THE DESIGN OF RHODIUM AND RUTHENIUM CATALYSTS FOR ASYMMETRIC ALDOL COUPLING

by

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DECLARATION

I hereby certify that this research is a result of my own investigation which has not already been accepted in substance for any degree and is not being submitted in candidature for any other degree.

Signed:_____

C.E. RAAB

I hereby certify that this statement is correct.

Signed:_____

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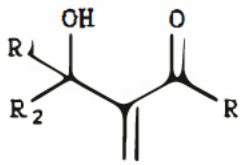
ABBREVIATIONS

Ac	-	acyl
BDPMC	-	1,2-bis(diphenylphosphinomethyl)cyclohexane
BINAP	-	bis(diphenylphosphino)-1,1'-binaphthyl
Bn	-	benzyl
Bu	-	butyl
^{t}Bu	-	tertiary butyl
Cbz	-	carbobenzoxy
c-Hex	-	cyclohexyl
Chiraphos	-	bis(diphenylphosphino)butane
COD	-	cycloocta-1,5-diene
DABCO	-	1,4-diazabicyclo[2.2.2]octane
de	-	diastereomeric excess
DIOP	-	O-isopropylidene-2,3-dihydroxy-1,4-bis-(diphenylphosphino)butane
DCPE	-	dicyclohexylphosphinoethane
DPPB	-	1,4-bis(diphenylphosphino)butane
ee	-	enantiomeric excess
Et	-	ethyl
EtOAc	-	ethyl acetate
Me	-	methyl
MeOH	-	methanol
NBD	-	norbornadiene
NMR	-	nuclear magnetic resonance
Ph	-	phenyl
^{i}Pr	-	isopropyl
Sol	-	solvent
THF	-	tetrahydrofuran
TLC	-	thin-layer chromatography
TMS	-	tetramethylsilane

SUMMARY

An investigation into the use of rhodium and ruthenium catalysts in the aldol-type coupling of α,β-unsaturated ketones and aldehydes was undertaken. This is similar to the Baylis Hillman reaction, in which the same coupling is catalysed by tertiary amines such as DABCO. The products of these coupling reactions are synthetically useful α-methylene β hydroxy carbonyl compounds **(i)**.

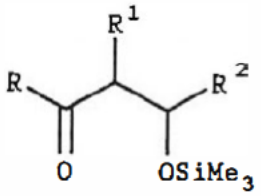


(i)

Simple rhodium and ruthenium catalysts, $[RhH(PPh_3)_4]$ and $[RuH_2(PPh_3)_4]$, were used to test the range of α,β-unsaturated compounds (such as methyl vinyl ketone, methyl acrylate and acrylonitrile) that could be coupled with a simple aldehyde such as propanal in the presence of these catalysts. It was found that both catalysts were successfully able to catalyse the coupling of methyl vinyl ketone and acrylonitrile with propanal respectively (overall yields in the range 40% to 70%), although the ruthenium catalyst did so to a larger degree. Neither catalyst was able to catalyse the coupling of methyl acrylate with propanal.

The mechanism of this catalysis involves the formation of a metal enolate intermediate. For this reason, preformed enolates

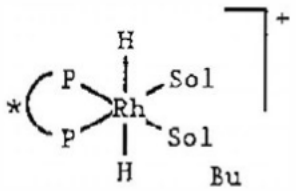
of the α,β-unsaturated ketones were also coupled with aldehydes in the presence of the catalyst $[Rh_4(CO)_{12}]$ to yield products **(ii)**.



(ii)

Enantioselective synthesis of **(ii)** was attempted by modifying the catalyst with a chiral diphosphine, however, with no success.

Chiral rhodium catalysts **(iii)** and **(iv)**, the former with chiral diphosphine ligands **(v)** to **(viii)**, were synthesised for the enantioselective direct coupling of α,β-unsaturated ketones and aldehydes.



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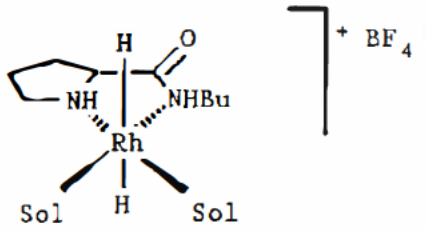
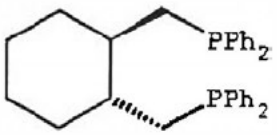


(iv)

Modest enantioselectivities were achieved in the coupling of methyl vinyl ketone and propanal using catalyst **(iii)** with ligands **(v)** to **(vii)**, and with catalyst **(iv)**. The enantiomeric excesses achieved were in the range 13% to 23%. The catalyst derived from diphosphine **(viii)** failed to catalyse the coupling reaction at all. The optical yields are low, but are novel and thus of interest. The catalytic systems and origins of asymmetry are discussed.



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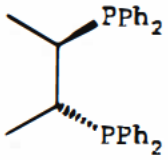

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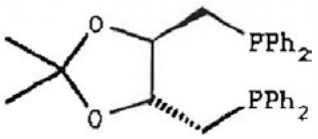

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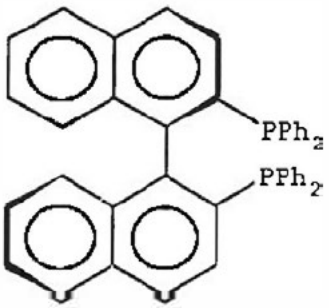
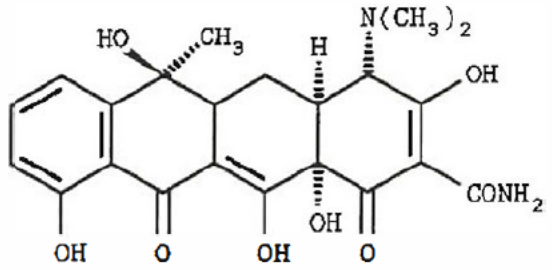


(viii)

1 INTRODUCTION

Over the last few decades, scientists have become aware that the biological activity of compounds often depends on their optical purity, in other words their degree of enantiomeric purity.[1-3] Because of the importance of biologically-active compounds, there has been a focus of activity in both academic and industrial spheres on stereochemical control in organic synthesis to produce enantiomerically pure products. These active compounds often have more than one chiral centre, with the specific activity being related to only one of the possible stereoisomers. An example is tetracycline **1** an antibiotic produced by ***Streptomyces spp.***



1

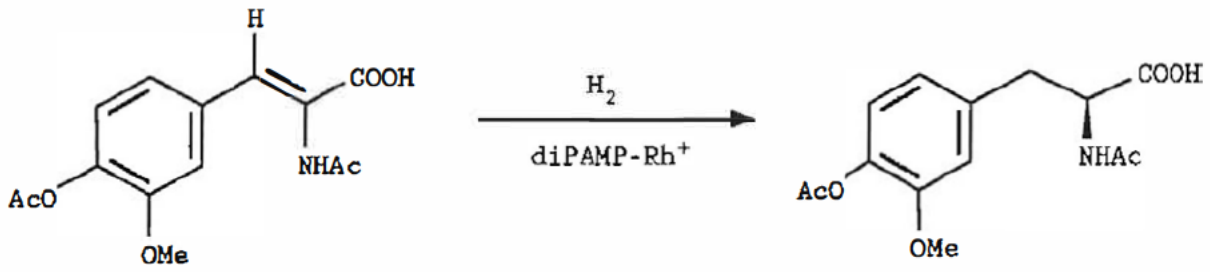
There are a number of different approaches to the preparation of enantiomerically pure compounds. Firstly, a homochiral compound may be used to convert a racemic mixture of enantiomers into diastereomers, which may then be separated in the process of resolution.[4-8] A potential disadvantage of this approach is that half of the material consists of the undesired enantiomer. A more serious drawback is that this method is not applicable to multi chiral centre molecules which are already diastereomeric. Resolution is largely an empirical method for the practising chemist.

