No Restrictions

MONASH UNIVERSITY
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DOCTOR OF PHILOSOPHY
ON..... 28 September 2004.....
..... [redacted] .....
Sec. Research Graduate School Committee

Errata

p. 19 line 7: should be 'phenomenon' for 'phenominun'

p. 22 line 7: should be 'leads' for 'lead'

p.86 line 1: should be 'Grignard' for 'Gringard'

p. 89, line 4: should be 'Scheme 4.17' for 'Scheme 4.16'

p. 120, line 7: should be 'undec-10-enylamine' for 'undec-10-amine'

p. 123, Table 6.1: should be 'Isolated yields of (161) (%)' for 'Isolated yields (%)', also it should be 'From resin attached (165)' and 'From solution of (175)' for 'Resin attached (165)' and 'Solution of (175)' respectively.

M O N A S H U N I V E R S I T Y

AUSTRALIA

Synthesis and Use of Nitrogen Heterocycles in Metal Mediated Reactions

Jayamini P. M. Illesinghe

B. Sc. (Biomedical) (Hons.) Monash

A thesis submitted to the Faculty of Science
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DOCTOR OF PHILOSOPHY

School of Chemistry, Monash University,
June 2004

Dedicated to my loving parents Prasantha and Jayanthi Illesinghe

Table of Contents

Part B

Chapter 6: Synthesis of Nitrogen Heterocycles by Rhodium Catalysed Hydroformylation of Polymer-Attached Amino Alkenes with Syn Gas

Chapter 7: Experimental

STATEMENT

To the best of the author's knowledge and belief, this thesis contains no material which has been accepted for the award of any other degree or diploma in any university, and contains no material previously published or written by another person except where due reference is made.

Jayamini P. M. Illesinghe

School of Chemistry

Monash University

June 2004

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The receipt of an Australian Postgraduate Award (APA) is gratefully acknowledged.

M; sincere gratitude goes to my family for always being there for me no matter what and supporting me 120%. Ammi (Jayanthi) and thathie (Prasantha) this is your PhD as much as it is mine because without your efforts and selfless sacrifices throughout all these years this would not have been possible. I would also like to thank my grandparents (Edna and Jerry) for the important role they play/played in my life. Your unconditional love and support has made me who I am. Thank you mallie (Suhith) for always listening to my boring chemistry problems although you had no idea as to what was going on. Last but not least, Suwan, thank you for coming into my life. Your love, support and belief in me has made this even more worthwhile.

Abbreviations

OsO_4 = Osmium tetroxide

DHQD = Dihydroquinidine

n-BuLi = *n*-Butyl lithium

$LiAlH_4$ = Lithium aluminium hydride

Wang resin = 4-(hydroxymethyl)phenoxymethyl polystyrene resin

THF = Tetrahydrofuran

$Na_2SO_4.10H_2O$ = Sodium sulfate decahydrate

DIAD = Diisopropyl azodicarboxylate

DHQ = Dihydroquinine

Binol = 1,1'-Bi-2-naphthol

TMEDA = *N*,*N*,*N*,*N*-Tetramethylethylenediamine

BSA = *N*,*O*-bis(trimethylsilyl)acetamide

MTPA = Mosher's acid

$[Rh(OAc)_2]_2$ = Rhodium(II) acetate dimmer

$BnV^{2+}2Br^-$ = Benzyl viologen (1,1'-dibenzyl-4,4'-bipyridinium) dibromide

DEAD = Diethyl azodicarboxylate

BIPHEPHOS = [6,6'-[[3,3'-bis(1,1-dimethyl)-5,5'-dimethoxy-1,1'-biphenyl]-2,2'-diyl]bis(oxy)]bisdibenzo[d,f][1,2,3]dioxaphosphepin

DMF = Dimethylformamide

TFA = Trifluoroacetic acid

Triton B = *N*-Benzyltrimethylammonium hydroxide

DIC = 1,3-diisopropylcarbodiimide

DMAP = *N*,*N*-Dimethylaminopyridine

$NaCNBH_3$ = Sodium cyanoborohydride

TMOF = Trimethyl orthoformate

Publications

Journals

Fallon, G., Illesinghe, J., Campi, E. M., Jackson, W. R., Robinson, A. J., *Acta. Crystallogr. E.*, 2003, 59, o1163.

Illesinghe, J., Ebeling, R., Ferguson, B., Patel, J., Campi, E.V., Jackson, W. R., Robinson, A. J., *Aust. J. Chem.*, **2004**, 57, 167.

Illesinghe, J., Campi, E. M., Jackson, W. R., Robinson, A. J., *Aust. J. Chem.*, **2004**, 57, 1.

Poster Presentations

19th Royal Australian Chemical Institute Organic Conference

Lorne, Melbourne, July 2003

Title: An Evaluation of Some Hindered Diamines as Chiral Modifiers of the Osmium Tetroxide Dihydroxylation of Stilbene

28th Annual Synthesis Symposium

Melbourne University, December 2003

Title: An Evaluation of Some Hindered Diamines as Chiral Modifiers of the Osmium Tetroxide Dihydroxylation of Stilbene

The New Zealand Institute of Chemistry (NZIC) Conference

Nelson, New Zealand, December 2003

Title: An Evaluation of Some Hindered Diamines as Chiral Modifiers of Metal Promoted Reactions

Abstract

The thesis describes the synthesis and application of some nitrogen heterocycles. The major part of the thesis is concerned with the synthesis of small chiral nitrogen heterocycles for the use as chiral modifiers in metal-promoted reactions. A study of the synthesis of large nitrogen heterocyles on a solid support is also included.

The chiral dimethylpyrrolidine ligands (43) and (44) were successfully synthesised from the key building block, (2*S*,5*S*)-2,5-hexanediol (49), which was prepared by a yeast reduction of 2,5-hexanedione (50). Both ligands, (43) and (44) were prepared in good yields and in excellent selectivity (>99% ee). Other modified pyrrolidine analogues ((55), (62), (63), (64), (65) and (66)) were also successfully prepared.

The chiral diamines (43), (44), were evaluated as ligands in the osmium tetroxide dihydroxylation of stilbene (12). ^{1}H n.m.r experiments showed that these ligands were too bulky to coordinate to osmium. Less hindered analogues ((55), (62), (63), (64), (65) and (66)) did act as ligands in the dihydroxylation reactions but with poor enantioselectivity (<10% ee). The chiral diamines were also evaluated as ligands in asymmetric Grignard reactions, Rh-catalysed hydroformylation reactions and copper-catalysed phenolic coupling reactions with very little success. However, asymmetric allylic alkylation reactions carried out using chiral pyrrolidine (43) showed excellent

enantioselectivity (75-85% ee). Good streoselectivity (51% ee) was achieved when ligand (66) was used.

Synthesis of the bis-aziridine ligands (56) and (57) were also attempted. The key building block in this reaction scheme was (2*R*,3*R*)-Butanediol (23). Synthesis of the chiral aziridine (25) was successfully carried out. However, reduction of the diamide (59) obtained following the coupling to oxalyl chloride failed to give the desired bis-aziridine ligand (56). The aniline (61) derivative used in the synthesis of the ligand (57) was prepared in a moderate yield (36%). However, the second coupling of the amine (61) with the cyclic sulfate (24) failed to give the desired ligand (57).

The second part of the thesis examined the rhodium(I)-phosphite catalysed hydroaminomethylation of resin-tethered amino alkenes (165a-d) with H_2/CO. These reactions gave moderate to good yields of 5-, 8-, 10- and 13-membered heterocycles (161a-d). Competing hydrogenation, dimerisation or polymerisation reactions were not observed using this methodology. Analogous reactions of untethered amines (175a-d) in solution gave more complex product mixtures with formation of polymers in most cases.

Chapter 1
Introduction

1.1 Introduction

Chirality is important in the context of biological activity because at a molecular level, asymmetry dominates biological processes.[1] Biologically active agents such as neurotransmitters, hormones and drugs often show a high degree of selectivity towards their molecular site of action.[2] Therefore it is not surprising that the pharmaceutical industry has become the driving force for the synthesis of enantiomerically pure compounds.[2]

The worldwide market for drugs sold as single enantiomers was $ (U.S) 159 billion in the year 2002[3] which was greater than in previous years, with $ 147 billion being recorded in the year 2001 and $ 133 billion in the year 2000.[4] Table 1.1 clearly shows that the majority of new drugs entering the market between 1998 – 2002 are chiral.[5-9] Figure 1.1 shows the percentage of chiral drugs sold as single enantiomers and in their racemic form. The trend that can be seen is that the ratio of new drugs entering the market as single enantiomers is on the rise and is nearing 100%. This is something of a sea change from the 1980's.[10] Data from 1982 show that 88% of chiral synthetic drugs were marketed as racemates.[11]

Table 1.1: New drugs entering the market from 1998 - 2002[5-9]

Year	Total new drugs	New chiral drugs	Single enantiomers	Nitrogen heterocycles
2002	33	22	20	22
2001	25	20	19	12
2000	35	23	22	24
1999	36	26	21	19
1998	26	21	15	21

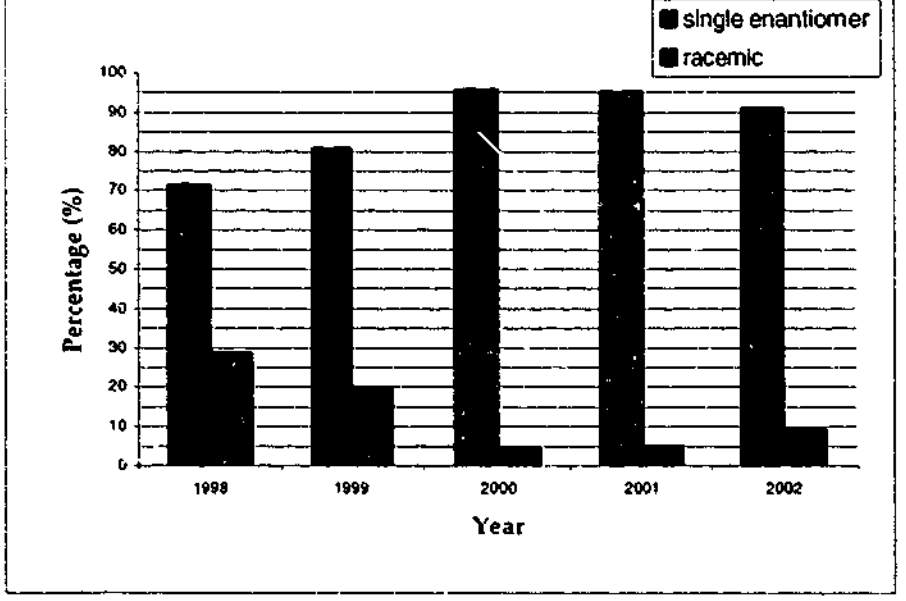


Figure 1.1: The increasing trend towards the single enantiomer drugs entering the market in the last five years[5-9]

Synthesis of enantiomerically pure compounds is by no means focused on the pharmaceutical industry. In fact, other industries, such as those involved in the production of agrochemicals and food (flavours and fragrances), are increasingly concerned with enantiomeric purity.[1,12-18] The major problem associated with the use of racemates is the often disparate biological activity and potency of each of the respective enantiomers as shown in Figure 1.2.[19]

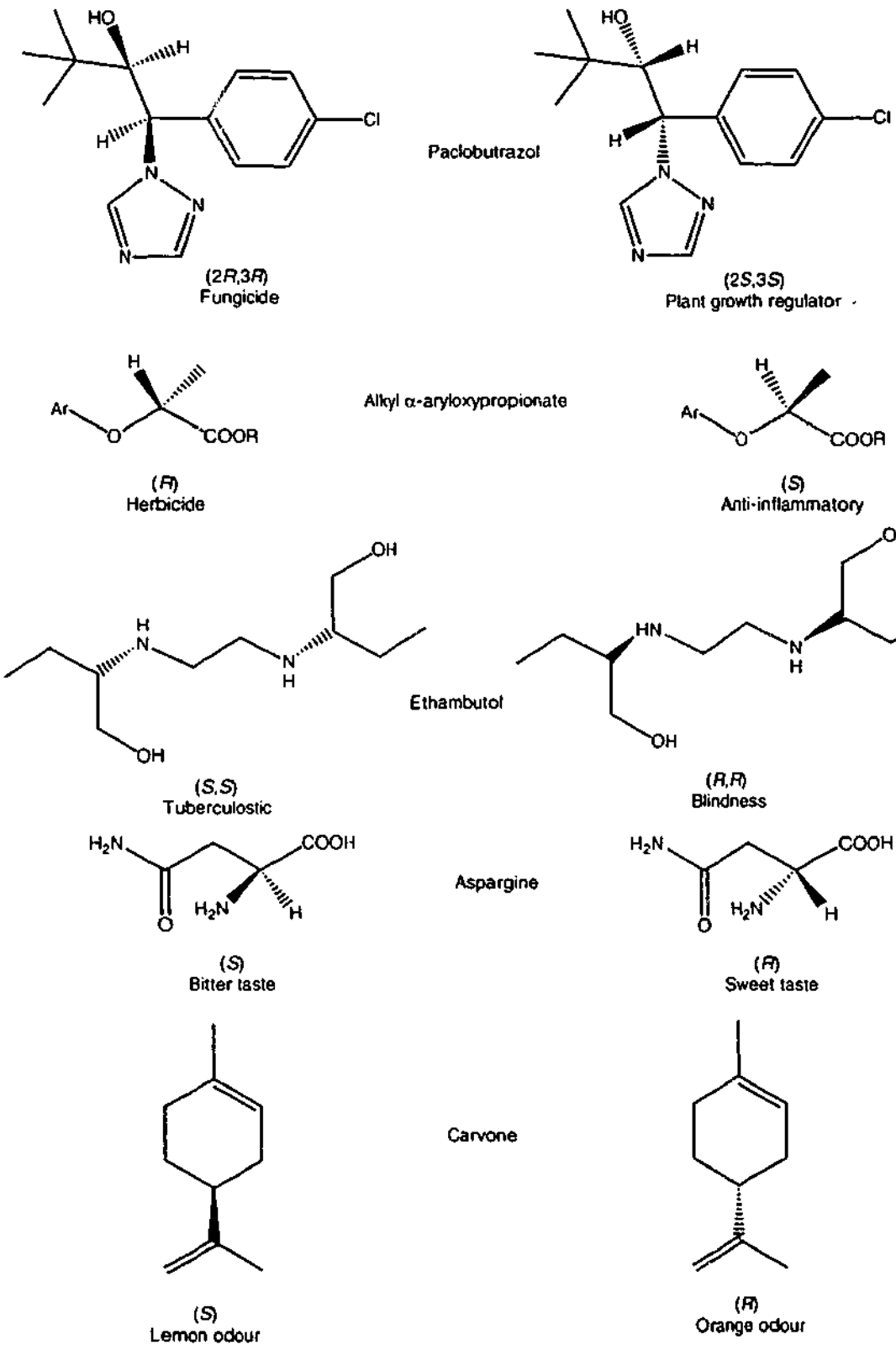


Figure 1.2: Differences in the properties of enantiomers

There are a variety of methods available for the synthesis of optically pure compounds. Methods include the use of chirality from the chiral pool, resolution of racemates, fermentation and enzymatic transformation, diastereomeric transformation,

resolution and asymmetric synthesis. All of these methods are used in industrial syntheses of enantiomerically pure compounds.

In the year 2002, the anti-infectives were the most active therapeutic area with eight new launches.[9] Of these, seven were chiral and all eight drugs contained nitrogen heterocycles in their structure. Examples of these include Omegacin® (biapenem) (1) and Pasil® (pazufloxacin) (2) (Figure 1.3). Nearly two thirds of the new drugs entering the market every year contain a nitrogen heterocycle moiety (Table 1.1). Nitrogen heterocycles have played a skeletal role in many synthetic drugs for a very long time and continue to do so. Penicillin (3), the first β-lactam antibiotic, was discovered in 1928 by Alexander Fleming. Enalapril (4) is a newer drug used to treat high blood pressure (Figure 1.3).

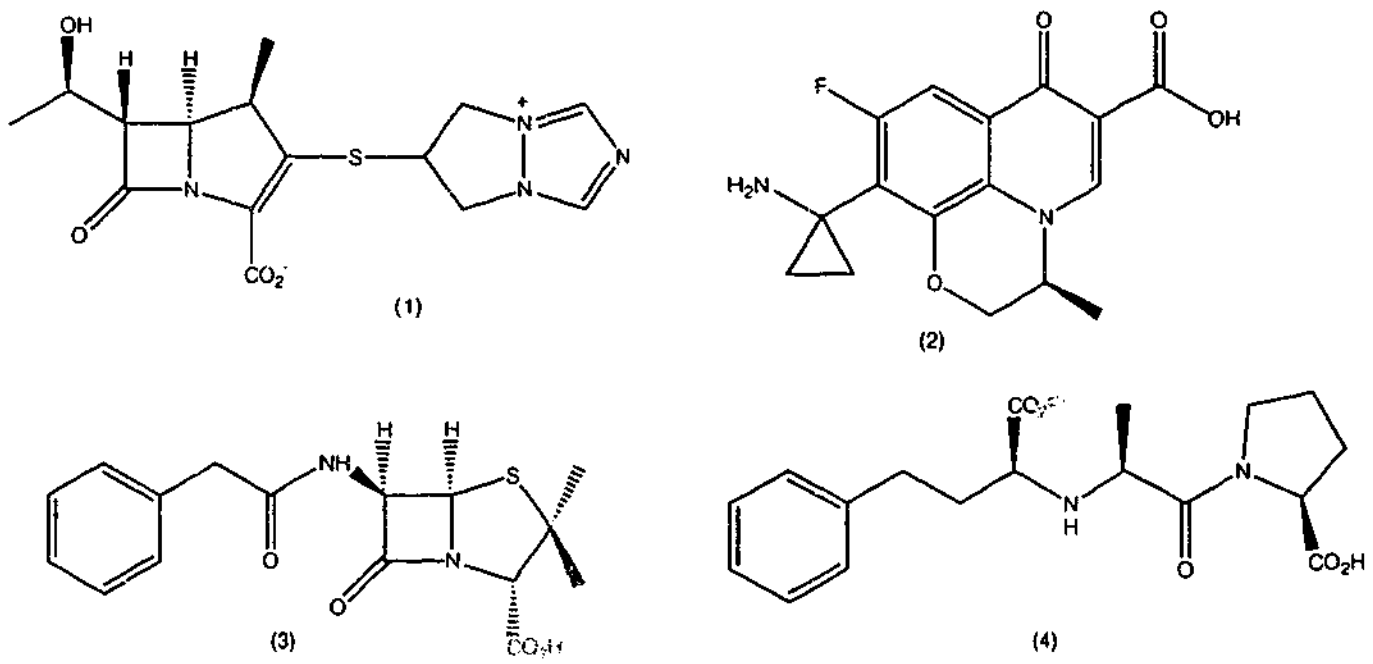


Figure 1.3: Some new and old drugs containing nitrogen heterocycles

Nitrogen heterocycles also make up the framework of many natural products such as alkaloids. The powerful euphoric and analgesic alkaloid morphine (5), which is isolated from poppy (*Papaver sominiferum*) seeds, possesses a piperidine moiety

(Figure 1.4).[20] Pyrrolizidine alkaloids such as retronecine (6), isolated from *Senecio douglasii var longilobus*, are naturally occurring carcinogens used as venoms (Figure 1.4).[21] Alkaloids related to aaptamines (7) were isolated from marine sponges of the genus *Xestospongia*.[22] These alkaloids (7) are topoisomerase II inhibitors that catenate DNA.

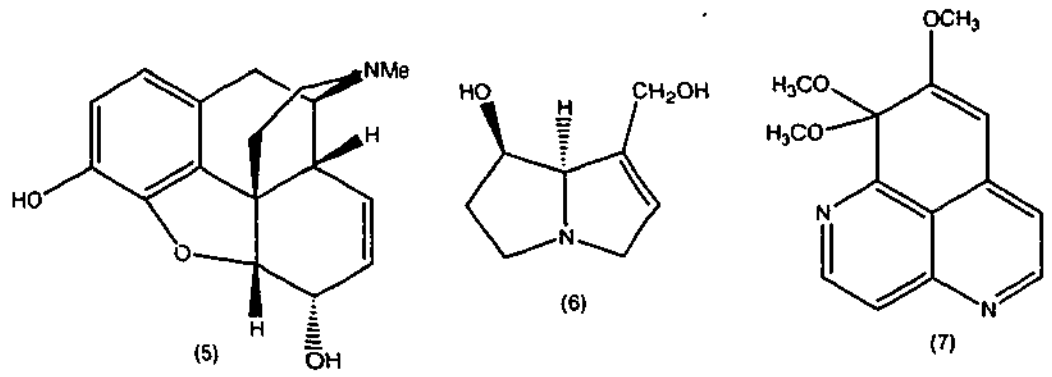


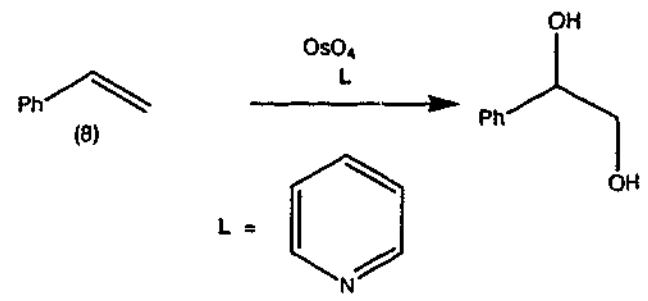
Figure 1.4: Plant alkaloids with nitrogen heterocycles[20,21,22]

The main focus of this project will be to synthesise chiral nitrogen heterocycles for use as ligands in asymmetric catalysis. This will form Part A of the thesis while Part B of this thesis will examine the synthesis of large nitrogen heterocycles.

1.2 Nitrogen heterocycles as ligands for metal mediated reactions

Many nitrogen heterocycles when incorporated with metals catalyse a variety of reactions.[23,24] Achiral reactions which use amine based ligands include dihydroxylation reactions, where pyridine is employed in conjunction with osmium tetroxide to carry out catalysis (Scheme 1.1 (a)).[25,26] Other examples include palladium catalysed co-polymerisation reactions of alkenes, such as styrene (8), using the 1,10-phenanthroline ligand (9) (Scheme 1.1 (b)).[27] Platinum based catalysts are used in Diels-Alder reactions (Scheme 1.1 (c)).[28]

(a)



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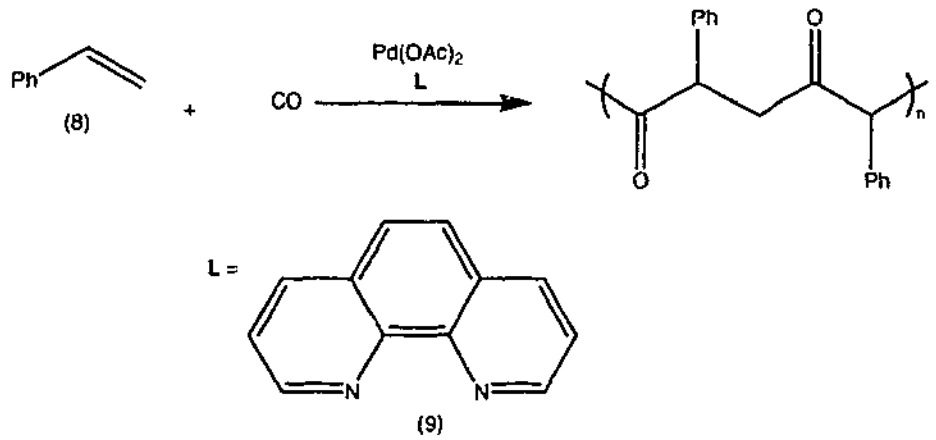

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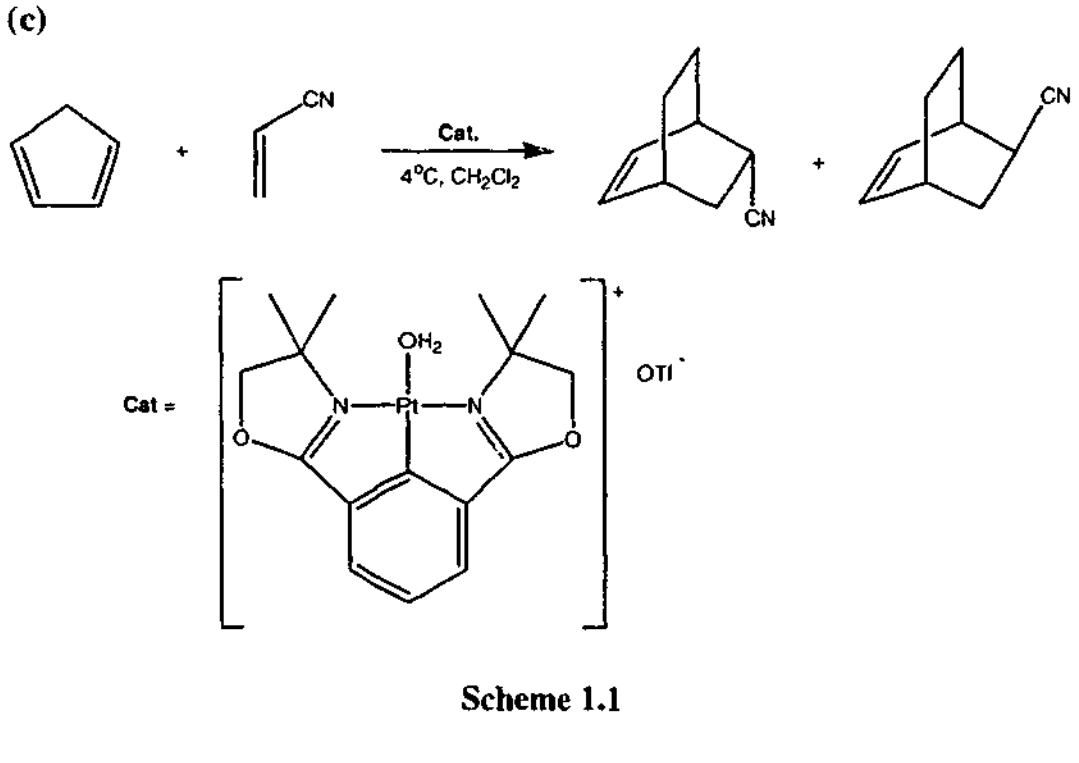


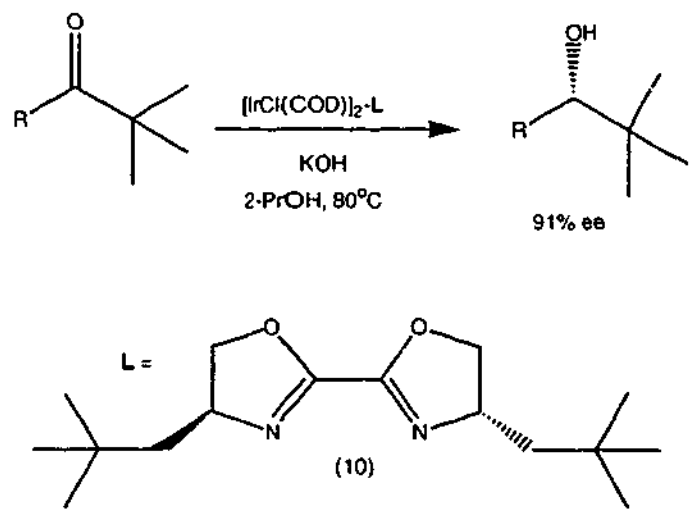
Scheme 1.1

Our main focus has been on the use of chiral amine ligands to aid asymmetric synthesis and hence to produce enantiomerically enriched material. This type of

synthesis is carried out under both stoichiometric and catalytic conditions. In both instances, amine ligands act as chiral auxiliaries and form complexes with metals which induce enantioselectivity.[29,30] Catalytic asymmetric synthesis is the ideal method to synthesise optically active material, as a small amount of the chiral catalyst can produce large quantities of enantiomerically pure material.[19] A number of asymmetric synthetic methods exist that utilise diamine ligands as chiral auxiliaries and some of these are discussed below.

(i) Asymmetric hydrogenation

Generally, asymmetric hydrogenation catalysts are ruthenium and rhodium based complexes with diphosphine ligands.[31] However, iridium complexes of the oxazolidine ligand (10) have also been used to reduce ketones to alcohols in good enantioselectivity (91% ee) (Scheme 1.2).[30,32-34]

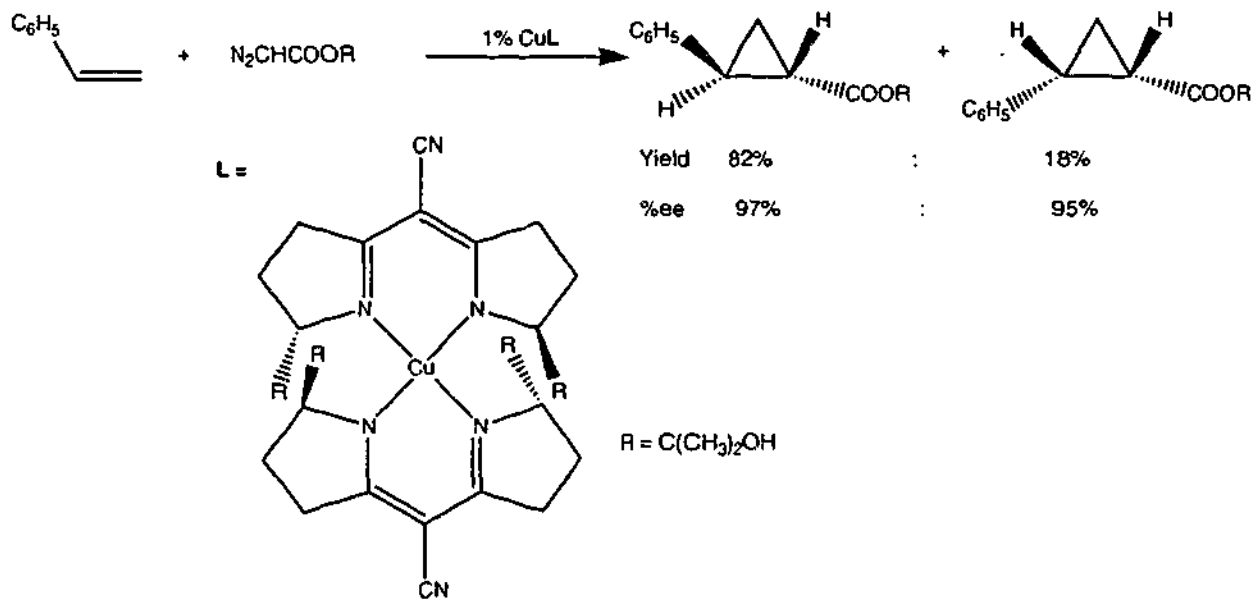


Scheme 1.2[32]

(ii) Asymmetric cyclopropanation

Cyclopropane formation is facilitated by a reaction between diazo compounds and alkenes and can be catalysed by a wide variety of transition metal compounds which facilitate the addition of a carbene entity to a carbon-carbon double bond.[31,34] The

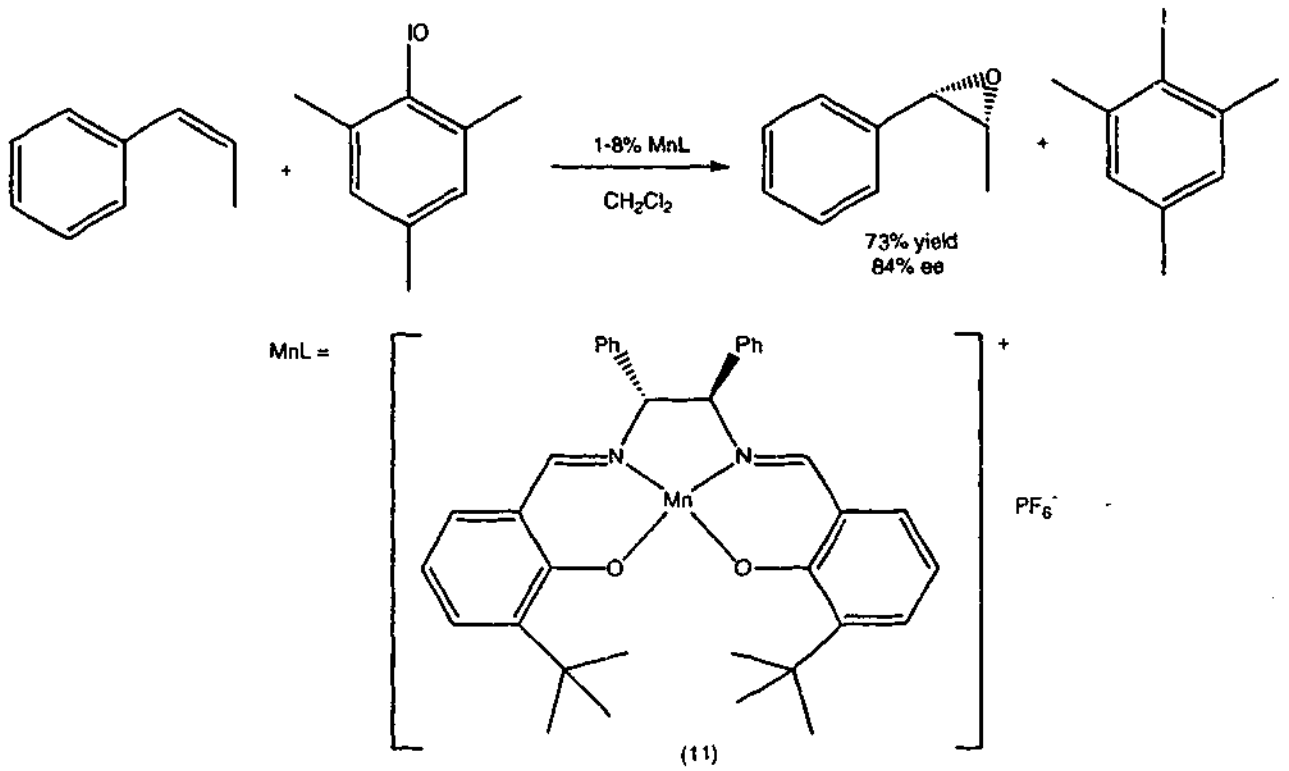
most widely used and established methodology for cyclopropanation reactions utilises copper.[35] Copper catalysed reactions have been known for over 80 years and these catalysts carry out cyclopropanation reactions with good regioselectivity and excellent enantioselectivity (Scheme 1.3).[35]



Scheme 1.3[35,36]

(iii) Asymmetric epoxidation

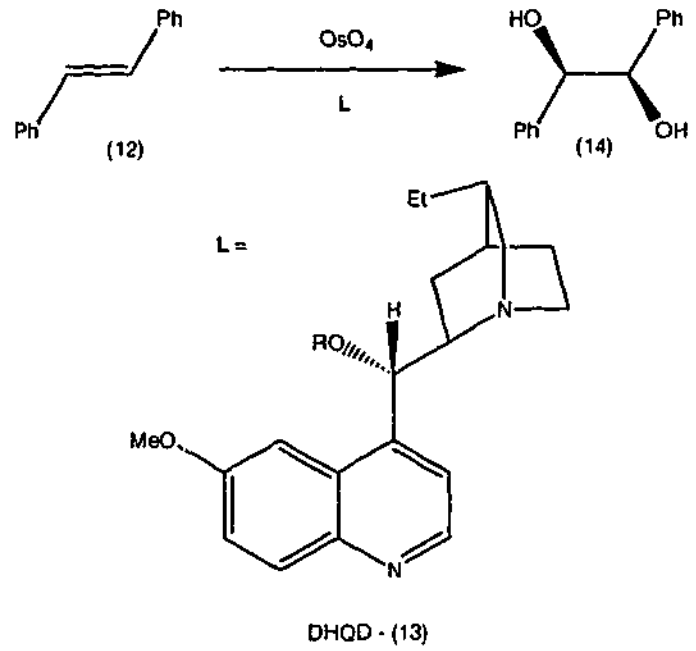
Enantioselective alkene epoxidation constitutes an extremely appealing strategy for the synthesis of optically active organic compounds. Manganese(III) complexes with C_2-symmetric chiral salen ligands, e.g. (11), promote epoxidation with high enantioselectivity as shown in Scheme 1.4.[31,37,38]



Scheme 1.4[38]

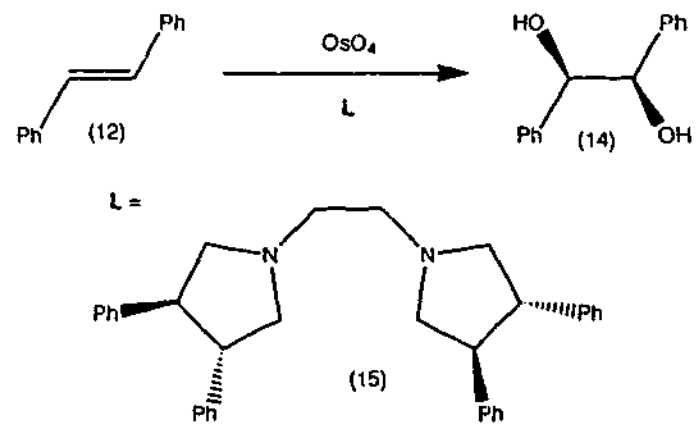
(iv) Asymmetric dihydroxylation

The *cis*-dihydroxylation of olefins such as stilbene (12) mediated by osmium tetroxide represents an important general method for olefin functionalisation. Sharpless and co-workers carry out asymmetric dihydroxylations of alkenes using cinchona alkaloid derivatives (13) as chiral ligands.[39,40] The ligands when coupled with osmium tetroxide allow dihydroxylation reactions to be carried out in excellent yield (>99%) and enantioselectivity (>97% ee) (Scheme 1.5).[41]



Scheme 1.5

A variety of chiral diamines such as (15) are elaborated into catalysts to facilitate asymmetric dihydroxylation (Scheme 1.6).[42] This reaction will be discussed in greater detail in Chapter 3.



Scheme 1.6[43]

1.3 Preparation of nitrogen heterocycles

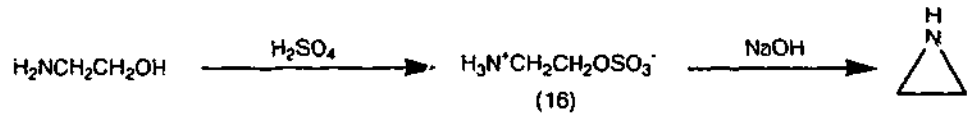
Many routes to nitrogen heterocycles are available including modification of existing heterocycles as well as cyclisation reactions. These syntheses can be discussed in two major parts.

(i) Preparation of small rings (3- and 5-membered heterocycles). These heterocycles can be formed as either achiral or chiral molecules.

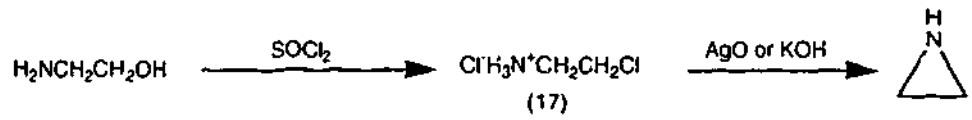
(ii) Preparation of large rings (8 – 13-membered heterocycles)

1.3.1. Preparation of achiral 3- or 5-membered heterocylces

The most common method used for the synthesis of aziridines is by heating 2-aminoethyl hydrogensulfate (16) with concentrated aqueous sodium hydroxide (Scheme 1.7, Method A).[44,45] Another method that is widely used involves a silver oxide or base catalysed cyclisation of 2-chloroethylamine hydrochloride salt (17) (Scheme 1.7, Method B).[45,46]



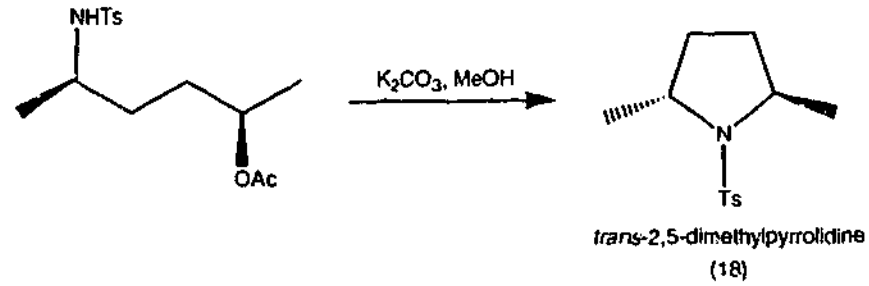
Method A[44]



Method B[46]

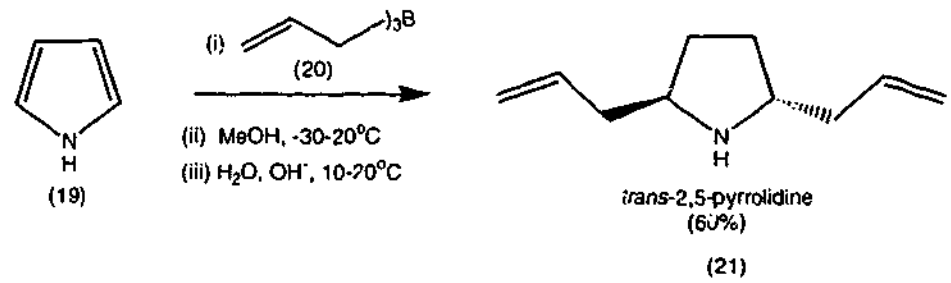
Scheme 1.7

The most reliable preparation of 5-membered nitrogen heterocycles is by intramolecular displacement of an activated alcohol by an amine.[47] This cyclisation is usually stereospecific (i.e. mainly the *trans*-isomer is formed opposed to the *cis*-isomer) with very little epimerisation. An example of this is the synthesis of the *trans*-2,5-disubtituted pyrrolidine (18) which was obtained in a >95% yield (Scheme 1.8).[47,48]



Scheme 1.8[48]

Another method for synthesising a 2,5-substituted pyrrolidine is by the reaction of pyrrole (19) with excess triallylborane (20). Using this method, *trans*-2,5-diallylpyrrolidine (21) was isolated as the main product in a 60% yield (Scheme 1.9).[48]



Scheme 1.9

1.3.2 Preparation of chiral 3- or 5-membered heterocycles

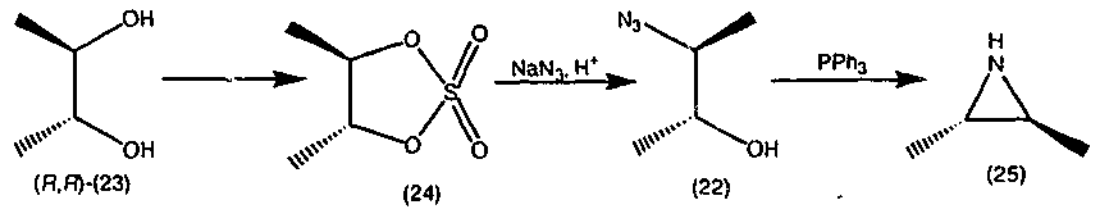
As with the achiral nitrogen heterocycles, there are many different ways to synthesise chiral aza-heterocycles.

(i) Preparation of chiral aziridines

Optically active aziridines are synthons for the preparation of amino acids, β-lactams, chiral reagents and show biological activity in their own right.[49] There are several methods for the synthesis of aziridines of which two will be discussed below.

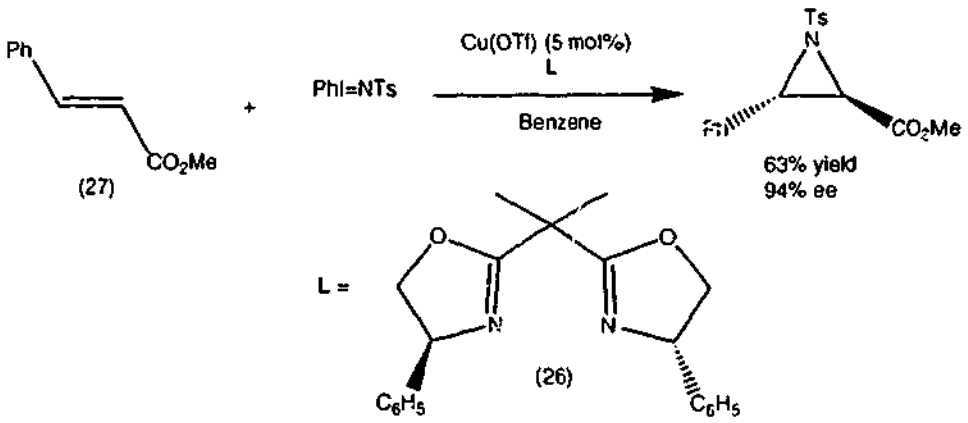
Ring closing aziridination leading to an azido alcohol (22) involves the reaction of a 1,2-glycol (23) which is activated as a cyclic sulfate (24).[50,51] The azide (22) was

formed by the use of sodium azide in an acidic medium. Ring closure to the aziridine (25) was performed by the exposure to triphenylphosphine (Scheme 1.10).[51]



Scheme 1.10

Another method utilises the Evans system of aziridination which employs a bis-oxazolidine ligand (26) with copper(I) triflate.[34] The aziridination of the cinnamate ester derivative (27) takes place in good yield and excellent enantioselectivity (Scheme 1.11).[30]



Scheme 1.11[52,53]

(ii) Preparation of chiral pyrrolidines

Since the first isolation of 2,5-substituted pyrrolidine alkaloids from ant venom (Figure 1.5),[54] chemists have extensively studied these natural products.[47,55] These heterocycles possess a wide range of biological activity which includes insecticidal, haemolytic and anticholinergic activity.[47]

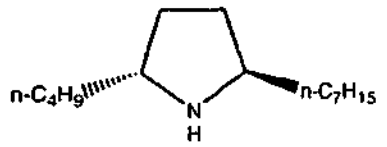
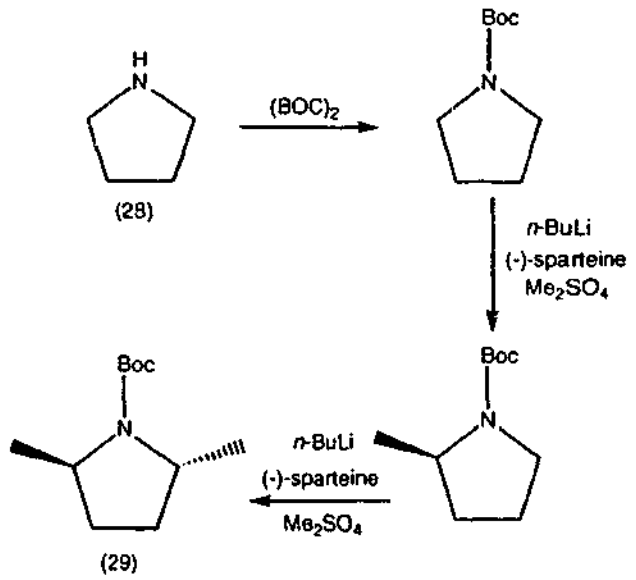


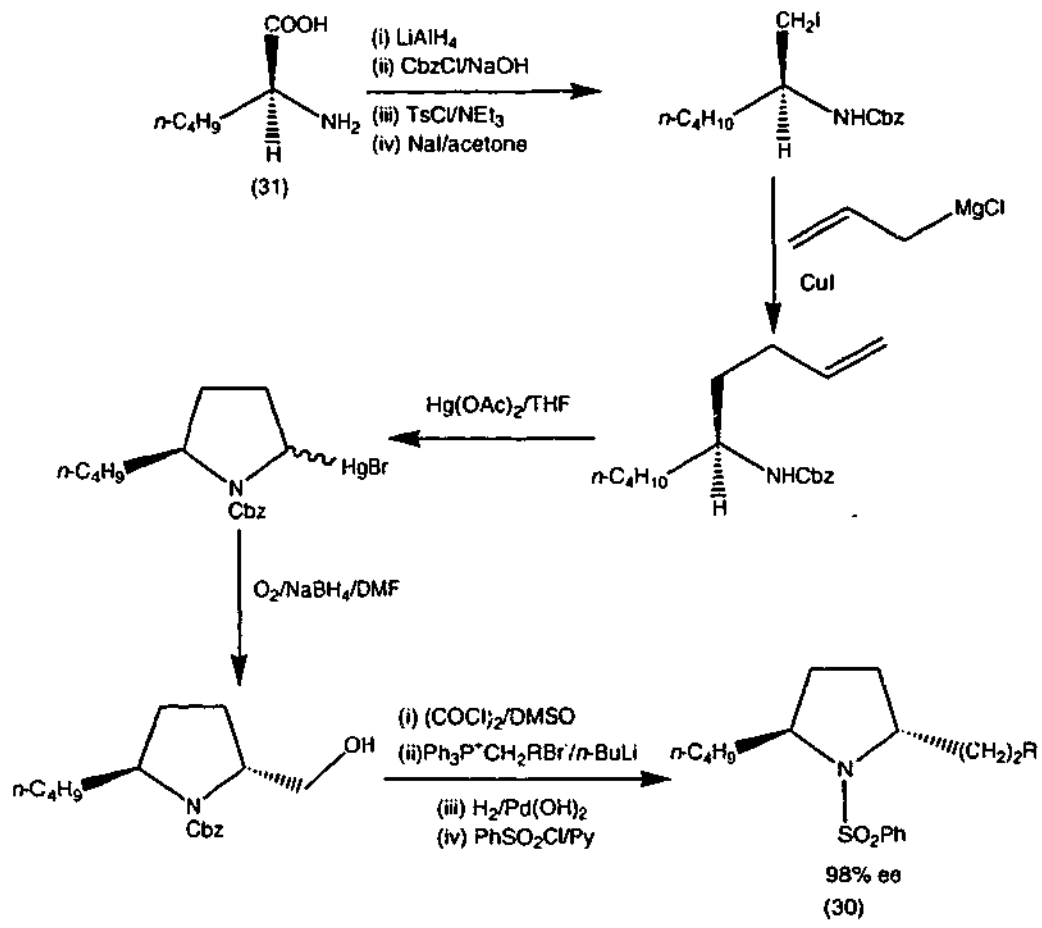
Figure 1.5: *trans*-2-heptyl-5-butylpyrrolidine[54]

Beak *et al.*[56,57] showed that the treatment of *N*-protected pyrrolidine with *n*-BuLi in the presence of (-)-sparteine affected asymmetric deprotonation. Subsequent stereoselective alkylation (Scheme 1.12) to give the (2*S*,5*S*)-*N*-Boc-2,5-dimethylpyrrolidine (29) occurred in 47% yield, with 80% diastereoselectivity and 90% enantioselectivity.



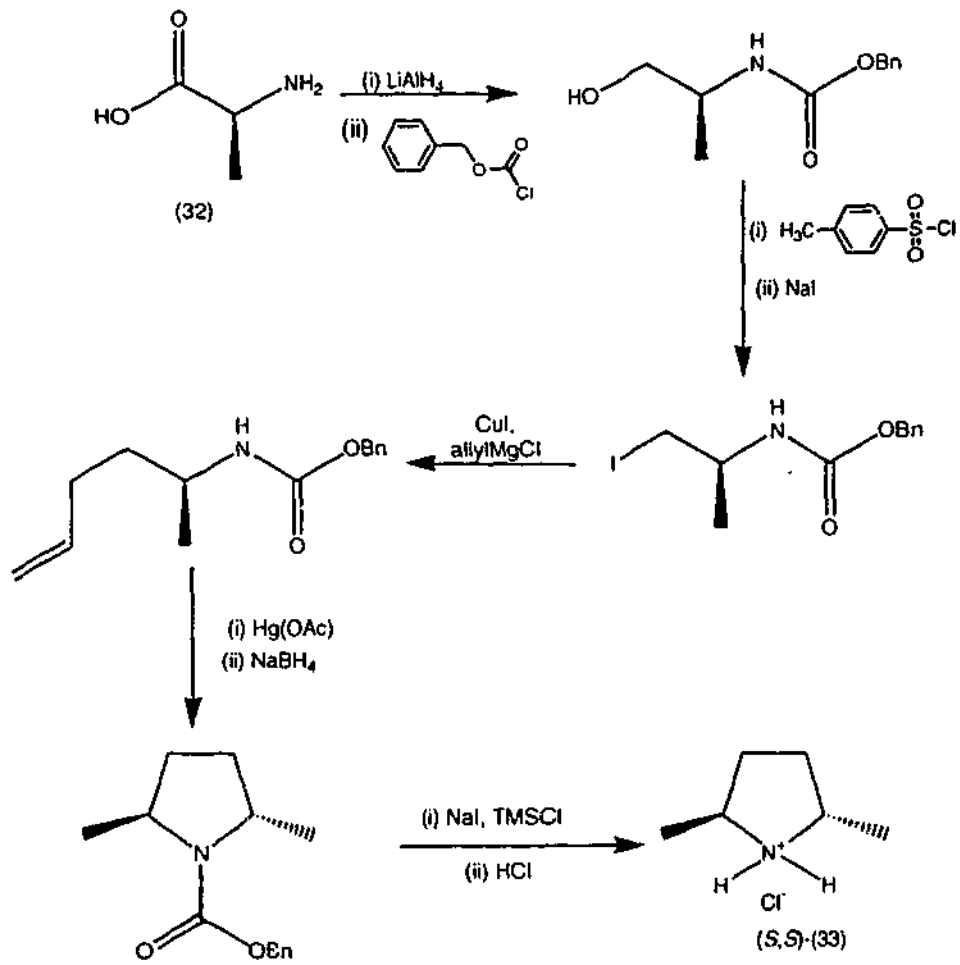
Scheme 1.12 [56]

Takahata *et al.*[55] showed that 2,5-dialkylpyrrolidines (30) could be synthesised from L-(+)-norleucine (31) using aminomercuration with a diastereoselectivity of 96% and an enantioselectivity of 98% (Scheme 1.13).



Scheme 1.13[55]

Another procedure utilises L-alanine (32) as the starting material, which is reduced and benzylated following a method described by Schlessinger and Iwanowicz (Scheme 1.14).[58] The alcohol is then converted to a halide before undergoing an organocuprate reaction. After carrying out a ring closing aminomercuration reaction, following a procedure described by Harding,[59,60] the benzoyl group is cleaved to give the desired product as its hydrochloride salt (33) in reasonable yield (40%) and in excellent stereoselectivity (>98% ee) (Scheme 1.14).[61]



Scheme 1.14

1.3.3 Preparation of medium and large rings

Cyclisation of small (3- and 4-membered) rings are governed by ring strain.[62,63] As the rings get larger in size the ring strain is no longer a problem. The medium sized rings (8 – 11-membered) suffer from transannular strain.[64] However, during the synthesis of large rings, the probability of coincidence of the reactive centers becomes very low.[65] A number of methods have been used to overcome this problem and some of them are briefly discussed below.

(i) High dilution principle

Conducting reactions under high dilution conditions encourages intramolecular cyclisation, while decreasing the probability of intermolecular reactions which leads to dimers, oligomers and polymers (Figure 1.6).[66]

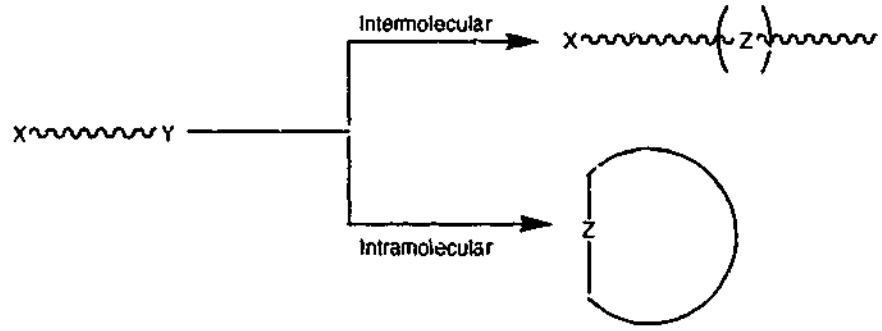
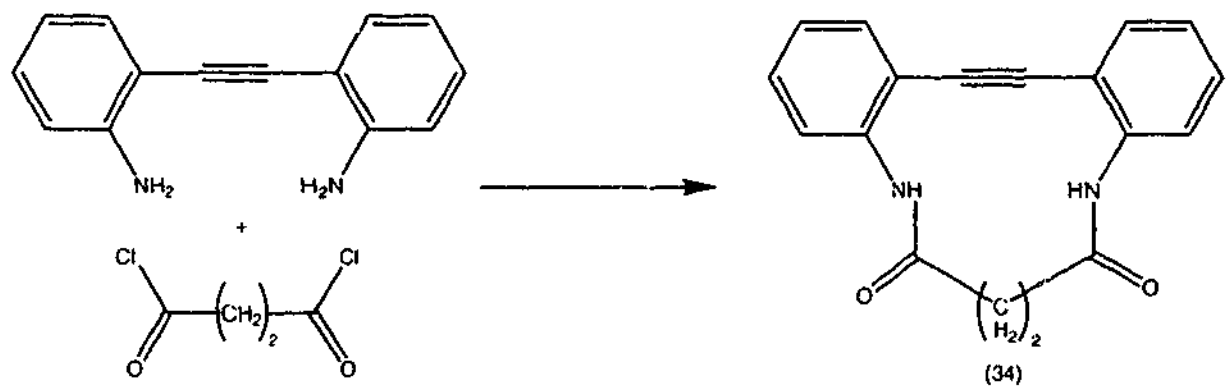


Figure 1.6: Difference between the intermolecular *vs* intramolecular reactions[67]

The concept was first formulated and applied in 1912 by P. Rouggli in the formation of cyclic amides (34) (Scheme 1.15).[68,69] High dilution does not necessarily imply large volumes of solvent. It can also mean the slow addition of a bis-functional reagent to a solution containing a promoter. This serves to maintain a continuous low concentration of the reactive species.[66] At low reactant concentrations, ring closure is favoured because the reacting molecules are "isolated" and more time is available for intramolecular reactions as opposed to intermolecular reactions.[70]



Scheme 1.15[68]

(ii) Templated ring closure

There are two main cyclisation methods which use either internal (endo) or external (exo) templates. The templates can be either temporary or permanent. They are chosen according to the specific reaction and the nature of the reacting groups.

(a) Endo templates

The term endo template is used to describe a process where a macrocycle is formed upon the template of a smaller ring. The ring is then enlarged to include all the pre-existing parts of the molecule, as shown in Figure 1.7.[69]

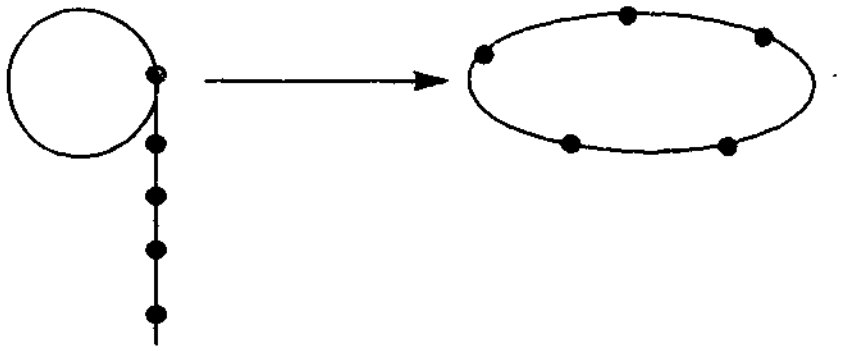
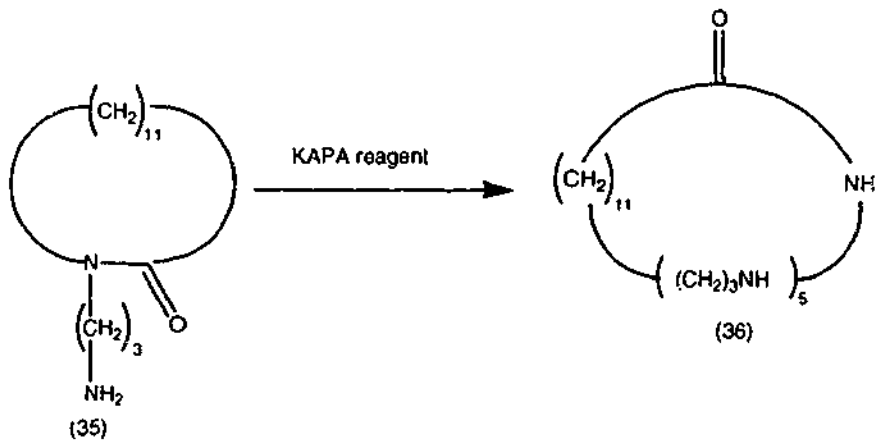


Figure 1.7: Ring expansion using internal templates[69]

This is observed in the conversion of the lactam (35) into amino amide (36) where ring enlargement is facilitated by the use of the KAPA (potassium aminopropylamide in 1,3-propanediamine) reagent (Scheme 1.16).[69] In this case, a 13-membered lactam (35) is transformed into a 33-membered amino amide (36) by five successive introductions of propylamine ($-CH_2CH_2CH_2NH_2$) units into the ring.[71]



Scheme 1.16[69]

(b) Exo templates

A temporary centre or group, which is either ionic or covalent, is used as a template in the cyclisation reaction (Figure 1.8). The template functions by self-assembling precursors molecules around it. Completion of the synthesis results in the elimination of the template.

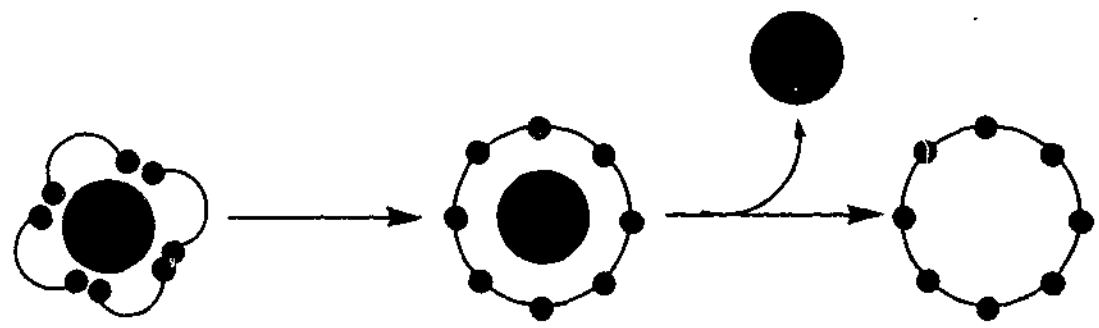
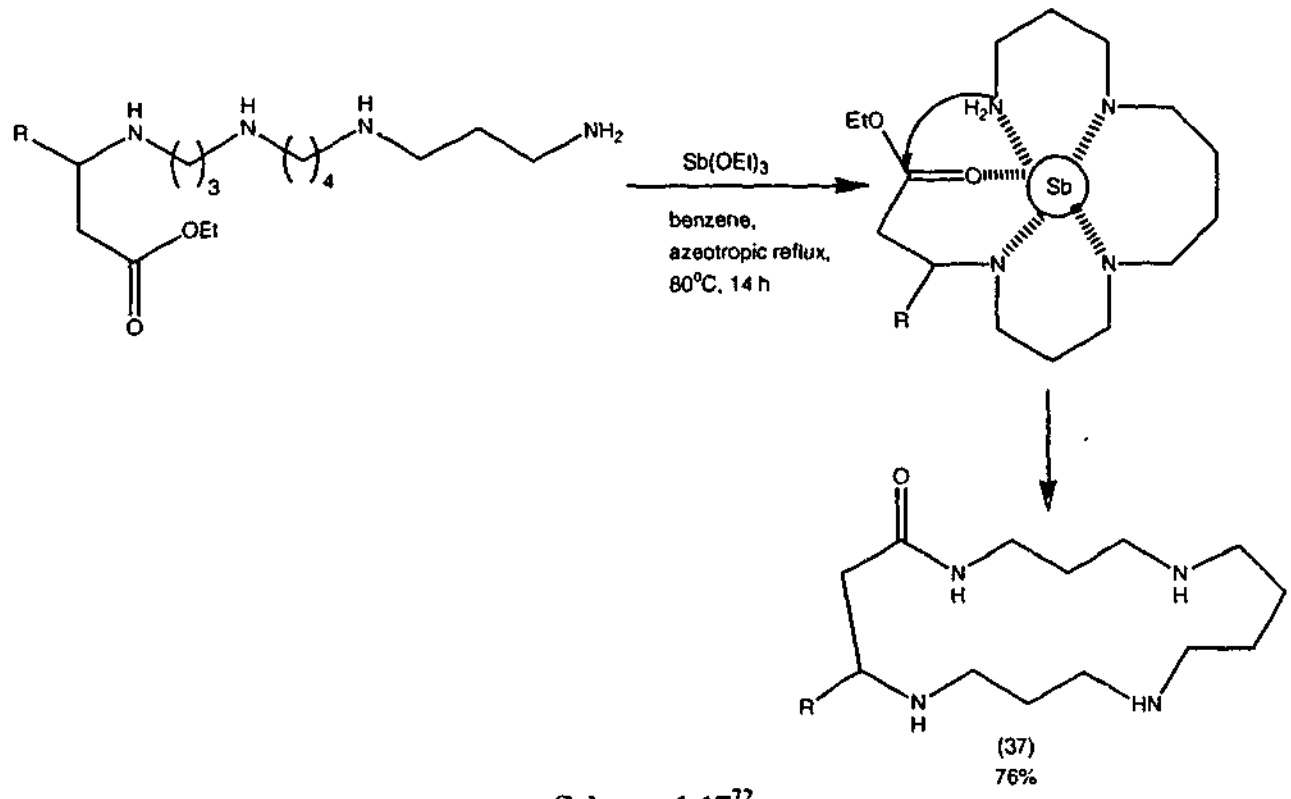


Figure 1.8: Cyclisation around a metal cation[69]

This phenominun can be observed in the synthesis of the 17-membered macrolactam (37) (Scheme 1.18).[72] The substrate is either covalently or coordinatively attached to the antimony template. Reaction of the amine with ester functional groups present at either end of the long open chain substrate results in cyclisation. The macrolactam (37) synthesis takes place in 76% yield with no polymerisation or regioisomer formation, and results in straightforward isolation of the lactam.[72]



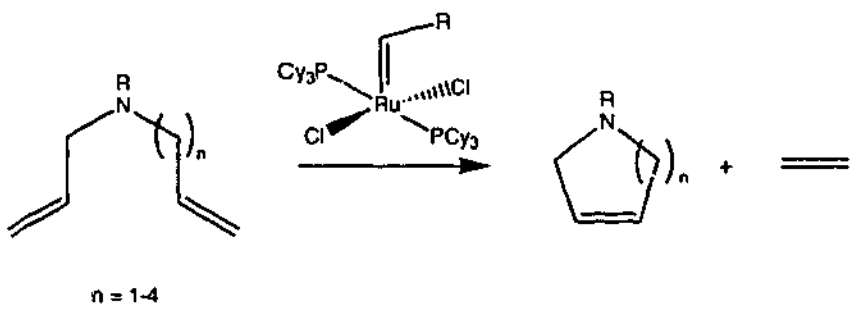
Scheme 1.17[72]

(iii) Homogenous metal catalysis

Metal catalysed reactions play an important role in the formation of nitrogen heterocycles and two approaches, namely ring closing metathesis and rhodium catalysed hydroformylation, will be discussed below.

(a) Ring Closing Metathesis

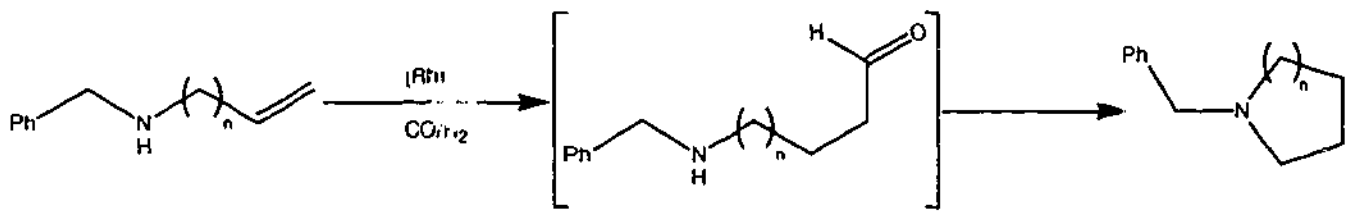
Reports have shown that ruthenium complexes, e.g. the Grubbs' catalyst, catalyse ring closing metathesis (RCM) reactions to form 5 - 8-membered heterocycles (Scheme 1.19).[73,74] Due to the extraordinary functional group tolerance of the ruthenium-based catalysts, cyclic amino acids, peptides and many natural products can be synthesised by this method.[75]



Scheme 1.18

(b) Rhodium catalysed cyclisation reactions

Hydroformylation is the reaction of olefins with CO and H_2 in presence of a catalyst to produce linear and branched aldehydes (Scheme 1.19).[76] Rhodium catalysed reactions of short chain alkenamines with CO/H_2 have been used in the preparation of 5 - 7-membered heterocycles when the intermediate aldehyde can react with the amino group in the substrate as shown in Scheme 1.20.[77-79] Rhodium catalysed hydroformylation reactions will be discussed in depth in Chapter 6.

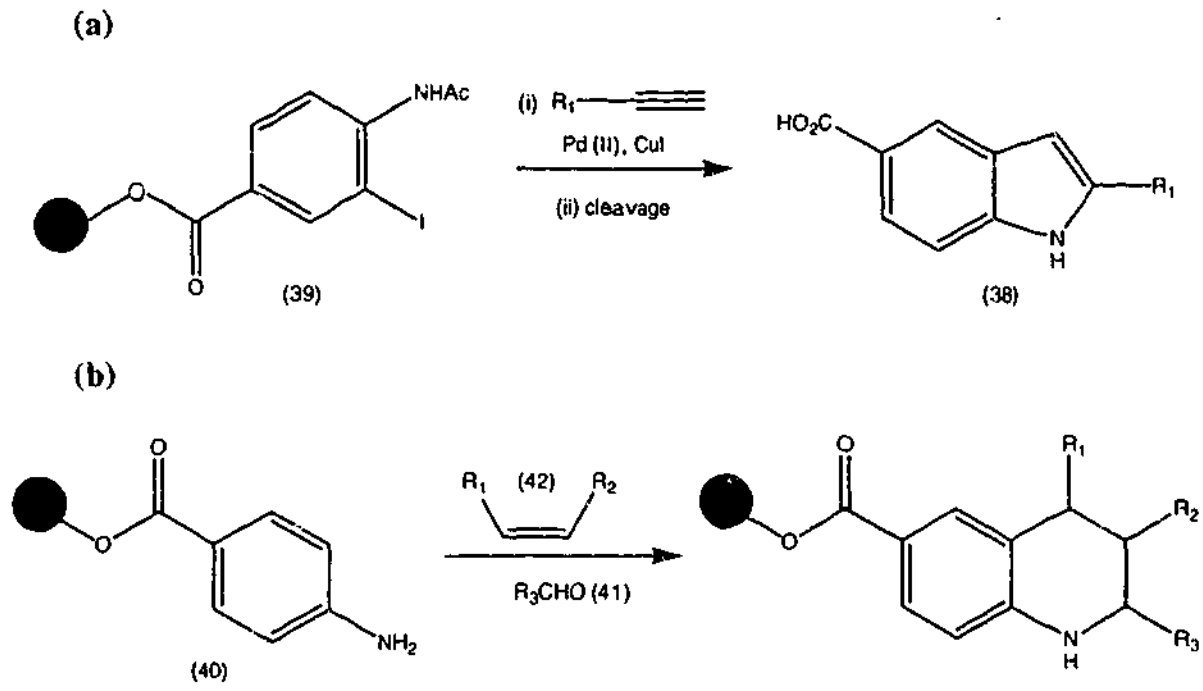


Scheme 1.19[77]

(iv) Solid support synthesis of heterocycles

Solid-phase synthesis of nitrogen heterocycles has emerged as an important tool in drug discovery and it also plays an integral part in the synthesis of many other natural products. Recent solid-phase synthesis literature describes many heterocyclic syntheses.[80]

Examples of this approach include the preparation of substituted indoles (38) from copper/palladium catalysed coupling of terminal acetylenes with resin-bound aryl iodides (39) (Scheme 1.20, (a)).[81] Another example is the condensation reaction carried out using arylamines (40), aldehydes (41) and olefins (42) (Scheme 1.20 (b)).[82]



Scheme 1.20[81,82]

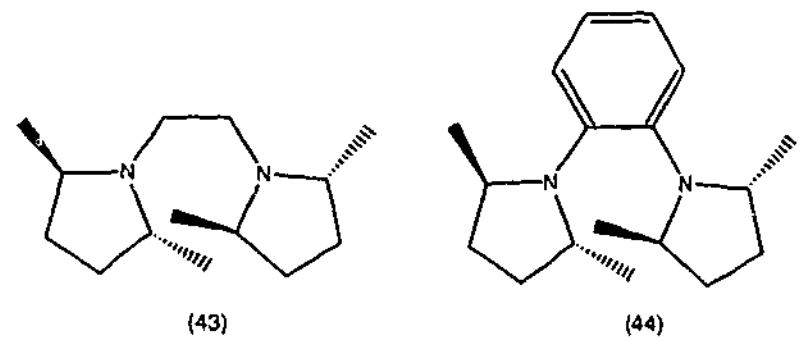
This approach involves the selection of a suitable solid polymer support and a linker, which binds to the substrate molecule. Use of these conditions lead to site isolation, effectively providing high dilution conditions.[83] Other benefits of doing a reaction on solid support include the separation of the intermediates from soluble reagents and solvents by simple filtration, consequently saving time and labour compared to solution phase synthesis. The excess reagents can be employed to help drive the reaction to completion and these reagents can be recovered and reused. In addition, the physical loss of the compound being synthesised is minimised as it remains attached to the solid support.

1.4 Aims of project

Part A

1.4.1 Preparation and applications of (2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl ligands ((43) and (44))

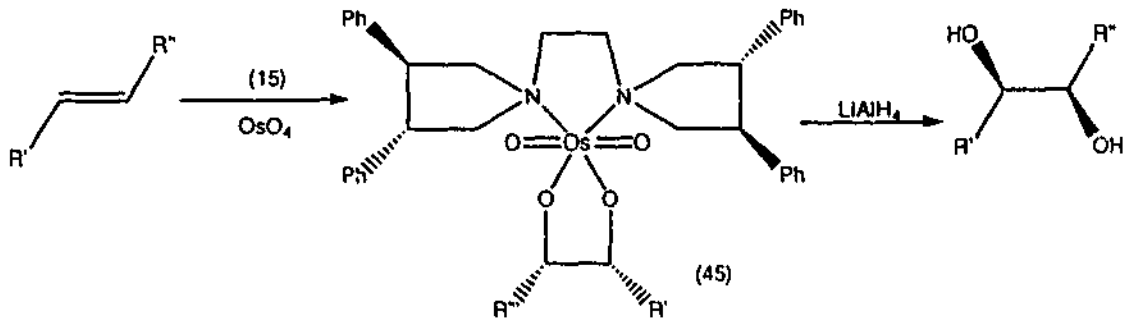
This project aims to synthesise 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethane (43) and 1,2-bis ((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (44) (Figure 1.9) and their analogues for use as ligands in asymmetric dihydroxylation reactions. The above mentioned ligands will also be evaluated as catalysts in other asymmetric reactions.



(43) (44)

Figure 1.9: (2*R*,5*R*)-2,5-Dimethylpyrrolidin-1-yl ligands ((43) and (44))[84]

These ligands (43) and (44) are very similar to the ligand (15) synthesised by Tomioka *et al.*.[85] Dihydroxylation of a variety of alkenes using osmium tetroxide with ligand (15) takes place in good yield and in excellent enantioselectivity (83-99% ee) (Scheme 1.21).[86] Osmium tetroxide is complexed to the chiral ligand which dictates facial diastereoselectivity when the osmium glycolate (45) is formed.[87-89] Cleaving the osmium glycolate (45) using $LiAlH_4$ releases the chiral diol in excellent yield and high enantioselectivity (Scheme 1.21).[86]



Scheme 1.21

1,2-Bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethane (43) is reported in the literature and used in the asymmetric palladium catalysed alkylations.[90] The ligands are also related to a class of chiral C_2-symmetric 2,5-disubstituted bis-(phospholano) ligands developed by Burk *et al.* and used in asymmetric hydrogenation reactions.[84] Both ethane bridged bis-(phospholano) analogue (BPE) (46), as well as the 1,2-bis-(phospholano)benzene analogue (DuPHOS) (47) (Figure 1.10), when incorporated into a rhodium complex result in the reduction of substituted alkenes in high yield and excellent enantioselectivity.

