

Hemiaminals: A New Chemotype for Organocatalysis

A dissertation submitted to the University of Cape Town in fulfilment of
the requirements for the degree
Masters in Chemistry

by

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February 2015

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Declaration

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Acknowledgements

Acknowledgements

I would like to acknowledge the following people and institutions for their support throughout this project:

My parents for their support and sacrifices they have done for me to be where I am. The long phone-call conversations really made a difference, I love you very much.

My supervisor Professor Roger Hunter for the long inspirational talks that encouraged me and were full of wisdom. Trust me rational intellect is my friend. Thank you for believing in me, you really made a difference in my life.

To the Hunter research group: thank you for patiently availing yourselves to help me with my project, not forgetting the laughter, there was never a dull moment in your presence.

To Ms. Deidre Brooks for just putting a smile on my face and enlightened my days whenever I was with you.

To my friends, Shankari, Khwezi and Latisa, a special thank you for the fun and inspiring conversations we had to keep the stress away, the laughter was worth every moment. I will forever remember your friendship.

To my sisters in Christ, Zanele, Lerato, Dimakatso, Hlengiwe, Ntombifikile and Keletso as well as the GBC-CPT family, I am really honoured to having met you. You will always remain in my heart.

The National Research Foundation for generously funding my studies.

Most importantly, I would like to thank my cornerstone, Jesus Christ, for remaining faithful to me and for keeping me free from worry. Indeed He is omnipotent, omniscient and omnipresent.

Abstract

Jorgensen and List introduced enantioselective α -amination of an aldehyde with an azodicarboxylate as the electrophile using L-proline enamine catalysis in 2002. Following borohydride reduction, the α -hydrazino alcohol was obtained in high yield (93-99%) and enantioselectivity (86-97%). Application of the enantioselective α -amination reaction to an acetal as a masked aldehyde was developed in our group recently, and in part I of this thesis results on extending this chemistry to the α -amination of *N*-protected hemiaminals from *N*-heterocycles are reported, in which it was found that the reaction only worked with the carbonyl group *exo* to the ring. In the case of the hemiaminal derived from *N*-Boc or *N*-CBz 2-pyrrolidinone an amination with proline catalyst in acetonitrile over 3 days gave α -aminated products in high ee (77-84%). N-N bond hydrogenolysis using Raney Nickel and hydrogen, followed by oxidation to the lactam afforded the *N*-protected α -amino lactam in high enantioselectivity (78% and 86%).

In part II the development of a mild reduction of the N-N bond of the α -hydrazino amination products of straight-chain aldehydes is reported. The corresponding oxazolidinone-hydrazides are reduced to their oxazolidinones via a modified E1cB elimination using ethyl bromomalonate and potassium carbonate in acetonitrile. The reactions gave high yields (76-96%) and ees (83-95%) with a good chemoselectivity profile.

Abbreviations

δ	chemical shift (NMR)
$^{\circ}\text{C}$	degrees centigrade
Ar	aromatic
Boc	<i>tert</i> -butoxycarbonyl
Bn	benzyl
(Boc) ₂ O	di- <i>tert</i> -butyl dicarbonate
br	broad
CBz	benzyloxycarbonyl
CDCl ₃	deuterated chloroform
CH ₃ CN	acetonitrile
d	doublet
dd	doublet of doublet
DCM	dichloromethane
DBAD	dibenzyl azodicarboxylate
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DMAP	4- <i>N,N</i> -dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
dr	diastereomeric ratio
DTBAD	di- <i>tert</i> -butyl azodicarboxylate
ee	enantiomeric excess
eq.	equivalents
g	gram(s)
h	hours
HPLC	high pressure liquid chromatography
HRMS	high-resolution mass spectroscopy
Hz	hertz
<i>J</i>	NMR spectra coupling constant
LiEt ₃ BH	lithium triethylborohydride
M	molarity
m	multiplet
Me	methyl
MeOH	methanol
mg	milligram(s)
min	minutes
mL	millilitre(s)
mmol	millimole(s)
<i>M/z</i>	mass-to-charge ratio
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
Pent	pentet

Abbreviations

Ph	phenyl
ppm	parts per million
q	quartet
RT	room temperature
R _t	retention time
s	singlet
t	triplet
td	triplet of doublet
THF	tetrahydrofuran
TLC	thin layer chromatography
TM	target molecule

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Chapter 1

Introduction

1.1 Chirality

Chirality is a property of three-dimensional molecules, in which a molecule is chiral if its mirror image cannot be superimposed on the original. An example in everyday life is hands and feet. Such non-superimposable mirror images are known as enantiomers, and they have identical chemical and physical properties, but may react differently in biological systems, which are themselves chiral. The predominant structural feature that makes a molecule chiral is the lack of mirror-plane symmetry, although a more comprehensive analysis reveals the lack of S_N symmetry (rotation-reflection symmetry). Enantiomers are characterised as stereoisomers, as they only differ in overall shape and not the connectivity of the atoms.¹ The origin of chirality lies in the existence of stereogenic units or elements, for which there are three types as: central, axis and plane. Centrally chiral molecules possess an asymmetric tetrahedral carbon atom bearing four different groups or atoms, termed a stereogenic or chiral centre. Axially chiral molecules arise from the arrangement of different groups about a stereogenic axis, while planar chirality is the result of arranging groups with respect to a stereogenic plane, Figure 1.²

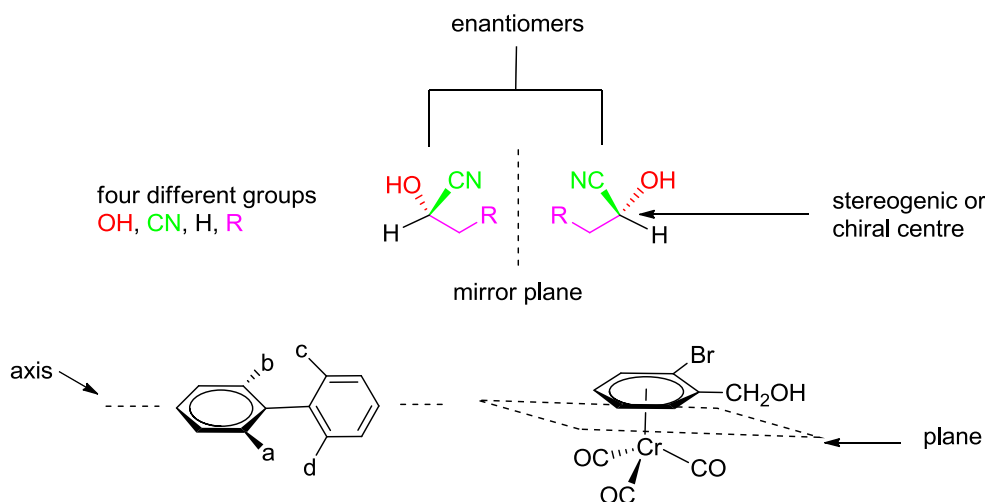


Figure 1: Examples of central, axial and planar chiral molecules.

Evidence for molecular chirality was discovered by the French chemist Louis Pasteur in 1848 when he resolved the structure of sodium ammonium (\pm)-tartrate, a side product from wine production, through studies in search of the origin of the optical activity in the crystals, Figure 2.^{3,4} However, it wasn't until 1874 that the Dutch chemist and winner of the first Nobel Prize in Chemistry, Jacobus Henricus van't Hoff, and French chemist Joseph Achille

Le Bel, independently explained optical activity in terms of the tetrahedral arrangement of the atoms around a carbon centre.⁵

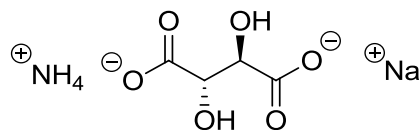


Figure 2: The structure of sodium ammonium (\pm)-tartrate.

Chemists use two main stereochemical conventions to differentiate between enantiomers based on the assignment of a stereodescriptor to each enantiomer. The first and most used is the IUPAC Cahn–Ingold–Prelog (CIP) system named after Robert Sidney Cahn, Christopher Kelk Ingold and Vladimir Prelog. Here, a set of rules assign the absolute configuration of a stereogenic centre based on the rotational direction of atoms around a chiral centre based on their relative priority, in which *R* denotes clockwise rotation (*rectus*) while *S* denotes anti-clockwise (*sinister*).^{6,7} Figure 3 illustrates the system for lactic acid.

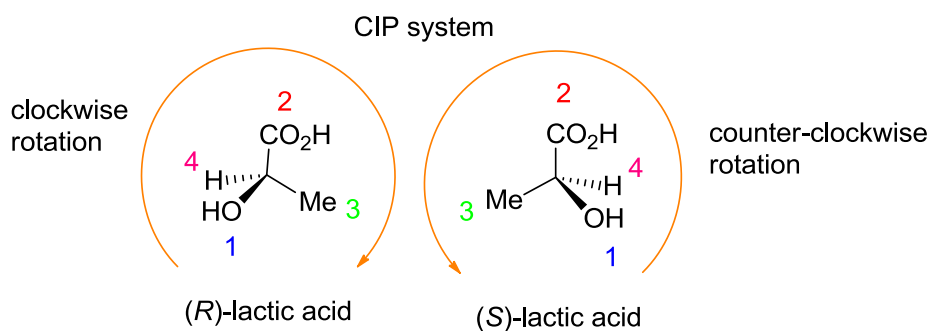


Figure 3: CIP stereochemical convention.

The second convention predates this by some fifty years or so and is the D- and L-convention due to the great German carbohydrate chemist Emil Fischer in the late 19th century. Before X-ray crystallography was developed chemists used glyceraldehyde as a standard that could be used as a comparison for deducing the configuration of other molecules based on their degradation to it. Fischer developed a 2D-convention in which the molecule is represented in a square planar fashion (glyceraldehyde as the prototype). In this the carbon backbone is placed vertically with the most oxidised carbon at the top, while the horizontal groups bear the H and OH substituents. The 2D-drawing has implied stereochemistry in which horizontal groups are taken as wedged while vertical groups are taken as dotted. Fischer designated the chiral centre of glyceraldehyde as D- or L- depending on whether the OH group was on the right or left respectively. He made the lucky guess, since it turned out to be correct, that the (+)-enantiomer of glyceraldehyde (based on optical rotation) was the D-isomer. This has been

proved to be correct by X-Ray crystallography and is equivalent to the R-enantiomer according to the CIP system, Figure 4.⁸

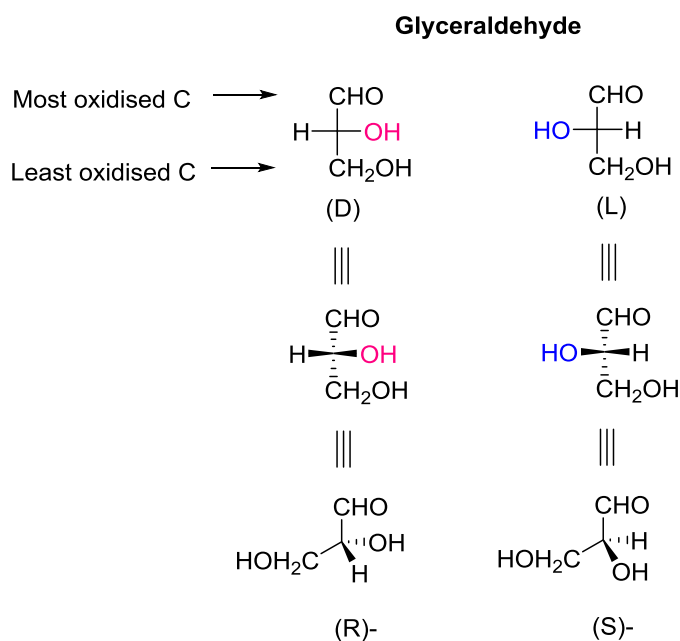


Figure 4: The Fischer convention.

In addition, the physical parameter of optical activity $[\alpha]_D$ is also used to assign a stereodescriptor to a particular enantiomer. This is based on the interaction of a chiral molecule with plane-polarized light in which the rotation of light to the right is given a (+) or *dextrorotatory* and to the left a (-) or *laevorotatory* descriptor.⁹ In the past, optical activity was the only measurable parameter for determining the enantiomeric purity of molecules but now there are techniques such as nuclear magnetic resonance (NMR) with a chiral shift reagent, and high pressure liquid chromatography (HPLC) using a chiral column.¹⁰ Equal quantities of two enantiomers in a mixture is called a racemic mixture, and this can be produced in a reaction from the addition of an achiral reagent to a prochiral centre in an achiral substrate. A classical example is the Strecker synthesis of amino acids as shown for acetaldehyde in Scheme 1. The reaction dates back to 1850, and involves reaction of an aldehyde with ammonium chloride to form an imine, which reacts with potassium cyanide (KCN) to produce an α -amino nitrile. The latter forms via a statistically equal addition to the two enantiotopic faces of the imine to afford a racemic mixture, which is then hydrolysed to the racemic α -amino acid, Scheme 1.¹¹

An example that led to the new legislation regarding the use of enantiomers in pharmaceuticals is that of thalidomide. Prescribed to pregnant women in the 1950's for treatment of insomnia and morning sickness, the company in question (Chemie Grünenthal) were unaware that while the *R*-isomer was indeed effective as a sedative, the *S*-isomer had teratogenic properties, Figure 6. This resulted in children being born with multiple birth defects and the drug was withdrawn from the market.^{14,15} Table 1 shows other drugs whose enantiomers produce different effects.¹⁶

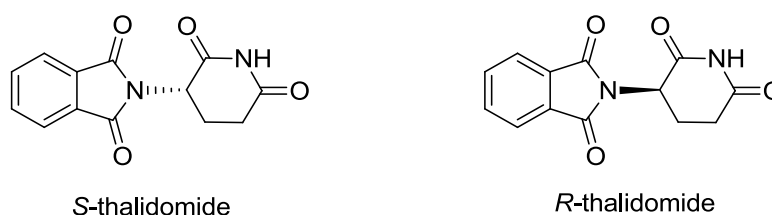


Figure 6: *S*- and *R*-isomers of thalidomide.

Table 1: List of drugs and effects of enantiomers

Drug	<i>R</i> -enantiomer	<i>S</i> -enantiomer
Ibuprofen	Slow acting	Fast acting
Prozac	Anti-depressant	Helps against migraine
Naproxen	Liver poison	Arthritis treatment
Dopa	Biologically inactive	Parkinson's disease

CC(C)C(C)C1=CC=C(C=C1)C(C)C(=O)O CN(C)CCOC1=CC=C(C=C1)C(F)(F)F CC(O)C(=O)Oc1ccc2cc(OC)ccc2c1 NC(C)C(O)C1=CC=C(O)C=C1
 Ibuprofen Prozac Naproxen Dopa

There are methods that can be used to resolve racemates into their enantiomers such as direct preferential crystallization, the crystallization of diastereomeric salts or via kinetic resolution, but industrial production needs to consider methods that are fast and cost-effective.¹⁷ The progression to synthetically produce enantiomerically pure molecules led to the concept of asymmetric synthesis.

1.2 Asymmetric synthesis

Asymmetric synthesis refers to when a prochiral centre is converted into a chiral one such that there is a preference for stereogenicity at the new chiral centre. If the starting material is achiral, enantiomers may be produced in unequal amounts using a chiral reagent, while if the starting material is chiral, diastereomers can be produced in unequal amounts regardless of whether the reagent is chiral or not. The respective terminology applied is enantioselective and diastereoselective, which reflects selectivity by degree, i.e. is rarely 100% selective. Racemic mixtures arise because the transition states of the products have the same energy. Asymmetric synthesis involves the manipulation of reaction parameters in order to create transition states with diastereo- character that have different energies, resulting in the favouring in formation of one product over the other, Figure 7.¹⁸ Understandably, the various methodologies can be divided into diastereoselective and enantioselective types, and these will now be discussed in that order.¹⁹

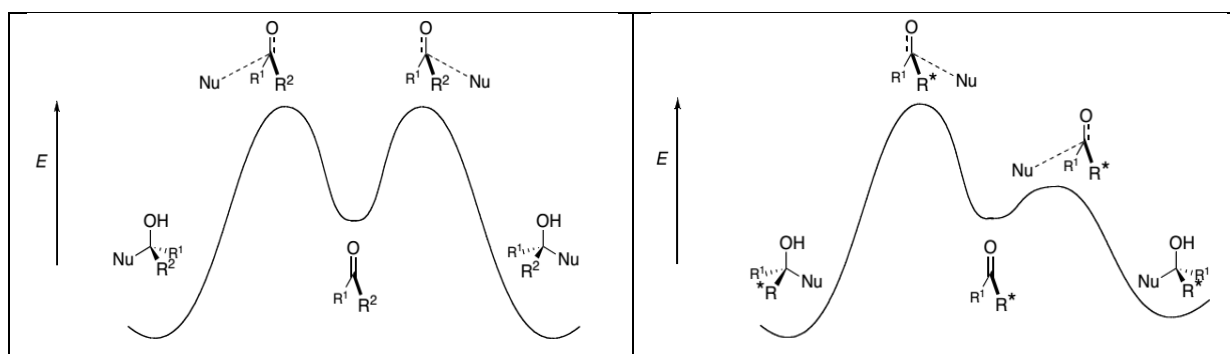


Figure 7: Equal transition state energies forming a racemic mixture (left), and unequal transition-state energies forming more of the desired product (right).

1.2.1 Diastereoselective Asymmetric Synthesis

Diastereoselective asymmetric synthesis is the formation of one diastereomer in excess over the other. The degree of diastereoselectivity is measured by a diastereomeric excess (de) and is calculated by subtracting minor from major isomer percentages (D as a percentage), Equation 1.²⁰

$$\text{de} = D_{\text{major}} - D_{\text{minor}} \text{ where } D_{\text{major}} + D_{\text{minor}} = 100\%$$

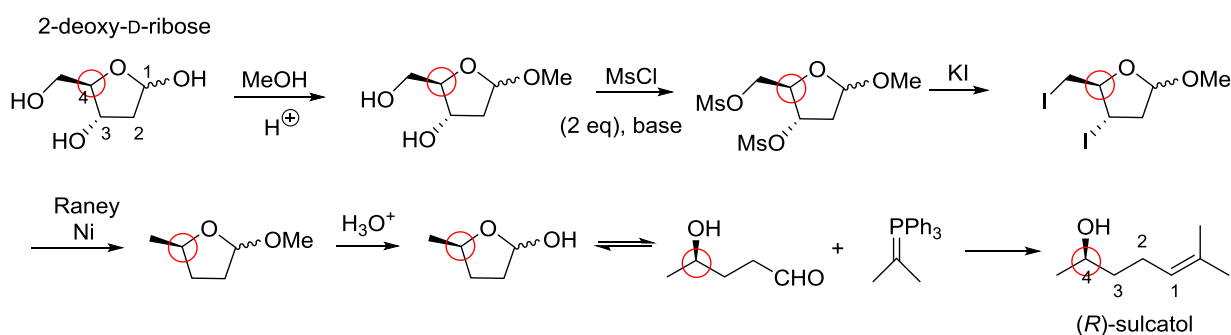
Equation 1: The equation for diastereomeric excess.

Alternatively, the two percentages of major and minor isomers can be reported as a diastereoisomeric ratio (dr), eg 95:5 dr = 90% de. A common type of this type of induction is

promoted when chirality is present in the substrate to direct the induction, and such a type of process is termed a substrate-controlled one. More often than not the reagent is achiral, but in some cases a double asymmetric induction approach is utilised involving chirality in both substrate and reagent, which can give rise to match and mis-match outcomes. The following sections describe the various categories that the literature has assigned to manipulating existing chirality in the substrate for asymmetric synthesis.

(i) Chiral pool

Chiral pool synthesis refers to having the chirality originating from a natural source such as a sugar (carbohydrate) or amino acid. Here the chirality starts as a pure enantiomer even if there is more than one chiral centre, even if not all centres are carried through into the target. New chirality created from prochirality is engineered from existing chirality in the starting material, and synthesis often involves several steps and may require complex transformations, Scheme 2.²¹ Problems using this strategy arise when the desired enantiomer is not available as a natural product. An example of a chiral pool synthesis that does start from the correct enantiomer is shown in Scheme 2 in which 2-deoxy-D-ribose is converted into the insect pheromone Sulcatol, and as a pure enantiomer (*R*). The chiral centre in the product is derived from C-4 of the ribose, while the C-3 hydroxyl of the ribose is reductively removed, and its anomeric centre (C-1) converted into the olefin.

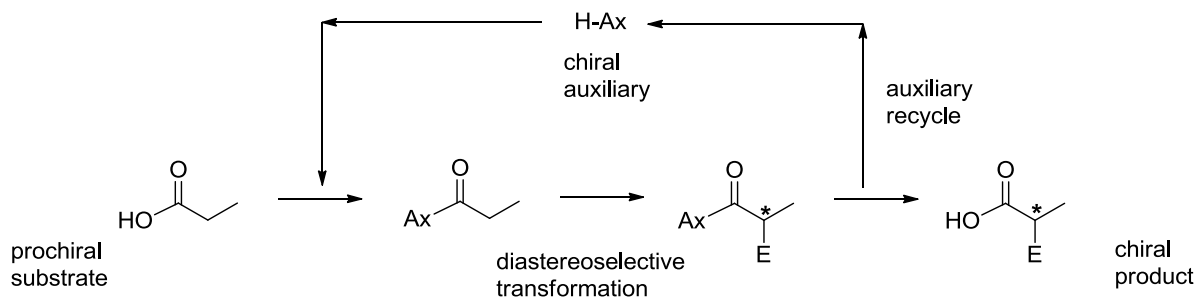


Scheme 2: Chiral pool synthesis from a sugar.

(ii) Chiral auxiliary

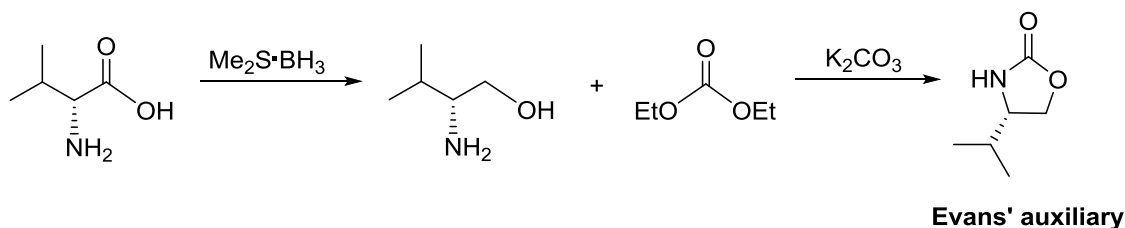
Chiral auxiliaries are enantiomerically pure organic compounds that are used to control the diastereoselectivity of asymmetric reactions. The auxiliary is first covalently bonded to the achiral substrate making it chiral. A diastereoselective reaction then follows. Finally, the auxiliary is removed without changing the configuration of the newly-formed chiral centre or

centres. The final product should be obtained in a high enantiomeric excess ultimately, and a good auxiliary is one that is easily removed intact and can thus be recycled, Scheme 3. Because the primary products are diastereomers, column chromatography or crystallization can often be used to separate them, but to be effective, drs need to be in the 90+ region.²² Scheme 3 illustrates an example for the α -alkylation of an acid.



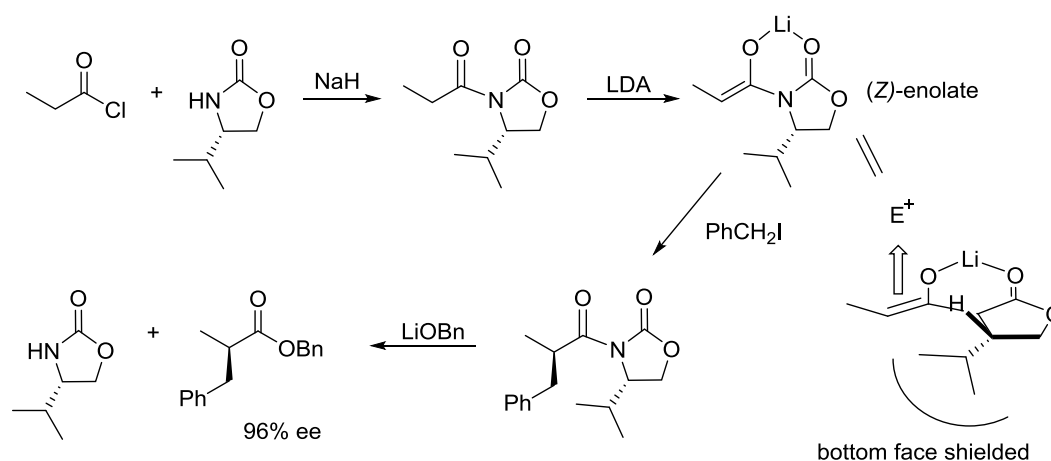
Scheme 3: Asymmetric α -alkylation using a chiral auxiliary

Although auxiliary-controlled methodology dates back to at least the 1970s, one of the most famous auxiliary-controlled methodologies is that developed in the early 1980s by David Evans at Harvard using oxazolidinones synthesized from amino acids using the chiral pool strategy, Scheme 4.



Scheme 4: Synthesis of chiral auxiliary from (*S*)-valine.

These have been used to bring about highly diastereoselective alkylations, as well as aldol and Diels-Alder reactions. Diastereoselectivity is achieved by the conformational preference of the auxiliary in the substrate intermediate (eg enolate), together with the shielding of one face of the prochiral functionality undergoing addition to create the new chiral centre through steric hindrance created by the chiral substituent attached to the auxiliary. Scheme 5 illustrates these ideas in a standard alkylation sequence in which, following *Z*-enolate formation, chelation of the lithium with the oxazolidinone carbonyl creates a flat enolate in a chiral environment as a single conformer (*s-cis*_{C-N}). Addition then proceeds from the face anti to the chiral substituent on the oxazolidinone ring. After reaction the auxiliary can be removed by $\text{S}_{\text{N}}\text{Ac}$ hydrolysis, without racemising the newly formed centre.²³



Scheme 5: Directed electrophilic attack using Evans' auxiliary.

1.2.2 Enantioselective Asymmetric Synthesis

Following the same trend as with diastereoselectivity, enantioselective asymmetric synthesis is the formation in a reaction of one enantiomer in excess over the other. The degree of enantioselectivity is measured by an enantiomeric excess (ee) and is recorded as a percentage, Equation 2, where E is the % of an enantiomer.²⁴ This type of induction generally implies the use of a chiral reagent or catalyst transferring asymmetry to a prochiral substrate and is therefore categorized as reagent-controlled asymmetric induction.

$$ee = E_{\text{major}} - E_{\text{minor}} \text{ where } E_{\text{major}} + E_{\text{minor}} = 100\%$$

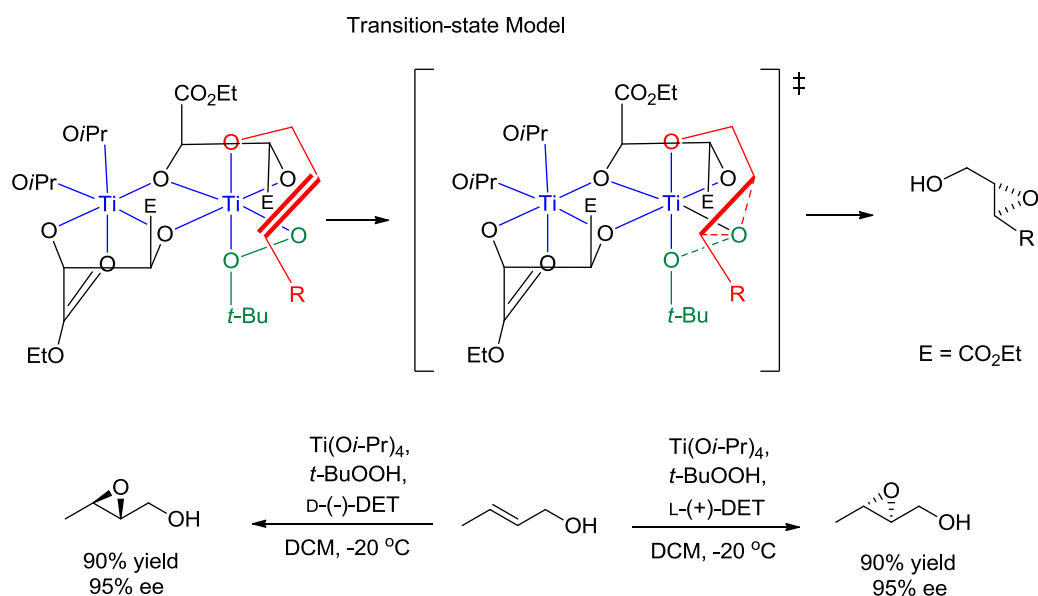
Equation 2: Equation for enantiomeric excess.

There are a plethora of enantioselective methodologies in the modern synthesis literature, so the examples that follow are key ones designed to illustrate the key principles.

(i) Epoxidation

Enantioselective epoxidation is a highly useful reaction, since the chiral epoxide can be ring-opened to afford a variety of highly functionalized chiral building blocks (chirons) such as alcohols, diols and amino alcohols.²⁵ In 1980, Karl Barry Sharpless developed a unique stereoselective epoxidation reaction that transforms primary and secondary allylic alcohols into epoxy alcohols, known as the Sharpless epoxidation.²⁶ Scheme 6 depicts the currently accepted transition-state model for this reaction involving the coordination of a chiral ligand, diethyl tartrate (DET), with a titanium catalyst, titanium tetra-isopropoxide, to form an active

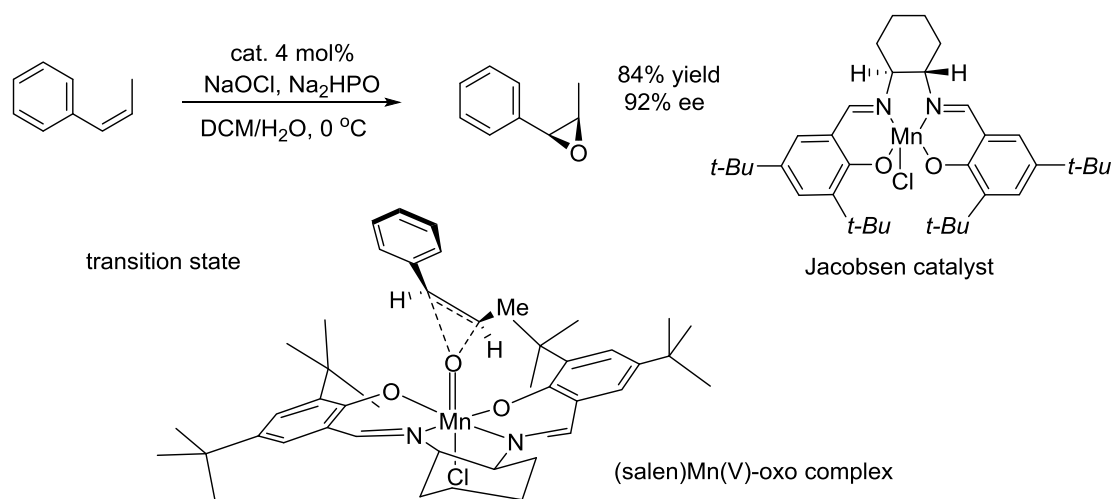
complex comprising two titanium atoms bridged by two tartrate ligands, which then reacts with an oxidizing agent *tert*-butyl hydroperoxide that displaces one of the isopropoxide ligands and one of the tartrate carbonyl groups. The allylic alcohol (here presented in a generalised form) then coordinates with the titanium by displacing a further isopropoxide ligand. The shape of the complex, which is depicted in Scheme 6 using L-(+)-DET, forces the reactive oxygen atom of the bound hydroperoxide to be delivered to a single face of the olefin. Also illustrated is the stereoselective outcome of the product which is controlled by the use of either L-(+)-DET which delivers the oxygen to the bottom face of the olefin, or D-(-)-DET which delivers the oxygen to the top face, according to the way structures are drawn. As shown, of significance here is the prior covalent attachment of reagent with substrate (here through a Ti-O bond) so that the reagent (an oxygen in this case) can be delivered selectively to one of the enantiotopic faces of the substrate (defined as such prior to co-ordination).



Scheme 6: Sharpless epoxidation.

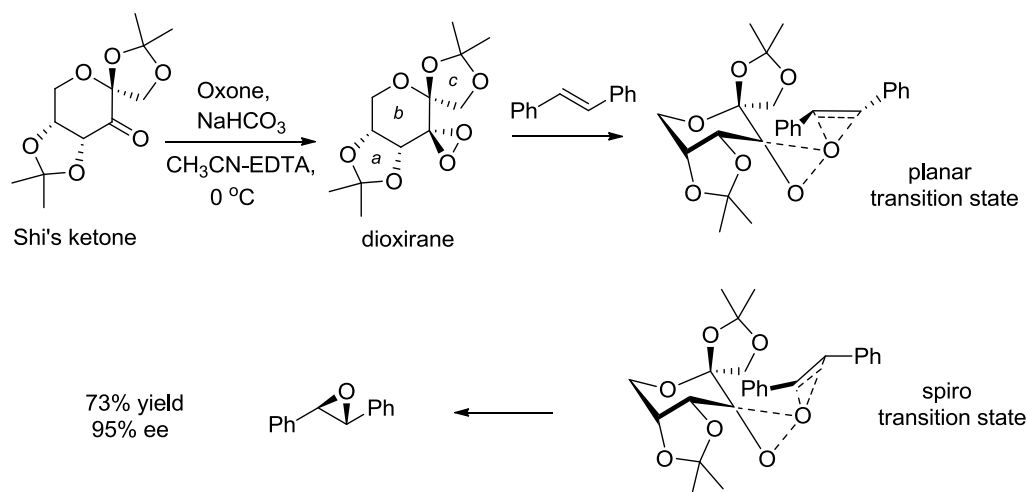
Later in the early 1990s, the Jacobsen-Katsuki epoxidation was developed by Eric Jacobsen and Tsutomu Katsuki who independently reported the use of a chiral manganese(III)-salen catalyst to transform unfunctionalized *cis*-olefins. In contrast to Sharpless epoxidation this reaction relies solely on attractive electrostatic interactions (not involving any covalent bonds between substrate and reagent), and hence doesn't require an adjacent functional group in the substrate like a hydroxyl group as in the Sharpless epoxidation case, Scheme 7.²⁷ The

(salen)Mn(V)-oxo complex has the two six-membered chelate rings distorted relative to one another in the transition state ensuring that the neighbouring *t*-butyl groups do not clash sterically. As a result of this positioning, the steric blocking of one face of the catalyst dominates more than the other forcing the incoming alkene to approach from the top in this case. Furthermore, the alkene approaches with the two R groups pointing away from the ligands, something that is not so clear-cut with a *trans* olefin.²⁸



Scheme 7: Jacobson-Katsuki epoxidation.

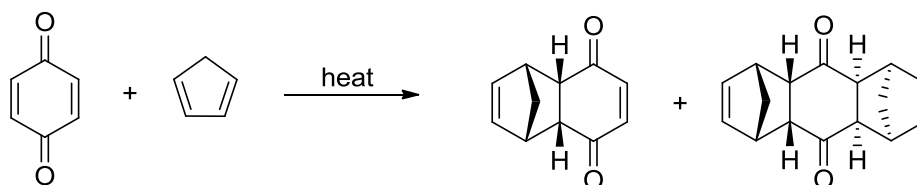
Another example is the Shi epoxidation developed in the mid 1990s by Yian Shi that utilizes a fructose-derived (chiral ketone) dioxirane catalyst that reacts with *trans* 1,2-di- and trisubstituted olefins as shown in Scheme 8 for *E*-stilbene. The catalyst is readily prepared by ketalization of D-fructose with acetone and perchloric acid followed by oxidation using pyridinium chlorochromate.²⁹ The epoxidation proceeds via a dioxirane intermediate produced by reaction of oxone (potassium peroxydisulfate) with the ketone carbonyl group, and transfer of oxygen to the alkene regenerates the ketone catalyst rendering the process catalytic.³⁰ The enantioselectivity in the product is controlled by either going through a planar or spiro transition states, with minimised steric interaction between the alkene substituent and the dioxolane *c* ring. Also, the lone pair of the oxygen involved in the transition state interaction lends stability via interaction with the alkene π^* orbital. In the transition state the alkene approaches the least-hindered equatorial oxygen of the dioxirane.³¹



Scheme 8: Shi epoxidation.

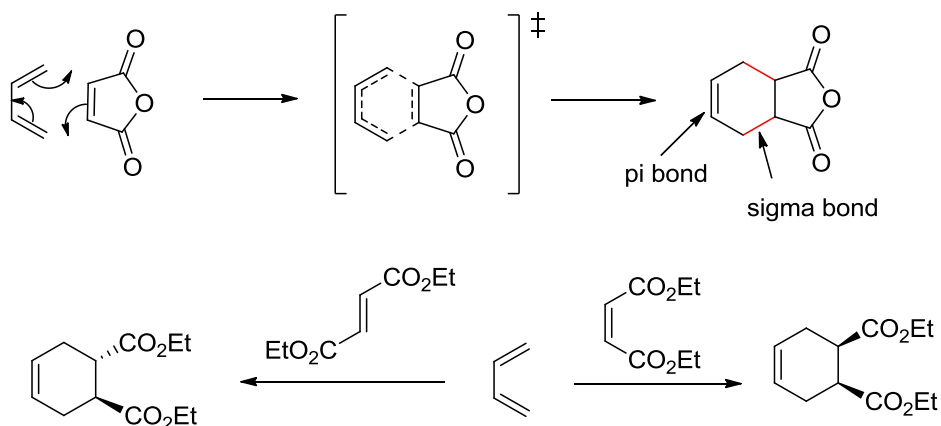
(ii) Diels-Alder Cycloaddition

The Diels-Alder reaction is named after Otto P. H. Diels and his student Kurt Alder who made the discovery jointly in 1928 during their studies on the reaction of benzoquinone with cyclopentadiene, Scheme 9.³²



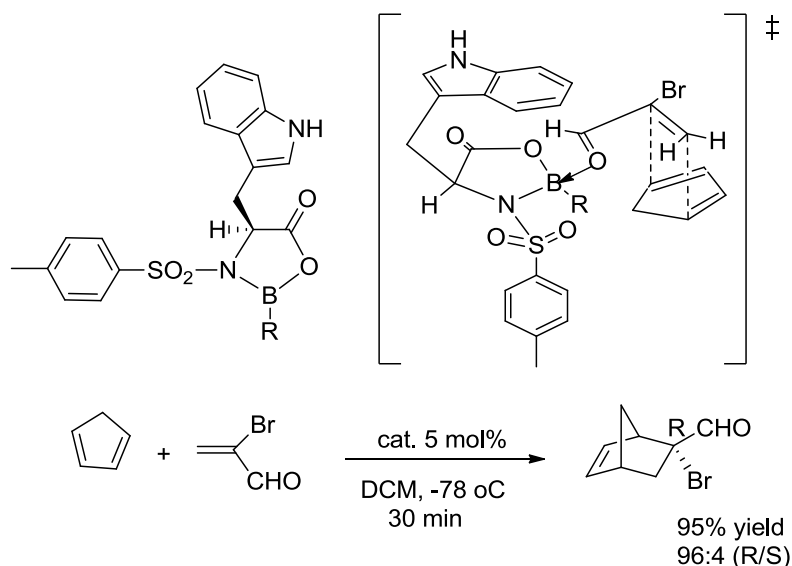
Scheme 9: Discovery of the Diels-Alder reaction.

This reaction is termed a cycloaddition and occurs between a conjugated diene in a *cis* conformation and a substituted alkene referred to as the dienophile. The concerted transition state has a cyclic geometry shaped like a six-membered ring formed from the delocalization of π electrons. It involves no ions or free radicals and has no intermediate. Two new σ bonds and one π bond are created in the product and any stereochemistry observed in the reactants is retained in the product (stereospecific), as depicted in Scheme 10.³³



Scheme 10: Cycloaddition of a diene and dienophile.

Following the discovery, researchers eventually developed Diels-Alder reactions using chiral Lewis acids for exploring the possibility of achieving enantioselectivity, in which Corey has made seminal contributions.³⁴ Corey found that oxazaborolidines derived from amino acids were particularly effective. Scheme 11 shows the case for a tryptophan-derived catalyst, where there is a proposed level of π -stacking between the π -excessive indole ring and the electron-deficient carbonyl group, rendering one face of the dienophile only as accessible for cycloaddition.^{35, 36}

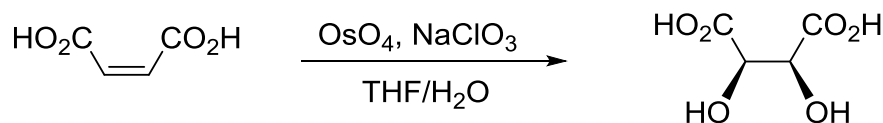


Scheme 11: Oxazaborolidine use in Diels-Alder reaction.

(iii) Dihydroxylation

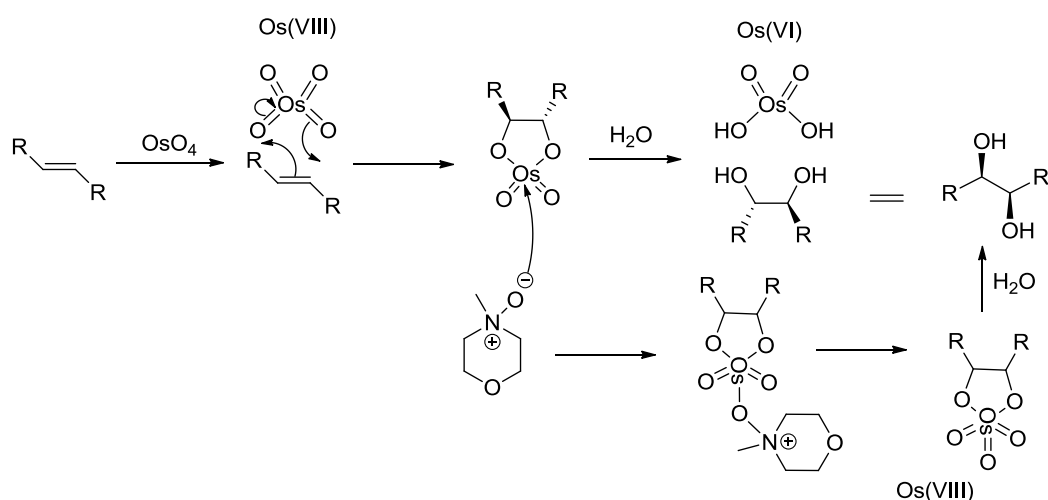
The use of osmium tetroxide (OsO_4) in the *cis*-dihydroxylation of prochiral olefins dates back to 1912 when Hoffmann carried out a reaction in the presence of a chlorate salt that acted as

an oxidant of the osmium once reacted, Scheme 12. About 30 years later, Rudolf Criegee and co-workers discovered that pyridine accelerated the rate of the reaction.³⁷



Scheme 12: Hoffmann dihydroxylation.

The dihydroxylation proceeds through a cycloaddition reaction of OsO_4 and the olefin to form an osmate ester, which is hydrolysed to give a 1,2-diol product. During this process osmium (VIII) is reduced to osmium (VI) necessitating the use of large amounts of this toxic and volatile reactant.³⁸ The introduction of *N*-methyl morpholine-*N*-oxide (NMO) as a co-oxidant by the Upjohn Company assisted in this aspect by transforming the process into the use of catalytic OsO_4 as shown in Scheme 13, and this paved the way for the development of the asymmetric dihydroxylation of olefins using a chiral ligand.³⁹



Scheme 13: Catalytic dihydroxylation.

Early attempts with chiral ligands gave low ees owing to the instability of the complex, but eventually excellent ees could be realised using cinchona-derived ligands,⁴⁰ and the use of a phthalazine spacer unit to create C-2 symmetry. The phthalazine spacer is attached to two chiral cinchona ligands (DHQ or DHQD – see Figure 8) placed on either side. Scheme 14 illustrates the reaction with osmium being added as potassium-osmate (VI) dehydrate ($\text{K}_2\text{Os}_2(\text{OH})_4$) along with potassium ferricyanide ($\text{K}_3\text{Fe}(\text{CN})_6$) as the oxidant together with other additives that speed up the reaction.⁴¹

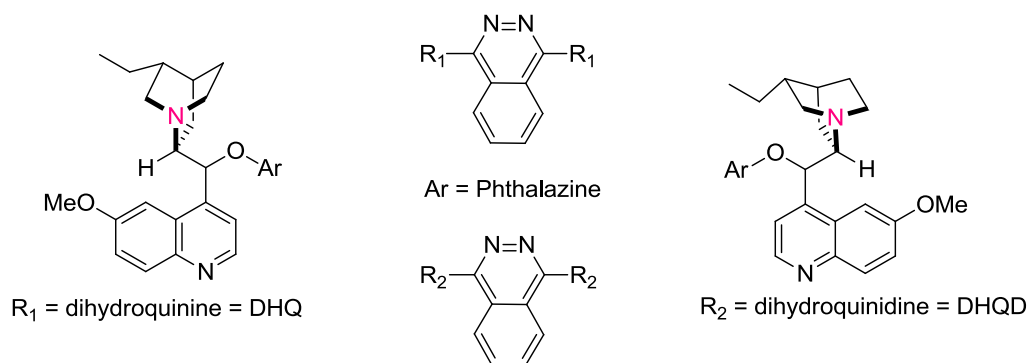
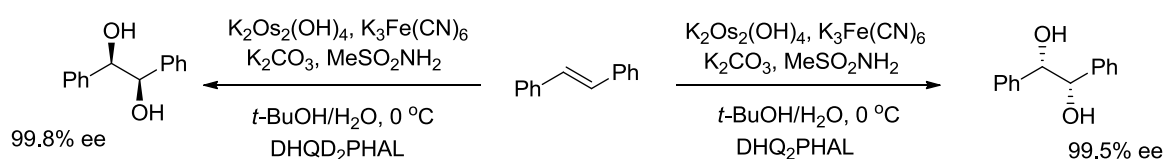


Figure 8: Phthalazine-based ligands.

