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# SYNTHESIS OF AMINO ACIDS BY METAL-CATALYSED REACTIONS

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***Dedicated to my family,***

***especially my parents***

***and grandma***

# TABLE OF CONTENTS

## CHAPTER 5 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.*

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July 2004

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# ABSTRACT

Prochiral dienamide esters ((46), (48) and (49)) were subjected to asymmetric hydrogenation with a chiral phosphine catalyst to yield chiral enamides ((51), (53) and (55)) with high enantiomeric excess (≥ 95%). High stereoselectivity was achieved using the Rh(I)-DuPHOS system where only the first double bond conjugated to the amide was reduced. The hydrogenation precursors ((46), (48) and (49)) were prepared by Horner-Emmons olefination where phosphonate (31) was reacted with a variety of aldehydes ((45), (47) and (41)).

Piperidines and pyrrolidines ((68), (69), (73) and (74)) were formed in two steps *via* tandem hydroformylation-cyclisation sequences. The catalyst systems used were Rh-$PPh_3$ and Rh-BIPHEPHOS. These catalyst systems exhibited different regioselectivity depending on the bulkiness of the ligand. In this project, 6- and 5-membered cyclic compounds ((68), (69), (73) and (74)) were successfully synthesised and the preparation of 8- and 7-membered ring compounds ((77) and (78)) was accomplished.

Tandem, enantioselective Rh(I)-DuPHOS catalysed asymmetric hydrogenation followed by a Rh-catalysed hydroformylation-cyclisation sequence lead to cyclic amino acids ((68), (69), (73) and (74)) with high enantiomeric excess (≥ 95%) in good yield and in a single pot. High yields and enantioselectivities were also obtained using Rh(I)-DuPHOS as the sole catalyst for both hydrogenation and hydroformylation.

Hydrogenation, hydroformylation, cyclisation and elimination reactions were also performed in a single pot using $scCO_2$ as the reaction solvent, and lead to highly

enantioselective (≥ 98% ee) conversions of dienamides ((46) and (48)) into cyclic α-amino acids ((68), (69), (73) and (74)).

Hydroformylation of (*E*)-*N*-(phenylethenyl)acetamide (91) using chiral catalysts, e.g. Rh(I)-Et-DuPHOS and Ru(III)-BINAP, gave low conversion to racemic aldehydes ((115) and (116)). Hydroformylation of longer chain enamides ((107) and (113)) gave the cyclic products, dehydropyrrolidine (125) and dehydropiperidine (130) when the reaction was carried out in benzene. The amidal pyrrolidine (124) and amidal piperidine (129) were formed when reactions were carried out in methanol. Unfortunately, the methoxy amidals ((124) and (129)) were also racemic.

Hydroformylation of styrene (15) using Rh(I)-DuPHOS and Rh(I)-BPE catalysts required severe conditions and gave racemic product (16). Hydroformylation of $\eta^6$-styrene chromium complex (18) using Rh(I)-DuPHOS could be carried out under milder reaction conditions and gave complete conversion to aldehyde (19) with moderate enantiomeric excess (56% and 50%).

# ABBREVIATIONS

| | |
|---|---|
| $H_2$ | hydrogen |
| CO | carbon monoxide |
| Me | methyl |
| Et | ethyl |
| Pr | propyl |
| *i*-Pr | *iso*-propyl |
| *t*-Bu | *tert*-butyl |
| Ph | phenyl |
| Cbz | benzyloxycarbonyl |
| Fmoc | fluorenylmethoxycarbonyl |
| atm | atmosphere |
| r.t. | room temperature |
| lit. | literature |
| b.p. | boiling point |
| h | hour |
| min | minute |
| psi | pounds per square inch |
| (-)-BPPM | (2*S*,4*S*)-4-(diphenylphosphino)-2-[(diphenylphosphino)-methyl]pyrrolidine |
| (*R*,*S*)-BINAPHOS | [(*R*)-2-diphenylphosphino-1,1'-dinaphthalen-2'-yl]-[(*S*)-1,1'-dinaphthalene-2,2'-diyl]phosphite |
| NAPHOS | diphosphine 2,2'-bis[(diphenylphosphino)methyl]-1,1'-binaphtyl |

| | |
|---|---|
| DIOP | (-)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane |
| CHIRAPHOS | (2*S*,3*S*)-bis(diphenylphosphino)butane |

# CHAPTER 1 INTRODUCTION

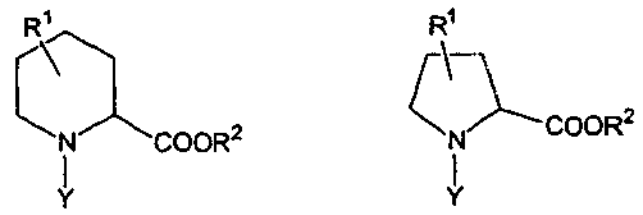
## *1.1 Background*

There is a growing trend in the pharmaceutical and fine chemical industries towards replacing classical organic synthesis with cleaner catalytic alternatives. Attention to the E factor,[1] and the amount of waste generated per kilo of product,[2] has driven chemists to reduce or eliminate the use of hazardous reagents and solvents. Tandem reaction sequences employing catalytic processes therefore offer an opportunity to conduct organic synthesis in a highly efficient manner. Furthermore, reaction sequences which possess high atom economy[3,4] and simultaneously incorporate stereochemistry into the framework of the desired target would be considered even more efficient.[5]

This project combines a number of green concepts through the study of domino catalytic asymmetric hydrogenation-hydroformylation sequences.[6,7] This sequential transformation facilitates the formation of a new C-C single bond and heterocycle with concomitant generation of a stereogenic centre in a single pot. Other highly efficient domino reactions have also been reported and include hydroformylation-Knoevenagel-hydrogenation,[8] hydroformylation-Wittig,[9] isomerisation-hydroformylation,[10] hydroformylation-conjugate addition,[11] and isomerisation-carbonylation sequences.[12] The use of supercritical carbon dioxide ($scCO_2$) as a green reaction solvent for a range of homogenous metal-catalysed reactions is also gaining popularity.[13,14] Some years ago, Burk and his colleagues showed that it was possible to carry out asymmetric catalytic hydrogenation reactions in supercritical carbon dioxide ($scCO_2$) with very high enantioselectivity. In fact, in some cases they were

able to achieve even higher enantiomeric excess (ee) than in conventional solvents.[15] There is also continued interest in atom efficient metal-catalysed hydroformylation reactions[16] and the incorporation of such reactions into tandem sequences, leading to the efficient synthesis of key synthetic intermediates.[17] These reactions feature strongly in the work described in this thesis.

The organic synthesis of biologically active cyclic amino acids is of both academic and pharmaceutical interest.[18,19] Such heterocycles are a sub-set of the larger group of compounds known as alkaloids (Figure 1.1). These alkaloids are of significant importance since they are key constituents of several pharmacologically active compounds as well as being of pharmacological interest in their own right.[18,19]




Piperidine Pyrrolidine

**Figure 1.1**

In addition, piperidine alkaloids are key intermediates in the synthesis of local anaesthetics (1),[20] neurotoxins (2),[18] the potent enzyme inhibitor (+)-Fagomine (3),[19] immunosuppressants (-)-FK-506 (4)[21] and therapeutic agents for cardiac insufficiency (5) (Figure 1.2).[22] Pyrrolidine alkaloids also attract great attention due to their unique biological properties. These alkaloids are found in ant venom (6)[23,24] and potent insecticides (-)-kainic acid (7),[25] and can mimic the β-turn function in peptides (8) (Figure 1.2).[26]

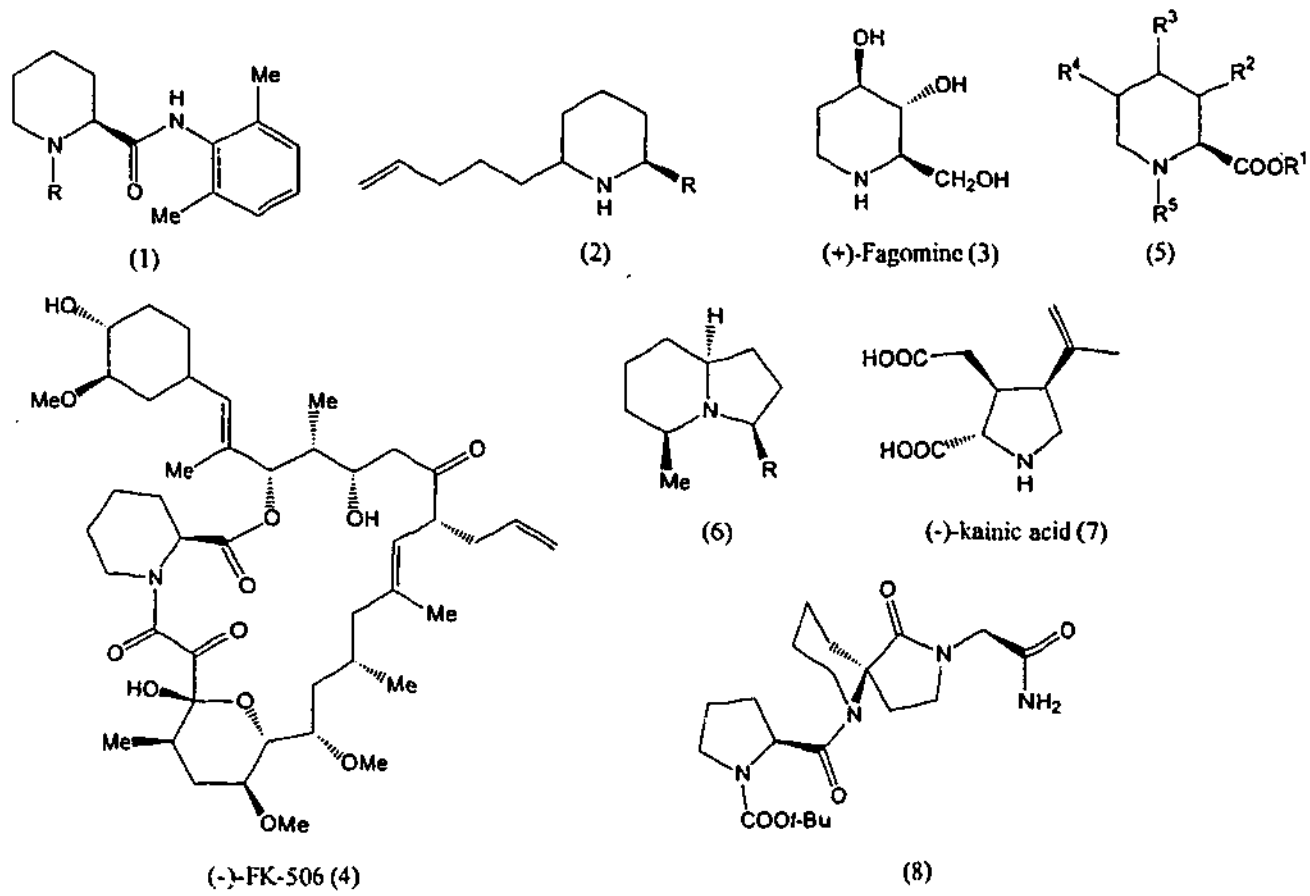
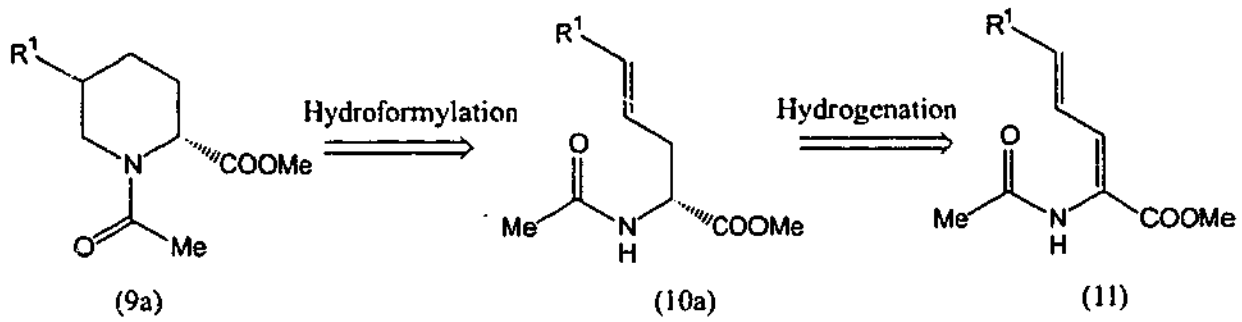



**Figure 1.2**

Recently, metal-catalysed routes to piperidine alkaloids involving hydrogenation and hydroformylation have been described. Ojima and co-workers reported a convenient synthesis of pipecolate derivatives (9a) from allylglycinate (10a).[27] Burk and co-workers have developed an efficient method for regio- and enantioselective hydrogenation of prochiral dienamide esters (11) to yield unsaturated amino acids (9a). This is achieved through the use of Rh(I)-DuPHOS, a very effective chiral catalyst for enantioselective hydrogenation reactions (refer to Section 1.2).[28] A retrosynthesis of cyclic amino acids (9a) involving dienamide esters (11) (hydrogenation precursors) and enamide esters (10a) (hydroformylation precursors) is illustrated below (Scheme 1.1).



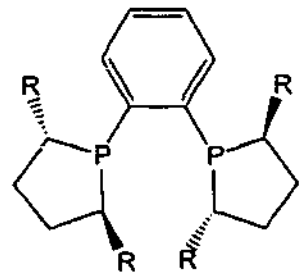

(9a) (10a) (11)

**Scheme 1.1**

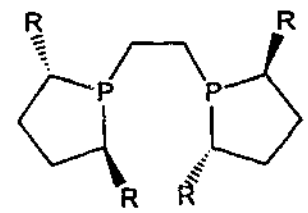
## *1.2 Asymmetric Hydrogenation*

Asymmetric hydrogenation is a key process in the production of valuable chemicals such as drugs, agricultural chemicals and food additives due to its ability to synthesise stereoisomers with very high selectivity.[29-31] Noyori and Knowles were awarded the Noble Prize for Chemistry in 2001 for their work in the area of asymmetric hydrogenation.[32] Chiral compounds that are biologically active are in general marketed as a single enantiomer because usually only one enantiomer possesses optimal activity while the other may be lethal, inactive or have undesirable metabolic profiles.[33]

The chiral bis-phosphine ligands, DuPHOS and BPE, developed by Burk, act as highly effective catalysts when complexed with rhodium for highly enantioselective hydrogenation of a wide variety of substrates (Figure 1.3).[34]



(*S*,*S*)-DuPHOS

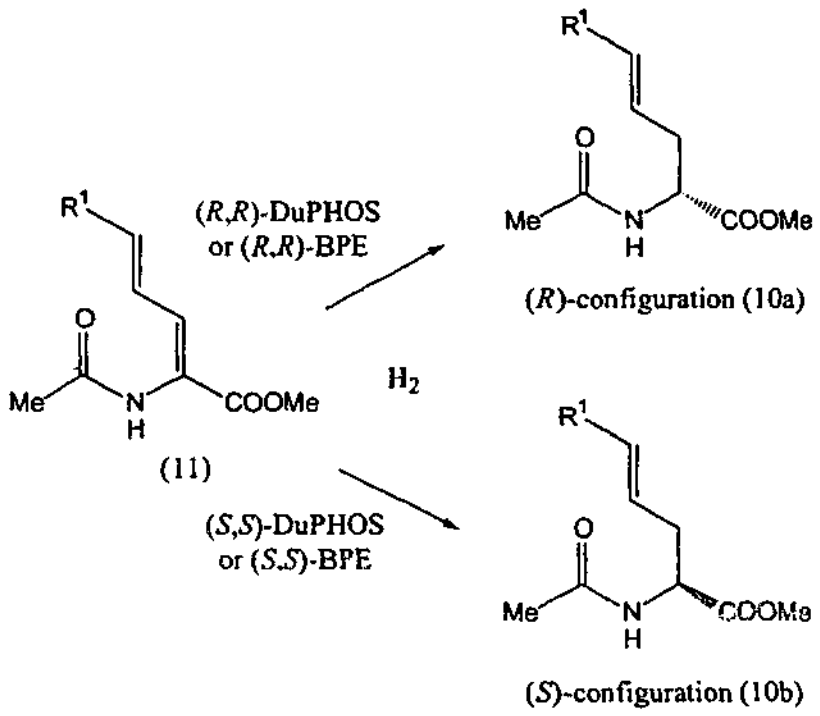


(*S*,*S*)-BPE

R = Me, Et, Pr or *i*-Pr

**Figure 1.3**

There are many literature reports of greater than 95% enantiomeric excess (ee) being achieved in the synthesis of chiral enamide esters,[28] amino alcohols[35,36] and amines.[37,38] When DuPHOS and BPE were used as ligands, only mild conditions, i.e. ambient temperature, short reaction times and low pressures, were needed to achieve excellent yields and enantioselectivity using a wide range of solvents, such as methanol, benzene[28,34,37] and tetrahydrofuran.[37] In addition, as outlined in Scheme 1.2, reduction of dienamide (11) with enantiopure DuPHOS or BPE ligands (i.e. (*R*,*R*) or (*S*,*S*)) allows equal access to both stereoisomers of enamide (10), *R*-10a and *S*-10b.[28] Optical rotation, chiral high performance liquid chromatography (HPLC) and chiral gas chromatography (GC) can be used to establish the enantioselectivity of the reduced products ((10a) and (10b)).




**Scheme 1.2**

The dialkyl substituents neighbouring the DuPHOS and BPE phosphorus atoms provides high electron density to the metal, encouraging strong binding to the prochiral olefin. The DuPHOS ligand induces chirality from the chiral 5-membered phospholane rings rather than through the 1,2-phenylene backbone. The rigid backbone in the DuPHOS ligand can be used to reduce conformational mobility and hence result in a more efficient chiral transfer. Enantioselectivity is significantly affected by the electronic properties of the olefin substrate, as stronger π-backbonding from the metal d-orbitals to the $\pi^*$-orbital of olefin gives tighter binding, leading to higher selectivity. The formation of a 6-membered chelate ring between the Rh atom, double bond and amide-carbonyl group of the substrate, is critical for stereoselective hydrogenation.[28,34,39] This chelation leads to reduction of the C=C bond which is α to the amide, leaving the distal C=C bond available for later hydroformylation (Figure 1.4).

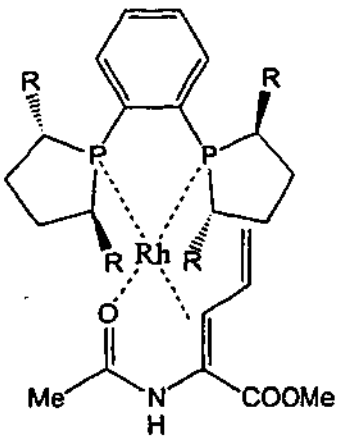
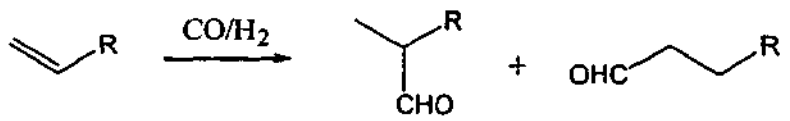



**Figure 1.4**

## *1.3 Hydroformylation*

Hydroformylation is one of the most widely used and studied homogenous metal-catalysed reactions of unsaturated compounds. It involves the addition of carbon monoxide and hydrogen to an alkene to give branched (*b*) and linear (*n*) aldehydes, a reaction also known as the oxo-process (Scheme 1.3).[40,41]




branched (*b*) linear (*n*)

**Scheme 1.3**

Aldehydes are important intermediates in the chemical industry and hydroformylation of alkenes yields about 4 million tons of aldehyde products per annum. These are used in the production of a range of chemicals including plasticizers, detergents, solvents and pharmaceutical chemicals.[40,42] Rhodium-based catalysts are now the most commonly used catalysts in the oxo-process as they enhance activity and increase regioselectivity under milder reaction conditions.[43,44] Early commercial plants were based on cobalt catalysts, however undesirable side reactions such as isomerisation, hydrogenation of double bonds and aldehyde condensation disadvantaged the use of

these catalysts. These undesirable outcomes can be avoided by the use of rhodium-based catalysts.[41,45]

The ratio of branched to linear aldehydes (*b* : *n*) formed is influenced by factors such as temperature, pressure, substrate structure, catalyst and ligand ratio as well as the ligands that are complexed with the metal.[46] In general, increasing the temperature and pressure of the reaction increases the reaction rate but many unwanted side products are also produced, giving a lower ratio of linear aldehydes.[16,41,44] The number of substituents on the unsaturated alkene will not only affect the branched to linear aldehyde ratio but also influence the reaction rate. The order of reactivity is illustrated below (Figure 1.5).[16]

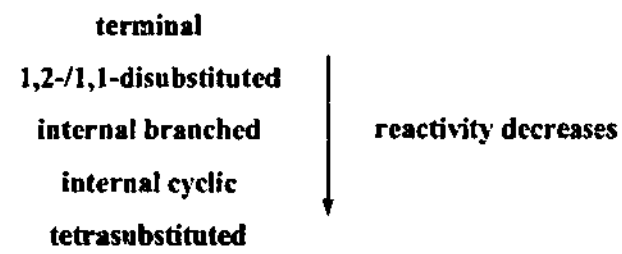
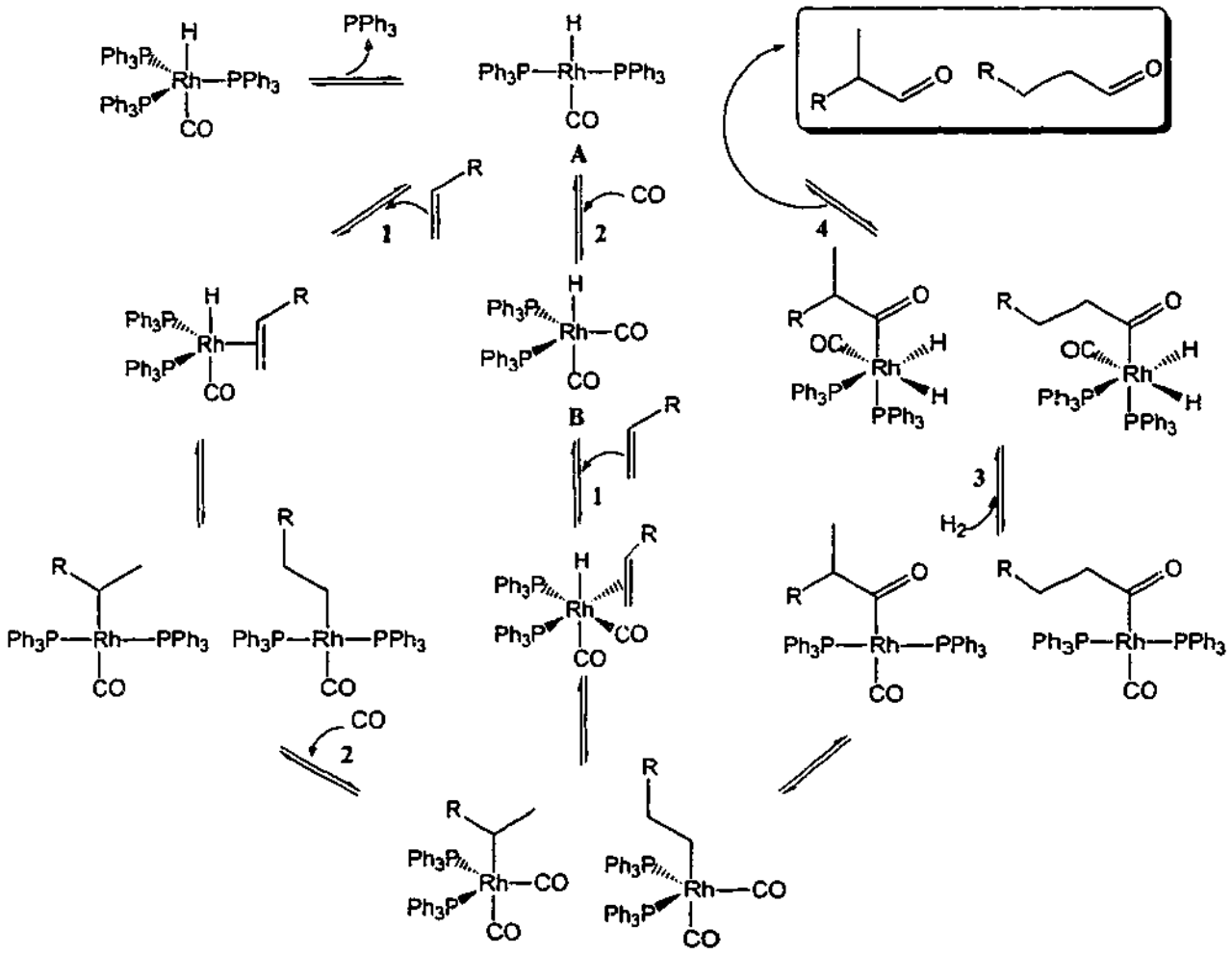



**Figure 1.5**

The catalyst to ligand ratio also plays a major role in affecting the regiochemistry of reaction. For example, an increase in the rhodium (Rh) to triphenylphosphine ($PPh_3$) ratio from 1 : 50 to 1 : 100 leads to a higher ratio of linear aldehydes. This increased steric hindrance is due to complexation of an additional phosphine ligand, which encourages addition of a formyl group to the terminal position of the alkene.[41]

Although Wilkinson and co-workers were the first to propose the associative mechanism of hydroformylation,[43,44,47] the dissociative mechanism that was proposed by Breslow and Heck is widely acknowledged and used.[48] The associative pathway is favored by a high concentration of ligand and $HRh(CO)_2(PPh_3)_2$ (**B**) is the active

species. Conversely, $HRh(CO)(PPh_3)_2$ (**A**) is the active species in the dissociative pathway.[16] The mechanism of rhodium-phosphine hydroformylation is summarised below (Scheme 1.4).[16,39,41]



**Scheme 1.4**

Fundamentally, the mechanism is comprised of 4 key steps:

1. Alkene insertion to give a trigonal bipyramidal complex.

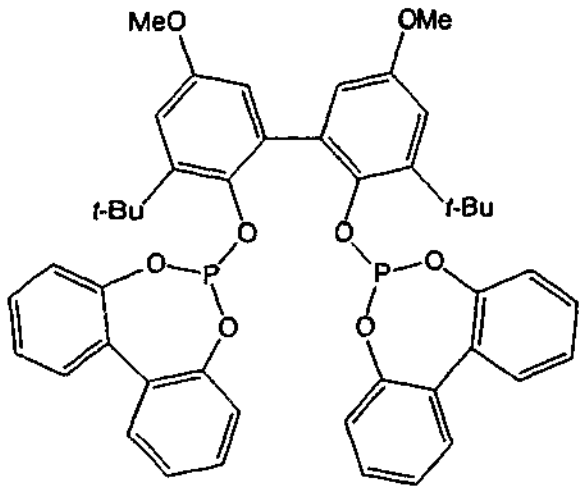
2. Carbon monoxide addition to give a trigonal bipyamidal complex.

3. Oxidative addition of hydrogen which is the rate determining step.

4. Reductive elimination to give products.

Triphenylphosphine is a commonly used ligand in hydroformylation reactions despite the fact that it gives relatively low regioselectivity for the terminal aldehyde isomer (*b* : *n* ratio = 20 : 80) from terminal alkenes.[49] Terminal aldehydes are converted into

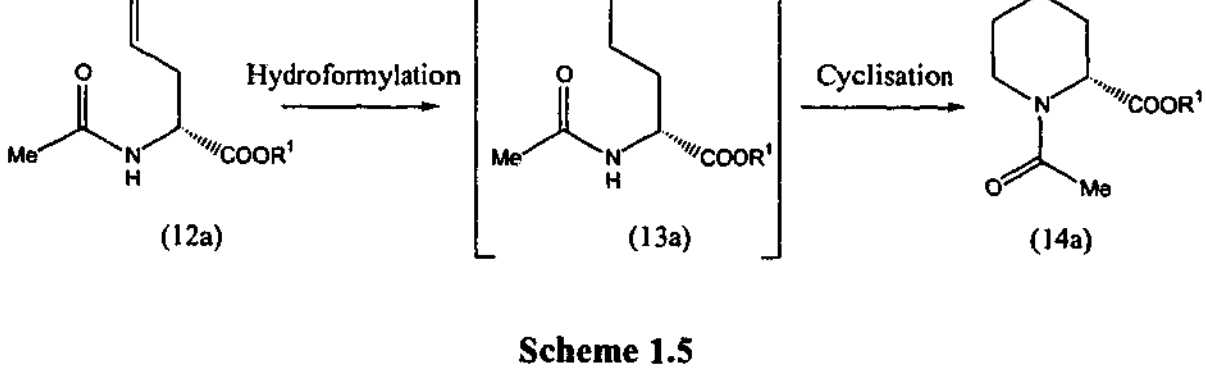
straight chain esters of phthalic anhydride for use as plasticizers.[40] The bulky ligand BIPHEPHOS can be used to give higher yields of linear aldehydes (*b* : *n* ratio = 2 : 98) (Figure 1.6).[50,51] The preference for linear over branched products is due to steric interactions resulting from the use of the bulky bis-phosphite ligand.[33,49]




BIPHEPHOS

**Figure 1.6**

The synthesis of cyclic compounds (14a) from unsaturated substrates (12a) described in this thesis involves two steps (Scheme 1.5). The Rh-BIPHEPHOS system will be used to control both the chemo- and regioselectivity of hydroformylation, leading to a predominance of linear aldehyde (13a) as demonstrated by Ojima.[33] The resulting aldehyde (13a) can be cyclised *in situ* to piperidine (14a), even though the amide group is a poor nucleophile.

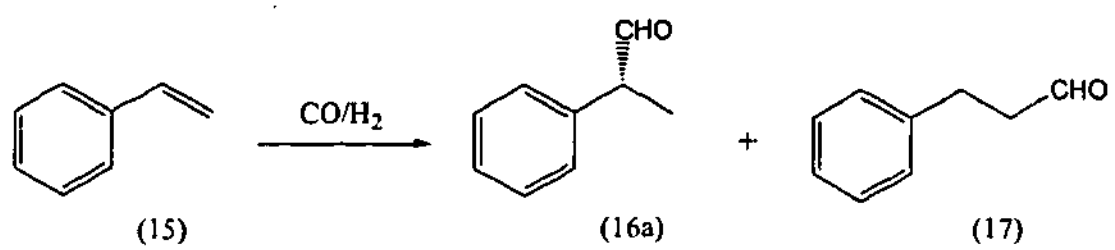



(12a) (13a) (14a)

**Scheme 1.5**

## *1.4 Asymmetric Hydroformylation*

In contrast to the hydroformylation of most terminal alkenes, the hydroformylation of styrene (15) gives a predominance of the branched chain isomer (16a) (Scheme 1.6).




**Scheme 1.6**

The resulting branched arylpropanals (16a) are chiral and their preparation by enantioselective hydroformylation has been widely explored as a direct route to precursors of anti-inflammatory drugs, e.g. Ibuprofen and Naproxen (Figure 1.7).[52]

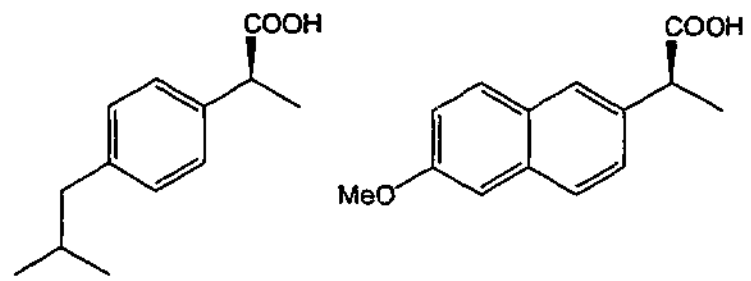
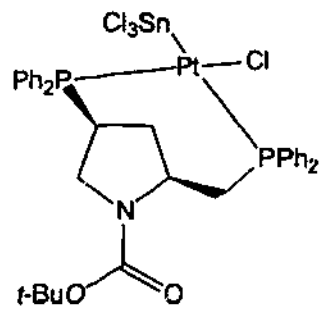



**Figure 1.7**

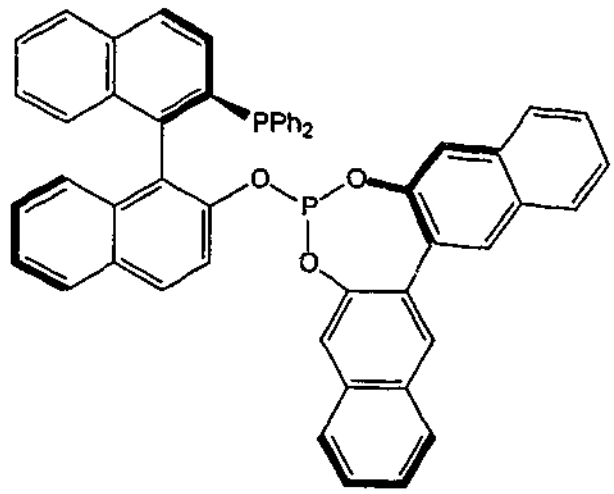
Stille and co-workers have reported that by using triethyl orthoformate as a trapping reagent, the hydroformylation of styrene (15) can be achieved with > 96% ee using [(-)-BPPM]$PtCl_2.SnCl_2$. The major limitation of this reaction is that the regioselectivity for the branched aldehyde (16) is always low (*b* : *n* ratio = 50 : 50) (Figure 1.8).[53] Several research groups have also commented that the reaction is very hard to reproduce.[52,54]




[(-)-BPPM]$PtCl_2.SnCl_2$

**Figure 1.8**

A few years later, Takaya *et al.* synthesised a new chiral ligand, (*R*,*S*)-BINAPHOS (Figure 1.9). The combination of this ligand with rhodium(I) generated a catalyst which hydroformylated styrene (15) with excellent conversion (> 99%) and enantioselectivity (94%), but suffered from the same regioselectivity problems (*b* : *n* ratio = 88 : 12).[55] This is due to the bulkiness of the ligand, causing an increase in the ratio of the linear aldehyde (17).

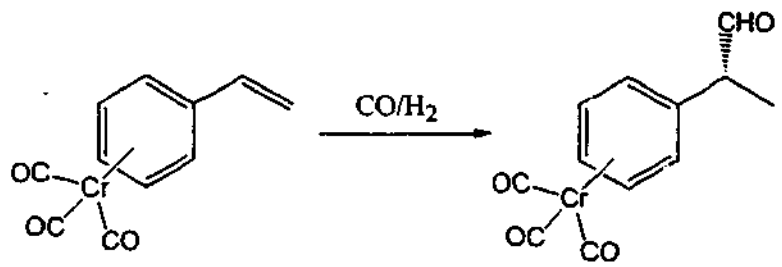



(*R*,*S*)-BINAPHOS

**Figure 1.9**

One way of overcoming the regioselectivity problem is to convert the styrene (15) into its tricarbonylchromium complex (18). The tricarbonylchromium is a very strong electron-withdrawing group which facilitates the predominant formation of the branched aldehyde (19a) (Scheme 1.7).[56] The reaction proceeds under very mild

conditions, e.g. with only 1 atm of $CO/H_2$.[57] In addition, the tricarbonylchromium group can be easily cleaved off by exposing the complex to sunlight and air.[58]

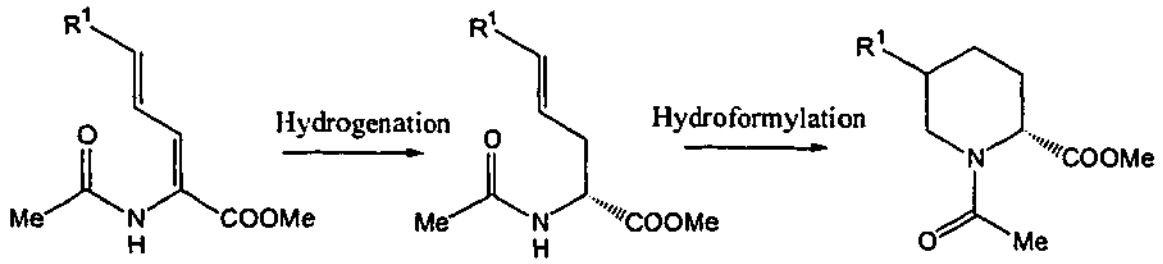



(18) (19a)

**Scheme 1.7**

## *1.5 The Research Project*

The aim of this project is to utilise the method devised by Burk for the hydrogenation of dienamide esters (11) to give chiral enamides (10a).[28] These can act as hydroformylation precursors for the synthesis of piperidine alkaloids (9a) as demonstrated by Ojima (Scheme 1.8).[27] The synthesis will then be extended to give larger ring amino acids.

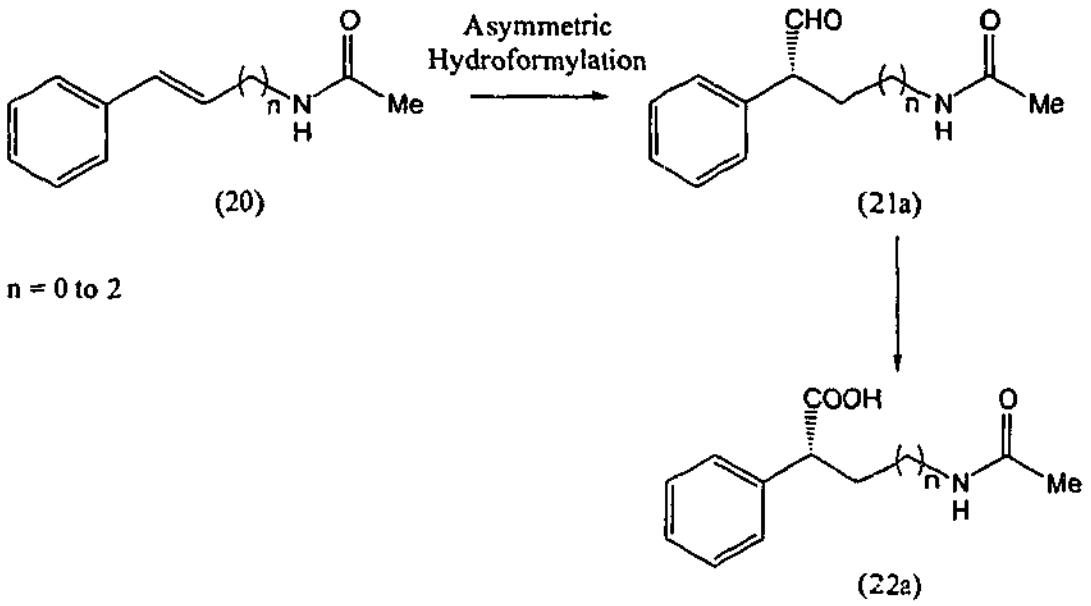



(11) (10a) (9a)

**Scheme 1.8**

Tandem reaction strategies will be devised utilising the above catalytic processes. The investigation will also be attempted in a solvent free medium, i.e. supercritical carbon dioxide ($scCO_2$).

In addition, Rh(I)-DuPHOS and Rh(I)-BPE will be investigated as hydroformylation catalysts. The prochiral enamide (20) will be converted to the chiral aldehyde (21a), which can be used to generate chiral amino acids (22a) (Scheme 1.9). These catalysts will also be evaluated as hydroformylation catalysts for reactions of styrene (15) with $CO/H_2$.



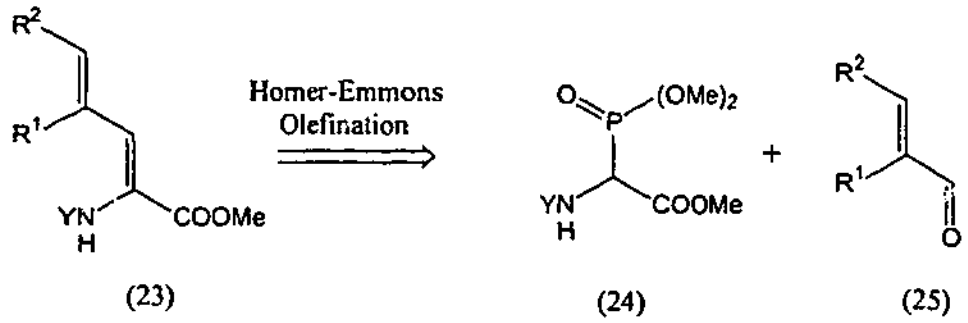

**Scheme 1.9**

# CHAPTER 2 SYNTHESIS OF CYCLIC α-AMINO ACIDS

## *2.1 Preparation of Hydrogenation Precursors*

### 2.1.1 General Introduction

This project begins with the synthesis of dienamide ester substrates (23) which can be subjected to asymmetric hydrogenation with chiral phosphine catalysts developed by Burk to yield chiral enamides.[28] These chiral enamides can then act as hydroformylation precursors for the synthesis of cyclic amino acids as demonstrated by Ojima.[27] Horner-Emmons olefination of phosphonate esters (24) with a variety of aldehydes (25) will initially be carried out to prepare the hydrogenation precursors (23) (Scheme 2.1).



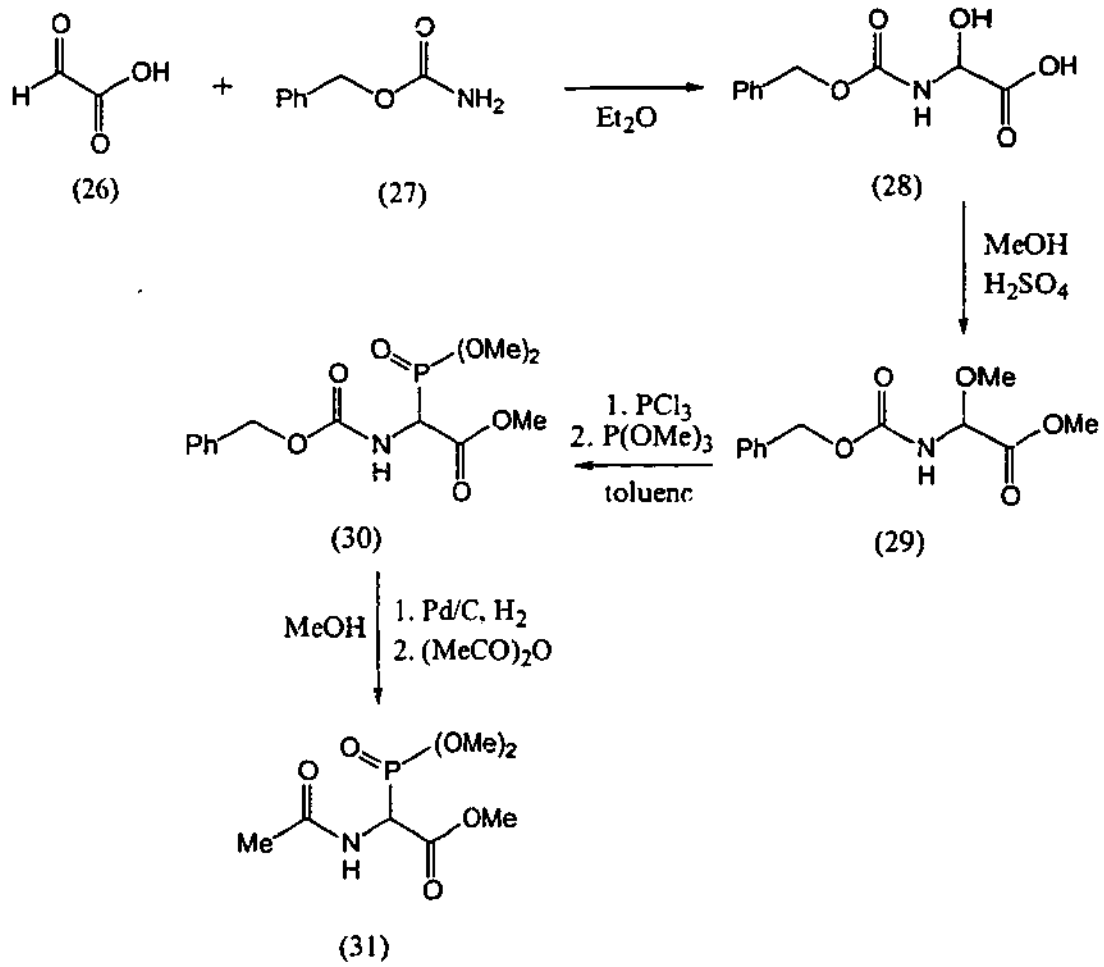

(23) (24) (25)

**Scheme 2.1**

### 2.1.2 Synthesis of Phosphonate Esters (24)

#### *2.1.2.1 Synthesis involving the benzyloxycarbonyl (Cbz)-protecting group*

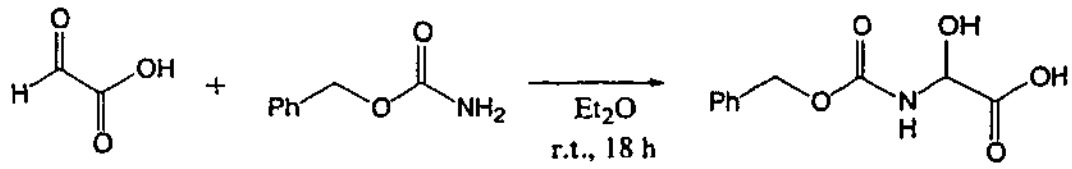
The phosphonate (31) was prepared by reacting glyoxylic acid (26) with benzyl carbamate (27) followed by several steps that are illustrated in Scheme 2.2.




(26) (27) (28) (29) (30) (31)

**Scheme 2.2**

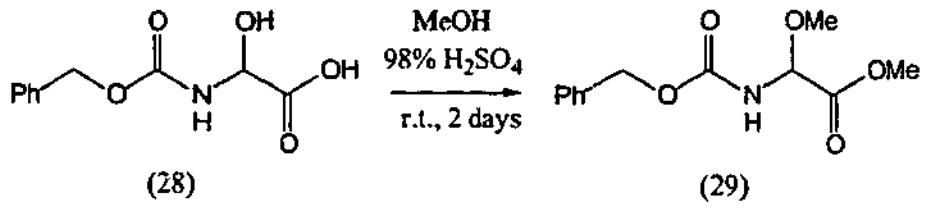
Commercially available benzyl carbamate (27) and glyoxylic acid monohydrate (26) were stirred overnight in diethyl ether to give pure *N*-benzyloxycarbonyl-2-hydroxyglycine (28) as a colourless solid (Scheme 2.3).




(26) (27) (28)

**Scheme 2.3**

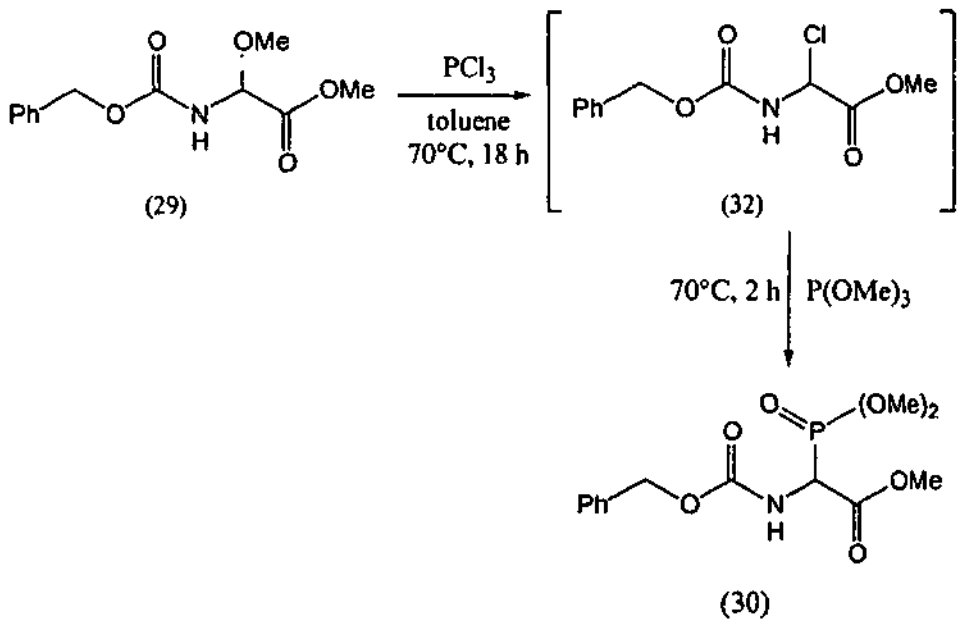
This compound (28) is reported in the literature and the observed melting point (199-200°C) of the prepared sample was close to the reported melting point (196-198°C).[59] The product (28) was obtained in quantitative yield showing improvement over the literature yield of 73%.




(28) (29)

**Scheme 2.4**

Methyl *N*-benzyloxycarbonyl-2-methoxyglycinate (29) was also obtained in quantitative yield, comparable to the reported yield (92%), by reaction of *N*-benzyloxycarbonyl-2-hydroxyglycine (28) with methanol and sulfuric acid as the catalyst. In the presence of methanol, the acid group underwent esterification to form the methyl ester while the alcohol group was converted into its methyl ether. The appearance of two new singlets in the $^1$H n.m.r. spectrum at δ 3.46 ($CHOC\underline{H}_3$) and at δ 3.80 ($COOCH_3$) and also the two new peaks in the $^{13}$C n.m.r. spectrum at δ 53.3 and 56.6 were consistent with this structural assignment. The melting point (78-80°C) was consistent with the literature melting point (76-78°C).[59]



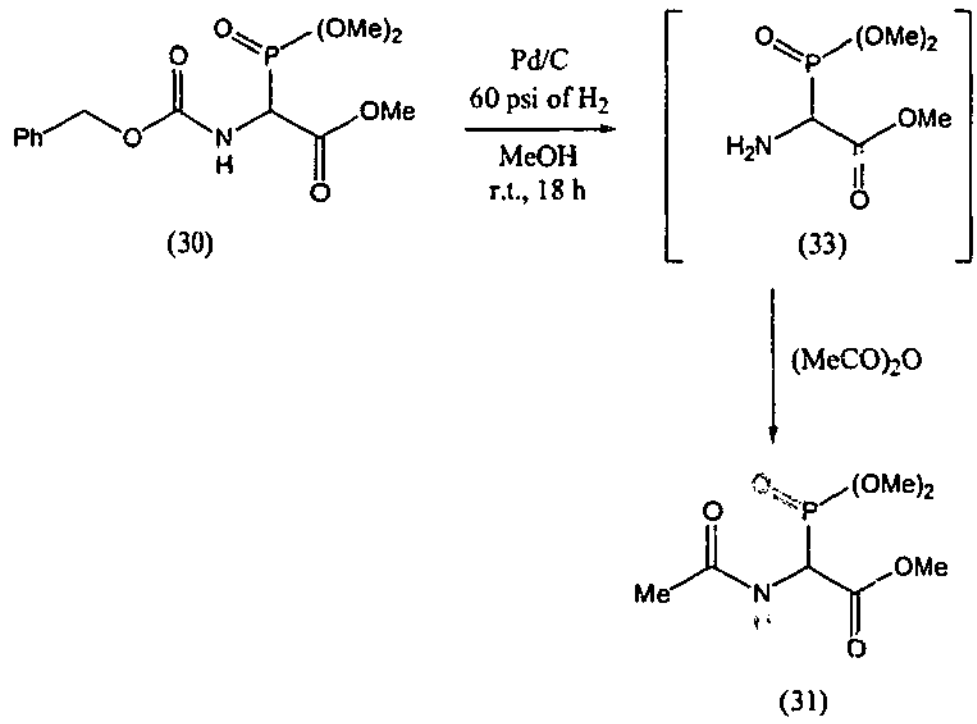

(29) (32) (30)

**Scheme 2.5**

Methyl *N*-benzyloxycarbonyl-2-methoxyglycinate (29) was reacted with phosphorus(III) chloride to give the intermediate chloro ester (32) in which the methoxyl group was replaced by a chloro substituent. The newly introduced chloro

substituent was then subjected to nucleophilic attack by trimethyl phosphite to give methyl 2-benzyloxycarbonyl-amino-2-(dimethoxyphosphinyl)acetate (30), isolated in 70% yield. The observed melting point (77-78°C) of this benzyloxycarbonyl-protected compound (30) was close to the literature melting point (80°C).[60]

In the $^{1}H$ n.m.r. spectrum, the H2 signal was seen as a doublet of doublets with a large coupling to the phosphorus (*J* 22 Hz) and additional coupling to the NH proton. The $^{13}C$ n.m.r. spectrum showed similar behaviour displaying the C2 methine as a doublet with large coupling to phosphorus (*J* 148 Hz).



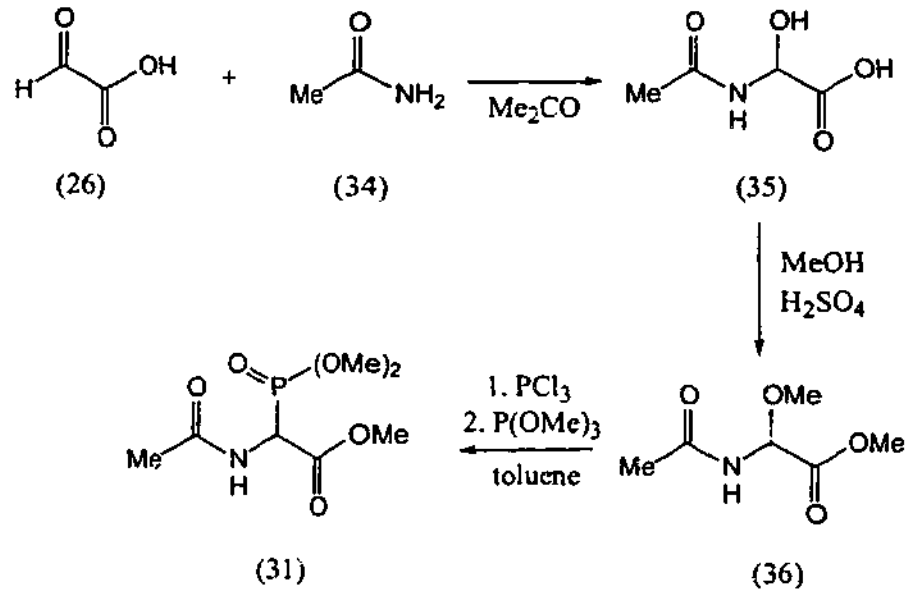

**Scheme 2.6**

Methyl 2-acetylamino-2-(dimethoxyphosphinyl)acetate (31) was prepared by hydrogenation of the benzyloxycarbonyl-protected compound (30) in the presence of acetic anhydride using palladium on charcoal as a catalyst. In this one pot reaction, cleavage of the benzyloxycarbonyl group gave the free amine intermediate (33) which was acylated *in situ* (Scheme 2.6).

Formation of product (31) was supported by the appearance of a new singlet for the acetyl methyl at δ 2.06 and the disappearance of signals arising from the benzyloxycarbonyl-protecting group at δ 5.13 and 7.32-7.40. The proton assigned to H2 was seen as a doublet of doublets in the $^{1}H$ n.m.r. spectrum due to coupling to the adjacent amide proton and also to the neighbouring phosphorus. In the $^{13}C$ n.m.r. spectrum, C2 of (31) was observed as a doublet due to the large coupling (*J* 147.2 Hz) to phosphorus analogous to that observed for benzyloxycarbonyl compound (30). Both COSY and HMQC n.m.r. experiments were done to enable complete assignment of the proton and carbon resonances. The observed melting point (90-92°C) was close to the reported melting point (88-89°C) supporting the formation of the target compound (31).[60]

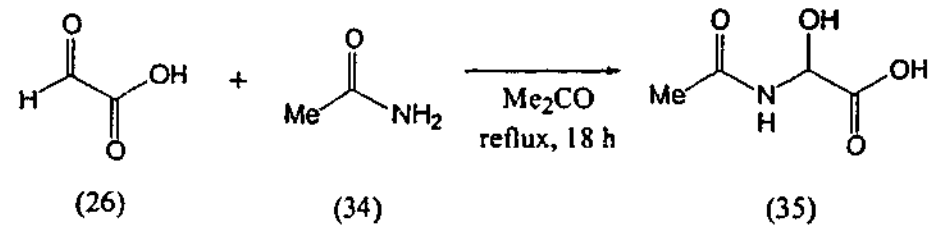
### *2.1.2.2 Attempted synthesis of (31) without the use of the benzyloxycarbonyl (Cbz)-protecting group*

An alternate, shorter route to the desired phosphonate (31) was also attempted (Scheme 2.7). The use of acetamide (34) instead of benzyl carbamate (27) in the first step would directly give the *N*-acetyl-protected phosphonate (31) and eliminate the need to cleave the benzyloxycarbonyl group prior to the alkylation step (refer to Scheme 2.2).



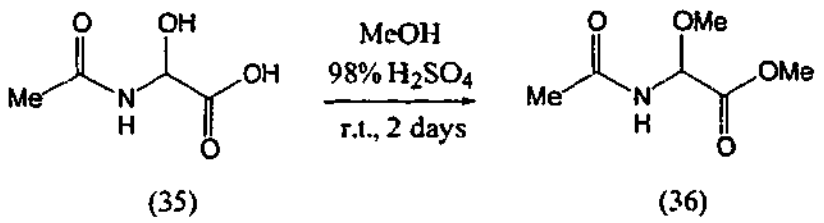

**Scheme 2.7**

*N*-Acetyl-2-hydroxyglycine (35) was prepared by refluxing the commercially available acetamide (34) with glyoxylic acid monohydrate (26) in acetone (Scheme 2.8). The compound (35) was obtained in quantitative yield as reported in literature.[61]




**Scheme 2.8**

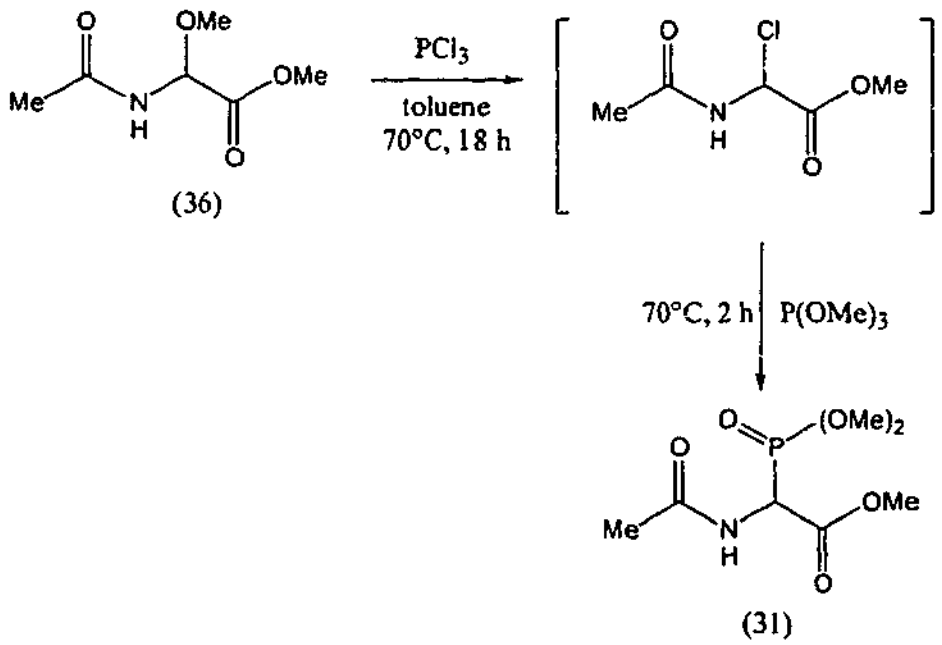
Reaction of *N*-acetyl-2-hydroxyglycine (35) in methanol with a catalytic amount of sulfuric acid gave methyl *N*-acetyl-2-methoxyglycinate (36) in 71% yield (Scheme 2.9). A modified work-up procedure to that reported in the literature[62] enabled an improved yield over the literature (32%) to be obtained. Purification of the product (36) by distillation as stated in literature[62] was not necessary as the $^{1}H$ and $^{13}C$ n.m.r. spectra of the product (36) showed that the product (36) was pure enough for the next step.




(35) (36)

**Scheme 2.9**

The final step in the alternate route to prepare methyl 2-acetylamino-2-(dimethoxyphosphinyl)acetate (31) involved reacting methyl *N*-acetyl-2-methoxyglycinate (36) with phosphorus(III) chloride and trimethyl phosphite (Scheme 2.10). As the compound (31) was highly soluble in water, continuous extraction was required.



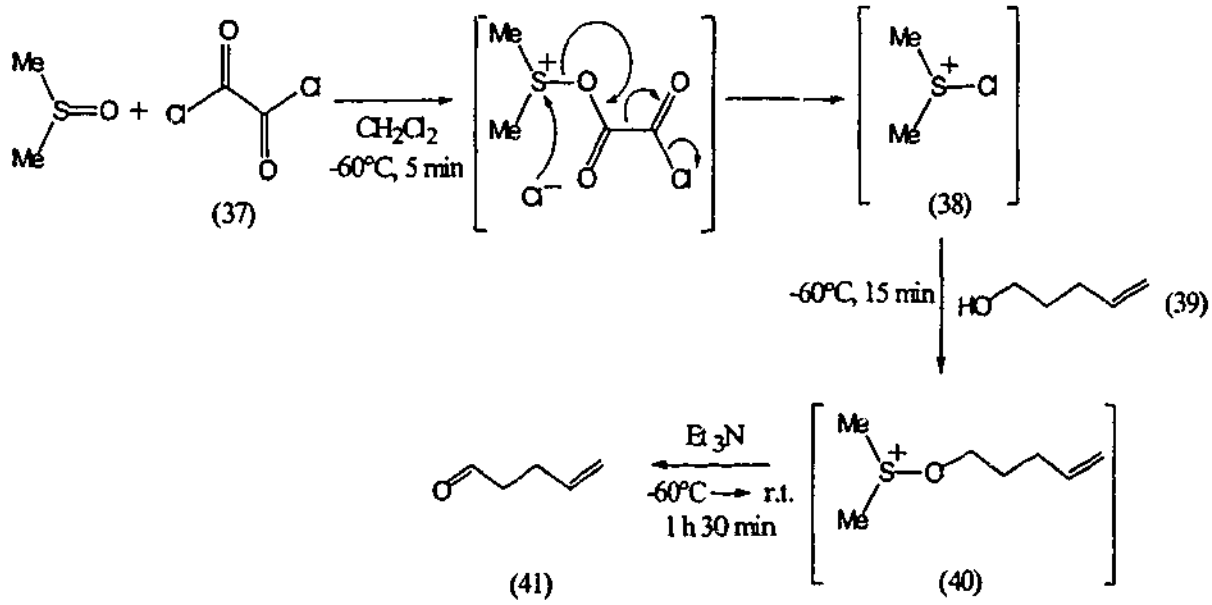

(36) (31)

**Scheme 2.10**

Only a low yield of 30% was obtained *via* this route and the alternative synthesis *via* the benzyloxycarbonyl-protecting compound (30), was more economical. Occasionally, however, hydrogenolysis of the Cbz-protecting group was temperamental. Reasons for this remain unknown.

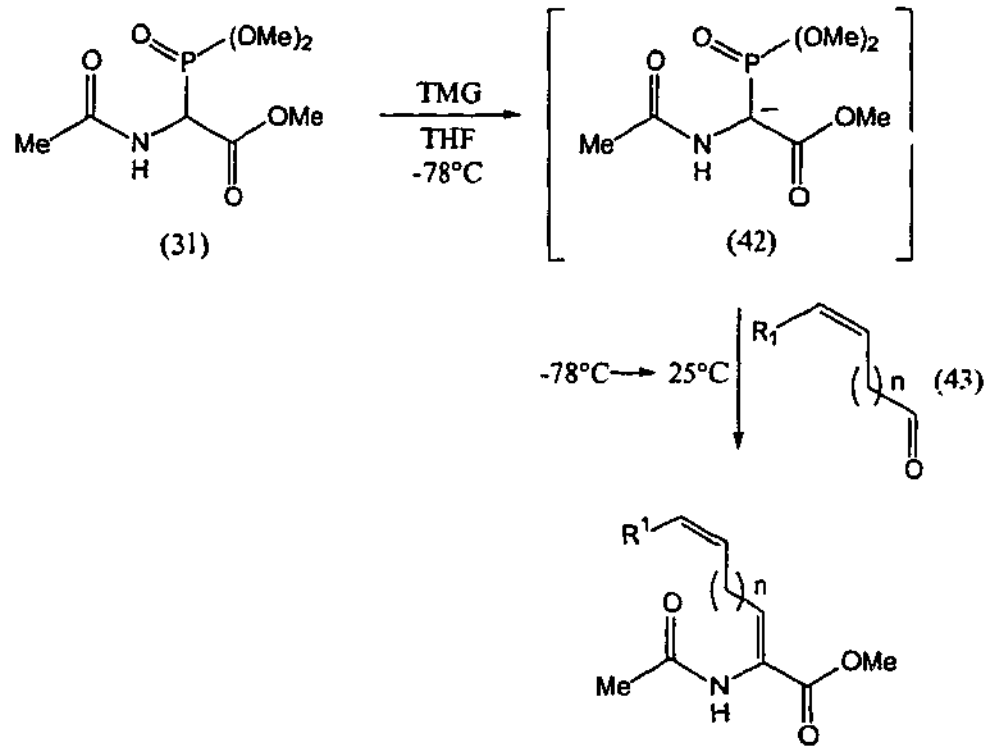
### 2.1.3 Preparation of Aldehydes

Acrolein (47) and crotonaldehyde (45) are commercially available. 4-Pentenal (41) was successfully prepared from 4-pentenol (39) by Swern oxidation[63,64] where dimethyl sulfoxide was firstly activated by oxalyl chloride (37) at approximately -60°C in dichloromethane, generating the intermediate (38) (Scheme 2.11). The hydroxyl group of the alcohol (39) then acts as a nucleophile, displacing the chlorine on sulfur, leading to the intermediate (40). Addition of triethylamine gave the desired product, 4-pentenal (41). The crude product comprised of a 17 : 83 mixture of the starting alcohol (39) and the desired aldehyde (41). The solvent was removed by distillation under atmospheric pressure and the aldehyde (41) was collected as a boiling point fraction at b.p. 103-104°C.[65] This fraction also contained some alcohol (39). Further purification was not attempted as it was believed the alcohol (39) would not adversely affect the Horner-Emmons olefination reaction. Unlike a previously reported method, no isomerisation to crotonaldehyde (45) was observed.[66]




**Scheme 2.11**

### 2.1.4 Horner-Emmons Olefination

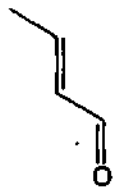
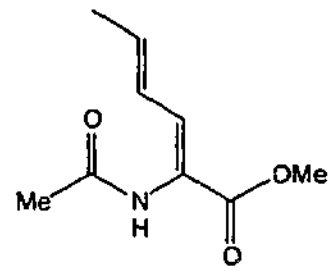
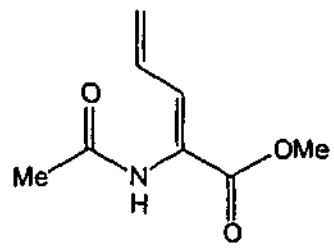
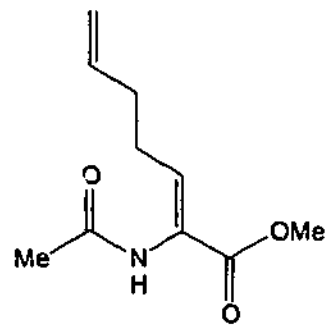



Hydrogenation Precursors (44)

**Scheme 2.12**

Hydrogenation precursors (44) were synthesised by olefination of the phosphonate (31) with 4-pentenal (41) and the commercially available aldehydes, acrolein (47) and crotonaldehyde (45) in the presence of tetramethylguanidine (TMG).[28] The reactions were carried out by firstly adding the base in tetrahydrofuran at -78°C, then warming to 25°C *via* a water bath to give dienamide esters (44) in variable yields. Deprotonation at C2 of the phosphonate (31) was achieved using tetramethylguanidine to generate the nucleophilic intermediate (42) which was then reacted with electrophilic aldehydes (43) to give dienamide esters (44) as illustrated in Scheme 2.12. The results are summarised in Table 2.1 and discussed below.

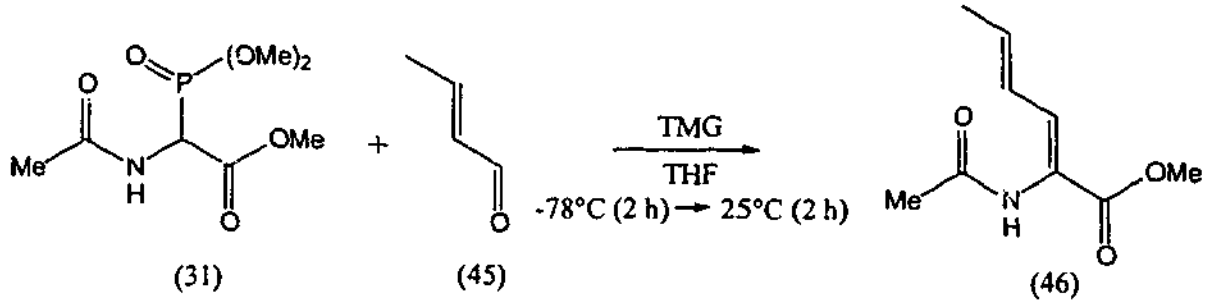
**Table 2.1 Preparation of hydrogenation precursors (44)**

| Aldehyde | Product | % Yield |
|---|---|---|
|  (45) |  (46) | 39[a]<br>55[b] |
|  (47) |  (48) | 87[b] |
|  (41) |  (49) | 38[b] |

[a] -78°C then warm to ambient temperature. [b] -78°C then warm to 25°C in a water bath.