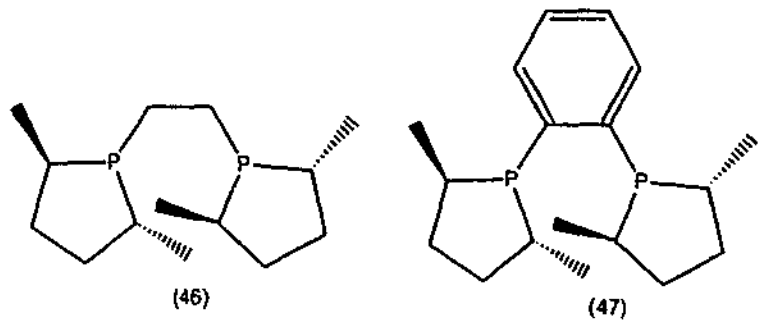
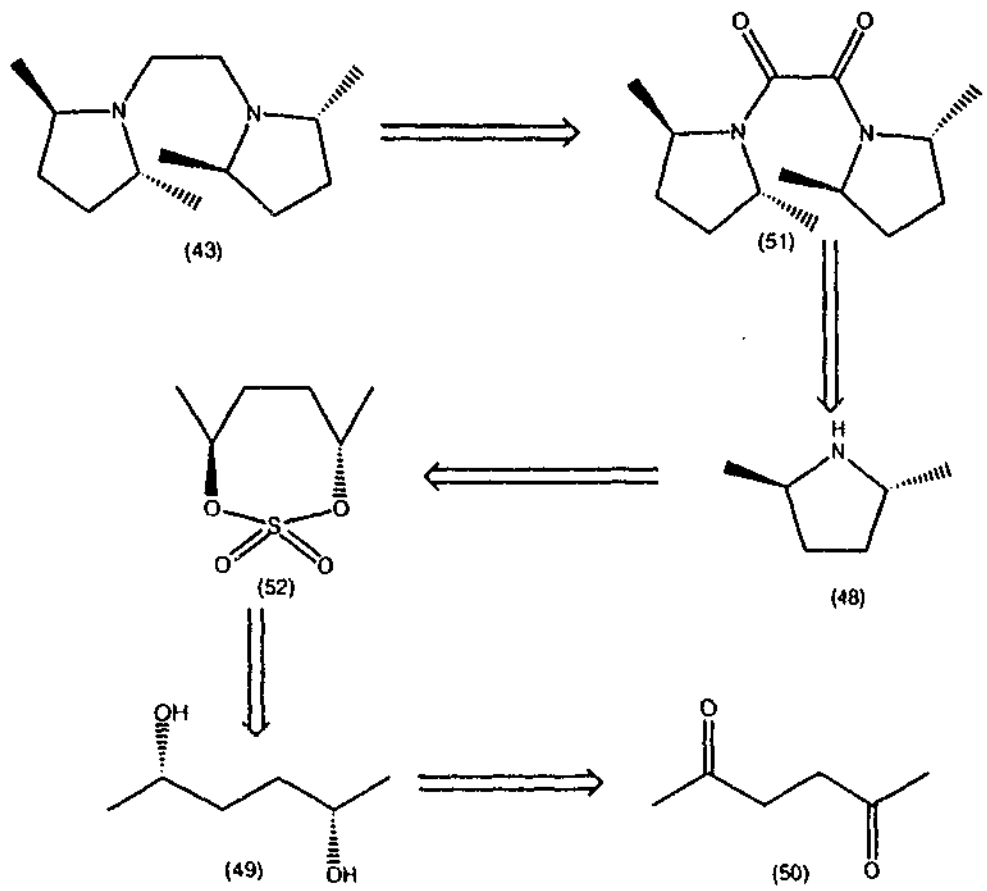


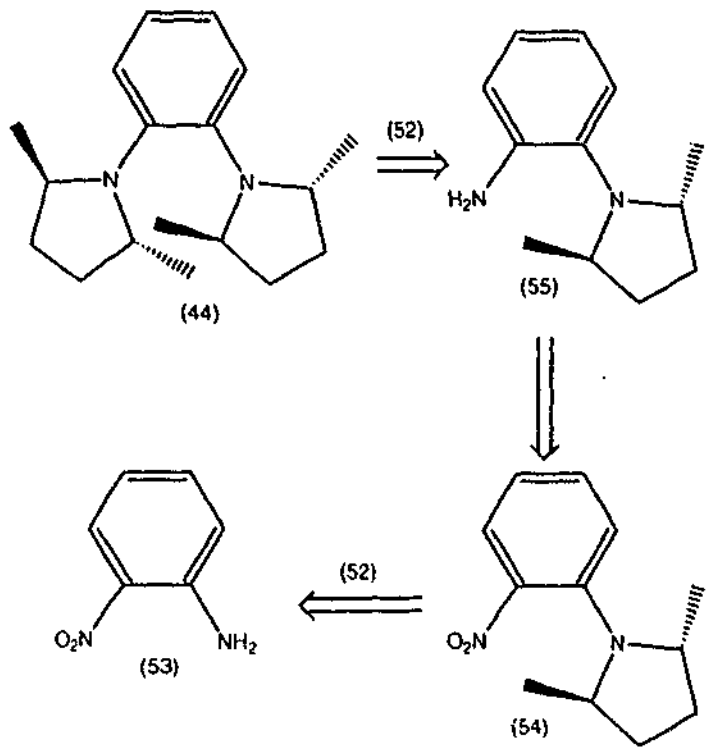
Figure 1.10: Bis-(phospholano) ligands ((46) and (47)) synthesised by Burk *et al.*[84]

The proposed reaction scheme (Scheme 1.22) consists of a coupling reaction between (2*R*,5*R*)-2,5-dimethylpyrrolidine (48) and oxalyl chloride followed by a reduction to produce the desired diamine (43). The chiral pyrrolidine (48) can be syntl esised from (2*S*,5*S*)-2,5-hexanediol (49) which can be obtained *via* a yeast reduction of 2,5-hexanedione (50).



Scheme 1.22

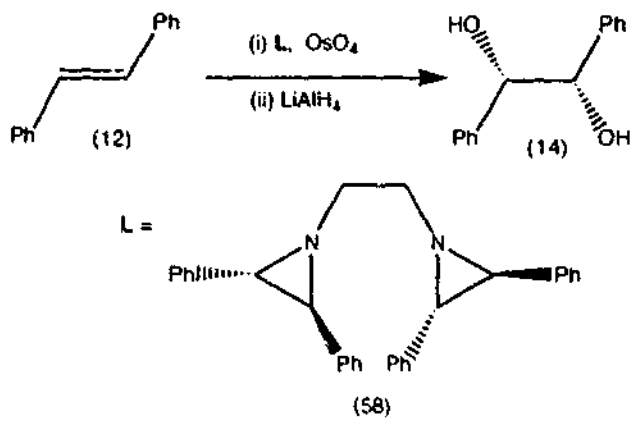
The cyclic sulfate (52) will also be reacted with *o*-nitroaniline (53) to give the nitro pyrrolidine product (54) (Scheme 1.23). Reduction of the nitro group (54) followed by a second coupling of the resulting amine (55) with cyclic sulfate (52) should provide the desired ligand (44) (Scheme 1.23).



Scheme 1.23

1.4.2 Proposed synthesis of (2*S*,3*S*)-2,3-dimethylaziridin-1-yl ligands ((56) and (57))

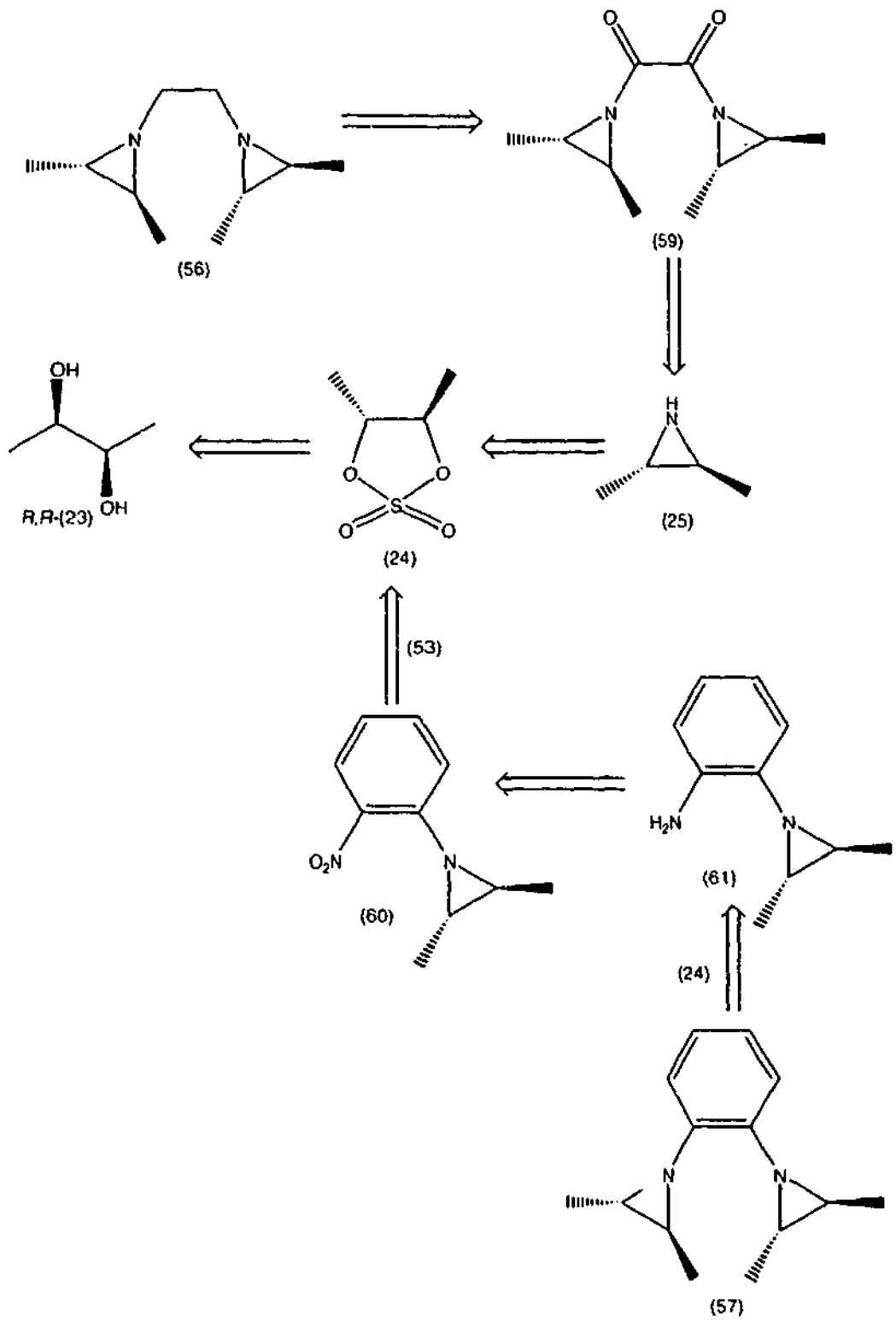
The bis-aziridine ligand (58) has been reported to be an excellent ligand for the osmium teroxide dihydroxylation of stilbene (12). The dihydroxylation reaction takes place in an excellent yield (90%) and enantioselectivity (95% ee) (Scheme 1.24).[91]



Scheme 1.24[91]

The corresponding methyl substituted derivatives (56) and (57) are not known and it was of interest to compare their efficiency with that of the pyrrolidine ligands (43)

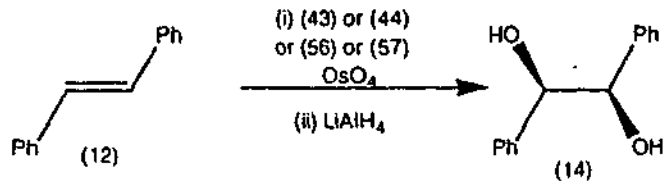
and (44). Synthesis of the methyl derivatives (56) and (57) were based on the same methodology described for the pyrrolidine ligands (43) and (44) (Scheme 1.25). The (2*R*,3*R*)-diol (23) can be obtained by a yeast reduction.



Scheme 1.25

1.4.3 Asymmetric synthesis

The chiral pyrrolidine ligands ((43) and (44)) and aziridine ligands ((56) and (57)) will firstly be examined in the asymmetric dihydroxylaton of stilbene (12) with OsO_4 under conditions described by Tomioka *et al.* (Scheme 1.26).[86]



Scheme 1.26

Some of these ligands will also be used in other asymmetric syntheses such as biaryl coupling reactions, palladium catalysed alkylation reactions, Grignard reactions and hydroformylation reactions.

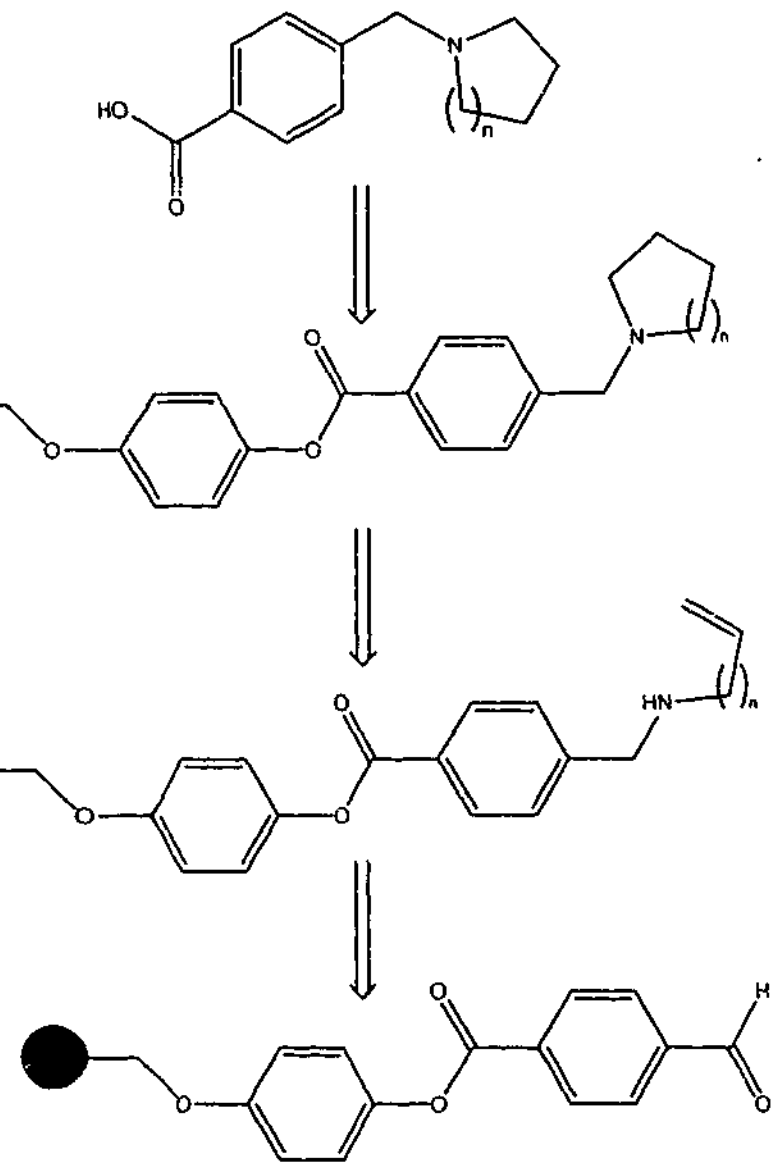
Part B

1.4.4 Preparation of nitrogen heterocycles by rhodium catalysed hydroformylation of polymer-attached amino alkenes

The preparation of nitrogen heterocycles, with ring sizes ranging from small to large (5, 8, 10 and 13), *via* an intramolecular hydroaminomethylation sequence was investigated. The synthesis of these nitrogen heterocycles was difficult in solution due to competing polymerisation reactions.[77] It was postulated that by performing the reactions on a solid support should favour intramolecular cyclisation and minimise intermolecular reations.

In this part of the project, Wang (4-(hydroxymethyl)phenoxymethyl polystyrene) resin was used to tether a starting aminoalkene (Scheme 1.27). This alkene was hydroformylated using a Rh-catalysed reaction with H_2/CO (syn gas). Ring formation

is then achieved *via* an intramolecular attack of the nucleophilic amino group on the initially formed aldehyde. Reduction of the resulting imine should give the desired heterocycle which can then be cleaved from the resin (Scheme 1.27).



Scheme 1.27

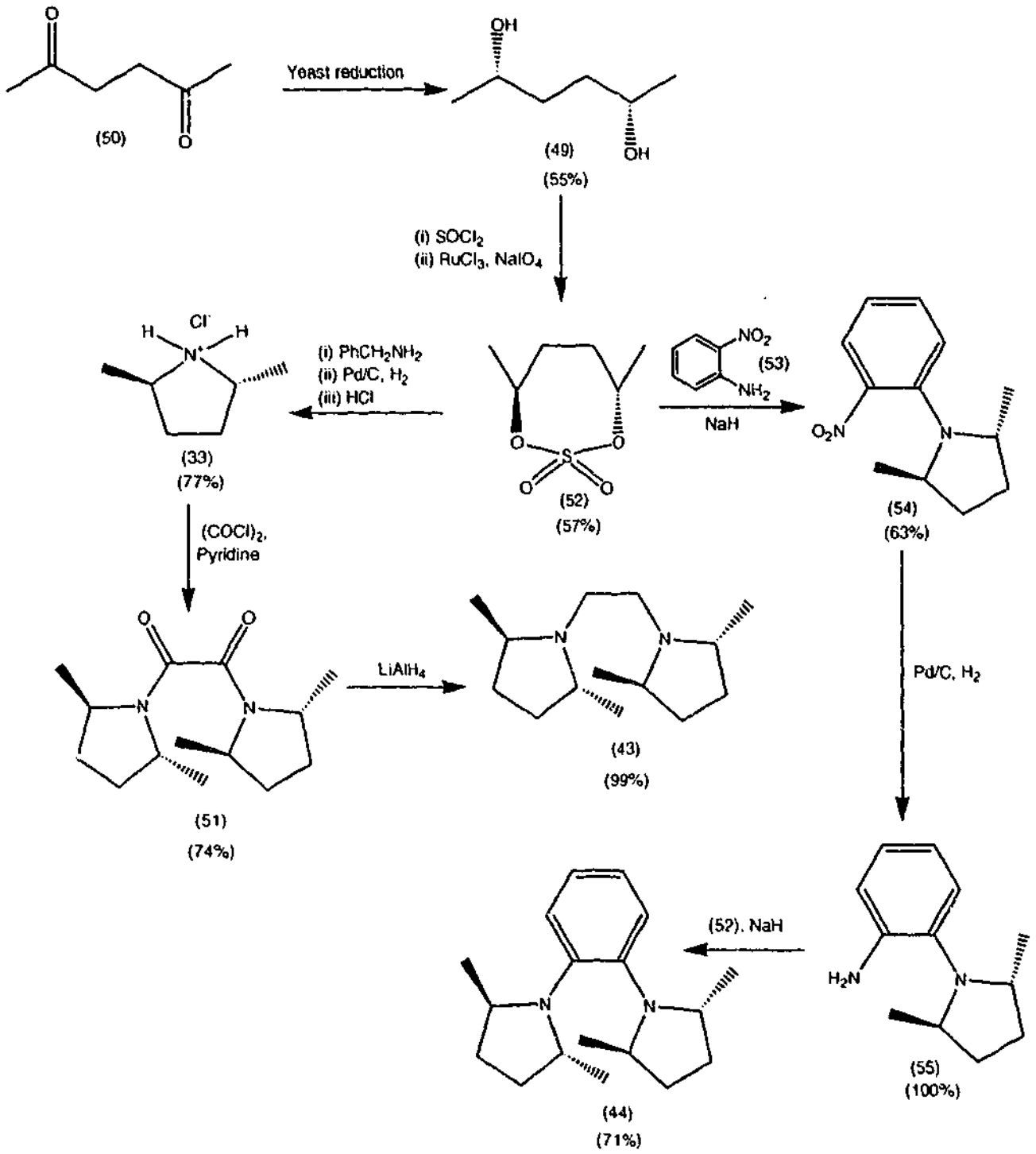
PART A

Chapter 2

Synthesis of (2R,5R)-2,5-Dimethylpyrrolidine Based Ligands

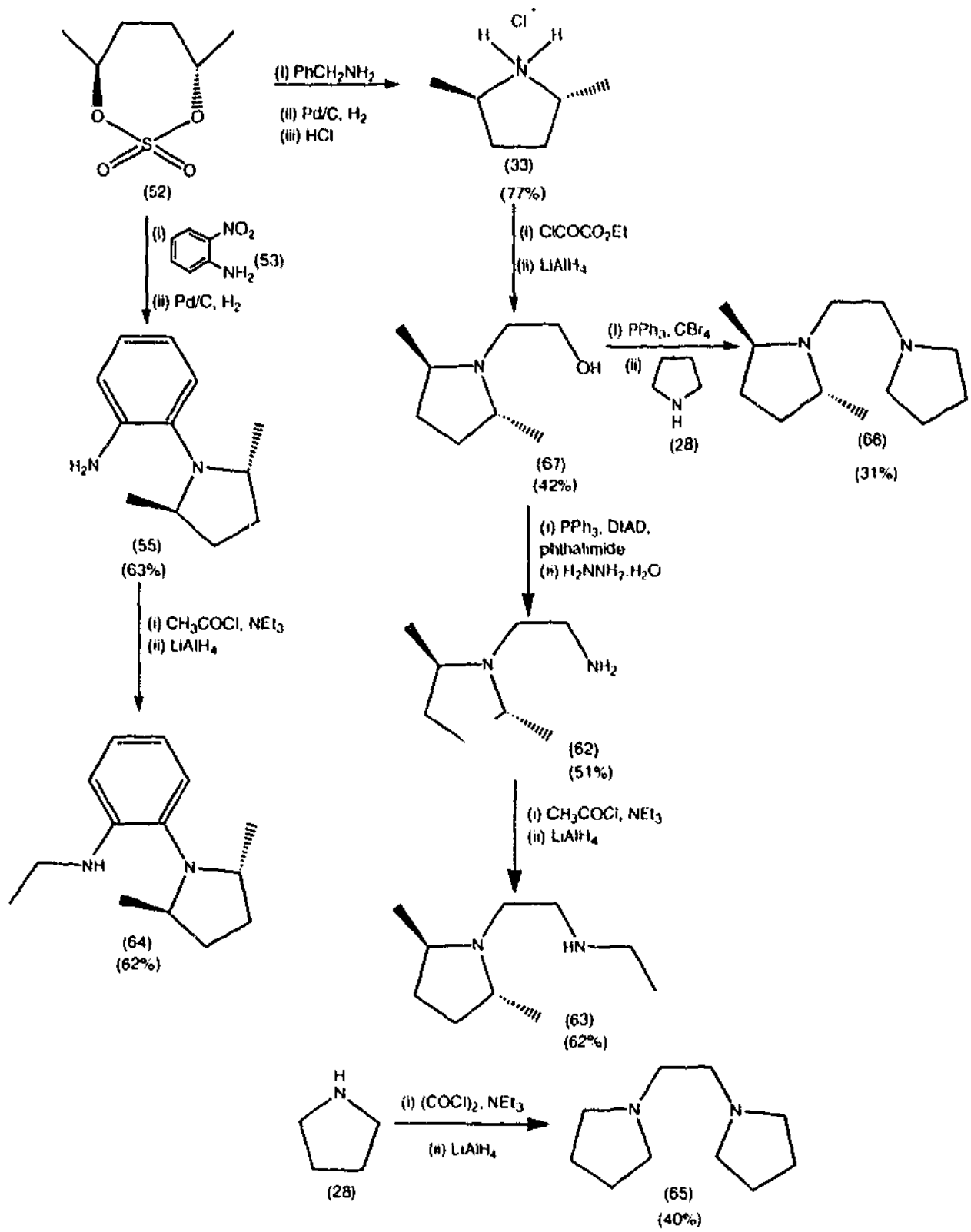
2.1 General summary of Chapter 2

The key building block for the synthesis of chiral dimethylpyrrolidine ligands (43) and (44) was (2*S*,5*S*)-2,5-hexanediol (49), which was prepared by a yeast reduction of 2,5-hexanedione (50). In order to synthesise 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethane (43), the activated diol (52) was converted to the (2*R*,5*R*)-2,5-dimethylpyrrolidine hydrochloride salt (33) and coupled with oxalyl chloride. The resulting compound (51) was reduced with $LiAlH_4$ to give the required chiral diamine (43) in good yield (Scheme 2.1). The synthesis of 1,2-bis-(2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (44) was achieved *via* the coupling of the activated diol (52) with *o*-nitroaniline (53). Subsequent reduction of the nitro group followed by a second coupling with the activated diol (52) afforded the desired chiral diamine (44) (Scheme 2.1).



Scheme 2.1

Of the six modified diamine ligands synthesised in this thesis, five were unsymmetrical and possessed only one (2*R*,5*R*)-2,5-dimethylpyrrolidine moiety. The second binding nitrogen was present as a primary ((55) and (62)), a secondary ((63) and (64)) or a tertiary ((65) and (66)) amine (Scheme 2.2). The diamine ligand (65) was a homologue of the chiral ethane bridged ligand (43). This ligand (65) was symmetrical but lacked chirality.



Scheme 2.2

2.2 Yeast reductions of the diketone (50)

Bakers' yeast (*Saccharomyces cerevisae*) has been extensively used in the synthesis of chiral compounds.[92] The attraction of Bakers' yeast is that it is cheap (250 g = A$

4.50), readily available (local supermarket) and reaction procedures are generally very simple.[93]

Bakers' yeast has been used extensively for the reduction of carbonyl groups.[94] In this study, (2*S*,5*S*)-2,5-hexanediol (49) was prepared by the reduction of 2,5-hexanedione (50) following a method described by Lieser *et al.*.[95] The reduction of the diketone (50) is a fermentation reaction utilising the alcohol dehydrogenase enzymes in yeast.[92] The sugar included in the reaction media helps the reduction in two ways. Firstly, sucrose is permeable through the yeast cell walls.[96] Therefore, once the sucrose is in the yeast cytosol, the yeast enzyme α-glycosidase breaks the sucrose down to its constituent monosaccarides, D-glucose and D-fructose.[96] The yeast survives and multiplies converting these simple sugars to carbon dioxide and ethanol, or water depending on the availability of oxygen. Secondly, glycolysis helps recycle the nicotinamide co-factors ($NADP^+$/NADPH) used in the reduction of the diketone (Figure 2.1).[92]

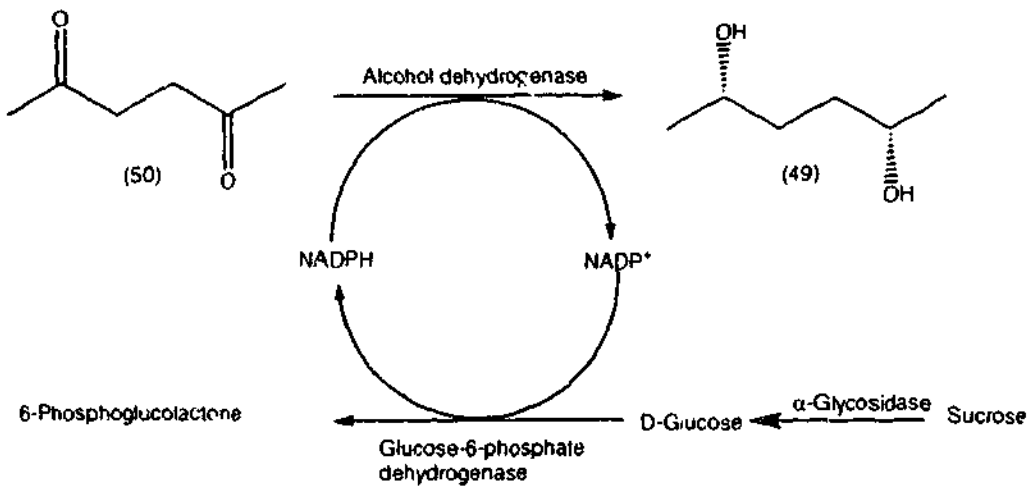


Figure 2.1: Reduction of the diketone (50) coupled with co-factor-recycling[92]

The yeast reduction of the hexanedione (50) was carried out under two different conditions as summarised in Table 2.1. Under fermentation conditions, using sugar

and water, the (2*S*,5*S*)-2,5-hexanediol (49) was isolated in a 46% yield with an enantioselectivity of >99% for the (2*S*,5*S*)-diol (49). The ^{1}H n.m.r. spectrum of the crude reaction mixture also showed the presence of (2*R*,3*R*)-butanediol (23) (~10%). This diol (23) was produced with an enantioselectivity of 89% and a diastereoselecti f 100%.

Yeast reduction of hexanedione (50) carried out under non-fermentation conditions, where no sugar was used, showed similar results to those observed by Lieser *et al*..[95] The yield was comparable (~50%) with that of the fermentation reaction and the high enantioselectivity (>99% ee) was also maintained. The reaction time, however, was considerably shorter *via* this method (27 h *vs* 7 days). The 'frothing' observed in fermentation reactions was avoided with the non-fermentation conditions and the products were much more readily isolated without the need for slow filtrations and continuous extractions of broths. In addition, production of 2,3-butanediol (23), obtained as an impurity from the fermentation reaction, was avoided. Further discussion about the 2,3-butanediol (23) formation in these fermentation reactions is presented in Chapter 5.

Table 2.1: Yeast reduction of 2,5-hexanedione (50)

Condition	**Under Fermentation conditions**	**Under Non-fermentation Conditions**
Reaction time	7 days	27 h
Main diol isolated	(2*S*,5*S*)-hexanediol (49)	(2*S*,5*S*)-hexanediol (49)
Isolated yield of (2*S*,5*S*)-hexanediol (49)	46%	55%
% ee of (2*S*,5*S*)-hexanediol (49)	>99%	>99%
By-products isolated	(2*R*,3*R*)-butanediol (23) (89% ee)	None

Without the presence of sugar in the reaction mixture (under non-fermentation conditions) it is unclear how the co-factors are recycled. The excess of yeast used may possibly eliminate the need to regenerate the yeast co-enzymes. The reduction of the hexanedione (50) proceeds to give exclusively (2*S*,5*S*)-2,5-hexanediol (49) following the 'Prelog rule'.[97] This rule basically says that during the course of the reaction the enzyme attacks the substrate from the less sterically hindered side as shown in Figure 2.2.

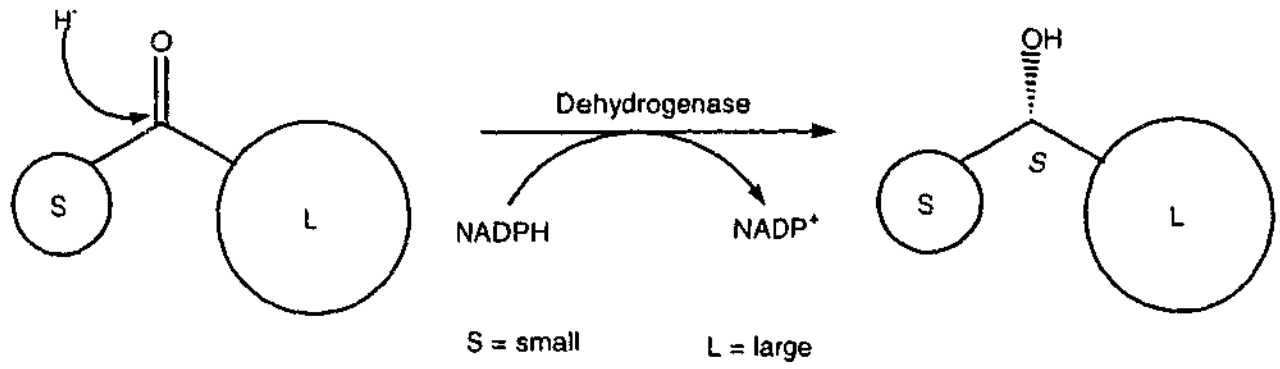
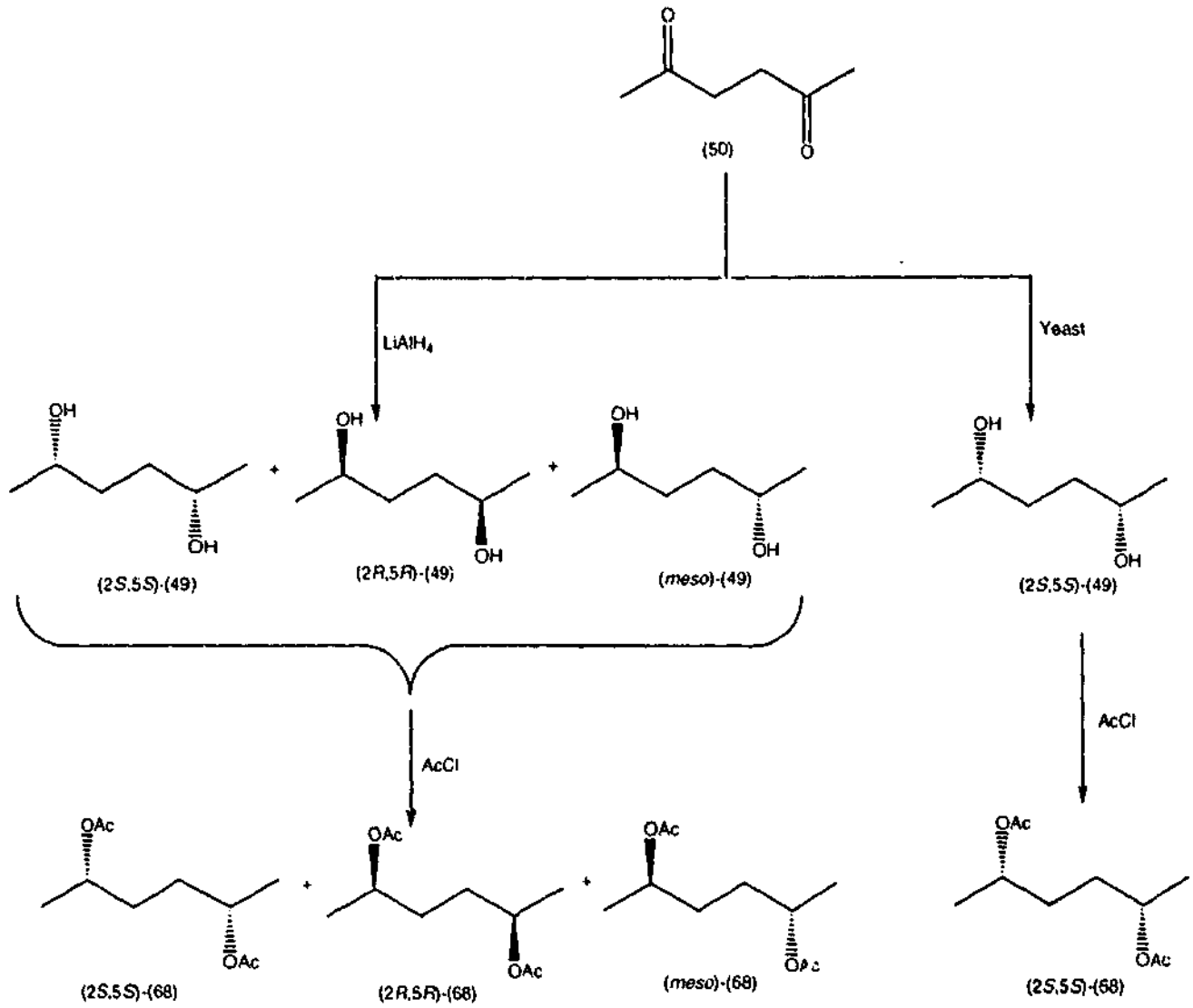


Figure 2.2. Prelog rule for asymmetric reduction of ketones

As the hexanediol (49) could not be resolved using a range of chiral GC columns it was converted to the corresponding diacetate (68) using acetyl chloride (Scheme 2.3). A sample containing all three isomers of hexanediol (49) was obtained by reduction of hexanedione (50) using $LiAlH_4$ (Scheme 2.3). The *meso*-hexanediol (49) showed similar ^1H n.m.r. and ^{13}C n.m.r. spectroscopy shifts to those of the racemic diol (49). This sample was also converted to the diacetate (68) using the same conditions used for (2*S*,5*S*)-hexanediol (49). Again there was no significant difference in the ^1H n.m.r. and ^{13}C n.m.r. spectra between the *meso*-(68) and the racemic compounds (68). Chiral GC, using the Chirasil-Dex CB column resolved the sample of the three diacetate stereoisomers (68) and displayed the expected peak area ratio of 1:2:1 for (2*S*,5*S*)-(68), (*meso*)-(68) and (2*R*,5*R*)-(68) respectively. Chiral GC of the (2*S*,5*S*)-diacetate

(68) obtained from the yeast reduction gave a single peak and none of the enantiomeric (2*R*,5*R*)- species could be detected.

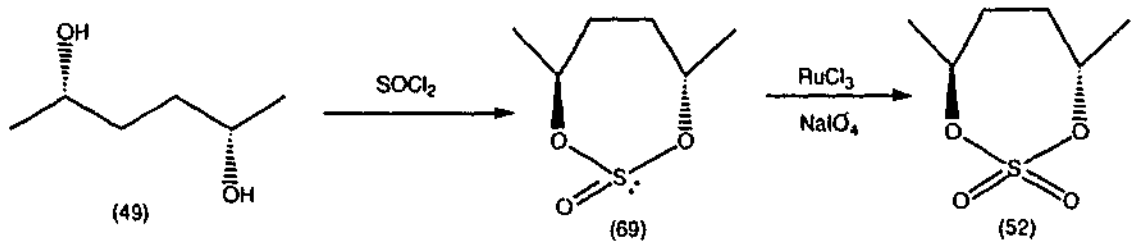


Scheme 2.3

2.3 Preparation of the activated hexanediol (52)

The (2*S*,5*S*)-2,5-hexanediol (49) was activated to nucleophilic attack by conversion to its cyclic sulfate (52) following the methods described by Caron and Kazlauskas[98] and Burk *et al*..[99] The diol (49) was first reacted with thionyl chloride to form the cyclic sulfite (69) which was isolated as a brown oil in good yield (Scheme 2.4). The appearance of two multiplets in the ^{1}H n.m.r spectrum at δ 4.33 and 5.16, corresponding to H2 and H5, is characteristic of the cyclic sulfite (69) due to its

unsymmetrical nature. This observation was consistent with the ^{13}C n.m.r. spectrum which showed two signals at δ 70.0 and 75.1 for C2 and C5.



Scheme 2.4

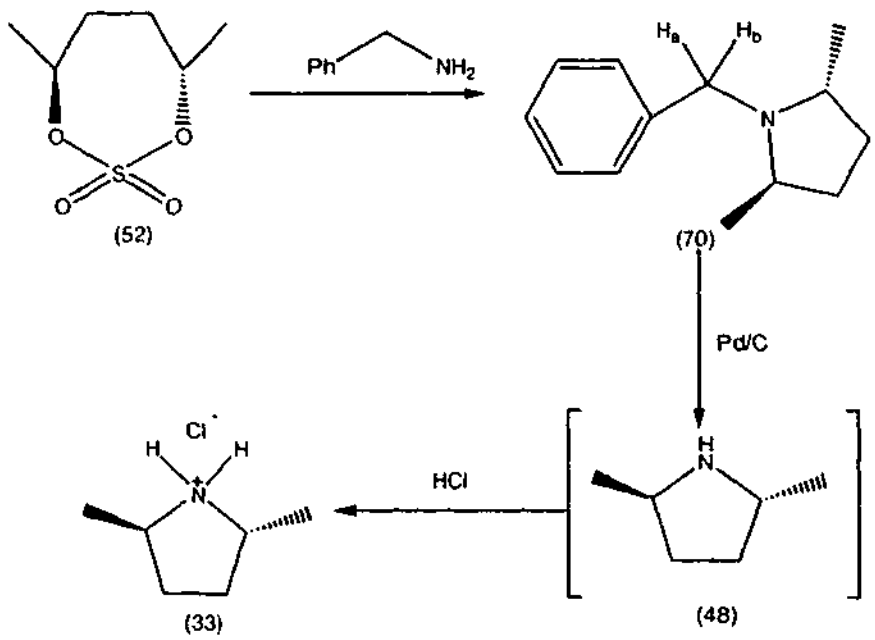
Oxidation of the cyclic sulfite (69) following a method described by Burk *et al.*[84] using ruthenium(III) chloride and sodium periodate, produced the cyclic sulfate (52) in reasonable yield (57%). This is a very colourful reaction in which the colour changes from green to red to light yellow and finally black during the workup. The formation of the cyclic sulfate (52) was verified by the appearance of the sulfate group in the infrared spectrum at stretching frequencies of 1376 and 1190 cm^{-1}. In addition, only one multiplet was observed for the H2 and H5 protons in the ^1H n.m.r. spectrum at δ 4.82 consistent with a symmetrical structure. The melting point and the optical rotation for this compound were also consistent with the literature.[99]

2.4 Preparation of (2*R*,5*R*)-dimethylpyrrolidine hydrochloride (33)

N-Benzyl dimethylpyrrolidine (70) was synthesised by reacting the cyclic sulfate (52) with neat benzylamine for 96 h following a modified method described by Short *et al.* (Scheme 2.5).[100] Excess benzylamine was removed from the crude product using dichloromethane after making the reaction mixture basic with sodium hydroxide. The product mixture was then continuously extracted into dichloromethane. The tertiary

amine (70) was found to give characteristic splitting (δ 3.51 (dd) and 3.84 (dd)) in the ^{1}H n.m.r. spectrum due to the diastereotopic benzylic protons H_a and H_b.

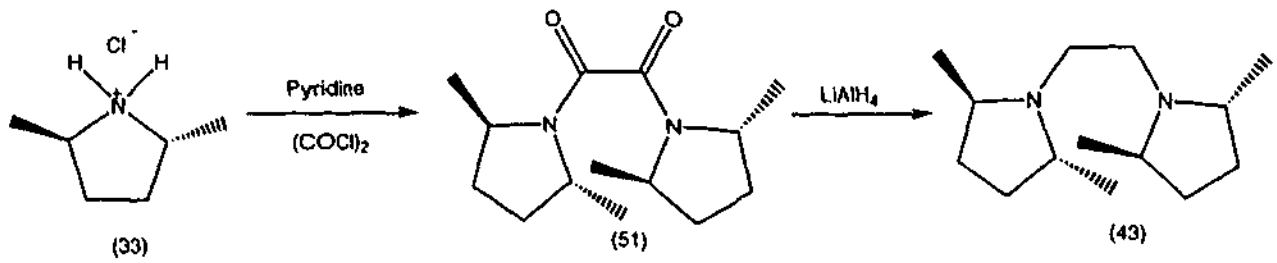
Hydrogenolysis of the benzyl pyrrolidine (70) over Pd/C gave (2*R*,5*R*)-2,5-dimethylpyrrolidine (48) which was immediately converted into its hydrochloride salt (33) in order to eliminate difficulties associated with handling the low boiling free amine (48) (Scheme 2.5).



Scheme 2.5

2.5 Preparation of 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethane (43)

The chiral pyrrolidine hydrochloride (33) was stirred with an excess of pyridine before being reacted with oxalyl chloride (Scheme 2.6). The pyridine acts as a base, not only neutralizing the chiral pyrrolidine salt (33) but also quenching the hydrochloric acid formed during the reaction.



Scheme 2.6

The amide (51) was isolated in 74% yield. The strong carbonyl stretching observed in the infrared spectrum at 1629 cm^{-1} is characteristic of the diamide (51) (Scheme 2.6). When the reaction was carried out for shorter periods (18 h), mono-substituted amide (71) was isolated. The synthesis of this amide (71) will be discussed in greater detail in Section 2.7.1.

Synthesis of the target chiral diamine (43) was achieved by reduction of the diamide (51) using $LiAlH_4$ under reflux in THF. The final diamine (43) had an optical purity of 99% for the (-)-enantiomer which was determined through comparison of experimental ($[\alpha]_D^{25}$ −181.1°) and literature ($[\alpha]_D^{25}$ −183°)[90] optical rotation values. This percentage value for optical purity was consistent with the optical purity observed for the chiral 2,5-hexanediol (49) used as the initial starting material for the preparation of the diamine (43). The ^1H n.m.r. and the ^{13}C n.m.r spectra of the chiral diamine (43) were consistent with those reported by Nakajima *et al.*.[90]

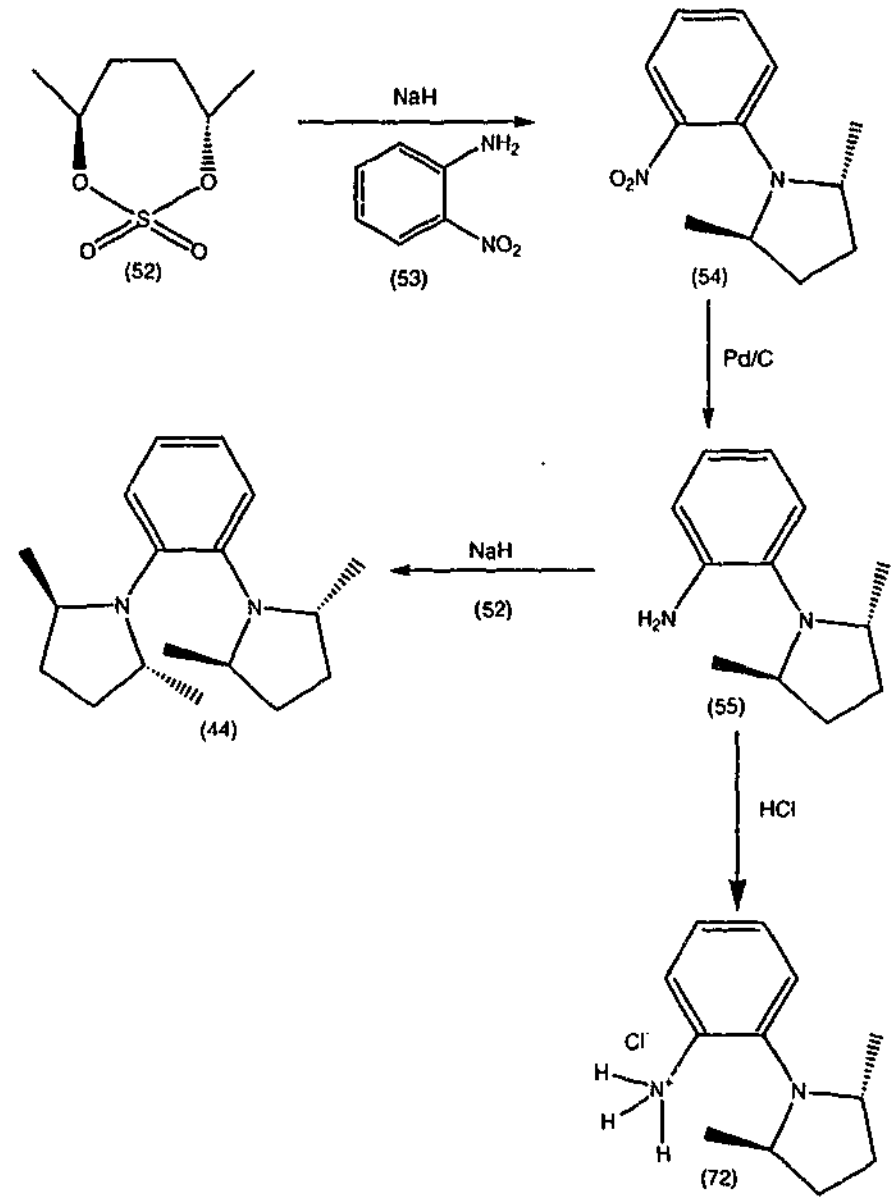
2.6 Preparation of 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (44)

The cyclic sulfate (52) synthesised above (see Section 2.3) was reacted with *o*-nitroaniline (53) in the presence of sodium hydride (Scheme 2.7). No reaction was observed when the sodium hydride was omitted. The reaction was carried out using a

modified method described by Cahill *et al.*.[101] The *o*-nitroaniline (53) was refluxed for two days with the cylic sulfate (52). The literature reports formation of a precipitate in the reaction mixture [101] but this was not observed in the present work. The reaction mixture became a deep orange/black colour and, addition of sodium hydride formed a deep red solution. The highly coloured nitrophenyl pyrrolidine (54) was isolated in 63% yield.

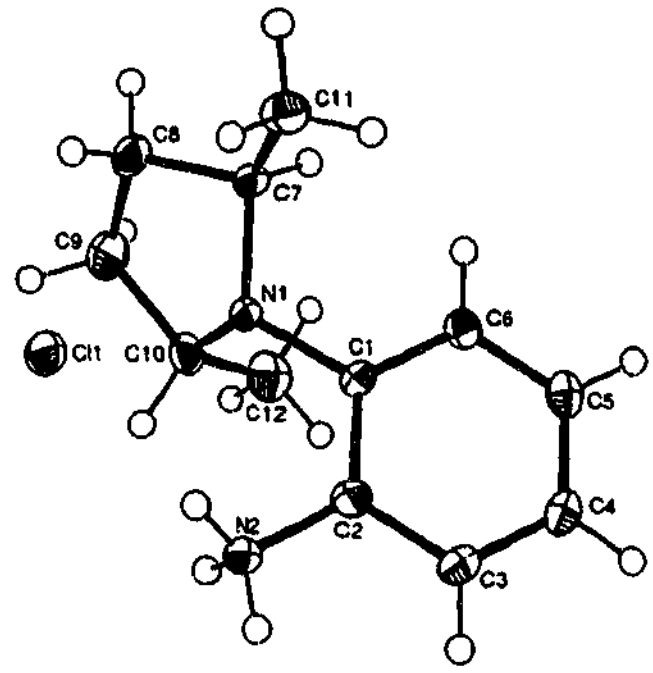
The accurate mass spectrum showed a $[M+Na]^+$ signal at 243.1101, confirming the presence of nitrophenyl pyrrolidine (54). The ^1H n.m.r. spectrum was largely inconclusive and showed some broad signals in the aliphatic region. This is probably due to the anisotrophy effect exerted by the nitrogens.[102] Pd/C has been used to successfully hydrogenate aromatic nitro compounds.[103] Using this methodology the nitrophenyl pyrrolidine (54) was readily hydrogenated to give the aminophenyl pyrrolidine (55) in excellent yield (100%). The IR spectrum showed a strong broad peak at 3433 cm^{-1} corresponding to the primary amine (55). A crystal structure of the hydrochloride salt (72) of this molecule was obtained (Figure 2.3a).[104]

The amino pyrrolidine (55) was coupled with a second molecule of cyclic sulfate (52) in the presence of sodium hydride to give the target chiral ligand (44) in good yield (71%) (Scheme 2.7). The ^1H n.m.r. spectrum showed a singlet at δ 6.84 for the equivalent aromatic protons. A crystal structure of this ligand (44) was also obtained (Figure 2.3b).[105] The crystal structure further confirmed the predicted (2*R*,5*R*)-stereochemistry of this ligand (44).



Scheme 2.7

(a)



(b)

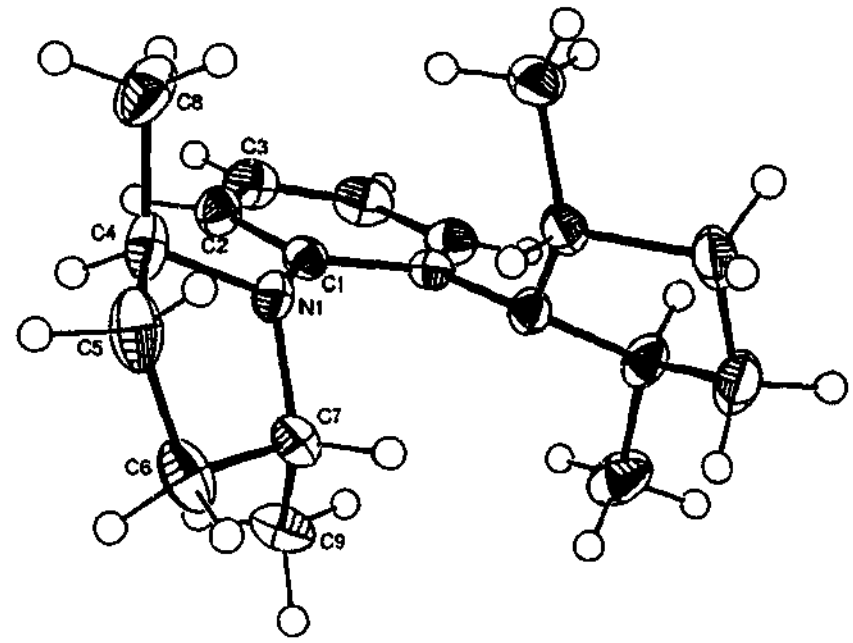


Figure 2.3: (a) ORTEP diagram of 1-amino-2-[(2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl]benzene hydrochloride salt (72);[104] (b) ORTEP diagram of 1,2-bis[(2*R*,5*R*)-2,5-dimethyl[pyrrolidin-1-yl]benzene (44)[105]

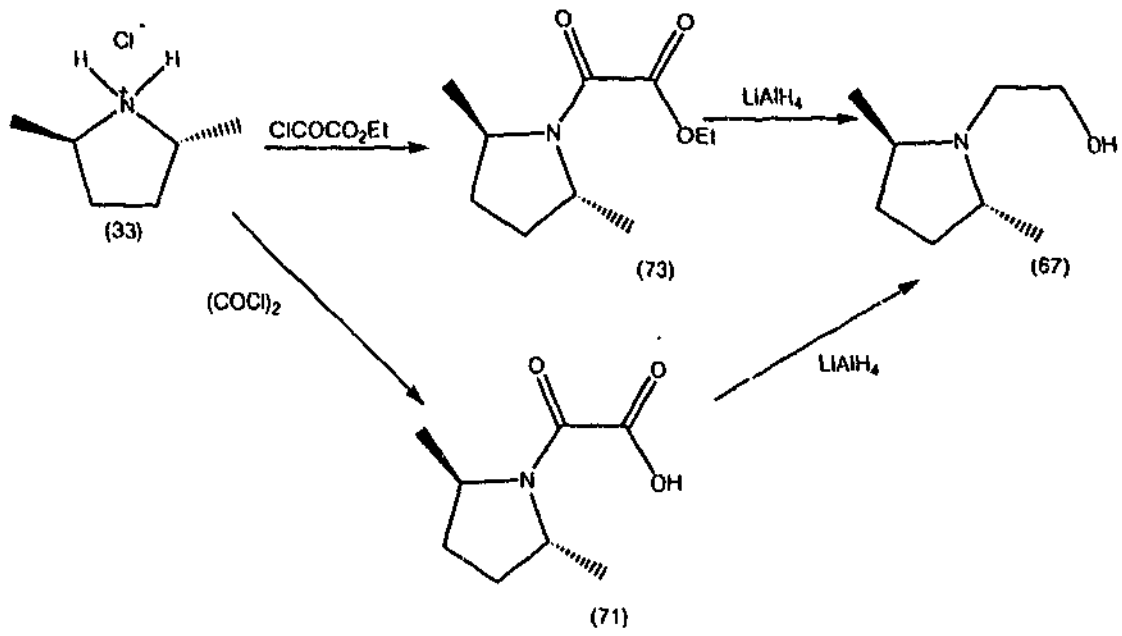
2.7 Preparation of modified pyrrolidine ligands

Less hindered analogues of the diamine ligands (43) and (44) were prepared as described in Scheme 2.2.

2.7.1 Preparation of chiral primary amine ligands

The mixed ligands of interest consisted of the chiral (2*R*,5*R*)-2,5-dimethylpyrrolidine moiety together with a second nitrogen as a primary amine. The ligands prepared were the 1-amino-2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene ligand (55) (see previous Section 2.6) which is the precursor of the dimethylpyrrolidne ligand (44) and 2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethylamine (62).

The precursor for the amine ligand (62) was the corresponding alcohol, 2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethanol (67). The synthesis of the alcohol (67) was carried out using two methods as described in Scheme 2.8. The first method involved the reaction of the pyrrolidine hydrochloride salt (33) with ethyl oxalyl chloride to give the amido ester, (2*R*,5*R*)-ethyl-2-(2,5-dimethylpyrrolidin-1-yl)-2-oxoethanoate (73). The formation of this molecule was confirmed by ^{1}H n.m.r. and ^{13}C n.m.r. spectroscopy. The I.R spectrum showed strong stretching bands at 1738 and 1650 cm^{-1} characteristic for the ester (73) and the amide carbonyl groups respectively. Reduction of this molecule using lithium aluminium hydride gave the desired alcohol (67).



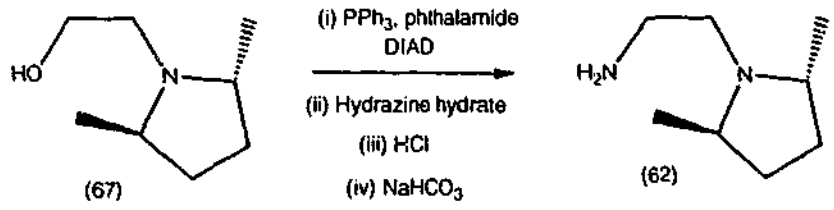
Scheme 2.8

The second method involved a reaction between the pyrrolidine hydrochloride salt (33) and oxalyl chloride (Scheme 2.8). Leaving the reaction for a short reaction time (18 h) with 2 equivalents of pyridine only one pyrrolidine coupled to the oxalyl chloride, in contrast to the reaction for a longer time (2 days) with more pyridine (see Scheme 2.6). After the aqueous work up, the corresponding acid (71) was isolated (see Section 2.6). This molecule was fully characterised using ^{1}H n.m.r. and ^{13}C n.m.r. spectrospcopy. The mass spectrum showed a molecular ion plus hydrogen signal at *m/z* 172.0, confirming the presence of the acid (71). Again, the reduction of the acid (71) using $LiAlH_4$ gave the desired alcohol (67).

Reduction of both the acid (71) and the ester (73) gave the alcohol (67) in modest yields 52% and 38% respectively. This is possibly because the alcohol (67) is hydrophilic and gets trapped in the precipitate formed by the addition of sodium sulfate decahydrate ($Na_2SO_4.10H_2O$). Of the two methods used, the first gave the better yield and control of the products isolated as only one pyrrolidine can react with

ethyl oxalyl chloride. Therefore, the method described first was generally used in the synthesis of the amine ligand (62).

In order to synthesise the amine ligand (62) (Scheme 2.9), the alcohol (67) was reacted with phthalimide under Mitsunobu conditions.[106,107] The pthalimide was immediately converted to the amine using hydrazine hydrate and isolated as the hydrochloric acid salt in 96% yield. It was readily converted to the free amine (62) in almost quantitative yield by neutralising with $NaHCO_3$. The free amine (62) was somewhat volatile and therefore needed to be handled with care.

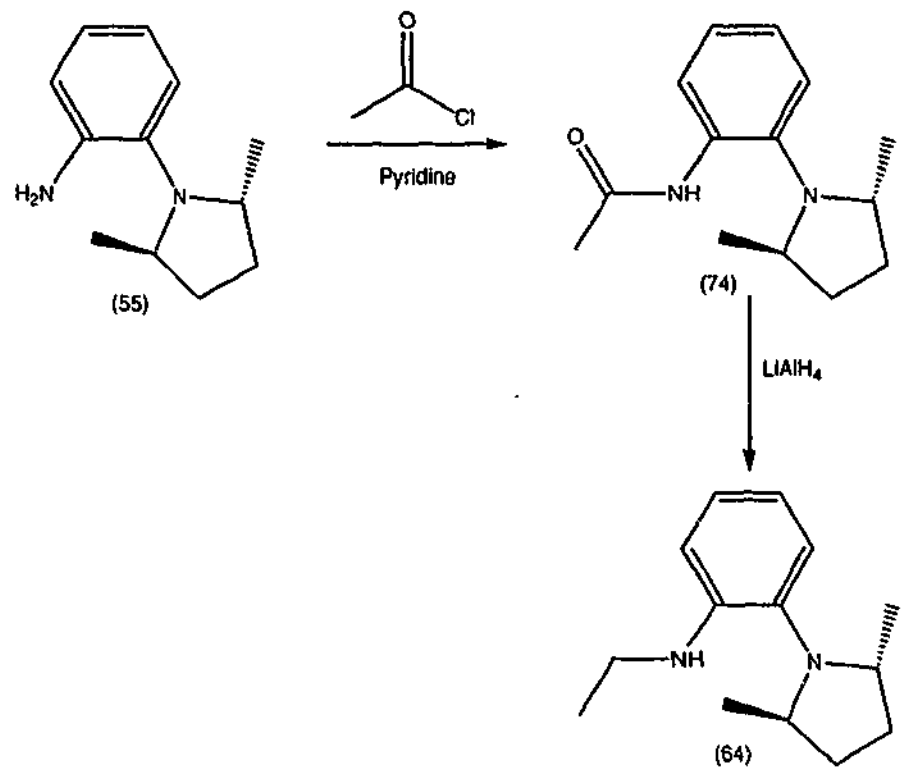


Scheme 2.9

2.7.2 Preparation of secondary amine ligands

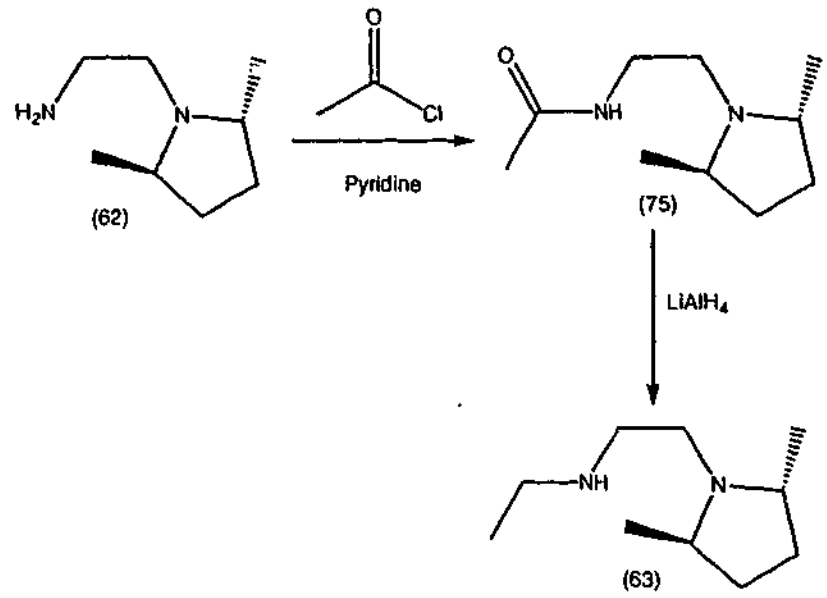
Preparation of mixed ligands (63) and (64) containing one chiral pyrrolidine moiety and a secondary amine was also undertaken. Reaction of 1-amino-2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (55) with acetyl chloride gave the amide (74) (Scheme 2.10) in a reasonable yield (63%). The structure was confirmed by ^{1}H n.m.r. and ^{13}C n.m.r. spectroscopy. Accurate mass spectroscopy gave a $[M+H]^+$ peak at 233.1641 consistent with the calculated value (233.1654).

The amide (74) was reduced with $LiAlH_4$ to give the secondary amine (64) in excellent yield (98%). A characteristic triplet was observed in the ^{1}H n.m.r. spectrum at δ 1.27 for the methyl protons within the ethyl group.



Scheme 2.10

A similar procedure was used in the acylation of pyrrolidine ethane ligand (63) to give the amide product (75) in 51% yield. The characteristic carbonyl stretch was observed at 1650 cm^{-1} in the infrared spectrum and a carbonyl carbon was present at δ 170.5 in the ^{13}C n.m.r. spectrum. Reduction of the amide (75) using $LiAlH_4$ gave the desired ligand (63) (Scheme 2.11). Again a characteristic triplet for the methyl group was observed at δ 1.12 in the ^{1}H n.m.r. spectrum.

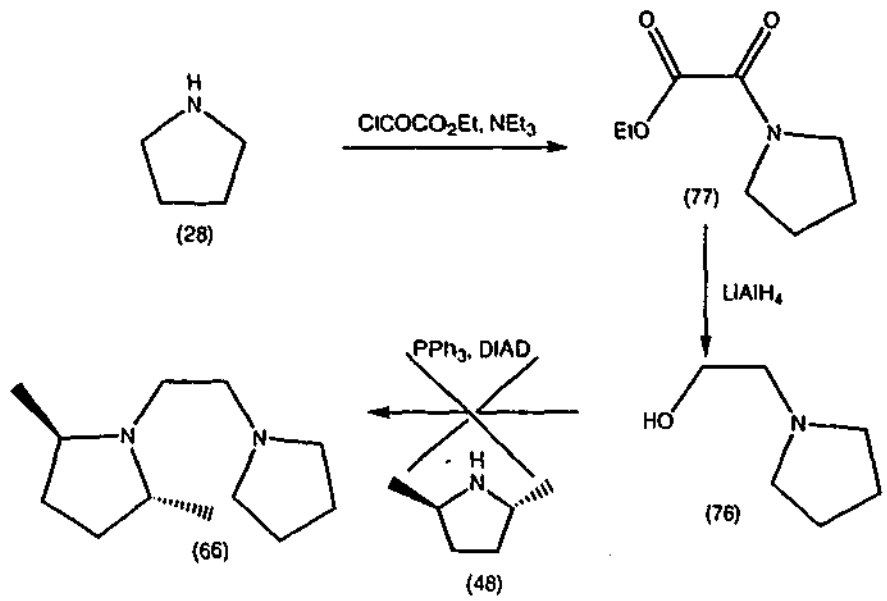


Scheme 2.11

2.7.3 Preparation of modified tertiary amine ligands

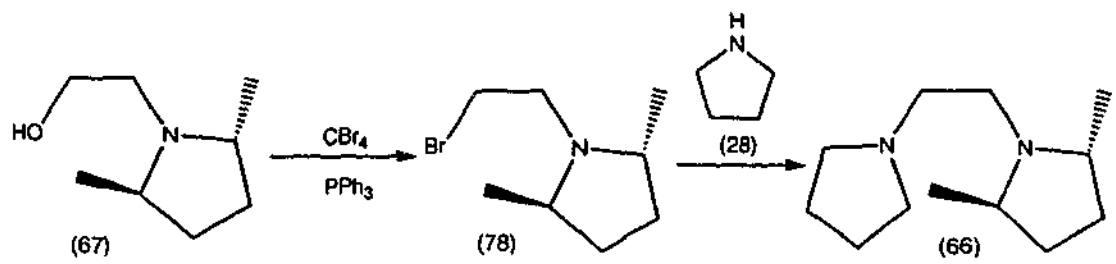
Two diamine ligands of interest fell into this category. The first ligand (66) was an unsymmetrical ligand containing one amine as a chiral dimethylpyrrolidine moiety and the second amine as an unsubstituted pyrrolidine. The second ligand (65) was a symmetrical ligand containing two pyrrolidine units.

Two methods were attempted for the synthesis of the unsymmetrical diamine ligand (66). The first attempted to use a Mitsunobu reaction[106,107] to convert the pyrrolidine alcohol (76) into the desired ligand (66) (Scheme 1.12). This route was undertaken so as to minimise the loss of any chiral material since the addition of the chiral amine (48) to the alcohol (76) would occur in the last step. Unfortunately this reaction failed, probably because the (2*R*,5*R*)-2,5-dimethypyrrolidine (48) was very difficult to obtain as the free amine under anhydrous conditions. The only products isolated at the end of the reaction were triphenylphosphine oxide, reduced DIAD and the alcohol (76). The amine (48) was not isolated as it is very volatile and is lost during the evaporatoration of the solvent.



Scheme 2.12

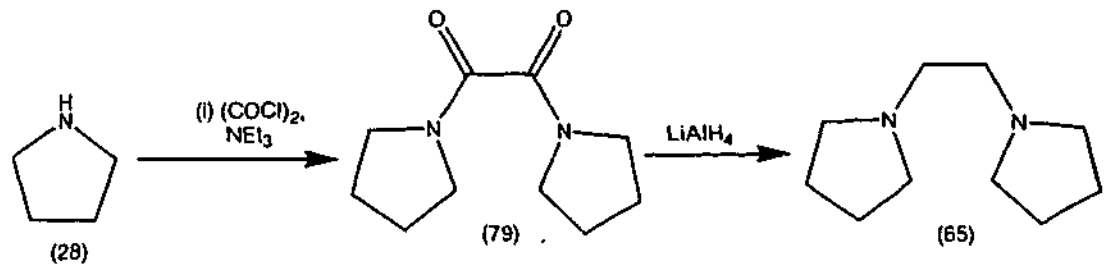
An alternative route involved bromination of the chiral alcohol (67) to give an unstable bromide (78) (Scheme 2.13). The presence of the brominated product (78) was confirmed with ^{1}H n.m.r. spectroscopy and mass spectroscopy. Addition of pyrrolidine (28) to the reaction mixture containing the bromo compound (78) gave the desired ligand (66) (Scheme 2.13) after stirring for 18 h and purification *via* its hydrochloride salt. The ^{1}H n.m.r and ^{13}C n.m.r spectra and mass spectrum confirmed the presence of this ligand (66).



Scheme 2.13

Synthesis of 1,2-di-(pyrrolidin-1-yl)ethane (65) was carried out using the same method that followed for the preparation of 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethane (43) (see also Section 2.5). Commercially available pyrrolidine (28) was used instead of the chiral dimethylpyrrolidine hydrochloride (33) to couple with

oxalyl chloride (Scheme 2.14). Reduction of the dioxo compound (79) provided the desired diamine (65) in a moderate yield (47%). The ^{1}H n.m.r. spectroscopy data was consistent with literature values.[108]



Scheme 2.14

2.8 Conclusion

2,5-Hexanedione (50) was reduced using yeast to give the corresponding diol (49) in moderate yield and in excellent stereoselectivity. The diol (49) was activated as the cyclic sulfate (52) which was then converted to the chiral 2,5-dimethylpyrrolidine salt (33) and coupled with oxalyl chloride. Reduction with $LiAlH_4$ gave the desired diamine ligand (43) in good yield and in excellent enantioselectivity (>99% ee).

In order to synthesise the 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene ligand (44), the cyclic sulfate (52) was reacted with 2-nitroaniline (53) followed by a hydrogenation to give the free aniline (55). A second coupling of the cyclic sulfate (52) produced the desired ligand (44) in good yield.

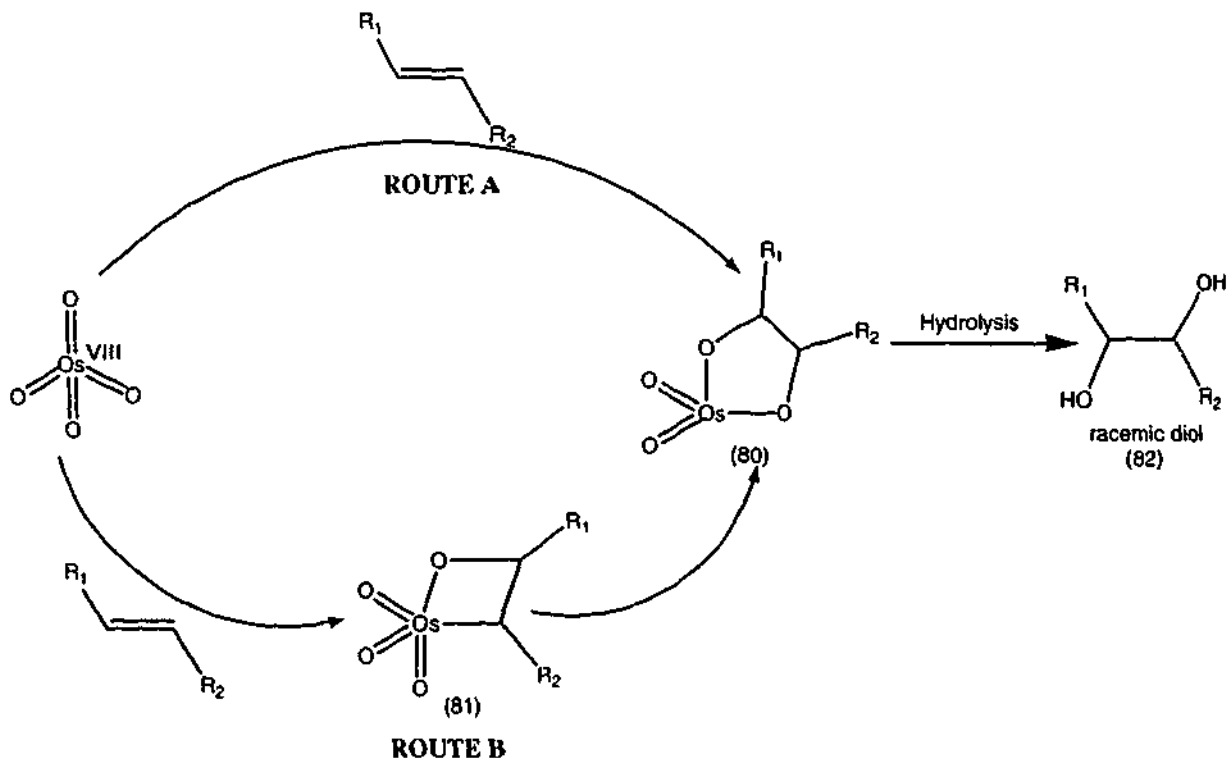
Modified pyrrolidine analogues with primary ((55), (62)), secondary ((63), (64)) and tertiary ((65), (66)) amine ligands were also successfully prepared.

Chapter 3

Asymmetric Dihydroxylation (AD) Reactions using Pyrrolidine Ligands

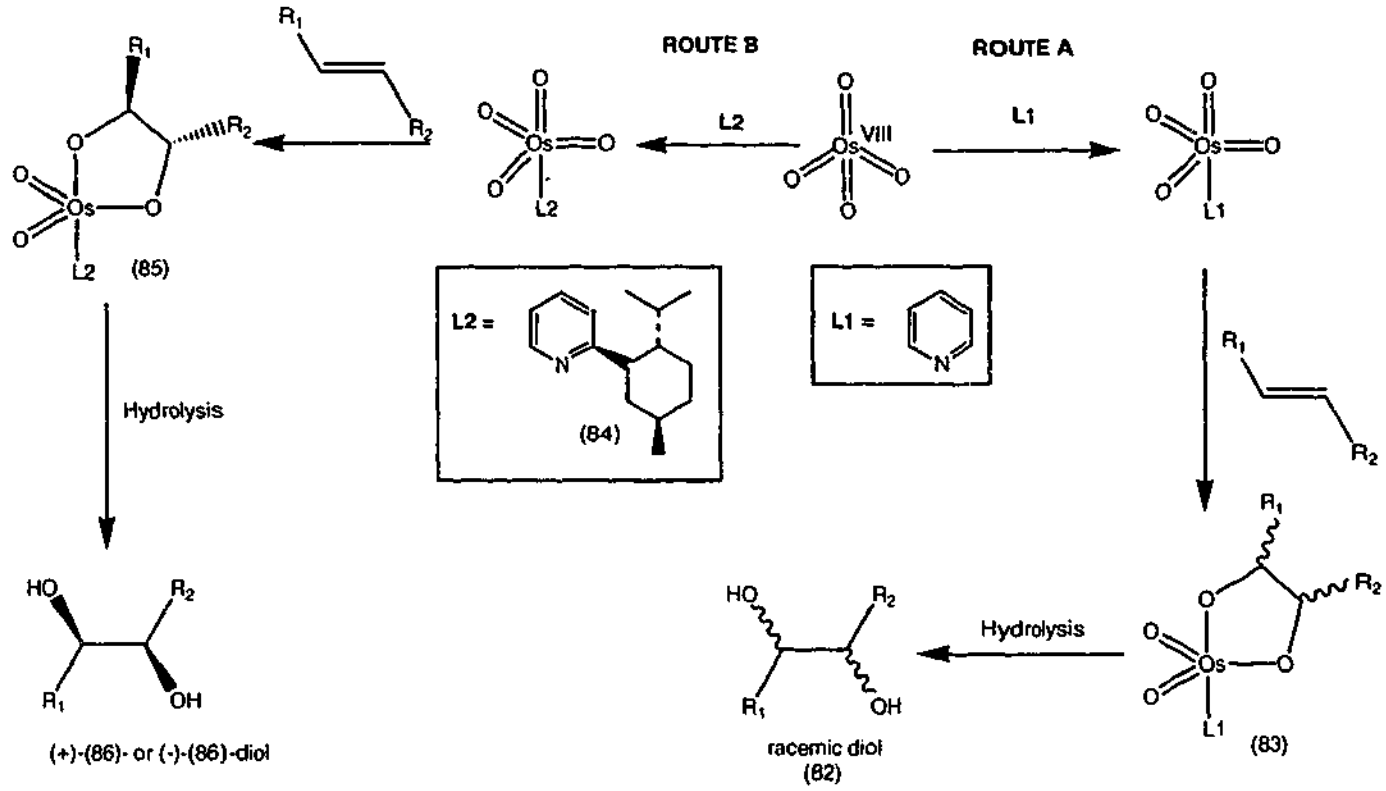
3.1 Introduction

The *cis*-dihydroxylation of olefins mediated by osmium tetroxide (OsO_4) is an important method for olefin functionalisation.[109] The osmylation process (Scheme 3.1) has been proposed to proceed *via* either a [3+2] cycloaddition leading directly to the monoglycolate ester (80) or a reversible [2+2] cycloaddition leading to a metallo-oxetane intermediate (81) (Scheme 3.1, Route A), which then undergoes irreversible rearrangement to the monoglycolate ester (80) (Scheme 3.1, Route B). Hydrolysis of the glycolate ester (80) releases the racemic diol (82).[110]



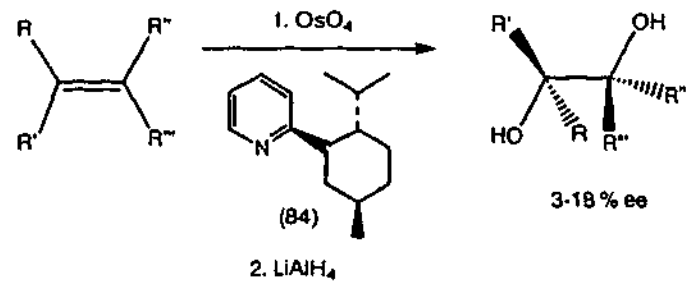
Scheme 3.1[34,110]

Criegee *et al.*[25] first reported the acceleration of osmium(VI) ester (83) formation by nucleophilic amine ligands such as pyridine (Scheme 3.2, Route A). The use of chiral amine ligands such as (84) not only accelerate the osmium(VI) ester (85) formation but also facilitate the formation of the chiral diol (86) (Scheme 3.2, Route B).



