c 1, H2O, 20 ºC); IR νmax/cm⁻¹ 3355, 3289, 1714, 1644, 1514; δH (400 MHz, DMSO-D6): 0.90 [3 H, d, J 7.2, one of CH(CH3)2], 0.98 [3 H, d, J 6.8, one of CH(CH3)2], 1.75-1.85 [2 H, m, CHCH(CH3)2 and one of CH2CH2CHC(O)], 2.22-2.38 [3 H, m, CH2CH2CHC(O) and one of CH2CH2CHC(O)], 3.26-3.36 [2 H, m, CH2OH], 3.49-3.56 [1 H, m, NHCHCH(CH3)], 3.70 [2 H, m, NHCH2C(O)], 3.99-4.04 [1 H, m, CH2CH2CH], 4.56 [1 H, t, J 5.6, CH2OH], 7.46 [1 H, d, J 9.2, one of CO(NH)], 7.81 [1 H, s, one of CO(NH)], 8.09 [1 H, t, J 5.6, one of CO(NH)]; δC (100 MHz, DMSO-D6): 18.7 [CH3, one of CHCH(CH3)2], 20.1 [CH3, one of CHCH(CH3)2], 25.8 [CH2, CH2CH2CH], 28.9 [CH, CHCH(CH3)2], 29.7 [CH2, CH2CH2CH], 47.6 [CH2, NHCH2C(O)], 61.2 [CH, one of CHCH(CH3)2 or CH2CH2CHC(O)], 61.3 [CH, one of CHCH(CH3)2 or CH2CH2CHC(O)], 66.8 [CH2, CH2OH], 170.4 [one of CO(NH)], 172.5 [one of CO(NH)], HRMS (ES'): found [M-H]- C12H20N3O4 270.1458, requires 270.1459.
(S)-N-[(R)-2-(2-hydroxyethylamino)-2-oxo-1-phenylethyl]-5-oxopyrrolidine-2-carboxamide L7

(R)-methyl2-[(S)-5-oxopyrrolidine-2-carboxamido]-2-phenylethanoate E5 (2.82g, 10.2mmol) and glycinol (2.44 g, 40 mmol) were added to a 10 mL Ace Pressure Tube with a magnetic stir bar inside. The tube was flushed with N$_2$ and sealed and heated to 150 °C in an oil bath. After 3 hr the reaction mixture solidified and stirring ceased. The reaction was heated for a further 3 hr, cooled in a water bath and the residue was dissolved into hot ethanol (25 mL). After cooling to rt, the suspension was filtered and the white powdery precipitate was rinsed with cold ethanol to give the product L7 (1.84 g, 59%): mp 177.9-180.3 °C; [α]$_D$ = -13.6 ° (c 1, H$_2$O , 20 °C), IR $\nu_{max}$/cm$^{-1}$, 3268, 2960, 1683, 690; $\delta$ H (400 MHz, DMSO-D6) 1.71-2.26 (4 H, m, CH$_2$CH$_2$CH and CH$_2$CH$_2$CH), 2.98-3.17 (2 H, m, NHCH$_2$), 3.27-3.40 (2 H, m, CH$_2$OH), 4.14-4.19 (1 H, m, CH$_2$CH$_2$CH), 4.65 (1 H, br s, OH), 5.46 [1 H, d, J 8.4, NHCH(Ph)], 7.20-7.41(5 H, m, ArCH), 7.87 [1 H, br s, one of C(O)NH], 8.39 [1 H, t, J 5.2, one of C(O)NH], 8.53 [1 H, d, J 8.0, one of C(O)NH], $\delta$C (100 MHz, DMSO-D6) 25.8 (CH$_2$, CH$_2$CH$_2$CH), 29.7 (CH$_2$, CH$_2$CH$_2$CH), 42.1 (CH$_2$, NHCH$_2$), 55.8 [CH, one of NHCH(Ph) or CH$_2$CH$_2$CH], 56.6 [CH, one of NHCH(Ph) or CH$_2$CH$_2$CH], 60.1 (CH$_2$, CH$_2$OH), 127.4 (CH, 2 x ArC), 128.0 (CH, ArCH), 128.8 (CH, 2 x ArCH), 139.5 (ArC), 170.2 [one of C(O)NH], 172.4 [one of C(O)NH], 178.0 [one of C(O)NH]; HRMS (ES$^+$): found [M-H] C$_{15}$H$_{16}$N$_3$O$_4$ 304.1300, requires 304.1303.
To a stirred mixture of methyl (2S)-5-oxopyrrolidine-2-carboxylate (2.14 g, 15 mmol) and 1, 5, 7-triazabicyclo [4.4.0] dec-5-ene (TBD) (0.60 g, 4.5 mmol) at 80 °C was added R-phenylglycinol (2.27 g, 16.5 mmol). The reaction mixture was warmed to 75 °C and stirred for 12 h, allowed to cool to ambient temperature. The residue obtained was chromatographed on silica gel using 8% methanol/ ethyl acetate as eluent to afford (S)-N-[(R)-2-hydroxy-1-phenylethyl]-5-oxopyrrolidine-2-carboxamide as a solid which was then triturated with cold acetonitrile to give the pure product D1 (2.60 g, 71 %) as a white solid; m.p. 189.8-191.1 °C; [α]D -81.6 (c 1, MeOH, 20 °C); IR νmax/cm⁻¹ 3372, 3287, 1655, 1638, 741: δ H (400 MHz, DMSO-D6) 1.72-1.81 (1 H, m, one of CH₂C₃H₂), 1.99-2.28 (3 H, m, CH₂CH₂CH, one of CH₂CH₂CH), 3.53 (2 H, t, J 5.9, CH₂OH), 4.02-4.08 (1H, m, CH₂CH₂CH), 4.77-4.84 (1 H, m, NHCHPh), 4.88 (1 H, t, J 5.8, OH), 7.17-7.23 (1 H, m, ArCH), 7.24-7.32 (4 H, m, ArCH), 7.85 (1 H, br s, one of NH), 8.29 (1 H, br d, J 8.2, one of NH); δC (100 MHz, DMSO-D6) 25.8 (CH₂, CH₂CH₂CH), 29.8 (CH₂, CH₂CH₂CH), 55.1 (CH, CH₂CH₂CH), 56.2 (CH, NHCHPh), 65.1 (CH₂, CH₂OH), 127.3 (CH, 2 x ArCH), 127.3 (CH, ArCH), 128.6 (CH, 2 x ArCH), 139.5 (ArC), 172.5 [one of C(O)NH], 177.9 [one of C(O)NH]; HRMS (ES⁻): found [M-H]⁻ C₁₃H₁₅N₂O₃ 247.1082, requires 247.1083.
(S)-N-[(S)-1-hydroxy-3-methylbutan-2-yl]-5-oxopyrrolidine-2-carboxamide D2