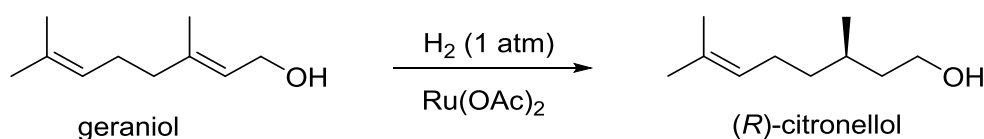


Scheme 14: Sharpless dihydroxylation.

A full description of the transition-state models accounting for enantioselectivity is complex and beyond the scope of this dissertation, but enantioselectivity relies on intermolecular interactions in a chiral environment.

(iv) Hydrogenation

The hydrogenation of unsaturated compounds such as alkenes, ketones and imines into chiral alkanes, alcohols, amino acids and amines respectively with asymmetric induction has been one of the most intensely studied objectives in transition-metal catalyzed reactions. Enantioselective hydrogenation requires a chiral catalyst, which directs the addition of hydrogen across the double bond, and is best carried out on an alkene with a heteroatom neighbour.⁴² Rhodium and ruthenium-based complexes are the most commonly used catalysts and these require the presence of a chelating functionality in the substrate, whereas iridium-based catalysts do not require coordination.⁴³ Since hydrogenation only requires a minuscule amount of the catalyst (2 mol%), this method is widely used in industry to synthesize chiral compounds, such as the terpene citronellol (see Scheme 15 below), which is used in fragrances.



Scheme 15: Hydrogenation using Ruthenium.

The first examples of homogenous asymmetric hydrogenation were independently reported by Leopold Horner and William Knowles in the late 1960s by modifying Wilkinson's catalyst $\text{RhCl}(\text{PPh}_3)_3$ with chiral monodentate phosphine ligands, but these provided poor enantioselectivities (8-15%).⁴⁴ Later, Henri Kagan and Knowles demonstrated that using bidentate chiral phosphine ligands improved enantioselectivity (88-96%). They each independently reported the C_2 -symmetric bisphosphine ligands, DIOP and DIPAMP, for rhodium-catalyzed asymmetric hydrogenation.^{45, 46} In 1980, Noyori and Takaya reported an atropisomeric (axial chirality about the bond joining the two naphthalene rings) C_2 -symmetric bisphosphine ligand, BINAP, which is now often used in ruthenium-based catalysis, Figure 9.⁴⁷ Researchers believed that the preferred mode of initial binding of the prochiral olefinic substrate to the catalyst determined the enantioselectivity, but in actual fact it is actually due to the difference in the rates of subsequent reactions of the catalyst-substrate adducts with H_2 .⁴⁸

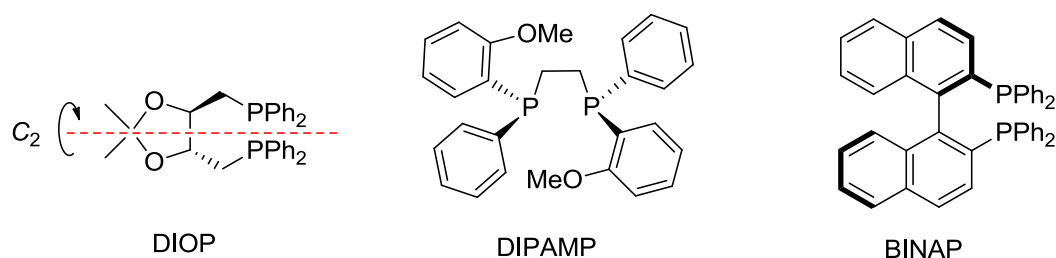
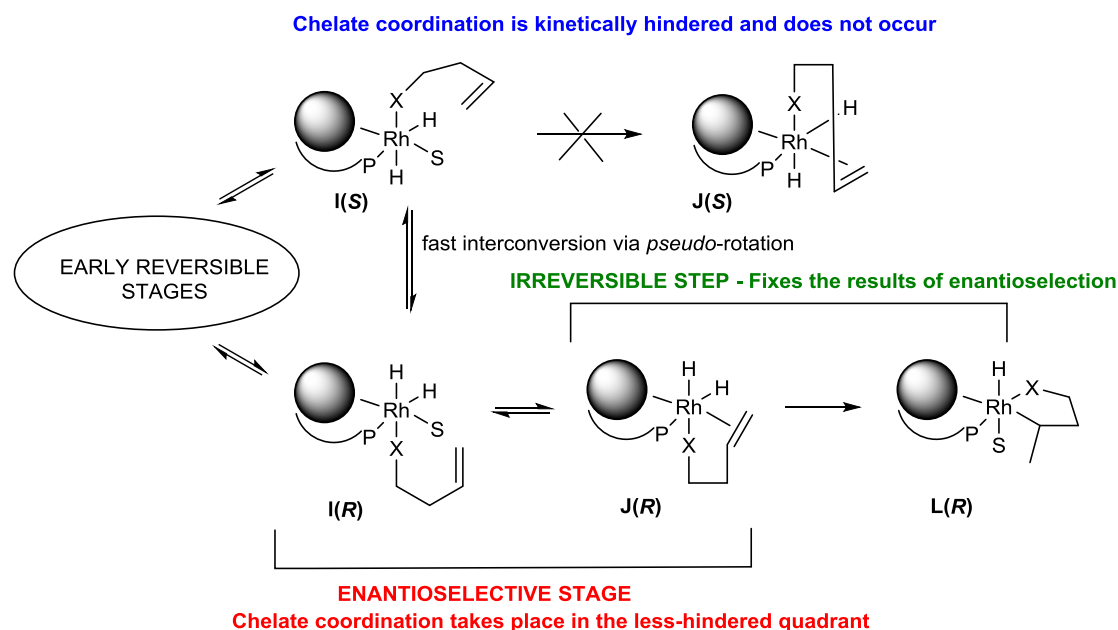
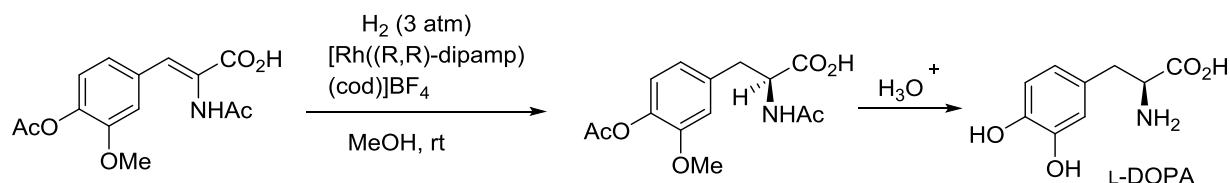


Figure 9: Bidentate ligands used for hydrogenation.

The enantioselectivity in simple terms results in the selective addition of hydrogen to the least hindered enantiotopic face of the double bond and with the substrate presenting itself to the catalyst in the energetically minimised way. The generally agreed mechanism is that the rhodium undergoes oxidative addition to the prochiral bond in which coordination of the metal to an adjacent donor atom in the substrate (eg N or O) together with non-bonded interactions between the chiral ligands and substrate determines facial selectivity. Thereafter, reductive elimination with retention of configuration leads to the chiral product with regeneration of catalyst. Ilya *et al.* conducted experiments which showed consistency with the idea that enantioselection takes place through the reversible coordination of the double bond in octahedral dihydride complexes, which can happen only if the resulting chelate cycle is formed in the less hindered quadrant, Scheme 16.⁴⁹ Some reaction examples are illustrated in Scheme 17.⁵⁰



Scheme 16⁴⁹: Stereoselection in Rh-catalyzed asymmetric hydrogenation through chelation with dihydride complexes.



Scheme 17: Examples of ruthenium and rhodium-based hydrogenations.

1.3 Organocatalysis

Chemical transformations that use organic catalysts such as those in enzymatic / bioorganic catalysis and as ligands in organometallic catalysis have been known over the past century but it was not until the late 1990s that the field of organocatalysis was made popular as one of the main branches of enantioselective synthesis.⁵¹ Organocatalysis is defined as the use of small organic molecules as metal-free catalysts. The advantages of organocatalysts include their stability in air and water, their ready availability in nature in both enantiomeric forms, and their relatively low cost and low toxicity, which presents a huge direct benefit in the production of pharmaceutical intermediates when compared with (transition) metal catalysts, which invariably leave trace amounts of heavy metals in the products.⁵² Organocatalysts can be synthesized or accessed from naturally occurring chiral molecules, and are also amenable to solid-phase synthesis and high-throughput screening techniques.

Essentially, organocatalysts can be classified as either Lewis bases, Lewis acids, Brønsted bases or Brønsted acids, examples of which are shown in Figure 10. Some catalysts are bifunctional having both an acid and base functionality. The catalytic cycles of these organocatalysts is initiated by either supplying or removing electrons or protons from a substrate or transition state.⁵³

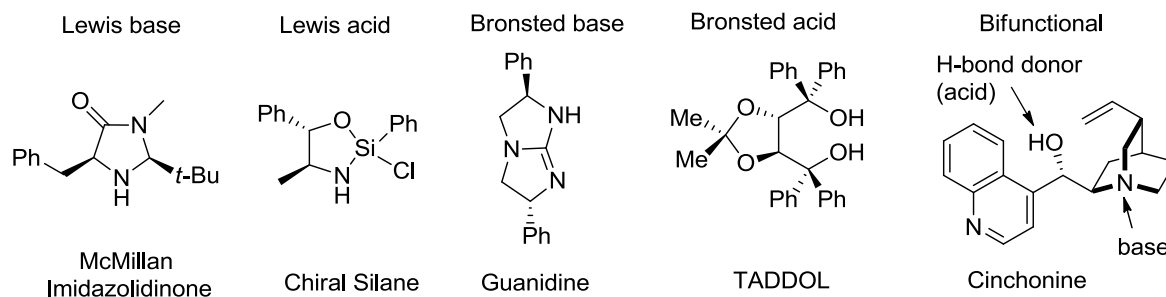
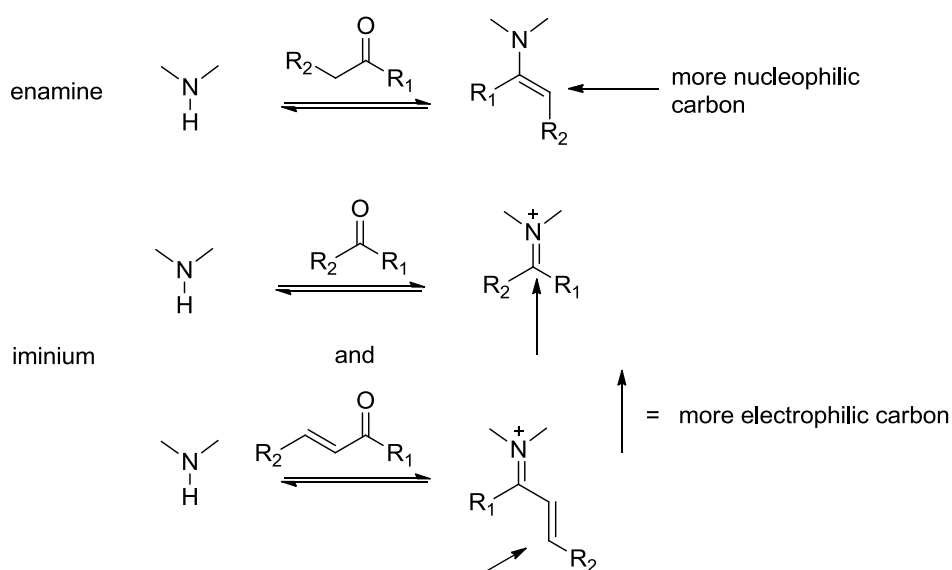


Figure 10: Different classifications of organocatalyst.

1.3.1 Aminocatalysis

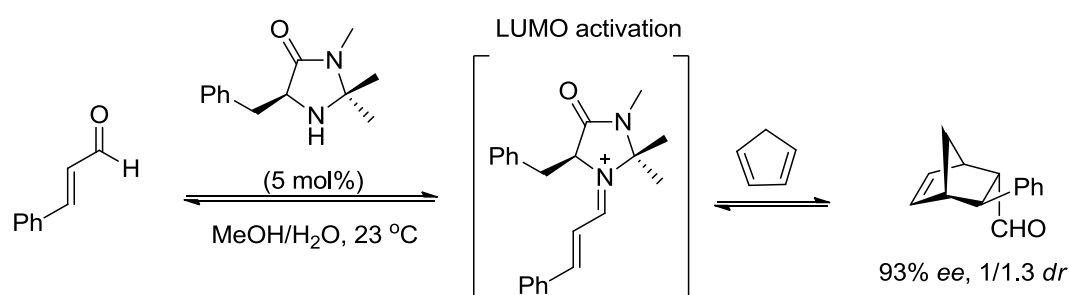
Owing to the natural abundance of nitrogen-centred compounds, most organocatalysts are found in a class termed aminocatalysts. Upon reaction these catalysts transform the substrates either into activated nucleophiles (increased electron density at reaction centre) or electrophiles (decreased electron density at reaction centre) through enamine or iminium ion reaction intermediates respectively.⁵⁴ These two forms are illustrated in Scheme 18 indicating the activated substrates. In such a way, the carbonyl group can manifest its well-known dual reactivity of electrophilic character at carbon and nucleophilic character at the α -position, depending on the reaction conditions.⁵⁵



Scheme 18: Equilibrium between iminium ion and enamine intermediates.

(i) Iminium catalysis

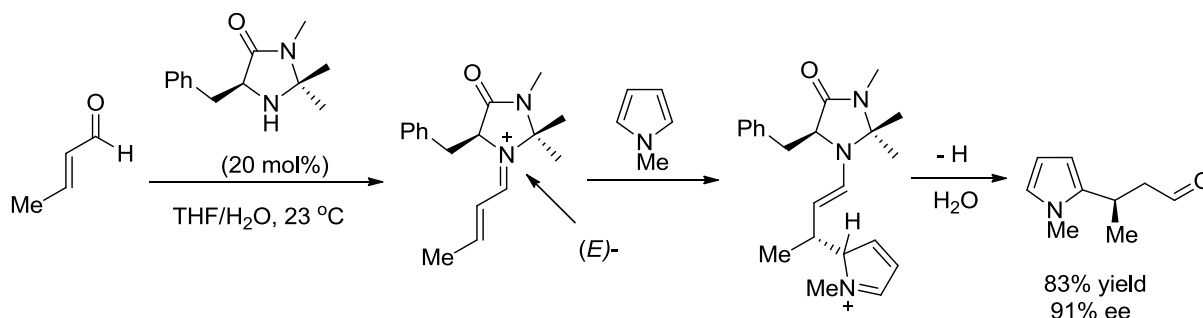
In iminium catalysis, the active species is an iminium ion which is formed by the reversible reaction of an amine catalyst with a carbonyl substrate. The higher reactivity of the iminium ion compared to the carbonyl species is used to assist reactions.⁵⁶ From Scheme 18 above, there are two types of iminium ions that can be formed; simple iminium ions that arise from simple carbonyl substrates like those of Mannich reactions and extended iminium ions from α - β -unsaturated carbonyls in nucleophilic 1-4-additions.⁵⁷ In 2000, the latter were exploited by David Macmillan and co-workers who established the first modern example of iminium catalysis in an enantioselective Diels–Alder reaction of α - β -unsaturated aldehydes and ketones with dienes using a chiral imidazolidinone catalyst, which is illustrated in Scheme 19. Reaction of the α - β -unsaturated aldehyde with the enantiopure amine catalyst formed an activated iminium ion with a lowered LUMO (lowest unoccupied molecular orbital) energy, which reacted with cyclopentadiene to afford a Diels–Alder [4+2] cycloaddition in high ee (> 90%).⁵⁸ Here, deprotonation of the iminium ion intermediate to an enamine cannot occur.



Scheme 19: Diels-Alder cycloaddition of an α - β -unsaturated aldehyde.

MacMillan and co-workers have also demonstrated the reaction capabilities of iminium catalysis for pyrrole 1,4-addition reactions with various α - β -unsaturated aldehydes as illustrated in Scheme 20.⁵⁹ The pyrrole undergoes preferential 1,4-addition (Michael) at the prochiral terminus of the conjugated iminium ion as shown. Furthermore, the reaction achieves high enantioselectivity in that *re*-face (underneath) attack at the prochiral terminus is favoured in order to minimise steric interference between the nucleophile and the benzyl group on the auxiliary. Of crucial importance to the stereoselectivity is the intermediacy of the configuration shown as (*E*-), since a configurational mixture would result in a mixture of

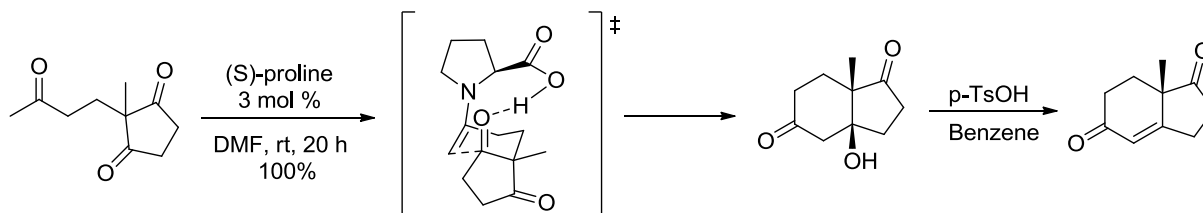
enantiomers. Deprotonation to regenerate aromaticity as well as hydrolysis of the enamine in order to turn over the catalyst generates the enantioenriched (*R*-) product as shown.



Scheme 20: Friedel-Crafts alkylation of α - β -unsaturated aldehydes.

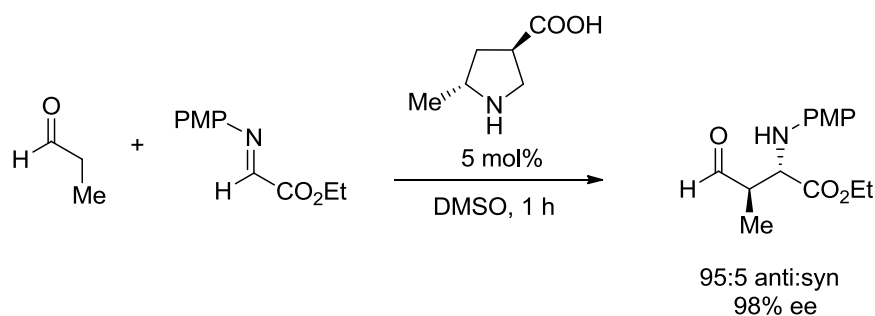
(ii) Enamine catalysis

By comparison, enamine catalysis involves the formation of an enamine intermediate that is generated through deprotonation of an iminium ion which then reacts with an electrophile or undergoes pericyclic reactions.⁶⁰ Reaction of the enamine can proceed via two different routes depending on the nature of the electrophile. If the electrophile contains a double bond such as that in an aldehyde or imine nucleophilic addition occurs resulting in α -substitution of the original carbonyl substrate. Conversely, single bond-containing electrophiles undergo a substitution reaction (Stork alkylation reaction). A key feature of enamine catalysis is that it involves involvement of a relatively high-lying HOMO (highest occupied molecular orbital) of the enamine. In the early 1970s the Hajos–Parrish–Eder–Sauer–Wiechert reaction was the first example reported of an asymmetric intramolecular aldol reaction involving enamine catalysis (catalyzed by proline), Scheme 21.⁶¹ This is a desymmetrization reaction that differentiates between two enantiotopic carbonyl groups by virtue of hydrogen bonds formed between the carboxylic moiety of proline in an enamine and a carbonyl group in the transition state.



Scheme 21: Intramolecular aldol reaction via enamine catalysis.

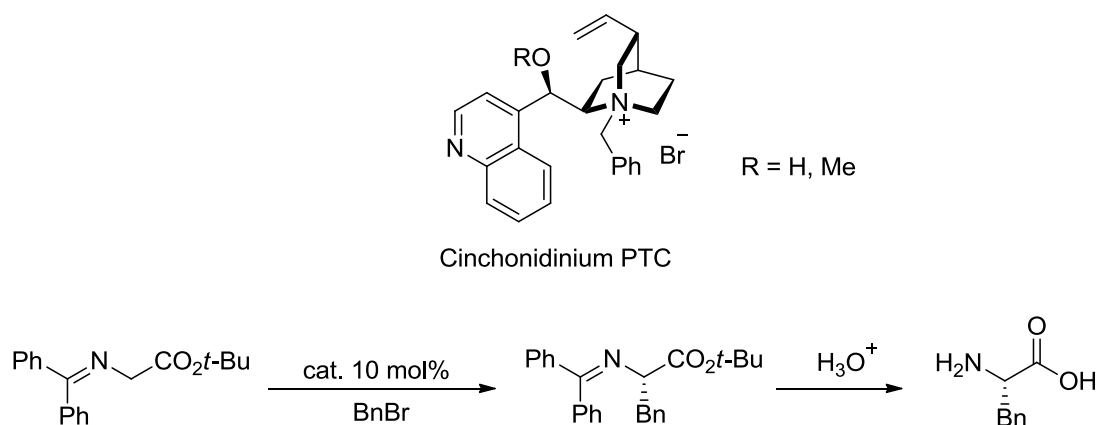
The asymmetric Mannich reaction is another useful methodology for the formation of C-C bonds in chiral products containing nitrogen. It involves the reaction between an enolisable substrate and an imine leading to the formation of a β -aminocarbonyl product, a motif commonly found in both natural products and pharmaceuticals.⁶² In 2000, Benjamin List and co-workers described the first Mannich reaction catalysed by L-proline, which stimulated the rapid development of many other asymmetric organocatalytic Mannich reactions.^{63, 64} Later in 2006, Barbas and co-workers synthesized an amino acid catalyst that is a highly anti-diastereo- and enantioselective Mannich catalyst for reactions involving simple aldehydes with *N*-*p*-methoxyphenyl (PMP)-protected imines, as shown in Scheme 22.⁶⁵



Scheme 22: *Anti*-diastereoselective and enantioselective Mannich reaction.

1.3.2 Phase-Transfer catalysis

Asymmetric phase-transfer catalysis (PTC) has been recognized as an alternative to many homogeneous synthetic organic transformations because of its preparative advantages, which include simple reaction procedures, mild conditions, and relatively inexpensive and environmentally friendly reagents.⁶⁶ Phase-Transfer catalysts are used to bring the reactant into contact with the substrate where each one has opposite solubilities in aqueous and organic media. This may occur by a reagent crossing over or via reaction at the media interface. Synthetically modified cinchona alkaloids (as ammonium salts) are typical chiral organocatalysts used in asymmetric PTC. In 1984 the Merck group reported the first efficient asymmetric PTC, in which methylation of a phenylindanone derivative was catalyzed by an *N*-alkylated (bridged nitrogen) cinchonidinium salt in high enantioselectivity.⁶⁷ In 1989, O'Donnell and co-workers developed cinchona alkaloid-derived chiral quaternary ammonium salts for the asymmetric synthesis of amino acids using a Schiff-base substrate.⁶⁸ Several generations of *O*-alkyl *N*-arylmethyl derivatives of the catalyst were developed, which led to highly enantioselective alkylation reactions of glycine imines for producing a range of α -amino acid derivatives, Scheme 23.⁶⁹



Scheme 23: Cinchona alkaloid-catalyzed phase-transfer reaction.

1.3.3 Hydrogen-Bonding catalysis

Hydrogen-bonding interaction is also a powerful tool for activating Lewis basic substrates via general acid catalysis. Much effort has been directed toward the development of new Brønsted acid catalysts, which has led to the discovery of several types of hydrogen-bonding donors such as ureas / thioureas, diols, and phosphoric acids, and these have become an important alternative to metal catalysts. Thioureas containing N-aryl groups bearing electron-withdrawing substituents at the *meta*- and *para*-positions, have a significant accelerating effect due to their rigid conformation, which minimizes the entropic penalty upon complexation with carbonyl compounds, Figure 11.⁷⁰

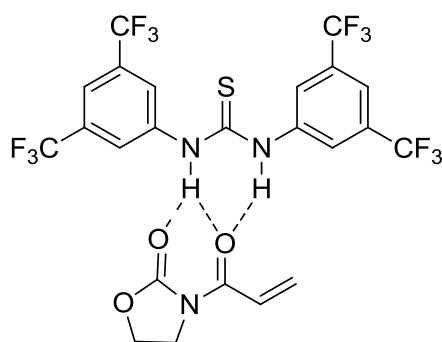
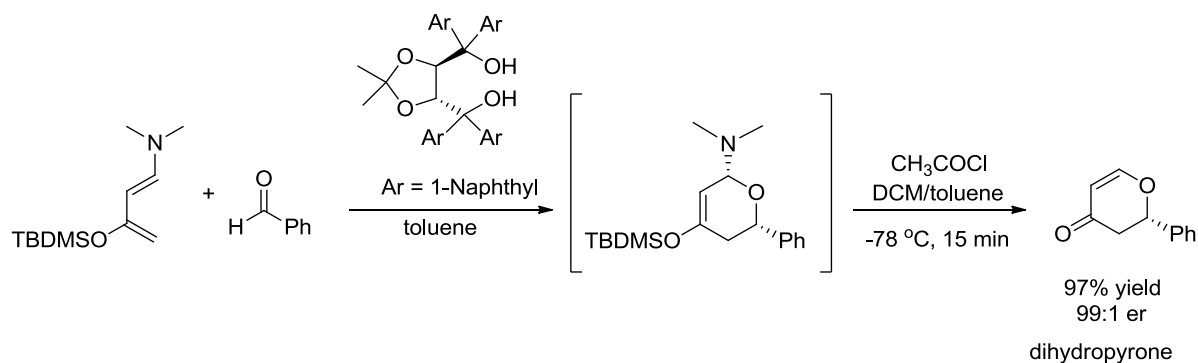


Figure 11: Proposed hydrogen-bonding interaction of a thiourea catalyst.

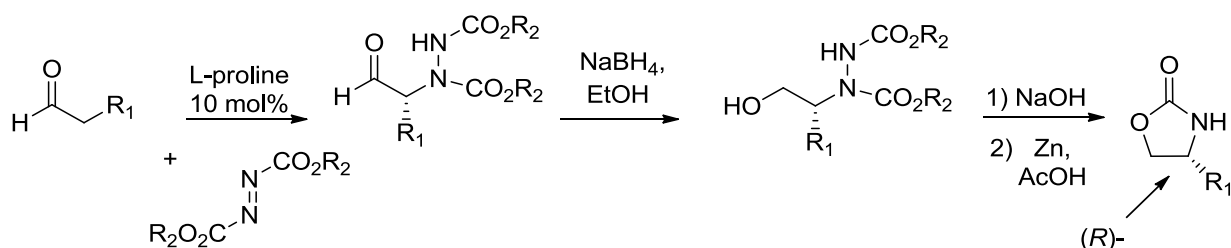
Similarly, Rawal and co-workers reported that TADDOLs could be used as weak Brønsted acid organocatalysts to achieve highly stereoselective hetero-Diels–Alder reactions via H-bonding between the Lewis basic carbonyl oxygen and the hydroxyl groups. Scheme 24 shows the reaction of a heterodiene with benzaldehyde to afford a dihydropyrone as a single stereoisomer.⁷¹



Scheme 24: Hetero-Diels-Alder reaction via hydrogen-bonding catalysis.

1.4 Amination

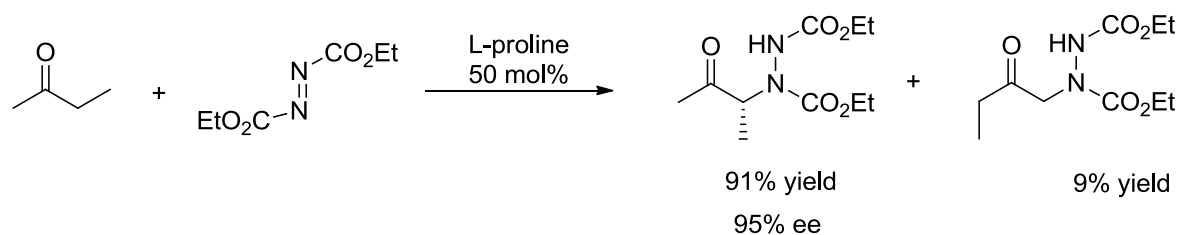
The introduction of nitrogen at the α -position of a carbonyl compound is a highly desirable transformation in synthesis, in which asymmetric catalysis offers opportunities to produce optically active α -amino acids, α -amino aldehydes and α -amino alcohols.⁷² In 2002, Benjamin List and Karl Jørgensen simultaneously reported a simple and efficient method for the direct α -amination of unbranched aldehydes using diazodicarboxylates as a nitrogen source and proline as a catalyst.^{73, 74} The α -hydrazino aldehyde products were configurationally unstable in that racemization occurred due to the presence of an acidic α -H thus, the aldehyde group was reduced *in situ* into α -amino alcohols using NaBH_4 , which resulted in a high yield (93-99%) and enantioselectivity (86-97%) of the α -hydrazino alcohols. These were subsequently cyclised under basic conditions, and their N-N bond reductively cleaved to afford chiral, non-racemic (*R*)-oxazolidinones, Scheme 25.⁷⁵



Scheme 25: L-Proline catalyzed α -amination of unbranched aldehydes.

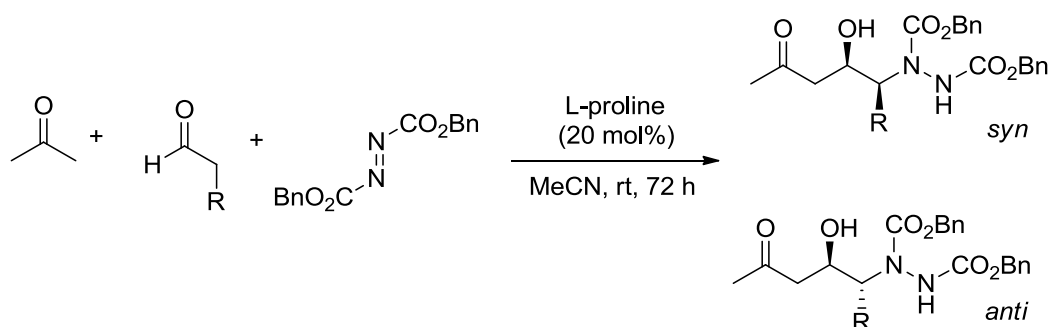
Jørgensen and co-workers also reported a proline-catalyzed enantioselective direct α -amination of ketones. The reaction of simple aliphatic ketones were found to be fairly regioselective, as the amination took place at the more highly substituted carbon atom, and

the reaction proceeded with high enantioselectivities. In later reports quaternary stereogenic centres were generated at the α -position of branched aldehydes and ketones, Scheme 26.⁷⁶



Scheme 26: α -Amination of ketones.

Barbas and co-workers extended the methodology by combining acetone, an aldehyde and dibenzyl azodicarboxylate, also using L-proline as the catalyst, in a one-pot synthesis to afford functionalized β -amino alcohols in high yields, with low diastereoselective control but good enantioselectivity (91-99%) of the *anti*-adducts, Scheme 27.⁷⁷



Scheme 27: Amination of β -amino alcohols.

The choice of proline as the aminating catalysts has been based on its bifunctional properties, involving both a nucleophilic secondary amino group that reacts as a Lewis base and a carboxylic acid moiety functioning as a Bronsted acid. This facilitates a highly pre-organized transition state during reactions involving enamines as intermediates, resulting in exceptionally high enantioselectivities.⁷⁸ In the transition state, the facial approach of the diazodicarboxylate is directed by interaction of the incoming nitrogen atom with the proton of the carboxylic acid of the L-proline-promoted enamine intermediate to produce the *R*-enantiomer (assisted model). The *S*-enantiomer can easily be formed using D-proline as the catalyst, although an alternative approach is to use Jorgensen's proline-derived steric catalyst (α,α -diarylprolinol silyl ether) which produces high enantioselectivities in a steric model. Here, the observed stereochemistry can be explained by considering

that steric repulsion between the catalyst side chain and the azodicarboxylate ester directs the electrophile anti (steric model), Figure 12.⁷⁹

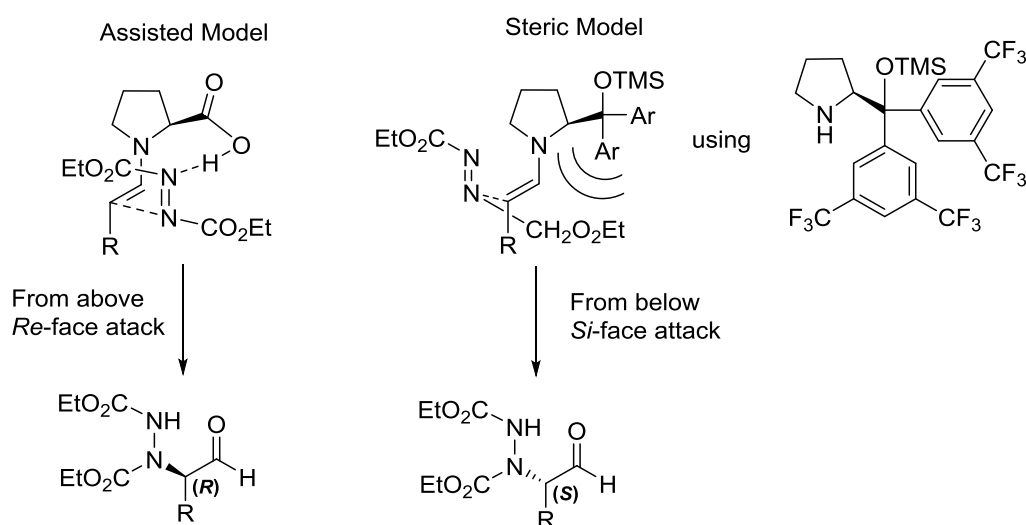
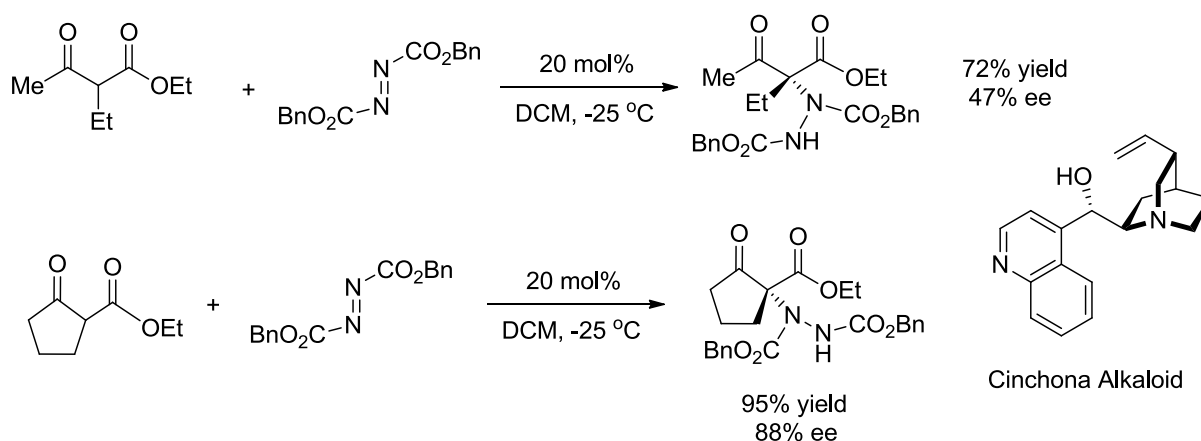


Figure 12: Enamine transition state models showing formation of the different enantiomers.

Cinchona alkaloids and their derivatives are also organocatalysts that have found extensive application in asymmetric amination in which good enantioselectivities can be secured with quaternary centres. In 2012, Russo and co-workers described the α -amination of cyclic β -ketoesters and lactones with dibenzyl azodicarboxylate in the presence of natural cinchona alkaloids such as cinchonine and cinchonidine. Cyclic β -ketoesters easily afforded both enantiomers in high yields and good enantioselectivities, Scheme 28.⁸⁰



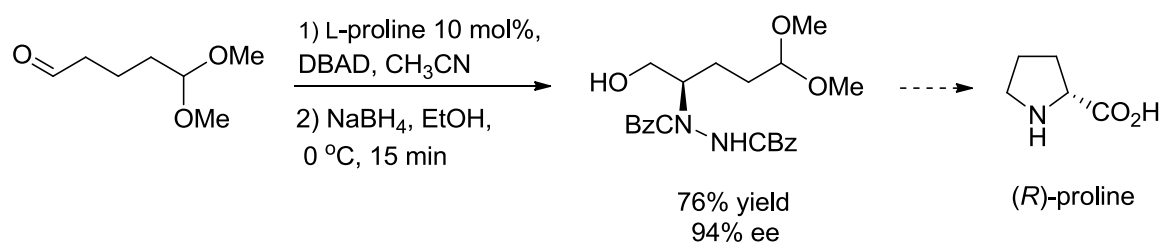
Scheme 28: α -Amination of β -ketoesters to form quaternary centres.

Chapter 2

Project Overview

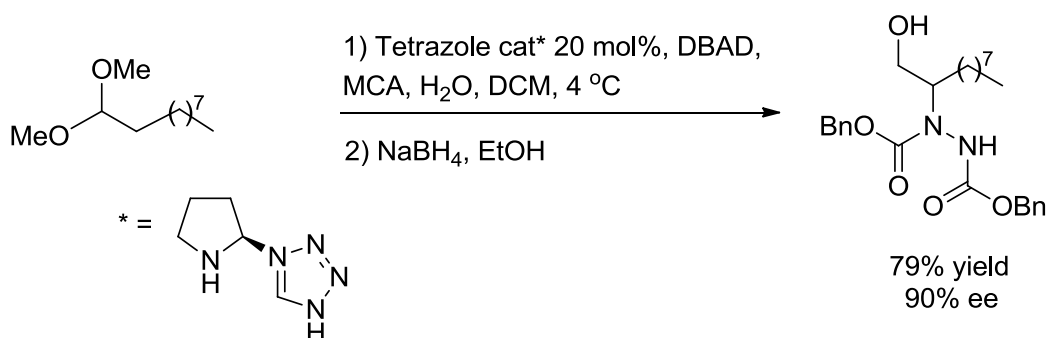
2.1 Scope

In the previous chapter the concept of enantioselective α -amination in organocatalysis was introduced. In 2008, Kalch and co-workers developed an enantioselective synthesis of cyclic amino acids using the organocatalytic α -amination reaction of aldehydes functionalized with an acetal group, shown in Scheme 29.⁸¹



Scheme 29: α -Amination of acetal functionalized aldehydes.

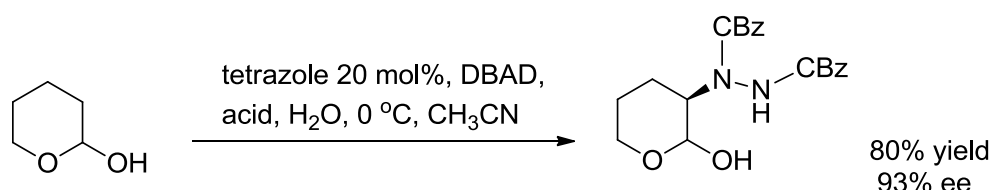
In 2014, a co-worker in our research group reported the first one-pot enantioselective α -amination of acetals, which gave good yields (70-81%) and enantioselectivities (70-86%), as illustrated in Scheme 30.⁸² The reaction conditions comprised of an acetal, aqueous monochloroacetic acid as Brønsted acid (with catalytic trifluoroacetic acid), proline or its tetrazole derivative as organocatalyst, and DBAD as the diazodicarboxylate nitrogen source. Reaction is thought to proceed via the oxocarbenium ion to the enamine rather than via hydrolysis to the aldehyde. A borohydride reduction as usual is then used to prevent racemisation.



Scheme 30: α -Amination of an acetals.

To widen the substrate scope, the α -amination of a δ -lactol was also conducted on the basis of it also being a masked carbonyl functionality (as a hemi-acetal). Using a low equivalent of

acid (0.1 eq.) in the reported conditions shown in Scheme 36 gave excellent enantioselectivity as shown in Scheme 31.



Scheme 31: α -Amination of a hemiacetal.

This interesting development led to the objective behind this project, which was to investigate whether these ideas could be extended to amination systems.

2.2 Aminals

Hemiaminals are a functional group having an amino and a hydroxyl group bonded to the same carbon atom, and are derived from the amination group, also known as an aminoacetal, which has two amino groups bonded to the same carbon atom. This group of functionalities appear in several natural and unnatural product structures as shown in Figure 13.

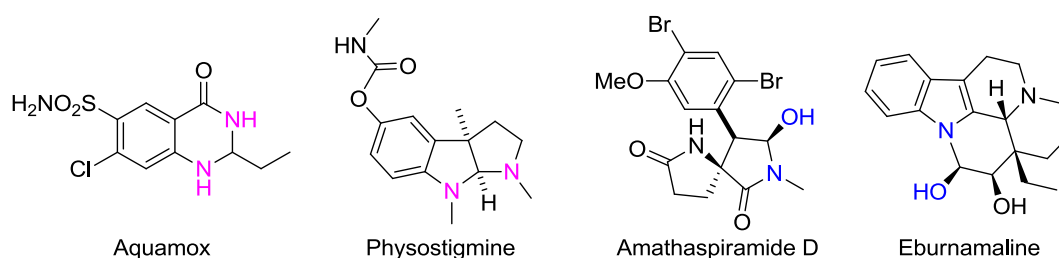
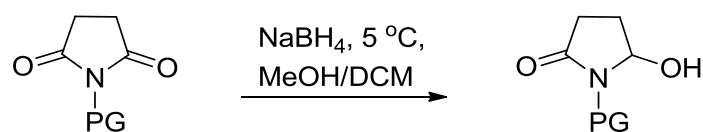


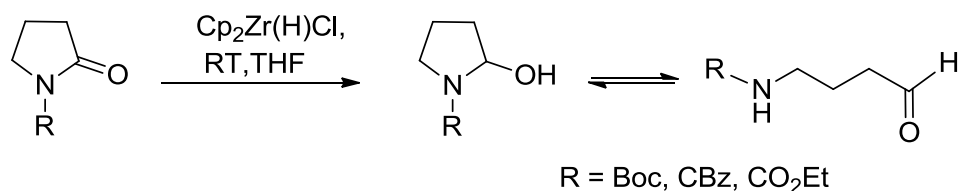
Figure 13: Examples of compounds containing amination and hemiaminal functionality.

Hemiaminals are important intermediates in the preparation of azanucleosides with antiviral, antiprotozoan and anticancer properties.⁸³ Hemiaminals have been mainly synthesized from the reduction of lactams rather than their amination precursors. Sadovoy and co-workers reported the use of NaBH_4 in methanol / dichloromethane (3 : 1) mixtures for reducing *N*-protected succinimides to the corresponding 5-hydroxypyrrolidin-2-ones, Scheme 32, which is more stable in the cyclic form.⁸⁴



Scheme 32: Reduction of succinimide to its hemiaminal.

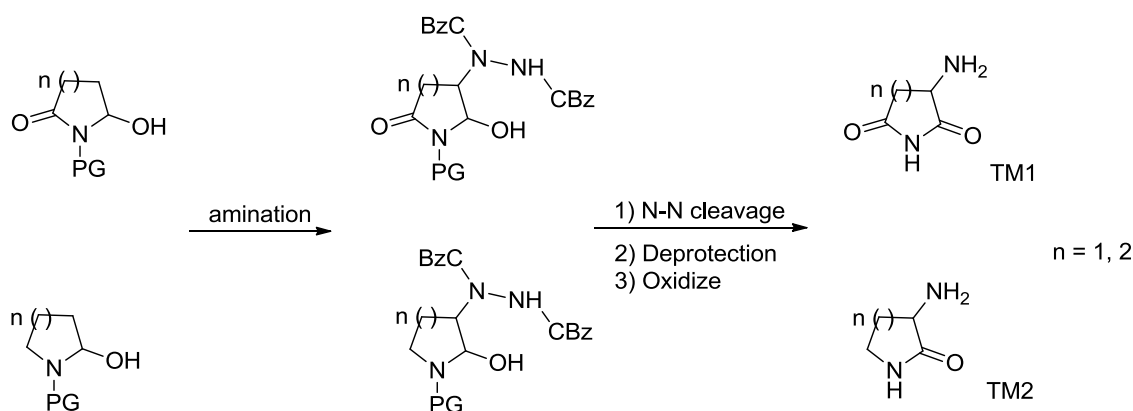
Piperno and co-workers used Schwartz reagent, $\text{Cp}_2\text{Zr(H)Cl}$, to reduce β -, γ -, δ - and ϵ -lactams through hydrozirconation into lactamols, while other literatures report the use of DIBAL-H or LiEt_3BH .⁸⁵ They also indicated that reduction of *N*-carbamate protected lactams affords the lactamol and the tautomeric aldehyde product by ring opening, Scheme 33, reminding us that the hemiaminal is indeed a masked aldehyde.