Scheme 3.2

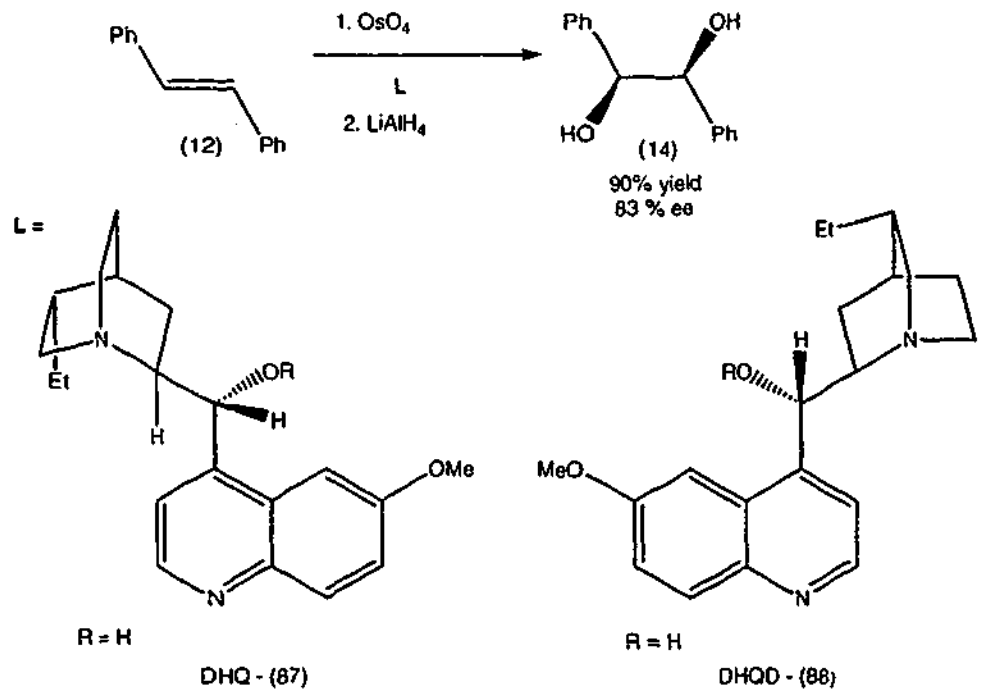
In the first example of metal mediated chiral induction, Sharpless and co-workers replaced the achiral *N*-donor ligands with chiral ligands such as (-)-2-(2-menthyl)pyridine (84). Initial work involved dihydroxylation reactions that took place with modest enantioselectivity (3-18% ee) (Scheme 3.3).[26]



Scheme 3.3[26]

Dihydroquinine (DHQ) (87) and dihydroquinidine (DHQD) (88) (Scheme 3.4) were prepared from naturally occurring cinchona alkaloids quinine and quinidine. These chiral ligands ((87) and (88)) were found to bind to osmium tetroxide through the quinuclidine nitrogen much more tightly than the chiral pyridine derivative (84) resulting in greater enantioselectivity (<83% ee).[26]

These ligands were tested on stilbene (12) which is the standard substrate of choice for testing ligands for asymmetric dihydroxylation reactions. Dihydroxylation reactions of stilbene (12) carried out using DHQ (87) and DHQD (88) ligands together with OsO_4 gave hydrobenzoin (14) in 90% yield and in 83% enantioselectivity.



Scheme 3.4

The dihydroquinidine (88) and dihydoquinine (87) ligands were further modified to increase the enantioselectivity. The 9-*O*-aryl ethers of DHQ (89) (R = Ar) and DHQD (90) (R = Ar) were reported to be the best ligands for asymmetric dihydroxylation of

dialkyl-substituted *trans*-olefins giving diols in high yields (>90%) and with excellent enantioselectivity (>98% ee).[39,41,111]

3.1.1 Chiral diamine ligands as chiral auxiliaries in asymmetric dihydroxylations

Since the initial reports of asymmetric dihydroxylation by Sharpless and Hentges,[26] a number of other groups have developed chiral ligands for this reaction. A class of ligands which has received a great deal of attention has been diamines[86,112-117] (Figure 3.1). The diamines allow for an increased binding affinity at low temperatures (-78, -100°C) to the osmium tetroxide,[118] relative to the monoamines. Hence, better stability of the osmate complexes results and improved enantioselectivity in the product is observed.

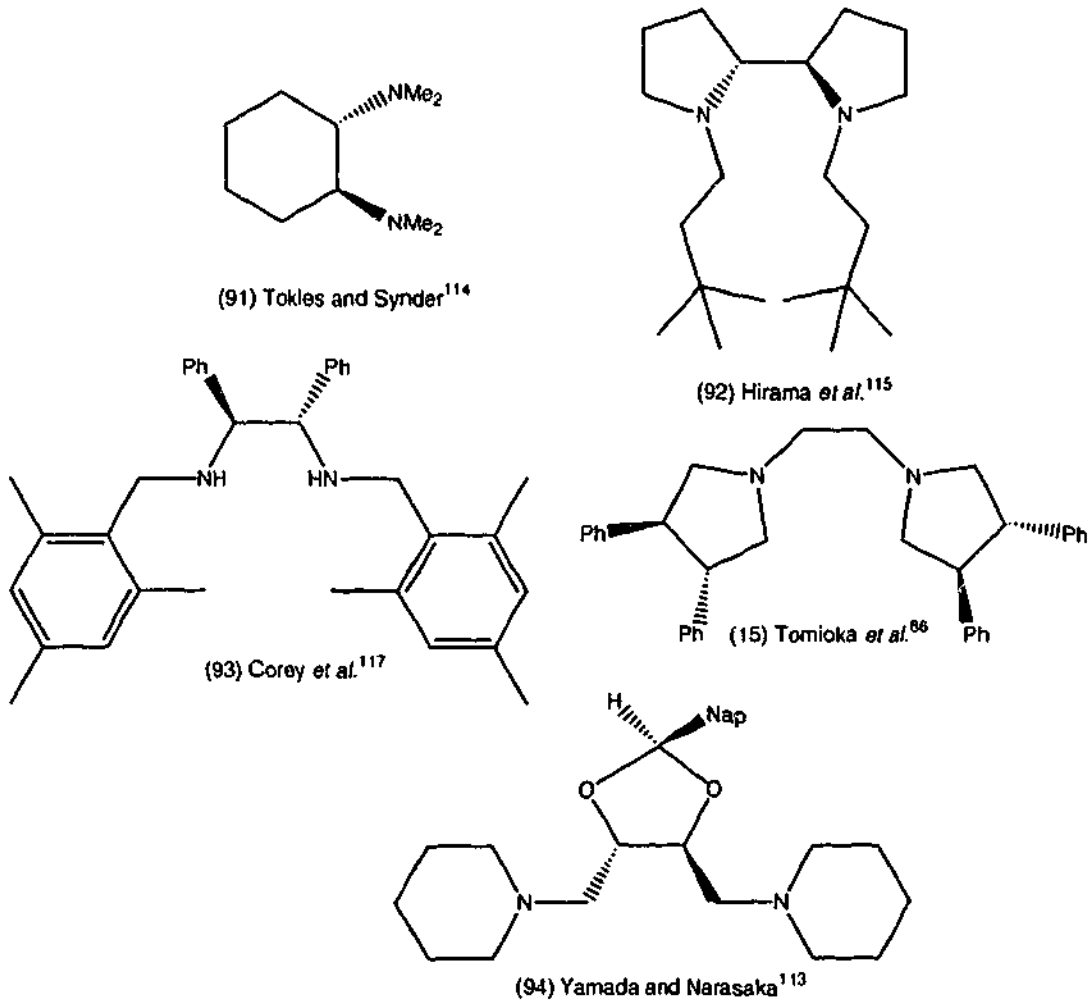


Figure 3.1:Chiral diamine ligands used in asymmetric dihydroxylation

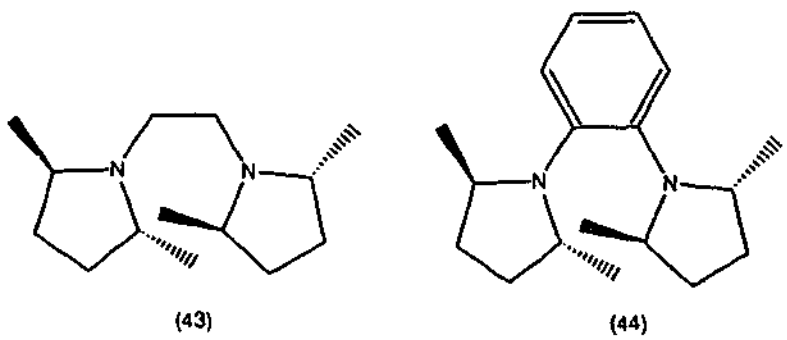
These chiral diamines together with OsO_4 perform dihydroxylation reactions on a number of different alkenes with good enantioselectivity (>98% ee). The yields and enantioselectvities achieved for the dihydroxylation of stilbene (12) using the diamines described in Figure 3.1 are summarised in Table 3.1.

Table 3.1: Asymmetric dihydroxylation of stilbene (12) using different diamine ligands

Entry	Ligand[a]	Yield (%)	Enantioselectivity (%)
1	Tokles and Synder (91)[114]	34	69
2	Tomioka (15)[86]	85	97
3	Hirama (92)[115]	80	91
4	Yamada and Narasaka (94)[113]	71	90
5	Corey et al. (93)[117]	95	92

a: Ligands identified by the authors

The diamine ligands (43) and (44) (Figure 3.2) are very similar to the ligand (15) synthesised by Tomioka *et al.*.[85] Dihydroxylation of stilbene (14) using osmium tetroxide with ligand (15) takes place in good yield and in excellent enantioselectivity (83-99% ee) (Table 3.1).[86]



(43) (44)

Figure 3.2: (2*R*,5*R*)-2,5-Dimethylpyrrolidin-1-yl ligands ((43) and (44))

These ligands (43) and (44) are also related to a class of chiral C_2-symmetric 2,5-disubstituted bis-(phospholano) ligands (46)[119] and (47)[119,120] developed by Burk *et al.* which have been used in enantioselective Rh-catalysed hydrogenation reactions.[84] Both the ethane bridged (46), as well as the benzene analogue (47) (Figure 3.3), when

incorporated into a rhodium complex result in the reduction of substituted alkenes in high yield and excellent enantioselectivity (>99% ee).[84]

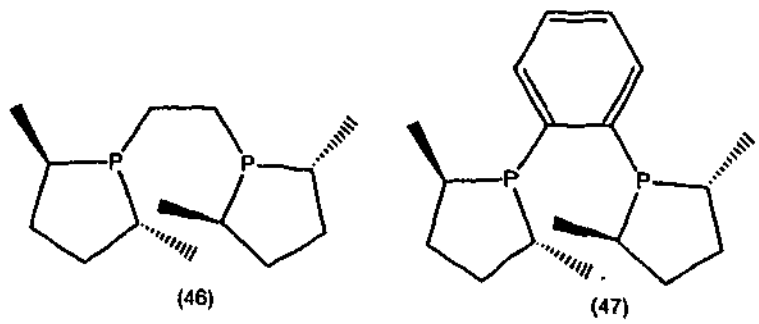
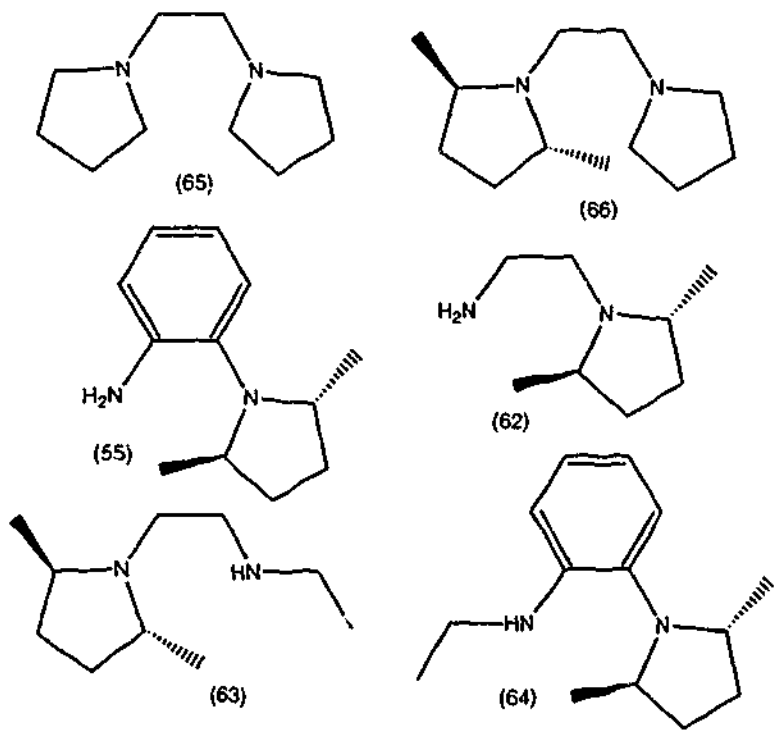


Figure 3.3: Bis-(phospholano) ligands ((46) and (47)) synthesised by Burk *et al.*

Diamine ligands (43) and (44) were evaluated as chiral modifiers of the osmium tetroxide dihydroxylation of stilbene (12) (Scheme 3.5). Unfortunately these reactions failed. ^{1}H n.m.r experiments and molecular modelling studies showed that these ligands ((43) and (44)) were too bulky to coordinate to osmium. Less hindered analogues ((55), (62), (63), (64), (65) and (66)) of these ligands were studied and some were shown to act as ligands in dihydroxylation reactions but with poor enantioselectivity (<10% ee).

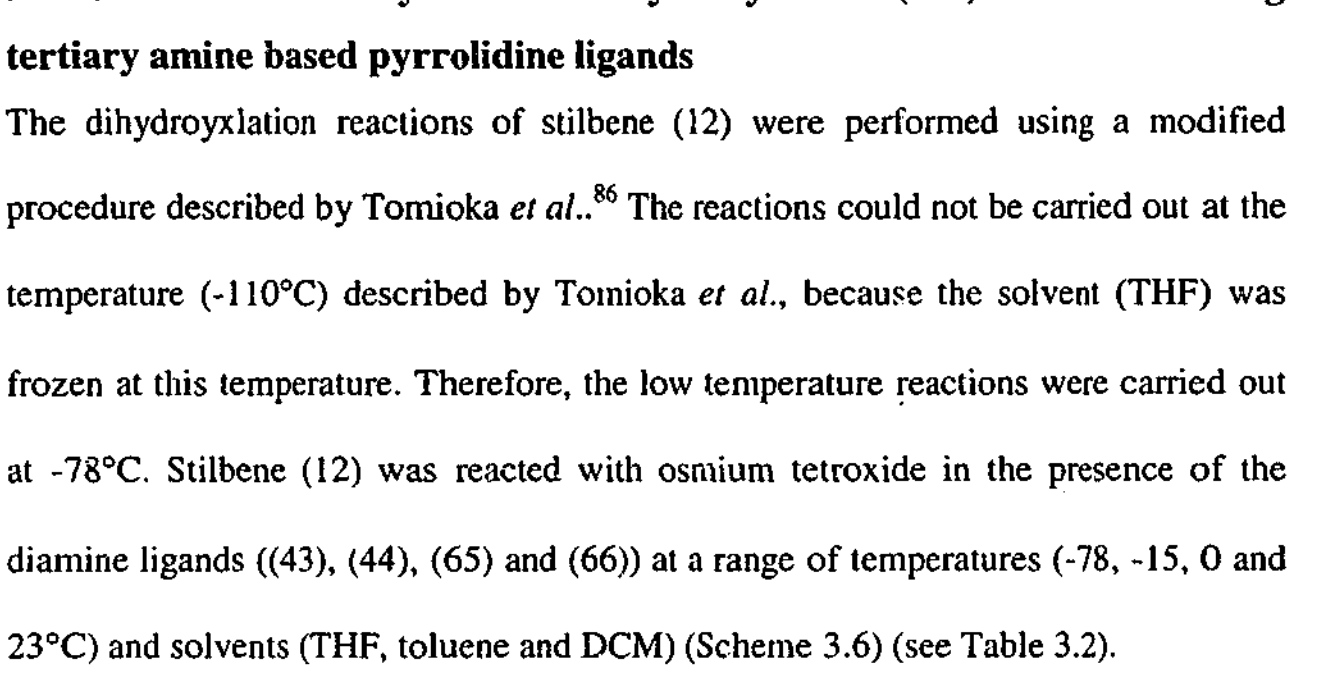


Scheme 3.5

3.2 Stoichiometric asymmetric dihydroxylation (AD) reactions using tertiary amine based pyrrolidine ligands

The dihydroyxlation reactions of stilbene (12) were performed using a modified procedure described by Tomioka *et al.*.[86] The reactions could not be carried out at the temperature (-110°C) described by Tomioka *et al.*, because the solvent (THF) was frozen at this temperature. Therefore, the low temperature reactions were carried out at -78°C. Stilbene (12) was reacted with osmium tetroxide in the presence of the diamine ligands ((43), (44), (65) and (66)) at a range of temperatures (-78, -15, 0 and 23°C) and solvents (THF, toluene and DCM) (Scheme 3.6) (see Table 3.2).

The reactions were performed firstly by mixing the desired ligand with OsO_4. The L-Os complex (95) formed provides the chiral environment required for the substrate (stilbene (12)) to chelate to form the stilbene-Os-L complex (96). $LiAlH_4$, when added to the reaction mixture, releases the desired diol (14) from the stilbene-Os-L complex (96) (Scheme 3.7).

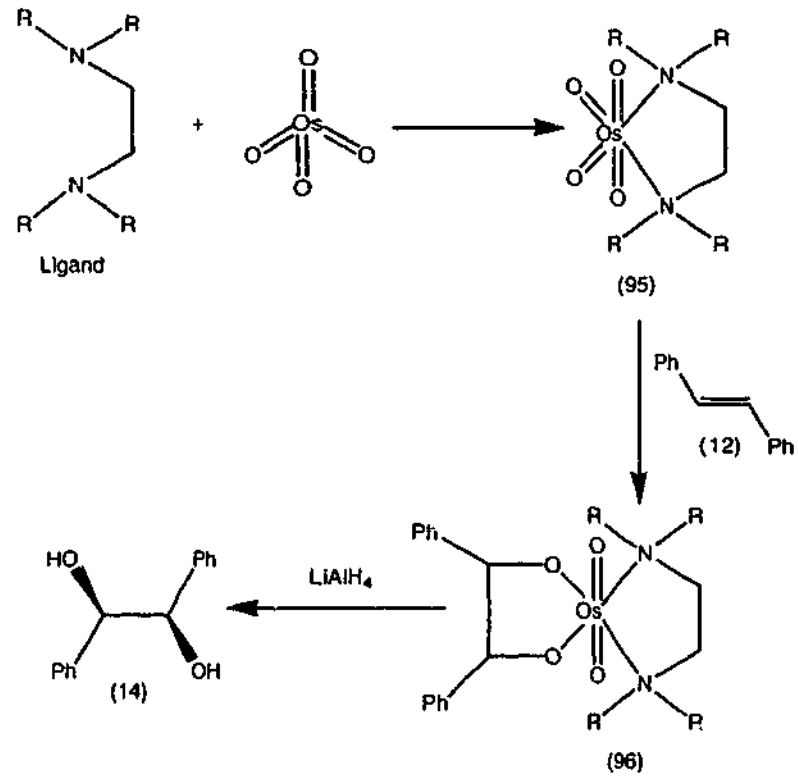


Scheme 3.6

Table 3.2: Stoichiometric AD reactions of stilbene (12) to hydrobenzoin (14)

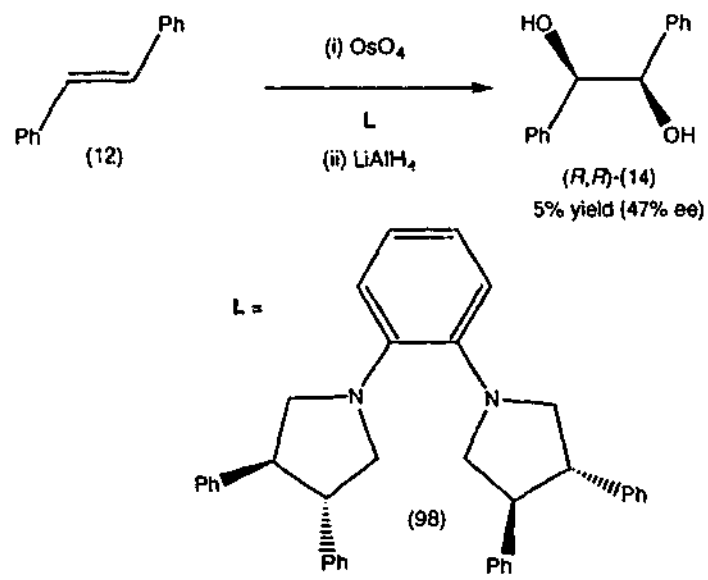
Entry	Ligand	Solvent	Temperature (°C)	Time (h)	Conversion to (14) (%)	% ee
1	No ligand	THF	-78	7	0	-
2	No Ligand	THF	23	4	93	-
3	(43)	THF	-78	8	0	-
4	(43)	THF	-15	8	0	-
5	(43)	THF	23	6	0	-
6	(43)	Toluene	-78	6	<1	-
7	(43)	Toluene	0	48	<3	-
8	(43)	Toluene	23	6	<1	-
9	(43)	DCM	0	8	0	-
10	(44)	THF	-78	6	0	-
11	(44)	THF	23	6	0	-
12	(44)	Toluene	0	8	0	-
13	(44)	Toluene	23	8	0	-
14	(65)	THF	-78	8	100	-
15	(65)	THF	23	8	37	-
16	(66)	THF	-78	7.5	0	-
17	(66)	THF	-15	7.5	50	9 (*R*,*R*)
18	(66)	THF	23	7.5	0	-
19[a]	(97)	THF	23	7.5	100	89 (*R*,*R*)
20[a]	(97)	THF	23	7.5	100	66 (*R*,*R*)

a: Ratio of stilbene: OsO_4: ligand of 0.8: 0.9: 2



Scheme 3.7

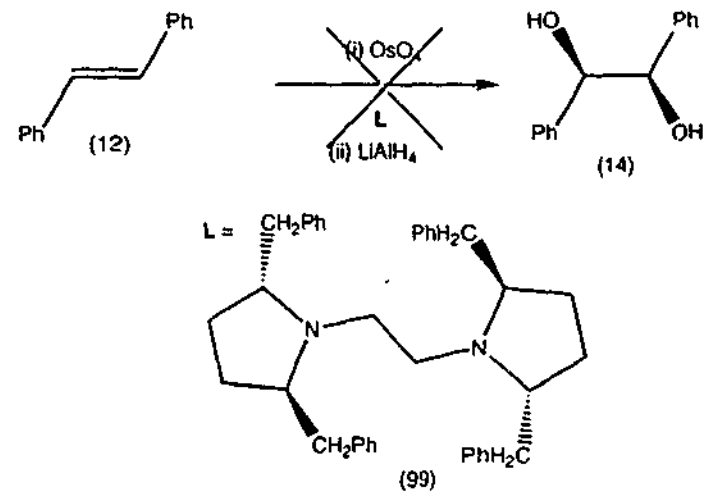
Reactions involving the ethane bridged and benzene bridged analogues ((43) and (44)) gave no conversion to diol (14) (Entries 3 – 13). Tomioka and co-workers commented that their benzene-linked ligand (98) failed to carry out dihydroxylations giving mainly starting material (12)[87,121] (Scheme 3.8). This observation was explained as being due to the aniline type nitrogens coordinating less effectively at the metal centre. These results were very similar to what was observed with ligand (44), which gave only starting material (12) when the reaction was carried out at -78°C.



Scheme 3.8[121]

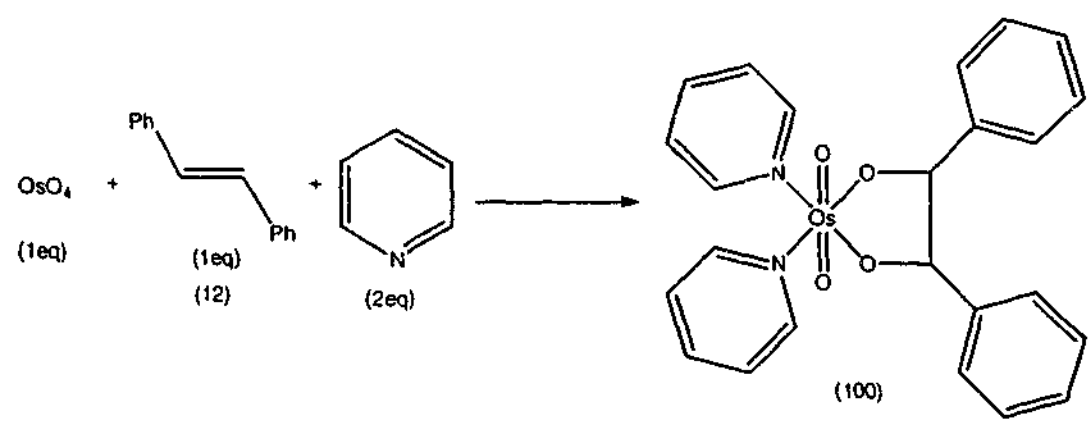
This explanation by Tomioka could be the reason why the benzene-linked ligand (44) was not facilitating the dihydroxylation reactions to take place but it does not explain why the dihydroxylation reactions using the ethane bridged ligand (43) were failing. In contrast, Tomioka's ligand (15) was very effective in dihydroxylation reactions of stilbene (12). It is more likely that steric effects exerted by the flanking methyl groups found at the 2 and 5 positions of the pyrrolidine ring were hindering the substrate binding to the osmium ligand complex. Tomioka and co-workers synthesised a pyrrolidine ligand (99) with benzyl groups at the 2 and 5 position of the pyrrolidine

ring,[85] but the Os-L complex of this ligand (99) gave only starting material (12) in dihydroxylation reactions (Scheme 3.9).[87]



Scheme 3.9

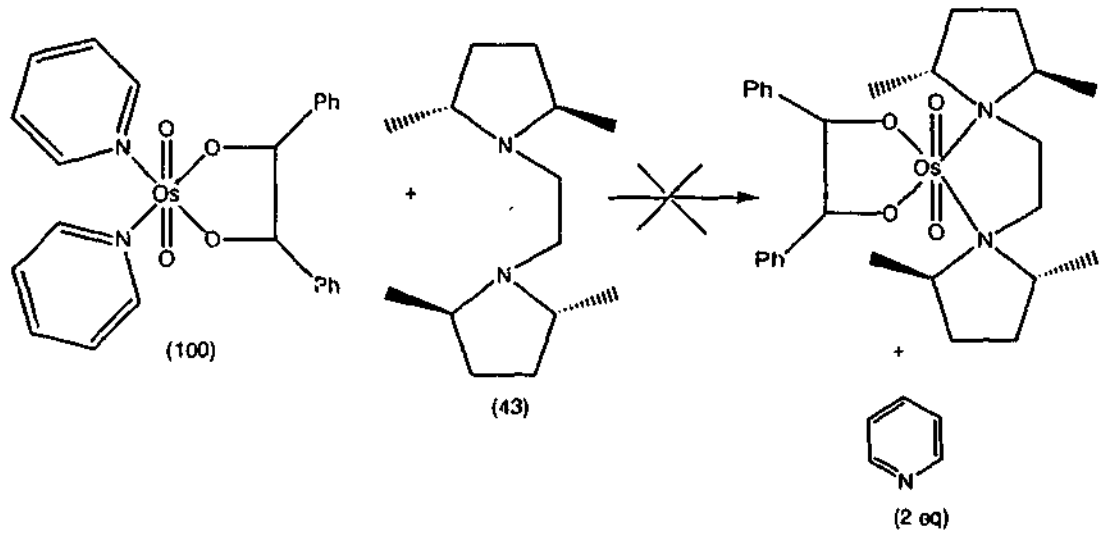
^{1}H n.m.r experiments were then conducted to establish a reason for the failure of these reactions. Firstly, a bis-pyridine osmium(VI) complex (100) was prepared as shown in Scheme 3.10 using methodology described by Sharpless *et al.*.[110] The presence of the bis-pyridine osmium glycolate (100) was confirmed by ^{1}H n.m.r and ^{13}C n.m.r. spectroscopy.



Scheme 3.10

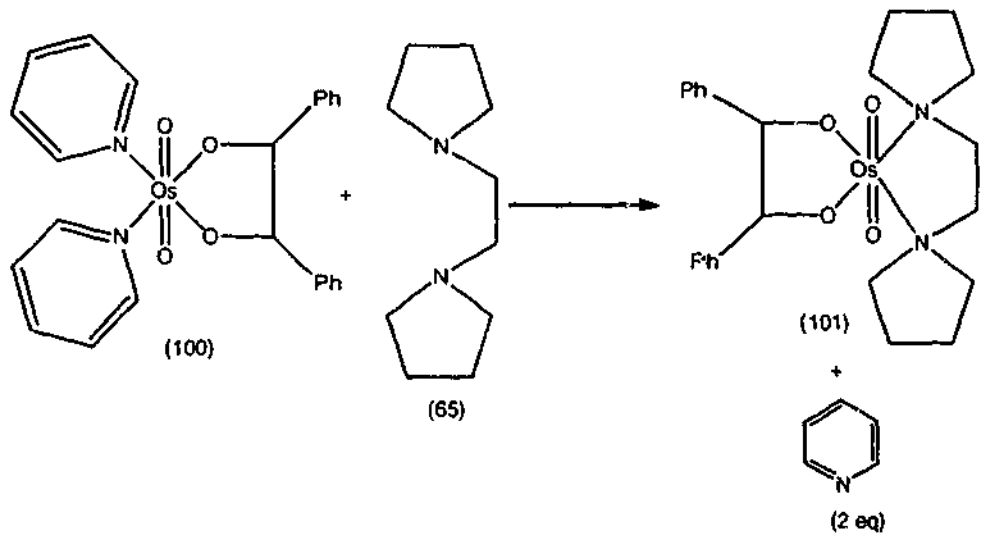
The ethane bridged analogue (43) was added to a solution of the bis-pyridine osmium glycolate (100) in deuterochloroform at room temperature (Scheme 3.11). It has been

previously shown that labile pyridine ligands can be displaced by competing diamine ligands.[87] No change in the ^{1}H n.m.r spectrum was observed when chiral diamine ligand (43) was used (Figure 3.4, (**b**)). Signals observed corresponded to either the ligand (43) or the osmium glycolate (100).



Scheme 3.11

In contrast, when the unsubsituted dipyrrolidine (65) was added (Scheme 3.12), peaks due to (100) and (65) were immediately replaced by a new set of resonances which were attributed to free pyridine and a new osmium-glycolate complex (101) (Figure 3.5, (**b**)). This reaction was repeated on a preparative scale and 1,2-di(pyrrolidin-1-yl)ethane osmium(VI) 1,2-diphenylglycolate (101) was isolated and characterised by elemental analysis, ^{1}H n.m.r and ^{13}C n.m.r. spectroscopy.



Scheme 3.12

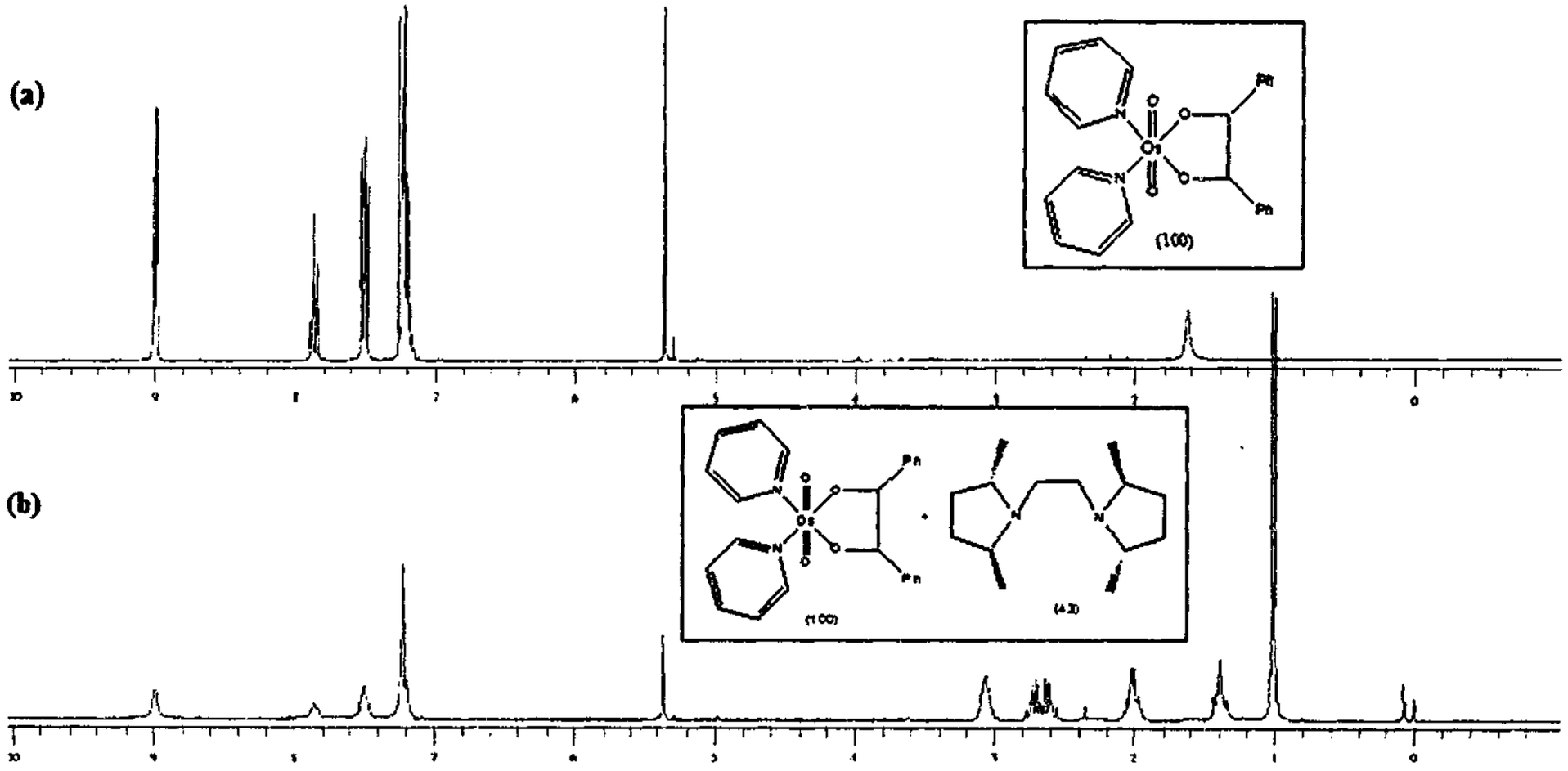


Figure 3.4: ^{1}H n.m.r. spectra of (a) The bis-pyridine osmium complex (100) and (b) The attempted displacement of pyridine by the addition of chiral dimethylpyrrolidine ethane (43)

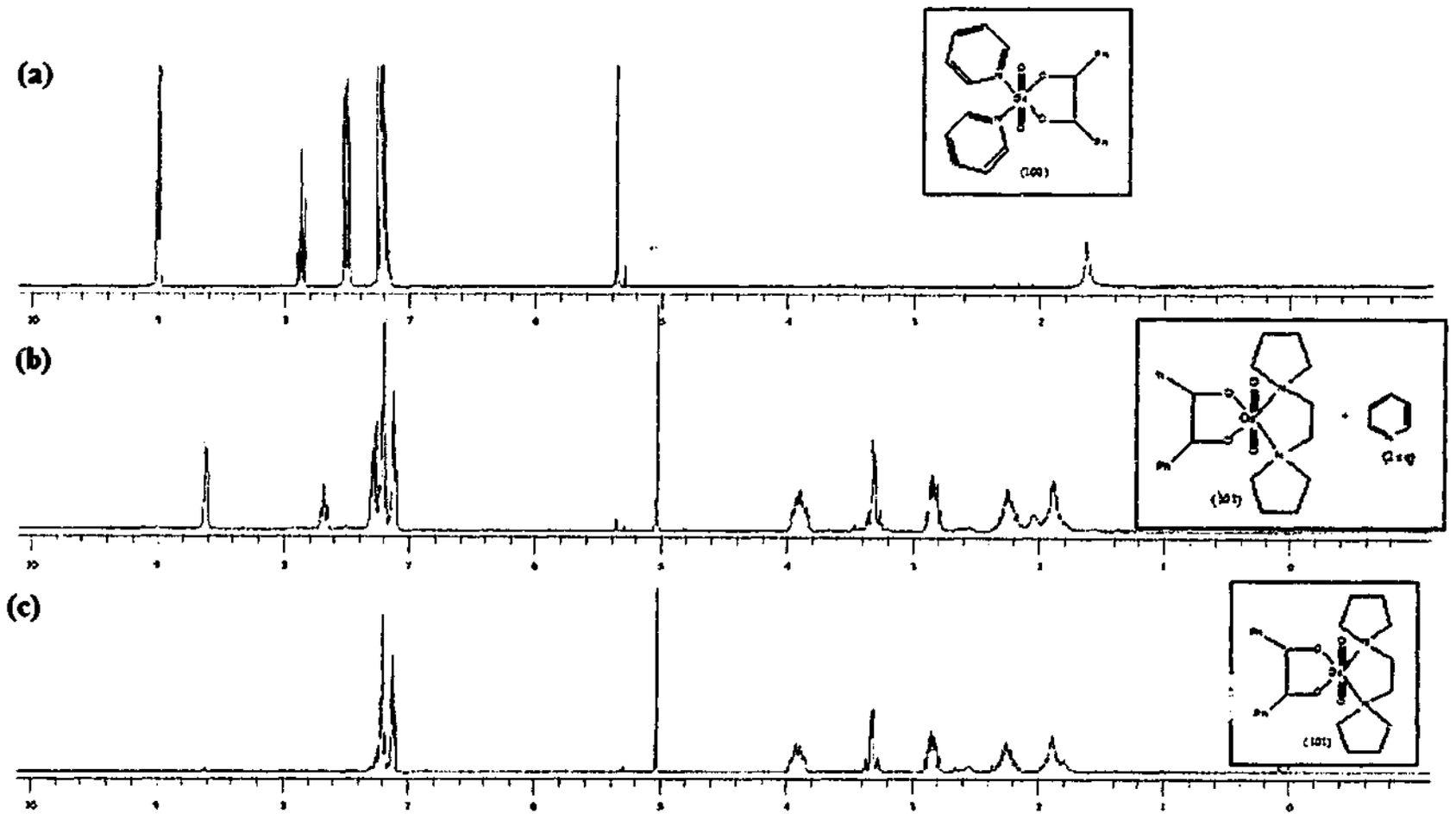


Figure 3.5: ^{1}H n.m.r. spectra of (a) The bis-pyridine osmium complex (100), (b) Displacement of pyridine by addition of 1,2-di(pyrrolidine-1-yl)ethane (65), (c) Pure, isolated 1,2-di(pyrrolidine-1-yl)ethane osmium glycolate complex (101)

Use of the diamine (65) in the dihydroxylation reaction led to complete conversion to the diol (14) at -78°C (Entry 14) and 37% conversion at room temperature (Entry 15) when the reaction was carried out in THF. Similar dramatic changes in the ^1H n.m.r spectrum were observed by Tomioka when he added the 3,4-diphenyl analogue (15) to complex (100).[87] This ligand gave high conversions of stilbene at -100°C and -78°C but reduced yields from reactions carried out at temperatures above -30°C due to some decomposition of the *in situ* formed Os-diamine complex.

Molecular modelling of the osmate ester (L-OsO_4) of the ethane bridged analogue (43) and 3,4-diphenyl analogue (15) using Insight II gave the space filling molecular mechanics structures shown in Figure 3.6

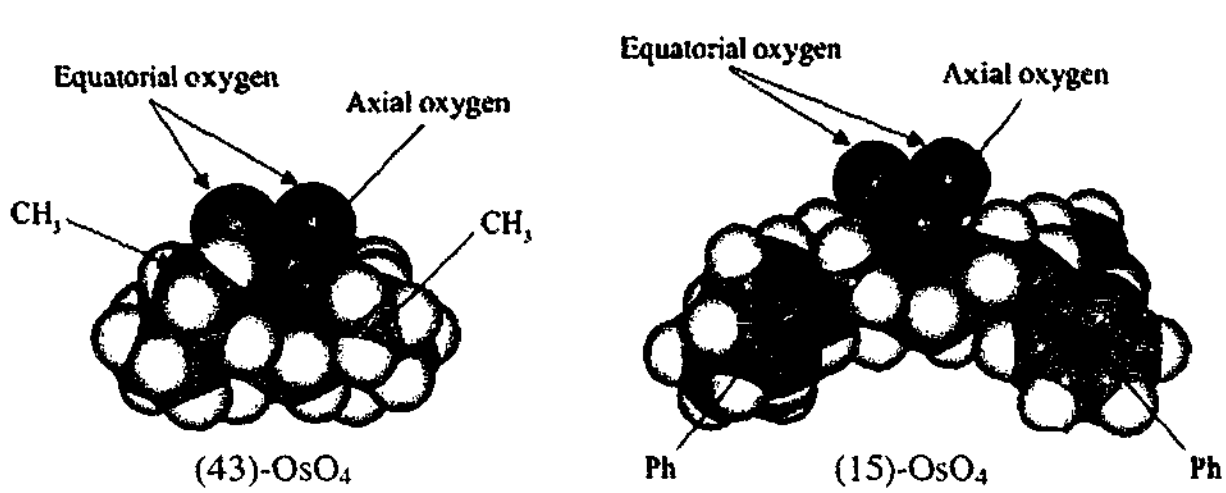


Figure 3.6: Structures of the osmium complexes of (43) and (15) minimised by molecular mechanics

The flanking methyl groups in the ester derived from (43) clearly impede access to the axial oxygens (only one visible) but allow free access to the equatorial oxygens. The ester from Tomioka's ligand (15), in contrast, allows clear access to both equatorial and axial oxygens. The lack of activity of osmium compounds derived from (43) thus

appears to be associated with lack of access to an axial oxygen. This result is in agreement with a mechanism proposed by Corey *et al.*[117] in which one axial and one equatorial oxygen are involved in forming a 5-membered transition state with the alkene (Figure 3.7).

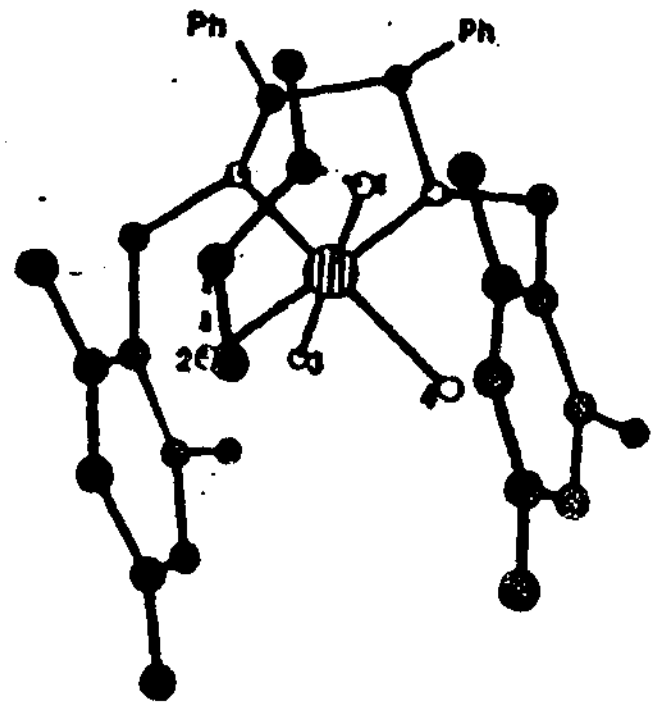


Figure 3.7: The complex formed with the ligand (93), OsO_4 and stilbene (12) postulated by Corey *et al.*[116]

Tomioka's earlier mechanistic suggestion was based on an X-ray crystal structure of the diamine osmium glycolate formed from (15), OsO_4 and stilbene (12) which showed that glycolate formation involved two equatorial oxygens (Figure 3.8).[86,89,121] Mechanistic models have been extensively discussed by several researchers[42,109,110,118,122,123] but full agreement has not been achieved on details of the reaction profile.

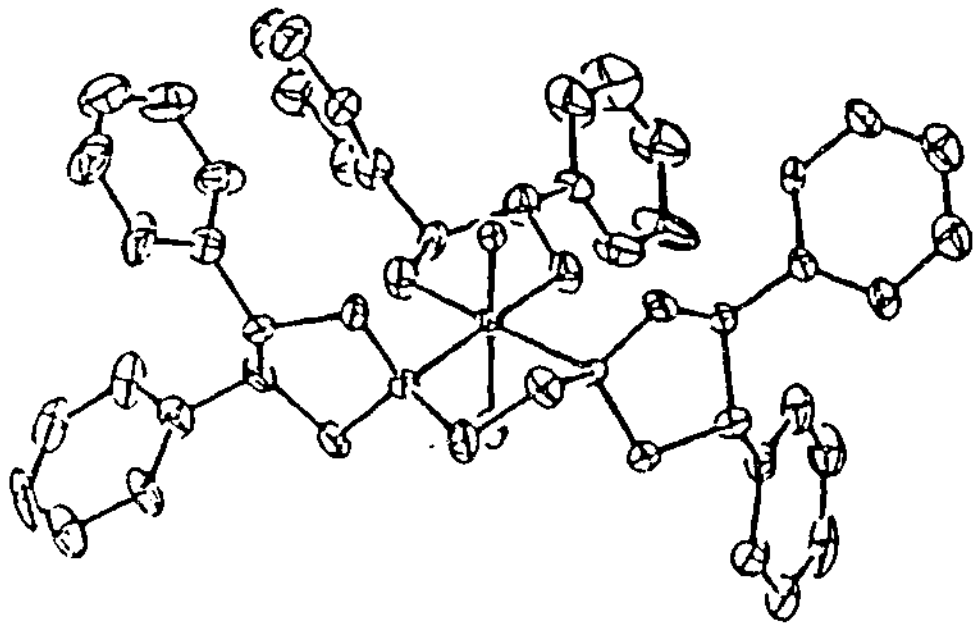
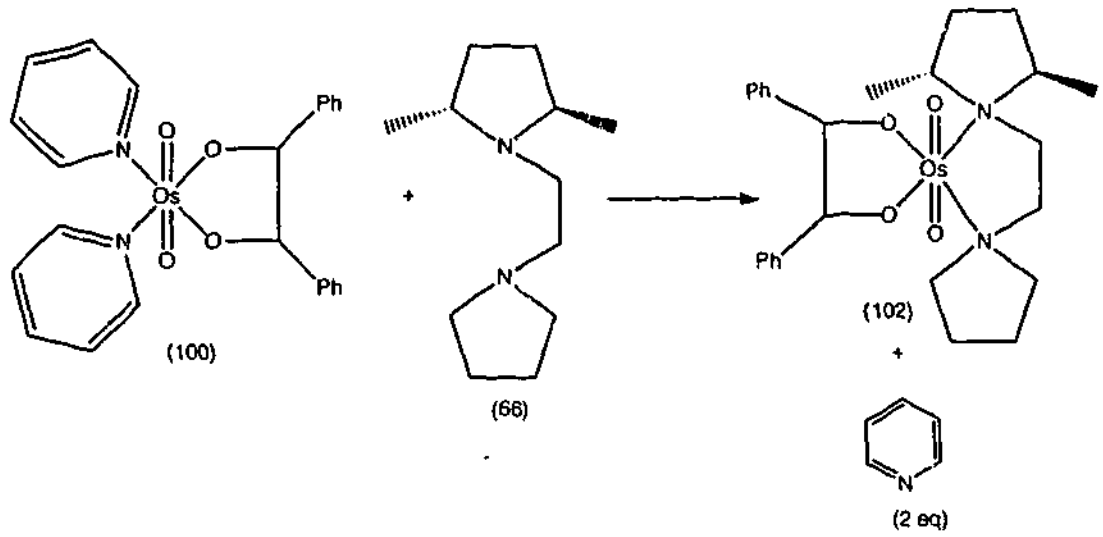


Figure 3.8: X-Ray crystal structure of diamine (15) osmium glycolate[121]

Reactions of the mixed ligand (66) bearing one 2,5-dimethyl- and one unsubstituted pyrrolidine group also gave no conversion to diol (14) at -78°C and room temperature (Entries 16 and 18), but at -15°C gave 50% conversion with a small but observable enantioselectivity (9% ee) (Entry 17). ^{1}H n.m.r. spectroscopy displacement studies using this ligand (66) (Scheme 3.13) showed that the reaction only went to 50% completion and that removal of pyridine *in vacuo* was required to facilitate the complete conversion to product (102). The ^{1}H n.m.r spectrum obtained was more complicated than that of the osmium glycolate (101) described previously, mainly because a mixture of two diastereoisomers ((*R*,*R*,*R*,*R*)-(102) and (*R*,*R*,*S*,*S*)-(102)) are formed when the racemic pyridine osmium glycolate (100) coordinates to the chiral ligand (66). This reaction was repeated on a preparative scale and 1-((2*R*,5*R*)-2,5-(dimethylpyrrolidinyl)-2-(pyrrolidinyl)ethane osmium glycolate (102) was isolated as a mixture of diastereoisomers and characterised by ^{1}H n.m.r and ^{13}C n.m.r. spectroscopy.



Scheme 3.13

Reactions of OsO_4 with stilbene (12) were carried out at -78°C and room temperature in the absence of added ligand. No conversion was obtained at -78°C (Entry 1) but 100% conversion was achieved at room temperature (Entry 2). Use of the Sharpless ligand (-)-DHQD-PHN (97)[41] at room temperature with ligand-to-OsO_4 ratios of 2:1 or 1:1 gave quantitative conversions and high ees (Entries 19 and 20).

These results are in agreement with the attempted reactions at -78°C which shows that with the poorly compexing ligands lead to no conversion as the unchanged OsO_4 is unreactive at this temperature. Attempted reactions involving the diamines as ligands at room temperature found that unreacted ligands could not be recovered from these reactions. Even (-)-DHQD-PHN (97) could not be recovered from successful dihydroxylation reactions of stilbene (12).

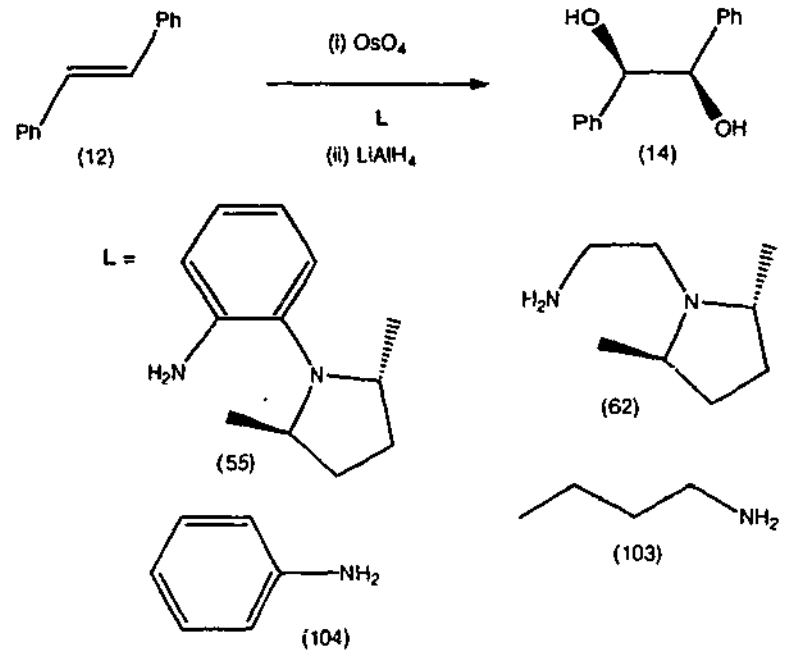
3.3 Dihydroxylation reactions using modified primary and secondary amine based pyrrolidine ligands

The flanking methyl groups of ligand (43) and (44) were thought to be causing problems in substrate chelation, and thus dihydroxylation reactions of stilbene (12) were undertaken using ligands with reduced steric bulk.

3.3.1 Primary amine ligands in dihydroxylations

Asymmetric dihydroxylations of stilbene (12) were carried out using ligands (55) and (62) containing a chiral 2,5-dimethylpyrrolidine and a primary amine (Scheme 3.14) (Table 3.3, Entries 1 – 4).

It was observed that the reactions proceeded partially at ambient temperature (Entries 2 and 4) using chiral ligands ((55) and (62)). However, the products (14) showed very poor enantioselectivity. The reactions failed to proceed at lower temperatures (<-60°C) giving only starting material (12) (Entries 1 and 3). It was not clear whether lack of dihydroxylation reactivity at low temperatures were due to the bulky pyrrolidine group or the primary amino group. Dihydroxylation reactions were thus carried out using two other primary amines, *N*-butylamine (103), an aliphatic primary amine, and aniline (104), an aromatic primary amine (Scheme 3.14). Two equivalents of these amines were used to maintain the coordinatively saturated system.



Scheme 3.14

Table 3.3: AD reactions of stilbene (12) using primary amine based ligands

Entry	Ligand	Temperature (°C)	Time (h)	Conversion to hydrobenzoin (14) (%)	% ee
1	(55)	-60	7.5	6	-
2	(55)	23	7.5	66	<1 (*R*,*R*)
3	(62)	-78	6.5	0	-
4	(62)	23	6.5	28	<6 (*R*,*R*)
5[a]	(103)	-78	7.5	0	-
6[a]	(103)	23	7.5	100	-
7[a]	(104)	-78	7.5	0	-
8[a]	(104)	23	7.5	100	-

a: Ratio of stilbene: OsO_4: ligand of 0.8: 0.9: 2

The results obtained from these reactions are summarised in Table 3.3 (Entries 5 – 8) and are similar to those obtained with the primary amine/pyrrolidine ligands (55) and (62). This result is consistent with what has been reported previously which states that tertiary amines coordinate to the osmium and increase its reactivity.[26] However, primary amines do not possess this ability. Also, due to the weak coordination of the primary amine to the osmium at ambient temperature, the osmium tetroxide is free to carry out the oxidation of the olefin. The reduced reactivity of the ligands (55) and

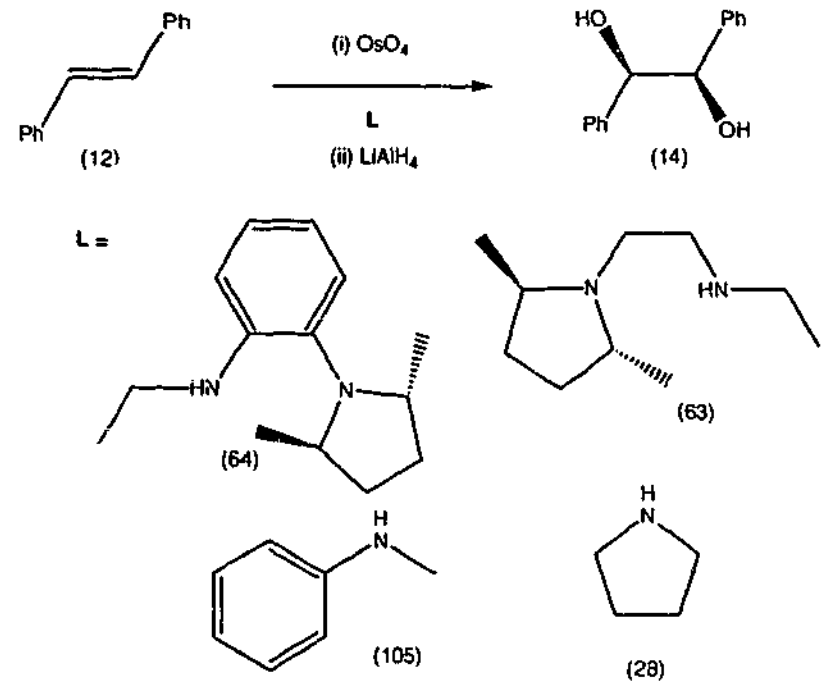
(62) (Entries 2 and 4), relative to aniline (104) and *N*-butylamine (103) (Entries 6 and 8) is difficult to understand and could be explained if the free osmium tetroxide is reacting more quickly with the ligand than with the alkene (12).

In view of the failure of ligands containing primary amines, ligands with secondary amines were investigated.

3.3.2 Secondary amine ligands in dihydroxylations

Attempted asymmetric dihydroxylation reactions carried out using the chiral ligands (63) and (64) gave only starting material (12) (Scheme 3.15) (Table 3.4). The complete lack of reactivity at both ambient and low temperatures (Entries 1 - 3) suggests that the free osmium tetroxide is not available to react with the alkene (12), but must react with the ligands ((63) and (64)) leading to its destruction. This is difficult to understand in view of Corey's[117] and Hannessian's[124] ligands. Both of these ligands containing secondary amines successfully carried out AD reactions at low temperatures in good yield (>70%) and with excellent enantioselectivity (>90% ee).[117,124]

AD reactions were attempted using two equivalents of pyrrolidine (28) and *N*-methylaniline (105) to evaluate the effectiveness of other secondary amines as ligands. The results of the attempted dihydroxylation reactions are also summarised in Table 3.4.



Scheme 3.15

Table 3.4: Dihydroxylation of stilbene (12) using secondary amine ligands

Entry	Ligand	Temperature (°C)	Time (h)	Conversion to hydrobenzoin (14) (%)
1	(64)	23	8	0
2	(63)	-78	8	6
3	(63)	23	8	0
4[a]	(28)	-78	6	0
5[a]	(28)	23	7.5	0
6[a]	(105)	-78	7.5	0
7[a]	(105)	23	7.5	70

a: Ratio of stilbene: OsO_4: ligand of 0.8: 0.9: 2

The reaction using *N*-methylaniline (105) did show some conversion to product (14) at room temperature but the conversion had dropped (Entry 7) from the 100% conversion observed when aniline (104) was used as a ligand (Table 3.3, Entry 6). It was also interesting to note that addition of pyrrolidine (28) to OsO_4 completely suppressed the reaction. These results suggest the osmium tetroxide is again reacting with the ligands ((64), (63), (28) and (105)) leading to its destruction rather than reacting with stilbene (12).

3.4 Conclusion

Chiral diamines based on *trans*-2,5-dimethylpyrrolidine appear to be too hindered to be of use as chiral modifiers of osmium tetroxide dihydroxylations of stilbene (12). Ligand 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethane (43) and 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (44) were not suitable as ligands for the asymmetric dihydroxylation of stilbene (12) under stoichiometric conditions. The reactions failed to proceed at either ambient or low temperatures.

A less hindered analogue (66) of ligand (43) was also used in dihydroxylation reactions and gave moderate conversion (50%) but poor enantioselectivity (9% ee). In contrast, reactions using the unsubstituted 1,2-di(pyrrolidine-1-yl)ethane ligand (65) gave complete conversion in the dihydroxylation of stilbene (12) at low temperature.

These results, together with the molecular modelling studies and ^{1}H n.m.r. spectroscopy studies, suggested that the steric interactions from the flanking methyl groups (2,5-disubstituted rings) found in chiral diamine ligands (43) and (44) were impeding the reaction. However, the reasons for the reactions failing at ambient temperature, are still unclear. A possible answer might involve an unproductive reaction between osmium tetroxide and the ligand resulting in the decomposition of both.

The use of two diamines incorporating one 2,5-dimethylpyrrolidine and a secondary amine, (63) and (64), also gave no conversion to the diol (14) at -78°C or at room temperature. In contrast, some conversion was achieved with the two diamines incorporating one 2,5-dimethylpyrrolidine and a primary amine, (55) and (62), but no

significant enantioselectivity was observed (<6% ee). These results are consistent with reactions involving pyrrolidine (28) and OsO_4 which under our conditions gave no diol (14) at -78°C or room temperature. Conversely, both butylamine (103) and aniline (104) gave 100% conversion at room temperature. However, osmium tetroxide alone in the absence of added ligand also gives complete conversion at ambient temperature.

Chapter 4

Other Asymmetric Reactions using (2R,5R)-2,5-Dimethylpyrrolidine Ligands

4.1 Introduction

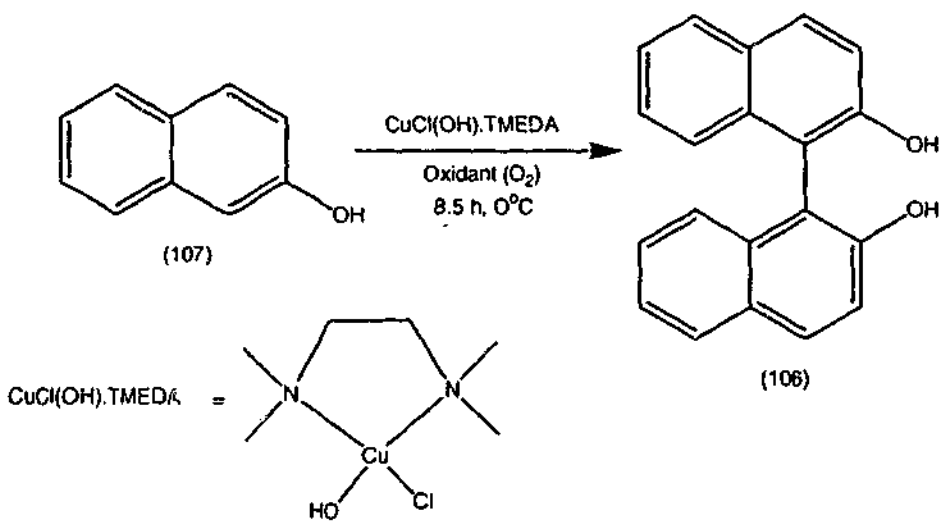
The limited success achieved using the chiral pyrrolidine ligands (43) and (44) in asymmetric dihydroxylation reactions led to a study of their use in other enantioselective catalytic reactions. Biaryl coupling, palladium catalysed allylic substitution, Grignard and hydroformylation reactions were studied. Other diamine ligands such as (43), (44), (62), (55), (65) and (66) were also used in these asymmetric reactions.

4.2 Copper catalysed oxidative coupling reactions

1,1'-Bi-2-naphthol (binol) (106) is a very useful compound in a variety of catalytic asymmetric reactions which include Diels-Alder, ene and Lewis acid catalysed reactions.[125-129] It can also be converted into enantiomerically pure 2,2'-bis(diphenylphosphino)-1,1-binapthyl (BINAP),[130] which is an excellent ligand for rhodium and ruthenium catalysed hydrogenation/hydroformylation reactions.[130-132]

The most widely used methods for obtaining enantiomerically pure binol (106) involve the optical resolution of racemic binol (106) through the formation of diastereomeric complexes.[125,128,133,134] The procedures developed in this way often require expensive chiral reagents and complicated techniques. On the other hand, Noji

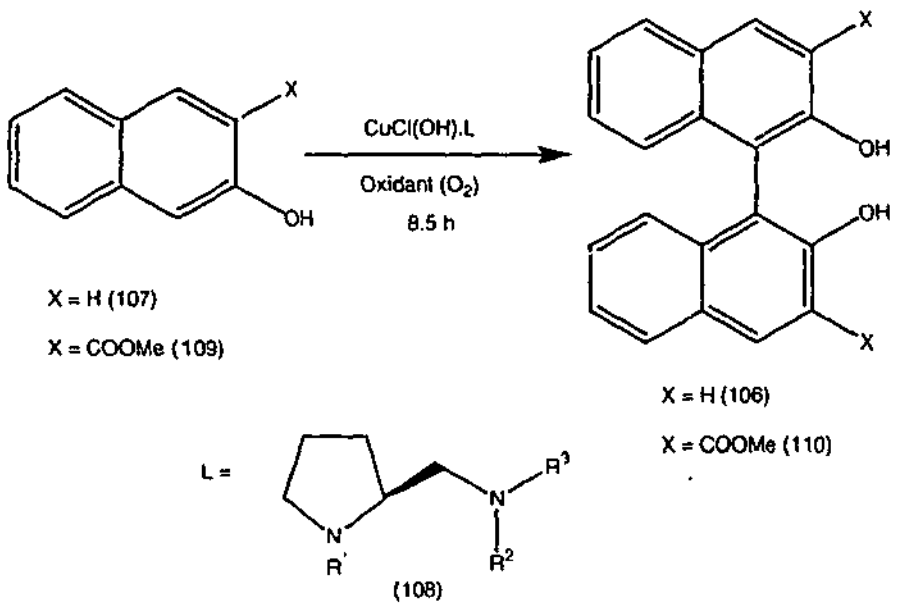
et al. reported a racemic synthesis of binol (106) involving a copper-TMEDA catalysed coupling of 2-naphthol (107) as shown in Scheme 4.1.[135]



Scheme 4.1

The same group further developed this reaction into an asymmetric synthesis of binol (106) through the use of chiral ligand (108) in the copper(II) amine catalyst system.[136] The coupling reaction gave binol (106) in 89% yield but with only 17% enantioselectivity. However, this same copper complex catalysed the oxidative coupling of methyl 3-hydroxy-2-naphthoate (109) to give the corresponding binaphthol compound (110) in 85% yield and 78% enantioselectivity (Scheme 4.2).[136]

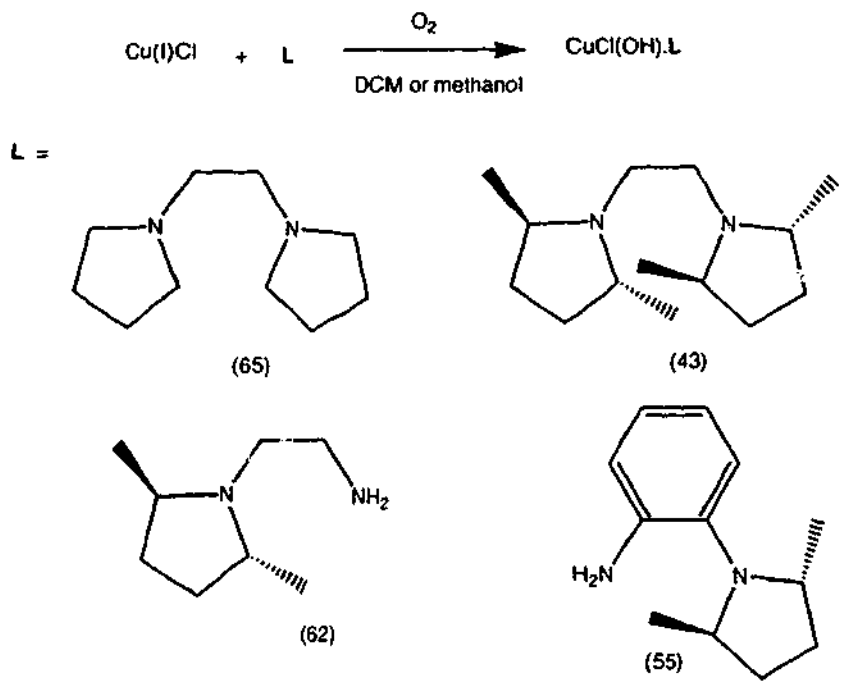
Other groups have also used chiral diamine ligands in Cu-catalysed oxidative reactions to achieve good coupling yields and excellent enantioselectivities.[137,138] As our diamine ligands (43), (55), (62) and (65) were very similar to those that examined by Nakajima *et al.*[136] it was decided to evaluate them in the oxidative coupling of 2-naphthol (107) and methyl 3-hydroxy-2-naphthoate (109).



Scheme 4.2[136]

4.2.1 Preparation of CuCl.diamine catalysts

All catalysts were synthesised by reacting Cu(I)Cl with the desired diamine under an oxygen atmosphere in either methanol or dichloromethane (Scheme 4.3).[136] The desired catalysts were isolated as solids after centrifugation.



Scheme 4.3

4.2.2 Oxidative coupling of 2-naphthol (107)

Coupling of 2-naphthol (107) was attempted with four different catalysts using a substrate to ligand ratio of 1:100 and the results are summarised in Table 4.1.

Table 4.1: Oxidative coupling of 2-naphthol (107) with copper complexes of diamine ligands

Entry	Ligand	Oxidant	Time (h)	Temp (°C)	Products (%)			S/m (107) (%)
					(106)	(111)	(112)	
1	(65)	air	18	23	100	0	0	0
2	(43)	air	48	23	5	3	trace	92
3	(43)	air	7 (days)	reflux	0	0	0	100
4	(43)	O_2	48	23	0	59	41	0
5	(43)	O_2	18	23	0	0	30	70
6	(62)	O_2	72	23	0	76	24	0
7	(62)	air	7 (days)	23	9	8	0	83
8	(62)	air	7 (days)	reflux	0	0	0	100
9	(55)	O_2	18	23	11	73	0	16

The best results were observed when the copper catalyst (CuCl(OH).(65)) incorporating the unsubstituted ligand was used. This system gave a 100% conversion to binol (106) (Entry 1). Low conversions to the desired binol (106) were obtained when Cu-complexes with the asymmetric ligands (43) and (62) were used (Entries 2 – 8). The main products were 1,2-naphthaquinone (111) and 2'-hydroxy-(1,1')-binaphthyl-3,4-dione (112) (Figure 4.1) (Entries 4-6). Noji *et al.* also reported the formation of quinones in the oxidative coupling of phenols.[135] Li *et al.* has reported the formation of the coupled quinone (112) in their reaction involving 2-naphthol (107) and methyl 3-hydroxy-2-naphthoate (109).[137]

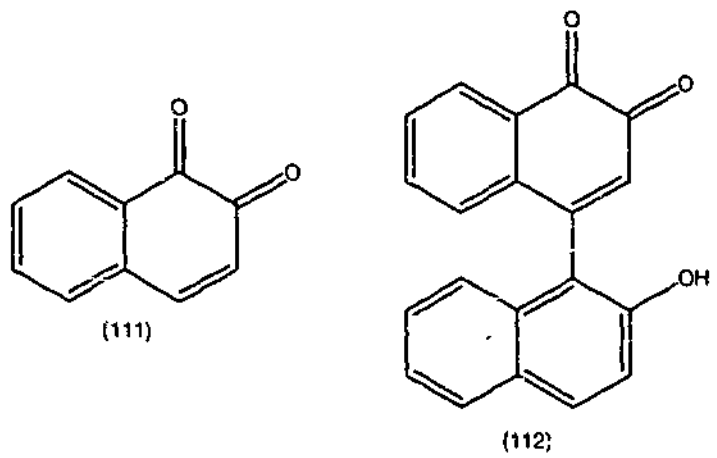


Figure 4.1: 1,2-Naphthaquinone (111) and 2'-hydroxy-(1,1')-binapthyl-3,4-dione (112)

4.2.3 Oxidative coupling of methyl 3-hydroxy-2-naphthoate (109)

Extensive studies have been carried out by Nakajima and co-workers to evaluate which substituents on the naphthol ring provide the best induction.[136] It was reported that an ester at the C2 position of the naphthalene ring encourages coupling reactions to take place in good yield and in excellent enantioselectivity. Li *et al.* reported that the substituent at the C2 position was critical for high induction. Hence, it was decided to carry out the coupling using methyl 3-hydroxy-2-napthoate (109) which was known to give the coupled product (110) with good selectivity (78% ee).

The postulated mechanism described in Figure 4.2[137] uses a copper catalyst incorporating 1,5-diaza-*cis*-decalin. This mechanism suggests that the substrate undergoes a ligand exchange with the catalyst to form a Cu(II)-ligand-substrate complex. Subsequent electron transfer from this complex would yield a tetrahedral copper radical complex (113). The model illustrates that due to steric reasons addition of the second substrate molecule to the complex is preferred from the top face giving the desired product (110).

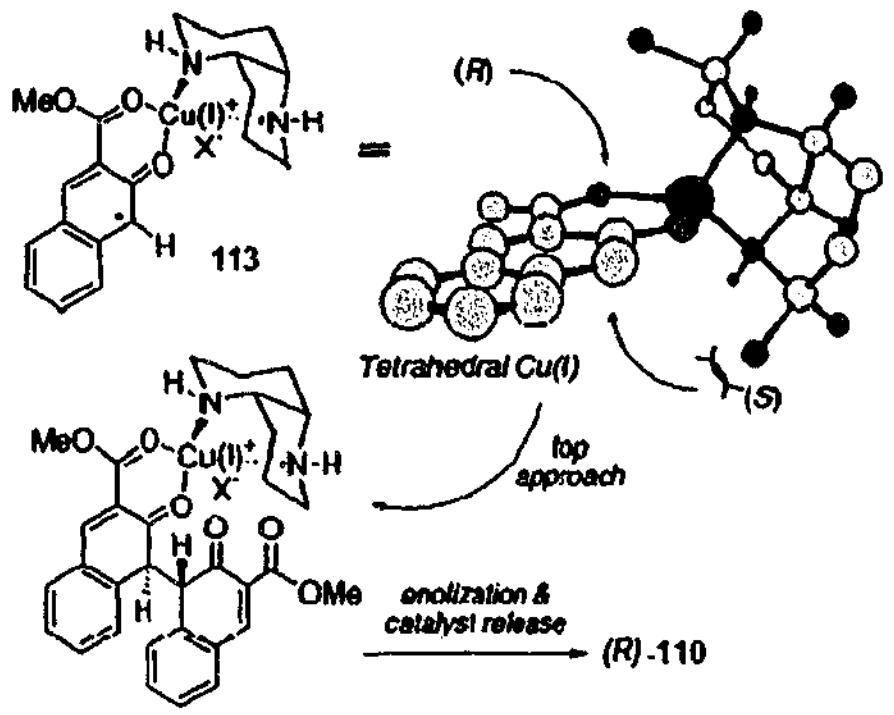
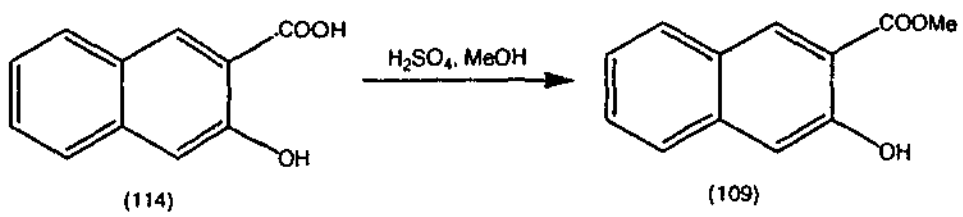


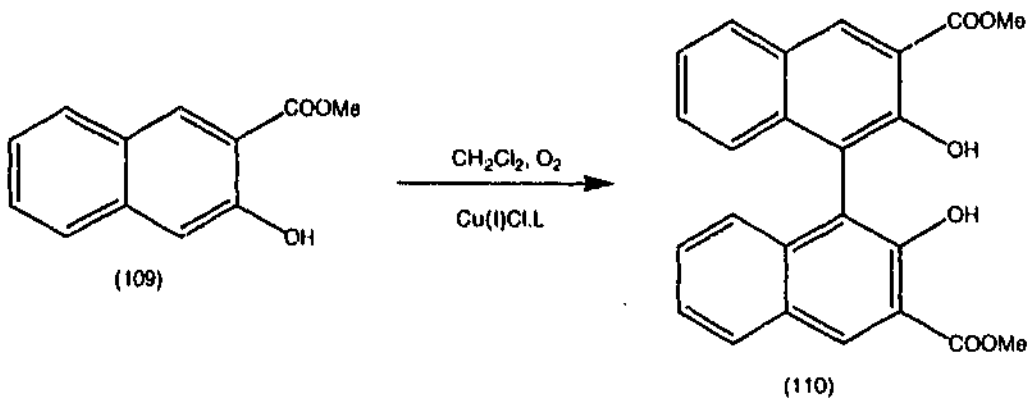
Figure 4.2: Tentative stereochemical model (only key hydrogens shown) for the biaryl coupling of methyl 3-hydroxy-2-naphthoate (109) using (*S*,*S*)-1,5-diazo-*cis*-decalin ligand[137]

Methyl 3-hydroxy-2-naphthoate (109) was prepared by esterification of the naphthoic acid (114) using methanol and concentrated sulfuric acid (Scheme 4.4). The product (109) showed a singlet in the ^{1}H n.m.r. spectrum at δ 4.02 and a signal at δ 52.4 in the ^{13}C n.m.r. spectrum for the methoxyl group.



Scheme 4.4

Coupling of the naphthoate (109) was carried out using air and oxygen as oxidants (Scheme 4.5) and the results for the copper complexes of the different ligands are summarised in Table 4.2.



Scheme 4.5

Table 4.2: Oxidative coupling of methyl 3-hydroxy-2-napthoate (109) with copper complexes of diamine ligands

Entry	Ligand	Oxidant	Time (h)	Temp (°C)	Conversion to (110) (%)	% ee of (110)
1	(65)	air	48	reflux	100	-
2	(65)	O_2	72	23	21	-
3	(65)	air	72	23	17	-
4	(43)	air	120	23	0	-
5	(43)	O_2	72	23	0	-
6	(43)	air	120	reflux	0	
7	(62)	O_2	72	23	17	23
8	(62)	air	7 (days)	reflux	100	6
9	(62)	O_2	10 (days)	23	13	-
10	(55)	O_2	18	23	0	-
11	(55)	air	18	reflux	0	-

Formation of the desired coupled product (110) was a very slow process, often requiring more than 24 hours. Only starting material was isolated with the use of the copper complex of the bis-2,5-substituted pyrrolidine ligand (43) (Entries 4 – 6) and the copper complex of the benzene ligand (55) (Entries 10 and 11), even at elevated temperatures. The copper complex of the bis-pyrrolidine ethane ligand (65) gave a 100% conversion at elevated temperature (Entry 1). However, only 21% conversion was observed when the reaction was carried out at room temperature (Entry 2).

Use of the copper complex of the mixed substituted/unsubstituted ligand (62) gave a 17% conversion at ambient temperature with an enantioselectivity of 23% (*S*) (Entry 7). Reactions carried out at higher temperature to increase the percentage conversion had a detrimental effect on the enantioselectivity dropping it down to 6% ee (Entry 8). These results are moderate compared to that reported in the literature (85% yield and 93% ee).[137]

4.3 Enantioselective palladium catalysed allylic substitutions

Enantioselective metal-catalysed allylic substitutions using phosphine ligands were first reported by Trost and Strege in 1977.[139] Since then, much research has been done to increase the selectivity of these reactions. A number of nitrogen based diamine ligands, such as the bis-oxazolidine (26)[140] and bis-aziridine (58)[141] ligands (Figure 4.3), have been used to carry out these reactions with excellent enantioselectivity (>90% ee).