The reaction was conducted as for the synthesis of (S)-N-[(R)-2-hydroxy-1-phenylethyl]-5-oxopyrrolidine-2-carboxamide above using methyl (2S)-5-oxopyrrolidine-2-carboxylate (2.00g, 14 mmol), 1, 5, 7-triazabicyclo [4.4.0] dec-5-ene (TBD) (0.49 g, 3.5 mmol) and (S)-valinol (1.52g, 14.7 mmol). The product (S)-N-[(S)-1-hydroxy-3-methylbutan-2-yl]-5-oxopyrrolidine-2-carboxamide D2 (2.22 g, 74 %) was isolated as a white solid; m.p. 144.1-145.9 °C ; [α]D -14.1 (c 0.8, H2O, 20 °C) IR ʋmax/cm⁻¹ 3396, 3323, 3215, 1680, 1640; δ H (400 MHz, DMSO-D6) 0.81 [3 H, d, J 6.8, one of CH(C₃H₅)₂], 0.85 [3 H ,d, J 6.8, one of CH(CH₃)₂], 1.75-1.94 [2 H, m, CH(CH₃)₂, one of CH₂CH₂CH], 2.01-2.21 (3H, m, CH₂CH₂CH, one of CH₂CH₂CH), 3.29-3.41 (2 H, m, CH₂OH) 3.51-3.60 [1 H, m, NHCHCH(CH₃)₂], 4.03-4.09 (1 H, m, CH₂CH₂CH), 4.60 (1 H, br s, OH), 7.59 (1 H,br d, J 8.9, one of NH), 7.82 (1 H, br s, one of NH); δC (100 MHZ, DMSO-D6) 18.8 (CH₃, one of CH₃), 20.2 (CH₃, one of CH₃), 26.0 (CH₂, CH₂CH₂CH), 28.7 [CH, CH(CH₃)₂], 29.8 (CH₂, CH₂CH₂CH), 56.3 [CH, CH₂CH₂CH], 61.7 [CH, NHCHCH(CH₃)₂], 62.9 (CH₂, CH₂OH), 172.8[amide C(O)NH] , 178.0 [lactam C(O)NH]; HRMS (ES⁺): found [M-H]⁻ C₁₀H₁₇N₂O₃ 213.1238, requires 213.1239.
(S)-N-((S)-1-hydroxy-3-phenylpropan-2-yl)-5-oxopyrrolidine-2-carboxamide D3

The reaction was conducted as for the synthesis of (S)-N-[((R)-2-hydroxy-1-phenylethyl]-5-oxopyrrolidine-2-carboxamide using methyl (2S)-5-oxopyrrolidine-2-carboxylate (1.43 g, 10 mmol), 1, 5, 7-triazabicyclo [4.4.0] dec-5-ene (TBD) (0.28 g, 30 mol %) and (S)-phenylalaninol (1.51 g, 10 mmol). The product (S)-N-((S)-1-hydroxy-3-phenylpropan-2-yl]-5-oxopyrrolidine-2-carboxamide D3 (1.76 g, 67%) was isolated as a white solid; m.p. 170.6–171.2 °C; [α]_D -32.9 (c 1, MeOH, 20 °C); IR υ_{max}/cm^{-1} 3299, 3228, 1686, 1645; δ_H (400 MHz, DMSO-D6) 1.63-1.72 (1 H, m, one of CH₂CH₂CH), 1.94-2.19 (3 H, m, CH₂CH₂CH, one of CH₂CH₂CH), 2.61 (1 H, dd, J 13.5, 8.3, one of CHCH₂Ph), 2.80 (1H, dd, J 13.5, 5.7, one of CHCH₂Ph), 3.27-3.39 (2 H, m, C_H₂OH), 3.83-3.92 (2 H, m, NHC_HCH₂Ph, CH₂CH₂CH), 4.77 (1 H, t, J 5.5, O_H), 7.13-7.27 (5 H, m, ArCH), 7.72 (1 H, br s, one of NH), 7.76 (1 H, br s, one of NH); δ_C (100 MHz, DMSO-D6) 25.9 (CH₂, CH₂CH₂CH), 29.6 (CH₂, CH₂CH₂CH), 36.9 (CH₂, CH₂Ph), 52.9 (CH, CH₂CH₂CH or NHCHCH₂Ph), 56.3 (CH, CH₂CH₂CH or NHCHCH₂Ph), 62.9 (CH₂, CH₂OH), 126.5 (CH, ArCH), 128.6 (CH, 2 x ArCH), 129.6 (CH, 2 x ArCH), 139.6 (ArC), 172.6 [one of C(O)NH], 177.9 [one of C(O)NH]; HRMS (ES^+): found [M-H]^− C_{14}H_{17}N_{2}O_{3} 261.1240, requires 261.1239.

(S)-N-((S)-1-hydroxy-4-methylpentan-2-yl)-5-oxopyrrolidine-2-carboxamide D4

The reaction was conducted as for the synthesis of (S)-N-[(R)-2-hydroxy-1-phenylethyl]-5-oxopyrrolidine-2-carboxamide using methyl (2S)-5-oxopyrrolidine-2-carboxylate (1.66 g, 11.6 mmol), 1, 5, 7-triazabicyclo [4.4.0] dec-5-ene (0.49 g, 3.5
mmol) and (S)-leucinol (1.36 g, 11.6 mmol). The product (S)-N-[(S)-1-hydroxy-4-methylpentan-2-yl]-5-oxopyrrolidine-2-carboxamide D4 was isolated as a white solid (2.07 g, 78 %); m.p. 122.4-123.9 ºC; [α]_D -21.9 (c 1, H₂O, 20 ºC); IR v_max/cm⁻¹ 3224, 3093, 1686, 1654; δ_H (400 MHz, DMSO-D6) 0.79 (3 H, d, J 6.7, one of CH₃), 0.83 (3 H, d, J 6.6, one of CH₃), 1.21-1.29 [2 H, m, CH₂CH(CH₃)], 1.49-1.59 [1 H, m, CH(CH₃)₂], 1.77-1.86 (1 H, m, one of CH₂CH₂CH), 1.98-2.24 (3 H, m, CH₂CH₂CH, one of CH₂CH₂CH), 3.17-3.30 (2 H, m, CH₂OH), 3.70-3.80 (1 H, m, NHCH₂CH₂ or CH₂CH₂CH), 3.93-4.02 (1 H, m, NHCH₂CH₂ or CH₂CH₂CH), 4.61 (1 H, t, J 5.7, OH), 7.57 (1 H, d, J 8.7, one of NH), 7.74 (1 H, br s, one of NH); (100 MHz, DMSO-D6) 22.4 (CH₃, one of CH₃), 23.9 (CH₃, one of CH₃), 24.7 [CH, CH(CH₃)₂], 26.1 (CH₂, CH₂CH₂CH), 29.8 (CH₂, CH₂CH₂CH), 39.9 [CH₂, CH₂CH(CH₃)], 49.2 (CH, NHCHCH₂CH or CH₂CH₂CH), 56.3 (CH, NHCHCH₂CH or CH₂CH₂CH), 64.2 (CH₂, CH₂OH), 172.6 [C(O)NH], 177.9 [C(O)NH]; HRMS (ES⁺): found [M-H]⁺ C₁₁H₁₉N₂O₃ 227.1394, requires 247.1396.