Scheme 33: Reduction of lactams.

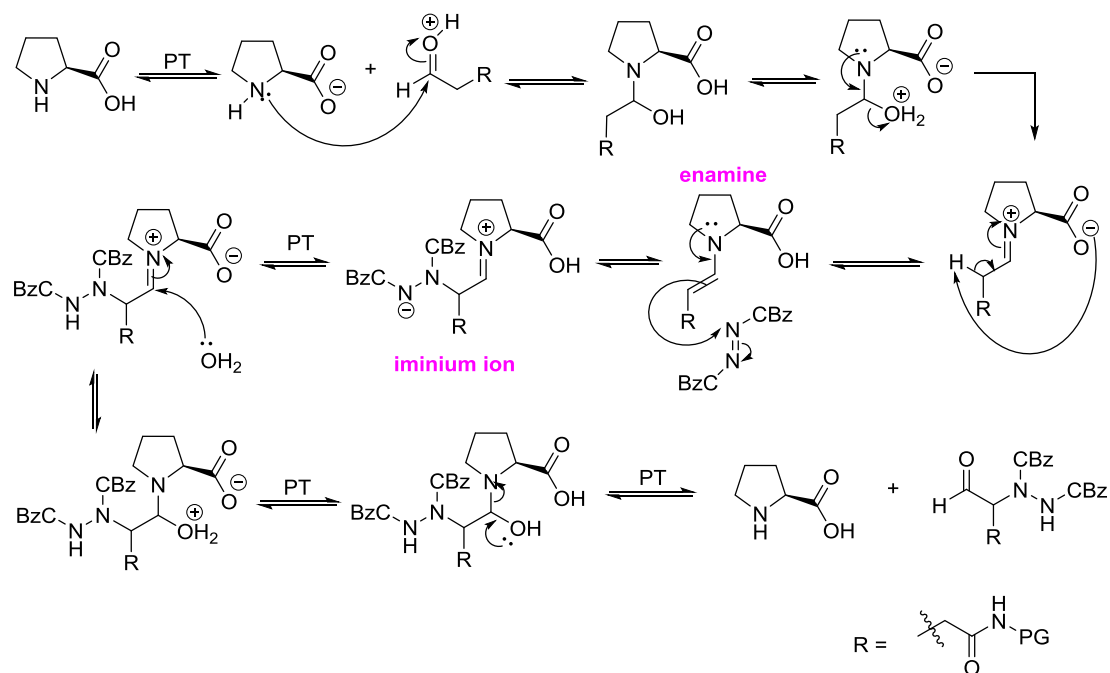
2.3 Aims and Objectives

The aim of this thesis was to take advantage of this equilibrium tautomerism to functionalize the masked aldehyde by the enantioselective α -amination reaction. Cleavage of the *N-N* bond followed by deprotection and oxidation would then afford the useful target α -amino lactams (TM1 and TM2) as illustrated in Scheme 34.



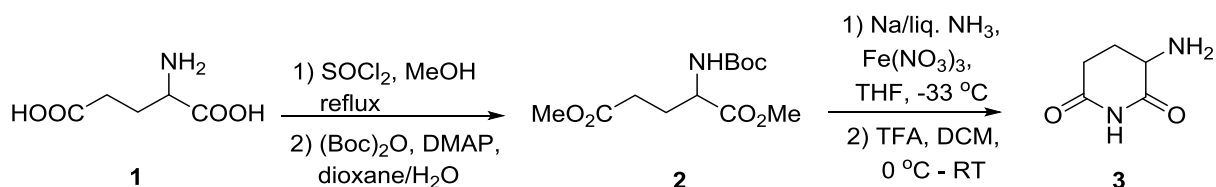
Scheme 34: α -Amination of hemiaminals.

Scheme 35 below shows the mechanism of proline reacting with an aldehyde forming an enamine which then reacts with the diazo-electrophile to form an iminium ion. After hydrolysis and subsequent proton transfer the aminated aldehyde is formed releasing proline back into the system.



Scheme 35: Proline-catalysed α -amination mechanism.

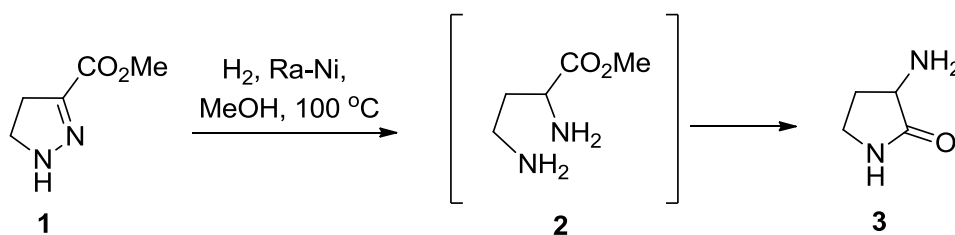
There are other methods that have been used to synthesize TM 1 and TM 2. Varala and co-workers⁸⁶ used a NaNH_2 / liq. NH_3 methodology for cyclisation, Scheme 36, which starts the synthesis by converting L-glutamic acid **1** into its bis-dimethyl ester by refluxing with thionyl chloride in methanol. The amino group was then protected with di-*tert*-butyl dicarbonate $(\text{Boc})_2\text{O}$ in a mixture of dioxane and water with a catalytic amount of 4-dimethylaminopyridine (DMAP) to afford *N*-Boc-L-glutamic dimethyl ester **2**. Treatment of **2** with Na / liq. NH_3 in dry THF then led to imide formation, which was then Boc-protected with trifluoroacetic acid in DCM to afford α -amino imide **3** in homochiral form.



Scheme 36: Synthesis by NaNH_2 /liq. NH_3 methodology.

Petrov and co-workers synthesized 2-pyrrolidinones with an amino group in 3 position.⁸⁷ The synthesis, Scheme 37, begins with a hydrogenation / hydrogenolysis sequence in methanol using Raney-Nickel to cleave the N-N bond of the pyrazoline-3-carboxylic acid methyl ester

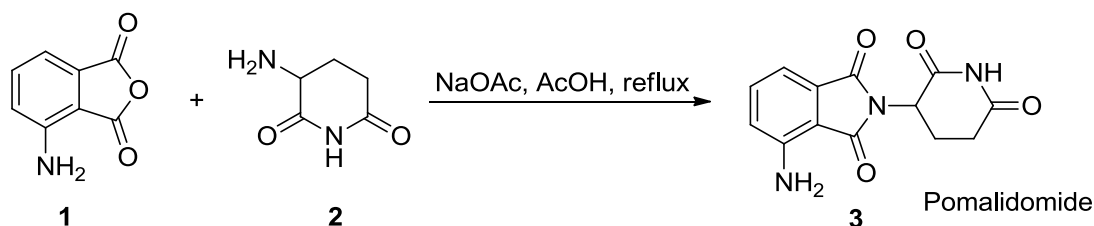
1 followed by cyclocondensation of diamine intermediate **2** to afford 3-aminopyrrolidin-2-one **3**. Here a racemic mixture of **3** was obtained.



Scheme 37: Synthesis by hydrogenation / hydrogenolysis.

2.4 Application

Target molecules **1** and **2** above can be used in the synthesis of biologically active compounds such as pomalidomide (Pomalyst[®]) illustrated in Scheme 38. This compound is a small molecule analogue of thalidomide developed by Celgene Corporation for the oral treatment of haematological and connective tissue diseases, and when used with low-dose dexamethasone can be used for the treatment of relapsed and refractory multiple myeloma.⁸⁸



Scheme 38: Synthesis of pomalidomide.

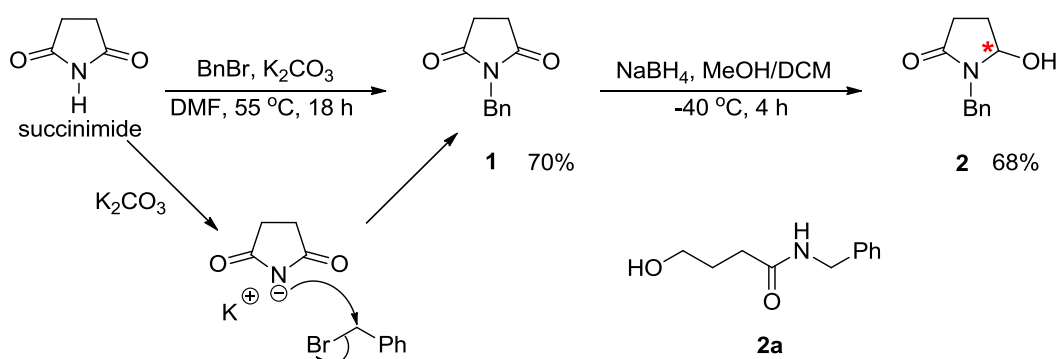
The general synthesis of pomalidomide **3** is a one-step reaction between amine-substituted phthalic anhydride **1** and α -aminoglutarimide **2** in a medium of sodium acetate in acetic acid.⁸⁹ It is administered as a racemate because it racemises *in vivo*. However, the importance of producing chiral, non-racemic compounds was discussed in Chapter one with thalidomide as an example. In this project the objective was to use enantioselective organocatalysis to produce chiral, non-racemic products derived from five- and six-membered cyclic hemiaminal starting materials with the carbonyl group inside (endo) or outside (exo) the ring.

Chapter 3

Results and Discussions

3.1 Synthesis of hemiaminal type 1

The first hemiaminal type 1 synthesised for amination studies was hemiaminal target **2** (Scheme 39) containing an endocyclic carbonyl group, which was prepared from succinimide. The first step involved *N*-benzylating with benzyl bromide and potassium carbonate via a known procedure⁹⁰ to afford *N*-benzyl succinimide **1**. This reaction proceeded through an S_N2 pathway, in which carbonate is basic enough to deprotonate the relatively acidic imide hydrogen. Following work-up and isolation via column chromatography, analysis of the ¹H NMR spectrum of product **1** showed a new multiplet between 7.36 - 7.14 ppm integrating for five aromatic protons as well as two benzylic protons as a singlet at 4.58 ppm. A singlet integrating for four equivalent protons was also observed as expected for the equivalent ring hydrogens (due to symmetry) at 2.61 ppm. Subsequent chemoselective reduction of **1** with sodium borohydride at low temperature afforded hemiaminal **2** in good yield (68%), Scheme 39.



Scheme 39: Synthesis of hemiaminal **2**.

Of key importance in the reduction was the need to avoid subsequent reduction of the aminal **2**, which occurred between 0 °C and room temperature to afford the ring-opened 4-hydroxybutyramide **2a**, Scheme 39. A mixture of methanol / dichloromethane (3 : 1) was used as solvent as suggested by the authors⁹¹ to avoid precipitation of the substrate that occurred in neat methanol at -40 °C. Analysis of the ¹H NMR spectrum of product **2**, Figure 14, showed the four heterocyclic ring protons originally in the form of a singlet in compound **1** to be much more complex, indicating that the protons were no longer equivalent. Overall, there was an upfield shift in line with the lower electron-withdrawing ability of the hydroxyl

group in **2** compared to the carbonyl group in **1**. Signals were complex in view of multiple couplings due to geminal and vicinal couplings in view of each methylene set being diastereotopic due to the newly introduced chiral centre (*). In addition, the two benzylic protons (H6) appeared as two distinct diastereotopic AB doublets at 4.76 ppm and 4.15 ppm because of the new chiral centre. A new signal integrating for one proton (H5) was observed at 5.02 ppm as a triplet due to coupling to the neighbouring two protons at H4 with an average J value of 5.3 Hz.

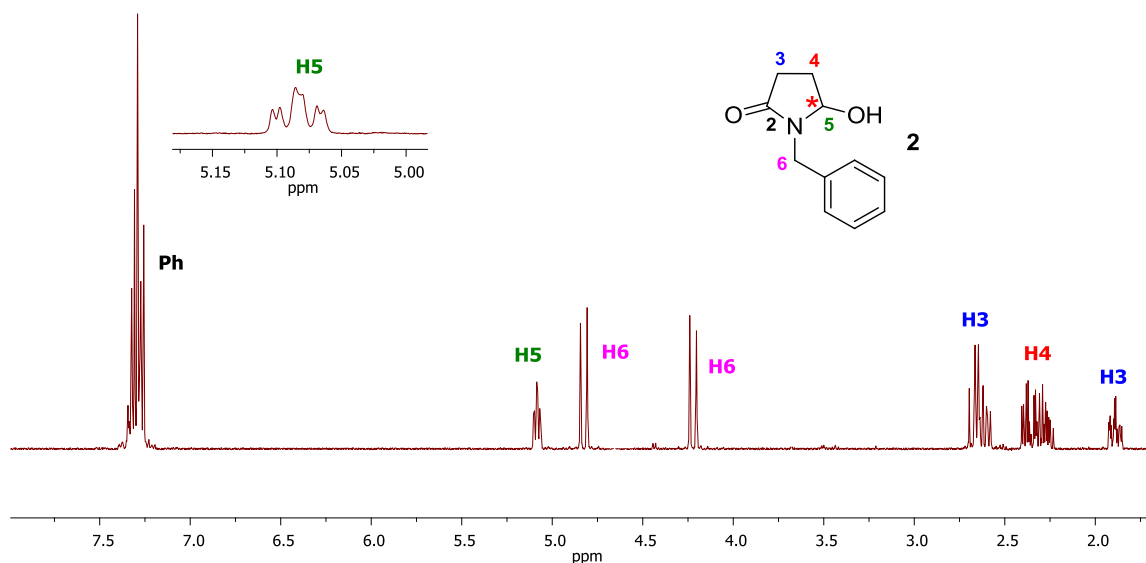


Figure 14: ¹H NMR spectrum of compound **2**.

Further reduction of the lactam carbonyl can be controlled as it enjoys greater resonance stabilization than the carbonyl groups of the imide due to a full donation of the nitrogen lone pair of electrons. This reduces the electrophilicity of the lactam carbonyl towards nucleophilic (hydride) attack compared to the case for the carbonyl groups of the imide, Figure 15.

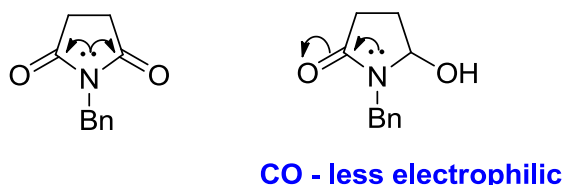
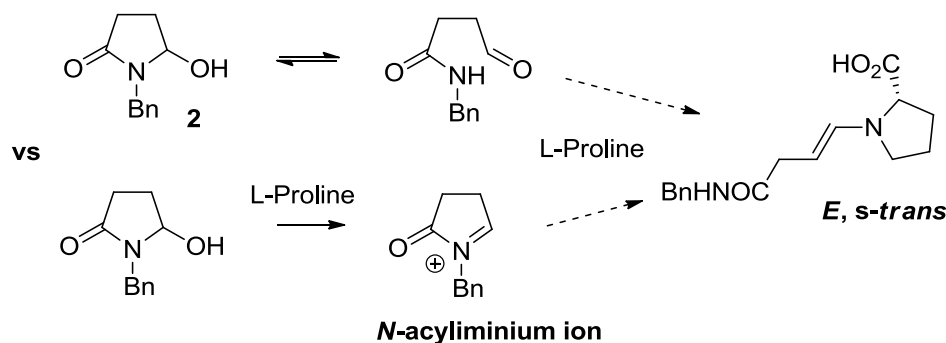


Figure 15: Resonance interpretation of the chemoselective reduction.

The next and key step addressed the essential issue of this thesis, namely that of enantioselective α -amination involving the reaction introduced by Jorgensen and List in 2002. The mechanism of this elegant reaction has already been described in Chapter 2 (page

29), in which an aldehyde transforms into its chiral enamine. Thus, the crucial issue here was whether the hemiaminal would open to the aldehyde in order to promote this. Alternatively, a mechanism via the *N*-acyliminium ion was thought possible, although this would need acid catalysis from the proline carboxyl group to be successful, which seemed unlikely. These ideas are depicted in Scheme 40.



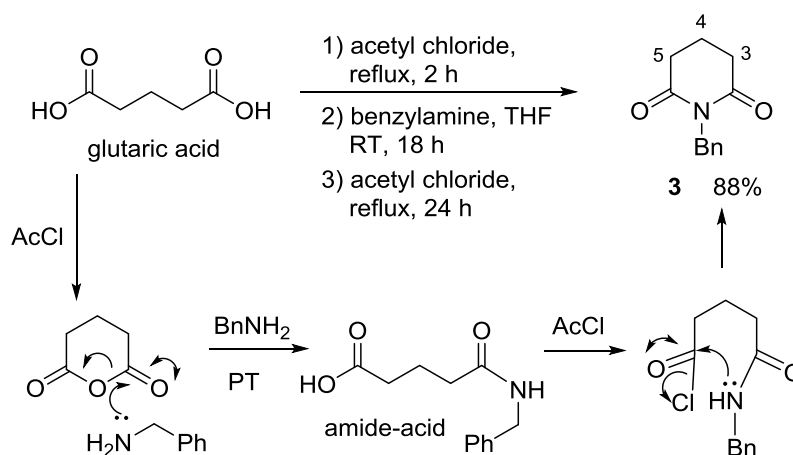
Scheme 44: Options for the enantioselective amination of **2**.

In the event a reaction was carried out between **2** (1.5 equivalents), diisopropyl azodicarboxylate (DIAD) as limiting reagent and 50 mol% L-proline in acetonitrile at three different temperatures of 0 °C, room temperature (RT) and 30 °C. Reactions were followed by TLC, but after 24 hours no reaction had occurred based on the retention of both reactants without any other spots forming on the TLC plate. The high amount of catalyst was used just to check for reactivity.

Based on this lack of reactivity, it was decided to resort to acid catalysis, which is not normally used for aldehyde amination, but does feature in a range of organo-aminocatalysis reactions.⁹⁹ The selection of acids tested as trifluoroacetic acid, monochloroacetic acid and acetic acid (at 1.0 equivalent to the limiting reagent) was made based on the acetal α -amination reaction mentioned in Chapter 2. After 15 minutes TLC showed that a reaction had occurred by virtue of the presence of a new non-polar spot. NMR spectroscopic analysis following work-up and isolation using column chromatography, however, revealed that amination as hoped for had not occurred, but rather that an adduct of proline and DIAD had formed without involvement of the substrate.

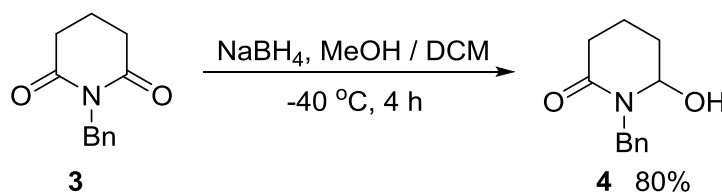
At this stage it was rationalised that the two likely reasons for failure were the size of the ring and / or the position of the carbonyl group to facilitate the ring-opening. The influence of changing the size of the ring while keeping the Bn protecting group constant was studied first, by

switching to the six-membered aminoral **4** derived from glutarimide **3**. The reaction began with refluxing glutaric acid in neat acetyl chloride to form the anhydride, which following the removal of excess acetyl chloride on the vacuum pump then underwent a nucleophilic acyl substitution (S_NAc) opening with benzylamine to the amide-acid. Ring closure of this intermediate was then achieved by a second treatment with acetyl chloride. The entire sequence could be successfully carried out in a one-pot sequence, Scheme 41.



Scheme 41: Synthesis of glutarimide **3**.

The 1H NMR spectrum of glutarimide **3** confirmed its formation in which five aromatic protons were observed between 7.30 - 7.08 ppm, two benzylic protons as a singlet at 4.85 ppm, a triplet at 2.55 ppm integrating for four protons (H3 and H5), and a quintet for the H4 protons at 1.82 ppm in accordance with the reported literature values.⁹² Thereafter, **3** was selectively reduced to 6-hydroxypiperidin-2-one **4** using sodium borohydride in a mixture (3 : 1) of methanol / dichloromethane as previously mentioned for **2**, Scheme 42. Analysis of its 1H NMR spectrum, Figure 16, again showed complex signals for the ring protons between 1.66 - 2.44 ppm, a set of AB doublets for the diastereotopic benzylic protons at 5.01 ppm and 4.29 ppm respectively, and a deshielded triplet at 4.85 ppm for H6 due to coupling with the adjacent H5 vicinal protons (average J value of 2.7 Hz).⁹³



Scheme 42: Reduction to hemiaminal **4**.

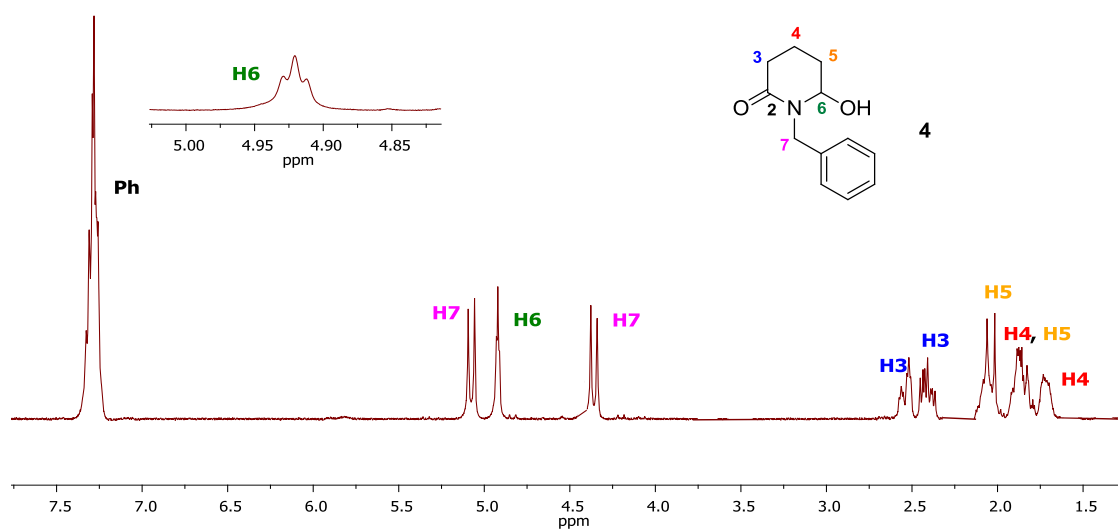
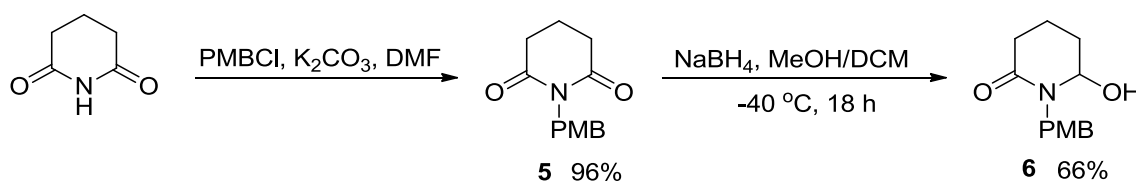


Figure 16: ¹H NMR spectrum of compound 4.

Unfortunately, once again all attempts to α -aminate **4** were unsuccessful even using acid catalysis. The remote possibility that the lack of reactivity had something to do with the choice of benzyl as *N*-protecting group, led to protection using a *para*-methoxybenzyl (PMB) protecting group.⁹⁴ This was achieved as before (Scheme 39) except using *para*-methoxybenzyl chloride to afford **5** as a white solid in an excellent yield of 96%, Scheme 43. Analysis of its ¹H NMR spectrum revealed an AB system in the aromatic region at 7.69 ppm and 6.72 ppm integrating for two protons each, which served as evidence of a 1,4-disubstituted benzene ring, together with a methoxy singlet seen slightly downfield as expected at 3.70 ppm.



Scheme 43: Synthesis of hemiaminal **6**.

As before, **5** was selectively reduced with sodium borohydride to afford **6** as a white solid with a corrected yield of 66% (at 60 % conversion). Figure 17 shows its ¹H NMR spectrum which confirmed the formation of **6** based on the appearance of H6 as a doublet of triplets due to a large ax-ax coupling at 5.05 ppm as well as an OH proton at 5.94 ppm. Also, interestingly H7 now appears as a singlet.

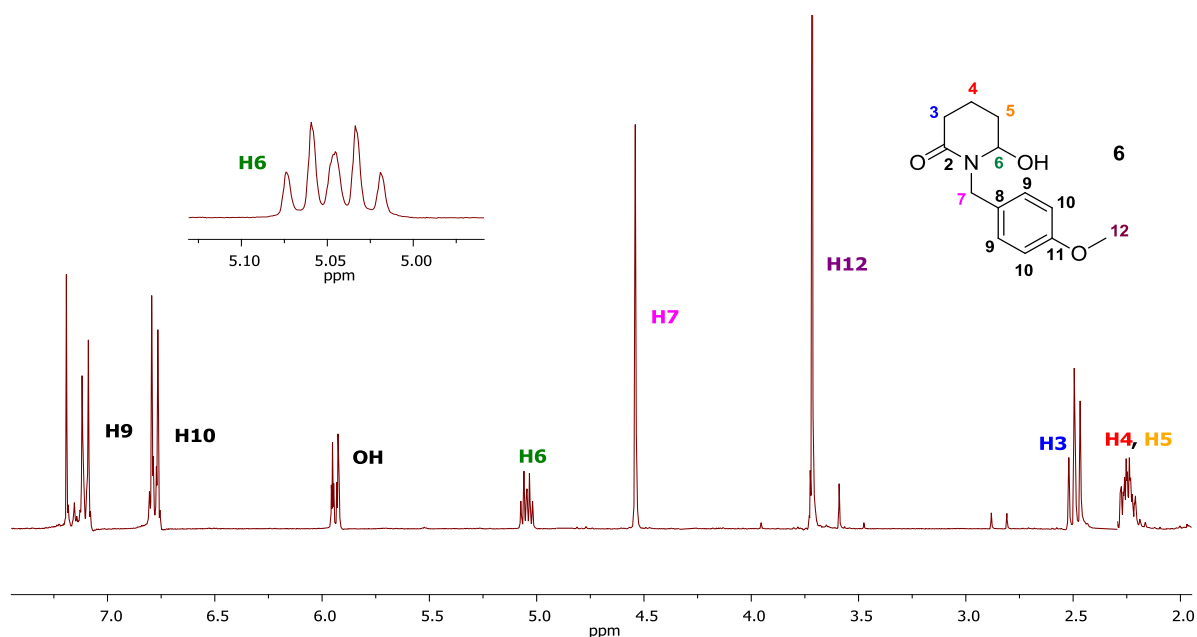
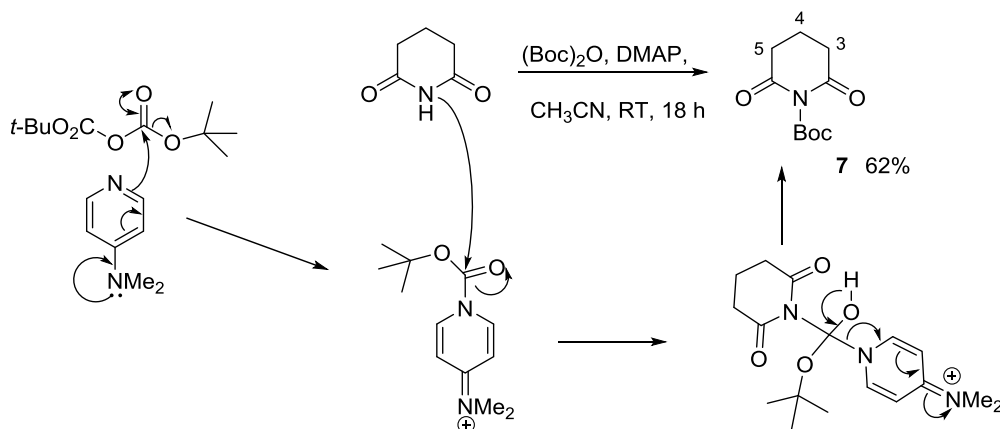


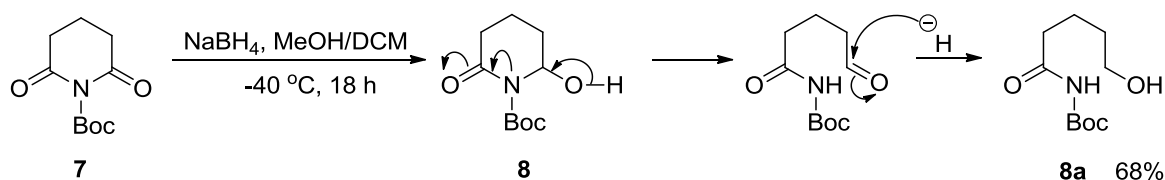
Figure 17: ¹H NMR spectrum of compound 6.

Amination reactions were again unsuccessful and so attention turned towards changing the protecting group to a more electron-withdrawing group in the hope of facilitating ring opening due to greater charge stabilization of the charge over a more delocalised system. For this purpose the carbamate protecting groups *tert*-butoxycarbonyl (Boc) and carboxybenzyl (CBz) groups were considered based on their use as standard protecting groups in peptide chemistry. The first one tried was Boc, which was introduced by reacting glutarimide with di-*tert*-butyl dicarbonate, (Boc)₂O, and 4-dimethylaminopyridine (DMAP) in acetonitrile via a S_NAc reaction. This afforded **7** in a moderate yield of 62% as an orange solid after work-up and isolation by column chromatography. The mechanism of acyl transfer is illustrated in Scheme 44 involving a sequence of S_NAc reactions with intermediacy of a highly electrophilic *N*-Boc-pyridinium species as the key event.



Scheme 44: Synthesis of imide **7**.

The structure of **7** was confirmed by ^1H NMR spectroscopy in which two sets of multiplets were observed at 2.51 ppm (H4) and 1.90 ppm (H3 and H5) as well as a singlet integrating for nine protons at 1.44 ppm as evidence of *t*-butyl group introduction. Attempts to chemoselectively reduce **7** with sodium borohydride at $-40\text{ }^\circ\text{C}$ disappointingly resulted in over reduction to alcohol **8a**, while carrying out the reaction at $-78\text{ }^\circ\text{C}$ or using lower equivalents also gave the same outcome. The ^1H NMR spectrum of **8a** is shown in Figure 18 revealing a NH singlet at 7.82 ppm, two sets of triplets at 3.57 ppm (H6) and 2.68 ppm (H3) integrating for two protons each and a broad OH singlet at 2.39 ppm. Formation of **8a** indicated the formation of hemiaminal **8** as an intermediate, which presumably opened up readily into the aldehyde, which in turn resulted in over-reduction, Scheme 45. However, these results suggested that the substrate structure was improving in terms of our desired aim.



Scheme 45: Reduction of compound **7**.

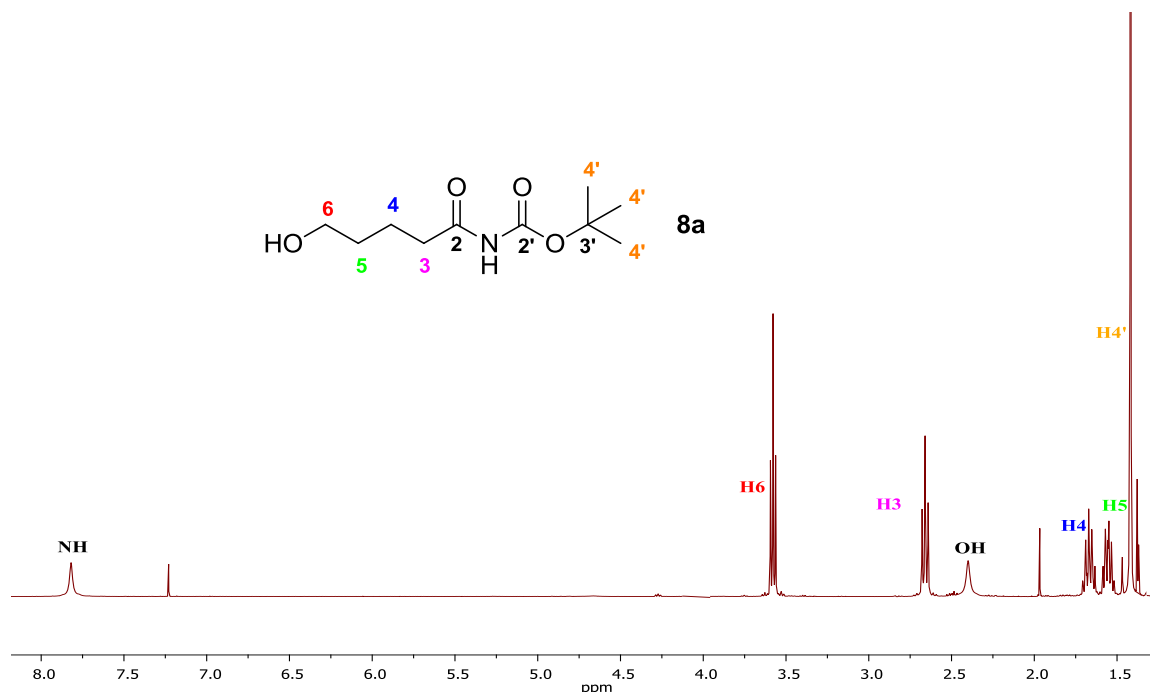
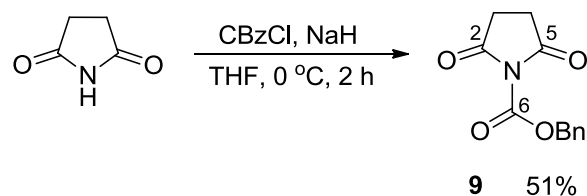


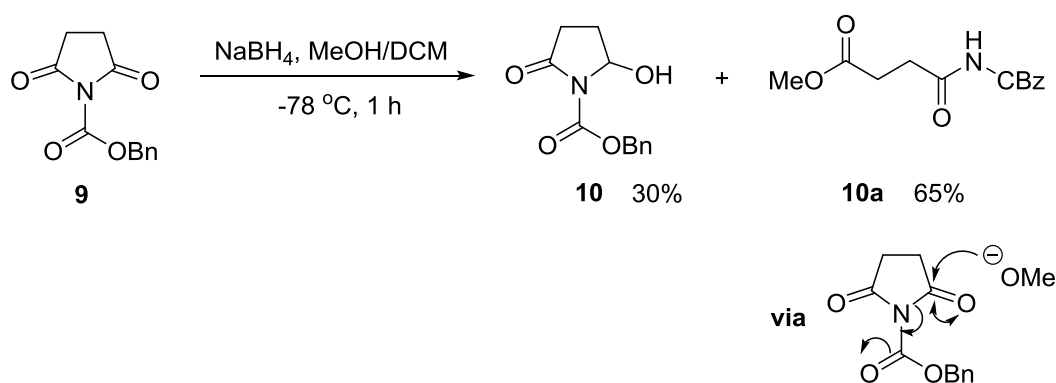
Figure 18: ^1H NMR spectrum of compound **8a**.

To this end, studies resorted back to the five-membered ring case, in which the anion of succinimide was reacted with benzyl chloroformate (CBzCl) to form compound **9** as a colourless solid, Scheme 46, in modest yield after work-up and column chromatography.



Scheme 46: Synthesis of CBz-protected succinimide **9**.

The structure of compound **9** was confirmed by analysis of the ^1H NMR spectrum, which showed a downfield singlet at 5.31 ppm for the newly introduced benzyl methylene group. Furthermore, the ^{13}C NMR spectrum confirmed the presence of a third carbonyl resonance at 152.3 ppm corresponding to C6 together with the existing carbonyl carbons (C2 and C5) at 176.6 ppm and infrared (IR) analysis further confirmed **9** by the presence of three $\text{C}=\text{O}$ peaks at 1785 cm^{-1} , 1779 cm^{-1} and 1798 cm^{-1} . Reduction to hemiaminal **10** using sodium borohydride in methanol / dichloromethane at $-40\text{ }^\circ\text{C}$ surprisingly did not result in an over-reduction even though it was thought that the five-membered ring was more likely to open up. The reaction gave a very low yield of **10** ($< 10\%$) with full conversion over an extended period of time and so the reaction was conducted at $-78\text{ }^\circ\text{C}$, which gave a 1 : 2 mixture of compound **10** and methyl ester **10a** in near quantitative yield overall following column chromatography. The formation of ring-opened compound **10a** may be explained by assuming that methanol, probably in the form of methoxide or a methoxyborate species was able to attack the relatively electrophilic imide endo-carbonyl group, which has an enhanced electrophilicity due to the extra CBz electron-withdrawing carbonyl group, Scheme 47.



Scheme 47: Reduction of CBz-protected succinimide **9**.

The structure of **10a** was supported by its ^1H NMR spectrum shown in Figure 19, which revealed a deshielded methoxy singlet at 3.58 ppm integrating for three protons, a singlet at 7.57 ppm (NH) and two sets of triplets at 2.99 ppm and 2.56 ppm for the desymmetrized methylene groups. The absence of chirality (compared to the hemiaminal) ensured a relatively simple spectrum, while the use of lithium aluminium hydride in THF at $-78\text{ }^\circ\text{C}$ gave no improvement (20% of **10**), presumably as a result of its higher reactivity.

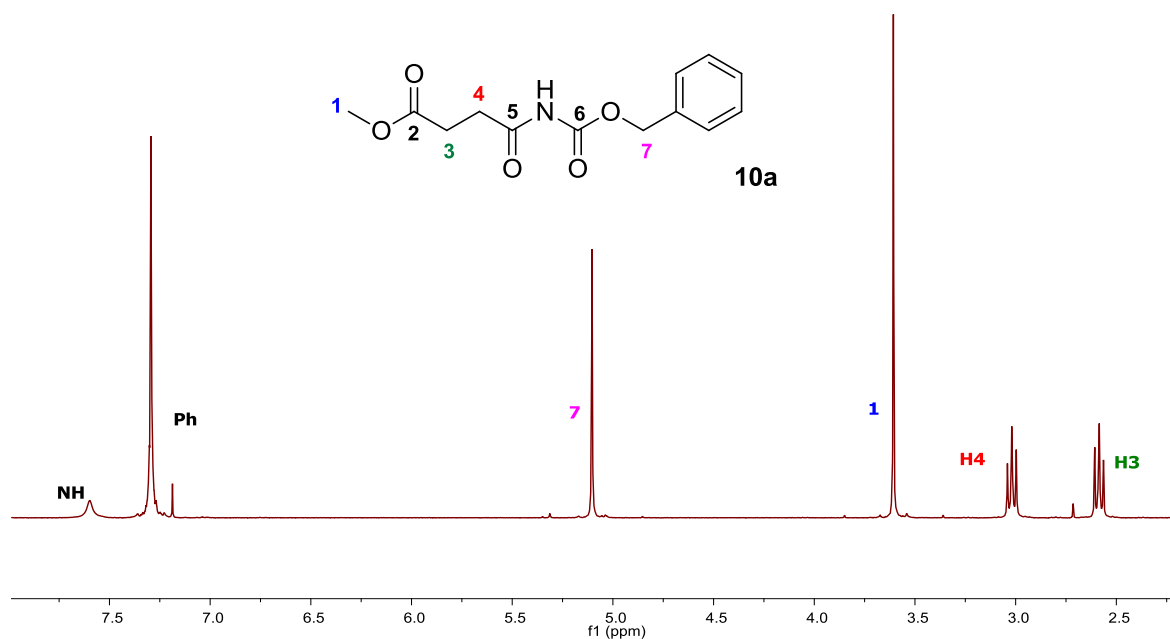


Figure 19: ^1H NMR spectrum of compound **10a**.

Formation of hemiaminal **10** was confirmed by a doublet at 5.68 ppm in the ^1H NMR spectrum integrating for one proton for H5, a doublet indicating in this case that one of the (vicinal) dihedral angles was close to 0 degrees according to the Karplus equation. Interestingly the doublet appeared twice (5.77) – see inset in Figure 20 – indicating the presence of $\text{N-CO}_{(\text{exo})}$ rotamers, in a ratio of about 4 : 1 by NMR. This was confirmed by the doubling of signals observed in the ^{13}C NMR spectrum of **10** at 86.3 ppm and 86.6 ppm for C-5. The two rotamer structures are shown in Figure 21.

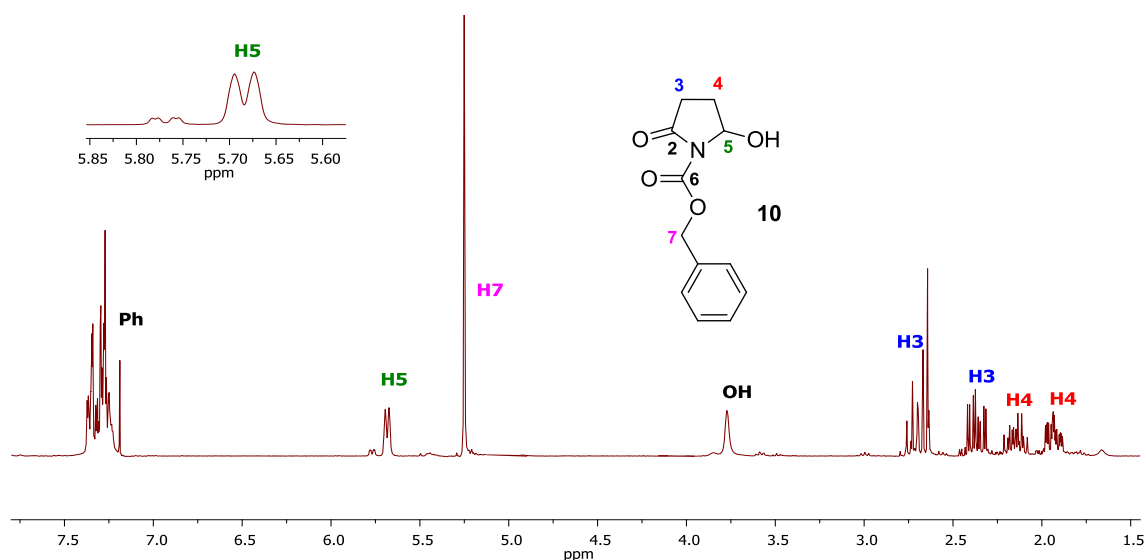


Figure 20: ^1H NMR spectrum of compound **10**.

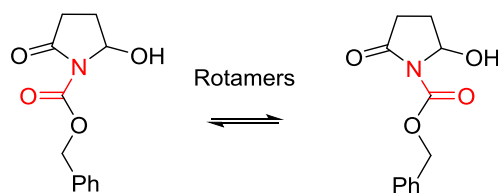
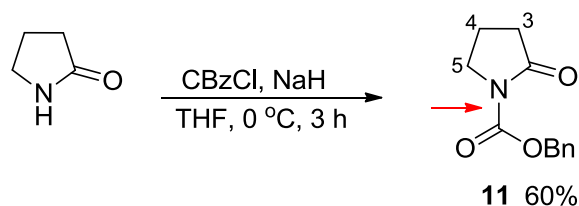


Figure 21: N-CO_(exo) rotamers.

Enantioselective α -amination of **10** was attempted using DIAD, 50 mol% L-proline in acetonitrile at 0 °C and at room temperature and at 30 °C and once again this reaction was unsuccessful. This significant set of results was interpreted as indicative that the reaction was not going to work with an endocyclic carbonyl group, and so the focus of attention now switched to hemiaminals of type 2 containing no endocyclic carbonyl group.

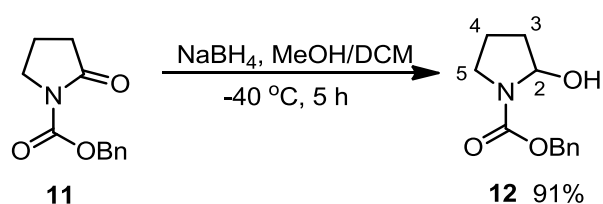
3.2 Synthesis of hemiaminal type 2

These hemiaminals contained the stabilizing carbonyl group exo to the ring and could be accessed from the corresponding lactam. Thus, reactions were conducted for the five-membered ring, and commercially available 2-pyrrolidinone was acylated with benzyl chloroformate via its anion formed using sodium hydride. In such a way *N*-protected lactam **11** could be produced in modest yield (60%) following a conventional work-up and column chromatography, Scheme 48. Analysis of its ^1H NMR spectrum confirmed the acylation with the introduction of benzyl signals. In this case, **11** was obtained as a single rotamer based on a single set of resonances in both the ^1H and ^{13}C NMR spectra, depicted in Scheme 48 as the *s-trans* configuration (red arrow) in order to minimise carbonyl / carbonyl repulsion.



Scheme 48: Synthesis of CBz protected 2-pyrrolidinone **11**.

Compound **11** was then selectively reduced to 2-hydroxypyrrolidine **12** using sodium borohydride in a methanol / dichloromethane mixture under conditions described for the imide cases before, Scheme 49. Following work-up and chromatography aminor **12** was obtained in an excellent yield of 91%. Its ^1H NMR spectrum shown in Figure 22 revealed a broad H2 multiplet centred at 5.51 ppm, although the presence of two signals again suggested rotamers with a minor H2 peak at 5.49 ppm, which was supported by the doubling of signals in the ^{13}C NMR spectrum at 81.2 ppm and 80.9 ppm for C2 as shown in Figure 23. Similarly, the introduction of a chiral centre at C2 resulted in the H5 protons appearing as diastereotopic multiplets with different chemical shifts (in **11** they were a triplet due to being enantiotopic).



Scheme 49: Reduction to exocyclic aminor **11**.