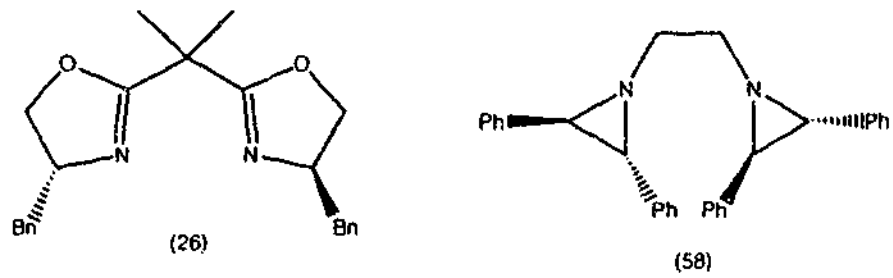


Figure 4.3: Chiral diamine ligands used in enantioselective allylic substitution reactions

The catalytic cycle of the palladium allylic alkylation reaction is illustrated in Figure 4.4.[35] Firstly the allylpalladium(II) chloride dimer is easily reduced *in situ* to the active Pd(0) form.[35] After the elimination of X^- (e.g. OAc^-) from the substrate a (η^3-allyl)palladium(II) complex (115) is formed. A soft nucleophile (pK_a <25),[142] such as a stabilised malonate anion, then attacks the allyl face opposite to the palladium. The

resulting unstable Pd(0)-olefin complex (116) readily releases the final product and regenerates the active palladium catalyst for the addition of another substrate molecule.[143]

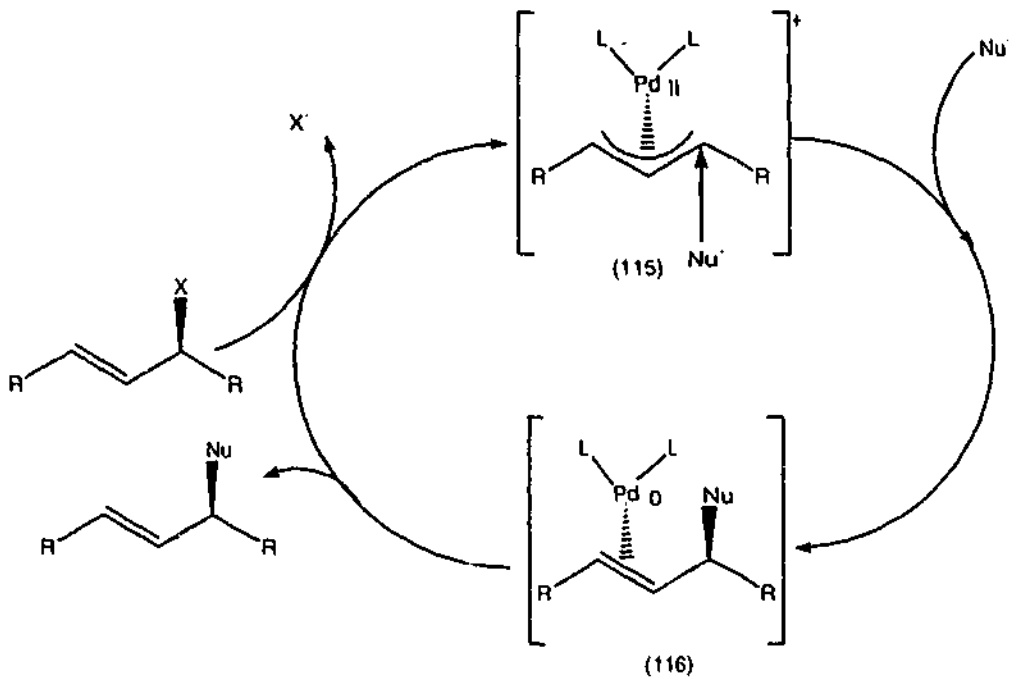


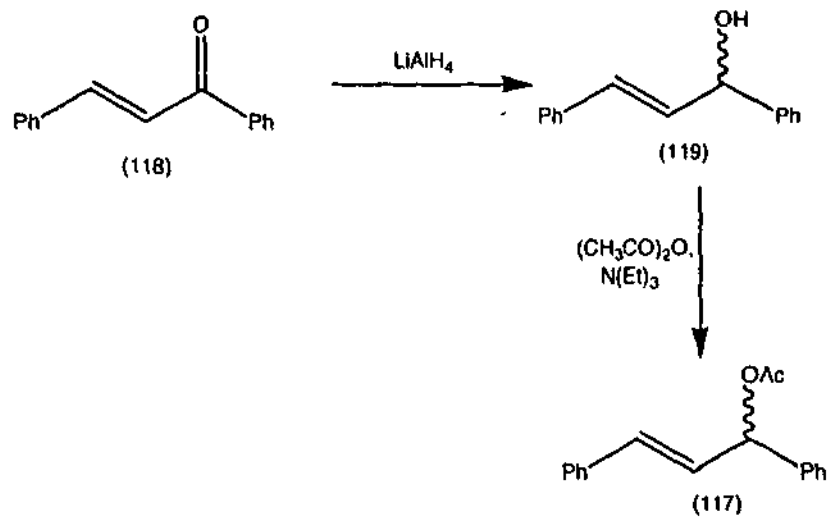
Figure 4.4: Mechanism of palladium catalysed allylic substitution[143]

The chiral diamine ligand (43) was used in asymmetric allylic alkylation reactions by Kubota *et al.*.[90] This reaction proceeded in excellent yield and enantioselectivity (89% ee). We intended to reproduce these results and investigate the use of the pyrrolidine ligands (43) and (66) to extend the scope and enantioselectivity of these allylic alkylation reactions.

4.3.1 Pd catalysed allylic alkylation reactions using tertiary diamine ligands

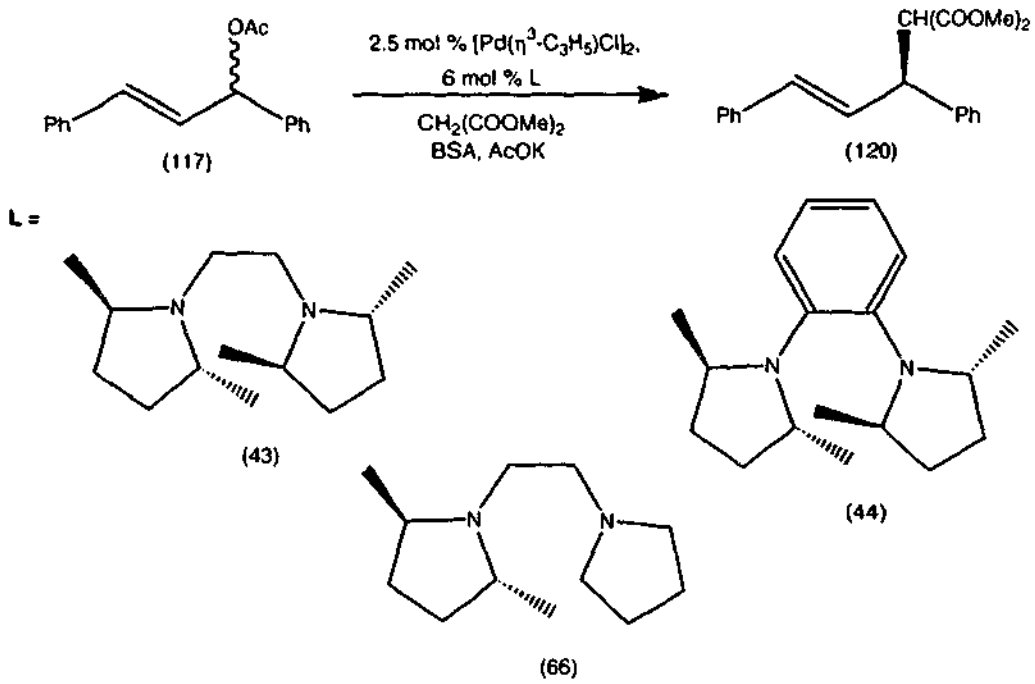
Before the reactions could be carried out, it was necessary to prepare (±)-1,3-diphenylprop-2-en-1-yl acetate (117) which has become a standard substrate for the evaluation of chiral ligands in Pd-catalysed allylic substitution reactions.[144] Reduction of 1,3-diphenylprop-2-en-1-one (118) to the alcohol (119) followed by an acetylation

(Scheme 4.6) gave the product (117) which was purified by column chromatography and characterised by the usual spectroscopic methods.[145]



Scheme 4.6

Palladium catalysed allylic alkylation reactions were carried out as described by Kubota *et al.*[90] (Scheme 4.7) in dichloromethane using dimethyl malonate as the nucleophile. The reactions were carried out using a catalyst: substrate ratio of 1:5 and the results are summarised in Table 4.3.



Scheme 4.7

Table 4.3: Allylic alkylation of (±)-1,3-diphenylprop-2-en-1-yl acetate (117) using Pd complexes with diamine ligands

Entry	Ligand	Time (h)	Temp (°C)	Conversion to (120) (%)	% ee
1	(43)	18	23	100	85 (*S*)
2	(43)	1	reflux	100	75 (*S*)
3	(44)	24	23	0	-
4	(44)	24	reflux	0	-
5	(66)	24	23	100	51 (*S*)

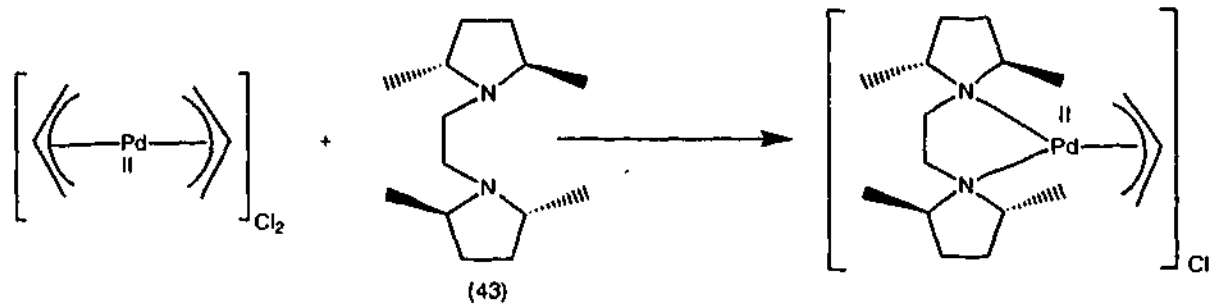
As shown in Table 4.3, the results obtained by Kubota *et al.*[90] were reproduced successfully. The reaction using ligand (43) was observed to give 100% conversion to product (120) in less time than reported (36 h)[90] in the literature (Entry 1). A reaction at reflux led to an increase in rate but resulted in reduced enantioselectivity (75% ee) (Entry 2). As expected, a reaction using ligand (66), with only one chiral pyrrolidine moiety, gave complete conversion to product (120) but showed a decline in the enantioselectivity (51% ee) (Entry 5).

It was hoped that use of ligand (44) with its more rigid benzene backbone would lead to a higher enantioselectivity. However, no conversion to product (120) occurred, suggesting that the anilino nitrogens were too weak to activate the Pd metal centre (Entries 3 and 4). In order to test this hypothesis, ^{1}H n.m.r. spectroscopy studies were used to observe the binding of ligands (43) and (44) with palladium.

4.3.2 ^{1}H n.m.r. spectroscopic studies using ligands (43) and (44) with allylpalladium(II) chloride dimer

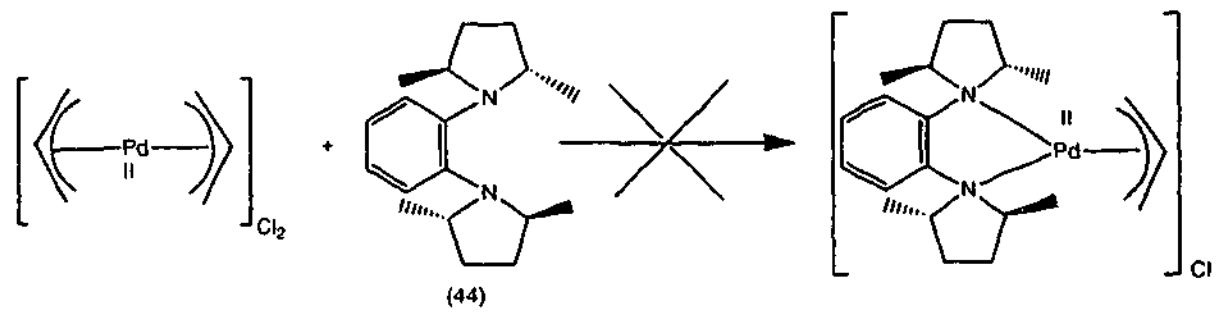
The ^{1}H n.m.r. spectrum of a mixture of allylpalladium(II) chloride dimer and 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethane (43) was recorded (Scheme 4.8). The ^{1}H n.m.r. spectrum showed shifts very different to those observed for the free ligand (43),

suggesting that the ligand was coordinating with the metal center. Hence, good yields and excellent enantioselectivities were observed in the allylic alkylation reactions.



Scheme 4.8

Mixing the allylpalladium dimer with 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (44) (Scheme 4.9) under the same conditions showed no change in the shifts in the ^{1}H n.m.r. spectrum compared to those of the free ligand (44), suggesting that the ligand was not coordinating to the metal. These observations are consistent with the results obtained in the allylic alkylation reactions.

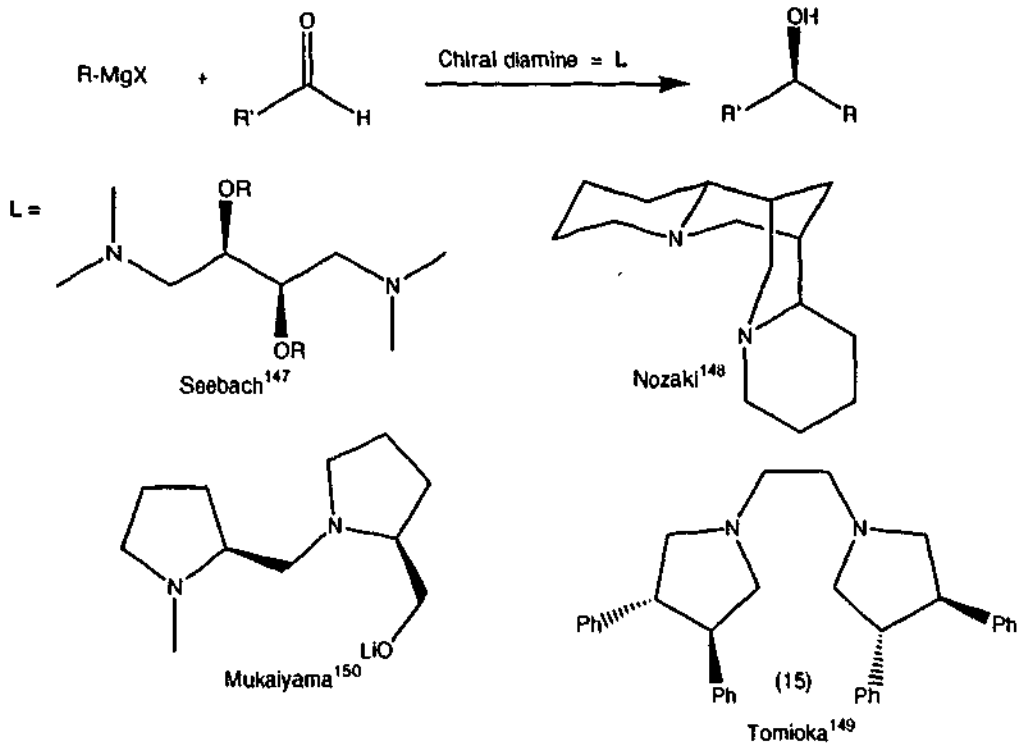


Scheme 4.9

4.4 Asymmetric Grignard reactions

A selection of chiral auxiliaries have been developed over the years for the synthesis of chiral alcohols from achiral aldehydes or ketones (Scheme 4.10). Cohen and Wright[146] first used 2,3-dimethoxybutane as a chiral solvent to carry out Grignard reactions. A few diamines have been used in the preparation of chiral secondary

alcohols under stoichiometric conditions.[147-152] Some of them are illustrated in Scheme 4.10.



Scheme 4.10

The possible origins of enantioselectivity were investigated by using the complex (121) (Figure 4.5).[147,153] The chiral ligand which is coordinated to the magnesium metal dictates the face in which the carbonyl group approaches the nucleophile.

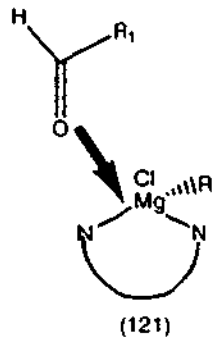
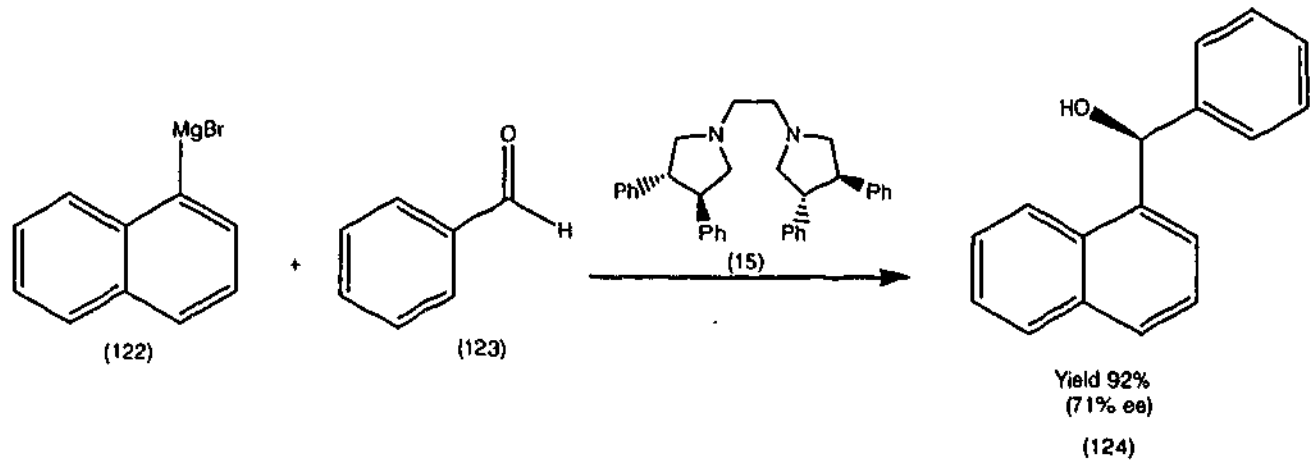


Figure 4.5

Tomioka's ligand (15) had been reported to give good enantioselectivity (71% ee) when used with α-naphthylmagnesium bromide (122) and benzaldehyde (123)

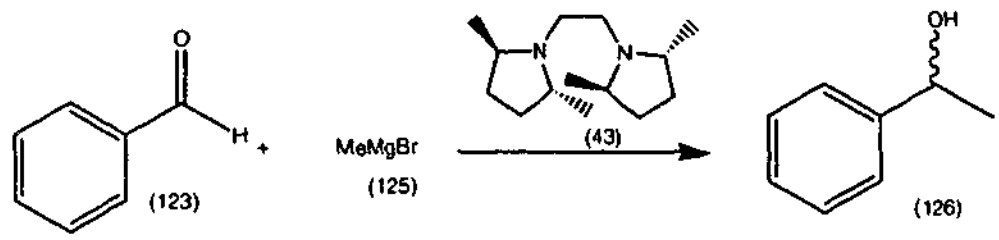
(Scheme 4.11).[149] Therefore, the use of the related pyrrolidine ligand (43) in Gringard reactions was of interest.



Scheme 4.11

4.4.1 Asymmetric Grignard reactions using 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethane (43)

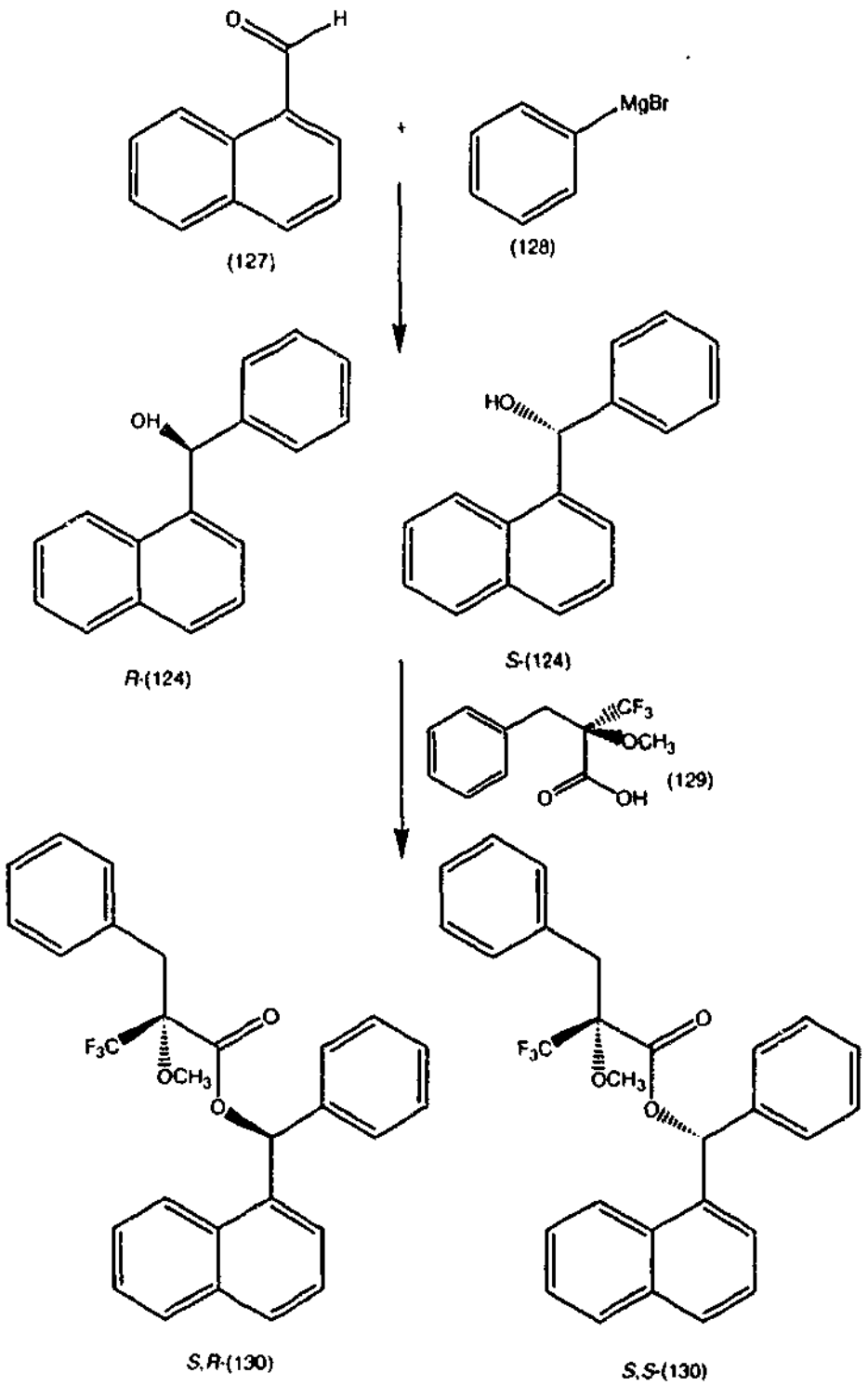
An asymmetric Grignard reaction was carried out using benzaldehyde (123) and methyl magnesium bromide (125) in the presence of the substituted pyrrolidine ligand (43) (Scheme 4.12). A control reaction was also carried out without the use of the chiral auxiliary (43). Both the reactions showed partial conversion to the alcohol (126). The product isolated from the reaction using the chiral auxiliary (43) showed no enantioselectivity. This result led to a study of α-naphthylbenzaldehyde (127), a more sterically demanding substrate.



Scheme 4.12

A Grignard reaction was carried out with the α-naphthaldehyde (127) and phenyl magnesium bromide (128). The reaction was monitored by ^{1}H n.m.r. spectroscopy.

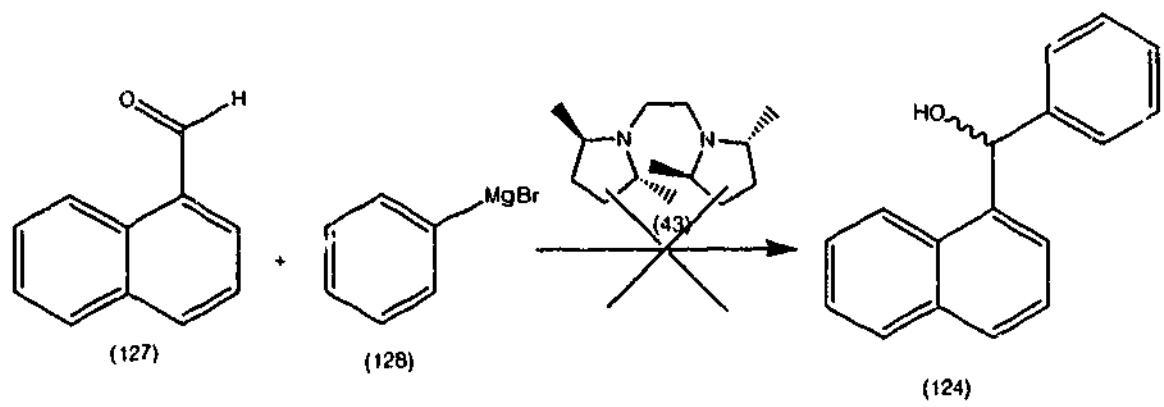
During the time specified (1 h) by Tomioka *et al.*, the reaction had not gone to completion, therefore the reaction was left for a further 36 hours. The racemic alcohol (124) was isolated and reacted with Mosher's acid ((-)-MTPA) (129) (Scheme 4.13) to give the Mosher's ester (130).[154]



Scheme 4.13

The ^{1}H n.m.r. spectrum of the two diastereoisomers showed two distinct multiplets for the methoxyl protons at δ 3.38-3.43 and 3.48-3.52. Two distinct peaks were also observed in the ^{19}F n.m.r. spectrum at δ 71.7 and 71.8 for the CF_3 groups.

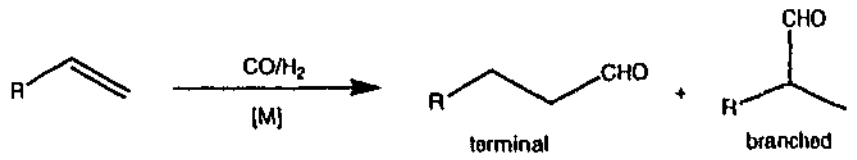
With this knowledge, an asymmetric Grignard reaction involving α-naphthaldehyde (127) (Scheme 4.14) was carried out using chiral ligand (43). Unfortunately, the reaction failed and gave only starting material (127). This again suggested that the steric effects exerted by the methyl group of the pyrrolidine ligand (43) was preventing the aldehyde (127) from binding to the metal ligand complex, as with the dihydroxylation reactions described in Chapter 3.



Scheme 4.14

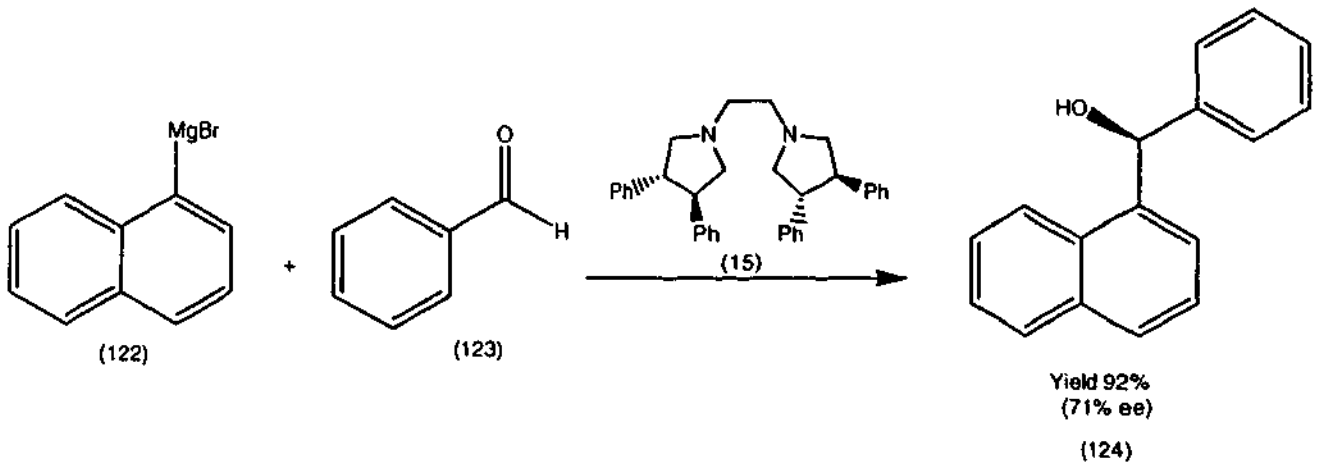
4.5 Asymmetric hydroformylation

The "oxo process" or "hydroformylation" is the metal catalysed addition of CO and H_2 to an olefin to produce an aldehyde.[155,156] Depending on the insertion point of the carbonyl group either a branched or a terminal aldehyde is produced (Scheme 4.15).[76] The formation of terminal aldehydes and their use in the synthesis of heterocycles will be extensively discussed in Chapter 6. In this section, the synthesis of chiral aldehydes was evaluated, which means that the insertion to favour the formation of branched aldehydes was desired.



Scheme 4.15

Styrene (8) is the substrate of choice for the evaluation of asymmetric hydroformylation reactions for a few reasons. Firstly, styrene (8) is highly reactive giving mainly the branched aldehyde (90:10, branched (131): terminal (132)) (Scheme 4.16).[157] Also, the branched aldehyde (131) is related to important chiral pharmaceuticals such as non-steroidal anti-inflammatory drugs based on 2-arylpropanoic acids.[158,159]



Scheme 4.16

A variety of chiral phosphorous containing ligands have been synthesised for use in the asymmetric metal catalysed hydroformylation reactions of styrene (8) and related compounds.[160] Most of the diphosphine ligands give poor to moderate enantioselectivities, but the mixed phosphine-phosphite ligand (Figure 4.6) reported by Takaya and co-workers gave excellent regioselectivity towards the branched aldehyde with an enantioselectivity of >90%.[161,162] However, the synthesis of this ligand is complicated and lengthy.[162]

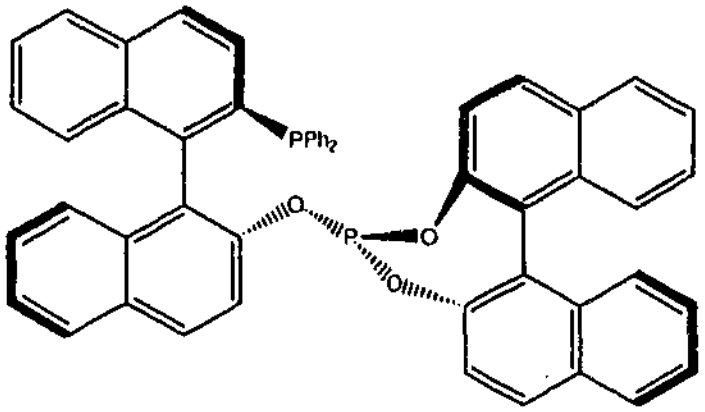


Figure 4.6: Ligand synthesised by Takaya[163]

Disulfide ligands have also been used in hydroformylation reactions of styrene (8) to give moderate enantioselectivities (4-58% ee).[164,165] Mixed ligands containing both phosphorus and sulfur heteroatoms (Figure 4.7) have also been synthesised and used to give quite satisfactory chemo- and regioselectivities but with low enantioselectivities (14% ee).[166] Other mixed ligands containing both N and P heteroatoms (Figure 4.7) have been used in the hydroformylation of styrene (8) with poor regio- and enantioselectivity.[160] Diamine ligands do not appear to have been used in hydroformylation reactions. A study was undertaken into the use of 1,2-bis-((2*R*,5*R*)-2, 5-dimethylpyrrolidin-1-yl)benzene (44) as a ligand in rhodium catalysed asymmetric hydroformylation of styrene (8).

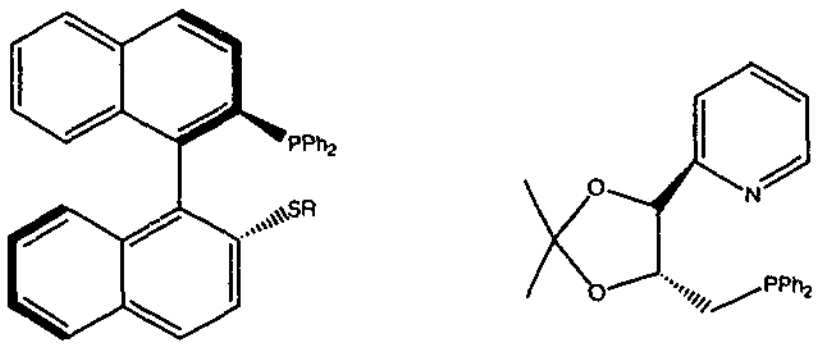
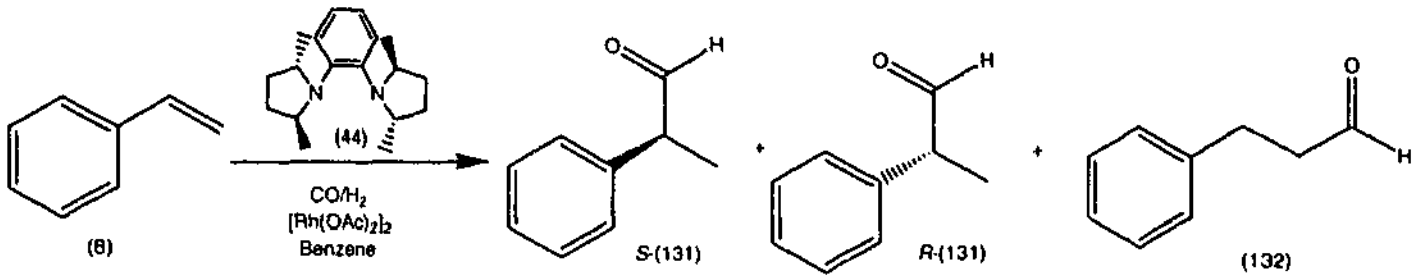


Figure 4.7: Phosphorus/sulfur and phosphorus/nitrogen mixed ligands

4.5.1 Asymmetric hydroformylations using 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (44)

Hydroformylation reactions were carried out using styrene (8) (Scheme 4.17) at two different *syn* gas pressures with a substrate: catalyst ratio of 1:100 to give branched (131) and linear (132) aldehydes (Table 4.4).



Scheme 4.17

Table 4.4: Asymmetric hydroformylations of styrene (8)

Entry	CO/H_2 (psi)	Temp (°C)	Time (h)	Products isolated (%)		
				S/m (8)	(131) (%ee)	(132)
1	1000	80	20	-	83 (-%)	17
2	400	50	20	50	44 (-%)	6
3	400	50	48	-	88 (15%)	12

The first reaction of styrene (8) was carried out at 1000 psi of hydrogen pressure and gave complete conversion to aldehyde after 20 hours (Entry 1). When the reaction pressure was decreased a longer reaction time was required for the reaction to go to completion (Entries 2 and 3). The enantioselectivity was measured by the use of a chiral shift reagent [$Eu(hfc)_3$] and ^1H n.m.r. spectroscopy. Although, only a 15% enantioselectivity was obtained, both this and the good regioselectivity were comparable with what has been reported with most phosphorus and the mixed ligands.[164]

4.6 Conclusion

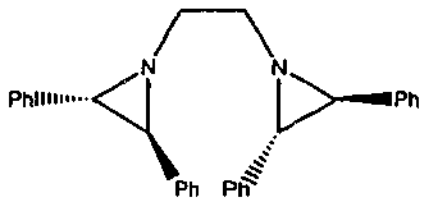
The chiral diamine ligand (43) based on 2,5-dimethylpyrrolidine was too hindered for the use in asymmetric Grignard reactions. However, the asymmetric allylic alkylation reactions carried out using chiral pyrrolidine (43) showed excellent enantioselectivity (75-85% ee). Good stereoselectivity (51% ee) was achieved when ligand (66) was used. Chiral diamine ligand (44) showed promise in Rh-catalysed hydroformylation of styrene (8). Cu-catalysed oxidative coupling of methyl 3-hydroxy-2-naphthoate (109) was successfully achieved with two ligands ((65), (62)). However, only ligand (62) was capable of inducing enantioselectivity (23% ee).

Chapter 5

Attempted Synthesis of Aziridine Based Ligands

5.1 Introduction

The three membered nitrogen heterocycle, aziridine, was first discovered by Gabriel in 1888.[167,168] Since then aziridines have played an important role in many industries, particularly in the synthesis of polymerisation products and adhesives.[169] They are also a rich source of important pharmaceuticals such as adrenoreceptor blocking agents and chemotherapeutic agents.[169] Tanner and co-workers have used the chiral bis-aziridine ligand (58) (Figure 5.1) in asymmetric transformations with great success.[170] Asymmetric reactions such as dihydroxylations, aziridinations, alkylations and cyclopropanations were studied by this group.[91,168,170,171]



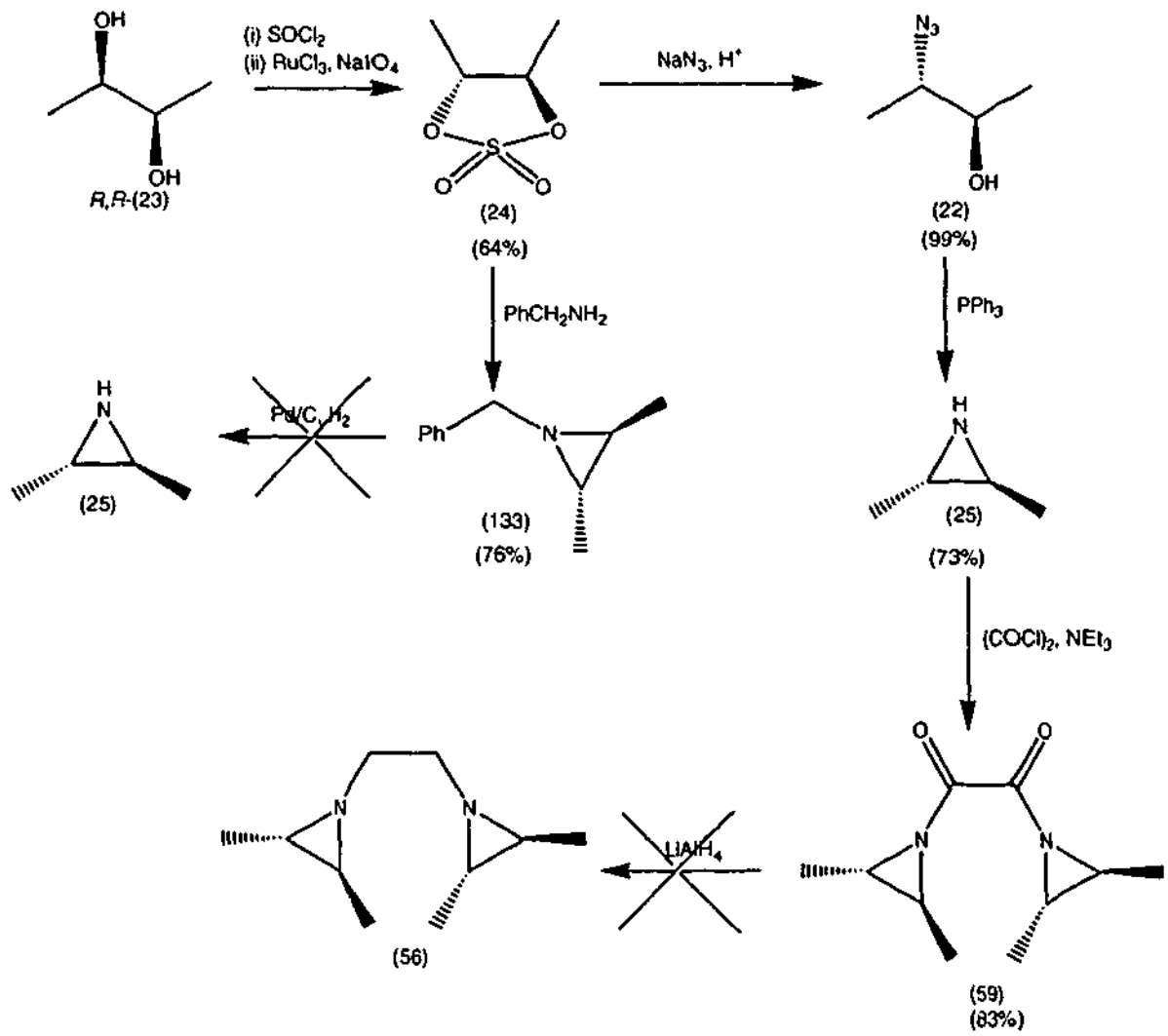
(58)

Figure 5.1: 1,2-Bis-(2,3-diphenylaziridin-1-yl)ethane (58)

Synthesis of ligand (56), very similar to that used by Tanner and co-workers, was attempted. This ligand (56) has methyl substituents at the two and three position of the aziridine ring instead of the phenyl substituents found in ligand (58). The ligands (56) and (57) were to be synthesised using similar methodology to that used for the pyrrolidine ligands (43) and (44). The (2*R*,3*R*)-butanediol (23) is produced from

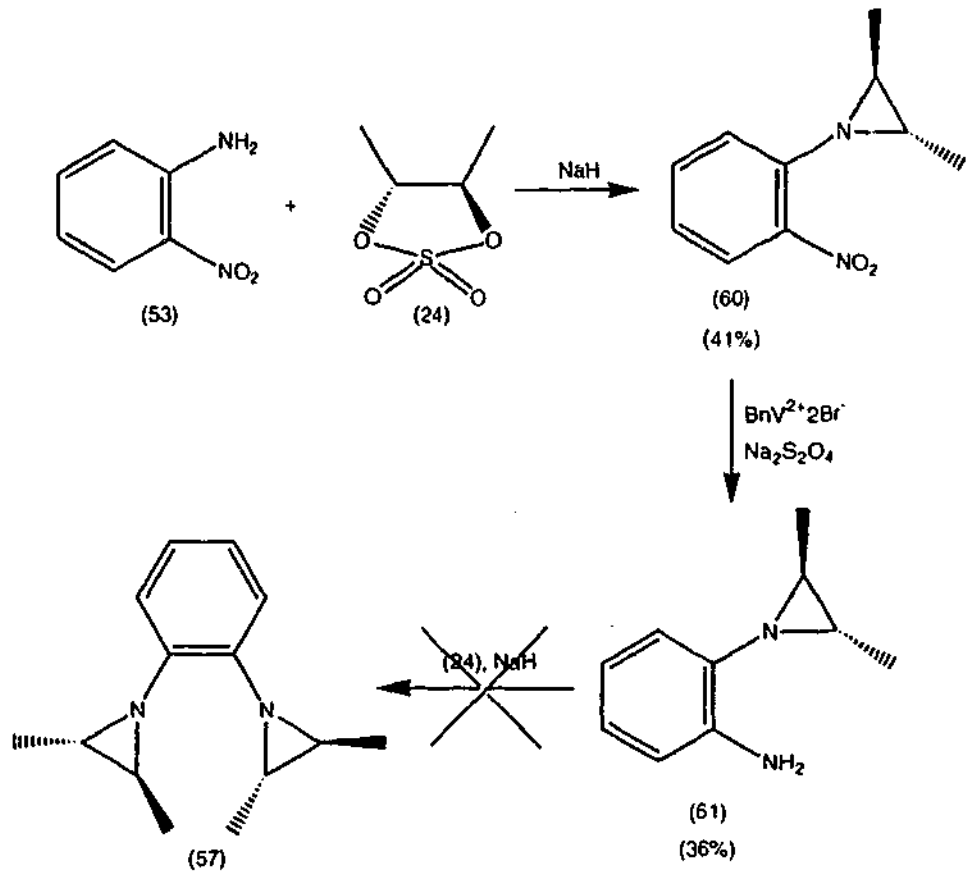
reactions involving yeast as a reducing agent. The chiral butanediol (23) is next converted to the cyclic sulfate (24) (Scheme 5.1).

Synthesis of the chiral ligand (56) was attempted by reacting the cyclic sulfate (24) with benzylamine. However, hydrogenolysis of the resulting benzyl aziridine (133) failed to give the desired product (25). Alternatively, the aziridine (25) was prepared by converting the cyclic sulfate (24) to the azido alcohol (22), followed by a cyclisation reaction. Next, the aziridine (25) was reacted with oxalyl chloride to give the diamide (59) but reduction with $LiAlH_4$ failed to give the desired ligand (56) (Scheme 5.1).



Scheme 5.1

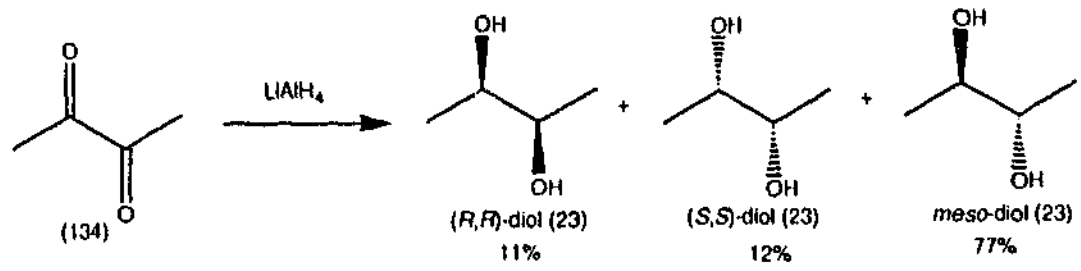
Attempts to synthesise the chiral ligand (57) involved the reaction of the cyclic sulfate (24) with *o*-nitroaniline (53). The product was reduced using benzyl viologen dibromide and sodium dithionate to afford the desired amine (57).[172,173] Coupling of the second cyclic sulfate (24) to the amine failed to give the desired ligand (57) (Scheme 5.2).



Scheme 5.2

5.2 Yeast reductions leading to (2*R*,3*R*)-2,3-butanediol (23)

It was observed that 2,3-butanediol (23) was produced as a by-product in the fermentation reaction leading to (2*S*,5*S*)-2,5-hexanediol (49) (Section 2.2). Samples of the racemic and *meso* diols (23) in a 33:67 ratio were obtained by $LiAlH_4$ reduction of butanedione (134) (Scheme 5.3).



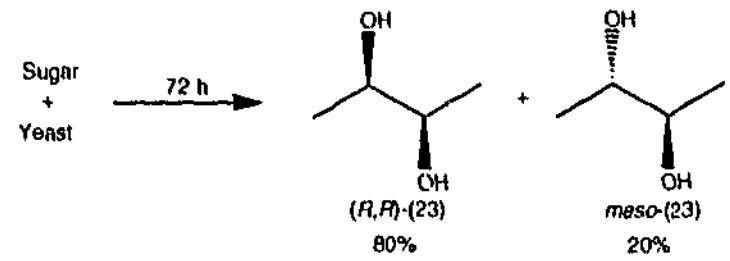
Scheme 5.3

The fermentation reaction of 2,3-hexanedione (50) produced (2*R*,3*R*)-2,3-butanediol (23) in a 89% enantioselectivity (Table 5.1, Entry 1). This result was quite intriguing since there was no obvious substrate present in the reaction mixture that could produce (2*R*,3*R*)-2,3-butanediol (23). A number of different yeast reductions were undertaken and they are summarised in Table 5.1.

Table 5.1: Yeast reduction to form butanediol (23)

Conditions used	Entry	Substrate used	Products isolated (%)				Reaction time (days)	Sugar Conc (g/ml)
			(*S*,*S*)-(49)	(*R*,*R*)-(23)	(*S*,*S*)-(23)	*meso*-(23)		
Fermentation	1	Hexanedione (50)	>90	9.45	0.55	0	7	0.22
	2	None	-	80	0	20	7	0.42
	3	Butanedione (134)	-	46	4	50	7	0.22
Non-Fermentation	4	Butanedione (134)	-	20	13	67	24 h	-

Fermentation reactions using sugar and yeast with no substrate gave the (2*R*,3*R*)-diol (23) and the *meso*-diol (23) in a 4:1 ratio (Scheme 5.4) (Table 5.1, Entry 2). This ratio was determined by ^{1}H n.m.r. spectroscopy. The optically active diol (23) was separated from the *meso*-diol (23) using column chromatography and its enantioselectivity measured using chiral gas chromatography. The (2*R*,3*R*)-diol (23) was the only enantiomer detected.



Scheme 5.4

This result was very similar to that reported by Romano *et al.*[174] and Roustan *et al.*.[175] The sugar (sucrose) in the reaction medium enters the yeast cell by facilitated diffusion. Sucrose is hydrolysed by the enzyme invertase to D-glucose and D-fructose, which is held in the yeast cell wall.[96] The monosaccharides are then transported through the plasma membrane by facilitated diffusion. Both D-glucose and D-fructose are converted to pyruvate (135) by glycolysis. The pyruvate (135) can then undergo transformation to a number of different products including ethanol, acetate and 2,3-butanediol (23) (Figure 5.2).[176] Low boiling materials such as ethanol, and water soluble products such as acetate, would be lost during the work up process.

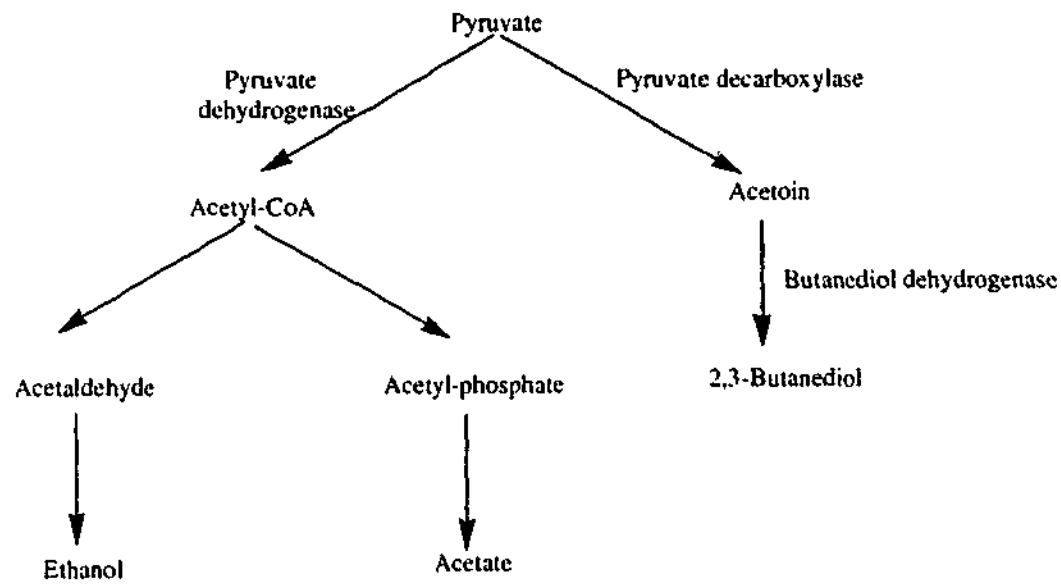
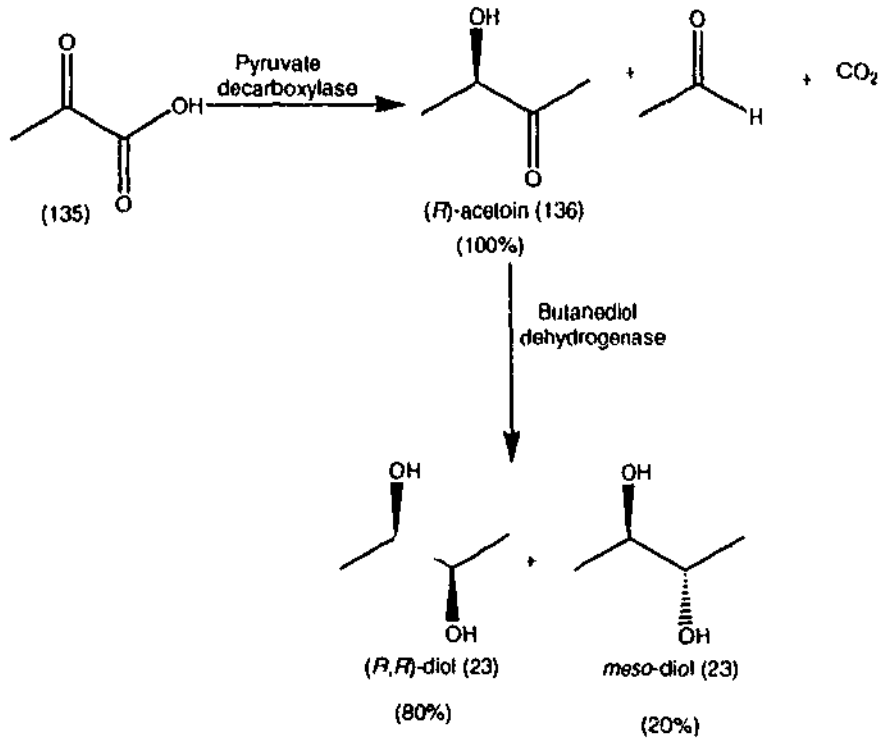


Figure 5.2: Products isolated by pyruvate metabolism

The absence of the (*S*,*S*)- configured diol (23) from the fermentation reaction suggested that decarboxylation of pyruvate (135) produces only the (*R*)-acetoin (136)

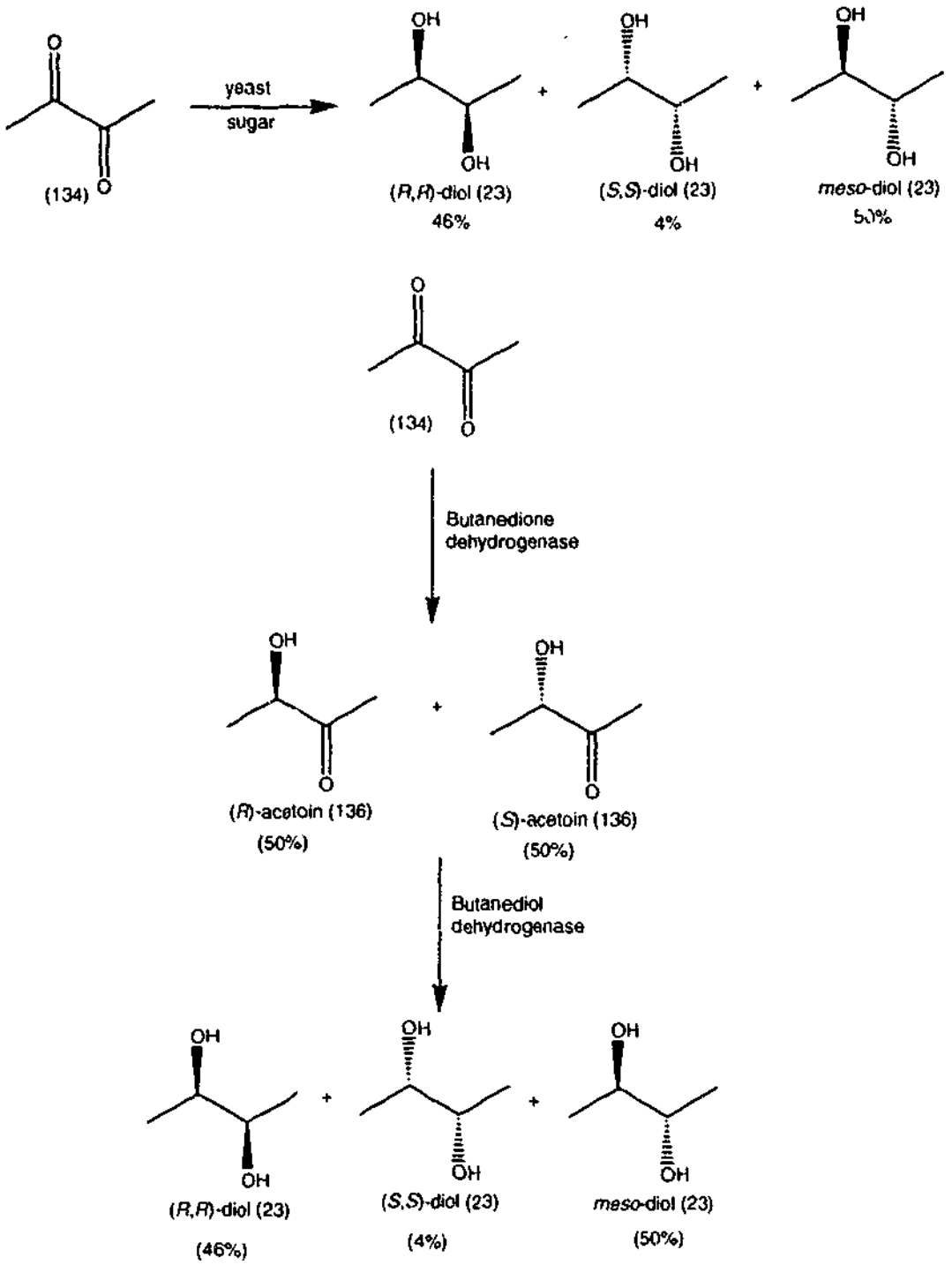
enantiomer (Scheme 5.5).[177] This result infers that the enzyme (pyruvate decarboxylase) responsible for this reaction is extremely enantioselective. However, the butanediol dehydrogenase which is the enzyme responsible for the second reduction[176] does not seem to be as streoselective. Therefore, two products, namely the (*R*,*R*)-diol (23) and the *meso*-diol (23), are formed.



Scheme 5.5

It was interesting that the 2,5-hexanedione (50) reduction produced both the (*S*,*S*)-diol (23) and the (*R*,*R*)-diol (23) with none of the *meso*-(23) (Entry 1), whereas in the absence of substrate none of the (*S*,*S*)-diol (23) but some *meso*-diol (23) was formed (Entry 2). This result suggests that either the hexanedione (50) or the increased sugar concentration (0.42 g/ml *vs* 0.22 g/ml)[176] in the reduction mixture affects the stereochemistry of the product. A similar observation was observed during the yeast reduction of 2,3-pentanedione.[178]

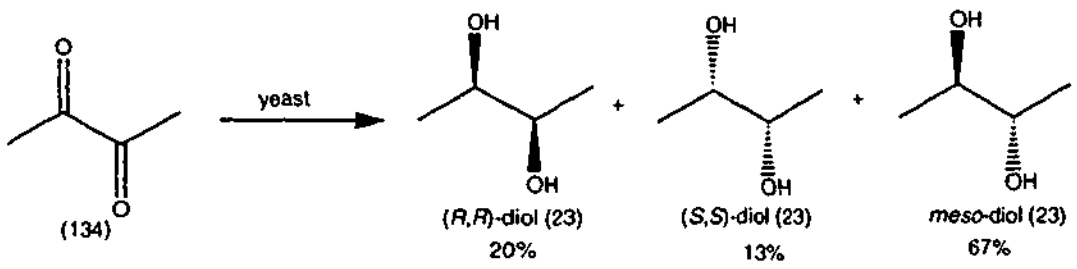
Reduction of 2,3-butanedione (134) under fermentation conditions gave 50% of the *meso*-diol (23) (Entry 3). This result is consistent with the literature.[175,178] Chiral gas chromatography was used to measure the enantioselectivity of the reaction and showed that 4% of the chiral material present was the (2*S*,3*S*)-diol (23) with 46% as the (2*R*,3*R*) isomer (23) (Scheme 5.6).



Scheme 5.6

This result suggests that the butanedione dehydrogenase does not exhibit high stereoselectivity in the reduction of butanedione (134) and results in both (*R*) and (*S*)-acetoin (136) in approximately 1:1 ratio (Scheme 5.6). The second reduction, which is similar to the route of pyruvate (135) (Scheme 5.5) reduction exhibits greater selectivity and gives all of the chiral products, (*R*,*R*)-(23), (*S*,*S*)-(23) and *meso*-(23), in a ratio of ~12:1:13. The sugar in the reaction mixture probably facilitates the production of the chiral material, however, the degree to which this contributes remains unknown.

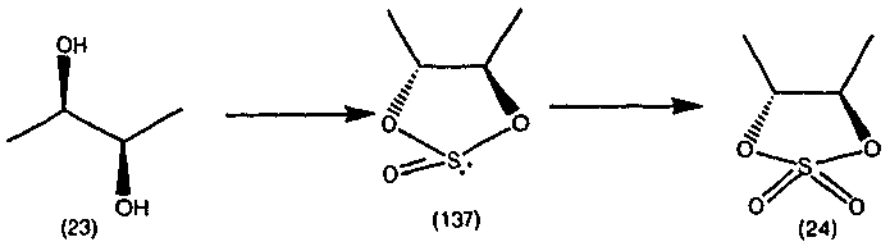
Reactions carried out under non-fermentation conditions showed reduced enantioselectivity for the (*R*,*R*)-diol (23) (Scheme 5.7) (Table 5.1, Entry 4). *Meso*-diol (23) formation also significantly increased. In this reaction, there is no effect from the sugar towards the butanediol (23) formation. The sugar is known to induce the activity of fermenting enzymes and hence change the stereochemistry of the products that are isolated.[178]



Scheme 5.7

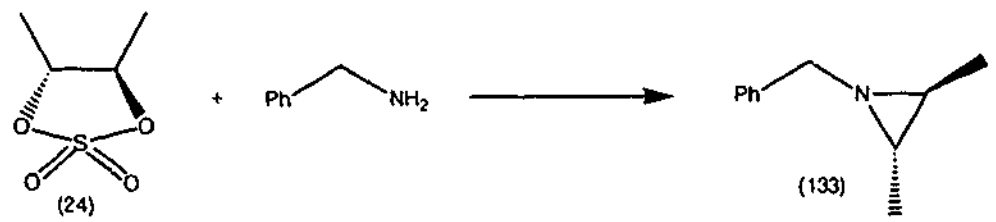
5.3 Synthesis of (2*R*,3*R*)-2,3-dimethylaziridine (25)

The cyclic sulfate (24) was prepared from (2*R*,3*R*)-butanediol (23) by reaction with thionyl chloride to give the cyclic sulfite (137). This was immediately oxidised with ruthenium trichloride and sodium periodate to give (24) (Scheme 5.8).



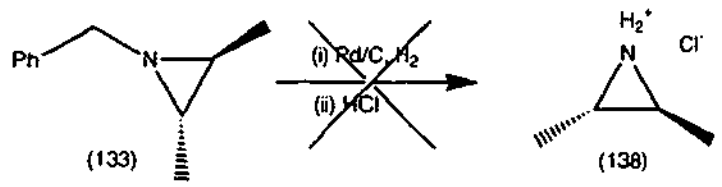
Scheme 5.8

The cyclic sulfate (24) was reacted with benzylamine to form the benzyl aziridine (133) (Scheme 5.9). The structure of this molecule was confirmed by ^{1}H n.m.r. spectroscopy where two doublets were recorded for the diastereotopic benzylic protons with a coupling constant of 14 Hz.



Scheme 5.9

This product was subjected to hydrogenolysis using Pd/C and H_2, followed by hydrochloride salt formation (Scheme 5.10). The ^{1}H n.m.r. spectrum of the isolated crude oil suggested that a mixture of compounds had been formed but none corresponded to the desired aziridine (25), the aziridine hydrochloride salt (138) or starting material (133).

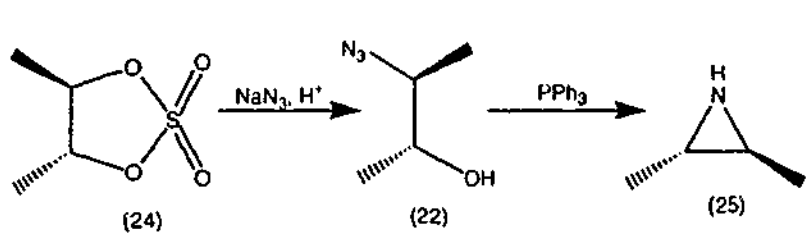


Scheme 5.10

Unlike the stable five membered pyrrolidine ring, the aziridine ring, is highly strained and is highly susceptible to ring opening.[91] Ibuka *et al.* showed that Pd(0) was

responsible for isomerisation reactions of aziridines involving ring opening.[179] Ambrosi *et al.* also showed the use of Pd/C led to ring opening of aziridines.[180] The attempted salt isolation involving acid may have also led to ring opening even though mild conditions were used. Aziridine ring opening by acids is well documented.[45,91]

The aziridine (25) was prepared following a method described by Shustov *et al.* (Scheme 5.11).[51] The cyclic sulfate (24) was converted to an azide (22) using sodium azide in an acidic medium (99% yield). The azide (22) was then reacted with triphenylphosphine to form the desired aziridine (25) which was distilled from the reaction mixture (73% yield). Much care was needed to isolate this low molecular weight amine (25) as it was highly volatile.

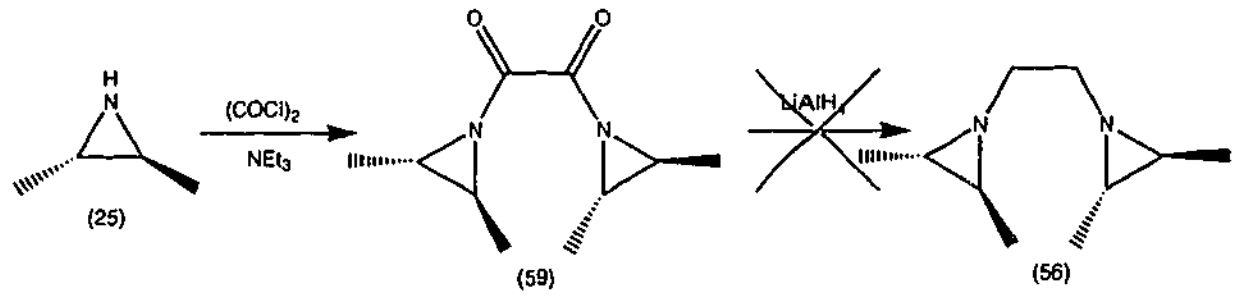


Scheme 5.11

5.4 Attempted synthesis of the chiral (2*S*,3*S*)-bis-aziridine ligand (56)

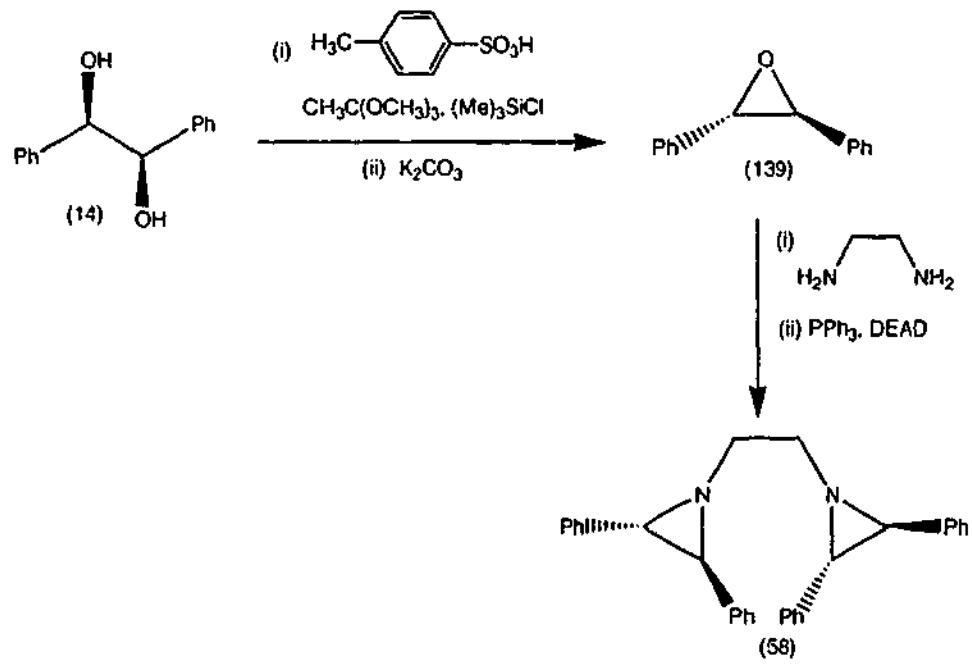
The aziridine (25) was reacted with oxalyl chloride in the presence of excess triethylamine to give the desired diamide (59) (Scheme 5.12). Excess triethylamine was crucial as this neutralised the hydrochloric acid that was being produced during the reaction, preventing any ring opening. The presence of the diamide (59) was confirmed by the strong infrared stretching observed at 1672 cm^{-1} and an accurate mass spectrum which showed a $[M+Na]^+$ peak at 219.1105. Unfortunately, the lithium aluminium hydride reduction, performed under varying experimental conditions, failed to give the desired ligand (56) (Scheme 5.12). The ^1H n.m.r. spectra isolated of

the crude oils showed multiple products. Mass spectra of the crude oils did not show the desired mass for the product (56).



Scheme 5.12

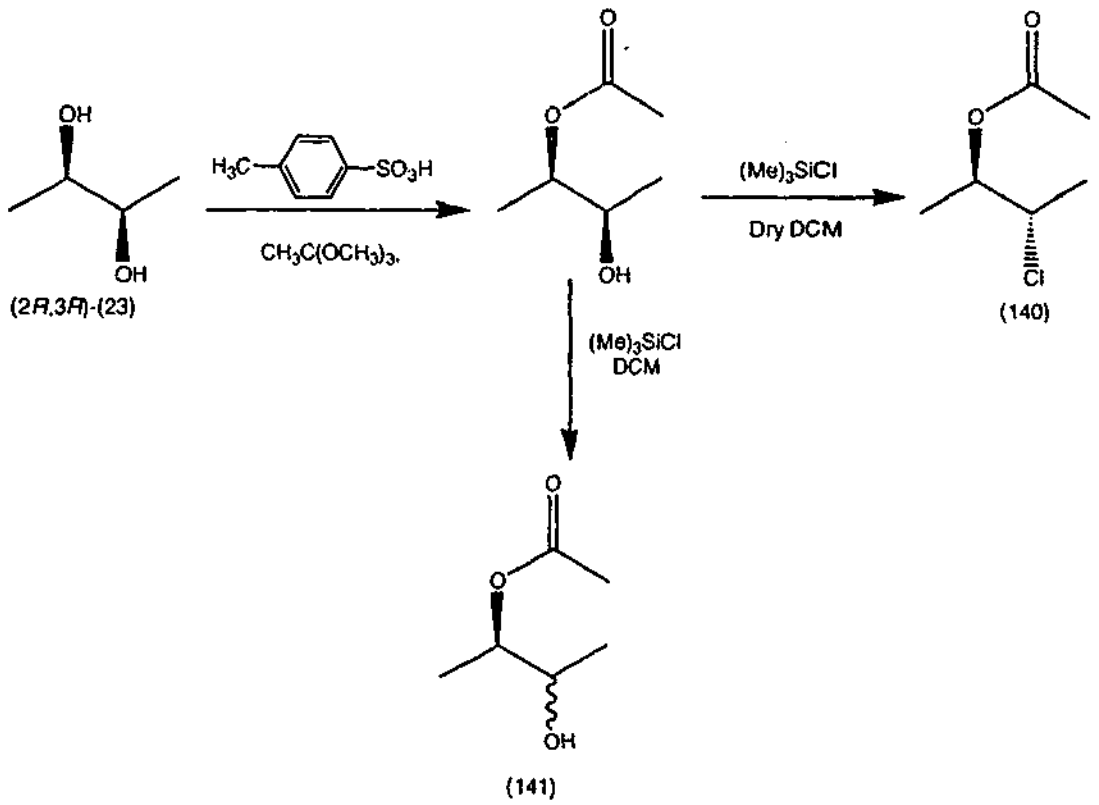
These results led us to investigate other avenues for the synthesis of the bis-aziridine (56) ligand. The Tanner group had synthesised[181] these ligands using an epoxide[182] route (Scheme 5.13). The diol (14) was converted to an epoxide (139) which was reacted with ethylenediamine followed by ring closure to give the desired ligand (58).[181]



Scheme 5.13

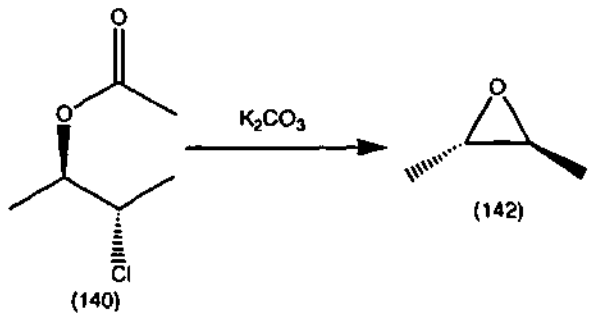
This same methodology was used in an attempted synthesis of the ethane bridged ligand (56). The (2*R*,3*R*)-butanediol (23) was reacted with *p*-toluenesulfonic acid and

trimethylorthoacetate, to activate one of the hydroxyl groups (Scheme 5.14). Trimethylsilyl chloride was added to produce the 2-acetoxy-3-chlorobutane (140). It was noted that when the dichloromethane was not vigorously dried hydroxy acetate (141) was formed.



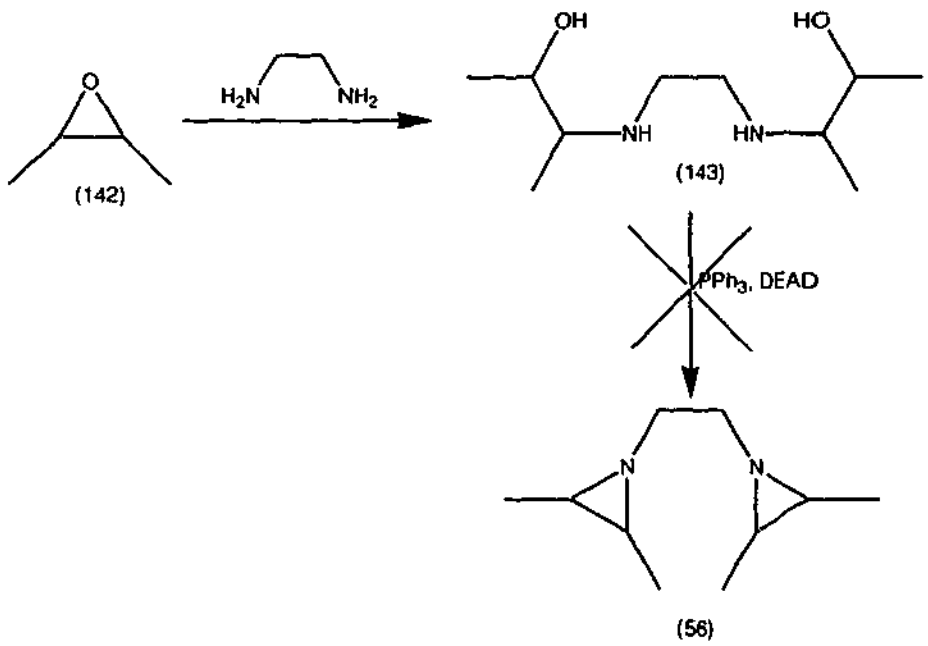
Scheme 5.14

The 2-acetoxy-3-chlorobutane (140) was reacted with potassium carbonate and the ^{1}H n.m.r. spectrum of the crude reaction mixture showed the presence of the epoxide (142) (Scheme 5.15). As the epoxide (142) was highly volatile isolation was not attempted.



Scheme 5.15

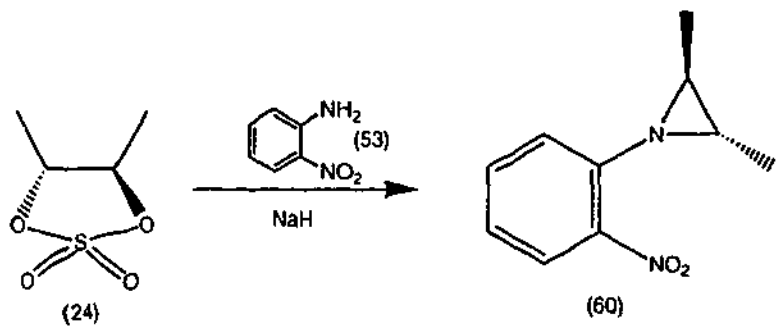
Attempted synthesis of the bis-aziridine ligand (56) was first carried out using a sample of racemic epoxide (142) which was reacted with ethylenediamine under the conditions described by Andersson *et al.*.[181] The ethane bridged bis-amino alcohol (143) that was isolated was a low melting solid (Scheme 5.16). A Mitsunobu reaction[106] was carried out on this solid in an attempt to form the desired bis-aziridine ligand (56). This reaction failed, and no signals were observed for the product (56) in the ^{1}H n.m.r. spectrum of the crude mixture. It is unclear as to why the reaction failed as triphenylphosphine oxide and reduced DEAD was isolated at the end of the reaction.



Scheme 5.16

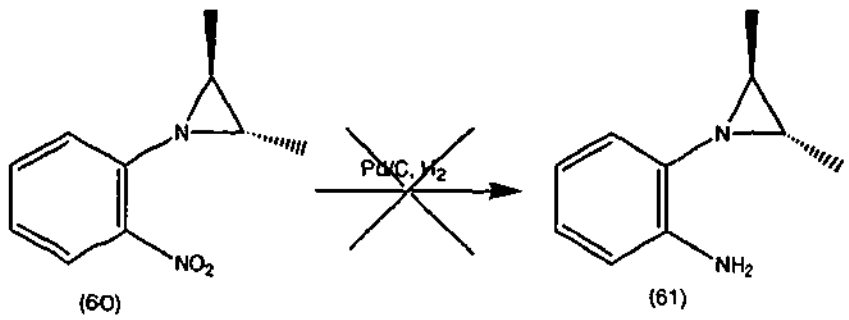
5.5 Attempted synthesis of the chiral (2*S*,3*S*)-bis-aziridine ligand (57)

Following the same procedure used to prepare the pyrrolidine ligand (44), the cyclic sulfate (24) was reacted with *o*-nitroaniline (53) in the presence of sodium hydride to afford the nitro aziridine (60) as a yellow solid (Scheme 5.17). An accurate mass spectrum was obtained which showed a peak corresponding to the $[M+Na]^+$ peak at 215.0794.