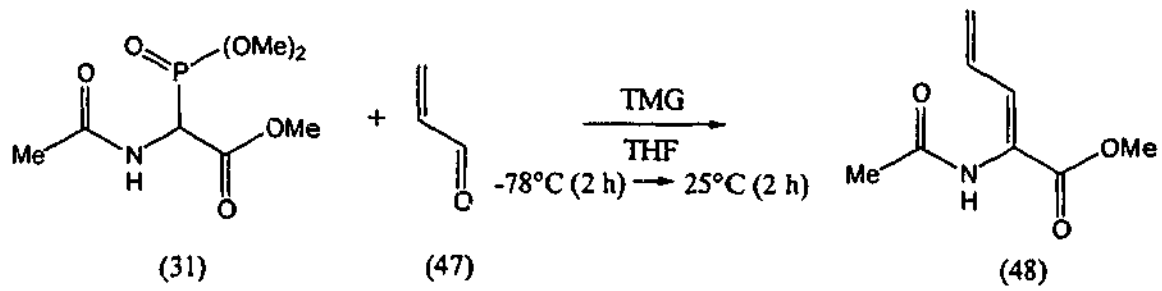
As shown in Scheme 2.13, (2*Z*,4*E*)-methyl 2-acetamidohexa-2,4-dienoate (46) was prepared from methyl 2-acetylamino-2-(dimethoxyphosphinyl)acetate (31) and crotonaldehyde (45). Different experimental conditions were explored to increase the yield of (2*Z*,4*E*)-methyl 2-acetamidohexa-2,4-dienoate (46). A satisfactory yield of 39% was obtained when the reaction mixture was allowed to warm from -78°C to ambient temperature and stirred for a further 2 h. When the -78°C bath was

immediately replaced by a 25°C warm water bath and the mixture was stirred at this higher temperature for a further 2 h, a higher yield (55%) was obtained. Using this modification, the reaction went to completion and the $^1$H n.m.r. spectrum of the crude oil showed no sign of starting materials ((31) and (45)). The observed melting point of 88-89°C was consistent with the literature melting point (89-90°C) for the dienamide (46).[28]




**Scheme 2.13**

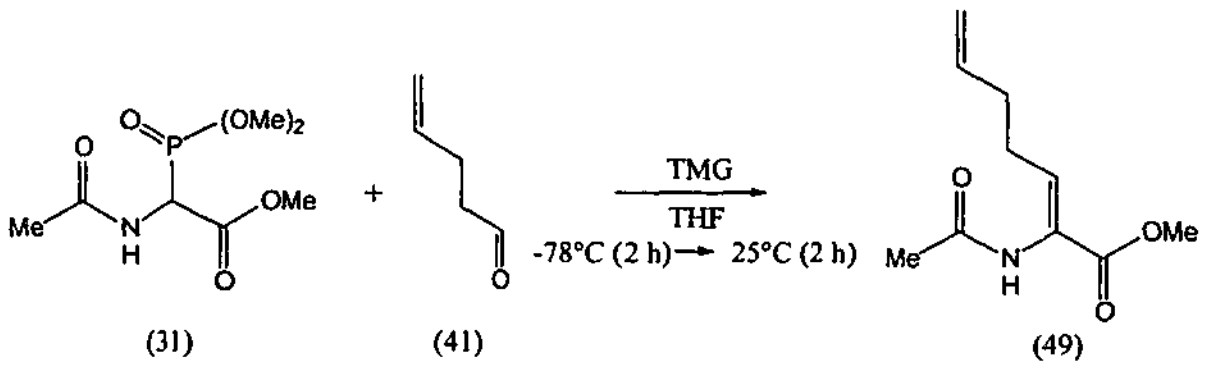
Preparation of (2*Z*)-methyl 2-acetamidopenta-2,4-dienoate (48) was carried out by reacting the phosphonate (31) with acrolein (47) as shown in Scheme 2.14. Hydroquinone was added as a stabilizer to prevent polymerisation of the acrolein (47). The product (48) was isolated in high yield (87%) after purification by chromatography.




**Scheme 2.14**

(2*Z*)-Methyl 2-acetamidohepta-2,6-dienoate (49) was synthesised in 38% yield by reacting 4-pentenal (41) with methyl 2-acetylamino-2-(dimethoxyphosphinyl)acetate

(31) as illustrated in Scheme 2.15. The formation of product (49) was supported by the disappearance of the aldehyde peak at ὸ 9.78 in the $^1$H n.m.r. spectrum and was consistent with the literature spectral data in every other respect.[60] The observed melting point (44-45°C) also matched the reported melting point (44°C).[60]




(31) (41) (49)

**Scheme 2.15**

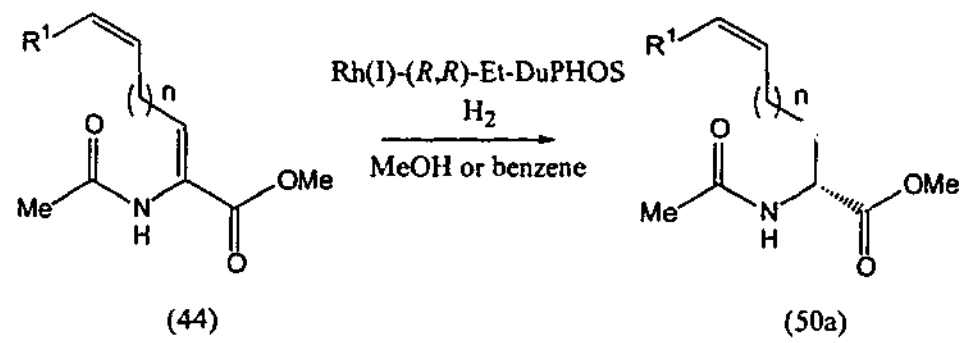
### 2.1.5 Summary

Use of the benzyloxycarbonyl-protecting group in the preparation of the phosphonate esters (31) gave a higher overall yield than a more direct route using the *N*-acetyl-protected analogues. Horner-Emmons olefination of phosphonate esters (31) with the aldehydes (43) gave the hydrogenation precursors (44) in acceptable yields.

## *2.2 Asymmetric Hydrogenations*

### 2.2.1 General Introduction

The DuPHOS ligand, developed by DuPont, when complexed to rhodium has been shown to give excellent enantioselectivity in the hydrogenation of prochiral substrates (44).[34] Recently, Burk *et al.* have demonstrated that high regio- and enantioselectivities can be achieved in the hydrogenation of prochiral dienamide esters (44).[28] In this project, the dienamide esters (44) were hydrogenated in either methanol or benzene with Rh(I)-Et-DuPHOS using short reaction times to give the chiral enamide esters (50a) (Scheme 2.16).




(44) (50a)

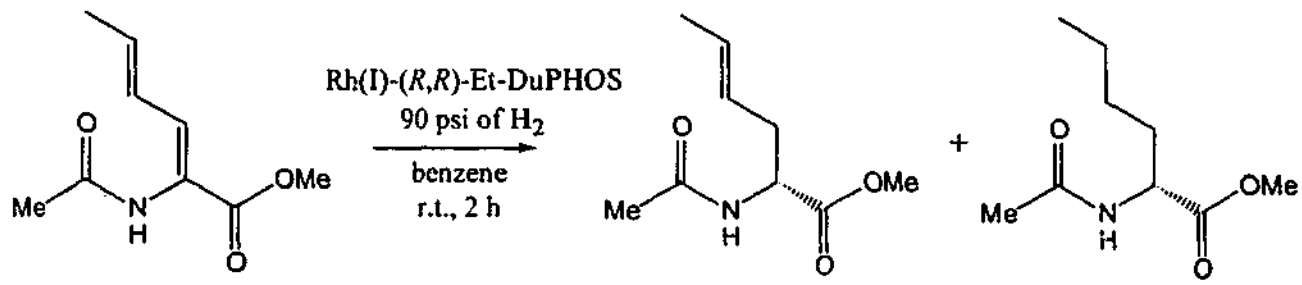
**Scheme 2.16**

The synthesised hydrogenation substrates (44) were predominantly (2*Z*)-isomers. This was confirmed by the chemical shift of the H3 resonance in the $^1$H n.m.r. spectrum. The presence of minute quantities of the (2*E*)-isomer however, would have little effect on enantioselectivity (< 0.1%) as both isomers would reduce to give the same configuration.[34] The substrates (44) were unstable at room temperature and were therefore stored under nitrogen in the freezer or subjected to hydrogenation promptly after isolation.

### 2.2.2 General Reaction Conditions

A catalyst to substrate ratio of 1 : 100, initial pressure (P) of 30-90 psi and 2-18 h reaction time (t) in methanol or benzene at ambient temperature were used. Optical rotations ($[\alpha]_D^{20}$) were measured using a polarimeter and enantiomeric excesses (% ee) were determined by chiral capillary GC or comparison of the optical rotations with literature values. In all cases, the Rh(I)-(*R*,*R*)-Et-DuPHOS and Rh(I)-(*S*,*S*)-Et-DuPHOS catalyst systems were used.

### 2.2.3 Preparation of (2*R*)-(4*E*)-Methyl 2-acetamidohex-4-enoate (51a)




(46) (51a) (52a)

**Scheme 2.17**

**Table 2.2 Rh(I)-catalysed asymmetric hydrogenation of the dienamide (46)**

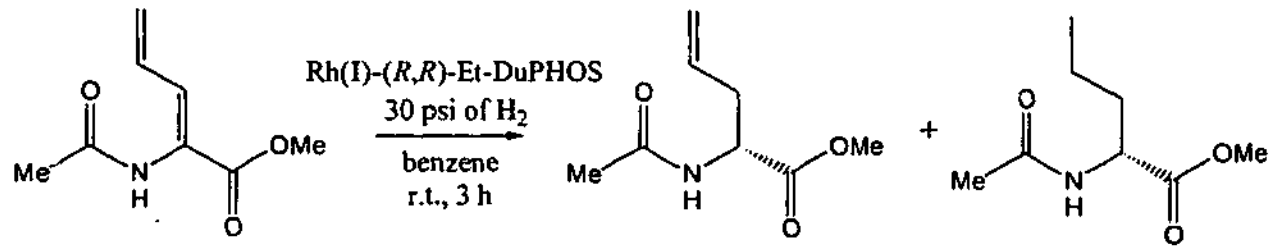
| Entry | Substrate : Catalyst | Solvent | t (h) | % Over-reduction |
|---|---|---|---|---|
| 1 | 50 : 1 | MeOH | 18 | 50 |
| 2 | 100 : 1 | MeOH | 18 | 14 |
| 3 | 100 : 1 | benzene | 2 | 6 |

The hydrogenation of (2*Z*,4*E*)-methyl 2-acetamidohexa-2,4-dienoate (46) was repeated three times with varying scale and reaction length. The first reaction involved 10 mg of substrate (46) for 18 h (Entry 1) The $^1$H n.m.r. spectrum indicated a 50 : 50 ratio of (2*R*)-(4*E*)-methyl 2-acetamidohex-4-enoate (51a) and the over-reduced by-product, (2*R*)-methyl 2-acetamidohexanoate (52a). The reaction was

repeated with 60 mg of substrate (46) with higher substrate to catalyst ratio under the same conditions (Entry 2). A 86 : 14 ratio of the desired product (51a) to the over-reduced by-product (52a) was observed in the $^1$H n.m.r. spectrum. The third reaction was carried out using 420 mg of substrate (46) in benzene, charged at the same pressure (90 psi) as the previous two runs but with a shorter reaction time of 2 h (Entry 3). The $^1$H n.m.r. spectrum of the product (51a) showed complete conversion to (51a) with only 6% of over-reduction. These results show that the amount of over-reduction was affected by the ratio of substrate to catalyst and reaction time.

Purification of product (51a) and by-product (52a) was attempted by preparative chromatography using silica precoated glass plates (2.5 x 7.5 cm); no separation was obtained as the two compounds ((51a) and (52a)) were found to possess same $R_f$ value. Simultaneously, chiral GC analysis using varied temperature programs (refer to Section 5.1) was unsuccessful and no resolution was obtained. Thus, an estimation of ee was made by comparing its optical rotation to a literature value, ignoring the contribution of the over-reduced compound (52a). An optical rotation of -55° was obtained for a sample of (51a) containing 6% of the over-reduced compound (52a) and compared favourably with Burk's rotation of –57.2° for a sample derived from a reaction with an ee of 99.3%.[34] This gave an estimated 95% ee for product (51a).

### 2.2.4 Preparation of (2*R*)-Methyl 2-acetamidopent-4-enoate (53a)




(48) (53a) (54a)

**Scheme 2.18**

**Table 2.3 Rh(I)-catalysed asymmetric hydrogenation of the dienamide (48)**

| Entry | Catalyst[a] | Substrate : Catalyst | Solvent | P (psi) | Time | % Conversion | % Over-reduction | % ee[b] |
|---|---|---|---|---|---|---|---|---|
| 1 | *(R,R)* | 100 : 1 | MeOH | 60 | 2 h | 100 | 85 | - |
| 2 | *(R,R)* | 100 : 1 | MeOH | 30 | 2 h | 82 | - | - |
| 3 | *(R,R)* | 50 : 1 | MeOH | 60 | 30 min | 100 | 21 | - |
| 4 | *(R,R)* | 50 : 1 | MeOH | 30 | 45 min | 100 | 17 | - |
| 5 | *(R,R)* | 100 : 1 | MeOH | 30 | 45 min | 38 | - | - |
| 6 | *(R,R)* | 50 : 1 | MeOH | 30 | 30 min | 65 | - | - |
| 7 | *(R,R)* | 100 : 1 | MeOH | 30 | 3 h | 100 | 5 | 76 |
| 8 | *(S,S)* | 100 : 1 | MeOH | 30 | 3 h | 100 | 5 | 95 |
| 9 | *(R,R)* | 100 : 1 | benzene | 30 | 3 h | 100 | 5 | 95 |
| 10 | *(S,S)* | 100 : 1 | benzene | 30 | 3 h | 100 | 5 | 95 |

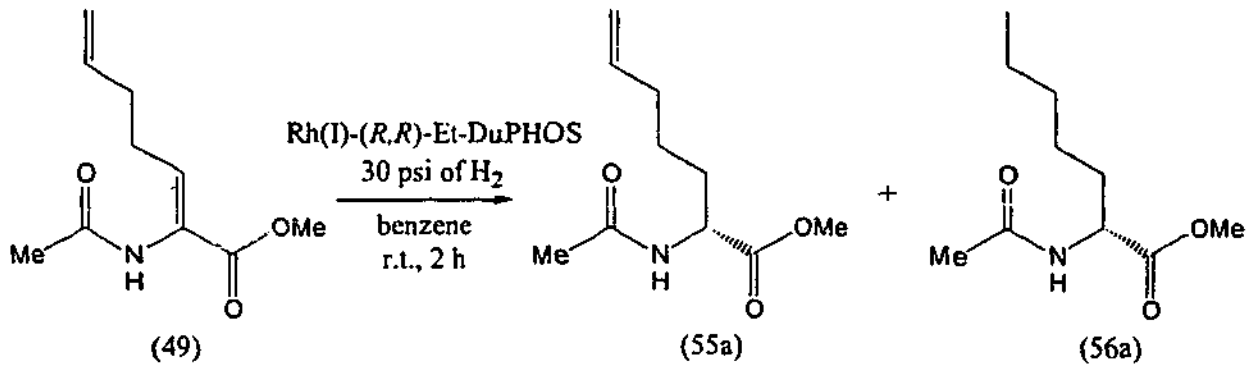
[a] (*R,R*) = Rh(I)-(*R,R*)-Et-DuPHOS and (*S,S*) = Rh(I)-(*S,S*)-Et-DuPHOS. [b] – signifies that the ee was not measured.

(2*R*)-Methyl 2-acetamidopent-4-enoate (53a) was produced in good yield and high purity after reaction optimization, which involved varying reaction time, pressure, substrate : catalyst ratio, catalyst and solvent. The substrate (48) was reacted under two different pressures (30 and 60 psi) with the same reaction duration (2 h) in methanol (Entries 1 and 2). The $^1$H n.m.r. spectra of the two reactions showed that

higher pressure increased the percentage of over-reduced product (54a) (85%) (Entry 1). The percentage of over-reduced product was still high (21%) using 60 psi of hydrogen pressure, even when the reaction time was shortened to 30 min (Entry 3). The substrate : catalyst ratio also had an effect on the percentage of over-reduction. A higher ratio of substrate to catalyst (50 : 1) at 30 psi for 45 min gave 17% of the saturated by-product (54a) (Entry 4) in contrast to the reaction with 100 : 1 ratio of substrate : catalyst which gave no over-reduction but only 38% conversion (Entry 5). A reaction with 50 : 1 ratio of substrate : catalyst for 30 min gave no over-reduction but only 65% conversion (Entry 6). Thus, the optimum hydrogenation conditions were found to be 30 psi of $H_2$, 100 : 1 ratio of substrate : catalyst for 3 h to give complete conversion to product (53a) with only 5% of over-reduction (Entry 7). These conditions gave complete conversion for reactions using Rh(I)-(*S*,*S*)-Et-DuPHOS and for reactions in benzene using both catalysts (Entries 8-10).

Very high ee (95%) was obtained for reactions using Rh(I)-(*S*,*S*)-Et-DuPHOS in both methanol and benzene (Entries 8 and 10). Reaction using Rh(I)-(*R*,*R*)-Et-DuPHOS in benzene also gave excellent enantioselectivity (95%) (Entry 9). Surprisingly, however, a much lower value (76% ee) was obtained from a reaction using Rh(I)-(*R*,*R*)-Et-DuPHOS in methanol (Entry 7). This result was never repeated and all future reactions were carried out in benzene. The enantiomeric excess (95% ee) was assessed using a chiral GC column (refer to Section 5.1).

### 2.2.5 Preparation of (2*R*)-Methyl 2-acetamidohept-6-enoate (55a)




(49) (55a) (56a)

**Scheme 2.19**

**Table 2.4 Rh(I)-catalysed asymmetric hydrogenation of the dienamide (49) in benzene**

| Entry | P (psi) | Time | % Conversion | % Over-reduction |
|---|---|---|---|---|
| 1 | 90 | 2 h | 100 | 40 |
| 2 | 30 | 15 min | 75 | - |
| 3 | 30 | 2 h | 100 | 8 |

Hydrogenation of (2*Z*)-methyl 2-acetamidohepta-2,6-dienoate (49) was performed three times with variation in the hydrogen pressure and reaction time. The first trial was carried out at 90 psi for 2 h with the $^1$H n.m.r. spectrum showing a 60 : 40 ratio of product, (2*R*)-methyl 2-acetamidohept-6-enoate (55a), to over-reduced compound, (2*R*)-methyl 2-acetamidoheptanoate (56a) (Entry 1). The reaction was repeated using a decreased pressure (30 psi) and time (15 min) but 25% of starting material (49) remained (Entry 2). In the third trial, substrate (49) was hydrogenated for 2 h at 30 psi. These were the optimal conditions and resulted in 100% conversion and only 8% over-reduction (Entry 3). It is interesting that the above compound (49) was hydrogenated under milder conditions than the previous compound (48) which has a conjugated system (Entry 9, Table 2.3). The enantiomeric excess (98%) was measured using a chiral GC column (refer to Section 5.1).

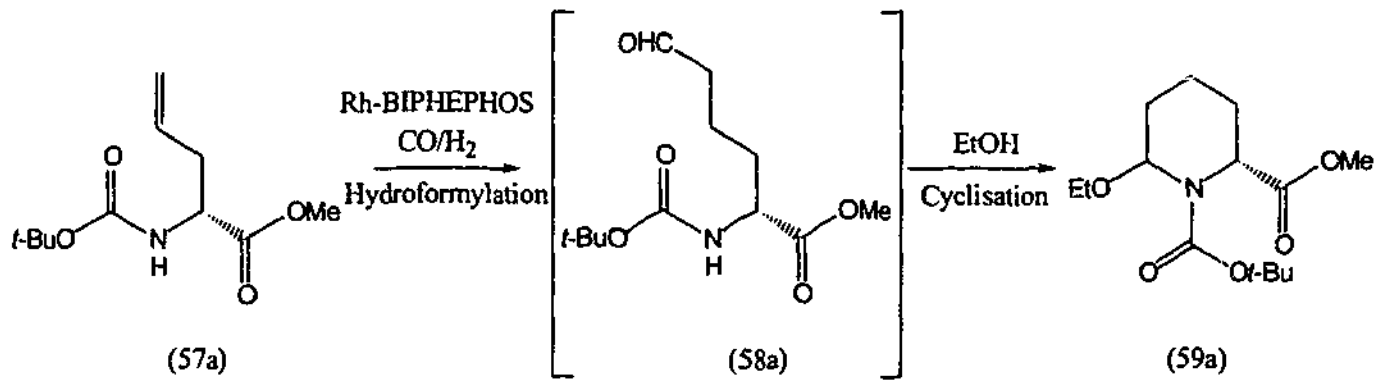
### 2.2.6 Summary

Three dienamides ((46), (48) and (49)) were hydrogenated using Rh(I)-(*S*,*S*)-Et-DuPHOS and Rh(I)-(*R*,*R*)-Et-DuPHOS with high regio- and enantioselectivity (≥ 95%) using short reaction times. For unsubstituted alkenes ((48) and (49)), the percentage of over-reduction was slightly higher than for the substituted alkene (46).

## *2.3 Hydroformylations*

### 2.3.1 General Introduction

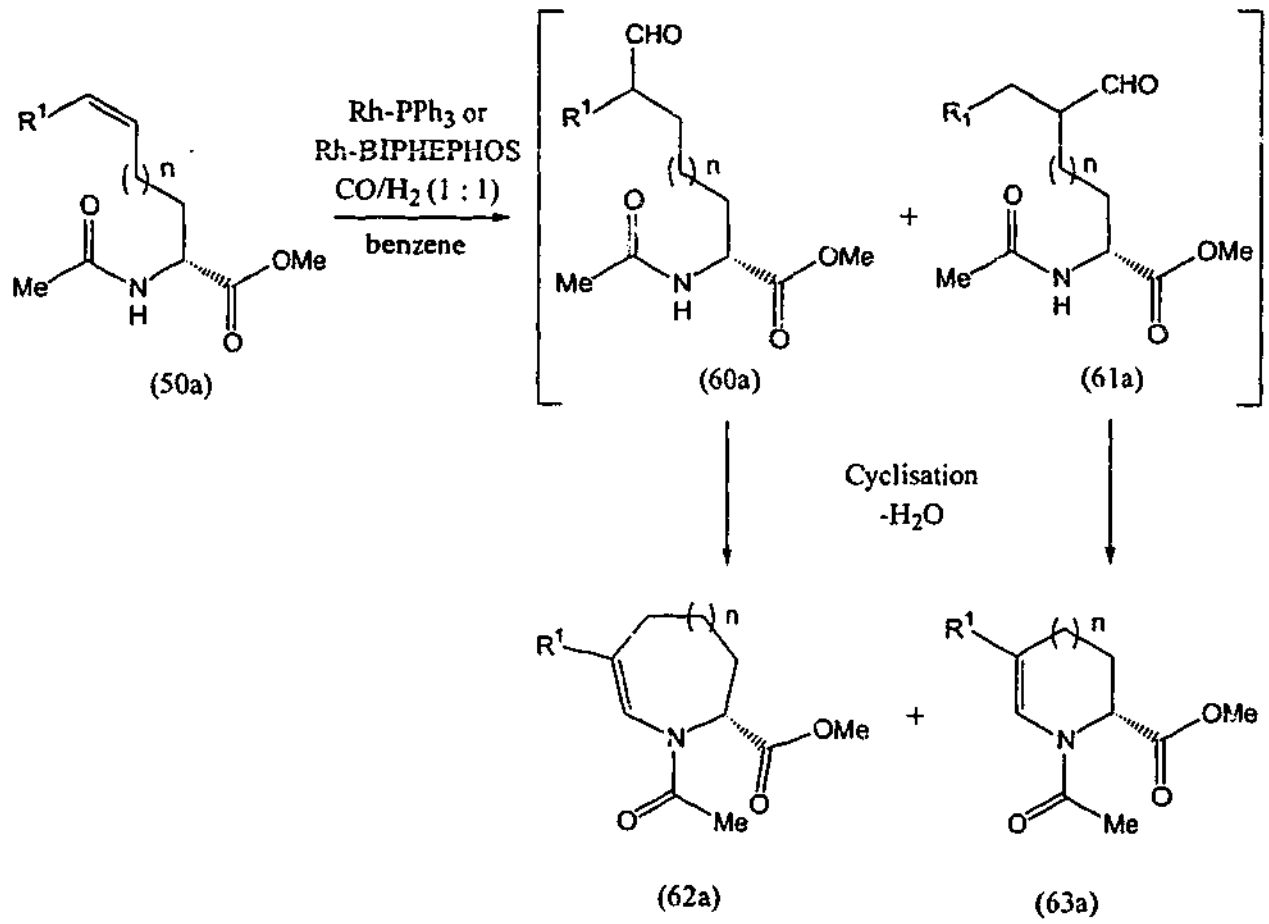
Ojima has demonstrated that regioselective synthesis of cyclic compounds (59a) from enamides (57a) is possible using the Rh-BIPHEPHOS catalytic system.[27] Two steps are involved: hydroformylation to give the intermediate aldehyde (58a) followed by cyclisation as illustrated in Scheme 2.20.




**Scheme 2.20**

In an extension of Ojima's reaction, the chiral enamides ((51a), (53a) and (55a)), synthesised as described in Section 2.2, were hydroformylated with the aim of forming the intermediates ((60a) and (61a)). Once formed, these aldehydes ((60a) and (61a)) could cyclise to give cyclic amides ((62a) and (63a)) as shown in Scheme 2.21. Reactions were carried out in benzene so that the cyclic products were isolated as

enamides ((62a) and (63a)) and not amidals, as was the case for Ojima when an alcohol was used as the reaction solvent.[27]



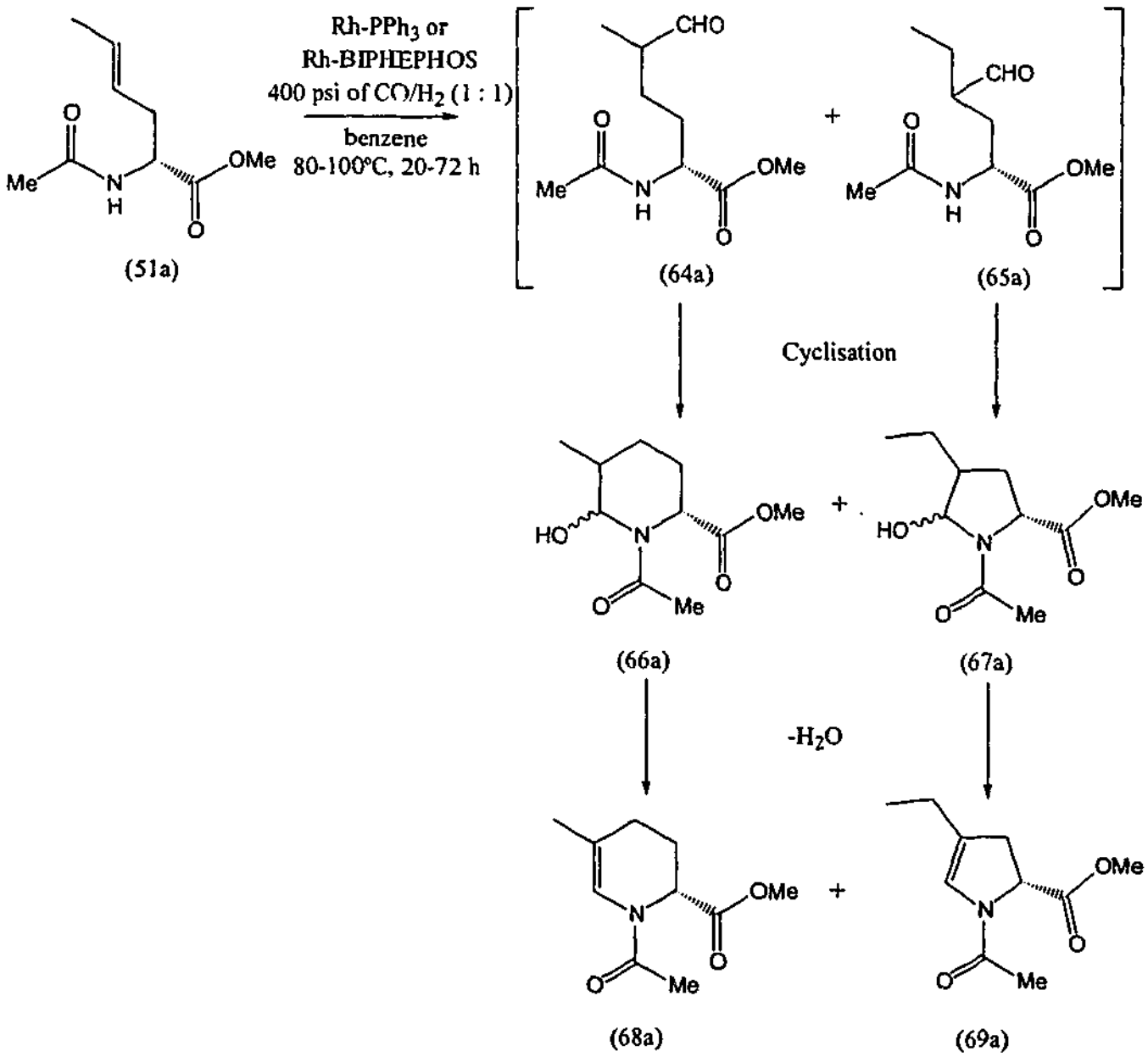

**Scheme 2.21**

### 2.3.2 General Reaction Conditions

The reaction was carried out using substrate, ligands ($PPh_3$ or BIPHEPHOS) and metal catalyst precursor ($[Rh(OAc)_2]_2$) in a ratio of 100 : 2 : 1, with an initial pressure (P) of 80-400 psi (1 : 1 ratio of $CO/H_2$). The temperature (T) was 80-100°C with reaction time (t) being between 20-72 h in benzene. Purification was performed using column or radial chromatography.

### 2.3.3 Rhodium-catalysed Reaction of (2*R*)-(4*E*)-Methyl 2-acetamidohex-4-enoate (51a)

$PPh_3$ and BIPHEPHOS were used as ligands to explore the regioselectivity of the reaction, leading to either 6 or 5-membered ring amides ((68a) and (69a)) (Scheme 2.22). The results are summarised in Table 2.5.




**Scheme 2.22**

**Table 2.5 Rh-catalysed hydroformylation of the enamide (51a) under 400 psi of $CO/H_2$ in benzene**

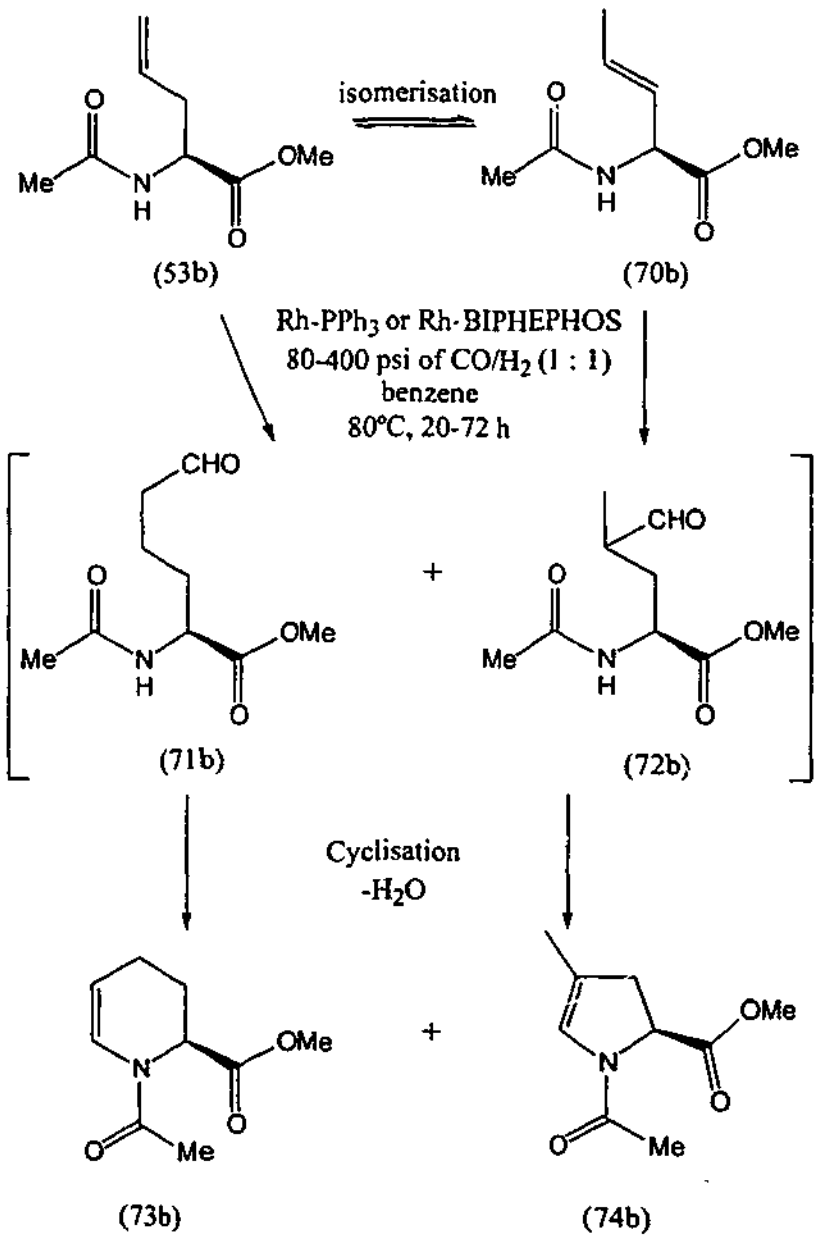
| Entry | Ligand | T (°C) | t (h) | Product ratio (68a) : (69a) | % Yield[a] | % ee[b] (68a) / (69a) |
|---|---|---|---|---|---|---|
| 1 | $PPh_3$ | 80 | 20 | 67 : 33 | 45 | 91 / 98 |
| 2 | BIPHEPHOS | 80 | 20 | 100 : - | 37[c] | - |
| 3 | BIPHEPHOS | 100 | 20 | 86 : 14 | 52[d] | 98 / 98 |
| 4 | BIPHEPHOS | 100 | 72 | 91 : 9 | 88 | 97 / 98 |
| 5 | $PPh_3$ | 80 | 20 | 75 : 25 | 47[e] | - |

[a] Isolated yield of cyclic products ((68a) and (69a)) after chromatography. [b] – signifies that the ee was not measured. [c] Crude product contained the aldehydes (2*R*)-methyl 2-acetamido-5-formylhexanoate (64a) and (2*R*)-methyl 2-acetamido-4-formylhexanoate (65a) in 1 : 1 ratio (*ca.* 40%). [d] Crude product contained only one aldehyde (64a) (*ca.* 30%). [e] Initially isolated as hemiaminals ((66a) and (67a)).

Hydroformylation of enamide (51a) using $PPh_3$ as the ligand gave (2*R*)-methyl *N*-acetyl-5-methyl-5,6-didehydropipecolate (68a) and (2*R*)-methyl-*N*-acetyl-4-ethyl-4,5-didehydroprolinate (69a) in a 67 : 33 ratio (Entry 1). Under the same conditions or at slightly increased temperature, use of the BIPHEPHOS ligand led to incomplete cyclisation and isolation of aldehydes (64a) and (65a) (Entries 2 and 3). Thus, the reaction was repeated using BIPHEPHOS at the same pressure but with increased temperature and reaction time. Complete conversion was achieved with these new conditions and a higher ratio of piperidine (68a) to pyrrolidine (69a) in 91 : 9 ratio was observed (Entry 4). This was consistent with the bulky ligand directing the initial hydroformylation to the less hindered carbon of the alkene. In one reaction using $PPh_3$, the initial product contained the hemiaminals (66a) and (67a). These dehydrated on standing in deuterated chloroform to give the unsaturated heterocyclic compounds (68a) and (69a) respectively (Entry 5).

The 6- and 5-membered ring products (68a) and (69a) were readily separated by chromatography and isolated in reasonable yield. Chiral HPLC showed that the enantiomeric excess (ee) of the reactant enamide (51a) was preserved in both these heterocycles.

### 2.3.4 Rhodium-catalysed Reaction of (2*S*)-Methyl 2-acetamidopent-4-enoate (53b)




**Scheme 2.23**

**Table 2.6 Rh-catalysed hydroformylation of the enamide (53b) at 80°C in benzene**

| Entry | Ligand | P (psi) | t (h) | Product ratio (73b) : (74b) | % Yield[a] | % ee[b] (73b) / (74b) |
|---|---|---|---|---|---|---|
| 1 | $PPh_3$ | 400 | 72 | 50 : 50 | 73 | - / 87 |
| 2 | BIPHEPHOS | 400 | 20 | 63 : 37 | 66 | 88 / - |
| 3 | BIPHEPHOS | 100 | 20 | 71 : 29 | 54[c] | - / 87 |
| 4 | BIPHEPHOS | 80 | 20 | 78 : 22 | -[d] | - |
| 5 | BIPHEPHOS | 80 | 72 | 66 : 34 | 75 | 99 / 99 |

[a] Isolated yield of cyclic products ((73b) and (74b)) after chromatography. [b] – signifies that the ee was not measured. [c] Crude product contained *ca.* 20% of the isomerised alkenamide ((2*S*)-methyl 2-acetamidopenta-3-enoate (70b)). [d] Crude product contained *ca.* 50% of the isomerised alkenamide (70b).

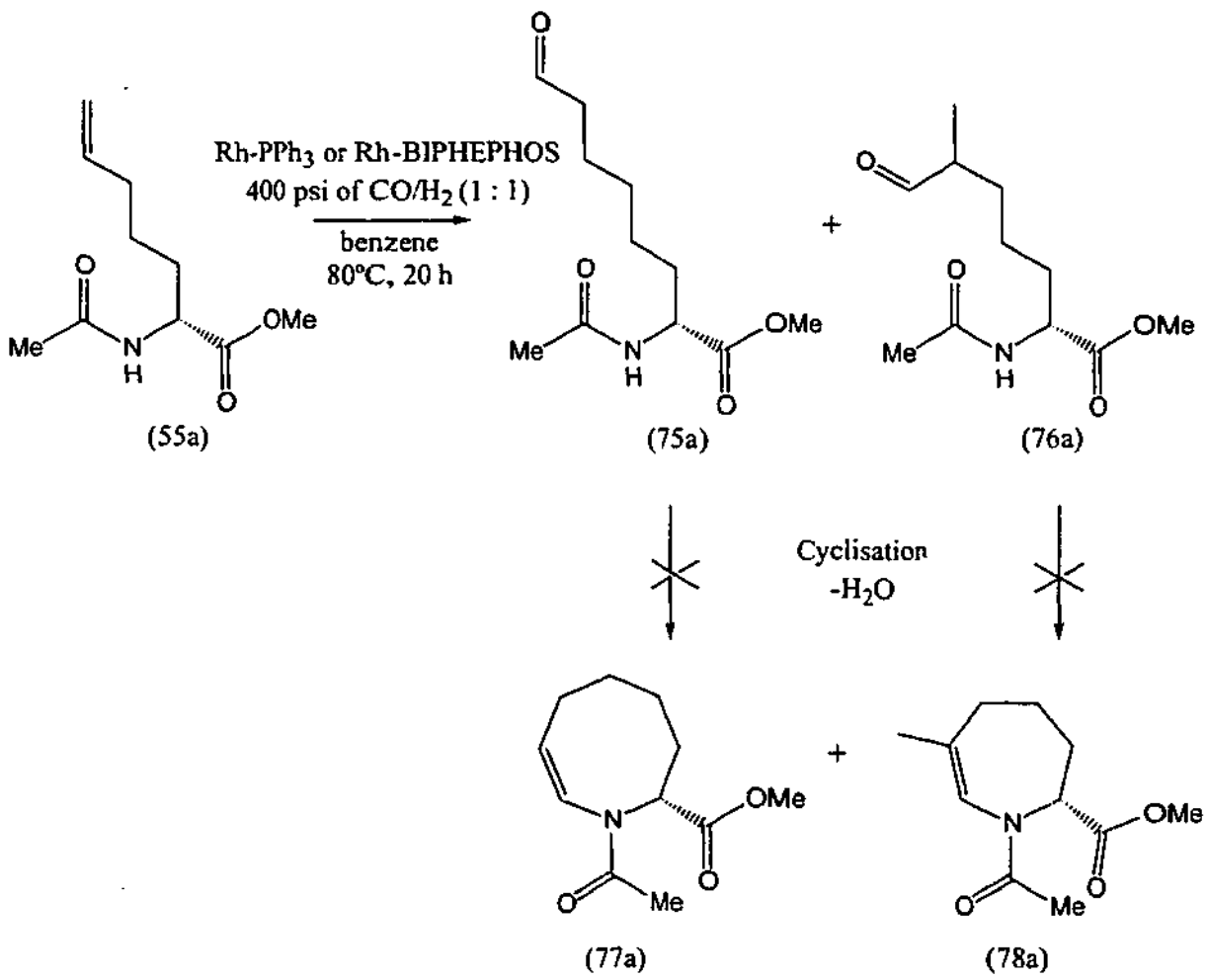
Hydroformylation of enamide (53b), containing a terminal alkene, surprisingly gave a lower than expected ratio of (2*S*)-methyl *N*-acetyl-5,6-didehydropipecolate (73b) : (2*S*)-methyl *N*-acetyl-4-methyl-4,5-didehydroprolinate (74b) in all cases. Reaction of substrate (53b) using the $PPh_3$ ligand gave a 50 : 50 ratio of cyclic amino acid derivatives ((73b) and (74b)) (Entry 1), in contrast to the 67 : 33 ratio obtained with substrate (51b) (Entry 1, Table 2.5). Reaction using BIPHEPHOS gave (73b) and (74b) in a ratio 63 : 37, again lower than the ratio of > 91 : 9 usually obtained for hydroformylation of terminal alkenes with this bulky ligand (Entry 2).[51] A reaction using 100 psi of $CO/H_2$ and the BIPHEPHOS ligand led to formation of the isomerised alkenamide (70b) in *ca.* 20% yield (Entry 3). This isomer (70b) would preferentially be hydroformylated and cyclised to give pyrrolidine (74b), which provides an explanation for the higher than unexpected ratio of the 5-membered ring product (74b). A reaction at even lower pressure (80 psi) gave *ca.* 50% of the isomerised alkenamide (70b) (Entry 4). Extending the reaction time under these

conditions gave the cyclic products ((73b) and (74b)) in 75% yield with high ee (Entry 5).

This result was quite unexpected in that, although alkene isomerisation by related rhodium compounds is well established, terminal alkenes normally hydroformylate faster than internal alkenes. The isomerisations are usually in equilibrium and the faster hydroformylation rate leads to almost exclusive formation of terminal product. This explanation is consistent with the recently reported high yields of straight chain aldehydes from hydroformylation of internal alkenes using a Rh-NAPHOS catalyst.[67] Similarly, a tandem isomerisation-carbonylation sequence gave linear esters from a Pd-catalysed carbonylation of internal alkenes.[12]

One possible explanation for this result is that chelation of rhodium to the amido carbonyl leads to preferential hydroformylation of the internal double bond as is the case for the preceding hydrogenation reaction involving dienamide substrates.[34,68]

### 2.3.5 Rhodium-catalysed Reaction of (2*R*)-Methyl 2-acetamidohept-6-enoate (55a)




**Scheme 2.24**

Hydroformylation of (2*R*)-methyl 2-acetamidohept-6-enoate (55a) using $PPh_3$ as the ligand and 400 psi of $CO/H_2$ (1:1) in benzene at 80°C for 20 h resulted in the formation of aldehydes ((75a) and (76a)) with no indication of cyclic compounds ((77a) and (78a)). The $^1H$ and $^{13}C$ n.m.r. spectra of the crude oil showed the linear and branched aldehydes ((75a) and (76a)) in an approximate ratio of 1 : 1. After purification by radial chromatography, (2*R*)-methyl 2-acetamido-7-formylheptanoate (75a) and (2*R*)-methyl 2-acetamido-6-formylheptanoate (76a), containing a small amount of the other isomer (75a), were isolated in 34% and 29% yields respectively. Cyclisation had not taken place under the reaction conditions used, possibly due to the temperature, pressure and the catalyst system. In addition, the formation of 7- and 8-

membered rings is more difficult than that of 5- and 6-membered rings. The $^{1}H$ n.m.r. spectrum showed that the branched chain aldehyde (76a) was a mixture of diastereoisomers, as two separate chemical shifts were observed for the aldehyde protons at $\delta$ 9.59 and 9.60.

The reaction was repeated with BIPHEPHOS as the ligand using 400 psi of $CO/H_2$ and 80°C in benzene for 20 h. The $^{1}H$ and $^{13}C$ n.m.r. spectra of the crude oil revealed that an approximate ratio of 1 : 1 of linear to branched aldehydes ((75a) and (76a)) had been synthesised as well as some unidentified by-products. The reaction in the presence of BIPHEPHOS did not show the expected regioselectivity in favour of the terminal aldehyde although many references have reported a > 98 : 2 ratio bias in favour of linear aldehydes using this bulky ligand.[27,69-71]

### 2.3.6 Summary

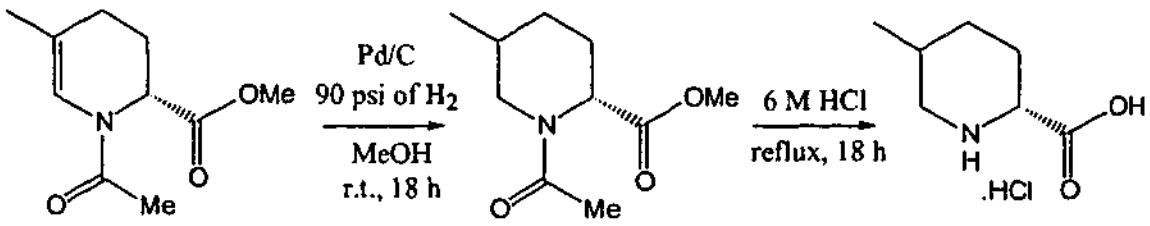
The 6- and 5-membered cyclic compounds ((68a), (69a), (73b) and (74b)) were successfully prepared from the hydroformylation reactions of enamides (51a) and (53b) using Rh-$PPh_3$ and Rh-BIPHEPHOS. The ee was assessed by HPLC and remained > 95%, proving that high pressure of *syn* gas and temperature did not affect the chiral purity. However, 8- and 7-membered cyclic compounds ((77a) and (78a)) were not obtained and instead the intermediate aldehydes ((75a) and (76a)) were isolated.

## 2.4 *Preparation of Cyclic α-Amino Acids*

### 2.4.1 Preparation of (2*R*)-Pipecolinic Hydrochlorides

Confirmation that Rh(I)-(*R*,*R*)-Et-DuPHOS gave the (*R*)-configuration at C2 in the previously synthesised piperidines was obtained by converting the prepared (*R*)-piperidines ((68a) and (73a)) into the (*R*)-pipecolinic hydrochlorides ((80a) and (82a)).

### 2.4.2 Preparation of (2*R*)-5-Methylpipecolinic Hydrochloride (80a)




(68a) (79a) (80a)

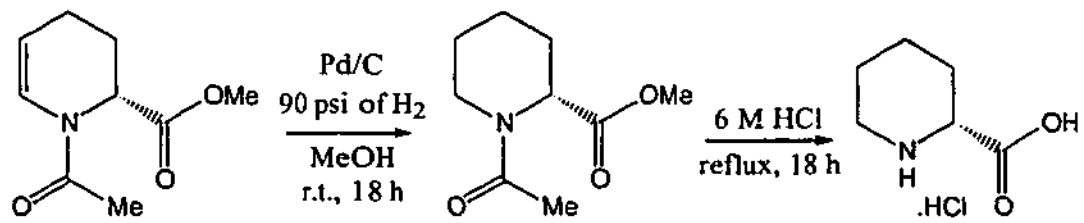
**Scheme 2.25**

(2*R*)-Methyl *N*-acetyl-5-methylpipecolate (79a) was prepared by reducing the C=C olefinic double bond in (2*R*)-methyl *N*-acetyl-5-methyl-5,6-didehydropipecolate (68a) using palladium on charcoal in the presence of $H_2$. In the $^1H$ and $^{13}C$ n.m.r. spectra, a 1 : 1 mixture of diastereomers was observed. The product (79a) was confirmed by the replacement of the two singlets at δ 1.70 (methyl at C5) and 6.40 (H6), by a doublet at δ 0.98 (methyl at C5) and two multiplets at δ 2.87 and 3.49 (H6). Pipecolate (79a) was isolated in high yield (83%).

Pipecolinic hydrochloride (80a) was synthesised by refluxing the methyl ester (79a) in 6 M HCl overnight. The harsh reaction conditions were needed as the amide-protecting group was not easily cleaved and under these conditions, the methyl ester group was converted to the carboxylic acid. Unfortunately, the resulting oil was

insoluble in common deuterated solvents and consequently made full characterisation impossible.

### 2.4.3 Preparation of (2*R*)-Pipecolinic Hydrochloride (82a)




(73a) (81a) (82a)

**Scheme 2.26**

Hydrogenation of (2*R*)-methyl *N*-acetyl-5,6-didehydropipecolate (73a) over Pd/C gave (2*R*)-methyl *N*-acetyl-pipecolate (81a) in good yield (84%). Rotamers were observed in the n.m.r. spectra probably due to restricted rotation around the amide bond.

Hydrolysis of the ester (81a) by heating at reflux in 6 M HCl gave (2*R*)-pipecolinic hydrochloride (82a) in 89% yield as a colourless solid. The product was fully characterised and its optical rotation (+10°) and melting point (260-264°C) were similar to reported literature values ($[\alpha]_D^{20}$ +10.8°, 256-257°C).[72] Thus, the initial enantioselective hydrogenation using the Rh(I)-(*R*,*R*)-Et-DuPHOS was highly selective for (*R*)-configured products at C2 which is in agreement with previous findings.[34,73]

### 2.4.4 Summary

The (*R*)-piperidine (73a) was successfully converted to (*R*)-pipecolinic hydrochloride (82a) in good yield. Its optical rotation was found to be identical to a literature reported value confirming the stereochemistry of the didehydropipecolate (73a) and hence the original enamide (53a) arising from Rh(I)-(*R*,*R*)-Et-DuPHOS catalysed asymmetric hydrogenation of dienamide (48).

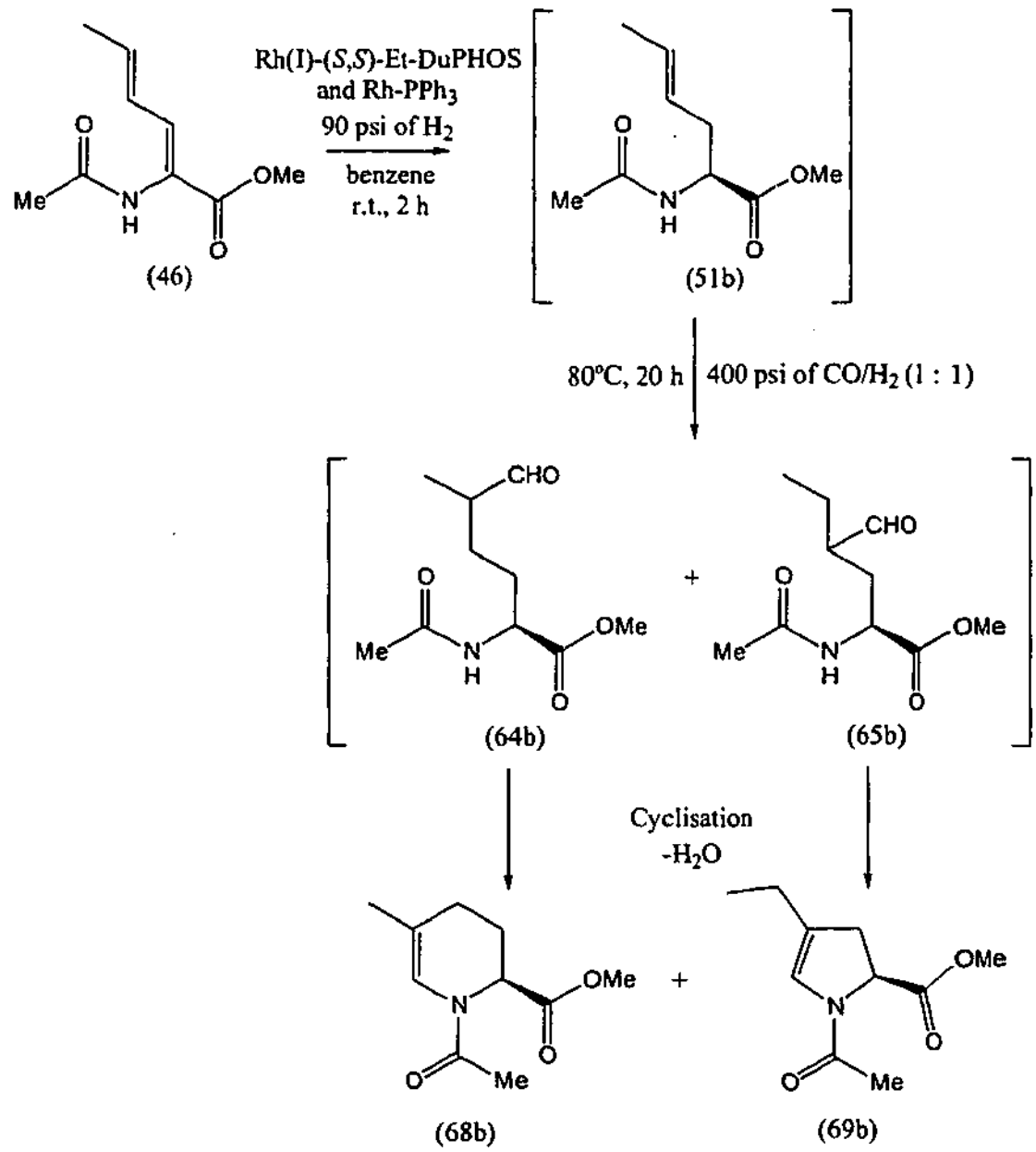
## *2.5 One-Pot Tandem Reactions*

### 2.5.1 Two Catalyst System

#### *2.5.1.1 General introduction*

After satisfactory conditions for the asymmetric hydrogenation and hydroformylation reactions leading to the synthesis of chiral cyclic α-amino acids had been established, a tandem route was explored. This sequential reaction involved two catalysts namely, Rh(I)-Et-DuPHOS and Rh-$PPh_3$ or Rh-BIPHEPHOS, in the one pot. Initially, the reaction vessel containing the prochiral dienamdes (44) was charged with hydrogen for the asymmetric hydrogenation step. After reaction was complete, the gas was vented and the vessel was filled with *syn* gas for the hydroformylation step to yield cyclic products ((62a) and (63a)). This reaction sequence therefore avoided the isolation and purification of the intermediate chiral enamides (50a).

### 2.5.1.2 Rhodium-catalysed tandem reaction of (2Z,4E)-methyl 2-acetamidohexa-2,4-dienoate (46)

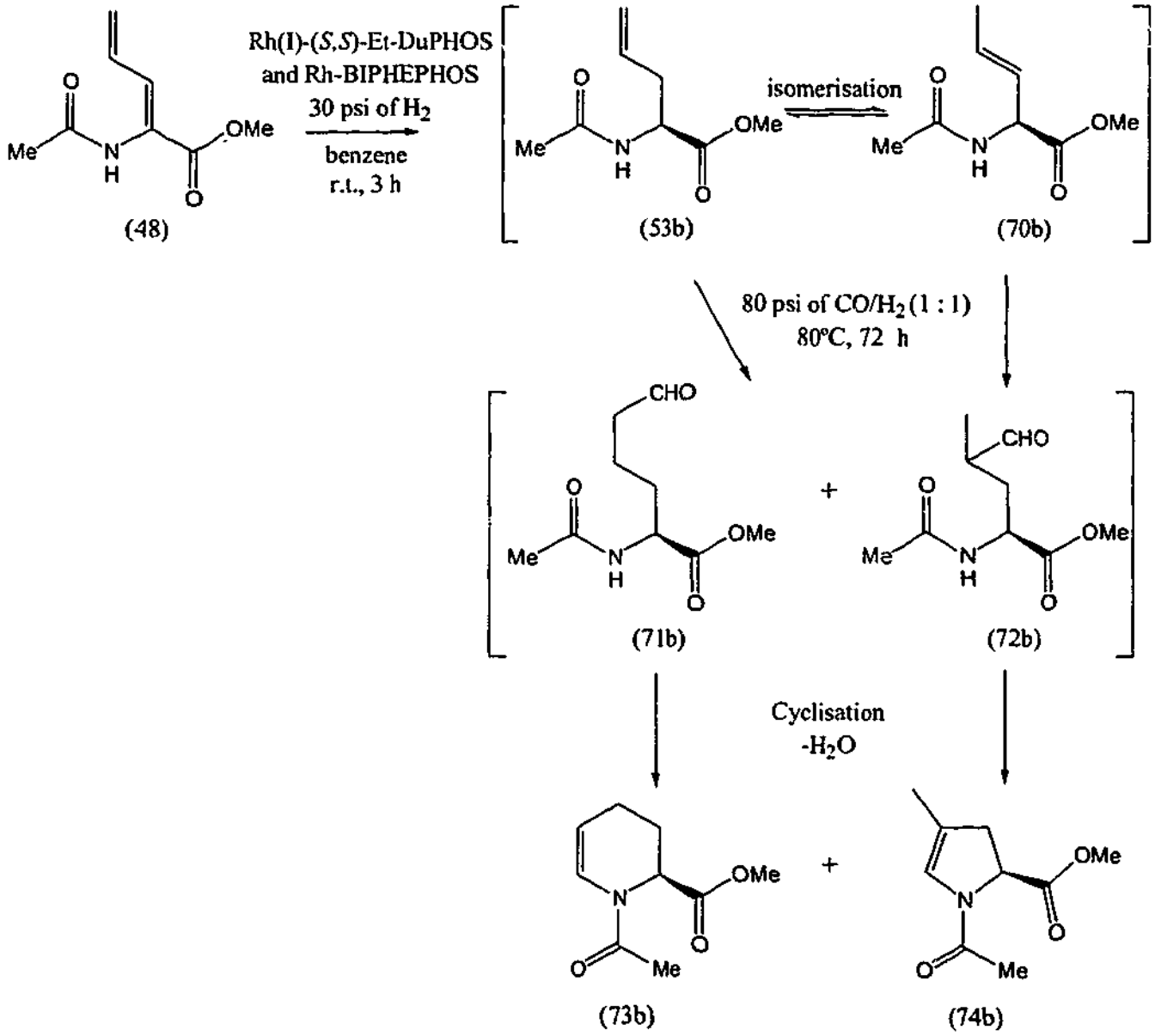



**Scheme 2.27**

The synthesis of cyclic amino acids was carried out in a 100 ml Parr autoclave containing both the Rh(I)-(*S*,*S*)-Et-DuPHOS and Rh-$PPh_3$ catalysts. The autoclave was charged with 90 psi of $H_2$ at room temperature. Under these conditions, Rh(I)-Et-DuPHOS catalyses the asymmetric hydrogenation of the prochiral dienamide (46) to the chiral enamide (51b). This intermediate (51b) was not isolated or purified and after 2 h, the gas was vented and replaced with a 1 : 1 molar $CO/H_2$ gas mixture. The temperature of the reaction was then raised to 80°C for a further 20 h. Under these

conditions, Rh-$PPh_3$ was activated to hydroformylate the remaining double bond to give aldehydes ((64b) and (65b)). *In situ* cyclisation then resulted to give cyclic products ((68b) and (69b)). It is interesting to note there is no significant competition by the Rh-$PPh_3$ in the hydrogenation step catalysed by Rh(I)-Et-DuPHOS since excellent enantioselectivity (> 95%) is maintained. In addition, the presence of Rh(I)-Et-DuPHOS during the hydroformylation step did not promote the hydrogenation of the second double bond, as the percentage of over-reduction was less than 7%. The ratio of the 6- and 5-membered cyclic amino acids ((68b) and (69b)) was 56 : 44, which is similar to that found previously when $PPh_3$ was used as the sole ligand (Entry 1, Table 2.5). Purification and characterisation were carried out as before and gave the piperidine (68b) in 51% yield and 95% ee and the pyrrolidine (69b) in 30% yield and 99% ee.

### 2.5.1.3 *Rhodium-catalysed tandem reaction of (2Z)-methyl 2-acetamidopenta-2,4-dienoate (48)*

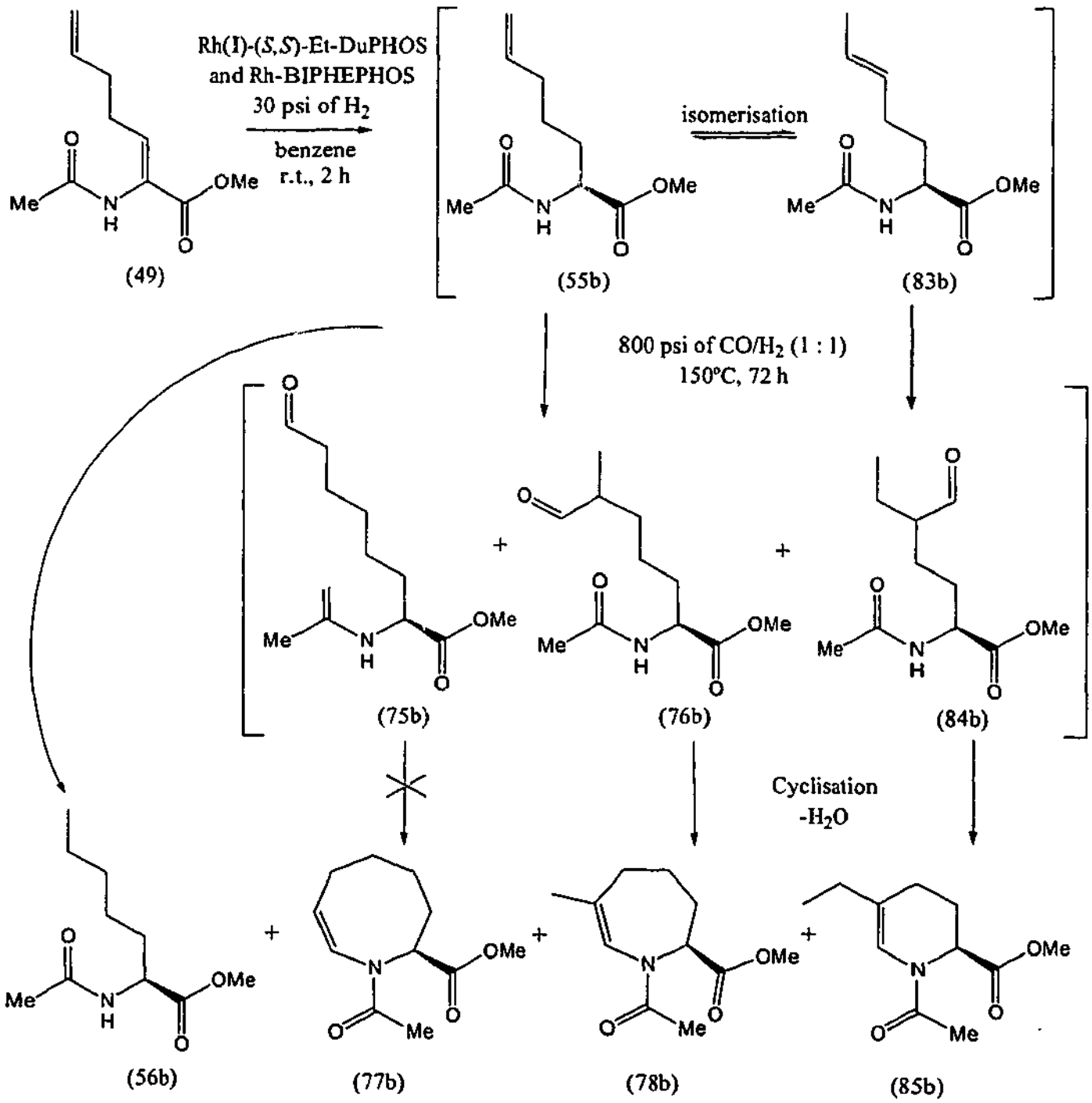



**Scheme 2.28**

Reaction of the terminal alkene (48) was performed in a vessel containing both the Rh(I)-(*S*,*S*)-Et-DuPHOS and Rh-BIPHEPHOS. The procedure was similar to the previous reaction, except lower hydrogen and *syn* gas pressures were used (refer to Section 2.5.1.2). After work-up, the crude $^1$H n.m.r. spectrum showed the presence of 6- and 5-membered compounds ((73b) and (74b)) in a 67 : 33 ratio. This product bias was created through the use of the bulky BIPHEPHOS ligand and was analogous to result found in Section 2.3.4 (Entry 5, Table 2.6). Purification gave the piperidine in

39% yield with 97% ee and pyrrolidine (74b) in 21% yield with 99% ee. Again some isomerised enamide (70b) was seen in the $^1$H n.m.r. spectrum.

### *2.5.1.4 Rhodium-catalysed tandem reaction of (2Z)-methyl 2-acetamidohepta-2,6-dienoate (49)*




**Scheme 2.29**

A one-pot tandem reaction was carried out on this longer chain alkene (49) using a higher hydrogen pressure and temperature for a longer period of time with a mixture of the Rh(I)-(*S*,*S*)-Et-DuPHOS and Rh-BIPHEPHOS catalysts. Chromatography gave a mixture of two heterocycles ((78b) and (85b)) in *ca.* 1 : 1 ratio and *ca.* 24% yield. No 8-membered ring compound (77b) was detected. Formation of the 6-membered ring compound (85b) arises from hydroformylation of isomerised starting enamide (83b). It appears that unsubstituted alkenes ((48) and (49)) are prone to isomerisation to generate the more stable substituted olefins: No isomerisation was observed for the non-terminal alkene (46). The major product of this reaction, however, was the hydrogenated enamide (56b) (*ca.* 74%). This over-reduction may be due to the high pressure of the *syn* gas and temperature used in this reaction. The reason for using such harsh conditions was to promote cyclisation, as the milder conditions used previously (400 psi of *syn* gas and 80°C in Section 2.3.5) did not give cyclic products and only intermediate aldehydes ((75a) and (76a)) were isolated.

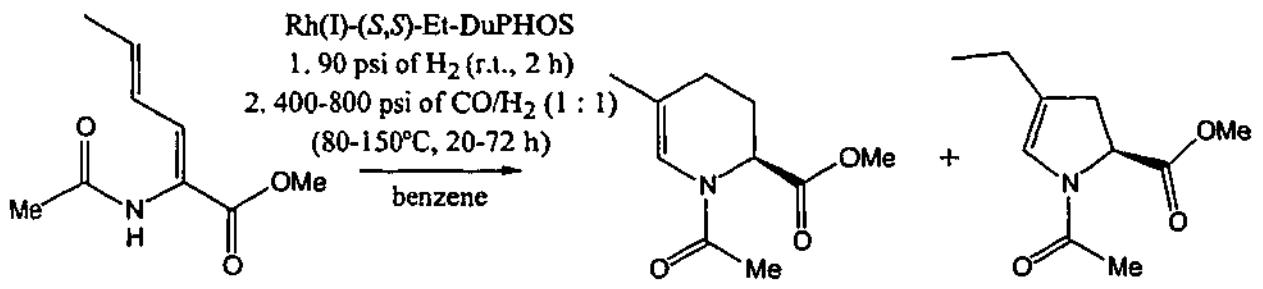
### *2.5.1.5 Summary*

The sequential one-pot synthesis of cyclic α-amino acids using the two catalysts, Rh(I)-Et-DuPHOS and Rh-$PPh_3$ or Rh-BIPHEPHOS, was a success. It gave cyclic α-amino acids derivatives in > 95% ee showing that the presence of the hydroformylation catalysts in the reaction mixture did not affect the enantioselectivity of the initial Rh(I)-Et-DuPHOS catalysed hydrogenation.

### 2.5.2 One Catalyst System

Investigation of tandem catalysis was extended to the use of only one catalyst, Rh(I)-Et-DuPHOS, for hydroformylation as well as hydrogenation. The use of Rh(I)-Et-DuPHOS as a hydroformylation catalyst had not been previously reported. The reaction sequence is identical to that carried out using the two catalyst system, i.e. first hydrogenation, then hydroformylation.