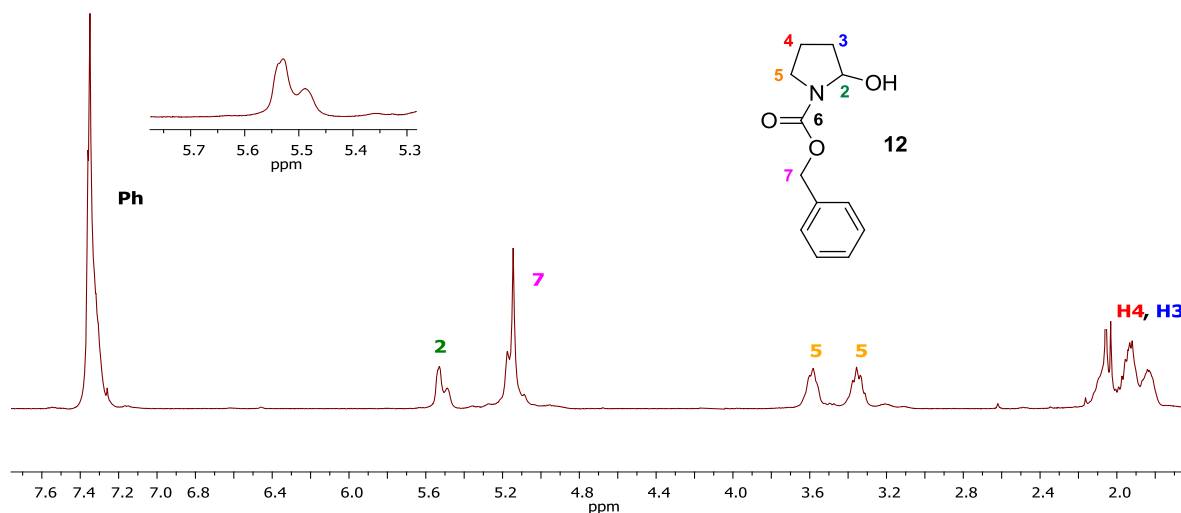


Figure 22: ^1H NMR spectrum of compound 12.

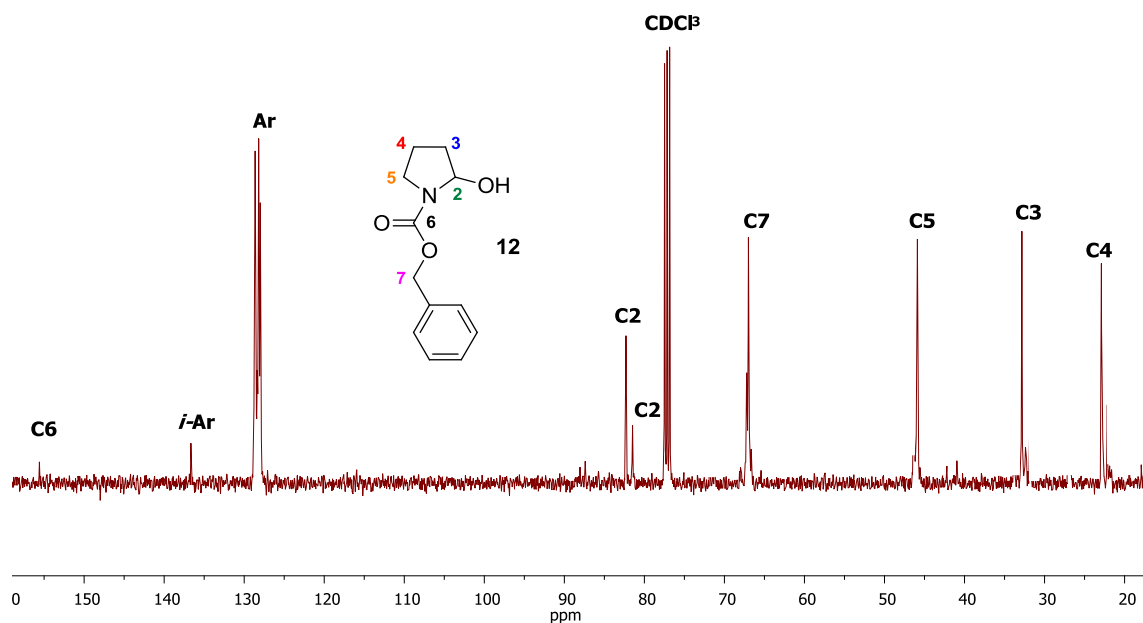
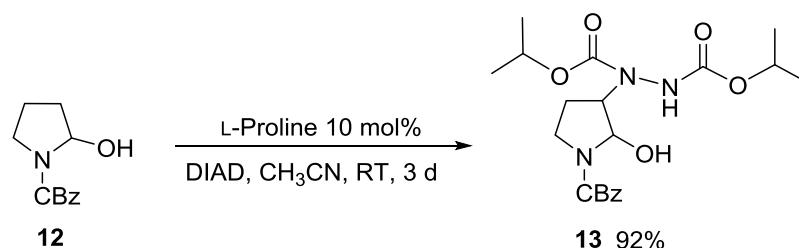


Figure 23: ^{13}C NMR spectrum of compound 12.

Enantioselective α -amination was attempted again using L-proline (50 mol%) and 1.0 equivalent of DIAD in acetonitrile at room temperature for 3 days without an acid catalyst to obtain a more polar product **13** in an excellent yield of 92% as a yellow oil following a work-up with aqueous ammonium chloride, and isolation using column chromatography.

Reactions were initially conducted using 50 mol% L-proline, but pleasingly, decreasing the catalyst load to 10 mol% gave similar results, Scheme 50.



Scheme 50: α -Amination of compound **12**.

The reason for the success this time is probably something to do with the hydrogen-bonding stabilisation in ring opening to the aldehyde that is offered by having the carbonyl group *exo*. Such stabilisation is denied in the *endo*-case. Figure 24 summarises:

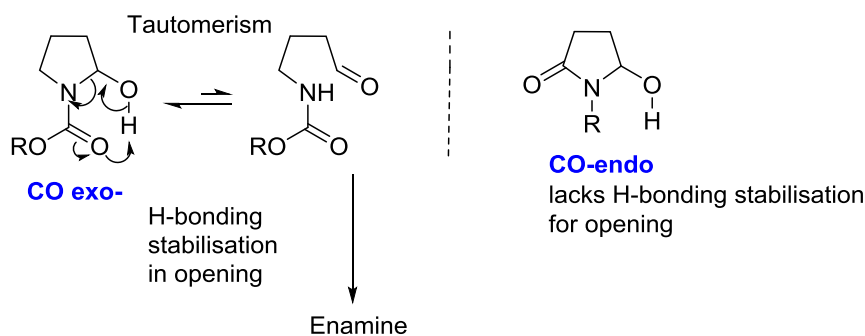


Figure 24: hydrogen-bonding stabilisation in ring opening.

An unambiguous structural assignment for **13** proved to be challenging in view of the various stereogenic elements possible in the product. Upon α -amination a further chiral centre is formed creating the possibility of diastereomers, and indeed **13** did appear on TLC as two closely-running spots. Other stereogenic elements for consideration, though, were the axial rotation axes of both the N-CBz moiety – this had shown to be operative in starting material **12** – as well as the hydrazide carbamate around the tertiary nitrogen centre. These possibilities are depicted individually in Figure 25.

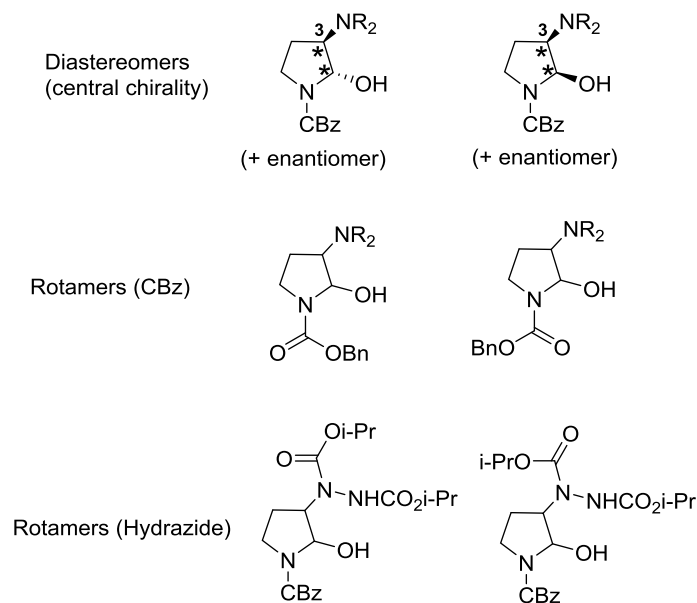


Figure 25: Illustration of stereogenic elements in **13**.

Needless to say this posed a difficult challenge. The ^1H NMR spectrum of **13** showed that amination had taken place by virtue of the appearance of high-field isopropyl resonances observed as a number of non-equivalent doublets integrating for 12H - see inlet in Figure 26 - against the 5H for the CBz phenyl group, as well as a deshielded signal for H3 (4.52 ppm) relative to its chemical shift in the starting material **12** (1.80 ppm). Signals appeared as broad and relatively unresolved indicating a complex mixture of conformers to be present. Regarding isomers, an approximately 2 : 1 mixture of compounds could be seen, based on the following resonances: the appearance of a singlet integrating for one NH proton observed at 6.67 ppm together with its minor signal at 6.51 ppm and an H3 major resonance at 4.52 ppm as a broad singlet with its minor singlet at 4.19 ppm. The ^{13}C NMR spectrum, Figure 27, of **13** revealed two distinct carbonyl resonances at 156.9 ppm for C6 and C4' and C3' overlapping at 155.4 ppm, showing that the isomers did not manifest differences in that region. In addition, there was doubling of signals in the isopropyl region at 22.1 ppm and 22.0 ppm, of C3 at 64.0 ppm and 60.5 ppm and of C4 at 34.0 ppm and 33.0 ppm to corroborate the notion of a 2 : 1 mix. Analysis of the infrared spectrum of **13** indicated a broad band of overlapping carbonyl stretches at 1684 cm^{-1} , a broad band at 3291 cm^{-1} corresponding to the O-H stretch and a shoulder band at 3384 cm^{-1} corresponding to the N-H stretch. High resolution mass spectroscopy (HRMS) using an electrospray ionization (ESI) mode found 446.1888 for $\text{C}_{20}\text{H}_{29}\text{N}_3\text{NaO}_7$ $[\text{M}+\text{Na}]^+$ which agreed well enough with the

calculated mass of 446.1903, lending further confidence to the assignment of structure **13** as shown.

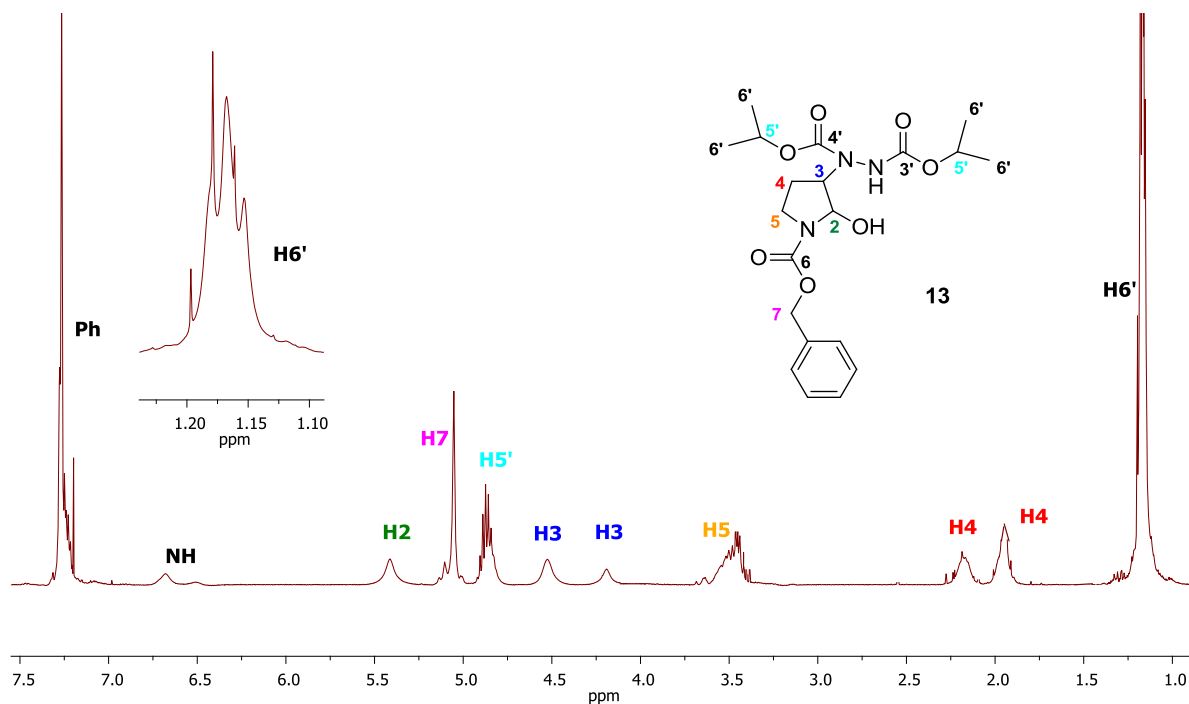


Figure 26: ^1H NMR spectrum of compound **13**.

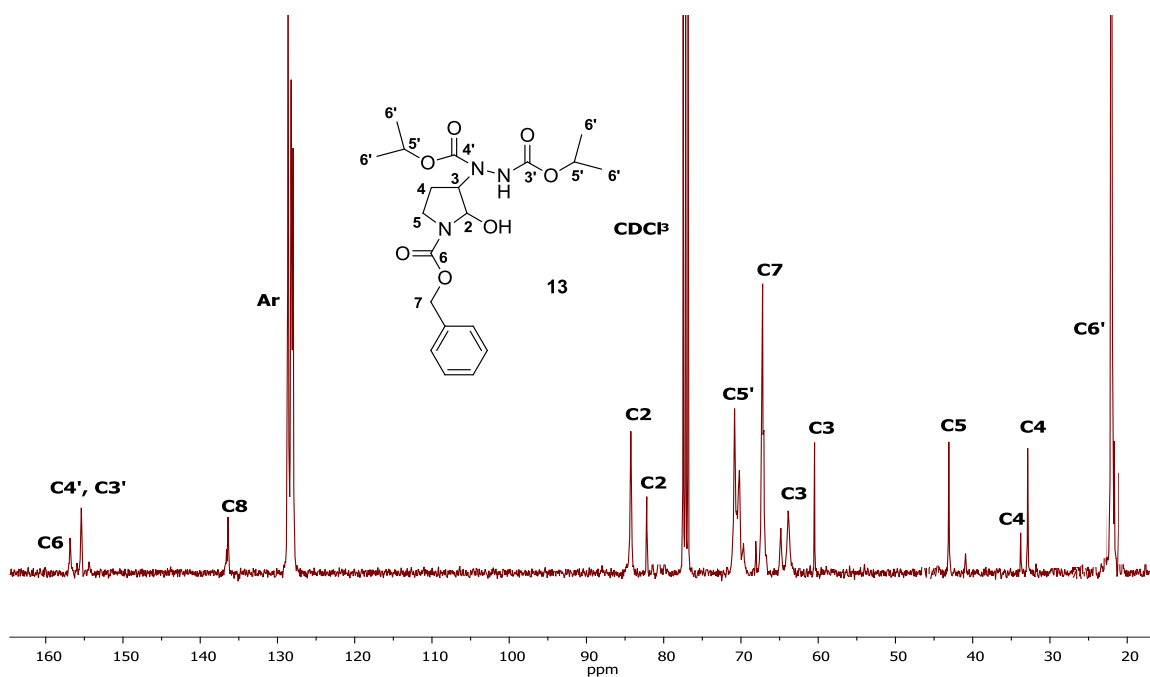


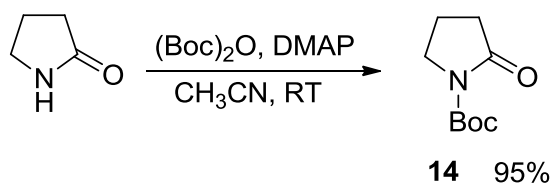
Figure 27: ^{13}C NMR spectrum of compound **13**.

Based on the data, it was attractive to suggest that the 2 : 1 ratio translates to a diastereomer level, and indeed this was what was observed later in high pressure liquid chromatography (HPLC) studies. Optimization studies of the reaction to obtain the greatest yield were carried out with respect to temperature and the addition of an acid catalyst, and the results are shown in Table 2, which showed that the best conditions for optimizing the yield were to run the reaction at room temperature (RT) for 3 days in the absence of acid, (Entry 2). The temperature of the optimized reaction as RT agreed with that of the original amination by List and Jorgensen, the much longer reaction time presumably reflected the issue of ring opening to the aldehyde. These reactions were stopped once 100% conversion of DIAD (as limiting reagent) had been achieved.

Table 2: Enantioselective α -amination of compound **12**.

Entry	Temp.	AcOH eq.	Time	Yield %
1	0 °C	-	4 d	62
2	RT	-	3 d	92
3	RT	1	3 d	48

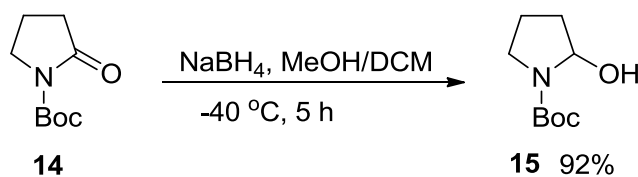
Since cleavage of the N-N bond required hydrogenation, which would cleave the CBz protecting group, it was decided to repeat the sequence with a Boc protecting group. To this end, commercially available 2-pyrrolidinone was Boc-protected using (Boc)₂O and DMAP in acetonitrile via a S_NAc reaction affording **14** in an excellent yield of 95% as a yellow oil after column chromatography, Scheme 51.⁹⁵ Analysis of its ¹H NMR spectrum confirmed its formation based on the appearance of a singlet observed at 1.45 ppm integrating for nine protons for the Boc *t*-butyl group, while the ¹³C NMR spectrum revealed two carbonyl signals only at 173.8 ppm and 149.8 ppm, as with **11** indicting the lack of rotamers.



Scheme 51: Synthesis of Boc protected 2-pyrrolidinone **14**.

As before, compound **14** was then selectively reduced to 2-hydroxypyrrolidine **15** using sodium borohydride in a methanol / dichloromethane mixture at -40 °C, Scheme 52.

Following work-up and chromatography hemiaminal **15** was obtained in an excellent yield of 92% as a colourless oil.⁹⁶ Analysis of the ¹H NMR spectrum shown in Figure 28 confirmed formation of **15** with an approximately 2 : 1 mixture of N-CO rotamers with evidence of a major H2 peak at 5.40 ppm was seen together with a minor peak at 5.38 ppm. Again, the presence of two closely separated signals for H2 suggested rotamers. Furthermore, the H5 protons now appeared as diastereotopic multiplets at 3.40 ppm and 3.21 ppm due to the newly introduced chiral centre at C2.



Scheme 52: Reduction to exocyclic hemiaminal **15**.

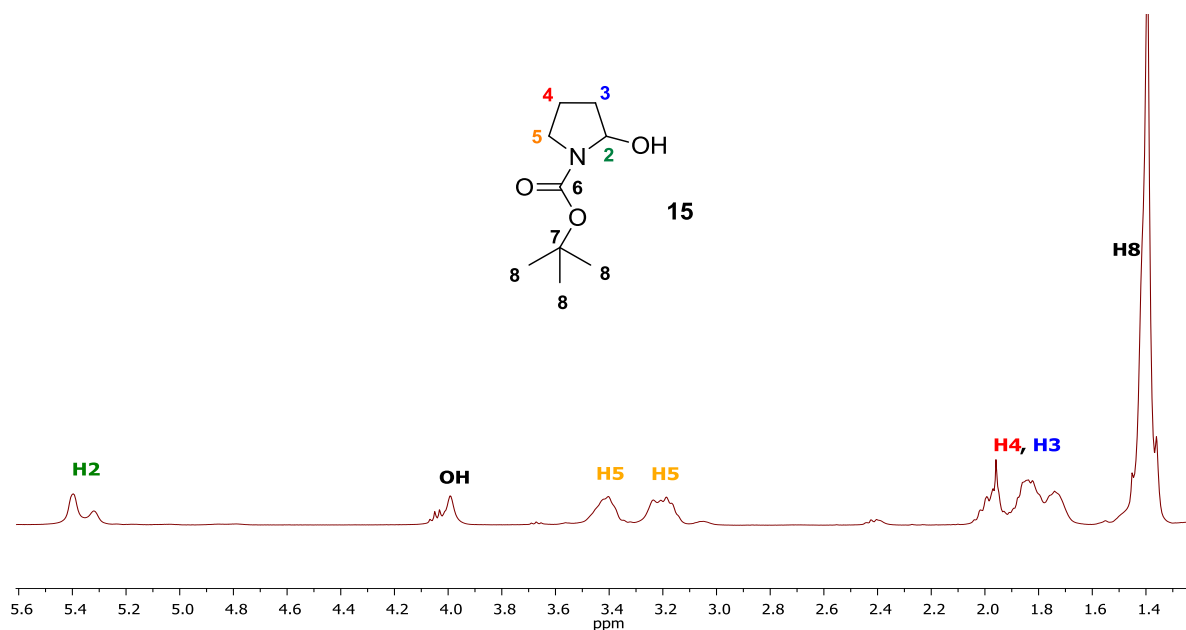
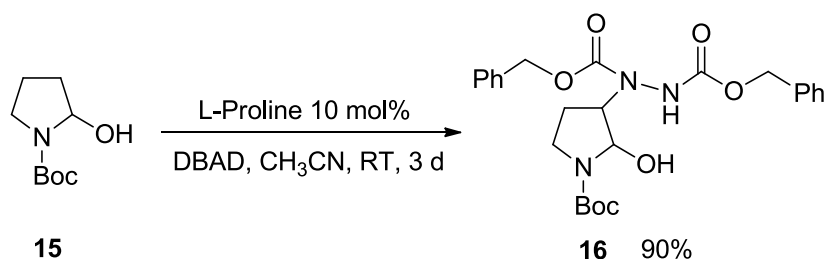


Figure 28: ¹H NMR spectrum of compound **15**.

Enantioselective α -amination of **15** was successful using the optimized results (Table 2, Entry 2) obtained for compound **13** and in which 10 mol% of L-proline was used with DBAD, which allowed for UV detection of the product, in acetonitrile at room temperature. The reaction took 3 days to reach completion which was in accord with that of entry 2 in Table 2. Aminated hemiaminal **16** was produced in an excellent yield of 90% as a yellow oil after

work-up with aqueous ammonium chloride and isolation via column chromatography, Scheme 53.



Scheme 53: α-Amination of hemiaminal **15**.

The ¹H NMR spectrum of **16**, Figure 29, showed that amination had taken place based on the appearance of phenyl signals integrating for ten protons as well as H3 shifting downfield (4.56 ppm) from its position in **15** (1.85 ppm). Moreover, once again the broad lines suggested interplay between several rotameric forms, and based on a major NH signal at 6.75 ppm and a minor one at 6.66 ppm as well as H3 appearing at 4.56 ppm and 4.02 ppm, a ratio of 2 : 1 for isomers was calculated as before. Likewise, the ¹³C NMR spectrum of **16**, Figure 30, indicated the presence of three carbonyl groups with signals at 156.1 ppm (C6), 155.6 ppm (C3') and 154.9 ppm (C4'), while the doubling of signals at 80.7 ppm and 79.8 ppm (C2) as well as at 44.6 ppm and 43.0 ppm (C5), supported the 2 : 1 mix. Analysis of the infrared spectrum of **16** indicated a broad band of overlapping carbonyl stretches at 1696 cm⁻¹, a broad band at 3185 cm⁻¹ corresponding to the O-H stretch and a shoulder band at 3300 cm⁻¹ corresponding to the N-H stretch. To further confirm the formation of **16**, HRMS using an ESI mode was conducted and found 508.2066 for C₂₅H₃₁N₃NaO₇ [M+Na]⁺, which agreed well enough with the calculated mass of 508.2060.

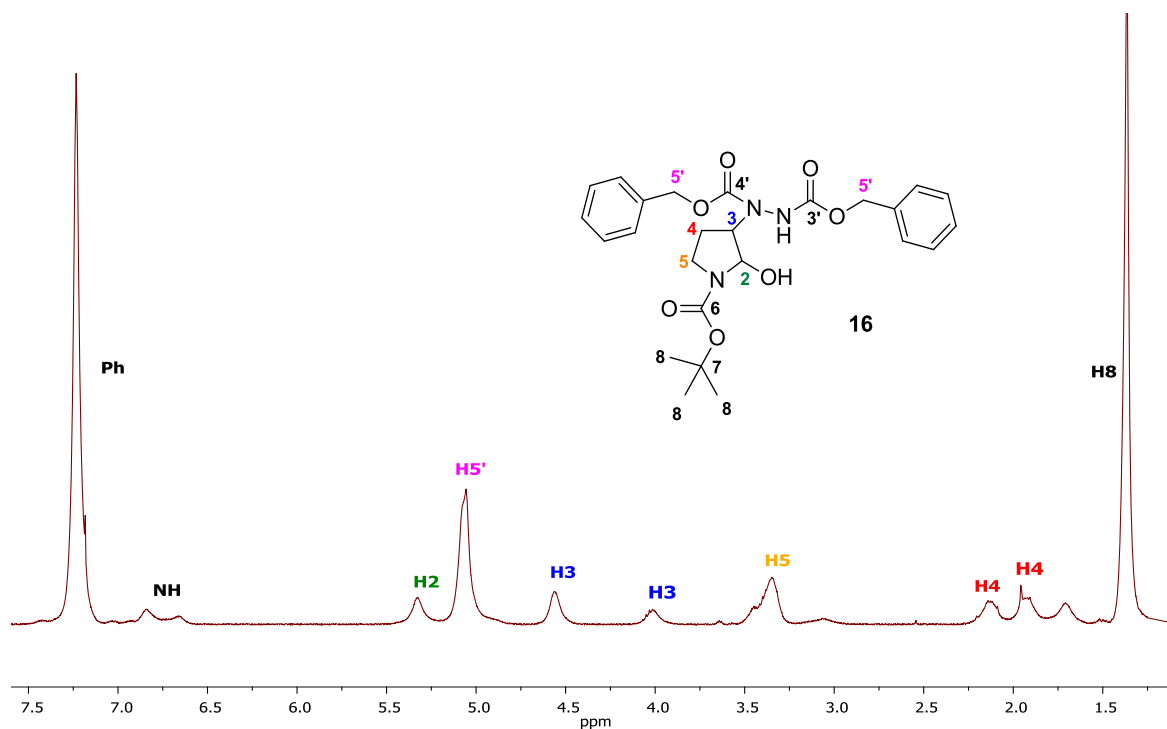


Figure 29: ^1H NMR spectrum of compound 16.

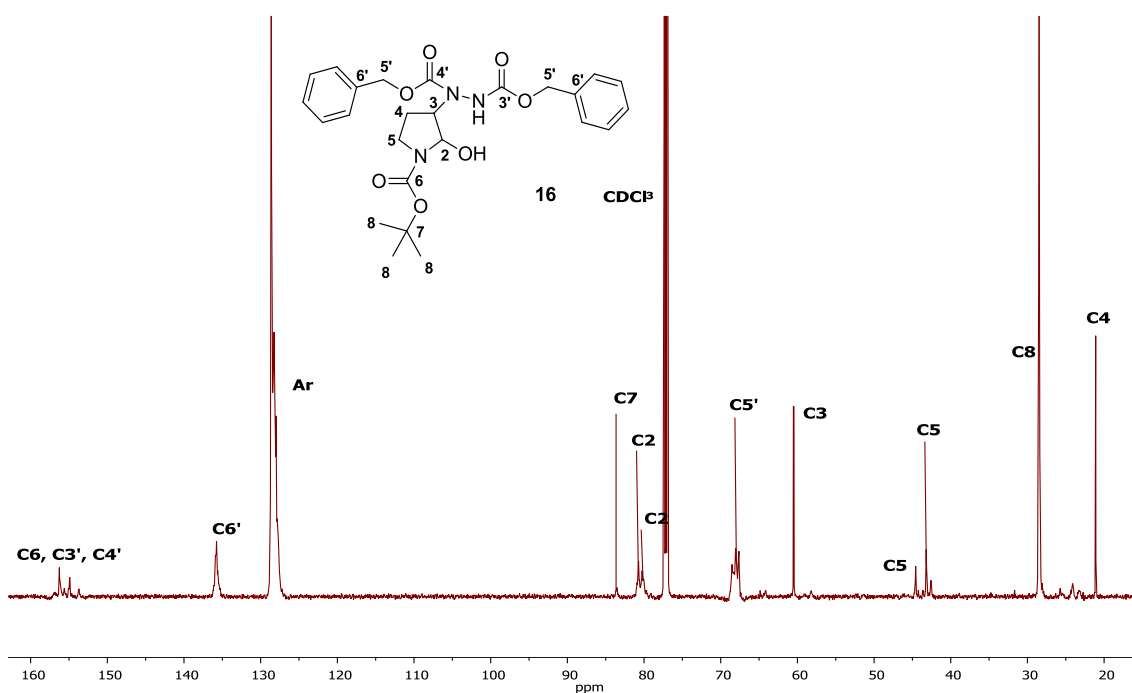


Figure 30: ^{13}C NMR spectrum of compound 16.

Finally, chiral HPLC was used to determine the number of individual peaks that could be identified. Enantiomeric excess (ee) measurements were carried out by HPLC using a Chiralpak AD column with a flow rate of 1 mL / min at 254 nm and a mobile phase of

2-propanol / hexane (1 : 9). The reaction was first repeated using DL-proline (racemic) in order to identify the various isomers. Analysis of the HPLC spectrum from the reaction, Figure 31, revealed four peaks as two sets of large(er) and small(er). The integration of the large to small in each pair agreed reasonably well with the NMR integration of a 2:1 mix of isomers suggesting that the NMR ratio corresponded to the large / small ratio of the HPLC. In turn this suggested that this ratio reflected the ratio of diastereomers. Conversely, the large / large or small / small ratio indicated the percentage of enantiomers, which within experimental error was 50 : 50 as expected. Peaks are labelled as follows:

Enantiomers of diastereomer 1 (E1D1; E2D1)

Enantiomers of diastereomer 2 (E1D2; E2D2)

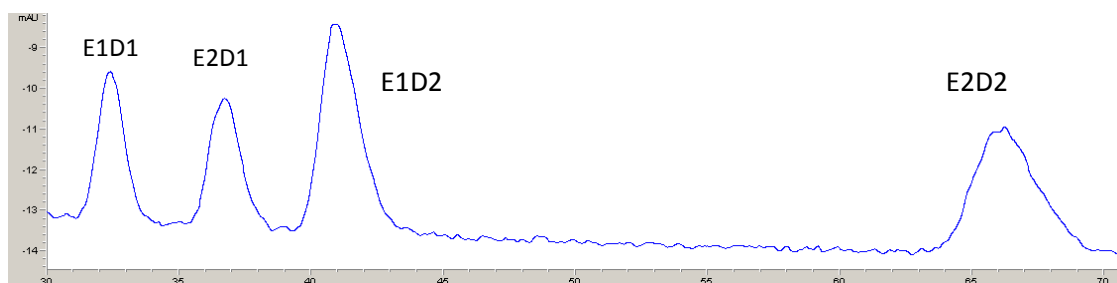


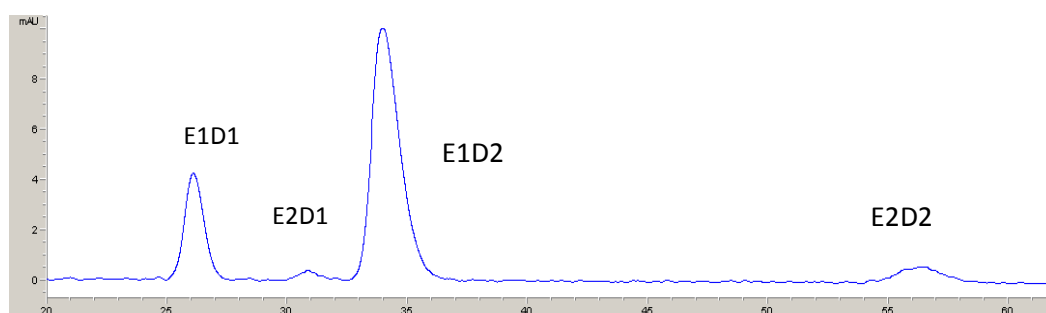
Figure 31: HPLC of racemic **16**.

Even though an excellent yield of 90% of the product was obtained, it was necessary to perform a study on the influence of reaction parameters on enantioselectivity. These were conducted with respect to temperature, solvent, catalyst and reagent respectively and once again reactions were monitored by the consumption of DBAD as a limiting reagent. Table 3 shows the results in which the racemic HPLC trace assisted in identifying both dr and ee.

Table 3: Temperature and acid additive studies.

Entry	Temp.	AcOH eq.	Time	Conversion (%)	Yield (%)	dr	ee (%)
1	0 °C	-	3 d	54	59	95 (5)	79 (82)
2	12 °C	-	3 d	57	63	87 (13)	88 (89)
3	12 °C	2	3 d	60	75	86 (14)	72 (79)
4	RT	-	3 d	100	90	84 (16)	85 (84)
5	RT	2	36 h	100	92	82 (18)	69 (70)
6	30 °C	-	2.8 d	100	93	81 (19)	80 (78)
7	30 °C	2	32 h	100	95	78 (22)	68 (77)

The results showed that RT or above was needed to get a high yield within three days (as an acceptable limit) in which the highest enantioselectivity (entry 4) was at RT without additional acid (AcOH). The trace corresponding to entry 4 is shown in Figure 32 revealing a diastereomeric ratio of about 3 : 1 based on the large / small ratios and an enantioselectivity of 85% (84%) based on the large / large (93:7) and small / small (92 : 8) ones. The diastereoselectivity fluctuated and was temperature dependent presumably because of the possibility of ring opening and closure (epimerisation) at the C2 hemiaminal centre. The structure of the major isomer was not ascertained because later the C2 centre would be removed by oxidation.

**Figure 32:** HPLC trace of Table 3 entry 4.

Although reactions conducted in acetonitrile seemed to give good results, a solvent study to confirm this was carried out, Table 4. A selection of relatively ‘green’ solvents was chosen

from a list published by the American Chemical Society Pharmaceutical Roundtable.⁹⁷ Reactions were conducted under the conditions from Entry 4 in Table 3 (see Scheme 53) with dry solvents and were left to go to 100% consumption of the DBAD, in which acetonitrile (Table 4, Entry 1) was confirmed as the best solvent as it gave the highest ee and yield in the shortest time. By comparison, ethanol gave no yield as this medium seemed to decompose the DBAD reagent (starting material remained intact while DBAD disappeared with the appearance of many spots).

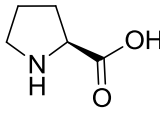
Table 4: Solvent studies using conditions from Scheme 57.

Entry	solvent	time	Yield (%)	dr	ee (%)
1	ACN	3 d	84	85 (15)	83 (84)
2	THF	5 d	45	89 (11)	78 (42)
3	Ethanol	6 d	0	-	-
4	EtOAc	4,5 d	68	87 (13)	74 (76)

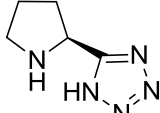
Similarly, catalyst studies were then conducted at room temperature in acetonitrile. The catalysts chosen were; **a.** L-Proline, **b.** (*S*)-(-)-5-(2-Pyrrolidinyl)-1*H*-tetrazole, **c.** (2*R*,5*R*)-2-*tert*-Butyl-3-methyl-5-phenylmethyl-4-imidazolidinone and **d.** diphenylprolinol silyl ether. Although tetrazole (b) has proved to be a remarkable catalyst for many published reactions and gave an increase of ee in the acetal amination compared to that from proline, in this study only L-proline worked, indicating the importance of having the free carboxyl group, presumably to catalyse ring-opening to the aldehyde.

Table 5: Catalyst studies.

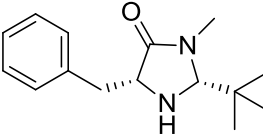
Entry	Catalyst	time	Yield (%)	dr	ee
1	a	3 d	93	86 (14)	82 (83)
2	b	5 d	0	-	-
3	c	6 d	0	-	-
4	d	6 d	0	-	-



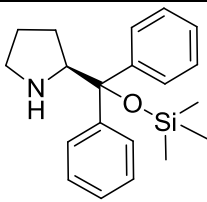
a



b

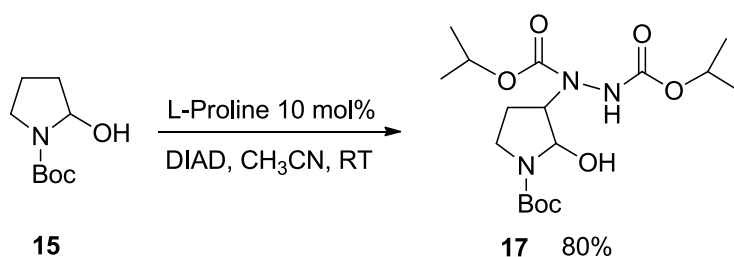


c



d

Lastly was the reagent study of DBAD vs DIAD (diisopropyl azodicarboxylate) and DTBAD (di-*tert*-butyl azodicarboxylate) to afford products **16**, **17** and **18** respectively. The formation of the DIAD product is described below, Scheme 54.

**Scheme 54:** Formation of aminated hemiaminal **17**.

As with **16**, the ^1H NMR spectrum of **17**, Figure 33, showed that amination using DIAD (1.0 eq.) and L-Proline (10 mol%) at room temperature in acetonitrile had taken place, and **17** was obtained in a yield of 80% as a yellow oil following a work-up with aqueous ammonium chloride, and isolation using column chromatography. Proof of structure was based on the appearance of isopropyl group signals integrating for twelve protons at 1.20 ppm as a series of doublets. Also, H3 again shifted downfield (4.54 ppm) from its position in **15** (1.85 ppm). Furthermore, an interplay between several isomeric forms was again observed as with **16** based on a major NH signal at 6.56 ppm and a minor one at 6.49 ppm, as well as a minor H3 signal appearing at 4.08 ppm, which allowed an approximate ratio of 2 : 1 for isomers to be calculated. Likewise, the ^{13}C NMR spectrum of **17** indicated the presence of three carbonyl

groups with signals at 156.8 ppm (C6), 156.0 ppm (C3') and 155.4 ppm (C4'), while the doubling of signals at 80.6 ppm and 79.2 ppm (C2) as well as at 44.7 ppm and 43.2 ppm (C5), supported the 2:1 mix. Analysis of the infrared spectrum of **17** indicated a broad band of overlapping carbonyl stretches at 1680 cm^{-1} , a broad band at 3290 cm^{-1} corresponding to the O-H stretch and a shoulder band at 3380 cm^{-1} corresponding to the N-H stretch. To further confirm the formation of **17**, HRMS was conducted and found 412.2054 for $\text{C}_{17}\text{H}_{31}\text{N}_3\text{NaO}_7 [\text{M}+\text{Na}]^+$ which agreed well enough with the calculated mass of 412.2060.

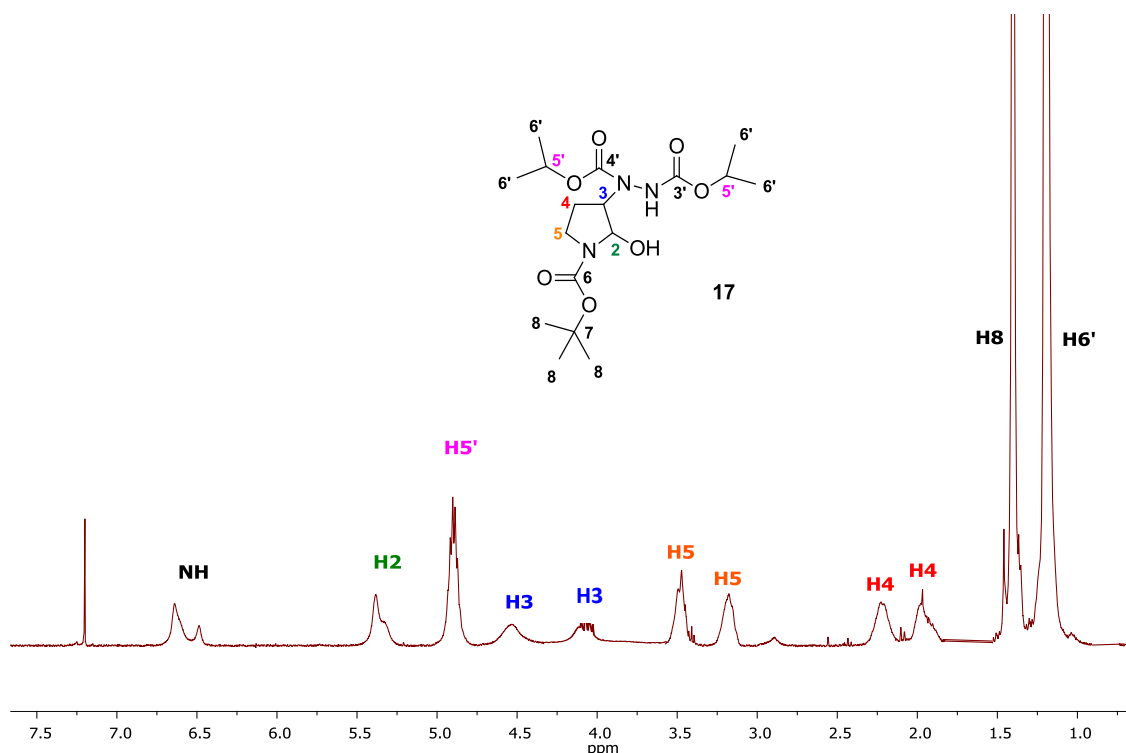
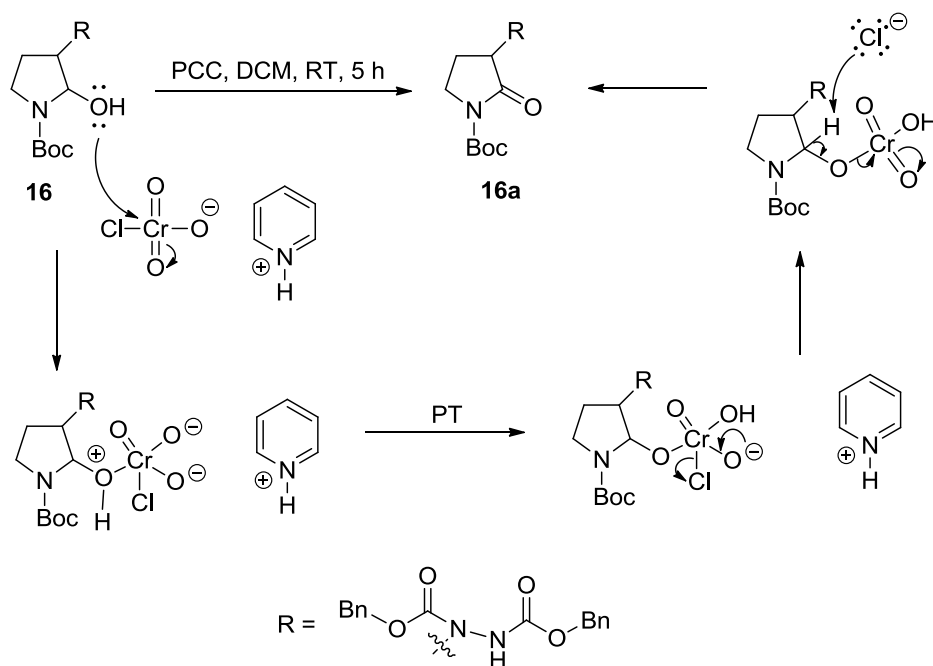


Figure 33: ^1H NMR spectrum of compound **17**.

Owing to the non-UV activity of the DIAD and DTBAD products **17** and **18** oxidation to the corresponding lactams was necessary. Various oxidants were tried out: SWERN, Dess-Martin periodinane, pyridinium dichlorochromate and pyridinium chlorochromate (PCC) – and of these only PCC was successful.⁹⁸ Scheme 55 indicates a general equation for the reaction together with a mechanism involving oxidation of a chromate ester with reduction at Cr. The products from PCC oxidation were isolated via filtration through Celite[®] and chromatography to afford oils **16a**, **17a** and **18a** in all three cases with yields of 68%, 67% and 66% for DBAD, DIAD and DTBAD respectively. A mechanism for the oxidation of hemiaminal **16** (R containing a UV-active benzyl groups), is described below.



Scheme 55: Oxidation of hemiaminal **16**.