A second approach to producing optically pure products is to use homochiral reagents.[9-11] By using homochiral reagents obtained from the "chiral pool", target molecules may be built up. Adventitious racemization of the chiral moeity must be avoided to preserve the original stereointegrity of the chiral centre. A major disadvantage of using homochiral reagents is that the original chiral molecule is of necessity consumed in the synthesis, having been incorporated into the target molecule.[12] This represents the "chiron" approach pioneered by Hannesian.[9]

A third approach is asymmetric synthesis,[1,4,13-16]an area in which considerable progress has been made in recent years. Morrison and Mosher[17] have described asymmetric synthesis as a reaction in which "an achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products are produced in unequal amounts." In other words, chirality is induced in an achiral system by a reactant that may be a chiral auxiliary, an enzyme, or a chiral catalyst. In asymmetric synthesis, enantiospecific syntheses, where one stereoisomer is formed exclusively, are rarely achieved, except in some instances where enzymes are used as catalysts.[12,18-21] Enzymes, being single enantiomers of amino acids, are able to function as the template for the synthesis of only one enantiomer of the product. For this reason enzymes are also very specific, and allow only a small range of reactants to be used in asymmetric synthesis. The use of a chiral auxiliary strategy reguires equimolar amounts of reactant and auxiliary. Unless the latter is recyclable or cheap, the process is unlikely to be cost-effective in practice.[22,23]

1.1 ASYMMETRIC CATALYSIS

The most desirable and most challenging of asymmetric reactions is catalytic asymmetric synthesis,[24-29] since one chiral catalyst molecule may in theory create millions of chiral product molecules, just as enzymes do in biological systems. This gives catalytic asymmetric synthesis a distinct advantage over traditional stoichiometric synthesis with chiral auxiliaries, especially on a large scale such as in industrial processes. The Monsanto Process[31] for L-Dopa synthesis via asymmetric hydrogenation is an example of such a strategy and was developed in the 1970s (**Scheme 1**). The further development in the 1980s of a number of industrial processes, such as the Takasago Process[25] for asymmetric isomerization, the Sumitomo Process[25] for asymmetric cyclopropanation, and the Arco Process[25] for asymmetric epoxidation, gives an indication of the emphasis being placed on research into asymmetric catalysis at this time.



Scheme 1

Asymmetric catalysis is more than likely to be the asymmetric synthetic approach of the future. This is reflected by the increasing number of research papers being published in this field.[24-30]

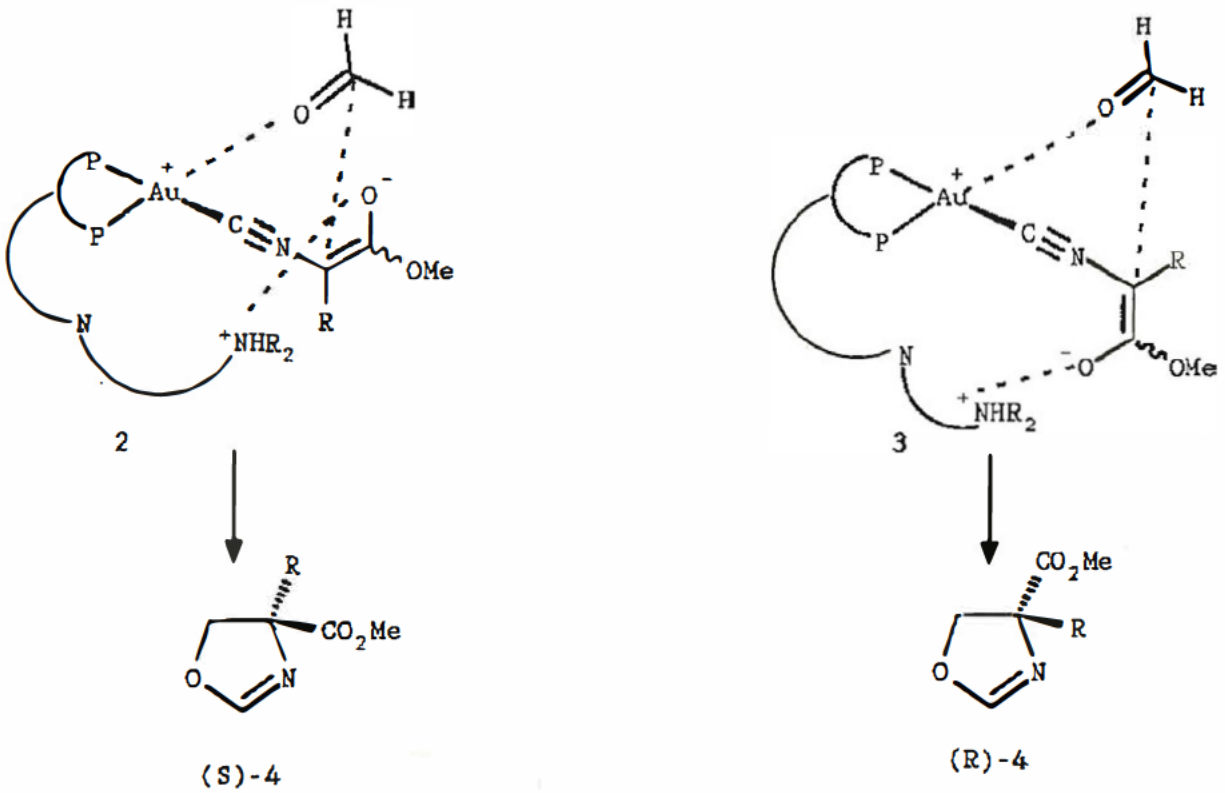
1.1.1 CATALYST FUNCTION

The majority of asymmetric catalysts, at present are metal complexes or coordination compounds. The role of the metal complex in organic synthesis is two-fold.[24] It may simply promote or catalyse a reaction which is viable even in its absence. Such a case is the Lewis-acid promoted Diels-Alder reaction in which the electrophilic character of the dieneophile is enhanced through coordination to the carbonyl oxygen.[32] Alternatively, the metal complex may be essential to the process, providing the necessary adjustment in activation energy for an achievable reaction pathway to be realised. For example, the metal complex may facilitate the cleavage of a covalent bond, without which step the reaction does not occur.

An enantioselective catalyst must not only perform the chemical catalysis (activating function), but it also has to control the stereochemical outcome of the reaction (controlling function).[26] In a catalytic process the reactive complex must be regenerated and the product released so that further reaction cycles can occur (turnover). The critical bond-forming steps may occur with one or both reactants coordinated to the metal centre. This represents "asymmetric" catalysis if a new stereogenic centre is formed during the reaction sequence. The metal provides a locus from which a reagent is delivered in the enantioselective step. If the metal centre carries optically active ligands or substituents, these may effect the relative energies of the pathways leading to the different stereoisomeric products. In favourable circumstances this can lead to a high enantiomeric excess (ee) of one of the products. The differentiation comes about through selective binding of the substrate, or alternatively through a lower intrinsic energy barrier of the rate-determining catalytic step, thereby enforcing a preferred diastereomeric pathway. In essence, the different diastereomeric pathways are a result of the two

possible transition-state complexes, which are both diastereomers. The transition state has two chiral centres, namely the fixed centre in the chiral ligand, and the newly-formed centre which can have either possible configuration. The size of the difference in transition-state energies will determine the degree of formation of the major enantiomeric product after cleavage from the metal catalyst. In general, it has been calculated that at ambient temperature a free energy difference of $\Delta G^{\ddagger}$= 12kJ/mol between the two paths, or transition states, is equivalent to an enantiomeric excess of 99%.[24] Relatively small energy differences may give rise to substantial enantioselection.

Examples of the different transition states which make up the diastereomeric pathways may be found in the gold(I) catalysed coupling of α-isocyanoacrylates and aldehydes (**Scheme 2**).[29]



Scheme 2

The transition state **2** is lower in energy than the transition state **3** and makes the diastereomeric pathway to the (S) product **4** favoured.