(S)-methyl 2-phenyl-4,5-dihydrooxazole-4-carboxylate 19

![Chemical Structure](image)

Triethylamine (1.6 mL, 9.1 mmol) was added slowly (15 minutes) to a solution of ethyl benzimidate hydrochloride (1.69 g, 9.1 mmol) in DCM (15 mL). The reaction mixture was stirred at room temperature for 30 min and L-serine methyl ester hydrochloride (1.57 g, 10.0 mmol) was added by portions. The resulting mixture was stirred for 48 h at room temperature. The solution was concentrated under reduced pressure. The residue was dissolved in acetone (25 mL), the insoluble salts were filtered off, and the filtrate was concentrated. Recrystallization of the crude material from diethyl ether gave the product as a colourless solid 19. (1.33 g, 71%): [α]_D +118.7 (c 1, EtOH, 20 ºC); IR v_max/cm⁻¹ 2989, 1735, 698; δ_H (400 MHz, CDCl₃) 3.82 (3 H, s, OCH₃), 4.59
(1H, dd, J 9.0, J 1.6, one of OCH₂), 4.69 (1 H, t, J 8.4, C(O)CHN), 4.95 (1 H, dd, J 8.0, 2.8, one of O-CH₂), 7.38-7.52 (3 H, m, ArCH), 7.97 (2 H, d, J 6.8, o-ArCH); δ C (100 MHz, CDCl₃) 52.8 (OCH₃), 68.6 [OCH₂ or C=NCHC(O)], 69.6 [OCH₂ or C=NCHC(O)], 127.3 (ArC), 128.5 (2xArC), 128.8 (2xArC), 131.9 (ArC), 166.2 (N=C-O), 171.5 [C(O)]; elemental analysis clad. (%) for C₁₁H₁₁NO₃ C 66.38, H 5.40, N 6.83; found: C 66.46, H 5.37, N 6.79.

(S)-N-[(S)-5-oxopyrrolidin-2-yl]methyl-2-phenyl-4,5-dihydrooxazole-4-carboxamide OX1

(S)-5-aminomethyl-2-pyrrolidone (1.33 g, 11.65 mmol), (S)-methyl 2-phenyl-4,5-dihydrooxazole-4-carboxylate (1.83 g, 8.83 mmol) and 1, 5, 7 triazabicyclo[4.4.0]decene (369 mg, 2.65 mmol) were stirred together at 80°C for 6 hr under a flow of nitrogen. On cooling to room temperature the solid product was recrystallized from THF/petrol to give an off-white powder (1.34 g, 53%): mp 101.6-102.4°C; [α]D -34.7 (c 1, CHCl₃, 20 °C); IR (solid) νmax/cm⁻¹ 3337, 2981, 1681, 1642; δ H (400 MHz, CDCl₃) 1.75-1.87 (1 H, m, one of CH₂CH₂CH), 2.19-2.36 (3 H, m, CH₂CH₂CH and one of CH₂CH₂CH), 3.32-3.43 [2 H, m, CH₂NHC(O)], 3.80-3.90 [1 H, m, CH₂CH₂CH], 4.60 [1 H, t, J 8.4, C(O)CHN=C], 4.71 [1 H, dd, J 8.8, 2.4, one of OCH₂], 4.87 [1 H, dd, J 8.8, 2.8, one of OCH₂], 5.82 [1 H, br s, one of NH(OC)], 6.99 [1 H, br s, one of NH(OC)], 7.41-7.61 (3 H, m, 3 x ArCH), 7.97 (2 H, br d, J 8.0, 2 x ArCH); δ C (100 MHz, CDCl₃) 24.5 (CH₂, CH₂CH₂CH), 29.8 (CH₂, CH₂CH₂CH), 45.9 (CH₂, CH₂NHC(O)), 56.1 (CH, NHCHCH₂), 68.8 (CH₂, OCH₂), 69.2 [CH, C=NCHC(O)], 127.5 (CH, ArCH), 128.7 (CH, 2 x ArCH), 128.8 (CH, 2 x ArCH), 197
132.0 (ArC), 166.8 [N=C-O], 172.5 [C(O)NHCH₂], 178.1 [C(O)NH lactam]; HRMS (ES²): found [M-H]⁻ C₁₁H₁₁NO₃ 286.1195, requires 286.1197.

(4S, 5R)-4-carbomethoxy-5-methyl-2-phenyloxazoline 20⁵

L-Threonine methyl ester (1.86 g, 14.11 mmol) and ethyl benzimidate hydrochloride (2.69 g, 14.11 mmol) were mixed in 1, 2 dichloroethane (25 mL). Triethylamine (1.98 mL, 197.0 mmol) was added and the mixture was stirred for 24 h. The insoluble salts were filtered off and the filtrate was washed with NaHCO₃ saturated aqueous solution (25 mL), dried over MgSO₄ and filtered. Evaporation of the solvent afforded product 20 (0.93 g, 30.0%) as a colourless oil. [α]D +97.0 (c 1.6, CHCl₃, 20 °C); [lit.⁵, [α]D]+96.7 (c 1.6, CHCl₃, 20 °C); IR νmax/cm⁻¹ 2985, 1740, 695; δ H (400 MHz, CDCl₃) 1.52 (3 H, d, J 6.4, CHCH₃), 3.80 (3 H, s, OCH₃), 4.45 [1H, d, J 7.6, CHC(O)OCH₃], 4.94-5.01 (1 H, m, CHCH₃), 7.37-7.50 (3 H, m, ArCH), 7.95-7.99 (2 H, m, ArCH); δ C (100 MHz, CDCl₃) 21.1 (CH₃), 52.7 (CH₃, OCH₃), 75.3 [CH, C=NCHC(O)], 78.5 [CH, OCH(CH₃)], 126.6 (CH, ArCH), 126.9 (CH, ArCH), 128.0 (ArC), 129.2 (CH, ArCH), 130.9(CH, ArCH), 131.5 (CH, ArCH), 165.2 (N=C-O), 171.3 [C(O)OCH₃]; elemental analysis clad (%) for C₁₂H₁₃NO₃ C 65.74, H 5.98, N6.39; found: C 65.83, H 5.84, N 6.31.
(4S,5R)-5-methyl-N-[(S)-oxopyrrolidin-2-yl]methyl]-2-phenyl-4,5-dihydrooxazole-4-carboxamide OX2