#### *2.5.2.1 Rhodium(I)-catalysed tandem reactions of (2Z,4E)-methyl 2-acetamidohexa-2,4-dienoate (46) using a single catalyst*




(46) (68b) (69b)

**Scheme 2.30** (Refer to Scheme 2.27 for intermediates)

**Table 2.7 Rh(I)-catalysed hydroformylation of the dienamide (46) in benzene**

| Entry | P (psi) | T (°C) | T (h) | Product ratio (68b) : (69b) | % Yield[a] | % ee[b] (68b) / (69b) |
|---|---|---|---|---|---|---|
| 1 | 400 | 80 | 20 | 83 : 17 | 42[c] | 99 / 99 |
| 2 | 800 | 150 | 72 | 100 : 0 | 58 | 96 / - |

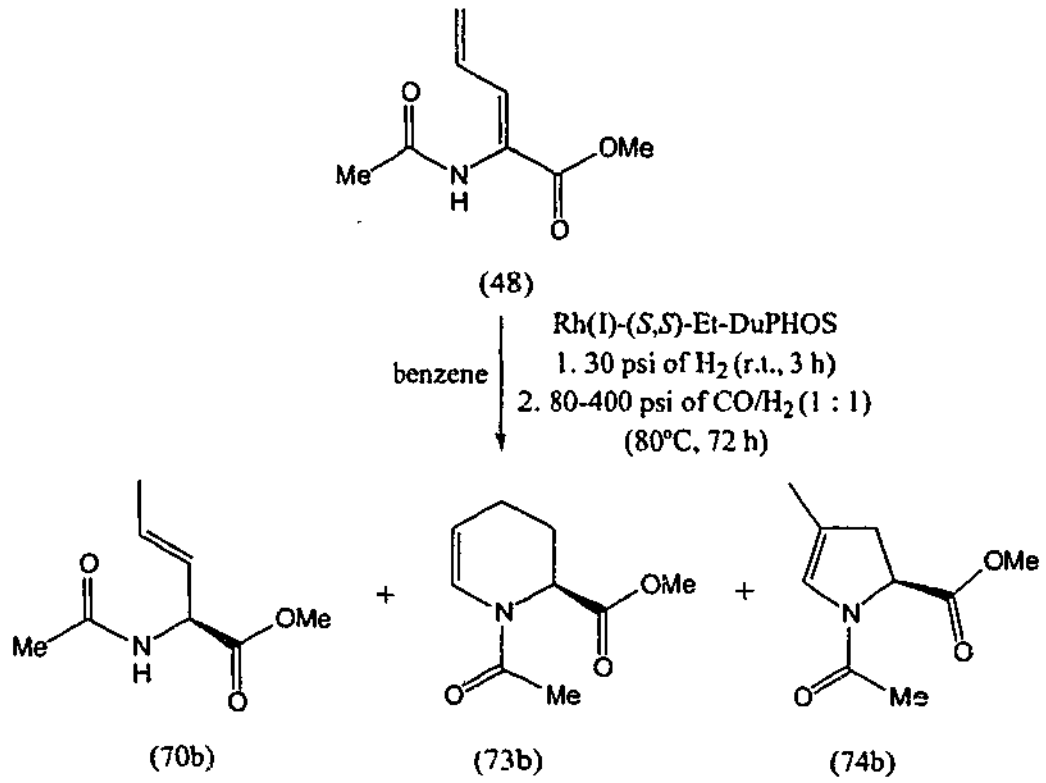
[a] Isolated yield of cyclic products ((68b) and (69b)) after chromatography. [b] – signifies that the ee was not measure. [c] Crude product contained aldehydes (64b) and (65b) (*ca.* 15%)

Reactions of the methyl-substituted dienamide substrate (46) using Rh(I)-Et-DuPHOS, under hydrogenation and hydroformylation conditions established earlier, gave the expected cyclic products (68b) and (69b) in reasonable yield and with

excellent enantiomeric excess (> 99%) (Entry 1). As substantial amounts of aldehydes ((64b) and (65b)) were also isolated, more forcing conditions (800 psi of *syn* gas, 150°C for 72 h) were applied to affect complete cyclisation. The piperidine (68b) was isolated as the sole product in 58% yield and 96% ee (Entry 2). Comparison of the results reported in Entry 4, Table 2.5 and Entry 2, Table 2.7 suggested that Rh(I)-Et-DuPHOS appears to be a slightly less efficient catalyst than Rh-BIPHEPHOS, as it needed harsher conditions to give complete conversion of the dienamide (46) to the cyclic products ((68b) and (69b)). Comparison of Entry 1, Table 2.5 and Entry 1, Table 2.7 showed that Rh(I)-Et-DuPHOS is also a less efficient catalyst than the Rh-$PPh_3$ system.

In terms of regioselectivity, each catalyst selected for the 6-membered ring compound (68a) in order of decreasing selectivity were: BIPHEPHOS (100%); DuPHOS (83%) and $PPh_3$ (67%). This was determined by comparing Entries 1 and 2, Table 2.5 and Entry 1, Table 2.7. All of these reactions were carried out under the same conditions (400 psi of $CO/H_2$, 80°C for 20 h).

### 2.5.2.2 *Rhodium(I)-catalysed tandem reactions of (2Z)-methyl 2-acetamidopenta-2,4-dienoate (48) using a single catalyst*




**Scheme 2.31** (Refer to Scheme 2.28 for intermediates)

**Table 2.8 Rh(I)-catalysed hydroformylation of the dienamide (48)**

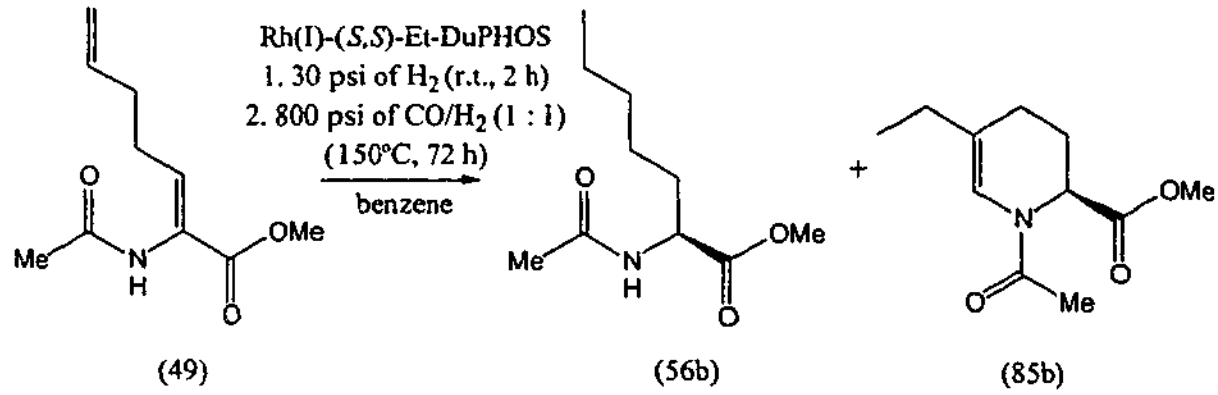
| Entry | P (psi) | T (°C) | T (h) | Product ratio (73b) : (74b) | % Yield[a] | % ee[b] (73b) / (74b) |
|---|---|---|---|---|---|---|
| 1 | 80 | 80 | 72 | 74 : 26 | -[c] | - |
| 2 | 400 | 80 | 72 | 54 : 46 | 91 | 95 / 99 |

[a] Isolated yield of cyclic products ((73b) and (74b)) after chromatography. [b] – siginifies that the ee was not measured. [c] Crude product contained isomerised alkenamide (70b) (*ca.* 40%).

Reaction of dienamide substrate (48) in the presence of Rh(I)-Et-DuPHOS alone, initially under an atmosphere of $H_2$ and then under $CO/H_2$ (80 psi) at 80°C, gave cyclic products ((73b) and (74b)) containing significant amounts of the isomerised alkene (70b) (Entry 1). In comparison to Entry 5, Table 2.6 where full conversion to cyclic products ((73b) and (74b)) was observed, this reaction showed a slower rate of hydroformylation. Although the ratio of piperidine (73b) and pyrrolidine (74b) (74 :

26) of this reaction was higher than the Rh-BIPHEPHOS system (66 : 34), the reaction contained *ca.* 40% of isomerised alkene (70b) which would give pyrrolidine (74b) as the product. A reaction using higher pressure (400 psi of $CO/H_2$) gave complete conversion to the piperidine (73b) and pyrrolidine (74b) in 91% isolated yield with high enantioselectivity (≥ 95%) (Entry 2). The ratio of piperidine (73b) to pyrrolidine (74b) was 54 : 46 which was slightly better than the Rh-$PPh_3$ system (50 : 50) under the same reaction conditions (compared to Entry 1, Table 2.6).

### *2.5.2.3 Rhodium(I)-catalysed tandem reaction of (2Z)-methyl 2-acetamidohepta-2,6-dienoate (49) using a single catalyst*




(49) (56b) (85b)

**Scheme 2.32** (Refer to Scheme 2.29 for intermediates)

A one-pot reaction using only the Rh(I)-(*S*,*S*)-Et-DuPHOS catalyst under the same conditions as the two catalyst system again gave predominantly the saturated compound (56b) (*ca.* 67%). Chromatography led to the isolation of the 6-membered ring compound (85b) in 12% yield. The difficulty associated with the formation of 8- and 7-membered rings ((77b) and (78b)) accounts for the low yields of heterocycles. The formation of a larger amount of hydrogenated rather than hydroformylated material is difficult to explain. Possible explanations for over-reduction include the

use of overly harsh reaction conditions and/or some catalyst decomposition to colloidal rhodium, an efficient hydrogenation catalyst.[34]

#### *2.5.2.4 Summary*

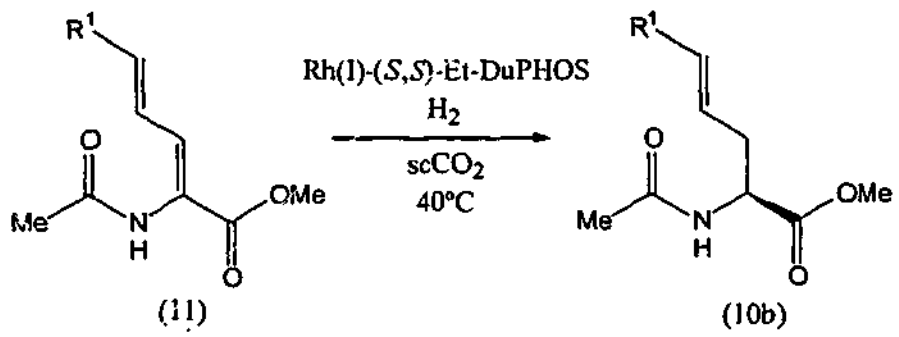
Rh(I)-Et-DuPHOS has proven to be not only a hydrogenation catalyst but also a hydroformylation catalyst. It appears that the Rh(I)-DuPHOS system is a slightly less efficient catalyst for hydroformylation than both Rh-$PPh_3$ and Rh-BIPHEPHOS. The regioselectivity of DuPHOS ligand in the hydroformylation step was between that of the $PPh_3$ and BIPHEPHOS ligands. The isolated yields of cyclic products were reasonable and their enantiomeric excess remained high.

## *2.6 Synthesis Of Cyclic α-Amino Acids In Supercritical Carbon Dioxide*

### 2.6.1 Asymmetric Hydrogenations

#### *2.6.1.1 General Introduction*

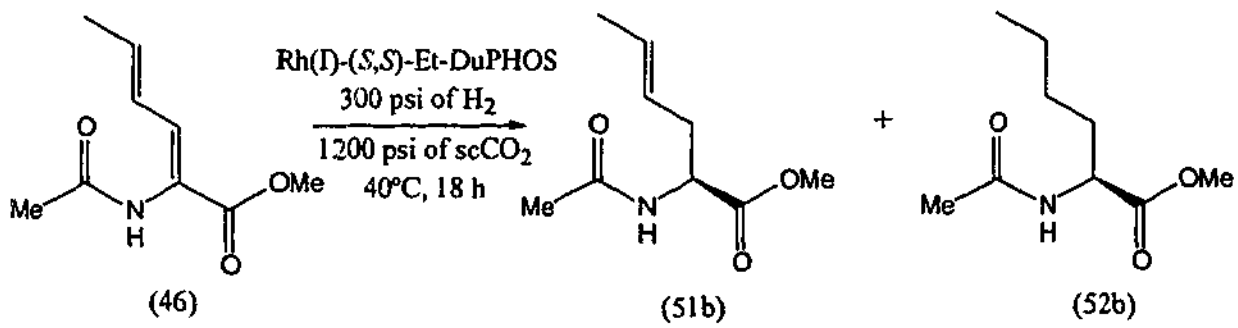
The enantioselective synthesis of cyclic α-amino acids using a tandem hydrogenation, hydroformylation, cyclisation, elimination sequence in which all of the reactions were carried out in a single pot, with a single catalyst were investigated in $scCO_2$. Enantioselective hydrogenation of the prochiral dienamide (11) was firstly carried out to establish appropriate conditions for reactions in $scCO_2$ (Scheme 2.33).




**Scheme 2.33**

Supercritical carbon dioxide has been widely explored as a potential solvent in many areas particularly in catalysis chemistry[74,75] as it eliminates environmental problems associated with toxic organic solvents.[76] It offers many advantages in that it is inexpensive and abundant, it has moderate critical properties (31°C at 1100 psi) and it is possible to control the rates and selectivities of reactions by altering the temperature and pressure of the $scCO_2$. The combination of this medium with catalysis offers many 'green' alternatives to conventional organic transformations.[77] There are many reports of the use of $scCO_2$ in asymmetric hydrogenation leading to enantioselective synthesis of α-amino acids,[15] carboxylic acids[78,79] and imines.[80]

### *2.6.1.2 Preparation of (2S)-(4E)-methyl 2-acetamidohex-4-enoate (51b)*




**Scheme 2.34**

**Table 2.9 Rh(I)-catalysed asymmetric hydrogenation of the dienamide ester (46)**

| Entry | Substrate : Catalyst | Solvent | P (psi) | T (°C) | t (h) | % Conversion | % Over-reduction |
|---|---|---|---|---|---|---|---|
| 1 | 50 : 1 | $scCO_2$ | 300 | 40 | 18 | 80 | - |
| 2[a] | 50 : 1 | MeOH | 90 | r.t. | 18 | 100 | 50 |
| 3[a] | 100 : 1 | MeOH | 90 | r.t. | 18 | 100 | 14 |
| 4[a] | 100 : 1 | benzene | 90 | r.t. | 2 | 100 | 6 |

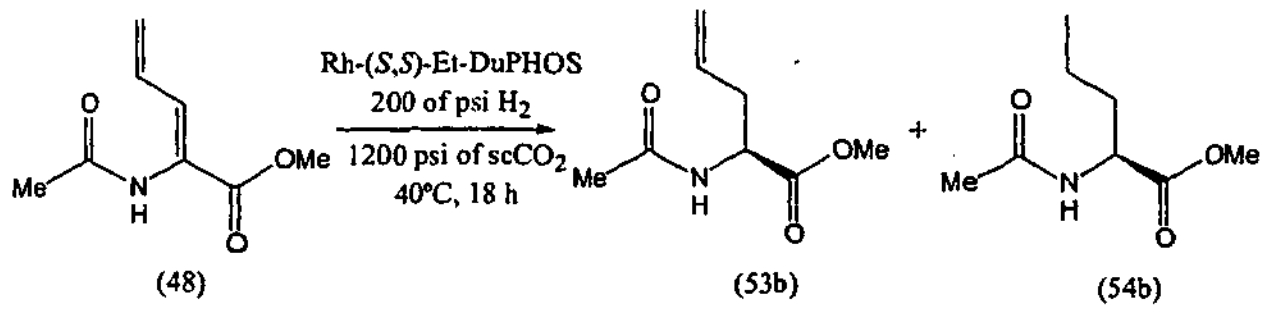
[a] These are repeat reactions from Table 2.2, Section 2.2.3.

The hydrogenation of (2*Z*,4*E*)-methyl 2-acetamidohexa-2,4-dienoate (46) was carried out under 300 psi of $H_2$ with 1200 psi of $CO_2$ at 40°C (Entry 1). After 18 h, the reaction was 80% complete with no sign of over-reduction. Warming and a high pressure of $CO_2$ are necessary to reach the critical point for $CO_2$ to become a supercritical fluid. Surprisingly, a longer reaction time and higher pressure of $H_2$ were needed compared to reactions carried out in methanol or benzene with a 100 : 1 of substrate to catalyst ratio (Entries 3 and 4). By comparison to the time and pressure used for reactions in benzene and methanol (Entries 2-4) there was no sign of over-reduced by-product (52b), although a 50 : 1 of substrate : catalyst ratio was used (Entry 1). Use of this higher catalyst loading in a reaction in methanol led to an increase of over-reduction to 50% (Entry 2). Interestingly, over-reduction of the dienamide substrate (46) did not occur in $scCO_2$; on the otherhand, 30% over-reduction of (48) resulted from reaction at 250 psi of $H_2$ (Entry 3, Table 2.10).

The lipophilic trifluoromethanesulfonate counter ion was essential in these reactions as it increases the solubility of the Rh(I)-DuPHOS cation in the supercritical fluid, allowing the catalysis to proceed.[15] It should be noted that these reactions were carried

out with readily accessible $CO_2$ pressures of 1200 psi, considerably lower than those used for previously reported hydrogenations (2500-5000 psi of $CO_2$).[15,78-80]

### *2.6.1.3 Preparation of (2S)-methyl 2-acetamidopent-4-enoate (53b)*




(48) (53b) (54b)

**Scheme 2.35**

**Table 2.10 Rh(I)-catalysed asymmetric hydrogenation of the dienamide ester (48)**

| Entry | Substrate : Catalyst | Solvent | P (psi) | T (°C) | t (h) | % Conversion | % Over-reduction |
|---|---|---|---|---|---|---|---|
| 1 | 50 : 1 | $scCO_2$ | 50 | 40 | 3 | 57 | 10 |
| 2 | 50 : 1 | $scCO_2$ | 100 | 40 | 18 | 70 | 17 |
| 3 | 50 : 1 | $scCO_2$ | 250 | 40 | 18 | 93 | 30 |
| 4 | 50 : 1 | $scCO_2$ | 200 | 40 | 18 | 88 | 16 |
| 5[a] | 100 : 1 | benzene | 30 | r.t. | 3 | 100 | 5 |

[a] This is repeat reaction from Table 2.3, Section 2.2.4.

Hydrogenation of (2*Z*)-methyl 2-acetamidopenta-2,4-dienoate (48) was first carried out in $scCO_2$ (1200 psi), with 50 psi of $H_2$ for 3 h. The low pressure and short reaction duration gave incomplete conversion (Entry 1). The reaction was repeated with 100 psi of $H_2$ for 18 h and gave a higher percentage of conversion to product (53b), however a substantial amount of starting material (48) was still present (Entry 2). Increasing the $H_2$ pressure to 250 psi gave a high conversion to product (53b) but also

resulted in an increase in over-reduced by-product (54b) (Entry 3). An intermediate $H_2$ pressure of 200 psi gave a comparable conversion but with less over-reduction and 72% conversion to the desired compound (53b) (Entry 4). A significant amount of over-reduced material (54b) was observed due to the higher loading of catalyst. In benzene, the reaction had gone to completion with only 30 psi of $H_2$ for 3 h (Entry 5). This hydrogenation is slower in the supercritical medium. One possible factor may be the limited solubility of the substrates in the fluid. A higher pressure gave improved conversion, which could be associated with an improvement in solvent properties of the $scCO_2$ at high pressures.[81] Unfortunately reactions at higher pressures of $H_2$ also gave higher amounts of the over-reduced product. This could be due to the high reactivity of the terminal double bond of the substrate (48) in comparison to the internal olefin (46) which gave no over-reduction even when 300 psi of $H_2$ was applied (Entry 1, Table 2.9).

#### *2.6.1.4 Summary*

The [(COD)Rh(I)((2*S*,5*S*)-Et-DuPHOS)]OTf catalyst was used to hydrogenate the dienamide substrates ((46) and (48)) in $scCO_2$ to give the chiral products ((51b) and (53b)). The results have shown that longer reaction times and higher pressures, compared to more conventional solvents, such as methanol and benzene, are needed to affect hydrogenations.

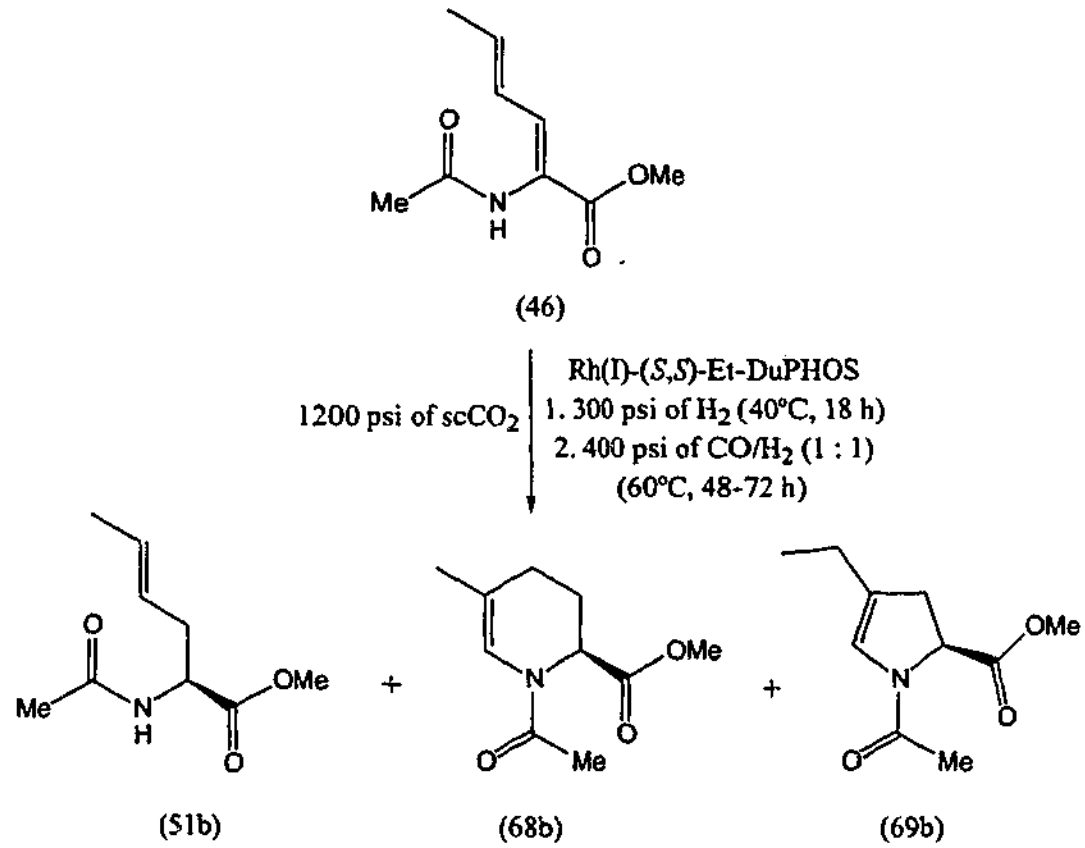
### 2.6.2 One-pot Tandem Reactions

#### *2.6.2.1 General Introduction*

After a few trials, optimum reaction conditions were obtained for a one-pot tandem reaction sequence in which the $H_2$ and $scCO_2$ were removed after the first step and replaced with $scCO_2$ and *syn* gas ($CO/H_2$ = 1:1) to give the cyclic amino acids as products. The [(COD)Rh(I)((2*S*,5*S*)-Et-DuPHOS)]OTf catalyst was used in the tandem reaction, as it was found previously to act as a hydroformylation catalyst in benzene.[6,7] The investigation was extended by using Rh(I)-Et-DuPHOS as the hydroformylation catalyst in $scCO_2$.

Several hydroformylation reactions in $scCO_2$ have been carried out since Rathke *et al.*[82] first reported the cobalt catalysed hydroformylation of propene in $scCO_2$.[13,14,83] Rhodium triarylphosphine complexes were also used in $scCO_2$ but problems have been reported due to the low solubility of the triarylphosphine ligands in the fluid.[84-86] However, this problem can be solved by the use of a modified fluorinated phosphine ligand.[87-91]

### 2.6.2.2 Rhodium(I)-catalysed tandem reaction of (2Z,4E)-methyl 2-acetamidohexa-2,4-dienoate (46) using a single catalyst in $scCO_2$




**Scheme 2.36** (Refer to Scheme 2.27 for intermediates)

**Table 2.11 Rh(I)-catalysed hydroformylation of the dienamide (46) under 400 psi of $CO/H_2$**

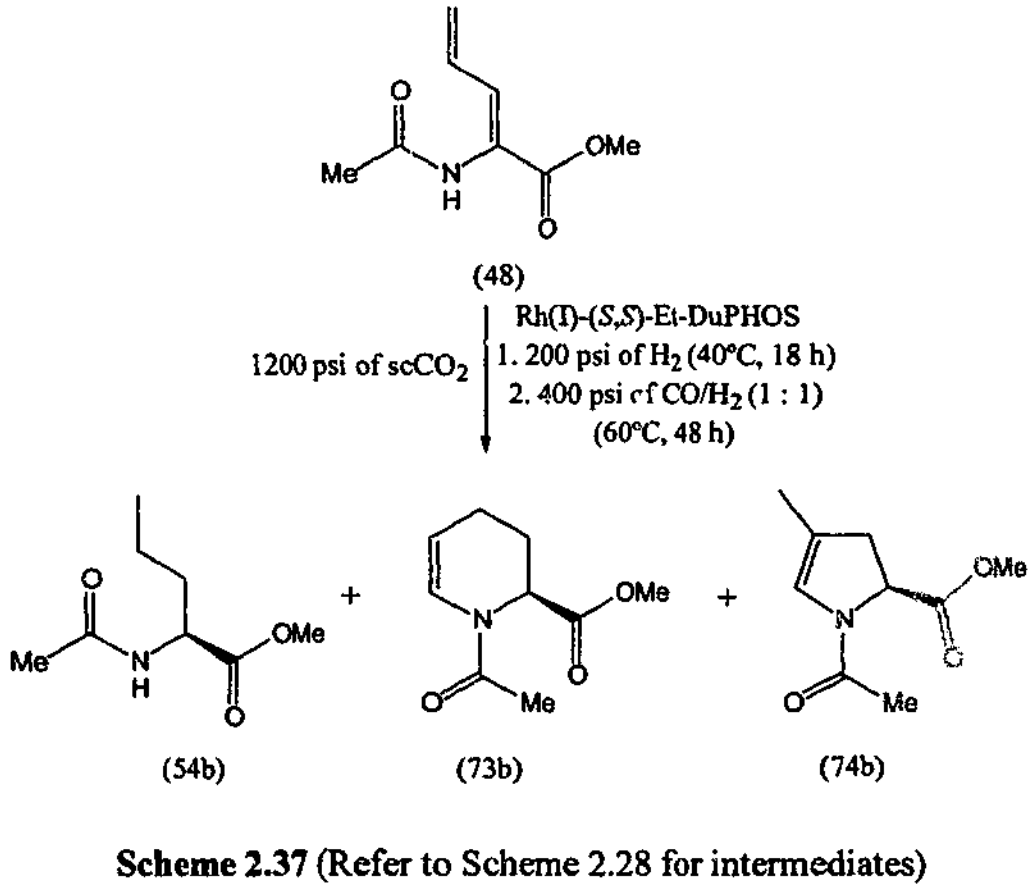
| Entry | Solvent | T (°C) | t (h) | Product ratio (51b) : (68b) : (69b) | % Yield[a] | % ee[b] (68b) / (69b) |
|---|---|---|---|---|---|---|
| 1 | $scCO_2$ | 60 | 72 | 20 : 54 : 26 | 86 | 99 / 99 |
| 2 | $scCO_2$ | 60 | 48 | - | -[c] | - |
| 3[d] | benzene | 80 | 20 | - : 83 : 17 | 42[e] | 99 / 99 |

[a] Isolated yield of cyclic products ((68b) and (69b)) after chromatography. [b] – signifies that the ee was not measured. [c] Crude only contained trace amount of cyclic products ((68b) and (69b)). [d] This is in Table 2.7, Section 2.5.2.1. [e] Crude product contained aldehydes ((64b) and (65b)) (*ca.* 15%).

Hydrogenation of the higher homologue (46), using 300 psi of $H_2$ for 18 h at 40°C followed by reaction with 400 psi of $CO/H_2$ for 72 h, gave some non-hydroformylated

material (51b) and 80% of a mixture of the cyclic products ((68b) and (69b)) in a ratio of 67 : 33 (Entry 1). Chromatographic separation gave clean samples of (68b) and (69b) each with an ee of 99% similar to that obtained from the reaction performed in benzene (Entry 3). The long reaction time was necessary as under similar conditions little cyclisation was observed after 48 h (Entry 2). The slower reaction in $scCO_2$ could be due to poor solubility of hydrogenated product (51b). There is also a slight difference in regioselectivity between the two reaction media (Entries 1 and 3). In the supercritical fluid, the ratio of 6-membered (68b) to 5-membered ring product (69b) was lower. This reaction was not repeated, however. the reproducibility is unknown.

### *2.6.2.3 Rhodium(I)-catalysed tandem reaction of (2Z)-methyl 2-acetamidopenta-2,4-dienoate (48) using a single catalyst in $scCO_2$*




**Scheme 2.37** (Refer to Scheme 2.28 for intermediates)

**Table 2.12 Rh(I)-catalysed hydroformylation of the dienamide (48) under 400 psi of $CO/H_2$**

| Entry | Solvent | T (°C) | t (h) | Product ratio (54b) : (73b) : (74b) : | % Yield[a] | % ee[b] (73b) / (74b) |
|---|---|---|---|---|---|---|
| 1 | $scCO_2$ | 60 | 48 | 30 : 52 : 18 | 44 | 98 / 98 |
| 2 | $scCO_2$ | 60 | 24 | - | -[c] | - |
| 3[d] | benzene | 80 | 72 | - : 54 : 46 | 91 | 95 / 99 |

[a] Isolated yield of cyclic products ((73b) and (74b)) after chromatography. [b] – signifies that the ee was not measured. [c] Crude product contained only trace amounts of cyclic products ((73b) and (74b)). [d] This is in Table 2.8, Section 2.5.2.2.

Reaction of (2*Z*)-methyl 2-acetamidopenta-2,4-dienoate (48) for 18 h under 200 psi of $H_2$, followed by reaction with 400 psi of $CO/H_2$ for 48 h at 60°C, gave 30% of over-reduced by-product (54b) and 70% of a mixture of the cyclic products, (73b) and (74b), in a ratio of 76 : 24 (Entry 1). The percentage of over-reduction was higher than expected since hydrogenation of (48) under similar reaction conditions had previously shown only 16% over-reduction (Entry 4, Table 2.10). This could be due to some catalyst decomposition to colloidal rhodium, which is an efficient hydrogenation catalyst. The long reaction time for the hydroformylation reaction was chosen as exploratory reactions showed little evidence for cyclic products when reaction times < 24 h were used (Entry 2, Table 2.11 and Entry 2, Table 2.12). The cyclic products ((73b) and (74b)) were separated and pure samples obtained in 24% and 20% yields respectively, both with 98% ee. In contrast to the previous reaction of the higher homologue (46) (Entry 1, Table 2.11), the use of $scCO_2$ gave more of the 6-membered heterocycle (68b) than the 5-membered cyclic product (69b). Again the reaction was not repeated and the reproducibility remains unknown.

#### *2.6.2.4 Summary*

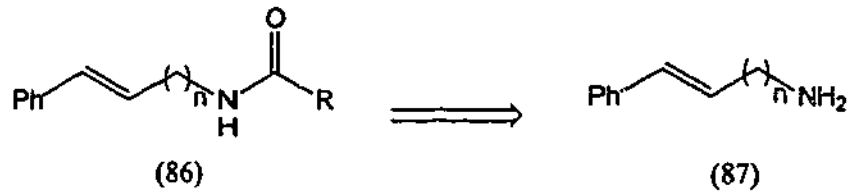
One-pot tandem synthesis of cyclic α-amino acids ((68b), (69b), (73b) and (74b)) in $scCO_2$ using [(COD)Rh(I)((2*S*,5*S*)-Et-DuPHOS)]OTf as the sole catalyst was successfully completed with reasonable yield and excellent enantioselectivity (> 98%).

# CHAPTER 3 SYNTHESIS OF AMINO ACIDS INVOLVING ENANTIOSELECTIVE HYDROFORMYLATION

## *3.1 Preparation of Hydroformylation Precursors*

### 3.1.1 General Introduction

This part of the project explores the use of Rh(I)-DuPHOS as a hydroformylation catalyst for the preparation of chiral amino acids. The scheme below shows the general route to the styryl enamides (86) from styryl amines (87) (Scheme 3.1). Variation of the chain length (n) and protecting group (R), e.g. acetyl, fluorenylmethoxycarbonyl (Fmoc) and benzyloxycarbonyl (Cbz), will be investigated.



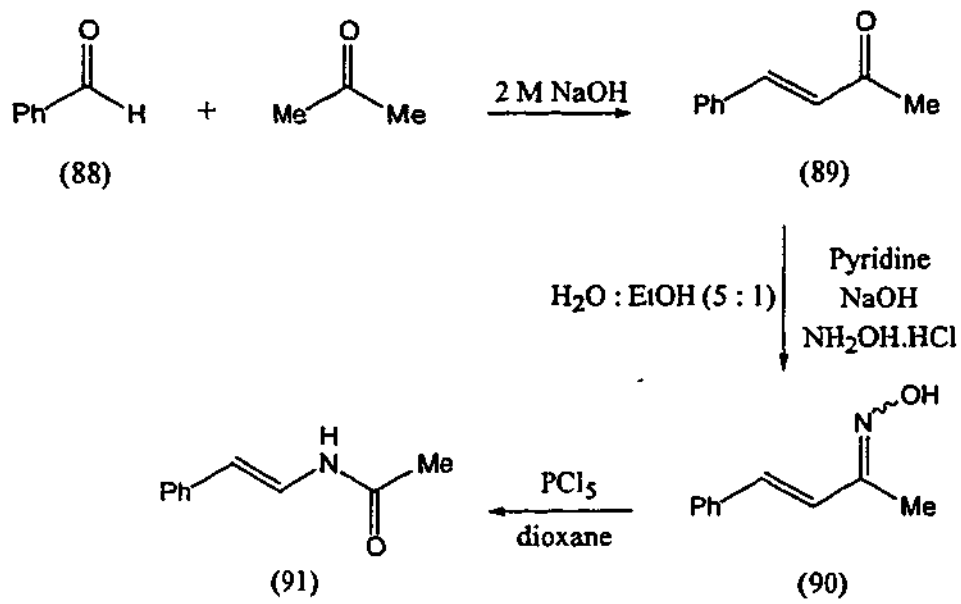

(86) (87)

**Scheme 3.1**

### 3.1.2 Preparation of (*E*)-*N*-(2-Phenylethenyl)acetamide (91)

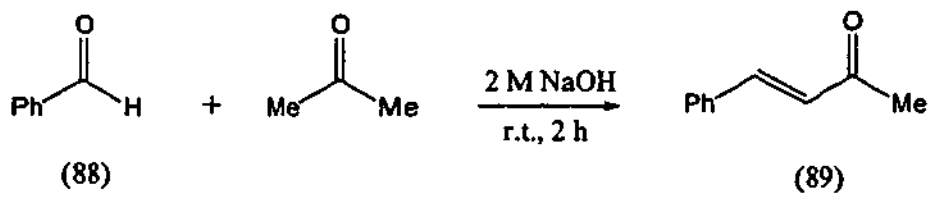
#### *3.1.2.1 Via 4-phenylbut-3-en-2-one oxime (90)*

A literature route was followed that involved several steps including formation of the oxime (90) and its Beckmann rearrangement to the targeted substrate, (*E*)-*N*-(2-phenylethenyl)acetamide (91) (Scheme 3.2).



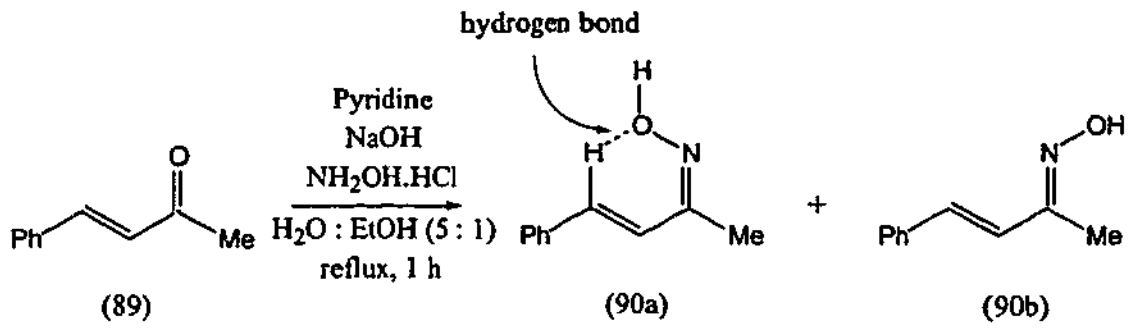

**Scheme 3.2**

Benzalacetone (89) was prepared by Claisen-Schmidt condensation between benzaldehyde (88) and acetone and was isolated as a yellow liquid in 89% yield (Scheme 3.3).[92] The $^1$H n.m.r. spectrum showed only the *trans*-isomer since the coupling constants of H3 and H4 were *J* 16.4, 16.2 Hz respectively.




**Scheme 3.3**

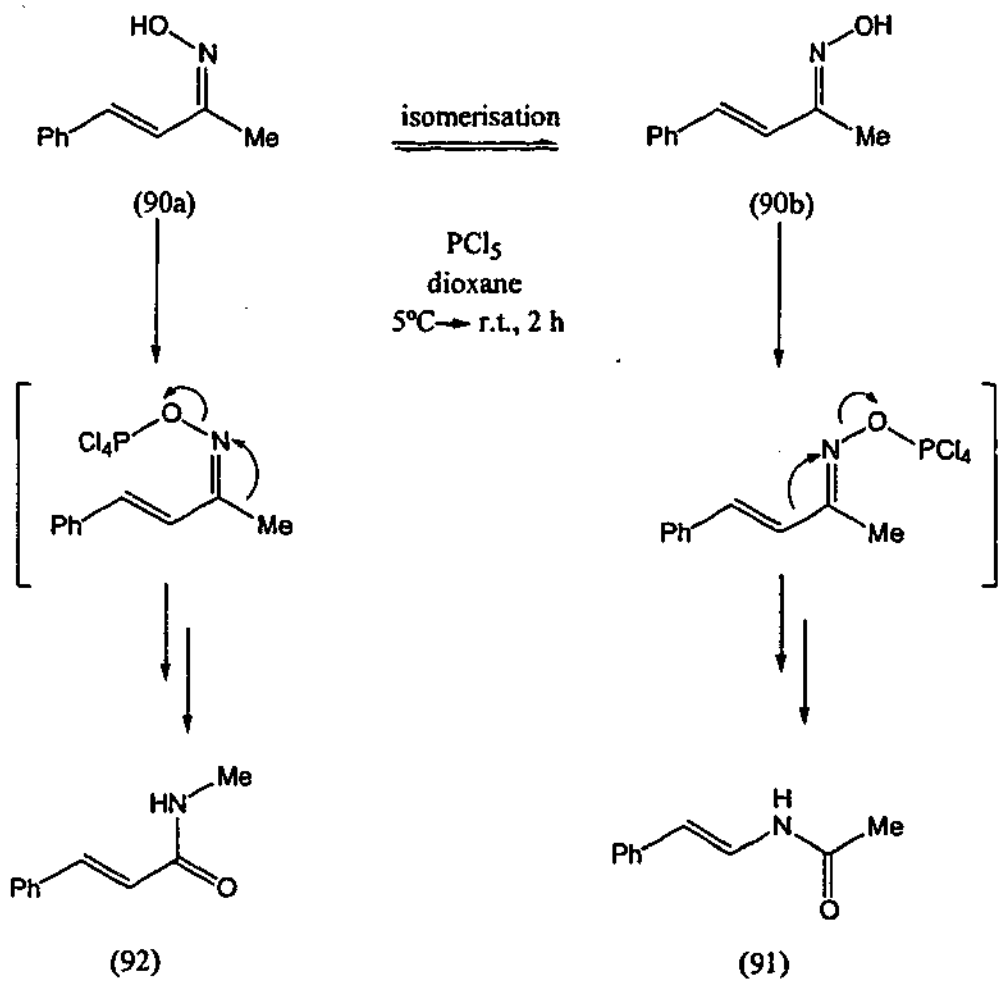
A mixture of *anti*- and *syn*-oximes ((90a) and (90b)) in a 75 : 25 ratio was formed by reacting (*E*)-benzalacetone (89) with hydroxylamine in the presence of pyridine (Scheme 3.4).[93] The oxime mixture ((90a) and (90b)) was purified by chromatography and individual isomers were isolated as semisolids. They were clearly identifiable by $^1$H n.m.r. spectroscopy as the H4 of the *anti*-oxime (90a) gave a resonance signal at δ 6.92, indicating hydrogen bonding to the adjacent hydroxyl group, whereas the H4 of the *syn*-oxime (90b) was more deshielded and it resonated at δ 7.60.




(89) (90a) (90b)

**Scheme 3.4**

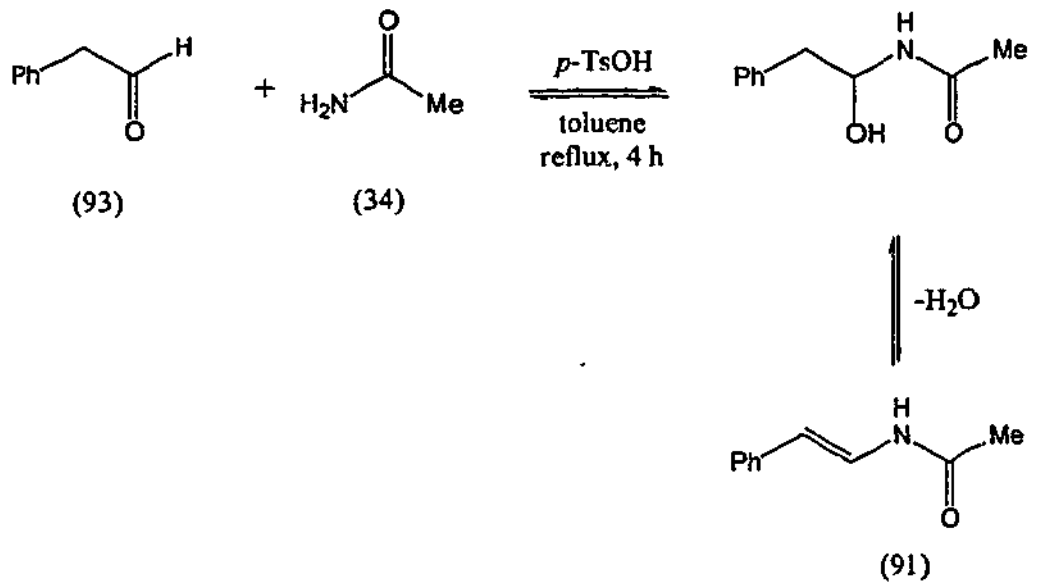
Reaction of the oxime mixture ((90a) and (90b) in a 75 : 25 ratio) with phosphorus pentachloride gave (*E*)-*N*-(2-phenylethenyl)acetamide (91) in only a poor yield (7%) even though it had been reported previously that Beckmann rearrangement of the mixed oximes ((90a) and (90b)) *via* this method gave the *E*-enamide (91) in 40% yield.[94,95] The major by-product of this reaction was (*E*)-*N*-methyl-3-phenylprop-2-enamide (92) formed from the isomeric *anti*-oxime (90a). The mechanism for this transformation is illustrated in Scheme 3.5. A similar reaction was carried out using pure *syn*-oxime (90b), however the $^1$H n.m.r. spectrum of the crude product showed a 25 : 75 product (91) to by-product (92) ratio and demonstrated that the *syn*-oxime (90b) isomerises under these reaction conditions to the *anti*-oxime (90a).




**Scheme 3.5**

### *3.1.2.2 Via phenylacetaldehyde (93)*

An alternative method involved the one-step condensation of acetamide (34) with phenylacetaldehyde (93) using a catalytic amount of *p*-toluenesulfonic acid in toluene (Entry 1). A Dean-Stark apparatus was employed to trap the water generated as the reaction was reversible (Scheme 3.6). Although the isolated yield (8%) had not improved, the use of toxic phosphorus pentachloride was avoided and the number of steps was reduced.




**Scheme 3.6**

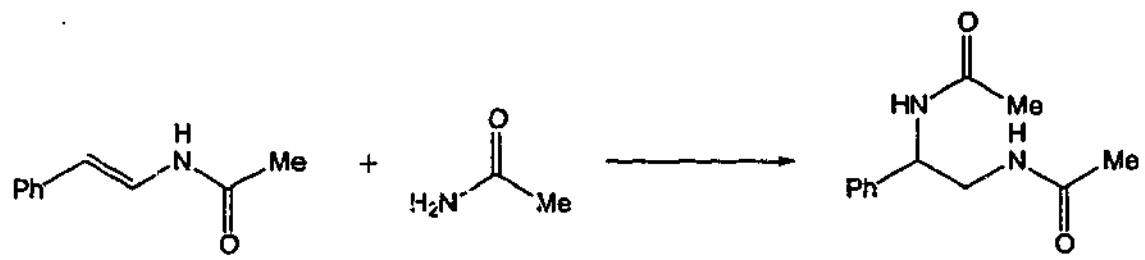
Similar reactions were carried out using varied conditions and the results are summarised in Table 3.1.

**Table 3.1 Preparation of (*E*)-*N*-(phenylethenyl)acetamide (91)**

| Entry | Catalyst | Solvent | T (°C) | Time | % Yield |
|---|---|---|---|---|---|
| 1 | *p*-toluenesulfonic acid | toluene | reflux[a] | 4 h | 8[b] |
| 2 | *p*-toluenesulfonic acid | neat | 70°C | 20 min | 15 |
| 3 | - | neat | 70°C | 120 h | 12 |

[a] Using Dean-Stark apparatus. [b] By-product, 2-acetamido-2-phenylethylacetamide (94) (*ca.* 50%) was isolated.

The poor yields were partly due to the formation of a by-product, 2-acetamido-2-phenylethylacetamide (94), generated from the Michael addition of a second molecule of acetamide (34) to the product (91) (Scheme 3.7).



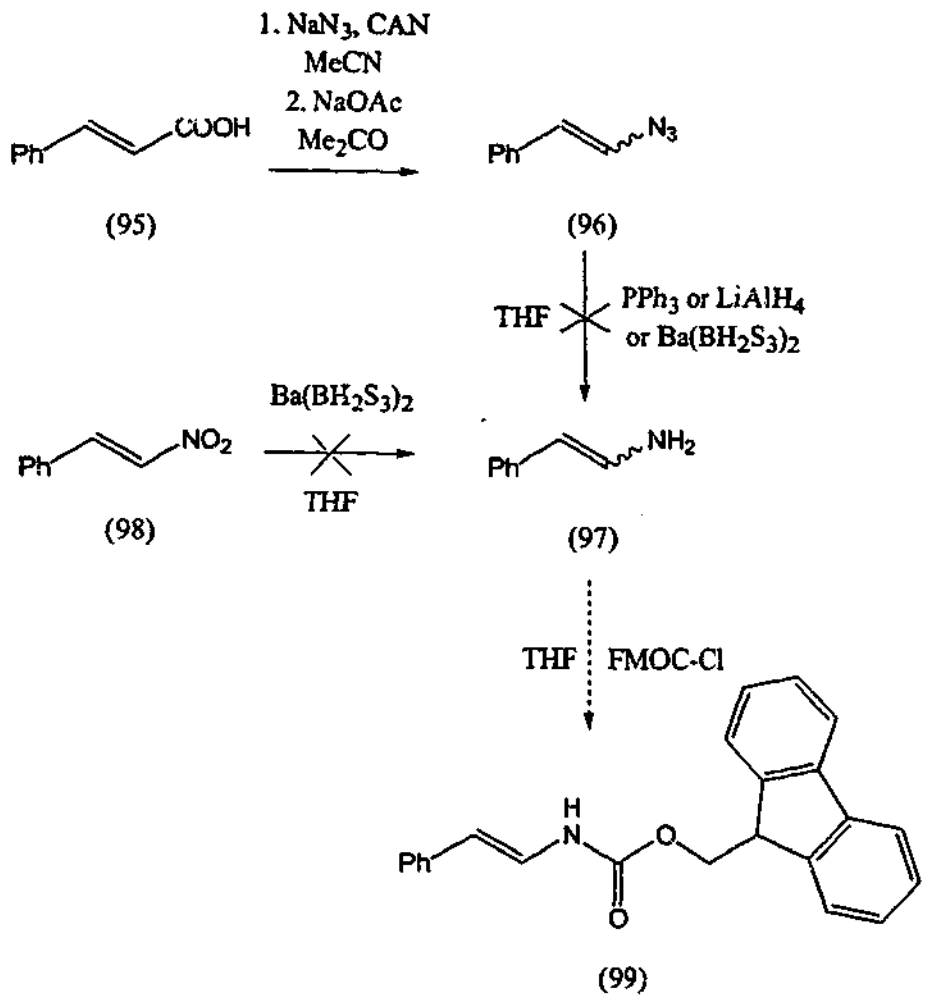

(9i) (34) (94)

**Scheme 3.7**

A greener, solventless route to enamines has been recently developed by Monash colleagues, Scott *et al.*,[96,97] (*E*)-*N*-(2-Phenylethenyl)acetamide (91) was prepared (*ca.* 15% yield) using this method and involved the heating of the two starting materials ((93) and (34)) together in a solvent free environment with a small amount of *p*-toluenesulfonic acid as catalyst. Column chromatography of the crude product gave a slightly higher yield than the other methods (Entries 1 and Section 3.1.2.1). The reaction was repeated without the addition of catalyst but took longer to generate the product (91) in similar yield (Entry 3).

### 3.1.3 Attempted Preparation of (*E*)-*N*-[9]-Fluorenylmethoxycarbonylamino-2-phenylethene (99)

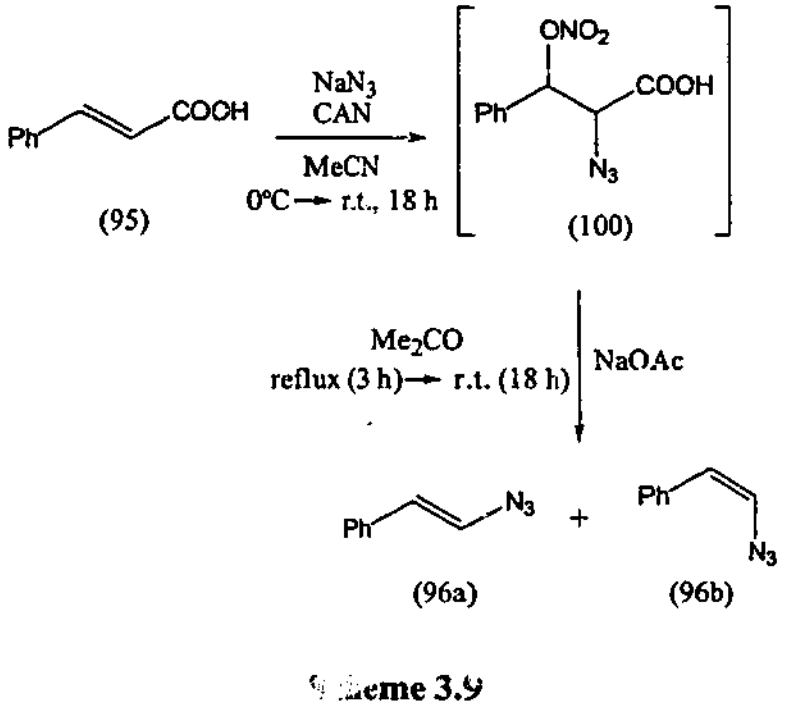
An endeavour was made to introduce a bulkier Fmoc-protecting group on the amino substituent to encourage the hydroformylation at the C2 position and hence promote selection for the desired β-amino acid. Different ways were tried to obtain the (*E*)-styrylamine (97), but were unsuccessful as summarised below (Scheme 3.8).




**Scheme 3.8**

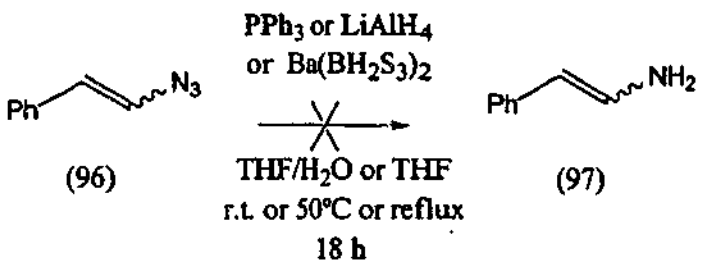
### *3.1.3.1 Via cinnamic acid (95)*

β-Azidostyrene (96) was prepared by reacting commercially available cinnamic acid (95) with sodium azide in the presence of cerium(IV) ammonium nitrate (CAN), followed by the addition of sodium acetate (Scheme 3.9). The intermediate (100) eliminated nitrate and carbon dioxide to give the desired product as a 1 : 1 mixture of (*E*)- and (*Z*)-isomers ((96a) and (96b)) with trace amounts of impurities. The crude yield was higher than reported (61%)[98] and separation was not carried out due to the instability of the products ((96a) and (96b)).




**Scheme 3.9**

Reduction of β-azidostyrene (96) was attempted several times with different reducing agents, i.e. $PPh_3$, $LiAlH_4$ and $Ba(BH_2S_3)_2$ (101), as summarised in Table 3.2. Following the method used by Knouzi *et al.*,[99] reactions were carried out in the presence of $PPh_3$ in a tetrahydrofuran/water solvent system at room temperature or 50°C. A complex mixture resulted and neither the starting material (96) or product (97) were isolated (Entries 1 and 2). The reaction was repeated using $LiAlH_4$, a stronger reductant, but a complex mixture also resulted and no starting material (96) or expected product (97) were recovered.




**Scheme 3.10**

**Table 3.2 Attempted preparation of (*E*)-styrylamine (97)**

| Entry | Reagent | Solvent | T (°C) | Time (h) | % Conversion |
|---|---|---|---|---|---|
| 1 | $PPh_3$[99] | $THF/H_2O$ | r.t. | 18 | -[a] |
| 2 | $PPh_3$[99] | $THF/H_2O$ | 50 | 18 | -[a] |
| 3 | $LiAlH_4$ | THF | r.t. | 18 | -[a] |
| 4 | $Ba(BH_2S_3)_2$[100] | THF | reflux | 18 | s/m recovered |

[a] The $^1H$ n.m.r. spectrum of the crude oil indicated neither starting material (96) nor product (97).

Thus, a milder reagent, $Ba(BH_2S_3)_2$ (101) was prepared as shown below (Scheme 3.11).

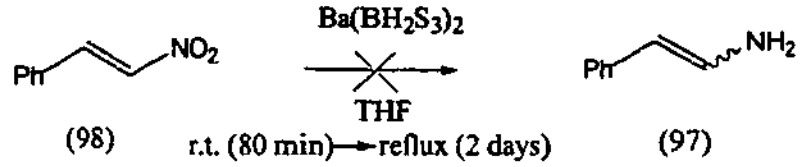
$$NaBH_4 \xrightarrow[\substack{THF \\ 0°C\ (20\ min) \rightarrow r.t.\ (30\ min)}]{1.\ Sulfur} \left[NaBH_2S_3\right] \xrightarrow[r.t.,\ 12\ h]{2.\ BaCl_2} Ba(BH_2S_3)_2 \quad (101)$$

**Scheme 3.11**

Barium sulfurated borohydride ($Ba(BH_2S_3)_2$) (101) can be used to selectively reduce aldehydes, ketones, azides and nitro-compounds without reducing carbon-carbon double bonds. Its reactivity lies between that of $LiAlH_4$ and $NaBH_4$. The hydride was sulfurated by the addition of sulfur to $NaBH_4$. Barium chloride was added to give the product (101) in 63% yield, which was lower than the reported yield (80-85%).[100] The product (101) was stored under nitrogen at low temperature, as exposure to air and moisture over time causes decomposition.[100,101]

Unfortunately, attempted reduction of the azide (96) with this reagent (101) only led to recovery of the starting material (96).

### 3.1.3.2 *Via (E)-β-nitrostyrene (98)*

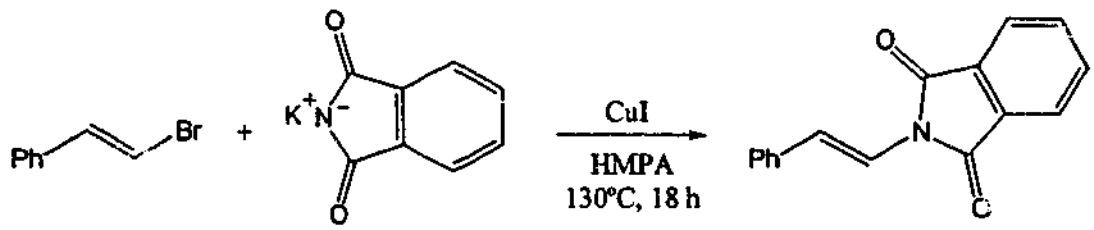



(98) (97)

**Scheme 3.12**

Attempts were also made to use $Ba(BH_2S_3)_2$ (101) to reduce the commercially available (*E*)-β-nitrostyrene (98) following a literature procedure.[100] No reaction occurred at ambient temperature. The $^1H$ n.m.r. spectrum of the crude oil, obtained after being heated at reflux for 2 days, indicated the presence of neither starting material (98) nor product (97). As the $^1H$ n.m.r. spectrum of the crude material was complex, this reaction was not investigated further.

## 3.1.4 Preparation of (*E*)-*N*-(2-Phenylethenyl)phthalimide (104)



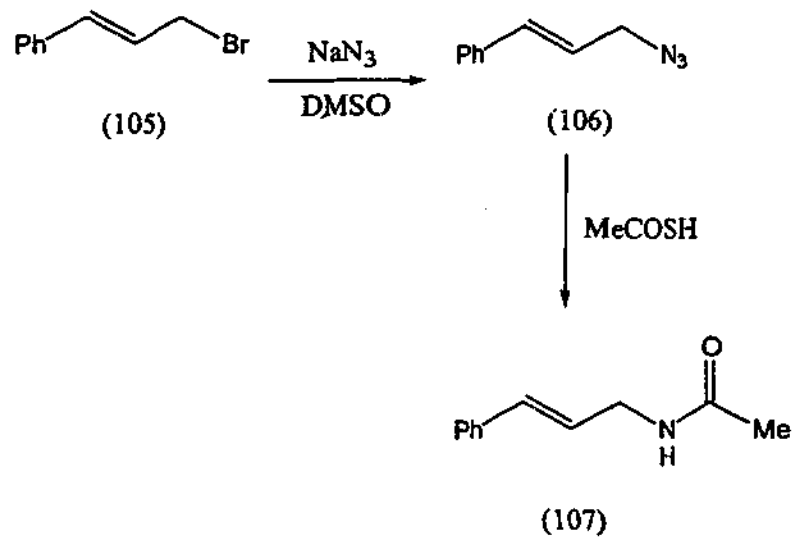

(102) (103) (104)

**Scheme 3.13**

As the preparation of (*E*)-*N*-[9]-Fluorenylmethoxycarbonylamino-2-phenylethene (99) was not successful, use of the alternative bulky phthalimide-protecting group was proposed. A mixture of β-bromostyrene (102), copper iodide and potassium phthalimide (103) in hexamethylphosphoric triamide was heated at 130°C for 18 h.[102] The $^1H$ n.m.r. spectrum of the crude oil indicated that the reaction was incomplete and that only 33% conversion had occurred. Separation of this complex mixture was not attempted.

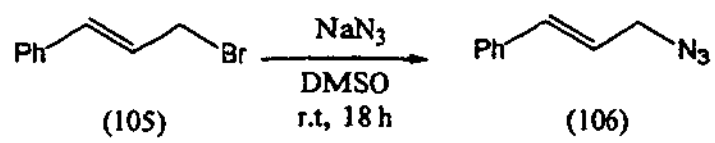
### 3.1.5 Preparation of (*E*)-*N*-(3-Phenylprop-2-enyl)acetamide (107)

The hydroformylation reactant, (*E*)-*N*-(3-phenylprop-2-enyl)acetamide (107), with one extra carbon in the chain, was prepared *via* the pathway shown below (Scheme 3.14).




**Scheme 3.14**

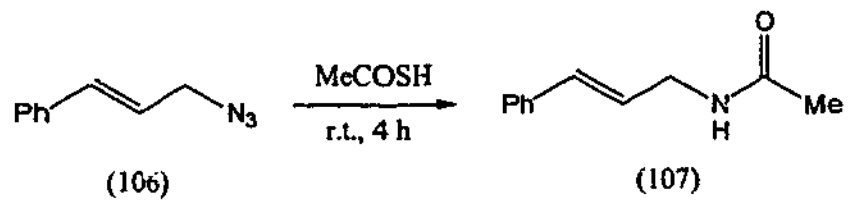
Cinnamyl azide (106) was prepared by stirring cinnamyl bromide (105) in a prepared 0.5 M solution of sodium azide in dimethyl sulfoxide (Scheme 3.15).[103] Complete conversion to the azide (106) was obtained after 18 h of stirring at ambient temperature.




**Scheme 3.15**

Reduction of the azide (106) was carried out with neat thioacetic acid as the reagent and solvent under mild experimental conditions (Scheme 3.16). Nitrogen gas evolved as the reaction proceeded and the pure product, (*E*)-*N*-(3-phenylprop-2-enyl)acetamide (107), was isolated after column chromatography in 72% yield. Thioacetic acid was a highly efficient reagent for this transformation as it selectively

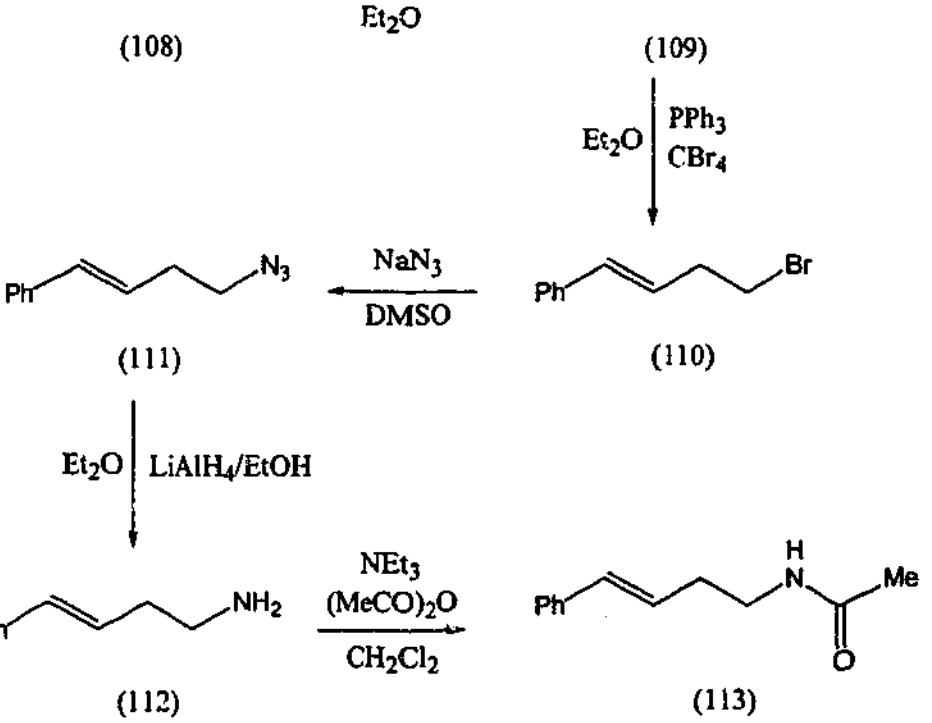
reduced the azide group and facilitated *in situ* acetylation. The observed melting point (87-89°C) was close to the reported melting point (88-90°C).[104]




(106) (107)

**Scheme 3.16**

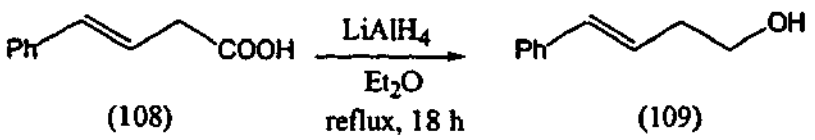
### 3.1.6 Preparation of (*E*)-*N*-(4-Phenylbut-3-enyl)acetamide (113)




(108) (109) (110) (111) (112) (113)

**Scheme 3.17**

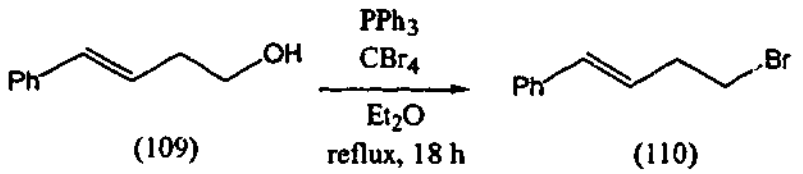
Commercially available styrylacetic acid (108) was reduced with $LiAlH_4$ in dry diethyl ether, under reflux for 18 h (Scheme 3.18). The excess $LiAlH_4$ was quenched with an aqueous $Na_2SO_4$ solution and subsequent removal of the aluminium salts by filtration gave the alcohol (109) in a 93% yield. This compound (109) was fully characterised and was consistent with literature data.[105]




(108) (109)

**Scheme 3.18**

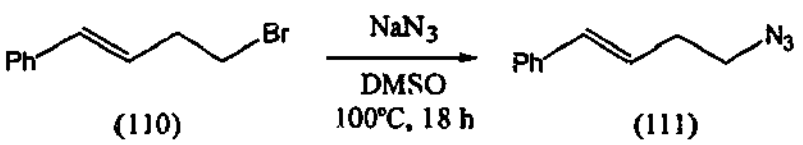
(*E*)-4-Bromobut-1-enylbenzene (110) was prepared from the alcohol (109) using a Mitsunobu reaction involving $PPh_3$ and carbon tetrabromide with heating under reflux in dry diethyl ether for 18 h (Scheme 3.19). Column chromatography gave the product (110) as an oil in quantitative yield.




(109) (110)

**Scheme 3.19**

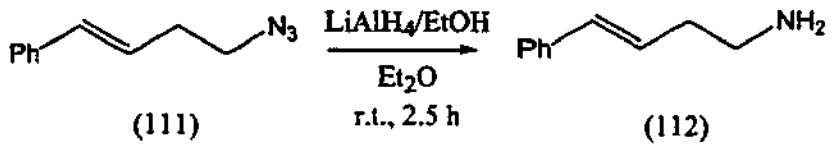
Conversion of (*E*)-4-bromobut-1-enylbenzene (110) to (*E*)-4-azidobut-1-enylbenzene (111) was carried out by heating the bromo compound (110) in a freshly prepared 0.5 M solution of sodium azide in dimethyl sulfoxide at 100°C for 18 h (Scheme 3.20). A higher temperature was needed for the reaction to go to completion compared to the reaction of cinnamyl bromide (105) (refer to Section 3.1.5), as the bromide (110) is no longer allylic. A yield of 75% was obtained.




(110) (111)

**Scheme 3.20**

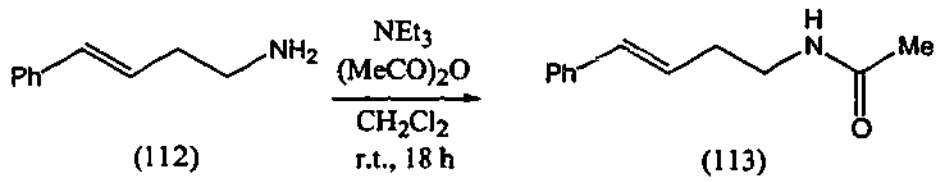
(*E*)-4-Phenylbut-3-enylamine (112) was prepared by reducing the (*E*)-4-azidobut-1-enylbenzene (111) with $LiAlH_3.OEt$, generated from $LiAlH_4$ and ethanol, in dry diethyl ether (Scheme 3.21). This reagent chemoselectively reduced the azide group without reduction of the olefin.




(111) (112)

**Scheme 3.21**

Acetylation of the amine (112) was carried out in dichloromethane using triethylamine and acetic anhydride at room temperature (Scheme 3.22). After 18 h, the reaction was worked up to give (*E*)-*N*-(4-phenylbut-3-enyl)acetamide (113) as the product, which did not require further purification.




(112) (113)

**Scheme 3.22**

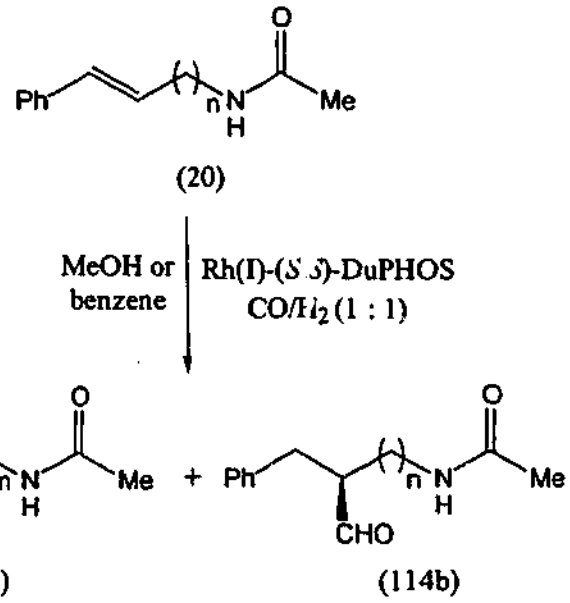
### 3.1.7 Summary

One of the β-amino acid precursors, (*E*)-*N*-(2-phenylethenyl)acetamide (91), was prepared in better yield through a one-pot, solventless reaction. Unfortunately, the preparation of (*E*)-*N*-fluorenylmethoxycarbonylamino-2-phenylethene (99) was not successful due to failed attempts to prepare the required (*E*)-styrylamine precursor (97). An attempt to prepare (*E*)-*N*-(2-phenylethenyl)phthalimide (104), which also contains a bulky amino-protecting group, was only partially successful. The synthesis of hydroformylation precursors containing longer carbon chains, (*E*)-*N*-(3-Phenylprop-2-enyl)acetamide (107) and (*E*)-*N*-(4-phenybut-3-enyl)acetamide (113), was successfully achieved in reasonable yield.

## 3.2 *Asymmetric Hydroformylations*

### 3.2.1 General Introduction

Preparation of chiral amino acid precursors ((21b) and (114b)) could be achieved *via* the enantioselective hydroformylation of amino alkenes (20) of different chain length (n). Rh(I)-DuPHOS will be evaluated as an enantioselective hydroformylation catalyst and compared with Rh-BINAP and Rh-$PPh_3$. Rh(I)-DuPHOS is known to act as a very effective enantioselective hydrogenation catalyst[34] and has been also shown to act as a hydroformylation catalyst,[6,7] however enantioselective hydroformylation reactions have not yet been evaluated.