The impressive enantioselectivity of enzymes, which often react with one enantiomer to the virtual exclusion of the other,[33] stems from molecular recognition at the active site. This phenomenon exploits all the structural features of the substrate, for instance hydrogen-bonding sites, steric factors, remote polar groups etc. The specificity of enzymes is necessarily restricted to a narrow range of reactants, as complex biological systems have many closely-related molecules present in comparable concentrations.

In contrast, current asymmetric catalysts function by recognition of only the reaction site in their substrate, which may arise from a simple steric interaction in the region of the reaction centre, with other structural features rarely being utilised. This means that chemical catalysts have a broad substrate tolerance. Furthermore, despite the recent advances in genetic engineering for enzyme modification, the "tuning" of chemical catalysts for specific purposes can be effected much more readily. As the factors leading to greater enantioselectivity become better understood, then the possibilty of designing catalysts incorporating optimal features improves.

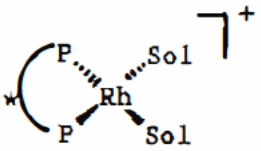
1.1.2 ASYMMETRIC TRANSFORMATIONS

Asymmetric catalysis has been used in a number of reaction types, but has been most widely studied and exploited for asymmetric hydrogenation. This is largely due to the fact that it was the basis for the first commercial catalytic process, Monsanto's L-Dopa synthesis (**Scheme 1**).[34] This acheivement by

Knowles and his collaborators spurred many chemists in the fields of catalysis, organometallic and synthetic organic chemistry, to initiate research on other related and asymmetric organic reactions.

1.1.2.1 Hydrogenation

Homogeneous Wilkinson-type catalysts **5** with a wide variety of chelating diphosphine ligands such as DIOP **6** and diPAMP **7** have afforded very high optical yields in the hydrogenation of olefins, with ee's often between 90 and 100%. They are also used for the hydrogenation of ketones, although with lower optical yields.[30]



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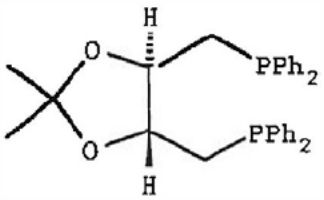
Sol = solvent



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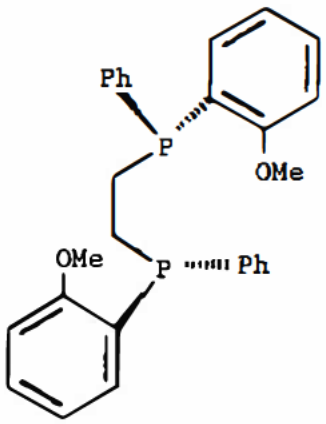

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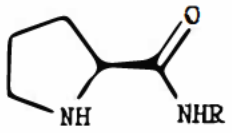
The hydrogenation of a number of substrates has been tabled by Koenig.[35] A necessity of these catalysts is that they have aryl

substituents on the phosphorus atoms of the ligands. It is the array of aryl rings in space around the metal that sterically transfers the chirality from ligand to substrate.[35,36] Corma and co-workers recently developed a chiral rhodium catalyst with a dinitrogen ligand **8** based on proline and have used it to hydrogenate olefins with ee's up to 99%.[37] The usefulness of this ligand is in the ready availability of homochiral proline as a starting material compared with the expense of corresponding chiral phosphines.



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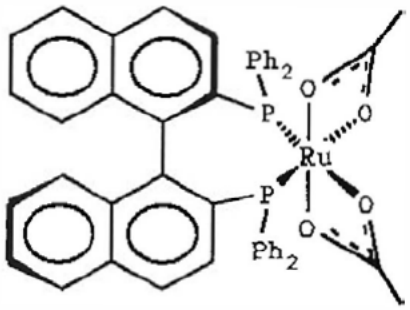
R = CMe_3 or $(CH_2)_3Si(OEt)_3$

Chiral ruthenium diphosphine complexes, such as the ruthenium η^2-acetate complex **9**, have proved more effective than many of the corresponding rhodium catalysts, being able to hydrogenate a wider range of prochiral olefins, often with greater enantioselectivity.[24,38,39]



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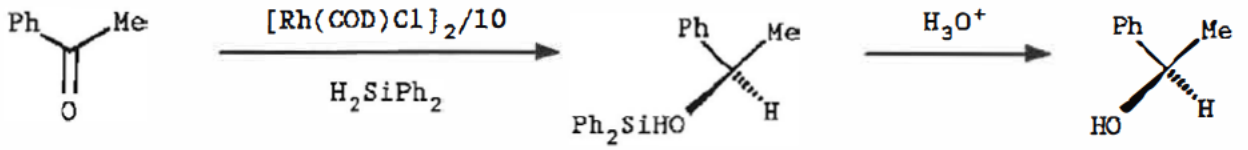
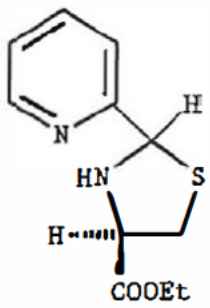
Whilst chiral catalysts have been used with varying success in a number of other asymmetric processes, few compete with the efficiency or scope of asymmetric catalytic hydrogenation.

1.1.2.2 Hydrosilylation

Asymmetric reduction of ketones via hydrosilylation by chiral rhodium complexes of the Wilkinson-type[40-43] has recently resulted in ee's of up to 97% (**Scheme 3**).[44]



97.6% (R)



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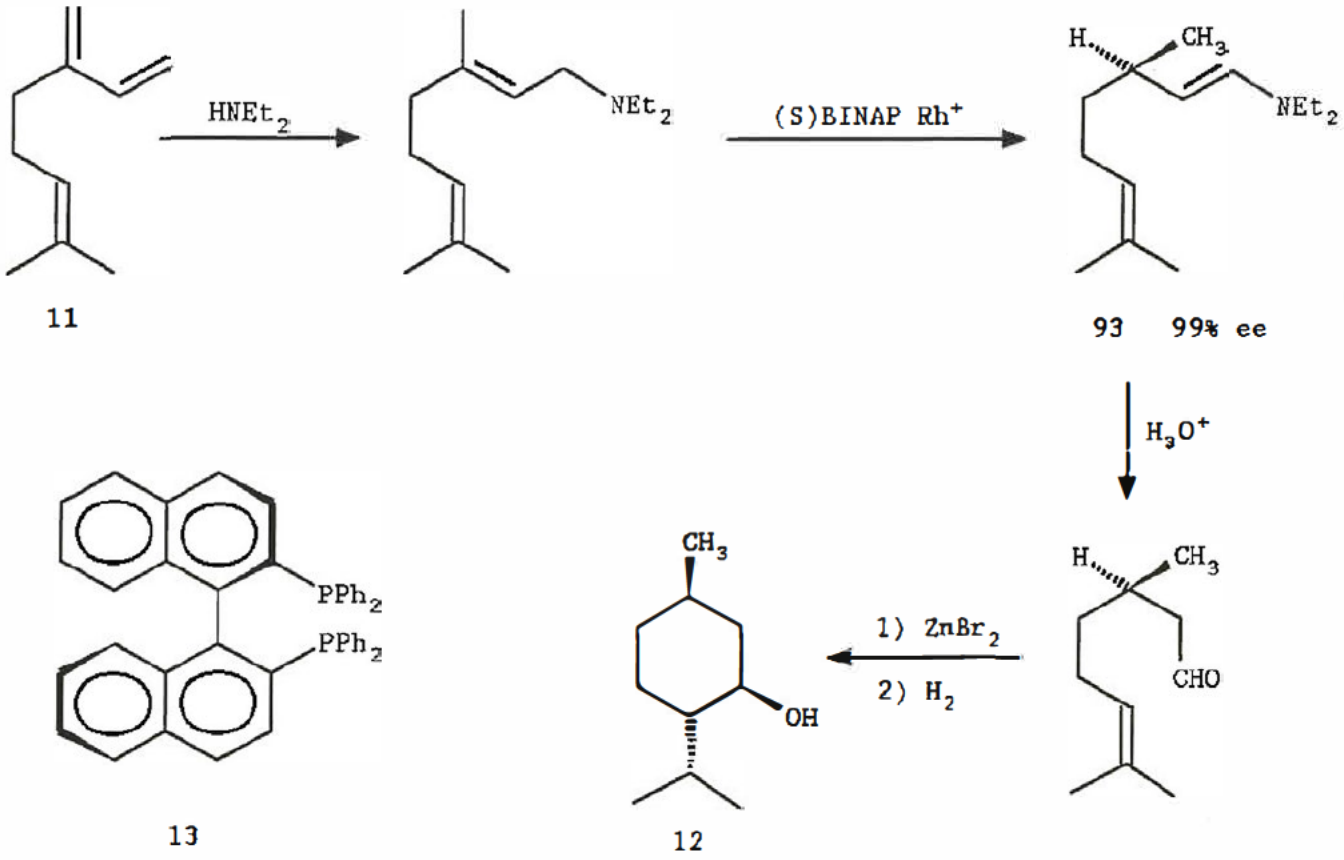
Scheme 3