(S)-5-aminomethyl-2-pyrrolidone (533mg, 4.67 mmol), (4S, 5R)-4-carbomethoxy-5-methyl-2-phenyloxazoline (930 mg, 4.24 mmol) and 1, 5, 7 triazabicyclo[4.4.0]decene (177 mg, 1.27 mmol) were stirred together at 80°C for 6 hr under a flow of nitrogen. On cooling to room temperature the solid product was recrystallized from THF/petrol to give an off white powder (0.60 g, 45%): mp 102.3-103.9°C; [α]D +17.4 (c 1, CHCl3, 20 ºC); IR (solid) υmax/cm⁻¹ 3330, 2978, 1684, 1649, 1518; δH (400 MHz, CDCl3) 1.57 (3 H, d, J 6.4, CH₃), 1.72-1.81 (1 H, m, one of CH₂CH₂CH), 2.15-2.31 (3 H, m, CH₂CH₂CH, one of CH₂CH₂CH), 3.22-3.30 [1 H, m, one of CH₂NHC(O)], 3.38-3.45 [1 H, m, one of CH₂NHC(O)], 3.80-3.87 (1H, m, CH₂CH₂CH/NH), 4.31 [1 H, d, J 8.0, C(O)CHN=C], 4.88 [1 H, m, CH(CHOH), 6.43 [1 H, br s, one of NHC(O)], 7.16 [1 H, br s, one of NHC(O)], 7.41 (2 H, br t, J 7.4, ArC-H), 7.50 (1 H, br t, J 7.4, ArC-H), 7.94 (2 H, br d, J 7.2, ArCH); δC (100 MHz, CDCl3) 21.9 (CH₃, CH₃), 24.6 (CH₂, CH₂CH₂CH), 29.8 (CH₂, CH₂CH₂CH), 44.2 [CH₂, CH₂NHC(O)], 54.0 (CH, NHCHCH₂), 75.3 [CH, NHC(O)CHN=C or OCH(CH₃)], 80.0 [CH, NHC(O)CHN=C or OCH(CH₃)], 127.2 (1 x ArC), 128.5 (CH, 2 x ArCH), 128.6 (CH, 2 x ArCH), 132.2 (CH, 1 x ArCH), 166.8 [N=C=O], 172.5 [one of C(O)NH], 178.1 [lactam C(O)NH]; HRMS (ES⁻): found [M-H] 300.1350 C₁₁H₁₁NO₃ requires 300.1354
To a stirring solution of (S)-N-2-[(S)-1-(hydroxymethyl)-3-methylbutan-2-ylamino]-2-oxoethyl]-5-oxopyrrolidine-2-carboxamide L1 (597 mg, 2.33 mmol, 1 equiv.) in THF (4 ml) was added triphenylphosphine (0.95 g, 3.61 mmol, 1.8 equiv.) in one portion. This was followed by dropwise addition, via syringe, of diisopropyl azodicarboxylate (0.72 mL, 3.61 mmol, 1.8 equiv.) to the reaction mixture. The reaction mixture was allowed to clear between drops. The progress of the reaction was monitored by TLC analysis. After 3 h of stirring the mixture was concentrated under reduced pressure. The residue was taken up in EtOAc (5 ml) and hexane (5 ml) was added to the mixture. The contents of the flask were allowed to stand for 20 min while a white precipitate (triphenylphosphene oxide) formed. The precipitate was removed via filtration. The filtrate was concentrated under reduced pressure and the process was repeated twice. The product was purified by column chromatography (hexane: EtOAc, gradient elution) and the product was dried in vacuo to yield a colourless powder (323 mg, 55%): mp 93.3-95.8 °C; [α]D -70.5 (c 0.25, MeOH, 20 °C); IR (solid) v max/cm -1 3219, 2959, 1681, 1640, 1532; δ H (400 MHz, CDCl3) 0.91 [3 H, d, J 6.8, one of CH(CH3)2], 1.00 [3 H, d, J 6.8, one of CH(CH3)2], 1.75-1.89 [2 H, m, CHCH(CH3)2 and one of CH2CH2CHC(O)], 2.23-2.40 [3 H, m, CH2CH2CHC(O) and one of CH2CH2CHC(O)], 3.38-3.51 (2 H, m, NHCH2), 3.88-3.97 (1 H, m, CH2CH2CH), 4.02-4.09 [1 H, m, C=NCH CH(CH3)2], 4.17 (1 H, t, J 8.8, one of OCH2), 4.48 (1 H, t, J 9.6, one of OCH2), 6.16 [1 H, br s, one of C(O)NH], 7.34 [1 H, br s, one of C(O)NH]; δ C 19.6 (CH3, one of CH3), 19.8 (CH3, one of CH3), 25.3 (CH2, CH2CH2CH), 28.9 [CH, CHCH(CH3)2], 29.4 (CH2, CH2CH2CH), 46.4 (CH2, NHCH2C=N), 57.6 [CH, CH2CH2CH], 70.8 (CH2, COCH2CH), 71.3 [CH, C=NCH(CH3)2], 167.4 (CH2C=N-O), 172.7 [one of C(O)NH], 177.2 [lactam C(O)NH]; HRMS (ES): found [M-H]- C12H18N3O3 252.1350, requires 252.1354.
(S)-N-[(S)-1-(4,5-dihydrooxazol-2-yl)-2-methylpropyl]-5-oxopyrrolidine-2-carboxamide OX4

Diethylaminosulfur trifluoride (0.36mL, 2.74 mmol) was added dropwise to a cold (-78 °C) solution of the (S)-N-[(S)-1-(2-hydroxyethylamino)-3-methyl-1-oxobutan-2-yl]-5-oxopyrrolidine-2-carboxamide L5 (0.68 g, 2.50 mmol) in DCM at -78 °C. After stirring for 1 h at -78 °C, anhydrous K₂CO₃ (0.52 g, 3.75 mmol) was added in one portion and the mixture was allowed to warm to ambient temperature. The reaction was poured into saturated aqueous NaHCO₃, and the biphasic mixture was separated and then extracted with DCM. The combined organic extracts were dried, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (SiO₂, hexane: ethyl gradient elution) led to the desired oxazoline product as a white solid (494 mg, 78%): mp 115.1-116.3 °C; [α]D -96.0 (c 0.25, CHCl₃, 20 °C); IR (solid) νmax/cm⁻¹ 3328, 2956, 2931, 2881, 1693, 1671, 1543; δ H (400 MHz, CDCl₃), 0.92 [3 H, d, J 6.6, one of CH(C₃H₃)], 0.98 [3 H, d, J 6.6, one of CH(CH₃)₂], 1.91-2.05 [2 H, m, CHCH(CH₃)₂ and one of CH₂CH₂], 2.20-2.48 (3 H, m, CH₂CH₂CH and one of CH₂CH₂CH), 3.34-3.51 (2 H, m, CH₂N), 3.77-3.88 (2 H, m, OCH₂), 3.98-4.09 [1 H, m, CH₂CH₂CHNH], 4.22-4.31 [1 H, m, NHCHCH(CH₃)₂], 6.22 [1H, s, one of C(O)NH], 7.39 (1 H, s, one of C(O)NH); δ C (100 MHz, CDCl₃) 18.7 [CH₃, one of CHCH(CH₃)₂], 19.8 [CH₃, one of CHCH(CH₃)₂], 25.5 (CH₂, CH₂CH₂CH), 28.8 (CH₂, CH₂CH₂CH), 31.1 [CH, CHCH(CH₃)₂], 52.4 [CH₂, C=NCH₂], 54.0 [CH, NHCHCH(CH₃)₂], 60.5 (CH, CH₂CH₂CH), 67.7(CH₂, 2 x OCH₂), 167.8 [N=C-O], 171.4 [CHC(O)NH], 177.8 [C(O)NH lactam]; HRMS (ES⁻): found [M-H]⁻ C₁₂H₁₈N₃O₃ 252.1356, requires 252.1354.
(S)-N-((S)-1-[(S)-4-benzyl-4,5-dihydrooxazol-2-yl]-2-methylpropyl)-5-oxopyrrolidine-2-carboxamide OX5