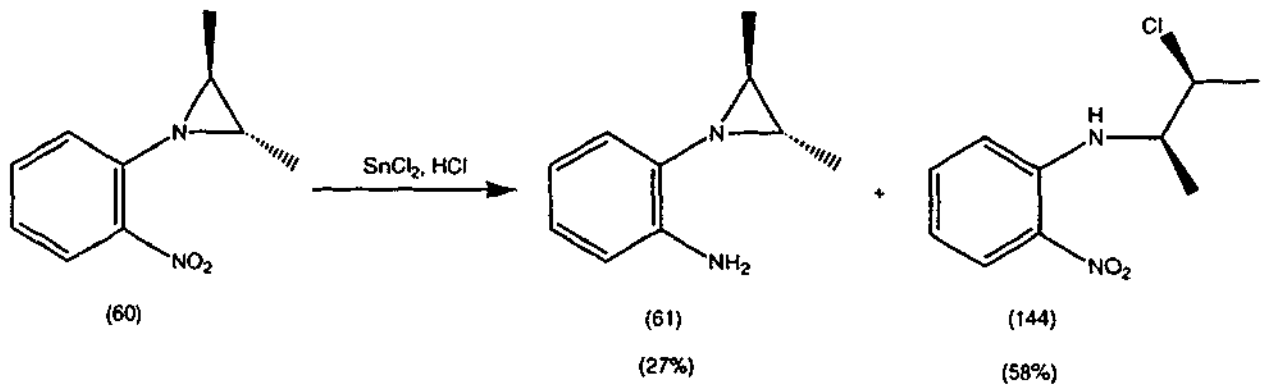
Scheme 5.17

Attempted reduction of the nitro group was carried out using a number of methods. The first method was to use Pd/C with H_2 at 60 psi (Scheme 5.18), a method successfully used to reduce the related pyrrolidine (54) (see Section 2.6). However, the results obtained were very similar to that resulting from the attempted hydrogenolysis of benzyl aziridine (133). Neither starting material (60) nor product (61) was isolated at the end of the reaction.



Scheme 5.18

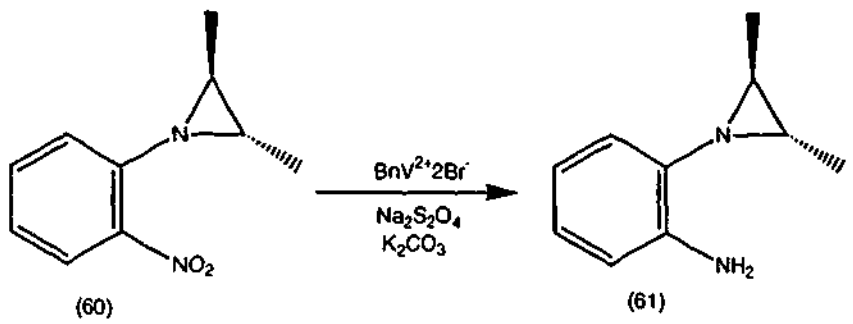
The second reduction method involved the use of stannous chloride with concentrated hydrochloric acid as described by Beckwith *et al.*.[183] Again, the hydrochloric acid caused the strained aziridine ring to open giving the chloro amine (144) as the major product (58%) (Scheme 5.19). The desired anilino aziridine (61) was however isolated, albeit in low yield (27%). The presence of the aziridine amine (61) was confirmed by accurate mass spectroscopy which showed a $[M+H]^+$ signal at 163.1235. Also, the infrared spectrum showed strong stretching at 3444 cm^{-1} characteristic of primary amines.



(60) (61) (27%) (144) (58%)

Scheme 5.19

Finally, an electron transfer catalyst, benzyl viologen (1,1'-dibenzyl-4,4'-pyridinium) dibromide, and sodium dithionate were used to affect reduction of the nitro group to give the amino aziridine (61) (Scheme 5.20).

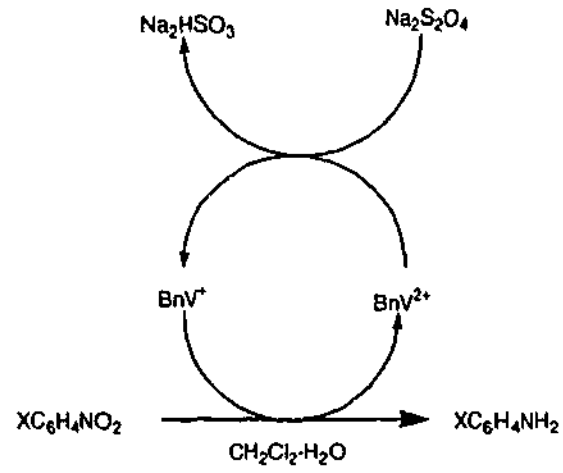


(60) (61)

Scheme 5.20

Reduction of the aromatic nitro group takes place in the following cycle where the benzyl viologen dibromide acts as the reductant, as shown in Figure 5.3 (a).[172,173] The reduction of the nitro group requires a total of six electrons. Four electrons are required to get to the hydroxylamine intermediate (ArNHOH) (Figure 5.3 (b)). This intermediate is then reduced to the aniline with two more electrons.

(a)



(b)

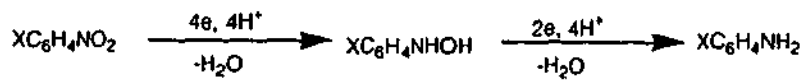
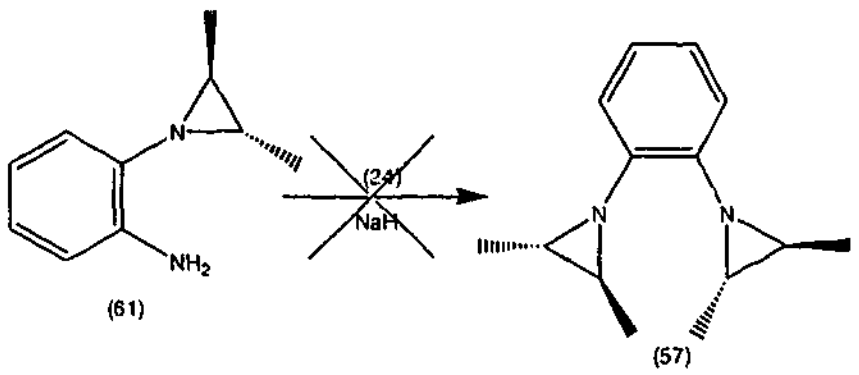


Figure 5.3: (a) Cyclic pathway for the viologen-mediated reduction of nitroarenes with sodium dithionate; (b) Electron transfer during the nitroarene reduction

The final step to prepare (57) required the coupling of the free amino group (61) with the cyclic sulfate (24). It had been previously shown that deprotonation of the aniline (61) by sodium hydride was required for successful preparation of pyrrolidine analogues (44) (Section 2.6). Reaction of (61) with sodium hydride and cyclic sulfate (24) (Scheme 5.21), gave a mixture of products none of which corresponded to either starting material (61) nor the desired product (57).



Scheme 5.21

5.6 Conclusion

(2*R*,3*R*)-Butanediol (23), produced *via* yeast reductions, was the key building block for the attempted synthesis of the bis-aziridine ligands (56) and (57). (2*R*,3*R*)-Butanediol (23) was converted to the cyclic sulfate (24) in a good yield (64%). Aziridine (25) was synthesised by the ringclosure of hydroxy azide (22) which was prepared by the cyclic sulfate (24). The aziridine (25) was successfully reacted with oxalyl chloride to form the desired diamide (59). Unfortunately, reduction of the amide failed to give the ethane bridged bis-aziridine ligand (56).

Synthesis of the ligand (57) was attempted by the reaction of the cyclic sulfate (24) with *o*-nitroaniline (53). The nitro group was then reduced to yield the aniline (61). Reduction using benzyl viologen dibromide and sodium dithionate gave a 36% yield of the desired aniline (61), whereas reduction using $SnCl_2$/HCl gave a 27% yield. The second coupling of the amine (61) with the cyclic sulfate (24), however, failed to give the desired ligand (57).

PART B

Chapter 6

Synthesis of Nitrogen Heterocycles by Rhodium Catalysed Hydroformylation of Polymer-Attached Amino Alkenes with Syn Gas

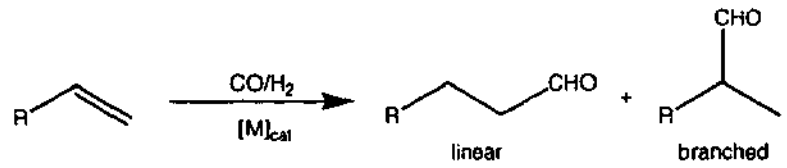
6.1 Introduction

Tandem reaction sequences are becoming increasingly important in organic synthesis and are often readily achieved through the use of metal catalysed reactions of difunctional molecules. A highly enantioselective route to five- and six-membered cyclic α-amino acids *via* a one pot, single catalyst, tandem hydrogenation-hydroformylation-cyclisation sequence was reported by Teoh *et al.*.[184] Bergmann *et al.* reported the synthesis of medium and large cyclic amines by rhodium-catalysed hydroformylation-reductive amination of amino alkenes.[185] The formation of larger sized heterocycles by this approach can, however, be challenged by competing dimerisation/polymerisation processes. Recently, Doyle and co-workers employed rhodium-carbenoid cyclisation to give high yields of medium and large rings in addition to five- and six-membered compounds.[186]

6.2 The hydroformylation reaction

Discovered in 1938 by Roelen, hydroformylation is one of the most important homogenous catalysed reactions in industry.[155,187,188] Also known as the "oxo process", hydroformylation is a metal catalysed addition of CO and H_2 to an alkene. Insertion of the CO takes place either at the terminal or the internal carbon of the

alkene giving rise to either a linear or branched aldehyde (Scheme 6.1).[31] Aldehydes are versatile chemical intermediates which can be readily converted into alcohols, amines, carboxylic acid derivatives *via* reduction, oxidation or other further reactions.[155] In industry terminal aldehydes are most sought after since they can be converted to primary alcohols which find application in the manufacture of solvents, plasticisers, detergents and coatings.[189-191]



Scheme 6.1

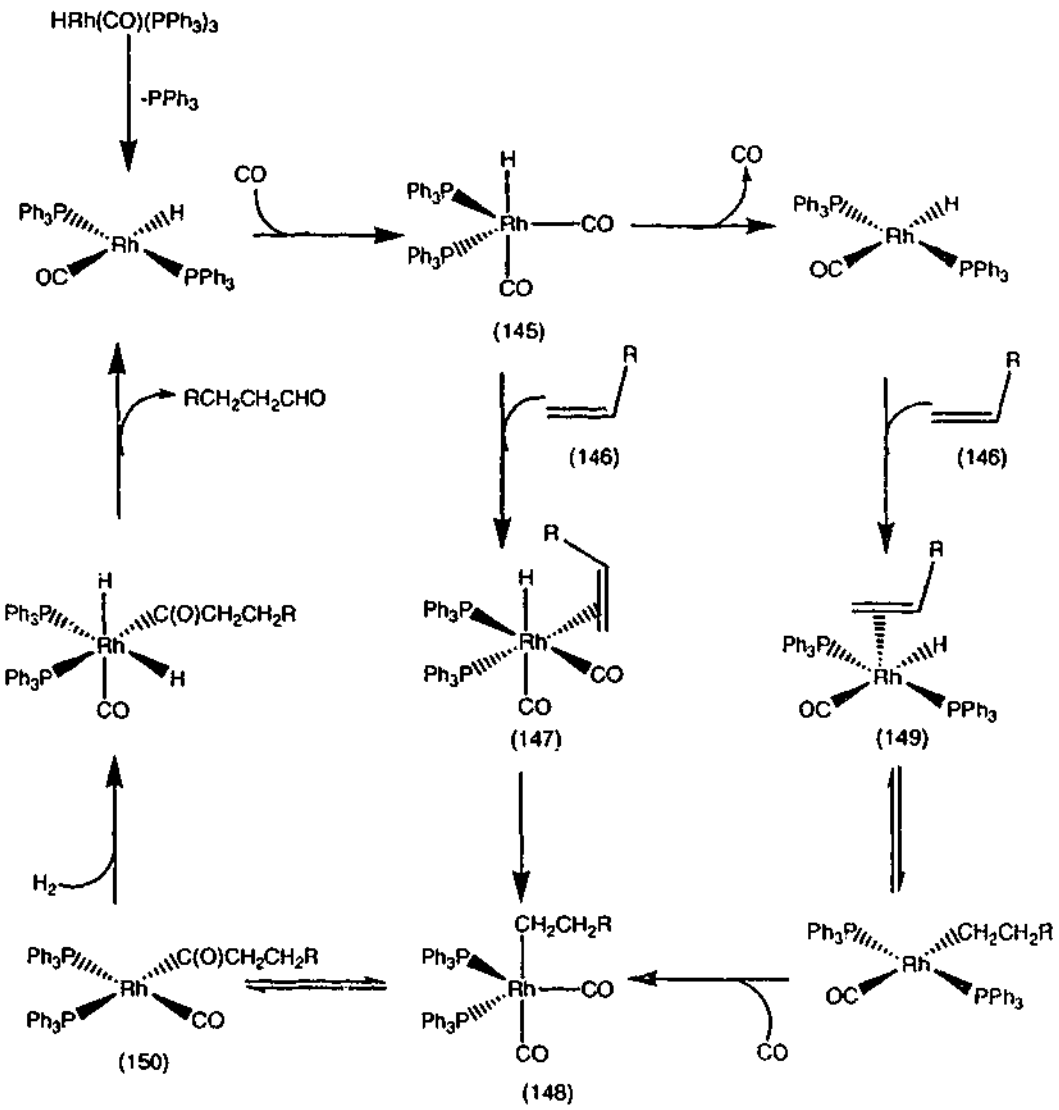
6.2.1 Hydroformylation catalysts

Hydroformylation catalysts which are used typically have the formula $H_xM_y(CO)_mL_n$. **M** is a transition metal atom with **L** being ligand/ligands capable of promoting the formation of metal carbonyl hydride species. The *x*, *y*, *m* and *n* factors of the formula can be modified according to the syn gas composition, pressure, temperature and ligand concentration.

Cobalt containing catalysts were the first catalysts used in hydroformylation reactions.[188] Several problems exist in the use of Cobalt carbonyl catalysts. The $HCo(CO)_4$ and $Co_2(CO)_8$ complexes are unstable or volatile making it difficult for product purification and catalyst recycling.[31] Also, limited selectivity towards the desired linear aldehyde and the severe reaction conditions[192] required for the reaction to take place makes these catalysts less attractive.[31] These short comings make rhodium phosphine catalysts much more attractive as they give high yields of the linear aldehydes under milder conditions. Hence, the rhodium based catalysts are

replacing the Co catalysts in most commercial plants such as for the hydroformylation of propylene.[193,194]

The mechanism of rhodium catalysed hydroformylation reactions using phosphine ligands was first proposed by Wilkinson and his co-workers.[195,196] They described both an associative and a dissociative mechanism as shown in Scheme 6.2.[197] (Note: For simplicity, Scheme 6.2 depicts the preparation of the linear isomer only).



Scheme 6.2

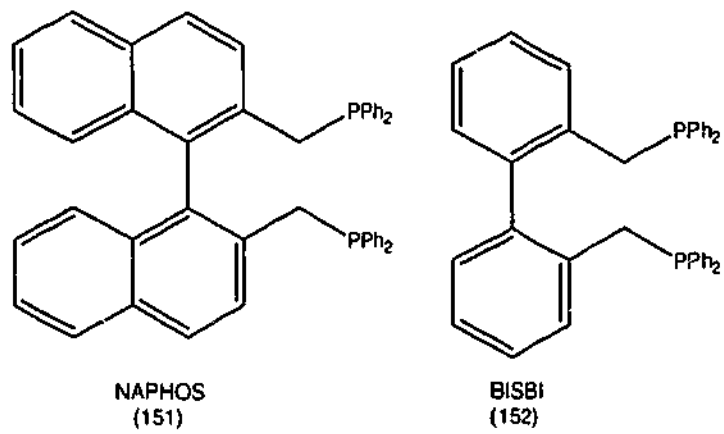
The $HRh(CO)_2(PPh_3)_2$ (145) complex is the key intermediate of both pathways.[198] The "associative pathway" (Blue) deals with the addition of the substrate (146) to complex (145) to form a six coordinate species (147) which is rapidly converted to the

alkyl complex (148). This pathway is preferred under high phosphine concentrations and low CO partial pressures. The "dissociative pathway" reaches the same complex (148) *via* the loss of a CO ligand followed by the addition of the substrate (146) to form a 5-membered complex (149). Both pathways undergo CO insertion to form the acyl complex (150), followed by the oxidative addition of H_2 which is believed to be the rate determining step.[199] Finally, the aldehyde is released *via* a reductive elimination and coordination of an additional CO ligand regenerating the Rh-complex (145).

6.2.2 Hydroformylation ligands

The phosphine ligands used in hydroformylation reactions play an important role as they dictate the regioselective outcome and the rate of the reaction. The ligands influence both the electronic and steric environment around the metal center.

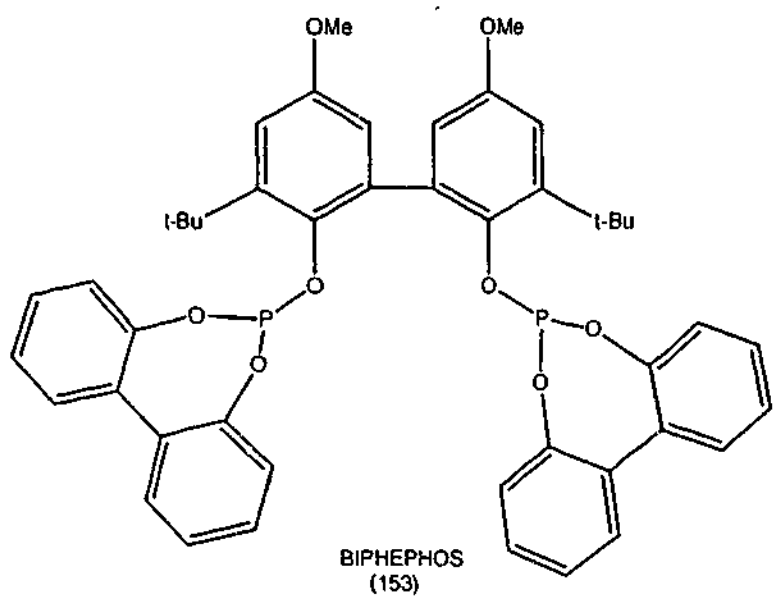
The use of diphosphine and phosphite ligands which have bite angles near 120° preferentially produced the terminal aldehyde rather than the branched aldehyde.[200-202] Examples of such ligands include NAPHOS (151) and BISBI (152) (Figure 6.1). Rh-complexes of these ligands are also known to increase the reactivity of the otherwise unreactive olefins.[203,204]



NAPHOS (151) BISBI (152)

Figure 6.1

Rhodium complexes of the BIPHEPHOS (153) (Figure 6.2) hydroformylate a variety of functionalised terminal alkenes with excellent regioselectivity (ratios of >40:1 for linear: branched aldehyde).[205] The rigid and sterically demanding bridge between the phosphorous atoms in the BIPHEPOS (153) ligand is believed to be reason for the high regioselectivity.[206]



BIPHEPHOS
(153)

Figure 6.2

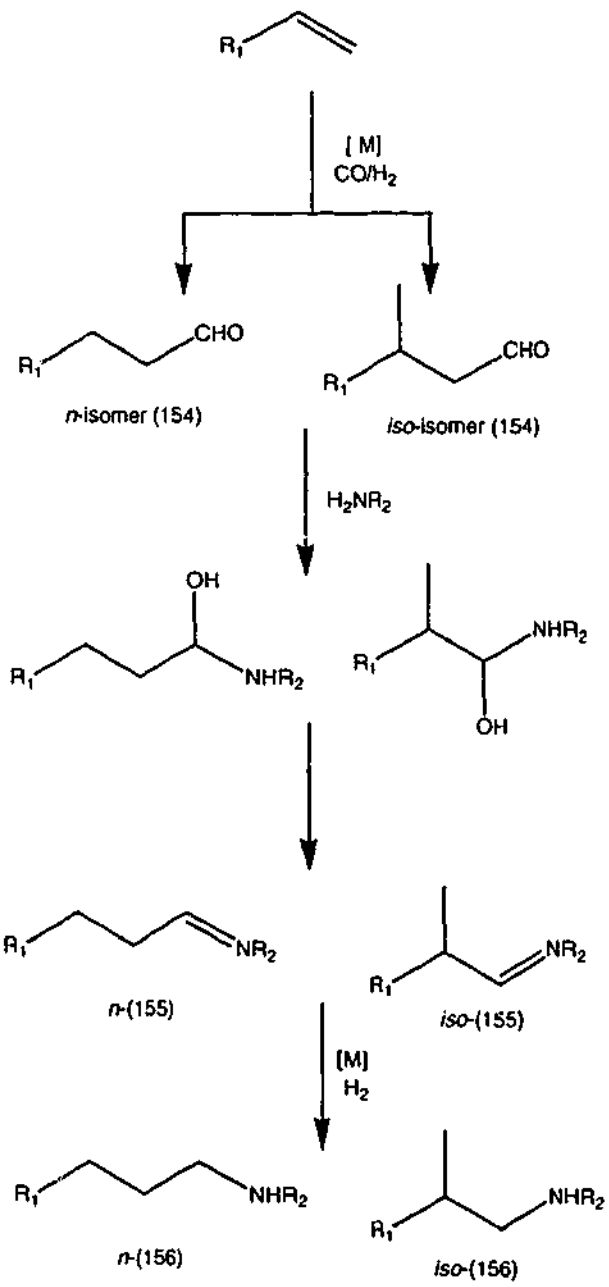
The basicity of the ligand also plays a role in the product formation. Rhodium complexes of the weakly basic triarylphosphines are more active hydroformylation catalysts than complexes of the strongly basic trialkylphosphines.[203,207] The electron-withdrawing properties of the aromatic phosphines shorten the metal-alkene bond, which results in a greater steric control to provide the linear aldehydes.[208]

The ligand concentration also plays a role in hydroformylation reactions. Utilising a higher ligand concentration increases the regioselectivity and decreases side reactions such as isomerisation and hydrogenation.[187,197]

Other factors such as temperature, carbon monoxide and hydrogen partial pressure and the steric and electronic properties of the substrate also effect the outcome of the hydroformylation reactions.

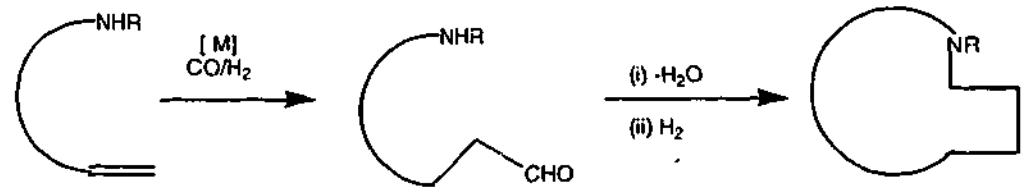
6.3 Tandem hydroformylation in the presence of *N*-nucleophiles

In this tandem reaction sequence, the initially formed aldehyde (154) reacts with an amine to form an intermediate imine (155) which is then hydrogenated in the presence of a rhodium catalyst to give a saturated amine (156) (Schene 6.3). This process, termed hydroaminomethylation, has recently been extensively reviewed.[155]



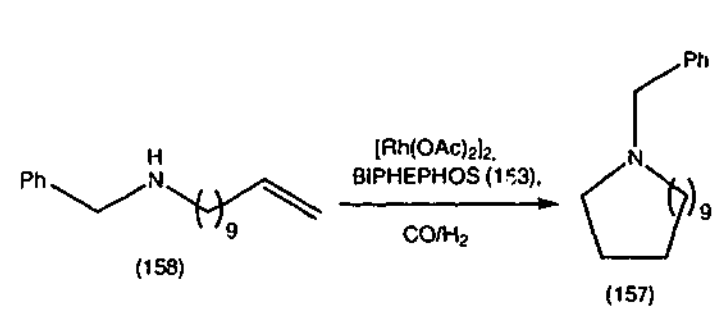
Scheme 6.3

If the reacting alkene molecule contains a primary or a secondary amine an intramolecular reaction can occur leading to cyclic amines (Scheme 6.4).



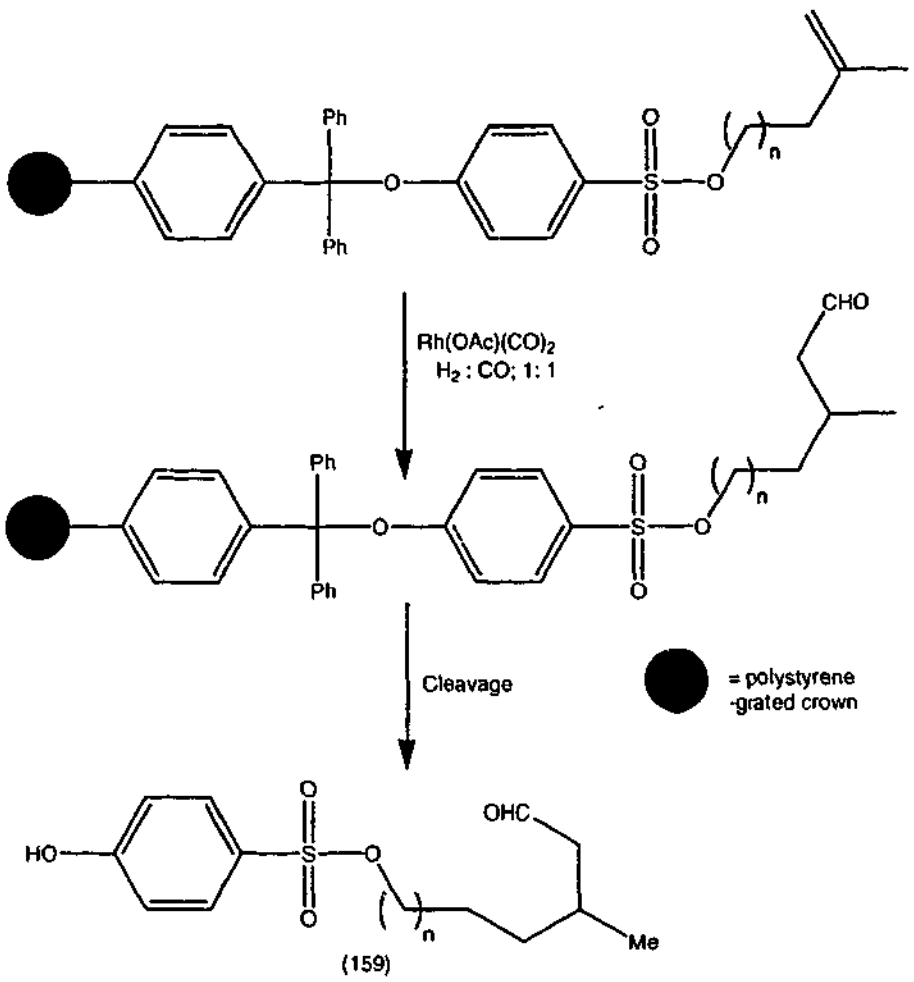
Scheme 6.4

Excellent yields of 13-membered ring (157) compounds were obtained by rhodium(I)-BIPHEPHOS catalysed reactions of *N*-benzyl-10-undecenamine (158) (Scheme 6.5).[185] However, hydroaminomethylation of other amino alkenes with varying chain length gave only modest yields of cyclised product due to competing reactions, notably polymerisation, dimerisation, and initial hydrogenation, rather than hydroformylation of the alkene.[185]



Scheme 6.5

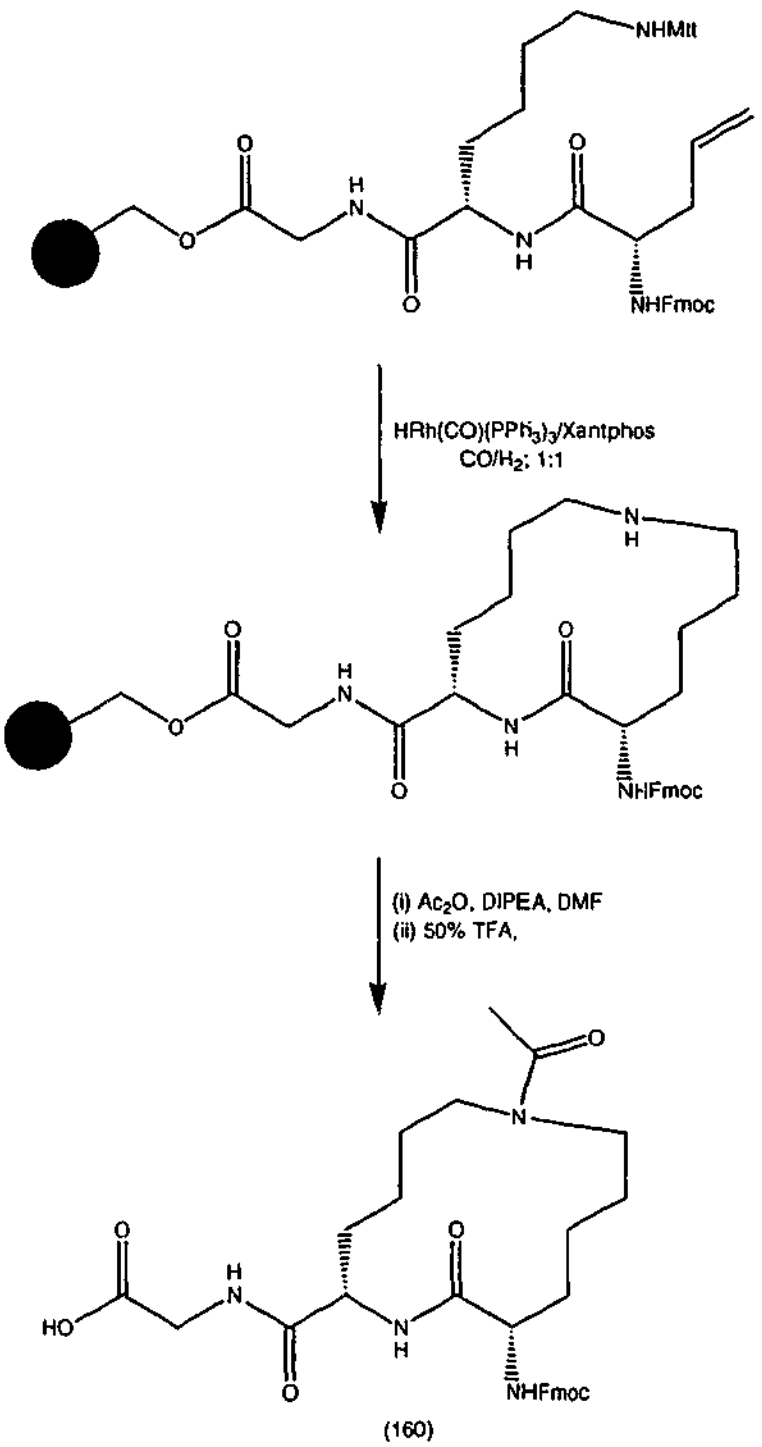
In order to overcome the formation of dimers and polymers a domino reaction sequence involving resin-supported amino alkenes has been investigated. Solid-phase synthesis, first developed by R. Bruce Merrifield,[209] avoids the formation of unwanted by-products by using a solid support (resin). Solid-phase hydroformylation of a tethered alkene was first reported by Takahashi *et al.* in a partial synthesis of muscone (159) (Scheme 6.6).[210]



(159)

Scheme 6.6

More recently, intermolecular hydroaminomethylation reactions of resin-tethered alkenes with *in situ* amines have been carried out leading to good to excellent yields of saturated amines.[211] One intramolecular hydroaminomethylation was also reported; rhodium-catalysed reaction of the unsaturated amine tethered by a Wang linker to PS-DVB (polystyrene divinyl benzene) resin with H_2/CO gave a 13-membered cyclic amine (160) in excellent yield (Scheme 6.7).[211] The authors reported that high yields were only obtained when the reactions were stirred and this necessitated the use of a specially modified glass vial to prevent destruction of the polymer beads.

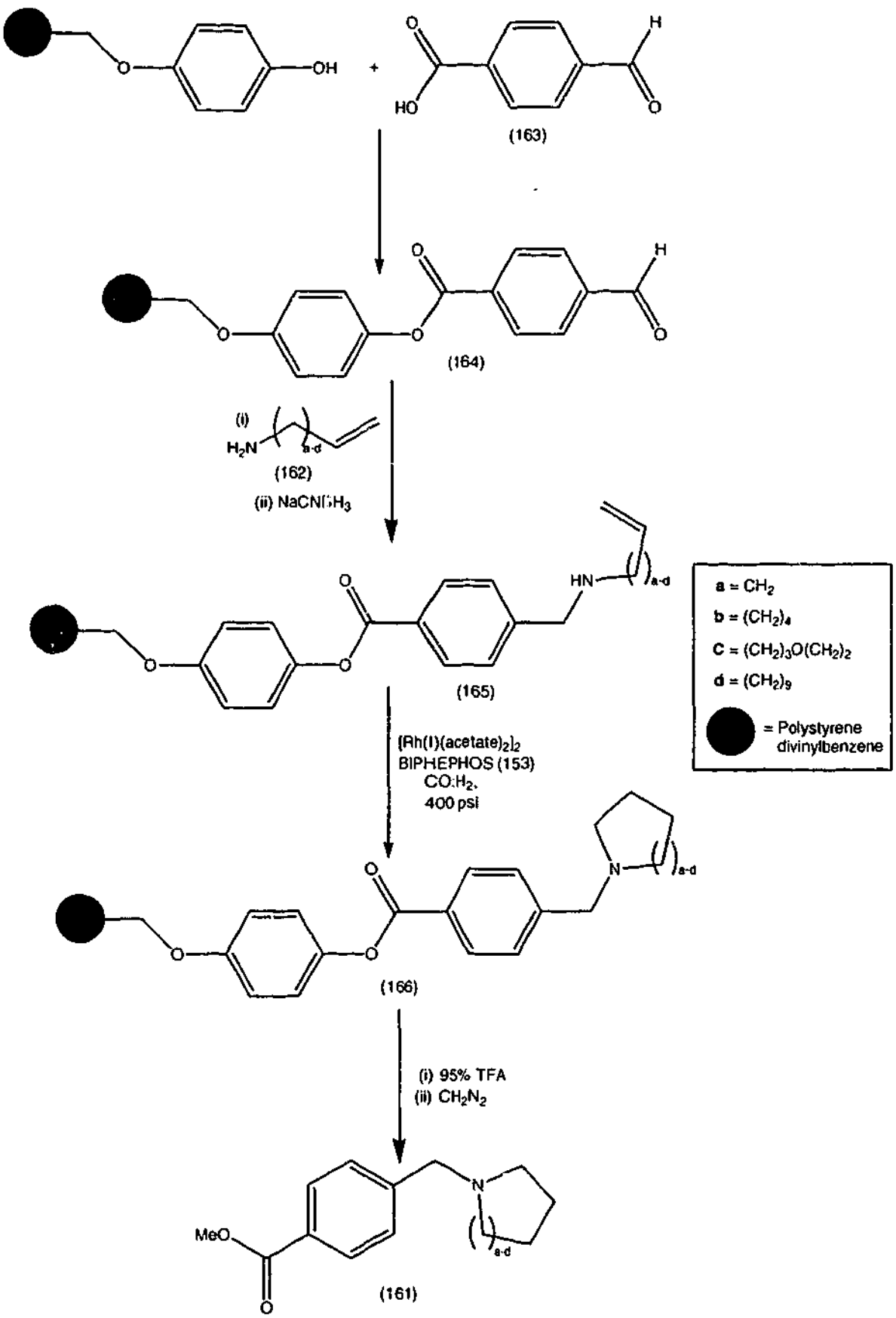


(160)

Scheme 6.7

This present study investigates the preparation of nitrogen heterocycles with ring sizes ranging from small to large *via* a similar intramolecular hydroaminomethylation sequence. The use of a Wang (4-(hydroxymethyl)phenoxymethyl) polystyrene resin has allowed us to carry out the reaction sequence without stirring, giving good to excellent yields of cyclic amines (161a-d) (Scheme 6.8). Also, a comparative study of

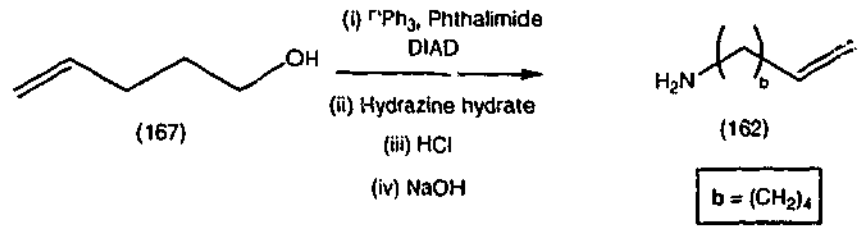
the formation of heterocycles from the respective amines (162a-d) without the use of the polystyrene resin was undertaken.



Scheme 6.8

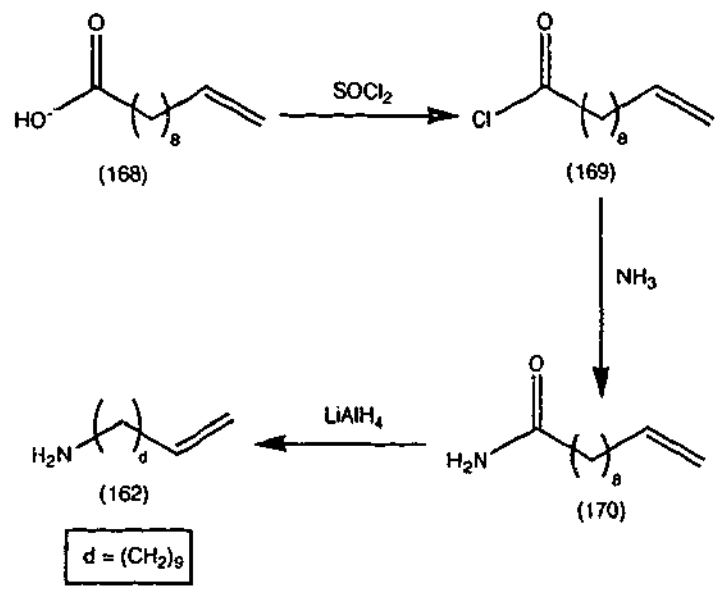
6.4 Preparation of amino alkenes

2-Propenamine (162a) was commercially available but all other amino alkenes needed to be prepared before the solid support reactions could be carried out. 5-Hexenamine (162b) was synthesised from the alcohol (167) using a Mitsunobu reaciton[106] (Scheme 6.9). Spectral data obtained were consistent with literature[212] values for the six carbon amine (162b).



Scheme 6.9

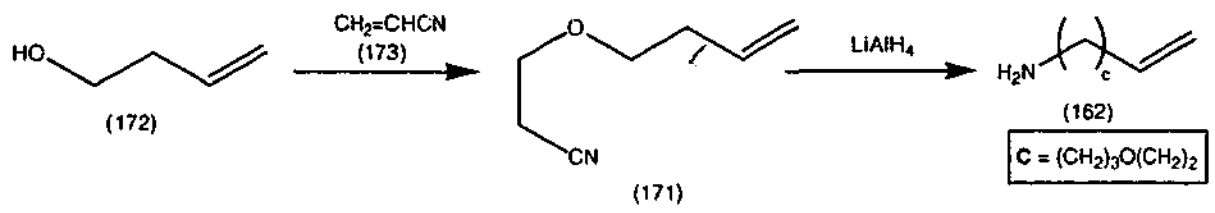
Undec-10-amine (162d) was synthesised from the undecanoic acid (168) by the preparation of the acid chloride (169), reaction with ammonia to produce the amide (170) and reduction with $LiAlH_4$ (Scheme 6.10).



Scheme 6.10

3-(But-3-enyloxy)propanamine (162c) was prepared from the nitrile (171). The nitrile (171), was synthesised by Michael addition of 3-butenol (172) to acrylonitrile (173) in

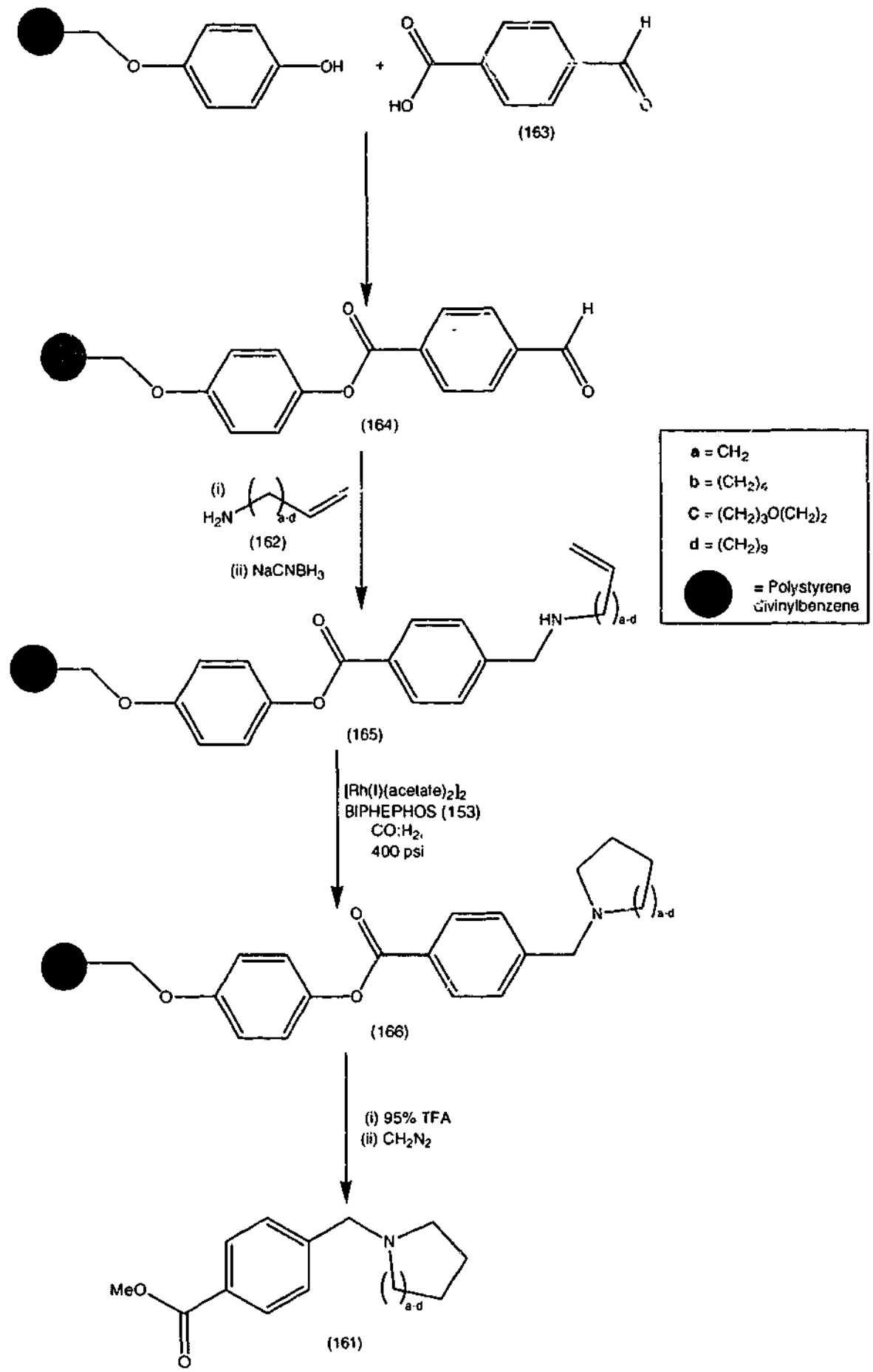
the presence of a phase transfer catalyst Triton B described by Simonot.[213] The nitrile (171) was reduced using $LiAlH_4$ to give the desired amine (162c) (Scheme 6.11).



Scheme 6.11

6.5 Preparation of nitrogen heterocyles

The hydroxymethyl Wang resin was reacted with *p*-carboxybenzaldehyde (163) to give the aldehyde functionalised resin (164) (Scheme 6.12). The resin was reacted with the unsaturated amines ((162a-d) and the resulting imines reduced with sodium cyanoborohydride to give the solid-phase amino alkenes (165a-d). Rhodium(I)-BIPHEPHOS catalysed hydroformylation of these alkenes with H_2/CO gave the polymer attached heterocycles (166a-d). The heterocycles were cleaved from the resin by treatment with 95% TFA and isolated as their methyl ester derivatives (161a-d) by reaction with diazomethane (Scheme 6.12).


OH
HO
(163)
(164)
(i)
(162)
(ii) NaCNBH3
HN
a-d
(165)
[Rh(I)(acetate)2]2
BIPHEPHOS (153)
CO:H2,
400 psi
N
(166)
(i) 95% TFA
(ii) CH2N2
MeO
(161)
a = CH2
b = (CH2)4
C = (CH2)3O(CH2)2
d = (CH2)9
= Polystyrene
divinylbenzene

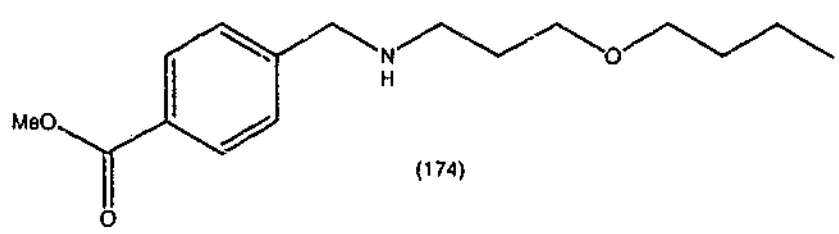
Scheme 6.12

The yields of the cyclic amines (161a-d) are given in Table 6.1. Modest yields of the amines (161b-d) and an excellent yield of 161a were obtained. No products arising from branched-chain aldehydes were detected. This high regioselectivity is in keeping with the catalyst's preference for terminal hydroformylation due to the bulky phosphite ligand (153).[205]

Products arising from competing hydrogenation rather than hydroformylation of the C=C double bond were not isolated with the exception of one reaction involving resin-tethered (165c) and a 100:1:2 ratio of alkene:rhodium(I):ligand which gave the saturated compound (174) (Figure 6.3). A higher catalyst loading was found to completely eliminate this side reaction. In all other cases, only a single product was obtained suggesting that the modest yields may be due to inefficient cleavage from the resin or incomplete product isolation.

Table 6.1: Yields of cyclic amines

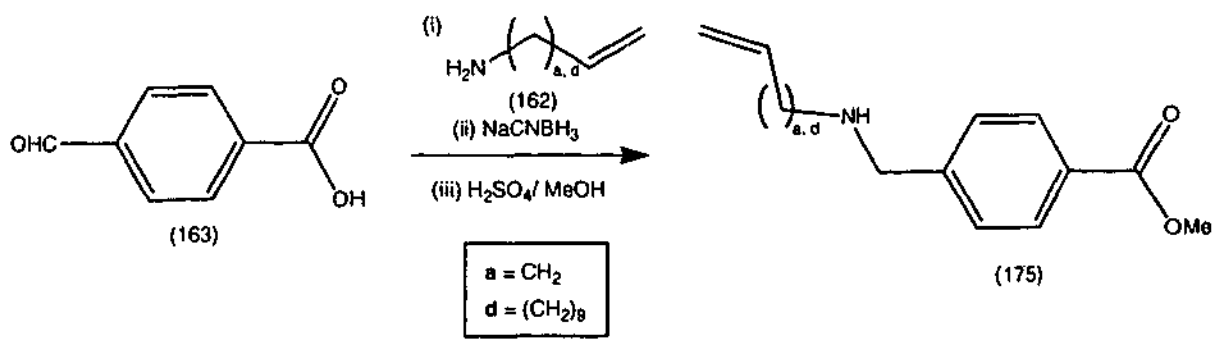
Amine	Ring size	Isolated Yields (%)	
		Resin attached (165)	Solution of (175)
161a	5	91	25 + polymer
161b	8	56	44
161c	10	61	49 + polymer
161d	13	50	14 + polymer



(174)

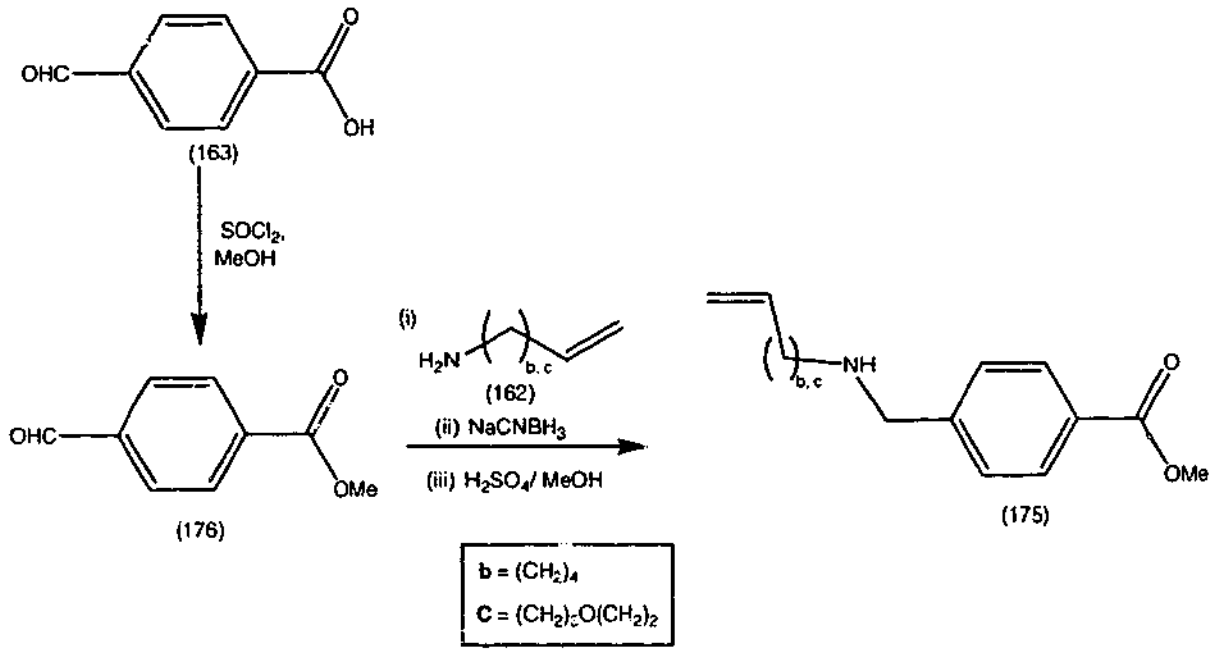
Figure 6.3: The saturated compound (174)

For the purpose of comparing solid and solution phase intramolecular hydroaminomethylation reactions, the amines (162a-d) were converted into their *N*-(4-methoxycarbonyl)benzyl derivatives (175a-d). The esters ((175a) and (175d)) from allyamine (162a) and the undec-10-enylamine (162d) were synthesised by reacting the respective amines with *p*-carboxybenzaldehyde (163) (Scheme 6.13). The imines which were not isolated were immediately reduced with $NaCNBH_3$ and the resulting carboxylic acids were esterified with sulphuric acid and methanol to give (175a) and (175d).



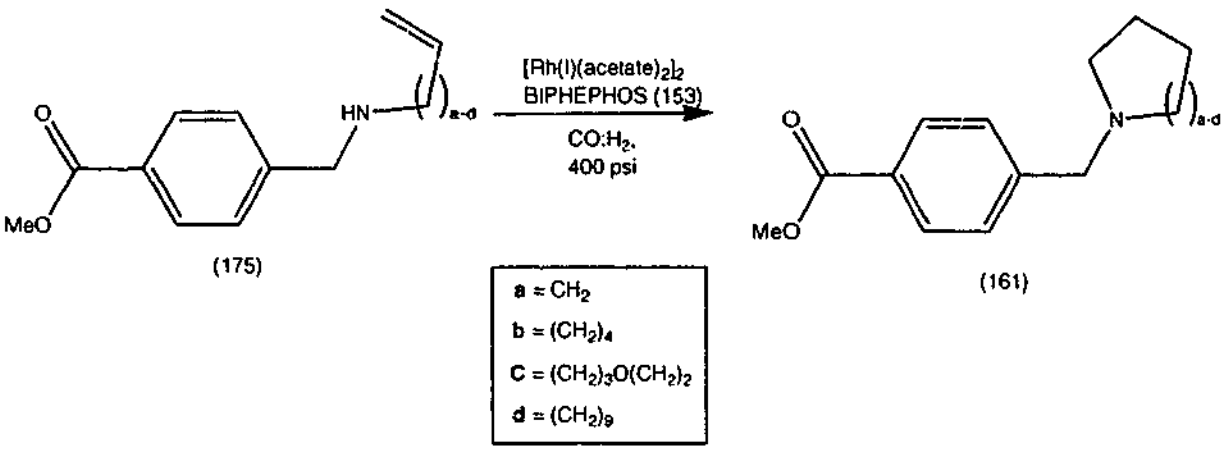
Scheme 6.13

The esters (175b-c) from 5-hexenamine (162b) and 3-(but-3-en-1-yloxy)propanamine (162c) were synthesised by firstly esterifying the *p*-carboxybenzaldehyde (163) with thionyl choride in the presence of methanol (Scheme 6.14). The resulting ester (176) was reacted with 5-hexenamine (162b) and 3-(but-3-en-1-yloxy)propanamine (162c) and the resulting imines immediately reduced using $NaCNBH_3$ to afford the desired alkene esters (175b) and (175c) (Scheme 6.14).



Scheme 6.14

These amino alkenes (175a-d) were then hydroformylated under the same reaction conditions used in the resin-supported examples (Scheme 6.15). In every case, more complex product mixtures were isolated and in reactions involving 175a, 175c and 175d, polymeric material was also isolated (Table 6.1).



Scheme 6.15

Surprisingly, hydroaminomethylation of the 4-methoxycarbonyl derivative of *N*-benzylundecenylamine (175d) gave only a low yield of cyclic product (161d) (14%). Previous investigations of solution phase hydroaminomethylation of the related *N*-

benzylundecenylamine gave the 13-membered *N*-benzylazacyclotridecane (157) in excellent yield (85%) (Scheme 6.5).[185]

6.6 Conclusion

Moderate to excellent yields of cyclic amines (161a-d) of varying ring size can be prepared by rhodium-catalysed hydroaminomethylation of unsaturated amines (162a-d) tethered to a Wang resin (165a-d). It is proposed that modest isolated yields from reactions performed on the solid-phase may be due to difficulties experienced during cleavage from the resin and/or product isolation. Analogous reactions of untethered amines (175a-d) in solution gave more complex product mixtures with formation of polymers in three cases.

Chapter 7

Experimental

7.1 General

Distillations were carried out using a Buchi Kugelrohr apparatus and oven temperatures reported serve only as a guide to boiling points. Melting points were determined on a Gallenkamp MFB-595 melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 141 polarimeter (in a cell length of 1 dm) at a wavelength of 589 nm (sodium D line) at a temperature of 25°C. Concentrations are expressed as *c* (g/100 ml).

Microanalyses were performed by Campbell Microanalytical Laboratory, Dunedin, New Zealand. Molecular modelling was carried out using Insight II 4.0 P+ (Accelrys, San Diego, CA, USA) with Discover Minimisation Module (97.0) using CVFF forcefields. The structures were minimised using the conjugate gradients algorithm with a convergence criterion of the average derivative being less than 0.001 kcal mol^{-1} (1 cal = 4.184 J).

Infrared (IR) spectra were recorded on a Perkin Elmer 1600 FTIR spectrometer (cm^{-1} scale) and refer to potassium bromide (KBr) disks of solids or thin films of liquids (neat) between sodium chloride discs. The intensity of the absorption bands (ν_{max}) for all samples is specified as either s (strong), m (medium) or w (weak) and prefixed b (broad) where appropriate.

Proton nuclear magnetic resonance (^{1}H n.m.r.) spectra were recorded at 300 MHz Varian Mercury 300 spectrometer, 300 MHz with Bruker DPX-300 spectrometer or 400 MHz with a Brucker-DRX 400 spectrometer. ^{1}H n.m.r. spectra refer to deuterochloroform ($CDCl_3$), solutions with tetramethylsilane (TMS) as the internal standard (δ 0.00 ppm) unless otherwise specified. Each resonance was assigned according to the following convention: chemical shift measured in parts per million (ppm) downfield from TMS, multiplicity, number of protons, observed coupling (*J* Hz) and assignment. Multiplicities were denoted as s (singlet), d (doublet), t (triplet),

q (quartet), p (pentet) or m (multiplet) and prefixed b (broad) where appropritate. Where ratio of compounds was determined from ^{1}H n.m.r. spectra, use was made of the relative integrations of signals due to comparable hydrogens, for example CH_3 or CH.

Carbon nuclear magnetic resonance (^{13}C n.m.r.) spectra were recorded at 100 MHz on Varian Mercury 300 spectrometer, on 100 MHz Brucker 300-DPX or on the Bruker DRX-400 spectrometer and were measured in deuterochloroform solutions as the solvent and internal standard (δ 77.04 ppm) unless otherwise specified. Each resonance was assigned according to the following convention: chemical shift (ppm) and assignment. Assignments were determined from J-modulated Spin Echo experiments for X-nuclei coupled to ^{1}H in order to determine the number of attached protons.

Fluorine nuclear magnetic resonance (^{19}F n.m.r.) spectra were recorded at 282.4 MHz with a Bruker DPX-300 spectrometer and refer to deuterochlroform ($CDCl_3$) solutions with fluorotrichloromethane as the internal standard (δ 0.00) unless otherwise stated.

Low resolution Electrospray Mass Spectroscopy (ESI) was carried out on a Micromass Platform II API QMS Electrospray Mass Spectroscopy with cone voltage at 25 V, using methanol as the mobile phase unless otherwise specified. Analyses were conducted in positive (ESI^{+}) mode. Electrospray Mass Spectroscopy (ESI) accurate mass measurements were obtained at high resolution with Bruker BioApex 4.7T ultrahigh resolution FT-ICR mass spectrometer and reported within ±5 pppm.

Gas Chromatography-Mass Spectroscopy (GCMS) was carried out using a Hewlett Packard 5890 gas chromatograph (column: 25 m x 0.32 mm ID, fused silica BP-5, film thickness 0.5 mm) with temperature programming (50°C for 2 min, to 280°C @ 10°C min^{-1}), coupled to a VG-TRIO mass spectrometer.

Gas Chromatography was carried out using a Hewlett Packard 5890 gas chromatograph. Instrument settings were kept at the following parameters during the analysis of the compounds: Detector temperature 260°; Injection temperature 200°;

Air 40 psi, 438 ml/min; Hydrogen 20 psi, 42 ml/min; Helium, 20 psi, 43.4 ml/min; Split flow 27.22 ml/min; Split ratio 42:1; Linear velocity, 25.78 cm/sec; Volumetric flow, 1.227 ml/min. GC analysis was performed on the Chrompak-WCOT fused silica, 25 m x 0.25 mm, coating CP Chirasil-DEX CB DF=0.25 column. Temperature programs used for GC analysis are listed in the following convention: Range from initial to final temperature, ramp rate (°/min). Product distributions were obtained from GLC peak areas using a Hewlett Packard 3396 Series II reporting integrator.

High Performance Liquid Chromatography (HPLC) was performed on Waters Model 5000 with a Varian UV-50 detector. Product distributions were obtained from peak areas in a peak printout using Class LC software. The columns used were Chiracel OJ (Column No. OJ00CE-JJ028), Chiracel OB (Column OB00CE-1H013) and Chiracel OD (Column No. OD00CE-HL011). Both the Chiracel OB and OJ columns have a cellulose ester derivative coated on silica gel absorbent while the Chiracel OD has a cellulose carbamate derivative on silica gel adsorbent. All columns are 0.46 cm ID x 25 cm with a particle size of 10 µm. Retention times (R_t) are reported as an average of two runs.

Flash column chromatography was carried using 40-63 µm (230-400 mesh) silica gel 60 (SiO_2) (Merck No-9385).[214] Analytical thin layer chromatography (t.l.c.) was performed on Polygram Sil G/UV_{254} coated with 0.25 mm of silica with flourescent idicator UV_{254} nm ultraviolet radiation or by staining with vanillin, ninhydrin and iodine when necessary.

Radial chromatography was performed using a chromatotron model 7924T on a glass plate coated with 2 mm of absorbent silica 60 PF_{254}.

7.1.1 Solvents and reagents

Diethyl ether (ether) (analytical grade) was dried over potassium hydroxide and either distilled from lithium aluminium hydride and stored over sodium wire (for anhydrous reactions) or distilled from fresh potassium hydroxide. Tetrahydrofuran (THF) was distilled from calcium hydride, stored over sodium wire and distilled under nitrogen from sodium and benzophenone prior to use. Dry dichloromethane (CH_2Cl_2) was

obtained by drying over calcium hydride and distilled before use. Benzene was dried over phosphorous pentoxide, decanted, distilled from fresh phosphorous pentoxide and stored over sodium wire. Dimethylformaide (DMF) (Analytical grade) was dried over calcium chloride and distilled. Hexane (boiling range 60-80°C) was dried over calcium chloride and stored over 4 Å molecular sieves. Distilled water was used for aqueous manipulations.

All commercially available chemicals were purchased from Sigma-Aldrich Pty Ltd.. Wang resin was supplied by Auspep. Bakers' yeast was purchased from the local supermarket.

Sodium cyanoborohydride ($NaCNBH_3$), NaH (60%) and $LiAlH_4$ was handled and stored with exclusion of moisture. Triton B (*N*-benzyltrimethylammonium hydroxide) and benzyl viologen (1,1'-benzyl-4-4'-pyridinium) bromide were used as a phase transfer catalysts.

NH_3/MeOH refers to saturated ammonia in methanol solution and was prepared by passing anhydrous ammonia gas through methanol (analytical grade) at 5°C (ice bath) for at least 0.5 h. Hydrogen chloride (HCl_g) was prepared[215] by the dropwise addition of conc. H_2SO_4 to NH_4Cl and dried bubbling through conc. H_2SO_4.

Deuterated solvents used in NMR were supplied by Cambridge isotopes laborataries. Anhydrous magnesium sulfate ($MgSO_4$) was used as the drying agent in the work up of all extraction.

Palladium on charcoal (10%) and osmium tetroxide were purchased from Sigma-Aldrich. Allylpalladium chloride dimer ($[(\eta^3\text{-}C_3H_5)PdCl]_2$) was purchased from Lancaster Scientific Pty Ltd.. Rhodium trichloride trihydrate ($RhCl_3.nH_2O$, n=approx. 3) was supplied by Johnson Mattey Pty Ltd. The Rhodium acetate dimer $[Rh(OAC)_2]_2$ was prepared by T. Ventrice following a procedure by Brown and Wilkinson.[195] BIPHEPHOS (153) [6,6'-[[3,3'-bis(1,1-dimethyl)-5,5'-dimethoxy-1,1'-biphenyl]-2,2'-diyl]bis(oxy)]bisdibenzo[d,f][1,2,3]dioxaphosphepin] was prepared by E. Campi according to a literature procedure.[205]

7.1.2 Conditions for hydrogenation reactions using 10% Pd/C

A Fisher-Porter tube was charged with palladium on charcoal, substrate (0.05g – 5.00 g) and solvent (methanol, benzene). After degassing the suspension with argon and three flushings with hydrogen, the reaction vessel was pressurised with hydrogen to the reported pressure and left stirring at ambient temperature for the reported period of time. Pressure was released and the catalyst removed by filtrations through a Celite pad. Removal of the solvents were carried out under reduced pressure.

7.1.3 Conditions for rhodium catalysed reactions with H_2/CO

Reactions with hydrogen (H_2) and carbon monoxide (CO) were carried out in a 100 ml starinless steel Parr autoclave with a pressure regulator, lined with a glass sleave and equipped with a magnetic Teflon coated stirrer bead. After the reagents had been added under nitrogen and the autoclave assembled, the vessel was flushed three times with 200 psi (1380 kPa) of H_2/CO (1:1 molar mixture) and then pressurised to the initial pressure of 400 psi (2750 kPa) or 800 psi (5500 kpa) of the same gases.

The temperature was controlled through a thermocouple inserted between the autoclave and the heating block and the reaction mixture stirred with a magnetic stirrer placed under the heating unit. The reactions were not stirred when the substrate was on a solid-phase. To prevent the temperature from overshooting, the temperature was set to 5°C less than the required reaction temperature. Once this temperature had been reached, the temperature was set to the reported reaction temperature. The time reported for the reaction refers to the duration of the heating at the reaction temperature. After the reaction time had elapsed, the autoclave was cooled to ambient temperature, the gases were slowly released and the contents, after removal of the solvent under reduced pressure, were analysed and treated as reported.

The standard conditions used for the rhodium-catalysed reactions with H_2/CO are as follows:

Substrate: 100 –500 mg

Catalyst Precursor: Rhodium(II) acetate dimer $[Rh(OAc)_2]_2$

Ligand: Posphite (BIPHEPHOS (153)), amine (44)

Ratio of substrate, ligand, catalyst precusor: 100:2:1 or otherwise specified

Synthesis gas: H_2/CO

Reaction Temperature: 80°C

Reaction time: 20 h

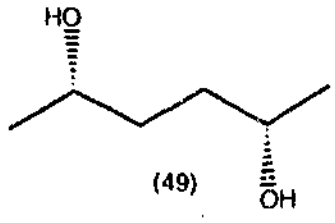
Solvent: Benzene

7.1.4 Solid-phase synthesis procedure

All solid-phase synthesis proceeded using plastic syringes (10 ml) fitted with frits which allowed for the filtration of solutions without loss of resin. The syringes were fitted on a vacuum tank and all the washings were removed *in vacuo*. Details of washing procedures are described in the experimental section. This generally involves soaking the resin in a specific amount (e.g 7 ml) of the desired solution for 1 min. These washings are necessary to remove excess reagents before the coupling reaction.

7.2 Synthesis of (2*R*,5*R*)-2,5-dimethyl pyrrolidine based ligands

7.2.1 Synthesis of (2*S*,5*S*)-2,5-hexanediol (49)

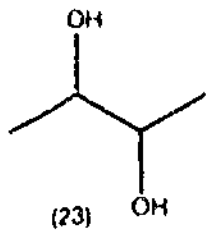


(49)

Method A

Using a modified yeast reduction method of Leiser[95] and Short.[100]

Baker's yeast (105 g) (Kitchen collection™) was added to a stirred solution of white sugar (CSR™) (175 g) in water (960 ml) and after 1 h, 2,5-hexanedione (50) (5.13 ml, 43.8 mmol) was added. Stirring was continued for 24 h before a second sugar solution (131.6 g in 580 ml of water) was added, followed by additional 2,5-hexanedione (50) (5.13 ml, 43.8 mmol) 1 h later. After stirring for 72 h, additional yeast (35 g) and sugar solution (70 g in 260 ml of water) were added. The reaction mixture was stirred for a further 72 h after which time t.l.c indicated that no more starting material (50) was present. The mixture was filtered through a Celite plug and the filtrate was continuously extracted for two days with dichloromethane. The extract was dried with $MgSO_4$, filtered and evaporated under reduced pressure to yield a light brown oil (8.93 g). The ^1H n.m.r. spectrum of this crude oil showed 2,5-hexanediol (49) together with 2,3-butanediol (23) (<10 %). Purification by column chromatography (SiO_2, ethyl acetate: hexane, 1:1) initially afforded the 2,3-butanediol (23) (100 mg).



(23)

^1H n.m.r. (300 MHz, $CDCl_3$): δ 1.17, d, *J* 6.1 Hz, 6H, H1, H4; 2.73, bs, 2H, 2 x OH; 3.46-3.58, m, 2H, H2, H3. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 19.5, C1, C4; 72.7, C2, C3. Mass Spectrum (ESI⁺, MeOH): *m/z* 112.8 ([M+Na]⁺). Analysis by GC indicated only two components: (Chrompack – WCOT Fused silica coating, CP chirasil-Dex CB; 100°, 12 min, 100-150°, 3°/min): R_t 12.4 min (89%) (2*R*,5*R*) and R_t 13.2 min (11%) (2*S*,5*S*). The spectral data were consistent with the literature.[216]

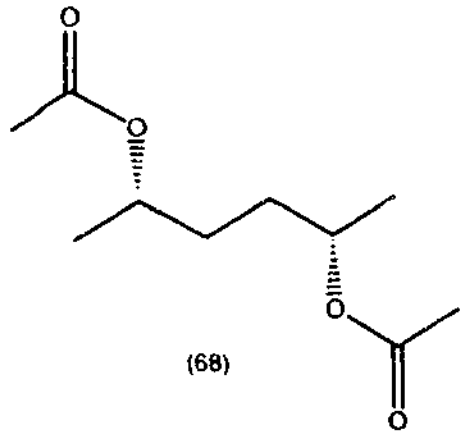
Next to elute was (2*S*,5*S*)-2,5-hexanediol (49), which solidified upon standing (4.77 g, 46%). $[\alpha]_D^{25}$ +33.4° (c 8 6, $CHCl_3$) (lit.[95] $[\alpha]_D^{25}$ +35° (c 9, $CHCl_3$). m.p. 52-54°C (lit.[95] 50-53°C). ν_{max} (KBr): 3322bs, 2935s, 2922s, 1705w, 1667w, 1461m, 1372s, 1333m, 1200w, 1150s, 1127s, 1061s, 1017s, 938s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 1.20, d, *J* 6.3 Hz, 6H, H1, H6; 1.42-1.60, m, 4H, H3, H4; 3.74-3.86, m, 2H, H2, H5. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 24.1, C1, C6; 36.4, C3, C4; 68.6, C2, C5. Mass Spectrum (ESI^+, MeOH): *m/z* 140.9 ($[M+Na]^+$). The spectral data were consistent with the literature.[95]

Method B

The reaction was carried out using a method described by Smallridge.[217]

2,5-Hexanedione (50) (0.51 ml, 4.23 mmol) was added to a paste of yeast (8.76 g) and water (7.0 ml). This paste was further ground using a mortar and pestle and was allowed to stand for 27 h in the mortar. The yeast was then transferred to a sinter and washed with ethyl acetate (250 ml). The organic layer was concentrated to afford the diol (49) as a light yellow oil (281 mg, 55%). The spectral data were consistent with that observed for (2*S*,5*S*)-2,5-hexanediol (49) in Method A.

7.2.2 Synthesis of (2*S*,5*S*)-2,5-hexanediiyl diacetate (68)



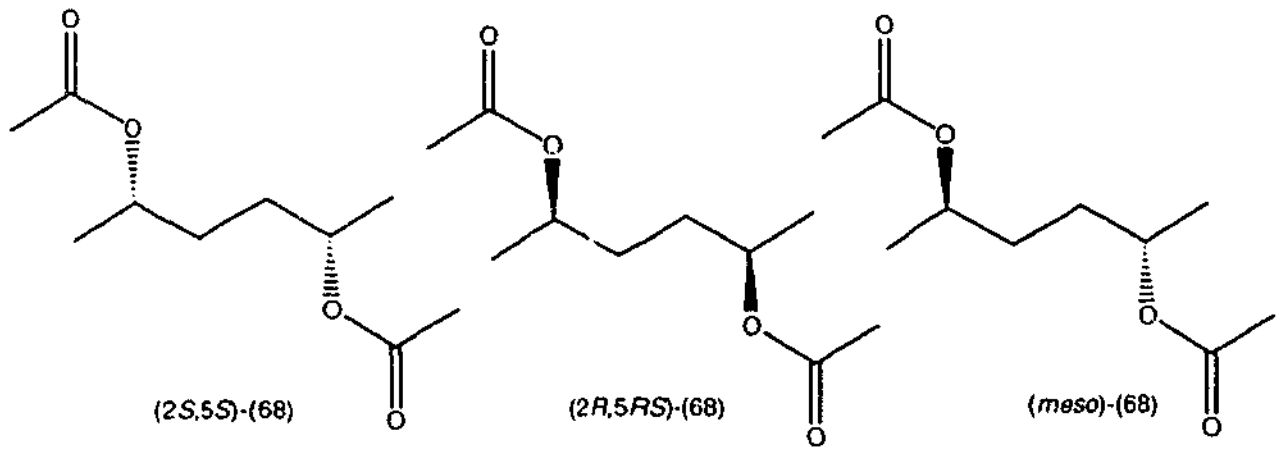
(68)

A mixture of (2*S*,5*S*)-2,5-hexanediol (49) (500 mg, 4.24 mmol) (obtained using Method A in the previous Section 7.2.1) and acetyl chloride (0.6 ml, 8.47 mmol) in dichloromethane (25 ml) was stirred at ambient temperature for 18 h. The reaction was quenched with sodium bicarbonate (sat.) (50 ml) and the mixture stirred for 10 minutes before the phases were separated. The organic layer was washed with water, dried with $MgSO_4$, filtered and evaporated under reduced pressure to give the diacetate (68) as a yellow oil (810 mg, 95%). ν_{max} (neat): 2968s, 2933s, 1733s, 1450s,

1372s, 1244s, 1133m, 1050s, 1022s, 950s, 844w cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 1.22, d, *J* 6.3 Hz, 6H, H1, H6; 1.42-1.70, m, 4H, H3, H4; 2.04, s, 6H, 2 x $C\underline{H}_3COO$; 4.82-4.96, m, 2H, H2, H5. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 20.2, C1, C6; 21.6, $\underline{C}H_3COO$; 31.9, C3, C4; 70.7, C2, C5; 170.7, CO. Mass Spectrum (ESI^+, MeOH): *m/z* 225.0 ($[M+Na]^+$). Analysis by GC indicated mainly one component: (Chrompack–WCOT Fused silica coating, CP Chirasil-Dex CB DF=0.25; 50-200°, 5°/min): R_t 17.04 min (>99.9%) (2*S*,5*S*) and 19.12 (trace) (2*R*,5*R*).

(2*S*,5*S*)-2,5-hexanediyl diacetate (68) was prepared as above using the (2*S*,5*S*)-hexanediol (49) (173 mg, 1.44 mmol) prepared using the Method B in Section 7.2.1. After the work up the diacetate (68) was obtained as a yellow oil (210 mg, 72%). The spectral data were consistent with that observed for (68) from above. Analysis by GC indicated two components: (Chrompak-WCOT fused silica, 25 m x 0.25 mm, coating CP Chirasil-DEX CB DF=0.25, 50-200°, 5°/min): R_t 17.04 min (>99.9%) (2*S*,5*S*) and 19.12 (trace) (2*R*,5*R*).

7.2.3 Synthesis of (2*S*,5*S*), (2*R*,5*R*) and (*meso*)-2,5-hexanediiyl diacetate (68)

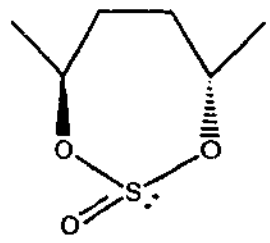


2,5-hexanedione (50) (0.51 ml, 4.23 mmol) was added to a stirred solution of $LiAlH_4$ (802 mg, 21.15 mmol) in THF (20 ml). After 10 min the reaction was cooled using an ice bath and sodium sulfate decahydrate ($Na_2SO_4.10H_2O$) was added until no further gas evolution was observed. The resulting precipitate was filtered and washed with THF (30 ml). The filtrate was evaporated to afford a mixture of (2*S*,5*S*), (2*R*,5*R*) and (*meso*)-2,5-hexanediol (49) as clear oil (503 mg, 99%). ^1H n.m.r. spectroscopy of the reaction mixture was identical to what was observed for the (2*S*,5*S*)-2,5-hexanediol

(49) discussed in Section 7.2.1 Method A. Both *meso*-diol (49) and the chiral diol (49) had identical ^{1}H n.m.r. spectra.

The clear oil was dissolved in dry dichloromethane (25 ml), acetyl chloride (0.60 ml, 8.38 mmol) was added and the mixture stirred for 18 h. The reaction was worked up as described in Section 7.2.2 to afford the diacetate (68) as a yellow oil (556 mg, 65%). The spectroscopic data was identical to that given for (2*S*,5*S*)-(68) in Section.7.2.2. Analysis by GC indicated three components: (Chrompak-WCOT fused silica, 25 m x 0.25 mm, coating CP Chirasil-DEX CB DF=0.25, 50-200°, 5°/min): R_t 17. 68 min (21.4%) (2*S*,5*S*), 18.57 min (57.3%) (*meso*), 19.12 (21.3%) (2*R*,5*R*).

7.2.4 Synthesis of (2*S*,5*S*)-2,5-hexanediol cyclic sulfite (69)

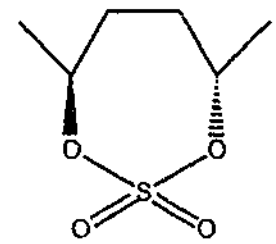


(69)

Sythesis of the cyclic sulfite (69) was achieved using the method described by Caron and Kazlauskas.[98]

Thionyl chloride (1.41 ml, 19.37 mmol) was added dropwise to a cooled solution (0°C) of (2*S*,5*S*)-2,5-hexanediol (49) (1.53 g, 12.95 mmol) in tetrachloromethane (25 ml). The reaction mixture was brought to ambient temperature and stirred at reflux for a further hour. The mixture was allowed to cool to 25°C before being evaporated under reduced pressure to afford the cyclic sulfite (69) as a brown oil (1.85 g, 87%).ν_{max} (neat): 2997s, 2922m, 1450m, 1378s, 1350w, 1200s, 1122m, 1089m, 905s, 856s, 816m, 739s cm^{-1}. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 1.32, d, *J* 6.4 Hz, 6H, H1, H6; 1.50-1.90, m, 4H, H3, H4; 4.33, m, 1H and 5.16, m, 1H, H2, H5. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 22.3, 22.6, C1, C6; 34.1, 36.0, C3, C4; 70.0, 73.1, C2, C5. Mass Spectrum (ESI$^+$, MeOH): *m/z* 186.8 ([M+Na]$^+$).