1.1.2.3 Epoxidation

Advances in catalytic asymmetric oxidation processes, particularly epoxidation, have had significant impact on organic chemistry.[45] Sharpless's chiral titanium tartrate complexes are amongst the most widely used,[46] successfully catalysing the epoxidation of a wide range of substrates, often with optical yields in excess of 94%. These catalysts are the basis of the Arco Process for the preparation of glycidol.[25]

1.1.2.4 Isomerization

The Takasago Process[25] for the commercial synthesis of (-)-menthol **12** from myrcene **11** is an example of a highly successful asymmetric isomerization catalysed by a chiral Wilkinson-type rhodium catalyst bearing the ligand BINAP **13** (**Scheme 4**).[47,48]



Scheme 4

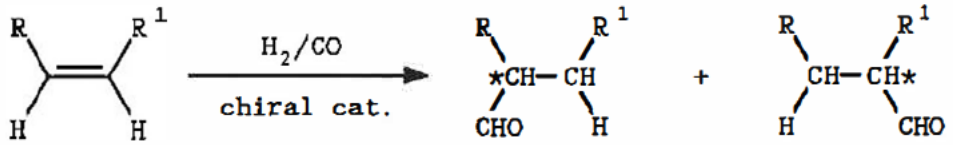
1.1.3 CARBON CARBON BOND FORMING PROCESSES.

All the catalytic processes reviewed so far, although useful, have involved functional group manipulations, and do not add to

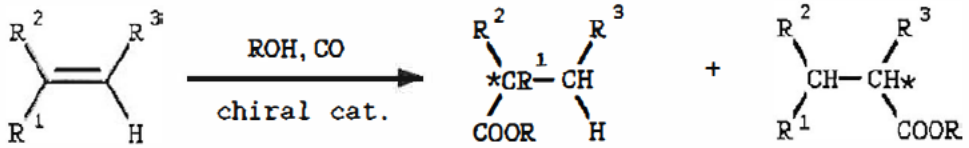
the carbon chain of the organic substrates. Carbon-carbon bond-forming processes are the backbone of organic synthesis. Whilst achiral and stoichiometric C-C bond-forming processes are well documented and successful, asymmetric catalytic equivalents are extremely rare, and not well understood.

1.1.3.1 Hydrocarbonylation

The simplest catalytic asymmetric C-C bond-forming process is hydrocarbonylation, which involves the addition of a carbonyl group (a formyl group in the case of hydroformylation and an ester in the case of hydroesterification) to the prochiral sp^2 carbon of a double bond (**Scheme 5**).[25,40,49,50]



Hydroformylation



Hydroesterification

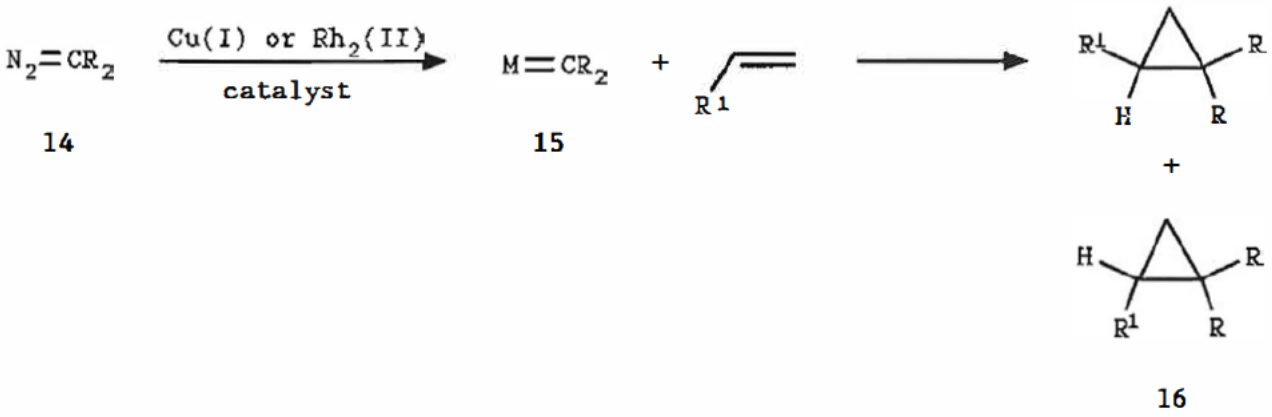
Scheme 5

The catalysts used are palladium, rhodium, or platinum/tin based, with chiral diphosphine ligands such as DIOP **6**. By fine tuning the catalyst, particularly the ligand structure, and optimising the reaction conditions (such as H_2/CO ratios and pressures), enantioselectivities of up to 98% have been

achieved.[51] The use of the process is illustrated by the oxidation of some of the chiral aldehydes obtained in order to provide a range of anti-inflammatory drugs.[52]

1.1.3.2 Cyclopropanation

A number of workers have been involved in the development of two basic catalytic systems for enantioselective carbenoid transformations, particularly the cyclopropanation of alkenes (**Scheme 6**).[27]



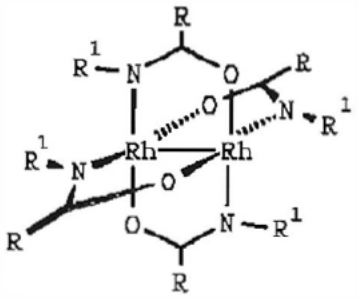
14 15 16

Scheme 6

Chiral copper(I) catalysts were developed initially by Aratani (working with salicylaldimine ligands) and Pfaltz (with semi-corrin/bis oxazoline ligands). Dirhodium(II) carboxylates or carboxamides were developed by M^{c}Kervey, Brunner, and Doyle independently. The success of a transition metal catalyst in the above reaction depends on its ability to convert a diazo compound **14** into a metal carbene with high turnover numbers, and a minimum of competing reactions. The metal-coordinated carbene **15** then reacts with a nucleophile, such as an alkene, to afford the cyclopropanation products **16**. The addition of the carbene to the alkene is the stereoselective step, and is influenced by the chiral environment created by the ligands.

The catalysts are *trans*-selective.The enantiopurity of the *trans* isomer is always higher than that of the *cis* isomer as well. Aratani-type catalysts have afforded cyclopropanes with ee's of up to 94%. Pfaltz-type Cu(I) semi-corrin/bis-oxazoline catalysts have given ee's up to 97%. Ligands developed by Evans and Masamune for Cu(I)-catalysed cyclopropanations have afforded *trans* isomers with ee's of up to 99%, and *cis* isomers with ee's of up to 97%.

Dirhodium(II) carboxylates have emerged as the most generally effective catalysts for carbenoid transformations, however the distance of the chiral centre in the ligand from the carbenoid centre seems to limit their stereoselectivity. This prompted Doyle and co-workers to develop dirhodium(II) carboxamides, in which the chiral centre is in close proximity to the carbenoid centre. These catalysts are of the general type **17**.