To a stirring solution of (S)-N-((S)-1-[(S)-1-hydroxy-3-phenylpropan-2-ylamino]-3-methyl-1-oxobutan-2-yl]-5-oxopyrrolidine-2-carboxamide L2 (0.90 g, 2.5 mmol) in THF (8 ml) was added triphenylphosphine (1.18 g, 4.5 mmol) in one portion. This was followed by dropwise addition of diisopropyl azodicarboxylate (0.90 mL, 4.5 mmol) via syringe, to the reaction mixture. The reaction mixture was allowed to clear between drops. The progress of the reaction was monitored by TLC analysis. After 3 h of stirring the mixture was concentrated under reduced pressure. The residue was taken up in EtOAc (8 mL) and hexane (8 mL) was added to the mixture. The contents of the flask were allowed to stand for 20 min while a white precipitate (triphenylphosphine oxide) formed. The precipitate was removed via filtration. The filtrate was concentrated under reduced pressure and the process was repeated twice. The product was purified by column chromatography (hexane: EtOAc, gradient elution) and the product was dried in vacuo to yield a colourless powder (836 mg, 49 %): mp 110.3-114.1°C; $[\alpha]_D$ - 45.6 (c 0.25, MeOH, 20 ºC); IR $\nu_{\text{max}}$/cm$^{-1}$ 3273, 3061, 2962, 2872, 1702, 1661; $\delta$ H (400 MHz, CDCl$_3$) 0.91 [3 H, d, $J$ 6.8 , one of CHCH($\text{C}_H_3$)$_2$], 0.96 [3 H, d, $J$ 6.8 , one of CHCH($\text{C}_H_3$)$_2$], 1.76-1.96 (2 H, m, CHCH($\text{C}_H_3$)$_2$ and one of $\text{CH}_2\text{CH}_2\text{CHC(O)}$), 1.99-2.26 [3 H, m, $\text{CH}_2\text{CH}_2\text{CHC(O)}$ and one of $\text{CH}_2\text{CH}_2\text{CHC(O)}$], 2.65 (1 H, dd, J 14.1, J 7.8, one of CHCH$_2$Ph), 3.00 (1 H, dd, J 14.1, J 5.8, one of CHCH$_2$Ph), 3.91-4.03 (1 H, m, CH$_2$CH$_2$CH), 4.20 [1 H, t, $J$ 8.8, NHCHCH($\text{CH}_3$)$_2$], 4.29-4.41 (2 H, m, C=NCHCH$_2$Ph, one of OCH$_2$), 4.54 (1 H, t, J 9.2, one of OCH$_2$), 6.80 [1 H, br s, one of C(O)NH], , 7.16-7.29 (5 H, 5 x ArCH), 7.81 [one of C(O)NH]; $\delta$ C (100 MHz, CDCl$_3$) 17.7 [CH$_3$, one of CHCH($\text{CH}_3$)$_2$], 18.9 [CH$_3$, one of CHCH($\text{CH}_3$)$_2$], 24.0 (CH$_2$, CH$_2$CH$_2$CH), 28.5 (CH$_2$, CH$_2$CH$_2$CH), 31.6 [CH, CHCH($\text{CH}_3$)$_2$], 41.8 (CH$_2$, CH$_2$Ph), 53.5[CH, CHCH($\text{CH}_3$)$_2$], 58.0 [CH, CH$_2$CH$_2$CH], 67.1(CH$_2$, OCH$_2$), 72.3(CH, C=NCHBn), 126.5 (CH, 1 x ArCH), 128.5 (CH, 2xArCH), 129.2 (CH, 2xArCH), 138.0
(1 x ArC), 166.5 (N=C-O), 171.9 [CHC(O)NH], 177.4 [C(O)NH lactam]; HRMS (ES‘): found [M-H]⁻ C₁₂H₁₈N₃O₃ 342.1820, requires 342.1823.

(S)-5-[(S)-4-isobutyl-4, 5-dihydrooxazol-2-yl]pyrrolidin-2-one OX6

Diethylaminosulfur trifluoride (0.16 mL, 1.20 mmol) was added dropwise to a -78 °C solution of the (S)-N-[(S)-1-hydroxy-4-methylpentan-2-yl]-5-oxopyrrolidine-2-carboxamide D₄ (0.25 g, 1.1 mmol) in DCM. After stirring for 2 h, anhydrous K₂CO₃ (0.23 g, 1.64 mmol) was added in one portion and the mixture was allowed to warm to ambient temperature. The reaction was poured into saturated aqueous NaHCO₃, and the biphasic mixture was separated and then extracted with DCM. The combined organic extracts were dried, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (SiO₂, hexane: ethyl acetate, gradient elution) led to the desired oxazoline product as colourless crystals (95 mg, 41%): mp 99.6-102.7°C; [α]D +12.3 (c 1, CHCl₃, 20 °C); IR νmax/cm⁻¹ 3077, 2935, 2863, 1683, 1666; δ H (400 MHz, CDCl₃) 0.86-0.98 (6 H, m, 2 x CH₃), 1.23-1.33 [1 H, one of CHCH₂CH(CH₃)₂], 1.51-1.60 [1 H, m, one of CHCH₂CH(CH₃)₂], 1.67-1.79 [1 H, m, CH(CH₃)₂], 2.22-2.49 (4 H, m, CH₂CH₂CH and CH₂CH₂CH), 3.86 (1 H, t, J 8.0, C=NCH), 4.07-4.18 (1 H, m, one of OCH₂), 4.31-4.42 (2 H, m, CH₂CH₂CH and one of OCH₂), 6.86 [C(O)NH]; δ C (100 MHz, CDCl₃) 22.7 [CH₃, one of CH(CH₃)₂], 22.8 [CH₃, one of CH(CH₃)₂], 25.1 [CH₂, CH₂CH₂CH], 25.4 [CH, CH(CH₃)₂], 29.4 [CH₂, CH₂CH₂CH], 45.4 [CH₂, CH₂CH(CH₃)₂], 51.3 [CH, CH₂CH₂CH], 64.7 (CH, C=NCH), 73.9 (CH₂, OCH₂), 166.0 (C=N), 178.0 [C(O)NH]; HRMS (ES‘): found [M-H]⁻ C₁₁H₁₇N₂O₂ 209.1299, requires 209.1296.
(S)-5-[(S)-5-benzyl-4, 5-dihydrooxazol-2-yl]pyrrolidin-2-one OX7