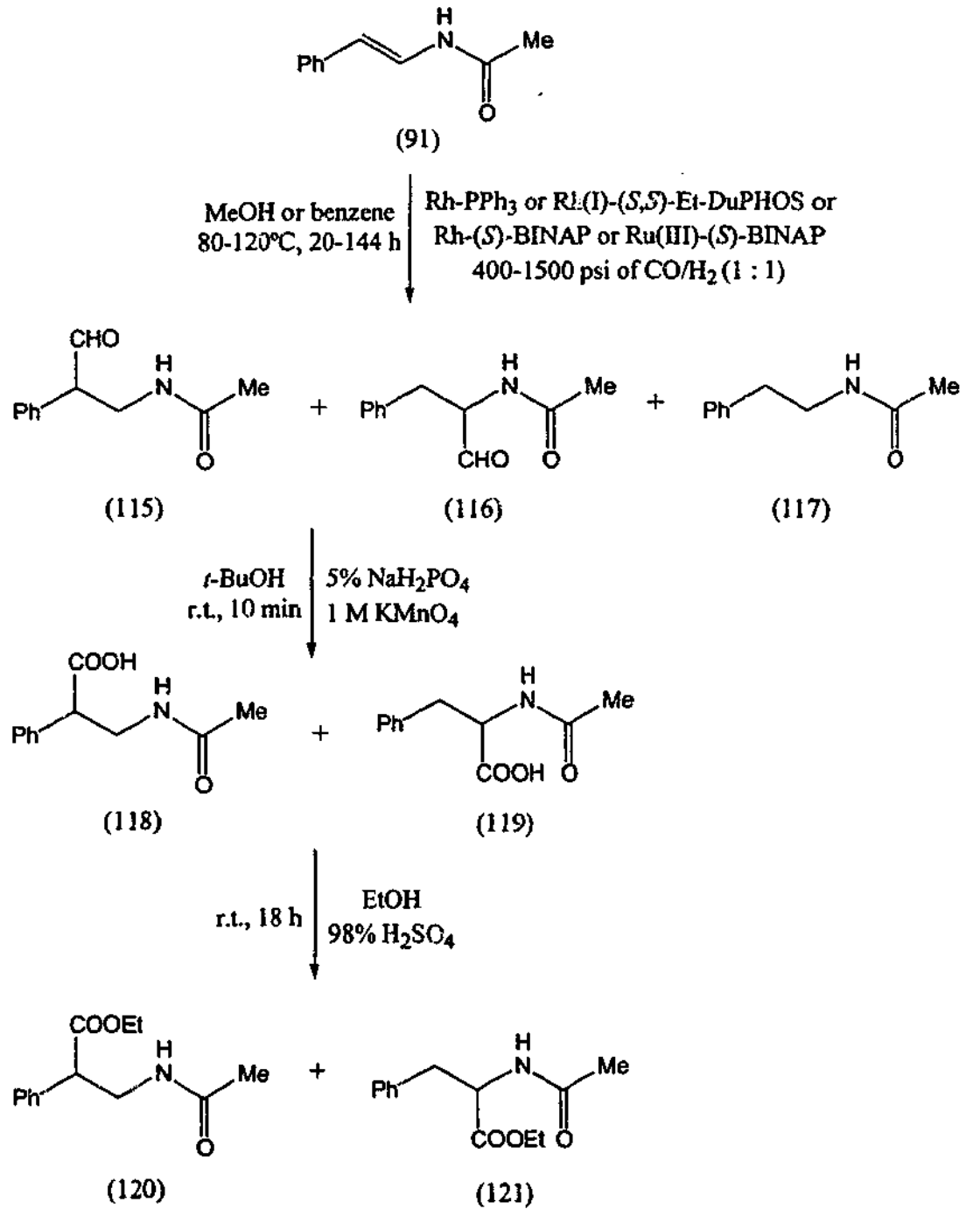

**Scheme 3.23**

### 3.2.2 General Reaction Conditions

Reactions were carried out using a: *i)* substrate : catalyst (Rh(I)-(*S*,*S*)-Et-DuPHOS / Ru(III)-(*S*)-BINAP) ratio of 100 : 1 or; a *ii)* substrate : metal catalyst precursor ($[Rh(OAc)_2]_2$) : ligand ((*S*)-BINAP) ratio of 100 : 1 : 2 or; a *iii)* substrate : metal catalyst precursor ($[Rh(OAc)_2]_2$) : ligand ($PPh_3$) ratio of 100 / 50 / 25 : 1 : 2 in benzene with an initial pressure (P) of 400-1500 psi $CO/H_2$ (1 : 1). The temperature

(T) was 80-200°C with reaction time (t) being 20-144 h. Purification was performed using a plug of silica.

### 3.2.3 Rhodium-catalysed Reactions of (*E*)-*N*-(2-Phenylethenyl)acetamide (91)




**Scheme 3.24**

**Table 3.3 Rh-catalysed hydroformylation of the enamide (91)**

| Entry | Catalyst[a] | Solvent | P (psi) | T (°C) | t (h) | Product ratio (115) : (116) : (117) | % Conversion |
|---|---|---|---|---|---|---|---|
| 1 | Rh-$PPh_3$[b] | MeOH | 400 | 80 | 96 | 67 : - : 33 | 50 |
| 2 | Rh-$PPh_3$[c] | benzene | 1000 | 100 | 20 | 58 : 19 : 23 | 60 |
| 3 | Rh-$PPh_3$[c] | benzene | 1000 | 100 | 96 | 56 : 22 : 22 | 60 |
| 4 | Rh-$PPh_3$[c] | benzene | 1500 | 120 | 20 | 54 : 27 : 19 | 60 |
| 5 | Rh-$PPh_3$[b] | benzene | 1500 | 120 | 72 | 59 : 29 : 12 | 60 |
| 6 | Rh-DuPHOS[d] | benzene | 400 | 80 | 20 | - | 0 |
| 7 | Rh-DuPHOS[d] | benzene | 400 | 80 | 48 | - | 0 |
| 8 | Rh-DuPHOS[d] | benzene | 400 | 80 | 72 | - | 0 |
| 9 | Ru-BINAP[d] | benzene | 500 | 80 | 144 | - | 0 |
| 10 | Rh-DuPHOS[d] | benzene | 500 | 50 | 144 | - | 0 |
| 11 | Rh-$PPh_3$[b] | benzene | 400 | 80 | 20 | - | 0[f] |
| 12 | Rh-$PPh_3$[b] | benzene | 400 | 80 | 20 | - | 0[f] |
| 13 | Rh-$PPh_3$[b] | benzene | 400 | 80 | 96 | - | 0[f] |
| 14 | Rh-$PPh_3$[c] | benzene | 500 | 50 | 144 | - | 0 |
| 15 | Rh-BINAP[c] | benzene | 1300 | 120 | 20 | - | 0 |
| 16 | Ru-BINAP[c] | benzene | 1300 | 120 | 72 | - | 0 |
| 17 | Rh-$PPh_3$[c] | benzene | 1000 | 120 | 20 | 67 : 33 : - | 38 |
| 18 | Rh-$PPh_3$[c] | benzene | 1000 | 120 | 20 | 67 : 33 : - | 16 |
| 19 | Rh-$PPh_3$[c] | benzene | 1000 | 200 | 20 | - : - : 100 | 0[f] |

[a] Rh-DuPHOS = Rh(I)-(*S*,*S*)-Et-DuPHOS, Ru-BINAP = Ru(III)-(*S*)-BINAP and Rh-BINAP = Rh-(*S*)-BINAP. [b] Substrate (91) : $[Rh(OAc)_2]_2$ : $PPh_3$ or (*S*)-BINAP ratio = 100 : 1 : 2. [c] Substrate (91) : $[Rh(OAc)_2]_2$ : $PPh_3$ ratio = 50 : 1 : 2. [d] Substrate (91) : Rh(I)-(*S*,*S*)-Et-DuPHOS or Ru(III)-(*S*)-BINAP ratio = 100 : 1. [e] Substrate (91) : $[Rh(OAc)_2]_2$ : $PPh_3$ ratio = 25 : 1 : 2. [f] Crude only contained trace amount of aldehydes ((115) and (116)).

Hydroformylation of (*E*)-*N*-(2-phenylethenyl)acetamide (91) was repeated numerous times under different reaction conditions and with a variety of catalysts. The results

are summarised in Table 3.3. The highest conversion was 60% and was accompanied by the hydrogenated by-product, *N*-(2-phenylethyl)acetamide (117) (Entries 1-5). Milder conditions (400-500 psi and 50-80°C) were used with chiral catalysts, i.e. Rh(I)-(*S*,*S*)-Et-DuPHOS and Ru(III)-(*S*)-BINAP, but the reactions did not proceed (Entries 6-10). When Rh-$PPh_3$ was used under the same conditions, only starting material (91) was recovered (Entries 11-14) revealing that more forcing conditions (1000-1500 psi and 80-120°C) were needed for the reaction to proceed. Previous workers have noted that high pressure (1200-1800 psi) and temperature (80-100°C) were required to achieve hydroformylation of similar substrates, e.g. *N*-allylamide, *N*-allylbenzamide and styryl dithianes.[106,107] In Entries 15 and 16, a higher pressure (1300 psi) and temperature (120°C) were employed using Rh- or Ru(III)-(*S*)-BINAP but only starting material was recovered. Moreover, the increased ratio of Rh-$PPh_3$ to substrate led to a decrease in the percentage of conversion (Entries 17 and 18) while a higher temperature (200°C) promoted hydrogenation to give more of the by-product (117) (Entry 19).

It was anticipated that the ratio of *N*-(2-formyl-2-phenylethyl)acetamide (115) to *N*-(1-formyl-2-phenylethyl)acetamide (116) would be relatively high and in favour of aldehyde (115) as hydroformylation of styrene (15) usually gives the branched aldehyde (16) as the major product (> 80%).[16] However, the ratios of aldehydes (115) and (116) were all less than 80 : 20 (Entries 2-5, 17 and 18), with the exception of a reaction in methanol (Entry 1) which had only gone to 30% conversion.

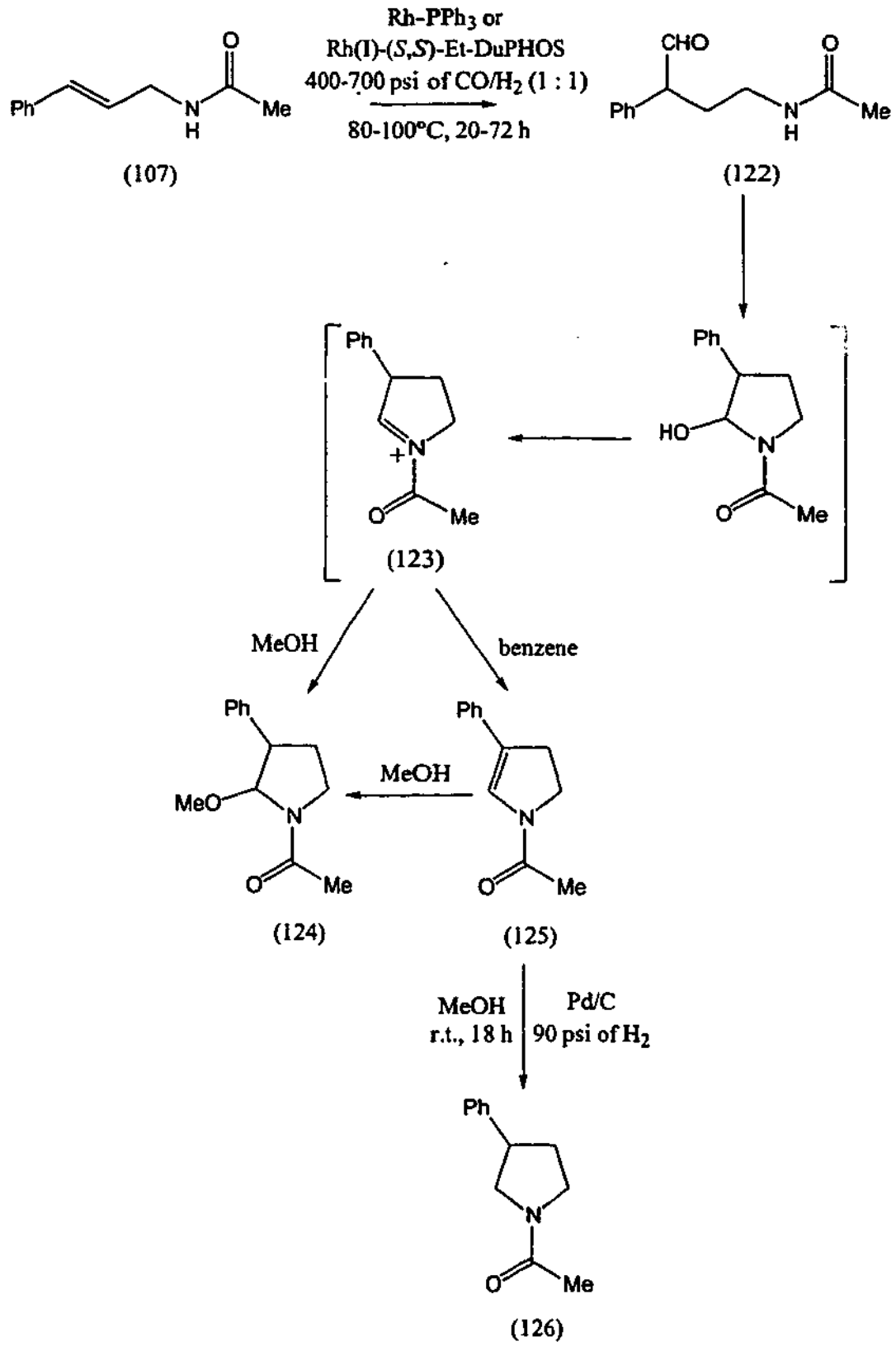
The aldehydes (115) and (116) were characterised by conversion to the corresponding acids, 3-acetamido-2-phenylpropanoic acid (118) and 2-acetamido-3-phenylpropanoic

acid (119). They were obtained by oxidation of the crude mixture of aldehydes ((115) and (116) in a 70 : 30 ratio) and amides ((91) and (117)) by $KMnO_4$. The carboxylic acids ((118) and (119)) were then readily separated from starting material (91) and hydrogenated compound (117). The $^1H$ n.m.r. spectrum showed the acids (118) and (119) in a 70 : 30 ratio, together with trace amount of impurities.

The carboxylic acids ((118) and (119) in 70 : 30 ratio) were esterified with a catalytic amount of concentrated sulfuric acid (98%) in ethanol to give a mixture of ethyl 3-acetamido-2-phenylpropanoate (120) and ethyl 2-acetamido-3-phenylpropanoate (121) which were not separated. The esterification reaction was repeated with a pure sample of 3-acetamido-2-phenylpropanoic acid (118) (obtained from a hydroformylation reaction in methanol (Entry 1)) and after purification, a pure sample of ethyl 3-acetamido-2-phenylpropanoate (120) was obtained. The $^1H$ and $^{13}C$ n.m.r. spectral data for the esters ((120) and (121)) was then fully explained and found to be consistent with literature values.[108-110]

### 3.2.4 Rhodium-catalysed Reaction of (*E*)-*N*-(3-Phenylprop-2-enyl)acetamide (107)

Hydroformylation of the enamide (107) should give the aldehyde (122) which would be expected to cyclise under the reaction conditions employed (refer to Chapter 2). It was hoped that the styryl group would accelerate the hydroformylation reaction and allow the use of mild reaction conditions to facilitate the isolation of the intermediate aldehyde (122). When the acetamide (107) was subjected to hydroformylation in benzene, the enamine (125) resulted with concomitant loss of chirality. For the reaction that was carried out in methanol, an amidal (124) was generated. However, no enantioselectivity was observed in product (124), possibly as a result of being formed *via* enamide (125) (Scheme 3.25).




(107) (122) (123) (124) (125) (126)

**Scheme 3.25**

**Table 3.4 Rh-catalysed hydroformylation of the enamide (107)**

| Entry | Catalyst[a] | Solvent | P (psi) | T (°C) | t (h) | Product ratio (122) : (124) : (125) | % Conversion |
|---|---|---|---|---|---|---|---|
| 1 | Rh-DuPHOS[b] | benzene | 400 | 80 | 20 | - | 0 |
| 2 | Rh-DuPHOS[b] | benzene | 700 | 80 | 72 | 37 : - : 63 | 45 |
| 3 | Rh-DuPHOS[b] | benzene | 700 | 100 | 72 | 26 : - : 74 | 84 |
| 4 | Rh-DuPHOS[b] | benzene | 700 | 100 | 20 | 20 : - : 80 | 33 |
| 5 | Rh-$PPh_3$[c] | benzene | 700 | 80 | 72 | - : - : 100 | 100[d] |
| 6 | Rh-$PPh_3$[c] | benzene | 700 | 100 | 72 | - : - : 100 | 100[d] |
| 7 | Rh-$PPh_3$[c] | MeOH | 700 | 100 | 72 | - : 100 : - | 100 |
| 8 | Rh-DuPHOS[b] | MeOH | 700 | 100 | 72 | - : 100 : - | 60 |

[a] Rh-DuPHOS = Rh(I)-(*S*,*S*)-Et-DuPHOS. [b] Substrate (107) : Rh(I)-(*S*,*S*)-Et-DuPHOS ratio = 50 : 1. [c] Substrate (107) : $[Rh(OAc)_2]_2$ : $PPh_3$ ratio = 50 : 1 : 2. [d] Crude product contained only trace amount of aldehyde (122).

Hydroformylation of (*E*)-*N*-(3-phenylprop-2-enyl)acetamide (107) was firstly carried out in benzene with Rh(I)-(*S*,*S*)-Et-DuPHOS at 400 psi of $CO/H_2$, 80°C for 20 h (Entry 1). The reaction gave only starting material (107) and no sign of aldehyde (122). A reaction using a higher pressure of *syn* gas (700 psi) and longer reaction time (72 h) was investigated and 45% conversion of starting material (107) was achieved (Entry 2). The majority of the product was *N*-acetyl-3-phenyl-2,3-didehydropyrrolidine (125) (63%). The remaining minor component was the desired aldehyde, *N*-(3-formyl-3-phenylpropyl)acetamide (122). An inability to isolate a clean sample of aldehyde (122) however, prevented assessment of enantioselectivity. The regioselectivity was found to be excellent as demonstrated by the addition of the formyl group only at the C3 position. The reaction was repeated at a higher temperature (100°C) and the percentage of conversion was increased to 84% but the ratio of aldehyde (122) to heterocycle (125) decreased (26 : 74) (Entry 3).

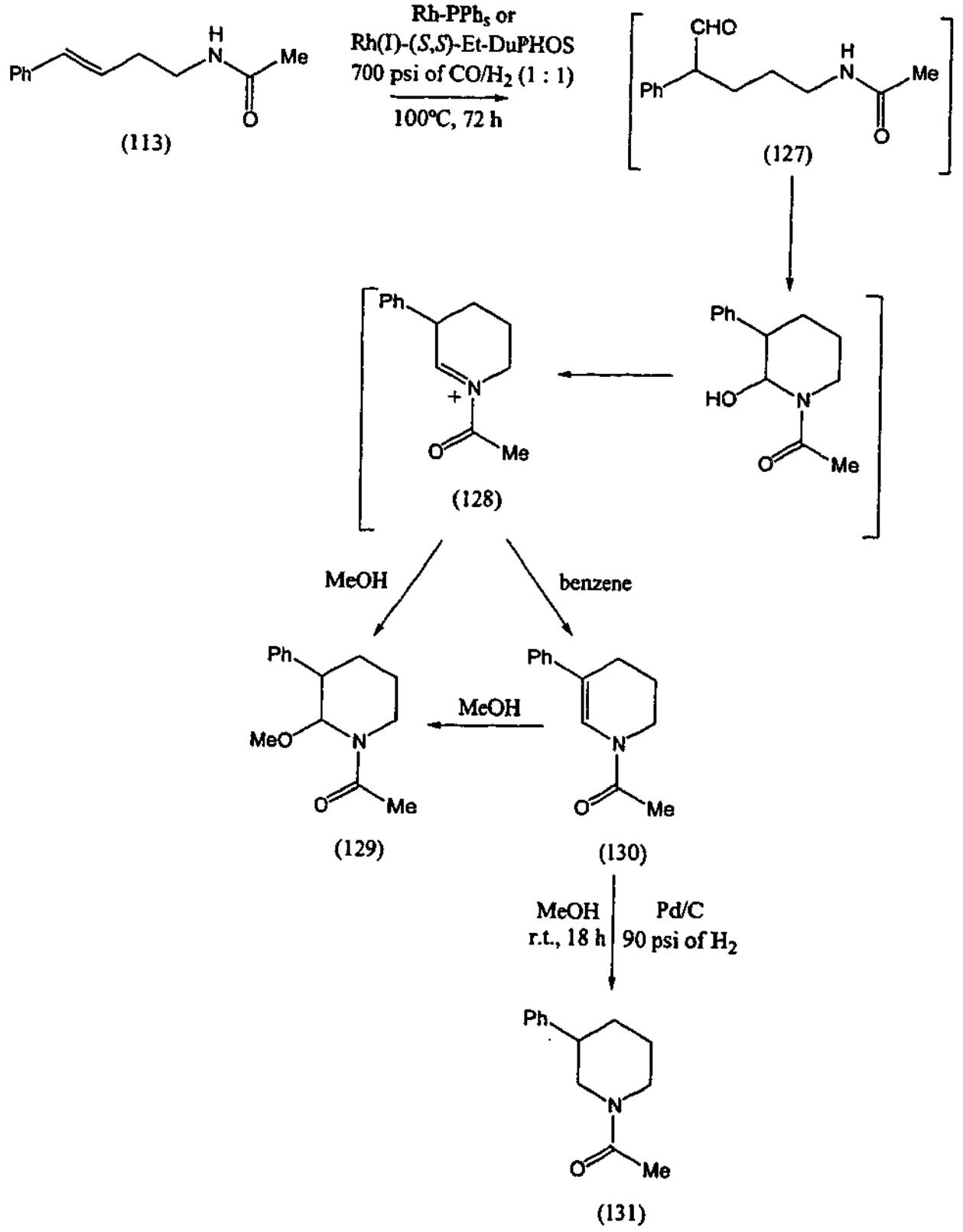
Furthermore, the ratio of aldehyde (122) to cyclised product (125) (20 : 80) was not improved by decreasing the reaction time to 20 h even though the conversion was only 33% (Entry 4). The reaction was also carried out with Rh-$PPh_3$ under 700 psi of $CO/H_2$ for 72 h in benzene at both 80 and 100°C (Entries 5 and 6). Both reactions gave full conversion of substrate (107) to the *N*-acetyl-3phenyl-2,3-didehydropyrrolidine (125) and only trace amounts of aldehyde (122) were observed. These results showed that higher pressure (700 psi), temperature (80-100°C) and longer reaction duration (72 h) were necessary to give high conversion. Unfortunately, the major material produced was the achiral dehydro-cyclic product (125).

Consequently, the hydroformylation of enamide (107) was continued by changing the solvent to methanol in an attempt to trap the intermediate iminium species (123). Initially, the reaction was done under 700 psi of $CO/H_2$ for 72 h at 100°C with Rh-$PPh_3$ as the catalyst. Under these conditions, full conversion to *N*-acetyl-2-methoxy-3-phenylpyrrolidine (124) was achieved (Entry 7). A reaction with Rh(I)-(*S*,*S*)-Et-DuPHOS under the same conditions also gave the amidal compound (124) as the sole product but the reaction only went to 60% completion (Entry 8) and after filtering off the catalyst, the optical rotation of 0° showed that the material (124) was racemic. This result was disappointing and implies that the hydroformylation step is not enantioselective.

The presence of *N*-acetyl-3-phenyl-2,3-didehydropyrrolidine (125) was confirmed by hydrogenation of its double bond with $H_2$ (90 psi) in methanol with a catalytic amount

of Pd/C. In the $^1$H n.m.r. spectrum, the H5 signal had moved significantly downfield. The product (126)[111] was isolated in quantitative yield.

### 3.2.5 Rhodium-catalysed Reaction of (*E*)-*N*-(4-Phenylbut-3-enyl)acetamide (113)




(113) (127) (128) (129) (130) (131)

**Scheme 3.26**

**Table 3.5 Rh-catalysed hydroformylation of the enamide (113)**

| Entry | Catalyst[a] | Solvent | P (psi) | T (°C) | t (h) | Product ratio (127) : (129) : (130) | % Conversion |
|---|---|---|---|---|---|---|---|
| 1 | Rh-DuPHOS[b] | benzene | 700 | 100 | 72 | - : - : 100 | 100 |
| 2 | Rh-$PPh_3$[c] | MeOH | 700 | 100 | 72 | - : 100 : - | 100 |
| 3 | Rh-DuPHOS[b] | MeOH | 700 | 100 | 72 | - : 100 : - | 58 |

[a] Rh-DuPHOS = Rh(I)-(*S*,*S*)-Et-DuPHOS. [b] Substrate (113) : Rh(I)-(*S*,*S*)-Et-DuPHOS ratio = 50 : 1.

[c] Substrate (113) : $[Rh(OAc)_2]_2$ : $PPh_3$ ratio = 50 : 1 : 2.

Hydroformylation of (*E*)-*N*-(4-phenylbut-3-enyl)acetamide (113) was first carried out in benzene using Rh(I)-(*S*,*S*)-Et-DuPHOS as the catalyst under 700 psi of $CO/H_2$ at 100°C for 72 h (Entry 1). The reaction gave full conversion of starting material (113) to the achiral *N*-acetyl-3-phenyl-2,3-didehydropiperidine (130). The reaction was repeated in methanol using Rh-$PPh_3$ under the same conditions and gave *N*-acetyl-2-methoxy-3-phenylpiperidine (129) as the only product (Entry 2). A reaction using Rh(I)-(*S*,*S*)-Et-DuPHOS in methanol gave the methoxy amidal (129) as the major product, together with some starting enamide (113), again showing that Rh-DuPHOS is a much less effective hydroformylation catalyst than Rh-$PPh_3$ (Entry 3). Disappointingly, the optical rotation of the purified cyclic product (129) again showed that the product was racemic.

Conversion of *N*-acetyl-3-phenyl-2,3-didehydropiperidine (130) to *N*-acetyl-3-phenylpiperidine (131) was carried out by reducing the double bond with Pd/C under 90 psi of $H_2$. The product (131)[112] was isolated in quantitative yield and was fully characterised by $^1H$ and $^{13}C$ n.m.r. spectroscopy.

### 3.2.6 Summary

Hydroformylation of (*E*)-*N*-(2-phenylethenyl)acetamide (91) was disappointing. No enantioselectivity was achieved with the chiral catalysts, Rh(I)-Et-DuPHOS, Ru(III)-BINAP and Rh-BINAP, even though excellent regioselectivity for branched aldehyde (115) was achieved. When Rh-$PPh_3$ was used, 60% conversion with 12% reduction was achieved. The aldehydes ((115) and (116)) were oxidised to their corresponding acids ((118) and (119)) and then esterified to known compounds ((120) and (121)). Hydroformylation of longer chain enamides ((107) and (113)) gave the cyclic products, dehydropyrrolidine (125) and dehydropiperidine (130) when the reaction was carried out in benzene, and amidal pyrrolidine (124) and amidal piperidine (129) when the reaction was carried out in methanol. Unfortunately, the resulting methoxy amidals ((124) and (129)) were racemic.

# CHAPTER 4 EVALUATION OF Rh(I)-DuPHOS AS A HYDROFORMYLATION CATALYST

## *4.1 Asymmetric Hydroformylation of Styrene (15)*

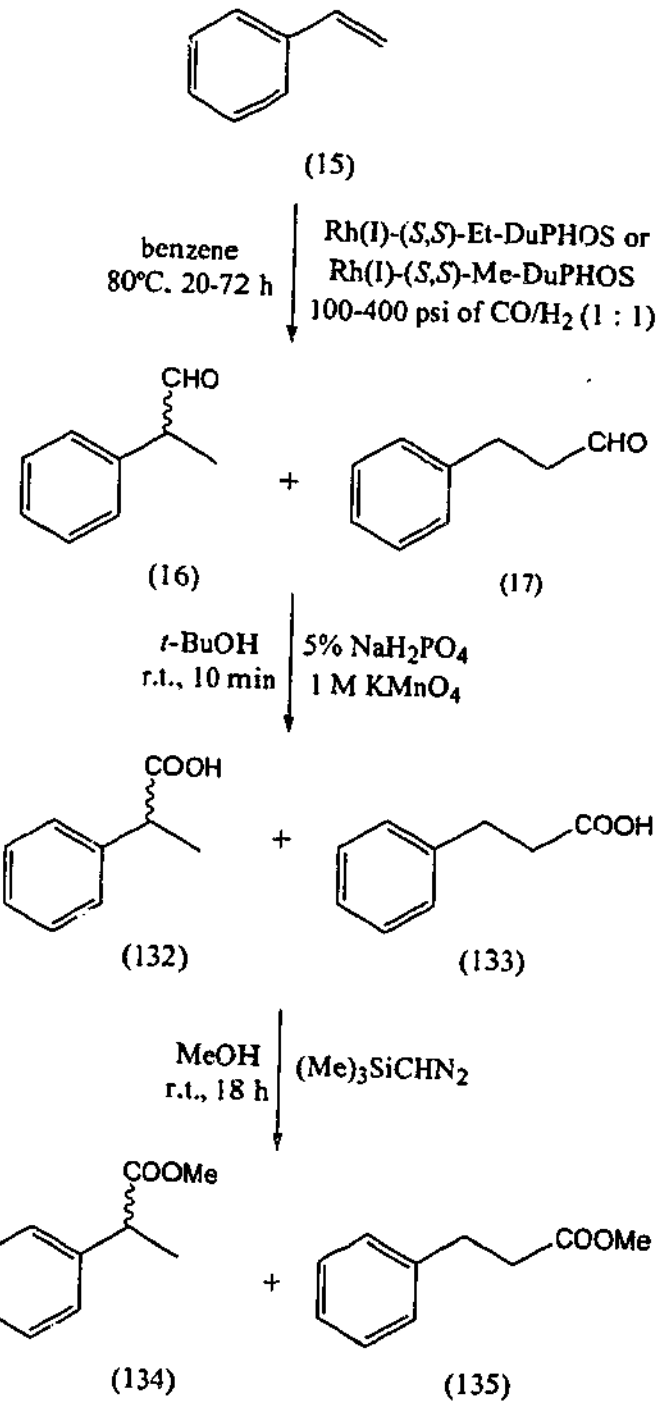
### 4.1.1 General Introduction

Asymmetric hydroformylation of olefins has been a desirable catalytic route for the synthesis of optically pure aldehydes.[42,52,113-115] These aldehydes are essential precursors for the production of a wide range of chemicals including pharmaceuticals and fine chemicals.[40,116] Rh(I)-DuPHOS has been shown to function efficiently as a hydroformylation catalyst in the preceding chapters (refer to Chapter 2 and Chapter 3). In view of its success in achieving very high enantioselectivity in hydrogenation reactions, it was of interest to see if it could give similar high ee's in hydroformylation reactions. Styrene (15) was chosen as the substrate in order to allow straight comparisons with the many different ligands that have been evaluated, examples of which include chiral phosphine-phosphites,[55,117-122] diphosphines[53,54,123-126] and diphosphites.[127-135]

### 4.1.2 General Reaction Conditions

The reaction conditions explored involved a catalyst to substrate ratio of 1 : 100, and an initial pressure (P) of 100-800 psi of $CO/H_2$ (1 : 1). The temperature (T) was 50-160°C with a 20-72 h reaction time (t) in benzene. Optical rotations ($[\alpha]_D^{20}$) were measured using a polarimeter and the enantiomeric excess (ee) was measured through comparison of the optical rotations with literature values. The Rh(I)-(*S*,*S*)-Et-DuPHOS, Rh(I)-(*S*,*S*)-Me-DuPHOS and Rh(I)-(*S*,*S*)-Me-BPE catalyst systems were used. Product purification was carried out using radial chromatography.

### 4.1.3 Rhodium(I)-catalysed Reaction of Styrene (15)




**Scheme 4.1**

**Table 4.1 Rh(I)-catalysed asymmetric hydroformylation of styrene (15) at 80°C**

| Entry | Catalyst | P (psi) | t (h) | % Conversion | Product ratio ((16) : (17)) | % ee[a] |
|---|---|---|---|---|---|---|
| 1 | Rh(I)-(*S,S*)-Et-DuPHOS | 400 | 20 | 35 | 56 : 44 | - |
| 2 | Rh(I)-(*S,S*)-Et-DuPHOS | 400 | 48 | 100 | 60 : 40 | 3 |
| 3 | Rh(I)-(*S,S*)-Et-DuPHOS | 100 | 48 | 45 | 45 : 55 | - |
| 4 | Rh(I)-(*S,S*)-Et-DuPHOS | 100 | 72 | 83 | 50 : 50 | - |
| 5 | Rh(I)-(*S,S*)-Me-DuPHOS | 400 | 48 | 100 | 60 : 40 | - |

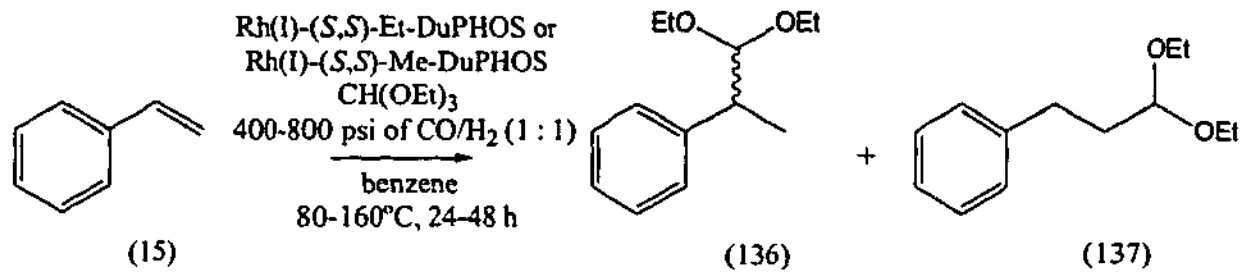
[a] – signifies that the ee was not measured

An initial reaction used Rh(I)-(*S,S*)-Et-DuPHOS in the presence of $CO/H_2$ (400 psi) at 80°C for 20 h. The $^1H$ n.m.r. spectrum showed only 35% conversion to the products, 2-phenylpropanal (16) and 3-phenylpropanal (17), which were obtained in a 56 : 44 ratio (Entry 1). Rh(I)-DuPHOS thus appears to be a less efficient catalyst than other Rh-based catalysts which give higher percentage of conversion, chemo- and regioselectivity.[52,113,115,136-138] The reaction was repeated with an extended reaction time (48 h) in order to achieve 100% conversion. The $^1H$ n.m.r. spectrum of the crude oil showed that branched and linear aldehydes ((16) and (17)) were present in a 60 : 40 ratio (Entry 2). Two reactions were carried out with lower pressure (100 psi) for 48 h (Entry 3) and 72 h (Entry 4). Full conversion was not achieved and the ratios of branched to linear aldehydes ((16) and (17)) were 45 : 55 and 50 : 50 for the two reactions respectively. The greater preference for the linear aldehyde (17) at lower pressures has previously been noted by Ojima.[136] As the Et-DuPHOS ligand is slightly bulkier compared to Me-DuPHOS, the reaction was carried out again with Rh(I)-(*S,S*)-Me-DuPHOS under the same conditions (Entry 5). Unexpectedly, the ratio of aldehydes ((16) and (17)) was the same as shown in Entry 2.

Although the branched aldehyde (16) was the major product, the proportion of branched aldehyde (16) was still low compared to other rhodium-based chiral diphosphine ligands, for example DIOP (71% of (16)),[139] CHIRAPHOS (94% of (16))[124] and BINAPHOS (90% of (16)).[140] Since the aldehydes ((16) and (17)) are unstable and possibly susceptible to racemization, purification was not attempted and they were oxidised to the corresponding carboxylic acids ((132) and (133)).

$KMnO_4$ was used as the oxidizing agent under mild conditions such that the chiral centre (C2) in the branched aldehyde (16) should not be affected. The yield obtained was reasonable (90%) and the $^1H$ n.m.r. spectrum showed that the ratio of isomers ((132) and (133)) was not altered (60 : 40 ratio). The mixture of acids ((132) and (133)) was not separated and the optical rotation was measured on the sample containing 40% of (133). The ee was extremely low (3%) when the optical rotation observed (+2.3°) was compared with the literature value (+78.9°).[141] An attempt to check the ee value involved conversion of the carboxylic acids ((132) and (133)) into their methyl esters ((134) and (135)) by reaction with (trimethylsilyl)diazomethane. The esters ((134) and (135)) were purified using radial chromatography. A sample of clean methyl esters ((134) and (135)) was analysed by HPLC using a OJ column (1.0 ml $min^{-1}$, 10% isopropanol : 90% hexane).[142] Unfortunately, no resolution of the enantiomers was obtained.

### 4.1.4 Rhodium(I)-catalysed Reaction of Styrene (15) with Trapping Reagent




(15) (136) (137)

**Scheme 4.2**

**Table 4.2 Rh(I)-catalysed asymmetric hydroformylation of styrene (15)**

| Entry | Catalyst[a] | P (psi) | T (°C) | t (h) | Product ratio ((136) : (137)) |
|---|---|---|---|---|---|
| 1 | Rh(I)-(*S*,*S*)-Et-DuPHOS | 400 | 80 | 48 | 77 : 23 |
| 2 | Rh(I)-(*S*,*S*)-Et-DuPHOS | 800 | 160 | 24 | 50 : 50[a] |
| 3 | Rh(I)-(*S*,*S*)-Me-BPE | 400 | 80 | 48 | 46 : 54 |

[a] Aldehydes ((16) and (17)) were obtained in a 3 : 1 ratio (*ca.* 66%).

Stille and co-workers pointed out that racemization of the branched aldehyde (16) may occur under the reaction conditions. Therefore, a trapping reagent, triethyl orthoformate, was added to the reaction mixture in order to prevent racemization by converting the aldehydes ((16) and (17)) into their acetals ((136) and (137)) *in situ*.[125] Reactions, Entry 1, Table 4.2 and Entry 2, Table 4.1 were carried out under the same conditions except for the absence of trapping reagent in the latter. Surprisingly the ratio of branched to linear products were determined to be 77 : 23 and 60 : 40 respectively. However, it is difficult to understand why the presence of the trapping reagent would affect the branched to linear aldehyde ratio, and a lack of reproducibility may be the reason for this result.

A reaction under more severe conditions (800 psi at 160°C) gave total conversion of styrene (15). However, most of the product was in the form of aldehydes ((16) and

(17)) rather than acetals ((136) and (137)) (Entry 2). The combined ratio of aldehydes ((16) and (17)) and acetals ((136) and (137)) was calculated to be approximately 67 : 33. The reaction using Rh(I)-Me-BPE unexpectedly gave a slight majority of linear acetal (137) (Entry 3). This could be due to the use of the less bulky Me-BPE ligand.

An optical rotation performed on the mixture of products ((136) and (137)) arising from conditions described in Entry 1, Table 4.2 gave only a very low value. This result was consistent with the low ee value obtained for the acid materials ((132) and (133)) (refer to Section 4.1.3).

### 4.1.5 Summary

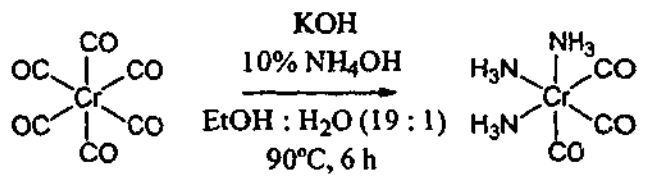
These results have shown that although Rh(I)-DuPHOS acts as a hydroformylation catalyst, the ratio of branched and linear aldehydes ((16) and (17)) obtained is lower than expected. Longer reaction times, higher temperatures and pressures are needed for the reaction to go to completion. Furthermore, the branched aldehydes (16) are racemic.

## 4.2 Asymmetric Hydroformylation of $\eta^6$-Styrene(tricarbonylchromium) (18)

### 4.2.1 General Introduction

The use of the bulky Rh(I)-DuPHOS required severe reaction conditions for the hydroformylation of styrene (15). Coordination of tricarbonylchromium to the arene ring has a large effect on the reactivity of the substituents attached to the ring as the tricarbonylchromium group is strongly electron withdrawing.[56,57] Hence, this group serves to stabilize the build-up of negative charge at the benzylic carbon during hydroformylation reactions and in turn leads to an increased ratio of branched aldehyde (16) under mild conditions. A related example also demonstrated an increased reactivity of styrene (15) involving the introduction of fluorine substituents into the aromatic ring. Ojima *et al.* has shown that hydroformylation of pentaflurostyrene gave excellent regioselectivity for the branched aldehyde (16) (> 97%).[136] It was hoped that reactions under mild conditions would lead to enhanced enantioselectivity by the Rh(I)-DuPHOS system.

### 4.2.2 Preparation of $\eta^6$-Styrene(tricarbonylchromium) (139)

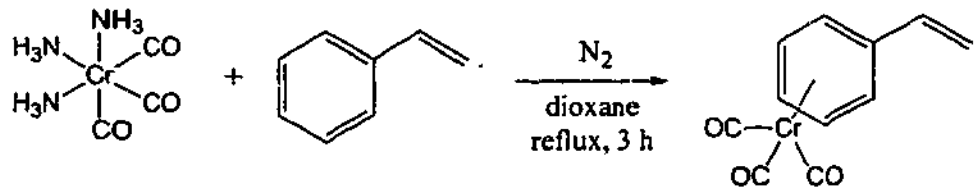



(138) (139)

**Scheme 4.3**

Triamminetricarbonylchromium (139) was prepared by reacting chromium hexacarbonyl (138) with KOH in degassed absolute ethanol and distilled water. After 6 h, the reaction mixture was quenched with 10% $NH_4OH$ to give the product (139) as

a yellow solid in 82% yield. It was found that the ethanol and water mixture used had to be degassed prior to reaction. The IR spectrum was consistent with literature values.[56,143] However, the melting point obtained (183-185°C) was quite different to that reported by Rausch *et al.* and Vebrel *et al.* (100°C[143] and 100-105°C[56]) but close to that reported by Doyle (> 180°C).[57]

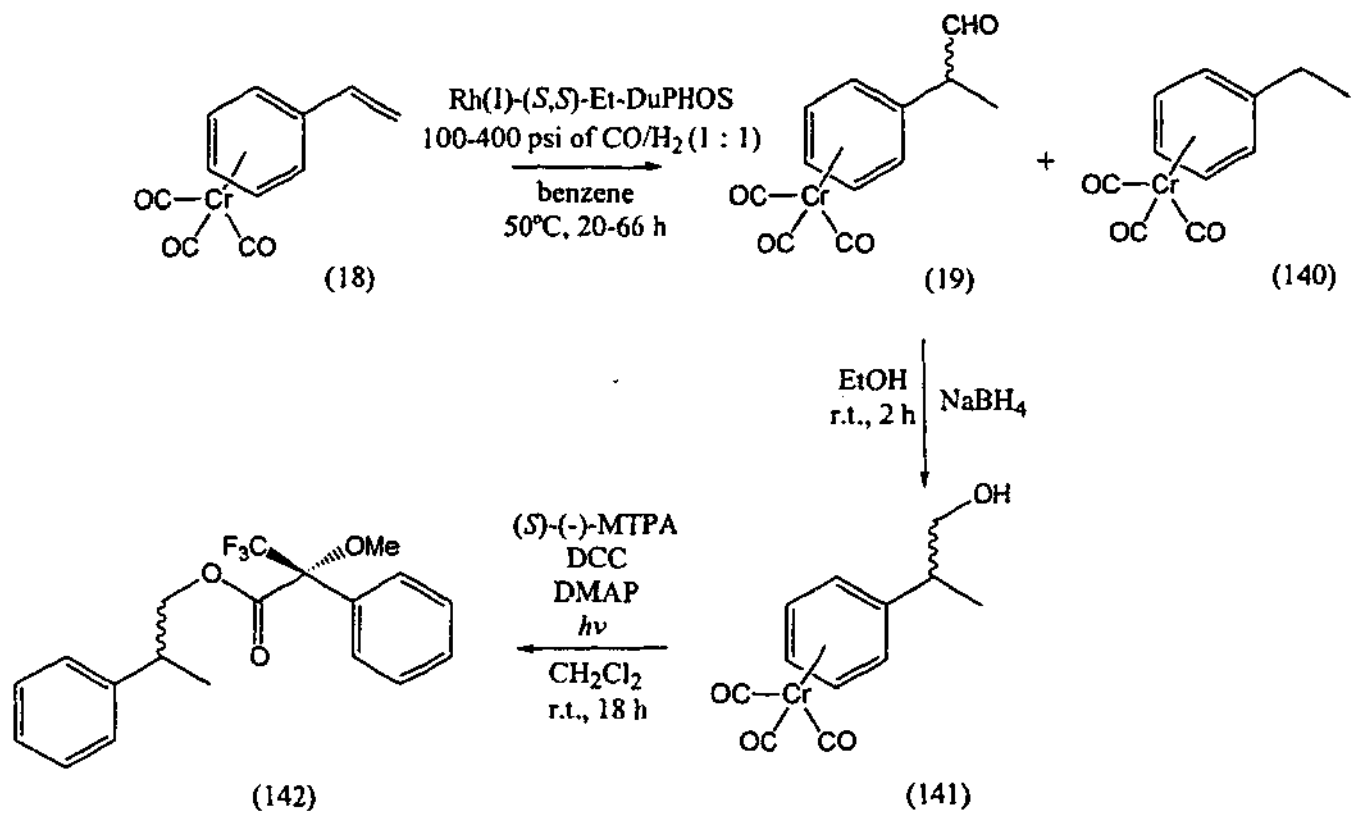



(139) (15) (18)

**Scheme 4.4**

Triamminetricarbonylchromium (139) was reacted with styrene (15) in dioxane. Filtration of the reaction mixture after heating at reflux for 3 h, gave an orange solid in 52% yield. It was crucial that all the steps were carried out under nitrogen using Schlenk techniques due to the styrene chromium complex (18) solutions being sensitive to air. The crude reaction solid collected was purified by sublimation and the pure product (18) s[illegible]ed under nitrogen at -10°C. The melting point and spectral data for the product (18) were in agreement with literature values.[56]

### 4.2.3 Rhodium(I)-catalysed Reactions of $\eta^6$-Styrene(tricarbonylchromium) (18)




(18) (19) (140) (142) (141)

**Scheme 4.5**

**Table 4.3 Rh(I)-catalysed hydroformylation of the the $\eta^6$-styrene chromium complex (18) at 50°C**

| Entry | P (psi) | t (h) | Product ratio (19) : (140) | % ee[a] |
|---|---|---|---|---|
| 1 | 400 | 66 | - : 100 | - |
| 2 | 100 | 66 | 100 : - | 0 |
| 3 | 100 | 20 | 100 : - | 56 |

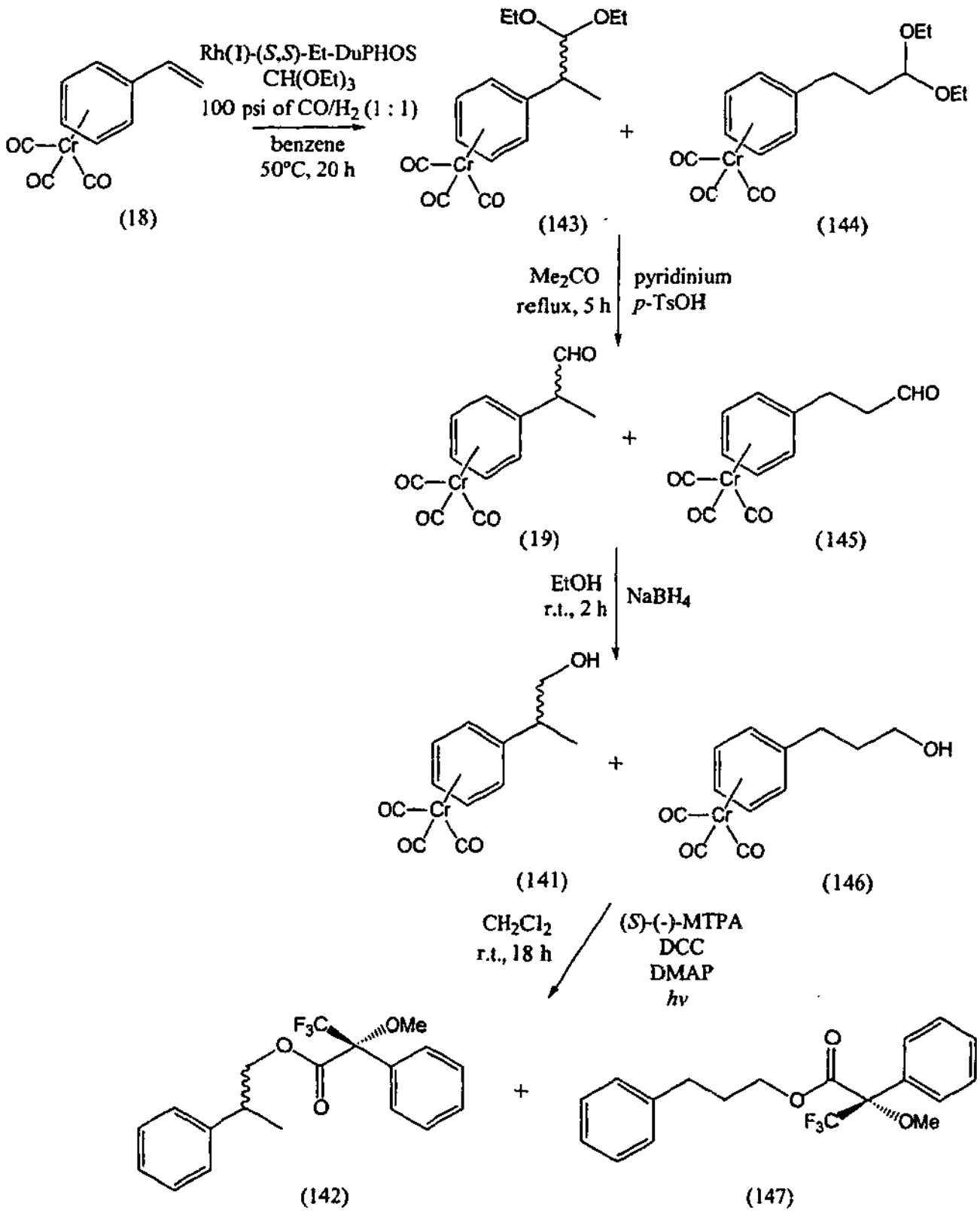
[a] - signifies that the ee was not measured.

Hydroformylation of the $\eta^6$-styrene chromium complex (18) using Rh(I)-Et-DuPHOS was firstly carried out under 400 psi of $CO/H_2$ for 66 h at 50°C (Entry 1). The reaction mainly gave the hydrogenated by-product (140) with no sign of the aldehyde (19). It was thought that the high pressure could be responsible for the strong preference for hydrogenation. Thus, the pressure was lowered to 100 psi and this change resulted in

the formation of the branched aldehyde (19) as the only product (Entry 2). Hence, complexation of the benzene ring with chromium tricarbonyl resulted in a dramatic increase in the reactivity of the styrene double bond.

The enantiomeric excess was determined *via* reduction of aldehyde (19) to the alcohol (141) and conversion to its Mosher's ester (142). The aldehyde generated (19) over this long reaction time (66 h) was found to be racemic by $^{19}F$ n.m.r. spectroscopy (Entry 2). Decreasing the reaction time to 20 h again led to only branched aldehyde (19) and this was now shown to have a higher ee (56%) (Entry 3). Significantly, the ratio of branched aldehyde (19) and ee were better than other rhodium-based chiral ligands, for example DIOP (90% of (19), 20% ee), BPPM (95% of (19), 14% ee) and BINAP (93% of (19), 7% ee) which were found by Doyle *et al.*.[57,144]

### 4.2.4 Rhodium(I)-catalysed Reaction of $\eta^6$-Styrene(tricarbonylchromium) (18) with Trapping Reagent




**Scheme 4.6**

Hydroformylation of $\eta^6$-styrene(tricarbonylchromium) (18) in the presence of triethyl orthoformate, as the trapping reagent, was carried out with 100 psi of *syn* gas at 50°C

for 20 h. The reagent was again added to prevent racemization of the aldehyde.[125] A mixture of 1,1-diethoxy-2-[$\eta^6$-phenyl(tricarbonylchromium)]propane (143) and 1,1-diethoxy-3-[$\eta^6$-phenyl(tricarbonylchromium)]propane (144) were formed in a 85 : 15 ratio. In this case, the addition of triethyl orthoformate led to an increase in linear aldehyde (145) (compared with Entry 3, Table 4.3). In contrast, the effect of this reagent on the hydroformylation of styrene (15) led to an increase in the branched isomer (compared Entry 2, Table 4.1 with Entry 1, Table 4.2).

The acetals ((143) and (144)) were cleaved using a catalytic amount of pyridinium *p*-toluensulfonic acid in acetone giving 2-[$\eta^6$-phenyl(tricarbonylchromium)]propanal (19) and 3-[$\eta^6$-phenyl(tricarbonylchromium)]propanal (145) with aldehyde peaks at $\delta$ 9.53 and 9.70 respectively in the $^1$H n.m.r. spectrum. The aldehydes ((19) and (145)) were reduced with $NaBH_4$ to the corresponding alcohols ((141) and (146)) which were then esterified with (*S*)-(-) -MTPA. The $^{19}$F n.m.r. spectrum gave an ee of 50% for the branched aldehyde (19), slightly lower than the value obtained without the triethyl orthoformate present. The tricarbonylchromium group was cleaved off by leaving the mixture exposed to light.

### 4.2.5 Summary

Hydroformylation of $\eta^6$-styrene chromium complex (18) using Rh(I)-DuPHOS gave a better product ratio than the non-complexed styrene (15). The reaction conditions required were mild and higher ee (56% and 50%) were obtained compared to the non-complexed styrene (15). The results of reactions using a trapping reagent showed there was no evidence for racemisation of the branched aldehyde (16).

# CHAPTER 5 EXPERIMENTAL

## *5.1 General*

Melting points (m.p.) were determined using a Gallenkamp melting point apparatus and are uncorrected. Microanalyses were carried out by Chemical and Microanalytical Services Pty. Ltd., Melbourne (CMAS).

Infrared (IR) spectra were recorded using a Perkin-Elmer 1600 series Fourier Transform infrared spectrophotometer as thin films of liquids (Film) or as potassium bromide (KBr) discs of solids. The IR data ($\nu_{max}$) were recorded in wavenumbers ($cm^{-1}$) with the relative intensities expressed as s (strong), m (medium), w (weak) and b (broad).

Proton nuclear magnetic resonance ($^1H$ n.m.r.) spectra were recorded at 300 MHz with a Varian Mercury 300 Q Spectrometer, at 300 MHz with a Bruk . AM-300 Spectrometer and at 400 MHz with a Bruker DRX400 Spectrometer as solutions in deuterated solvents as stated. Each resonance was assigned according to the following convention: chemical shift, measured in parts per million (ppm) relative to the internal reference tetramethylsilane (TMS) (0.00 ppm); multiplicity, denoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and b (broad); number of protons; observed coupling constants (*J* Hz) and proton assignment.

Carbon nuclear magnetic resonance ($^{13}C$ n.m.r.) spectra were recorded at 75 MHz with a Varian Mercury 300 Q Spectrometer, at 75 MHz with a Bruker AM-300 Spectrometer and at 100 MHz with a Bruker DRX400 Spectrometer in deuterated

solvents as specified with TMS (0.00 ppm) as the internal reference. Chemical shifts were measured in ppm and assignments for identifiable carbons are given.

Phosphorus nuclear magnetic resonance ($^{31}P$ n.m.r.) spectra were recorded at 121.5 MHz on a Bruker AM-300 spectrometer in deuterated solvents with 85% phosphoric acid ($H_3PO_4$) as the external standard (0.00 ppm). The chemical shifts were quoted with positive values downfield from $H_3PO_4$.

Correlation Spectroscopy (COSY) was used to correlate the chemical shifts of proton that were coupled to one another. Heteronuclear Multiple Quantum Correlation (HMQC) was used to determine the corresponding $^{13}C$ to which $^{1}H$ were attached. Heteronuclear Multiple Bond Correlation (HMBC) spectroscopy was used to determine long range $^{13}C$-$^{1}H$ connectivity. All experiments were carried out using a Bruker DRX400 spectrometer.

Low resolution electron impact mass spectra (EI) were obtained using a VG TRIO-1 mass spectrometer at 70 eV. $M^+$ denotes the molecular ion. Electrospray mass spectra ($ESI^+$) were recorded on a Micromass Platform Electrospray mass spectrometer using methanol as the mobile phase. Accurate mass measurements were obtained at high resolution with a Bruker BioApex 47 e FTMS (4.7 Telsa magnet) fitted with an analytical electrospray source.

Analytical thin layer chromatography (t.l.c.) was performed on plastic plates coated with 0.25 mm of silica gel (Polygram SIL G/$UV_{254}$). Flash chromatography was carried out using Merck silica gel 60, 0.063-0.200 mm (70-230 mesh). Preparative

radial chromatography was carried out using a Chromatotron model 7924T on glass plates coated with 2 mm of absorbent (Silica Gel $F_{254}$). The compounds were visualized under 254 nm ultraviolet irradiation or by exposure to iodine vapour. Eluent mixtures were expressed as volume to volume ratios.

Analytical gas chromatography (GC) was carried out on a capillary column Model C-002 (column: 0.53 mm x 30 cm, 30QCS/BPX5) and chiral column Model C-024 (column: 0.25 mm x 50 cm, 50 CP2/XE60-SVALSAPEA) using helium as the carrier gas. The capillary column was operated on temperature programs: *i)* the initial column temperature was 50°C for 1 min, then heated to 280°C at 10°C $min^{-1}$ or *ii)* the initial column temperature was 80°C for 3 min, then heated to 280°C at 10°C $min^{-1}$. The chiral column was operated isothermally: 130°C, 140°C, 150°C or 165°C for 20 min and on a temperature program: the initial column temperature was 100°C for 1 min, then heated to 280°C at 5°C $min^{-1}$ and maintained at 280°C for 9 min.

High performance liquid chromatography (HPLC) was performed on a Waters Model 6000 using a Waters gradient program Model 660 and Waters Model 481 detector. It was carried out on a Varian Variable Wavelength Model UV/VIS 50 detector, $\lambda = 254$ nm and a Rheodyne 712S (100 µl) injector. Before analysis, samples were purified through silica precoated glass plates (Silica Gel $F_{254}$, 2.5 x 7.5 cm. thickness 250 µm) and grated silica powder was filtered by 25 mm syringe filters (0.46 cm x 25 cm, 0.2 U, 100/PK). Analysis was performed using DAICEL Chirasil® OD, 0.46 mm x 25 cm or DAICEL Chirasil® OJ, 0.46 mm x 25 cm columns. The solvent system applied was 10% isopropanol : 90% light petroleum with a flow rate of 1.0 ml $min^{-1}$.

Optical rotations ($[\alpha]_D^{20}$) were measured using Perkin Elmer Model 141 Polarimeter. The radiation source employed was a sodium (Na) lamp at 589 nm. The sample cell used was 1 ml in volume with path length of 10 cm.

### 5.1.1 Materials and Reagents

Acetone ($Me_2CO$), absolute ethanol (EtOH), acetonitrile (MeCN), dichloromethane ($CH_2Cl_2$), ethyl acetate (EtOAc), diethyl ether ($Et_2O$), *iso*-propanol (*i*-PrOH), methanol (MeOH), *tert*-butanol (*t*-BuOH), triethylamine ($NEt_3$), toluene, dioxane, magnesium sulfate ($MgSO_4$), sodium sulfate ($Na_2SO_4$), sodium chloride (NaCl), sodium bicarbonate ($NaHCO_3$), sodium sulfate decahydrate ($Na_2SO_4.10H_2O$), potassium carbonate ($K_2CO_3$) were used as supplied by BDH. Light petroleum (b.p. range 60-70°C) was dried over calcium chloride ($CaCl_2$), distilled from $CaCl_2$. Anhydrous tetrahydrofuran (THF) and diethyl ether ($Et_2O$) were stored over sodium (Na) wire and then distilled from sodium and benzophenone prior to use. Benzene was stored over sodium wire. Dimethyl sulfoxide (DMSO) and common reagents were used as supplied by Aldrich. Chloroform ($CHCl_3$) was used as supplied by Merck. Deuterated solvents were used as supplied by Cambridge Isotopes Laboratories.

Palladium on charcoal (Pd/C) with 10% Pd concentration, sodium borohydride ($NaBH_4$) and lithium aluminium hydride ($LiAlH_4$) were used as supplied by Sigma-Aldrich and stored in dessicators.

### 5.1.2 Hydrogenation Procedures

***Asymmetric catalysts and materials:***

[(1,2-Bis((2*R*,5*R*)-2,5-diethylphospholano)benzene-(1,5-cyclooctadiene)rhodium(I)]-trifluoromethanesulfonate ([(COD)Rh(I)((2*R*,5*R*)-Et-DuPHOS)]OTf or Rh(I)-(*R*,*R*)-Et-DuPHOS) and [(1,2-bis((2*S*,5*S*)-2,5-diethylphospholano)benzene-(1,5-cyclooctadiene)rhodium(I)]-trifluoromethanesulfonate ([(COD)Rh(I)((2*S*,5*S*)-Et-DuPHOS)]OTf or Rh(I)-(*S*,*S*)-Et-DuPHOS) were used as supplied from Strem Chemicals.

Hydrogen and Nitrogen – High purity (< 10 ppm of oxygen) and purified by passage through columns which removed traces of water, oxygen and hydrocarbon were obtained from BOC gases.

Reaction vessels – Fisher-Porter tubes (100 ml) fitted with pressure gauge heads and stirrer beads were employed.

***General palladium on charcoal hydrogenation:***

Substrate, solvent and palladium on charcoal (Pd/C) were placed in a Fischer-Porter tube. The tube was evacuated before it was pressurized with hydrogen to the stated pressure (P) and left stirring at ambient temperature for the reported period of time (t).

***General asymmetric hydrogenation:***

In a drybox , the substrate, catalyst (substrate : catalyst = 100 : 1) and deoxygenated methanol or benzene were added into a Fischer-Porter tube. Three vacuum/nitrogen cycles were used to purge the gas line of any oxygen, followed by three vacuum/nitrogen cycles and three vacuum/hydrogen cycles of the vessel before the

vessel was pressurized to the stated pressure with hydrogen. The vessel was left stirring at ambient temperature for the reported period of time.

For liquid substrates, a freeze-pump-thaw cycle was applied, the solution was transferred into a drybox and loaded into a Fischer-Porter tube as above.

***General freeze-pump-thaw:***

The substrate was dissolved in methanol or benzene in a sealed vessel which was immersed in liquid nitrogen and the contents frozen. The vessel was opened to vacuum in order to remove most of the gas, then resealed again. The solution was thawed before being frozen again. The above steps were repeated > three times until gas evolution was no longer observed during the thaw cycle.

### 5.1.3 Hydroformylation Procedures

***Catalysts and materials:***

Rhodium acetate dimer ($[Rh(OAc)_2]_2$) was prepared as in the literature[43] and 6, 6'-((3, 3'-bis(1, 1-dimethylethyl)-5, 5'-dimethoxy-1, 1'-biphenyl)-2, 2'-diyl)bis(dibenzo(d,f)(1,3,2)dioxaphosphepin) (BIPHEPHOS) was prepared by Eva M. Campi. Triphenylphosphine ($PPh_3$) and dichloro[(*S*)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl] ((*S*)-BINAP) were commercially available from Aldrich. [(COD)Rh(I)((2*S*,5*S*)-Et-DuPHOS)]OTf or Rh(I)-(*S*,*S*)-Et-DuPHOS, [(1,2-bis((2*S*,5*S*)-2,5-dimethylphospholano)benzene-(1,5-cyclooctadiene)rhodium(I)]-trifluoromethanesulfonate ([(COD)Rh(I) ((2*S*,5*S*)-Me-DuPHOS)]OTf or Rh(I)-(*S*,*S*)-Me-DuPHOS), [(1,2-bis((2*S*,5*S*)-2,5-dimethylphospholano)ethane-(1,5-cyclooctadiene)rhodium(I)]-trifluoromethanesulfonate ([(COD)Rh(I)((2*S*,5*S*)-Me-BPE)]OTf or Rh(I)-(*S*,*S*)-Me-BPE) and dichloro[(*S*)-(-)-2,2'-bis(diphenylphosphino)-

1,1'-binaphthyl]ruthenium(III) (Ru(III)-(*S*)-BINAP) were used as supplied from Strem Chemicals.

A 1 : 1 molar mixture of $CO/H_2$ was obtained from BOC gases.

Reaction vessels – stainless steel Parr autoclave (100 ml) fitted with teflon coated pressure gauge heads, glass liner, stirrer bead, thermocouple and heating block were employed.

***General hydroformylation:***

The reagents and substrate were added under nitrogen into the autoclave which was flushed three times with 100 psi of $CO/H_2$ (1 : 1) and then pressurized to the stated pressure (P) of the same gases. The autoclave was inserted to the heating block where its temperature was controlled by a thermocouple and the reaction was stirred with a magnetic stirrer under the heating block. The vessel was left stirring at the reported temperature (T) for the reported period of time (t). At the end of the reaction, the vessel was left to cool to ambient temperature. The gas mixture was released slowly and the contents were treated and analysed as reported.

### 5.1.4 Supercritical Carbon Dioxide ($scCO_2$) Reactions Procedures

***Catalysts and materials:***

[(COD)Rh(I)((2*S*,5*S*)-Et-DuPHOS)]OTf or Rh(I)-(*S*,*S*)-Et-DuPHOS was used as supplied from Strem Chemicals.

High purity hydrogen (< 10 ppm of oxygen) and 1 : 1 molar mixture of $CO/H_2$ were obtained from BOC gases. High purity of liquid carbon dioxide (SCF grade) (< 4 ppm of oxygen and water) was obtained from BOC gases.

Reaction vessels – stainless steel Parr autoclave (100 ml) fitted with teflon coated pressure gauge heads, glass liner, stirrer bead, thermocouple and heating block were employed.

High pressure syringe pump (Model 260D) from ISCO which was connected to the liquid $CO_2$ cylinder, was used to charge the reaction vessels in high pressure (> 1200 psi).

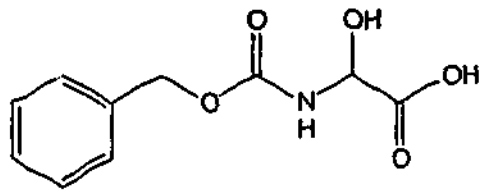
***General supercritical carbon dioxide reactions:***

In a drybox, the reagents and substrate were added into the autoclave. The gas line was flushed three times with $H_2$ or $CO/H_2$ (1 : 1) and then pressurized to the stated pressure (P) of the same gases. The vessel was then charged with 1200 psi of liquid $CO_2$. The autoclave was inserted to the heating block where its temperature was controlled by a thermocouple and the reaction was stirred with a magnetic stirrer under the heating block. The vessel was left stirring at the reported temperature (T) for the reported period of time (t). At the end of the reaction, the vessel was cooled with ice (0°C). The gas mixture was released very slowly over 1 h and the contents were treated and analysed as reported.

# *Experimental For Chapter 2*

## *5.2 Preparation of Hydrogenation Precursors*

### 5.2.1 Preparation of *N*-Benzyloxycarbonyl-2-hydroxyglycine (28)



(28)

A mixture of benzyl carbamate (27) (15.0 g, 99.2 mmol) and glyoxylic acid monohydrate (26) (10.01 g, 109.1 mmol) in dry diethyl ether (170 ml) was stirred for 18 h as described by Zoller *et al.*.[59] The white crystalline product which formed was collected by filtration and washed with diethyl ether to give the acid (28) (22.7 g, 100%), m.p. 199-200°C (lit.[59] 196-198°C).

$\nu_{max}$ (KBr): 3334s, 1729s, 1701s, 1531s, 1452m, 1272s, 1250s, 1092s, 1020w, 893w, 695w $cm^{-1}$.

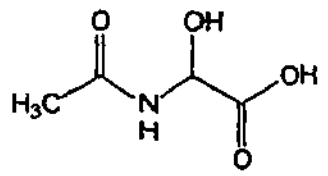
$^1$H n.m.r. (300 MHz, DMSO): δ 5.03, s, 2H, $CH_2O$; 5.20, d, 1H, *J* 8.9 Hz, H2; 7.28-7.49, m, 5H, ArH; 8.14, d, 1H, *J* 8.9 Hz, NH.

$^{13}$C n.m.r. (75 MHz, DMSO): δ 66.5, $CH_2O$; 74.1, C2; 128.7, C2', 6' and C3', 5'; 129.2, C4'; 137.7, C1'; 156.3, CONH; 171.9, C1.

Mass spectrum ($ESI^+$, MeOH): *m/z* 248.0 $(M+Na)^+$.

The spectral data were consistent with those reported in the literature.[59]

### 5.2.2 Preparation of *N*-Acetyl-2-hydroxyglycine (35)



(35)

Acetamide (34) (6.1 g, 103.26 mmol) and glyoxylic acid monohydrate (26) (10.6 g, 115.15 mmol) were dissolved in acetone (150 ml) and the mixture was heated at reflux as reported by Williams *et al.*.[61] After 18 h, the reaction mixture was concentrated *in vacuo* to give the product (35) (14.86 g, 100%) as a thick yellow oil.