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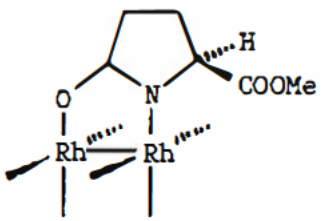

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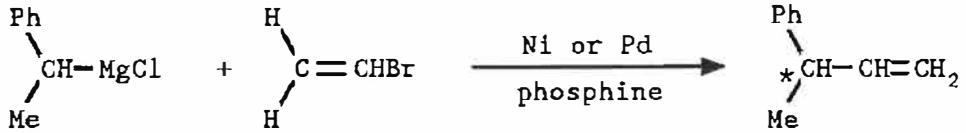
Development of the chiral proline-based ligand 5S-MEPY, shown in **18**, resulted in ee's of >94% being attained in intra molecular cyclopropanations.[27]

Hydrocarbonylation and cyclopropanation, however, only add one carbon at a time to the substrate. For this reason asymmetric coupling reactions, where two carbon chains are joined at a prochiral sp^2 centre, are of considerable importance to the synthetic organic chemist. There has recently been a significant input of research into such catalytic asymmetric

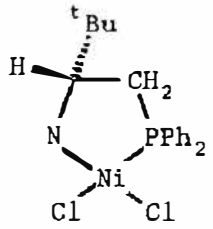
coupling reactions.

1.1.3.3 Cross-coupling with Organometallic Reagents

Asymmetric cross-coupling of alkenyl or aryl halides with organometallic reagents, effectively catalysed by the Group VIII transition metals (particularly nickel and palladium) bearing optically-active phosphine ligands, has been extensively studied by Hayashi, Kumada and co-workers.[53] Their studies included cross-Grignard couplings. A typical example is the coupling of 1-phenylethylmagnesium chloride **19** and vinyl bromide **20**, catalysed by nickel or palladium phosphine complexes (**Scheme 7**).[54]



19 **20** 0 - 83% ee



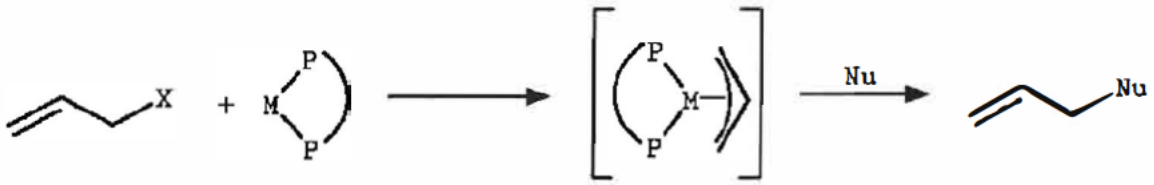
21

Scheme 7

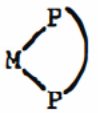
The Ni R-^{t}Leuphos complex **21** gave the highest optical yield of 83%. Alkylzinc reagents, such as 1-phenylethylzinc chloride, gave higher optical yields than the corresponding Grignard reagents in the same reactions.[55]

1.1.3.4 Allylic Alkylation

Asymmetric allylic alkylation is also catalysed by nickel and palladium diphosphine complexes, and involves the addition of a carbon nucleophile to a π-allylmetal complex **22** (**Scheme 8**).[24,25,29,53]



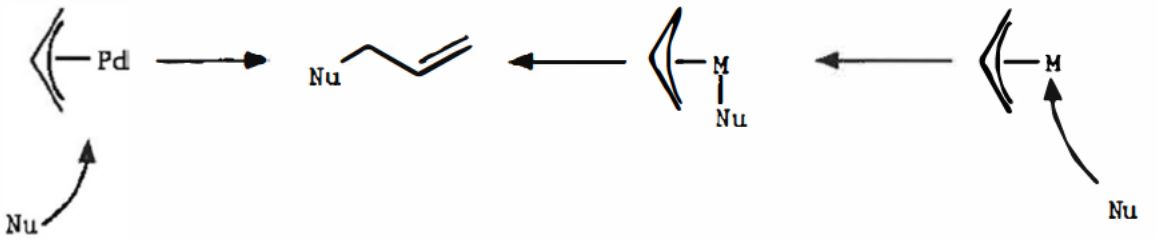
22



= Ni or Pd diphosphine

Scheme 8

Stereochemical studies have shown that a soft carbon nucleophile, such as acetylacetonate, attacks a π-allyl carbon of a palladium-allyl complex on the side opposite to the metal, whereas a hard carbon nucleophile such as a Grignard or organozinc reagent coordinates to the metal before attacking a π-allyl carbon from the same side as the metal (Ni or Pd) (**Scheme 9**).[56,57]



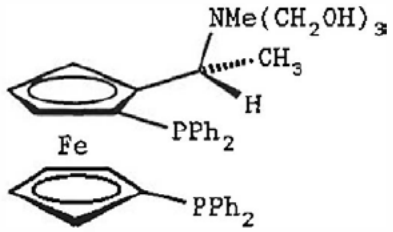
"Soft" nucleophile

"Hard" nucleophile

Scheme 9

In the asymmetric allylation with soft nucleophiles by palladium catalysts bearing traditional diphosphine ligands,

such as DIOP **6**, enantioselectivities were disappointingly low (<10% ee), as the incoming nucleophile is far removed from the chiral environment of the ligand. This has lead to the development of new ligands, which have pendant side-chains with chirotopic groups, which are able to direct the incoming nucleophile by means of a 2° coordinative interaction.[29] An example of such a ligand is the ferrocenylphosphine **23**. Hayashi *et al.* have developed a range of ligands of similar type which enhance stereoselectivty by 2° interaction with the substrate.



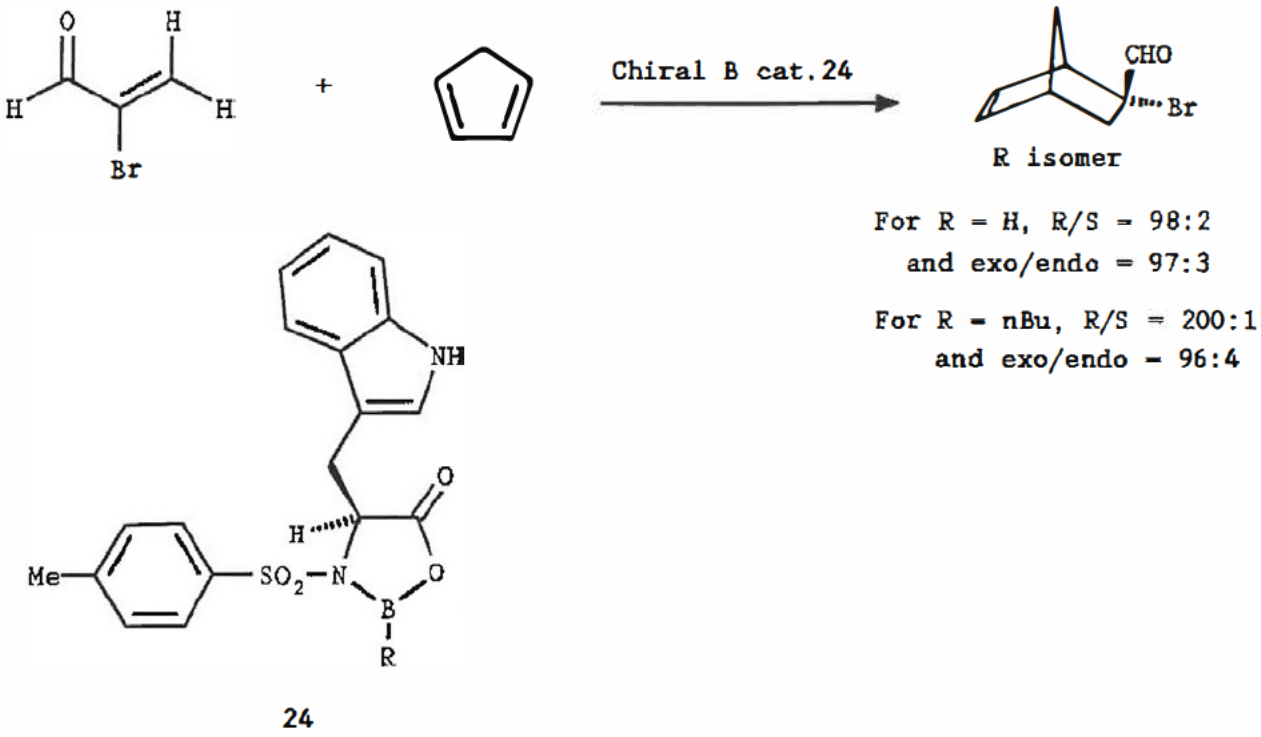
23

Ito, Sawamura,Hayashi, and co-workers have reported optical yields of up to 96% with palladium catalysts bearing ligands similar to **23**.[58] This is an example of successful catalyst design through an understanding of mechanistic detail of the reaction.