7.2.5 Synthesis of (2*S*,5*S*)-2,5-hexanediol cyclic sulfate (52)

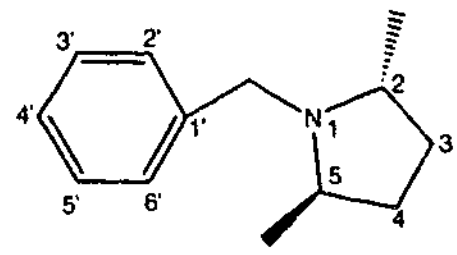


(52)

Synthesis of the cyclic sulfate (52) was achieved according to the method described by Burk *et al.*.[84]

Tetrachloromethane (20 ml), acetonitrile (20 ml) and water (25 ml) were added to the cyclic sulfite (69) (1.85 g, 11.25 mmol) and the mixture was cooled to 0°C. Ruthenium(III) chloride (30 mg, 0.14 mmol) and sodium periodate (4.81 g, 22.5 mmol) were added and the mixture was stirred at 25°C for 1 h. After quenching the reaction with water (100 ml), the mixture was extracted with diethyl ether (4 x 50 ml). The combined ether extracts were washed with brine (2 x 25 ml), dried ($MgSO_4$), filtered and evaporated. The resulting solid was dissolved in ether (20 ml) and filtered through a silica plug to remove any ruthenium salts. The resulting solution was evaporated under reduced pressure to afford the title compound (52) as colourless crystals (1.32 g, 65%). $[\alpha]_D^{25}$ +33.0° (c 1.15, $CHCl_3$) (lit.[84] $[\alpha]_D^{25}$ +32.4° (c 1, $CHCl_3$). m.p. 108-112°C (lit. 109.5-110.5°C). ν_{max} (KBr): 2989m, 2933m, 2355m, 1459w, 1376s, 1347s, 1190s, 1128m, 1100m, 1021s, 943m, 903s, 814m cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 1.44, d, *J* 6.4 Hz, 6H, H1, H6; 1.82-2.08, m, 4H, H3, H4; 4.82, m, 2H, H2, H5. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 22.4, C1, C6; 35.3, C3, C4; 82.1, C2, C5. Mass Spectrum (ESI^+, MeOH): *m/z* 202.9 ($[M+Na]^+$). The spectral data were consistent with the literature.[84]

7.2.6 Synthesis of (2*R*,5*R*)-*N*-benzyl-2,5-dimethylpyrrolidine (70)



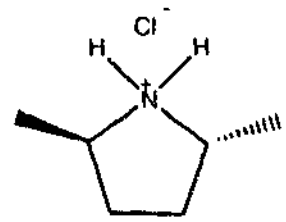
(70)

Method A

Synthesis of the benzyl pyrrolidine (70) was carried using a modified method of Short *et al.*.[100]

A mixture of cyclic sulfate (52) (7.78 g, 43.2 mmol) and benzylamine (23.16 ml, 216.13 mmol) was stirred at ambient temperature for 96 h. The reaction was quenched with sodium hydroxide (2 M, 300 ml). The resulting solution was extracted with dichloromethane (3 x 250 ml) to remove the excess benzylamine. The aqueous layer was continuously extracted with dichloromethane overnight to afford the required product (70) as a yellow oil (7.05 g, 86%). $[\alpha]_D^{25}$ –112.0° (c 2.1, MeOH) (lit. [100] $[\alpha]_D^{25}$ -109.7° (c 1.97, MeOH). ν_{max} (neat): 3077w, 3022w, 2955s, 2867m, 2800m, 1600w, 1489m, 1450s, 1367s, 1327m, 1294w, 1150m, 1027w, 766w, 727s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 0.97, d, *J* 6.4 Hz, 6H, 2 x CH_3; 1.29-1.44, m, 2H and 1.91-2.01, m, 2H, H3, H4; 2.98-3.10, m, 2H, H2, H5; 3.51, d, *J* 13.7 Hz, 1H and 3.84, d, *J* 13.7 Hz, 1H, $C\underline{H}_2Ph$; 7.17-7.40, m, 5H, ArH. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 17.4, 2 x CH_3; 31.3, C3, C4; 52.0, $\underline{C}H_2Ph$; 55.3, C2, C5; 126.6, C4'; 128.2, 128.7, C2', C3', C5', C6'; 140.9, C1'. Mass Spectrum (ESI^+, MeOH): *m/z* 190.1 ($[M+H]^+$). The spectral data were consistent with the literature.[100]

7.2.7 Synthesis of (2*R*,5*R*)-2,5-dimethylpyrrolidine hydrochloride (33)



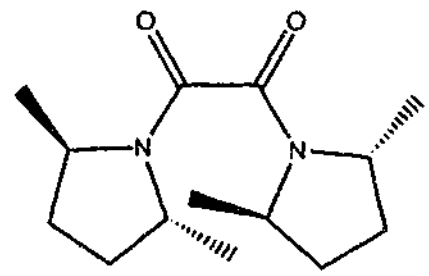
(33)

The pyrrolidine hydrochloride (33) was synthesised using the modified method of Short *et al.*.[100]

The *N*-benzyl pyrrolidine (70) (2.31 g, 12.22 mmol) was dissolved in methanol (20 ml) and the solution transferred to a Fisher Porter tube to which 10% Pd/C (30 mg) was added following the general hydrogenation procedure described in Section 7.1.2. The mixture was stirred under hydrogen (100 psi) for 18 h. The catalyst was removed by filtration through a Celite pad with cooling (0°C). Dry HCl gas (described in Section 7.1.1) was bubbled into the filtrate for 1 h and the solution was evaporated to dryness to give the desired product (33) as a colourless solid (1.50 g, 90%). $[\alpha]_D^{25}$

+5.01° (c 3.0, CH_2Cl_2) (lit.[100] $[\alpha]_D^{25}$ +5.57° (c 1.18, CH_2Cl_2). m.p. 196-202°C (lit.[100] 197-200°C). ν_{max} (KBr): 3389bs, 2977s, 2889s, 2789s, 2689s, 22489s, 2055s, 1594s, 1455s, 1411s, 1389s, 1338s, 1277w, 1216w, 1161m, 1122s, 1677s, 1050s, 988s, 950s, 844s, 744s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 1.53, d, *J* 6.7 Hz, 6H, 2 x CH_3; 1.60–1.78, m, 2H and 2.14–2.30, m, 2H, H3, H4; 3.72–3.94, m, 2H, H2, H5; 9.52, bs, 2H, 2 x NH. ^{13}C n.m.r. (100 MHz,$CDCl_3$): δ 18.7, 2 x CH_3; 32.7, C3, C4; 55.3, C2, C5. Mass Spectrum (GCMS, MeOH): *m/z* 99 ($[M-HCl]^+$). The spectral data were consistent with the literature.[100]

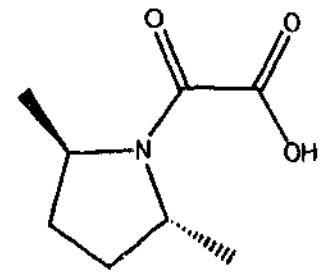
7.2.8 Synthesis of 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)-1,2-dioxo-ethane (51)



(51)

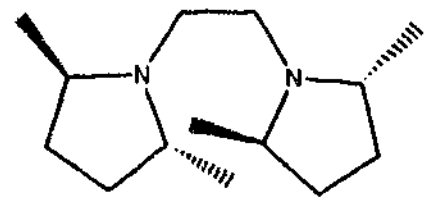
Pyridine (15.7 ml, 195.8 mmol) was added to a solution of the dimethylpyrrolidine hydrochloride (33) (2.67 g, 19.58 mmol) in dichloromethane (150 ml) at -78°C under a N_2 atmosphere and the mixture was stirred for 15 minutes. Oxalyl chloride (0.85 ml, 9.79 mmol) was added dropwise to the reaction mixture and the mixture was stirred for 2 days. The reaction was quenched with water (100 ml) and diluted with dichloromethane (150 ml). The organic layer was separated and washed successively with 1 M HCl (150 ml x 3), water (150 ml) and brine (150 ml), dried over $MgSO_4$, filtered and evaporated to afford the desired product (51) as a colourless solid (1.81 g, 74%). $[\alpha]_D^{25}$ –220.5° (c 1.03, $CHCl_3$). m.p. 184-186 °C. (Found: *m/z* 275.1727. $[C_{14}H_{24}O_2N_2Na]^+$ ($[M+Na]^+$) requires 275.1735). ν_{max} (KBr): 2963s, 2874m, 1654m, 1629s, 1602m, 1560m, 1481s, 1444s, 1375s, 1308s, 1209m, 1163s, 1087s, 1033s, 967w, 916w, 800w, 772s, 694s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 1.14, d, *J* 6.6 Hz, 6H and 1.24, d, *J* 6.4 Hz; 6H, 4 x CH_3; 1.52–1.66, m, 4H and 2.00–2.34, m, 4H, H3', H4'; 4.24–4.34, m, 2H and 4.38–4.48, m, 2H, H2', H5'. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 18.9, 22.8, 4 x CH_3; 29.2, 31.4, C3', C4'; 53.8, 54.1, C2', C5'; 163.0, C1, C2. Mass Spectrum (ESI^+, MeOH): *m/z* 253.2 ($[M+H]^+$).

A reaction using pyridine (0.11 ml, 1.33 mmol), (2*R*,5*R*)-2,5-dimethylpyrrolidine hydrochloride (33) (0.90 g, 0.66 mmol) and oxalyl chloride (0.03 ml, 0.33 mmol) in dichloromethane: diethyl ether (2:1) (15 ml) was stirred for 18 h. Work up gave (2*R*,5*R*)-2-*N*-(2,5-dimethylpyrrolidin-1-yl)-2-oxoethanoic acid (71) as a colourless solid (91 mg, 80%). For spectral data, refer to Section 7.2.14.



(71)

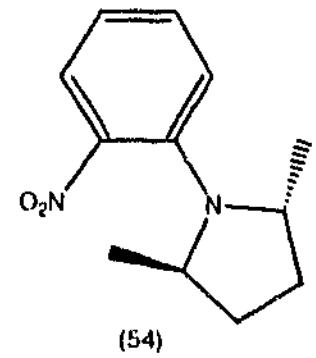
7.2.9 Synthesis of 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethane (43)



(43)

A solution of the diamide (51) (1.21 g, 4.77 mmol) dissolved in THF (10 ml), was added to a refluxing solution of $LiAlH_4$ (900 mg, 23.85 mmol) in THF (200 ml). The reaction mixture was vigorously stirred at this temperature for a further 2 h. The mixture was cooled to 0°C and sodium sulfate decahydrate ($NaSO_4.10H_2O$) was added until no further gas evolution was observed. The resulting precipitate was filtered and washed with THF (100 ml). The filtrate was evaporated to afford the title compound (43) as a yellow oil (1.07 g, 99%). $[\alpha]_D^{25}$ –181.1° (c 3.0, $CHCl_3$) (lit.[90] $[\alpha]_D^{25}$ -183° (c 3.05, $CHCl_3$). (Found: *m/z* 225.2321. $[C_{14}H_{29}N_2]^+$ ($[M+H]^+$) requires 225.2331). ν_{max} (neat): 2955s, 2877s, 2811s, 2688w, 1667w, 1638w, 1455m, 1300s, 1350m, 1322m, 1294m, 1194w, 1166w, 1116m, 1005w, 966w, 866m cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 1.01, d, *J* 6.4 Hz, 12 H, 4 x CH_3; 1.33–1.45, m, 4H and 1.92-2.08, m, 4H, H3', H4'; 2.54–2.79, m, 4H, H1, H2; 3.02–3.24, m, 4H, H2', H5'. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 17.2, 4 x CH_3; 31.0, C3', C4'; 47.1, C1, C2; 55.2, C2', C5'. Mass Spectrum (ESI$^+$, MeOH): *m/z* 225.2 ($[M+Na]^+$). The spectral data were consistent with the literature.[90]

7.2.10 Synthesis of 1-nitro-2-((2*R*,5*R*)-(2,5-dimethylpyrrolidin-1-yl)benzene (54)



(54)

Method A

The nitrophenly pyrrolidine (54) was synthesised using the modified method of Cahill *et. al.*,[101]

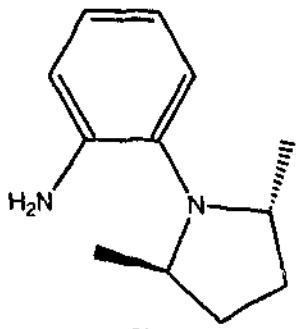
o-Nitroaniline (53) (77 mg, 0.56 mmol) was added to a solution of the cyclic sulfate (52) (100 mg, 0.56 mmol) in THF (20 ml). The resulting yellow solution was refluxed for 2 days after which 80% sodium hydride (101 mg, 3.30 mmol) was added. After refluxing for a further 24 h, the reaction was quenched with 10% NH_4Cl (20 ml). The THF was removed under reduced pressure and the resulting aqueous solution extracted with dichloromethane (3 x 100 ml). The combined organic extracts were successively washed with water (100 ml) and brine (100 ml), dried with $MgSO_4$, filtered and evaporated to afford an orange semi-solid (95 mg). Purification by column chromatography (SiO_2, ethyl acetate: hexane, 1: 10) afforded the required product (54) as a yellow oil (78 mg, 63%). $[\alpha]_D^{25}$ -1803.7° (c 0.41, $CHCl_3$). (Found: *m/z* 243.1101. $[C_{12}H_{16}O_2N_2Na]^+$ ([M+Na]$^+$) requires 243.1109). ν_{max} (neat): 2956s, 2855s, 2356s, 1600s, 1561m, 1505s, 1477m, 1450m, 1350m, 1272s, 1172m, 1150m, 1044m, 922w, 838m cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 0.80-1.22, bm, 6H, 2 x CH_3; 1.46- 1.68, m, 2H and 2.10-2.28, m, 2H, H3', H4'; 3.82-4.10, bs, 2H, H2', H5'; 6.80, t, *J* 7.0 Hz, 1H, H4; 7.06, dd, *J* 8.5, 1.2 Hz, 1H, H6; 7.39, t, *J* 7.0 Hz, 1H, H5; 7.82, dd, *J* 8.2, 1.7 Hz, H1, H3. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 20.1, 2 x CH_3; 30.1, C3', C4'; 55.8, C2', C5'; 117.6, 121.7, 126.7, 132.9, ArCH; 140.9, ArC. Mass Spectrum (ESI$^+$, MeOH): *m/z* 221.1 ([M+H]$^+$).

Method B

A solution of the cyclic sulfate (52) (100 mg, 0.55 mmol) and *o*-nitroaniline (53) (309 mg, 2.24 mmol) in toluene (20 ml) was refluxed for 4 days. The solvent was

evaporated and a ^{1}H n.m.r. spectrum of the resulting black solid (366 mg), showed only the presence of 2-nitroaniline (53).

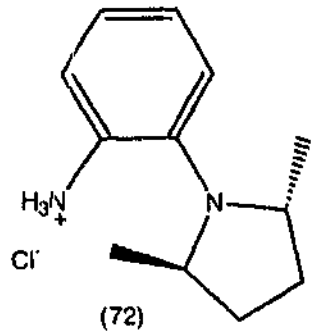
7.2.11 Synthesis of 1-amino-2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (55)



(55)

The nitrophenyl pyrrolidine (54) (441 mg, 2.00 mmol) was dissolved in benzene (10 ml) and placed in a Fisher Porter tube to which 10% Pd/C (10 mg) was added following the general procedure for hydrogenations described in Section 7.1.2. The reaction mixture was pressurised with hydrogen gas to 60 psi and stirred overnight. The Pd/C was removed using a Celite plug and the filtrate concentrated to afford an orange oil. The oil was purified using column chromatography (SiO_2, ethyl acetate: hexane, 1: 10) to give the desired product (55) as a red/orange oil (380 mg, 100%). $[\alpha]_D^{25}$ +79.5° (c 0.86, $CHCl_3$). (Found: *m/z* 191.1535. $[C_{12}H_{19}N_2]^+$ ($[M+H]^+$) requires 191.1548). ν_{max} (neat): 3433s, 3333s, 3055w, 3022w, 2955s, 2855s, 2822m, 2600w, 1605s, 1500s, 1455s, 1366s, 1322m, 1277s, 1250s, 1150s, 1133m, 1050m, 1016w, 922w, 844w, 744s cm^{-1}. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 0.60–0.80, m, 3H and 0.90–1.02, m, 3H, 2 x CH_3; 1.38–1.58, m, 2H, and 2.00–2.24, m, 2H, H3', H4'; 3.60–3.98, m, 4H, H2', H5', NH_2; 6.65–6.75, m, 2H, H3, H6; 6.82–6.95, m, 2H, H4, H5. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 18.6, 2 x CH_3; 32.1, 32.8, C3', C4'; 52.8, 54.3, C2', C5'; 115.2, 118.1, C4, C5; 123.2, 123.6, C3, C6; 133.5, 143.2, C1, C2. Mass Spectrum (ESI$^+$, MeOH): *m/z* 191.0 ($[M+H]^+$).

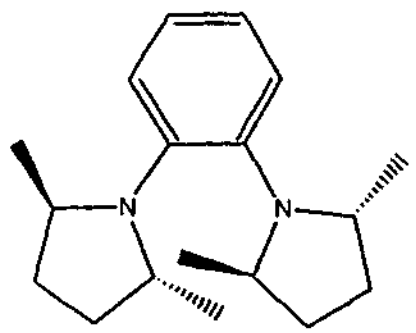
7.2.12 Synthesis of 1-amino-2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene hydrochloride salt (72)



(72)

HCl gas (prepared as described in Section 7.1.1) was passed through a stirred solution of 1-amino-2-((2*R*, 5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (55) (200 mg, 1.05 mmol) in methanol (20 ml). The mixture was concentrated to give the desired hydrochloride salt (72) as a colourless soild (269 mg, 93%). m.p. 182-184°C. (Found: *m/z* 191.1541. $[C_{12}H_{19}N_2]^+$ ($[M+H-HCl]^+$) requires 191.1548). ν_{max} (KBr): 3322s, 3200s, 2977m, 2822w, 2733w, 2556bm, 1661s, 1605s, 1500s, 1466m, 1444s, 1383w, 1311w, 1277w, 1022m, 783s, 755s cm^{-1}. ^1H n.m.r. (300 MHz, CD_3OD): δ 0.86, d, *J* 6.7 Hz, 3H and 1.32, d, *J* 6.1 Hz, 3H, 2 x CH_3; 1.72-1.88, m, 1H, 1.88-2.08, m, 1H, 2.25-2.40, m, 1H and 2.40-2.55, m, 1H, H3', H4'; 4.13-4.20, m, 1H and 4.20-4.35, m, 1H, H2', H5'; 7.03, d, *J* 7.3, 1.5 Hz, 1H, H5; 7.11, ddd, *J* 8.4, 6.9, 1.3 Hz, 1H, H3; 7.26, d, *J* 7.3, 1.5 Hz, 1H, H4; 7.32, ddd, *J* 8.4, 6.9, 1.3 Hz, 1H, H6. ^{13}C n.m.r. (100 MHz, CD_3OD): δ 18.7, 19.9, 2 x CH_3; 33.7, C3', C4'; 61.9, 63.6, C2', C5'; 123.5, 124.9, 127.0, 131.8, ArCH; 130.0, 141.2, C1, C2. Mass Spectrum (ESI^+, MeOH): *m/z* 190.8 ($[M+H-HCl]^+$). Crystals of the hydrochloride salt suitable for X-ray diffraction were obtained from a diethyl ether: hexane mixture. The X-ray structure was determined and details are attached in the Appendix.[104]

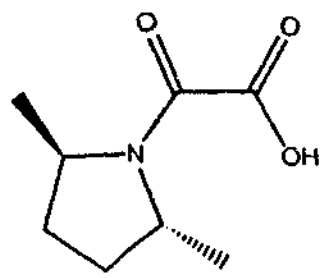
7.2.13 Synthesis of 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (44)



(44)

The aminophenyl pyrrolidine (55) (400 mg, 2.11 mmol) was added to a solution of the cyclic sulfate (52) (379 mg, 2.11 mmol) in THF (100 ml). The resulting orange solution was refluxed for 2 days after the addition of 80% sodium hydride (633 mg, 21.10 mmol). As t.l.c. indicated the presence of unreacted aminophenyl pyrrolidine (55), more cyclic sulfate (52) (379 mg, 2.11 mmol) dissolved in THF (30 ml) was added. The mixture was stirred at reflux for a further 2 days and quenched with 10% NH_4Cl (30 ml). The THF was removed under reduced pressure and the aqueous mixture extracted with dichloromethane (3 x 100 ml). The combined organic layers were washed with water (100 ml) and brine (100 ml), dried with $MgSO_4$, filtered and evaporated to afford a brown semi-solid. Purification using column chromatography (SiO_2, ethyl acetate: hexane, 1:10) afforded the title compound (44) as a colourless solid (408 mg, 71%). $[\alpha]_D^{25}$ +18° (c 0.51, $CHCl_3$). m.p. 108-112°C. (Found: *m/z* 273.2320. $[C_{18}H_{29}N_2]^+$ ($[M+H]^+$) requires 273.2331). ν_{max} (KBr): 2955s, 2922s, 2867s, 2811s, 1583s, 1494s, 1450s, 1367s, 1322m, 1294s, 1256m, 1194w, 1150s, 1100w, 1044w, 994m, 956w, 916w, 744s, cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 0.58, d, *J* 6.4 Hz, 6H, 1.10, d, *J* 5.8 Hz, 6H, 2 x CH_3; 1.32–1.58, m, 4H and 2.02–2.20, m, 4H, H3', H4'; 3.68–3.80, m, 2H and 4.06–4.18, m, 2H, H2', H5'; 6.84, s, 4H, H3, H4, H5, H6. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 19.6, 19.9, 2 x CH_3; 32.3, 33.2, C3' C4'; 51.9, 52.1, C2', C5'; 120.0, C3, C6; 120.6, C4, C5; 140.4, C1, C2. Mass Spectrum (ESI^+, MeOH): *m/z* 273.2 ($[M+H]^+$). Crystals of the diamine (44) suitable for X-ray diffraction were obtained by the slow evaporation of a diethyl ether solution of (44). The X-ray structure was determined the details are attached in the Appendix.[105]

7.2.14 Synthesis of (2*R*,5*R*)-2-(2,5-dimethylpyrrolidin-1-yl)-2-oxoethanoic acid (71)

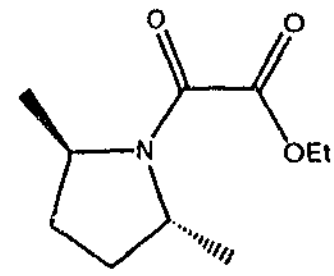


(71)

The reaction was carried out as described in Section 7.2.8 to give the desired product (71) as colourless solid (91 mg, 80%). m.p. 126-132°C. ν_{max} (KBr): 3415s, 1736s,

1618s, 1239 cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 1.23, d, *J* 6.41 Hz, 6H, 2 x CH_3; 1.56–1.66, m, 2H, H3', H4'; 1.66–1.81, m, 1H, OH; 2.07–2.32, m, 2H, 4,29–4.44, m, and 1H, 4.91–5.02, m, 1H, H2' H5'. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 18.4, 22.4, 2 x CH_3; 28.5, C3', C4'; 55.4, C2', C5'; 157.6, 159.9, C1, C2. Mass Spectrum (ESI^+, MeOH): *m/z* 172.0 ($[M+H]^+$)

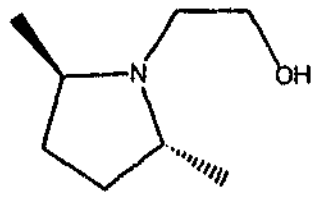
7.2.15 Synthesis of ethyl (2*R*,5*R*)-2-(2,5-dimethylpyrrolidin-1-yl)-2-oxoethanoate (73)



(73)

Pyridine (7.0 ml, 87.0 mmol) was added dropwise to a stirred solution of (2*R*,5*R*)-2,5-dimethylpyrrolidine hydrochloride (33) (2.38 g, 17.47 mmol) in dichloromethane: diethyl ether (2:1; 100 ml) at 0°C. After stirring for 15 min, ethyl oxalyl chloride (1.94 ml, 17.4 mmol) was added dropwise and an immediate formation of white precipitate was observed. The reaction was allowed to stir at room temperature for 18 h. It was acidified with 1 M HCl (75 ml) and extracted with dichloromethane (3 x 75 ml). The combined organic layers were dried with $MgSO_4$, filtered and evaporated to obtain the desired product (73) as a yellow oil (2.87 g, 83%). $[\alpha]_D^{25}$ -88.4° (c 2.0, $CHCl_3$). (Found: *m/z* 222.1093. $[C_{10}H_{17}NO_3Na]^+$ ($[M+Na]^+$) requires 222.1106). ν_{max} (neat): 2967s, 2878s, 1738s, 1650s, 1433s, 1383m, 1300m, 1277s, 1183s, 1161s, 1088s, 1017s, 983m, 911m, 861s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 1.15, d, *J* 6.3 Hz, 3H and 1.22, d, *J* 6.4 Hz, 3H, 2 x CH_3; 1.37, t, *J* 7.2 Hz, 3H, $OCH_2C\underline{H}_3$; 1.55-1.68, m, 2H and 2.04-2.34, m, 2H, H3', H4'; 4.24-4.42, m, 4H, H2', H5', $OC\underline{H}_2CH_3$. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 14.0, $OCH_2\underline{C}H_3$; 18.6, 22.3, 2 x $\underline{C}H_3$; 28.8, 30.8, C3', C4'; 53.9, 53.9, C2', C5'; 61.9, $O\underline{C}H_2CH_3$; 159.2, 162.5, C1, C2. Mass Spectrum (ESI^+, MeOH): *m/z* 222.1 ($[M+Na]^+$).

7.2.16 Synthesis of 2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethanol (67)

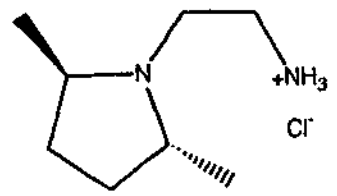


(67)

The $LiAlH_4$ reduction was carried out as described in Section 7.2.9 using ethyl (2*R*,5*R*)-(2,5-dimethylpyrrolidin-1-yl)-2-oxo-ethanoate (73) (1.78g, 8.92 mmol). The orange oil obtained after the work up was purified using column chromatography (SiO_2, ethyl acetate followed by NH_3 in methanol) to give the desired product (67) (660 mg, 52%). $[\alpha]_D^{RT}$ -55.1° (c 2.3, $CHCl_3$). (Found: *m/z* 144.1382. $[C_8H_{18}NO]^+$ ($[M+H]^+$) requires 144.1388). ν_{max} (neat): 3383bs, 2963s, 2360s, 2341m, 1654s, 1560w, 1456s, 1379s, 1050s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 0.97, d, *J* 6.3 Hz, 6H, 2 x CH_3; 1.30–1.46, m, 2H and 1.89–2.07, m, 2H, H3', H4'; 2.64-2.80, m, 2H, H2', H5'; 3.05–3.23, m, 1H, H2; 3.23, bs, 1H, OH, 3.48–3.63, m, 1H, H1. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 17.7, 2 x $\underline{C}H_3$; 31.2, C3', C4'; 48.4, C2; 55.2, C2', C5'; 59.2, C1. Mass Spectrum (ESI$^+$, MeOH): *m/z* 144.0 ($[M+H]^+$).

The reaction was carried out as described in Section 7.2.9, using (2*R*,5*R*)-2-(2,5-dimethylpyrrolidin-1-yl)-2-oxoethanoic acid (71) (91 mg, 0.35 mmol) to give the desired product (67) as a yellow oil (30 mg, 38%). The spectroscopic data were consistent with that obtained for (67) from above.

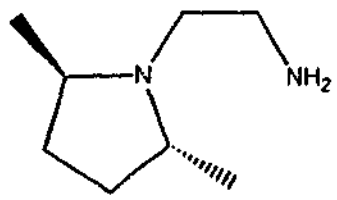
7.2.17 Synthesis of 2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethylamine hydrochloride



The reaction was carried out using a modified method of Mitsunobu *et al.*.[106]
2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethanol (67) (746 mg, 5.21 mmol) dissolved in distilled THF (5 ml) and diisopropyl azodicarboxylate (DIAD) (1.03 ml, 5.21 mmol) dissolved in distilled THF (5 ml) were added dropwise simultaneously under a

nitrogen atmosphere to a stirred solution of phthalimide (767 mg, 5.21 mmol) and triphenylphosphine (1.37 g, 5.21 mmol) in freshly distilled THF (20 ml) at 0°C. Stirring was continued at ambient temperatures for 3 days and the solvent was removed under reduced pressure to give a yellow oil. The oil was redissolved in methanol (50 ml) before adding hydrazine hydrate (0.3 ml, 6.25 mmol) and refluxing for a further 8 h. Concentrated HCl (5 ml) was added to the reaction mixture, which was then refluxed for 2 h. After cooling the mixture, the methanol was removed under reduced pressure. The resulting semi-solid was dissolved in water and extracted with dichloromethane (3 x 100 ml). The aqueous layer was concentrated to afford the titled amine salt as a yellow semi-solid (887 mg, 96 %). $[\alpha]_D^{25}$ –41.3° (c 0.62, H_2O). (Found: *m/z* 143.1545. $[C_8H_{19}N_2]^+$ ($[M+H-HCl]^+$) requires 143.1548). ν_{max} (KBr): 3411bs, 2989s, 1728s, 1650m, 1455s, 1394s, 1278s, 1150w, 1100m, 1055m, 800w cm^{-1}. ^1H n.m.r. (300 MHz, D_2O): δ 1.27, d, *J* 6.8 Hz, 3H and 1.40, d, *J* 6.6 Hz, 3H, 2 x CH_3; 1.71, m, 1H, 1.85, m, 1H, 2.18, m, 1H and 2.39, m, 1H, H3', H4'; 3.24-3.54, m, 4H, H1, H2; 3.68, m, 1H and 4.01, m, 1H, H2', H5'. ^{13}C n.m.r. (100 MHz, DMSO): δ 13.4, 15.9,2 x CH_3; 28.5, C3', C4'; 34.4, C1; 43.3, C2; 57.9, 60.1, C2', C5'. Mass Spectrum (ESI$^+$, MeOH): *m/z* 142.7 ($[M+H-HCl]^+$).

7.2.18 Synthesis of 2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethylamine (62)

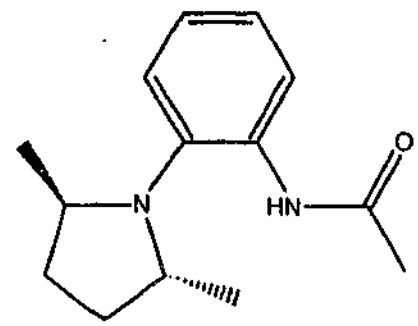


(62)

Sodium bicarbonate (sat.) solution was added to the amine hydrochloride salt (from Section 7.2.17) (600 mg, 3.37 mmol) and the mixture extracted with dichloromethane (3 x 20 ml). The combined organic layers were washed with water, dried with $MgSO_4$, filtered and evaporated to afford the desired product (62) as an orange oil (513 mg, 99%). $[\alpha]_D^{25}$ –112° (c 0.5, $CHCl_3$). (Found: *m/z* 143.1546. $[C_8H_{19}N_2]^+$ ($[M+H]^+$) requires 143.1548). ν_{max} (neat): 3288bs, 3189 bs, 2953s, 2866s, 2822s, 1718s, 1664s, 1534m, 1450s, 1375s, 1238s, 1112s, 1036s, 927s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 0.96, d, *J* 6.4 Hz, 6H, 2 x CH_3; 1.20-1.42, m, 4H, H3', H4'; 1.92-2.08, m, 2H and 2.48-2.68, m, 2H, H1, H2; 2.77, bs, 2H, NH_2; 2.98-3.10, m, 2H, H2',

H5', ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 17.2, 2 x CH_3; 31.04, C1, C2, C3', C4'; 55.2, C2', C5'. Mass Spectrum (ESI^+, MeOH): *m/z* 142.8 ($[M+H]^+$).

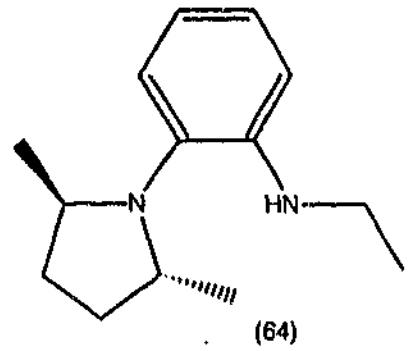
7.2.19 Synthesis of 1-acetylamino-2-((2*R*,5*R*)-dimethylpyrrolidine-1-yl)benzene (74)



(74)

Acetyl chloride (0.07 ml, 1.05 mmol) was added dropwise to a cooled (0°C) and stirred solution of 1-amino-2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (55) (200 mg, 1.05 mmol) and pyridine (0.09 ml, 1.16 mmol) in dichloromethane: diethyl ether (2:1; 20 ml). The mixture was brought to room temperature and stirred for 1.5 h. The reaction was quenched with 1 M HCl (20 ml) and extracted with dichloromethane (6 x 20 ml). The combined organic layers were dried with $MgSO_4$, filtered and evaporated to afford the desired product (74) as an orange solid (158 mg, 63%). $[\alpha]_D^{25}$ –62.3° (c 0.94, $CHCl_3$). m.p. 158-168°C. (Found: *m/z* 233.1641. $[C_{14}H_{20}N_2O]^+$ ($[M+H]^+$) requires 233.1654). ν_{max} (KBr): 3411sb, 3309s, 3166s, 3111s, 2989s, 2956s, 2544s, 2447s, 2355s, 1700s, 1600s, 1533s, 1489s, 1439s, 1367m, 1289s, 1239s, 1117m, 1072m, 1033m cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 0.86, d, *J* 7.0 Hz, 3H and 1.66, d, *J* 6.3 Hz, 3H, 2 x CH_3; 1.68-1.82, m, 2H, H3' or H4'; 2.34, s, 3H, CH_3CO; 2.42-2.78, m, 2H, H3' or H4'; 4.02-4.16, m, 1H and 4.48-4.62, m, 1H, H2', H5'; 7.20, d, *J* 7.6 Hz, 1H, H3; 7.30, t, *J* 7.2 Hz, 1H, H5; 7.50, t, *J* 7.5 Hz, 1H, H4; 7.94, d, *J* 8.1 Hz, 1H, H6; 10.97, bs, 1H, NH. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 14.9, 17.6, 2 x CH_3; 24.0, $\underline{C}H_3CO$; 30.0, 30.5, C3', C4'; 60.1, 62.1, C2', C5'; 122.4, C5; 125.9, C4; 126.2, C2; 128.3, C3; 130.2, C6; 133.6, C1; 170.5, CO. Mass Spectrum (ESI^+, MeOH): *m/z* 233.2 ($[M+H]^+$).

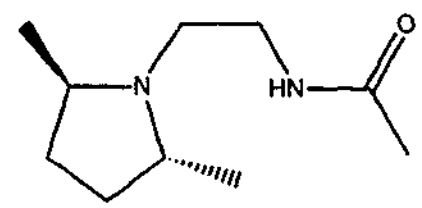
7.2.20 Synthesis of (2*R*,5*R*)-dimethylpyrrolidin-1-yl)-1-ethylamino-2-benzene (64)



(64)

The reduction of 1-acetylamino-2-((2*R*,5*R*)-dimethylpyrrolidin-1-yl)benzene (74) (137 mg, 1.04 mmol) using $LiAlH_4$ (392 mg, 10.37 mmol) was carried out as described in Section 7.2.9. The reaction was refluxed for 24 h after the addition of $LiAlH_4$. After working up with $Na_2SO_4.10H_2O$ as described previously (Section 7.2.9), a yellow oil was isolated and purified using column chromatography (SiO_2, ethyl acetate: hexane, 1:10) to afford the desired product (64) as a yellow oil (120 mg, 98%). $[\alpha]_D^{25}$ +14.6° (c 0.56, $CHCl_3$). (Found: *m/z* 219.1861. $[C_{14}H_{23}N_2]^+$ ($[M+H]^+$) requires 219.1861). ν_{max} (neat): 3355bs, 3044m, 2967s, 1650w, 1595s, 1505s, 1455m, 1433s, 1372s, 1322s, 1261s, 1156s, 1044m cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 0.70, d, *J* 6.4 Hz, 3H and 0.99, d, *J* 5.3 Hz, 3H, 2 x CH_3; 1.27, t, *J* 7.2 Hz, 3H, $CH_2\underline{CH_3}$; 1.40-1.58, m, 2H and 2.04-2.28, m, 2H, H3', H4'; 3.02-3.30, m, 2H, $\underline{CH_2}CH_3$; 3.62-3.74, m, 1H and 3.86-3.94, m, 1H, H2', H5'; 4.38, bs, 1H, NH; 6.60-6.68, m, 2H, H3, H5; 6.92, dd, *J* 7.6, 1.4 Hz, 1H, H6; 6.99, t, *J* 7.5 Hz, 1H, H4. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 15.5, 18.7, 2 x CH_3, $CH_2\underline{C}H_3$; 32.2, 32.8, C3', C4'; 38.9, $\underline{C}H_2CH_3$; 53.1, 54.3, C5', C2'; 110.2, 116.7, 123.1, 124.1, C3, C4, C5, C6; 132.9, C2; 145.5, C1. Mass spectrum (ESI^+, MeOH): *m/z* 219.2 ($[M+H]^+$).

7.2.21 Synthesis of 1-acetylamino-2-((2*R*,5*R*)-dimethylpyrrolidine-1-yl)ethane (75)

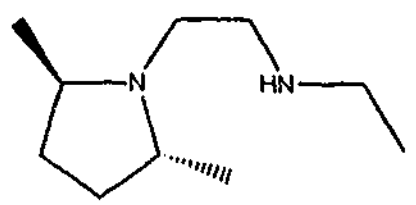


(75)

Acetyl chloride (0.15 ml, 2.05 mmol) was added dropwise to a cooled (0°C) and stirred solution of 1-amino-2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethane (62) (292 mg, 2.05 mmol) and pyridine (0.18 ml, 2.26 mmol) in dichloromethane: diethyl ether

(2:1; 20 ml). The mixture was brought to room temperature and stirred for 4 h. The reaction was quenched with water (20 ml) and extracted with dichloromethane (3 x 20 ml). The combined organic layers were dried with $MgSO_4$, filtered and evaporated to give a black oil (100 mg). ^{1}H n.m.r spectroscopy of this oil showed mainly unreacted pyridine together with other impurities. The aqueous layer was basified using NaOH (4 M) and extracted with dichloromethane (3 x 20 ml). The combined organic layers were dried with $MgSO_4$, filtered and evaporated to afford the desired amide (75) as a orange oil (192 mg, 51%). $[\alpha]_D^{25}$ –127.6° (c 0.21, $CHCl_3$). (Found: *m/z* 185.1653. $[C_{10}H_{21}N_2O]^+$ ($[M+H]^+$) requires 185.1653). ν_{max} (neat): 3289bs, 3089w, 2967s, 2922s, 2867s, 2822s, 1722s, 1650s, 1550s, 1450s, 1372s, 1277s, 1167m, 1111m, 1033w cm^{-1}. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 0.97, d, *J* 6.3 Hz, 6H, 2 x CH_3; 1.32-1.44, m, 2H and 1.92-2.08, m, 5H, H3', H4', OCH_3; 2.61-2.69, 2H, H1; 2.98-3.18, m, 3H, H2 and H2' or H5'; 3.44, 3.56, m, 1H, H2' or H5'. ^{13}C n.m.r. (100MHz, $CDCl_3$): δ 17.3, 2 x CH_3; 23,6, $\underline{C}H_3CO$; 31.0, C3', C4'; 37.9, C1; 45.8, C2; 55.1, C2', C5'; 170.5, CO. Mass spectrum (ESI$^+$, MeOH): *m/z* 184.9 ($[M+H]^+$).

7.2.22 Synthesis of ((2*R*,5*R*)-dimethylpyrrolidin-1-yl)-1-ethylamino-2-ethane (63)

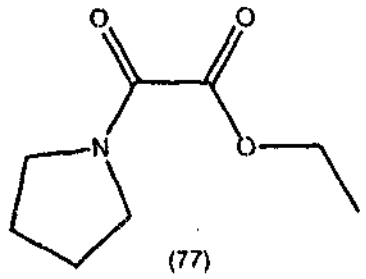


(63)

The reduction of 1-acetylamino-2-((2*R*,5*R*)-dimethylpyrrolidin-1-yl)ethane (75) (192 mg, 1.05 mmol) using $LiAlH_4$ (199 mg, 5.27 mmol) was carried out as described in Section 7.2.9. The desired product (63) was isolated as a yellow oil (133 mg, 75%). $[\alpha]_D^{25}$ –94.7° (c 0.95, $CHCl_3$). (Found: *m/z* 171.1855. $[C_{10}H_{23}N_2]^+$ ($[M+H]^+$) requires 171.1861). ν_{max} (neat): 3300bs, 1455s, 1372s, 1327m, 1133m, 1122s, 733w cm^{-1}. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 0.96, d, *J* 6.2 Hz, 6H, 2 x CH_3; 1.12, t, *J* 7.2 Hz, 3H, $CH_2C\underline{H}_3$; 1.28-1.42, m, 2H and 1.90-2.08, m, 2H, H3', H4'; 2.48-2.82, m, 6H and 2.98-3.08, m, 2H, $C\underline{H}_2CH_3$, H1, H2, H2', H5'. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 15.4,

$CH_2\underline{C}H_3$; 17.1, 2 x CH_3; 31.0, H3', H4'; 44.3, 46.8, 48.1, $\underline{C}H_2CH_3$, C1, C2; 55.3, C2', C5'. Mass spectrum (ESI$^+$, MeOH): *m/z* 171.1 ($[M+H]^+$).

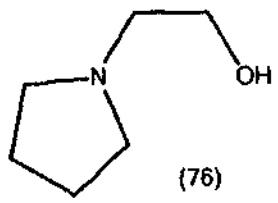
7.2.23 Synthesis of ethyl 2-oxo-2-(pyrrolidin-1-yl)ethanoate (77)



(77)

Ethyl oxalyl chloride (7.85 ml, 0.07 mol) was added to a solution of triethylamine (9.35 ml, 0.14 mol) and pyrrolidine (28) (5.86 ml, 0.07 mol) in dichloromethane at 0°C. The mixture was brought to room temperature and allowed to stir for 18 h. The reaction was quenched with HCl (1 M) and extracted with dichloromethane (3 x 75 ml). The combined organic layers were washed with water (75 ml) and brine (75 ml), dried with $MgSO_4$, filtered and evaporated to afford the amido ester (77) as an orange oil[218] (11.0 g, 92%). ν_{max} (neat): 2978s, 2889s, 1739s, 1655s, 1450s, 1389w, 1366s, 1339s, 1250s, 1189s, 1167s, 1106m, 1017s, 861m cm^{-1}. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 1.37, t, *J* 7.2 Hz, 3H, $CH_2\underline{C}H_3$; 1.84-2.02, m, 4H, H3', H4'; 3.54, t, *J* 6.6 Hz, 2H and 3.63, t, *J* 6.5 Hz, 2H, H2', H5'; 4.33, q, *J* 7.2 Hz, 2H, $\underline{C}H_2CH_3$. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 14.1, $CH_2\underline{C}H_3$; 24.0, 26.0, C3', C4'; 46.1, 47.4, C2', C5'; 62.0, $\underline{C}H_2CH_3$; 158.6, 162.1, C1, C2. Mass Spectrum (ESI$^+$, MeOH): *m/z* 172.0 ($[M+H]^+$).

7.2.24 Synthesis of 2-(pyrrolidin-1-yl)-ethanol (76)

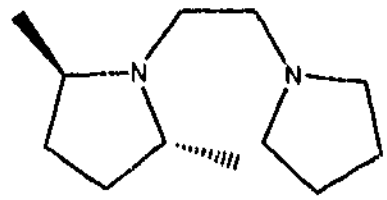


(76)

The reduction of the pyrrolidine ethyl ester (77) (6.00g, 0.04 mol) was carried out using $LiAlH_4$ (6.8 g, 0.18 mol) as described in Section 7.2.9. The desired alcohol (76) was isolated as a yellow oil (1.55 g, 34%). (Found: *m/z* 116.1069. $[C_6H_{14}NO]^+$ ($[M+H]^+$) requires 116.1075). ν_{max} (neat): 3378bs, 2956s, 2800s, 1461m, 1344w, 1289m, 1244w, 1194w, 1139m,1056s, 873m cm^{-1}. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 1.74-1.82, m, H3', H4'; 2.50-2.60, m, H2', H5'; 2.65, t, *J* 5.5 Hz, 2H, H2; 3.64, t, *J* 5.5 Hz, 2H, H1. ^{13}C n.m.r. (100MHz, $CDCl_3$): δ 23.8, C3', C4'; 54.1, C2', C5'; 57.9, C2;

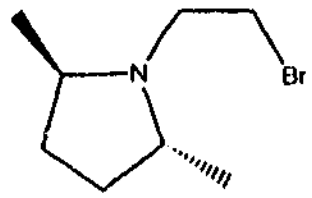
60.2, C1. Mass Spectrum (ESI$^+$, MeOH): *m/z* 115.8 ([M+H]$^+$). The spectral data were consistent with the literature.[108]

7.2.25 Synthesis of 1-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)-2-(pyrrolidin-1-yl)ethane (66)



(66)

Method A: From 2-bromo-1-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethane (78)



(78)

A solution of triphenylphosphine (915 mg, 3.49 mmol) in anhydrous diethyl ether (15 ml) was added to a cooled (0°C) and stirred solution of 2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethanol (67) (500 mg, 3.49 mmol) and carbon tetrabromide (1.16g, 3.49 mmol) in anhydrous diethyl ether (20 ml). External cooling was discontinued and the reaction mixture was heated at reflux for 1 h. The mixture was then cooled in ice before a small sample was removed and concentrated under vacuum to give a pale brown solid. The ^{1}H n.m.r spectrm of this solid showed the formation of 2-bromo-1-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethane (78) and triphenylphosphine oxide. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 1.01, d, *J* 6.3 Hz, 6H, 2 x CH_3; 1.35-1.45, m, 2H and 1.98-2.08, m, 2H, H3', H4'; 2.93, dt, *J* 7.9, 2.1 Hz, 2H, H2; 3.06-3.16, m, 2H, H2', H5'; 3.41, t, *J* 7.9 Hz, 2H, H1. Mass Spectrum (ESI$^+$, MeOH): *m/z* 208.0 ([M(^{81}Br)+H]$^+$), 206.0 ([M(^{79}Br)+H].

The bromo compound (78) was extremely unstable and the crude solution was used immediately in the next step.

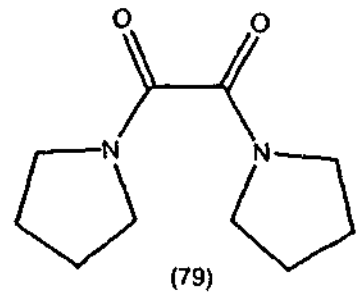
Pyrrolidine (28) (0.32 ml, 3.84 mmol) was added to this cold reaction mixture and the mixture was brought to room temperature. The mixture was stirred for 18 h before the solvent was evaporated. The resulting brown oil was dissolved in methanol (50 ml) and dry HCl gas (see Section 7.1.1) was bubbled through it (20 mins). The methanol was evaporated and the resulting black oil was dissolved in water (30 ml) and

dichloromethane (30 ml), and the layers separated and extracted with dichloromethane (3 x 30 ml). The aqueous layer was reduced *in vacuo*, the pH was adjusted to 11 using NaOH pellets and the mixture extracted with dichloromethane (3 x 50 ml). The combined organic layers were washed with water, brine, dried with $MgSO_4$, filtered and evaporated to afford a dark brown oil. This oil was run through a silica plug (ethyl acetate followed by NH_3 in methanol) to afford the amine (66) as a brown oil (214 mg, 31%). $[\alpha]_D^{25}$ –80.5° (c 0.2, $CHCl_3$). (Found: *m/z* 197.2010. $[C_{12}H_{25}N_2]^+$ ($[M+H]^+$) requires 197.2018). ν_{max} (neat): 2955s, 2800s, 2689m, 1456s, 1372s, 1344m, 1327m, 1294m, 1238w, 1194s, 1122s, 1000m, 967s, 922m, 887m, 722s, 694s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 0.99, d, *J* 6.2 Hz, 6H, 2 x CH_3; 1.32-1.46, m, 2 H and 1.92-2.08, m, 2H, H3', H4'; 1.72-1.88, m, 4H, H3", H4"; 2.52–2.86, m, 8H, H2", H5", H1, H2; 3.00–3.12, m, 2H, H2', H5'. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 16.7, 2 x CH_3; 23.4, 30.6, C3', C4', C3", C4"; 46.4, 55.1, C1, C2; 54.6, C2", C5"; 55.7, C2', C5'. Mass Spectrum (ESI^+, MeOH): *m/z* 196.9 ($[M+H]^+$).

Method B: From Mitsunobu reaction with alcohol (76)[106]

(2*R*,5*R*)-2,5-dimethylpyrrolidine hydrochloride (33) (1.17 g, 8.70 mmol) was dissolved in diethyl ether, and basified with $NaHCO_3$ (sat.). The organic layer was dried using NaOH pellets. The resulting solution was stirred for 30 min. under a N_2 atmosphere before decanting in to a three necked R.B.F. to which THF (20 ml) and triphenylphosphine (1.14 g, 4.35 mmol) were added. The solution was cooled to 0°C and the pyrrolidinyl alcohol (76) (500 mg, 4.35 mmol) and diisopropyl azodicarboxylate (0.86 ml, 4.35 mmol) were added dropwise simultaneously. Stirring was continued at ambient temperature for 3 days and the solvent was removed under reduced pressure. ^1H n.m.r. spectroscopy of the crude oil showed only the starting alcohol (76) together with triphenylphosphine oxide and the reduced DIAD.

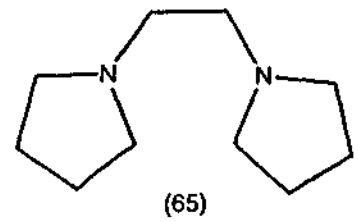
7.2.26 Synthesis of 1,2-dioxo-1,2-di(pyrrolidine-1-yl)ethane (79)



(79)

Oxalyl chloride (6.10 ml, 70.1 mmol) was added dropwise to a stirred solution of pyrrolidine (28) (11.4 ml, 142 mmol) and triethylamine (25 ml, 185 mmol) in dichloromethane (70 ml) at 0°C. The solution was stirred for 12 h and then diluted with dichloromethane (50 ml). The reaction mixture was acidified with 1 M HCl and extracted with dichloromethane (3 x 50 ml). The combined organic layers were washed with water (50 ml), brine (50 ml) dried with $MgSO_4$, filtered and evaporated to afford the desired product (79) as a cream solid (11.70 g, 85%). m.p. 73-75°C (lit.[219] m.p. 77-78°C). ν_{max} (KBr): 2967s, 2878s, 1633s, 1461w, 1400s, 1333w, 1222w, 1172w, 772m cm^{-1}. ^1H n.m.r. (400 MHz, $CDCl_3$): δ 1.88–2.05, m, 8H, H2', H3'; 3.47–3.58, m, 8H, H1', H4'. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 24.1, 26.1, C2', C3'; 42.3, 47.1, C1', C4'; 163.3, C1, C2. Mass Spectrum (ESI^+, MeOH): *m/z* 218.8 ($[M+Na]^+$). The spectral data were consistent with the literature.[219]

7.2.27 Synthesis of 1,2-di(pyrrolidin-1-yl)ethane (65)

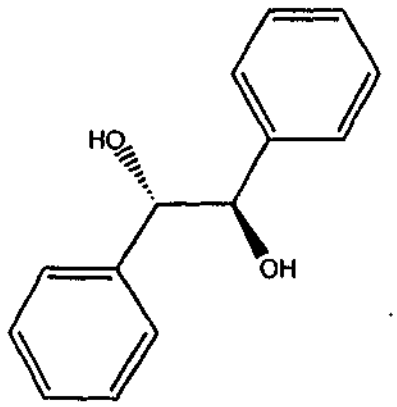


(65)

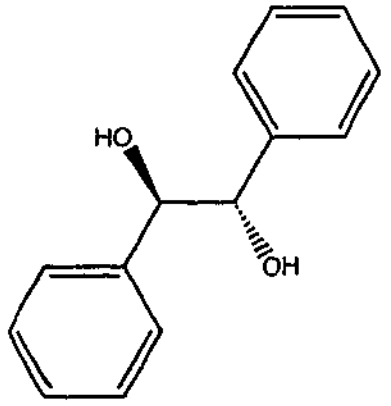
1,2-Dioxo-1,2-di(pyrrolidine-1-yl)ethane (79) (5.00 g, 25.5 mmol) in THF (50 ml) was added to a suspension of $LiAlH_4$ (4.81 g, 127.4 mmol) in THF (70 ml) at 0°C under an atmosphere of nitrogen. The mixture was stirred for 2 h at reflux, cooled to 0°C and $NaSO_4.10H_2O$ was added until no further gas evolution was observed. The resulting suspension was filtered and the solid washed with THF (50 ml). The filtrate was evaporated to afford the title compound (65) as a pale yellow oil (2.00 g, 47 %). ν_{max} (neat): 2967s, 2748s, 1450w, 1344w, 1294w, 1281w, 1144s, 1111s, 978m cm^{-1}. ^1H n.m.r. (400 MHz, $CDCl_3$): δ 1.74-1.82, m, 8H, H2', H3'; 1.82-2.48, m, 8H, H1', H4'; 2.65, s, 4H, H1, H2. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 23.7, C2', C3'; 54.8, C1', C4'; 55.9, C1, C2. Mass Spectrum (ESI^+, MeOH): *m/z* 190.8 ($[M+Na]^+$). The spectral data were consistent with the literature.[108]

7.3 Asymmetric dihydroxylation using pyrrolidine ligands

7.3.1 Synthesis of (±)-1,2-diphenylethane-1,2-diol ((±)hydrobenzoin) (14)



(*S,S*)- (14)



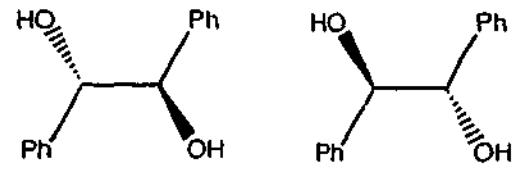
(*R,R*)-(14)

Stilbene (12) (32 mg, 0.178 mmol) was added to a stirred solution of OsO_4 (51 mg, 0.201 mmol) in THF (15 ml) to give a black mixture. The reaction was stirred at ambient temperature for 4 h. Lithium aluminium hydride (49 mg, 1.22 mmol) was added and the mixture was stirred for a further 18 h. $Na_2SO_4.10H_2O$ was added until no further gas evolution was observed. The resulting precipitate was filtered and the filtrate evaporated to afford the desired product (14) as a colourless solid (37 mg, 97%). m.p. 145-149°C (lit.[220] 149-151°C). ν_{max} (KBr): 3488s, 3389bs, 3022m, 2889s, 1672m, 1655s, 1594m, 1577m, 1489s, 1450s, 1383s, 1357s, 1250s, 1194s, 1039s, 778s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 2.93, bs, 2H, 2 x OH; 4.68, s, 2H, H1, H2; 7.07–7.14, m, 4H, H3' H5'; 7.20–7.25, m, 6H, H2', H6', H4'. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 79.4, C1, C2; 127.2, C3', C5'; 128.1, C4'; 128.3, C2', C6'; 140.0, C1'. Mass Spectrum (ESI^+, MeOH): *m/z* 237.1 ($[M+Na]^+$).

The crude diol (14) was purified for HPLC analysis *via* t.l.c. (Silica gel $60F_{254}$, 2.5 x 7.5 cm, 250 μm; ethyl acetate: hexane, 1:1). Fraction of silica containing the required product was scraped off the plate as a powder. Isopropanol (HPLC grade) (1 ml) was added to the silica powder and the resulting suspension was filtered through a syringe filter (25 mm, 0.46 cm x 25 cm, 0.2 U) to give a solution of the purified hydrobenzoin (14). The solution of diol (14) in isopropanol (20 μl) was injected in to the HPLC apparatus containing the chiral OJ column (1.0 ml/min, detection at 250 nm, 10% isopropanol: 90% hexane) to give two peaks: R_t = 12.0 mins, R_t = 13.3 mins.

The reaction was carried out using stilbene (12) (32 mg, 0.18 mmol) and OsO_4 (51 mg, 0.20 mmol) following the procedure described above but at -78°C for 7 h. The reaction was worked up to obtain a colourless solid (30 mg). ^1H n.m.r. spectroscopy of this solid showed only starting material (12).

7.3.2 Asymmetric dihydroxylations of stilbene (12)



(*S,S*)- (14) (*R,R*)-(14)

(i) Using 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethane (43)

Reactions were carried out using the general method described by Tomioka *et al.*.[43] A typical procedure is outlined below.

OsO_4 (51 mg, 0.201 mmol) was added to a stirred solution of chiral diamine (43) (50 mg, 0.22 mmol) in THF (10 ml) at the desired temperature (e.g. ambient temperature (23°C), -78 °C, 0 °C) and the mixture stirred for 15 minutes before stilbene (12) (32 mg, 0.178 mmol) was added. The mixture was stirred at the same temperature for a further 6 h before $LiAlH_4$ (59 mg, 1.56 mmol) was added and stirred for 18 h at ambient temperature. Two different work up procedures were followed:

Work up A

$NaSO_4.10H_2O$ was added until no further gas evolution was observed. The resulting precipitate was removed by filtration and the filtrate was evaporated.

Work up B

The $LiAlH_4$ was hydrolysed by quenching with water (~2 ml). The resulting precipitate was removed by filtration. Most of the solvent was removed under reduced pressure and the pH adjusted to 2 using a 10% HCl solution and the resulting mixture was extracted with diethyl ether (3 x 20 ml). The combined organic layers were washed with brine (10 ml), dried with $MgSO_4$, filtered and evaporated.

^1H n.m.r spectroscopy of the crude sample was used in identifying the products formed using both work up methods.

The reactions were carried out using varying temperature, reaction times and solvents and the results are summarised in Table 7.3.1.

Table 7.3.1:

Entry[a,b]	Solvent	Temp (°C)	Time (h)	Conversion to (14) (%)
1[a,d]	THF	-78	8	0[c]
2[a]	THF	-15	8	0[c]
3[a]	THF	23	6	0[c]
4[b]	Toluene	-78	6	<1[c]
5[b]	Toluene	0	48	<3[c]
6[b]	Toluene	23	6	<1[c]
7[b]	DCM	0	8	0[c]

a, Refers to Work up A from above; *b*, Refers to Work up B from above; *c*, The % conversion was determined by ^{1}H n.m.r. spectroscopy of the crude sample. The % conversion was determined relative to the amount of starting material (12) and product (14) present in the ^{1}H n.m.r. spectrum; *d*, In Entry 1 a stirred solution of chiral diamine (43) (50 mg, 0.22 mmol) in THF (10 ml) was cooled to <-100°C. As the THF froze at this temperature, the reaction was warmed to -78°C before a solution of OsO_4 (51 mg, 0.201 mmol) dissolved in THF (3 ml) was added.

(ii) Using 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (44)

Reactions were carried out as described in Section 7.3.2 (i). and results presented in Table 7.3.2. All four reactions were carried out using the same ratio of reactants. Entries 1 and 4 used chiral diamine (44) (50 mg, 0.18 mmol), OsO_4 (42 mg, 0.17 mmol), stilbene (12) (27 mg, 0.15 mmol) and $LiAlH_4$ (49 mg, 1.29 mmol). Entry 2 was done using chiral diamine (44) (43 mg, 0.16 mmol), OsO_4 (36 mg, 0.14 mmol), stilbene (12) (23 mg, 0.13 mmol) and $LiAlH_4$ (42 mg, 1.11 mmol). Entry 3 was done using chiral diamine (44) (60 mg, 0.22 mmol), OsO_4 (50 mg, 0.20 mmol), stilbene (12) (32 mg, 0.17 mmol) and $LiAlH_4$ (58 mg, 1.53 mmol). The reactions were carried out using different temperatures, solvents and reaction times (Table7.3.2). Both work up methods (Work up A and Work up B) described in Section 7.3.2 (i) were used in isolating the product and ^{1}H n.m.r spectroscopy of the crude samples was used to identify the products formed.

Table 7.3.2:

Entry[a,b]	Solvent	Temp (°C)	Time (h)	Conversion to (14) (%)
1[a]	THF	-78	6	0[c]
2[a]	THF	23	6	0[c]
3[a]	THF	reflux	72	0[c]
4[b]	Toluene	0	8	0[c]
5[d]	Toluene	23	8	0[c]

a, *b*, *c*; As for Table 7.3.1; *d*, The reaction was worked up using water (1 ml) instead of $Na_2SO_4.10H_2O$. The resulting precipitate was filtered and the filtrate evaporated to afford a yellow oil.

(iii) Using 1,2-di(pyrrolidin-1-yl)ethane (65)

Reactions were carried out as described in Section 7.3.2 (i). The reactions were carried out using the diamine (65) (37 mg, 0.22 mmol), OsO_4 (51 mg, 0.20 mmol), stilbene (12) (32 mg, 0.18 mmol) and $LiAlH_4$ (141 mg, 3.75 mmol). The reactions were worked up (Work up A) as described in Section 7.3.2 (i). ^1H n.m.r. spectroscopy of the crude samples were used to identify the products formed in all entries and the results are summarised in Table 7.3.3.

Table 7.3.3:

Entry	Solvent	Temp (°C)	Time (h)	Conversion to (14) (%)
1	THF	-78	8	100
2	THF	23	8	37[a]

a, The % conversion was determined by ^1H n.m.r. spectroscopy of the crude sample. The % conversion was determined relative to the amount of starting material (12) and product (14) present in the ^1H n.m.r. spectrum.

(iv) Using 1-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)-2-(pyrrolidin-1-yl)ethane (66)

The reactions were carried out as described in Section 7.3.2 (i), using 1-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)-2-(pyrrolidin-1-yl) ethane (66) (44 mg, 0.22 mmol), OsO_4 (51 mg, 0.20 mmol) and stilbene (12) (32 mg, 0.18 mmol) in THF. Quenching, work up (Work up A) and the product identification of the reactions were carried out as described in Section 7.3.2 (i) and the results are summarised in Table 7.3.4.

Table 7.3.4:

Entry	Temp (°C)	Time (h)	Conversion to (14) (%)	% ee
1	-78	7.5	0[a]	-
2	-15	7.5	50[a]	9 (*R*,*R*)[b]
3	23	7.5	0[a]	-

a, The % conversion was determined by ^{1}H n.m.r. spectroscopy of the crude sample. The % conversion was determined by ^{1}H n.m.r. spectroscopy of the crude sample. The % conversion was determined relative to the amount of starting material (12) and product (14) present in the ^{1}H n.m.r. spectrum; *b*, % ee was measured using chiral HPLC using chiral OJ column described in Section 7.3.1.

(v) Using (-) hydroquinidine-9-phenanthryl ether (97)

Reactions were carried out as described in Section 7.3.2 (i). Entry 1 was carried out using the chiral amine (97) (112 mg, 0.22 mmol), OsO_4 (51 mg, 0.20 mmol) and stilbene (12) (32 mg, 0.18 mmol). Entry 2 was done using the chiral amine (97) (22 mg, 0.45 mmol), OsO_4 (51 mg, 0.20 mmol) and stilbene (12) (32 mg, 0.18 mmol). Both reactions were carried out in THF at room temperature for 7.5 h. Quenching, work up (Work up A) and the product identification of the reactions were carried out as described in Section 7.3.2 (i) and the results are summarised in Table 7.3.5.

Table:7.3.5:

Entry	Amine:Os	Conversion to (14) (%)	% ee	Optical rotation ($[\alpha]_D^{25}$)
1	1:1	100	69 (*R*,*R*)[a]	Not measured
2	2:1	100	89 (*R*,*R*)[a]	+87 (c 1.5, EtOH)[b]

a, % ee was measured using chiral HPLC using chiral OJ column as described in Section 7.3.1; *b*, lit[86] for (*S*,*S*)-(14) is $[\alpha]_D^{25}$ –88.8 (EtOH) (97% ee).

(vi) Using 2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethylamine (62)

Reactions were carried out as described Section 7.3.2 (i) using the chiral diamine (62) (28 mg, 0.197 mmol), OsO_4 (50 mg, 0.197 mmol) and stilbene (12) (32 mg, 0.18 mmol) in THF. Quenching and the work up (Work up A) of the reactions were carried

out as described in Section 7.3.2 (i). ^{1}H n.m.r spectroscopy of the crude samples was used to identify the products isolated. The reactions are summarised in Table 7.3.6.

Table 7.3.6:

Entry	Temp (°C)	Time (h)	Conversion to (14) (%)	% ee
1	-78	6.5	0[a]	-
2	23	6.5	28[a]	<6 (*R*,*R*)[b]

a and *b*, as for Table 7.3.4

(vii) Using 1-amino-2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (55)

Reactions were carried out as described Section 7.3.2 (i) using chiral diamine (55) (42 mg, 0.22 mmol), OsO_4 (51 mg, 0.20 mmol) and stilbene (12) (32 mg, 0.18 mmol) in THF. Quenching, work up (Work up A) and the product identification of the reactions were carried out as described in Section 7.3.2 (i) and the results are summarised in Table 7.3.7.

Table 7.3.7:

Entry	Temp (°C)	Time (h)	Conversion to (14) (%)	% ee
1	-60	7.5	6[a]	-
2	23	7.5	66[a]	<1 (*R*,*R*)[b]

a and *b* as described in Table 7.3.4.

(viii) Using butylamine (103)

Reactions was carried out as described in Section 7.3.2 (i), using butylamine (103) (29 mg, 0.39 mmol), OsO_4 (50 mg, 0.20 mmol) and stilbene (12) (32 mg, 0.18 mmol) in THF. Quenching, work up (Work up A) and the product identification of the reactions were carried out as described in Section 7.3.2 (i) and the results are summarised in Table 7.3.8.

Table 7.3.8:

Entry	Solvent	Temp (°C)	Time (h)	Conversion to (14) (%)
1	THF	-78	7.5	0[a]
2	THF	23	7.5	100

a, as described in Table 7.3.3

(ix) Using aniline (104)

Reactions were carried out as described in Section 7.3.2. (i), using aniline (104) (37 mg, 0.393 mmol), OsO_4 (50 mg, 0.197 mmol) and stilbene (12) (32 mg, 0.18 mmol) in THF. Quenching, work up (Work up A) and the product identification of the reactions were carried out as described in Section 7.3.2 (i) and the results are summarised in Table 7.3.9.

Table 7.3.9:

Entry	Solvent	Temp (°C)	Time (h)	Conversion to (14) (%)
1	THF	-78	7.5	0[a]
2	THF	23	7.5	100

a, as with Table 7.3.3

(x) Using 1-ethylamino-2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (64)

A reaction was carried out as described in Section 7.3.2 (i), using the chiral diamine (64) (49 mg, 0.22 mmol), OsO_4 (51 mg, 0.20 mmol) and stilbene (12) (32 mg, 0.18 mmol). The reaction was carried out for 8 h in THF at ambient temperature before the addition of $LiAlH_4$ (49 mg, 1.28 mmol). The reaction was worked up (Work up A) as described in Section 7.3.2 (i). A black solid (50 mg) was isolated. The ^1H n.m.r. spectrum of the crude showed no conversion to product (14).

(xi) Using ((2*R*,5*R*)-dimethylpyrrolin-1-yl)-1-ethylamino-2-ethane (63)

Reactions were carried out as described in Section 7.3.2 (i), using chiral diamine (63) (38 mg, 0.22 mmol), OsO_4 (51 mg, 0.20 mmol) and stilbene (12) (32 mg, 0.18 mmol) in THF. Quenching, work up (Work up A) and the product identification of the reactions were carried out as described in Section 7.3.2 (i) and the results are summarised in Table 7.3.10.

Table 7.3.10:

Entry	Solvent	Temp (°C)	Time (h)	Conversion to (14) (%)
1	THF	-78	8	6[a]
2	THF	23	8	0[a]

a, as with Table 7.3.3

(xii) Using pyrrolidine (28)

Reactions were carried out as described in Section 7.3.2 (i), using amine (28) (28 mg, 0.393 mmol), OsO_4 (50 mg, 0.197 mmol) and stilbene (12) (32 mg, 0.18 mmol) in THF. Quenching, work up (Work up A) and the product identification of the reactions were carried out as described in Section 7.3.2 (i) and the results are summarised in Table 7.3.11

Table 7.3.11:

Entry	Solvent	Temp (°C)	Time (h)	Conversion to (14) (%)
1	THF	-78	6	0[a]
2	THF	23	7.5	0[a]

a, as with Table 7.3.3

(xiii) Using *N*-methylaniline (105)

The reaction was carried out as described in Section 7.3.2 (i) using *N*-methylaniline (105) (42 mg, 0.39 mmol), OsO_4 (50 mg, 0.20 mmol) and stilbene (12) (32 mg, 0.18 mmol) in THF. Quenching, work up (Work up A) and the product identification of the

reactions were carried out as described in Section 7.3.2 (i) and the results are summarised in Table 7.3.12.

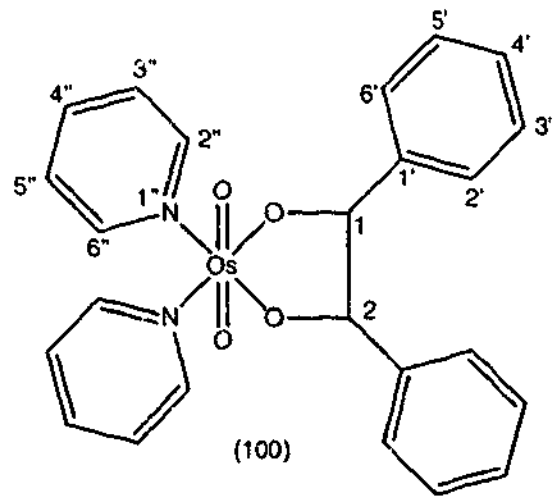
Table 7.3.12:

Entry	Solvent	Temp (°C)	Time (h)	Conversion to (14) (%)
1	THF	-78	7.5	0[a]
2	THF	23	7.5	70[a]

a, is as with Table.7.3.3

7.3.3 ^{1}H n.m.r displacement studies using pyrrolidine based ligands

7.3.3.1 Synthesis of the bis-(pyridine)osmium(VI)-1,2-diphenylethyleneglycolate (100)



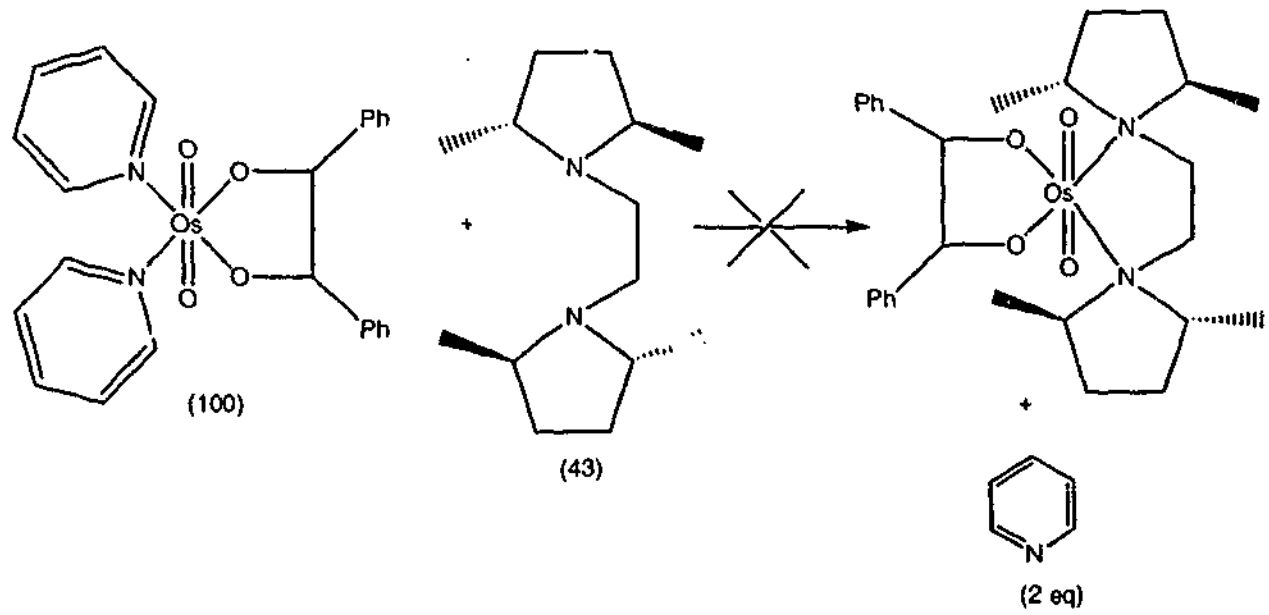
(100)

Synthesis of the glycolate (100) was achieved using a modified method described by Sharpless *et al.*.[110]

A solution of pyridine (168 mg, 2.0 mmol) in toluene (4 ml) and a solution of OsO_4 (200 mg, 0.8 mmol) in toluene (1 ml) were added *via* syringe to a round bottom flask containing a magnetic stirrer bar. Stilbene (12) (144 mg, 0.8 mmol) was dissolved in toluene (2 ml) and the solution added *via* syringe to the reaction mixture. An immediate formation of a orange/brown precipitate was observed. The mixture was stirred for 2 h and filtered. The resulting brown solid was dissolved in dichloromethane (20 ml) and precipitated using pentane (100ml). The precipitate was collected by filtration and dried to give the glycolate (100)[87] as a pink brown solid (416 mg, 87%). ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 5.36, s, 2H, H1, H2; 7.10-7.40, m,

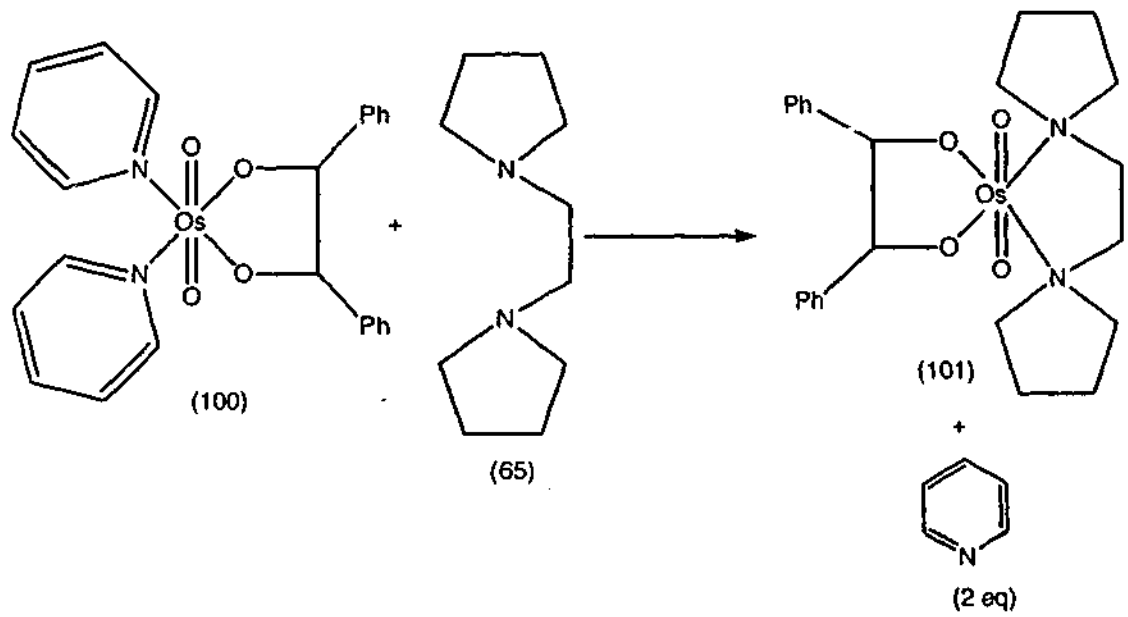
10H, H2', H3', H4', H5', H6'; 7.48 – 7.53, m, 4H, H3", H5"; 7.87, tt, *J* 7.7, 1.5 Hz, 2H, H4"; 9.00, dd, *J* 5.2, 1.5 Hz, 4H, H2", H6". ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 99.4, C1, C2; 125.6, C3', C5'; 127.7, C4'; 128.0, C2', C6'; 128.2, 140.7, C3", C4", C5"; 141.0, C1'; 149.8, C2", C6".

7.3.3.2 ^{1}H n.m.r studies of the reaction between bis-pyridine osmium(VI) glycolate (100) and 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethane (43)



A solution of the bis-pyridine osmium(VI) glycolate (100) (16 mg, 2.81 x 10^{-2} mmol) in base washed $CDCl_3$ was syringed into an n.m.r tube. After running the ^{1}H n.m.r spectrum of the complex (spectroscopic values as in Section 7.3.3.1), the contents were transferred into a sample vial containing 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethane (43) (7.0 mg, 3.09 x 10^{-2} mmol). The resulting solution was syringed into the n.m.r tube and the ^{1}H n.m.r spectrum was recorded. The spectrum showed no shift changes in the peaks of either the ligand (43) (See Section 7.2.9) or the osmium complex (100) (Section 7.3.3.1).