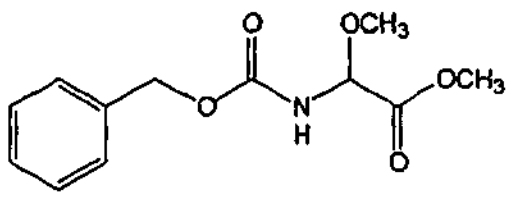
$\nu_{max}$ (Film): 3344b, 1733s, 1661s, 1538s, 1422w, 1377m, 1233m, 1111m, 1077m $cm^{-1}$.

$^1$H n.m.r. (300 MHz, DMSO): δ 1.84, s, 3H, $COCH_3$; 5.38, d, 1H, *J* 8.7 Hz, H2; 8.66, d, 1H, *J* 8.4 Hz, NH.

$^{13}$C n.m.r. (75 MHz, DMSO): δ 22.9, $CO\underline{C}H_3$; 71.2, C2; 169.7, CONH; 171.5, C1.

The spectral data were consistent with those reported in the literature.[61]

### 5.2.3 Preparation of Methyl *N*-benzyloxycarbonyl-2-methoxyglycinate (29)



(29)

Following the method described by Zoller *et al.*,[59] concentrated sulfuric acid ($H_2SO_4$) (98%, 3.2 ml) was added to a cooled (0°C) and stirred solution of *N*-benzyloxycarbonyl-2-hydroxyglycine (28) (22.7 g, 100.7 mmol) in methanol (240 ml). The mixture was stirred for 2 days at ambient temperature then poured into an ice cooled saturated $NaHCO_3$ solution (500 ml). The mixture was extracted with ethyl

acetate (3 x 300 ml), the combined extract was dried over $MgSO_4$ and concentrated under reduced pressure to give an oil. Crystallization was initiated on addition of light petroleum and the crystal was collected by filtration to give the product (29) (27.72 g, 100%) as colourless needles flakes, m.p. 78-80°C (lit.[59] 76-78°C).

$\nu_{max}$ (KBr): 3312s, 3036m, 2946s, 2845m, 1752s, 1688s, 1440s, 1362s, 1263s, 1226s, 1103s, 881s, 739s $cm^{-1}$.

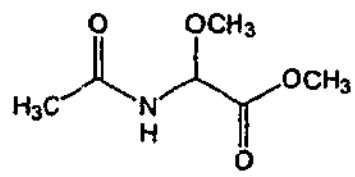
$^1H$ n.m.r. (300 MHz, DMSO): δ 3.46, s, 3H, $CHOC\underline{H}_3$; 3.80, s, 3H, $COOCH_3$; 5.15, s, 2H, $CH_2O$; 5.36, d, 1H, *J* 9.6 Hz, H2; 5.87, d, 1H, *J* 8.6 Hz, NH; 7.31-7.39, m, 5H, ArH.

$^{13}C$ n.m.r. (75 MHz, DMSO): δ 53.3, 56.6, $CHO\underline{C}H_3$ and $COO\underline{C}H_3$; 67.7, $CH_2O$; 80.9, C2; 128.4, 128.8, C2', 6' and C3', 5'; 128.6, C4'; 135.9, C1'; 155.8, CONH; 168.1, C1.

Mass spectrum ($ESI^+$, MeOH): *m/z* 276.1 $(M+Na)^+$.

The spectral data were consistent with those reported in the literature.[59]

### 5.2.4 Preparation of *N*-Acetyl-2-methoxyglycinate (36)




(36)

Using an identical method as described above (refer to Section 5.2.3), concentrated sulfuric acid ($H_2SO_4$) (98%, 7.7 ml) was added to a stirred solution of *N*-acetyl-2-hydroxyglycine (35) (27.52 g, 206.52 mmol) in methanol (480 ml). After work-up, the mixture was concentrated to give the product (36) (23.66 g, 71%) as a yellow oil.

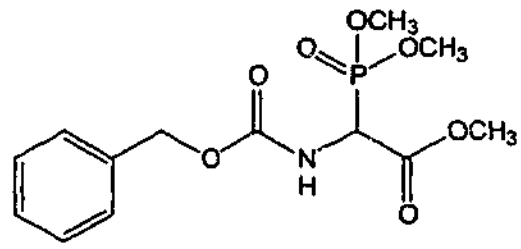
$\nu_{max}$ (Film): 3333b, 3066w, 29455w, 1750s, 1672s, 1527s, 1438s, 1372s, 1222s, 1105s, 944w, 783w $cm^{-1}$.

$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 2.11, s, 3H, $COCH_3$; 3.45, s, 3H, $CHOCH_3$; 3.81, s, 3H, $COOCH_3$; 5.55, d, 1H, *J* 9.3 Hz, H2; 7.28, bs, 1H, NH.

$^{13}$C n.m.r. (75 MHz, $CDCl_3$): δ 22.97, $COCH_3$; 52.79, $COOCH_3$; 56.38, $CHOCH_3$; 78.17, C2; 168.4, CONH; 170.9, C1.

The spectral data were consistent with those reported in the literature.[62]

### 5.2.5 Preparation of Methyl 2-benzyloxycarbonylamino-2-dimethoxyphosphinyl)acetate (30)




(30)

Using the identical method described by Schmidt *et al.*,[60] methyl *N*-benzyloxycarbonyl-2-methoxyglycinate (29) (23.0 g, 90.81 mmol) was dissolved in toluene (100 ml) at 70°C and phosphorus(III) chloride ($PCl_3$) (8.0 ml, 90.81 mmol) was added. The mixture was stirred for 18 h, trimethyl phosphite ($P(OMe)_3$) (10.7 ml, 90.81 mmol) was added dropwise and the mixture was stirred for another 2 h at 70°C. The mixture was concentrated under reduced pressure and redissolved in ethyl acetate. The solution was washed with saturated $NaHCO_3$ solution (3 x 50 ml) and the organic layer was dried over $MgSO_4$. The solvent was evaporated *in vacuo* and light petroleum was added to the oil with vigorous stirring to give the title compound (30) (24.33 g, 81%) as a white solid, m.p. 77-78°C (lit.[60] 80°C).

$\nu_{max}$ (KBr): 3322s, 3034m, 2946s, 2860w, 1750s, 1717s, 1457m, 1335s, 1276s, 1240s $cm^{-1}$.

$^{1}$H n.m.r. (300 MHz, $CDCl_3$): δ 3.77-3.83, m, 9H, $COOCH_3$ and 2 x $CH_3OP$; 4.93, dd, 1H, *J* 22.4, 9.3 Hz, H2; 5.13, d, 1H, *J* 12.2 Hz and 5.15, d, 1H, *J* 12.1 Hz, $CH_2O$; 5.77, bd, 1H, *J* ~8.2 Hz, NH; 7.32-7.40, m, 5H, ArH.

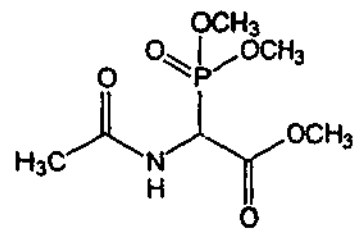
$^{13}$C n.m.r. (75 MHz, $CDCl_3$): δ 52.4, d, *J* 148.0 Hz, C2; 53.7, $COO\underline{C}H_3$; 54.4, d, *J* 6.9 Hz and 54.5, d, *J* 6.6 Hz, $CH_3OP$; 67.7, $CH_2O$; 128.4, 128.5, 128.8, ArCH; 136.0, C1'; 155.8, CONH; 167.3, C1.

$^{31}$P n.m.r. (121.5 MHz, $CDCl_3$): δ 19.62, s.

Mass spectrum ($ESI^+$, MeOH): *m/z* 354.1 $(M+Na)^+$.

The spectral data were consistent with those reported in the literature.[60]

### 5.2.6 Preparation of Methyl 2-acetylamino-2-(dimethoxyphosphinyl)acetate (31)



(31)

Methyl 2-benzyloxycarbonylamino-2-(dimethoxyphosphinyl)acetate (30) (10.0 g, 30.18 mmol) was dissolved in methanol (80 ml). The solution was added to a Fischer-Porter tube followed by palladium on charcoal (10%, 0.75 g) and acetic anhydride ($(MeCO)_2O$) (7.7 ml, 81.49 mmol). The mixture was hydrogenated at 60 psi for 18 h (refer to Section 5.1.2) as stated by Schmidt *et al.*.[60] The catalyst was removed by filtration through a Celite pad and the filtrate was concentrated *in vacuo* to give the title compound (31) (8.06 g, 100%) as a colourless solid, m.p. 90-92°C (lit.[60] 88-89°C).

$\nu_{max}$ (KBr): 3281m, 3050w, 2852w, 1749m, 1673m, 1540m, 1309m, 1287w, 1232w, 1133m, 1061m, 1028m $cm^{-1}$.

$^1H$ n.m.r. (300 MHz, $CDCl_3$): δ 2.06, s, 3H, $COCH_3$; 3.79-3.81, m, 9H, $COOCH_3$ and 2 x $CH_3OP$; 5.24, dd, 1H, *J* 22.3, 8.5 Hz, H2; 6.74, d, 1H, *J* 8.6 Hz, NH.

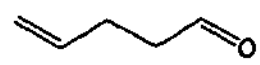
$^{13}C$ n.m.r. (75 MHz, $CDCl_3$): δ 23.3, $CO\underline{C}H_3$; 49.3, d, *J* 147.2 Hz, C2; 53.7, $COO\underline{C}H_3$; 54.3, d, *J* 6.6 Hz, and 54.6, d, *J* 6.3 Hz, $CH_3OP$; 167.3, d, *J* 2.0 Hz, C1; 169.7, d, *J* 5.7 Hz, CONH.

Mass spectrum ($ESI^+$, MeOH): *m/z* 262.0 $(M+Na)^+$.

The spectral data were consistent with those reported in the literature.[60]

Reaction of *N*-acetyl-2-methoxyglycinate (36) (1.01 g, 6.27 mmol) with phosphorus(III) chloride ($PCl_3$) (0.55 ml, 6.27 mmol) and trimethyl phosphite ($P(OMe)_3$) (0.74 ml, 6.27 mmol) at 70°C was carried out as described in Section 5.2.5. The concentrated mixture was redissolved in dichloromethane (50 ml), then washed with saturated $NaHCO_3$ solution (3 x 30 ml). The combined aqueous layers were extracted in a continuous extractor with dichloromethane (100 ml). After 2 days, the organic layer was concentrated *in vacuo* to give product (31) (0.43 g, 30%) as a colourless solid. The spectral data were identical to those above.

### 5.2.7 Preparation of 4-Pentenal (41)



(41)

Following the method by described by Mancuso *et al.*,[63,64] dimethyl sulfoxide (1.52 ml, 21.34 mmol) in dichloromethane (5 ml) was added dropwise to a solution of oxalyl chloride (37) (0.93 ml, 10.67 mmol) in dichloromethane (20 ml) at –60°C under nitrogen. The mixture was stirred for 5 min before the addition of 4-pentenol

(39) (1.0 ml, 9.7 mmol) in dichloromethane (5 ml). The mixture was stirred for 15 min prior to the addition of triethylamine ($NEt_3$) (6.76 ml, 48.5 mmol), then allowed to warm to ambient temperature. After 1.5 h, the mixture was quenched with water (100 ml) and the aqueous layer was extracted with dichloromethane (2 x 100 ml). The combined organic layer was washed saturated with saturated NaCl solution (2 x 200 ml), 1 M HCl solution (2 x 50 ml), saturated $Na_2CO_3$ solution (2 x 50 ml) and water (50 ml), dried over $MgSO_4$. The solvent was removed by distillation at atmospheric pressure to give a residual oil (1.30 g). The $^1H$ and $^{13}C$ n.m.r. spectra indicated that the crude oil was a mixture of the desired product, 4-pentenal (41) and starting material (39) (δ 3.62, t, 2H, $C\underline{H_2}OH$) in a approximate ratio of 83 : 17 (a approximate yield for (41) as 0.68 g, 83%). The crude product was used in a subsequent reaction (Section 5.2.10).

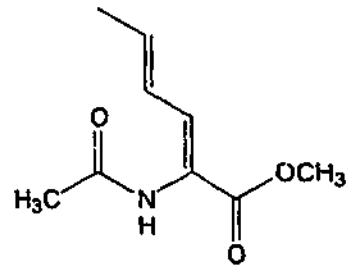
$\nu_{max}$ (Film): 3498b, 3077m, 2937s, 1736m, 1641s, 1439m, 1372m, 1125m, 1069m, 993m, 911m $cm^{-1}$.

$^1H$ n.m.r. (300 MHz, $CDCl_3$): δ 2.13, q, 2H, *J* 7.0 Hz, H3; 2.39, td, 2H, *J* 7.0, 1.4 Hz, H2; 4.94-5.10, m, 2H, H5; 5.82, ddt, 1H, *J* 17.1, 10.2, 6.3 Hz, H4; 9.78, t, 1H, *J* 1.5 Hz, H1.

$^{13}C$ n.m.r. (75 MHz, $CDCl_3$): δ 26.2, C3; 42.8, C2; 115.5, C5; 136.4, C4; 201.7, C1.

The spectral data were consistent with those reported in the literature.[145]

### 5.2.8 Preparation of (2*Z*,4*E*)-Methyl 2-acetamidohexa-2,4-dienoate (46)




(46)

Using the modified method described by Burk *et al.*,[28] tetramethylguanidine (TMG) (0.61 ml, 4.89 mmol) was added to a solution of methyl 2-acetylamino-2-(dimethoxyphosphinyl)acetate (31) (0.88 g, 3.68 mmol) in distilled tetrahydrofuran (15 ml) at -78°C. After 15 min, crotonaldehyde (45) (0.4 ml, 4.42 mmol) was added and the mixture was stirred for 2 h at -78°C. The mixture was warmed to 25°C using a warm water bath for a further 2 h. The mixture was diluted with dichloromethane (20 ml), washed with 1 M HCl solution (2 x 10 ml), 1 M $CuSO_4$ solution (2 x 10 ml), saturated $NaHCO_3$ solution (2 x 10 ml) and 1 M NaCl solution (10 ml). The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to give an oil (0.90 g). Purification by flash chromatography on silica gel using ethyl acetate and light petroleum (2 : 1) gave the product (46) (0.37 g , 55%), ($R_f$ 0.21) as a white solid, m.p. 88-90°C (lit.[28] 89-90°C).

$\nu_{max}$ (Nujol): 2855s, 1722w, 1655w, 1616w, 1511w, 1305w, 1233w, 1166w, 1116w $cm^{-1}$.

$^1H$ n.m.r. (300 MHz, $CDCl_3$): δ 1.88, d, 3H, *J* 5.2 Hz, H6; 2.16, s, 3H, $COCH_3$; 3.17, s, 3H, $COOCH_3$; 6.18, d, 2H, *J* 10.9 Hz, H4 and H5; 6.90, bs, 1H, NH; 7.08, d, 1H, *J* 10.1 Hz, H3.

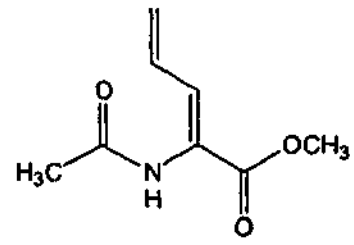
$^{13}C$ n.m.r. (75 MHz, $CDCl_3$): δ 19.3, C6; 23.6, $CO\underline{C}H_3$; 52.6, $COO\underline{C}H_3$; 121.6, C2; 126.9, 134.5, 139.7, C3, C4 and C5; 165.7, 169.2, C1 and CONH.

Mass spectrum ($ESI^+$, MeOH): *m/z* 206.0 $(M+Na)^+$.

The spectral data were consistent with those reported in the literature.[28]

A similar reaction was warmed at ambient temperature for 2 h after the removal of -78°C bath to give the title compound (46) in 39% yield after chromatography.

### 5.2.9 Preparation of (2*Z*)-Methyl 2-acetamidopenta-2,4-dienoate (48)




(48)

Using the modified method as described in Section 5.2.8, tetramethylguanidine (TMG) (1.9 ml, 14.9 mmol) and hydroquinone (5 mg) were added to a solution of methyl 2-acetylamino-2-(dimethoxyphosphinyl)acetate (31) (3.0 g, 11.23 mmol) in distilled tetrahydrofuran (35 ml) at -78°C. After 15 min, acrolein (47) (0.9 ml, 13.47 mmol) was added, the mixture stirred at -78°C for 2 h then at 25°C using a water bath for 2 h and work-up as before to give an oil (2.81 g). Purification by flash chromatography on silica gel using ethyl acetate and light petroleum (1 : 1) gave (2*Z*)-methyl 2-acetamidopent-2,4-dienoate (48) (1.65 g, 87%), ($R_f$ 0.2) as a white solid, m.p. 61-63°C.

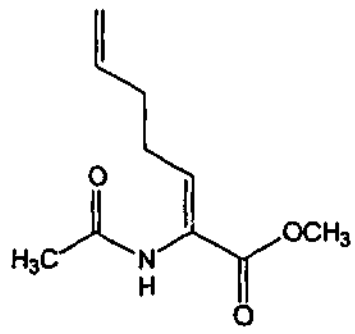
$\nu_{max}$ (KBr): 3277m, 3011m, 2955m, 1733s, 1655s, 1594m, 1518s, 1438m, 1377w, 1350w, 1250w, 1113s, 1016m, 994m, 950s, 768m $cm^{-1}$.

$^1H$ n.m.r. (300 MHz, $CDCl_3$): δ 2.14, s, 3H, $COCH_3$; 3.79, s, 3H, $COOCH_3$; 5.47, d, 1H, *J* 10.1 Hz, H5(*Z*); 5.59, d, 1H, *J* 16.9 Hz, H5(*E*); 6.39-6.52, m, 1H, H4; 7.03, d, 1H, *J* 11.3 Hz, H3; 7.12, bs, 1H, NH.

$^{13}$C n.m.r. (75 MHz, $CDCl_3$): δ 23.8, CO<u>C</u>H$_3$; 52.8, COO<u>C</u>H$_3$; 132.1, 132.9, C3 and C4; 123.7, C2; 125.2, C5; 165.6, 168.8, C1 and CONH.

Microanalysis: Found: H 6.67, C 56.66, N 8.29, O 28.38%. Calculated $C_8H_{11}NO_3$: H 6.54, C 56.78, N 8.28, O 28.38%.

### 5.2.10 Preparation of (2*Z*)-Methyl 2-acetamidohepta-2,6-dienoate (49)




(49)

Reaction of tetramethylguanidine (TMG) (0.31 ml, 3.95 mmol) and methyl 2-acetylamino-2-(dimethoxyphosphinyl)acetate (31) (0.71 g, 2.97 mmol) in distilled tetrahydrofuran (10 ml) with 4-pentenal (41) (0.69 ml, 3.57 mmol) as described in Section 5.2.8 gave an oil (0.47 g). Purification by flash chromatography on silica gel using ethyl acetate and light petroleum (1 : 1) gave (2*Z*)-methyl 2-acetamidohept-2,6-dienoate (49) (0.22 g , 38%), ($R_f$ 0.24) as a white solid m.p. 44-45°C (lit.[60] 44°C).

$\nu_{max}$ (KBr): 3268m, 3018w, 2957w, 1742s, 1664s, 1518s, 1434m, 1376m, 1269s, 1157m, 916m, 768m cm$^{-1}$.

$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 2.10, s, 3H, COC<u>H</u>$_3$; 2.16-2.29, m, 4H, H4 and H5; 3.75, s, 3H, COOC<u>H</u>$_3$; 4.97-5.08, m, 2H, H7; 5.79, ddt, 1H, *J* 17.1, 10.4, 6.4 Hz, H6; 6.64, t, 1H, *J* 6.6 Hz, H3; 7.90, bs, 1H, NH.

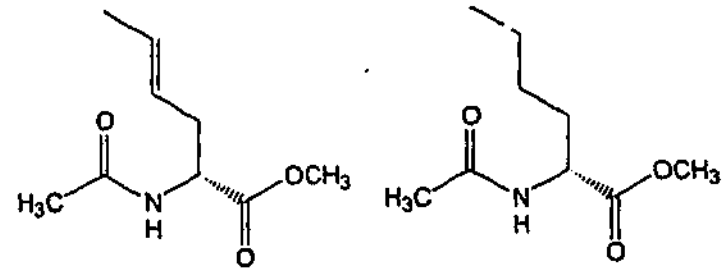
$^{13}$C n.m.r. (75 MHz, $CDCl_3$): δ 23.2, CO<u>C</u>H$_3$; 28.0, C4; 32.3, C5; 52.3, COO<u>C</u>H$_3$; 115.5, C7; 125.9, C2; 137.0, C3; 138.0, C6; 165.0, 169.2, C1 and CONH.

Mass spectrum (ESI$^+$, MeOH): *m/z* 220.1 (M+Na)$^+$.

The spectral data were consistent with those reported in the literature.[60]

## 5.3 Asymmetric Hydrogenations

### 5.3.1 Preparation of (2*R*)-(4*E*)-Methyl 2-acetamidohex-4-enoate (51a)



(51a) (52a)

(2*Z*,4*E*)-Methyl 2-acetamidohexa-2,4-dienoate (46) (0.42 g, 2.18 mmol) and [(COD)Rh(I)((*R*,*R*)-Et-DuPHOS)]OTf (substrate : catalyst ratio = 100 : 1) were dissolved in benzene (10 ml). The vessel was charged with hydrogen (90 psi) and the mixture was stirred for 2 h (refer to Section 5.1.2) as described by Burk *et al.*.[28] The hydrogen was vented and the mixture was concentrated to give an oil (0.42 g). Purification by passing through a short silica plug with ethyl acetate gave an oil (0.4 g, 99%). The $^1$H n.m.r. spectrum of the oil indicated the product, (2*R*)-(4*E*)-methyl 2-acetamidohex-4-enoate (51a) and fully saturated compound, (2*R*)-methyl 2-acetamidohexanoate (52a) (δ 0.89, m, 3H, H6; 1.22-1.39, m, 2H, H5) in a ratio of 94 : 6 ratio respectively.

$\nu_{max}$ (Film): 3284s, 2066w, 2954m, 2856w, 1747s, 1658s, 1547s, 1437s, 1375s, 1217m, 1142m, 1072w, 1016w, 968m, 848w cm$^{-1}$.

$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 1.67, ddt, 3H, *J* 6.4, 1.7, 1.1 Hz, H6; 2.03, s, 3H, $COCH_3$; 2.45-2.51, m, 2H, H3; 3.67, s, 3H, $COOCH_3$; 4.63, dt, 1H, *J* 7.8, 5.6 Hz, H2; 5.28, m, 1H, H5; 5.55, dtq, 1H, *J* 15.1, 6.4, 1.2, H4; 5.98, bs, 1H, NH.

$^{13}C$ n.m.r. (75 MHz, $CDCl_3$): δ 18.3, C6; 23.4, $CO\underline{C}H_3$; 35.6, C3; 52.3, 52.6, C2 and $COO\underline{C}H_3$; 124.6, 130.1, C4 and C5; 169.8, 172.6, C1 and CONH.

Mass spectrum ($ESI^+$, MeOH): *m/z* 207.9 $(M+Na)^+$.

$[\alpha]_D^{20}$ -55° (c 1.18, $CHCl_3$) containing 6% of (52a) (lit.[28] $[\alpha]_D^{20}$ -57.2° (c 1.18, $CHCl_3$) containing < 2% of (52a)). The enantiomeric excess (ee) was 99%.

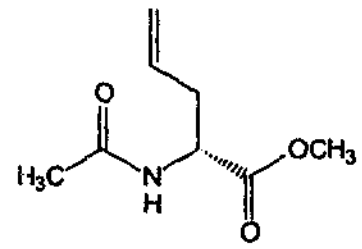
The spectral data were consistent with those reported in the literature.[28]

Similar reactions were carried out in methanol varying the substrate : catalyst ratio at 90 psi of $H_2$ for 18 h and the results are summarised in Table 5.1.

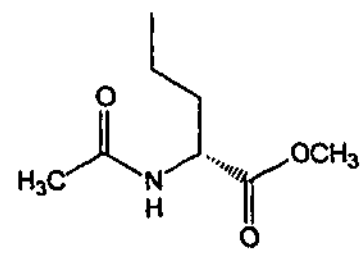
**Table 5.1**

| Entry | Substrate : Catalyst | % Over-reduction |
|---|---|---|
| 1 | 50 : 1 | 50 |
| 2 | 100 : 1 | 14 |

### 5.3.2 Preparation of (2*R*)-Methyl 2-acetamidopent-4-enoate (53a)




(53a)




(54a)

Using the method described in Section 5.1.2, hydrogenation of (2*Z*)-methyl 2-acetamidopenta-2,4-dienoate (48) (40 mg, 0.24 mmol) in benzene was carried out at 30 psi for 3 h using [(COD)Rh(I)((*R*,*R*)-Et-DuPHOS)]OTf. Purification by passing through a short plug of silica with ethyl acetate gave an oil (36 mg, 88%). The $^1H$ n.m.r. spectrum indicated the known title product, (2*R*)-methyl 2-acetamidopent-4-enoate (53a) and the fully saturated compound, (2*R*)-methyl 2-acetamidopentanoate (54a) (δ 0.93, t, 3H, *J* 7.3 Hz, H5; 1.25-1.44, m, 2H, H4) in a 95 : 5 ratio respectively.

A solution of the oil in dichloromethane (2 ml) was injected into the GC chiral column (Model C-024) with the following conditions: the initial column temperature was 100°C for 1 min, then raised at 5°C $min^{-1}$ to 280°C and held at 280°C for 9 min to give two peaks; (*R*) $t_1$ = 18.2 min with 97.67% area, (*S*) $t_2$ = 18.6 min with 2.33% area. The enantiomeric excess (ee) was 95.3%.

$\nu_{max}$ (Film): 3278s, 3079w, 2955w, 1744s, 1657s, 1546m, 1438m, 1375m, 1275w, 1226w, 1151m, 997w, 924w $cm^{-1}$.

$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 2.00, s, 3H, $COCH_3$; 2.42-2.61, m, 2H, H3; 3.72, s, 3H, $COOCH_3$; 4.66, m, 1H, H2; 5.09, d, 1H, *J* 16.2 Hz, H5(*E*); 5.10, d, 1H, *J* 10.1 Hz, H5(*Z*); 5.65, m, 1H, H4; 6.14, bs, 1H, NH.

$^{13}$C n.m.r. (75 MHz, $CDCl_3$): δ 23.4, $CO\underline{C}H_3$; 35.6, C3; 51.8, 52.5, C2 and $COO\underline{C}H_3$; 119.2, C5; 132.2, C4; 169.7, 172.2, C1 and CONH.

Mass spectrum ($ESI^+$, MeOH): Found: *m/z* 194.0785. Calculated $(C_8H_{13}NO_3+Na)^+$: *m/z* 194.0793.

$[\alpha]_D^{20}$ -43° (c 0.047, $CHCl_3$) containing 5% of (54a).

The spectral data were consistent with those reported in the literature.[146]

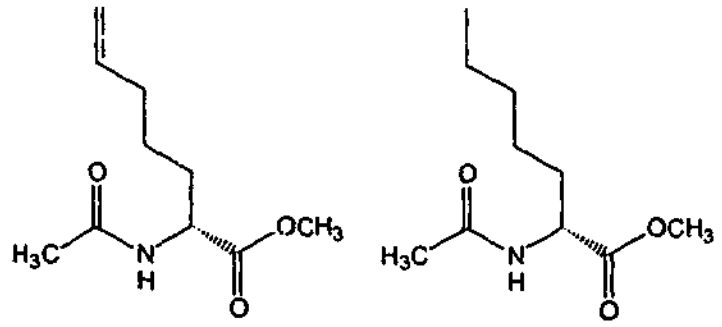
Similar reactions were carried out by varying catalyst, solvent, substrate : catalyst ratio, pressure (P) and reaction time (t). The results are summarised in Table 5.2.

**Table 5.2**

| Entry | Catalyst[a] | Substrate : Catalyst | Solvent | P (psi) | Time | % Conversion | % Over-reduction | % ee[b] |
|---|---|---|---|---|---|---|---|---|
| 1 | *(R,R)* | 100 : 1 | MeOH | 60 | 2 h | 100 | 85 | - |
| 2 | *(R,R)* | 100 : 1 | MeOH | 30 | 2 h | 82 | - | - |
| 3 | *(R,R)* | 50 : 1 | MeOH | 60 | 30 min | 100 | 21 | - |
| 4 | *(R,R)* | 50 : 1 | MeOH | 30 | 45 min | 100 | 17 | - |
| 5 | *(R,R)* | 100 : 1 | MeOH | 30 | 45 min | 38 | - | - |
| 6 | *(R,R)* | 50 : 1 | MeOH | 30 | 30 min | 65 | - | - |
| 7 | *(R,R)* | 100 : 1 | MeOH | 30 | 3 h | 100 | 5 | 76 |
| 8 | *(S,S)* | 100 : 1 | MeOH | 30 | 3 h | 100 | 5 | 95 |
| 9 | *(R,R)* | 100 : 1 | benzene | 30 | 3 h | 100 | 5 | 95 |

[a] (*R,R*) = Rh(I)-(*R,R*)-Et-DuPHOS and (*S,S*) = Rh(I)-(*S,S*)-Et-DuPHOS. [b] – signifies that the ee was not measured.

### 5.3.3 Preparations of (2*R*)-Methyl 2-acetamidohept-6-enoate (55a)




(55a) (56a)

Using the method to that described in Section 5.1.2, hydrogenation of (2*Z*)-methyl 2-acetamidohepta-2,6-dienoate (49) (40 mg, 0.20 mmol) in benzene was carried out at 30 psi for 2 h using [(COD)Rh(I)((*R,R*)-Et-DuPHOS)]OTf. Purification by passing through a short plug of silica with ethyl acetate gave an oil (36 mg, 90%). The $^1$H n.m.r. spectrum indicated the titled product, (2*R*)-methyl 2-acetamidohept-6-enoate

(55a) and the fully saturated compound, (2*R*)-methyl 2-acetamidoheptanoate (56a) (δ 0.88, t, 3H, *J* 6.6 Hz, H7) in a 92 : 8 ratio respectively. A solution of the oil in dichloromethane (2 ml) was injected into the GC chiral column (Model C-024) with the following conditions: the initial column temperature was 100°C for 1 min, then was raised at 5°C $min^{-1}$ to 280°C held and at 280°C for 9 min to give two peaks; (*R*) $t_1$ = 25.9 min with 99.20% area, (*S*) $t_2$ = 26.1 min with 0.80% area. The enantiomeric excess (ee) was 98.4%.

$\nu_{max}$ (Film): 3286s, 3075w, 2954m, 2862w, 1745s, 1658s, 1547s, 1436m, 1374m, 1264m, 1210m, 1153w, 1019w, 913w, 793w $cm^{-1}$.

$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 1.26-1.53, m, 2H, H4; 1.58-1.91, m, 2H, H3; 2.03, s, 3H, $COCH_3$; 2.06-2.10, m, 2H, H5; 3.75, s, 3H, $COOCH_3$; 4.61, td, 1H, *J* 7.7, 5.5 Hz, H2; 4.95-5.05, m, 2H, H7; 5.75, ddt, 1H, *J* 17.0, 10.4, 6.5 Hz, H6; 6.30, bs, 1H, NH.

$^{13}$C n.m.r. (75 MHz, $CDCl_3$): δ 23.5, $CO\underline{C}H_3$; 24.8, C4; 32.2, C3; 33.5, C5; 52.4, 52.7, C2 and $COO\underline{C}H_3$; 115.3, C7; 138.0, C6; 170.1, 173.3, C1 and CONH.

Mass spectrum (EI): Found: *m/z* 156.1024. Calculated ($C_{10}H_{17}NO_3$-$COCH_3$): *m/z* 156.1024.

$[\alpha]_D^{20}$ -60° (c 0.15, $CHCl_3$) containing 8% of (56a).

Similar reactions were carried out in methanol by varying pressure (P) and reaction time (t). The results are summarised in Table 5.3.

**Table 5.3**

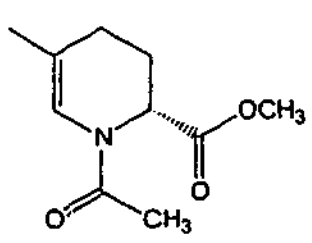
| Entry | P (psi) | Time | % Conversion | % Over-reduction |
|---|---|---|---|---|
| 1 | 90 | 2 h | 100 | 40 |
| 2 | 30 | 15 min | 75 | - |

## 5.4 *Hydroformylations*

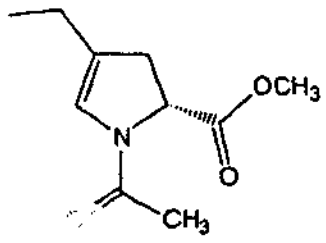
### 5.4.1 Rhodium-catalysed Reactions of (2*R*)-(4*E*)-Methyl 2-acetamidohex-4-enoate (51a)

**(2*R*)-Methyl *N*-acetyl-5-methyl-5,6-didehydropipecolate (68a)**

**(2*R*)-Methyl *N*-acetyl-4-ethyl-4,5-didehydroprolinate (69a)**




(68a)




(69a)

(2*R*)-(4*E*)-Methyl 2-acetamidohex-4-enoate (51a) (40 mg, 0.22 mmol), rhodium(II) acetate dimer (1.0 mg, 2.2 μmol) and BIPHEPHOS (3.5 mg, 4.4 μmol) were dissolved in deoxygenated benzene (5 ml) in a 100 ml Parr autoclave (refer to Section 5.1.3). The autoclave was pressurized to 400 psi of $CO/H_2$ (1 : 1 molar ratio) and heated to 100°C. After 72 h, the autoclave was cooled to ambient temperature and the solvent was removed under reduced pressure to give a brown oil (50 mg). The $^1H$ n.m.r. and $^{13}C$ n.m.r. spectra of the crude oil showed the presence of the two compounds ((2*R*)-methyl *N*-acetyl-5-methyl-5,6-didehydropipecolate (68a) and (2*R*)-methyl *N*-acetyl-4-ethyl-4,5-didehydroprolinate (69a)) in 91 : 9 ratio. The separation of the two products ((68a) and (69a)) was done with chromatography on silica gel using ethyl acetate and light petroleum (3 : 1 ratio).

(2*R*)-Methyl *N*-acetyl-5-methyl-5,6-didehydropipecolate (68a) (30 mg, 70%), ($R_f$ 0.51) was isolated as clear oil. A solution of the purified compound (68a) in HPLC grade isopropanol (10 μl) was injected into the HPLC containing a OD chiral column (1.0 ml $min^{-1}$, 10% isopropanol : 90% hexane) to give two peaks; (*S*) $t_1$ = 7.9 min with

1.32% area, (*R*) $t_2$ = 10.5 min with 98.68% area. The enantiomeric excess was 97.4%.

$\nu_{max}$ (Film): 2925w, 1744s, 1654s, 1404s, 1205m, 1174m, 1019w, 956w $cm^{-1}$.

$^1$H n.m.r. (300 MHz, $CDCl_3$) (minor rotamer in brackets): δ 1.70, s, 3H, (1.74, s, 3H), $CH_3C5$; 1.80-2.00, m, 3H, H3 and H4; 2.22, s, 3H, (2.11, s, 3H), $COCH_3$; 2.37, m, 1H, H4; 3.71, s, 3H, (3.76, s, 3H), $COOCH_3$; 5.23, m, 1H, (4.60, bs, 1H), H2; 6.40, s, 1H, (7.04, s, 1H), H6.

$^{13}$C n.m.r. (75 MHz, $CDCl_3$) (minor rotamer in brackets): δ 21.4, (21.2), $\underline{C}H_3C5$; 21.8, (21.9), $CO\underline{C}H_3$; 23.7, (24.2), C3; 24.7, (24.3), C4; 51.3, (53.1), C2; 52.7, (55.4), $COO\underline{C}H_3$; 116.1, (116.7), C5; 120.1, (118.4), C6; 168.2, 171.3, CON and $\underline{C}OOCH_3$.

Microanalysis: Found: H 7.69, C 60.74, N 6.96, O 24.61%. Calculated $C_{10}H_{14}NO_3$: H 7.67, C 60.88, N 7.10, O 24.34%.

$[\alpha]_D^{20}$ +138° (c 0.034, $CHCl_3$).

(2*R*)-Methyl *N*-acetyl-4-ethyl-4,5-didehydroprolinate (69a) (5 mg, 11%), ($R_f$ 0.34) was obtained as clear oil.

$\nu_{max}$ (Film): 2858m, 1750s, 1647s, 1438s, 1208m, 1026w $cm^{-1}$.

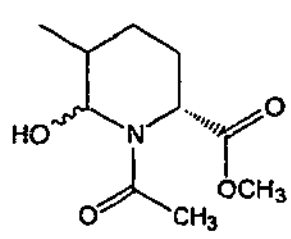
$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 1.08, t, 3H, *J* 7.5 Hz, $CH_2C\underline{H}_3$; 2.03-213, m, 2H, $C\underline{H}_2CH_3$; 2.15, s, 3H, $COCH_3$; 2.52, dd, 1H, *J* 16.8, 5.1 Hz, and 2.96, dd, *J* 16.7, 11.7 Hz, 1H, H3; 3.76, s, 3H, $COOCH_3$; 4.82, dd, 1H, *J* 11.7, 5.2 Hz, H2; 6.19-6.21, m, 1H, H5.

$^{13}$C n.m.r. (75 MHz, $CDCl_3$): δ 12.5, $CH_2\underline{C}H_3$; 21.8, C3; 21.9, $CO\underline{C}H_3$; 36.7, $\underline{C}H_2CH_3$, 52.7, 58.7, C2 and $COO\underline{C}H_3$; 122.9, C5; 126.4, C4; 166.0, 171.9, CON and $\underline{C}OOCH_3$.

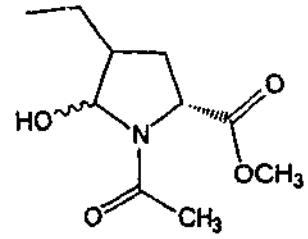
Mass spectrum (EI): Found: *m/z* 197.1046. Calculated $C_{10}H_{15}NO_3$: *m/z* 197.1052.

$[\alpha]_D^{20}$ +114° (c 0.028, $CHCl_3$).

A reaction of (2*R*)-(4*E*)-methyl 2-acetamidohex-4-enoate (51a) (50 mg, 0.27 mmol), rhodium(II) acetate dimer (1.2 mg, 2.7 μmol) and $PPh_3$ (1.4 mg, 5.4 μmol) at 80°C with 400 psi of $CO/H_2$ (1 : 1 molar ratio) for 20 h gave a brown oil (64 mg). The $^1H$ n.m.r. spectrum of the crude oil showed (2*R*)-methyl *N*-acetyl-5-methyl-6-hydroxypipecolate (66a) and (2*R*)-methyl *N*-acetyl-4-ethyl-5-hydroxyprolinate (67a) in 75 : 25 ratio. The compounds were separated using column chromatography (ethyl acetate).




(66a)




(67a)

(2*R*)-Methyl *N*-acetyl-5-methyl-6-hydroxypipecolate (66a):

$^1H$ n.m.r. (300 MHz, $CDCl_3$): δ 1.07, d, 3H, *J* 9.0 Hz, $CH_3C5$; 1.31-1.79, m, 5H, H3, H4 and H5; 2.22, s, 3H, $COCH_3$; 3.71, s, 3H, $COOCH_3$; 4.39, t, 1H, *J* 8.9 Hz, H2; 5.05, m, 1H, H6.

(2*R*)-Methyl *N*-acetyl-4-ethyl-5-hydroxyprolinate (67a):

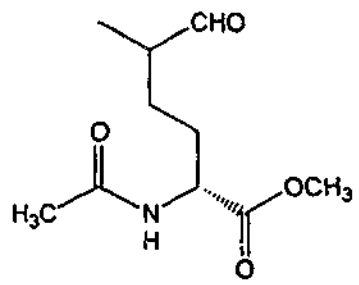
$^1H$ n.m.r. (300 MHz, $CDCl_3$): δ 1.08, t, 3H, *J* 7.5 Hz, $CH_2C\underline{H_3}$; 1.31-1.73, m, 3H, $C\underline{H_2}CH_3$ and H4; 2.15, s, 3H, $COCH_3$; 2.37-2.47, m, 2H, H3; 3.76, s, 3H, $COOCH_3$; 4.44-4.53, m, 1H, H2; 5.29, m, 1H, H5.

Similar reactions were carried out in benzene by varying ligand, pressure (P), temperature (T) and reaction time (t). The results are summarised in Table 5.4.

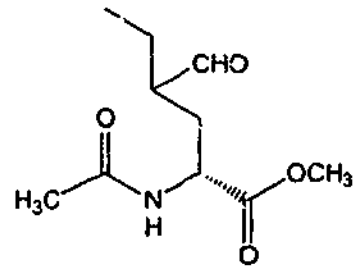
**Table 5.4**

| Entry | Ligand | P (psi) | T (°C) | t (h) | Product ratio (68a) : (69a) | % Yield[a] | % ee[b] (68a) / (69a) |
|---|---|---|---|---|---|---|---|
| 1 | $PPh_3$ | 400 | 80 | 20 | 67 : 33 | 45 | 91 / 98 |
| 2 | BIPHEPHOS | 400 | 80 | 20 | 100 : 0 | 37[c] | - |
| 3 | BIPHEPHOS | 400 | 100 | 20 | 86 : 14 | 52[d] | 98 / 98 |

[a] Isolated yield of cyclic products ((68a) and (69a)) after chromatography. [b] – signifies that the ee was not measured. [c] Crude product contained aldehydes (2*R*)-methyl 2-acetamido-5-formylhexanoate (64a) (δ 9.61, d, 1 H, *J* 1.5 Hz, H6) and (2*R*)-methyl 2-acetamido-4-formylhexanoate (65a) (δ 9.76, d, 1H, *J* 1.5 Hz, H5) in 1 : 1 ratio (*ca.* 40%). [d] Crude product contained only one aldehyde (64a) (*ca.* 30%).




(64a)

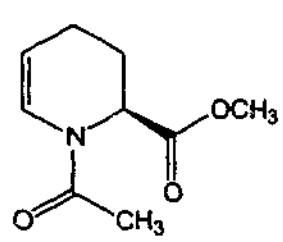



(65a)

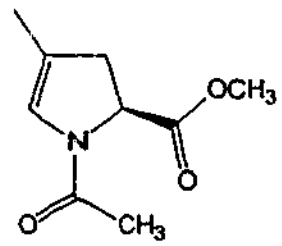
### 5.4.2 Rhodium-catalysed Reactions of (2*S*)-Methyl 2-acetamidopent-4-enoate (53b)

**(2*S*)-Methyl *N*-acetyl-5,6-didehydropipecolate (73b)**

**(2*S*)-Methyl *N*-acetyl-4-methyl-4,5-didehydroprolinate (74b)**




(73b)




(74b)

Using the method described in Section 5.1.3, (2*S*)-methyl 2-acetamidopent-4-enoate (53b) (74 mg, 0.43 mmol), rhodium(II) acetate dimer (1.9 mg, 4.3 μmol) and BIPHEPHOS (6.8 mg, 8.6 μmol) in deoxygenated benzene (10 ml) were reacted with

$CO/H_2$ (1 : 1 molar ratio) (80 psi) at 80°C. After 72 h, the autoclave was cooled to ambient temperature and the solvent was removed under reduced pressure to give a brown oil (80 mg). The $^1H$ n.m.r. spectrum indicated the two compounds ((2*S*)-methyl *N*-acetyl-5,6-didehydropipecolate (73b) and (2*S*)-methyl *N*-acetyl-4-methyl-4,5-didehydroprolinate (74b)) were present in a 66 : 34 ratio. The two compounds ((73b) and (74b)) were separated using column chromatography (3 : 1 of ethyl acetate : light petroleum).

(2*S*)-Methyl *N*-acetyl-5,6-didehydropipecolate (73b) (38 mg, 48%), ($R_f$ 0.5) was isolated as clear oil. A solution of the purified compound (73b) in HPLC grade isopropanol (10 µl) was injected into the HPLC containing a OD chiral column (1.0 ml $min^{-1}$, 10% isopropanol : 90% hexane) to give two peaks; (*S*) $t_1$ = 9.3 min with 99.79% area, (*R*) $t_2$ = 26.5 min with 0.21% area. The enantiomeric excess was 99.6%.

$\nu_{max}$ (Film): 3468b, 2955w, 2847w, 1744m, 1674m, 1645s, 1437w, 1417m, 1383m, 1347m, 1208m, 1045m, 989m, 887w, 721w $cm^{-1}$.

$^1H$ n.m.r. (300 MHz, $CDCl_3$) (minor rotamer in brackets): δ 1.80-2.12, m, 3H, H3 and H4; 2.23, s, 3H, (2.13, s, 3H), $COCH_3$; 2.38, m, 1H, H4; 3.73, s, 3H, (3.75, s, 3H), $COOCH_3$; 4.97, m, 1H, (5.05, m, 1H), H5; 5.24, m, 1H, (4.66, m, 1H), H2; 6.63, d, *J* 8.6 Hz, 1H, H6.

$^{13}C$ n.m.r. (75 MHz, $CDCl_3$) (minor rotamer in brackets): δ 18.9, (18.6), C3; 21.5, $CO\underline{C}H_3$; 23.3, (23.9), C4; 51.7, (55.7), C2; 52.3, (52.6), $COO\underline{C}H_3$; 107.1, (107.0), C5; 125.1, (123.2), C6; 168.5, CON; 171.0, $\underline{C}OOCH_3$.

Microanalysis: Found: C 59.01, H 7.12, N 7.60, O 26.27%. Calculated $C_9H_{13}NO_3$: C 58.99, H 7.16, N 7.65, O 26.21%.

$[\alpha]_D^{20}$ -64° (c 0.016, $CHCl_3$).

(2*S*)-Methyl *N*-acetyl-4-methyl-4,5-didehydroprolinate (74b), (20 mg, 27%), ($R_f$ 0.3) was isolated as clear oil. A solution of the purified compound (74b) in HPLC grade isopropanol (10 µl) was injected into the HPLC containing a OD chiral column (1.0 ml $min^{-1}$, 10% isopropanol : 90% hexane) to give two peaks; (*S*) $t_1$ = 12.2 min with 99.81% area, (*R*) $t_2$ = 26.2 min with 0.19% area. The enantiomeric excess was 99.6%.

$\nu_{max}$ (Film): 3296b, 2958w, 2874w, 1746m, 1654m, 1542s, 1438w, 1375m, 1273w, 1208m, 1156w, 1023w, 968w, 884w $cm^{-1}$.

$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 1.74, s, 3H, $CH_3$C4; 2.14, s, 3H, $COCH_3$; 2.50, m, 1H, and 2.95, m, 1H, H3; 3.76, s, 3H, $COOCH_3$; 4.82, dd, *J* 11.7, 5.1 Hz, 1H, H2; 6.25, s, 1H, H5.

$^{13}$C n.m.r. (75 MHz, $CDCl_3$): δ 13.8, $\underline{C}H_3$C4; 21.9, CO$\underline{C}H_3$; 38.8, C3; 52.8, COO$\underline{C}H_3$; 58.5, C2; 120.2, C4; 124.3, C5; 165.9, 171.9, CON and $\underline{C}OOCH_3$.

Mass spectrum ($ESI^+$, MeOH): Found: *m/z* 206.0787. Calculated $(C_9H_{13}NO_3+Na)^+$: *m/z* 206.0793.

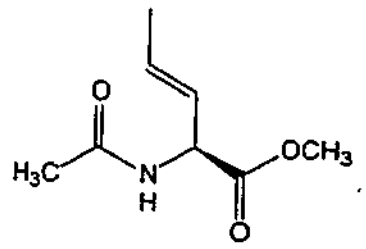
Similar reactions were carried out in benzene by varying ligand, pressure (P) and reaction time (t) at 80°C. The results are summarised in Table 5.5.

**Table 5.5**

| Entry | Ligand | P (psi) | t (h) | Product ratio (73b) : (74b) | % Yield[a] | % ee[b] (73b) / (74b) |
|---|---|---|---|---|---|---|
| 1 | $PPh_3$ | 400 | 72 | 50 : 50 | 73 | - / 87 |
| 2 | BIPHEPHOS | 400 | 20 | 63 : 37 | 66 | 88 / - |
| 3 | BIPHEPHOS | 100 | 20 | 71 : 29 | 54[c] | - / 87 |
| 4 | BIPHEPHOS | 80 | 20 | 78 : 22 | -[d] | - |

[a] Isolated yield of cyclic products ((73b) and (74b)) after chromatography. [b] – signifies that the ee was not measured. [c] Crude product contained *ca.* 20% of the isomerised alkenamide ((2*S*)-methyl 2-

acetamidopenta-3-enoate (70b)). [d] Crude product contained *ca.* 50% of the isomerised alkenamide (70b).



(70b)

(2*S*)-(3*E*)-Methyl 2-acetamidopent-3-enoate (70b) ($R_f$ 0.4) was isolated as clear oil.

$\nu_{max}$ (Film): 3283b, 2956w, 1746s, 1655m, 1542s, 1438w, 1375m, 1248w, 1203w, 1160w, 968w $cm^{-1}$.

$^1H$ n.m.r. (300 MHz, $CDCl_3$): δ 1.70, ddd, 3H, *J* 6.5, 1.7, 1.2 Hz, H5; 2.03, s, 3H, $COCH_3$; 3.75, s, 3H, $COOCH_3$; 5.03, m, 1H, H2; 5.46, ddq, 1H, *J* 15.3, 6.4, 1.7 Hz, H4; 5.77, m, 1H, H3; 6.16, bs, 1H, NH.

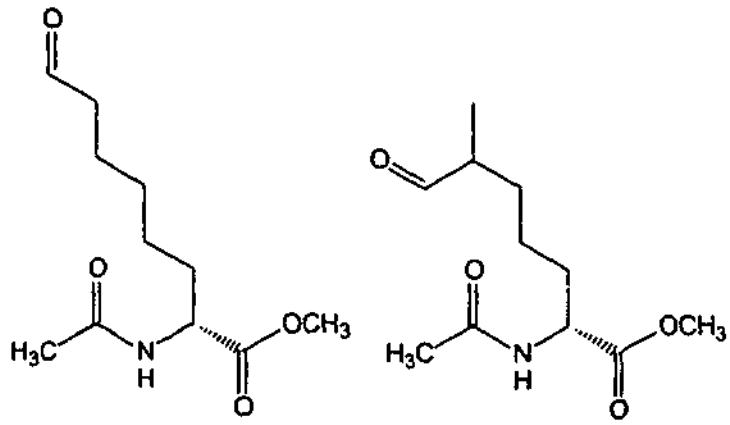
$^{13}C$ n.m.r. (75 MHz, $CDCl_3$): δ 18.2, C5; 23.5, $CO\underline{C}H_3$; 53.0, 54.5, C2 and $COO\underline{C}H_3$; 125.2, 130.3, C3 and C4; 169.6, 171.8, C1 and CONH.

Mass spectrum ($ESI^+$, MeOH): Found: *m/z* 172.0964. Calculated $(C_8H_{13}NO_3+H)^+$: *m/z* 172.0974.

### 5.4.3 Rhodium-catalysed Reactions of (2*R*)-Methyl 2-acetamidohept-6-enoate (55a)

**(2*R*)-Methyl 2-acetamido-7-formylheptanoate (75a)**

**(2*R*)-Methyl 2-acetamido-6-formylheptanoate (76a)**



(75a) (76a)

Using the same method described in Section 5.1.3, (2*R*)-methyl 2-acetamidohept-4-enoate (55a) (70 mg, 0.36 mmol), rhodium(II) acetate dimer (1.6 mg, 3.6 μmol) and $PPh_3$ (1.9 mg, 7.2 μmol) in deoxygenated benzene (10 ml) were reacted with $CO/H_2$ (1 : 1 molar ratio) (400 psi) at 80°C. After 20 h, the autoclave was cooled to ambient temperature and the solvent was removed under reduced pressure to give a brown oil (80 mg). The $^1H$ and $^{13}C$ n.m.r. spectra indicated the two compounds ((2*R*)-methyl 2-acetamido-7-formylheptanoate (75a) and (2*R*)-methyl 2-acetamido-6-formylheptanoate (76a)) were present in a 50 : 50 ratio. The two aldehydes ((75a) and (76a)) were partially separated using radial chromatography (1 : 1 of ethyl acetate : light petroleum) to give (75a) and a sample of (76a) containing 20% of the other isomer (75a).

(2*R*)-Methyl 2-acetamido-7-formylheptanoate (75a) (28 mg, 34%), ($R_f$ 0.86) was isolated as a yellow oil.

$\nu_{max}$ (Film): 3296s, 3010w, 2938m, 2862w, 2728w, 1744s, 1657s, 1542s, 1438s, 1438m, 1375s, 1211m, 1167m, 1031w, 735w $cm^{-1}$.

$^1$H n.m.r. (300 MHz, $CDCl_3$) (minor rotamer in brackets): δ 1.20-1.37, m, 4H, H4 and H5; 1.55-1.69, m, 2H, H6; 1.77-1.83, m, 2H, H3; 2.00, s, 3H, (2.02, s, 3H), $COCH_3$; 2.41, td, 2H, *J* 7.2, 1.7 Hz, H7; 3.75, s, 3H, (3.72, s, 3H), $COOCH_3$; 4.62, m, 1H, H2; 6.14, bs, 1H, NH; 9.73, t, 1H, *J* 1.7 Hz, (9.75, m, 1H), CHO.

$^{13}$C n.m.r. (75 MHz, $CDCl_3$): δ 24.5, $CO\underline{C}H_3$; 22.1, C6; 25.3, C4; 29.0, C5; 32.6, C3; 44.0, C7; 52.3, 52.7, C2 and $COO\underline{C}H_3$; 170.0, 173.2, C1 and CONH; 202.6, CHO.

Mass spectrum (EI): Found: *m/z* 186.1133. Calculated ($C_{11}H_{19}NO_4$-$COCH_3$): *m/z* 186.1130.

(2*R*)-Methyl 2-acetamido-6-formylheptanoate (76a) (24 mg, 29%), ($R_f$ 0.95) containing 20% of (75a) was obtained as a yellow oil.

$\nu_{max}$ (Film): 3304w, 2953w, 2865w, 1740s, 1656s, 1545s, 1438s, 1375s, 1212m, 1178m, 1153w, 1039w $cm^{-1}$.

$^1$H n.m.r. (300 MHz, $CDCl_3$) (1 : 1 mixture of two diastereoisomers): δ 1.10, d, 3H, *J* 7.0 Hz, H7; 1.23-1.46, m, 3H, H4 and H5; 1.58-1.90, m, 3H, H3 and H5; 2.03, s, 3H, $COCH_3$; 2.24-2.38, m, 1H, H6; 3.75, s, 3H, $COOCH_3$; 4.63, m, 1H, H2; 6.21, bs, 1H, NH; 9.60, m, 1H, CHO[†].

$^{13}$C n.m.r. (75 MHz, $CDCl_3$) (1:1 mixture of two diastereoisomers): δ 13.8, C7; 23.0, C4; 24.5, $CO\underline{C}H_3$; 30.2, C5; 32.9, C3; 46.5, C6; 52.2, 52.8, C2 and $COO\underline{C}H_3$; 170.1, 173.2, C1 and CONH; 204.9, CHO.

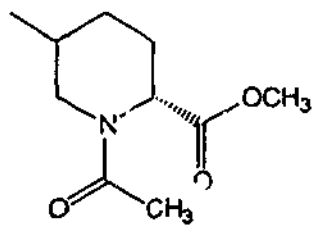
Mass spectrum (EI): Found: *m/z* 186.1133. Calculated ($C_{11}H_{19}NO_4$-$COCH_3$): *m/z* 186.1130.

[†] In 400MHz, all chemical shifts were the same except for two CHO peaks at δ 9.59, d, 1H, *J* 1.9 Hz and 9.60, d, 1H, *J* 1.8 Hz.

A similar reaction was carried out using the same substrate (55a) (37 mg), rhodium(II) acetate dimer (0.9 mg, 8.4 μmol) and BIPHEPHOS (3.0 mg, 3.8 μmol). The $^{1}H$ and $^{13}C$ n.m.r. spectra indicated the presence of ((2*R*)-Methyl 2-acetamido-7-formylheptanoate (75a) and (2*R*)-methyl 2-acetamido-6-formylheptanoate (76a) in approximately 50 : 50 ratio.

## *5.5 Preparation of Cyclic α-Amino Acids*

### 5.5.1 Preparation of (2*R*)-Methyl *N*-acetyl-5-methylpipecolate (79a)




(79a)

A solution of (2*R*)-methyl *N*-acetyl–5-methyl-5,6-didehydropipecolate (68a) (56 mg, 0.28 mmol) in methanol (5 ml) was added to a Fischer-Porter tube followed by palladium on charcoal (10%). The mixture was hydrogenated at 90 psi for 18 h (refer to Section 5.1.2). The catalyst was removed by filtration through a Celite pad and the filtrate was concentrated *in vacuo* to give the product (79a) (46 mg, 83%) as an oil.

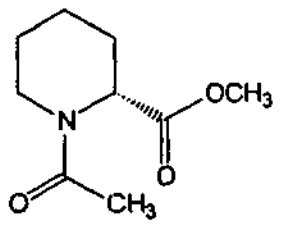
$\nu_{max}$ (Film): 3425m, 2955m, 1740s, 1640s, 1434s, 1368w, 1334w, 1265w, 1211m, 1163w, 1076w, 1031w, 1004w, 961w $cm^{-1}$.

$^{1}H$ n.m.r. (300 MHz, $CDCl_3$) (a mixture of diastereomers with rotamers in brackets): δ 0.98, d, 3H, *J* 3.1 Hz, $CH_3C5$; 1.51-1.64, m, 4H, H3, H4 and H5; 2.15, s, 3H, (2.08, s, 3H), $COCH_3$; 2.28, m, 1H, H4; 2.87, m, 1H and 3.49, m, 1H, H6; 3.73, s, 3H, (3.77, s, 3H), $COOCH_3$; 5.40, m, 1H, (4.50, m, 1H), H2.

$^{13}C$ n.m.r. (75 MHz, $CDCl_3$) (a mixture of diastereomers with minor rotamers in brackets): δ 19.3, $\underline{C}H_3C5$; 21.8, $CO\underline{C}H_3$; 26.7, (27.4), C4; 29.8, (29.6), C3; 31.4, C5; 51.2, (56.5), C2; 51.1, C6; 52.3, (52.7), $COO\underline{C}H_3$; 170.4, 171.7, CON and $\underline{C}OOCH_3$.

Mass spectrum ($ESI^+$, MeOH): Found: *m/z* 222.1099. Calculated $(C_{10}H_{17}NO_3+Na)^+$: *m/z* 222.1106

### 5.5.2 Preparation of (2*R*)-Methyl *N*-acetyl-pipecolate (81a)




(81a)

Using the method described above in Section 5.5.1, (2*R*)-methyl *N*-acetyl-5,6-didehydropipecolate (73a) (59 mg, 0.32 mmol) was dissolved in methanol (5 ml) and reacted with palladium on charcoal (10%) at 90 psi of $H_2$ for 18 h. After work-up, the solution was concentrated to give product (81a) (50 mg, 84%) as an oil.

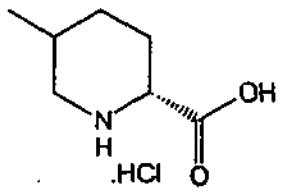
$\nu_{max}$ (Film): 3433m, 2944w, 1738s, 1638s, 1550w, 1433s, 1373w, 1261w, 1211m, 1166m, 1005w $cm^{-1}$.

$^1H$ n.m.r. (300 MHz, $CDCl_3$) (minor rotamer in brackets): δ 1.25-1.87, m, 5H, H3, H4 and H5; 2.14, s, 3H, (2.08, s, 3H), $COCH_3$; 2.25, m, 1H, H4; 3.28, m, 1H, (2.61, m, 1H), H6; 3.75, m, 1H, (4.58, m, 1H) and 3.73, s, 3H, (3.77, s, 3H), $COOCH_3$; 5.39, m, 1H, (4.53, m, 1H), H2.

$^{13}C$ n.m.r. (75 MHz, $CDCl_3$) (minor rotamer in brackets): δ 21.0, (20.9), C5; 21.8, (21.6), $CO\underline{C}H_3$; 25.4, (24.6), C3; 26.7, (27.4), C4; 44.3, (39.3), C6; 51.8, (52.6), $COO\underline{C}H_3$; 52.3, (56.9), C2; 170.5, (170.3), 171.8, (171.2), CON and $\underline{C}OOCH_3$.

Mass spectrum ($ESI^+$, MeOH): Found: *m/z* 208.0943. Calculated $(C_{10}H_{15}NO_3+Na)^+$: *m/z* 208.0949.

### 5.5.3 Preparation of (2*R*)-5-Methylpipecolinic hydrochloride (80a)

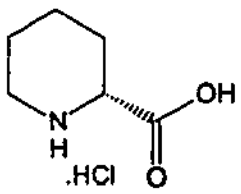



(80a)

A solution of (2*R*)-methyl *N*-acetyl-5-methylpipecolate (79a) (50 mg, 0.25 mmol) in 6 M HCl solution was refluxed overnight. The mixture was concentrated to give a green oil (40 mg, 89%). As the oil was insoluble in most common deuterated solvents (i.e. $CD_3OD$, $D_2O$ and $CDCl_3$), full characterisation was not carried out. However, mass spectroscopy showed the presence of product (80a).

Mass spectrum ($ESI^+$, MeOH): Found: *m/z* 166.0844. Calculated $(C_7H_{13}NO_2+Na)^+$: *m/z* 166.0844.

### 5.5.4 Preparation of (2*R*)-Pipecolinic hydrochloride (82a)




(82a)

Using the method described above in Section 5.5.3, (2*R*)-methyl *N*-acetyl-pipecolate (81a) (50 mg, 0.27 mmol) was refluxed in 6 M HCl solution. After work-up, the solution was concentrated to give the product (82a) (40 mg, 89%) as a white solid, m.p. 260-264°C (lit.[72] 256-257°C).

$\nu_{max}$ (KBr): 3428b, 2958b, 1741s, 1578s, 1459m, 1396s, 1258m, 1193s, 1082w, 926w, 829w, 716w, 530w $cm^{-1}$.

$^1H$ n.m.r. (300 MHz, $D_2O$): δ 1.56-1.78 m, 3H, H3 and H5; 1.80-1.94, m, 2H, H3 and H4; 2.26, m, 1H, H4; 3.01, m, 1H and 3.43, m, 1H, H6; 3.70, m, 1H, H2.

$^{13}C$ n.m.r. (75 MHz, $D_2O$): δ 28.7, C3 and C5; 46.1, C4; 47.9, C6; 59.5, C2; 174.0, COOH.

Mass spectrum ($ESI^+$, MeOH): Found: *m/z* 152.0680. Calculated $(C_6H_{11}NO_2+Na)^+$: *m/z* 152.0688.

$[\alpha]_D^{20}$ +10° (c 0.002, $H_20$) (lit.[72] $[\alpha]_D^{20}$ +10.8° (c 2, $H_20$)).

The spectral data were consistent with those reported in the literature.[147,148]

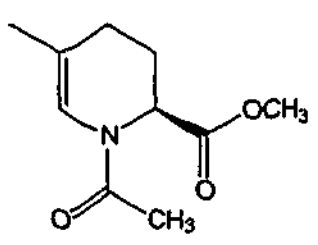
## *5.6 One-pot Tandem Reactions*

### 5.6.1 Two Catalyst System

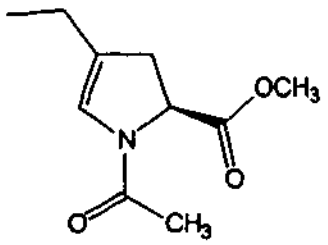
#### *5.6.1.1 Rhodium-catalysed reaction of (2Z,4E)-methyl 2-acetamidohexa-2,4-dienoate (46)*

**(2*S*)-Methyl *N*-acetyl-5-methyl-5,6-didehydropipecolate (68b)**

**(2*S*)-Methyl *N*-acetyl-4-ethyl-4,5-didehydroprolinate (69b)**




(68b)




(69b)

(2*Z*,4*E*)-Methyl 2-acetamidohexa-2,4-dienoate (46) (50 mg, 0.27 mmol), [(COD)Rh(I)((*S*,*S*)-Et-DuPHOS)]OTf (substrate : catalyst ratio = 100 : 1), rhodium(II) acetate dimer (1.2 mg, 2.7 μmol) and $PPh_3$ (1.4 mg, 5.4 μmol) were

dissolved in deoxygenated benzene (10 ml) in a 100 ml Parr autoclave (refer to Section 5.3.1). The autoclave was charged with hydrogen (90 psi) and the mixture was stirred for 2 h (refer to Section 5.1.2). The hydrogen was then vented and the autoclave was pressurized to 400 psi of $CO/H_2$ (1 : 1 molar ratio) and heated to 80°C (refer to Section 5.1.3). After 20 h, the autoclave was cooled to ambient temperature and the solvent was removed *in vacuo* to give a brown oil (50 mg). The $^1H$ n.m.r. spectrum of the crude oil showed the presence of the two compounds ((2*S*)-methyl *N*-acetyl-5-methyl-5,6-didehydropipecolate (68b) and (2*S*)-methyl *N*-acetyl-4-ethyl-4,5-didehydroprolinate (69b)) in a 56 : 44 ratio). The products ((68b) and (69b)) was separated by using chromatography (ethyl acetate : light petroleum = 3 : 1).

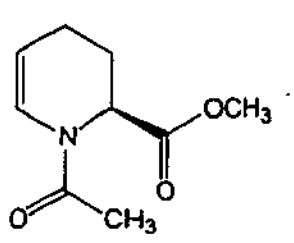
(2*S*)-Methyl *N*-acetyl-5-methyl-5,6-didehydropipecolate (68b) (27 mg, 51%), ($R_f$ 0.51) was isolated as clear oil. A solution of the purified compound (68b) in HPLC grade isopropanol (10 µl) was injected into the HPLC containing a OD chiral column (1.0 ml $min^{-1}$, 10% isopropanol : 90% hexane) to give two peaks; (*S*) $t_1$ = 8.0 min with 97.63% area, (*R*) $t_2$ = 10.8 min with 2.37% area. The enantiomeric excess was 95.3%. Refer to Section 5.4.1 for full characterisation.

(2*S*)-Methyl *N*-acetyl-4-ethyl-4,5-didehydroprolinate (69b) (16 mg, 30%), ($R_f$ 0.34) was obtained as clear oil. A solution of the purified compound (69b) in HPLC grade isopropanol (10 µl) was injected into the HPLC containing a OD chiral column (1.0 ml $min^{-1}$, 10% isopropanol : 90% hexane) to give two peaks; (*S*) $t_1$ = 11.1 min with 99.55% area, (*R*) $t_2$ = 18.9 min with 0.45% area. The enantiomeric excess was 99.1%. Refer to Section 5.4.1 for full characterisation.

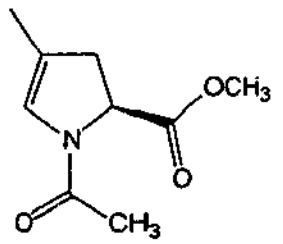
### 5.6.1.2 *Rhodium-catalysed reaction of (2Z)-methyl 2-acetamidopenta-2,4-dienoate (48)*

**(2*S*)-Methyl *N*-acetyl-5,6-didehydropipecolate (73b)**

**(2*S*)-Methyl *N*-acetyl-4-methyl-4,5-didehydroprolinate (74b)**




(73b)




(74b)

Using an identical method to that described in Section 5.6.1.1, (2*Z*)-methyl 2-acetamidopenta-2,4-dienoate (48) (40 mg, 0.24 mmol), [(COD)Rh(I)((*S,S*)-Et-DuPHOS)]OTf (substrate : catalyst ratio = 100 : 1), rhodium(II) acetate dimer (1.0 mg, 2.4 μmol) and BIPHEPHOS (3.4 mg, 5.4 μmol) were dissolved in deoxygenated benzene (10 ml) in a 100 ml Parr autoclave and reacted with $H_2$ at 30 psi for 3 h (refer to Section 5.1.2). The hydrogen was vented and the autoclave was pressurized to 80 psi of $CO/H_2$ (1 : 1 molar ratio) and heated to 80°C for 72 h. After work-up, the $^1H$ n.m.r. spectrum of the crude oil (40 mg) showed the presence of cyclic products, (2*S*)-methyl *N*-acetyl-5,6-didehydropipecolate (73b) and (2*S*)-methyl *N*-acetyl-4-methyl-4,5-didehydroprolinate (74b) in 67 : 33 ratio respectively as well as the isomerised alkene, (2*S*)-methyl 2-acetamidopenta-3-enoate (70b) (*ca.* 25%). The separation of the products ((73b) and (74b)) was done using chromatography (ethyl acetate : light petroleum = 3 : 1).

(2*S*)-Methyl *N*-acetyl-5,6-didehydropipecolate (73b) (17 mg, 39%), ($R_f$ 0.5) was isolated as clear oil. A solution of the purified compound (73b) in HPLC grade isopropanol (10 μl) was injected into the HPLC containing a OD chiral column (1.0 ml $min^{-1}$, 10% isopropanol : 90% hexane) to give two peaks; (*S*) $t_1$ = 8.8 min with

98.55% area, (*R*) $t_2$ = 25.0 min with 1.45% area. The enantiomeric excess was 97.1%. Refer to Section 5.4.2 for full characterisation.