1.1.3.5 Diels-Alder Reactions

Corey and Loh have demonstrated the usefulness of chiral catalysts in asymmetric Diels-Alder reactions promoted by a chiral oxazaborolidine catalyst **24** (**Scheme 10**).[59]

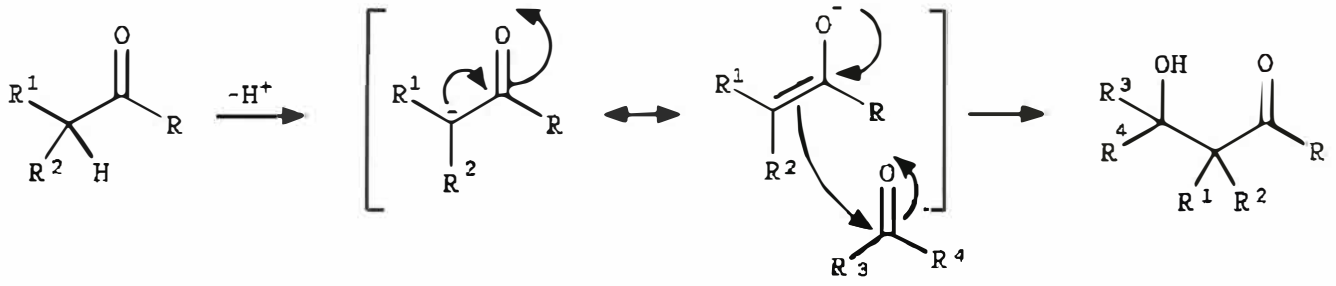
The Diels-Alder reaction holds great promise in asymmetric synthesis, because up to four new stereocentres can be formed as a result of the cycloaddition reaction. The chiral titanium catalysts of Narasaka *et al.*[60] have yielded ee's approaching 94% with endo:exo ratios of the order 95:5 in the reaction of α,β-unsaturated N-acyloxazolidinones with cyclopentadienes.



Scheme 10

1.1.4 THE ALDOL REACTION

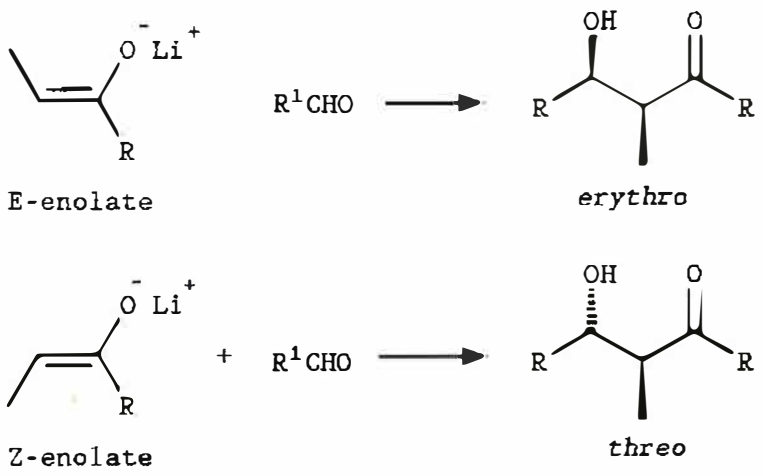
The aldol reaction remains a very useful organic synthetic procedure for coupling carbonyl compounds (**Scheme 11**). The reaction products are β hydroxycarbonyl compounds. Many biologically active compounds are of this type and can be made using aldol procedures. The β-hydroxycarbonyls are useful in having two new chiral centres and two functional groups as well.



Scheme 11

1.1.4.1 Preformed Enolates in Aldol Couplings

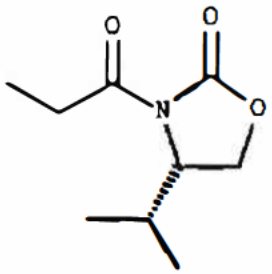
The aldol reaction may be performed on a preformed enolate instead of an enolizable carbonyl compound used in basic conditions. Stereoselectivity of the products can be controlled in this way.[61] E-enolates give rise predominately to *erythro* products, while Z-enolates produce the *threo* products (**Scheme 12**).[62]



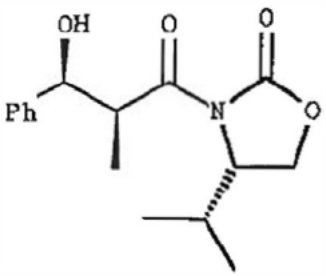
Scheme 12

The larger is the R-group in the enolate, the greater the selection for the *erythro* product. With this in mind, researchers introduced chiral auxiliaries as the R-group on the enolate. This enhances *erythro* selectivity as well as the

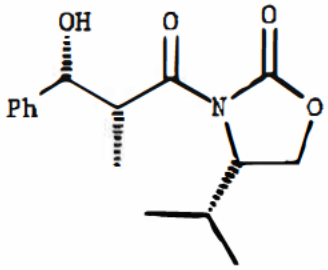
diastereoface selectivity of the enolate addition to the aldehyde. For example, the dibutylboron enolate of the Evans reagent **25** reacted with benzaldehyde, giving exclusively the *erythro* products **26** and **27**, with a diastereomer ratio of 332:1.[61]



25

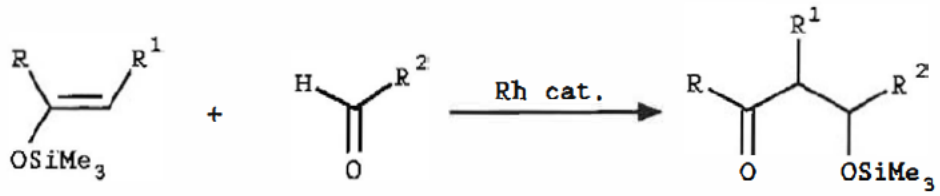


26



27

Using preformed enolates in aldol chemistry can have disadvantages. The enolates can be acid or base sensitive.[63] Matsuda and co-workers have reported the rhodium catalysed aldol coupling of enol silyl ethers with aldehydes and ketones under almost neutral conditions (**Scheme 13**).[64,65]



enol silylether

Rh cat. = $[Rh_4(CO_{12})]$ or $[(COD)Rh(DPPB)]^+ X^-$

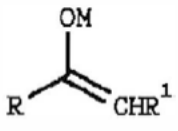
COD = 1,5-cyclooctadiene

DPPB = bis(1,4-diphenylphosphino)-butane

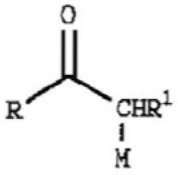
$X^- = ClO_4^-$ or PF_6^-

Scheme 13

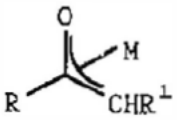
These workers proposed the intermediacy of an oxygen-bound rhodium enolate species. Oxygen-bound early transition metal enolates **28** had previously been generated *in situ*, and were found to be useful in controlling the stereochemistry in aldol reactions with aldehydes.[66] Several relatively stable carbon-bound late transition-metal enolates **29** had been generated and isolated, but were unable to induce carbon-carbon bond formations, except when converted to η^3-enolates **30** where possible.