The ^1H NMR spectrum of **16a**, Figure 34, once again revealed broad signals but did suggest that oxidation had taken place based on the disappearance of the H2 proton. In addition, the spectrum indicated one set of signals for the NH hydrogen at 6.75 ppm and H3 at 5.09 ppm overlapping with the benzylic protons H5'. The spectral data indicated that our interpretation of the 2 : 1 ratio (or thereabouts) in **16** being due to diastereomers (based on the HPLC data) was indeed correct. Also, only one spot was observed on TLC. The H3 proton shifted downfield to 5.09 ppm from 4.56 ppm due to the presence of the vicinal withdrawing carbonyl group. The ^{13}C NMR spectrum of **16a**, Figure 35, further proved the formation of **16a** by the appearance of a new carbonyl signal at 169.8 ppm in addition to the existing three carbonyl groups, and a single signal of H3 signals at 71.4 ppm. Analysis of the infrared spectrum of **16a** indicated a broad band of four carbonyl stretches at 1713 cm^{-1} (two $\text{C}=\text{O}$ stretches overlapping), 1787 cm^{-1} and 1798 cm^{-1} , and a broad band at 3377 cm^{-1} corresponding to the N-H stretch – see overlap in Figure 36. Additional confirmation was conducted using HRMS that found 506.1904 for $\text{C}_{25}\text{H}_{29}\text{N}_3\text{NaO}_7$ $[\text{M}+\text{Na}]^+$, which agreed well enough with the calculated mass of 506.1903.

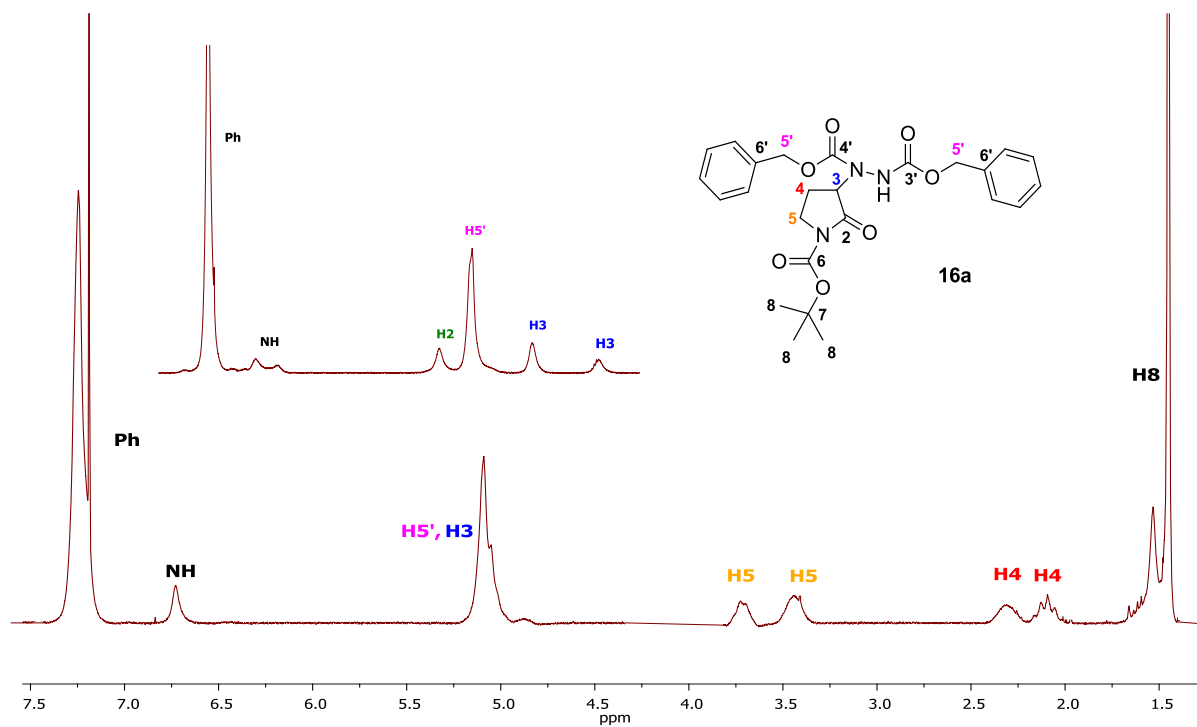


Figure 34: ^1H NMR spectrum of compound 16a.

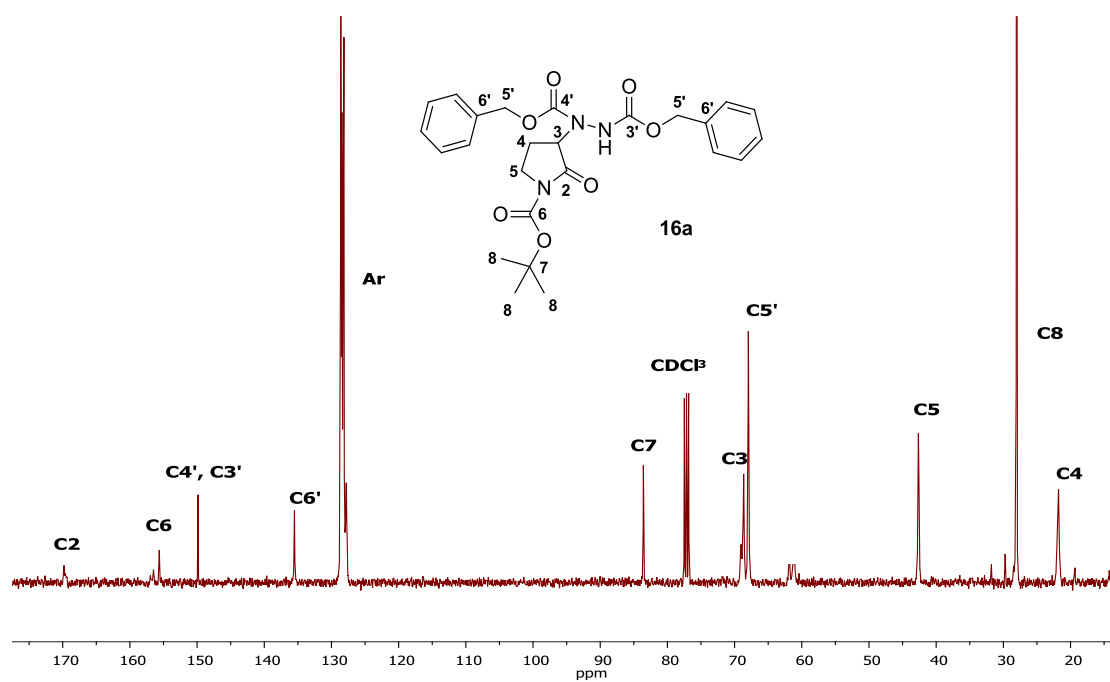
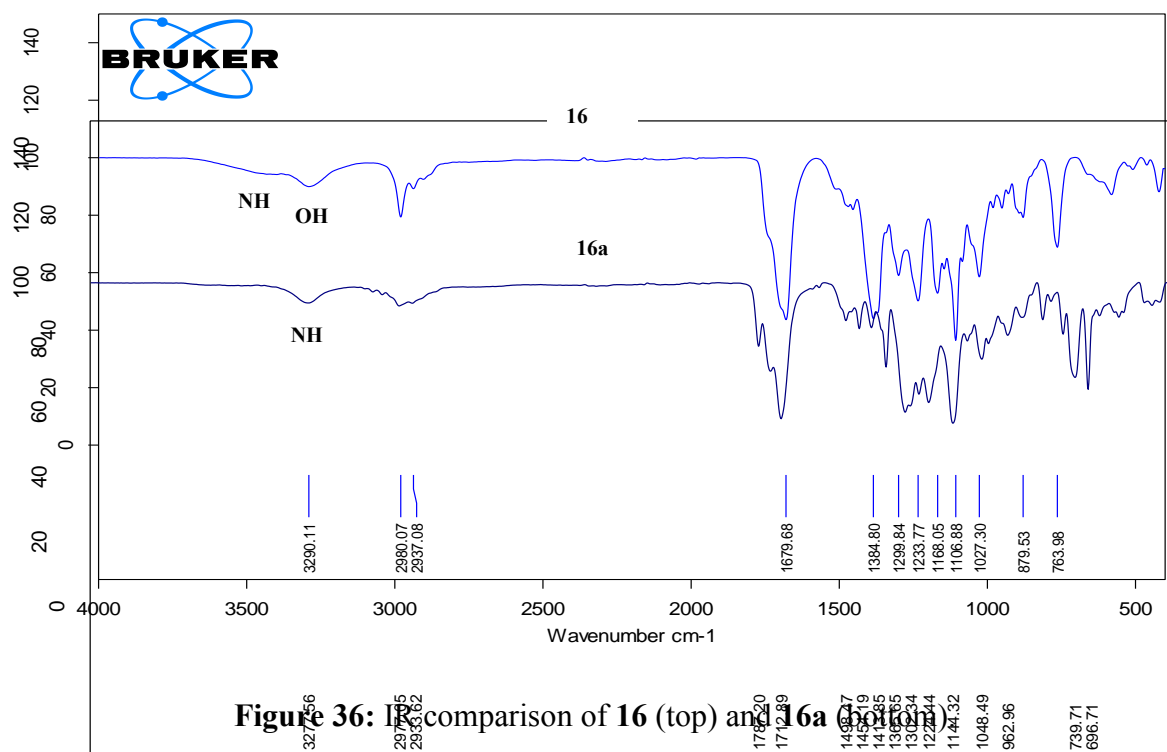


Figure 35: ^{13}C NMR spectrum of compound 16a.



We led the final word to chiral HPLC analysis. Pleasantly, only two peaks were observed, and based on the trace of the racemic product obtained from using DL-Proline, which showed two separated peaks for the enantiomers in a 1:1 ratio, an enantioselectivity of 84% was calculated (92:8), which did not change from an ee average of 84% in **16**. This evidence demonstrated that indeed no racemization at the α -aminated centre via enolization had taken place by introducing a carbonyl group next to it, Figure 37.

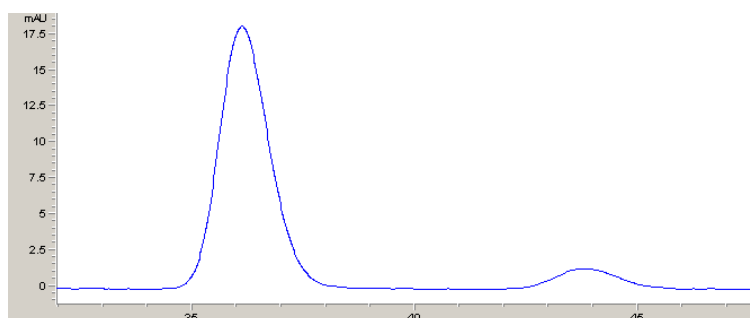
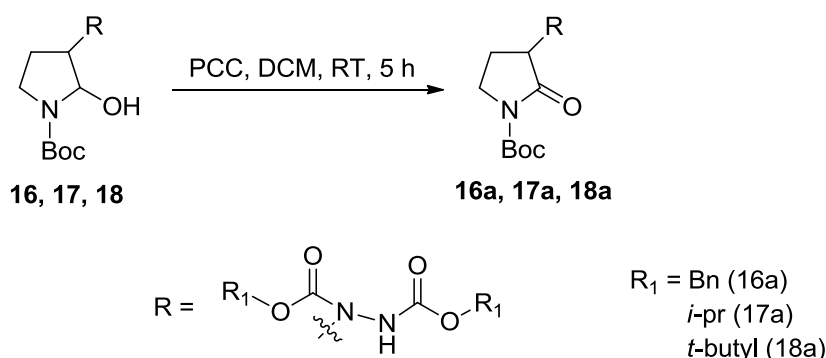


Figure 37: HPLC spectrum of 16a.

Results of the amination reagent study are shown in Table 6 and these were calculated on the basis of 100% conversion of the amination reagent as before followed by oxidation with PCC, Scheme 56. The results revealed DBAD to be the best reagent with respect to yield and enantioselectivity. It was also observed that the reaction time increased with an increase in

bulkiness of the carbamate ester groups. Reaction with DTBAD formed many spots, creating isolation difficulty, which resulted in a low yield of product.



Scheme 56: Oxidation of hemiaminals using PCC.

Table 6: Reagent studies of the oxidized products.

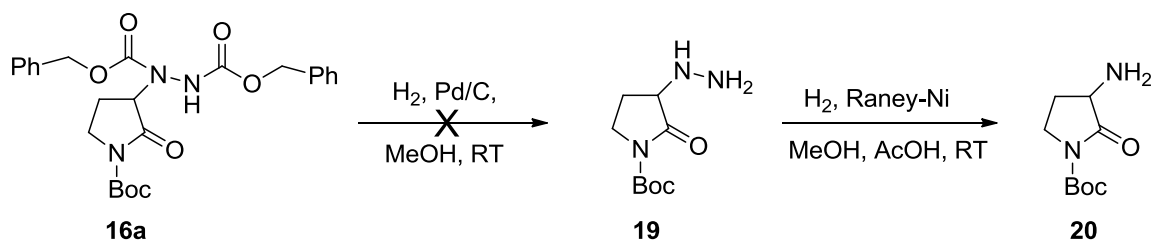
Cpd No	electrophile	Time	Yield ^a (%)	Yield ^b (%)	ee ^b (%)
16	DBAD	3 d	90	68	85
17	DIAD	6 d	80	67	80
18	DTBAD	4 d	46	66	68

a. Calculated after amination; b. Calculated after oxidation.

The next step in the methodology development was to cleave the hydrazide N-N bond to afford the α -amino lactam as a useful synthesis intermediate.

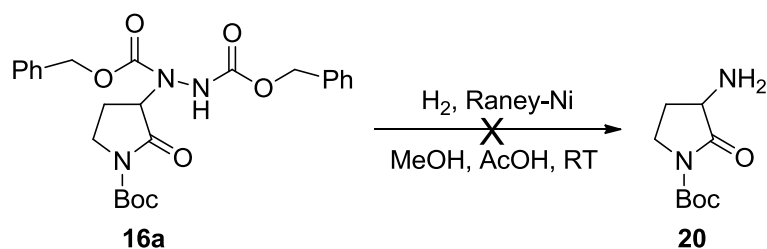
3.3 N-N bond cleavage

Various methods have been reported for this conversion including: samarium diiodide,⁹⁹ lithium / liquid ammonia,¹⁰⁰ hydrogenolysis with Palladium-on-carbon¹⁰¹ or Raney Nickel,¹⁰² Zinc in acetone / acetic acid, and finally NaNO₂ in an acetic acid / hydrochloric acid mixture. In the event lactam **16a** was subjected to hydrogenolysis using palladium on carbon (2.0 eq.) in dry methanol at room temperature to remove the benzyl groups to afford hydrazine **19**, followed by the addition of Raney Nickel to give **20**, Scheme 57.



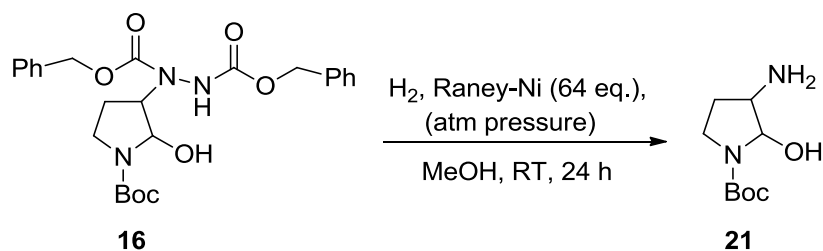
Scheme 57: Hydrogenolysis of lactam using palladium.

Surprisingly, the reaction to produce **19** did not work, giving inconclusive results (multiple spots and unassignable NMR spectra). Moreover, attempts to run the reaction at lower palladium equivalents (0.5 eq.), at higher temperatures, in different solvents or under pressure using a hydrogenator were unsuccessful. As such the conditions were changed to using Raney Nickel (2 eq.) in methanol and acetic acid at atmospheric pressure directly, which would hopefully afford amine **20**, Scheme 58.



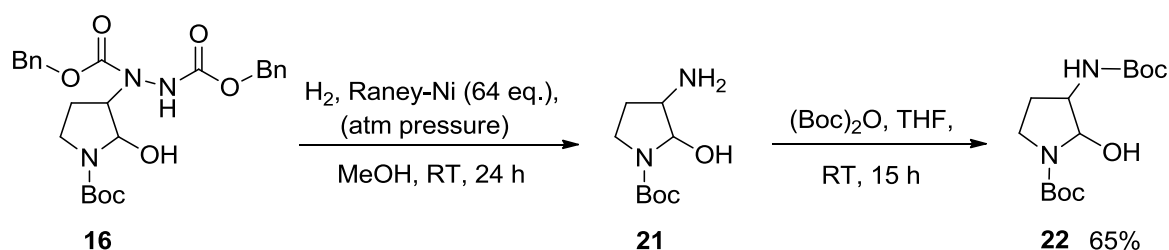
Scheme 58: Atmospheric pressure hydrogenolysis of lactam using Raney Nickel.

Yet again the reaction was unsuccessful with no reaction occurring and the starting material recovered. At this stage it was decided to attempt N-N cleavage prior to hemiaminal oxidation. Owing to the sensitivity of the hydroxyl group to acid medium the reactions were conducted in the absence of acetic acid. Hydrogenolysis using the protocol in Scheme 57 resulted in deamination back to **15** according to ^1H NMR analysis and so it was decided to proceed directly with Raney Nickel at 8 equivalents, which resulted in a 20% conversion of **16** to a more polar non-UV active spot on TLC which suggested the formation of an amine **21** based on TLC staining, Scheme 59. Increasing the catalyst load to 64 equivalents gave 100% conversion after 24 hours. The results suggested that coordination of the hydroxyl to the nickel metal through hydrogen bonding facilitated the reaction. Conducting reactions under pressure at 2 bar, 2.5 bar and 4 bar gave no improvement in the amount of catalyst that needed to be used.



Scheme 59: Atmospheric pressure hydrogenation of hemiaminal **16**.

Owing to the polarity of the product and thus the difficulty to isolate the α -amino hemiaminal, the reaction was filtered over Celite[®] and the crude product reacted with (Boc)₂O in THF at room temperature to afford compound **20** in a yield of 65% over the two steps as a colourless oil, Scheme 60.



Scheme 60: Formation of α -amino protected hemiaminal **22**.

Figure 38 shows the ¹H NMR spectrum of **22** that confirmed N-N cleavage by the disappearance of the phenyl signals as well as the benzyl methylene groups. In addition, two Boc singlets at 1.38 ppm and 1.41 ppm were observed integrating for 18H (H8 and H4'). The presence of diastereomers was supported by the presence of extra peaks at 5.11 ppm. The ¹³C NMR spectrum further confirmed the formation **22** as two carbonyl signals were observed at 155.1 ppm (C-2') and 155.0 ppm (C-6) instead of three as seen in **16**. Analysis of the infrared spectrum of **22** indicated a broad band of two overlapping carbonyl stretches at 1700 cm⁻¹ and 1695 cm⁻¹ for the two carbamate carbonyl groups, a broad O-H band at 3290 cm⁻¹ and a shoulder band at 3387 cm⁻¹ corresponding to the N-H stretch. Additional confirmation was conducted using HRMS that found 302.1743 for C₁₄H₂₆N₂NaO₅ [M+Na]⁺ which agreed well enough with the calculated mass of 302.1740. This evidence was sufficient to confirm that **21** was indeed afforded as an intermediate product.

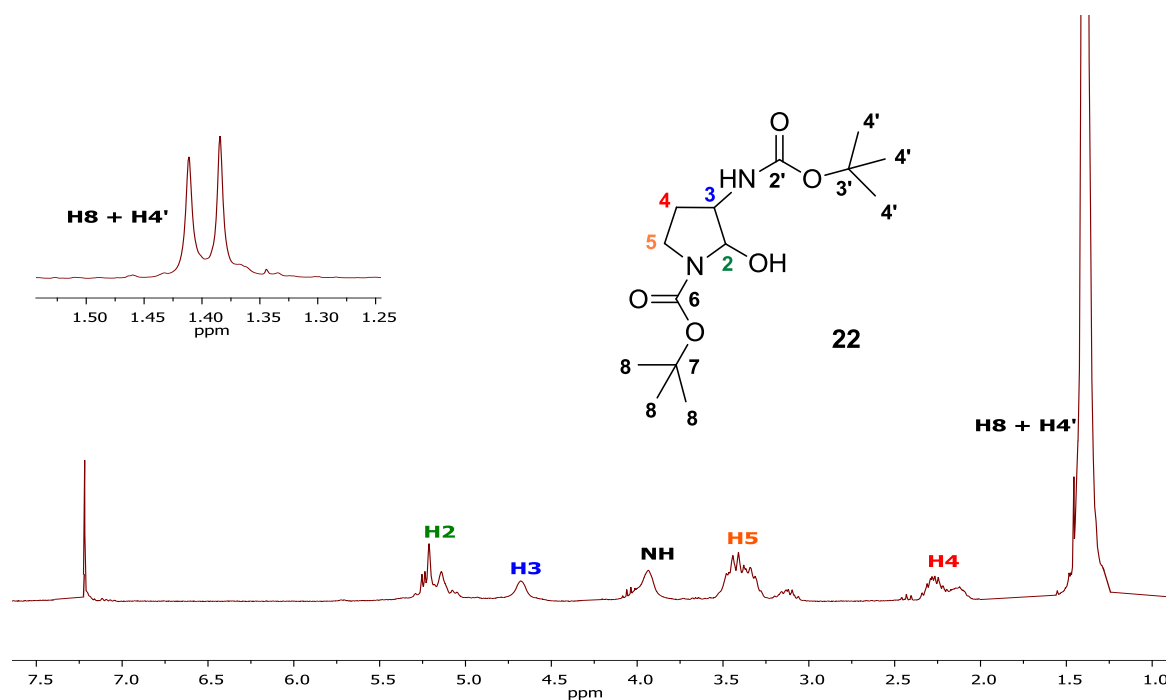
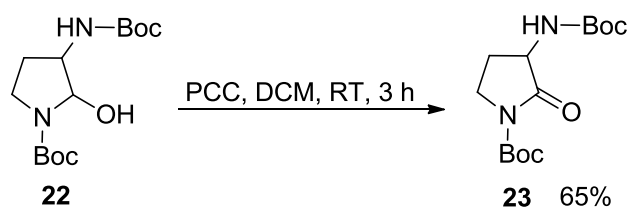


Figure 38: ^1H NMR spectrum of **22**.

Oxidation of **22** was accomplished using PCC in dry DCM at room temperature to afford **23** in 65% yield as an oil after filtration through Celite[®] and column chromatography, Scheme 61.



Scheme 61: Oxidation of **22**.

Figure 39 depicts the ^1H NMR spectrum which supports the formations of compound **23**. The disappearance of H2 and the appearance of a third carbonyl signal at 171.6 ppm in the ^{13}C NMR spectrum provided significant diagnostic peaks. Analysis of the infrared spectrum of **23** indicated a broad band of two overlapping carbonyl stretches at 1725 cm^{-1} and a band at 1698 cm^{-1} , as well as a broad band at 3389 cm^{-1} corresponding to the N-H stretch. Further confirmation was obtained by HRMS that found 323.1586 for $\text{C}_{14}\text{H}_{24}\text{N}_2\text{NaO}_5$ $[\text{M}+\text{Na}]^+$, which agreed well enough with the calculated mass of 323.1583. Determination of the enantioselectivity by chiral HPLC revealed an ee of 78% (89:11), Figure 40, which had

reduced from an ee average of 84% in **16** indicating that a small amount of racemisation had occurred.

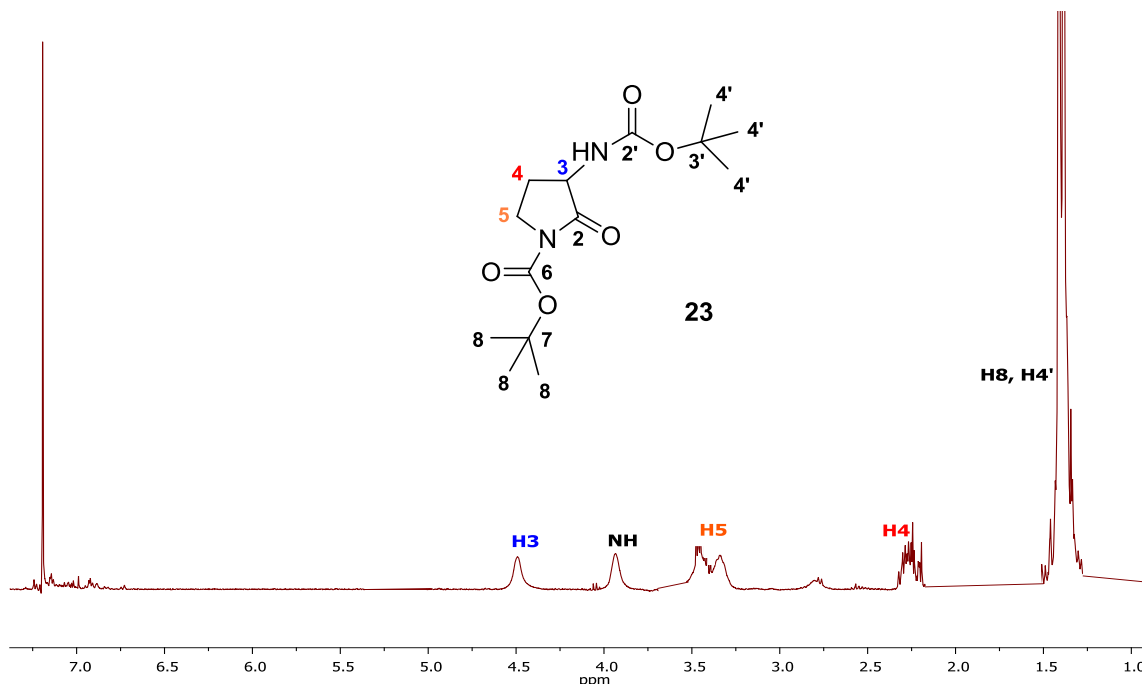


Figure 39: ¹H NMR spectrum of **23**.

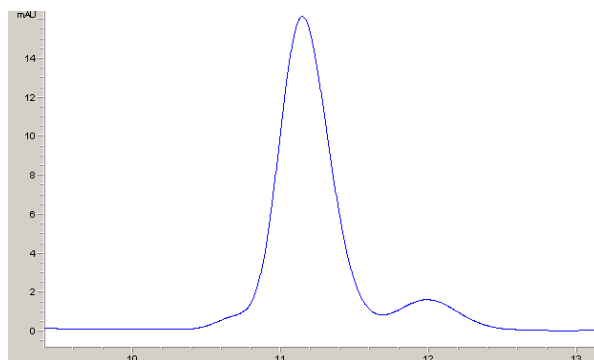
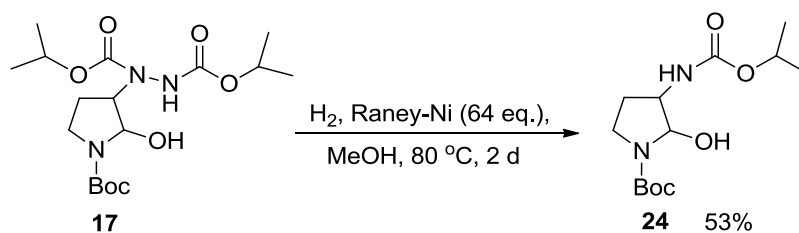


Figure 40: HPLC spectrum of **23**.

Further N-N cleavage studies were conducted on aminal **17** in which cleavage also required 64 equivalents of Raney Nickel in methanol at 80 °C under reflux, Scheme 62. Moreover, the TLC profile obtained was different to that in Scheme 59 showing a spot which did not corroborate to amine formation. Upon filtration through celite[®] and isolation by chromatography, the desired compound **24** was obtained in 53% yield as a colourless oil, Scheme 62.



Scheme 62: Atmospheric pressure hydrogenation of **17**.

Analysis of the ^1H NMR spectrum, Figure 41, supported the formation of **24**. Although the spectrum profile was similar to that of compound **17**, proton integration of the isopropyl group signal was halved in **24**. Further confirmation was supported by the appearance of only two carbonyl signals in the ^{13}C NMR spectrum at 156.5 ppm (C6) and 155.2 ppm (C2'). Analysis of the infrared spectrum of **24** indicated a broad band of two carbonyl stretches at 1739 cm^{-1} and 1694 cm^{-1} , a broad band at 3292 cm^{-1} corresponding to the O-H stretch and a shoulder band at 3368 cm^{-1} corresponding to the N-H stretch. Additional confirmation was obtained using HRMS which found 311.1584 for $\text{C}_{13}\text{H}_{24}\text{N}_2\text{NaO}_5 [\text{M}+\text{Na}]^+$ which agreed well enough with the calculated mass of 311.1583.

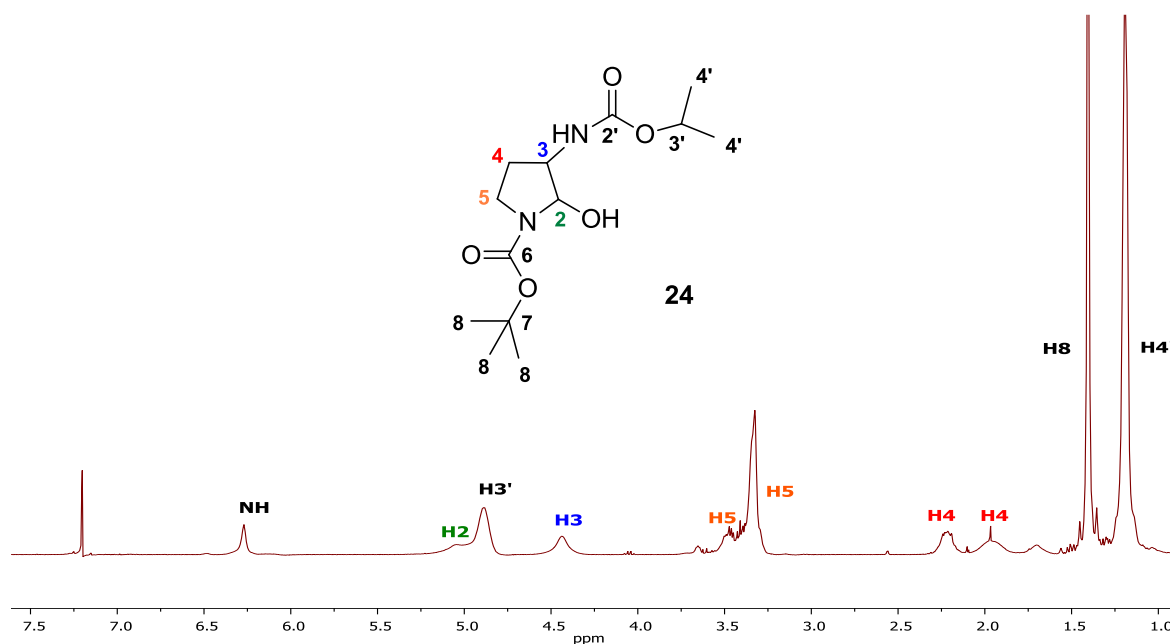
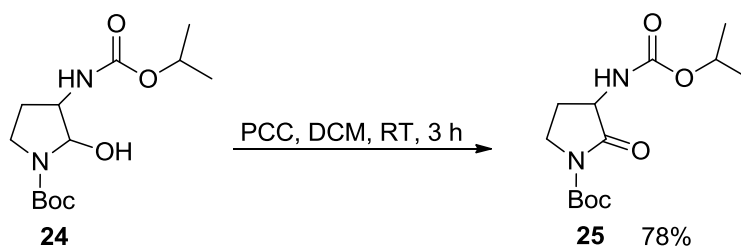


Figure 41: ^1H NMR spectrum of **24**.

Finally, **24** was oxidized using PCC in dry DCM at room temperature to afford **25** as a colourless oil in 78% yield after filtration through Celite[®] and chromatography, Scheme 63.



Scheme 63: Oxidation of **24**.

Analysis of the NMR spectra, Figure 42, showed the disappearance of H2 in the ^1H NMR spectrum and the appearance of a third carbonyl signal at 171.6 ppm in the ^{13}C NMR spectrum lending sufficient support evidence for the structure of **25** with the product obtained as a single diastereomer. Analysis of the infrared spectrum of **25** indicated a broad band of three carbonyl stretches at 1741 cm^{-1} , 1725 cm^{-1} and 1695 cm^{-1} and a broad band at 3362 cm^{-1} corresponding to the N-H stretch. Further confirmation was obtained by HRMS that found 309.1429 for $\text{C}_{13}\text{H}_{22}\text{N}_2\text{NaO}_5$ $[\text{M}+\text{Na}]^+$ which agreed well enough with the calculated mass of 309.1427. Pleasingly, the ee by chiral HPLC was determined to be 86% (93:7), Figure 43.

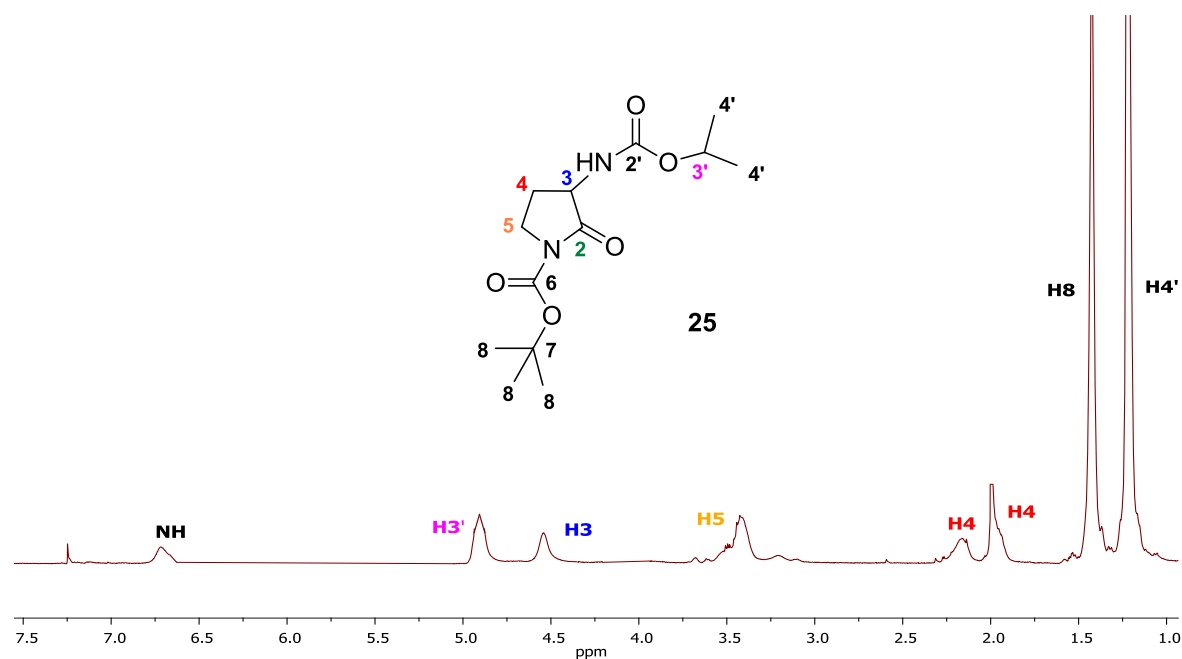


Figure 42: ^1H NMR spectrum of **25**.

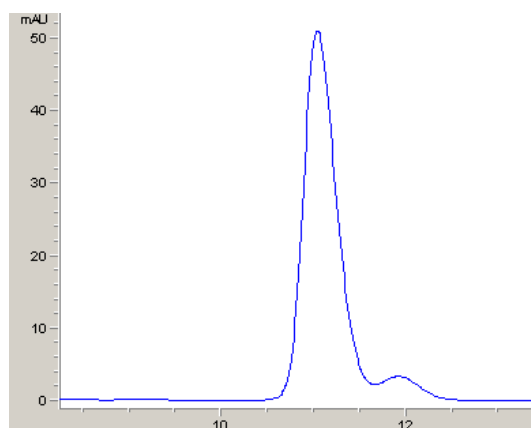


Figure 43: HPLC spectrum of **25**.

Since cleavage of the hemiaminal hydrazide **16** using Raney Nickel required a large excess of the catalyst and was hardly ‘green’ we sought for a milder, greener, and more importantly, safer method. One such method involved a novel *in situ* elimination reaction (E1cB) developed by Phillip Magnus and co-workers, which led to a further modification developed in our laboratory, which will be discussed in the next chapter. In conclusion, successful enantioselective α -amination of a five-membered hemiaminal containing an *exo*- carbamate *N*-protecting group has been achieved. Cleavage with Raney Nickel followed by hydroxyl group oxidation afforded the *N*-protected-3-amino-2-pyrrolidinone in high ee. This new methodology opens up the way for enantioselectively α -aminating lactams of different ring sizes. Interestingly, the equivalent *N*-protected 5-hydroxy-2-pyrrolidinone variant containing an *endo*-carbonyl group did not aminate under any conditions, probably due to a lack of hydrogen-bonding stabilisation in the ring opening step to generate the aldehyde for enamine formation and amination ultimately.

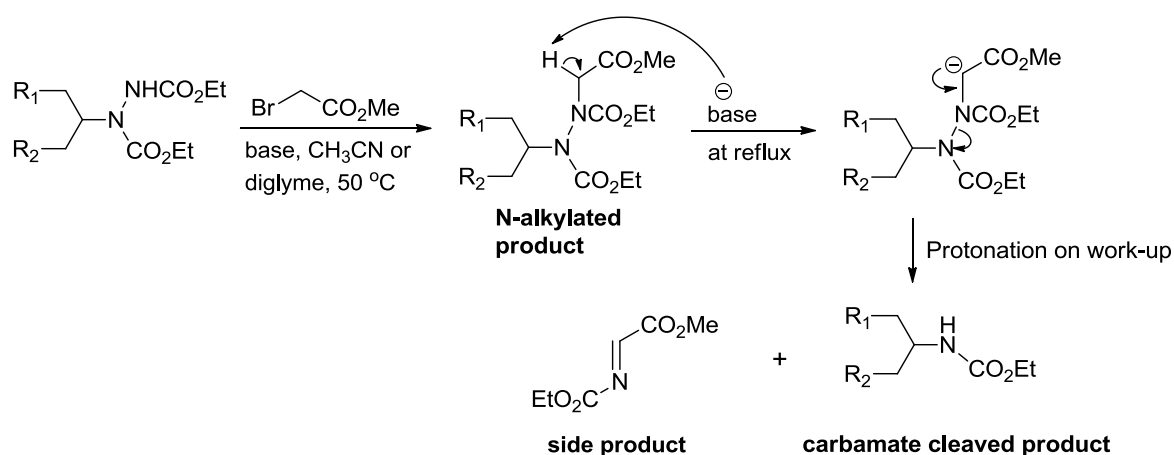
Chapter 4

N-N cleavage via E1cB

4.1 E1cB N-N cleavage introduction

The conventional cleavage methods mentioned in Chapter 3 (section 3.3) are conducted under harsh conditions, and cause chemoselective problems with substrates containing hydrogen-responsive functionalities (eg. benzyl ethers or alkenes), thus limiting the substrate scope. In 2009, Magnus developed a method¹⁰³ which made use of an E1cB mechanism (unimolecular elimination via the conjugate base) for reductive cleavage of the N-N bond of mono-*N*-alkylated hydrazine dicarboxylates to form carbamates. The reaction occurs under mild basic conditions and proceeds by first deprotonation to form a carbanion followed by the loss of the leaving group. This type of reaction occurs when there is an electron-withdrawing group adjacent to the C-H bond to be deprotonated, which stabilizes the conjugate base.¹⁰⁴

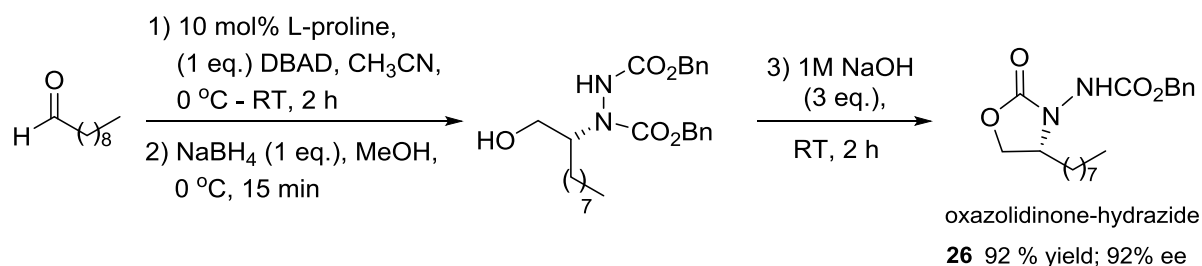
In their research Magnus discovered that reacting the secondary nitrogen of the hydrazide with ethyl or methyl bromoacetate in acetonitrile or diglyme in the presence of a base, (Cs₂CO₃ or NaH), resulted in *N*-alkylation, which subsequently underwent E1cB elimination involving the acidic methylene hydrogen of the newly introduced alkoxy carbonylmethylene group to afford a carbamate in an excellent yield of 80-98% together with a dehydroglycine derivative side product, Scheme 64. The reaction could be conducted in two separate steps with isolation of the *N*-alkylated intermediate prior to the elimination step or in a one-pot procedure when using NaH as a base.¹⁰⁵



Scheme 64: E1cB N-N cleavage methodology developed by Magnus.

4.2 Model study

This method, published in 2009, had never before been applied to enantioselectively α -aminated substrates when this work began. In order to test the degree of its application, a model study was conducted on α -aminated decanal, which was chosen as a non-volatile aldehyde due to its long chain. Owing to the presence of a nucleophilic primary hydroxyl group in the α -hydrazino alcohol product produced after α -amination of decanal with proline and DBAD, application of the base-mediated Magnus procedure would inevitably cause cyclisation to form an *N*-substituted oxazolidinone. Thus the α -aminated product was first converted into an oxazolidinone-hydrazide using 1 M sodium hydroxide (NaOH). The three-step sequence from decanal to the (*R*)-oxazolidinone-hydrazide was achieved in an overall yield of 92% and an ee of 92%, as shown in Scheme 65 below.



Scheme 65: Formation of decanal oxazolidinone **26**.

The formation of oxazolidinone-hydrazide **26** was confirmed by the ¹H NMR and ¹³C NMR spectra, shown in Figures 44 and Figure 45 respectively. The ¹H NMR spectrum revealed aromatic signals integrating for five protons at 7.29 ppm and a benzyl (H3') singlet at 5.12 ppm for two protons. In addition, diastereotopic H5 protons were observed quite far apart at 4.39 ppm and 3.90 ppm due to an alkyl shielding effect, while H4 integrating for one proton appeared between the two H5 signals, which was indicated by hsqc. The broad resonances were due to the presence of hydrazide rotamers. Additionally, the ¹³C NMR spectrum revealed two deshielded resonances at 68.2 ppm and 67.8 ppm for the C3' and C5 carbons bonded to oxygen, while the C4 carbon, being bonded to nitrogen, appeared more upfield as expected at 56.9 ppm. In addition, the oxazolidinone carbonyl (C2) and the CBz carbonyl (C2') resonances appeared in close proximity in the ¹³C NMR spectrum. Additional confirmation of **26** was obtained using high resolution mass spectroscopy, which found 349.2131 for C₁₉H₂₉N₂O₄ [M+H]⁺; calculated mass was 349.2127.

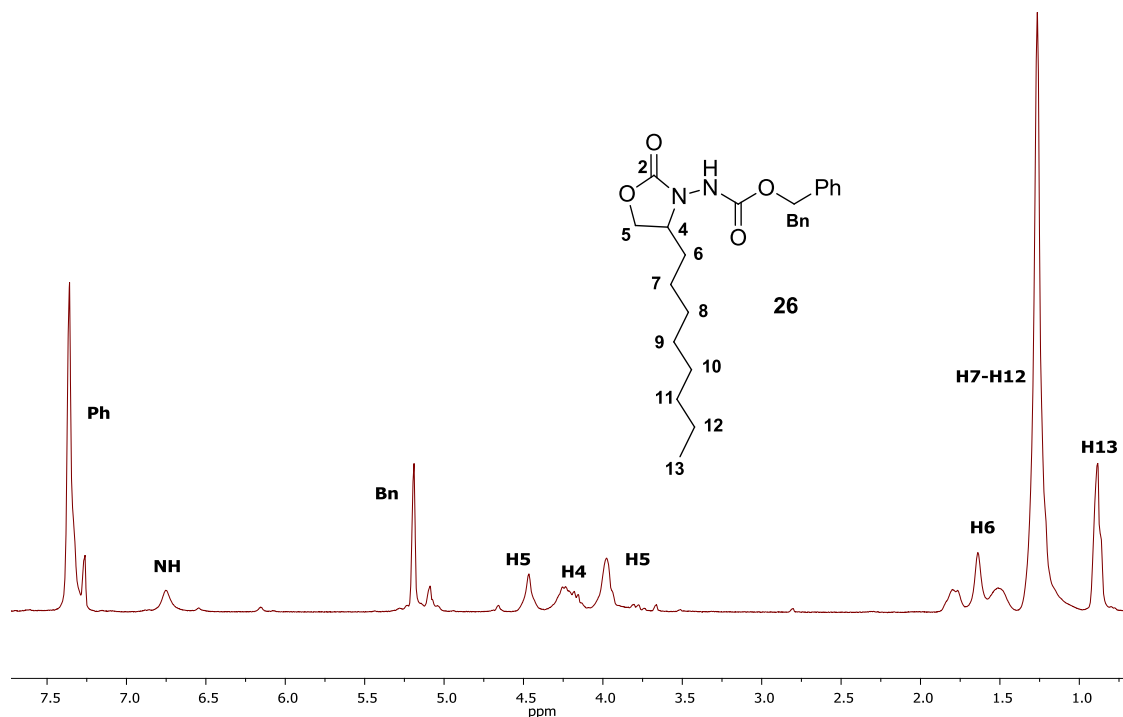


Figure 44: ^1H NMR spectrum of decanal oxazolidinone.