(2*S*)-Methyl *N*-acetyl-4-methyl-4,5-didehydroprolinate (74b), (9 mg, 21%), ($R_f$ 0.3). A solution of the purified compound (74b) in HPLC grade isopropanol (10 μl) was injected into the HPLC containing a OD chiral column (1.0 ml $min^{-1}$, 10% isopropanol : 90% hexane) to give two peaks; (*S*) $t_1$ = 12.2 min with 99.81% area, (*R*) $t_2$ = 26.2 min with 0.19% area. The enantiomeric excess was 99.6%. Refer to Section 5.4.2 for full characterisation.

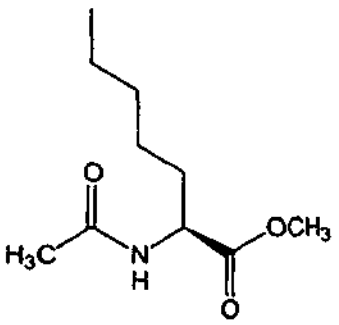
(2*S*)-Methyl 2-acetamidopenta-3-enoate (70b), refer to Section 5.4.2 for full characterisation.

### *5.6.1.3 Rhodium-catalysed reaction of (2Z)-methyl 2-acetamidohepta-2,6-dienoate (49)*

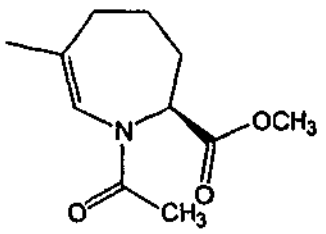
**(2*S*)-Methyl 2-acetamidoheptanoate (56b)**

**(2*S*)-Methyl *N*-acetyl-6-methyl-6,7-didehydroazepanyl-2-carboxylate (78b)**

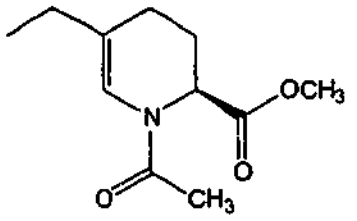
**(2*S*)-Methyl *N*-acetyl-5-ethyl-5,6-didehydropipecolate (85b)**




(56b)




(78b)




(85b)

Using the method described in Section 5.6.1.1, (2*Z*)-methyl 2-acetamidohepta-2,6-dienoate (49) (40 mg, 0.2 mmol) and [(COD)Rh(I)((*S*,*S*)-Et-DuPHOS)]OTf (substrate

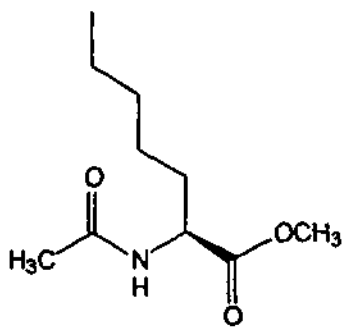
: catalyst ratio = 100 : 1), rhodium(II) acetate dimer (1.1 mg, 2.5 μmol) and BIPHEPHOS (3.9 mg, 5.0 μmol) were dissolved in deoxygenated benzene (10 ml) in a 100 ml Parr autoclave and reacted with $H_2$ at 30 psi for 2 h (refer to Section 5.1.3). The hydrogen was vented and the autoclave was pressurized to 800 psi of $CO/H_2$ (1 : 1 molar ratio) and heated to 150°C for 72 h. After work-up, the $^1H$ n.m.r. spectrum of the crude oil (40 mg) showed the presence of three compounds, (2*S*)-methyl *N*-acetyl-6-methyl-6,7-didehydroazepanyl-2-carboxylate (78b), (2*S*)-methyl *N*-acetyl-5-ethyl-5,6-didehydropipecolate (85b) and (2*S*)-methyl 2-acetamidoheptanoate (56b) in 13 : 13 : 74 ratio. Purification using radial chromatography (ethyl acetate : light petroleum = 1 : 1) gave a sample of the cyclic products ((78b) and (85b) in a *ca.* 50 : 50 ratio) (10 mg, 24%), ($R_f$ 0.33) was isolated as a yellow oil.

(2*S*)-Methyl 2-acetamido-6-methyl-6,7-didehydroazepanyl-2-carboxylate (78b):

$^1H$ n.m.r. (300 MHz, $CDCl_3$): δ 1.60-2.20, m, 6H, H3, H4 and H5; 1.74, d, 3H, *J* 1.3 Hz, $CH_3C6$; 2.09, s, 3H, $COCH_3$; 3.70, s, 3H, $COOCH_3$; 5.14, dd, 1H, *J* 7.4, 5.2 Hz, H2; 6.10, s, 1H, H7.

Mass spectrum ($ESI^+$, MeOH): Found: *m/z* 234.1104. Calculated: $(C_{11}H_{17}NO_3+Na)^+$ *m/z* 234.1106.

(2*S*)-Methyl *N*-acetyl-5-ethyl-5,6-didehydropipecolate (85b), refer to Section 5.6.2.3 for full characterisation.




(56b)

(2*S*)-Methyl 2-acetamidoheptanoate (56b), ($R_f$ 0.44) was isolated as a yellow oil.

$\nu_{max}$ (Film): 3311b, 2955w, 2855w, 1738s, 1655s, 1538s, 1438s, 1372s, 1211w $cm^{-1}$.

$^1H$ n.m.r. (300 MHz, $CDCl_3$): δ 0.88, t, 3H, *J* 6.6 Hz, H7; 1.21-1.41, m, 6H, H3, H4, H5 and H6; 1.65, m, 1H, H6; 1.88, m, 1H, H3; 2.03, s, 3H, $COCH_3$; 3.75, s, 3H, $COOCH_3$; 4.61, m, 1H, H2; 6.19, bd, 1H, *J* 7.2 Hz, NH.

$^{13}C$ n.m.r. (75 MHz, $CDCl_3$): δ 14.3, C7; 22.8, C4; 23.6, $CO\underline{C}H_3$; 25.2, C5; 31.7, C6; 32.9, C3; 52.5, 52.7, C2 and $COO\underline{C}H_3$; 169.9, 173.4, C1 and CONH.

Mass spectrum ($ESI^+$, MeOH): *m/z* 224.3 $(M+Na)^+$.

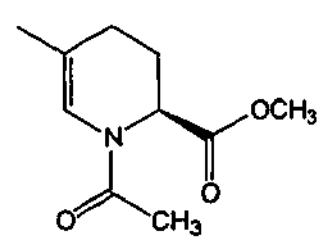
The spectral data were consistent with those reported in literature.[149]

### 5.6.2 One Catalyst System

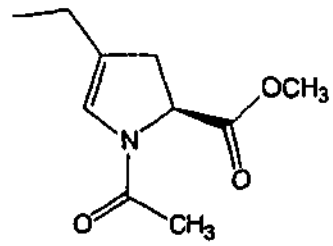
#### *5.6.2.1 Rhodium(I)-catalysed reactions of (2Z,4E)-methyl 2-acetamidohexa-2,4-dienoate (46)*

**(2*S*)-Methyl *N*-acetyl-5-methyl-5,6-didehydropipecolate (68b)**

**(2*S*)-Methyl *N*-acetyl-4-ethyl-4,5-didehydroprolinate (69b)**




(68b)




(69b)

Using the method to that described in Section 5.6.1.1, (2*Z*,4*E*)-methyl 2-acetamidohexa-2,4-dienoate (46) (40 mg, 0.22 mmol) and [(COD)Rh(I)((*S*,*S*)-Et-DuPHOS)]OTf (substrate : catalyst ratio = 100 : 1) were dissolved in deoxygenated benzene (10 ml) in a 100 ml Parr autoclave and reacted with $H_2$ at 90 psi for 2 h (refer to Section 5.1.2). The hydrogen was vented and the autoclave was pressurized to 800 psi of $CO/H_2$ (1 : 1 molar ratio) and heated to 150°C for 72 h (refer to Section 5.1.3).

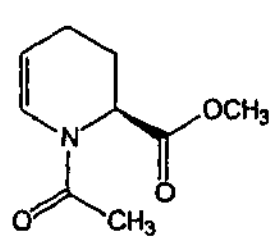
After work-up, the $^1$H n.m.r. spectrum of the crude oil (40 mg) showed only the presence of (2*S*)-methyl *N*-acetyl-5-methyl-5,6-didehydropipecolate (68b). Purification was done using chromatography (ethyl acetate : light petroleum = 3 : 1). (2*S*)-Methyl *N*-acetyl-5-methyl-5,6-didehydropipecolate (68b) (25 mg, 58%), ($R_f$ 0.51) was isolated as clear oil. A solution of the purified compound (68b) in HPLC grade isopropanol (10 μl) was injected into the HPLC containing a OD chiral column (1.0 ml min$^{-1}$, 10% isopropanol : 90% hexane) to give two peaks; (*S*) $t_1$ = 8.0 min with 98.12% area, (*R*) $t_2$ = 10.6 min with 1.88% area. The enantiomeric excess was 96.2%. Refer to Section 5.4.1 for full characterisation.

A similar reaction was carried out at 400 psi, 80°C for 20 h gave a mixture of products, (2*S*)-methyl *N*-acetyl-5-methyl-5,6-didehydropipecolate (69b) (35% yield, 99% ee) and (2*S*)-methyl *N*-acetyl-4-ethyl-4,5-didehydroprolinate (69b) (7% yield, 99% ee) in 83 : 17 ratio as well as *ca.* 15% of the aldehydes ((64b) and (65b)).

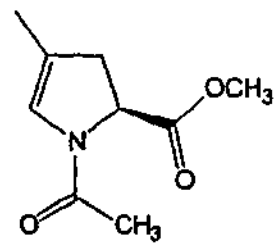
### *5.6.2.2 Rhodium(I)-catalysed reactions of (2Z)-methyl 2-acetamidopenta-2,4-dienoate (48)*

**(2*S*)-Methyl *N*-acetyl-5,6-didehydropipecolate (73b)**

**(2*S*)-Methyl *N*-acetyl-4-methyl-4,5-didehydroprolinate (74b)**




(73b)




(74b)

Using the method to that described in Section 5.6.1.1, (2*Z*)-methyl 2-acetamidopenta-2,4-dienoate (48) (50 mg, 0.30 mmol) and [(COD)Rh(I)((*S*,*S*)-Et-DuPHOS)]OTf

(substrate : catalyst ratio = 100 : 1) were dissolved in deoxygenated benzene (10 ml) in a 100 ml Parr autoclave and reacte with $H_2$ at 30 psi for 3 h (refer to Section 5.1.2). The hydrogen was vented and the autoclave was pressurized to 400 psi of $CO/H_2$ (1 : 1 molar ratio) and heated to 80°C for 72 h (refer to Section 5.1.3). After work-up, the $^1$H n.m.r. spectrum of the crude oil (40 mg) showed the presence of two compounds, ((2*S*)-methyl *N*-acetyl-5,6-didehydropipecolate (73b) and (2*S*)-methyl *N*-acetyl-4-methyl-4,5-didehydroprolinate (74b)) in a 54 : 46 ratio). The products ((73b) and (74b)) were separated using chromatography (ethyl acetate : light petroleum = 3 : 1).

(2*S*)-Methyl *N*-acetyl-5,6-didehydropipecolate (73b) (22 mg, 40%), ($R_f$ 0.5) was isolated as clear oil. A solution of the purified compound (73b) in HPLC grade isopropanol (10 µl) was injected into the HPLC containing a OD chiral column (1.0 ml min$^{-1}$, 10% isopropanol : 90% hexane) to give two peaks; (*S*) $t_1$ = 9.3 min with 97.29% area, (*R*) $t_2$ = 26.2 min with 2.71% area. The enantiomeric excess was 94.6%. Refer to Section 5.4.2 for full characterisation.

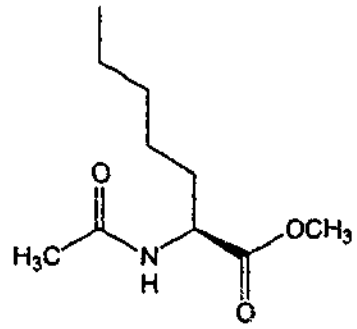
(2*S*)-Methyl *N*-acetyl-4-methyl-4,5-didehydroprolinate (74b), (28 mg, 51%), ($R_f$ 0.3). A solution of the purified compound (74b) in HPLC grade isopropanol (10 µl) was injected into the HPLC containing a OD chiral column (1.0 ml min$^{-1}$, 10% isopropanol : 90% hexane) to give two peaks; (*S*) $t_1$ = 12.2 min with 99.81% area, (*R*) $t_2$ = 26.2 min with 0.19% area. The enantiomeric excess was 99.6%. Refer to Section 5.4.2 for full characterisation.

A similar reaction was carried out at 80 psi, 80°C for 72 h and gave the products ((73b) and (74b)) in a 74 : 26 ratio. Crude product also contained *ca.* 40% isomerised alkenamide (70b).

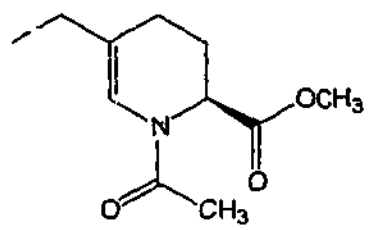
### 5.6.2.3 *Rhodium(I)-catalysed reactions of (2Z)-methyl 2-acetamidohepta-2,6-dienoate (49)*

**(2*S*)-Methyl 2-acetamidoheptanoate (56b)**

**(2*S*)-Methyl *N*-acetyl-5-ethyl-5,6-didehydropipecolate (85b)**




(56b)




(85b)

Using an identical method to that described in Section 5.6.1.1, (2*Z*)-methyl 2-acetamidohepta-2,6-dienoate (49) (40 mg, 0.2 mmol) and [(COD)Rh(I)((*S*,*S*)-Et-DuPHOS)]OTf (substrate : catalyst ratio = 100 : 1) were dissolved in deoxygenated benzene (10 ml) in a 100 ml Parr autoclave at 30 psi for 2 h (refer to Section 5.1.2). The hydrogen was vented and the autoclave was pressurized to 800 psi of $CO/H_2$ (1 : 1 molar ratio) and heated to 150°C for 72 h. After work-up, the $^1H$ n.m.r. spectrum of the crude oil (40 mg) showed the presence of two compounds ((2*S*)-methyl *N*-acetyl-5-ethyl-5,6-didehydropipecolate (85b) and (2*S*)-methyl 2-acetamidoheptanoate (56b)) in 33 : 67 ratio. The products ((85b) and (56b)) were separated using radial chromatography (ethyl acetate : light petroleum = 1 : 1).

(2*S*)-Methyl *N*-acetyl-5-ethyl-5,6-didehydropipecolate (85b) (5 mg, 12%), ($R_f$ 0.35) was isolated as a yellow oil.

$\nu_{max}$ (Film): 3339b, 2953m, 1744s, 1656s, 1406s, 1378m, 1311m, 1205m, 1172m, 1033m, 978w, 839w $cm^{-1}$.

$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 1.03, t, 3H, *J* 7.4 Hz, $CH_2\underline{C}H_3$; 1.84, m, 1H, H3; 1.93-2.09, m, 4H, H4 and $C\underline{H}_2CH_3$, 2.23, s, 3H, $COCH_3$; 2.37, m, 1H, H3; 3.71, s, 3H, $COOCH_3$; 5.20, m, 1H, H2; 6.39, bs, 1H, H6.

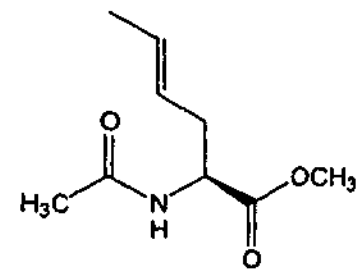
$^{13}$C n.m.r. (75 MHz, $CDCl_3$): δ 12.7, $CH_2\underline{C}H_3$; 21.6, $CO\underline{C}H_3$; 22.6, C4; 23.7, C3; 28.4, $\underline{C}H_2CH_3$; 51.7, C2; 52.[illegible]$O\underline{C}H_3$; 119.1, C6; 121.7, C5; 168.2, 171.2, $\underline{C}OOCH_3$ and CON.

Mass spectrum ($ESI^+$, MeOH): Found: *m/z* 234.1097. Calculated: $(C_{11}H_{17}NO_3+Na)^+$ *m/z* 234.1106.

## *5.7 Synthesis of Cyclic α-Amino Acids in Supercritical Carbon Dioxide*

### 5.7.1 Asymmetric Hydrogenations

#### *5.7.1.1 Preparation of (2S)-(4E)-methyl 2-acetamidohex-4-enoate (51b)*




(51b)

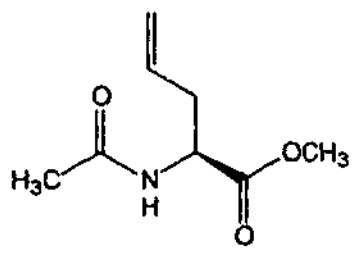
(2*Z*,4*E*)-Methyl 2-acetamidohexa-2,4-dienoate (46) (20 mg, 0.11 mmol) and [(COD)Rh(I)((*S*,*S*)-Et-DuPHOS)]OTf (substrate : catalyst ratio = 50 : 1) were loaded in a 100 ml Parr autoclave in a drybox. The vessel was charged with hydrogen (300 psi) and followed by 1200 psi of liquid $CO_2$ by using a high pressure pump (refer to Section 5.1.4). The autoclave was heated to 40°C and stirred for 18 h. Before work-up, the autoclave was cooled to 0°C by immersing into a bucket of ice. Subsequently,

the hydrogen and $CO_2$ were vented very slowly. The crude product which was left in the vessel was retrieved by dissolving the oil with dichloromethane and the mixture was then concentrated to give a yellow oil (22 mg). Purification by passing through a short silica plug with ethyl acetate gave an oil (20 mg, 98%). The $^1$H n.m.r. spectrum of the oil indicated the product, (2*S*)-(4*E*)-methyl 2-acetamidohex-4-enoate (51b) and starting material, (2*Z*,4*E*)-methyl 2-acetamidohexa-2,4-dienoate (46) in 80 : 20 ratio respectively.

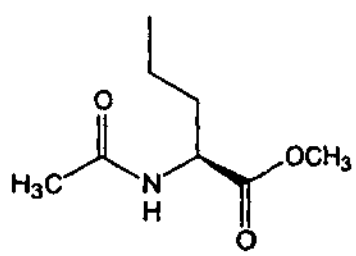
(2*Z*,4*E*)-Methyl 2-acetamidohexa-2,4-dienoate (46), refer to Section 5.2.8 for full characterisation.

(2*S*)-(4*E*)-Methyl 2-acetamidohex-4-enoate (51b), refer to Section 5.3.1 for full characterisation.

### *5.7.1.2 Preparation of (2S)-methyl 2-acetamidopent-4-enoate (48)*




(53b)




(54b)

Using the method described in Section 5.7.1.1, hydrogenation of (2*Z*)-methyl 2-acetamidopenta-2,4-dienoate (48) (35 mg, 0.21 mmol) was carried out at 200 psi of $H_2$ and 1200 psi of $CO_2$ with [(COD)Rh(I)((*S*,*S*)-Et-DuPHOS)]OTf. The vessel was heated to 40°C for 18 h. Purification by passing through a short plug of silica with ethyl acetate gave an oil (40 mg, 100%). The $^1$H n.m.r. spectrum indicated the title product, (2*S*)-methyl 2-acetamidopent-4-enoate (53b), the fully saturated compound,

(2*S*)-methyl 2-acetamidopentanoate (54b) and starting material, (2*Z*)-methyl 2-acetamidopenta-2,4-dienoate (48) in a 72 : 16 : 12 ratio respectively.

(2*Z*)-Methyl 2-acetamidopenta-2,4-dienoate (48), refer to Section 5.2.9 for full characterisation.

(2*S*)-Methyl 2-acetamidopent-4-enoate (53b), refer to Section 5.3.2 for full characterisation.

Similar reactions were carried out by varying pressure (P) and reaction time (t). The results are summarised in Table 5.6.

**Table 5.6**

| Entry | Pressure (psi) | Time (h) | % Conversion | % Over-reduction |
|---|---|---|---|---|
| 1 | 50 | 3 | 57 | 10 |
| 2 | 100 | 18 | 70 | 17 |
| 3 | 250 | 18 | 93 | 30 |

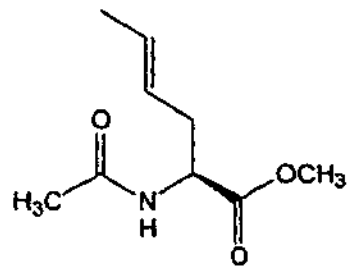
### 5.7.2 One-pot Tandem Reactions

#### *5.7.2.1 Rhodium(I)-catalysed reactions of (2Z,4E)-methyl 2-acetamidohexa-2,4-dienoate (46)*

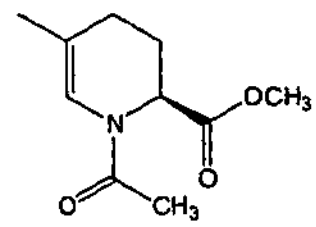
**(2*S*)-(4*E*)-Methyl 2-acetamidohex-4-enoate (51b)**

**(2*S*)-Methyl *N*-acetyl-5-methyl-5,6-didehydropipecolate (68b)**

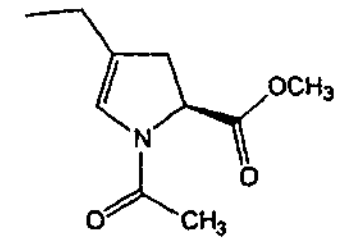
**(2*S*)-Methyl *N*-acetyl-4-ethyl-4,5-didehydroprolinate (69b)**




(51b)




(68b)




(69b)

(2*Z*,4*E*)-Methyl 2-acetamidohexa-2,4-dienoate (46) (50 mg, 0.27 mmol), [(COD)Rh(I)((*S*,*S*)-Et-DuPHOS)]OTf (substrate : catalyst ratio = 50 : 1) were loaded into a 100 ml Parr autoclave in a drybox. The vessel was charged with hydrogen (300 psi) and 1200 psi of liquid $CO_2$ by using a high pressure pump (refer to Section 5.1.4) and it was then heated to 40°C. After 18 h, the autoclave was cooled to 0°C by immersing into a bucket of ice. Subsequently, the hydrogen and $CO_2$ were vented very slowly and the autoclave was pressurized to 400 psi of $CO/H_2$ (1 : 1 molar ratio) and 1200 psi of liquid $CO_2$. The autoclave was heated to 60°C for 72 h. Work-up as above (refer to Section 5.7.1.1) gave a brown oil (58 mg). The $^1$H n.m.r. spectrum of the crude oil showed the presence of the three compounds, (2*S*)-methyl *N*-acetyl-5-methyl-5,6-didehydropipecolate (68b), (2*S*)-methyl *N*-acetyl-4-ethyl-4,5-didehydroprolinate (69b) and the non-hydroformylated material, (2*S*)-(4*E*)-methyl 2-acetamidohex-4-enoate (51b) in 54 : 26 : 20 ratio. Purification was done using chromatography (ethyl acetate : light petroleum = 3 : 1).

(2*S*)-(4*E*)-Methyl 2-acetamidohex-4-enoate (51b), refer to Section 5.3.1 for full characterisation.

(2*S*)-Methyl *N*-acetyl-5-methyl-5,6-didehydropipecolate (68b) (22 mg, 41%), ($R_f$ 0.51) was isolated as clear oil. A solution of the purified compound (68b) in HPLC grade isopropanol (10 μl) was injected into the HPLC containing a OD chiral column (1.0 ml $min^{-1}$, 10% isopropanol : 90% hexane) to give two peaks; (*S*) $t_1$ = 8.3 min with 97.96% area, (*R*) $t_2$ = 11.4 min with 0.44% area. The enantiomeric excess was 99.1%. Refer to Section 5.4.1 for full characterisation.

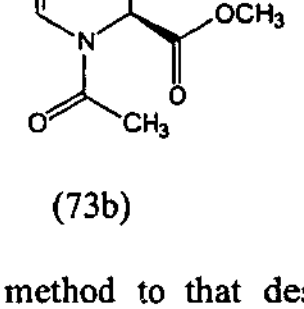
(2*S*)-Methyl *N*-acetyl-4-ethyl-4,5-didehydroprolinate (69b) (24 mg, 45%), ($R_f$ 0.34) containing 38% of (2*S*)-methyl *N*-acetyl-5-methyl-5,6-didehydropipecolate (68b) was obtained as clear oil. A solution of the purified compound (69b) in HPLC grade isopropanol (10 μl) was injected into the HPLC containing a OD chiral column (1.0 ml $min^{-1}$, 10% isopropanol : 90% hexane) to give two peaks; (*S*) $t_1$ = 11.6 min with 99.05% area, (*R*) $t_2$ = 22.1 min with 0.39% area. The enantiomeric excess was 99.2%. Refer to Section 5.4.1 for full characterisation.

A similar reaction was carried out for 48 h and the $^1$H n.m.r. spectrum of the crude oil showed a trace amount of cyclic products ((68b) and (69b)).

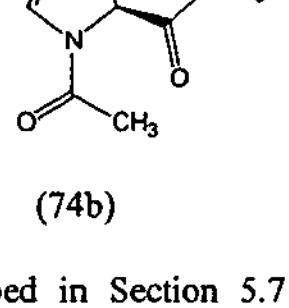
### *5.7.2.2 Rhodium(I)-catalysed reactions of (2S)-methyl 2-acetamidopenta-2,4-dienoate (48)*

**(2*S*)-Methyl *N*-acetyl-5,6-didehydropipecolate (73b)**

**(2*S*)-Methyl *N*-acetyl-4-methyl-4,5-didehydroprolinate (74b)**




(73b)




(74b)

Using an identical method to that described in Section 5.7.2.1, (2*Z*)-methyl 2-acetamidopenta-2,4-dienoate (48) (50 mg, 0.3 mmol) and [(COD)Rh(I)((*S*,*S*)-Et-DuPHOS)]OTf (substrate : catalyst ratio = 50 : 1) ) in a 100 ml Parr autoclave in a drybox. The vessel was charged with hydrogen (200 psi) and 1200 psi of liquid $CO_2$ by using a high pressure pump (refer to Section 5.1.4), it was then heated to 40°C. After 18 h, the autoclave was cooled to 0°C by immersing into a bucket of ice. Subsequently, the hydrogen and $CO_2$ were vented very slowly and the autoclave was pressurized to 400 psi of $CO/H_2$ (1 : 1 molar ratio) and 1200 psi of liquid $CO_2$. The autoclave was heated to 60°C for 48 h. Work-up as above (refer to Section 5.7.1.1) to give a brown oil (58 mg). The $^1H$ n.m.r. spectrum of the crude oil showed the presence of three compounds, (2*S*)-methyl *N*-acetyl-5,6-didehydropipecolate (73b), (2*S*)-methyl *N*-acetyl-4-methyl-4,5-didehydroprolinate (74b) and the fully saturated compound, (2*S*)-methyl 2-acetamidopentanoate (54b) in 52 : 18 : 30 ratio. Purification was done using chromatography (ethyl acetate : light petroleum = 3 : 1).

(2*S*)-Methyl *N*-acetyl-5,6-didehydropipecolate (73b) (13 mg, 24%), ($R_f$ 0.5) was isolated as clear oil. A solution of the purified compound (73b) in HPLC grade isopropanol (10 μl) was injected into the HPLC containing a OD chiral column (1.0

ml $min^{-1}$, 10% isopropanol : 90% hexane) to give two peaks; (*S*) $t_1$ = 9.9 min with 96.77% area, (*R*) $t_2$ = 29.29 min with 1.12% area. The enantiomeric excess was 97.7%. Refer to Section 5.4.2 for full characterisation.

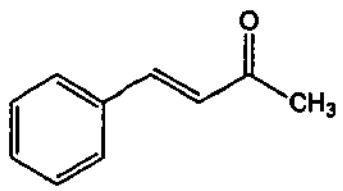
(2*S*)-Methyl *N*-acetyl-4-methyl-4,5-didehydroprolinate (74b), (11 mg, 20%), ($R_f$ 0.3) containing 55% of (2*S*)-methyl 2-acetamidopentanoate (54b). A solution of the purified compound (74b) in HPLC grade isopropanol (10 μl) was injected into the HPLC containing a OD chiral column (1.0 ml $min^{-1}$, 10% isopropanol : 90% hexane) to give two peaks; (*S*) $t_1$ = 13.0 min with 95.87% area, (*R*) $t_2$ = 30.3 min with 0.88% area. The enantiomeric excess was 98.2%. Refer to Section 5.4.2 for full characterisation.

A similar reaction was carried out for 24 h and the $^1$H n.m.r. spectrum of the crude oil showed no sign of cyclic products ((73b) and (74b)).

## *Experimental For Chapter 3*

## *5.8 Preparation of β-Amino Acids Precursors*

### 5.8.1 Preparation of (*E*)-Benzalacetone (89)




(89)

A solution of 2 M NaOH (10 ml) was added dropwise to a stirred mixture of benzaldehyde (88) (25 ml, 250 mmol) and acetone (50 ml, 700 mmol) over 15 min according to method described by Drake *et al.*.[92] After 2 h of stirring at ambient temperature, the mixture was acidified with 1.2 M HCl solution (20 ml). The organic layer was separated and the aqueous layer was extracted with toluene (3 x 20 ml). The

combined organic layer was then washed with water (3 x 20 ml), dried over $Mg_2SO_4$ and concentrated *in vacuo* to give product (89) (32.64 g, 89%) as yellow liquid.

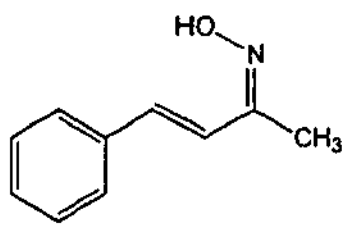
$\nu_{max}$ (Film): 3457w, 1717m, 1690m, 1668s, 1609s, 1495w, 1450m, 1358m, 1257s, 1204m, 1183m, 975s, 750s, 690s $cm^{-1}$.

$^1H$ n.m.r. (300 MHz, $CDCl_3$): δ 2.34, s, 3H, H1; 6.68, d, 1H, *J* 16.4 Hz, H3; 7.31-7.39, m, 5H, ArH; 7.49, d, 1H, *J* 16.2 Hz, H4.

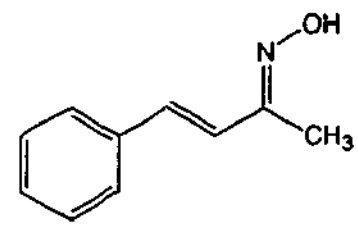
$^{13}C$ n.m.r. (75 MHz, $CDCl_3$): δ 27.3, C1; 128.2, C3; 128.0, 128.7, C2', 6' and C3', 5'; 130.3, C4'; 134.1, C1'; 143.2, C4; 198.1, C2.

Mass spectrum ($ESI^+$, MeOH): *m/z* 168.7 $(M+Na)^+$.

### 5.8.2 Preparation of 4-Phenylbut-3-en-2-one oxime (90)




(90a)




(90b)

Following the method described by Schenck *et al.*,[93] hydroxylamine hydrochloride ($NH_2.OH.HCl$) (43.04 g, 0.62 mol) and NaOH (86.08 g, 1.05 mol) were added to a solution of (*E*)-benzalacetone (89) (21.52 g, 0.15 mol) in water and ethanol (5 : 1). After 1 h of reflux, the mixture was concentrated under reduced pressure to give an oil. The oil was diluted with dichloromethane (80 ml) and was washed with water (3 x 100 ml) and 2 M HCl solution (3 x 50 ml). The solvent was evaporated *in vacuo* to give a thick yellow oil. The $^1H$ n.m.r. spectrum of the crude oil showed a mixture of *anti*- and *syn*-oximes ((90a) and (90b) in a 75 : 25 ratio). A portion (5 g) of the crude oil was purified by flash chromatography on silica gel using ethyl acetate and light

petroleum (4 : 1) and firstly gave *anti*-4-phenylbut-3-en-2-one oxime (90a) followed by *syn*-4-phenylbut-3-en-2-one oxime (90b).

*Anti*-4-Phenylbut-3-en-2-one oxime (90a) (1.94 g, 35%), ($R_f$ 0.21) was isolated as pale yellow paste.

$\nu_{max}$ (KBr): 3327b, 1670s, 1578m, 1492m, 1442m, 1420m, 1332w, 1290w, 1246m, 1209w, 1185m, 1168m, 1076w, 961s, 830m, 751s, 691s $cm^{-1}$.

$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 2.15, s, 3H, H1; 6.84, d, 1H, *J* 16.5 Hz, H3; 6.92, d, 1H, *J* 16.5 Hz, H4; 7.28-7.38, m, 3H, H3', H4' and H5'; 7.46-7.49, m, 2H, H2' and H6'.

$^{13}$C n.m.r. (75 MHz, $CDCl_3$): δ 9.9, C1; 125.8, C3; 126.9, 128.8, C2', 6' and C3', 5'; 128.5, C4'; 133.5, C4; 136.3, C1'; 156.8, C2.

Mass spectrum ($ESI^+$, MeOH): *m/z* 161.9 $(M)^+$.

*Syn*-4-Phenylbut-3-en-2-one oxime (90b) (0.45 g, 10%), ($R_f$ 0.26) was obtained as a pale yellow paste.

$\nu_{max}$ (KBr): 3421b, 1654s, 1518m, 1508m, 1449m, 1031w, 972s, 749s, 691s $cm^{-1}$.

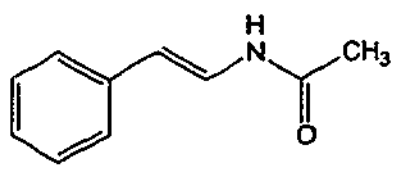
$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 2.15, s, 3H, H1; 6.96, d, 1H, *J* 16.7 Hz, H3; 7.30-7.40, m, 3H, H3', H4' and H5'; 7.52-7.56, m, 2H, H2' and H6'; 7.60, d, 1H, *J* 16.5 Hz, H4.

$^{13}$C n.m.r. (75 MHz, $CDCl_3$): δ 17.1, C1; 116.8, C3; 127.6, 128.8, C2', 6' and C3', 5'; 129.2, C4'; 136.2, C1'; 136.6, C4; 153.5, C2.

Mass spectrum ($ESI^+$, MeOH): *m/z* 161.9 $(M)^+$.

The spectral data were consistent with those reported in the literature.[93]

### 5.8.3 Preparation of (*E*)-*N*-(2-Phenylethenyl)acetamide (91)



(91)

#### *5.8.3.1 Via 4-phenylbut-3-en-2-one oxime (90)*

Using the method described by Zielinski *et al.*,[95] phosphorus pentachloride ($PCl_5$) (10.95 g, 52.58 mmol) was added portionwise to a stirred and cooled (5°C) solution of *anti*- and *syn*-4-phenylbut-3-en-2-one oximes ((90a) and (90b) in a 75 : 25 ratio) (7.68 g, 47.64 mmol) in dioxane (100 ml). The reaction mixture was warmed to ambient temperature and allowed to stir for a further 2 h. The mixture was then poured into a cooled $Na_2CO_3$ solution (100 ml) and extracted with diethyl ether (3 x 100 ml) and concentrated *in vacuo* to give a dark red oil. The $^1H$ n.m.r. spectrum of the crude oil showed the desired product, (*E*)-*N*-(2-phenylethenyl)acetamide (91) and by-product, (*E*)-*N*-methyl-3-phenylprop-2-enamide (92) in a 30 : 70 ratio. Purification by column chromatography using ethyl acetate and light petroleum (3 : 1) gave (*E*)-*N*-(2-phenylethenyl)acetamide (91) as a pale yellow solid (0.54 g, 7%), ($R_f$ 0.38), m.p. 106-108°C (lit.[94,150] 113-114°C).

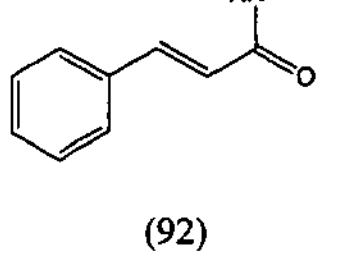
$\nu_{max}$ (KBr): 3414s, 3291b, 3055s, 1670s, 1646s, 1578w, 1534m, 1448w, 1370m, 1304m, 1165m, 941m, 747m, 692m, 600w $cm^{-1}$.

$^1H$ n.m.r. (300 MHz, $CDCl_3$): δ 2.12, s, 3H, $COCH_3$; 6.18, d, 1H, *J* 14.6 Hz, H2; 7.25-7.34, m, 5H, ArH; 7.52, dd, 1H, *J* 14.6, 10.8 Hz, H1.

$^{13}C$ n.m.r. (75 MHz, $CDCl_3$): δ 23.8, $CO\underline{C}H_3$; 112.6, C2; 122.8, C1; 125.8, 128.0, C2', 6' and C3', 5'; 126.9, C4'; 136.1, C1'; 167.4, CONH.

Mass spectrum ($ESI^+$, MeOH): *m/z* 161.8 $(M)^+$.

The spectral data were consistent with those stated in the literatures.[94,150]




(92)

(*E*)-*N*-Methyl-3-phenylprop-2-enamide (92) (1.59 g, 21%), ($R_f$ 0.25) was obtained as a yellow oil.

$\nu_{max}$ (Film): 3282b, 1656s, 1619s, 1549m, 1494m, 1449m, 1345m, 1284w, 1165m, 978m, 766m, 601w $cm^{-1}$.

$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 2.87, bs, 3H, $CH_3$; 6.56, d, 1H, *J* 15.7 Hz, H2; 7.02-7.52, m, 5H, ArH; 7.59, d, 1H, *J* 15.5 Hz, H3.

$^{13}$C n.m.r. (75 MHz, $CDCl_3$): δ 26.5, $CH_3$; 120.8, C2; 127.5, 128.6, C2', 6' and C3', 5'; 129.4, C4'; 134.6, C1'; 140.2, C3; 167.0, C1.

Mass spectrum ($ESI^+$, MeOH): *m/z* 161.9 $(M)^+$.

The spectral data were consistent with those stated in the literatures.[151]

A similar reaction was carried out as above using pure *syn*-oxime (90b) (0.1 g, 0.62 mmol) and phosphorus pentachloride ($PCl_5$) (0.14 g, 0.67 mmol) in tetrahydrofuran (10 ml). The $^1$H n.m.r. spectrum of the crude showed product (91) : by-product (92) in 25 : 75 ratio.

### *5.8.3.2 Via phenylacetaldehyde (93)*

Using the modified method described by Correa *et al.*,[96,97] a neat mixture of phenylacetaldehyde (93) (1.0 g, 3.32 mmol) and acetamide (34) (0.49 g, 8.32 mmol) was heated at 70°C. The mixture was stirred for 20 min before the addition of *p*-toluenesulfonic acid (*p*-TsOH) (50 mg). The $^1$H n.m.r. spectrum of the crude solid

showed desired product, (*E*)-*N*-(2-phenylethenyl)acetamide (91) and starting materials ((93) and (34)). Purification by flash chromatography on silica gel using ethyl acetate and light petroleum (3 : 1) gave the product (91), (0.20 g, 15%), ($R_f$ 0.32) as a pale yellow solid.

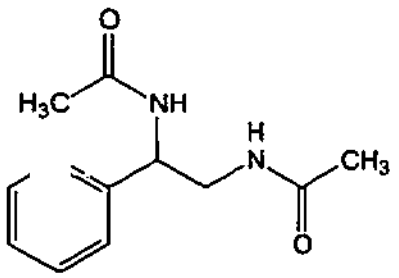
Refer to Section 5.8.3.1 for full characterisation.

Similar reactions were carried out by varying the conditions. The results are summarised in Table 5.7.

**Table 5.7**

| Entry | Catalyst | Solvent | T (°C) | Time (h) | % Yield |
|---|---|---|---|---|---|
| 1 | *p*-toluene sulfonic acid | Toluene | reflux[a] | 4 | 8[b] |
| 2 | - | Neat | 70°C | 120 | 12 |

[a] Using Dean-Stark apparatus. [b] By-product, 2-acetamido-2-phenylethylacetamide (94) (*ca.* 50%) was isolated.



(94)

2-Acetamido-2-phenylethylacetamide (94):

$\nu_{max}$ (KBr): 3290b, 3262b, 3926w, 1245w, 1643s, 1538w, 1490w, 1372m, 1286s, 1182m, 1084m, 1041m, 1020m, 977m, 949w, 910s, 732s, 646w $cm^{-1}$.

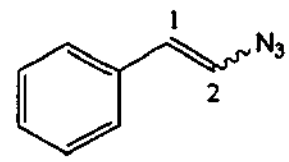
$^1H$ n.m.r. (300 MHz, $CDCl_3$): δ 1.96, s, 3H, $C\underline{H_3}CONHC2$; 2.12, s, 3H, $C\underline{H_3}CONHC1$; 2.77, m, 2H, H1; 5.18, m, 1H, H2; 6.82, bd, 1H, *J* 9.6 Hz, NH; 7.13-7.23, m, 5H, ArH; 10.15, bd, 1H, *J* 9.7 Hz, NH.

$^{13}$C n.m.r. (75 MHz, $CDCl_3$): δ 23.2, $\underline{C}H_3CONHC2$; 23.8, $\underline{C}H_3CONHC1$; 39.0, C1; 49.8, C2; 126.8, C4'; 128.6, 128.9, C2', 6' and C3', 5'; 137.6, C1'; 169.0, $CH_3\underline{C}ONHC2$; 171.7, $CH_3\underline{C}ONHC1$.

Mass spectrum ($ESI^+$, MeOH): *m/z* 161.9 $(M\text{-}C_2H_4NO)^+$.

The spectral data were consistent with those reported in the literature.[152]

### 5.8.4 Preparation of β-Azidostyrene (96)




(96)

A degassed solution of cerium(IV) ammonium nitrate (CAN) (1.85 g, 3.38 mmol) in acetonitrile (10 ml) was added dropwise to a stirred, cooled (0°C) mixture of cinnamic acid (95) (0.2 g, 1.35 mmol) and sodium azide ($NaN_3$) (0.13 g, 2.03 mmol) in acetonitrile (20 ml) according to the method described by Nair *et al.*.[98] The reaction mixture was left stirring at ambient temperature for 18 h. The reaction mixture was diluted with dichloromethane (40 ml), washed with water (2 x 20 ml) and the organic phase was dried over $MgSO_4$ and concentrated to give a yellow oil. The oil was redissolved with acetone (20 ml) prior to the addition of sodium acetate (NaOAc) (0.17 g, 2.03 mmol). The reaction mixture was heated at reflux for 3 h and then stirred at ambient temperature for further 18 h. Work-up as before gave products, (*E*)-β-azidostyrene (96a) and (*Z*)-β-azidostyrene (96b) (50 : 50 ratio) (0.34 g, 100%) as a yellow oil. Separation was not carried out due to instability of the products ((96a) and (96b)).

$\nu_{max}$ (Film): 3460b, 2974m, 2112s, 1702s, 1635m, 1400s, 1364m, 1275m, 1219m, 1180m, 1147m, 1021w, 933w, 844w, 751w $cm^{-1}$.

$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 5.68, d, 1H, *J* 8.5 Hz, H2(*Z*) ; 6.27, d, 1H, *J* 13.9 Hz, H2(*E*), 6.3[illegible], 1H, *J* 8.4 Hz, H1(*Z*); 6.60, d, 1H, *J* 13.9 Hz, H1(*E*); 7.18-7.35, m, 8H, ArH; 7.57-7.60, m, 2H, ArH.

$^{13}$C n.m.r. (75 MHz, $CDCl_3$): δ 118.0, 119.9, C2; 125.3, 126.8, C1; 128.4, 125.9, 128.9, 129.1, C2', 6' and C3', 5'; 127.4, 137.5, C4'; 134.7, 135.1, C1'.

The spectral data were consistent with those reported in the literature.[98]

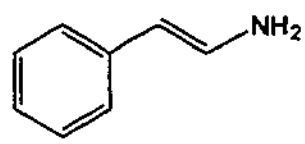
### 5.8.5 Preparation of Barium Sulfurated Borohydride (101)

$Ba(BH_2S_3)_2$

(101)

Following the method described by Firouzabadi *et al.*,[100] sulfur (1.27 g, 39.75 mmol) was added to a cooled (0°C) solution of $NaBH_4$ (0.5 g, 13.2 mmol) in tetrahydrofuran (25 ml) over 20 min. The reaction mixture was left stirring at ambient temperature for further 30 min followed by the addition of barium chloride ($BaCl_2$) (1.37 g, 6.6 mmol). After 12 h, the mixture was concentrated *in vacuo* and the solid was washed with light petroleum (3 x 20 ml) to give product (101) (2.96 g, 63%) as yellow powder.

### 5.8.6 Attempted Preparation of (*E*)-Styrylamine (97)




(97)

#### *5.8.6.1 Via β-azidostyrene (96)*

$PPh_3$ (0.56 g, 2.13 mmol) was added to a stirring mixture of β-azidostyrene (96) (0.31 g, 2.13 mmol) in tetrahydrofuran (5 ml) and water (0.1 ml) as according to the method

described by Knouzi *et al.*.[99] The reaction mixture was left stirring at ambient temperature for 18 h. It was concentrated and the residual oil was diluted with ethyl acetate and light petroleum (1 : 1 ratio) (10 ml) to initiate the formation of triphenylphosphine oxide. Unfortunately, no solids were formed and the solution was concentrated again to give an yellow oil (0.7 g). The $^1$H n.m.r. spectrum of the crude oil indicated neither starting material (96) nor product (97).

A similar reaction was carried out using the same substrate (96) (0.06 g, 0.41 mmol) and $PPh_3$ (0.11 g, 0.41 mmol) in tetrahydrofuran (5 ml) and water (0.1 ml). The reaction mixture was left heated at 50°C for 18 h. Work-up as above to give a yellow oil (0.06 g). The $^1$H n.m.r. spectrum of the crude oil indicated neither starting material (96) nor product (97).

Another reaction was carried out using the same substrate (96) (0.10 g, 0.69 mmol) with $LiAlH_4$ (0.13 g, 3.45 mmol) in tetrahydrofuran (10 ml). After 18 h of stirring at ambient temperature, the reaction was quenched with $Na_2SO_4.10H_2O$, followed by filtration. The filtrate was concentrated to give an oil (0.06 g). The $^1$H n.m.r. spectrum of the crude oil indicated neither starting material (96) nor product (97).

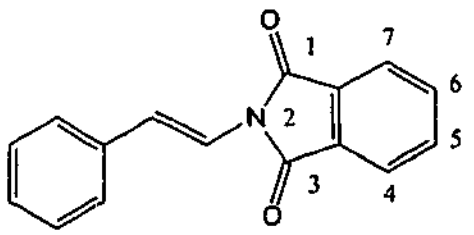
The reaction was attempted using $Ba(BH_2S_3)_2$ (101) (0.16 g, 0.45 mmol) with the same substrate (0.07 g, 0.45 mmol) as stated by Firouzabadi *et al.*.[100] After 18 h of reflux, the catalyst was filtered through a Celite pad. The filtrate was concentrated to give a dark brown oil (0.05 g). The $^1$H n.m.r. spectrum of the crude oil indicated starting material (96).

#### *5.8.6.2 Via (E)-β-nitrostyrene (98)*

Following method described by Firouzabadi *et al.*,[100] $Ba(BH_2S_3)_2$ (101) (0.72 g, 1.5 mmol) was added to a stirring solution of (*E*)-β-nitrostyrene (98) (0.25 g, 2.0 mmol)

in tetrahydrofuran (10 ml) in 4 portions with 20 min intervals at ambient temperature. The reaction mixture was then heated at reflux. After 2 days, the reaction mixture was quenched with 5% NaOH solution (15 ml) and left stirring at ambient temperature for further 18 h. The organic layer was concentrated to give an oil (0.3 g). The $^1$H n.m.r. spectrum of the crude oil indicated neither starting material (98) nor product (97).

### 5.8.7 Preparation of (*E*)-*N*-(2-Phenylethenyl)phthalimide (104)



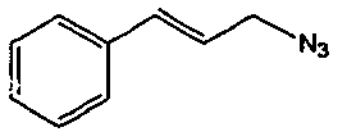

(104)

Copper iodide (CuI) (0.53 g, 2.73 mmol) was added to a stirring mixture of β-bromostyrene (102) (0.5 g, 2.73 mmol) and potassium phthalimide (103) (1.52 g, 8.19 mmol) in hexamethylphosphoric triamide (HMPA) (15 ml) as according to Ogawa *et al.*.[102] The reaction mixture was heated at 130°C for 18 h, cooled and quenched with 5% HCl solution (30 ml) and NaCl solution (30 ml), followed by extraction with benzene (30 ml). The organic layer was concentrated to give a dark brown oil (1.0 g). The $^1$H n.m.r. spectrum of the crude oil indicated the presence of starting material (102) (δ 6.77, d, 1H, *J* 13.9 Hz, CHBr; 7.11, d, 1H, *J* 14.0 Hz, CHPh) and product (104) in an approximately 67 : 33 ratio.

$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 6.84, d, 1H, *J* 15.0 Hz, H2; 7.25-7.41, m, 5H, ArH; 7.67, d, 1H, *J* 15.2 Hz, H1; 7.77, m, 2H, H5 and H6; 7.90, m, 2H, H4 and H7.

The spectral data were consistent with those reported in the literature.[102]

### 5.8.8 Preparation of (*E*)-3-Azidoprop-1-enylbenzene (106)




(106)

Using the method described by Alvarez *et al.*,[103] cinnamyl bromide (105) (2.0 g, 10.16 mmol) was added to a freshly prepared solution of sodium azide ($NaN_3$) in dimethyl sulfoxide (0.5 M, 22.3 ml). The reaction mixture was left stirring at ambient temperature for 18 h. The reaction mixture was quenched with water (50 ml) and extracted with diethyl ether (3 x 30 ml). The combined organic layer was extracted with water (2 x 30 ml) and saturated NaCl solution (2 x 30 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give product, (*E*)-3-azidoprop-1-enylbenzene (106) (1.67 g, 100%) as a yellow liquid.

$\nu_{max}$ (Film): 3028w, 2924w, 2100s, 1658w, 1598w, 1492w, 1428w, 1351w, 1236w, 1028w, 957w, 882w, 746m, 692m $cm^{-1}$.

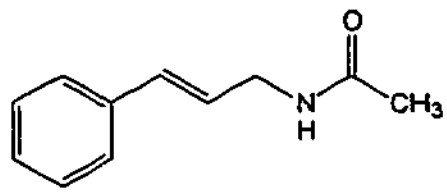
$^1H$ n.m.r. (300 MHz, $CDCl_3$): δ 3.91, bd, 2H, *J* 6.4 Hz, H3; 6.24, dt, 1H, *J* 15.8, 6.6 Hz, H2; 6.63, d, 1H, *J* 15.9 Hz, H1; 7.21-7.40, m, 5H, ArH.

$^{13}C$ n.m.r. (75 MHz, $CDCl_3$): δ 53.0, C3; 122.5, C2; 128.2, C1; 126.7, 128.7, C2', 6' and C3', 5'; 134.5, C4'; 136.0, C1'.

Mass spectrum (EI): *m/z* 159.0 $(M)^+$.

The spectral data were consistent with those reported in literature.[103]

### 5.8.9 Preparation of (*E*)-*N*-(3-Phenylprop-2-enyl)acetamide (107)



(107)

Thioacetic acid (MeCOSH) (3.28 ml, 44.73 mmol) was added to (*E*)-3-azidoprop-1-enylbenzene (106) (1.78 g, 11.82 mmol) as described by Rosen *et al.*.[104] The neat mixture was stirred at ambient temperature for 4 h. Purification was done through a silica plug with gradient solvent system (1 : 1 ratio of ethyl acetate : light petroleum to ethyl acetate) gave the product, (*E*)-*N*-(3-phenylprop-2-enyl)acetamide (107) (1.48 g, 72%) as a white solid, m.p. 87-89°C (lit.[104] 88-90°C).

$\nu_{max}$ (KBr): 3248b, 3095w, 2920w, 1646s, 1560s, 1426s, 1374s, 1266w, 1227m, 1099m, 1030m, 963s, 753s, 693s, 596m, 494w, 460w, 430w $cm^{-1}$.

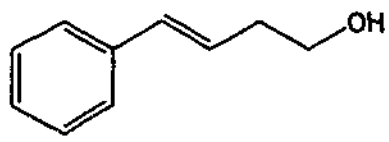
$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 2.0, s, 3H, $COCH_3$; 3.99, m, 2H, H1; 6.16, m, 1H, H2; 6.24, bs, 1H, NH; 6.49, d, 1H, *J* 15.8 Hz, H3; 7.20-7.35, m, 5H, ArH.

$^{13}$C n.m.r. (75 MHz, $CDCl_3$): δ 23.2, $CO\underline{C}H_3$, 41.7, C1; 125.6, C2; 127.7, C3; 126.4, 128.6, C2', 6' and C3', 5'; 132.1, C4'; 136.6, C1'; 170.3, CONH.

Mass spectrum ($ESI^+$, MeOH): *m/z* 197.9 $(M+Na)^+$.

The spectral data were consistent with those reported in literature.[104]

### 5.8.10 Preparation of (*E*)-4-Phenylbut-3-enol (109)



(109)

Using the method described by Padwa *et al.*,[105] a solution of *E*-styrylacetic acid (108) (1.0 g, 6.17 mmol) in dry diethyl ether (20 ml) was added dropwise into a solution of

$LiAlH_4$ (0.23 g, 6.17 mmol) in dry diethyl ether (30 ml). The reaction mixture was then heated at reflux for 18 h. It was quenched by the addition of $Na_2SO_4.10H_2O$. After filtration, the filtrate was concentrated to give product, (*E*)-4-phenylbut-3-enol (109) (0.85 g, 93%) as yellow oil.

$\nu_{max}$ (KBr): 3363b, 3026m, 2932m, 1947w, 1877w, 1803w, 1650w, 1597w, 1493m, 1448m, 1178w, 1046s, 965s, 743s, 693w $cm^{-1}$.

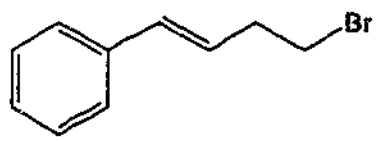
$^1H$ n.m.r. (300 MHz, $CDCl_3$): δ 2.42, m, 2H, H2; 2.60, bs, 1H, OH; 3.67, t, 2H, *J* 6.5 Hz, H1; 6.16, m, 1H, H3; 6.44, d, 1H, *J* 15.8 Hz, H4; 7.15-7.34, m, 5H, ArH.

$^{13}C$ n.m.r. (75 MHz, $CDCl_3$): δ 36.3, C2; 61.9, C1; 126.1, 128.5, C2', 6' and C3', 5'; 126.5, 127.2, C3 and C4; 132.5, C4'; 137.3, C1'.

Mass spectrum ($ESI^+$, MeOH): *m/z* 130.9 $(M+H-OH)^+$.

The spectral data were consistent with those reported in literature.[105]

### 5.8.11 Preparation of (*E*)-4-Bromobut-1-enylbenzene (110)




(110)

Following the modified method described by Shuto *et al.*,[153] $PPh_3$ (2.65 g, 10.12 mmol) and carbon tetrabromide ($CBr_4$) (3.36 g, 10.12 mmol) were added to a stirred solution of (*E*)-4-phenylbut-3-enol (109) (0.5 g, 3.37 mmol) in diethyl ether (20 ml). The reaction mixture was heated at reflux for 18 h. It was quenched with saturated NaCl solution (30 ml), extracted with ethyl acetate (2 x 20 ml), dried over $Na_2SO_4$ and concentrated to give an oil. Purification through a silica plug (9 : 1 ratio of light petroleum : ethyl acetate) gave the product, (*E*)-4-bromobut-1-enylbenzene (110) (1.03 g, 100%) as a yellow oil.

$\nu_{max}$ (Film): 3026m, 2922m, 2854w, 1995w, 1947w, 1723m, 1597m, 1492m, 1447m, 1257m, 1207m, 1071w, 1028w, 965s, 909w, 741s, 692m, 668m $cm^{-1}$.

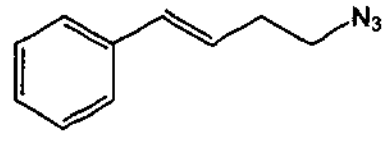
$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 2.75, qd, 2H, *J* 7.0, 1.5 Hz, H3; 3.45, t, 2H, *J* 7.1 Hz, H4; 6.16, m, 1H, H2; 6.47, d, 1H, *J* 15.8 Hz, H1; 7.18-7.37, m, 5H, ArH.

$^{13}$C n.m.r. (75 MHz, $CDCl_3$): δ 32.4, C3; 36.4, C4; 126.3, 128.7, C2', 6' and C3', 5'; 126.7, 127.6, C1 and C2; 132.8, C4'; 137.1, C1'.

Mass spectrum (EI): *m/z* 212 $(M)^+$.

The spectral data were consistent with those reported in literature.[154]

### 5.8.12 Preparation of (*E*)-4-Azidobut-1-enylbenzene (111)




(111)

Following the modified method descried by Alvarez *et al.*,[103] (*E*)-4-bromobut-1-enylbenzene (110) (2.01 g, 9.52 mmol) was added to a solution of sodium azide ($NaN_3$) in dimethyl sulfoxide (0.5 M, 20.9 ml). The reaction was heated at 100°C for 18 h. Work-up as described in Section 5.8.8 gave the product, (*E*)-4-azidobut-1-enylbenzene (111) (1.23 g, 75%) as a dark brown oil.

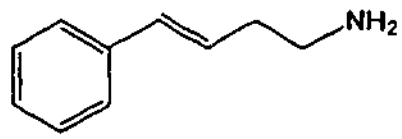
$\nu_{max}$ (Film): 3026w, 2932w, 2100s, 1729w, 1702w, 1598w, 1493m, 1449m, 1372w, 1347w, 1264m, 1146w, 1045w, 966m, 909m, 734s, 693m $cm^{-1}$.

$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 2.51, qd, 2H, *J* 7.0, 1.4 Hz, H3; 3.39, t, 2H, *J* 6.9 Hz, H4; 6.17, m, 1H, H2; 6.52, d, 1H, *J* 15.9 Hz, H1; 7.18-7.40, m, 5H, ArH.

$^{13}$C n.m.r. (75 MHz, $CDCl_3$): δ 32.7, C3; 51.0, C4; 125.9, C2; 126.2, 128.6, C2', 6' and C3', 5'; 127.5, C1; 132.8, C4'; 137.1, C1'.

The spectral data were consistent with those reported in the literature.[155]

### 5.8.13 Preparation of (*E*)-4-Phenylbut-3-enylamine (112)




(112)

Using the modified method as described by Davidson *et al.*,[156] freshly distilled ethanol (0.09 ml) was added to a suspension of $LiAlH_4$ (0.58 g, 15.24 mmol) in dry ether (26.2 ml). A fraction of this $LiAlH_4$ solution (2.6 ml) was added to a stirred solution of (*E*)-4-phenylbut-3-enylazide (111) (0.87 g, 5.02 mmol) in dry ether (10 ml). The addition was repeated for 3 times at 30 min intervals. The reaction mixture was left stirring for further 30 min before being quenched with $Na_2SO_4.10H_2O$. After filtration, the filtrate was concentrated to give the product, (*E*)-4-phenylbut-3-enylamine (112) (0.58 g, 58%) as a yellow liquid.

$\nu_{max}$ (Film): 3364w, 3025m, 2926m, 2856w, 1597m, 1492s, 1449m, 1381w, 1308w, 1027w, 966s, 1146w, 1045w, 966m, 743s, 693s $cm^{-1}$.

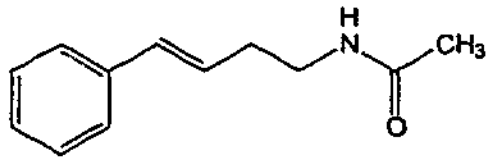
$^1H$ n.m.r. (300 MHz, $CDCl_3$): δ 1.91, bs, 2H, $NH_2$; 2.35, q, 2H, *J* 6.7 Hz, H2; 2.81, t, 2H, *J* 6.7 Hz, H1; 6.17, m, 1H, H3; 6.44, d, 1H, *J* 15.8 Hz, H4; 7.16-7.36, m, 5H, ArH.

$^{13}C$ n.m.r. (75 MHz, $CDCl_3$): δ 27.2, C1; 41.6, C2; 126.0, 128.5, C2', 6' and C3', 5'; 127.1, 127.8, C3 and C4; 132.0, C4'; 137.5, C1'.

Mass spectrum ($ESI^+$, MeOH): *m/z* 147.9 $(M+H)^+$.

The spectral data were consistent with those reported in the literature.[157]

### 5.8.14 Preparation of (*E*)-*N*-(4-Phenylbut-3-enyl)acetamide (113)




(113)

Triethylamine ($NEt_3$) (0.46 ml, 3.21 mmol) and acetic anhydride ($(MeCO)_2O$) (0.29 ml. 3.21 mmol) were added to a stirred solution of (*E*)-4-phenylbut-3-enylamine (112) (0.43 g, 2.92 mmol) in dichloromethane (20 ml). The reaction mixture was left stirring at ambient temperature for 18 h. The reaction mixture was quenched with water (20 ml), extracted with dichloromethane (2 x 20 ml) and the organic layer was dried over $MgSO_4$. The filtrate was concentrated to give the product, (*E*)-*N*-(4-phenylbut-3-enyl)acetamide (113) (0.43 g, 78%) as a brown solid, m.p. 38-40°C.

$\nu_{max}$ (KBr): 3300b, 3083w, 2856m, 1793w, 1651s, 1557s, 1447s, 1366m, 1297m, 1196w, 1097m, 970s, 744s, 693s, 603w $cm^{-1}$.

$^1H$ n.m.r. (300 MHz, $CDCl_3$): δ 1.97, s, 3H, $COCH_3$; 2.40, q, 2H, *J* 6.7 Hz, H2; 3.38, q, 2H, *J* 6.7 Hz, H1; 5.10, bs, 1H, NH; 6.15, m, 1H, H3; 6.45, d, 1H, *J* 15.9 Hz, H4; 7.19-7.40, m, 5H, ArH.

$^{13}C$ n.m.r. (75 MHz, $CDCl_3$): δ 22.1, $CO\underline{C}H_3$; 33.0, C1; 39.0, C2; 126.0, 128.5, C2', 6' and C3', 5'; 127.0, 127.3, C3 and C4; 132.2, C4'; 137.2, C1'; 166.4, CONH.

Mass spectrum ($ESI^+$, MeOH): *m/z* 190.1 $(M+H)^+$.

The spectral data were consistent with those reported in the literature.[158]

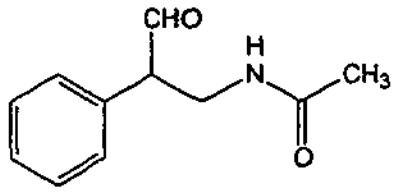
## 5.9 *Asymmetric Hydroformylations*

### 5.9.1 Rhodium-catalysed Reactions of (*E*)-*N*-(2-Phenylethenyl)acetamide (91)

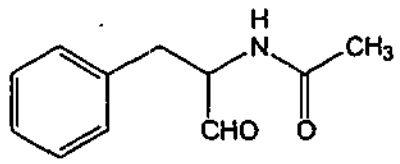
**_N_-(2-Formyl-2-phenylethyl)acetamide (115)**

**_N_-(1-Formyl-2-phenylethyl)acetamide (116)**

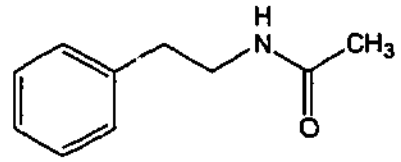
**_N_-(2-Phenylethyl)acetamide (117)**




(115)




(116)




(117)

(*E*)-*N*-(2-Phenylethenyl)acetamide (91) (50 mg, 0.32 mmol), rhodium(II) acetate dimer (2.8 mg, 6.2 μmol) and $PPh_3$ (3.2 mg, 12.4 μmol) were dissolved in deoxygenated benzene (10 ml) in a 100 ml Parr autoclave (refer to Section 5.1.3). The autoclave was pressurized to 1500 psi of $CO/H_2$ (1 : 1 molar ratio) and heated to 120°C. After 20 h, the autoclave was cooled to ambient temperature and the solvent was removed under reduced pressure to give a brown oil (53 mg). The $^1H$ n.m.r. spectrum of the crude oil indicated *ca.* 40% of starting material (91) and hydroformylated products, *N*-(2-formyl-2-phenylethyl)acetamide (115), *N*-(1-formyl-2-phenylethyl)acetamide (116) as well as the hydrogenated by-product, *N*-(2-phenylethyl)acetamide (117) in 54 : 27 : 19 ratio. As the products were unstable, separation was not carried out.

*N*-(2-Formyl-2-phenylethyl)acetamide (115):

$^1H$ n.m.r. (300 MHz, $CDCl_3$): δ 1.93, s, 3H, $COCH_3$; 3.92, m, 2H, H1; 3.92, m, 1H, H2; 7.27-7.35, m, 5H, ArH; 9.71, bs, 1H, CHO.

Mass spectrum ($ESI^+$, MeOH): Found: *m/z* 192.1022. Calculated $(C_{11}H_{13}NO_2+H)^+$: *m/z* 192.1024.

*N*-(1-Formyl-2-phenylethyl)acetamide (116):

$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 2.07, s, 3H, $COCH_3$; 3.14-3.17, m, 2H, H2; 4.71, m, 1H, H1; 7.27-7.35, m, 5H, ArH; 9.62, bs, 1H, CHO.

The spectral data was consistent with that reported in the literature.[159]

*N*-(2-Phenylethyl)acetamide (117):

$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 1.93, s, 3H, $COCH_3$; 2.81, t, 2H, *J* 7.0 Hz, H1; 3.51, m, 2H, H2; 7.20, s, 5H, ArH.

Mass spectrum ($ESI^+$, MeOH): *m/z* 163.8 $(M+H)^+$.

Similar reactions were carried out by varying catalyst, substrate to catalyst ratio, solvent, pressure (P), temperature (T) and reaction time (t). The results are summarised in Table 5.8.

**Table 5.8**

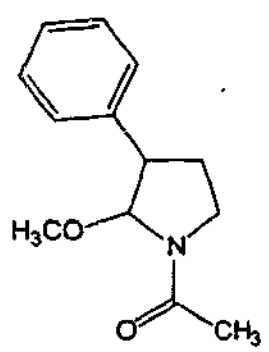
| Entry | Catalyst[a] | Solvent | P (psi) | T (°C) | t (h) | Product ratio (115) : (116) : (117) | % Conversion |
|---|---|---|---|---|---|---|---|
| 1 | Rh-$PPh_3$[b] | MeOH | 400 | 80 | 96 | 67 : - : 33 | 50 |
| 2 | Rh-$PPh_3$[c] | benzene | 1000 | 100 | 20 | 58 : 19 : 23 | 60 |
| 3 | Rh-$PPh_3$[c] | benzene | 1000 | 100 | 96 | 56 : 22 : 22 | 60 |
| 4 | Rh-$PPh_3$[b] | benzene | 1500 | 120 | 72 | 59 : 29 : 12 | 60 |
| 5 | Rh-DuPHOS[d] | benzene | 400 | 80 | 20 | - | 0 |
| 6 | Rh-DuPHOS[d] | benzene | 400 | 80 | 48 | - | 0 |
| 7 | Rh-DuPHOS[d] | benzene | 400 | 80 | 72 | - | 0 |
| 8 | Ru-BINAP[d] | benzene | 500 | 80 | 144 | - | 0 |
| 9 | Rh-DuPHOS[d] | benzene | 500 | 50 | 144 | - | 0 |
| 10 | Rh-$PPh_3$[b] | benzene | 400 | 80 | 20 | - | 0[f] |
| 11 | Rh-$PPh_3$[b] | benzene | 400 | 80 | 20 | - | 0[f] |
| 12 | Rh-$PPh_3$[b] | benzene | 400 | 80 | 96 | - | 0[f] |
| 13 | Rh-$PPh_3$[c] | benzene | 500 | 50 | 144 | - | 0 |
| 14 | Rh-BINAP[c] | benzene | 1300 | 120 | 20 | - | 0 |
| 15 | Ru-BINAP[c] | benzene | 1300 | 120 | 72 | - | 0 |
| 16 | Rh-$PPh_3$[c] | benzene | 1000 | 120 | 20 | 67 : 33 : - | 38 |
| 17 | Rh-$PPh_3$[e] | benzene | 1000 | 120 | 20 | 67 : 33 : - | 16 |
| 18 | Rh-$PPh_3$[c] | benzene | 1000 | 200 | 20 | - : - : 100 | 0[f] |

[a] Rh-DuPHOS = Rh(I)-(*S*,*S*)-Et-DuPHOS, Ru-BINAP = Ru(III)-(*S*)-BINAP and Rh-BINAP = Rh-(*S*)-BINAP. [b] Substrate (91) : $[Rh(OAc)_2]_2$ : $PPh_3$ or (*S*)-BINAP ratio = 100 : 1 : 2. [c] Substrate (91) : $[Rh(OAc)_2]_2$ : $PPh_3$ ratio = 50 : 1 : 2. [d] Substrate (91) : Rh(I)-(*S*,*S*)-Et-DuPHOS or Ru(III)-(*S*)-BINAP ratio = 100 : 1. [e] Substrate (91) : $[Rh(OAc)_2]_2$ : $PPh_3$ ratio = 25 : 1 : 2. [f] Crude only contained trace amount of aldehydes ((115) and (116)).