28

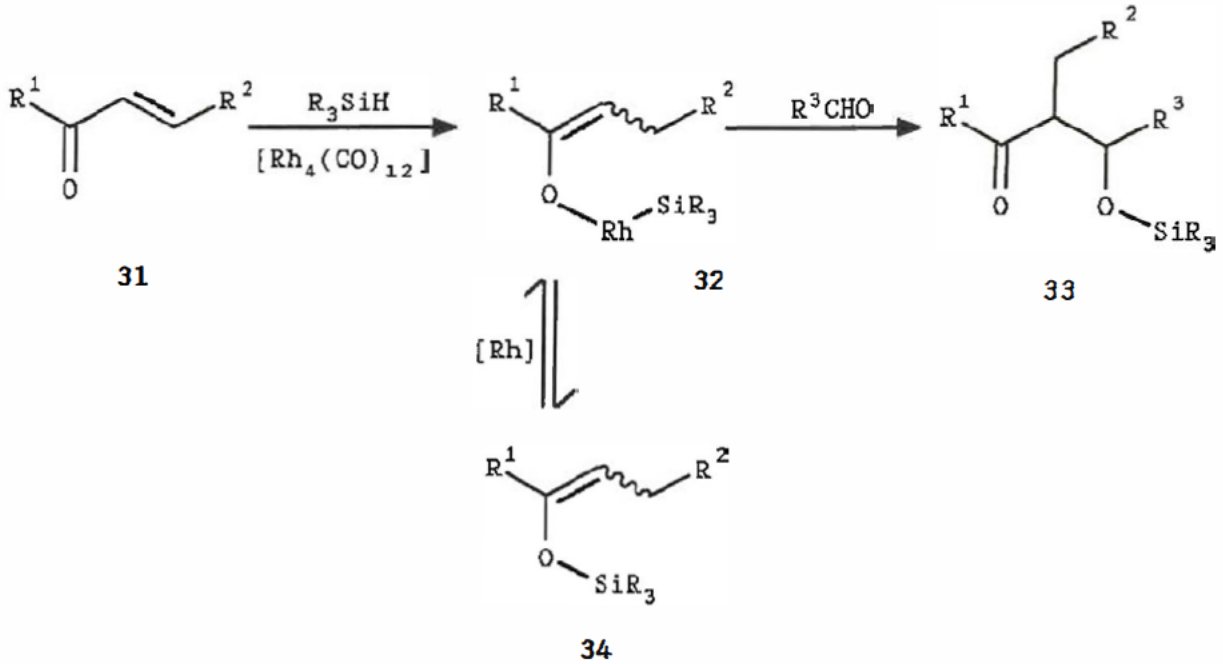


29



30

The promising use of oxygen-bound rhodium enolates **28** in C-C bond formations, prompted Heathcock and co-workers to synthesise and isolate some of these complexes and then apply them to aldol type reactions.[67] The isolation of these rhodium enolates **32** by the Heathcock group allowed Matsuda *et al*. to develop a one-pot enolization and aldol coupling reaction of an α,β-unsaturated carbonyl compound **31**, trialkylsilane and aldehyde to give the aldol product **33** (**Scheme 14**).[68]

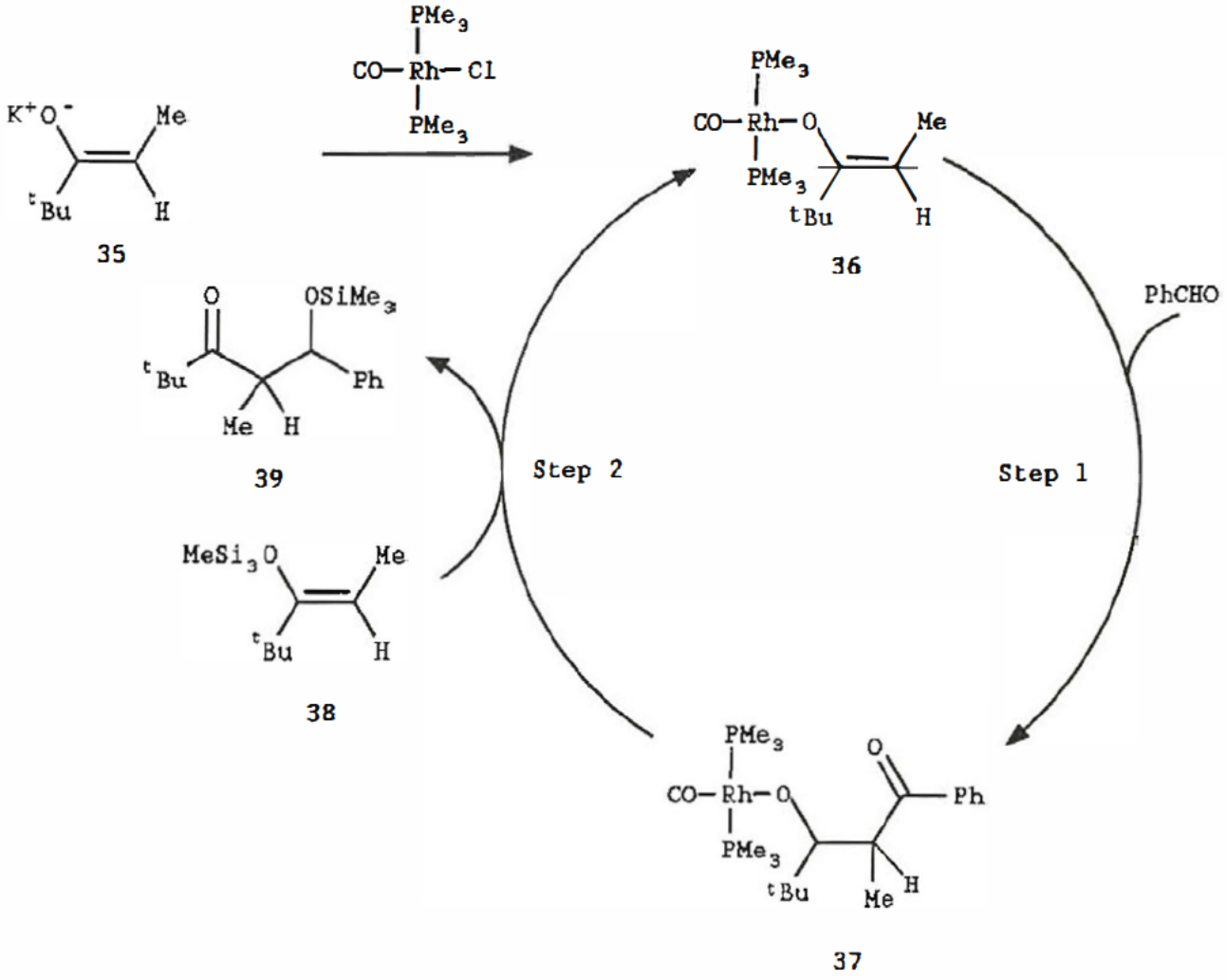


31 32 33 34

Scheme 14

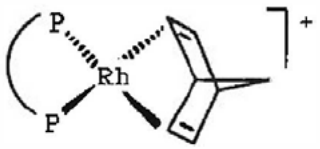
The *syn*:*anti* ratios of the products were as high as 88:12 for the most effective catalyst $[Rh_4(CO)_{12}]$.

The Heathcock group[67] prepared oxygen-bound rhodium enolates by reaction of potassium enolates **35** with rhodium halide derivatives, such as $[ClRh(PMe_3)_2CO]$. The rhodium enolates **36** reacted stoichiometrically with benzaldehyde to produce rhodium aldolate complexes **37**. The rhodium aldolate in turn reacts with an enol silane **38** (the enolate source), regenerating the rhodium enolate **36** and forming the silylated aldol product **39**. This group found that in favourable conditions, (that is excluding enolizable aldehydes, which are able to act as acids which protonate the rhodium enolate, seriously limiting the scope of the rhodium aldol chemistry) a catalytic aldol cycle could be achieved. **Scheme 15** outlines the catalytic cycle. Step 1 was found to be fast and reversible, while Step 2 was effectively irreversible under the reaction conditions.