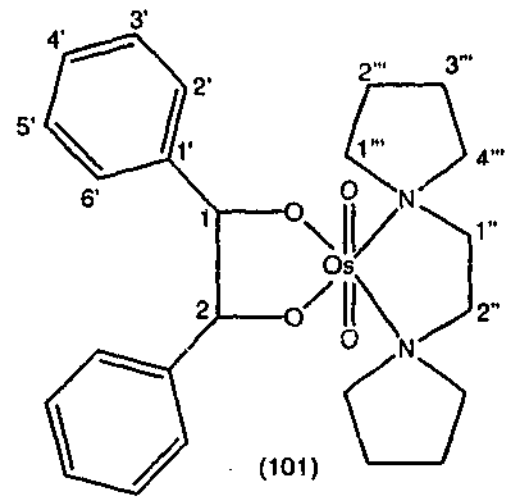
7.3.3.3 ^{1}H n.m.r studies of the reaction between bis-pyridine osmium(VI) glycolate (100) and 1,2-di(pyrrolidin-1-yl)ethane (65)



A solution of the bis-pyridine osmium(VI) glycolate (100) (16 mg, 2.81 x 10^{-2} mmol) was dissolved in base washed $CDCl_3$ and syringed into a n.m.r tube. The ^{1}H n.m.r spectrum (spectroscopic values as in Section 7.3.3.1), was recorded and the contents were then transferred into a sample vial containing 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethane (65) (5.2 mg, 3.09 x 10^{-2} mmol). The contents of the sample vial were syringed into the n.m.r tube and the ^{1}H n.m.r spectrum was recorded. ^{1}H n.m.r (300 MHz, $CDCl_3$): δ 1.78–2.00, m, 2H and 2.12-2.34, m, 2H, H3''', H4'''; 2.76-2.94, m, 2H and 3.24-3.40, m, 2H, H2''', H5'''; 3.80-4.00, m, 4H, H1'', H2''; 5.03, s, 2H, H1, H2; 7.08-7.32, m, 14H, H2', H3', H4', H5', H6', pyridine H3, H5; (Pyridine protons: δ 7.63, m, 2H, H4; 8.58-8.62, m, 4H, H2, H6).

The displaced pyridine was removed *in vacuo* and the resulting pink solid was dissolved in fresh base washed $CDCl_3$ and the ^{1}H n.m.r spectrum recorded. ^{1}H n.m.r spectrum was identical to that above minus the peaks due to pyridine.

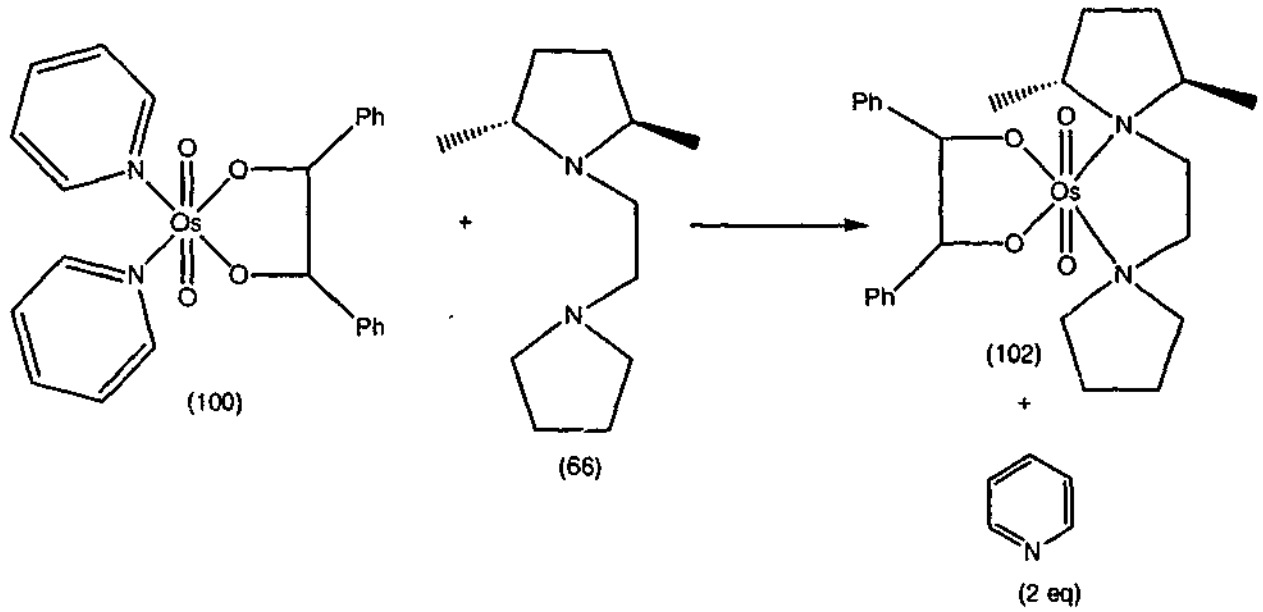
7.3.3.4 Synthesis of 1,2-di(pyrrolidin-1-yl)ethane osmium(VI) 1,2-diphenylglycolate.CH_2Cl_2 (101)



(101)

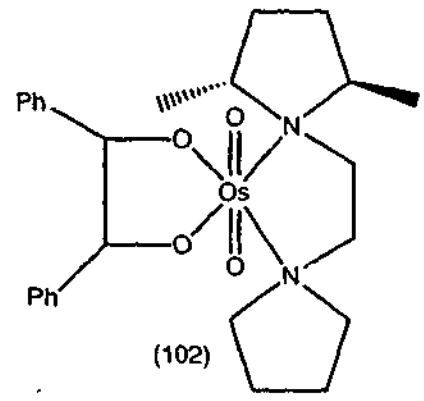
The bis-pyrrolidine (65) (27 mg, 0.16 mmol) was added to a stirring solution of the pyridine osmium complex (100) (87 mg, 0.15 mmol) in dry toluene (5 ml). The brown suspension was stirred for 10 min before the solvent was removed. The resulting solid was washed with pentane (3 x 3 ml), dissolved in dichloromethane and the solvent evaporated to afford a light brown solid. The solvent was removed and the resulting solid washed with pentane (3 x 3 ml), and dichloromethane (3 x 3 ml) to afford the 1,2-di(pyrrolidin-1-yl)ethane osmium(VI) 1,2-diphenylglycolate (101) as a pink solid (75 mg, 90 %). (Found: C, 44.3, H, 4.9, N, 4.1. $C_{25}H_{34}Cl_2N_2O_4Os$ requires C, 43.7, H, 4.9, N, 4.1). ν_{max} (KBr): 3044w, 3022m, 2966w, 2900w, 2856s, 1650s, 1638s, 1600w, 1444s, 1333w, 1277m, 1105m, 1055s, 1000s, 955s, 827s, 730m, 686s, 672sm 605s, 583 cm^{-1}. ^1H n.m.r (300 MHz, $CDCl_3$): δ 1.78–2.00, m, 2H and 2.12-2.34, m, 2H, H3''', H4'''; 2.76-2.94, m, 2H and 3.24-3.40, m, 2H, H2''', H5'''; 3.80-4.00, m, 4H, H1'', H2''; 5.03, s, 2H, H1, H2; 7.08-7.32, m, 10H, ArH. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 22.0, 22.1, C2''', C3'''; 61.1, 61.1, C1''', C4'''; 63.12, C1'', C2''; 99.0, C1, C2; 127.2, C5'; 127.6, C2', C6'; 127.9, C3', C5'; 142.0, C1'. Mass Spectrum (ESI^+, MeOH): *m/z* 627.2 ($[M+Na]^+$) $C_{24}H_{32}O_4N_2OsNa$.

7.3.3.5 ^{1}H n.m.r studies of the reaction between bis-pyridine osmium(VI) glycolate (100) and 1-((2*R*,5*R*)-2,5-(dimethylpyrrolidin-1-yl)-2-(pyrrolidin-1-yl))ethane (66)



A solution of the bis-pyridine osmium(VI) glycolate (100) (10 mg, 1.7 x 10^{-2} mmol) in base washed $CDCl_3$ was syringed into an n.m.r tube. The ^{1}H n.m.r spectrum recorded (spectroscopic values as in Section 7.3.3.1), and the contents were then emptied in to a sample vial containing 1-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)-2-(pyrrolidin-1-yl)ethane (66) (5.0 mg, 2.60 x 10^{-2} mmol). The solution was syringed into the n.m.r tube and the ^{1}H n.m.r spectrum was recorded. The ^{1}H n.m.r. spectrum showed that the reaction had gone to 50% completion. The displaced pyridine was removed *in vacuo* and the resulting solid was washed with dichloromethane (3 x 20 ml) to facilitate the complex formation. The resulting brown solid was dried and redissolved in fresh, base washed $CDCl_3$ and the ^{1} H n.m.r spectrum recorded. The ^{1}H n.m.r spectrum showed that the reaction had gone to completion. Two diasterionieric osmium complexes ((*R*,*R*,*R*,*R*)-(102) and (*R*,*R*,*S*,*S*)-(102) were observed. Separation of the diastereoisomers was not attempted.^{1}H n.m.r (300 MHz, $CDCl_3$): δ 1.20, d, *J* 7.0 Hz, 3H, 1.24, d, *J* 6.7 Hz, 3H, 1.32, d, *J* 6.5 Hz, 3H and 1.56, d, *J* 6.5Hz, 3H, 2 x (2 x CH_3); 1.67-2.30, m, 16H, 2 x (H3‴, H4‴, H3⁗, H4⁗); 2.50-3.68, m, 14H and 3.81-3.88, m, 4H, 2 x (H1″, H2″, H2‴, H5⁗); 4.32-4.48, m, 2H, 2 x (H2‴); 4.92, dd, *J* 9.2, 5.3 Hz, 2H and 5.03, d, *J* 9.2 Hz, 2H, 2 x (H1, H2); 7.02-7.12, m, 8H, 2 x (H3', H5'); 7.16-7.24, m, 12H, 2 x (H2', H6', H4').

7.3.3.6 Synthesis of the 1-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)-2-(pyrrolidin-1-yl)ethane osmium glycolate (102)



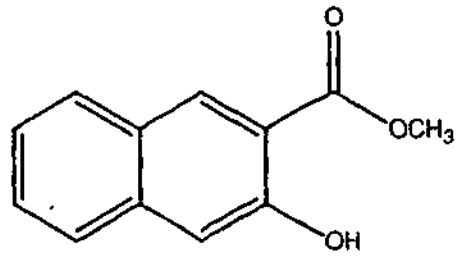
(102)

The bis-pyrrolidine (66) (20 mg, 0.102 mmol) was added to a stirring solution of the bis-pyridine osmium complex (100) (43 mg, 7.30 x 10^{-2} mmol) in dry dichloromethane (5 ml). The brown suspension was stirred for 3 hours before the solvent was evaporated. The resulting brown solid was redissolved in dichloromethane (3 x 3 ml) and the solvent evaporated. The brown solid was dissolved in a minimum amount of dichloromethane, and pentane was added. The black precipitate formed was removed by filtration and the filtrate concentrated to afford the desired complex (102) as a light brown solid (35 mg, 76%). ^{1}H n.m.r. (300 MHz, $CDCl_3$): As given in Section 7.3.3.5. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 15.0, 15.9, 17.9, 19.0, 2 x (2 x CH_3); 21.6, 21.7, 21.8, 21.9, 28.9, 28.9, 29.2, 29.4, 2 x (C3‴, C4‴, C3⁗, C4⁗); 55.1, 55.5, 60.0, 60.4, 61.4, 62.2, 62.4, 62.7, 2 x (C1", C2", C2⁗, C5⁗); 60.8, 61.3, 65.6, 66.2, 2 x (C2‴, C5⁗); 98.8, 98.9, 99.4, 99.5, 2 x (C1, C2); 127.2, 127.3, 127.8, 128.1, 128.2, 2 x (C2', C3', C4', C5', C6'); 141.9, 142.1, 2 x (C1').

7.4 Other asymmetric reactions using (2*R*,5*R*)-2,5-dimethyl pyrrolidine ligands

(i) Asymmetric biaryl coupling reactions using copper catalysts

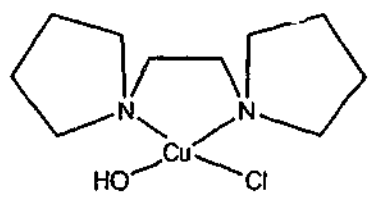
7.4.1 Synthesis of methyl 3-hydroxy-2-naphthoate (109)



(109)

Concentrated sulphuric acid (0.8 ml) was added to a stirring solution of 3-hydroxy-2-napthoic acid (114) (4.00g, 21.3 mmol) in methanol (28 ml) and the resulting yellow solution was refluxed for 18 h. After cooling the reaction mixture, the methanol was removed under reduced pressure. The resulting yellow solid was dissolved in diethyl ether (200 ml) and the pH adjusted to 8 using a $NaHCO_3$ (sat.) solution. The aqueous layer was extracted with diethyl ether (3 x 100 ml). The combined organic layers were washed with water and brine, dried with $MgSO_4$, filtered and evaporated to afford the desired product (109) as a yellow solid (1.84 g, 43%). m.p. 75-77°C (lit.[221] 73-74 °C). ν_{max} (KBr): 3178bs 1683s, 1627m, 1577w, 1505s, 1439s, 1416m, 1316s, 1277s, 1211s, 1144m, 1072s, 950m, 866m, 789s, 589s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 4.02,s, 3H, OCH_3; 7.29-7.35, 2H, m, H4, H7; 7.49, dt, *J* 6.7, 1.2 Hz, 1H, H6; 7.68, d, *J* 8.4 Hz, 1H, H5; 7.79, d, *J* 8.4 Hz, 1H, H8; 8.49, s, H1; 10.43, s, 1H, OH. ^{13}C n.m.r. (100MHz, $CDCl_3$): δ 52.4, OCH_3; 111.37, C4; 113.85, C2; 123.62, C7; 126.0, C5; 126.7, C8a; 128.9, C6, C8; 132.1, C1; 137.5, C4a; 155.9, C3; 169.9, CO. Mass Spectrum (ESI^+, MeOH): *m/z* 224.9 ($[M+Na]^+$).

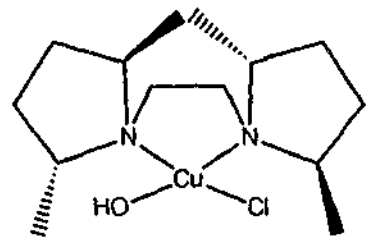
7.4.2 Synthesis of Cu(OH)Cl.1,2-di(pyrrolidine-1-yl) ethane (Cu(OH)Cl.(65))



Reactions were carried out using the general procedure described by Nakajima *et al.*.[136]

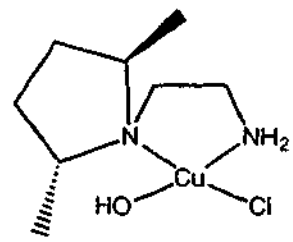
A mixture of Cu(I)Cl (59 mg, 0.595 mmol) and 1,2-di(pyrrolidine-1-yl)ethane (65) (200 mg, 1.19mmol) in methanol (20 ml) was stirred under an oxygen atmosphere at room temperature for 2 days. After reducing the methanol (to 5 ml) the reaction mixture was centrifuged. The filtrate was decanted and the resulting solid was washed with a small amount of cold methanol. A green solid was isolated of the tilted compound (99 mg, 59%). m.p. 110-115°C.

7.4.3 Synthesis of Cu(OH)Cl.1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethane (Cu(OH)Cl.(43))



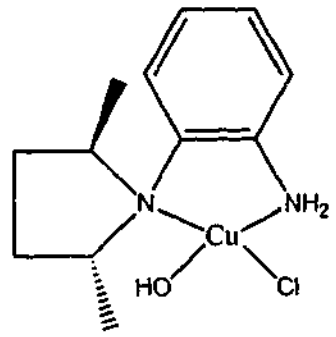
A mixture of Cu(I)Cl (70 mg, 0.711 mmol) and 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethane (43) (319 mg, 1.42mmol) as described above (Section 7.4.2) gave the titled copper complex as a chocolate brown solid (166 mg, 69%). m.p. 100-105°C.

7.4.4 Synthesis of Cu(OH)Cl.2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethylamine (Cu(OH)Cl.(62))



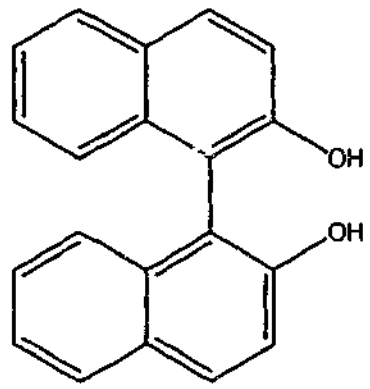
A mixture of Cu(I)Cl (179 mg, 1.81 mmol) and 2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethylamine (62) (514 mg, 3.61 mmol) in dichloromethane (10 ml) as described in Section 7.4.2 gave the titled compound as a khaki green solid (260 mg, 71%). m.p. 107-110°C.

7.4.5 Synthesis of Cu(OH)Cl.1-amino-2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (Cu(OH)Cl.(55))



A mixture of Cu(OH)Cl (39 mg, 0.395 mmol) and 1-amino-2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (55) (150 mg, 0.789 mmol) in dichloromethane (10 ml) as described in Section 7.4.2 afforded a the titled complex as a khaki green solid (113 mg, 93%).

7.4.6 Oxidative coupling of 2-naphthol (107)



(106)

7.4.6.1 Using Cu(OH)Cl.1,2-di(pyrrolidine-1-yl) ethane (Cu(OH)Cl.(65))

A mixture of the titled copper catalyst (Cu(OH)Cl.(65)) (10 mg, 3.47 x 10^{-2} mmol) and 2-naphthol (107) (500 mg, 3.47 mmol) in dichloromethane (10 ml) were stirred at room temperature for 18 h in open air. The reaction mixture had gone dry over the course of the reaction to afford a brown solid. ^{1}H n.m.r. spectrum of the crude solid showed 100% conversion to product (106). Purification of the crude solid using column chromatography (SiO_2, ethyl acetate) afforded 1,1'-binaphthalene-2,2' diol (106) (450 mg, 90%) as a colourless solid. m.p. 206-210 °C (lit.[222] 208-210°C). ν_{max} (KBr): 3500s, 3422bs, 1615s, 1594s, 1511s, 1461s, 1383s, 1344m, 1311m, 1255w, 1216s, 183s, 1144s, 811s, 750s, 667s cm^{-1}. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 5.01, bs, 2H, 2 x OH; 7.15, d, *J* 8.2 Hz, 2H, H3, H3'; 7.28 –7.44, m, 6H H4, H4', H6, H6', H7, H7'; 7.89, d, *J* 8.5 Hz, 2H and 7.98, d, *J* 8.8 Hz, 2H, H5, H5', H8, H8'. ^{13}C n.m.r. (100

MHz, $CDCl_3$): δ 111.06, C1, C1'; 118.0, C3, C3'; 124.3, 124.4, 127.7, 128.6, C5, C5', C6, C6', C7, C7'; C8, C8'; 129.7, C4a, C4a'; 131.6, C4, C4'; 133.6, C8a, C8a'; 152.9, C2, C2'. Mass Spectrum (ESI$^+$, MeOH): *m/z* 271.1 ($[M\text{-}OH+2H]^+$). The spectral data were consistent with those of an authentic sample.

7.4.6.2 Using Cu(OH)Cl.1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethane (Cu(OH)Cl.(43))

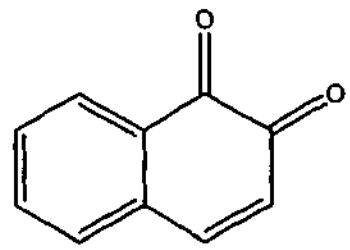
The reactions were carried out as described in Section 7.4.6.1 using 2-naphthol (107) (100 mg, 0.69 mmol) and the titled copper complex (Cu(OH)Cl.(43)) (3 mg, 6.94 x 10^{-2} mmol) under varying conditions and the results are summarised in Table 7.4.1

Table 7.4.1:

Entry	Oxidant	Time (h)	Temp (°C)	Mass isolated (mg)	Products isolated (%)[a]			
					(106)	(111)	(112)	S/m (107)
1	air	48	23	103	5	3	trace	92
2	air	7 (days)	reflux	128	0	0	0	100
3	O_2	48	23	105	0	59	41	0
4	O_2	18	23	112	0	0	30	70

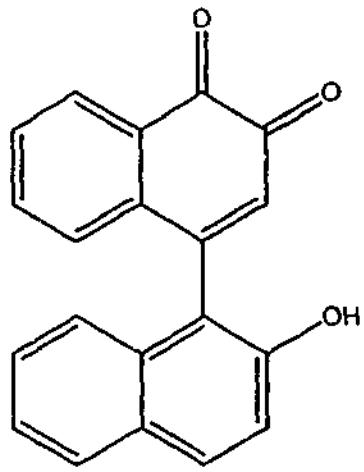
a: The ratios of products isolated (%) were determined by ^{1}H n.m.r. spectroscopy of the crude sample.

Reaction mixture from Entry 3 was purified using column chromatography (SiO_2, ethyl acetate: hexane, 1:5). First to elute was 1,2-napthaquinone (111) as a yellow solid (47 mg, 24%). m.p. 135-138°C (lit.[223] m.p. 143°C). ν_{max} (KBr): 1654s, 1611s, 1560m, 1459s, 1400s, 1287s, 1247s, 1197m, 1131w, 957m, 849s, 764s, 681m cm^{-1}. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 6.44, d, *J* 10.2 Hz, 1H, H3; 7.34-7.38, m, 1H, 8.08-8.14, m, 1H, H5, H8; 7.44, d, *J* 10.2 Hz, 1H, H4; 7.51, td, *J* 7.6, 1.4 Hz, 1H and 7.65, td, *J* 7.6, 1.4 Hz, 1H, H6, H7. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 128.1, C3; 130.0, 130.4, 131.0, 136.0, C5, C6, C7, C8; 131.7, 134.9, C4a, C8a; 145.5, C4; 178.9, 180.9, C1, C2. Mass Spectrum (GCMS/EI$^+$, MeOH): *m/z* 159.2 ($[M+H]^+$). The spectral data were consistent with the literature.[223]



(111)

Next to elute was 2'-hydroxy-(1,1')-binapthyl-3,4-dione (112) as a red/orange solid (47 mg, 24%). m.p. 138-148°C (lit.[136] m.p. 143°C). ν_{max} (KBr): 3388b, 1688m, 1644m, 1622m, 1578s, 1511s, 1428s, 1333m, 1288s, 1244m, 1136w, 1067w, 972m, 906m, 877m, 805s, 777s, 733s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 5.91, s, 1H, OH; 6.56, s, 1H, H2; 6.89, dd, *J* 7.4, 1.4 Hz, 1H, 7.34-7.58, m, 5H, 7.82-7.88, m, 1H, 8.20, dd, *J* 7.4, 1.4 Hz, 1H, ArH'; 7.29, d, *J* 8.8 Hz, 1H, 7.91, d, *J* 8.8 Hz, 1H, ArH. ^1H n.m.r. (300 MHz, DMSO): δ 6.36, s, H2; 6.71, dd, *J* 7.0, 1.9 Hz, 1H, ArH; 7.28-7.41, m, 3H, 7.48-7.60, m, 2H, 7.73, m, 1H, 7.88, m, 1H, 7.93, d, *J* 8.8 Hz, 1H, 8.07, dd, 6.9, 1.5 Hz, 1H, ArH; 9.8, s, 1H, OH. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 115.8, 118.1, 129.1, 131.9, 132.3, 135.2, 150.1, 152,6, ArC; 124.3, 124.4, 127.7, 128.6, 129.3, 130.6, 131.0, 131.3, 131.4, 136.0, ArCH; 179.5, 180.4, CO. Mass Spectrum (ESI^+, MeOH): *m/z* 323.1 ($[M+Na]^+$). The spectral data were consistent with the literature.[136]



(112)

7.4.6.3 Using Cu(OH)Cl.2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethylamine (Cu(OH)Cl.(62))

The reactions were carried out as described in Section 7.4.6.1 using 2-napthol (107) (100 mg, 0.69 mmol) and the titled copper complex (Cu(OH)Cl.(62)) (2 mg, 6.94 x 10^{-2} mmol) under varying conditions and the results are summarised in Table 7.4.2.

Table 7.4.2

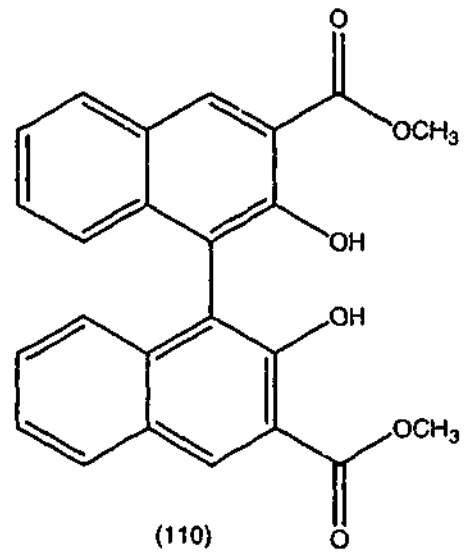
Entry	Oxidant	Time (h)	Temp (°C)	Mass isolated (mg)	Products isolated (%)[a]			
					(106)	(111)	(112)	(107)
1	O_2	72	23	133	0	76	24	0
2	air	7 (days)	23	118	9	8	0	83
3	air	7 (days)	reflux	102	0	0	0	100

a: The ratios of products isolated (%) were determined by ^{1}H n.m.r. spectroscopy of the crude sample.

7.4.6.4 Using Cu(OH)Cl.1-amino-2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (Cu(OH)Cl.(55))

The reaction was carried out as described in Section 7.4.6.1 using 2-napthol (107) (100 mg, 0.69 mmol) and the catalyst (Cu(OH)Cl.(55)) (2 mg, 6.94 x 10^{-2} mmol) in dichloromethane (10 ml) under an atmosphere of O_2 at 23°C for 18 h. The reaction was worked up as described in Section 7.4.6.1 to afford a brown solid (128 mg). ^{1}H n.m.r. spectroscopy of this solid showed that there was 16% starting material (107), 73% of the quinone (111) and 11% product (106).

7.4.7 Oxidative coupling of methyl 3-hydroxy-2-naphthoate (109)



(110)

7.4.7.1 Using Cu(OH)Cl.1,2-di(pyrrolidine-1-yl) ethane (Cu(OH)Cl.(65))

The reaction was carried out as described in Section 7.4.7.1 using methyl 3-hydroxy-2-naphthoate (109) (100 mg, 0.49 mmol) as the substrate and the titled copper catalyst (Cu(OH)Cl.(65)) (2 mg, 0.49 x 10^{-2} mmol). The reaction was refluxed for 2 days. The resulting brown solid was purified using column chromatography to afford dimethyl 2,2'-dihydroxy-1,1'-binapthalene-3,3'-dicarboxylate (110)[136] as a colourless solid (100

mg, 100%). m.p. 280-283°C. ν_{max} (KBr): 3478bs, 3179bs, 2953m, 1689s, 1624m, 1600m, 1500s, 1438s, 1322s, 1283s, 1222s, 1150s, 1078s, 800s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 4.05, s, 6H, 2 x OCH_3; 7.05-7.19, m, 2H, 7.30-7.38, m, 4H and 7.88-7.96, m, 2H, H5, H5', H6, H6', H7, H7', H8, H8'; 8.68, s, 2H, H4, H4'; 10.72, s, 2H, 2 x OH. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 53.1, 2 x OCH_3; 114.4, C2, C2'; 117.2, 127.4, 137.3, C1,C1', C4a, C4a', C8a, C8'; 124.2, 124.9, 129.6, 130.0, ArCH; 133.1, C4, C4'; 154.1, C3, C3'; 170.7, 2 x CO. Mass Spectrum (FST^+, MeOH): *m/z* 425.2 ($[M+Na]^+$).

Similar reactions were carried out at room temperature under air and in an atmosphere of oxygen and the results are summarised in Table 7.4.3.

Table 7.4.3:

Entry	Oxidant	Time (h)	Temp (°C)	Mass isolated (mg)	Products isolated[a] (%)	
					S/m (109)	P (110)
1	air	48	reflux	100	0	100
2	O_2	72	23	102	79	21
3	air	72	23	101	83	17

a: The ratios of products isolated (%) were determined by ^1H n.m.r. spectroscopy of the crude sample.

7.4.7.2 Using Cu(OH)Cl.1,2-bis((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethane (Cu(OH)Cl.(43))

The reactions were carried out as described in Section 7.4.7.1 using the titled catalyst (Cu(OH)Cl.(43)) (2 mg, 4.95 x 10^{-3} mmol) and the hydroxy naphthoate (109) (100 mg, 0.49 mmol) and the results are summarised in Table 7.4.4.

Table 7.4.4:

Entry	Oxidant	Time (h)	Temp (°C)	Mass isolated (mg)	Products isolated (%)[a]	
					S/m (109)	P (110)
1	air	120	23	110	100	0
2	O_2	72	23	110	100	0
3	air	120	reflux	100	100	0

a: The ratios of products isolated (%) were determined by ^1H n.m.r. spectroscopy of the crude sample.

7.4.7.3 Using Cu(OH)Cl. 2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethylamine (Cu(OH)Cl.(62))

The reactions were carried out as described in Section 7.4.7.1 using the titled catalyst (Cu(OH)Cl.(62)) (2 mg, 4.95 x 10^{-3} mmol) and the hydroxy naphthoate (109) (100 mg, 0.49 mmol) and the results are summarised in Table 7.4.6.

Table 7.4.5

Entry	Oxidant	Time (h)	Temp (°C)	Mass isolated (mg)	Products isolated (%)[a]			
					S/m (109)	P (110)	ee (%)	Optical rotation $[\alpha]_D^{25}$
1	O_2	72	23	110	83	17	23[b] (*S*)	-38° (c 0.44, THF)
2	Air	7 (days)	reflux	121	0	100	6	not measured
3	O_2	10 (days)	23	111	87	13	-	-

a: The ratios of products isolated (%) were determined by ^{1}H n.m.r. spectroscopy of the crude sample. *b*, % ee was measured by comparing the measured optical rotation value with the literature optical rotation lit for (*R*)-(110) is $[\alpha]_D^{25}$ + 172° (c 0.82, THF).

7.4.7.4 Using Cu(OH)Cl.1-amino-2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (Cu(OH)Cl.(55))

The reactions were carried out as described in Section 7.4.7.1 using the titled catalyst (Cu(OH)Cl.(55)) (2 mg, 4.95 x 10^{-3} mmol) and the hydroxy naphthoate (109) (100 mg, 0.495 mmol) with dichloromethane (10 ml) and the results are summarised in Table 7.4.7.

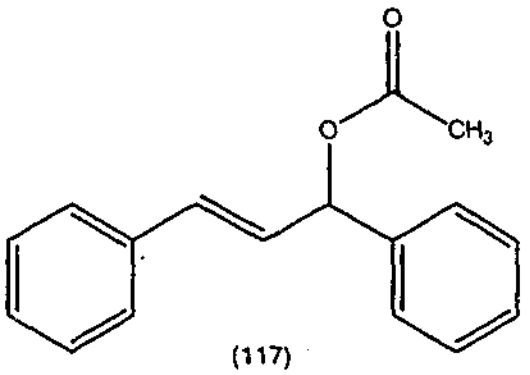
Table 7.4.6

Entry	Oxidant	Time (h)	Temp (°C)	Mass isolated (mg)	Products isolated (%)[a]	
					S/m (109)	P (110)
1	O_2	18	23	128	100	0
2	air	18	reflux	121	100	0

a: The ratios of products isolated (%) were determined by ^{1}H n.m.r. spectroscopy of the crude sample.

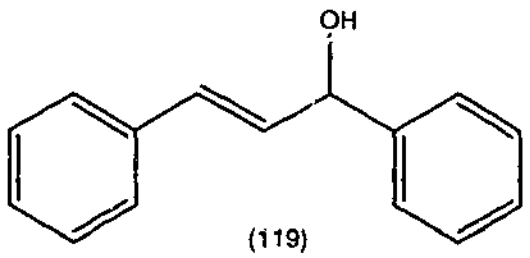
(ii) Asymmetric palladium-catalysed allylic alkylation reactions

7.4.8 Synthesis of (±)-1,3-diphenylprop-2-en-1-yl acetate (117)



(117)

The acetate (117) was synthesised using the method described by Wang *et al.*.[145] 1,3-diphenylprop-2-en-1-one (118) (5.00 g, 22.7 mmol) in diethyl ether (40 ml) was added dropwise to a suspension of $LiAlH_4$ (431 mg, 11.4 mmol) in diethyl ether (20 ml). After addition was completed, water (40 ml) was added dropwise (CAUTION!). The mixture was extracted with diethyl ether (7 x 40 ml) and the organic phase was washed with $NaHCO_3$ (sat.), water, brine, dried over $MgSO_4$ and concentrated under reduced pressure to afford (±)-1,3-diphenylprop-2-en-1-ol (119) as a yellow oil (4.54 g, 90%). ν_{max} (neat): 3356bs, 3056s, 3022s, 1600s, 1489s, 1444s, 1394m, 1094s, 1067s, 1011s, 961s, 744s, 694s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 5.39, m, 1H, H1; 6.38, dd, *J* 15.9, 6.5 Hz, 1H, H2; 6.69, d, *J* 15.9 Hz, 1H, H3; 7.16-7.46, m, 10H, ArH. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 75.4, C1; 126.6, 126.9, C2', C6', C2", C6"; 128.1, C4', C4"; 128.8, 128.9, C2', C6', C2", C6"; 130.8, C2; 131.7, C3; 136.7, C1'; 143.0, C1".



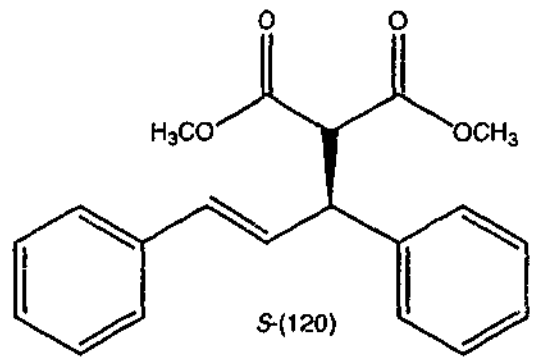
(119)

Acetic anhydride (1.13 ml, 12 mmol) and triethylamine (20 ml) were added to (±)-1,3-diphenylprop-2-en-1-ol (119) (4.54 g, 20.4 mmol) and stirred at ambient temperature for 18 h. The reaction mixture was then poured into water and extracted with diethyl ether (3 x 50 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified using flash chromatography (SiO_2, ethyl acetate: hexane, 1:4) to give the desired acetate (117) as a yellow oil (4.98 g, 97%). ν_{max} (neat): 3055s, 3022s, 2922m, 1733s, 1683m, 1594w, 1489s, 1444m, 1367s, 1233s, 1056m, 1017m, 961s,

911m, 739s, 694s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 2.14, s, 3H, OCH_3; 6.35, dd, *J* 15.7, 6.8 Hz, 1H, H2; 6.44, d, *J* 7.3 Hz, 1H, H1; 6.64, d, *J* 15.7 Hz, 1H, H3; 7.20-7.42, m, 10H, ArH. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 21.6, OCH_3; 76.4, C1; 126.9, 127.2, C3', C5', C3", C5"; 127.7, 128.3, 128.4, 132.8, C2, C3, C4', C4"; 128.8, 128.9, C2', C6', C2", C6"; 136.4, 139.5, C1', C1"; 170.3, CO. Mass Spectrum (ESI^+, MeOH): *m/z* 237.1 ($[M+Na]^+$). The spectral data were consistent with the literature.[145]

7.4.9 Preparation of (-)-dimethyl 2-(1,3-diphenylprop-2-en-1-yl)malonate (120)

7.4.9.1 Using 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethane (43)



S-(120)

Reactions were carried out using a modified procedure described by Leutenegger *et al.*[140] and a typical procedure is outlined below.

The diamine ligand (43) (7.6 mg, 0.04 mmol) in degassed dichloromethane (5 ml) was added to a three necked flask under N_2 containing allylpalladium chloride dimer ($[(\eta^3-C_3H_5)PdCl]_2$) (5.8 mg, 16 x 10^{-3} mmol). The solution was subjected to three freeze-pump-thaw cycles and refluxed for 2 h and cooled to ambient temperature. In a separate flask under N_2, anhydrous potassium acetate (spatula tip) was added to a solution of the acetate (117) (100 mg, 0.40 mmol), dimethyl malonate (118 mg, 0.89 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (0.29 ml, 1.19 mmol) in dichloromethane (10 ml). The suspension was subjected to three freeze-pump-thaw cycles, after which the first palladium solution was transferred by canula into the suspension, and the resulting mixture stirred for 18 h. The reaction was quenched with HCl (1 M) (5 ml) and extracted with dichloromethane (3 x 20 ml). The combined organic layers were dried and concentrated to afford (-)-dimethyl 2-(1,3-diphenylprop-2-en-1-yl)malonate (120) as an opaque oil (128 mg, 100%). ν_{max} (neat): 3033s, 2955s, 1750s, 1733s, 1594m, 1494s, 1450s, 1433s, 1316s, 1255s, 1194s, 1155s, 1022s, 967s, 744s, 694s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 3.51, s, 3H, and

3.70, s, 3H, 2 x OCH_3; 3.96, d, *J* 10.8 Hz, 1H, H1; 4.26, dd, *J* 11.0, 8.4 Hz, 1H, H1'; 6.33, dd, *J* 15.8, 8.5 Hz, 1H, H2'; 6.48, d, *J* 15.8, 1H, H3'; 7.18-7.34, m, 10H, ArH. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 49.5, C2; 52.7, 52.9, 2 x OCH_3; 58.0, C1'; 126.7, 128.2, C3'', C5'', C3''', C5'''; 127.5, 127.9, C4'', C4'''; 128.8, 129.0, C2'', C6'', C2''', C6'''; 129.4, 132.1, C2', C3'; 137.1, C1''; 140.5, C1'''; 168.1, 168.5, 2 x CO. Mass Spectrum (ESI^+, MeOH): *m/z* 347.1 ($[M+Na]^+$). The acetate was further purified as described in Section 7.3.1 and injected in to the HPLC instrument containing the chiral OD column (0.2 ml/min, detection at 250 nm, 2% isopropanol: 98% hexane) to give two peaks: The (*R*) acetate (120) R_t = 52.7 min (6%) and the (*S*) acetate (120) R_t = 13.3 min (94%). The spectral data were consistent with the literature.[140]

A similar reaction was carried out as above, but after the canula transfer the reaction mixture was heated at reflux for 1 h. The reaction was worked up as above to afford a brown oil (120 mg). ^1H n.m.r. spectroscopy showed 100% conversion to the desired malonate (120) with an enantioselectivity of 75% ((*S*)).

7.4.9.2 Using 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (44)

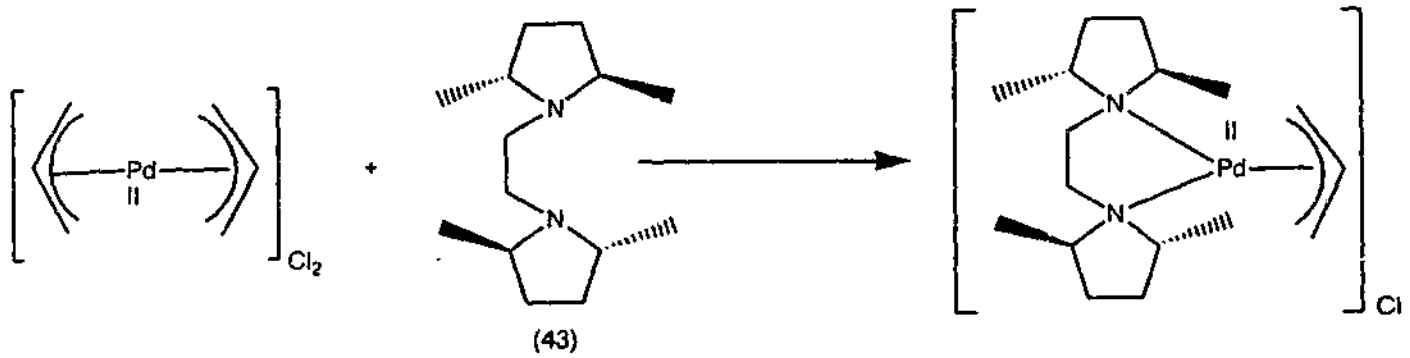
Reactions were carried out as described in Section 7.4.9.1 using 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (44) (10.8 mg, 0.04 mmol). The reactions were carried out at ambient temperature and at reflux. After working up the reactions brown oils were isolated. ^1H n.m.r. spectroscopy of this crude oil showed that only the presence of starting material (117) and dimethyl malonate.

7.4.9.3 Using 1-((2*R*,5*R*)-2,5-(dimethylpyrrolidin-1-yl)-2-(pyrrolidin-1-yl)ethane (66)

Reactions were carried out as described in Section 7.4.9.1 using ligand (66) (6.6.mg, 0.04 mmol) at ambient temperature. After working up the reaction a brown solid (122 mg) was isolated. ^1H n.m.r spectroscopy of the crude solid showed 100% conversion to the malonate (120) with an enantioselectivity of 51% for the (*S*)-malonate (120).

7.4.10 ^{1}H n.m.r studies with allylpalladium chloride dimer

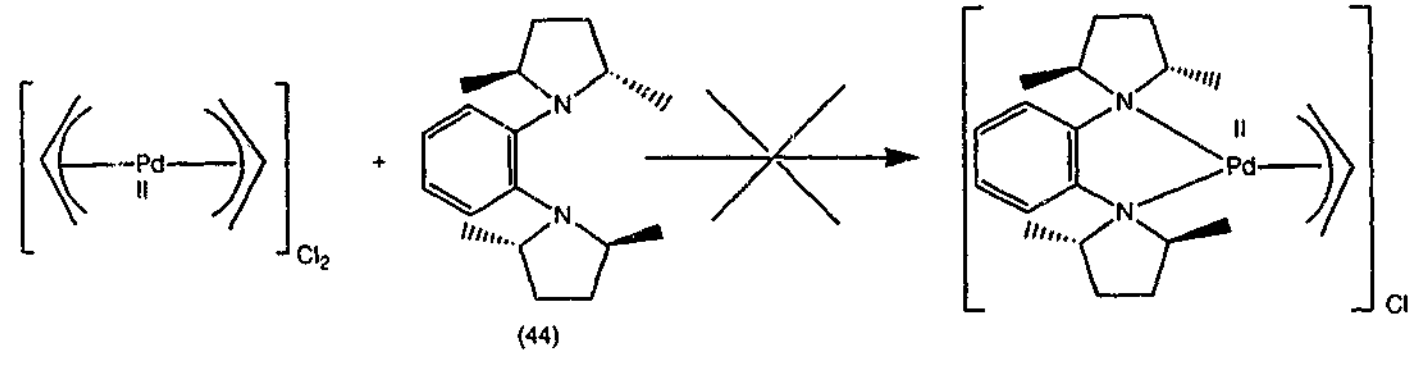
7.4.10.1 Using 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethane (43)



Diamine ligand (43) (12 mg, 6.32 x 10^{-3} mmol) was dissolved in CD_2Cl_2 (2 ml) and the solvent transferred to an n.m.r. tube. ^{1}H n.m.r. (300 MHz, CD_2Cl_2): δ 0.96, d, *J* 6.2 Hz, 12H, 4 x CH_3; 1.28-1.42, m, 4H and 1.86-2.08, m, 4H, H3, H4 and 2.48-2.70, m, 4H, 2.94-3.04, m, 4H, H2, H5, H1', H2'.

After the ^{1}H n.m.r. spectrum was recorded the contents were transferred to a three necked flask, under nitrogen containing allylpalladium chloride dimer $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (11.5 mg, 3.16 x 10^{-3} mmol). The solution was subjected to three freeze-pump-thaw cycles and refluxed for 2 h. The reaction mixture was cooled to ambient temperature and the contents were transferred by canula to a n.m.r. tube and the ^{1}H n.m.r. spectrum recorded. ^{1}H n.m.r. (300 MHz, CD_2Cl_2): δ 1.27, d, *J* 6.6 Hz, 12H, 4 x CH_3; 1.70-1.82, m, 4H and 2.01-2.43, m, 4H, H3, H4; 2.82-2.96, m, 2H, 2.96-3.00, m, 4H and 3.22-3.42, m, 2H, H2, H5, H1', H2'.

7.4.10.2 Using 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (44)



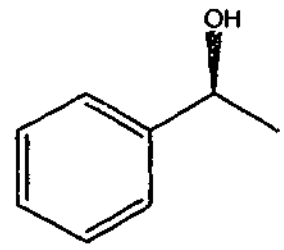
The reaction was carried out as described in Section 7.4.10.1 using 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (44) (1.7 mg, 6.32 x 10^{-3} mmol). Diamine ligand (44) was dissolved in CD_2Cl_2 (2 ml) and the solvent transferred to an n.m.r. tube and

the ^{1}H n.m.r. spectrum recorded. ^{1}H n.m.r. (300 MHz, CD_2Cl_2): δ 0.57, d, *J* 6.3 Hz, 6H, 1.10, d, *J* 5.8 Hz, 6H, 6 x CH_3; 1.38-1.58, m, 4H, 2.04-2.20, m, 4H, H3, H4; 3.70-3.80, m, 2H, 4.10-4.20, m, 2H, H2, H5; 6.82, s, 4H, ArH.

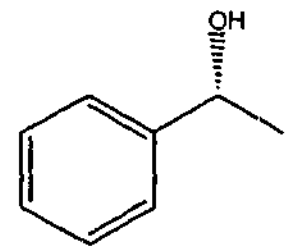
After the ^{1}H n.m.r. spectrum was recorded the contents were transferred to a three necked flask, under nitrogen containing allylpalladium chloride dimer $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (11.5 mg, 3.16 x 10^{-3} mmol) and the identical procedure as described in section 7.4.10.1.was followed. ^{1}H n.m.r. spectrum carried out after refluxing the reaction mixture for 2 h. The ^{1}H n.m.r. spectrum was identical to that recorded before the addition of the allylpalladium choloride.

(iii) Asymmetric grignard reactions

7.4.11 Synthesis of (±)-2-phenylethan-2-ol (126)



R-(126)

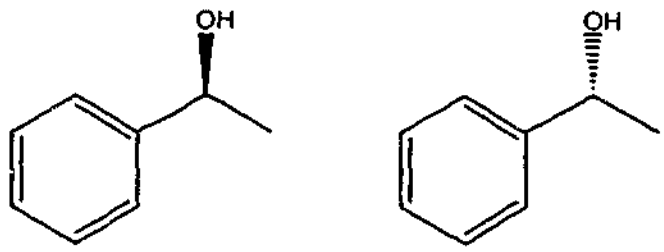


S-(126)

Benzaldehyde (123) (0.01 ml, 0.134 mmol) was added to a stirring solution methylmagnesium bromide (125) (0.04 ml, 0.36 mmol) in toluene (10 ml) under nitrogen at -78°C. The mixture was stirred at this temperature for a further 4 h. The reaction mixture was quenched with 10% HCl (10ml) and extracted with diethyl ether (3 x 20 ml). The combined organic layers were evaporated to afford a colourless oil. The ^{1}H n.m.r. spectrum showed a mixture of product (126) (37% conversion) and starting material (126) ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 1.49, d, *J* 6.4 Hz, 3H, H1; 4.89, q, *J* 6.4 Hz, 1H, H2; 7.20-7.42, m, 5H, H2', H3', H4', H5', H6'.

The crude alcohol was purified for HPLC analysis using t.l.c. as described in Section 7.3.1. The solution of diol in isopropanol (20 μl) was injected into the HPLC instrument containing the chiral OB column (1.0 ml/min, detection at 250 nm, 10% isopropanol: 90% hexane) to give two peaks. R_t = 12.09 min, R_t = 15.33 min in a ratio of 1:1. The spectral data were consistent with those of an authentic sample.

7.4.12 Asymmetric synthesis of 2-phenyl-ethan-2-ol (126)

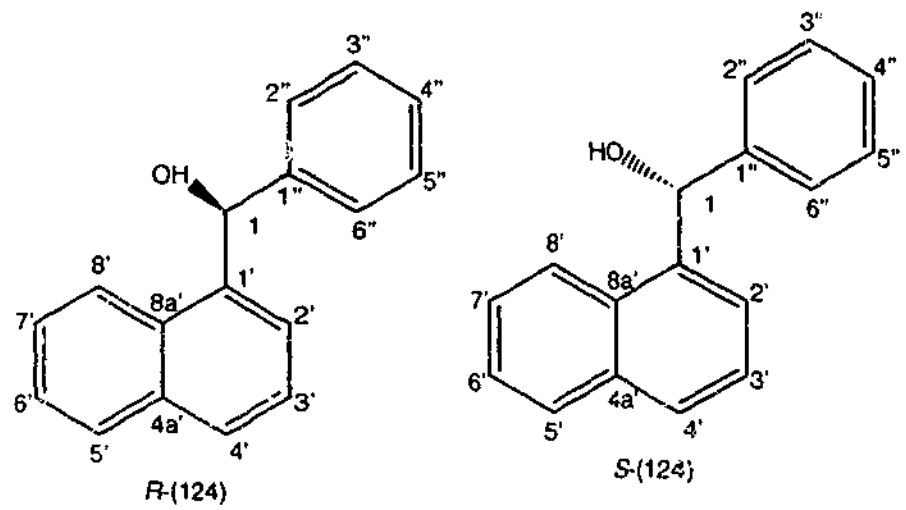


R-(126) *S*-(126)

Reaction was carried out as described by Tomioka *et al.*.[224]

Methylmagnesium bromide (125) (0.04 ml, 0.36 mmol) was added to a stirring solution of chiral diamine (43) (100 mg, 0.45 mmol) in toluene under nitrogen at -78°C. The mixture was stirred for 45 min before benzaldehyde (123) (0.01 ml, 0.134 mmol) was added. The reaction mixture was stirred at -78°C for a further 2 h. The reaction was worked up as described in Section 7.4.11 to afford a colourless oil (86 mg). The ^{1}H n.m.r. spectrum of this crude oil showed 35% conversion to product (126) together with starting material (123) and the ligand (43). Purification for HPLC was carried out as described in Section 7.4.11, gave two peaks at R_t = 12.02 min (50%) and R_t = 15.31 min (50%).

7.4.13 Synthesis of α-naphthylphenylcarbinol (124)

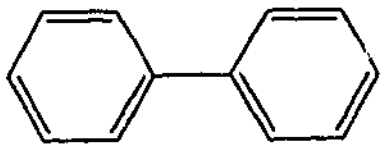


R-(124) *S*-(124)

The reaction was carried out as described in Section 7.4.11 using phenylmagnesium bromide (128) (0.62 ml, 1.66 mmol) and α-naphthaldehyde (127) (100 mg, 0.64 mmol). The reaction mixture was stirred at ambient temperature 1.5 days. The yellow oil (244 mg) isolated, after work up, was purified using radial chromatography.

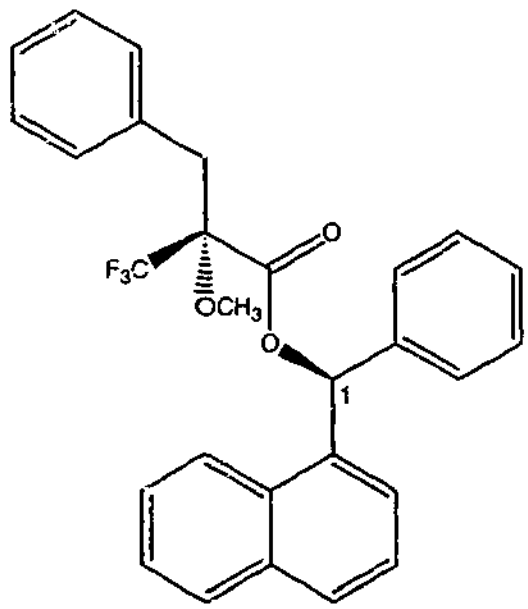
The first to elute was biphenyl (51 mg, 52%) as a colourless solid. m.p. 68-70°C (lit.[225] 69-72). ν_{max} (KBr): 3055s, 3832s, 2996m, 1944w, 1597m, 1569m, 1479s,

1429s, 1343m, 1169m, 729s, 696s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 7.33, tt, *J* 7.4, 2.2 Hz, 2H, H4; 7.43, t, 7.4, 4H, H3, H5; 7.58, d, *J* 7.4 Hz, H2, H6. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 123.6, C3, C4, C5; 124.5, C2, C6; 140.8, C1. Mass Spectrum (ESI^+, MeOH): *m/z* 140.9 ($[M+Na]^+$). The spectral data were consistent with the literature.[225]

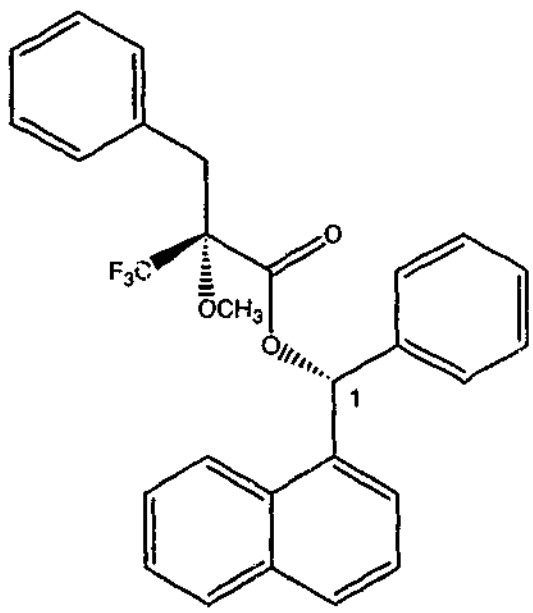


Next to elute was the titled alcohol (124) as a orange oil (80 g, 53%). ν_{max} (neat): 3354bs, 3060s, 2380s, 1950s, 1706m, 1674m, 1596s, 1513s, 1452s, 1395m, 1373m, 1231m, 1165s, 1051s, 989s, 909 cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 2.48, bs, 1H, OH; 6.46, s, 1H, H1; 7.18-7.48, m, 8H, H3', H5', H6', H7', H8', H3", H4", H5"; 7.57, d, *J* 7.1 Hz, 1H, H4'; 7.77, d, *J* 8.1Hz, 1H, 7.82, d, *J* 5.9 Hz, 1H, 7.98, d, *J* 8.9 Hz, 1H, H2', H2", H6". ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 73.8, C1; 115.5, 124.2, 124.8, 125.5, 125.7, 126.3, 127.3, 127.8, 128.6, 128.7, 128.9, 129.7, ArCH; 130.9, 134.1, 138.9, 143.2, ArC. Mass Spectrum (ESI^+, MeOH): *m/z* 235.0 ($[M+H]^+$).

7.4.14 Synthesis of the Moshers ester of α-naphthylphenylcarbinol (130)



S,R-(130)

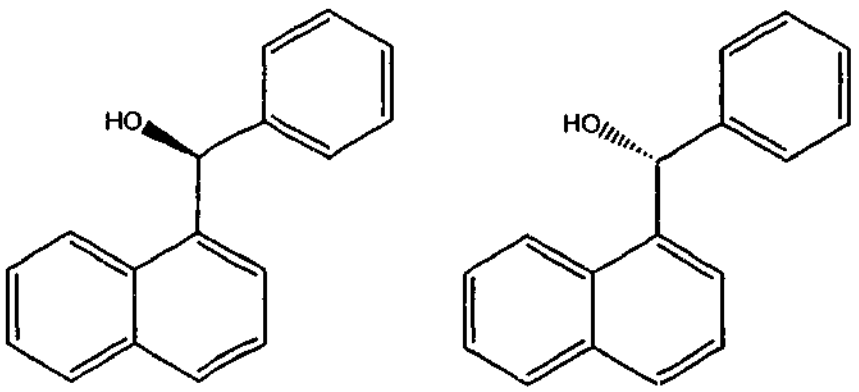


S,S-(130)

A solution of 1,3-dicyclohexylcarbodiimide (94 mg. 0.455 mmol) in dry dichloromethane (10 ml) and 4-dimethylaminopyridine (<10 mg) was added to a stirred solution of α-naphthylphenylcarbinol (124) (71 mg, 0.303 mmol) and (*S*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ((-)-MTPA) (129) (107 mg, 0.455

mmol) in dry dichloromethane (10 ml). The reaction was stirred under nitrogen at room temperature for 2.5 h. The reaction mixture was quenched with water and extracted with dichloromethane (3 x 10 ml). The combined organic layers were washed with water, dried ($MgSO_4$), filtered and evaporated to afford a cream solid. Column chromatography afforded the two diastereoisomers as a colourless solid (130) (100 mg, 73%). ^{1}H n.m.r. (300 MHz, $CDCl_3$) (two diastereoisomers): δ 3.38-3.43, m, 3H and 3.48-3.52, m, 3H, 2 x OCH_3; 7.18-8.00, m, 36H, H1, 34ArH. ^{19}F n.m.r (300Mz, $CDCl_3$) (two diastereoisomers): δ 71.7, and 71.8, 2 x CF_3. Mass Spectrum (ESI$^+$, MeOH): *m/z* 473.3 ([M+Na]$^+$).

7.4.15 Asymmetric synthesis of α-naphthylphenylcarbinol (124)

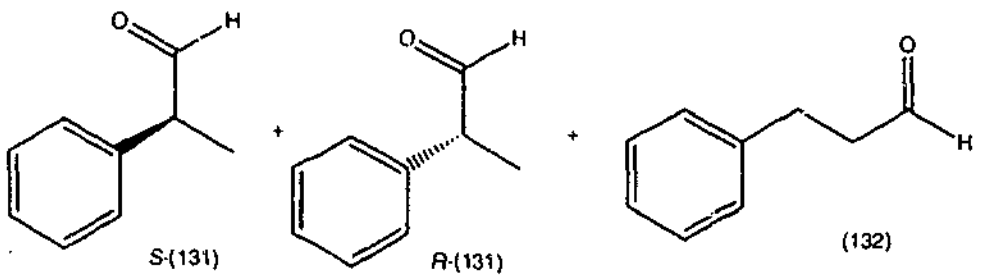


R-(124) *S*-(124)

The reaction was carried out as described in Section 7.4.12 using chiral diamine (43) (115 mg, 0.513 mmol), α-napthaldehyde (127) (0.02 ml, 0.155 mmol) and phenylmagnesium bromide (128) (0.15 ml, 0.404 mmol) in toluene (10 ml) for 13 h at –78°C. The reaction was worked up as described in Section 7.4.11 to afford a yellow oil (220 mg). ^{1}H n.m.r. specroscopy showed that the reaction showed only starting material (127), ligand (43) and residual solvent.

(iii) Asymmetric hydroformylation of styrene (8)

7.4.16 Using 1,2-bis-((2*R*,5*R*)-2, 5-dimethylpyrrolidin-1-yl)benzene (44)



S-(131) *R*-(131) (132)

Hydroformylation was carried out using the general procedure described in Section 7.1.3. Styrene (8) (100 mg, 0.96 mmol), chiral diamine (44) (5 mg, 1.9 x 10^{-2} mmol) and rhodium(II) acetate dimer (4 mg, 9.8 x 10^{-3} mmol) were dissolved in deoxygenated benzene (10 ml) in a 100 ml Parr autoclave which then was pressurised with CO/H_2 (e.g, 1000 psi, 400 psi). The reaction mixture was heated (e.g 50°C, 80°C) for the desired time (18 h, 48 h). At the end of each reaction period, the autoclave was cooled to ambient temperature before the pressure was released. The mixture was concentrated and the ^1H n.m.r. spectrum of the crude material showed a mixture of terminal (132) and branched (131) aldehydes (see Table 7.4.7 for ratios). Terminal aldehyde (132) (3-phenylpropanaldehyde (132)). ^1H n.m.r. (300 MHz, $CDCl_3$): δ 2.78, t, *J* 7.3 Hz, 2H, H2; 2.97, t, *J* 7.5 Hz, 2H, H3; 7.17-7.45, m, 5H, ArH; 9.83, t, *J* 1.4 Hz, 1H, CHO.

The branched aldehyde (131) ((*R*)-2-methyl-2-phenyl-ethylaldehyde (*R*-(131))) and (*S*)-2-methyl-2-phenyl-ethylaldehyde (*S*-(131))). ^1H n.m.r. (300 Mz, $CDCl_3$): δ 1.44, d, *J* 7.0 Hz, 3H, CH_3; 3.63, qd, *J* 7.0, 1.4 Hz; 1H, CH; 7.17-7.45, m, 5H, ArH; 6.88, d, *J* 1.4 Hz; 1H, CHO.

The enantiomeric excess of the branched aldehyde was determined from the ^1H n.m.r spectrum using shift reagent $[Eu(hfc)_3]$.[226]

The reactions carried out at varying temperatures, pressures and times and the results are summarised in Table 7.4.7.

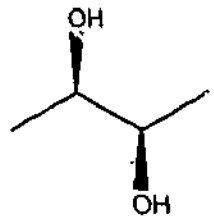
Table 7.4.7:

Entry	CO/H_2 (psi)	Temp (°C)	Time (h)	Mass isolated (mg)	Products isolated (%)		
					S/m (8)	(131) (% ee)	(132)
1	1000	80	20	135	0	83	17
2	400	50	20	130	50	44	6
3	400	50	48	104	0	88 (15% ee)	12

a: The ratios of products isolated (%) were determined by ^1H n.m.r. spectroscopy of the crude sample.

7.5 Attempted synthesis of (2*S*,5*S*)-2,5-dimethyl aziridine based ligands (56) and (57)

7.5.1 Synthesis of (2*R*,3*R*)-2,3-butanediol (23)



(*R,R*)-(23)

Method A

Baker's yeast (150 g) was added to a solution of white sugar (CSR^{TM}) (350 g) in 1.5 L. After stirring this mixture for 24 h, 250 g of sugar was added to the reaction mixture. Stirring was continued for 24 h before a further 70 g of sugar was added followed by 35 g of yeast. The reaction mixture was stirred for 72 h before being filtered through a Celite plug. The filtrate was reduced in volume (300 ml) and continuously extracted with dichloromethane (500 ml) for 48 h, to afford an orange oil (3.00 g). The ^{1}H n.m.r. spectrum of the crude oil showed (2*R*,3*R*)-butanediol (23) (80%) together with *meso*-butanediol (23) (20%). Purification by column chromatography (SiO_2, ethyl acetate: hexane, 1:4) afforded the titled product (23) as a yellow oil (600 mg). $[\alpha]_D^{25}$ −13.3° (neat) (lit.[216] $[\alpha]_D^{25}$ −13.3° (neat)). ν_{max} (neat): 3400bs, 2977s, 2900s, 1722s, 1605w, 1650m, 1377s, 1272s, 1161s, 1083s, 1011s, 994s, 968s, 933s, 889s, 811s cm^{-1}. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 1.17, d, *J* 6.1 Hz, 6H, H1, H4; 3.46-3.58, m, 2H, H2, H3; 2.73, bs, 2H, 2 x OH. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 19.5, C1, C4; 72.7, C2, C3. Mass Spectrum (ESI$^+$, MeOH): *m/z* 112.8 ([M+Na]$^+$). Analysis by GC indicated only one component: (Chrompack–WCOT Fused silica coating, CP Chirasil-Dex CB DF=0.25; 50-200°, 5°/min): R_t 14.1 min (100%) (2*R*,3*R*). The spectral data were consistent with the literature. [216]

Note: Spectroscopy details of the *meso*-diol (23) are given in Method B.

Method B

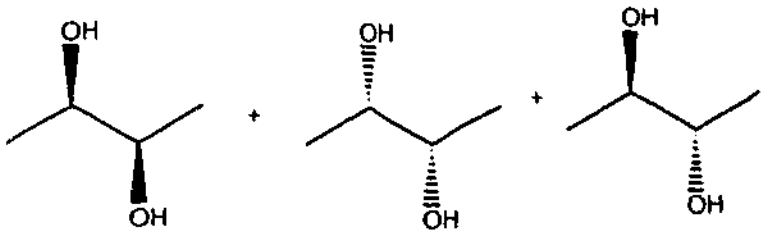
Synthesis of the diol (23) was achieved using the modified method of Leiser *et al.*.[95] Reaction was carried out as described in Section 7.2.1 Method A using butanedione (134) (2 x 5 g, 116 mmol). An orange oil (5.00 g) was isolated after continuously extracting the filtrate. ^{1}H n.m.r. spectroscopy of the crude oil showed a mixture of the

chiral diol (23) (50%) and the *meso*-2,3-butanediol (23) (50%). Column chromatography was attempted to separate the products but was unsuccessful. The ^{1}H n.m.r and ^{13}C n.m.r. spectra were consistent with the spectra quoted in Method A for the (2*R*,3*R*) diol (23). Spectral details for the *meso*-diol (23) are as below:
^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 1.12, d, *J* 6.3 Hz, 6H, 2 x CH_3; 3.32, bs, 2H, 2 x OH; 3.73-3.83,m, 2H, H2, H3. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 17.1, C1, C4; 71.0, C2, C3. The spectral data were consistent with the literature.[216] Analysis by GC indicated three components: (Chrompack–WCOT Fused silica coating, CP Chirasil-Dex CB DF=0.25; 50-200°, 5°/min): R_t 12.1 min (4%) (2*S*,3*S*), R_t 12.2 min (46%) (2*R*,3*R*) and 12.7 min (50%) (*meso*).

Method C

Synthesis of the diol (23) was achieved using the modified method of Smallridge.[217]
2,3-Butanedione (134) (0.37 ml, 4.23 mmol) was added to a paste of yeast (8.76 g) and water (7.0 ml). This paste was further ground using a mortar and pestle and was allowed to stand for 27 h. The yeast washed with ethyl acetate (250 ml) and the organic layer concentrated to afford 2,3-butanediol (23) as a light yellow oil (300 mg, 79%). ^{1}H n.m.r. spectroscopy showed a 2:1 mixture of the *meso*-diol (23): chiral ((*R*,*R*) and (*S*,*S*)) diol (23). Analysis by GC indicated three components: (Chrompack-WCOT Fused silica coating, CP Chirasil-Dex CB DF=0.25; 50-200°, 5°/min): R_t 12.1 min (13%) (2*S*,3*S*), R_t 12.2 min (20%) (2*R*,3*R*) and 12.7 min (67%) (*meso*).

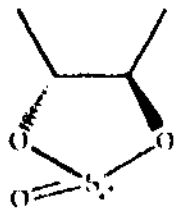
7.5.2 Synthesis of (±)-2,3-butanediol (23) and *meso*-butanediol (23)



Butanedione (134) was added to a stirring suspension of $LiAlH_4$ (1.09 g, 29.1 mmol) in freshly distilled THF (20 ml) under an atmosphere of N_2. The resulting suspension was further stirred for 15 mins. The reaction mixture was cooled to 0°C and $NaSO_4.10H_2O$ was added until no further gas evolution was observed. The resulting precipitate was filtered and washed with THF (100 ml). The filtrate was evaporated to afford a 2,3-butanediol (23) as a yellow oil (450 mg, 86%). The ^{1}H n.m.r. spectrum of

this oil showed a 1:2 mixture of the racemic diol (23): the *meso*-diol (23). Analysis by GC indicated three components: (Chrompack-WCOT Fused silica coating, CP Chirasil-Dex CB DF=0.25; 50-200°, 5°/min): R_t 13.8 min, (11%), (2*S*,3*S*), 14.1 min, (12%), (2*R*,3*R*), 14.2 min, (67%) (*meso*).

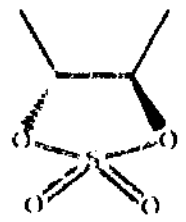
7.5.3 Synthesis of (2*R*,3*R*)-2,3-butanediol cyclic sulfite (137)



(137)

The reaction was carried as described in Section 7.2.4, (2*R*,3*R*)-Butanediol (23) (383 mg, 4.26 mmol) and thionyl chloride (0.47 ml, 6.38 mmol) were reacted to afford the desired product (137) as a brown oil (721 mg). Further purification was not undertaken and the crude material was used to synthesise the cyclic sulfate (24). ν_{max} (neat): 2978s, 2933s, 1772w, 1733m, 1511w, 1444s, 1377s, 1200s, 1033s, 906s, 828s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 1.43, d, *J* 6.1 Hz, 3H, 1.52, d, *J* 6.2 Hz, 3H, 2 x CH_3, 4.09, dq, *J* 9.0, 6.3 Hz, 1H and 4.65, dq, *J* 9.0, 6.2 Hz, 1H, H2, H3. ^{13}C n.m.r. (100MHz, $CDCl_3$): δ 16.3, 18.3, C1, C4, 82.2, 85.6, C2, C3. Mass Spectrum (GCMS, MeOH): *m/z* 120 ($[M-O]^+$).

7.5.4 Synthesis of (2*R*,3*R*)-2,3-butanediol cyclic sulfate (24)

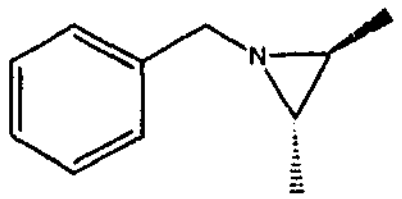


(24)

The reaction was carried out as described in Section 7.2.5. The cyclic sulfite (137) (721 mg, 5.30 mmol), sodium periodate (2.27 g, 10.6 mmol) and ruthenium(III) chloride (20 mg) gave the desired product (24) as an orange oil (515 mg, 64%). $[\alpha]_D^{25}$ -5.74° (c 5.7, $CHCl_3$). ν_{max} (neat): 2989s, 2933s, 1733w, 1694w, 1450s, 1372s, 1294m, 1205s, 1117m, 1039s, 917s, 844s, 828s, 733s, 644s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 1.55, d, *J* 6.0 Hz, 6H, 2 x CH_3; 4.76-4.87, m, 2H, H2, H3. ^{13}C n.m.r

(100 MHz, $CDCl_3$): δ 16.7, C1, C4; 85.5, C2, C3. Mass Spectrum (GCMS, MeOH): *m/z* 152 ($[M]^+$). The spectral data were consistent with the literature.[51]

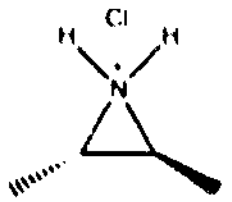
7.5.5 Synthesis of *N*-benzyl-(2*S*,3*S*)-2,3-dimethylaziridine (133)



(133)

The reaction was carried out as described in Section 7.2.6. The cyclic sulfate (24) (1.2 g, 7.89 mmol) and benzylamine (4.31 ml, 39.5 mmol) gave the desired product (133) as a yellow oil (960 mg, 76%). (Found: *m/z* 184.1098. $[C_{11}H_{15}NNa]^+$ ($[M+Na]^+$) requires 184.1102). ν_{max} (neat): 3022s, 2978s, 2922s, 2878s, 1600m, 1489s, 1450s, 1422s, 1383s, 1350s, 1261m, 1156s, 1111s, 1088s, 1027s, 788s, 722s, 6[illegible]s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 1.20, d, *J* 5.3 Hz, 3H and 1.30, d, *J* 6.0 Hz, 3H, 2 x CH_3; 1.85-1.93, m, 1H and 1.98-2.04, m, 1H, H2, H3; 3.54, d, *J* 14.2 Hz, 1H and 3.89, *J* 14.2 Hz, 1H, CH_2Ph; 7.20-7.40, m, 5H, ArH. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 11.76, 18.8, 2 x CH_3; 39.3, 42.2, C2, C3; 55.6, CH_2Ph; 126.8, C4', 127.9, C3', C5'; 128.5, C2', C6'; 140.7, C1'. Mass Spectrum (ESI$^+$, MeOH): *m/z* 183.7 ($[M+Na]^+$).

7.5.6 Attempted synthesis of (2*S*,3*S*)-2,3-dimethylaziridine hydrochloride salt (138)

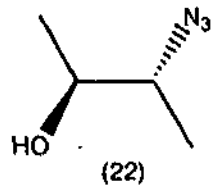


(138)

The hydrogenolysis of the *N*-benzyl aziridine (133) was carried out as described in Section 7.2.7. The *N*-benzyl aziridine (133) (900 mg, 5.59 mmol) was dissolved in methanol (20 ml). The solution was transferred to a Fisher porter tube to which 10% Pd/C (3 mg) was added. The mixture was stirred under hydrogen (60 psi) for 18 h following the general hydrogenation procedure described in Section 7.1.2. The catalyst was removed by filtration through a Celite pad with cooling. Dry HCl gas (Section 7.1.1) was bubbled into the filtrate for 1 h followed by evaporation to afford

a colourless solid. The ^{1}H n.m.r. spectrum of the crude solid showed neither product (138) or starting material (133).

7.5.7 Synthesis of (2*R*,3*S*)-3-azidobutan-2-ol (22)

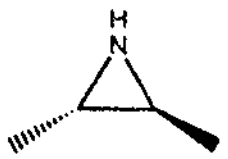


(22)

Prepared using a method described by Shustov *et al.*[51]

Sodium azide was added to a stirring solution of the cyclic sulfate (24) in acetone (10 ml) and the mixture stirred for 9.5 h. The reaction mixture was evaporated to dryness and the solid redissolved in diethyl ether (10 ml), 3 M H_2SO_4 (1 ml) was added and stirred for 3 days. After basifying with $NaHCO_3$ (sat.), the mixture was extracted with diethyl ether (3 x 10 ml). The combined organic layers were evaporated to afforded the desired product (22) as a yellow oil (355 mg, 99%). ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 1.19, d, *J* 6.4 Hz, 3H, H1; 1.25, d, *J* 6.7, 3H, H4; 1.82, d, *J* 4.7, 1H, OH; 3.55, dq, *J* 6.7, 3.9 Hz, 1H, H3; 3.80, m, 1H, H2. The spectral data were consistent with the literature.[51]

7.5.8 Synthesis of (2*S*,3*S*)-2,3-dimethylaziridine (25)

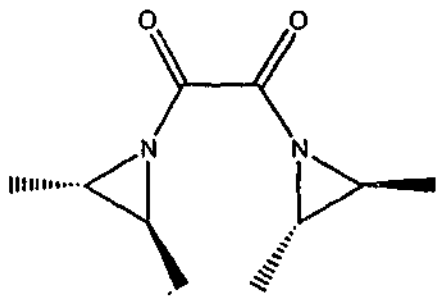


(25)

Prepared using a method described by Shustov *et al.*.[51]

Triphenylphosphine (12.9 g, 49 mmol) was added to the azido alcohol (22) (1.88 g, 16.3 mmol) under N_2 and the whole was stirred for 7 h. After which the product (25) (1.01 g, 73%) was isolated as a clear liquid from vacuum distillation. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 0.16, bs, 1H, NH; 1.18, d, *J* 5.3 Hz, 6H, 2 x CH_3; 1.64, m, 2H, C2, C3. The spectral data were consistent with the literature.[51]

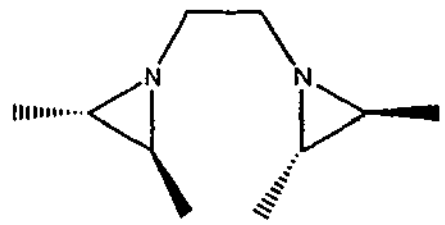
7.5.9 Synthesis of 1,2-bis-((2*S*,3*S*)-2,3-dimethylaziridin-1-yl)-1,2-dioxo-ethane (59)



(59)

Triethylamine (1.06 ml, 7.62 mmol) was added to a solution of the dimethylaziridine (25) (360 mg, 5.07 mmol) in dichloromethane (50 ml) at -78°C under a N_2 atmosphere and the mixture was stirred for 15 minutes. Oxalyl chloride (0.22 ml, 2.54 mmol) was added dropwise and the resulting mixture was stirred for 2 days. The reaction was quenched with water (100 ml) and diluted with dichloromethane (150 ml). The organic layer was separated and washed successively with 1 M HCl (150 ml x 3), water (150 ml) and brine (150 ml), dried over $MgSO_4$, filtered and evaporated to afford the desired product (59) as a yellow oil (412 mg, 83%). (Found: *m/z* 219.1105. $[C_{14}H_{24}O_2N_2Na]^+$ ($[M+Na]^+$) requires 219.1109). ν_{max} (neat): 2967s, 2922s, 1738s, 1672s, 1433s, 1372s, 1333s, 1305s, 1239s, 1167s, 1133m, 1044, 833m, 761w cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 1.37, d, *J* 5.2 Hz, 12H, 4 x CH_3; 2.48-2.58, m, 4H, 4 x H2, H3. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 16.7, 16.8, 4 x CH_3; 41.3, C2, C3; 168.9, CO. Mass Spectrum (ESI^+, MeOH): *m/z* 198.0 ($[M+H]^+$).

7.5.10 Attempted synthesis of 1,2-bis-((2*S*,3*S*)-2,3-dimethylaziridin-1-yl)ethane (56)



(56)

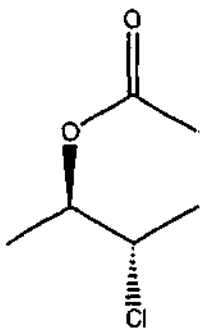
A solution of the diamide (59) (152 mg, 0.78 mmol) dissolved in diethyl ether (10 ml), was added to a refluxing suspension of $LiAlH_4$ (146 mg, 3.88 mmol) in diethyl ether (10 ml). The reaction mixture was vigorously stirred at this temperature for a further 2 h. The mixture was cooled to 0°C and $NaSO_4.10H_2O$ was added until no further gas evolution was observed. The resulting precipitate was filtered and washed

with THF (100 ml) and the filtrate was evaporated to afford a yellow oil (100 mg). ^{1}H n.m.r. spectroscopy showed neither starting material (59) or product (56).

A reaction was carried out as described above using diamide (59) (50 mg, 0.26 mmol) and $LiAlH_4$ (48 mg, 1.28 mmol) at ambient temperature for 24 h. The reaction was worked up as above to give a yellow oil (38 mg). ^{1}H n.m.r. spectroscopy showed neither starting material (59) or product (56).

A similar reaction was carried out using diamide (59) (50 mg, 0.26 mmol) and $LiAlH_4$ (48 mg, 1.28 mmol) at ambient temperature for 0.5 h. The reaction was worked up as above to give a yellow oil (72 mg). ^{1}H n.m.r. spectroscopy showed neither starting material (59) or product (56).