Diethylaminsulfur trifluoride (0.19 mL, 1.43 mmol) was added dropwise to a -78 °C solution of the (S)-N-[(S)-1-hydroxy-3-phenylpropan-2-yl]-5-oxopyrrolidine-2-carboxamide D3 (0.34 g, 1.3 mmol) in DCM. After stirring for 2 h, anhydrous K$_2$CO$_3$ (0.27 g, 1.95 mmol) was added in one portion and the mixture was allowed to warm to ambient temperature. The reaction was poured into saturated aqueous NaHCO$_3$, and the biphasic mixture was separated and then extracted with DCM. The combined organic extracts were dried, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (SiO$_2$, hexane: ethyl acetate, gradient elution) led to the desired oxazoline product as colourless crystals (184 mg, 58%): mp 100.4-103.1°C; [$\alpha$]$_D$ -52.7 (c 1, CHCl$_3$, 20 °C); IR $\nu_{\text{max}}$/cm$^{-1}$ 3077, 2935, 2863, 1687, 1670, 695; $\delta$ H (400 MHz, CDCl$_3$) 2.16-2.47 (4 H, m, CH$_2$CH$_2$), 2.70 (1 H, dd, J 14.0, J 7.8 one of CH$_2$Ph), 3.04 (1 H, dd, J 14.0, J 7.8 one of CH$_2$Ph), 4.05 (1 H, dd, J 8.4, J 7.2, one of OCH$_2$), 4.25 (1 H, t, J 9.0, one of OCH$_2$), 4.28-4.34 (1 H, m, CH$_2$CH$_2$CH), 4.38-4.47 (1 H, m, C=NCHCH$_2$Ph), 6.73 [1 H, br s, C(O)NH], 7.15-7.32 (5 H, m, 5 x ArCH); $\delta$ C (100 MHz, CDCl$_3$) 26.1 (CH$_2$, CH$_2$CH$_2$), 29.3 (CH$_2$, CH$_2$CH$_2$CH), 41.8 (CH$_2$, CH$_2$Ph), 58.7 (CH$_2$, CH$_2$CH$_2$CHNH), 62.4 (CH, C=NCHCH$_2$Ph), 74.7 (CH$_2$, OCH$_2$), 126.3 (CH, ArCH), 128.4 (CH, 2 x ArCH), 129.9 (CH, 2 x ArCH), 136.6 (1 x ArC), 167.3 (C=N), 176.9 [C(O)NH]; m/z (ESI) 244 ([M$^-$], 100%), HRMS (ES$^+$): found [M-H]$^-$ C$_{14}$H$_{13}$N$_2$O$_2$ 243.1135, requires 243.1139.
3.3 Syntheses of Substrates

**(rac)-(E)-1, 3-Diphenyl-3-hydroxyprop-1-ene 82**

![Structure](image)

Cerium (III) trichloride heptahydrate (14.9 g, mmol) was added to a solution of trans-chalcone 81 (8.32 g, 40 mmol) in methanol (100 ml). The solution was cooled to 0° C, before sodium borohydride (1.92 g, mmol) was added in small portions (H₂ gas evolved). Once effervescence had ceased, the solution was allowed to warm to ambient temperature with stirring overnight. The pH of the reaction mixture was adjusted to 7 with 10% HCl (aqueous), water (50 ml) was added and the product was extracted in diethyl ether (5 x 50 ml), dried over MgSO₄ and concentrated in vacuo. The crude product was purified by column chromatography (pet. Ether/ EtOAc, 10:1), affording the desired product 82 (rac)-(E)-1, 3-Diphenyl-3-hydroxyprop-1-ene as white solid (5.32 g, 64%); mp 55.2-57.1°C (lit., 7 54-56 °C); IR νmax /cm⁻¹ 3345, 3031,1503, 692; δ H (400 MHz, CDCl₃) 2.15 (1 H, br s, OH), 5.38 (1 H, d, 6.4, CH(OH)), 6.39 [1 H, dd, J15.8,6.4, CHCHCH(OH)], 6.69 [1 H, d, 15.8, CHCHCH(OH)], 7.17-7.45 (10 H, m, 10 x ArCH); δ C (100 MHz, CDCl₃) 75.2 (CHOH), 126.4 (2 x ArC), 126.7 (2 x ArC), 127.8 (ArC), 127.9 (ArC), 128.6 (ArC), 128.7 (2 x ArC), 130.6 [CHCHCH(OH)], 131.6 [CHCHCH(OH)], 136.2 (ArCCHCH), 142.8 [ArCCH(OH)].

**(rac)-(E)-1,3-diphenylallyl acetate 79**

![Structure](image)

4-dimethylaminopyridine (0.1 g, 0.08 mmol, 5 mol%) was added to a solution of (rac)-(E)-1, 3-Diphenyl-3-hydroxyprop-1-ene 82 (3.31 g, 15.7 mmol) in pyridine (15 mL) at 0 °C. Acetic anhydride (4.5 mL, 48.0 mmol) was added dropwise over 10 min, and the mixture was allowed warm to room temperature with stirring overnight. On confirmation of the reaction by TLC analysis (hexane:diethyl ether, 4:1), diethyl ether
(200 mL) was added and the reaction mixture was successively washed with saturated CuSO4 solution (5 x mL), 10% NaHCO3 solution and water (2 x 25 mL). The organic layer was dried and concentrated in vacuo to yield the crude allyl acetate, which was purified by flash chromatography (pet. Ether/ EtOAc, 20:1) to give the product 79 (rac)-(E)-1,3-diphenylallyl acetate as a yellow oil (3.44 g, 87 %): IR \( \nu_{\text{max}} / \text{cm}^{-1} \) 3058, 1740, 1366, 692; \( \delta \text{H} \) (400 MHz, CDCl3) 2.15 (3 H, s, CH3), 6.36 [1 H, dd, \( J \) 15.8, 6.8, CHCHCH(O)], 6.46 [1 H, d, \( J \) 6.8, CHCHCH(O)], 6.65 [1 H, d, \( J \) 15.8, CHCHCH(O)], 7.25-7.44 (10 H, m, 10 x ArCH); \( \delta \text{C} \) (100 MHz, CDCl3) 21.2 [CH3, C(O)CH3], 75.7 [CH, CHCHCH(O)], 126.8 (2 x ArCH), 127.1 (2 x ArCH), 127.5 (1 x ArCH), 128.1 (ArCH), 128.2 (2 x ArCH), 128.7 (2 x ArCH) 132.6 [CHCHCH(O)], 136.2 [CHCHCH(O)], 139.3 (ArCCHCH), 140.7 [ArCCH(O)], 170.1 [C(O)]

**Cinnamyl methyl carbonate 74**

Cinnamyl alcohol 83 (5 g, 37.3 mmol), K2CO3 (10.3 g, 74.5 mmol) and methyl chloroformate (2.9 mL, 37.3 mmol) were stirred in DCM (100 mL) at room temperature overnight and then refluxed for 4 h. After cooling to room temperature, the reaction was quenched by the addition of water (100 mL), the organic layer separated and the aqueous layer washed with DCM (30 mL). The combined organic extracts were dried over MgSO4 and concentrated in vacuo. The crude product was purified by column chromatography (hexane: EtOAc, gradient elution) yielding the product cinnamyl methyl carbonate 74 as a clear oil (2.39 g, 36 %): IR \( \nu_{\text{max}} / \text{cm}^{-1} \) 3028,1741, 690; \( \delta \text{H} \) (400 MHz, CDCl3) 3.80 (3 H, s, CH3), 4.78 (2 H, d, \( J \) 6.4, CHCHCH2O), 6.29 (1 H, dt, \( J \) 16.0, 6.4,CHCH2O), 6.68 (1 H, d, \( J \) 16.0, CHCHCH2O), 7.23-7.54 (5 H, m, ArCH); \( \delta \text{C} \) (100 MHz, CDCl3) 54.9 (CH3, OCH3), 68.5 (CH2, CHCHCH2O), 122.4 (CHCHCH2O), 126.7 (2 x ArCH), 128.3 (ArCH), 128.7 (2 x ArCH), 134.6 (CHCHCH2O), 135.9 (ArC), 155.5 (C=O)
3.4 Asymmetric Transformations