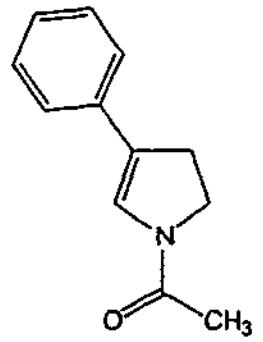
### 5.9.2 Rhodium-catalysed Reactions of (*E*)-*N*-(3-Phenylprop-2-enyl)acetamide (107)

**_N_-Acetyl-2-methoxy-3-phenylpyrrolidine (124)**

**_N_-Acetyl-3-phenyl-2,3-didehydropyrrolidine (125)**




(124)




(125)

(*E*)-*N*-(3-Phenylprop-2-enyl)acetamide (107) (50 mg, 0.29 mmol), rhodium(II) acetate dimer (2.6 mg, 5.8 μmol) and $PPh_3$ (3.0 mg, 11.6 μmol) were dissolved in deoxygenated methanol (10 ml) in a 100 ml Parr autoclave (refer to Section 5.1.3). The autoclave was pressurized to 700 psi of $CO/H_2$ (1 : 1 molar ratio) and heated to 100°C. After 72 h, the autoclave was cooled to ambient temperature and the solvent was removed under reduced pressure to give a brown oil (59 mg). The $^1H$ n.m.r. spectrum of the crude oil indicated a mixture of isomers of the cyclic product, *N*-acetyl-2-methoxy-3-phenylpyrrolidine (124). Purification was done using a silica plug (ethyl acetate) to give product (124) (21 mg, 33%) as a yellow oil.

$\nu_{max}$ (Film): 3517b, 2936w, 1661s, 1495w, 1406s, 1353w, 1185w, 1079s, 1032w, 970w, 850w, 756w, 700w $cm^{-1}$.

$^1H$ n.m.r. (300 MHz, $CDCl_3$) (minor diastereoisomer in brackets): δ 2.01, m, 1H, H4; 2.14, s, 3H, $COCH_3$; 2.39-2.67, m, 2H, H4 and H5; 3.37, s, 3H, (3.46, s, 3H), $OCH_3$; 3.46-3.83, m, 2H, H3 and H5; 4.93, bd, 1H, *J* 1.5 Hz, (5.53, s, 1H), H2; 7.09-7.36, m, 5H, ArH.

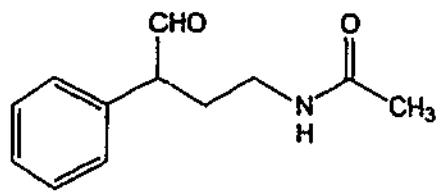
$^{13}C$ n.m.r. (75 MHz, $CDCl_3$) (minor diastereoisomer in brackets): δ 22.1, (23.0), $CO\underline{C}H_3$; 29.0, (30.8), C4; 45.0, (46.2), C5; 49.3, (48.9), C3; 54.4, (56.9), $OCH_3$; 95.6, (91.9), C2; 127.0, 129.1, (126.8, 128.9), C2', 6' and C3', 5'; 127.2, C4'; 141.5, (141.2), C1'; 170.7, (171.1), CON.

Mass spectrum ($ESI^+$, MeOH): Found: *m/z* 242.1152. Calculated $(C_{13}H_{17}NO_2+Na)^+$: *m/z* 242.1157.

A similar reaction was carried out using Rh(I)-(*S,S*)-Et-DuPHOS and (*E*)-*N*-(3-phenylprop-2-enyl)acetamide (107) (50 mg, 0.29 mmol) (substrate : catalyst ratio = 50 : 1 ) at 100°C with 700 psi of $CO/H_2$ (1 : 1 molar ratio) for 72 h in methanol (10 ml) and gave a brown oil (64 mg). The $^1H$ n.m.r. spectrum of the crude oil indicated *ca.* 40% of starting material (107) and the cyclic product, *N*-acetyl-2-methoxy-3-phenylpyrrolidine (124). After the crude sample was purified through a silica plug (ethyl acetate), optical rotation of the clean product was assessed.

$[\alpha]_D^{20}$ 0° (c 0.1, $CH_2Cl_2$).

A reaction of (*E*)-*N*-(3-phenylprop-2-enyl)acetamide (107) (50 mg, 0.29 mmol), rhodium(II) acetate dimer (2.6 mg, 5.8 μmol) and $PPh_3$ (3.0 mg, 11.6 μmol) at 100°C with 700 psi of $CO/H_2$ (1 : 1 molar ratio) for 72 h in benzene (10 ml) gave a brown oil (45 mg). The $^1H$ n.m.r. spectrum of the crude oil showed only the dehydro-cyclic material, *N*-acetyl-3-phenyl-2,3-didehydropyrrolidine (125), no starting material (107) and trace amount aldehyde, *N*-(3-formyl-3-phenylpropyl)acetamide (122) (δ 9.72, bs, CHO).




(122)

*N*-Acetyl-3-phenyl-2,3-didehydropyrrolidine (125):

$\nu_{max}$ (Film): 3396b, 2924s, 2854s, 1642s, 1626s, 1450m, 1376w, 1274w, 1081w, 1030s, 891w, 756w, 700w $cm^{-1}$.

$^1H$ n.m.r. (300 MHz, $CDCl_3$) (minor rotamor in brackets): δ 2.21, s, 3H, (2.12, s, 3H), $COCH_3$; 2.98, m, 1H, and 3.10, m, 1H, H4; 3.99, m, 2H, H5; 6.90, bt, 1H, *J* 1.9 Hz, (7.46, bt, 1H, *J* 1.9 Hz), H2; 7.16-7.35, m, 5H, ArH.

$^{13}C$ n.m.r. (75 MHz, $CDCl_3$) (minor rotamer in brackets): δ 21.9, $CO\underline{C}H_3$; 29.2, (30.8), C4; 45.5, (47.0), C5; 110.0, C3; 124.6, (124.4), C2; 124.8, C4'; 127.1, 128.8, C2', 6' and C3', 5'; 129.0, C1'; 166.4, CON.

Mass spectrum ($ESI^+$, MeOH): *m/z* 188.0 $(M+H)^+$.

Similar reactions were carried out in benzene by varying catalyst, pressure (P), temperature (T) and reaction time (t). The results are summarised in Table 5.9.

**Table 5.9**

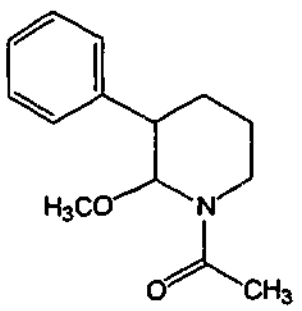
| Entry | Catalyst[a] | P (psi) | T (°C) | t (h) | Product ratio (122) : (124) : (125) | % Conversion |
|---|---|---|---|---|---|---|
| 1 | Rh-DuPHOS[b] | 400 | 80 | 20 | - | 0 |
| 2 | Rh-DuPHOS[b] | 700 | 80 | 72 | 37 : - : 63 | 45 |
| 3 | Rh-DuPHOS[b] | 700 | 100 | 72 | 26 : - : 74 | 84 |
| 4 | Rh-DuPHOS[b] | 700 | 100 | 20 | 20 : - : 80 | 33 |
| 5 | Rh-$PPh_3$[c] | 700 | 80 | 72 | - : - : 100 | 100[d] |

[a] Rh-DuPHOS = Rh(I)-(*S*,*S*)-Et-DuPHOS. [b] Substrate (107) : Rh(I)-(*S*,*S*)-Et-DuPHOS ratio = 50 : 1. [c] Substrate (107) : $[Rh(OAc)_2]_2$ : $PPh_3$ ratio = 50 : 1 : 2. [d] Crude product contained only trace amount of aldehyde (122).

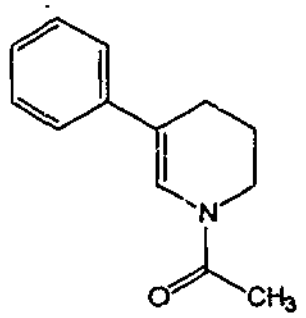
### 5.9.3 Rhodium-catalysed Reactions of (*E*)-*N*-(4-Phenylbut-3-enyl)acetamide (113)

**N-Acetyl-2-methoxy-3-phenylpiperidine (129)**

**N-Acetyl-3-phenyl-2,3-didehydropiperidine (130)**




(129)




(130)

(*E*)-*N*-(4-Phenylbut-3-enyl)acetamide (113) (250 mg, 1.3 mmol), rhodium(II) acetate dimer (11.5 mg, 26..0 μmol) and $PPh_3$ (13.5 mg, 52.0 μmol) were dissolved in deoxygenated methanol (30 ml) in a 100 ml Parr autoclave (refer to Section 5.1.3). The autoclave was pressurized to 700 psi of $CO/H_2$ (1 : 1 molar ratio) and heated to 100°C. After 72 h, the autoclave was cooled to ambient temperature and the solvent was removed under reduced pressure to give a brown oil (320 mg). The $^1H$ n.m.r. spectrum of the crude oil indicated a mixture of isomers of cyclic product, *N*-acetyl-2-methoxy-3-phenylpiperidine (129). Purification was done through column chromatography (ethyl acetate) to give *N*-acetyl-2-methoxy-3-phenylpiperidine (129) (130 mg, 43%), ($R_f$ 0.4) as a yellow oil.

$\nu_{max}$ (Film): 3465b, 2939s, 1651s, 1495w, 1418s, 1372w, 1350w, 1307w, 1267w, 1180w, 1162m, 1130m, 1103m, 1076s, 1048w, 1023w, 947m, 905w, 879w, 804w, 750s, 700s $cm^{-1}$.

$^1H$ n.m.r. (300 MHz, $CDCl_3$) (minor diastereoisomer in brackets): δ 1.52-1.70, m, 2H, H5; 1.73-1.89, m, 2H, H4; 2.17, s, 3H, (2.18, s, 3H), $COCH_3$; 2.75-2.85, m, 1H, H3;

3.12, s, 3H, (3.15, s, 3H), $OCH_3$; 3.54-3.62, m, 2H, (4.46-4.52, m, 2H), H6; 5.84, bd, 1H, *J* 2.7 Hz, (4.95, bd, 1H, *J* 2.6 Hz), H2; 7.14-7.38, m, 5H, ArH.

$^{13}C$ n.m.r. (75 MHz, $CDCl_3$) (minor diastereoisomer in brackets): δ 22.0, (21.8), $CO\underline{C}H_3$; 24.4, C5; 25.0, C4; 40.1, C6; 46.7, (48.5), C3; 55.4, (54.5), $OCH_3$; 82.5, (88.1), C2; 126.6, C4'; 128.3, C2', 6' and C3', 5'; 141.8, (141.7), C1'; 170.2, (168.8), CON.

Microanalysis: Found: H 8.25, C 71.10, N 5.82, O 14.83%. Calculated $C_{14}H_{19}NO_2$: H 8.21, C 72.07, N 6.00, O 13.72%.

Mass spectrum ($ESI^+$, MeOH): Found: *m/z* 256.1307. Calculated $(C_{14}H_{19}NO_2+Na)^+$: *m/z* 256.1313.

A similar reaction was carried out using Rh(I)-(*S*,*S*)-Et-DuPHOS and (*E*)-*N*-(4-phenylbut-3-enyl)acetamide (113) (50 mg, 0.26 mmol) (substrate : catalyst ratio = 50 : 1 ) at 100°C with 700 psi of $CO/H_2$ (1 : 1 molar ratio) for 72 h in methanol (10 ml) gave a brown oil (64 mg). The $^1H$ n.m.r. spectrum of the crude oil indicated *ca.* 42% of starting material (113) and the cyclic product, *N*-acetyl-5-phenyl-6-methoxypiperidine (129). The crude sample was purified through a silica plug (ethyl acetate) and the optical rotation of the clean product was measured.

$[\alpha]_D^{20}$ 0° (c 0.08, $CHCl_3$).

A reaction of (*E*)-*N*-(4-phenylbut-3-enyl)acetamide (113) (50 mg, 0.26 mmol), Rh(I)-(*S*,*S*)-Et-DuPHOS (substrate : catalyst ratio = 50 : 1) at 100°C with 700 psi of $CO/H_2$ (1 : 1 molar ratio) for 72 h in benzene (10 ml) gave a brown oil (84 mg). The $^1H$ n.m.r. spectrum of the crude oil showed only the dehydro-cyclic material, *N*-acetyl-3-phenyl-2,3-didehydropiperidine (130).

*N*-Acetyl-3-phenyl-2,3-didehydropiperidine (130):

$\nu_{max}$ (Film): 3466b, 2933s, 1666s, 1638s, 1494m, 1405s, 1316m, 1255m, 1200s, 1150m, 1072s, 1027w, 983w, 944w, 883w, 750s, 705s $cm^{-1}$.

$^1H$ n.m.r. (300 MHz, $CDCl_3$) (minor rotamor in brackets): δ 1.92-2.10, m, 2H, H5; 2.25, s, 3H, (2.20, s, 3H), $COCH_3$; 2.50, m, 2H, H4; 3.74, m, 2H, (3.62, m, 2H), H6; 6.98, bt, 1H, *J* 1.6 Hz, (7.17, bt, 1H), H2; 7.17-7.43, m, 5H, ArH.

$^{13}C$ n.m.r. (75 MHz, $CDCl_3$) (minor rotamer in brackets): δ 21.6, C5; 21.7, $CO\underline{C}H_3$; 24.8, C4; 40.1, (40.1), C6; 119.5, C3; 123.3, (121.4), C2; 124.8, 128.4, C2', 6' and C3', 5'; 126.8, C4'; 140.1, C1'; 168.5, CON.

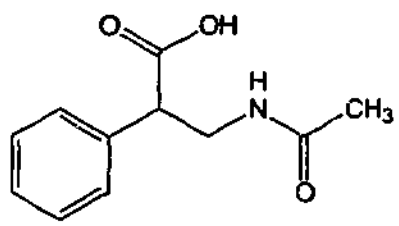
Mass spectrum ($ESI^+$, MeOH): *m/z* 202.0 $(M+H)^+$.

## *5.10 Conversions of Products*

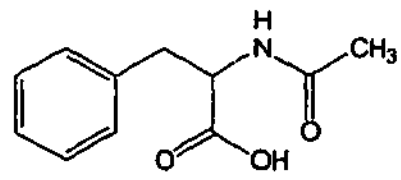
### 5.10.1 Oxidation of Aldehydes ((115) and (116))

**3-Acetamido-2-phenylpropanoic acid (118)**

**2-Acetamido-3-phenylpropanoic acid (119)**




(118)




(119)

A 5% aqueous $NaH_2PO_4$ buffer solution (25 ml) was added to a stirred crude mixture of *N*-(2-formyl-2-phenylethyl)acetamide (115) and *N*-(1-formyl-2-phenylethyl)acetamide (116) (70 : 30 ratio) containing 50% of starting material (91) (320 mg, 1.67 mmol) in *t*-butanol (25 ml) to give a solution of pH 5. A 1 M $KMnO_4$ solution (25 ml) was then added to this vigorously stirred solution. After 10 min of stirring at ambient temperature, saturated $Na_2SO_4$ solution (30 ml) was added to quench the oxidation followed by the addition of cold 1.2 M HCl solution until the

mixture reached a pH of 3. The mixture was extracted with dichloromethane (4 x 50 ml) and the combined organic layer was washed with saturated $NaHCO_3$ solution (2 x 40 ml). Cold 1.2 M HCl solution was added to acidify the basic aqueous layer followed by extraction with dichloromethane (4 x 50 ml). The second organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give the products ((118) and (119)) as a yellow oil (80 mg). The $^1H$ n.m.r. spectrum of the crude oil showed the presence of carboxylic acids ((118) and (119)) in a 70 : 30 ratio.

3-Acetamido-2-phenylpropanoic acid (118):

$^1H$ n.m.r. (300 MHz, $CDCl_3$): δ 1.97, s, 3H, $COCH_3$, 3.66-3.74, m, 2H, H3; 3.96, m, 1H, H2; 7.35, s, 5H, ArH.

Mass spectrum ($ESI^+$, MeOH): Found: *m/z* 230.0788. Calculated $(C_{11}H_{13}NO_2+Na)^+$: *m/z* 230.0793.

2-Acetamido-3-phenylpropanoic acid (119):

$^1H$ n.m.r. (300 MHz, $CDCl_3$): δ 1.99, s, 3H, $COCH_3$; 3.19, m, 1H, and 3.70, m, 1H, H3; 4.91, m, 1H, H2; 7.35, s, 5H, ArH.

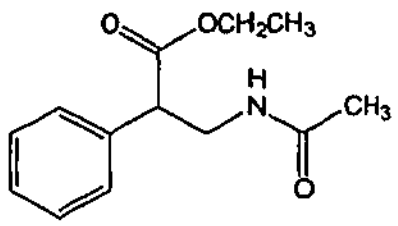
The spectral data were consistent with those reported in the literature.[160]

A reaction of a crude mixture containing only the aldehyde, *N*-(2-formyl-2-phenylethyl)acetamide (115) (250 mg, 1.31 mmol) gave 3-acetamido-2-phenylpropanoic acid (118) (200 mg, 74%) as an oil.

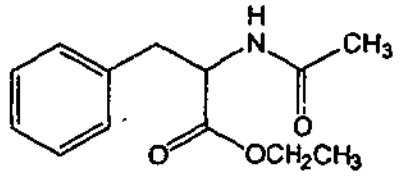
### 5.10.2 Esterification of Carboxylic Acids ((118) and (119))

**Ethyl 3-acetamido-2-phenylpropanoate (120)**

**Ethyl 2-acetamido-3-phenylpropanoate (121)**



(120)



(121)

Concentrated sulfuric acid (98%, 3.0 ml) was added stirred mixture of 3-acetamido-2-phenylpropanoic acid (118) and 2-acetamido-3-phenylpropanoic acid (119) (70 : 30 ratio) (70 mg, 0.34 mmol) in ethanol (20 ml). After 18 h of stirring at ambient temperature, the reaction mixture was concentrated. The residual oil was redissolved in dichloromethane and then was washed with saturated $NaHCO_3$ solution (3 x 20 ml), dried over $MgSO_4$ and concentrated under reduced pressure to give a yellow oil (70 mg). The $^1H$ n.m.r. spectrum of the crude oil showed the presence of branched and linear ethyl esters ((120) and (121)). Purification was done through a silica plug (1 : 1 ratio of ethyl acetate : light petroleum) to give a sample of the ethyl esters ((120) and (121) in a 70 : 30 ratio) (20 mg, 25%) isolated as a yellow oil.

Ethyl 3-acetamido-2-phenylpropanoate (120), refer below for full characterisation.

Ethyl 2-acetamido-3-phenylpropanoate (121):

$^1H$ n.m.r. (300 MHz, $CDCl_3$): δ 1.20, m, 3H, $OCH_2C\underline{H}_3$; 1.99, s, 3H, $COCH_3$; 3.13, dd, 2H, *J* 5.9, 2.2 Hz, H3; 4.15, m, 2H, $OC\underline{H}_2CH_3$; 4.87, dt, 1H, *J* 7.8, 5.8 Hz, H2; 5.88, bs, 1H, NH; 7.16-7.37, m, 5H, ArH.

$^{13}C$ n.m.r. (75 MHz, $CDCl_3$): δ 14.2, $OCH_2\underline{C}H_3$; 23.3, $CO\underline{C}H_3$; 38.1, C3; 53.3, C2; 61.6, $O\underline{C}H_2CH_3$; 127.8, C4'; 128.7, 129.5, C2', 6' and C3', 5'; 136.1, C1'; 169.7, CONH; 171.8, C1.

Mass spectrum ($ESI^+$, MeOH): *m/z* 258.0 $(M+Na)^+$.

The spectral data were consistent with those reported in the literatures.[108,109]

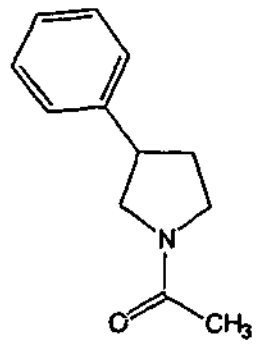
A reaction of 3-acetamido-2-phenylpropanoic acid (118) (200 mg, 0.97 mmol) with concentrated sulfuric acid ($H_2SO_4$) (98%, 3.0 ml) in ethanol (20 ml) gave a crude yellow oil (170 mg). Purification was done through a silica plug (1 : 1 ratio of ethyl acetate : light petroleum) to give the product, ethyl 3-acetamido-2-phenylpropanoate (120) (40 mg, 18%) as a yellow oil.

$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 1.19, m, 3H, $OCH_2C\underline{H}_3$; 1.92, s, 3H, $COCH_3$; 3.66, m, 2H, H3; 3.89, dd, 1H, *J* 8.6, 6.2 Hz, H2; 4.14, m, 2H, $OC\underline{H}_2CH_3$; 6.05, bs, 1H, NH; 7.24-7.36, m, 5H, ArH.

$^{13}$C n.m.r. (75 MHz, $CDCl_3$): δ 14.3, $OCH_2\underline{C}H_3$; 23.4, $CO\underline{C}H_3$; 42.5, C3; 51.3, C2; 61.3, $O\underline{C}H_2CH_3$; 127.9, C4'; 128.1, 129.1, C2', 6' and C3', 5'; 136.7, C1'; 170.4, CONH; 173.2, C1.

The spectral data were consistent with those reported in the literature.[110]

### 5.10.3 Preparation of *N*-Acetyl-3-phenylpyrrolidine (126)




(126)

Using an identical method to that described in Section 5.5.1, *N*-acetyl-3-phenyl-2,3-didehydropyrrolidine (125) (30 mg, 0.16 mmol) was dissolved in methanol (5 ml) and reacted with Pd/C and $H_2$ (90 psi). After work-up, the solution was concentrated to give product (126) (40 mg, 100%) as an oil.

$\nu_{max}$ (Film): 3403b, 2932m, 2858w, 1725w, 1642s, 1495w, 1438m, 1364w, 1261m, 1124w, 1072w, 981w, 922w, 852w, 733w, 700w $cm^{-1}$.

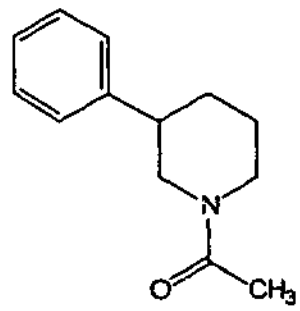
$^1H$ n.m.r. (300 MHz, $CDCl_3$): δ 2.55, m, 2H, H4; 2.09, s, 3H, $COCH_3$; 3.09, m, 1H, H3; 3.46, m, 2H, H5; 3.86, m, 2H, H2; 7.15-7.37, m, 5H, ArH.

$^{13}C$ n.m.r. (75 MHz, $CDCl_3$): δ 21.6, $CO\underline{C}H_3$; 31.7, C4; 38.8, C3; 47.0, C5; 53.5, C2; 127.1, C4'; 128.6, 128.8, C2', 6' and C3', 5'; 143.2, C1'; 169.0, CON.

Mass spectrum ($ESI^+$, MeOH): *m/z* 190.1 $(M+Na)^+$.

The spectral data were consistent with those reported in literature.[111]

### 5.10.4 Preparation of *N*-Acetyl-3-phenylpiperidine (131)




(131)

Using an identical method to that described in Section 5.5.1, *N*-acetyl-5-phenyl-5,6-didehydropiperidine (130) (50 mg, 0.25 mmol) was dissolved in methanol (5 ml) reacted with Pd/C and $H_2$ (90 psi). After work-up, the solution was concentrated to give the product (131) (50 mg, 100%) as an oil.

$\nu_{max}$ (Film): 3403b, 2932m, 2858w, 1725w, 1642s, 1495w, 1438m, 1364w, 1261m, 1124w, 1072w, 981w, 922w, 852w, 733w, 700w $cm^{-1}$.

$^1H$ n.m.r. (300 MHz, $CDCl_3$): δ 1.70-1.80, m, 2H, H5; 1.80-1.90, m, 2H, H4; 2.08, s, 3H, $COCH_3$; 2.65, m, 1H, H3; 3.27-3.31, m, 2H, H6; 3.63-3.66, m, 2H, H2; 7.16-7.37, m, 5H, ArH.

$^{13}$C n.m.r. (75 MHz, $CDCl_3$): δ 22.6, CO<u>C</u>H$_3$; 31.3, C5; 33.6, C4; 42.9, C3; 47.3, C6; 51.6, C2; 127.1, C4'; 128.8, 128.9, C2', 6' and C3', 5'; 141.6, C1'; 170.2, CON.

Mass spectrum (ESI$^+$, MeOH): *m/z* 204.3 $(M+H)^+$.

The spectral data were consistent with those reported in literature.[112]

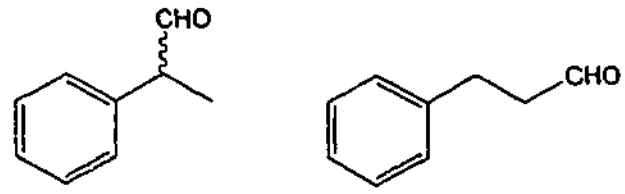
## *Experimental For Chapter 4*

## *5.11 Asymmetric Hydroformylations of Styrene (15)*

### 5.11.1 Rhodium(I)-catalysed Reaction of Styrene (15)

**2-Phenylpropanal (16)**

**3-Phenylpropanal (17)**




(16) (17)

Styrene (15) (65 mg, 0.62 mmol) and [(COD)Rh(I)((*S*,*S*)-Et-DuPHOS)]OTf (substrate: catalyst ratio = 100 : 1) were dissolved in deoxygenated benzene (10 ml) and placed in a 100 ml Parr autoclave (refer to Section 5.1.3). The autoclave was charged with $CO/H_2$ (1 : 1 molar ratio) (400 psi) and heated at 80°C. After 48 h, the autoclave was cooled to ambient temperature and the solvent was concentrated *in vacuo* to give a yellow oil (70 mg, 84%). The $^1$H n.m.r. spectrum of the crude oil showed the presence of branched and linear aldehydes, 2-phenylpropanal (16) and 3-phenylpropanal (17) in a 60 : 40 ratio.

2-Phenylpropanal (16):

$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 1.36, d, 3H, *J* 7.0 Hz, H3; 3.49, qd, 1H, *J* 7.0, 1.2 Hz, H2; 7.21-7.36, m, 5H, ArH; 9.58, d, 1H, *J* 1.4 Hz, H1.

3-Phenylpropanal (17):

$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 2.60, td, 2H, *J* 7.0, 1.3 Hz, H2; 2.84, t, 2H, *J* 7.4 Hz, H3; 7.21-7.36, m, 5H, ArH; 9.64, t, 1H, *J* 1.3 Hz, H1.

Similar reactions were carried out by varying catalyst, pressure (P) and reaction time (t) at 80°C. The results are summarised in Table 5.10.

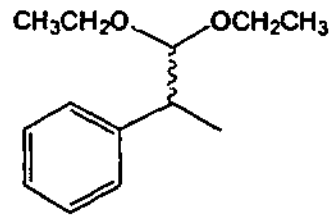
**Table 5.10**

| Entry | Catalyst | P (psi) | t (h) | % Conversion | Product ratio ((16) : (17)) |
|---|---|---|---|---|---|
| 1 | Rh(I)-(*S*,*S*)-Et-DuPHOS | 400 | 20 | 35 | 56 : 44 |
| 2 | Rh(I)-(*S*,*S*)-Et-DuPHOS | 100 | 48 | 45 | 45 : 55 |
| 3 | Rh(I)-(*S*,*S*)-Et-DuPHOS | 100 | 72 | 83 | 50 : 50 |
| 4 | Rh(I)-(*S*,*S*)-Me-DuPHOS | 400 | 48 | 100 | 60 : 40 |

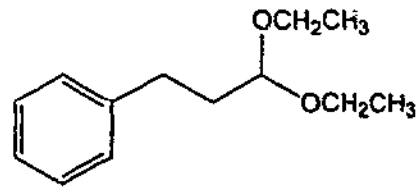
### 5.11.2 Rhodium(I)-catalysed Reaction of Styrene (15) with Trapping Reagent

**1,1-Diethoxy-2-phenylpropane (136)**

**1,1-Diethoxy-3-phenylpropane (137)**




(136)




(137)

Styrene (15) (500 mg, 4.8 mmol), [(COD)Rh(I)((*S*,*S*)-Et-DuPHOS)]OTf (substrate: catalyst ratio = 100 : 1) and triethyl orthoformate (3.2 ml, 19.2 mmol) were dissolved in deoxygenated benzene (20 ml) in a 100 ml Parr autoclave (refer to Section 5.1.3). The autoclave was charged with $CO/H_2$ (1 : 1 molar ratio) (400 psi) at 80°C. After 48 h, the autoclave was cooled to ambient temperature and the solvent was concentrated *in vacuo* to give a yellow oil (550 mg). The $^1$H n.m.r. spectrum of the crude oil

showed the presence of branched and linear products, 1,1-diethoxy-2-phenylpropane (136) and 1,1-diethoxy-3-phenylpropane (137) in 77 : 23 ratio.

1,1-Diethoxy-2-phenylpropane (136):

$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 1.02-1.19, m, 6H, 2 x $OCH_2C\underline{H}_3$; 1.29, d, 3H, *J* 7.1 Hz, H3; 2.99, m, 1H, H2; 3.36-3.71, m, 4H, 2 x $OC\underline{H}_2CH_3$; 4.44, d, 1H, *J* 6.5 Hz, H1; 7.13-7.33, m, 5H, ArH.

1,1-Diethoxy-3-phenylpropane (137):

$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 1.18-1.23, m, 6H, 2 x $OCH_2C\underline{H}_3$; 1.90-1.97, m, 2H, H2; 2.66-2.71, m, 2H, H3; 3.36-3.71, m, 4H, 2 x $OC\underline{H}_2CH_3$; 4.48, t, 1H, *J* 5.7 Hz, H1; 7.13-7.33, m, 5H, ArH.

Mass spectrum ($ESI^+$, MeOH): *m/z* 231.2 $(M+Na)^+$.

$[\alpha]_D^{20}$ +0.4° (c 0.81, EtOH) containing 23% of (137).

Similar reactions were carried out by varying catalyst, temperature (T), pressure (P) and reaction time (t). The results are summarised in Table 5.11.

**Table 5.11**

| Entry | Catalyst[a] | P (psi) | T (°C) | t (h) | Product ratio ((136) : (137)) |
|---|---|---|---|---|---|
| 1 | Rh(I)-(*S*,*S*)-Et-DuPHOS | 800 | 160 | 24 | 50 : 50[a] |
| 2 | Rh(I)-(*S*,*S*)-Me-BPE | 400 | 80 | 48 | 46 : 54 |

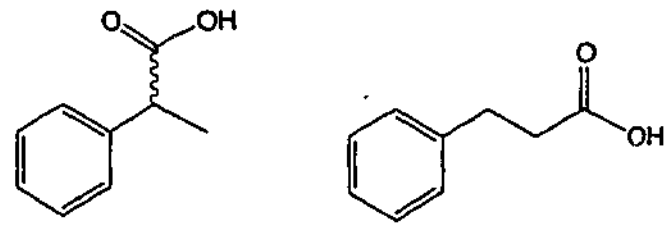
[a] Aldehydes ((16) and (17)) were obtained in a 3 : 1 ratio (*ca.* 66%).

## *5.12 Conversion of Products*

### 5.12.1 Oxidation of Aldehydes ((16) and (17))

**2-Phenylpropionic acid (132)**

**3-Phenylpropionic acid (133)**



(132) (133)

Using the method as described in Section 5.10, 1 M $KMnO_4$ solution (15 ml) was added to a vigorously stirring mixture of 2-phenylethanal (16) and 3-phenylpropanal (17) (60 : 40 ratio) (70 mg, 5.22 mmol) in *t*-butanol (15 ml) and 5% aqueous $NaH_2PO_4$ buffer solution (15 ml). After 10 min of stirring at ambient temperature, worked up as described previously gave the products ((132) and (133)) as a yellow oil (70 mg, 90%). The $^1H$ n.m.r. spectrum of the crude oil showed the presence of branched and linear carboxylic acids, 2-phenylpropionic acid (132) and 3-phenylpropionic acid (133) in a 60 : 40 ratio.

2-Phenylpropionic acid (132):

$^1H$ n.m.r. (300 MHz, $CDCl_3$): δ 1.51, d, 3H, *J* 7.2 Hz, H3; 3.73, q, 1H, *J* 7.2 Hz, H2; 7.17-7.35, m, 5H, ArH.

3-Phenylpropionic acid (133):

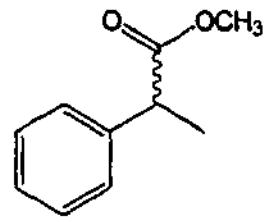
$^1H$ n.m.r. (300 MHz, $CDCl_3$): δ 2.66, t, 2H, *J* 7.5 Hz, H2; 2.94, t, 2H, *J* 7.6 Hz, H3; 7.17-7.35, m, 5H, ArH.

$[\alpha]_D^{20}$ +2.3° (c 1, EtOH) containing 40% of (133) (lit.[141] $[\alpha]_D^{20}$ +78.9° (c 1, EtOH)). The enantiomeric excess (ee) was 3%.

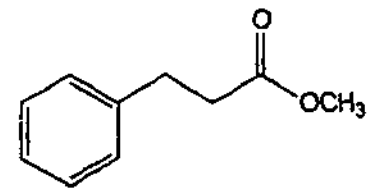
### 5.12.2 Esterification of Carboxylic Acids ((132) and (133))

**Methyl 2-phenylpropionate (134)**

**Methyl 3-phenylpropionate (135)**




(134)




(135)

(Trimethylsilyl)diazomethane ($Me_3SiCHN_2$) (2.0 M in hexane) was added dropwise to a stirred mixture of 2-phenylpropionic acid (132) and 3-phenylpropionic acid (133) (60 : 40 ratio) (68 mg, 0.45 mmol) in methanol (20 ml) to give a permanent yellow solution. The reaction mixture was left to stir at ambient temperature for 18 h. The solvent was then removed under reduced pressure to yield the products ((134) and (135)) as a yellow oil (70 mg). The $^1$H n.m.r. spectrum of the crude oil showed the presence of branched and linear esters, methyl 2-phenylpropionate (134) and methyl 3-phenylpropionate (135) in a 60 : 40 ratio. Purification using radial chromatography (6 : 1 = ethyl acetate : light petroleum) first gave a mixture of methyl 2-phenylpropionate (134) and methyl 3-phenylpropionate (135) (56 : 44 ratio) (30 mg, 41%) which was isolated as a yellow oil.

Methyl 2-phenylpropionate (134):

$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 1.50, d, 3H, *J* 7.1 Hz, H3; 3.66, s, 3H, $COOCH_3$; 3.73, q, 1H, *J* 7.0 Hz, H2; 7.25-7.36, m, 5H, ArH.

Mass spectrum ($ESI^+$, MeOH): *m/z* 187.1 $(M+Na)^+$.

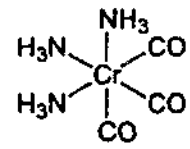
Further elution gave methyl 3-phenylpropionate (135) (5 mg, 7%) isolated as a yellow oil.

$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 2.64, t, 2H, *J* 7.5 Hz, H2; 2.96, t, 2H, *J* 7.6 Hz, H3; 3.67, s, 3H, $COOCH_3$; 7.25-7.36, m, 5H, ArH.

Assessment of ee was attempted using the HPLC containing a OJ column (1.0 ml $min^{-1}$, 10% isopropanol : 90% hexane) but no resolution was obtained.

### 5.12.3 Synthesis of $\eta^6$-Styrene(tricarbonylchromium) (18)

#### *5.12.3.1 Preparation of triamminetricarbonylchromium (139)*

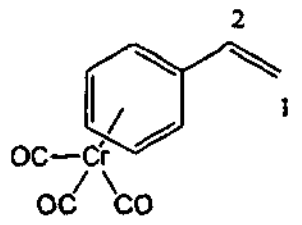



(139)

Chromium hexacarbonyl (138) was dissolved in a solution of KOH (3.75 g, 66.8 mmol) in degassed ethanol (47.5 ml) and water (2.5 ml) in a 100 ml autoclave as described by Vebrel[143] and Rausch *et al.*.[56] The mixture was stirred and heated at 90°C. After 6 h, the autoclave was cooled and the CO was vented. The orange suspension was poured into a flask containing 10% $NH_4OH$ solution (75 ml) under nitrogen. The mixture was stirred vigorously for further 1 h. The yellow solid was filtered off and washed with 10% $NH_4OH$ solution (100 ml) and degassed ethanol (100 ml) under nitrogen. It was dried under vacuum to give the product (139) (1.56 g, 82%) as yellow solid, m.p. 183-185°C (lit. 100°C[143] and 100-105°C[56]).

$\nu_{max}$ (KBr): 3378s, 3290b, 1883s, 1718b, 1594s, 1209s, 734m, 642m, 499m $cm^{-1}$.

### 5.12.3.2 *Preparation of $\eta^6$-styrene(tricarbonylchromium) (18)*




(18)

Following the method described by Rausch *et al.*,[56] a mixture of styrene (15) (1.0 g, 9.6 mmol) and triamminetricarbonylchromium (139) (1.98 g, 10.6 mmol) in dioxane was heated at reflux under nitrogen. After 3 h of stirring, the reaction mixture was filtered under $N_2$ through a Celite to remove a green precipitate. The filtrate was concentrated under vacuum to give the product (18) (1.19 g, 52%) as orange solid, m.p. 78-80°C (lit.[56] 78-79°C). Purification can be carried out using a cold-finger sublimation apparatus (0.33 mmHg at 85°C).

$\nu_{max}$ (KBr): 3483b, 1968s, 1870s, 1636ms, 1262w, 821m, 661m, 631m, 534w, $cm^{-1}$.

$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 5.28-5.44, m, 6H, H1 and ArH; 5.66, d, 1H, *J* 17.6 Hz, H1; 6.28, dd, 1H, *J* 17.5, 10.9 Hz, H2.

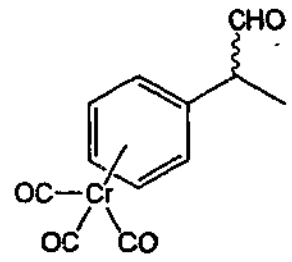
$^{13}$C n.m.r. (75 MHz, $CDCl_3$): δ 67.3, C1; 91.4, C4'; 90.7, 92.7, 128.8, C2', 6' and C3', 5'; 116.7, C2; 133.7, C1'.

The spectral data were consistent with those reported in the literature.[56]

## 5.13 *Hydroformylations of $\eta^6$-Styrene(tricarbonylchromium) (18)*

### 5.13.1 Rhodium(I)-catalysed Reaction of $\eta^6$-Styrene(tricarbonylchromium) (18)

**2-[$\eta^6$-Phenyl(tricarbonylchromium)]propanal (19)**




(19)

$\eta^6$-Styrene(tricarbonylchromium) (18) (50 mg, 0.21 mmol) and [(COD)Rh(I)((*S*,*S*)-Et-DuPHOS)]OTf (substrate: catalyst ratio = 100 : 1) were dissolved in deoxygenated benzene (10 ml) and placed in a 100 ml Parr autoclave (refer to Section 5.1.3). The autoclave was charged with $CO/H_2$ (1 : 1 molar ratio) (100 psi) and heated at 50°C. After 20 h, the autoclave was cooled to ambient temperature and the solvent was concentrated *in vacuo* to give the aldehyde (19) as a yellow oil (55 mg, 100%). The $^1H$ n.m.r. spectrum of the crude oil showed only the presence of branched aldehyde, 2-[$\eta^6$-phenyl(tricarbonylchromium)]propanal (19).

$^1H$ n.m.r. (300 MHz, $CDCl_3$): δ 1.44, m, 3H, H3; 3.33, m, 1H, H2; 5.1-5.4, m, 5H, ArH; 9.70, bs, 1H, H1.

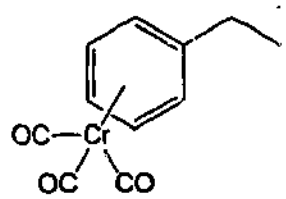
The spectral data was consistent with that reported in literature.[57]

Similar reactions were carried out by varying pressure (P) and reaction time (t) at 50°C. The results are summarised in Table 5.12.

**Table 5.12**

| Entry | P (psi) | Time (h) | Product ratio ((19) : (140)[a]) |
|---|---|---|---|
| 1 | 400 | 66 | - : 100 |
| 2 | 100 | 66 | 100 : - |

[a] Hydrogenated by-product, 2-[$\eta^6$-phenyl(tricarbonylchromium)]ethane (140) (δ 0.9, bs, H1).

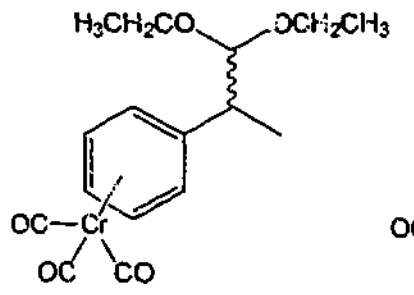



(140)

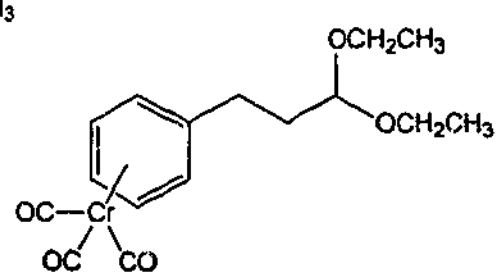
### 5.13.2 Rhodium(I)-catalysed Reaction of $\eta^6$-Styrene(tricarbonylchromium) (18) with Trapping Reagent

**1,1-Diethoxy-2-[$\eta^6$-phenyl(tricarbonylchromium)]propane (143)**

**1,1-Diethoxy-3-[$\eta^6$-phenyl(tricarbonylchromium)]propane (144)**




(143)




(144)

$\eta^6$-Styrene(tricarbonylchromium) (18) (50 mg, 0.21 mmol), [(COD)Rh(I)((*S*,*S*)-Et-DuPHOS)]OTf (substrate: catalyst ratio = 100 : 1) and triethyl orthoformate (0.14 ml, 0.83 mmol) were dissolved in deoxygenated benzene (20 ml) in a 100 ml Parr autoclave (refer to Section 5.1.3). The autoclave was charged with $CO/H_2$ (1 : 1 molar ratio) (100 psi) and heated at 50°C. After 20 h, the autoclave was cooled to ambient temperature and the solvent was concentrated *in vacuo* to give the products ((143) and (144)) as a yellow oil (0.13 g, 100%). The $^1H$ n.m.r. spectrum of the crude oil showed

the presence of branched and linear products, 1,1-diethoxy-2-[$\eta^6$-phenyl(tricarbonylchromium)]propane (143) and 1,1-diethoxy-3-[$\eta^6$-phenyl(tricarbonylchromium)]propane (144) in a 85 : 15 ratio and only a trace of aldehydes ((19) and (145)).

1,1-Diethoxy-2-[$\eta^6$-phenyl(tricarbonylchromium)]propane (143):

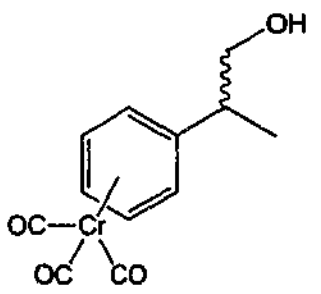
$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 1.23, m, 9H, 2 x $OCH_2C\underline{H_3}$ and H3; 3.36-3.71, m, 6H, 2 x $OC\underline{H_2}CH_3$, H1 and H2; 5.33, m, 5H, ArH.

1,1-Diethoxy-3-[$\eta^6$-phenyl(tricarbonylchromium)]propane (144):

$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 1.23, m, 6H, 2 x $OCH_2C\underline{H_3}$; 1.45, bs, 2H, H2; 3.36-3.71, m, 7H, 2 x $OC\underline{H_2}CH_3$, H1 and H3; 5.33, m, 5H, ArH.

## *5.14 Conversion of Products*

### 5.14.1 Reduction of 2-[$\eta^6$-Phenyl(tricarbonylchromium)]propanal (19) 2-[$\eta^6$-Phenyl(tricarbonylchromium)]propanol (141)




(141)

A solution of $NaBH_4$ (15 mg, 0.43 mmol) in ethanol (5 ml) was added to a stirring solution of 2-[$\eta^6$-phenyl(tricarbonylchromium)]propanal (19) (55 mg, 0.22 mmol) in ethanol (5 ml). The reaction mixture was left stirring at ambient temperature for 2 h, then was concentrated *in vacuo*. The oil was redissolved in ether (20 ml), water (10 ml) and the mixture was stirred vigorously for 10 min. The organic layer was separated and washed with water (20 ml), NaCl solution (20 ml) and dried over

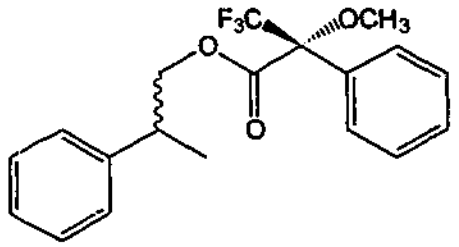
$MgSO_4$. The solvent was evaporated to give product (141) (58 mg, 100%) as a green oil.

$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 1.27, m, 3H, H3; 1.6, bs, 1H, OH; 2.63, m, 1H, H2; 3.70, m, 2H, H1; 5.30, m, 5H, ArH.

The spectral data was consistent with that reported in literature.[57]

### 5.14.2 Esterification of Alcohol (141) with (*S*)-(-)-α-Methoxy-α-(trifuoromethyl)-phenylacetic acid ((*S*)-(-)-MTPA)

**2-Phenylpropyl (*S*)-(-)-α-methoxy-α-(trifuoromethyl)phenylacetate (142)**




(142)

Using the method described by Doyle,[57] a solution of 1,3-dicyclohexylcarbodiimide (DCC) (58 mg. 0.24 mmol) and a few crystals of 4-dimethylaminopyridine (DMAP) in dichloromethane (6 ml) was added to a stirring solution of 2-[$\eta^6$-phenyl(tricarbonylchromium)]propanol (141) (58 mg. 0.22 mmol) and (*S*)-(-)-MTPA (54 mg, 0.22 mmol) in dichloromethane (9 ml). The reaction mixture was left stirring at ambient temperature. After 18 h of exposing to light, water (20 ml) was added and the mixture was left stirring for further 10 min. The organic layer was separated, dried over $MgSO_4$, filtered through silica and concentrated *in vacuo* to give the product (142) (0.32 g, 90%) as a yellow oil.

$^1$H n.m.r. (300 MHz, $CDCl_3$) (minor diastereoisomer in brackets): δ 1.29, m, 3H, H3; 3.16-3.20, m, 1H, H2; 3.39, bs, 3H, (3.41, bs, 3H), $OCH_3$; 4.45, m, 2H, H1; 7.16-7.44, m, 10H, 2 x ArH.

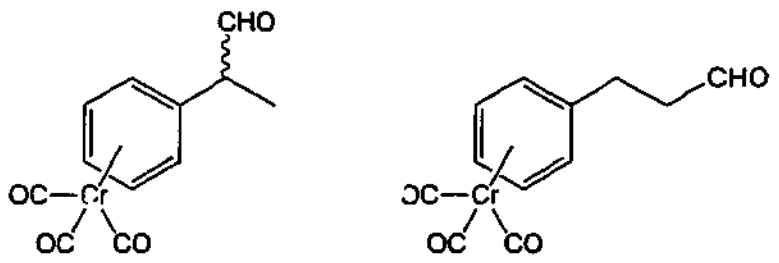
$^{19}F$ n.m.r. (300 MHz, $CDCl_3$) (minor diastereoisomer in brackets): δ -72.16 (1.23), bs, (-72.12 (0.35), bs), $CF_3$. The enantiomeric excess was 56%.

The spectral data were consistent with those reported in literature.[57]

### 5.14.3 Cleavage of Trapping Reagent

**2-[η$^6$-Phenyl(tricarbonylchromium)]propanal (19)**

**3-[η$^6$-Phenyl(tricarbonylchromium)]propanal (145)**




(19) (145)

A few crystals of pyridinium *p*-toluenesulfonic acid (*p*-TsOH) was added to a stirring mixture of 1,1-diethoxy-2-[η$^6$-phenyl(tricarbonylchromium)]propane (143) and 1,1-diethoxy-3-[η$^6$-phenyl(tricarbonylchromium)]propane (144) (85 : 15 ratio) (0.13 g, 0.40 mmol) in acetone (10 ml) as according to method described by Parrinello *et al.*.[125] The mixture was heated at reflux for 5 h. It was then concentrated, redissolved in ether (10 ml), washed with a saturated $NaHCO_3$ solution (2 x 10 ml) and dried over $MgSO_4$. The solvent was evaporated to give the aldehydes ((19) and (145) in a 85 : 15 ratio) (60 mg, 59%) as a green oil.

2-[η$^6$-Phenyl(tricarbonylchromium)]propanal (19), refer to Section 5.13.1 for full characterisation.

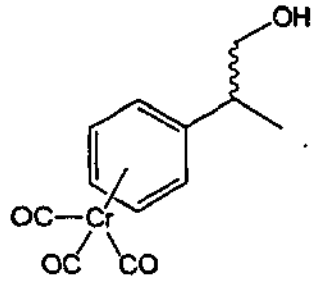
3-[η$^6$-Phenyl(tricarbonylchromium)]propanal (145):

$^1H$ n.m.r. (300 MHz, $CDCl_3$): δ 1.44, m, 2H, H3; 2.45, m, 2H, H2; 2.65; 5.32, m, 5H, ArH; 9.53, bs, 1H, H1.

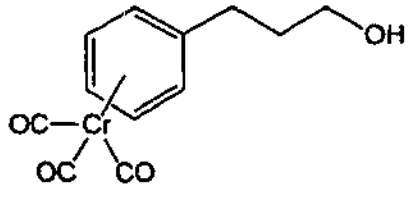
### 5.14.4 Reduction of $\eta^6$-Tricarbonylchromium Aldehydes ((19) and (145))

**2-[$\eta^6$-Phenyl(tricarbonylchromium)]propanol (141)**

**3-[$\eta^6$-Phenyl(tricarbonylchromium)]propanol (146)**




(141)




(146)

Using the method as described in Section 5.14.1, a solution of $NaBH_4$ (16 mg, 0.47 mmol) in ethanol (5 ml) was added to a stirring solution of 2-[$\eta^6$-phenyl(tricarbonylchromium)]propanal (19) and 3-[$\eta^6$-phenyl(tricarbonylchromium)]propanal (145) (85 : 15 ratio) (60 mg, 0.22 mmol) in ethanol (10 ml). The mixture was stirred for 2 h. Work-up as before to give the products ((141) and (146) in 85 : 15 ratio) (65 mg, 100%) as a green oil.

2-[$\eta^6$-Phenyl(tricarbonylchromium)]propanol (141), refer to Section 5.14.1 for full characterisation

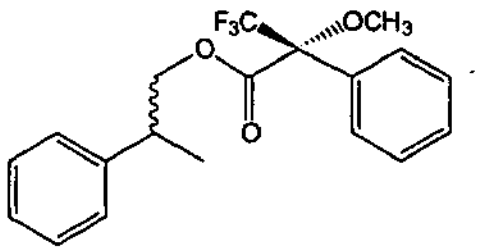
3-[$\eta^6$-Phenyl(tricarbonylchromium)]propanol (146):

$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 1.65, m, 2H, H2; 2.46, m, 2H, H3; 3.49, m, 2H, H1; 5.32, m, 5H, ArH.

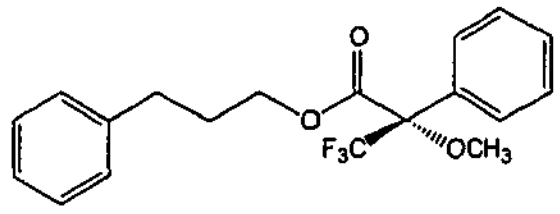
### 5.14.5 Esterification of Alcohols ((141) and (146)) with (*S*)-(-)-α-Methoxy-α-(trifuoromethyl)-phenylacetic acid ((*S*)-(-)-MTPA)

**2-Phenylpropyl (*S*)-(-)-α-methoxy-α-(trifuoromethyl)phenylacetate (142)**

**3-Phenylpropyl (*S*)-(-)-α-methoxy-α-(trifuoromethyl)phenylacetate (147)**




(142)




(147)

Using the method described in Section 5.14.2, a solution of 1,3-dicyclohexylcarbodiimide (DCC) (70 mg. 0.28 mmol) and a few crystals of 4-dimethylaminopyridine (DMAP) in dichloromethane (6 ml) was added to a stirring mixture of 2-[$\eta^6$-phenyl(tricarbonylchromium)]propanol (141) and 3-[$\eta^6$-phenyl(tricarbonylchromium)]propanol (146) (85 : 15 ratio) (65 mg. 0.25 mmol) and (*S*)-(-)-MTPA (60 mg, 0.25mmol) in dichloromethane (9 ml). Work-up as before to products ((142) and (147) in 85 : 15 ratio) (90 mg, 100%) as a yellow oil.

2-Phenylpropyl (*S*)-(-)-α-methoxy-α-(trifuoromethyl)phenylacetate (142), refer to Section 5.14.2 for full characterisation.

$^{19}$F n.m.r. (300 MHz, $CDCl_3$) (minor diastereoisomer in brackets): δ -72.15 (0.27), bs, (-72.09 (0.09), bs), $CF_3$. The enantiomeric excess was 50%.

3-Phenylpropyl (*S*)-(-)-α-methoxy-α-(trifuoromethyl)phenylacetate (147):

$^1$H n.m.r. (300 MHz, $CDCl_3$): δ 2.05, m, 2H, H2; 2.54, m, 2H, H3; 3.55, m, 3H, $OCH_3$; 4.35, m, 2H, H1; 7.16-7.44, m, 10H, 2 x ArH.

The spectral data were consistent with those reported in literature.[57]

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# A highly enantioselective synthesis of cyclic α-amino acids involving a one-pot, single catalyst, tandem hydrogenation–hydroformylation sequence†

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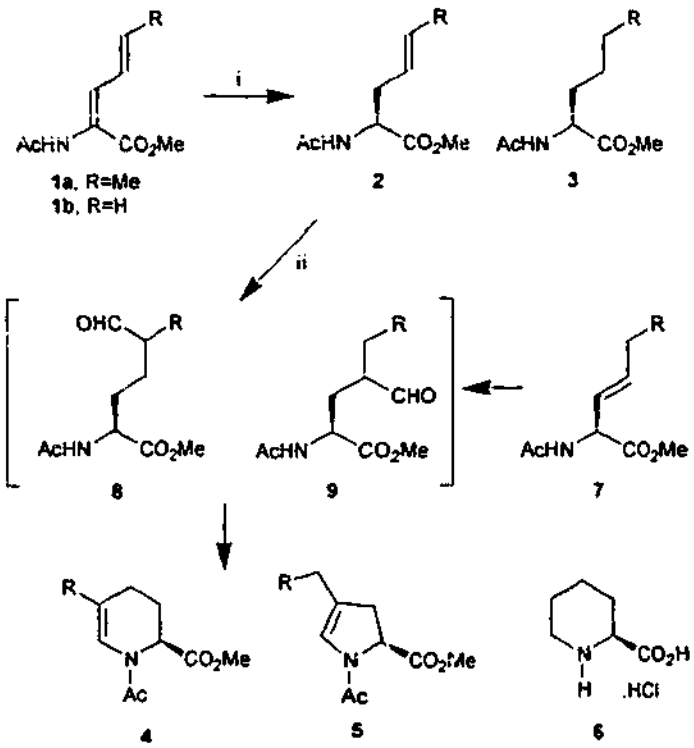
**Tandem enantioselective hydrogenation followed by a hydroformylation–cyclisation sequence leading to cyclic α-amino acids with ee's > 95% can be achieved in a single pot, one catalyst system by successive reactions of prochiral dienamide esters with $H_2$ followed by $H_2$/CO using Rh(I)-DuPHOS.**

Cyclic amino acids are of increasing biological importance because of their relationship to naturally occurring biological molecules, *e.g.* the izidine alkaloids[1] (piperidines), kainic acid analogues[2] (pyrrolidines), and their use in peptidomimetics.[3] Recent syntheses of pipecolic acid derivatives have involved aldol condensation–reductive amination of aspartate β-aldehyde,[4] intramolecular cyclohydrocarbonylation of unsaturated amides[5] and ruthenium catalysed ring closing metathesis.[6] Both of these latter preparations start with allylglycine which is available in both enantiomeric forms.[7] In spite of these recent advances, there appears to be a demand for facile routes to this class of compound as other general syntheses are relatively limited in scope. In this communication we describe a general synthesis of either enantiomer of piperidino- and pyrrolidino-based α-amino acids by a sequence which, in its final form, involves a single pot, one catalyst reaction sequence. Such tandem sequences are becoming increasingly important in organic synthesis and have recently been used for isomerisation–carbonylation of alkenes.[8] Domino reactions employing hydroformylation–condensation–hydrogenation sequences have also recently been reported.[9]

Rhodium catalysed hydrogenation of the prochiral dienamide ester **1a** under conditions reported by Burk[10] gave the allylglycine derivative **2a** in high enantiomeric excess (>95%) and yield (98%) (Scheme 1). Either enantiomer of **2a** could be obtained by the use of (*R*,*R*)- or (*S*,*S*)-Et-DuPHOS with the (*R*,*R*)-catalyst giving the (*R*)-enantiomer of **2a**.[10,11] Excellent regioselectivity was observed with <5% of the saturated product **3a** being produced. The unsubstituted analogue **1b** was also hydrogenated under milder conditions to give **2b** with excellent regioselectivity but with a slightly increased amount of over-reduced material **3b** (5–15%). The enantioselectivity was again >95% as shown by chiral gas chromatography (Scheme 1).

Ojima and co-workers have previously reported preparation of pipecolic acid derivatives from protected allylglycines closely related to **2b**.[5] Reactions of **2b** using rhodium–phosphine catalysts with $H_2$/CO under conditions previously used in our work[12] gave very good isolated yields (*ca.* 70%) of the cyclic amino acid derivatives **4b** and **5b** (Table 1, entries 1 and 2) (Scheme 1). The compounds were readily separated and chiral hplc showed that the enantiomeric excess had not been compromised. Confirmation that the (*R*)-configuration was present in samples of **4b** prepared using (*R*,*R*)-Et-DuPHOS was obtained by conversion of **4b** to (*R*)-pipecolic acid hydrochloride **6** and comparison of optical rotation values.[13]

The isolated piperidine **4**:pyrrolidine **5** ratio originates from the regioselectivity exhibited during hydroformylation. The observed selectivity (<2:1 for **4b**:**5b**), however, was considerably lower than expected given that hydroformylation of a terminal alkene using $PPh_3$ as ligand would be expected to yield a piperidine:pyrrolidine ratio of *ca.* 2:1, whereas the bulkier BIPHEPHOS ligand should bias this ratio to *ca.* 9:1.[12,14] An




**Scheme 1** (i) **1a**: (*S*,*S*)-Et-DuPHOS-Rh(I), $H_2$ (90 psi), 2 h, PhH, rt; **1b**: (*S*,*S*)-Et-DuPHOS-Rh(I), $H_2$ (30 psi), 3 h, PhH, rt. (ii) $H_2$/CO (1:1), 80–400 psi, 80–100 °C, 20–72 h. [$Rh(OAc)_2]_2$, $PPh_3$ or BIPHEPHOS with substrate:Rh(I):phosphine ratio of 100:1:2.

**Table 1** Rhodium catalysed hydroformylation of chiral enamides **2a** (R = Me) and **2b** (R = H)[a]

| Entry | R | Catalyst System[b] | $H_2$:CO (psi) | T (°C) | Time (h) | Product Ratio (4 : 5) | Yield (%)[c] | % ee (4/5)[e] |
|---|---|---|---|---|---|---|---|---|
| 1 | H | A | 400 | 80 | 72 | 50:50 | 73 | --/87 |
| 2 | H | B | 400 | 80 | 20 | 63:37 | 66 | 88/-- |
| 3 | H | B | 100 | 80 | 20 | 71:29 | 54[d] | --/87 |
| 4 | H | B | 80 | 80 | 20 | 78:22 | —[f] | |
| 5 | H | B | 80 | 80 | 72 | 66:34 | 75 | 99/-- |
| 6 | Me | A | 400 | 80 | 20 | 67:33 | 45 | 91/98 |
| 7 | Me | B | 400 | 80 | 20 | 100:0 | 37[g] | |
| 8 | Me | B | 400 | 100 | 72 | 91:9 | 81 | 97/-- |

[a] Reaction conditions: Substrate (0.3 mmol) : $[Rh(OAc)_2]_2$ : $PPh_3$ or BIPHEPHOS ratio = 100:1:2 in benzene (5–10 ml) with $H_2$/CO (1:1). [b] Catalyst code: A = Rh-$PPh_3$, B = Rh-BIPHEPHOS. [c] Isolated yield of cyclic products **4** and **5** after chromatography. [d] Crude product contained *ca.* 20% isomerised alkenamide **7**. [e] Crude product contained *ca.* 50% isomerised alkenamide **7**. [f] Aldehydes **8a** and **9a** (*ca.* 1:1) also obtained. [g] -- Signifies that enantioselectivity was not assessed.

† Electronic supplementary information (ESI) available: experimental information. See http://www.rsc.org/suppdata/cc/b2/b200374k/

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explanation for this anomaly became apparent after conducting the hydroformylation experiments under milder conditions. Reaction of **2b** at 80 °C with 100 psi of $H_2$/CO over 20 h (entry 3) gave a modest yield (54%) of **4b** and **5b** and *ca.* 20% of the isomerised alkenamide **7**. Significantly, Rh(I)-BIPHEPHOS catalysed hydroformylation of **7** would favour reaction remote from the bulky amino acid moiety resulting in pyrrolidine **5b** after cyclisation and dehydration (Scheme 1). This secondary route to **5b** explains the higher than expected amounts of pyrrolidine in reactions involving **2b**. Under lower hydroformylation pressure (80 psi) an even greater percentage of **7** (*ca.* 50%) was observed after 20 h (entry 4) and extended reaction over 72 h gave significant amounts of **5b** (entry 5).

Hydroformylation of the homologue **2a** at 80 °C with 400 psi $H_2$/CO using $PPh_3$ as ligand gave **4a** and **5a** in a 2:1 ratio (entry 6) whilst a similar reaction using BIPHEPHOS gave a significant amount of the uncyclised aldehydes **8a** and **9a** together with piperidine **4a** (entry 7). Increasing the temperature and reaction time led to complete conversion and isolation of cyclic compounds **4a** and **5a** in high yield and in a ratio of 9:1.

A tandem reaction was then investigated which capitalized on the disparate operating conditions of the two Rh-DuPHOS and Rh-BIPHEPHOS catalysts. Under mild reaction pressures, only the Rh-DuPHOS catalyst would be expected to facilitate hydrogenation of the enamide substrates **1** ensuring the maintenance of high enantioselectivity. Hence, in the presence of *both* Rh-DuPHOS and Rh-BIPHEPHOS, hydrogenation of **1b** (rt, 30 psi of $H_2$, 3 h) followed by hydroformylation (80 °C, 80 psi of $H_2$/CO) gave **4b** and **5b** in a 2:1 ratio and 63% isolated yield. Importantly, the enantiomeric excess of **4b** and **5b** was found to be >95% (entry 9, Table 2). A similar reaction sequence involving **1a** with Rh-DuPHOS and Rh-$PPh_3$ gave **4a** and **5a** in *ca.* 1:1 ratio in 81% isolated yield (entry 10). The ee of **4a** and **5a** were also shown to be ≥ 95% by chiral hplc.

Next we investigated whether a single catalyst, namely Rh(I)-DuPHOS, could be employed to facilitate both hydrogenation and hydroformylation. To our knowledge, the use of Rh-DuPHOS as a hydroformylation catalyst has not been previously reported. Reaction of dienamide **1b** in the presence of Rh-DuPHOS alone, initially with $H_2$ at ambient temperature and then with $H_2$/CO (80 psi) at 80 °C, gave a product containing significant amounts of the isomerised alkene **7** (entry 11). Reaction using a higher pressure of $H_2$/CO (400 psi) gave complete conversion to **4b** and **5b** in *ca.* equimolar ratio in 91% isolated yield with excellent enantioselectivity (entry 12). It appears that the Rh-DuPHOS system is slightly less efficient for hydroformylation than the Rh-BIPHEPHOS system (compare entries 5 and 11). A similar diminution in rate was observed for a reaction of **1a** in the presence of Rh-DuPHOS where hydroformylation under conditions giving complete conversion using Rh-$PPh_3$ (entry 6, Table 1; entry 10, Table 2) gave substantial amounts of aldehydes (**8a** and **9a**) (entry 13). A reaction under more forcing conditions gave complete conversion to the piperidine **4a** which was isolated as the sole product in 58% yield and with 96% ee (entry 14).

These results clearly establish that it is possible to obtain cyclic α-amino acids in good to very good yields and with excellent enantioselectivity using a single catalyst in a single pot *via* a tandem reaction sequence.

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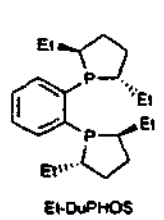
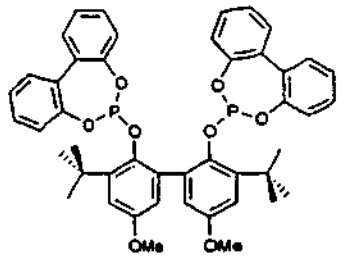
**Table 2** Rhodium catalysed tandem hydrogenation and hydroformylation of dienamides **1a** (R = Me) and **1b** (R (R = H)[a]

| Entry | R | Catalyst System[b] | $H_2$/CO (psi) | $T$ (°C) | Time (h) | Product Ratio (4 : 5) | Yield (%)[c] | % ee (4/5) |
|---|---|---|---|---|---|---|---|---|
| 9 | H | B + C | 30 | 80 | 72 | 67:33 | 63 | 95/95 |
| 10 | Me | A + C | 400 | 80 | 20 | 56:44 | 81 | 95/99 |
| 11 | H | C | 80 | 80 | 72 | 74:26 | —[d] | |
| 12 | H | C | 400 | 80 | 72 | 54:46 | 91 | 95/99 |
| 13 | Me | C | 400 | 80 | 20 | 83:17 | 35[e] | 99/99 |
| 14 | Me | C | 800 | 150 | 72 | 100:0 | 58 | 96/—[f] |



Et-DuPHOS



BIPHEPHOS

[a] Reaction conditions: Substrate (0.3 mmol) : Rh-Et-DuPHOS: $Rh[(OAc)_2]_2$ : $PPh_3$ or BIPHEPHOS ratio = 100:1:1:2 in benzene (5–10 ml) with $H_2$ (30 psi, 3 h for **1b** and 90 psi, 2 h for **1a**) at ambient temperature followed by $H_2$/CO (1:1). [b] Catalyst code: A = Rh-$PPh_3$, B = Rh-BIPHEPHOS, C = Rh-Et-DuPHOS. [c] Isolated yield of cyclic products **4** and **5** after chromatography. [d] Crude product contained *ca* 40% isomerised alkenamide **7**. [e] Aldehydes **8a** and **9a** also obtained. [f] Enantioselectivity was not assessed.

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# One-pot tandem enantioselective hydrogenation–hydroformylation synthesis of cyclic α-amino acids

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Five- and six-membered cyclic amino acids can be prepared in good yield with high ee (> 95%) *via* tandem rhodium-DuPHOS catalysed asymmetric hydrogenation followed by a rhodium-catalysed hydroformylation–cyclisation sequence in a single pot. The synthesis can be achieved using Rh-DuPHOS as the sole catalyst.

## Introduction

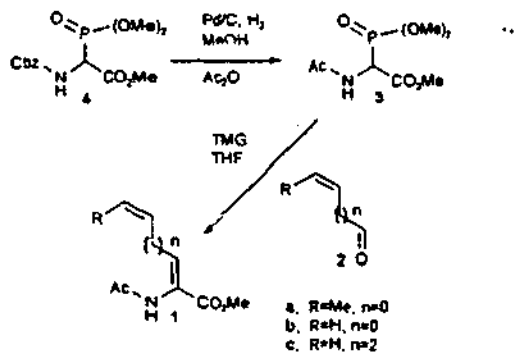
There is a growing trend in the pharmaceutical and fine chemicals industries towards replacing classical organic synthesis with cleaner catalytic alternatives. Attention to E factor,[1] the amount of waste generated per kilo of product,[2] has driven chemists to reduce or eliminate the use and generation of toxic and hazardous reagents and solvents. Tandem reaction sequences employing catalytic processes therefore offer a remarkable opportunity to conduct organic synthesis in a highly efficient manner. Furthermore, reaction sequences which possess high atom economy[3] and simultaneously incorporate stereochemistry into the framework of the desired target would be considered even more efficient.[4] In this context, we have recently developed an enantioselective synthesis of cyclic α-amino acids *via* domino catalytic asymmetric hydrogenation–hydroformylation protocol.[5] Cyclic amino acids are of increasing biological importance because of their relationship to naturally occurring biological molecules, *e.g.* the izidine alkaloids[6] (piperidines) and kainic acid[7] (pyrrolidines), and their use in peptidomimetics.[8] The sequential transformation described herein allows the formation of a new C–C single bond and heterocycle formation with concomitant generation of a stereogenic centre. Other highly efficient domino reactions have also recently been reported and include hydroformylation–Knoevenagel–hydrogenation,[9] hydroformylation–Wittig,[10] isomerization–hydroformylation,[11] hydroformylation–conjugate addition[12] and isomerisation–carbonylation[13] sequences.

In this paper, we describe an enantioselective tandem hydrogenation–hydroformylation–cyclisation sequence leading to cyclic α-amino acid derivatives.