7.5.11 Synthesis of (2*R*,3*S*)-2-acetoxy-3-chlorobutane (140)

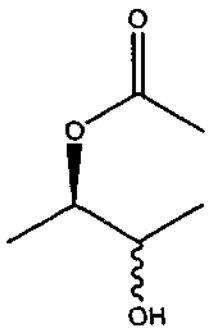


(140)

Synthesis of the 2-acetoxy-3-chlorobutane (140) was achieved using the method described by Tanner *et al.*.[170]

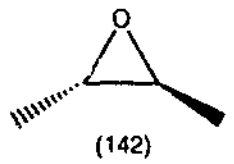
p-Toluenesulfonic acid (5 mg) followed by trimethyl orthoacetate (0.14 ml, 1.10 mmol) was added to a stirring solution of diol (23) (100 mg, 1.11 mmol) in DRY dichloromethane (10 ml) under nitrogen. The mixture was stirred for 1 h and trimethylsilyl chloride (0.14 ml, 1.11 mmol) was added. The reaction was stirred for a further 2 h before the dichloromethane was evaporated to afford the desired product (140) (167 mg, 100%) as a yellow oil. ν_{max} (neat): 3456bs, 2977s, 2933s, 2878w, 1736s, 1449m, 1373s, 1239s, 1160w, 1102m, 1053m, 1022s cm^{-1}. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 1.30, d, *J* 6.3 Hz, 3H, H1; 1.48, d, *J* 6.7 Hz, 3H, H4; 2.09, s, 3H, $COCH_3$; 4.12, dq, *J* 6.8, 4.4 Hz, 1H, H3; 4.98, dq, *J* 6.3, 4.4 Hz, 1H, H2. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 15.7, C1; 21.0, C4; 21.4, $\underline{C}H_3CO$; 59.4, C3; 73.3, C4; 170.3, CO. Mass Spectrum (ESI$^+$, MeOH): *m/z* 154.7 ([M-Cl+H+K]$^+$).

A similar reaction carried using reagent grade dichloromethane produced 3-hydroxy-2-acetate (141) as a yellow oil. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 1.19, d, *J* 6.5Hz, 1H, H1; 1.23, d, *J* 6.5 Hz, 1H, H4; 2.09, s, 3H, OCH_3; 2.13, bs, 1H, OH; 3.75, p, *J* 6.5 Hz, 1H, H3; 4.75, p, *J* 6.5 Hz, 1H, H2. Mass Spectrum (ESI$^+$, MeOH): *m/z* 170.6 ($[M+K]^+$).



(141)

7.5.12 Synthesis of (2*S*,3*S*)-2,3-dimethyloxirane (142)

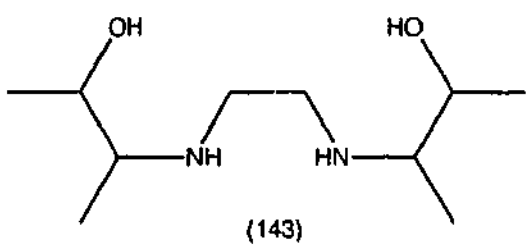


(142)

Synthesis of the epoxide (142) was achieved using the method described by Tanner *et al.*.[170]

K_2CO_3 (307 mg, 2.22 mmol) was added to a stirring solution of the chlorobutane (140) (167 mg, 1.11 mmol) in methanol (2 ml), and the resulting mixture was stirred for 18 h. As the epoxide (142) was highly volatile a small sample was removed and ^{1}H n.m.r. spectroscopy carried out showed 100% conversion to the desired product (142). ^{1}H n.m.r. (300 MHz, MeOH): 1.27, d, *J* 4.9 Hz, 2 x CH_3; 2.66–2.78, m, 2H, H2, H3. Isolation of the epoxide (28) was not attempted. The spectral data were consistent with the literature.[227]

7.5.13 Synthesis of (±)-1,2-bis-[(3-hydroxybutan-2-yl)amino]ethane (143)

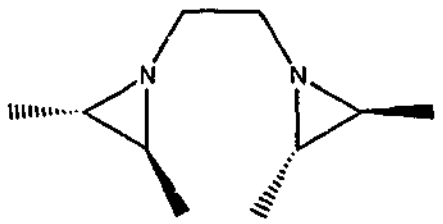


(143)

Synthesis of the hydroxy amino ethane (143) was achieved using the method described by Tanner *et al.*.[170]

Ethylenediamine (0.1 ml, 1.39 mmol) was added to a solution of *trans*-epoxybutane (142) (200 mg, 2.78 mmol) in THF, under N_2 in a Carius tube. The sealed tube was at reflux for 5 days before a small sample was removed. The solvent was removed *in vacuo* to afford the desired product (143) (70mg, 25%) as a clear semi-solid. (Found: *m/z* 205.1906. $[C_6H_{12}O_2]^+$ ($[M+H]^+$) requires 205.1916). ν_{max} (neat): 3289bs, 2970s, 1667s, 1600s, 1449s, 1373s, 1304m, 1122s, 1005s, 902m, 822m cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 1.00, d, *J* 6.4 Hz, 6H, H4'; 1.10, d, *J* 6.4 Hz, 6H, H1'; 1.86, bs, 4H, 2 x OH, 2 x NH; 2.57–2.84, m, 4H, H1, H2; 3.80, dq, *J* 6.5, 3.2 Hz, 2H, H3'. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 14.7, C1', C2'; 18.2, C3', C4', 42.3, 50.0, C1, C2; 57.8, C2'; 67.5, C3'. Mass Spectrum (ESI^+, MeOH): *m/z* 205.2 ($[M+H]^+$).

7.5.14 Attempted synthesis of *trans*-1,2-bis-(2,3-dimethylaziridin-1-yl)ethane (56)

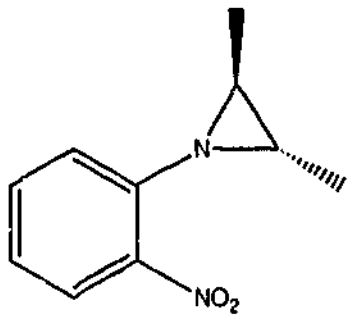


(56)

Synthesis of the bis-aziridine (56) was attempted using the method described by Tanner *et al.*.[170]

Triphenylphosphine (180 mg, 0.69 mmol) and diethyl azodicarboxylate (DEAD) (0.02 ml, 0.69 mmol) were added to a stirred solution of the diamine (143) (70 mg, 0.69 mmol) in a Carius tube at 0°C. The reaction mixture was stirred at ambient temperature for 4 days. The THF was removed by distillation to leave a pink white solid (301 mg). ^1H n.m.r. spectroscopy of this solid showed triphenylphosphine oxide, $DEADH_2$ and peaks that did not correspond to either product (56) or starting material (143). Mass spectrometry too didn't show any peaks corresponding to the required product (56).

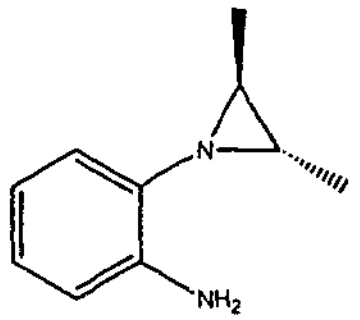
7.5.15 Synthesis of 2-nitro-1-(2*S*,3*S*)-2,5-dimethylaziridin-1-yl)benzene (60)



(60)

Sodium hydride (60% suspension oil 158 mg, 3.95 mmol) was added to a solution of the cyclic sulfate (24) (400 mg, 2.63 mmol) in THF (20 ml) under N_2 and the mixture refluxed for 15 min before *o*-nitroaniline (53) (363 mg, 2.63 mmol) was added. The resulting deep red suspension was refluxed overnight. The mixture was quenched with 10% NH_4Cl (100 ml) and the THF removed under reduced pressure. The resulting solid was dissolved in diethyl ether and washed with 10% NH_4Cl (3 x 30 ml), water, and brine, dried with $MgSO_4$, filtered and evaporated to afford a dark orange oil. Purification by column chromatography (SiO_2, ethyl acetate: hexane, 1:7) afforded the desired product (60) as a yellow solid (210 mg, 41%). $[\alpha]_D^{25}$ +620.4° (c 1.07, $CHCl_3$). (Found: *m/z* 215.0794. $[C_{10}H_{12}N_2O_2Na]^+$ ($[M+Na]^+$) requires 215.0797). m.p. 96-100°C. ν_{max} (KBr): 3438s, 2980s, 1604s, 1570s, 1509s, 1442s, 1341s, 1262s, 1143s, 1024m, 958m, 852m, 782m, 704m, 854m, 601s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 1.22, d, *J* 5.2 Hz, 6H, 2 x CH_3; 2.30–2.41, m, 2H, H2', H3'; 6.98–7.07, 2H, H3, H5; 7.45, t, *J* 7.9 Hz, 1H, H4; 8.01, d, *J* 8.6 Hz, 1H, H6. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 16.7, C1', C4'; 44.0, C2', C3'; 121.9, 124.5, 126.5, 134.5, C3, C4, C5, C6; 159.5, C1, C2. Mass Spectrum (ESI^+, MeOH): *m/z* 192.9 ($[M+H]^+$).

7.5.16 Synthesis of 1-amino-2-(2*S*,3*S*)-(2,5-dimethylaziridin-1-yl)benzene (61)



(61)

Method A

Synthesis of the amino benzene (61) was achieved using the method described by Park *et al.*.[172,173]

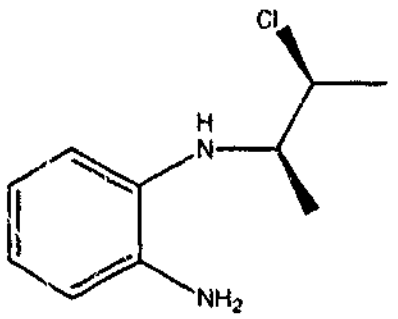
An aqueous solution (2 ml) containing potassium carbonate (214 mg, 1.55 mmol) and sodium dithionate (359 mg, 2.06 mmol) was added dropwise to the nitro aziridine (60) (50 mg, 0.26 mmol) and benzyl viologen dibromide (10 mg, 2.6×10^{-2} mmol) in acetonitrile (12 ml) and water (1 ml). An immediate purple colour was observed which lasted until the end of the reaction (2 h). The reaction was quenched with 2 M NaOH and the pH adjusted to 12 before extraction with dichloromethane (3 x 50 ml). The combined organic layer was dried with $MgSO_4$, filtered and evaporated to afford a dark brown oil. Purification using radial chromatography (SiO_2, ethyl acetate: hexane, 1: 4) afforded the desired product (61) as an orange oil (15 mg, 36%). (Found: *m/z* 163.1235. $[C_{10}H_{15}N_2]^+$ ($[M+H]^+$) requires 163.1235). ν_{max} (neat): 3444bs, 3356bs, 3033s, 2978s, 2922s, 2867s, 1611s, 1494s, 1455s, 1422s, 1378s, 1328s, 1328s, 1278s, 1268s,1169s, 1139s, 1094m, 1022s, 739s cm^{-1}. ^1H n.m.r. (400 MHz $CDCl_3$): δ 1.23, bs, 6H, 2 x CH_3; 2.10–2.30, bm, 2H, H2', H3'; 3.82, bs, 2H, NH_2; 6.62–6.73, m, 3H, H3, H4, H6; 6.84, td, *J* 6.4, 1.9 Hz, 1H, H5. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 15.8, 2 x CH_3; 40.3, C2', C3'; 114.8, 118.3, C3, C6; 120.1, C4; 122.9, C5; 135.7, C2; 141.0, C1. Mass Spectrum (ESI^+, MeOH): *m/z* 163.2 ($[M+H]^+$).

Method B

Synthesis of the amino benzene (61) was achieved using the method described by Beckwith *et al.*.[183]

The nitro aziridine (60) (220 mg, 1.13 mmol) was suspended in concentrated hydrochloric acid (2 ml) and ethanol (R.W.S) (2 ml) and the mixture stirred for 30 min during the addition of stannous chloride (537 mg, 2.84 mmol) in ethanol (4 ml). The mixture was then stirred for further 12 h, made basic by the addition of 15% potassium hydroxide solution in water and extracted with dichloromethane (3 x 50 ml). The combined organic layers were dried with $MgSO_4$, filtered and evaporated to afford a dark orange oil. The oil was purified using column chromatography (SiO_2, ethyl acetate: hexane, 1:7). 2-(3'-chlorobutyl-2-amino)aniline (144) (150 mg, 58%) eluted first as a deep orange oil. $[\alpha]_D^{25}$ +134.8° (c 1.10, $CHCl_3$). (Found: *m/z* 251.0553. $[C_{10}H_{13}N_2O_2{}^{35}ClNa]^+$ ($[M(^{35}Cl)+Na]^+$) requires 251.0563 and *m/z*

253.0527. $[C_{10}H_{13}N_2O_2{}^{37}ClNa]^+$ ($[M(^{37}Cl)+Na]^+$) requires 253.0527). ν_{max} (neat): 3344bs, 3089m, 2993m, 1615s, 1572s, 1506s, 1416s, 1350s, 1265s, 1228s, 1161s, 1072s, 1044s, 861s, 739s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 1.39, d, *J* 6.5 Hz, 3H, H1'; 1.62, d, *J* 6.8 Hz, 3H, H4'; 3.90–4.04, m, 1H, H2'; 4.35, qd, *J* 6.8, 3.4 Hz, 1H, H3'; 6.68, t, 7.0 Hz, 1H, H5; 8.20, dd, *J* 8.7, 1.7 Hz, 1H, H6; 8.32, bd, *J* 8.4 Hz, 1H, NH. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 15.3, C1', 21.9, C4'; 53.0, C2'; 61.0, C3'; 114.0, 115.6, C3, C6; 127.3, 136.3, C4, C5; 144.1, C1, C2. Mass Spectrum (ESI^+, MeOH): *m/z* 229.1 ($[M(^{35}Cl)+H]^+$), 231.0 ($[M(^{37}Cl)+H]^+$).



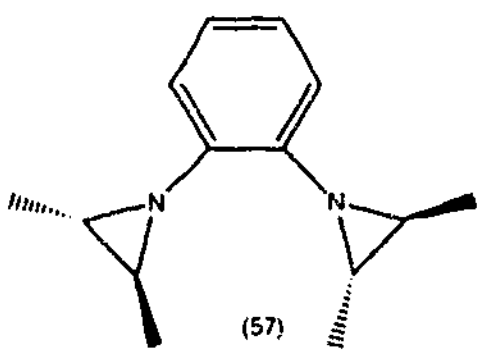
(144)

Next to elute was the desired amine (61) as an orange oil (50 mg, 27%). The spectral data were consistent with what was described in Method A.

Method C

Reactions were carried out as described in Section 7.2.11 using the nitro aziridine (60) (38 mg, 0.198 mmol) with benzene (5 ml) and Pd/C under a hydrogen pressure of 60 psi. The reaction mixture was worked up as before (Section 7.2.11) after 18 h to give a dark orange oil (35 mg). ^1H n.m.r. spectroscopy of the crude showed no starting material (60) or product (61).

7.5.17 Attempted synthesis of 1,2-bis-(2*S*,3*S*)-2,5-dimethylaziridin-1-yl)benzene (57)

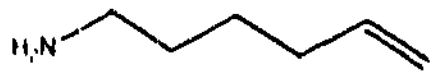


(57)

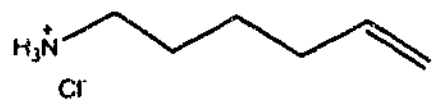
The reaction was carried out using a similar method described in Section 7.2.12. The aminophenyl aziridine (61) (22 mg, 0.14 mmol) was added to a solution of the cyclic sulfate (24) (21 mg, 0.14 mmol) in THF (100 ml). The resulting orange solution was refluxed for 2 days after the addition of 60% sodium hydride (8.5 mg, 0.20 mmol). The mixture was stirred at reflux for a further 2 days and quenched with 10% NH_4Cl (30 ml). The THF was removed under reduced pressure and the aqueous mixture extracted with dichloromethane (3 x 100 ml). The combined organic layers were washed with water (100 ml) and brine (100 ml), dried with $MgSO_4$, filtered and evaporated to afford a brown semi-solid (300 mg). ^1H n.m.r. spectrospcopy showed no signals corresponding to either starting materials ((61) and (24)) or product (57).

7.6 Synthesis of Nitrogen Heterocycles by Rhodium Catalysed Hydroformylation of Polymer-Attached Amino Alkenes with Syn gas

7.6.1 Synthesis of 5-hexenamine (162b)

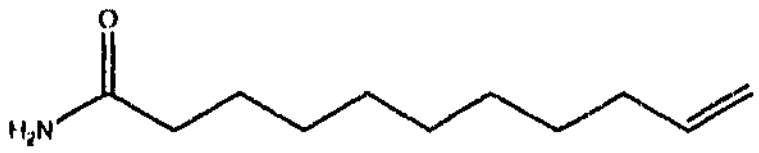


5-Hexenol (167) (3.6 ml, 30.0 mmol) in distilled THF (10 ml) and Diisopropylazodicarboxylate (DIAD) (5.90 ml, 30.0 mmol) in distilled THF (10 ml) were added dropwise and simultaneously under a N_2 atmosphere to a stirred suspension of phthalimide (4.41 g, 30.0 mmol) and triphenylphosphine (7.85 g, 30.0 mmol) in freshly distilled THF (40 ml) at 0°C. The resulting yellow solution was stirred at ambient temperature for 18 h and the solvent was removed under reduced pressure to give a yellow oil. The oil was redissolved in methanol (50 ml) before hydrazine hydrate (1.5 ml, 35.94 mmol) was added and the mixture refluxed for a further 8 h, followed by standing overnight. Concentrated HCl (5 ml) was added and the reaction mixture refluxed for a further 2 h. After cooling the mixture, the methanol was removed under reduced pressure. The resulting semi-solid was dissolved in water and extracted with dichloromethane (3 x 100 ml). The aqueous layer was concentrated to afford a white solid (3.9 g, 96%). ^{1}H n.m.r. spectroscopy of this solid showed that it was the 5-hexenamine hydrochoride salt. ^{1}H n.m.r. (300 MHz, D_2O): δ 1.46, p, *J* 7.2 Hz, 2H, H3; 1.66, p, *J* 7.3 Hz, 2H, H2; 2.09, q, *J* 7.3 Hz, 2H, H4; 2.99, t, *J* 7.3Hz, 2H, H1; 4.96-5.11, m, 2H, H6; 5.84, m, 1H, H5.



The white solid was dissolved in the minimum amount of water to which NaOH pellets were added. The desired product (162b) separated as a clear oil and collected by pipette (2.75 g, 93%). ν_{max} (neat): 3377bs, 2922s, 2856s, 1655s, 1033s, 1572m, 1501m, 1500w, 1461s, 1439s, 905s cm^{-1}. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 1.41-1.48, m, 6H, H2, H3, NH_2; 2.07, q, *J* 7.0 Hz, 2H, H4; 2.69, t, *J* 6.6 Hz, 2H, H1, 4.91-4.99, m, 2H, H6; 5.78-5.91, m, 1H, H5. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 26.[illegible], H3; 33.4, 33.8,H2, H4; 42.3, H1, 114.7, H6; 139.0, H5. Mass Spectrum (ESI^+, MeOH): *m/z* 99.8 ($[M+H]^+$). The spectral data were consistent with the literature.[212]

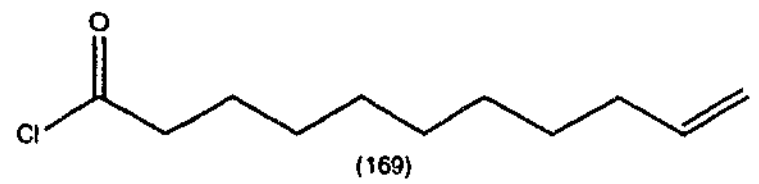
7.6.2 Synthesis of undec-10-enamide (170)



(170)

The reaction was carried out using the method described by Furniss *et al.*.[215]

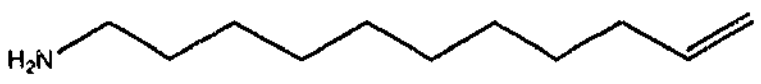
Thionyl chloride (3.96 ml, 54.3 mmol) was added to undec-10-enoic acid (168) (10.0 g, 54.3 mmol) under an atmosphere of nitrogen and the mixture allowed to stir under mild warming (hot water) for 2 h. The resulting mixture was flash distilled to afford undec-10-oyl chloride (169) as a colourless oil (6.66 g, 61%). ν_{max} (neat): 3078s, 2922s, 2855s, 1800s, 1638s, 1455s, 1411s, 1338w, 1127m, 989s, 961s, 911s, 722s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 1.20-1.42, m, 12H, H4, H5, H6, H7, H8; 1.62-1.78, m, 2H, H3; 2.03, q, *J* 6.3 Hz, 2H, H9; 2.88, t, *J* 7.3 Hz, H2; 4.88-5.04, m, 2H, H11; 5.72-5.88, m, 2H, H10. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 25.3, 28.6, 29.1, 29.2, 29.4, C3, C4, C5, C6, C7, C8; 33.9, C9; 47.3, C2; 114.5, C11; 139.3, C10; 174.1, C1.



(169)

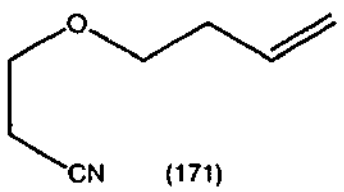
The acid chloride (169) (6.66 g, 30.6 mmol) was dissolved in dichloromethane (10 ml) and was added dropwise to chilled (-78°C) liquid ammonia (100 ml) stirred under nitrogen. The reaction was stirred at -78°C for 1 h, allowed to warm to ambient temperature for 2 h and the resulting solid was dissolved in 2 M HCl (50 ml) and dichloromethane (100 ml). The aqueous phase was removed and the organic phase washed with 2 M HCl (2 x 50 ml), and $NaHCO_3$ (3 x 50 ml), dried ($MgSO_4$), filtered and concentrated to give the desired product (170) as a light brown solid (5.50 g, 98%). m.p. 85-86°C (lit.[228] 88.5-89°C). ν_{max} (KBr): 3358, 3078s, 2922s, 2855s, 1800s, 1638s, 1455s, 1411s, 1338w, 1127m, 989s, 961s, 911s, 722s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 1.30, m, 10H, H4, H5, H6, H7, H8; 1.62, m, 2H, H3; 2.03, m, 2H, H9; 2.21, t, 2H, *J* 7.2 Hz, H2; 4.89-5.04, m, 2H, H11; 5.68, bs, 1H (D_2O exch.), NH; 5.71-5.91, ddt, *J* 16.9, 10.1, 6.6 Hz, H10; 6.18, bs, 1H (D_2O exch.), NH. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 25.5, 28.8, 29.0, 29.2, 29.2, C3, C4, C5, C6, C7, C8; 33.7, C9; 35.9, C2; 114.1, C11; 139.1, C10; 176.1, CO. Mass spectrum (ESI^+): *m/z* 183.9 ($[M+H]^+$). The spectral data were consistent with the literature.[228]

7.6.3 Synthesis of undec-10-enammine (162d)



Undec-10-enamide (170) (5.50 g, 30.05 mmol) was added to a cooled (0°C) stirred suspension of $LiAlH_4$ (2.31 g, 72.1 mmol) in anhydrous diethyl ether (50 ml). The mixture was refluxed for 4 h, cooled (0°C) and terminated by the addition of $NaSO_4.10H_2O$ until effervescence ceased. The suspension was filtered using a Celite plug and the filtrate was flash distilled to afford the desired product (162d) as a clear oil (3.00g, 58%). ν_{max} (neat): 3334bs, 2924s, 2853s, 1641w, 1571s, 1487s, 1466s, 1319m, 992w, 910m cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 1.24-1.46, m, 16H, H2, H3, H4, H5, H6, H7, H8, NH_2; 1.98-2.08, m, 2H, H9; 2.67, t, *J* 6.8 Hz, 2H, H1; 4.89-5.04, m, 2H, H11; 5.81, ddt, *J* 16.9, 10.1, 6.6 Hz, 1H, H10. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 26.8, 28.8, 29.0, 29.3, 29.4, 29.5, C3, C4, C5, C6, C7, C8; 33.7, 33.8, C2, C9; 42.2, C1, 114.0, C11; 139.0, C10. Mass spectrum (ESI^+): *m/z* 170.1 ($[M+H]^+$). The spectral data were consistent with the literature.[228]

7.6.4 Synthesis of 3-(but-3'-enyloxy)propanenitrile (171)



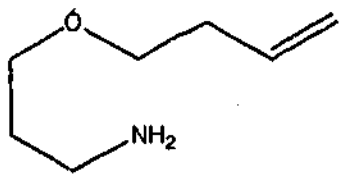
(171)

The reaction was performed as described by Simonot and Rousseau.[213]

3-Butenol (172) (6.0 ml, 69.3 mmol) was added to stirred Triton B (40% in MeOH) (1.2 ml). After 10 min, acrylonitrile (173) (5.5 ml, 83.16 mmol) was added dropwise and stirring continued for 24 h at ambient temperature with exclusion of light. The excess acrylonitrile (173) was removed under reduced pressure and the residue acidified with acetic acid (4 ml). The mixture was diluted with water (50 ml) and extracted with ether (70 ml). The organic phase was washed with water (3 x 30 ml), dried ($MgSO_4$), filtered and concentrated to give a brown oil. Kugelrohr distillation 110°C/18 mm. (lit.[213] 105-107°C/18 mm) gave 3-(but-3'-en-1-yloxy)propanenitrile (171) as a clear oil (4.85 g, 56%). ν_{max} (neat): 3079m, 2875s, 2252m,1753w, 1719w, 1642m, 1417m, 1364s, 1228m, 1116s, 999m, 920s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 2.26, qt, 2H, *J* 6.7, 1.3 Hz, H2'; 2.52, t, 2H, *J* 6.3 Hz, H2; 3.46, t, 2H, *J* 6.7

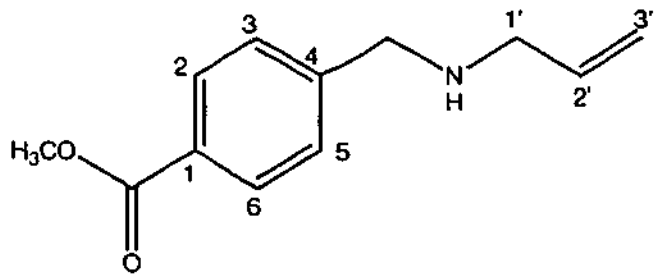
Hz, H1'; 3.56, t, 2H, *J* 6.3 Hz, H3; 4.93-5.08, m, 2H, H4'; 5.74, ddt, 1H, *J* 17.0, 10.2, 6.7 Hz, H3'. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 18.4, C2; 33.54, C2'; 64.9, C3; 70.2, C1'; 116.3, C4'; 117.7, C1; 134.4, C3'. Mass Spectrum (ESI^+, MeOH): *m/z* 125.8 ($[M+H]^+$). The spectral data were consistent with the literature.[213]

7.6.5 Synthesis of 3-(but-3-en-1-yloxy)propanamine (162c)



The nitrile (171) (4.85 g, 38.8 mmol) was dissolved in anhydrous ether (20 ml) and added dropwise to a stirred suspension of $LiAlH_4$ (2.21 g, 58.2 mmol) in anhydrous diethyl ether (50 ml) at 0°C under a nitrogen atmosphere. The reaction was heated at reflux for 2 h, cooled to 0°C and the reaction terminated by the addition of $Na_2SO_4.10H_2O$ portionwise until effervescence ceased. The mixture was filtered and the filtrate concentrated to give the desired amine (162c) as a clear oil (4.85 g, 97%). ν_{max} (neat): 3365s, 3297s, 3077s, 2864s, 1641m, 1600m, 1467w, 1432s, 1368m, 1227w, 1112s, 995m, 913s cm^{-1}. ^{1}H n.m.r. (300 MHz, $CDCl_3$): δ 1.70, p, *J* 6.3 Hz, 2H, H2; 1.95, bs, 2H, NH_2; 2.32, qt, *J* 6.6, 1.3 Hz, 2H, H2'; 2.78, t, *J* 6.7 Hz, 2H, H1; 3.46, t, *J* 6.7 Hz, 2H, H1'; 3.50, t, *J* 6.2 Hz, 2H, H3; 4.98-5.13, m, 2H, H4'; 5.81, ddt, *J* 17.0, 10.2, 6.7 Hz, 1H, H3'. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 32.8, C2; 39.1, C1; 68.4, C3; 69.6, C1'; 115.6, C4'; 134.7, C3'. Mass Spectrum (ESI^+, MeOH): *m/z* 129.7 ($[M+H]^+$). The spectral data were consistent with the literature.[229]

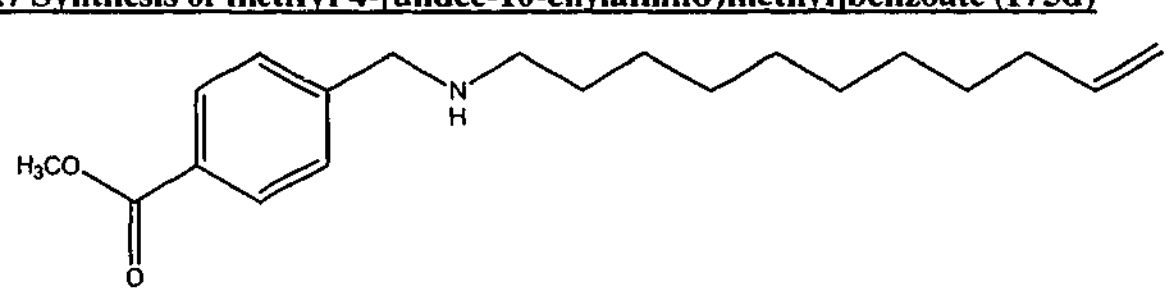
7.6.6 Synthesis of methyl 4-[(allylamino)methyl]benzoate (175a)



2-Propenamine (162a) (0.24 ml, 3.33 mmol) was added to a stirring solution of *p*-carboxybenzaldehyde (163) (500 mg, 3.33 mmol) in ethanol (20 ml). The mixture was refluxed for 2 h before sodium cyanoborohydride ($NaCNBH_3$) (251 mg, 4.0 mmol), was added and the mixture refluxed for a further 1 h. The mixture was concentrated under reduced pressure to afford a white solid. Concentrated H_2SO_4 (5

ml) was added followed by methanol (20 ml) and the resulting mixture was stirred for 18 h. After removing the methanol, the reaction mixture was basified with NaOH (4 M) before extraction with dichloromethane (3 x 50 ml). The combined organic layers were dried with $MgSO_4$, filtered and evaporated to afford a yellow oil which was purified using column chromatography (SiO_2, ethyl acetate: hexane, 1:1) to afford the desired product (175a) as a yellow oil (283 mg, 42%). (Found: *m/z* 206.1178. $[C_{12}H_{16}O_2N]^+$ ($[M+H]^+$) requires 206.1181). ν_{max} (neat): 3450bs, 3077m, 3000m, 2944m, 2811m, 1717s, 1611s, 1433s, 1377m, 1278s, 1183m, 1111s, 1016m, 922m, 856w, 756s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 3.28, dt, *J* 6.0, 1.6 Hz, 2H, H1'; 3.85, s, 2H, $ArC\underline{H}_2$; 3.91, s, 3H, OCH_3; 5.10-5.25, m, 2H, H3'; 5.93, ddt, *J* 17.2, 10.3, 6.0 Hz, 1H, H2'; 7.41, d, *J* 8.1 Hz, 2H, H3, H5; 8.00, d, *J* 8.4 Hz, 2H, H2, H6. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 51.5, C1; 52.3, OCH_3; 52.5, $Ar\underline{C}H_2$; 117.4, C3'; 128.5, C3, C5; 129.3, C1; 130.0, C2, C6, 135.7, C4; 144.6, C2'; 167.1, CO. Mass Spectrum (ESI^+, MeOH): *m/z* 206.1 ($[M+H]^+$).

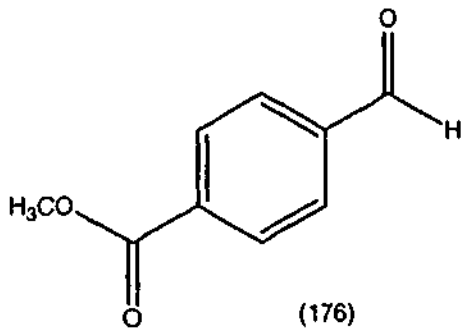
7.6.7 Synthesis of methyl 4-[undec-10-enylamino)methyl]benzoate (175d)



The reaction was carried out as described for the synthesis of methyl 4-[(allylamino)methyl]benzoate (175a) in Section 7.6.6 Method A, using 10-undecenamine (162d) (563 mg, 3.33 mmol). After working up the reaction, a yellow oil was isolated and purification using column chromatography (SiO_2, ethyl acetate: hexane, 1:1) afforded the desired product (175d) as a yellow oil (390 mg, 33%). (Found: *m/z* 318.2433. $[C_{20}H_{32}O_2N]^+$ ($[M+H]^+$) requires 318.2433). ν_{max} (neat): 3450bs, 3078s, 2922s, 2856s, 1717s, 1638s, 1611s, 1572m, 1455s, 1433s, 1411s, 1278s, 1178s, 1107s, 1010s, 905s, 856s, 755s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 1.21-1.55, m, 14H, H2', H3', H4', H5', H6', H7', H8'; 2.03, q, *J* 6.7 Hz, 2H, H9'; 2.61, t, *J* 7.2 Hz, 2H, H1'; 3.84, s, 2H, $ArC\underline{H}_2$; 3.90, s, 3H, OCH_3; 4.89-5.04, m, 2H, H11'; 5.80, ddt, *J* 17.0, 10.3, 6.7 Hz, 1H, H10'; 7.39, d, *J* 8.4 Hz, 2H, H3, H5; 7.99, d, *J* 8.4 Hz, H2, H6. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 27.5, 29.1, 29.3, 29.6, 29.7, 30.3, C2', C3', C4', C5', C6', C7', C8'; 34.0, C9'; 49.7, C1'; 52.2, OCH_3; 53.9, $Ar\underline{C}H_2$; 114.3,

C11'; 128.1, C3, C5; 128.9, C1; 129.9, C2, C6; 139.4, C10'; 146.2, C4; 167.2, CO. Mass Spectrum (ESI^+, MeOH): *m/z* 318.3 ($[M+H]^+$).

7.6.8 Synthesis of methyl-4-formylbenzoate (176)

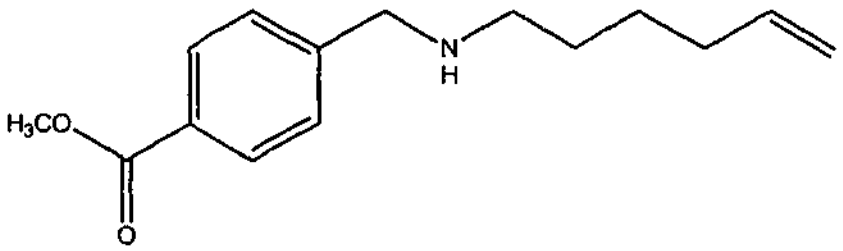


(176)

The reaction was performed as described by Sharma and Tandon.[230]

Thionyl chloride (6 ml) was added to a suspension of *p*-carboxybenzaldehyde (163) (5.00g, 33.3 mmol) in dry methanol (0°C). The mixture was brought to ambient temperature and stirred for a further 2 h. The solvent removed and the excess thionyl chloride was removed using dichloromethane (2 x 100 ml). The desired product (176) was isolated as a orange yellow solid (4.82 g, 88%). m.p. 60-62°C (lit.[230] 61-63°C). ν_{max} (KBr): 3022w, 2977w, 2989m, 1727s, 1685s, 1577s, 1503s, 1435m, 1392m, 1288s, 1204s, 1108s, 1013m, 958m, 852s, 810m, 757s, 687s cm^{-1}. ^1H n.m.r. (300 MHz, DMSO): δ 3.90, s, 3H, OCH_3; 8.05, d, *J* 8.4 Hz, 2H, H3, H5; 8.16, d, *J* 8.5 Hz, 2H, H2, H6; 10.11, s, 1H, CHO. ^{13}C n.m.r. (100 MHz, DMSO): δ 52.6, OCH_3; 129.7, 129.8, C2, C3, C5, C6; 134.3, C4; 139.1, C1; 165.5, $\underline{C}OOCH_3$; 193.0, CHO.

7.6.9 Synthesis of methyl 4-[(hex-5-enylamino)methyl]benzoate (175b)



Method A

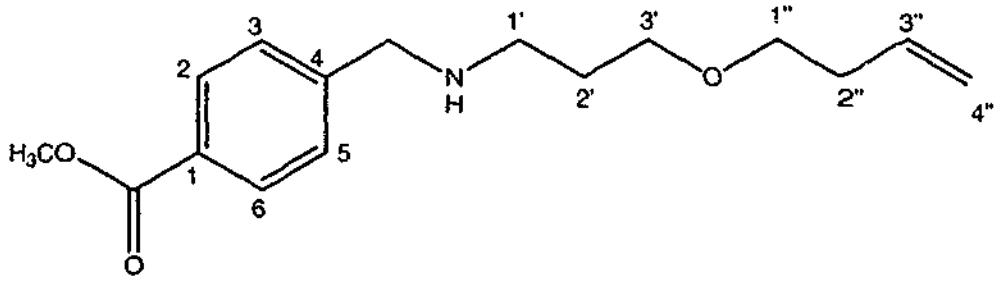
5-Hexenamine (162b) (302 mg, 3.05 mmol) was added to a stirring solution of methyl 4-formylbenzoate (176) (500 mg, 3.05 mmol) in ethanol (20 ml). The mixture was refluxed for 2 h before sodium cyanoborohydride ($NaCNBH_3$) (220 mg, 6.10 mmol), was added and the mixture refluxed for a further 1 h. The mixture was concentrated under reduced pressure and quenched with HCl (1 M, 100 ml). Once the H_2 gas evolution had ceased, the reaction mixture was basified with NaOH (4 M) and

extracted with diethyl ether (3 x 50 ml). The combined organic layers were dried with $MgSO_4$, dried and evaporated to afford the desired product (175b) as an orange oil (602 mg, 80%). (Found: *m/z* 248.1642. $[C_{15}H_{22}O_2N]^+$ ($[M+H]^+$) requires 248.1650)ν_{max} (neat): 3333bs, 3066m, 2911s, 2855s, 1716s, 1638s, 1611s, 1577m, 1433s, 1416s, 1277s, 1172s, 989s, 911s, 727s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 1.36-1.58, m, 4H, H2', H3'; 2.05, q, *J* 7.0 Hz, 2H, H4'; 2.62, t, *J* 7.1 Hz, 2H, H1'; 3.84, s 2H, Ar$\underline{C}H_2$; 3.91, s, 3H, OCH_3; 4.90-5.04, m, 2H, H6'; 5.80, m, 1H, H5'; 7.39, d, *J* 8.4 Hz, 2H, H3, H5; 7.99, d, *J* 8.4 Hz, 2H, H2, H6. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 26.7, 29.7, C2', C3'; 33.8, C4'; 49.5, C1'; 52.2, OCH_3; 53.9, Ar$\underline{C}H_2$; 114.7, C6'; 128.1, 129.9, C2, C3, C5, C6; 128.9, C1; 138.9, C5'; 146.2, C4; 167.2, CO. Mass Spectrum (ESI^+, MeOH): *m/z* 248.0 ($[M+H]^+$).

Method B

The reaction was carried out as described for the preparation of methyl 4-[(allylamino)methyl]benzoate (175a) in Section 7.6.6, using 5-hexenamine (162b) (330 mg, 3.33 mmol) and *p*-carboxybenzaldehyde (163) (500 mg, 3.33 mmol). During the work up after esterification strong emulsions were encountered. The ^1H n.m.r. spectrum of the resulting oil showed no peaks corresponding to the product (175b).

7.6.10 Synthesis of methyl 4-({[3-but-3-en-1-yloxy)propyl]amino}methyl)benzoate (175c)



Method A

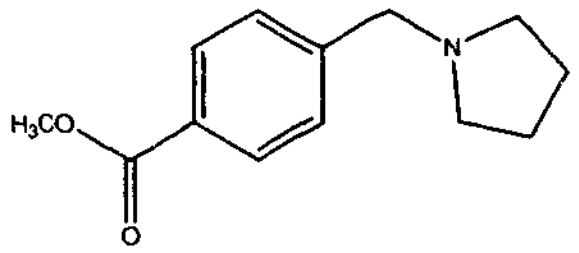
The reaction was carried out as described for the synthesis of methyl 4-[(hex-5-enylamino)methyl]benzoate (175b) in Section 7.6.9 Method A. Reaction of 3-(but-3-en-1-yloxy)propanamine (162c) (390 mg, 3.05 mmol) and methyl 4-formylbenzoate (176) (500 mg, 3.05 mmol) gave an orange oil (602 mg). Purification using column chromatography afforded the desired product (175c) as an orange oil (278 mg, 35%). (Found: *m/z* 278.1751. $[C_{16}H_{24}O_3N]^+$ ($[M+H]^+$) requires 278.1756). ν_{max} (neat): 3333sb, 3077m, 2944s, 2855sm 1727s, 1716s, 1644w, 1611s, 1433s, 1278s, 1106s,

1022m, 917s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 1.80, p, *J* 6.4 Hz, 2H, H2'; 2.31, qt, *J* 6.7, 1.3 Hz, 2H, H2"; 2.49, s, 1H, NH; 2.73, t, *J* 6.8 Hz, 2H, H1'; 3.46, t, *J* 6.8 Hz, 2H, 3.51, t, *J* 6.0 Hz, H3', H1"; 3.85, s, 2H, $ArC\underline{H}_2$; 3.91, s, 3H, OCH_3; 4.97-5.12, m, 2H, H4"; 5.80, m, 1H, H3"; 7.40, d, *J* 8.5 Hz, 2H, H3, H5; 7.99, d, *J* 8.4 Hz, H2, H6. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 29.9, 34.3, C2', C2"; 47.2, C1'; 52.2, OCH_3; 53.7, $Ar\underline{C}H_2$; 69.7, 70.3, C3', C1"; 116.6, C4"; 128.1, 129.9, C2, C3, C5, C6; 128.9, C1; 135.4, C3"; 145.7, C4; 167.2,CO. Mass Spectrum (ESI^+, MeOH): *m/z* 278.1 ($[M+H]^+$).

Method B

The reaction was carried out as described for the preparation of methyl 4-[(allylamino)methyl]benzoate (175a) in Section 7.6.6, using 3-(but-3-enyloxy)propanamine (162c) (430 mg, 3.33 mmol) and *p*-carboxybenzaldehyde (163) (500 mg, 3.33 mmol). During the work up after esterification strong emulsions were encountered. The ^1H n.m.r. spectrum of the resulting oil showed no peaks corresponding to the product (175c).

7.6.11 Synthesis of methyl 4-[(pyrrolidin-1-yl)methyl]benzoate (161a)

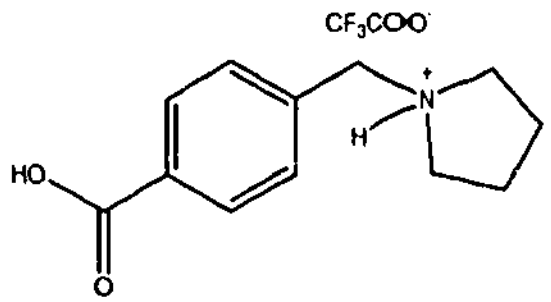


Method A

The reactions were carried out following the general method described for the solid phase synthesis in Section 7.1.4.

The Wang resin (500 mg, 0.45 mmol) was pre-swollen in DMF (3 x 10 ml), and a solution of 4,4'-dimethylaminopyridine (DMAP) (27 mg, 0.22 mmol) in DMF (1 ml) was then added to the resin. In a separate vial, *p*-carboxybenzaldehyde (163) (338 mg, 0.25 mmol) was also dissolved in DMF (1 ml), and was then added to a solution of DMAP (54 mg, 0.45 mmol) and 1,3-diisopropylcarbodiimide (DIC) (0.35 ml, 2.25 mmol) in DMF (1 ml). This mixture was then added to the swollen resin and was shaken overnight. The resultant orange suspension was filtered and the resin was washed with DMF (5 x 10 ml). The resin then was dried for 1.5 h before trimethyl

orthoformate (TMOF) (2 ml) and 3-propenamine (162a) (0.27 ml, 3.6 mmol) were added and the mixture agitated for a further 18 h. Acetic acid (0.2 ml) in methanol (0.5 ml) followed by $NaCNBH_3$ (680 mg suspended in 2 ml THF) were added into the resin mixture. The mixture was left standing for 30 min and manually shaken for 30 min. The resin was hydroformylated using the general procedure described in Section 7.1.3. The resin, BIPHEPHOS (153) (7.2 mg, 8.00 x 10^{-3} mmol) and rhodium(II) acetate dimer (2.0 mg, 0.45 x 10^{-2} mmol) were dissolved in deoxygenated benzene (20 ml) in a 100 ml Parr autoclave which was pressurised with CO/H_2 at 400 psi, and heated at 80°C for 18 h. The autoclave was cooled to ambient temperature before the pressure was released and the resin drained and washed with benzene. After drying the resin for 1 h, the resin was cleaved using TFA (95%, 10 ml) and the resulting solution evaporated (using N_2) to afford 4-(pyrrolidin-1-yl-methyl)-benzoic acid TFA salt as an orange oil (250 mg). (Found: *m/z* 206.1178. $[C_{12}H_{16}O_2N]^+$ ($[M+H-CF_3COOH]^+$) requires 206.1181). ^1H n.m.r. (300 MHz, D_2O) δ 1.93, m, 2H, 2.14, m, 2H and H3', H4'; 3.15, m, 2H and 3.49, m, 2H, H2', H5'; 4.40, s, 2H, $ArC\underline{H}_2$; 7.55, d, *J* 8.0 Hz, 2H, H3, H5; 8.06, d, *J* 8.0 Hz, 2H, H2, H6. Mass Spectrum (ESI$^+$, MeOH): *m/z* 219.9 ($[M+H-CF_3COOH]^+$). The spectral data were consistent with the literature.[231]



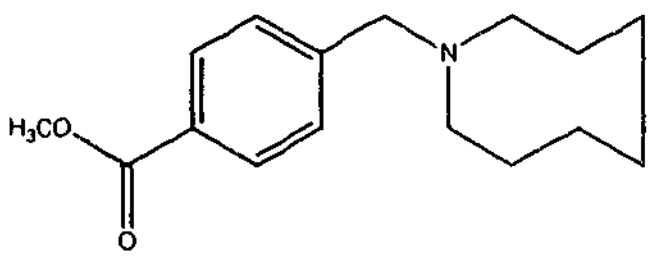
The crude oil was dissolved in methanol (10 ml) to which trimethylsilyldiazomethane (~ 3 ml) was added until a canary yellow colour appeared. The reaction mixture was stirred for 18 h before the methanol was evaporated and the residue basified using $NaHCO_3$ (sat.) and extracted with dichloromethane (3 x 20 ml). The combined organic layers were dried with $MgSO_4$ filtered and evaporated to afford an orange oil (112 mg). The orange oil was purified using column chromatography (SiO_2, ethyl acetate: hexane, 1:3) to afford the desired product (161a) as a yellow oil (90 mg, 91%). (Found: *m/z* 220.1340. $[C_{13}H_{18}O_2N]^+$ ($[M+H]^+$) requires 220.1334). ^1H n.m.r. (300 MHz, $CDCl_3$): δ 1.78-1.86, m, 4H, H3', H4'; 2.54-2.62, m, 4H, H2', H5'; 3.70, s, 2H, $ArC\underline{H}_2$; 3.91, s, 3H, OCH_3; 7.42, d, *J* 8.1 Hz, 2H, H3, H5; 7.99, d, *J* 8.2 Hz, 2H,

112, 116. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 23.6, C3', C4'; 52.3, OCH_3; 54.3, C2', C5'; 60.3, $ArCH_2$; 129.2, C3, C5; 129.4, C1; 129.9, C2, C6; 145.6, C4; 167.2, CO. Mass Spectrum (ESI^+, MeOH): *m/z* 220.3 ($[M+H]^+$). The spectral data were consistent with the literature.[232,233]

Method B

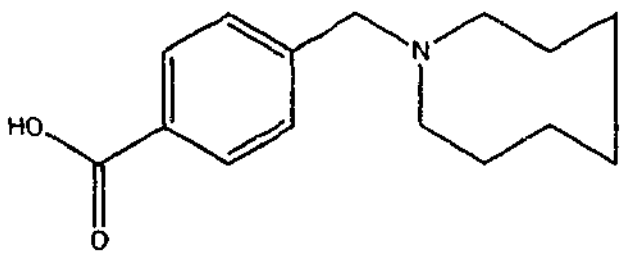
Methyl 4-[(allylamino)methyl]benzoate (175a) (150 mg, 0.73 mmol) was hydroformylated in the presence of BIPHEPHOS (153) (3.2 mg) and rhodium(II) acetate dimer (11.5 mg) with CO/ H_2 (400 psi) according to the general conditions outlined in Section 7.1.3. After 18 h, the vessel pressure was released to reveal that the glass sleave was outlined with insoluble polymeric material. The remaining solution was concentrated to afford a brown oil (70 mg). After purification using column chromatography (SiO_2, ethyl acetate: hexane, 1:1) afforded the desired product (161a) as a yellow oil (40 mg, 25%). Spectroscopic data were consistent with those described for (161a) obtained *via* Method A.

7.6.12 Synthesis of methyl 4-[(azacyclooctan-1-yl)methyl]benzoate (161b)



Method A

The reaction was performed in the manner described for methyl 4-[(pyrrolidin-1-yl)methyl]benzoate (161a) in Section 7.6.11, but 5-hexenamine (162b) (356 mg, 3.6 mmol) was used as the starting material. Subsequent TFA (6 ml, 95%) cleavage of the amine from the resin afforded the TFA salt of 4-(Azocan-1-ylmethyl)benzoic acid as a clear oil (157 mg).[234] (Found: *m/z* 248.1648. $[C_{15}H_{22}O_2N]^+$ ($[M+H\text{-}CF_3COOH]^+$) requires 248.1650). Mass Spectrum (ESI^+, MeOH): *m/z* 248.3 ($[M+H\text{-}CF_3COOH]^+$).

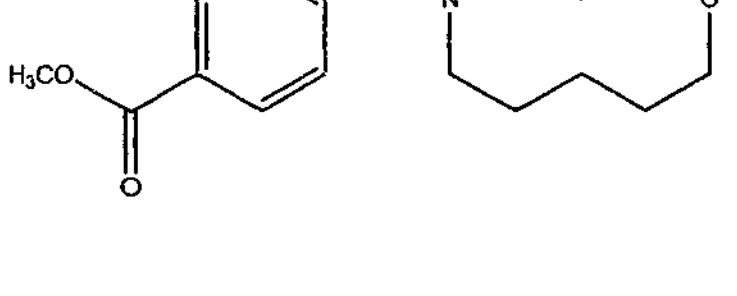


Esterification was performed in the manner described for methyl 4-[(pyrrolidin-1-yl)methyl]benzoate (161a) in Section 7.6.11 to afford an orange oil (95 mg). Purification of the crude product by column chromatography (SiO_2, ethyl acetate: hexane, 1:1) afforded the titled product (161b) as a yellow oil (66 mg, 56%). (Found: *m/z* 262.1803. $[C_{16}H_{24}O_2N]^+$ ($[M+H]^+$) requires 262.1807). ν_{max} (neat): 2911s, 2856s, 2789s, 1722s, 1611s, 1572m, 1433s, 1411m, 1350m, 1278s, 1105s, 1017s, 967s, 850m, 756s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 1.46-1.72, m, 10H, H3', H4', H5', H6', H7'; 2.54, t, *J* 5.8 Hz, 4H, H2', H8'; 3.64, s, 2H, $ArC\underline{H}_2$; 3.91, s, 3H, OCH_3; 7.44, d, *J* 8.1 Hz, 2H, H3, H5; 7.98, d, *J* 8.4 Hz, 2H, H2, H6. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 26.3, 28.0, C3', C4', C5', C6', C7'; 52.2, $O\underline{C}H_3$; 54.6, C2', C8'; 63.6, $Ar\underline{C}H_2$ 128.9, C1; 129.1, C3, C5; 129.7, C2, C6; 147.2, C4; 167.4, CO. Mass Spectrum (ESI^+, MeOH): *m/z* 262.4 ($[M+H]^+$).

Method B

Methyl 4-[(hex-5-enylamino)methyl]benzoate (175b) (176 mg, 0.71 mmol) was hydroformylated in the presence of BIPHEPHOS (153) (3.2 mg) and rhodium(II) acetate dimer (11.5 mg) with CO/ H_2 (400 psi) according to the general conditions outlined in Section 7.1.3. After 18 h, the vessel pressure was released and the reaction solvent was concentrated to afford a brown oil (111 mg). After purification using column chromatography (SiO_2, ethyl acetate: hexane, 1:1) afforded the desired product (161b) as a yellow oil (82 mg, 44%). Spectroscopic data were consistent with those described for (161b) obtained *via* Method A.

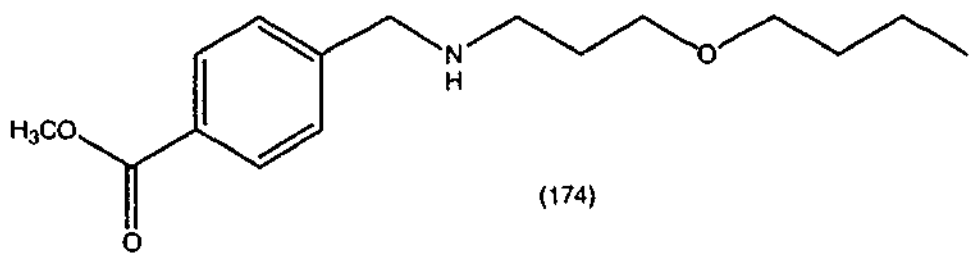
7.6.13 Synthesis of methyl 4-(1,5-oxazanan-5-ylmethyl)benzoate (161c)



Method A

The reaction was performed in the manner described for methyl 4-[(pyrrolidin-1-yl)methyl]benzoate (161a) in Section 7.6.11, but 3-(but-3-en-1-yloxy)propan-1-amine (162c) (461 mg, 3.6 mmol) was used as the starting material. Subsequent TFA (6 ml,

95%) cleavage of the amine from the resin afforded a clear oil (196 mg). Esterification was performed in the manner described for methyl 4-[(pyrrolidin-1-yl)methyl]benzoate (161a) in Section 7.6.11 to afford a yellow oil of 4-({[3-butoxy)propyl]amino}methyl)benzoate (174) (87 mg, 70%) (trace amounts of the titled benzoate (161c) was observed in the mass spectrum). (Found: *m/z* 280.1908. $[C_{16}H_{25}O_3N]^+$ ($[M+H]^+$) requires 280.1913). ν_{max} (neat): 3322 sb, 2944s, 2856s, 1722s, 1611s, 1455s, 1433s, 1367m, 1277s, 1183m, 1111s, 1017s, 967m, 750s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 0.89, t, *J* 7.4 Hz, 3H, H4''; 1.32, sextet, *J* 7.4 Hz, H2, H3''; 1.52, p, *J* 7.0 Hz, H2, H2''; 1.77, *J* 6.5 Hz, H2, H2'; 2.71, t, *J* 6.8 Hz, 2H, H1'; 3.38, t, *J* 6.6 Hz, 2H, 3.47, t, *J* 6.2 Hz, 2H, H3', H1''; 3.83, s, 2H, Ar$\underline{C}H_2$; 3.90, s, 3H, OCH_3; 7.38, d, *J* 8.5 Hz, H3, H5; 7.97, d, *J* 8.4 Hz, H2, H6. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 14.1, C4''; 19.6, C3''; 30.2, 32.0, C2', C2''; 47.3, C1''; 52.2, OCH_3; 53.9, H3'; 69.7, 71.0, Ar$\underline{C}H_2$, C1'; 128.1, C3, C5; 128.9, C1; 129.9, C2, C6; 146.2, C4; 167.3, CO. Mass Spectrum (ESI^+, MeOH): *m/z* 280.2 ($[M+H]^+$).



(174)

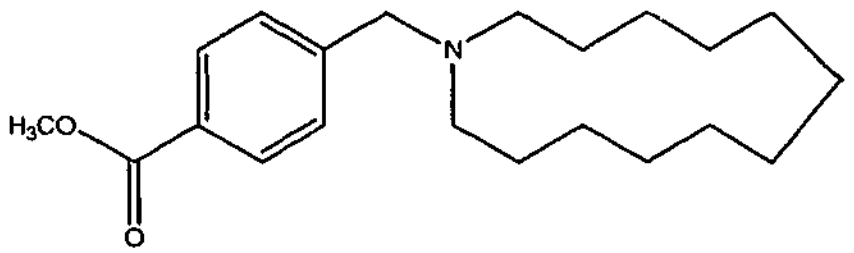
The hydroformylation reaction was carried out as described in above, but with a higher catalyst loading was used, where BIPHEPHOS (153) (14.4 mg, 16 x 10^{-3} mmol) and rhodium(II) acetate (4.0 mg, 9.0 x 10^{-3} mmol). Subsequent TFA (6 ml, 95%) cleavage of the amine from the resin afforded an orange oil. Esterification was performed in the manner described for methyl 4-[(pyrrolidin-1-yl)methyl]benzoate (161a) in Section 7.6.11 to afford an orange oil (110 mg). Purification of the crude product using column chromatography (SiO_2, ethyl acetate: hexane, 1:1) afforded the titled product (161c) as a yellow oil (80 mg, 61%). (Found: C, 69.98, H, 8.71, N, 4.84% . $C_{17}H_{25}NO_3$ requires C, 70.06, H, 8.65, N, 4.81%). (Found: *m/z* 292.1902. $[C_{17}H_{26}O_3N]^+$ ($[M+H]^+$) requires 292.1913). ν_{max} (neat): 3000sb, 2922s, 2844s, 1722s, 1605s, 1600w, 1427s, 1272s, 1106s, 1022s, 944m, 855m, 761s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 1.45-1.74, m, 8H, H3', H7', H8', H9'; 2.39, t, *J* 5.3 Hz, 2H and 2.53, t, *J* 6.1 Hz, 2H, H2', H10'; 3.55, s, 2H, Ar$\underline{C}H_2$; 3.65, t, *J* 5.3 Hz, 4H, H4', H6'; 3.91, s, 3H, OCH_3; 7.42, d, *J* 8.1 Hz, 2H, H3, H5; 7.99, d, *J* 8.3 Hz, 2H, H2, H6. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 26.2, 27.3, H3', H7', H8', H9'; 48.7, 55.3, C2', C10'; 52.2,

OCH_3; 61.1, 66.6, C4', C6'; 72.8, Ar$\underline{C}H_2$; 128.9, C1; 129.4, C3, C5; 129.7, C2, C6; 146.1, C4; 167.4, CO. Mass Spectrum (ESI^+, MeOH): *m/z* 292.1 ($[M+H]^+$).

Method B

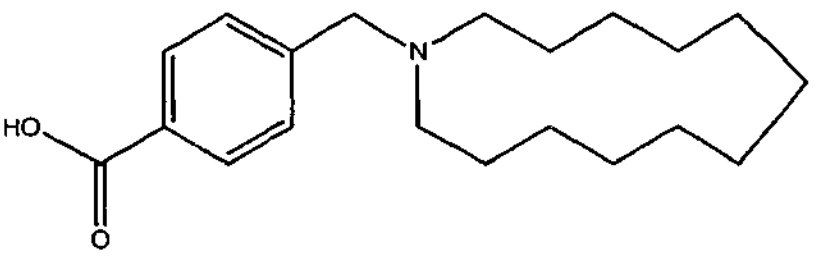
Methyl 4-({[3-but-3-en-1-yloxy)propyl]amino}methyl)benzoate (175c) (193 mg, 0.70 mmol) was hydroformylated in the presence of BIPHEPHOS (153) (6.2 mg) and rhodium(II) acetate dimer (21.9 mg) with CO/ H_2 (400 psi) according to the general conditions outlined in Section 7.1.3 After 18 h, the vessel pressure was released to reveal that the glass sleave was outlined with insoluble polymeric material. The remaining solution was concentrated to afford a brown oil (183 mg). The crude product was purified by column chromatography (SiO_2, ethyl acetate: hexane, 1:5) afforded the desired product (161c) as a yellow oil (100 mg, 49%). Spectroscopic data were consistent with those described for (161c) obtained *via* Method A.

7.6.14 Synthesis of methyl 4-[(azacyclotridecan-1-yl)methyl]benzoate (161d)



Method A

The reaction was performed in the manner described for methyl 4-[(pyrrolidin-1-yl)methyl]benzoate (161a) in Section 7.6.11, but undec-10-enamine (162d) (608 mg, 3.6 mmol) was used as the starting material. Subsequent TFA (6 ml, 95%) cleavage of the amine from the resin afforded the TFA salt of 4-[(azacyclotridecan-1-ylmethyl]benzoic acid as a clear oil (247 mg). Mass Spectrum: *m/z* 306.3 ($[M+H-CF_3COOH]^+$).



Esterification was performed in the manner described for methyl 4-[(pyrrolidin-1-yl)methyl]benzoate (161a) in Section 7.6.11 to afford an orange oil (150 mg). Purification of the crude product by column chromatography (SiO_2, ethyl acetate:

hexane, 1:5) afforded the titled product (161d) as a yellow oil (74 mg, 50%). m.p 98-102°C. (Found: *m/z* 332.2587. $[C_{21}H_{33}O_2N]^+$ ($[M+H]^+$) requires 332.2589). ν_{max} (neat): 3411sb, 2966m, 2911s, 2844s, 2777m, 1716s, 1611m, 1561s, 1461s, 1433s, 1272s, 1100s cm^{-1}. ^1H n.m.r. (300 MHz, $CDCl_3$): δ 1.18-1.50, m, 20H, H3', H4', H5', H6', H7', H8', H9', H10', H11', H12'; 2.28-2.42, m, 4H, H2', H13'; 3.56, s, 2H, $ArC\underline{H}_2$; 3.90, s, 3H. OCH_3; 7.40, d, *J* 8.1 Hz, 2H, H3, H5; 7.97, d, *J* 8.2 Hz, 2H, H2, H6. ^{13}C n.m.r. (100 MHz, $CDCl_3$): δ 27.0, 27.1, 29.3, 29.5, C3', C4', C5', C6', C7', C8', C9', C10', C11', C12'; 53.8, 55.8, C2', C13'; 59.2, $Ar\underline{C}H_2$; 128.7, C3, C5; 129.1, C1; 129.4, C2, C6; 138.9, C4; 167.2, CO. Mass Spectrum (ESI^+, MeOH): *m/z* 332.3 ($[M+H]^+$).

Method B

Methyl 4-[(undec-10-enylamino)methyl]benzoate (175d) (341 mg, 1.07 mmol) was hydroformylated in the presence of BIPHEPHOS (153) (34 mg) and rhodium(II) acetate dimer (9.5 mg) with CO/ H_2 (400 psi) according to the general conditions outlined in Section 7.1.3. After 18 h, the vessel pressure was released to reveal that the glass sleave was outlined with insoluble polymeric material. The remaining solution was concentrated to afford a brown oil (356 mg). The crude product was purified by column chromatography (SiO_2, ethyl acetate: hexane, 1:5) afforded the desired product (161d) as a yellow oil (50 mg, 14%). Spectroscopic data were consistent with those described for (161d) obtained *via* Method A.

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Appendix

Table 1: Crystal data and structure refinement for 1-amino-2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene hydrochloride salt (72)

Identification code	k11_02	
Empirical formula	C12 H19 Cl N2	
Formula weight	226.74	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 8.0618(1) Å	α= 90°.
	b = 9.4707(1) Å	β= 90°.
	c = 16.0182(2) Å	γ = 90°.
Volume	1223.00(3) $Å^3$	
Z	4	
Density (calculated)	1.231 Mg/m^3	
Absorption coefficient	0.284 mm^{-1}	
F(000)	488	
Crystal size	0.20 x 0.16 x 0.14 mm^3	
Theta range for data collection	3.32 to 28.27°.	
Index ranges	-10<=h<=10, -12<=k<=12, -21<=l<=21	
Reflections collected	17235	
Independent reflections	3018 [R(int) = 0.0400]	
Completeness to theta = 27.50°	99.6 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3018 / 0 / 139	
Goodness-of-fit on F^2	1.084	
Final R indices [I>2sigma(I)]	R1 = 0.0326, wR2 = 0.0904	
R indices (all data)	R1 = 0.0358, wR2 = 0.0920	
Absolute structure parameter	0.00(5)	
Largest diff. peak and hole	0.505 and -0.550 $e.Å^{-3}$	

Table 2: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 1-amino-2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene hydrochloride salt (72). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	6725(2)	7079(2)	4016(1)	16(1)
C(2)	7782(2)	7570(2)	3379(1)	18(1)
C(3)	8069(2)	9036(2)	3344(1)	20(1)
C(4)	7339(2)	9953(2)	3904(1)	21(1)
C(5)	6339(2)	9448(2)	4544(1)	22(1)
C(6)	6034(2)	8003(2)	4595(1)	19(1)
C(7)	5582(2)	4934(2)	4800(1)	20(1)
C(8)	4957(2)	3511(2)	4482(1)	26(1)
C(9)	4178(2)	3818(2)	3629(1)	33(1)
C(10)	4905(2)	5240(2)	3332(1)	23(1)
C(11)	6887(2)	4856(2)	5479(1)	26(1)
C(12)	3613(2)	6406(2)	3277(1)	30(1)
Cl(1)	9136(1)	3573(1)	3542(1)	25(1)
N(1)	6241(2)	5577(1)	3998(1)	17(1)
N(2)	8427(2)	6699(2)	2768(1)	23(1)

Table 3: Bond lengths [Å] and angles [°] for 1-amino-2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene hydrochloride salt (72)

C(1)-C(6)	1.392(2)
C(1)-C(2)	1.409(2)
C(1)-N(1)	1.4753(18)
C(2)-N(2)	1.381(2)
C(2)-C(3)	1.409(2)
C(3)-C(4)	1.381(2)
C(3)-H(3)	0.9500
C(4)-C(5)	1.389(2)
C(4)-H(4)	0.9500
C(5)-C(6)	1.392(2)
C(5)-H(5)	0.9500
C(6)-H(6)	0.9500
C(7)-C(11)	1.515(2)
C(7)-N(1)	1.5172(19)
C(7)-C(8)	1.526(2)
C(7)-H(7)	1.0000
C(8)-C(9)	1.531(3)
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.544(2)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-C(12)	1.521(2)
C(10)-N(1)	1.549(2)
C(10)-H(10)	1.0000
C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
N(2)-H(2A)	0.9100
N(2)-H(2B)	0.9100

N(2)-H(2C)	0.9100
C(6)-C(1)-C(2)	121.14(14)
C(6)-C(1)-N(1)	120.90(14)
C(2)-C(1)-N(1)	117.68(13)
N(2)-C(2)-C(1)	122.92(14)
N(2)-C(2)-C(3)	119.89(14)
C(1)-C(2)-C(3)	117.01(14)
C(4)-C(3)-C(2)	121.57(15)
C(4)-C(3)-H(3)	119.2
C(2)-C(3)-H(3)	119.2
C(3)-C(4)-C(5)	120.68(15)
C(3)-C(4)-H(4)	119.7
C(5)-C(4)-H(4)	119.7
C(4)-C(5)-C(6)	118.99(15)
C(4)-C(5)-H(5)	120.5
C(6)-C(5)-H(5)	120.5
C(1)-C(6)-C(5)	120.54(15)
C(1)-C(6)-H(6)	119.7
C(5)-C(6)-H(6)	119.7
C(11)-C(7)-N(1)	112.60(13)
C(11)-C(7)-C(8)	115.18(14)
N(1)-C(7)-C(8)	100.80(12)
C(11)-C(7)-H(7)	109.3
N(1)-C(7)-H(7)	109.3
C(8)-C(7)-H(7)	109.3
C(7)-C(8)-C(9)	105.37(13)
C(7)-C(8)-H(8A)	110.7
C(9)-C(8)-H(8A)	110.7
C(7)-C(8)-H(8B)	110.7
C(9)-C(8)-H(8B)	110.7
H(8A)-C(8)-H(8B)	108.8
C(8)-C(9)-C(10)	106.58(14)
C(8)-C(9)-H(9A)	110.4
C(10)-C(9)-H(9A)	110.4
C(8)-C(9)-H(9B)	110.4
C(10)-C(9)-H(9B)	110.4

H(9A)-C(9)-H(9B)	108.6
C(12)-C(10)-C(9)	113.07(14)
C(12)-C(10)-N(1)	111.51(12)
C(9)-C(10)-N(1)	103.37(13)
C(12)-C(10)-H(10)	109.6
C(9)-C(10)-H(10)	109.6
N(1)-C(10)-H(10)	109.6
C(7)-C(11)-H(11A)	109.5
C(7)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
C(7)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
C(10)-C(12)-H(12A)	109.5
C(10)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
C(10)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(1)-N(1)-C(7)	117.59(12)
C(1)-N(1)-C(10)	113.33(12)
C(7)-N(1)-C(10)	104.88(11)
C(2)-N(2)-H(2A)	109.5
C(2)-N(2)-H(2B)	109.5
H(2A)-N(2)-H(2B)	109.5
C(2)-N(2)-H(2C)	109.5
H(2A)-N(2)-H(2C)	109.5
H(2B)-N(2)-H(2C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for k11_02. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	15(1)	15(1)	19(1)	1(1)	0(1)	-1(1)
C(2)	17(1)	18(1)	19(1)	2(1)	-1(1)	1(1)
C(3)	20(1)	19(1)	22(1)	4(1)	-2(1)	-3(1)
C(4)	22(1)	15(1)	26(1)	0(1)	-7(1)	-1(1)
C(5)	21(1)	19(1)	25(1)	-5(1)	-4(1)	3(1)
C(6)	17(1)	21(1)	20(1)	-2(1)	1(1)	1(1)
C(7)	23(1)	17(1)	19(1)	2(1)	6(1)	-2(1)
C(8)	30(1)	17(1)	31(1)	1(1)	10(1)	-5(1)
C(9)	37(1)	25(1)	36(1)	-3(1)	0(1)	-9(1)
C(10)	26(1)	22(1)	21(1)	-6(1)	1(1)	-4(1)
C(11)	26(1)	26(1)	25(1)	5(1)	2(1)	2(1)
C(12)	28(1)	31(1)	30(1)	-5(1)	-9(1)	1(1)
Cl(1)	28(1)	19(1)	28(1)	2(1)	10(1)	5(1)
N(1)	20(1)	14(1)	18(1)	0(1)	4(1)	-2(1)
N(2)	28(1)	19(1)	22(1)	2(1)	8(1)	1(1)

Table 5: Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 1-amino-2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene hydrochloride salt (72)

	x	y	z	U(eq)
H(3)	8782	9403	2924	24
H(4)	7522	10940	3852	25
H(5)	5870	10078	4940	26
H(6)	5349	7646	5029	23
H(7)	4620	5505	5004	24
H(8A)	4124	3110	4869	31
H(8B)	5886	2833	4426	31
H(9A)	2957	3882	3679	39
H(9B)	4454	3058	3228	39
H(10)	5447	5112	2776	27
H(11A)	7876	4379	5262	38
H(11B)	6448	4325	5955	38
H(11C)	7181	5813	5658	38
H(12A)	2793	6164	2848	44
H(12B)	4157	7297	3128	44
H(12C)	3057	6509	3817	44
H(2A)	8824	5896	3008	35
H(2B)	9266	7153	2499	35
H(2C)	7617	6475	2396	35

Table 6: Hydrogen bonds for 1-amino-2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene hydrochloride salt (72) [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(2)-H(2A)...Cl(1)	0.91	2.37	3.2602(14)	164.6
N(2)-H(2B)...Cl(1)#1	0.91	2.50	3.3787(14)	162.4

Symmetry transformations used to generate equivalent atoms:

#1 -x+2,y+1/2,-z+1/2

Table 7: Crystal data and structure refinement for 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (44)

Identification code	k10_02	
Empirical formula	C18 H28 N2	
Formula weight	272.42	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 2 21 21	
Unit cell dimensions	a = 8.5423(2) Å	α= 90°.
	b = 8.8892(2) Å	β= 90°.
	c = 10.6486(2) Å	γ = 90°.
Volume	808.59(3) $Å^3$	
Z	2	
Density (calculated)	1.119 Mg/m^3	
Absorption coefficient	0.065 mm^{-1}	
F(000)	300	
Crystal size	0.24 x 0.20 x 0.18 mm^3	
Theta range for data collection	3.82 to 28.27°.	
Index ranges	-11<=h<=11, -11<=k<=11, -14<=l<=14	
Reflections collected	11552	
Independent reflections	2003 [R(int) = 0.0419]	
Completeness to theta = 27.50°	99.4 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2003 / 0 / 93	
Goodness-of-fit on F^2	0.952	
Final R indices [I>2sigma(I)]	R1 = 0.0353, wR2 = 0.1074	
R indices (all data)	R1 = 0.0402, wR2 = 0.1125	
Absolute structure parameter	3(3)	
Largest diff. peak and hole	0.170 and -0.175 $e.Å^{-3}$	

Table 8: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (44) U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	4352(1)	4491(1)	515(1)	22(1)
C(2)	5789(1)	4055(1)	1022(1)	30(1)
C(3)	7198(1)	4537(1)	521(1)	34(1)
C(4)	2840(1)	3321(1)	2264(1)	32(1)
C(5)	1158(1)	2752(2)	2303(1)	40(1)
C(6)	938(1)	2071(1)	1010(1)	37(1)
C(7)	1879(1)	3094(1)	126(1)	26(1)
C(8)	3209(2)	4468(2)	3278(1)	45(1)
C(9)	2768(1)	2197(1)	-853(1)	35(1)
N(1)	2913(1)	3961(1)	990(1)	23(1)

Table 9: Bond lengths [Å] and angles [°] for 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (44)

C(1)-C(2)	1.3958(14)
C(1)-N(1)	1.4104(12)
C(1)-C(1)#1	1.4214(19)
C(2)-C(3)	1.3849(15)
C(2)-H(2)	0.9500
C(3)-C(3)#1	1.381(2)
C(3)-H(3)	0.9500
C(4)-N(1)	1.4719(12)
C(4)-C(8)	1.5188(18)
C(4)-C(5)	1.5237(18)
C(4)-H(4)	1.0000
C(5)-C(6)	1.516(2)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-C(7)	1.5364(15)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-N(1)	1.4904(13)
C(7)-C(9)	1.5164(15)
C(7)-H(7)	1.0000
C(8)-H(8A)	0.9800
C(8)-H(8B)	0.9800
C(8)-H(8C)	0.9800
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(2)-C(1)-N(1)	122.30(9)
C(2)-C(1)-C(1)#1	118.39(6)
N(1)-C(1)-C(1)#1	119.31(5)
C(3)-C(2)-C(1)	121.94(10)
C(3)-C(2)-H(2)	119.0
C(1)-C(2)-H(2)	119.0
C(3)#1-C(3)-C(2)	119.60(6)

C(3)#1-C(3)-H(3)	120.2
C(2)-C(3)-H(3)	120.2
N(1)-C(4)-C(8)	112.74(9)
N(1)-C(4)-C(5)	101.18(9)
C(8)-C(4)-C(5)	113.52(10)
N(1)-C(4)-H(4)	109.7
C(8)-C(4)-H(4)	109.7
C(5)-C(4)-H(4)	109.7
C(6)-C(5)-C(4)	102.98(9)
C(6)-C(5)-H(5A)	111.2
C(4)-C(5)-H(5A)	111.2
C(6)-C(5)-H(5B)	111.2
C(4)-C(5)-H(5B)	111.2
H(5A)-C(5)-H(5B)	109.1
C(5)-C(6)-C(7)	104.78(9)
C(5)-C(6)-H(6A)	110.8
C(7)-C(6)-H(6A)	110.8
C(5)-C(6)-H(6B)	110.8
C(7)-C(6)-H(6B)	110.8
H(6A)-C(6)-H(6B)	108.9
N(1)-C(7)-C(9)	113.54(8)
N(1)-C(7)-C(6)	103.77(9)
C(9)-C(7)-C(6)	111.85(9)
N(1)-C(7)-H(7)	109.2
C(9)-C(7)-H(7)	109.2
C(6)-C(7)-H(7)	109.2
C(4)-C(8)-H(8A)	109.5
C(4)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	109.5
C(4)-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5
C(7)-C(9)-H(9A)	109.5
C(7)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(7)-C(9)-H(9C)	109.5

H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(1)-N(1)-C(4)	119.80(8)
C(1)-N(1)-C(7)	117.87(8)
C(4)-N(1)-C(7)	110.09(8)

Symmetry transformations used to generate equivalent atoms:

#1 x,-y+1,-z

Table 10: Anisotropic displacement parameters ($Å^2 x\ 10^3$)for 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (44) The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	24(1)	21(1)	22(1)	-2(1)	1(1)	2(1)
C(2)	30(1)	29(1)	30(1)	0(1)	-3(1)	7(1)
C(3)	24(1)	36(1)	43(1)	-6(1)	-5(1)	4(1)
C(4)	34(1)	36(1)	26(1)	11(1)	7(1)	11(1)
C(5)	37(1)	40(1)	43(1)	18(1)	15(1)	8(1)
C(6)	32(1)	26(1)	54(1)	9(1)	12(1)	0(1)
C(7)	24(1)	21(1)	33(1)	1(1)	2(1)	-1(1)
C(8)	50(1)	61(1)	23(1)	2(1)	1(1)	14(1)
C(9)	37(1)	28(1)	39(1)	-9(1)	7(1)	-7(1)
N(1)	25(1)	25(1)	20(1)	3(1)	1(1)	1(1)

Table 11: Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 1,2-bis-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzene (44)

	x	y	z	U(eq)
H(2)	5800	3409	1733	36
H(3)	8159	4232	891	41
H(4)	3579	2452	2330	39
H(5A)	1019	1986	2969	48
H(5B)	414	3587	2448	48
H(6A)	-183	2061	773	45
H(6B)	1343	1028	985	45
H(7)	1147	3803	-306	31
H(8A)	2458	5299	3230	67
H(8B)	4271	4857	3154	67
H(8C)	3136	3989	4105	67
H(9A)	3502	1514	-434	52
H(9B)	3349	2886	-1400	52
H(9C)	2028	1611	-1358	52