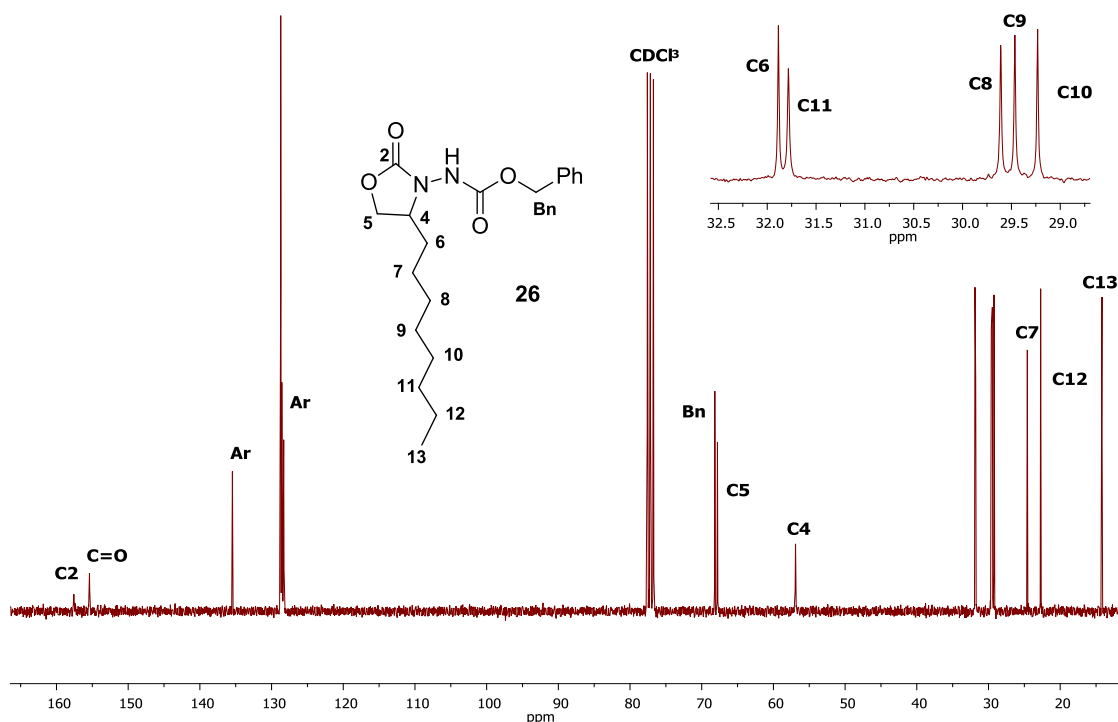
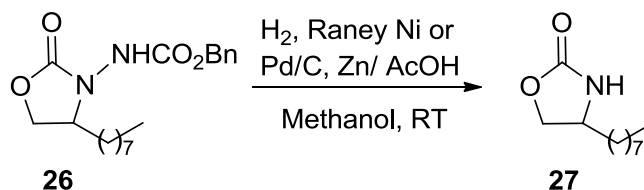


Figure 45: ^{13}C NMR spectrum of the decanal oxazolidinone-hydrazide.

Before proceeding with applying Magnus' methodology, a conventional hydrogenolysis was first applied to oxazolidinone **26** (Scheme 66), which with Raney Nickel (2 eq.) gave a disappointing yield of 53% while hydrogenation with Pd-C (7 mol%) followed by Zn (37 eq.)

in acetic acid (4 mL) gave a very low overall yield of 24%, with a full consumption of starting material as monitored by TLC in each case.



Scheme 66: Hydrogenolysis of oxazolidinone-hydrazide **26**.

Formation of **27** was confirmed by ¹H NMR and ¹³C NMR spectra, Figure 46 and Figure 47 respectively. The prominent observations noted were the disappearance of the benzyl methylene and phenyl resonances in both spectra as well as the C2' carbonyl carbon in the ¹³C NMR spectrum. Furthermore, the resolved ¹H NMR spectrum was due to the absence of rotamers that arose with the hydrazide. Likewise, further confirmation of **27** was obtained using HRMS that found 200.1652 for C₁₁H₂₂NO₂ [M+H]⁺, which was in agreement with the calculated mass of 200.1651.

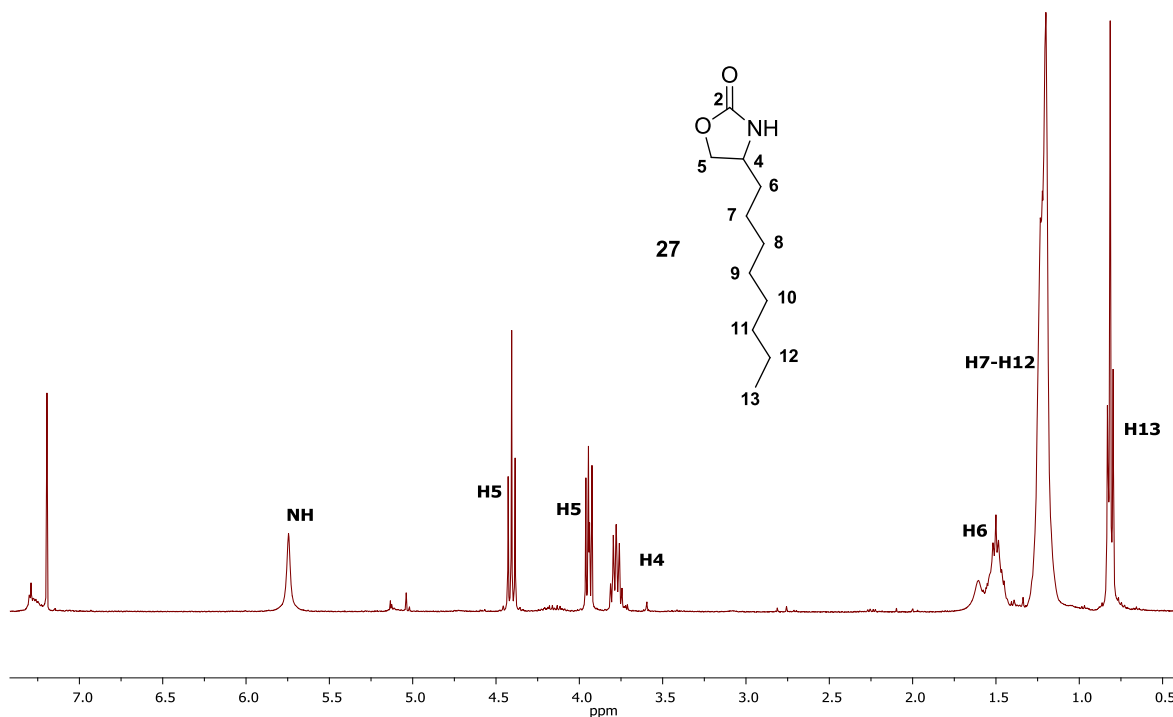


Figure 46: ¹H NMR spectrum of N-N cleaved decanal oxazolidinone.

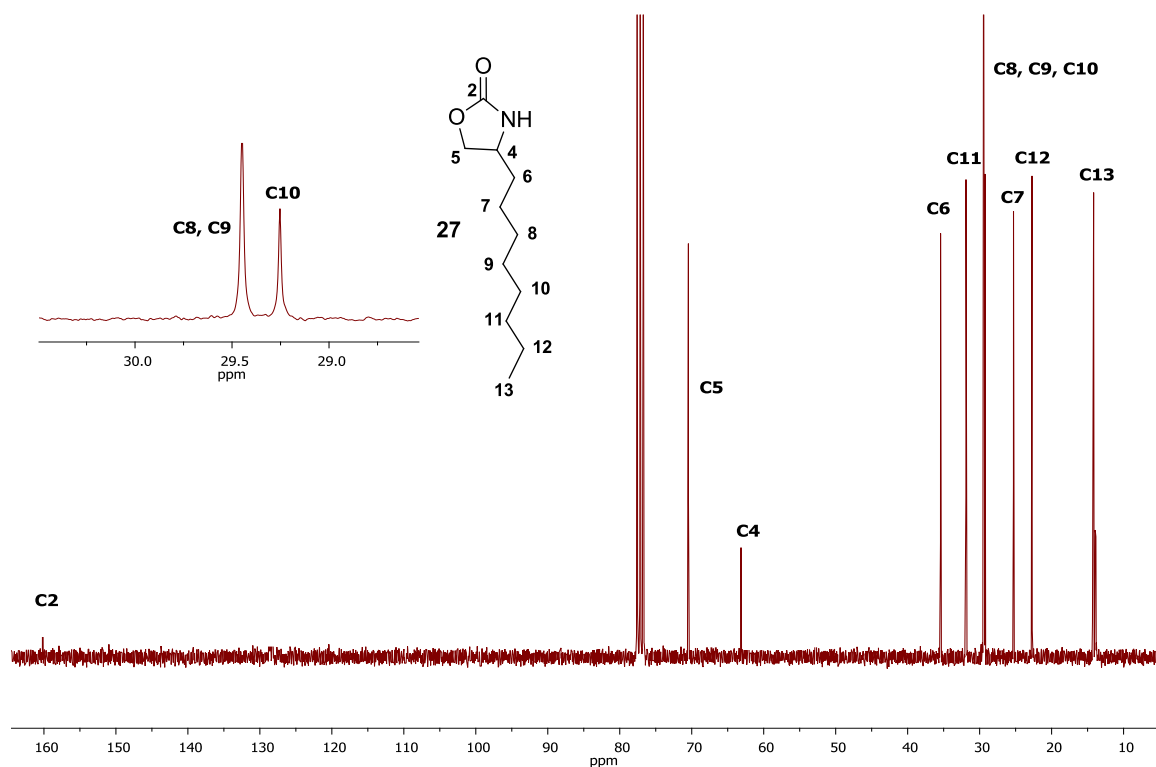
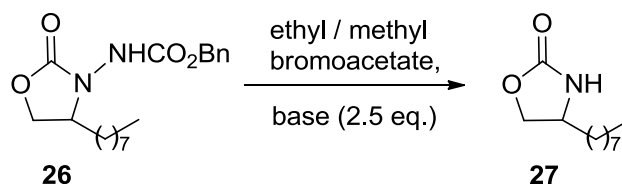


Figure 47: ^{13}C NMR spectrum of N-N cleaved decanal oxazolidinone.

4.3 Reaction study using Magnus' methodology

With a reference for the cleaved product now in hand, the oxazolidinone-hydrazide **26** was subjected to E1cB cleavage studies using Magnus' conditions with either ethyl or methyl bromoacetate (2 eq.) in varying solvents (0.25 M), Scheme 67.



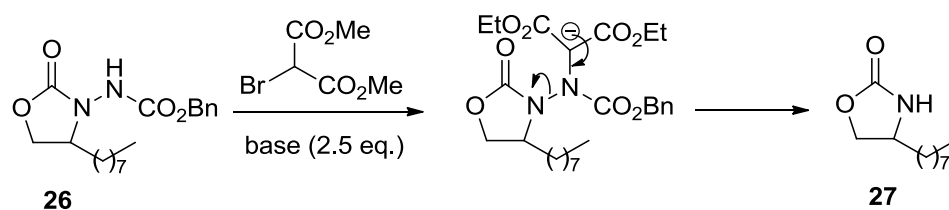
Scheme 67: Application of Magnus' conditions.

Table 7 shows the results in which Magnus-1 refers to the one-pot procedure (without isolation of alkylated product) using Cs_2CO_3 in CH_3CN , while Magnus-2 refers to using NaH in diglyme, also in a one-pot procedure. Dry solvents were used, as reaction times increased with wet solvents.

Table 7: Studies of Magnus' conditions with varying solvents.

Entry	Procedure	Base	Alkylating agent	Solvent	Temp (°C)	Time	Yield (%)
1	Magnus-1	Cs ₂ CO ₃	Methyl bromoacetate	CH ₃ CN	80	>2 d	-
2		Cs ₂ CO ₃	Ethyl bromoacetate	CH ₃ CN	80	>2 d	-
3	Magnus-2	NaH	Ethyl bromoacetate	Diglyme	50	17 h	16
4		NaH	Ethyl bromoacetate	CH ₃ CN	50-80	2 d	-
5		NaH	Ethyl bromoacetate	THF	50-80	2 d	-
6		NaH	Ethyl bromoacetate	DMF	50	24 h	46

Reactions conducted using the Magnus-1 procedure (Entries 1 and 2) were unsuccessful. Both the alkylating agent and the starting material were recovered (identified by NMR) even after extended reaction times of more than 2 days. An improvement was observed with the Magnus-2 conditions in which NaH was used as a base giving a very low yield of 16% with 100% conversion after 17 hours (Entry 3). However, the low yield was to a degree a result of the difficulty in separating the product from diglyme even after multiple washings and chromatography. This led to the study of other solvents that could be easily removed by an aqueous work-up, but attempts in acetonitrile and THF also failed, with recovery of the starting material (Entries 4 and 5) even after extended reaction times at high temperatures. Progress was eventually achieved in DMF giving an improved yield of 46%. The poor outcomes compared to Magnus' work may have been due to the change in substrate from that shown in Scheme 64 to our oxazolidinone-hydrazide. Whatever the reason it was thought that switching to the more electrophilic bromomalonate would not only facilitate the N-alkylation step but also the E1cB elimination on account of the proton being abstracted being more acidic due to the presence of two electron-withdrawing groups in the reagent, (Scheme 68). Table 8 shows a preliminary set of results varying the various reaction parameters of base, solvent, reagent equivalents, and reaction temperature.

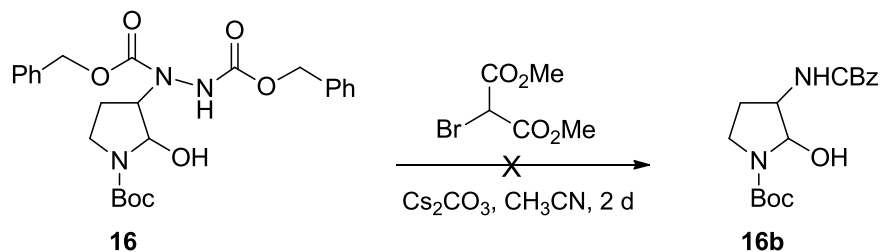
**Scheme 68:** New E1cB conditions.**Table 8:** Studies using bromomalonate.

Entry	diethyl bromomalonate (eq)	Base (eq)	Solvent (0.25 M)	Time	Temp (°C)	Yield (%)
1	1.5	NaH (3)	THF	24 h	0 – 50	48
2	1.5	NaH (3)	DMF	2 d	50	29
3	1.5	NaH (3)	CH ₃ CN	2 d	50	-
4	2	Cs ₂ CO ₃ (2.5)	CH ₃ CN	2 d	RT	64
5	2	Cs ₂ CO ₃ (2.5)	CH ₃ CN	4 h	50	64
6	5	Cs ₂ CO ₃ (2.5)	CH ₃ CN	5 h	50	66
7	2	Cs ₂ CO ₃ (5)	CH ₃ CN	5 h	50	68
8	5	Cs ₂ CO ₃ (5)	CH ₃ CN	5 h	50	80

Although there were many parameter changes, the mini-study identified that using Cs₂CO₃ in CH₃CN at room temperature at two equivalents of bromomalonate and 2.5 equivalents of base looked promising (entry 4), giving a 64% yield after chromatography. Heating the reaction with 5 equivalents each increased the yield to 80% (entry 8), which, however, was not cost efficient.

Consequently, the conditions of entry 4 in Table 8 were applied to hemiaminal hydrazide **16** with diethyl bromomalonate in acetonitrile at 0 °C, room temperature and 50 °C, but unfortunately the reaction was unsuccessful, with recovery of both starting materials at 0 °C

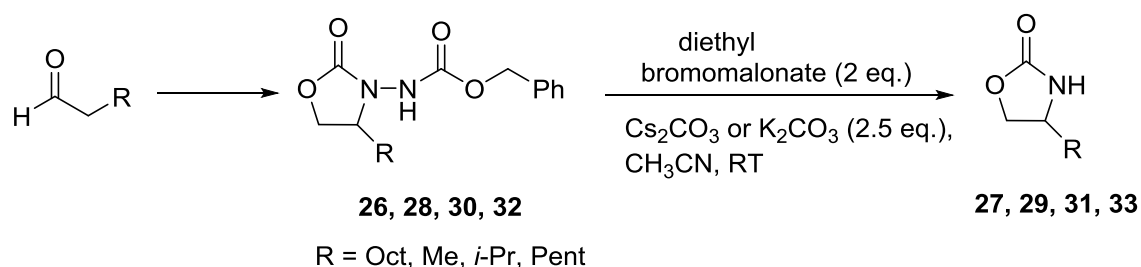
and room temperature after work-up, and multiple unidentifiable spots at higher temperature, Scheme 69. Therefore, cleavage of the hemiaminal hydrazide remained using Raney Nickel. However, a study on other α -aminated aldehydes was pursued to explore the scope of the bromomalonate reaction.



Scheme 69: Attempted Alkylation of hemiaminal hydrazide **16**.

4.4 New methodology applied to other simple aldehydes

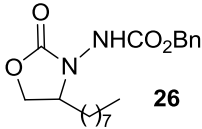
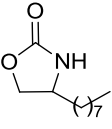
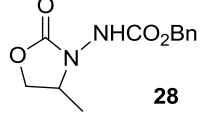
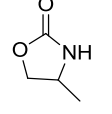
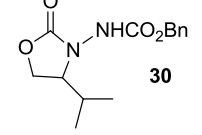
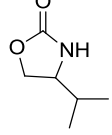
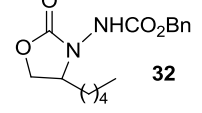
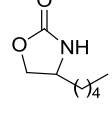
Hence the study was resumed with extension to other oxazolidinone-hydrazides (**26**, **28**, **30**, **32**) derived from other simple aldehydes such as propanal, *iso*-valeraldehyde and heptaldehyde, in which it was decided to retain the stoichiometry of the reagents in entry 4 but also change the relatively expensive caesium carbonate base to the cheaper potassium carbonate, Scheme 70.



Scheme 70: Extension of E1cb elimination to other aldehydes.

Oxazolidinone-hydrazides **26**, **28**, **30** and **32** in high ee were converted to cleaved products **27**, **29**, **31**, and **33** using the new optimized conditions, and the results are shown in Table 9 in which the yield and ee in the left-hand column refers to the results for aldehyde α -amination followed by base-promoted cyclisation to form the oxazolidinone hydrazide.

Table 9: Oxazolidinone formation via the E1cB protocol.

Entry	Oxazolidinone-hydrazide (1 eq)	Yield (%)	ee (%)	N-N cleaved oxazolidinone product	Base			
					K ₂ CO ₃		Cs ₂ CO ₃	
					time	Yield (%)	time	Yield (%)
1	 26	92	92	 27	23 h	90	48h	64
2	 28	88	90	 29	48 h	61	20 h	88
3	 30	91	91	 31	48 h	62	20 h	96
4	 32	89	93	 33	2 d	76 (85% conv)	2 d	63 (53% conv)

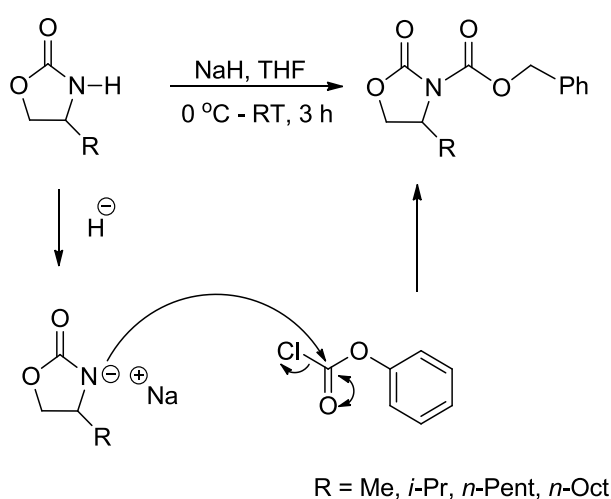
Gratifyingly K₂CO₃ proved to improve the yield of the cleaved product **27** (R = Oct) from 64% (with Cs₂CO₃; entry 1) to 90% as well as promote a marginal improvement for **32** (entry 4; R = Pent) from 63% to 76% respectively, albeit that the reactions in entry 4 failed to go to completion. However, for smaller chains Cs₂CO₃ proved to give superior yields in lower reaction times (entries 2 and 3). A solvent compatibility study with K₂CO₃ was conducted using oxazolidinone-hydrazide **26**, and the results shown in Table 10 indicate that acetonitrile was indeed the best solvent, giving the highest yield in the shortest time. Reactions in DMF and toluene gave low yields, with completion of the reactions only possible by adding extra base and heating at 50 °C. Methanol gave no yield, with the degradation of bromomalonate observed on TLC.

Table 10: Solvent study using decanal oxazolidinone.

Entry	Solvent	Temp.	Time	Yield %
1	Acetonitrile	RT	23 hrs	90
2	DMF	RT – 50 °C	3 d	30
3	Toluene	RT -50 °C	3 d	44
4	Methanol	RT	43 hrs	0

4.5 Derivatization of oxazolidinones

Owing to the non-UV activity of the cleaved products, derivatization of the oxazolidinone NH using benzyl chloroformate was conducted to install a UV-active chromophore for measuring the ees. In the event, sodium hydride (NaH) was used as a base to deprotonate the oxazolidinone forming an anion strong enough to attack the reagent through a S_NAc reaction, Scheme 71. Figure 48 shows the 1H NMR and ^{13}C NMR spectra of the CBz-derivatized propanal oxazolidinone **29a** as representative, with evidence of formation indicated by the reappearance of benzyl methylene (Bn) and phenyl resonances in the place of an NH signal, and a C=O resonance appearing in the ^{13}C NMR spectrum.



Scheme 71: Derivatization of N-N cleaved oxazolidinones.

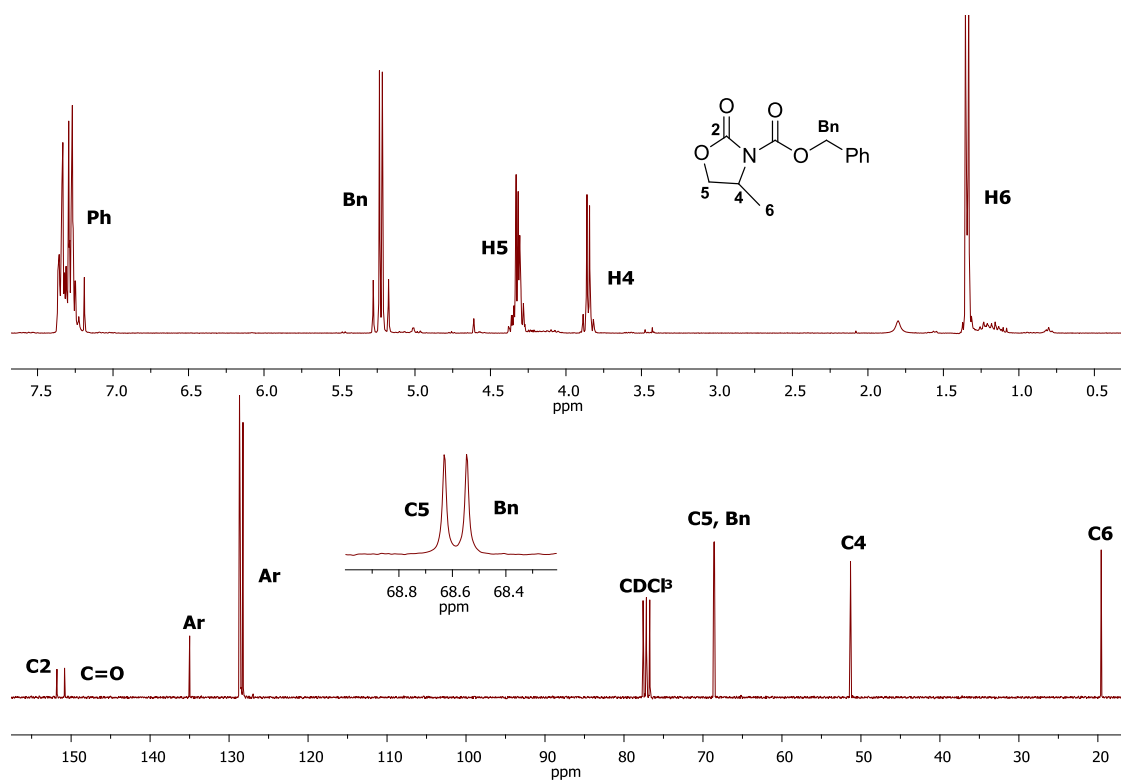
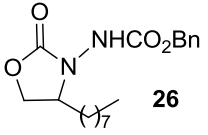
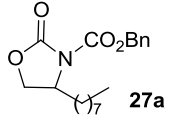
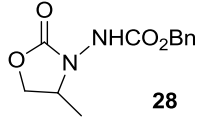
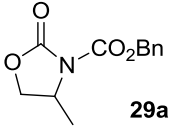
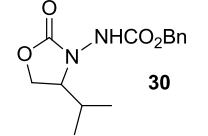
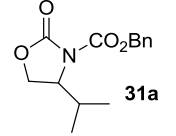
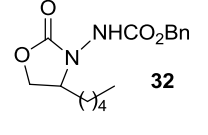
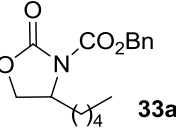


Figure 48: ¹H NMR and ¹³C NMR spectra of cbz-derivatized propanal oxazolidinone.

Table 11 shows a comparison of ees of oxazolidinones **26**, **28**, **30** and **32** before cleavage against those obtained after derivatization on cleaved product **27**, **29**, **31** and **33** and results suggested negligible racemization overall (a little with entry 1), within experimental error.

Table 11: Derivatization results.

Entry	Oxazolidinone	ee (%)	Derivatized cleaved product	Yield (%)	ee (%)
1	 26	92	 27a	94	83
2	 28	90	 29a	89	95
3	 30	91	 31a	92	92
4	 32	93	 33a	92	88

4.6 Extension to functionalized aldehydes

To explore scope the methodology was extended to a range of functionalized aldehydes containing various unsaturated functional groups. Fully assigned ^1H NMR spectra for one of the oxazolidinone hydrazides **36** is shown in Figure 49 together with its cleaved product **37**, which show a significant sharpening of the resonances in the latter as a result of rotamer disappearance.

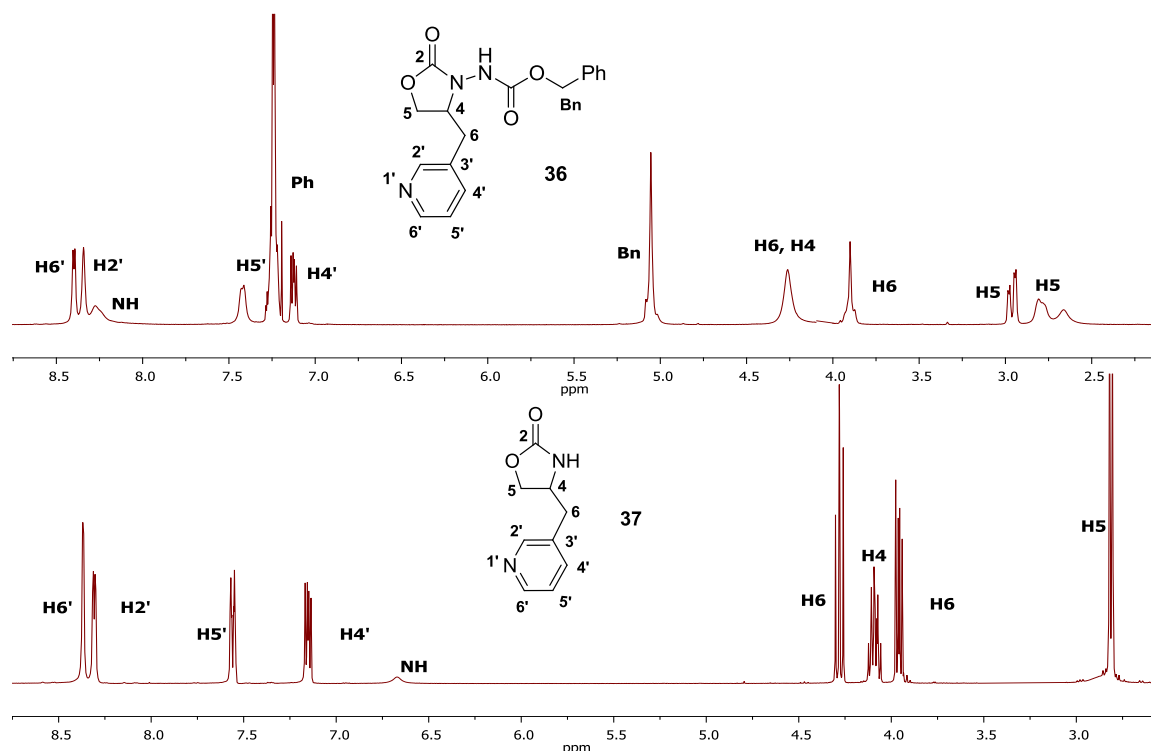
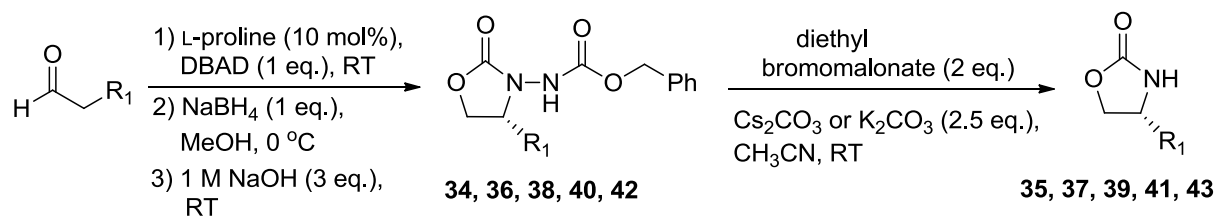


Figure 49: Comparison of the ¹H NMR spectra of pyridine functionalized oxazolidinone-hydrazide and its cleaved product.

Table 12 below shows the results obtained for the full series of oxazolidinone-hydrazides together with their cleaved products, Scheme 72.



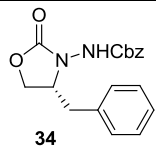
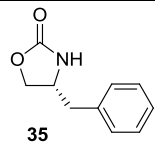
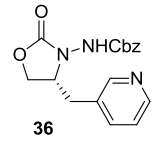
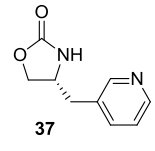
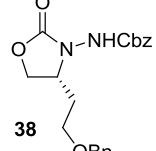
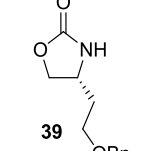
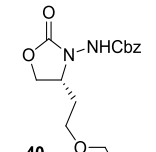
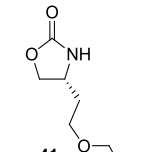
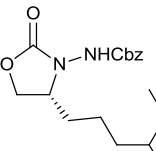
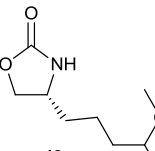
R₁ = alkyl or aryl

Scheme 72: α-Amination reaction followed by E1cB elimination.

Formation of the oxazolidinone-hydrazides via enantioselective amination followed by ring closure gave high yields in the range 72% - 91% and high ees of 86% - 95%. Thereafter, E1cB cleavage results gave high yields for both bases although a greater advantage lay with the Cs₂CO₃ in which reaction times were in the range between 2 to 5 hours as compared to 24 hours for K₂CO₃. An exception was observed with bis-acetal **43**, which formed over an extended reaction time of 48 hours with both bases and gave a lower yield of 57% with Cs₂CO₃ (Entry 5). Comparison of the oxazolidinone-hydrazide and cleaved oxazolidinone ees

indicated negligible racemization as before (Entries 1 to 3). Derivatization of **41** and **43** to install a UV-active CBz functionality for ee determination was unsuccessful owing to the instability of the substrates.

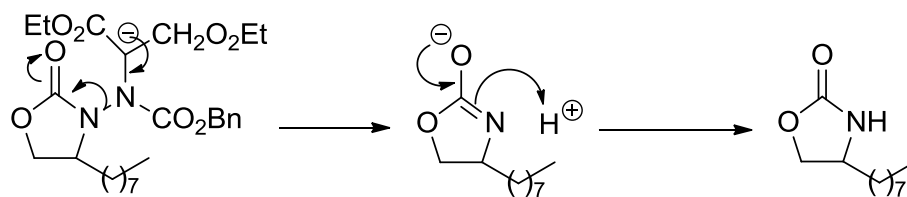
Table 12: Modified E1cb elimination of functionalized substrates.

Entry	Oxazolidinone-hydrazide from amination	Yield (%) ^a	ee (%) ^a	N-N Cleaved oxazolidinone	K ₂ CO ₃		Cs ₂ CO ₃		ee (%)
					time	Yield (%)	time	Yield (%)	
1		91	86		20 h	84	3 h	82	84
2		87	95		24 h	75	2 h	90	91
3		86	92		24 h	82	5 h	84	87
4		87	90		24 h	80	4 h	81	-
5		72	86*		48 h	86 (70% conv)	48 h	57 (89% conv)	-

a. Yield and ee after amination, * Obtained from α -hydrazino alcohol.

In conclusion, an improved methodology has been developed for the N-N cleavage of oxazolidinone-hydrazides derived from straight-chain aldehydes via an E1cB modified Magnus protocol using bromomalonate and either K₂CO₃ or Cs₂CO₃ as base. The success of this procedure on oxazolidinone-hydrazides, while failing on the hemiaminal open hydrazide, possibly suggests a stereoelectronic element involving appropriate orbital alignment operating within the oxazolidinone as opposed to the open hydrazide, although further experimental support for this idea will need to be obtained, Scheme 73. However, the

mystery as to why Magnus' procedure on our oxazolidinone hydrazides was virtually ineffective is not understood.



Scheme 73: Assisted elimination through delocalization.

Chapter 5

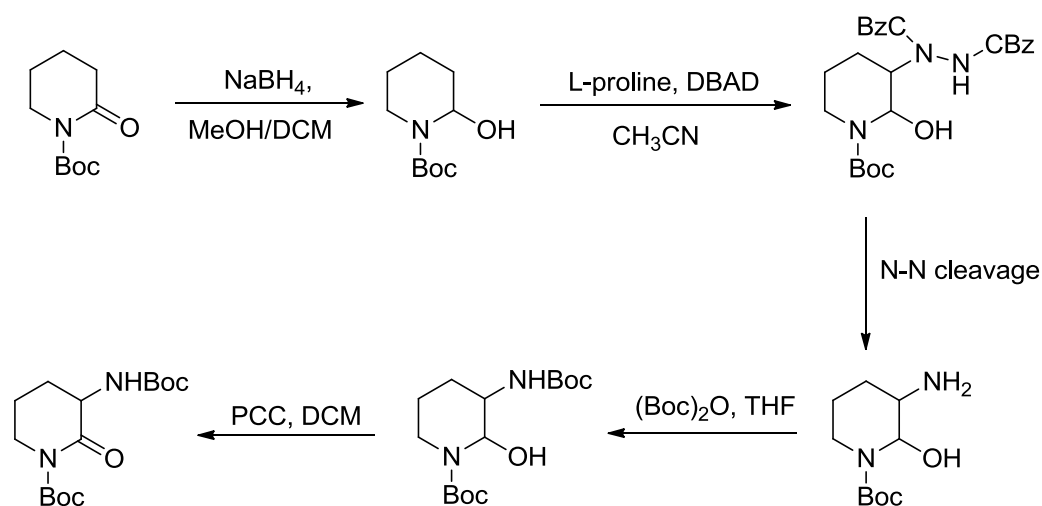
Conclusion and Future work

5.1 Conclusion

The use hemiaminals as masked aldehydes was proven successful through asymmetric α -amination of *N*-CBz and *N*-Boc protected hemiaminals with L-proline and DIAD, DBAD or DTBAD which were synthesized from 2-pyrrolidinone. Cleavage of the N-N bond of the resultant hydrazides was achieved with excess Raney Nickel followed by oxidation with PCC to afford the chiral α -aminated lactams with high ees of 78% and 86%. A new methodology was also developed for the N-N cleavage of the oxazolidinone hydrazides via an E1cB protocol using diethyl bromomalonate and a base (Cs_2CO_3 or K_2CO_3) which gave high yields and ees. Successful synthesis was established using various spectroscopic and analytical techniques, such as ^1H NMR, ^{13}C NMR, IR and mass spectrometry.

5.2 Future work

Future work would include the extension of the synthesis to six-membered (2-piperidinone) rings with exocyclic carbonyl as masked aldehydes, Scheme 74.



Scheme 74: α -Amination, cleavage and oxidation of six-membered hemiaminal.

Chapter 6 Experimental

6.1 General procedures

All reactions were carried out in oven-dried glassware. Dry solvents were distilled under nitrogen before being used: acetonitrile from calcium hydride, tetrahydrofuran from sodium and benzophenone and dichloromethane from phosphorous pentoxide. All reagents and solvents were used without further purification from commercial sources. Thin Layer Chromatography analysis was carried out on aluminium sheets pre-coated with silica (Merck Silica Gel 60 F254), which was visualized by ultraviolet light and sprayed with ninhydrin or a 2.5% solution of anisaldehyde in a mixture of sulfuric acid under heat. Column chromatography was carried out using silica gel (Fluorochem Silica Gel 60, 40-63 micron) as the stationary phase.

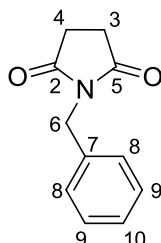
Nuclear Magnetic Resonance spectra were recorded in CDCl_3 solutions using a Bruker Avance III 400 MHz or a Varian Unity XR (300 and 400 MHz) or Varian Mercury 300 spectrometer for ^1H NMR and a Bruker Ultrashield 400 Plus (101 MHz) or a Bruker Avance III (75 MHz) for ^{13}C NMR. Chemical shifts are reported relative to tetramethylsilane as the internal standard at 0.00 ppm for ^1H NMR and CDCl_3 at 77.16 ppm for ^{13}C NMR as the internal standard. Spectral features for ^1H NMR were recorded in the following order: chemical shift (δ_{H} , ppm); multiplicity; coupling constant(s) (J , Hz); number of protons; assignment. ^{13}C NMR spectral data is recorded in the form: chemical shift (δ_{C} , ppm); assignment.

High-resolution mass spectra (HRMS) were obtained using a Waters Synapt G2 instrument. Infrared (IR) spectra were obtained on a Bruker Platinum ATR Tensor 27 or Perkin Elmer uATR Two spectrometer instruments with neat samples. Spectral features are tabulated as wavenumbers (cm^{-1}). Enantiomeric excess (ee) measurements were carried out by high pressure liquid chromatography (HPLC) on an Agilent 1220 Infinity LC series machine using a Chiralpak AD or OD column (250 x 4.6 mm) with a chiral stationary phase. All known compounds afforded as solids were pure enough to proceed to the next step unless stated otherwise.

6.2 Synthesis and Characterization of products

6.2.1 Synthesis of hemiaminal type 1

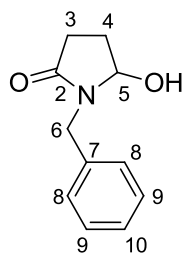
1-(Benzyl)-2,5-pyrrolidinedione, **1**⁹¹



To a solution of 2,5-pyrrolidinedione (2.50 g, 25.2 mmol, 1.0 eq.) in DMF (30 mL) was added anhydrous potassium carbonate (4.18 g, 30.3 mmol, 1.2 eq.) followed by benzyl bromide (3.00 mL, 25.2 mmol, 1.0 eq.) and the reaction mixture was refluxed overnight at 55 °C. The reaction mixture was then cooled to room temperature and water (200 mL) was added forming a precipitate. The precipitate was filtered, washed with water and dried to afford compound **1** (3.34 g, 70%) as a colourless solid. ¹H NMR spectroscopic analysis showed it to be pure enough to proceed to the next step.

δ_{H} (300 MHz, CDCl₃) 7.36 – 7.14 (m, 5H, Ar-H), 4.58 (s, 2H, H-6), 2.61 (s, 4H, H-4, H-3);
 δ_{C} (101 MHz, CDCl₃) 176.9 (C-5, C-2), 136.0 (C-7), 129.0 (C-8), 128.8 (C-9), 128.1 (C-10), 42.5 (C-6), 28.3 (C-4, C-3).

1-(Benzyl)-5-hydroxypyrrolidin-2-one, **2**⁹¹

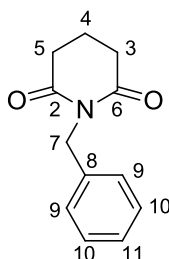


To a solution of compound **1** (1.00 g, 5.29 mmol, 1.0 eq.) in a mixture (3 : 1) of MeOH (30 mL) and DCM (10 mL) at -40 °C was added sodium borohydride (999 mg, 26.4 mmol, 5.0 eq.) in portions and the reaction mixture was stirred at -40 °C until the starting material was consumed. The reaction mixture was then quenched with aqueous ammonium chloride (30 mL) at -40 °C and allowed to warm to room temperature. The mixture was then extracted

with dichloromethane (3 x 50 mL) and the combined organic layers were dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel with an ethyl acetate / hexane (4 : 6) mixture to afford compound **2** (688 mg, 68%) as a colourless solid.

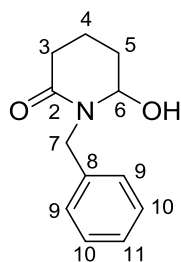
δ_{H} (400 MHz, CDCl_3) 7.29 - 7.17 (m, 5H, Ar-H), 5.02 (t, $J = 5.3$ Hz, 1H, H-5), 4.76 (d, $J = 8.0$ Hz, 1H, H-6), 4.15 (d, $J = 6.0$ Hz, 1H, H-6), 2.64 - 2.50 (m, 1H, H-3), 2.35 - 2.16 (m, 2H, H-4), 1.82 (t, $J = 8.0$ Hz, 1H, H-3); δ_{C} (101 MHz, CDCl_3) 174.7 (C-2), 136.8 (C-7), 128.9 (C-8), 128.5 (C-9), 127.8 (C-10), 82.8 (C-5), 43.8 (C-6), 28.9 (C-3), 28.4 (C-4).

1-(Benzyl)-2,6-piperidinedione, 3¹⁰⁶



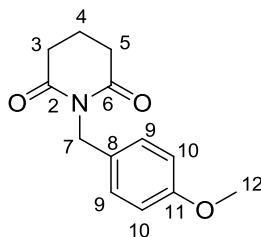
A solution of glutaric acid (2.00 g, 15.1 mmol, 1.0 eq.) in acetyl chloride (20.0 mL, 280 mmol, 18.5 eq.) was refluxed at 55 °C for 2 hours. The excess acetyl chloride was removed in vacuo and the residue dried under high vacuum for 1 hour. The residue was then dissolved in THF (40 mL) and benzylamine (3.00 mL, 27.4 mmol, 1.8 eq.) was added and the mixture was stirred at room temperature for 18 hours. The mixture was then concentrated and re-dissolved in acetyl chloride (30.0 mL, 420 mmol, 28 eq.) which was refluxed for a further 24 hours, upon which the solution was concentrated and dissolved in ethyl acetate (30 mL). This was then washed with saturated sodium carbonate (50 mL) and the organic layer was dried over magnesium sulfate and concentrated. The crude residue was chromatographed on silica gel using an ethyl acetate / hexane (4 : 6) mixture to give compound **3** (2.63 g, 88%) as a colourless oil.

δ_{H} (300 MHz, CDCl_3) 7.30 - 7.08 (m, 5H, Ar-H), 4.85 (s, 2H, H-7), 2.55 (t, $J = 5.0$ Hz, 4H, H-3, H-5), 1.82 (pent, $J = 5.4$ Hz, 2H, H-4); δ_{C} (101 MHz, CDCl_3) 172.5 (C-6, C-2), 137.4 (C-8), 128.7 (C-9), 128.4 (C-10), 127.4 (C-11), 42.7 (C-7), 32.9 (C-3, C-5), 17.1 (C-4).

1-(Benzyl)-6-hydroxypiperidin-2-one, 4¹⁰⁷

To a solution of compound **3** (200 mg, 0.984 mmol, 1.0 eq.) in a mixture (3 : 1) of MeOH (9 mL) and DCM (3 mL) at -40 °C was added sodium borohydride (186 mg, 4.92 mmol, 5.0 eq.) in portions and the reaction mixture was stirred at -40 °C until the starting material was consumed. The reaction mixture was then quenched with aqueous ammonium chloride (20 mL) at -40 °C and allowed to warm to room temperature. The mixture was then extracted with dichloromethane (3 x 50 mL) and the combined organic layers were dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel with an ethyl acetate / hexane (4 : 6) mixture to afford compound **4** (162 mg, 80%) as a colourless solid.

δ_{H} (400 MHz, CDCl_3) 7.32 - 7.13 (m, 5H, Ar-H), 5.01 (d, $J = 6.0$ Hz, 1H, H-7), 4.85 (t, $J = 5.3$ Hz, 1H, H-6), 4.29 (d, $J = 8.0$ Hz, 1H, H-7), 2.60 - 2.50 (m, 1H, H-3), 2.47 - 2.34 (m, 1H, H-3), 2.11 - 1.99 (m, 1H, H-5), 1.95 - 1.81 (m, 2H, H-5, H-4), 1.78 - 1.66 (m, 1H, H-4); δ_{C} (101 MHz, CDCl_3) 170.7 (C-2), 137.8 (C-8), 128.8 (C-9), 128.3 (C-10), 127.6 (C-11), 79.2 (C-6), 47.3 (C-7), 32.6 (C-5), 31.1 (C-3), 16.0 (C-4).