## Results and discussion

### Synthesis of hydrogenation precursors

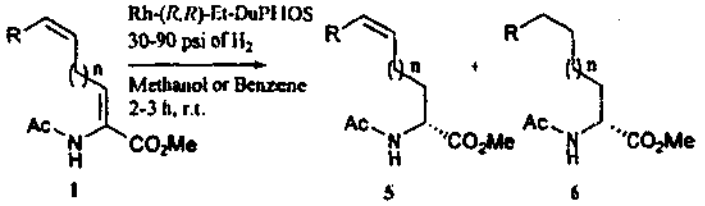
The hydrogenation precursors, the dienamide esters **1**, were readily accessible by reaction of unsaturated aldehydes **2** with the phosphonate **3**[14,15] (Scheme 1). The Cbz-protected phosphonate **4**[15] was prepared in 81% yield and converted quantitatively into the N-acetyl-protected phosphonate **3**.[15] An alternative route to **3** from methyl *N*-acetyl-2-methoxyglycinate[16,17] gave the phosphonate in a poor yield (30%). Horner–Emmons olefination[18] of the phosphonate **3** was carried out using the unsaturated aldehydes **2a–2c** (Scheme 1). The use of tetramethylguanidine (TMG) as base at low temperature in THF has been described by Burk *et al.* and the dienamide esters **1a–1c** were obtained in acceptable yields (**1a**, 55%; **1b**, 87%; **1c**, 38%) using this method.[14]




Scheme 1

### Asymmetric hydrogenations

The DuPHOS ligand developed by the DuPont company has been shown to give complexes with rhodium which give excellent enantioselectivities when used as catalysts in hydrogenation of prochiral substrates.[19] Recently Burk *et al.* have demonstrated that high regio- and enantioselectivities can be achieved in the hydrogenation of prochiral dienamide esters.[14] In this paper, the dienamide esters **1** were hydrogenated in either methanol or benzene with Rh-Et-DuPHOS using short reaction times (Scheme 2). Full conversions and high enantioselectivity (ee) were achieved in methanol (> 80% ee) and benzene (> 95% ee) (Table 1). As the substrates were more soluble




a; R=Me, n=0; b; R=H, n=0; c; R=H, n=2

Scheme 2

DOI: 10.1039/b209087m

**Table 1** Rh-catalysed asymmetric hydrogenation of dienamide esters 1[a]

| Entry | Substrate | R | n | Pressure/ psi | Time/ h | Product | Ratio[b] 5:6 | Yield (%)[c] | % ee[d] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | Me | 0 | 90 | 2 | **5a** | 94:6 | 99 | 95 |
| 2 | **1a** | Me | 0 | 90 | 2 | **5a** | 95:5 | 98 | 95[e] |
| 3 | **1b** | H | 0 | 30 | 3 | **5b** | 95:5 | 88 | 95 |
| 4 | **1b** | H | 0 | 30 | 3 | **5b** | 95:5 | 90 | 76[f] |
| 5 | **1b** | H | 0 | 30 | 3 | **5b** | 95:5 | 90 | 95[e] |
| 6 | **1c** | H | 2 | 30 | 2 | **5c** | 92:8 | 90 | 98 |

[a] All reactions were performed in benzene using Rh-(*R*,*R*)-Et-DuPHOS with substrate:catalyst ratio = 100:1 at ambient temperature, 100% conversion was observed in all cases. For specific conditions, refer to experimental. [b] % Over-reduction was estimated by $^1$H NMR. [c] Isolated yield of 5 + 6 after passage through a short plug of silica. [d] % ee of 5 was assessed by chiral capillary GC column (CP-Chirasil Val). [e] Reaction using Rh-(*S*,*S*)-Et-DuPHOS giving (*S*)-5. [f] Reaction carried out in methanol.

**Table 2** Rh-catalysed hydroformylation of hydrogenated enamides 5a: R = Me and 5b: R = H[a]

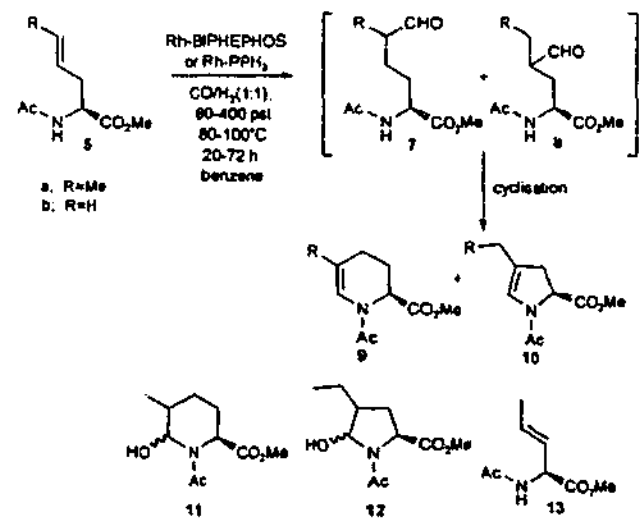
| Entry | R | Catalyst system | CO/ $H_2$/psi | $T$/°C | Time/ h | Product ratio 9:10 | Yield (%)[b] | % ee[c] 9/10 |
|---|---|---|---|---|---|---|---|---|
| 7 | Me | A | 400 | 80 | 20 | 67:33 | 45 | 91/98 |
| 8 | Me | B | 400 | 80 | 20 | 100:0 | 37[d] | — |
| 9 | Me | B | 400 | 100 | 72 | 91:9 | 81 | 97/98 |
| 10 | Me | A | 400 | 80 | 20 | 80:20 | 47[e] | — |
| 11 | H | A | 400 | 80 | 72 | 50:50 | 73 | – /87 |
| 12 | H | B | 400 | 80 | 20 | 63:37 | 66 | 88/— |
| 13 | H | B | 100 | 80 | 20 | 71:29 | 54[f] | – /87 |
| 14 | H | B | 80 | 80 | 20 | 78:22 | [g] | — |
| 15 | H | B | 80 | 80 | 72 | 66:34 | 75 | 99/99 |

[a] Reaction conditions: substrate:[$Rh(OAc)_2$]$_2$:$PPh_3$ or BIPHEPHOS ratio = 100:1:2 in benzene (5–10 mL). A = Rh-$PPh_3$ and B = Rh-BIPHEPHOS. For specific conditions, refer to experimental. [b] Isolated yield of cyclic products 9 and 10 after chromatography. [c] % ee was assessed by chiral HPLC column (DAICEL Chiralcel® OD); — Signifies that enantiomeric excess (ee) was not assessed. [d] Aldehydes 7a and 8a (*ca.* 1:1) also obtained. [e] Initial isolation of amidals 11 and 12. [f] Crude product contained *ca.* 20% isomerised alkenamide 13. [g] Crude product contained *ca.* 50% isomerised alkenamide 13.

in benzene and the % ee was found to be higher, subsequent reactions were carried out in benzene. An increase in pressure, reaction duration and catalyst loading increased the amount of over-reduction.[14] For unsubstituted dienamide esters **1b** and **1c** (entries 3 to 6), a low pressure (30 psi of $H_2$) and short reaction time (2–3 h) were used to give < 8% of the over-reduced by-product **6** with 100% conversion of starting material **1**. In contrast for the substituted substrate **1a** (entries 1 and 2), higher pressure (90 psi of $H_2$) was needed for the hydrogenation to go to completion in 2 h. In all cases, the products were isolated in high yields. Enantiomeric excess was assessed by chiral capillary GC.

## Hydroformylation

**Preparation of pyrrolidine and piperidine derivatives.** Heterocyclic compounds can be obtained in good yields by a hydroformylation–cyclisation reaction sequence from unsaturated amines and amides.[20,21] Ojima *et al.* have applied this methodology to the preparation of pipecolic acid derivatives by hydroformylation of enamides related to **1b**.[22] High regioselectivity was obtained when the bulky phosphite BIPHEPHOS[23] was used as a ligand. The methodology has now been applied to reactions of the chiral enamides **5**, leading predominantly to the cyclic amido esters **9** and **10** presumably *via* the aldehydes **7** and **8** as shown in Scheme 3. The reactions were carried out using $Rh/PPh_3$ or Rh/BIPHEPHOS under 400 psi of $CO/H_2$ (1:1) and gave the piperidine **9** and pyrrolidine **10** derivatives. The 5- and 6-membered ring compounds were readily separated by chromatography and chiral HPLC showed that the enantiomeric excess (ee) of these compounds was preserved (Table 2). Hydroformylation of enamide **5a** using the $PPh_3$ ligand gave **9a** and **10a** in a 2:1 ratio (entry 7), whilst under the same conditions, use of the BIPHEPHOS ligand led to incomplete cyclisation and isolation of aldehydes **7a** and **8a** (entry 8). Reaction using BIPHEPHOS at the same pressure but with increased temperature and reaction time gave complete conversion with a higher ratio of piperidine **9a** to pyrrolidine **10a** (9:1 ratio) (entry 9) consistent with the bulky ligand directing the initial hydroformylation to the less hindered carbon of the alkene. In one reaction using $PPh_3$ as ligand, the initial product contained the amidals **11** and **12** which dehydrated on standing in $CDCl_3$ to give the enamides **9a** and **10a** (entry 10). Similar amidals have been isolated by Ojima and coworkers.[20,22]

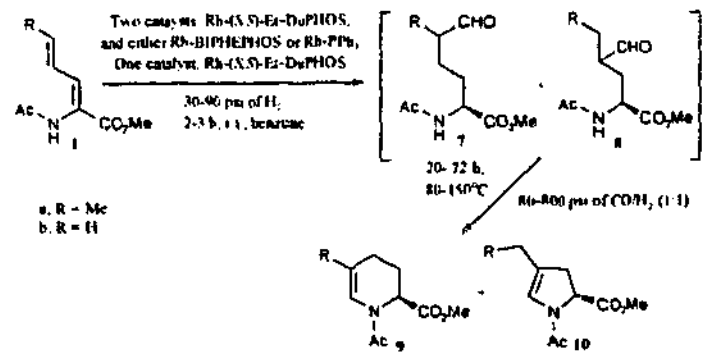



Scheme 3

Hydroformylation of **5b**, containing a terminal alkene, surprisingly gave a lower than expected piperidine **9b**:pyrrolidine **10b** ratio in all cases. Reaction of **5b** using the $PPh_3$ ligand gave a 1:1 ratio of the cyclic amino acid derivatives **9b** and **10b** (entry 11), in contrast to the *ca.* 2:1 ratio obtained with **5a**. Reaction using BIPHEPHOS gave **9b** and **10b** in a ratio of 2:1, again lower than the ratio of > 9:1 usually obtained for hydroformylation of terminal alkenes with this ligand[23] (entry 12). A reaction using 100 psi $CO/H_2$ and the BIPHEPHOS ligand led to formation of the isomerised alkenamide **13** in *ca.* 20% yield (entry 13). This isomer would preferentially be hydroformylated and cyclised to give pyrrolidine **10b**, which explains the unexpected higher ratio of pyrrolidine **10b** in the reactions. A reaction at even lower pressure (80 psi) gave *ca.* 50% of the isomerised alkenamide **13** (entry 14). Extending the reaction time under these conditions gave the cyclic products **9b** and **10b** in 75% yield (entry 15).

This result is very unexpected in that, although alkene isomerisation by related rhodium compounds is well established, the terminal alkene normally hydroformylates faster than internal alkenes. Thus, such a phenomenon is consistent with the recently reported high yields of straight chain aldehydes from hydroformylation of internal alkenes using a Rh-NAPHOS catalyst.[24] Similarly, a tandem isomerisation–carbonylation sequence gave linear esters from a Pd-catalysed carbonylation of internal alkenes.[13] One possible explanation for this result is that chelation of rhodium to the amido carbonyl leads to preferential hydroformylation of the internal double bond as is the case for the preceding hydrogenation reaction.[19,25]

**One-pot tandem reactions.** The possibility of carrying out the hydrogenation–hydroformylation sequence in a single pot was examined (Scheme 4). Hydrogenation of the dienamides **1a** and **1b** was carried out in a vessel containing both the Rh-DuPHOS and either Rh-BIPHEPHOS or $Rh-PPh_3$ catalysts.

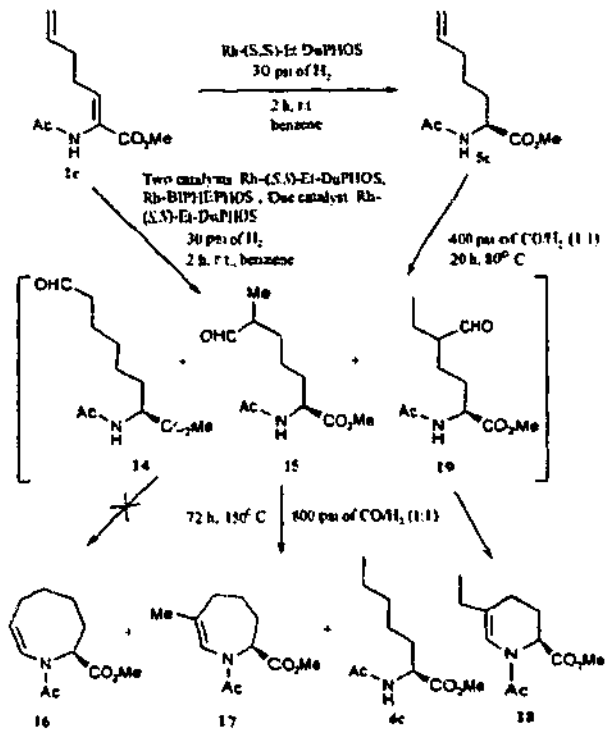


Scheme 4

After the low pressure hydrogenation was complete, the gas was vented and replaced by a 1:1 $CO/H_2$ gas mixture and the temperature raised to 80 °C. Good to very good yields of the heterocycles **9** and **10** were obtained (Table 3, entries 16 and 17). Excellent enantioselectivity (> 95% ee) of **9** and **10** was maintained, showing that there was no significant competition by Rh-BIPHEPHOS or Rh-$PPh_3$ in the hydrogenation step catalysed by Rh-DuPHOS. Reaction of the terminal alkene **1b** gave some isomerised alkene **13** (25%) in addition to the heterocycles **9b** and **10b** (Table 3, entry 17).

The possibility of using Rh-DuPHOS as a catalyst for both reactions was investigated. This catalyst has not been used previously for hydroformylation reactions. Reactions of dienamide substrates **1a** and **1b** using Rh-Et-DuPHOS, initially under hydrogenation conditions and then under hydroformylation conditions, gave the expected cyclic products **9** and **10** in reasonable yields (Table 3). Again, the enantiomeric excess (ee) was found to be excellent (> 98%). Comparison of the results reported in entries 9 (Table 2) and 19 (Table 3) suggests that Rh-DuPHOS appears to be a slightly less efficient catalyst than Rh-BIPHEPHOS as it needed more forcing conditions to give complete conversion of dienamide **1a** to cyclic products **9a** and **10a**. Comparison of entries 7 (Table 2) and 18/19 (Table 3) shows that Rh-DuPHOS is also less efficient than the Rh-$PPh_3$ system. A similar scenario was observed in reaction of dienamide **1b**, as it too required higher pressure to achieve 100% completion and 91% isolated yield of **9b** and **10b** (compare entries 15 (Table 2) and 20/21 (Table 3)).

**Attempted preparation of 7- and 8-membered cyclic amino acid derivatives.** Attempts were made to extend the method to the preparation of larger ring cyclic amido esters from a longer chain hydrogenation precursor (Scheme 5) and the results are summarised in Table 4. The enamide ester **5c** was



Scheme 5

hydroformylated using the Rh-$PPh_3$ and Rh-BIPHEPHOS systems and gave the aldehydes **14** and **15** (entries 22 and 23). No cyclic material was observed.

A one-pot tandem reaction was carried out using a higher pressure and temperature for a longer period of time with the mixed Rh-DuPHOS and Rh-BIPHEPHOS catalysts (Table 4, entry 24). The major product was the saturated compound **6c**. Chromatography gave a mixture of the two heterocycles **17** and **18** in *ca.* 1:1 ratio and *ca.* 24% yield. No 8-membered ring compound **16** was detected. Formation of **18** means that some of the aldehyde **19** has been generated *via* initial alkene isomerisation.

A one-pot reaction using only Rh-DuPHOS as catalyst under the same conditions again gave predominantly the saturated compound **6c** (Table 4, entry 25). Chromatography led to the isolation of the 6-ring compound **18** in 12% yield. The difficulty associated with the formation of 7- and 8-membered rings accounts for the low yields of heterocycles but the formation of large amounts of hydrogenated rather than hydroformylated material is hard to understand.

**Preparation of a cyclic α-amino acid.** The piperidine **9b** prepared using (R,R)-Et-DuPHOS-Rh was converted into the pipecolic acid hydrochloride **21** (Scheme 6)and its optical

**Table 3** One-pot tandem reaction of dienamide esters **1a**; R = Me and **1b**; R = H[a]

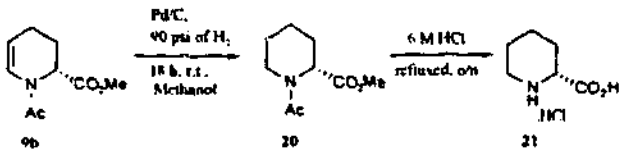
| Entry | R | Catalyst system | $CO/H_2$/psi | T/°C | Time/h | Product ratio 9:10 | Yield (%)[b] | % ee[c] 9/10 |
|---|---|---|---|---|---|---|---|---|
| 16 | Me | A + C | 400 | 80 | 20 | 56:44 | 81 | 95/99 |
| 17 | H | B + C | 80 | 80 | 72 | 67:33 | 60[d] | 95/95 |
| 18 | Me | C | 400 | 80 | 20 | 83:17 | 35[e] | 99/99 |
| 19 | Me | C | 800 | 150 | 72 | 100:0 | 58 | 96/— |
| 20 | H | C | 80 | 80 | 72 | 74:26 | [f] | — |
| 21 | H | C | 400 | 80 | 72 | 54:46 | 91 | 95/99 |

[a] Reaction conditions: substrate:Rh-Et-DuPHOS:$[Rh(OAc)_2]_2$:$PPh_3$ or BIPHEPHOS ratio = 100:1:1:2 in benzene (5–10 mL) with $H_2$ (90 psi, 2 h for **1a** and 30 psi, 3 h for **1b**) at ambient temperature followed by $CO/H_2$ (1:1 ratio). A = Rh-$PPh_3$, B = Rh-BIPHEPHOS and C = Rh-Et-DuPHOS. [b] Isolated yield of cyclic products **9** and **10** after chromatography. [c] % ee was assessed by chiral HPLC column (DAICEL Chiralcel® OD); — Signifies that enantioselectivity was not assessed. [d] Isomerised alkene **13** also isolated (25% yield). [e] Aldehydes **7a** and **8a** also obtained (*ca.* 15%). [f] Crude product contained *ca.* 40% isomerised alkenamide **13**.

**Table 4** Attempted synthesis of 7- and 8-membered cyclic amino acids[a]

| Entry | Substrate | Catalyst system | $CO/H_2$/psi | T/°C | Time/h | Product ratio[b] 17:18 | Yield (%)[c] |
|---|---|---|---|---|---|---|---|
| 22 | 5c | A | 400 | 80 | 20 | [d] | — |
| 23 | 5c | B | 400 | 80 | 20 | [e] | — |
| 24 | 1c | B + C | 800 | 150 | 72 | 50:50[f] | 12 |
| 25 | 1c | C | 800 | 150 | 72 | 0:100[g] | 24 |

[a] Reaction conditions: substrate:Rh-Et-DuPHOS:$[Rh(OAc)_2]_2$:$PPh_3$ or BIPHEPHOS ratio = 100:1:1:2 in benzene (5–10 mL) with 30 psi of $H_2$ for 2 h at ambient temperature followed by $CO/H_2$ (1:1 ratio). A = Rh-$PPh_3$, B = Rh-BIPHEPHOS and C = Rh-Et-DuPHOS. [b] — Signifies that no cyclic products were observed. [c] Isolated yield of cyclic products **17** and **18** after chromatography. [d] Aldehydes **14** and **15** were obtained in 1:1 ratio (63% yield). [e] Aldehydes **14** and **15** present in 1:1 ratio; not isolated. [f] Crude product contained *ca.* 74% over-reduced by-product **6c**. [g] Crude product contained *ca.* 67% over-reduced by-product **6c**.




Scheme 6

rotation, $[\alpha]_D$ +10° was almost identical to a literature $[\alpha]_D$ +10.8° for the (*R*)-enantiomer.[26] Thus the initial enantioselective hydrogenation using Rh-(*R*,*R*)-Et-DuPHOS was highly selective for the (*R*)-configuration of the product in agreement with previous findings.[19,27]

## Conclusion

High yields of 5- and 6-membered ring α-amino acid derivatives, *viz.* the piperidines **9** and pyrrolidines **10**, can be obtained with high ee using one or two catalysts in a one-pot reaction. The reaction involves a tandem hydrogenation, hydroformylation, cyclisation sequence. It has been demonstrated that Rh-DuPHOS can act as an efficient catalyst for hydroformylation as well as hydrogenation reactions.

Reactions of glycine derivatives **1a** and **1b**, substituted with 1,3-dienes, gave surprisingly high ratios of products arising from branched as opposed to linear aldehydes. Similarly, reactions of the homologous 1,5-diene derivative **1c** gave the 6- and 7-membered ring heterocycles **18** and **17**, suggesting that isomerisation competes with hydroformylation and that formation of internal aldehydes is favoured, possibly because of intramolecular chelation of the rhodium catalyst to the oxygen of the acetamido carbonyl group.

## Experimental

$^1$H NMR and $^{13}$C NMR spectra were recorded at 300 MHz and 75 MHz respectively with a Varian Mercury 300 Q Spectrometer in $CDCl_3$ and referenced to $Me_4Si$ unless otherwise stated. $^{31}$P NMR spectra were recorded at 121.5 MHz on a Bruker AM-300 spectrometer in deuterated solvents with 85% phosphoric acid ($H_3PO_4$) as the external standard. EI mass spectra were recorded on a Hewlett Packard Trio-1 spectrometer operating at 200°C/70 eV. ESI mass spectra were recorded on a Micromass Platform spectrometer. HRMS were recorded on a Bruker BioApex 47e Fourier transform mass spectrometer.

Analytical gas chromatography (GC) was carried out using a Chrompack CP-Chirasil Val chiral column (column: 0.25 mm × 50 m, 50 CP2/XE-60-S-VAL-S-A-PEA) using helium as the carrier gas and follows the temperature program: initial column temperature was 100°C for 1 min, then heated to 280°C for 9 min at 5°C min$^{-1}$. High performance liquid chromatography (HPLC) was carried out on a Varian LC Model 5000 instrument with a Varian UV-50 detector and using a DAICEL Chiralcel® OD column. The solvent system used was 10% isopropanol:90% hexane with a flow rate of 1.0 mL min$^{-1}$. A solution (10 μL) of the purified compound in HPLC grade isopropanol was used for injection. Optical rotations $[\alpha]_D^{20}$ were measured using a Perkin Elmer Model 141 Polarimeter. Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. Microanalysis were carried out by Chemical and Microanalytical Services Pty. Ltd., Melbourne (CMAS).

### Materials

[(COD)Rh-((2*R*,5*R*)-Et-DuPHOS)]OTf and [(COD)Rh-((2*S*,5*S*)-Et-DuPHOS)]OTf were used as supplied from Strem Chemicals. $[Rh(OAc)_2]_2$ and BIPHEPHOS[22] were prepared by Eva M. Campi. $PPh_3$ was obtained from Aldrich. $H_2$ and 1:1 molar mixture of $CO/H_2$ were obtained from BOC gases.

### Synthesis of hydrogenation precursors

**Methyl 2-benzyloxycarbonylamino-2-(dimethoxyphosphinyl)-acetate 4.** The Cbz-protected phosphonate **4** was prepared as described by Schmidt[15] from methyl *N*-benzyloxycarbonyl-2-methoxyglycinate[16,17] (23.0 g, 90.81 mmol) as a white solid, (24.33 g, 81%); mp 77–78°C (lit.[15] 80°C). $^1$H NMR: δ [minor rotamer in brackets] 3.77–3.83 (m, 9H, $COOCH_3$, 2 × $CH_3OP$), 4.93 (dd, 1H, $J$ = 22.4, 9.3 Hz, [5.12, bd, $J$ ~8.2 Hz], H2), 5.13 (d, 1H, $J$ = 12.2 Hz) and 5.15 (d, 1H, $J$ = 12.1 Hz, $CH_2O$), 5.77 (bd, 1H, $J$ ~8.2 Hz, [6.21, bs], NH), 7.32–7.40 (m, 5H, ArH). $^{13}$C NMR: δ [minor rotamer in brackets] 52.4 (d, $J$ = 148.0 Hz, [73.9, s], C2), 53.7 [53.5] ($COOCH_3$), 54.4 (d, $J$ = 6.9 Hz, $CH_3OP$), 54.5 (d, $J$ = 6.6 Hz, $CH_3OP$), 67.9 [67.7] ($CH_2O$), 128.4, 128.5, 128.8 (ArCH), 136.0 (C1'), 155.8 [155.9] (CONH), 167.3 [170.0] (C1). $^{31}$P NMR: δ 19.62 (s). MS (ESI$^+$, MeOH): $m/z$ 354.1 $(M + Na)^+$.

**Methyl 2-acetylamino-2-(dimethoxyphosphinyl)acetate 3.** The *N*-acetyl phosphonate **3** was prepared as described by Schmidt *et al.*[15] from the phosphonate **4** (10.0 g, 30.18 mmol) as a white solid (8.06 g, 100%); mp 90–92°C (lit.[15] 88–89°C). $^1$H NMR: δ 2.06 (s, 3H, $COCH_3$), 3.79–3.81 (m, 9H, $COOCH_3$, 2 × $CH_3OP$), 5.24 (dd, 1H, $J$ = 22.3, 8.5 Hz, H2), 6.74 (d, 1H, $J$ = 8.6 Hz, NH). $^{13}$C NMR: δ 23.3 ($COCH_3$), 49.3 (d, $J$ = 147.2 Hz, C2), 53.7 ($COOCH_3$), 54.3 (d, $J$ = 6.6 Hz, $CH_3OP$), 54.6 (d, $J$ = 6.3 Hz, $CH_3OP$), 167.3 (d, $J$ = 2.0 Hz, C1), 169.7 (d, $J$ = 5.7 Hz, CONH). MS (ESI$^+$, MeOH): $m/z$ 262.0 $(M + Na)^+$.

An alternative route to the phosphonate **3** involved reaction of methyl *N*-acetyl-2-methoxyglycinate[16,17] (1.01 g, 6.27 mmol) with phosphorus(III) chloride (0.55 mL, 6.27 mmol) and trimethyl phosphite (0.74 mL, 6.27 mmol) at 70°C as described for the preparation of the Cbz-protected phosphonate **4**[15] to give **3** as a white solid (0.43 g, 30%).

**4-Pentenal 2c.** Following the method described by Swern *et al.*,[28,29] reaction of 4-penten-1-ol (1.0 mL, 9.70 mmol) with dimethyl sulfoxide (1.52 mL, 21.34 mmol), oxalyl chloride (0.93 mL, 10.67 mmol) and triethylamine (6.76 mL, 48.50 mmol) gave an oil (1.30 g). The $^1$H and $^{13}$C NMR spectra indicated that the crude oil was a mixture of 4-pentenal **2c** and starting material (δ 3.62, t, $CH_2$) in an ratio of ~1:0.2. (approximate yield for **2c** was 83%). The crude product was used in the preparation of (2*Z*)-methyl 2-acetamidohepta-2,6-dienoate **1c**. $^1$H NMR: δ 2.13 (q, 2H, $J$ = 7.0 Hz, H3), 2.39 (td, 2H, $J$ = 7.0, 1.4 Hz, H2), 4.94–5.10 (m, 2H, H5), 5.82 (ddt, 1H, $J$ = 17.1, 10.2, 6.3 Hz, H4), 9.78 (t, 1H, $J$ = 1.5 Hz, H1). $^{13}$C NMR: δ 26.2 (C3), 42.8 (C2), 115.5 (C5), 136.4 (C4), 201.7 (C1). The spectral data were consistent with literature data.[30]

**(2*Z*,4*E*)-Methyl 2-acetamidohexa-2,4-dienoate 1a.** Tetramethylguanidine (0.61 mL, 4.89 mmol) was added to a solution of methyl 2-acetylamino-2-(dimethoxyphosphinyl) acetate **3** (0.88 g, 3.68 mmol) in distilled THF (15 mL) at −78°C following the method described by Burk.[14] After 15 min, crotonaldehyde **2a** (0.40 mL, 4.42 mmol) was added and the mixture was stirred for 2 h at −78°C. The mixture was warmed to 25°C using a warm water bath and stirred at this temperature for a further 2 h. The mixture was diluted with $CH_2Cl_2$ (20 mL), washed with 1 M HCl (2 × 10 mL), 1 M $CuSO_4$ (2 × 10 mL), saturated $NaHCO_3$ (2 × 10 mL) and 1 M NaCl (10 mL). The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to give an oil (0.90 g). Purification by flash chromatography on silica gel using

ethyl acetate and light petroleum (2:1) gave the dienoate **1a** as a white solid (0.37 g, 55%), ($R_f$ 0.21), mp 88–90°C (lit.[14] 89–90.1°C). $^1$H NMR: $\delta$ 1.88 (d, 3H, $J$ = 5.2 Hz, H6), 2.16 (s, 3H, $COCH_3$), 3.17 (s, 3H, $COOCH_3$), 6.16–6.20 (m, 2H, H4, H5), 6.90 (bs, 1H, NH), 7.08 (d, 1H, $J$ = 10.1 Hz, H3). $^{13}$C NMR: $\delta$ 19.3 (C6), 23.6 ($COCH_3$), 52.6 ($COOCH_3$), 121.6 (C2), 126.9, 134.5, 139.7 (C3, C4, C5), 165.7, 169.2 (C1, CONH).MS (ESI$^+$, MeOH): $m/z$ 206.0 $(M + Na)^+$.

**(2*Z*)-Methyl 2-acetamidopenta-2,4-dienoate 1b.** Using the method described above, tetramethylguanidine (1.90 mL, 14.90 mmol) and hydroquinone (5 mg) were added to a solution of the phosphonate **3** (3.0 g, 11.23 mmol) in distilled THF (35 mL) at −78°C. After 15 min, acrolein **2b** (0.90 mL, 13.47 mmol) was added, the mixture stirred at −78°C for 2 h then at 25°C for 2 h and worked up to give an oil (2.81 g). Purification by flash chromatography on silica gel using ethyl acetate and light petroleum (1:1) gave the (2*Z*)-dienoate **1b** as a white solid (1.65 g, 87%), ($R_f$ 0.2); mp 61–63°C. IR (KBr): 3277, 3011, 2955, 1733, 1655, 1594, 1518, 1438, 1113, 1016, 994, 950, 768 cm$^{-1}$. $^1$H NMR: $\delta$ 2.14 (s, 3H, $COCH_3$), 3.79 (s, 3H, $COOCH_3$), 5.47 (d, 1H, $J$ = 10.1 Hz, $H5_{(E)}$), 5.59 (d, 1H, $J$ = 16.9 Hz, $H5_{(Z)}$), 6.39–6.52 (m, 1H, H4), 7.03 (d, 1H, $J$ = 11.3 Hz, H3), 7.12 (bs, 1H, NH). $^{13}$C NMR: $\delta$ 23.8 ($COCH_3$), 52.8 ($COOCH_3$), 132.1, 132.9 (C3, C4), 123.7 (C2), 125.2 (C5), 165.6, 168.8 (C1, CONH). Calc. for $C_8H_{11}NO_3$: C, 56.78; H, 6.54; N, 8.28. Found: C, 56.66; H, 6.67; N, 8.29%.

**(2*Z*)-Methyl 2-acetamidohepta-2,6-dienoate 1c.** Reaction of tetramethylguanidine (0.31 mL, 3.95 mmol) and the phosphonate **3** (0.71 g, 2.97 mmol) in distilled THF (10 mL) with 4-pentenal **2c** (0.69 mL, 3.57 mmol) as described above gave an oil (0.47 g). Purification by flash chromatography on silica gel using ethyl acetate and light petroleum (1:1) gave the (2*Z*)-dienoate **1c** as a white solid (0.22 g, 38%), ($R_f$ 0.24); mp 44–45°C (lit.[15] 44°C). $^1$H NMR: $\delta$ 2.10 (s, 3H, $COCH_3$), 2.16–2.29 (m, 4H, H4, H5), 3.75 (s, 3H, $COOCH_3$), 4.97–5.08 (m, 2H, H7), 5.79 (ddt, 1H, $J$ = 17.1, 10.4, 6.4 Hz, H6), 6.64 (t, 1H, $J$ = 6.6 Hz, H3), 7.90 (bs, 1H, NH). $^{13}$C NMR: $\delta$ 23.2 ($COCH_3$), 28.0 (C4), 32.3 (C5), 52.3 ($COOCH_3$), 115.5 (C7), 125.9 (C2), 137.0 (C3), 138.0 (C6), 165.0, 169.2 (C1, CONH). MS (ESI$^+$, MeOH): $m/z$ 220.1 $(M + Na)^+$.

### Asymmetric hydrogenations

In a dry box, the substrate, catalyst (substrate:catalyst = 100:1) and deoxygenated methanol or benzene were added into a Fischer–Porter tube. Three vacuum/nitrogen cycles were used to purge the gas line of any oxygen, followed by three vacuum/nitrogen cycles and three vacuum/hydrogen cycles of the vessel before the vessel was pressurized to the stated pressure with hydrogen. The vessel was left stirring at ambient temperature for the reported period of time. For liquid substrates, a freeze–pump–thaw cycle was applied, the solution was transferred into a dry box and loaded into a Fischer–Porter tube.

**(2*R*,4*E*)-Methyl 2-acetamidohex-4-enoate 5a.** (2*Z*,4*E*)-Methyl 2-acetamidohexa-2,4-dienoate **1a** (0.42 g, 2.18 mmol) and [(COD)Rh-(*R*,*R*)-Et-DuPHOS]OTf were dissolved in benzene (10 mL). The vessel was charged with hydrogen (90 psi) and the mixture stirred for 2 h. The hydrogen was vented and the mixture was concentrated to give an oil (0.42 g). Purification by passing through a short silica plug with ethyl acetate gave an oil (0.40 g, 99%). The $^1$H NMR spectrum of the oil indicated the (2*R*,4*E*)-hex-4-enoate **5a** and the fully saturated compound, (2*R*,4*E*)-methyl 2-acetamidohexanoate **6a** [$\delta$ 0.89 (m, $CH_3$), 1.22–1.39 (m, $CH_2$)] in a 94:6 ratio respectively. IR (neat) 3284, 2954, 1747, 1658, 1547, 1437, 1375, 1217, 1142, 968 cm$^{-1}$. $^1$H NMR: $\delta$ 1.67 (ddt, 3H, $J$ = 6.4, 1.7, 1.1 Hz, H6), 2.03 (s, 3H, $COCH_3$), 2.43–2.51 (m, 2H, H3), 3.75 (s, 3H, $COOCH_3$), 4.63 (dt, 1H, $J$ = 7.8, 5.6 Hz, H2), 5.28 (m, 1H, H5), 5.55 (dqt, 1H, $J$ = 15.1, 6.4, 1.2 Hz, H4), 5.98 (bs, 1H, NH). $^{13}$C NMR: $\delta$ 18.3 (C6), 23.4 ($COCH_3$), 35.6 (C3), 52.3, 52.6 (C2, $COOCH_3$), 124.6, 130.1 (C4, C5), 169.8, 172.6 (C1, CONH). MS (ESI$^+$, MeOH): $m/z$ 207.9 $(M + Na)^+$. $[\alpha]_D^{22}$ −55° ($c$ 1.18, $CHCl_3$) containing 6% of **6a** (lit.[14] $[\alpha]_D^{20}$ −57.2° ($c$ 1.18, $CHCl_3$) containing < 2% of **6a**).

**(2*R*)-Methyl 2-acetamidopent-4-enoate 5b.** Hydrogenation of (2*Z*)-methyl 2-acetamidopenta-2,4-dienoate **1b** (40 mg, 0.24 mmol) in benzene was carried out at 30 psi for 3 h using Rh-(*R*,*R*)-Et-DuPHOS. Purification by passing through a short plug of silica with ethyl acetate gave an oil (36 mg, 88%). The $^1$H NMR spectrum indicated the (2*R*)-pent-4-enoate **5b** and the fully saturated compound, (2*R*)-methyl 2-acetamidopentanoate **6b** [$\delta$ 0.93 (t, $J$ = 7.3 Hz, $CH_3$), 1.25–1.44 (m, $CH_2$)] in a 95:5 ratio respectively. A solution of the oil in dichloromethane (2 mL) was injected into the GC chiral column to give two peaks: (*R*), $t_1$ = 18.2 min; (*S*), $t_2$ = 18.6 min; ee 95% (*R*). IR (neat): 3278, 1744, 1657, 1546, 1438, 1375, 1151 cm$^{-1}$. $^1$H NMR: $\delta$ 2.00 (s, 3H, $COCH_3$), 2.42–2.61 (m, 2H, H3), 3.72 (s, 3H, $COOCH_3$), 4.66 (m, 1H, H2), 5.09 (d, 1H, $J$ = 16.2 Hz, $H5_{(Z)}$), 5.10 (d, 1H, $J$ = 11.1 Hz, $H5_{(E)}$), 5.65 (m, 1H, H4), 6.14 (bs, 1H, NH). $^{13}$C NMR: $\delta$ 23.4 ($COCH_3$), 51.8, 52.5 (C2, $COOCH_3$), 119.2 (C5), 132.2 (C4), 169.7, 172.2 (C1, CONH). HRMS (ESI$^+$, MeOH): calc. for $(C_8H_{13}NO_3 + Na)^+$ $m/z$ 194.0793, found 194.0785 $(M + Na)^+$. $[\alpha]_D^{22}$ −43° ($c$ 0.047, $CH_3Cl$) containing 5% of **6b**.

**(2*R*)-Methyl 2-acetamidohept-6-enoate 5c.** Hydrogenation of (2*Z*)-methyl 2-acetamidohepta-2,6-dienoate **1c** (40 mg, 0.20 mmol) in benzene was carried out at 30 psi for 2 h using Rh-(*R*,*R*)-Et-DuPHOS. Purification by passing through a short plug of silica with ethyl acetate gave an oil (36 mg, 90%). The $^1$H NMR spectrum indicated the (2*R*)-hept-6-enoate **5c** and the fully saturated compound, (2*R*)-methyl 2-acetamidoheptanoate **6c** [($\delta$ 0.88 (t, $J$ = 6.6 Hz, $CH_3$)] in a 92:8 ratio respectively. A solution of the oil in dichloromethane (2 mL) was injected into the GC chiral column to give two peaks: (*R*), $t_1$ = 25.9 min; (*S*), $t_2$ = 26.1 min; ee 98% (*R*). IR (neat): 3286, 2954, 1745, 1658, 1547, 1436, 1374, 1264, 1210 cm$^{-1}$. $^1$H NMR: $\delta$ 1.26–1.53 (m, 2H, H4), 1.58–1.91 (m, 2H, H3), 2.03 (s, 3H, $COCH_3$), 2.06–2.10 (m, 2H, H5), 3.75 (s, 3H, $COOCH_3$), 4.61 (td, 1H, $J$ = 7.7, 5.5 Hz, H2), 4.95–5.05 (m, 2H, H7), 5.75 (ddt, 1H, $J$ = 17.0, 10.4, 6.5 Hz, H6), 6.30 (bs, 1H, NH). $^{13}$C NMR: $\delta$ 23.5 ($COCH_3$), 24.8 (C4), 32.2 (C3), 33.5 (C5), 52.4, 52.7 (C2, $COOCH_3$), 115.3 (C7), 138.0 (C6), 170.1, 173.3 (C1, CONH). HRMS (EI, MeOH): calc. for $(C_{10}H_{17}NO_3–COCH_3)$ $m/z$ 156.1024, found 156.1024 (M–$COCH_3$). $[\alpha]_D^{22}$ −60° ($c$ 0.15, $CH_3Cl$) containing 8% of **6c**.

### Hydroformylations

Reactions with $CO/H_2$ were carried out in a 100 mL Parr stainless steel autoclave fitted with a glass liner and magnetic stirrer bead.[21,31] After the reagents and substrate had been added under nitrogen into the autoclave, the vessel was flushed three times with 100 psi of $CO/H_2$ (1:1 molar ratio) and then pressurized to the stated pressure of the same gases. The autoclave was inserted to the heating block where its temperature was controlled by a thermocouple and the reaction was stirred with a magnetic stirrer under the heating block. The vessel was left stirring at the reported temperature for the reported period of time. At the end of the reaction, the vessel was left to cool to ambient temperature. The gases were

released slowly and the contents were treated and analyzed as reported.

**Reaction of (2*R*,4*E*)-methyl 2-acetamidohex-4-enoate 5a.** *(2R)-Methyl N-acetyl-5-methyl-5,6-didehydropipecolate* **9a** *and (2R)-methyl N-acetyl-4-ethyl-4,5-didehydroprolinate* **10a**. (2*R*,4*E*)-Methyl 2-acetamidohex-4-enoate **5a** (40 mg, 0.22 mmol), rhodium(II) acetate dimer (1.0 mg, 2.2 μmol) and BIPHEPHOS (3.5 mg, 4.4 μmol) were dissolved in deoxygenated benzene (5 mL). The autoclave was pressurized to 400 psi of $CO/H_2$ (1:1 molar ratio) and heated to 100°C. After 72 h, the autoclave was cooled to ambient temperature and the solvent was removed under reduced pressure to give an brown oil (50 mg). The $^1H$ and $^{13}C$ NMR spectra of the crude oil showed the pipecolate **9a** and the prolinate **10a** in a 91:9 ratio respectively. The compounds were separated by chromatography on silica gel using ethyl acetate and light petroleum (3:1 ratio).

(2*R*)-Methyl *N*-acetyl-5-methyl-5,6-didehydropipecolate **9a** was isolated as clear oil (30 mg, 70%), ($R_f$ 0.51). HPLC: (*S*), $t_1$ = 7.9 min; (*R*), $t_2$ = 10.5 min; ee 97% (*R*). IR (neat): 1744, 1654, 1404, 1205, 1174 $cm^{-1}$. $^1H$ NMR: $\delta$ [minor rotamer in brackets] 1.70 (s, 3H, [1.74, s], $CH_3C5$), 1.80–2.00 (m, 3H, H3, H4a), 2.22 (s, 3H, [2.11, s], $COCH_3$), 2.37 (m, 1H, H4b), 3.71 (s, 3H, [3.76, s], $COOCH_3$), 5.23 (m, 1H, [4.60, bs], H2), 6.40 (s, 1H, [7.04, s], H6). $^{13}C$ NMR: $\delta$ [minor rotamer in brackets] 21.4 [21.2] ($CH_3C5$), 21.75 [21.85] ($COCH_3$), 23.7 [24.2] (C3), 24.7 [24.3] (C4), 51.3 [53.1] (C2), 52.7 [55.4] ($COOCH_3$), 116.1 [116.7] (C5), 120.1 [118.4] (C6), 168.2, 171.3 (C1, CONH). Calc. for $C_{10}H_{14}NO_3$: C, 60.88; H, 7.67; N, 7.10. Found: C, 60.74; H, 7.69; N, 6.96%. $[\alpha]_D^{20}$ +138° (*c* 0.034, $CH_3Cl$).

(2*R*)-Methyl *N*-acetyl-4-ethyl-4,5-didehydroprolinate (**10a**) was obtained as clear oil (5 mg, 11%), ($R_f$ 0.34). HPLC: (S), $t_1$ = 11.0 min; (R), $t_2$ = 18.7 min; ee 98% (*R*). IR (neat): 2858, 1750, 1647, 1438, 1208 $cm^{-1}$. $^1H$ NMR: $\delta$ 1.08 (t, 3H, $J$ = 7.5 Hz, $CH_3CH_2$), 2.03–213 (m, 2H, $CH_3CH_2$), 2.15 (s, 3H, $COCH_3$), 2.52 (dd, 1H, $J$ = 16.8, 5.1 Hz, H3a), 2.96 (dd, 1H, $J$ = 16.7, 11.7 Hz, H3b), 3.76 (s, 3H, $COOCH_3$), 4.82 (dd, 1H, $J$ = 11.7, 5.2 Hz, H2), 6.19–6.21 (m, 1H, H5). $^{13}C$ NMR: $\delta$ 12.5 ($CH_3CH_2$), 21.8 (C3), 21.9 ($COCH_3$), 36.7 ($CH_3CH_2$), 52.7, 58.7 (C2, $COOCH_3$), 122.9 (C5), 126.4 (C4), 166.0, 171.9 (C1, CONH). HRMS (EI, MeOH): calc. for $C_{10}H_{15}NO_3$ *m/z* 197.1052, found 197.1046 (M). $[\alpha]_D^{20}$ +114° (*c* 0.028, $CH_3Cl$).

A similar reaction using BIPHEPHOS at 80°C, 400 psi gave a mixture of the aldehydes **7a** and **8a** (ratio *ca.* 1:1) and the pipecolate **9a**. $^1H$ NMR: $\delta$ for **7a**, 9.61 (d, $J$ = 1.5 Hz, CHO); for **8a**, 9.76 (d, $J$ = 1.5 Hz, CHO). The pipecolate **9a** was isolated in 37% yield.

A reaction of the hex-4-enoate **5a** (50 mg, 0.27 mmol), rhodium(II) acetate dimer (1.2 mg, 2.7 μmol) and triphenylphosphine (1.4 mg, 5.4 μmol) at 80°C with 400 psi of $CO/H_2$ for 20 h gave a brown oil (64 mg). The $^1H$ and $^{13}C$ NMR spectra of the crude oil showed (2*R*)-methyl *N*-acetyl-5-methyl-6-hydroxypipecolate **11** and (2*R*)-methyl *N*-acetyl-4-ethyl-5-hydroxyprolinate **12** in 4:1 ratio. The compounds were separated using column chromatography (ethyl acetate).

(2*R*)-methyl *N*-acetyl-5-methyl-6-hydroxypipecolate **11**: $^1H$ NMR. $\delta$ 1.07 (d, 3H, $J$ = 9.0 Hz, $CH_3$–C5), 1.31–1.79 (m, 5H, H3, 4 5), 2.22 (s, 3H, $COCH_3$), 3.71 (s, 3H, $COOCH_3$), 4.39 (t, 1H, $J$ = 8.9 Hz, H2), 5.05 (m, 1H, H6).

(2*R*)-methyl *N*-acetyl-4-ethyl-5-hydroxyprolinate **12**: $^1H$ NMR. $\delta$ 1.08 (t, 3H, $J$ = 7.5 Hz, $CH_3CH_2$), 1.31–1.73 (m, 3H, $CH_3CH_2$, H4), 2.15 (s, 3H, $COCH_3$), 2.37–2.47 (m, 2H, H3), 3.76 (s, 3H, $COOCH_3$), 4.44–4.53 (m, 1H, H2), 5.29 (m, 1H, H5).

The $CDCl_3$ solutions of **11** and **12** on storing for several hours underwent dehydration to give (2*R*)-methyl *N*-acetyl-5-methyl-5,6-didehydropipecolate **9a** in 30% yield and (2*R*)-*N*-acetyl-4-ethyl-4,5-didehydroprolinate **10a** in 17% yield respectively.

Similar reactions were carried out by varying ligand, pressure, temperature and reaction time. The results are summarised in Table 2.

**Reaction of (2*S*)-methyl 2-acetamidopent-4-enoate 5b.** *(2S)-Methyl N-acetyl-5,6-didehydropipecolate* **9b** *and (2S)-methyl N-acetyl-4-methyl-4,5-didehydroprolinate* **10b**. The (2*S*)-pent-4-enoate **5b** (74 mg, 0.43 mmol), rhodium(II) acetate dimer (1.9 mg, 4.3 μmol) and BIPHEPHOS (6.8 mg, 8.6 μmol) in deoxygenated benzene (10 mL) were reacted with $CO/H_2$ (80 psi) at 80°C for 72 h to give a brown oil (80 mg). The $^1H$ NMR spectrum indicated the pipecolate **9b** and the prolinate **10b** were present in a 66:34 ratio respectively. The two compounds were separated using column chromatography (3:1 of ethyl acetate:light petroleum).

(2*S*)-Methyl *N*-acetyl-5,6-didehydropipecolate **9b** was isolated as clear oil (38 mg, 48%), ($R_f$ 0.5). HPLC: (*S*), $t_1$ = 9.3 min (*R*), $t_2$ = 26.5 min; ee 99% (*S*). IR (neat): 3468, 1744, 1674, 1645, 1417, 1383, 1347, 1208, 1045 $cm^{-1}$. $^1H$ NMR: $\delta$ [minor rotamer in brackets] 1.80–2.12 (m, 3H, H3, H4a), 2.23 (s, 3H, [2.13, s], $COCH_3$), 2.35–2.41 (m, 1H, H4b), 3.73 (s, 3H, [3.75, s], $COOCH_3$), 4.97 (m, 1H, [5.00–5.10, m], H5), 5.24 (m, 1H, [4.65–4.66, m], H2), 6.63 (d, 1H, $J$ 8.6 Hz, H6). $^{13}C$ NMR: $\delta$ [minor rotamer in brackets] 18.9 [18.6] (C3), 21.5 ($COCH_3$), 23.3 [23.9] (C4), 51.7 [55.7] (C2), 52.3 [52.6] ($COOCH_3$), 107.1 [107.0] (C5), 125.1 [123.2] (C6), 168.5, 171.0 (C1, CONH). Calc. for $C_9H_{13}NO_3$: C, 58.99; H, 7.16; N, 7.65. Found: C, 59.01; H, 7.12; N, 7.60%. $[\alpha]_D^{20}$ −64° (*c* 0.016, $CH_3Cl$).

(2*S*)-Methyl *N*-acetyl-4-methyl-4,5-didehydroprolinate **10b** was isolated as a colourless oil (21 mg, 27%), ($R_f$ 0.3). HPLC: (*S*), $t_1$ = 12.2 min; (*R*), $t_2$ = 26.2 min; ee 99% (*S*). IR (neat): 3296, 1746, 1654, 1542, 1375, 1208 $cm^{-1}$. $^1H$ NMR: $\delta$ 1.74 (s, 3H, $CH_3C4$), 2.14 (s, 3H, $COCH_3$), 2.50 (m, 1H, H3a), 2.94 (m, 1H, H3b), 3.76 (s, 3H, $COOCH_3$), 4.82 (dd, 1H, $J$ = 11.7, 5.1 Hz, H2), 6.22 (q, 1H, $J$ = 1.8 Hz, H5). $^{13}C$ NMR: $\delta$ 13.8 ($CH_3C4$), 21.9 ($COCH_3$), 38.3 (C3), 52.8 ($COOCH_3$), 58.5 (C2), 120.2 (C4), 124.3 (C5), 165.9, 171.9 (C1, CONH). HRMS ($ESI^+$, MeOH): calc. for $(C_9H_{13}NO_3 + Na)^+$ *m/z* 206.0793, found, 206.0787 $(M + Na)^+$.

Reaction of **5b** (40 mg, 0.23 mmol) using BIPHEPHOS at 80°C, 80 psi for 20 h gave a crude oil containing *ca.* 50% of the pent-3-enoate **13** and the cyclic compounds **9b** and **10b** in a ratio of 78:22. (2*S*,3*E*)-Methyl 2-acetamidopent-3-enoate **13** was isolated as a clear oil, ($R_f$ 0.4). IR (neat): 3283, 1746, 1655, 1542, 1375 $cm^{-1}$. $^1H$ NMR: $\delta$ 1.70 (ddd, 3H, $J$ = 6.5, 1.7, 1.2 Hz, H5), 2.03 (s, 3H, $COCH_3$), 3.75 (s, 3H, $COOCH_3$), 5.03 (m, 1H, H2), 5.46 (ddq, 1H, $J$ = 15.3, 6.4, 1.7 Hz, H4), 5.77 (m, 1H, H3), 6.16 (bs, 1H, NH). $^{13}C$ NMR: $\delta$ 18.2 (C5), 23.5 ($COCH_3$), 53.0, 54.5 (C2, $COOCH_3$), 125.2, 130.3 (C3, C4), 169.6, 171.8 (C1, CONH). HRMS ($ESI^+$, MeOH): calc. for $(C_8H_{13}NO_3 + H)^+$ *m/z* 172.0974, found, 172.0964 $(M + H)^+$.

Similar reactions were carried out by varying ligand, pressure, temperature and reaction time. The results are summarised in Table 2.

**Reaction of (2*R*)-methyl 2-acetamidohept-6-enoate 5c.** *(2R)-Methyl 2-acetamido-7-formylheptanoate* **14** *and (2R)-methyl 2-acetamido-6-formylheptanoate* **15**. The (2*R*)-hept-4-enoate **5c** (70 mg, 0.36 mmol), rhodium(II) acetate dimer (1.6 mg, 3.6 μmol) and triphenylphosphine (1.9 mg, 7.2 μmol) in deoxygenated benzene (10 mL) were reacted with $CO/H_2$ (400 psi) at 80°C for 20 h to give a brown oil (80 mg). The $^1H$ and $^{13}C$ NMR spectra indicated the two aldehydes **14** and **15** were present in a 50:50 ratio. The aldehydes were partially separated using radial chromatography (ethyl acetate:light petroleum,

1:1) to give a sample of **14** and a sample of **15** containing 20% of the isomer **14**.

The (2*R*)-heptanoate **14** was isolated as a yellow oil (28 mg, 34%), ($R_f$ 0.86). IR (neat): 3296, 2938, 1744, 1657, 1542, 1438, 1438, 1375, 1211, 1167 $cm^{-1}$. $^1H$ NMR: $\delta$ [minor rotamer in brackets] 1.20–1.37 (m, 4H, H4, H5), 1.55–1.69 (m, 2H, H6), 1.77–1.83 (m, 2H, H3), 2.00 (s, 3H, [2.02, s], $COCH_3$), 2.41 (td, 2H, $J$ = 7.2, 1.7 Hz, H7), 3.75 (s, 3H, [3.72, s], $COOCH_3$), 4.62 (m, 1H, H2), 6.14 (bs, 1H, NH), 9.73 (t, 1H, $J$ = 1.7 Hz, [9.75, m], CHO). $^{13}C$ NMR: $\delta$ 24.5 ($COCH_3$), 22.1 (C6), 25.3 (C4), 29.0 (C5), 32.6 (C3), 44.0 (C7), 52.3, 52.7 (C2, $COOCH_3$), 170.0, 173.2 (C1, CONH), 202.6 (CHO). HRMS (EI, MeOH): calc. for ($C_{11}H_{19}NO_4$–$COCH_3$) $m/z$ 186.1130, found, 186.1133 (M–$COCH_3$).

The (2*R*)-heptanoate **15** was obtained as a yellow oil (24 mg, 29%), ($R_f$ 0.95) containing 20% of **14**. IR (neat): 1740, 1656, 1545, 1438, 1375, 1212, 1178 $cm^{-1}$. $^1H$ NMR: $\delta$ (1:1 mixture of two diastereoisomers) 1.10 (d, 3H, $J$ = 7.0 Hz, H7), 1.23–1.46 (m, 3H, H4, H5a), 1.58–1.90 (m, 3H, H3, H5b), 2.03 (s, 3H, $COCH_3$), 2.24–2.38 (m, 1H, H6), 3.75 (s, 3H, $COOCH_3$), 4.63 (m, 1H, H2), 6.21 (d, 1H, $J$ = 7.8 Hz, NH), 9.60 (m, 1H, CHO).† $^{13}C$ NMR: $\delta$ (1:1 mixture of two diastereoisomers) 13.8 (C7), 23.0 (C4), 30.2 (C5), 32.9 (C3), 46.5 (C6), 52.2, 52.8 (C2, $COOCH_3$), 170.1, 173.2 (C1, CONH), 204.9 (CHO). HRMS (EI, MeOH): calc. for ($C_{11}H_{19}NO_4$–$COCH_3$) $m/z$ 186.1130, found, 186.1133 (M–$COCH_3$). A similar reaction was carried out using **5c** (37 mg), rhodium(II) acetate dimer (0.9 mg, 8.4 μmol) and BIPHEPHOS (3.0 mg, 3.8 μmol) also gave a 1:1 mixture of the aldehydes **14** and **15**.

### One-pot tandem hydrogenation and hydroformylation reactions

Reactions were carried out in a 100 mL Parr autoclave (see previous conditions used for hydroformylation reactions).

### Two catalyst system

The ratio of substrate:Rh-DuPHOS:[$Rh(OAc)_2$]$_2$:BIPHEPHOS or $PPh_3$ was 100:1:1:2; $CO/H_2$ (1:1 molar mixture).

**Reaction of (2*Z*,4*E*)-methyl 2-acetamidohexa-2,4-dienoate 1a.** The (2*Z*,4*E*)-hexa-2,4-dienoate **1a** (50 mg, 0.27 mmol), [(COD)Rh-(*S*,*S*)-Et-DuPHOS]OTf, rhodium(II) acetate dimer (1.2 mg, 2.7 μmol) and triphenylphosphine (1.4 mg, 5.4 μmol) were dissolved in deoxygenated benzene (10 mL) as described previously. The autoclave was charged with hydrogen (90 psi) and the mixture was stirred for 2 h. The hydrogen was vented and the autoclave was pressurized to 400 psi of $CO/H_2$ and heated to 80 °C for 20 h to give a brown oil (50 mg). The $^1H$ NMR spectrum of the crude oil showed two compounds, the pipecolate **9a** and the prolinate **10a** in a 56:44 ratio respectively. The compounds were separated as described previously. The (2*S*)-pipecolate **9a** was isolated as a clear oil (27 mg, 51%). HPLC showed the ee as 95% (*S*). The (2*S*)-prolinate **10a** was obtained as a clear oil (16 mg, 30%). HPLC showed the ee as 99% (*S*).

**Reaction of (2*Z*)-methyl 2-acetamidopenta-2,4-dienoate 1b.** A solution of the (2*Z*)-penta-2,4-dienoate **1b** (40 mg, 0.24 mmol), [(COD)Rh-(*S*,*S*)-Et-DuPHOS]OTf, rhodium(II) acetate dimer (1.0 mg, 2.4 μmol) and BIPHEPHOS (3.4 mg, 5.4 μmol) in deoxygenated benzene (10 mL) was reacted with hydrogen at 30 psi for 3 h. The hydrogen was vented and the autoclave was pressurized to 80 psi of $CO/H_2$ and heated to 80 °C for 72 h. After work up, the $^1H$ NMR spectrum of the crude oil (40 mg) showed the pipecolate **9b** and the prolinate **10b** in a 67:33 ratio respectively as well as the isomerised alkene **13** (*ca.* 25%). The compounds were separated as described previously. The (2*S*)-pipecolate **9b** was isolated as a clear oil (17 mg, 39%). HPLC showed the ee as 97% (*S*). The (2*S*)-prolinate **10b** was obtained as a colourless oil (9 mg, 21%). HPLC showed the ee as 99% (*S*).

**Reaction of (2*Z*)-methyl 2-acetamidohepta-2,6-dienoate 1c.** *(2S)-Methyl N-acetyl-6-methyl-6,7-didehydroazepan-1-yl-2-carboxylate* **17** *and (2S)-methyl N-acetyl-5-ethyl-5,6-didehydropipecolate* **18**. The (2*Z*)-hepta-2,6-dienoate **1c** (40 mg, 0.20 mmol), [(COD)Rh-(*S*,*S*)-Et-DuPHOS]OTf, rhodium(II) acetate dimer (1.1 mg, 2.5 μmol) and BIPHEPHOS (3.9 mg, 5.0 μmol) in deoxygenated benzene (10 mL) were reacted with hydrogen at 30 psi for 2 h. The hydrogen was vented and the autoclave was pressurized to 800 psi of $CO/H_2$ and heated to 150 °C for 72 h. After work up, the $^1H$ NMR spectrum of the crude oil (40 mg) showed three compounds, (2*S*)-methyl *N*-acetyl-6-methyl-6,7-didehydroazepan-1-yl-2-carboxylate **17**, (2*S*)-methyl *N*-acetyl-5-ethyl-5,6-didehydropipecolate **18** and (2*S*)-methyl 2-acetamidoheptanoate **6c** in a 13:13:74 ratio respectively. Purification using radial chromatography (ethyl acetate:light petroleum = 1:1) gave a sample of the cyclic products **17** and **18** in a *ca.* 1:1 ratio as a yellow oil (10 mg, 24%), ($R_f$ 0.33). HRMS ($ESI^+$, MeOH): calc. for $(C_{11}H_{17}NO_3 + Na)^+$ $m/z$ 234.1106, found, 234.1097 $(M + Na)^+$.

(2*S*)-Methyl 2-acetamido-6-methyl-6,7-didehydroazepan-1-yl-2-carboxylate **17**, $^1H$ NMR: $\delta$ 1.6–2.2 (m, 6H, H3, H4, H5), 1.74 (d, 3H, $J$ = 1.3 Hz, $CH_3$), 2.09 (s, 3H, $COCH_3$), 3.70 (s, 3H, $COOCH_3$), 5.14 (dd, 1H, $J$ = 7.4, 5.2 Hz, H2), 6.10 (s, 1H, H7).

(2*S*)-Methyl *N*-acetyl-5-ethyl-5,6-didehydropipecolate **18**,$^1H$ NMR: $\delta$ 1.03 (t, 3H, $J$ = 7.4 Hz, $CH_3CH_2$), 1.78–1.90 (m, 1H, H3), 1.93–2.09 (m, 4H, H4, $CH_3CH_2$), 2.23 (s, 3H, $COCH_3$); 2.33–2.40 (m, 1H, H3); 3.71 (s, 3H, $COOCH_3$); 5.20 (m, 1H, H2); 6.39 (bs, 1H, H6).

(2*S*)-Methyl 2-acetamidoheptanoate **6c**, ($R_f$ 0.44) was isolated as a yellow oil. IR (neat) 3311, 1738, 1656 $cm^{-1}$. $^1H$ NMR: $\delta$ 0.88 (t, 3H, $J$ = 6.6 Hz, H7), 1.21–1.41 (m, 6H), 1.59–1.71 (m, 1H), 1.78–1.97 (m, 1H), 2.03 (s, 3H, $COCH_3$), 3.75 (s, 3H, $COOCH_3$), 4.61 (m, 1H, H2), 6.19 (bd, 1H, $J$ 7.2 Hz, NH). $^{13}C$ NMR: $\delta$ 14.3 (C7), 22.8 (C4), 23.6 ($COCH_3$), 25.2 (C5), 31.7, 32.9 (C3, C6), 52.5, 52.7, C2, $COOCH_3$), 169.9, 173.4 (C1, CONH). MS ($ESI^+$, MeOH): $m/z$ 224.3 $(M + Na)^+$.

### One catalyst system

The ratio of substrate:Rh-DuPHOS was 100:1; $CO/H_2$ (1:1 molar mixture).

**Reaction of (2*Z*,4*E*)-methyl 2-acetamidohexa-2,4-dienoate 1a.** The (2*Z*,4*E*)-hexa-2,4-dienoate **1a** (40 mg, 0.22 mmol) and [(COD)Rh-(*S*,*S*)-Et-DuPHOS]OTf in deoxygenated benzene (10 mL) were reacted with hydrogen at 90 psi for 2 h. The hydrogen was vented and the autoclave was pressurized to 800 psi of $CO/H_2$ and heated to 150 °C for 72 h. After work up, the $^1H$ NMR spectrum of the crude oil (40 mg) showed only the pipecolate **9a**. Purification using chromatography (ethyl acetate:light petroleum = 3:1) gave the (2*S*)-pipecolate **9a** as a clear oil (25 mg, 58%). HPLC showed the ee as 96% (*S*).

A similar reaction was carried out at 400 psi, 80 °C for 20 h gave a mixture of **9a** and **10a** (ratio 83:17) as well as *ca.* 15% of the aldehydes **7a** and **8a** ($^1H$ NMR: $\delta$ 9.76).

**Reaction of (2*Z*)-methyl 2-acetamidopenta-2,4-dienoate 1b.** The (2*Z*)-penta-2,4-dienoate **1b** (50 mg, 0.30 mmol) and [(COD)Rh-(*S*,*S*)-Et-DuPHOS]OTf in deoxygenated benzene (10 mL) were reacted with hydrogen at 30 psi for 3 h. The hydrogen was vented and the autoclave was pressurized to 400 psi of $CO/H_2$ and heated to 80 °C for 72 h. After work

† At 400 MHz using a Bruker-DRX spectrometer, all chemical shifts were the same except for the CHO peaks at $\delta$ 9.59 (d, 1H, $J$ = 1.9 Hz) and 9.60 (d, 1H, $J$ = 1.8 Hz). CHO.

up, the $^1$H NMR spectrum of the crude oil (40 mg) showed the pipecolate **9b** and the prolinate **10b** in a 54:46 ratio respectively. The compounds were separated as described previously. The (2*S*)-pipecolate **9b** was isolated as a clear oil (22 mg, 40%). HPLC showed the ee as 94% (*S*). The (2*S*)-prolinate **10b** was isolated as an oil (28 mg, 51%). HPLC showed the ee as 99% (*S*).

A similar reaction was carried out at 80 psi, 80 °C for 72 h gave **9b** and **10b** in a 74:26 ratio respectively as well as *ca.* 40% of the isomerised alkene **13**. The spectral data were consistent with those described above.

**Reaction of (2*Z*)-methyl 2-acetamidohepta-2,6-dienoate 1c.** The (2*Z*)-hepta-2,6-dienoate **1c** (40 mg, 0.20 mmol) and [(COD)Rh-(*S*,*S*)-Et-DuPHOS]OTf in deoxygenated benzene (10 mL) were reacted with hydrogen at 30 psi for 2 h. The hydrogen was vented and the autoclave was pressurized to 800 psi of $CO/H_2$ and heated to 150 °C for 72 h. After work up, the $^1$H NMR spectrum of the crude oil (40 mg) showed the (2*S*)-methyl *N*-acetyl-5-ethyl-5,6-didehydropipecolate **18** and (2*S*)-methyl 2-acetamidoheptanoate **6c** in a 33:67 ratio respectively.

The pipecolate **18** was isolated using radial chromatography (ethyl acetate:light petroleum = 1:1) as a yellow oil (5 mg, 12%), ($R_f$ 0.35). IR (neat) 3339, 2953, 1744, 1656, 1406, 1378, 1311, 1205, 1172, 1033 cm$^{-1}$. $^1$H NMR: $\delta$ 1.03 (t, 3H, $J$ = 7.4 Hz, $CH_3CH_2$), 1.78–1.90 (m, 1H, H3), 1.93–2.09 (m, 4H, H4, $CH_3CH_2$), 2.23 (s, 3H, $COCH_3$); 2.33–2.40 (m, 1H, H3); 3.71 (s, 3H, $COOCH_3$); 5.20 (m, 1H, H2); 6.39 (bs, 1H, H6). $^{13}$C NMR: $\delta$ 12.7 ($CH_3CH_2$), 21.6 ($COCH_3$), 22.6 (C4), 23.7 (C3), 28.4 ($CH_3CH_2$), 51.7 (C2), 52.6 ($COOCH_3$), 119.1 (C6), 121.7 (C5), 168.3, 171.2 (C1, CONH). HRMS (ESI$^+$, MeOH): calc. for $(C_{11}H_{17}NO_3 + Na)^+$ $m/z$ 234.1106, found, 234.1097 $(M + Na)^+$.

### Cyclic amino acids

**(2*R*)-Methyl *N*-acetylpipecolate 20.** (2*R*)-Methyl *N*-acetyl-5,6-didehydropipecolate **9a** (prepared by hydrogenation of **5a** using Rh-(*R*,*R*)-Et-DuPHOS) (59 mg, 0.32 mmol) was dissolved in methanol (5 mL) and added to a Fischer–Porter tube followed by palladium on charcoal (10%). The mixture was hydrogenated at 90 psi for 18 h. The catalyst was removed by filtration through a Celite pad and the filtrate was concentrated *in vacuo* to give the ester **20** as an oil (50 mg, 84%). $^1$H NMR:[32] $\delta$ [minor rotamer in brackets] 1.25–1.87 (m, 5H), 2.14 (s, 3H, [2.08, s]), 2.21–2.28 (m, 1H), 3.28 (m, 1H, [2.61, m]), 3.71–3.78 (m, 1H, [4.58, m]), 3.73 (s, 3H, [3.77, s]), 5.39 (m, 1H, [4.53, m]). $^{13}$C NMR: $\delta$ [minor rotamer in brackets] 21.0 [20.9], 21.8 [21.6] ($COCH_3$), 25.4 [24.6], 26.7 [27.4], 44.3 [39.3] (C6), 51.8 [52.6] ($COOCH_3$), 52.3 [56.9] (C2), 170.5 [170.3] and 171.8 [171.2] (C1, CONH). HRMS (ESI$^+$, MeOH): calc. for $(C_{10}H_{15}NO_3 + Na)^+$ $m/z$ 208.0949, found, 208.0943 $(M + Na)^+$.

**(2*R*)-Pipecolinic acid hydrochloride 21.** (2*R*)-Methyl *N*-acetylpipecolate **20** (50 mg, 0.27 mmol) was refluxed in 6 M HCl overnight. After work up, the solution was concentrated to give the salt **21** as white solid (40 mg, 89%) mp 260–264 °C (lit.[26] 256–257 °C). The $^1$H and $^{13}$C NMR spectra in $D_2O$ were consistent with literature data.[33] $^1$H NMR: $\delta$ ($CD_3OD$) 1.56–1.78 (m, 3H), 1.80–1.94 (m, 2H), 2.26 (m, 1H), 3.01 (m, 1H), 3.43 (m, 1H), 3.77 (m, 1H). HRMS (ESI$^+$, MeOH): calc. for $(C_6H_{11}NO_2 + Na)^+$ $m/z$ 152.0688, found, 152.0680 $(M + Na)^+$. $[\alpha]_D^{20}$ +10° (*c* 0.002, $H_2O$) (lit.[26] for (2R)-**21**, $[\alpha]_D^{20}$ +10.8° (*c* 2, $H_2O$)).

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