3.4.1 Asymmetric Diethylzinc Addition to Benzaldehyde

General Procedure A

A flame-dried (under vacuum) Schlenk tube was charged with ligand (0.1 mmol) and toluene (2 mL) was added. The solvent was degassed by three freeze-thaw cycles. Titanium isopropoxide (72 µL, 0.20 mmol) was added and the mixture was stirred for 1 hr under an N₂ atmosphere. Diethylzinc solution (1 M in hexanes, 2 mL, 2 mmol) was added to the reaction mixture in one portion. Upon the addition of diethylzinc the solution turned green in colour. The Schlenk tube was partially submerged in methanol in a Lauda cooling bath (-30 °C) and a solution of benzaldehyde (102 µL, 1 mmol) in toluene (1 mL) was charged to the tube. The reaction was continued for 16 h with stirring and then the vessel was removed from the cooling bath and allowed to reach room temperature. The reaction was quenched with saturated ammonium chloride solution (3 mL) and extracted with DCM (3 x 5 ml), washed with brine (5 ml) and the combined organic extracts dried with MgSO₄. The organics were concentrated in vacuo (toluene removed by azeotropic distillation with methanol) and the residue was purified by flash column chromatography (hexane: EtOAc, 5:1 v/v) to yield 1-phenyl-1-propanol as a colourless oil. The enantioselectivity was determined by HPLC analysis [Daicel Chiralcel OD column, hexane/2-propanol 98:2, 0.5 mL/min, 254 nm (tᵣ 24.4 min, tₛ 31.8 min)]. \(^{10}\) \(\delta\) \(H\) (400 MHz, CDCl₃) 0.91 (3 H, t, \(J\) 7.6, CH₃), 1.23-1.29 (1 H, m, OH), 1.71-1.86 (2 H, m, CH₂), 4.58 (1 H, \(J\) 6.8, OCH), 7.21-7.38 (5 H, m, 5 x ArCH); \(\delta\) \(C\) (100 MHz, CDCl₃) 10.1 (CH₃), 31.9 (CH₂), 76.0 (CHOH), 125.9 (1 x ArCH), 127.5 (2 x ArCH), 128.4 (2 x ArCH), 144.6 (ArC).
3.4.2 Asymmetric Addition of Phenylacetylene to Benzaldehyde

**General Procedure B**

Under dry nitrogen, the ligand (0.20 mmol) and titanium tetraisopropoxide (0.4 mmol) were mixed in dry DCM (3.0 mL) at room temperature. Then diethylzinc (2.0 mL, 1.0 M solution in hexane) was added. After the mixture was stirred at room temperature for 2 h, phenylacetylene (3.3 mL, 3 mmol) was added and the mixture was stirred for 1 h. Then the solution was treated with benzaldehyde (102 μL, 1.0 mmol). After the reaction was completed (TLC, 18 h), the reaction solution was cooled to 0 °C and quenched by 5% aqueous HCl. The mixture was extracted with diethyl ether (3 x 10 mL). The extract was washed with brine (3 x 15 mL), dried over anhydrous MgSO₄, and concentrated under vacuum. The crude product was purified by flash column chromatography (silica gel, 12.5% EtOAc in petroleum ether) to give 1,3-diphenylprop-2-yn-1-ol as a colourless oil. The enantioselectivity was determined by HPLC analysis [Daicel Chiralcel OD column, hexane/2-propanol 90.0: 10.0, 1.0 mL/min, 254 nm (t (R) 10.0 min, t(S) 17.8 min)]. The predominant configuration of the products was given by the sign of the optical rotation compared with the literature data. δ H (400 MHz, CDCl₃) 2.26 (1 H, d, J 6.2, CHO), 5.69 (1 H, d, J 6.0, ArCCHOH), 7.30-7.65 (10 H, m, ArCH); δ C (100 MHz, CDCl₃) 65.2 [ArCCH(OH)], 86.4 [ArCCCH], 88.3 [ArCCH(OH)C], 122.3 (ArCCCH), 126.6 (2 x ArC), 128.2 (2 x ArC), 128.3 (ArC), 128.5 (2 x ArC), 128.6 (2 x ArC), 131.6(ArC), 140.5 [ArCCH(OH)]
3.4.3 Asymmetric Transfer Hydrogenation Reaction

General Procedure C

Ligand (0.022 mmol) and [RuCl\(_2\)(p-cymene)]\(_2\) (6.1 mg, 0.01 mmol) were dried under vacuum in a dry Schlenck tube for 15 min. 2-Propanol (degassed, 10 mL) and NaOH (4 mg, 0.1 mmol) were added under a nitrogen atmosphere. The solution was stirred for 30 min and acetophenone (2 mmol) was added. The reaction mixture was stirred at room temperature for 24 h. The reaction was quenched by addition of aqueous NH\(_4\)Cl, extracted with EtOAc (3 x 3mL) and the organic phase was subsequently passed through a pad of silica and evaporated under vacuum. The product was purified using SiO\(_2\) column chromatography. Enantiomeric excess (ee) determination was carried out using HPLC with a Daice Chiralcel OD HPLC instrument [solvent, 95:5 hexane/isopropanol; flow rate 1 ml/min; 254 nm UV detection, t \((R)\) 11.3 min, t \((S)\) 13.6 min]. The configuration was assigned by comparison with the sign of specific rotation of the known compounds.\(^{12}\) 1-phenylethanol: \(\delta_H\) (400 MHz, CDCl\(_3\)) 1.50 (3 H, d, \(J\ 6.6, CH_3\)), 1.80 (1 H, br s, OH), 4.91 (1 H, q, \(J\ 5.6, CHOH\)), 7.27-7.39 (5 H, m, ArH); \(\delta_C\) (100 MHz, CDCl\(_3\)) 25.3 (CH\(_3\)), 70.5(CHOH), 125.6 (2 x ArC), 127.6 (2 x ArC), 128.7 (2 x ArC), 146.2 (ArC).
3.4.4 Nozaki-Hiyama-Kishi Allylation of Benzaldehyde

![Chemical structure]