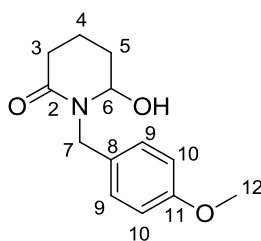
1-(*p*-Methoxybenzyl)piperidine-2,6-dione, 5¹⁰⁸

To a solution of glutarimide (500 mg, 4.42 mmol, 1.0 eq.) in DMF (5 mL) at room temperature was added potassium carbonate (1.20 g, 8.84 mmol, 2.0 eq) and 4-methoxybenzyl chloride (0.60 mL, 4.42 mmol, 1.0 eq). The reaction mixture was left to stir overnight before being diluted with water (100 mL) and extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over magnesium sulfate and

concentrated. Crystallization from a mixture of DCM and hexane afforded compound **5** (990 mg, 96%) as a colourless solid.

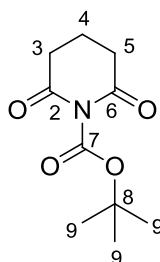
δ_{H} (300 MHz, CDCl_3) 7.69 (d, $J = 4.5$ Hz, 2H, H-9), 6.72 (d, $J = 4.5$ Hz, 2H, H-10), 4.81 (s, 2H, H-7), 3.70 (s, 3H, H-12), 2.57 (d, $J = 4.0$ Hz, 4H, H-5, H-3), 1.84 (pent, $J = 5.4$ Hz, 2H, H-4); δ_{C} (101 MHz, CDCl_3) 172.5 (C-6, C-2), 159.1 (C-11), 130.6 (C-9), 129.8 (C-8), 113.9 (C-10), 55.3 (C-12), 42.2 (C-7), 33.0 (C-5, C-3), 17.2 (C-4).

6-Hydroxy-1-(*p*-methoxybenzyl)piperidin-2-one, **6¹⁰⁹**



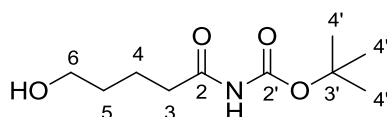
To a solution of compound **5** (400 mg, 1.71 mmol, 1.0 eq.) in a mixture (2 : 1) of MeOH (10 mL) and DCM (5 mL) at -20 °C was added sodium borohydride (195 mg, 5.14 mmol, 5.0 eq.) and the reaction mixture was stirred at -20 °C overnight. The reaction mixture was quenched with aqueous ammonium chloride (20 mL) at -20 °C and allowed to warm to room temperature with stirring. The mixture was then extracted with dichloromethane (3 x 30 mL) and the combined organic layers were dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel with an ethyl acetate / hexane (1 : 1) mixture to afford compound **6** (160 mg, 66%) as a colourless solid with recovery of the starting material (240 mg, 1.03 mmol), 60% conversion.

δ_{H} (300 MHz, CDCl_3) 7.10 (d, $J = 4.5$ Hz, 2H, H-9), 6.78 (d, $J = 4.5$ Hz, 2H, H-10), 5.94 (dt, $J = 2.0$ Hz, 1H, O-H), 5.05 (dt, $J = 5.2$ Hz, 1H, H-6), 4.54 (s, 2H, H-7), 3.72 (s, 3H, H-12), 2.49 (t, $J = 5.0$ Hz, 2H, H-3), 2.30 - 2.20 (m, 4H, H-5, H-4); δ_{C} (101 MHz, CDCl_3) 169.5 (C-2), 159.2 (C-11), 129.5 (C-9), 129.2 (C-8), 114.2 (C-10), 79.2 (C-6), 55.4 (C-12), 48.5 (C-7), 32.6 (C-5), 31.6 (C-3), 20.5 (C-4).

tert-Butyl 2,6-dioxopiperidine-1-carboxylate, **7**¹¹⁰

To a solution of 2,6-piperidinedione (5.00 g, 60.0 mmol, 1.0 eq.) in CH₃CN (150 mL) at room temperature, was added di-*tert*-butyl dicarbonate (13.0 mL, 60.0 mmol, 1.0 eq) followed by 4-dimethylaminopyridine (1.50 g, 12.0 mmol, 0.2 eq.). The reaction mixture was stirred for 18 hours at room temperature before being quenched with aqueous ammonium chloride (50 mL) and extracted with ethyl acetate (3 x 100 mL), dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel with an ethyl acetate / hexane (1 : 1) mixture to give compound **7** (12.2 g, 95%) as a yellow oil.

δ_{H} (400 MHz, CDCl₃) 2.68 - 2.52 (m, 4H, H-5, H-3), 2.04 -1.90 (m, 2H, H-4), 1.44 (s, 9H, H-9); δ_{C} (101 MHz, CDCl₃) 170.2 (C-6, C-2), 149.1 (C-7), 86.4 (C-8), 32.0 (C-5, C-3), 27.6 (C-9), 17.2 (C-4).

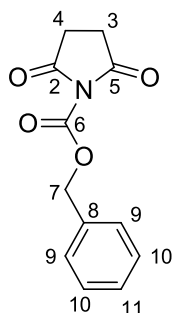
tert-Butyl ((6-hydroxypentanoyl)amino)carbamate, **8a**

To a solution of compound **7** (200 mg, 0.938 mmol, 1.0 eq.) in a mixture (3 : 1) of MeOH (9 mL) and DCM (3 mL) at -40 °C was added sodium borohydride (177 mg, 4.69 mmol, 5.0 eq.) in portions and the reaction mixture was stirred at -40 °C until the starting material was consumed. The reaction mixture was then quenched with aqueous ammonium chloride (20 mL) at -40 °C and allowed to warm to room temperature. The mixture was then extracted with dichloromethane (3 x 50 mL) and the combined organic layers were dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel with an ethyl acetate / hexane (4 : 6) mixture to afford compound **8** (139 mg, 68%) as a colourless oil.

IR ν_{max} / cm⁻¹ 3322 (N-H), 3275 (O-H), 1699 (2 x C=O); HRMS (ESI): 240.1215 [M+Na]⁺, C₁₀H₁₉NNaO₄ requires 240.1216; δ_{H} (400 MHz, CDCl₃) 7.82 (s, 1H, N-H), 3.57

(t, $J = 4.0$ Hz, 2H, H-6), 2.68 (t, $J = 5.3$ Hz, 2H, H-3), 2.39 (s, 1H, O-H), 1.71 - 1.63 (m, 2H, H-4), 1.59 - 1.51 (m, 2H, H-5), 1.42 (s, 9H, H-4'); δ_C (101 MHz, CDCl_3) 171.2 (C-2), 157.3 (C-2'), 82.5 (C-3'), 60.8 (C-6), 33.6 (C-3), 29.8 (C-5), 27.6 (C-4'), 19.7 (C-4).

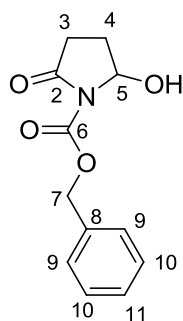
1-(Benzyloxycarbonyl)-2,5-pyrrolidinedione, **9**¹¹¹



To a solution of 2,5-pyrrolidinedione (991 mg, 10.2 mmol, 1.7 eq.) dissolved in DMF (3 mL) and THF (10 mL) at 0 °C, was added sodium hydride (319 mg, 60%, 7.80 mmol, 1.3 eq.) and the reaction mixture was stirred for 15 minutes at 0 °C. Benzyl chloroformate (0.90 mL, 6.00 mmol, 1.0 eq.) was then added to the reaction mixture which was left to stir at 0 °C until complete. The reaction mixture was then quenched with aqueous ammonium chloride (20 mL) and extracted with ethyl acetate (3 x 50 mL), dried with magnesium sulfate and concentrated. The residue was chromatographed on silica gel with an ethyl acetate / hexane (3 : 7) mixture to afford compound **9** (714 mg, 51%) as a colourless solid.

IR ν_{max} / cm^{-1} 1785 (C=O), 1779 (C=O), 1798 (C=O); δ_H (400 MHz, CDCl_3) 7.40 - 7.25 (m, 5H, Ar-H), 5.31 (s, 2H, H-7), 2.72 (s, 4H, H-4, H-3); δ_C (75 MHz, CDCl_3) 176.6 (C-5, C-2), 152.3 (C-6), 134.1 (C-8), 128.8 (C-9), 128.7 (C-10), 128.4 (C-11), 70.0 (C-7), 28.6 (C-4, C-3).

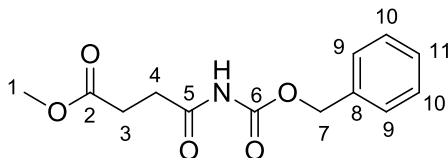
1-(Benzyloxycarbonyl)-5-hydroxypyrrolidin-2-one, **10**



To a suspension of lithium aluminium hydride (60.0 mg, 1.60 mmol, 1.0 eq.) in THF (10 mL) at -78 °C was added dropwise compound **9** (371 mg, 1.60 mmol, 1.0 eq.) in THF (5 mL) over 30 minutes. After completion the mixture was warmed to -40 °C, quenched with 1M HCl (10 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layers were washed with brine (2 × 20 mL), dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel with an ethyl acetate / hexane (2 : 8) mixture to afford compound **10** (113 mg, 30%) as a yellow oil and an approximately 4 : 1 mixture of N-CO rotamers.

IR ν_{\max} / cm^{-1} 1658 (2 x C=O); HRMS (ESI): 258.0746 $[\text{M}+\text{Na}]^+$, $\text{C}_{12}\text{H}_{13}\text{NNaO}_4$ requires 258.0742; δ_{H} (300 MHz, CDCl_3) major rotamer 7.39 - 7.21 (m, 5H, Ar-H), 5.68 (d, $J = 5.0$ Hz, 1H, H-5), 5.25 (s, 2H, H-7), 3.77 (brs, 1H, OH), 2.78 - 2.63 (m, 1H, H-3), 2.44 - 2.31 (m, 1H, H-3), 2.22 - 2.07 (m, 1H, H-4), 1.99 - 1.88 (m, 1H, H-4); δ_{C} (75 MHz, CDCl_3) 175.5 (C-2), 152.6 (C-6), 135.3 (C-8), 128.7 (C-9), 128.6 (C-10), 128.5 (C-11), 86.3 (C-5), 65.5 (C-7), 27.6 (C-4), 26.5 C-3); δ_{H} minor rotamer 5.77 (d, $J = 5.2$ Hz, 1H, H-5); δ_{C} minor rotamer 86.6 (C-5).

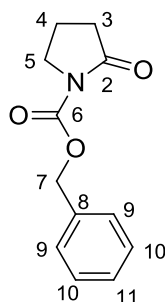
Methyl 5-(((benzyloxy)carbonyl)amino)-5-oxobutanoate, **10a**



To a suspension of lithium aluminium hydride (60.0 mg, 1.60 mmol, 1.0 eq.) in THF (10 mL) at -78 °C was added dropwise compound **9** (371 mg, 1.60 mmol, 1.0 eq.) in THF (5 mL) over 30 minutes. After completion the mixture was warmed to -40 °C, quenched with 1M HCl (10 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layers were washed with brine (2 × 20 mL), dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel with an ethyl acetate / hexane (2 : 8) mixture to afford compound **10a** (276 mg, 65%) as a yellow oil.

IR ν_{\max} / cm^{-1} 3281 (N-H), 1678 (3 x C=O); HRMS (ESI): 279.0851 $[\text{M}+\text{Na}]^+$, $\text{C}_{13}\text{H}_{15}\text{NNaO}_5$ requires 279.0854; δ_{H} (300 MHz, CDCl_3) 7.57 (s, 1H, N-H), 7.32 - 7.27 (m, 5H, Ar-H), 5.10 (s, 2H, H-7), 3.58 (s, 3H, H-1), 2.99 (t, $J = 4.0$ Hz, 2H, H-4), 2.56 (t, $J = 5.0$ Hz, 2H, H-3); δ_{C} (75 MHz, CDCl_3) 172.8 (C-5), 172.3 (C-2), 150.3 (C-6), 135.7 (C-8), 128.9 (C-9), 128.5 (C-10), 127.9 (C-11), 65.4 (C-7), 49.6 (C-1), 29.8 (C-3), 29.6 (C-4).

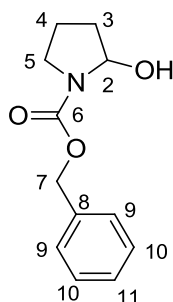
6.2.3 Synthesis of hemiaminal type 2

1-(Benzyloxycarbonyl)pyrrolidin-2-one, **11**¹¹²

To a solution of 2-pyrrolidinone (0.30 mL, 4.00 mmol, 2.0 eq.) in THF (10 mL) at 0 °C, was added sodium hydride (120 mg, 60%, 3.00 mmol, 1.5 eq.) and the reaction was stirred for 15 minutes at 0 °C. This mixture was then added to a solution of benzyl chloroformate (0.30 mL, 2.00 mmol, 1.0 eq.) in THF (10 mL) cooled to 0 °C. The reaction was then stirred for 3 hours before being quenched with aqueous ammonium chloride (20 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over magnesium sulfate and concentrated. The crude residue was chromatographed on silica gel with an ethyl acetate / hexane (2 : 8) mixture to afford compound **11** (263 mg, 60%) as a yellow oil and a single

N-CO rotamer.

δ_{H} (300 MHz, CDCl_3) 7.35 - 7.16 (m, 5H, Ar-H), 5.16 (s, 2H, H-7), 3.68 (t, $J = 6.0$ Hz, 2H, H-5), 2.39 (t, $J = 6.0$ Hz, 2H, H-3), 1.90 (pent, $J = 6.0$ Hz, 2H, H-4); δ_{C} (101 MHz, CDCl_3) 172.5 (C-2), 150.0 (C-6), 134.0 (C-8), 127.1 (C-9), 126.9 (C-10), 126.7 (C-11), 66.4 (C-7), 45.0 (C-5), 31.3 (C-3), 16.1 (C-4).

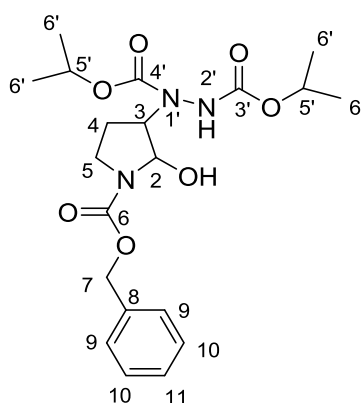
1-(Benzyloxycarbonyl)-2-hydroxypyrrolidine, **12**¹¹³

To a solution of compound **11** (500 mg, 2.28 mmol, 1.0 eq.) in a mixture (3 : 1) of MeOH (9 mL) and DCM (3 mL) at -40 °C was added sodium borohydride (431 mg, 11.4 mmol, 5.0 eq.) in portions and the reaction mixture was stirred at -40 °C for 5 hours. The reaction

mixture was then quenched with aqueous ammonium chloride (20 mL) at $-40\text{ }^{\circ}\text{C}$ and allowed to warm to room temperature. The mixture was then extracted with dichloromethane (3 x 50 mL) and the combined organic layers were dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel with an ethyl acetate / hexane (1 : 1) mixture to give compound **12** (459 mg, 91%) as a colourless oil and an approximately 2 : 1 mixture of N-CO rotamers.

δ_{H} (400 MHz, CDCl_3) major rotamer 7.35 (s, 5H, Ar-H), 5.55 - 5.51 (m, 1H, H-2), 5.16 (s, 2H, H-7), 3.64 - 3.54 (m, 1H, H-5), 3.46 - 3.26 (m, 1H, H-5), 2.16 - 1.72 (m, 4H, H-4, H-3); δ_{C} (101 MHz, CDCl_3) 155.6 (C-6), 136.6 (C-8), 128.6 (C-9), 128.2 (C-10), 128.0 (C-11), 82.3 (C-2), 67.0 (C-7), 45.9 (C-5), 32.8 (C-3), 22.9 (C-4); δ_{H} minor rotamer 5.51 - 5.45 (m, 1H, H-2); δ_{C} minor rotamer 80.9 (C-2).

Diisopropyl 1-(1-(benzyloxycarbonyl)-2-hydroxypyrrolidin-3-yl)hydrazine-1,2-dicarboxylate, 13

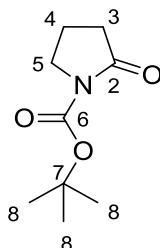


To a solution of compound **12** (100 mg, 0.452 mmol, 1.5 eq.) in CH_3CN (3 mL) was added L-proline (3.47 mg, 0.030 mmol, 0.1 eq.) and diisopropyl azodicarboxylate (60.9 mg, 0.301 mmol, 1.0 eq.) and the reaction was left to stir at room temperature for 3 days in which it had turned colourless. The reaction mixture was then quenched with aqueous ammonium chloride (10 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel using an ethyl acetate / hexane (3 : 7) mixture to give compound **13** (117 mg, 92%) as a yellow oil and an approximately 2 : 1 mixture of diastereomers.

IR ν_{max} / cm^{-1} 3384 (N-H), 3291 (O-H), 1684 (3 x C=O); HRMS (ESI): 446.1888 $[\text{M}+\text{Na}]^+$, $\text{C}_{20}\text{H}_{29}\text{N}_3\text{NaO}_7$ requires 446.1903; δ_{H} (400 MHz, CDCl_3) major isomer 7.26 (s, 5H, Ar-H), 6.67 (s, 1H, NH), 5.50 - 5.34 (m, 1H, H-2), 5.41 (s, 2H, H-7), 4.90 - 4.84 (m, 2H, H-5'),

4.57 - 4.45 (m, 1H, H-3), 3.60 - 3.39 (m, 2H, H-5), 2.27 - 2.05 (m, 1H, H-4), 2.02 - 1.86 (m, 1H, H-4), 1.29 - 1.02 (m, 12H, H-6'); δ_C (101 MHz, $CDCl_3$) major isomer 156.9 (C-6), 155.4 (C-4', C-3'), 136.3 (C-8), 128.6 (C-9), 128.2 (C-10), 128.0 (C-11), 84.3 (C-2), 70.8 (C-5'), 67.3 (C-7), 64.0 (C-3), 43.1 (C-5), 34.0 (C-4), 22.1 (C-6'); δ_H minor isomer 6.51 (s, 1H, N-H), 4.27 - 4.12 (m, 1H, H-3); δ_C minor isomer 60.5 (C-3), 33.0 (C-4), 22.0 (C-6').

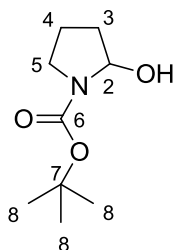
1-(*tert*-Butoxycarbonyl)pyrrolidin-2-one, **14**¹¹⁴



To a solution of 2-pyrrolidinone (5.00 g, 60.0 mmol, 1.0 eq.) in CH_3CN (150 mL) at room temperature, was added di-*tert*-butyl dicarbonate (13.0 g, 60.0 mmol, 1.0 eq) followed by 4-dimethylaminopyridine (1.50 g, 12.0 mmol, 0.2 eq.). The reaction mixture was stirred overnight at room temperature, before being quenched with aqueous ammonium chloride (50 mL) and extracted with ethyl acetate (3 x 100 mL), dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel with an ethyl acetate / hexane (1 : 1) mixture to give compound **14** (10.6 g, 95%) as a yellow oil and as a single C-N rotamer.

δ_H (300 MHz, $CDCl_3$) 3.67 (t, $J = 5.0$ Hz, 2H, H-5), 2.43 (t, $J = 5.0$ Hz, 2H, H-3), 1.93 (pent, $J = 6.0$ Hz, 2H, H-4), 1.45 (s, 9H, H-8); δ_C (101 MHz, $CDCl_3$) 173.8 (C-2), 149.8 (C-6), 82.0 (C-7), 46.1 (C-5), 32.5 (C-3), 27.6 (C-8), 17.0 (C-4).

1-(*tert*-Butoxycarbonyl)-2-hydroxypyrrolidine, **15**¹¹⁵

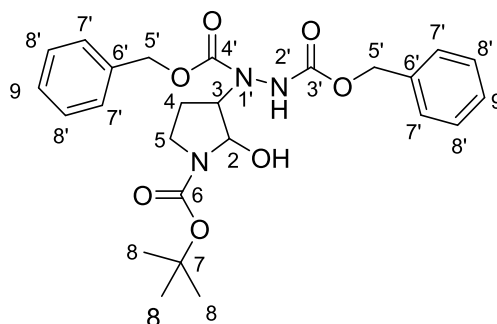


To a solution of compound **14** (500 mg, 2.70 mmol, 1.0 eq.) in a mixture (3 : 1) of MeOH (15 mL) and DCM (5 mL) at -40 °C was added sodium borohydride (510 mg, 13.5 mmol,

5.0 eq.) and the reaction mixture was stirred at $-40\text{ }^{\circ}\text{C}$ for 5 hours until the starting material was consumed. The reaction mixture was quenched with aqueous ammonium chloride (15 mL) at $-40\text{ }^{\circ}\text{C}$ and allowed to warm to room temperature with stirring. The mixture was then extracted with dichloromethane (3 x 30 mL) and the combined organic layers were dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel with an ethyl acetate / hexane (2 : 8) mixture to afford compound **15** (465 mg, 92%) as a colourless oil and as an approximately 2 : 1 mixture of N-CO rotamers.

δ_{H} (400 MHz, CDCl_3) major rotamer 5.45 - 5.40 (m, 1H, H-2), 4.01 (br s, 1H, OH), 3.49 - 4.34 (m, 1H, H-5), 3.28 - 3.12 (m, 1H, H-5), 2.08 - 1.63 (m, 4H, H-4, H-3), 1.40 (s, 9H, H-8); δ_{C} (300 MHz, CDCl_3) major rotamer 155.1 (C-6), 81.5 (C-2), 79.9 (C-7), 45.9 (C-5), 32.8 (C-3), 28.4 (C-8), 22.7 (C-4); δ_{H} minor rotamer 5.34 - 5.27 (m, 1H, H-2); δ_{C} minor rotamer 79.8 (C-2).

Dibenzyl 1-(1-(*tert*-butoxycarbonyl)-2-hydroxypyrrolidin-3-yl)hydrazine-1,2-dicarboxylate, 16

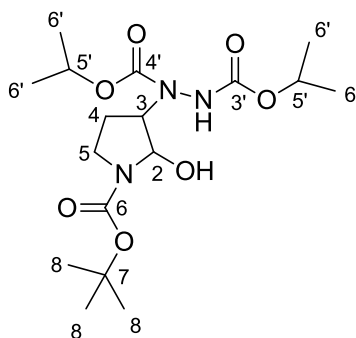


To a solution of compound **15** (100 mg, 0.534 mmol, 1.5 eq.) in CH_3CN (3 mL) was added L-proline (4.10 mg, 0.036 mmol, 0.1 eq.) and dibenzyl azodicarboxylate (106 mg, 0.356 mmol, 1.0 eq.). Aqueous ammonium chloride (10 mL) was added once the reaction mixture had become colourless (3 days) and was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel with an ethyl acetate / hexane (2 : 8) mixture to give compound **16** (156 mg, 90%) as a yellow oil and as an approximately 2 : 1 mixture of diastereomers and ee of 83% and 84%.

IR ν_{max} / cm^{-1} 3300 (N-H), 3185 (O-H), 1696 (3 x C=O); HRMS (ESI): 508.2066 $[\text{M}+\text{Na}]^+$, $\text{C}_{25}\text{H}_{31}\text{N}_3\text{NaO}_7$ requires 508.2060; δ_{H} (400 MHz, CDCl_3) major isomer 7.21 (s, 10H, Ar-H), 6.75 (s, 1H, NH), 5.44 - 5.25 (m, 1H, H-2), 5.15 - 4.95 (m, 4H, H-5'), 4.63 - 4.48 (m, 1H,

H-3), 3.52 - 3.25 (m, 2H, H-5), 2.21 - 2.06 (m, 1H, H-4), 1.98 - 1.86 (m, 1H, H-4), 1.37 (s, 9H, H-8) δ_C (300 MHz, CDCl_3) major isomer 156.1 (C-6), 155.6 (C-3'), 154.9 (C-4'), 135.6 (C-6'), 128.5 (C-7'), 128.2 (C-8'), 127.8 (C-9'), 83.0 (C-7), 80.7 (C-2), 68.4 (C-5'), 53.7 (C-3), 44.6 (C-5), 28.2 (C-8), 25.3 (C-4); δ_H minor isomer 6.66 (s, 1H, N-H), 4.11 - 3.93 (m, 1H, H-3); δ_C minor isomer 79.8 (C-2), 43.0 (C-5); Chiralpak AD hexane / *i*-propanol (1 : 9), flow rate = 1 mL / min, λ = 254 nm; R_t (major diastereomer 1) = 26.09 min, R_t (minor diastereomer 1) = 30.83 min; R_t (major diastereomer 2) = 33.98 min, R_t (minor diastereomer 2) = 56.55 min, 83% *ee*.

Diisopropyl 1-(1-(*tert*-butoxycarbonyl)-2-hydroxypyrrolidin-3-yl)hydrazine-1,2-dicarboxylate, **17**

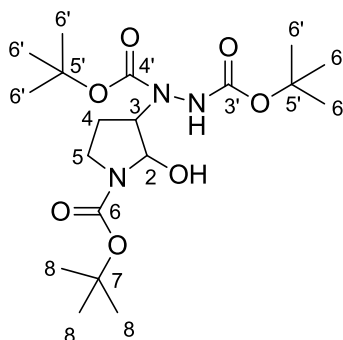


To a solution of **15** (100 mg, 0.534 mmol, 1.5 eq.) in acetonitrile (3 mL) was added L-proline (4.10 mg, 0.036 mmol, 0.1 eq.) and diisopropyl azodicarboxylate (72.0 mg, 0.356 mmol, 1.5 eq.) and the reaction was left to stir at room temperature for 6 days after which it had become colourless. The reaction mixture was quenched with aqueous ammonium chloride (10 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was chromatographed over silica gel using ethyl acetate / hexane (3 : 7) mixture to give compound **17** (111 mg, 80%) as a colourless oil and 2 : 1 mixture of diastereomes.

IR ν_{max} / cm^{-1} 3380 (N-H), 3290 (O-H), 1680 (3 x C=O); HRMS (ESI): 412.2054 $[\text{M}+\text{Na}]^+$, $\text{C}_{17}\text{H}_{31}\text{N}_3\text{NaO}_7$ requires 412.2060; δ_H (400 MHz, CDCl_3) major isomer 6.56 (s, 1H, N-H), 5.46 - 5.29 (m, 1H, H-2), 5.01 - 4.83 (m, 2H, H-5'), 4.67 - 4.44 (m, 1H, H-3), 3.57 - 3.41 (m, 1H, H-5), 3.27 - 3.11 (m, 1H, H-5), 2.32 - 2.13 (m, 1H, H-4), 2.02 - 1.86 (m, 1H, H-4), 1.38 (s, 9H, H-8), 1.22 - 1.06 (m, 12H, H6'); δ_C (151 MHz, CDCl_3) major isomer 156.8 (C-6), 156.0 (C-3'), 155.4 (C-4'), 80.6 (C-2), 70.2 (C-5'), 57.8 (C-3), 44.7 (C-5), 28.5 (C-8),

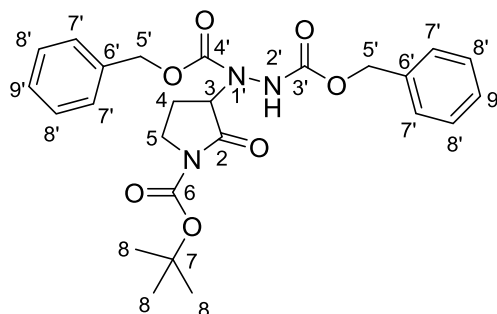
25.8 (C-4), 21.1 (C-6'); δ_{H} minor isomer 6.49 (s, 1H, N-H), 4.12 - 3.98 (m, 1H, H-3); δ_{C} minor isomer 79.2 (C-2), 43.2 (C-5).

Di-*tert*-butyl 1-(1-(*tert*-butoxycarbonyl)-2-hydroxypyrrolidin-3-yl)hydrazine-1,2-dicarboxylate, **18**



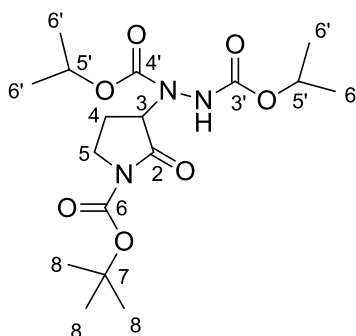
To a solution of **15** (100 mg, 0.534 mmol, 1.5 eq.) in acetonitrile (3 mL) was added L-proline (4.10 mg, 0.036 mmol, 0.1 eq.) and di-*tert*-butyl azodicarboxylate (82.0 mg, 0.356 mmol, 1.0 eq.) and the reaction was left to stir at room temperature for 4 days after which it had turned colourless. The reaction mixture was quenched with aqueous ammonium chloride (10 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over magnesium sulfate and concentrated. The residue was chromatographed over silica gel using ethyl acetate / hexane (3 : 7) mixture to give compound **18** (68 mg, 46%) as a colourless oil and 2 : 1 mixture of diastereomes.

IR ν_{max} / cm^{-1} 3389 (N-H), 3291 (O-H), 1700 (3 x C=O); HRMS (ESI): 440.2375 $[\text{M}+\text{Na}]^+$, $\text{C}_{19}\text{H}_{35}\text{N}_3\text{NaO}_7$ requires 440.2373; δ_{H} (400 MHz, CDCl_3) major isomer 6.56 (s, 1H, N-H), 5.42 - 5.20 (m, 1H, H-2), 4.56 - 4.36 (m, 1H, H-3), 3.56 - 3.08 (m, 2H, H-5), 2.28 - 1.81 (m, 2H, H-4), 1.49 - 1.27 (m, 27H, H-8, H-6'); δ_{C} (101 MHz, CDCl_3) major isomer 156.1 (C-6), 155.1 (C-3'), 154.8 (C-4'), 84.5 (C-2), 82.1 (C-7), 80.4 (C-5'), 63.6 (C-3), 43.3 (C-5), 28.6 (C-8, C-6'), 25.9 (C-4); δ_{H} minor isomer 6.30 (s, 1H, N-H), 4.05 (m, 1H, H-3); δ_{C} minor isomer 84.1 (C-2), 63.3 (C-3).

Dibenzyl 1-(1-(*tert*-butoxycarbonyl)-2-oxopyrrolidin-3-yl)hydrazine-1,2-dicarboxylate,**16a**

To a solution of compound **16** (230 mg, 0.474 mmol, 1.0 eq.) in DCM (5 mL) was added pyridinium chlorochromate (306 mg, 1.42 mmol, 3.0 eq.) and the reaction mixture was stirred at room temperature for 5 hours, after which it was filtered through Celite[®] and the solvent removed in vacuo. The crude residue was chromatographed on silica gel with an ethyl acetate / hexane mixture (3 : 7) to afford compound **16a** (156 mg, 68%) as a colourless oil with ee of 84% and isomer ratio of (92 : 8).

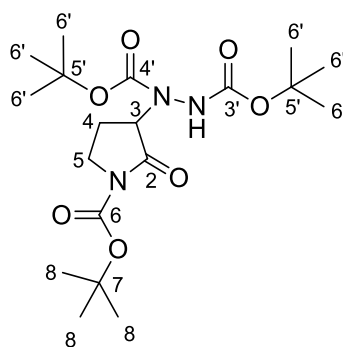
IR ν_{\max} / cm^{-1} 3377 (N-H), 1713 (2 x C=O), 1787 (C=O), 1798 (C=O); HRMS (ESI): 506.1904 [M+Na]⁺, C₂₅H₂₉N₃NaO₇ requires 506.1903; δ_{H} (400 MHz, CDCl₃) 7.24 (s, 10H, Ar-H), 6.75 (s, 1H, NH), 5.16 - 4.95 (m, 5H, H-5', H-3), 3.81 - 3.65 (m, 1H, H-5), 3.50 - 3.35 (m, 1H, H-5), 2.40 - 2.22 (m, 1H, H-4), 2.19 - 2.02 (m, 1H, H-4), 1.43 (s, 9H, H-8); δ_{C} (101 MHz, CDCl₃) 169.8 (C-2), 155.6 (C-6), 149.9 (C-4', C-3'), 135.5 (C-6'), 128.5 (C-7'), 128.1 (C-8'), 127.8 (C-9'), 83.6 (C-7), 76.8 (C-3), 68.7 (C-5'), 42.6 (C-5), 28.0 (C-8), 21.8 (C-4); Chiralpak AD hexane / *i*-propanol (1 : 9), 1mL / min, 254 nm; R_t (major) = 36.11 min, R_t (minor) = 43.77 min, 84% *ee*.

Diisopropyl 1-(1-(*tert*-butoxycarbonyl)-2-oxopyrrolidin-3-yl)hydrazine-1,2-dicarboxylate, 17a

To a solution of **17** (150 mg, 0.385 mmol, 1.0 eq.) in DCM (3 mL) was added pyridinium chlorochromate (249 mg, 1.16 mmol, 3.0 eq.) and the reaction mixture was stirred at room temperature for 5 hours, filtered through Celite[®] and the solvent was concentrated. The crude residue was chromatographed over silica gel with ethyl acetate / hexane mixture (3 : 7) to afford compound **17a** (99 mg, 67%) as a colourless oil with ee of 80% and isomer ratio of (89 : 11).

IR ν_{\max} / cm^{-1} 3261 (N-H), 141 (2 x C=O), 1695 (2 x C=O); HRMS (ESI): 410.1896 $[\text{M}+\text{Na}]^+$, $\text{C}_{17}\text{H}_{29}\text{N}_3\text{NaO}_7$ requires 410.1903; δ_{H} (400 MHz, CDCl_3) 6.52 (s, 1H, N-H), 4.96 - 4.80 (m, 2H, H-5'), 4.40 - 4.26 (m, 1H, H-3), 3.78 - 3.70 (m, 1H, H-5), 3.50 - 3.41 (m, 1H, H-5), 2.35 - 2.20 (m, 1H, H-4), 2.15 - 1.99 (m, 1H, H-4), 1.46 (s, 9H, H-8), 1.25 - 1.12 (m, 12H, H-6'); δ_{C} (101 MHz, CDCl_3) 171.3 (C-2), 156.0 (C-3', C-4'), 150.1 (C-6), 83.6 (C-7), 71.2 (C-3), 70.2 (C-5'), 42.7 (C-5), 28.1 (C-8), 22.1 (C-6'), 17.1 (C-4); Chiralpak AD hexane / *i*-propanol (1 : 9), flow rate = 1 mL / min, λ = 254 nm; R_t (major) = 11.18 min, R_t (minor) = 12.03 min, 80% ee.

Di-*tert*-butyl 1-(1-(*tert*-butoxycarbonyl)-2-oxopyrrolidin-3-yl)hydrazine-1,2-dicarboxylate, **18a**

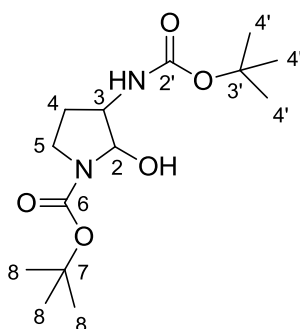


To a solution of **18** (150 mg, 0.287 mmol, 1.0 eq.) in DCM (3 mL) was added pyridinium chlorochromate (186 mg, 0.861 mmol, 3.0 eq.) and the reaction mixture was stirred at room temperature for 5 hours, filtered through Celite[®] and the solvent was concentrated under reduced pressure. The crude residue was chromatographed over silica gel with ethyl acetate / hexane mixture (3 : 7) to afford compound **18a** (79 mg, 66%) as a colourless oil with an ee of 68% and isomer ratio of (83 : 17).

IR ν_{\max} / cm^{-1} 3379 (N-H), 1798 (C=O), 1786 (C=O), 1715 (2 x C=O); HRMS 438.2218 $[\text{M}+\text{Na}]^+$, $\text{C}_{19}\text{H}_{33}\text{N}_3\text{NaO}_7$ requires 438.2220; δ_{H} (400 MHz, CDCl_3) 6.34 (s, 1H, N-H),

4.55 -4.52 (m, 1H, H-3), 3.61 - 3.12 (m, 2H, H-5), 2.32 - 1.85 (m, 2H, H-4), 1.53 - 1.32 (m, 27H, H-8, H-6'); δ_C 171.8 (C-2), 156.2 (C-3'), 155.9 (C-4'), 151.4 (C-6), 81.6 (C-7), 80.1 (C-5'), 73.5 (C-3), 38.7 (C-5), 29.3 (C-8, C-6'), 15.7 (C-4); Chiralpak AD hexane / *i*-propanol (1 : 9), flow rate = 1 mL / min, λ = 254 nm; R_t (major) = 35.81 min, R_t (minor) = 40.22 min, 68% *ee*.

***tert*-Butyl 3-((*tert*-butoxycarbonyl)amino)-2-hydroxypyrrolidine-1-carboxylate, 22**

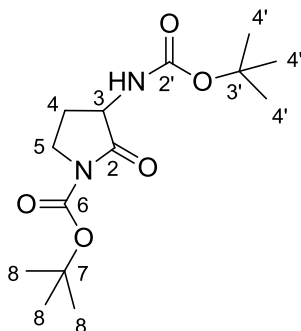


To a solution of compound **16** (246 mg, 0.507 mmol, 1.0 eq.) in MeOH (5 mL) was added Raney Nickel (952 mg, 16.2 mmol, 32 eq.) in MeOH (2 mL) and the reaction mixture was purged with hydrogen then hydrogenated at room temperature and atmospheric pressure for 6 hours. After this time, further Raney Nickel (952 mg, 16.2 mmol, 32 eq.) in MeOH (2 mL) was added and the reaction was left to stir for a further 18 hours under a hydrogen atmosphere. The mixture was then filtered through Celite[®] and the solvent evaporated in vacuo. The crude product **21** was then dissolved in THF (5 mL) and di-*tert*-butyl dicarbonate (332 mg, 1.52 mmol, 3.0 eq.) was added and the reaction was left to stir at room temperature for 15 hours. The reaction mixture was then quenched with aqueous ammonium chloride (10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was chromatographed over silica gel with an ethyl acetate / hexane (3 : 7) mixture to give compound **22** (180 mg, 65%) as a colourless oil with an approximately 2 : 1 mixture of isomers.

IR ν_{\max} / cm^{-1} 3387 (N-H), 3290 (O-H), 1722 (C=O), 1695 (C=O); HRMS (ESI): 302.1743 $[\text{M}+\text{Na}]^+$, $\text{C}_{14}\text{H}_{26}\text{N}_2\text{NaO}_5$ requires 302.1740; δ_H (300 MHz, CDCl_3) major isomer 5.40 - 5.06 (m, 1H, H-2), 4.79 - 4.65 (m, 1H, H-3), 4.12 - 3.85 (m, 1H, N-H), 3.56 - 3.26 (m, 2H, H-5), 2.42 - 2.05 (m, 2H, H-4), 1.41 (s, 9H, H-8), 1.38 (s, 9H, H-4'); δ_C (75 MHz, CDCl_3) major

isomer 155.1 (C-2'), 155.0 (C-6), 85.5 (C-2), 80.9 (C-3'), 79.0 (C-7), 52.2 (C-3), 43.5 (C-5), 29.6 (C-4), 28.5 (C-8), 28.5 (C-4'); δ_{H} minor isomer 5.11 (m, 1H, H-2); δ_{C} minor isomer 86.3 (C-2).

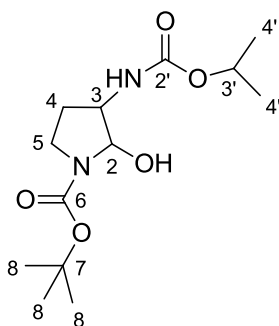
tert*-Butyl 3-((*tert*-butoxycarbonyl)amino)-2-oxopyrrolidine-1-carboxylate, **23*



To a solution of **22** (90.0 mg, 0.298 mmol, 1.0 eq.) in DCM (5 mL) was added pyridinium chlorochromate (192 mg, 0.893 mmol, 3.0 eq.) and the reaction mixture was stirred at room temperature for 12 hours, filtered through Celite[®] and the solvent was concentrated. The crude residue was chromatographed over silica gel with ethyl acetate / hexane mixture (1 : 1) to afford compound **23** (57 mg, 65%) as a yellow oil with an ee of 78% and an isomer ratio of (89 : 11).

IR ν_{max} / cm^{-1} 3389 (N-H), 1725 (2 x C=O), 1698 (C=O); HRMS (ESI): m/z 323.1586 $[\text{M}+\text{Na}]^+$, $\text{C}_{14}\text{H}_{24}\text{N}_2\text{NaO}_5$ requires 323.1583; δ_{H} (400 MHz, CDCl_3) 4.57 - 4.43 (m, 1H, H-3), 3.93 (s, 1H, NH), 3.51 - 3.24 (m, 2H, H-5), 2.34 - 2.14 (m, 2H, H-4), 1.44 - 1.32 (m, 18H, H-8, H4'); δ_{C} (300 MHz, CDCl_3) 171.6 (C-2), 150.0 (C-2'), 149.5 (C-6), 83.2 (C-7), 79.9 (C-3'), 59.2 (C-3), 42.5 (C-5), 27.9 (C-8), 27.9 (C-4'), 22.3 (C-4); Chiralpak AD hexane / *i*-propanol (1 : 9), flow rate = 1mL / min, λ = 254 nm; R_t (major) = 11.14 min, R_t (minor) = 11.98 min, 78% ee.

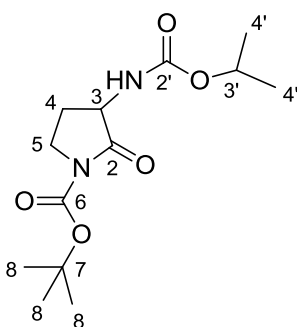
tert*-Butyl 2-hydroxy-3-((*isopropoxycarbonyl*)amino)pyrrolidine-1-carboxylate, **24*



To a solution of **17** (156 mg, 0.401 mmol, 1.0 eq.) in methanol (5 mL) was added Raney Nickel (1.50 g, 25.6 mmol, 64 eq.) dissolved in methanol (2 mL) and the reaction mixture was purged with hydrogen then hydrogenated at atmospheric pressure at 80 °C for 2 days. The mixture was then filtered through Celite[®] and concentrated under reduced pressure. The reaction mixture was dissolved with aqueous ammonium chloride (20 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over magnesium sulfate and concentrated. The residue was chromatographed over silica gel with ethyl acetate / hexane (3 : 7) to give **24** (61 mg, 53%) as a colourless oil and as a single isomer.

IR ν_{\max} / cm^{-1} 3368 (N-H), 3292 (O-H), 1694 (C=O), 1739 (C=O); HRMS (ESI): m/z 311.1584 $[\text{M}+\text{Na}]^+$, $\text{C}_{13}\text{H}_{24}\text{N}_2\text{NaO}_5$ requires 311.1583; δ_{H} (400 MHz, CDCl_3) 6.27 (s, 1H, N-H), 5.16 - 4.79 (m, 2H, H-3', H-2), 4.53 - 4.35 (m, 1H, H-3), 3.55 - 3.23 (m, 2H, H-5), 2.28 - 2.15 (m, 1H, H-4), 2.09 - 1.87 (m, 1H, H-4), 1.40 (s, 9H, H-8), 1.24 (s, 6H, H-4'); δ_{C} (101 MHz, CDCl_3) 156.5 (C-6), 155.2 (C-2'), 91.5 (C-2), 80.3 (C-7), 72.8 (C-3'), 54.6 (C-3), 44.9 (C-5), 29.7 (C-4), 28.4 (C-8), 21.9 (C-4').

tert*-Butyl 3-((isopropoxycarbonyl)amino)-2-oxopyrrolidine-1-carboxylate, **25*



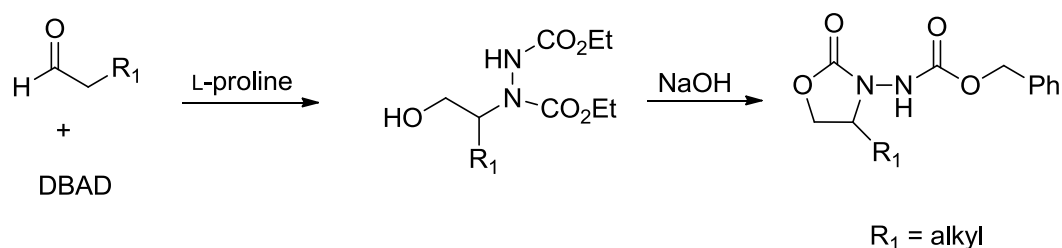
To a solution of **24** (135 mg, 0.468 mmol, 1.0 eq.) in DCM (3 mL) was added pyridinium chlorochromate (302 mg, 1.40 mmol, 3.0 eq.) and the reaction mixture was stirred at room temperature for 12 hours, filtered through Celite[®] and the solvent was concentrated under reduced pressure. The crude residue was chromatographed over silica gel with ethyl acetate / hexane mixture (3 : 7) to afford compound **25** (105 mg, 78%) as a colourless oil with an ee of 86% and an isomer ratio of (93 : 7).