General procedure D

A flame-dried Schlenk tube was charged with dry THF (1 mL) and dry acetonitrile (150 µL). Anhydrous chromium (III) chloride (4.0 mg, 25.3 mmol) and manganese (41.7 mg, 0.76 mmol) were added simultaneously to the solvent mixture. The resulting suspension was allowed to stand at room temperature for approximately 30 minutes until the characteristic purple colour of the chromium (III) salt disappeared. The mixture was stirred vigorously under an atmosphere of nitrogen for 1 h resulting in a green reaction mixture. DIPEA (13 µL, 75.9 mmol) was added followed by the ligand (30.4 mmol) resulting in an immediate green catalyst mixture. This was stirred at room temperature for 1 hour prior to the addition of the allyl bromide (0.51 mmol) with the resulting chromium(III) allyl solution being stirred for a further 1 hour. The reaction was initiated by the addition of aldehyde (0.25 mmol) and chlorotrimethylsilane (64 µL, 0.51 mmol) and stirred under an atmosphere of nitrogen at room temperature for 16 hours. The resulting green–brown suspension was quenched with saturated aqueous NaHCO₃ (1 mL) and extracted with Et₂O (3 × 1mL). The combined organic layers were concentrated in vacuo to give a green residue. This was flushed through a small silica gel column (1.5×5 cm, pentane–AcOEt 9:1) to remove the catalyst and, after evaporation of the solvent, the reaction products were isolated as oil. The % conversion of the reaction are determined from the ¹H NMR spectrum of the crude product by measuring the ratio of the formyl proton of benzaldehyde (10.03 ppm) to the CH(OH) (4.57 ppm) of the product and assuming that all aldehyde consumed went to product. The crude product was dissolved in THF (1 mL), a few drops of aqueous 1 M HCl were added to complete desilylation. The solvent was removed in vacuo and the resulting aqueous phase was extracted with Et₂O (3 × 2 mL). The organic layers were combined, dried over anhydrous Na₂SO₄ and concentrated in vacuo to give a yellow oil. This was purified by flash column chromatography on silica gel (1 × 15 cm) using hexane–AcOEt 5:1 as the eluent to give the required product as an oil. Enantioselectivity was
determined using HPLC with a Daicel Chiralcel OD HPLC instrument (solvent, 90:10 hexane/isopropanol; flow rate 0.5 ml/min; 254 nm UV detection. Retention times were 25.1 min and 27.3 min for the racemic product and were not assigned to specific enantiomers.

3.4.5 Palladium Catalyzed Asymmetric Allylic Alkylation Reaction

\[ \text{Ligand/} \text{Pd}(\text{dba})_3 \text{CH}_2(\text{COOCH}_3)_2, \text{NaH} \]

\[ \text{H}_3\text{C}=\text{O} \]

\[ \text{O} \]

\[ \text{O} \]

\[ \text{CH}_3 \]

\[ \text{O} \]

\[ \text{O} \]

\[ \text{84} \]

\[ \text{85} \]

General Procedure E

A flame-dried N\textsubscr{2} filled Schlenk, was charged with tris(benzylideneacetone)dipalladium (5 mol\%) and the ligand (15 mol\%) before being degassed by three freeze-pump-thaw cycles. Dry toluene (3 ml) was then transferred under N\textsubscr{2}, into the Schlenk. The resulting mixture was then stirred for 2 h at 85°C. NaH (2.0 equiv.), dimethyl malonate (2.2 equiv.) and toluene (8 ml), were charged into a second flame-dried N\textsubscr{2} filled Schlenk. The resulting gel was stirred at 85°C for 15 min, before the addition of (\textit{rac})-(E)-1, 3-diphenyl-3-hydroxyprop-1-ene 73 (1 equiv.) in toluene (1 ml), and was stirred for a further 15 min. The catalyst was transferred to the substrate-nucleophile mixture via a gas-tight syringe, along with a toluene rinse (1 ml). This reaction mixture was then stirred at the appropriate temperature for 48 h. At that point saturated NH\textsubscr{4}Cl solution (10 ml) was added, the organic layer was separated and the aqueous layer was extracted with diethyl ether (3 x 10 ml). The combined organics were washed with brine (10 ml), dried, filtered and concentrated in vacuo to yield the appropriate crude product. A \textsuperscript{1}H NMR spectrum was recorded to determine the % conversion [unreacted (\textit{rac})-(E)-1,3-diphenyl-3-hydroxyprop-1-ene signal at 6.65 (1H, d) compared to product signal at 4.27 (1H, dd)]. Spectral characterisation was consistent with that reported for the product. In the case where conversion was achieved, the enantiomeric excess was investigated by HPLC analysis [Daicel Chiralcel OD, 254 nm, hexane (0.1% diethylamine): isopropyl alcohol, 99:1, 0.5 ml/min], t\textsubscript{R} = 19.9 min, t\textsubscript{S} = 22.0 min,
confirmed by comparison with the literature for similar HPLC system.\textsuperscript{4} There was no enantiomeric excess determined in any of the catalytic runs. $\delta_H$ (400 MHz, CDCl\textsubscript{3}) 3.53 (3H, s, one of OCH\textsubscript{3}), 3.70 (3H, s, one of OCH\textsubscript{3}), 3.96 (1H, d, $J$ = 11.0, COCHCO), 4.27 (1H, dd, $J$ = 10.5, 8.7, CH=CHCH), 6.34 (1H, dd, $J$ = 15.6, 8.7 Hz, CH=CHCH), 6.48 (1H, d, $J$ = 15.6 Hz, CH=CHCH), 7.34-7.17 (10H, m, 10 x ArCH), $\delta_C$ (100 MHz, CDCl\textsubscript{3}) 49.2 (CH=CHC\textsubscript{H}), 52.4 (OCH\textsubscript{3}), 52.6 (OCH\textsubscript{3}), 57.7 [C(O)CHC(O)], 126.3 (2 x ArCH), 126.6 (1 x ArCH), 127.2 (1 x ArCH), 127.6 (2 x ArCH), 127.9 (2 x ArCH), 128.5 (2 x ArCH), 129.1 (CH=CHCH), 131.9 (CH=CHCH), 136.8 (1 x ArC), 140.2 (1 x ArC), 167.7 (CO), 168.2 (CO).

3.4.6 Molybdenum Complex catalyzed Asymmetric Allylic Alkylation of 3-phenyl-prop-2-enyl methyl carbonate

![Chemical Structure]

**General Procedure F**

A flame dried Schlenk tube was charged with ligand (15 mol\%), and molybdenum hexacarbonyl (26.4 mg, 0.10 mmol, 10 mol\% Mo) before being degassed by three freeze-pump-thaw cycles. Toluene (3 ml) was added to this and the resulting mixture heated to 85°C for 2 h. Separately, a flame-dried Schlenk tube was charged with sodium hydride (60% dispersion in mineral oil, 80 mg, 2 mmol) and degassed before the addition of toluene (8 ml) and dimethyl malonate (0.25 ml, 2.2 mmol). The resulting gel was stirred at 85°C for 15 min, before 3-phenyl-prop-2-enyl acetate 79 (176.2 mg, 1 mmol) was added in toluene (1 ml), and stirred for a further 15 mins. The catalyst solution was then transferred to the substrate-nucleophile mixture via a gas-tight syringe, along with a toluene rinse (1 ml). The reaction mixture was then stirred at 85°C for 48 h before quenching with ammonium chloride (10% aq.), separation of the aqueous and organic layers, and the aqueous layer was further extracted with diethyl ether (3 x 10 ml). The combined organics were washed with brine (10 ml), dried and concentrated in vacuo, affording the crude products. Analysis by $^1$H NMR showed no conversion to the desired products in each catalytic reaction run.
REFERENCES