IR ν_{\max} / cm^{-1} 3362 (N-H), 1741 (C=O), 1725 (C=O), 1695 (C=O); HRMS (ESI): m/z 309.1429 $[\text{M}+\text{Na}]^+$, $\text{C}_{13}\text{H}_{22}\text{N}_2\text{NaO}_5$ requires 309.1427; δ_{H} (400 MHz, CDCl_3) 6.72 (s, 1H, N-H), 4.95 - 4.82 (m, 1H, H-3'), 4.57 - 4.48 (m, 1H, H-3), 3.60 - 3.32 (m, 2H, H-5), 2.27 - 2.11 (m, 1H, H-4), 2.03 - 1.88 (m, 1H, H-4), 1.37 (s, 9H, H-8), 1.22 (s, 6H, H-4');

δ_{C} (151 MHz, CDCl_3) 171.2 (C-2), 156.8 (C-2'), 153.8 (C-6), 83.7 (C-7), 70.7 (C-3'), 60.5 (C-3), 36.2 (C-5), 28.5 (C-8), 22.0 (C-4'), 21.1 (C-4); Chiralpak AD hexane / *i*-propanol (1 : 9), flow rate = 1 mL / min, $\lambda = 254$ nm; R_t (major) = 11.04 min, R_t (minor) = 11.91 min, 86% *ee*.

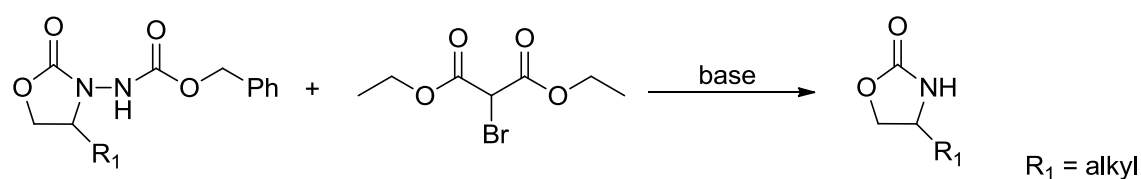
6.2.3 Synthesis of E1cb products

General procedure 1 for synthesis of oxazolidinone-hydrazides

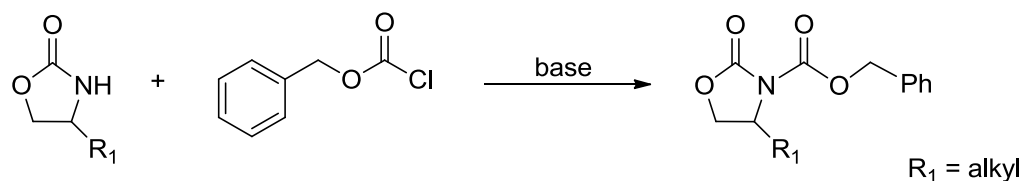


To a solution of the aldehyde (1.66 mmol, 1.5 eq.) and L-proline (13.0 mg, 0.11 mmol, 0.1 eq.) in CH₃CN (10 mL) at 0 °C was added dibenzyl azodicarboxylate (330 mg, 1.11 mmol, 1.0 eq.) and the reaction mixture was left to stir at 0 °C for 30 minutes then at room temperature until the complete consumption of DBAD. The reaction mixture was then cooled to 0 °C and diluted with methanol (20 mL) followed by sodium borohydride (42 mg, 1.11 mmol, 1.0 eq.). After 15 minutes, 1 M sodium hydroxide (3.3 mL, 3.32 mmol, 3.0 eq.) was added and after an additional 2 hours the resulting mixture was quenched with aqueous ammonium chloride (15 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (20 mL) and dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel with an ethyl acetate / hexane mixture to afford the product.

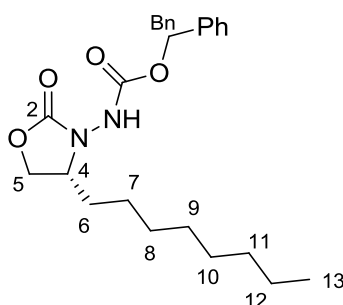
General procedure 2 for synthesis of oxazolidinones



To a solution of the oxazolidinone-hydrazide (0.26 mmol, 1.0 eq.) in dry CH₃CN (1 mL) at 20 °C under nitrogen, was added either Cs₂CO₃ or K₂CO₃ as base (0.65 mmol, 2.5 eq.) followed by the addition of diethyl bromomalonate (0.09 mL, 0.52 mmol, 2.0 eq.). The reaction mixture was left to stir at 20 °C until the starting material was consumed before being quenched with aqueous ammonium chloride (5 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel with an ethyl acetate / hexane mixture to afford the oxazolidinone product.

General procedure 3 for synthesis of CBz-protected oxazolidinones

To a solution of oxazolidinone (4.00 mmol, 1.0 eq.) in THF (10 mL) at 0 °C, was added sodium hydride (120 mg, 60%, 3.00 mmol, 1.5 eq.) and the reaction was stirred for 15 minutes at 0 °C. A solution of benzyl chloroformate (0.30 mL, 2.00 mmol, 1.0 eq.) in THF (10 mL) was then added dropwise and the reaction mixture was stirred for 3 hours before being quenched with aqueous ammonium chloride (10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over magnesium sulfate and concentrated. The crude residue was chromatographed on silica gel with an ethyl acetate / hexane (3 : 7) mixture to afford the product.

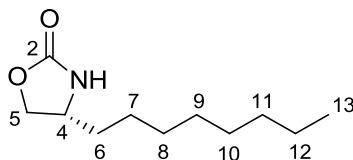
(R)-Benzyl (4-octyl-2-oxo-oxazolidin-3-yl)carbamate, 26

Synthesized from decanal (0.31 mL) and according to **General procedure 1** gave compound **26** (356 mg, 92%) as a colourless oil in 90% ee.

$[\alpha]_D^{20}$ -12.9 ($c = 1.0$, EtOAc); IR (neat) $\nu_{\text{max}} / \text{cm}^{-1}$ 3323 (N-H), 1740 (2 x C=O); HRMS (ESI): m / z 349.2131 $[\text{M} + \text{H}]^+$, $\text{C}_{19}\text{H}_{29}\text{N}_2\text{O}_4$ requires 349.2127; δ_{H} (300 MHz, CDCl_3) 7.36 - 7.22 (m, 5H, Ar), 6.68 (s, 1H, N-H), 5.12 (s, 2H, Bn), 4.25 - 4.05 (m, 1H, H-5), 4.01 - 3.84 (m, 2H, H-5, H-4), 1.80 - 1.65 (m, 1H, H-6), 1.50 - 1.33 (m, 1H, H-6), 1.29 - 1.06 (m, 12H, H-7 to H-12), 0.81 (t, $J = 6.0$ Hz, 3H, H-13); δ_{C} (75 MHz, CDCl_3) 157.6 (C-2), 155.4 (C=O), 135.4 (*i*-Ar), 128.7 (Ar), 128.6 (Ar), 128.3 (Ar), 68.2 (Bn), 67.8 (C-5), 56.9 (C-4), 31.9 (C-6), 31.8 (C-11), 29.6 (C-8), 29.4 (C-9), 29.2 (C-10), 24.6 (C-7), 22.8 (C-12),

14.2 (C-13); Chiralpak OD hexane / *i*-propanol (1 : 9), flow rate = 1 mL / min, λ = 256 nm; R_t (major) = 23.60 min, R_t (minor) = 15.37 min.

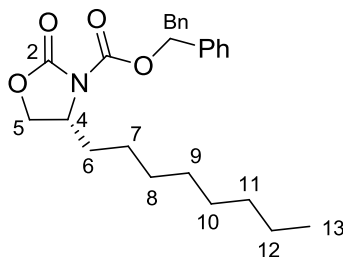
(R)-4-Octyloxazolidin-2-one, 27



Hydrazide **26** (90.0 mg) according to **General procedure 2** with anhydrous potassium carbonate (89.2 mg) for 23 hours gave compound **27** (46.6 mg, 90%) as a colourless oil.

$[\alpha]_D^{20}$ +29.0 (c = 1.0, EtOAc); IR (neat) ν_{\max} / cm^{-1} 3270 (N-H), 1746 (C=O), 1239 (C-O); HRMS (ESI): m/z 200.1652 $[M + H]^+$, $\text{C}_{11}\text{H}_{22}\text{NO}_2$ requires 200.1651; δ_{H} (400 MHz, CDCl_3) 5.75 (s, 1H, N-H), 4.41 (t, J = 5.3 Hz, 1H, H-5), 3.94 (t, J = 5.3 Hz, 1H, H-5), 3.83 - 3.71 (pent, J = 5.6 Hz, 1H, H-4), 1.70 - 1.39 (m, 2H, H-6), 1.30 - 1.12 (m, 12H, H-7 to H-12), 0.81 (t, J = 6.0 Hz, 3H, H-13); δ_{C} (75 MHz, CDCl_3) 160.2 (C-2), 70.5 (C-5), 67.9 (C-4), 35.4 (C-6), 31.9 (C-11), 29.5 (C-8), 29.5 (C-9), 29.3 (C-10), 25.6 (C-7), 22.7 (C-12), 14.2 (C-13).

(R)-Benzyl 4-octyl-2-oxo-oxazolidine-3-carboxylate, 27a

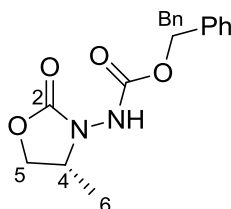


Synthesized from **27** (80.0 mg) according to **General procedure 3** to afford compound **27a** (96.0 mg, 72%) as a colourless oil in 83% ee.

$[\alpha]_D^{20}$ -7.0 (c = 1.0, EtOAc); IR (neat) ν_{\max} / cm^{-1} 1792 (C=O), 1725 (C=O); HRMS (ESI): m/z 356.1831 $[M + \text{Na}]^+$, $\text{C}_{19}\text{H}_{27}\text{NNaO}_4$ requires 356.1838; δ_{H} ^1H NMR (300 MHz, CDCl_3) 7.37 - 7.19 (m, 5H, Ar-H), 4.58 (s, 2H, Bn), 4.28 - 4.13 (m, 2H, H-5, H-4), 3.99 - 3.90 (m, 1H, H-5), 2.01 - 1.53 (m, 2H, H-6), 1.26 - 1.11 (m, 12H, H-7 to H-12), 0.80 (t, J = 6.0 Hz, 3H, H-13); δ_{C} (75 MHz, CDCl_3) 151.8 (C=O), 151.6 (C-2), 135.6 (*i*-Ar), 128.9 (Ar), 128.7 (Ar), 128.5 (Ar), 69.6 (C-5), 66.5 (Bn), 50.9 (C-4), 35.4 (C-6), 31.5 (C-11), 29.6

(C-8), 29.6 (C-9), 29.3 (C-10), 24.6 (C-7), 22.5 (C-12), 14.3 (C-13); Chiralpak OD hexane / *i*-propanol (1 : 9), flow rate = 0.3 mL / min, λ = 258 nm; $R_t(\text{major})$ = 51.16 min, $R_t(\text{minor})$ = 54.96 min.

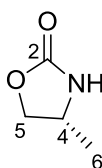
(R)-Benzyl (4-methyl-2-oxo-3-oxazolidinyl)carbamate, 28



Synthesized from propanal (0.12 mL) according to **General procedure 1** to afford compound **28** (244 mg, 88%) as a white solid in 90% ee.

$[\alpha]_D^{20}$ -12.7 (c = 1.0, EtOAc); IR (neat) ν_{max} / cm^{-1} 3270 (N-H), 1772 (C=O), 1704 (C=O); HRMS (ESI): m/z 251.1036 $[\text{M} + \text{H}]^+$, $\text{C}_{12}\text{H}_{15}\text{N}_2\text{O}_4$ requires 251.1032; δ_{H} (400 MHz, CDCl_3) 7.34 - 7.22 (m, 5H, Ar-H), 6.73 (s, 1H, N-H), 5.11 (s, 2H, Bn), 4.41 (t, J = 5.3 Hz, 1H, H-5), 4.12 - 3.97 (m, 1H, H-4), 3.82 (t, J = 5.3 Hz, 1H, H-5), 1.21 (d, J = 6.0 Hz, 3H, H-6); δ_{C} (101 MHz, CDCl_3) 155.6 (C-2), 154.2 (C=O), 135.4 (*i*-Ar), 128.8 (Ar), 128.6 (Ar), 128.4 (Ar), 68.9 (Bn), 68.3 (C-5), 53.0 (C-4), 17.0 (C-6); Chiralpak OD hexane / *i*-propanol (1 : 9), flow rate = 1 mL / min, λ = 256 nm; $R_t(\text{major})$ = 31.62 min, $R_t(\text{minor})$ = 23.81 min.

(R)-4-Methyloxazolidin-2-one, 29

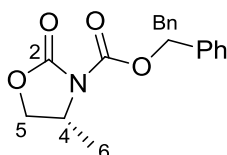


To hydrazide **28** (65.0 mg) according to **General procedure 2** with anhydrous caesium carbonate (212 mg) for 20 hours to afford compound **29** (23.6 mg, 88%) as a colourless solid.

$[\alpha]_D^{20}$ +22.3 (c = 1.0, EtOAc); IR (neat) ν_{max} / cm^{-1} 3286 (N-H), 1721 (C=O), 1238 (C-O); HRMS (ESI): m/z 102.0541 $[\text{M} + \text{H}]^+$, $\text{C}_4\text{H}_8\text{NO}_2$ requires 102.0555; δ_{H} (300 MHz, CDCl_3) 6.47 (s, 1H, N-H), 4.42 (t, J = 5.0 Hz, 1H, H-5), 4.00 - 3.90 (m, 2H, H-5, H-4), 1.22

(d, $J = 6.0$ Hz, 3H, H-6); δ_{C} (101 MHz, CDCl_3) 160.2 (C-2), 71.7 (C-5), 48.3 (C-4), 20.7 (C-6).

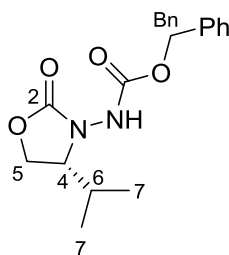
(R)-Benzyl 4-methyl-2-oxo-oxazolidine-3-carboxylate, 29a



Synthesized from **29** (40.0 mg) according to **General procedure 3** to afford compound **29a** (73.3 mg, 78%) as a colourless oil in 95% ee.

$[\alpha]_{\text{D}}^{20} -9.0$ ($c = 1.0$, EtOAc); IR (neat) $\nu_{\text{max}} / \text{cm}^{-1}$ 1735 (C=O), 1718 (C=O), 1251 (C-O); HRMS (ESI): m/z 236.0925 $[\text{M} + \text{H}]^+$, $\text{C}_{12}\text{H}_{14}\text{NO}_4$ requires 236.0923; δ_{H} (300 MHz, CDCl_3) δ 7.38 – 7.21 (m, 5H, Ar-H), 5.23 (s, 2H, Bn), 4.36 - 4.27 (m, 2H, H-5, H-4), 3.91 - 3.81 (m, 1H, H-5), 1.34 (d, $J = 6.0$ Hz, 3H, H-6); δ_{C} (75 MHz, CDCl_3) δ 151.8 (C=O), 150.8 (C-2), 135.0 (*i*-Ar), 128.7 (Ar), 128.6 (Ar), 128.2 (Ar), 68.6 (Bn), 68.6 (C-5), 51.3 (C-4), 19.6 (C-6); Chiralpak OD hexane / *i*-propanol (1 : 9), flow rate = 1mL / min, $\lambda = 256$ nm; R_{t} (major) = 23.60 min, R_{t} (minor) = 15.37 min.

(R)-Benzyl (4-isopropyl-2-oxo-3-oxazolidinyl)carbamate, 30

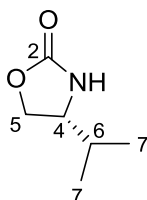


Synthesized from isovaleraldehyde (0.18 mL) according to **General procedure 1**, to afford compound **30** (281 mg, 91%) as a colourless oil in 91% ee.

$[\alpha]_{\text{D}}^{20} -12.5$ ($c = 1.0$, EtOAc); IR (neat) $\nu_{\text{max}} / \text{cm}^{-1}$ 3319 (N-H), 1764 (C=O), 1726 (C=O); HRMS (ESI): m/z 279.1345 $[\text{M} + \text{H}]^+$, $\text{C}_{14}\text{H}_{19}\text{N}_2\text{O}_4$ requires 279.1345; δ_{H} (300 MHz, CDCl_3) 7.31 - 7.23 (m, 5H, Ar), 6.96 (s, 1H, N-H), 5.09 (s, 2H, Bn), 4.37 - 4.23 (m, 1H, H-5), 4.09 - 3.80 (m, 2H, H-5, H-4), 2.03 - 1.85 (m, 1H, H-6), 0.91 (t, $J = 7.2, 6.6$ Hz, 3H, H-7);

δ_{C} (300 MHz, CDCl_3) 156.1 (C-2), 155.1 (C=O), 135.3 (*i*-Ar), 128.6 (Ar), 128.5 (Ar), 128.2 (Ar), 68.1 (Bn), 64.1(C-4), 60.9 (C-5), 28.5 (C-6), 17.8 (C-7), 15.9 (C-7); Chiralpak OD hexane / *i*-propanol (1 : 9), flow rate = 0.5 mL / min, λ = 258 nm; R_{t} (major) = 41.41 min, R_{t} (minor) = 44.61 min.

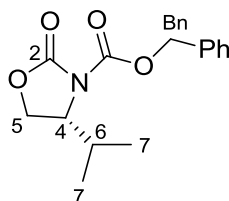
(*R*)-4-Isopropylloxazolidin-2-one, 31



To hydrazide **30** (73.0 mg) according to **General procedure 2** and anhydrous caesium carbonate (214 mg) for 20 hours to afford compound **31** (32.2 mg, 96%) as a colourless oil.

$[\alpha]_{\text{D}}^{20}$ +22.3 (c = 1.0, EtOAc); IR (neat) ν_{max} / cm^{-1} 3236 (N-H), 1728 (C=O), 1224 (C-O); HRMS (ESI): m/z 130.0873 $[\text{M} + \text{H}]^+$, $\text{C}_6\text{H}_{12}\text{NO}_2$ requires 130.0868; δ_{H} (300 MHz, CDCl_3) 6.88 (s, 1H, N-H), 4.36 (t, J = 6.0 Hz, 1H, H-5), 4.09 - 3.96 (t, J = 5.0, 1H, H-5), 3.60 - 3.48 (q, J = 5.3 Hz, 1H, H-4), 1.74 - 1.57 (oct, J = 5.6 Hz, 1H, H-6), 0.88 (d, J = 6.9 Hz, 3H, H-7), 0.93 (d, J = 6.6 Hz, 3H, H-7); δ_{C} (101 MHz, CDCl_3) 160.6 (C-2), 68.6 (C-5), 58.4 (C-4), 32.7 (C-6), 17.9 (C-7), 17.6 (C-7).

(*R*)-Benzyl 4-isopropyl-2-oxo-oxazolidine-3-carboxylate, 31a

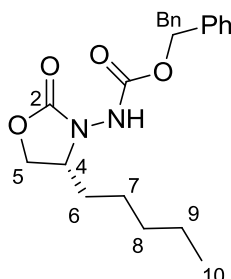


Synthesized from **31** (51.7 mg) according to **General procedure 3** to afford compound **31a** (84.2 mg, 80%) as a colourless oil in 92% ee.

$[\alpha]_{\text{D}}^{20}$ -8.0 (c = 1.0, EtOAc); IR (neat) ν_{max} / cm^{-1} 1800 (C=O), 1714 (C=O); HRMS (ESI): m/z 286.1048 $[\text{M} + \text{Na}]^+$, $\text{C}_{14}\text{H}_{17}\text{NNaO}_4$ requires 286.1055; δ_{H} (300 MHz, CDCl_3) 7.41 - 7.22 (m, 5H, Ar-H), 5.25 (s, 2H, Bn), 4.24 - 4.05 (m, 3H, H-5, H-4), 2.33 - 2.21 (m, 1H, H-6), 0.91 (d, J = 4.5 Hz, 3H, H-7), 0.84 (d, J = 6.6 Hz, 3H, H-7); δ_{C} (300 MHz, CDCl_3) 155.8 (C-2), 155.1 (C=O), 136.1 (*i*-Ar), 128.7 (Ar), 128.6 (Ar), 128.2 (Ar), 67.1 (Bn), 65.2(C-4), 60.7 (C-5), 28.5 (C-6), 17.2 (C-7), 16.9 (C-7); Chiralpak OD hexane /

i-propanol (1 : 9), flow rate = 0.5 mL / min, λ = 258 nm; R_t (major) = 26.70 min, R_t (minor) = 29.63 min.

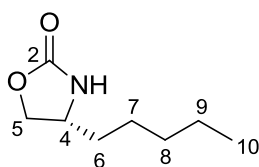
(*R*)-Benzyl (2-oxo-4-pentylloxazolidin-3-yl)carbamate, 32



Synthesized from heptanal (0.23 mL) according to **General procedure 1** to afford compound **32** (303 mg, 89%) as a colourless oil in 93% ee.

$[\alpha]_D^{20}$ -12.8 (c = 1.0, EtOAc); IR (neat) ν_{\max} / cm^{-1} 3285 (N-H), 1770 (C=O), 1722 (C=O); HRMS (ESI): m/z 307.1657 $[\text{M} + \text{H}]^+$, $\text{C}_{16}\text{H}_{23}\text{N}_2\text{O}_4$ requires 307.1658; δ_{H} (400 MHz, CDCl_3) 7.33 - 7.22 (m, 5H, Ar-H), 6.74 (s, 1H, N-H), 5.10 (s, 2H, Bn), 4.43 - 4.34 (m, 1H, H-5), 4.00 - 3.83 (m, 2H, H-5, H-4), 1.76 - 1.36 (m, 2H, H-6), 1.29 - 1.14 (m, 6H, H-7, H-8, H-9), 0.91 (t, J = 6.8 Hz, 3H, H-10); δ_{C} (75 MHz, CDCl_3) 159.2 (C-2), 155.4 (C=O), 136.2 (*i*-Ar), 128.9 (Ar), 128.8 (Ar), 127.7 (Ar), 68.3 (Bn) 66.5 (C-5), 54.6 (C-4), 33.3 (C-6), 31.7 (C-8), 26.1 (C-7), 22.8 (C-9), 14.3 (C-10); Chiralpak OD hexane / *i*-propanol (1 : 9), flow rate = 1 mL / min, λ = 256 nm; R_t (major) = 26.03 min, R_t (minor) = 17.21 min.

(*R*)-4-Pentylloxazolidin-2-one, 33

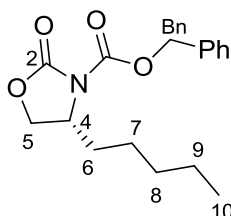


To hydrazide **32** (80.0 mg) according to **General procedure 2** with anhydrous potassium carbonate (90.2 mg) for 2 days to afford compound **33** (37.4 mg, 76%) as a colourless oil.

$[\alpha]_D^{20}$ +25.1 (c = 1.0, EtOAc); IR (neat) ν_{\max} / cm^{-1} 3308 (N-H), 1742 (C=O), 1233 (C-O); HRMS (ESI): m/z 158.1183 $[\text{M} + \text{H}]^+$, $\text{C}_8\text{H}_{16}\text{NO}_2$ requires 158.1181; δ_{H} (300 MHz, CDCl_3) 6.26 (s, 1H, N-H), 4.41 (t, J = 6.3 Hz, 1H, H-5), 3.94 (dd, J = 6.3, 4.8 Hz, 1H, H-5), 3.78

(pent, $J = 5.4$ Hz, 1H, H-4), 1.60 - 1.39 (m, 2H, H-6), 1.34 - 1.14 (m, 6H, H-7, H-8, H-9), 0.82 (t, $J = 5.8$ Hz, 3H, H-10); δ_{C} (75 MHz, CDCl_3) 160.1 (C-2), 70.5 (C-5), 52.8 (C-4), 35.4 (C-6), 31.6 (C-8), 25.0 (C-7), 22.5 (C-9), 14.0 (C-10).

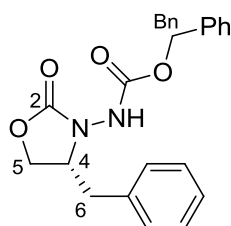
(R)-Benzyl 2-oxo-4-pentyloxazolidine-3-carboxylate, 33a



Synthesized from **33** (62.9 mg) according to **General procedure 3** to afford compound **33a** (90 mg, 78%) as a colourless oil in 88% ee.

$[\alpha]_{\text{D}}^{20}$ -9.0 ($c = 1.0$, EtOAc); IR (neat) $\nu_{\text{max}} / \text{cm}^{-1}$ 1737 (C=O), 1726 (C=O), 1251 (C-O); HRMS (ESI): m/z 292.1537 $[\text{M} + \text{H}]^+$, $\text{C}_{16}\text{H}_{22}\text{NO}_4$ requires 292.1549; δ_{H} (300 MHz, CDCl_3) 7.39 - 7.22 (m, 5H, Ar-H), 5.25 (s, 2H, Bn) 5.20 (t, $J = 6.3$ Hz, 2H, H-5, H-4), 4.02 (t, $J = 6.0$ Hz, 1H, H-5), 2.52 - 2.11 (m, 2H, H-6), 2.18 - 1.78 (m, 6H, H-7, H-8, H-9), 0.91 (t, $J = 6.2$ Hz, 3H, H-10); δ_{C} (75 MHz, CDCl_3) 152.8 (C=O), 151.7 (C-2), 135.5 (*i*-Ar), 128.7 (Ar), 128.7 (Ar), 128.5 (Ar), 69.5 (C-5), 66.2 (Bn), 51.8 (C-4), 35.6 (C-6), 31.8 (C-8), 23.0 (C-7), 22.4 (C-9), 14.0 (C-10); Chiralpak OD hexane / *i*-propanol (1 : 9), flow rate = 0.3 mL / min, $\lambda = 258$ nm; R_{t} (major) = 41.29 min, R_{t} (minor) = 44.52 min.

Benzyl (R)-(4-benzyl-2-oxo-oxazolidin-3-yl)carbamate, 34

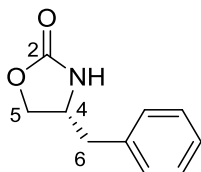


Synthesized from the corresponding aldehyde (224 mg, 1.66 mmol) using **General procedure 1** to give **34** (327 mg, 91%) as a colourless oil in 86% ee.

$[\alpha]_{\text{D}}^{20}$ -19.5 ($c = 1.0$, DCM); IR (neat) $\nu_{\text{max}} / \text{cm}^{-1}$ 1774 (C=O), 1728 (C=O), 1217 (C-O); HRMS (ESI): m/z 327.1338 $[\text{M} + \text{H}]^+$, $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_4$ requires 327.1345; δ_{H} (400 MHz, CDCl_3) 7.53 (br s, 1H, NH), 7.51 - 7.21 (m, 8H, Ar-H), 7.25 - 6.95 (m, 2H, Ar-H), 5.13

(s, 2H, Bn), 4.37 - 4.18 (m, 2H, H-4, H-5), 4.13 - 3.85 (m, 1H, H-5), 3.28 - 2.95 (m, 1H, H-6), 2.91 - 2.73 (m, 1H, H-6); δ_C (101 MHz, CDCl_3) 157.3 (C-2), 155.3 (C=O), 135.3 (*i*-Ar), 135.3 (*i*-Ar), 128.8 (Ar), 128.7 (Ar), 128.4 (Ar), 128.2 (Ar), 128.0 (Ar), 127.0 (Ar), 67.8 (Bn), 67.0 (C-5), 57.6 (C-4), 37.6 (C-6); Chiralpak OD column hexane / *i*-propanol (1 : 1), flow rate = 0.5 ml / min, $\lambda = 258$ nm; $R_t(\text{major}) = 17.10$ min, $R_t(\text{minor}) = 15.69$ min.

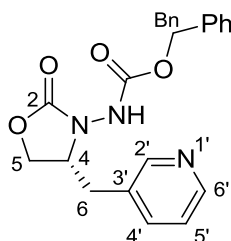
(*R*)-4-Benzylloxazolidin-2-one, 35



Synthesised using **General procedure 2** with oxazolidinone **34** (80.0 mg, 0.250 mmol) and anhydrous potassium carbonate to give **35** (38.0 mg, 84%) after 20 hours as a colourless oil in 84% ee.

$[\alpha]_D^{20} +51.4$ ($c = 1.0$, DCM); IR (neat) $\nu_{\text{max}} / \text{cm}^{-1}$ 1738 (C=O), 1246 (C-O); HRMS (ESI): m / z 178.0864 $[\text{M} + \text{H}]^+$, $\text{C}_{10}\text{H}_{12}\text{NO}_2$ requires 178.0868; δ_H (400 MHz, CDCl_3) 7.42 - 7.32 (m, 2H, Ar-H), 7.31 - 7.25 (m, 1H, Ar-H), 7.50 - 7.18 (m, 2H, Ar-H), 6.08 (br s, 1H, NH), 4.43 (t, $J = 5.7$ Hz, 1H, H-5), 4.22 - 4.09 (m, 2H, H-4, H-5), 3.09 - 2.69 (m, 2H, H-6); δ_C (101 MHz, CDCl_3) 159.6 (C-2), 135.9 (*i*-Ar), 129.0 (Ar), 128.9 (Ar), 127.1 (Ar), 69.5 (C-5), 53.7 (C-4), 41.3 (C-6); Chiralpak OD column hexane / *i*-propanol (1 : 1), flow rate = 1 ml / min, $\lambda = 258$ nm; $R_t(\text{major}) = 6.71$ min, $R_t(\text{minor}) = 6.04$ min.

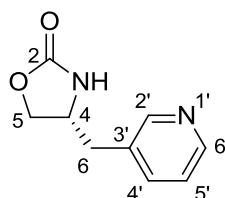
Benzyl (*R*)-(2-oxo-4-(pyridin-3-ylmethyl)oxazolidin-3-yl)carbamate, 36



Synthesised from the corresponding aldehyde (328 mg, 1.10 mmol) using **General procedure 1** to give **36** (450 mg, 87%) as a colourless oil in 95% ee.

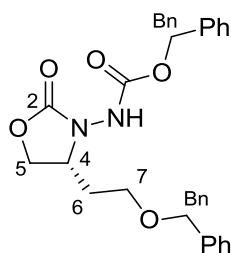
$[\alpha]_D^{20}$ -12.8 ($c = 1.0$, MeOH); IR (neat) $\nu_{\max} / \text{cm}^{-1}$ 1777 (C=O), 1718 (C=O), 1215 (C-O); HRMS (ESI): m/z 328.1298 $[\text{M} + \text{H}]^+$, $\text{C}_{17}\text{H}_{18}\text{N}_3\text{O}_4$ requires 328.1297; δ_{H} (400 MHz, CDCl_3) 8.47 (d, $J = 4.4$ Hz, 1H, H-6'), 8.41 (s, 1H, H-2'), 8.34 (br s, 1H, NH), 7.53 - 7.44 (m, 1H, H-5'), 7.37 - 7.26 (m, 5H, Ar-H), 7.19 (dd, $J = 7.6, 4.4$ Hz, 1H, H-4'), 5.12 (s, 2H, Bn), 4.25 - 4.23 (m, 2H, H-5, H-4), 3.06 - 2.96 (m, 1H, H-5), 3.03 (dd, $J = 14.4, 4.6$ Hz, 1H, H-6), 2.89 - 2.80 (m, 1H, H-6); δ_{C} (101 MHz, CDCl_3) 157.1 (C-2), 155.6 (C=O), 149.8 (C-6'), 148.1 (C-2'), 136.9 (C-3'), 135.4 (C-4'), 131.2 (*i*-Ar), 128.5 (Ar), 128.4 (Ar), 128.1 (Ar), 123.7 (C-5'), 67.9 (Bn), 66.5 (C-5), 57.1 (C-4), 34.8 (C-6); Chiralpak OD column hexane / *i*-propanol (4 : 6), flow rate = 1 ml / min, $\lambda = 258$ nm; $R_t(\text{major}) = 8.95$ min, $R_t(\text{minor}) = 17.86$ min.

(R)-4-(Pyridin-3-ylmethyl)oxazolidin-2-one, 37



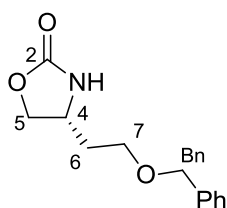
Synthesised using **General procedure 2** with oxazolidinone **36** (80.0 mg, 0.250 mmol) and anhydrous cesium carbonate to give **37** (40.0 mg, 90%) after 2 hours as a colourless oil in 91% ee.

$[\alpha]_D^{20}$ +18.5 ($c = 1.0$, MeOH); IR (neat) $\nu_{\max} / \text{cm}^{-1}$ 1771 (C=O), 1726 (C=O), 1222 (C-O); HRMS (ESI): m/z 179.0819 $[\text{M} + \text{H}]^+$, $\text{C}_9\text{H}_{11}\text{N}_2\text{O}_2$ requires 179.0821; δ_{H} (400 MHz, CDCl_3) 8.51 (d, $J = 4.7$ Hz, 1H, H-6'), 8.45 (s, 1H, H-2'), 7.90 - 7.50 (m, 1H, H-5'), 7.30 (dd, $J = 7.6, 4.7$ Hz, 1H, H-4'), 6.79 (br s, 1H, NH), 4.42 (t, $J = 8.6$ Hz, 1H, H-5), 4.43 - 4.13 (m, 1H, H-4), 4.10 (dd, $J = 8.6, 5.4$ Hz, 1H, H-5), 2.98 (s, 1H, H-6), 2.96 (s, 1H, H-6); δ_{C} (101 MHz, CDCl_3) 159.7 (C-2), 151.6 (C-6'), 149.1 (C-2'), 137.8 (C-4'), 133.6 (C-3'), 124.5 (C-5'), 69.8 (C-5), 53.9 (C-4), 39.0 (C-6); Chiralpak OD column hexane: *i*-propanol (4 : 6), flow rate = 1 ml / min, $\lambda = 258$ nm; $R_t(\text{major}) = 14.92$ min, $R_t(\text{minor}) = 13.44$ min.

Benzyl (R)-4-(7-(benzyloxy)ethyl)-2-oxooxazolidin-3-yl)carbamate, 38

Synthesized from the corresponding aldehyde (295 mg, 1.10 mmol) using **General procedure 1** to give **38** (354 mg, 86 %) as a colourless oil in 92% ee.

$[\alpha]_{\text{D}}^{20}$ -8.0 ($c = 1.0$, CHCl_3); IR (neat) $\nu_{\text{max}} / \text{cm}^{-1}$ 1774 (C=O), 1730 (C=O), 1221 (C-O); HRMS (ESI): m / z 371.1601 $[\text{M} + \text{H}]^+$, $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_5$ requires 371.1607; δ_{H} (400 MHz, CDCl_3) 7.25 - 7.40 (m, 10H, Ar-H), 6.94 (br s, 1H, NH), 5.19 (s, 2H, Bn), 4.55 - 4.50 (m, 1H, H-7), 4.45 (s, 2H, Bn), 4.22 - 4.00 (m, 2H, H-4, H-7), 3.64 - 3.42 (m, 2H, H-5), 2.06 - 1.81 (m, 2H, H-6); δ_{C} (101 MHz, CDCl_3) 157.3 (C-2), 155.3 (C=O), 137.6 (*i*-Ar), 135.4 (*i*-Ar), 128.6 (Ar), 128.5 (Ar), 128.4 (Ar), 128.2 (Ar), 127.9 (Ar), 127.7 (Ar), 73.5 (Bn), 68.0 (Bn), 68.0 (C-7), 66.3 (C-5), 56.1 (C-4), 31.9 (C-6); Chiralpak OD column hexane / *i*-propanol (1 : 1), flow rate = 1 ml / min, $\lambda = 258$ nm; R_{t} (major) = 25.92 min, R_{t} (minor) = 25.92 min.

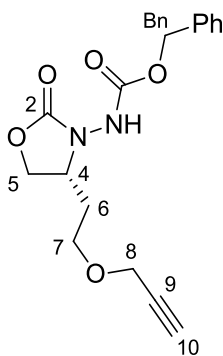
(R)-4-(7-(Benzyloxy)ethyl)oxazolidin-2-one, 39

Synthesised using **General procedure 2** with oxazolidinone **38** (200 mg, 0.54 mmol) and anhydrous cesium carbonate to give **39** (100 mg, 84%) after 5 hours as a colourless oil in 87% ee.

$[\alpha]_{\text{D}}^{20}$ +22.0 ($c = 1.0$, CHCl_3); IR (neat) $\nu_{\text{max}} / \text{cm}^{-1}$ 1738 (C=O), 1243 (C-O); HRMS (ESI): m / z 222.1119 $[\text{M} + \text{H}]^+$, $\text{C}_{12}\text{H}_{16}\text{NO}_3$ requires 222.1130; δ_{H} (400 MHz, CDCl_3) 7.45 - 7.23 (m, 5H, Ar-H), 6.33 (br s, 1H, NH), 4.50 (s, 2H, Bn), 4.47 - 4.32 (m, 1H, H-7), 4.10 - 4.05 (m, 2H, H-4, H-7), 3.58 (t, $J = 5.7$ Hz, 2H, H-5), 2.05 - 1.68 (m, 2H, H-6);

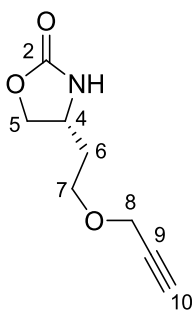
δ_C (101 MHz, $CDCl_3$) 137.7 (C-2), 129.8 (*i*-Ar), 128.6 (Ar), 128.0 (Ar), 127.7 (Ar), 73.5 (Bn), 70.4 (C-7), 67.6 (C-5), 52.0 (C-4), 35.1 (C-6); Chiralpak OD column hexane / *i*-propanol (7 : 3), flow rate = 1 ml / min, λ = 258 nm; R_t (major) = 8.62 min, R_t (minor) = 9.71 min.

Benzyl (*R*)-(2-oxo-4-(7-(prop-9-yn-7-yloxy)ethyl)oxazolidin-3-yl)carbamate, 40



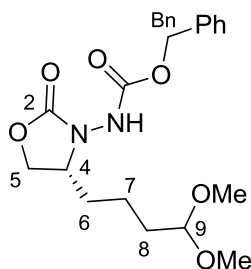
Synthesized from the corresponding aldehyde (209 mg, 1.10 mmol) using **General procedure 1** to give **40** (304 mg, 87 %) as a yellow oil in 90% ee.

$[\alpha]_D^{20}$ -12.9 (c = 1.0, $CHCl_3$); IR (neat) ν_{max} / cm^{-1} 1771 (C=O), 1726 (C=O), 1222 (C-O); HRMS (ESI): m/z 319.1281 $[M + H]^+$, $C_{16}H_{19}N_2O_5$ requires 319.1294; δ_H (300 MHz, $CDCl_3$) 7.46 - 7.29 (m, 5H, Ar-H), 6.80 (br s, 1H, NH), 5.18 (s, 2H, Bn), 4.54 - 4.48 (m, 1H, H-7), 4.21 - 4.00 (m, 4H, H-4, H-7, H-8), 3.69 - 3.61 (m 1H, H-5), 3.60 - 3.50 (m, 1H, H-5), 2.42 (t, J = 2.4 Hz, 1H, H-10), 2.09 - 1.84 (m, 2H, H-8); δ_C (101 MHz, $CDCl_3$) 157.2 (C-2), 155.3 (C=O), 135.3 (*i*-Ar), 128.7 (Ar), 128.5 (Ar), 128.3 (Ar), 79.1 (C-9), 74.9 (C-10), 68.2 (Bn), 68.0 (C-7), 66.0 (C-5), 58.4 (C-8), 56.1 (C-4), 31.7 (C-6); Chiralpak OD column hexane / *i*-propanol (1 : 1), flow rate = 0.5 ml / min, λ = 258 nm; R_t (major) = 16.53 min, R_t (minor) = 15.64 min.

(R)-4-(7-(Prop-9-yn-7-yloxy)ethyl)oxazolidin-2-one, 41

Synthesised using **General procedure 2** with oxazolidinone **40** (100 mg, 0.310 mmol) and anhydrous cesium carbonate to give **41** (42.0 mg, 81%) after 4 hours as a colourless oil.

$[\alpha]_D^{20} +21.3$ ($c = 1.0$, DCM); IR (neat) $\nu_{\max} / \text{cm}^{-1}$ 1733 (C=O), 1243 (C-O); HRMS (ESI): m/z 170.0809 $[\text{M} + \text{H}]^+$, $\text{C}_8\text{H}_{12}\text{NO}_3$ requires 170.0817; δ_{H} (400 MHz, CDCl_3) 6.30 (br s, 1H, NH), 4.56 - 4.39 (m, 1H, H-7), 4.14 (d, $J = 2.4$ Hz, 2H, H-8), 4.07 - 3.92 (m, 2H, H-4, H-7), 3.63 (t, $J = 5.7$ Hz, 2H, H-5), 2.46 (t, $J = 2.4$ Hz, 1H, H-10), 1.98 - 1.70 (m, 2H, H-6); δ_{C} (101 MHz, CDCl_3) 159.7 (C-2), 79.3 (C-9), 74.9 (C-10), 70.4 (C-7), 67.1 (C-5), 58.4 (C-8), 51.6 (C-4), 34.9 (C-6).

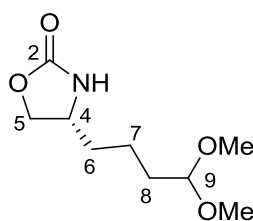
Benzyl (R)-(4-(9,9-dimethoxybutyl)-2-oxooxazolidin-3-yl)carbamate, 42

To a solution of bis-acetal α -hydrazino alcohol (780 mg, 1.69 mmol, 1.0 eq.) in MeOH (15 mL) was added NaOH (5.1 mL, 1M, 5.10 mmol, 3.0 eq.) and the reaction was stirred for 1 hour at room temperature, when complete consumption of the hydrazine was observed on TLC. The reaction was quenched with saturated ammonium chloride solution (20 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layers were dried with magnesium sulfate and the solvent evaporated *in vacuo*. The crude residue was then chromatographed on silica gel with ethyl acetate / hexane (4 : 6) mixture to give **42** (430 mg, 72% yield) as a

colourless gum. The ee could not be determined as none of our HPLC columns could separate the enantiomers of this compound – ee is inferred from the ee of the hydrazino alcohol starting material as 90%.

$[\alpha]_D^{20}$ -12.2 ($c = 0.5$, DCM); IR (neat) $\nu_{\max} / \text{cm}^{-1}$ 1780 (C=O), 1740 (C=O), 1236 (C-O), 1125 (C-O); HRMS (ESI): m / z 375.1529 $[\text{M} + \text{Na}]^+$, $\text{C}_{17}\text{H}_{24}\text{N}_2\text{NaO}_6$ requires 375.1532; δ_{H} (300 MHz, CDCl_3) 7.39 - 7.27 (m, 5H, Ar-H), 7.19 (br s, 1H, NH), 5.22 (s, 2H, Bn), 4.47 - 4.43 (m, 1H, H-5), 4.33 (t, $J = 5.4$ Hz, 1H, H-9), 4.12 - 3.87 (m, 2H, H-4, H-5), 3.30 (s, 3H, OMe), 3.29 (s, 3H, OMe), 1.85 - 1.69 (m, 1H, H-6), 1.62 - 1.41 (m, 3H, H-6, H-8) 1.39 - 1.20 (m, 2H, H-7); δ_{C} (101 MHz, CDCl_3) 201.3 (C-2), 155.3 (C=O), 135.3 (*i*-Ar), 128.5 (Ar), 128.4 (Ar), 128.1 (Ar), 104.1 (C-9), 67.9 (Bn), 67.4 (C-5), 56.6 (C-4), 52.9 (OMe), 52.9 (OMe), 32.2 (C-6), 31.3 (C-8), 19.3 (C-7).

(R)-4-(9,9-dimethoxybutyl)oxazolidin-2-one, 43



To hydrazide **42** (88.0 mg) and according to **General procedure 1** with anhydrous potassium carbonate for 48 hours to afford compound **43** (30.5 mg, 86%) as a colourless oil in a corrected yield based on a 70% conversion of **42**.

$[\alpha]_D^{20}$ +27.1 ($c = 0.5$, DCM); IR (neat) $\nu_{\max} / \text{cm}^{-1}$ 1748 (C=O), 1263 (C-O); HRMS (ESI): m / z 226.1052 $[\text{M} + \text{Na}]^+$, $\text{C}_9\text{H}_{17}\text{NNaO}_4$ requires 226.1055; δ_{H} (300 MHz, CDCl_3) 6.36 (br s, 1H, NH), 4.45 (t, $J = 8.3$ Hz, 1H, H-5), 4.33 (t, $J = 5.4$ Hz, 1H, H-9), 3.99 (dd, $J = 8.3$, 6.0 Hz, 1H, H-5), 3.93 - 3.76 (m, 1H, H-4), 3.30 (s, 3H, OMe), 3.29 (s, 3H, OMe), 1.70 - 1.51 (m, 4H, H-6, H-8), 1.46 - 1.24 (m, 2H, H-7); δ_{C} (101 MHz, CDCl_3) 157.0 (C-2), 104.2 (C-9), 80.6 (C-5), 68.8 (C-4), 55.2 (OMe), 50.0 (OMe), 30.3 (C-6), 29.4 (C-8), 17.5 (C-7).

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