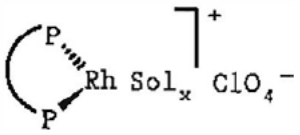


Scheme 15

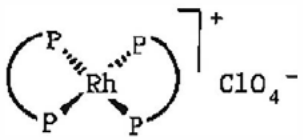
Prompted by the first reported rhodium-catalysed crossed aldol reaction by Matsuda and co-workers,[64] Reetz and Vougioukas released their results of rhodium-catalysed aldol additions.[69] They too coupled preformed enolates as enol silanes with aldehydes, using rhodium diphosphines **40-42**.



40



41

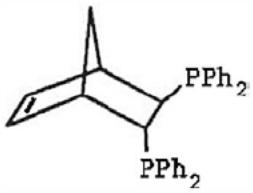


42

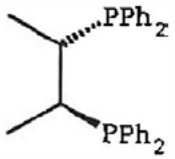
P P = $Ph_2P(CH_2)_nPPh_2$, n = 2 or 4

Sol = solvent

Their results indicate that the most effective catalyst for the coupling was **40**. They then continued to perform the first examples of enantioselective aldol additions using rhodium catalysts bearing chiral diphosphine ligands such as (R,R)-Norphos **43** and (S,S)-Chiraphos **44** on the catalysts.

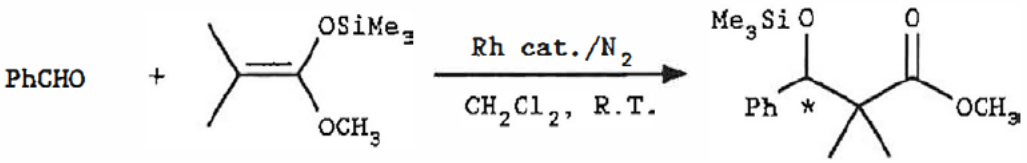


43



44

In the coupling of enol silane and aldehyde (**Scheme 16**) with Rh-Chiraphos and Rh-Norphos catalysts, the enantioselectivities achieved are low (**Table 1**), but are nevertheless significant, being novel.

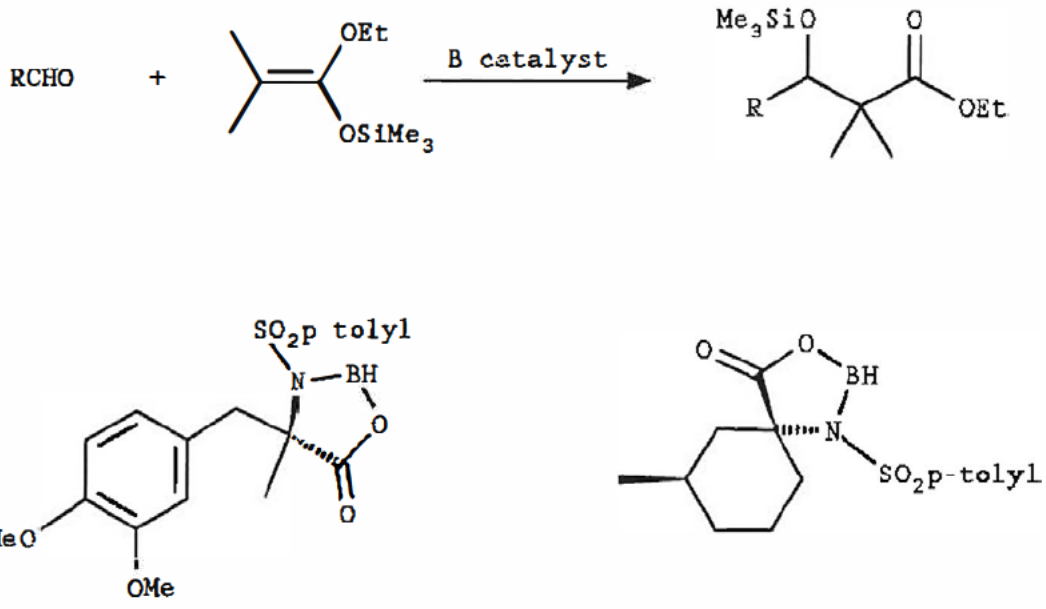


Scheme 16

Table 1

Catalyst	Mol. %	Ee(%)	Configuration
Rh-Chiraphos	5	5	S
Rh-Norphos	5	7	R
Rh-Norphos	5	12	R

Masamune and co-workers have developed a catalytic asymmetric aldol addition of enolsilanes to aldehydes, catalysed by chiral boron complexes **45** and **46** with very high enantio selectivity (**Scheme 17**).[70] The results of the reaction are shown in **Table 2**.



45 46

Scheme 17

Table 2

Entry	Aldehyde	Catalyst	Yield	Ee(%)	Configuration
1	PhCHO	45	80	84	R
2	PhCHO	46	83	91	R
3	c $C_6H_{11}CHO$	45	68	91	R
4	c-$C_6H_{11}CHO$	46	59	96	R
5	$CH_3(CH_2)_2CHO$	45	81	>98	
6	$CH_3(CH_2)_2CHO$	46	82	>98	
7	$(CH_3)_2CHCH_2CHO$	45	87	97	
8	$(CH_3)_2CHCH_2CHO$	46	89	>98	
9	$Ph(CH_2)_2CHO$	45	83	>98	
10	$Ph(CH_2)_2CHO$	46	83	>98	
11	$BnO(CH_2)_2CHO$	45	86	99	

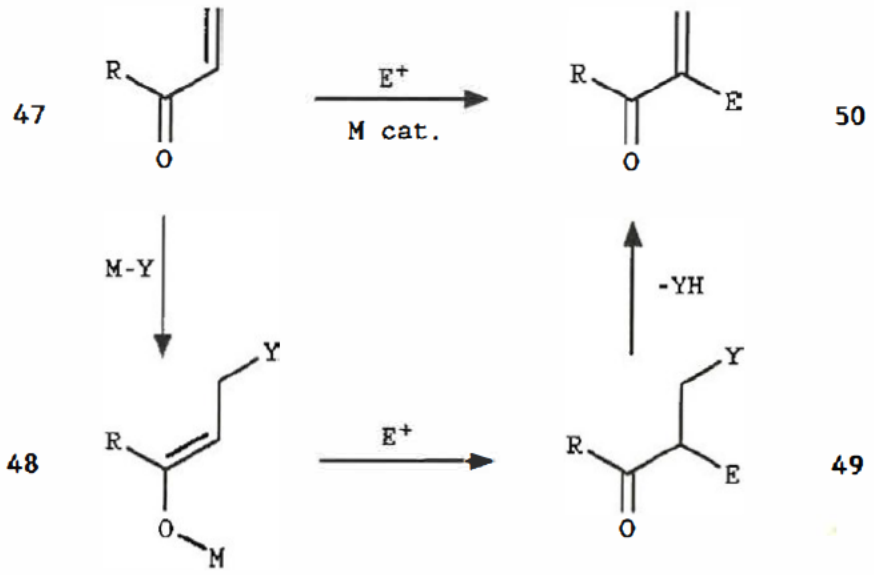
Although the mechanism is not completely understood, nor the structure of the catalysts unequivocal, the high degree of enantiopurity of the products should allow this procedure to be used by synthetic chemists.

These examples reflect the advances in the use of preformed enolates in aldol couplings.

1.1.4.2 Direct Aldol Couplings

The direct coupling of ketones and aldehydes is a more recent development. In 1985 Matsuda and co-workers reported a rhodium-catalysed, direct aldol cross-coupling of α,β-unsaturated ketones (also called α,β-enones) and aldehydes.[71] α,β Unsaturated ketones have been widely used as electrophiles at the carbonyl carbon as well as the β-carbon. To give these compounds nucleophilic character at the α-carbon is very difficult. Since the introduction of an electrophile to the

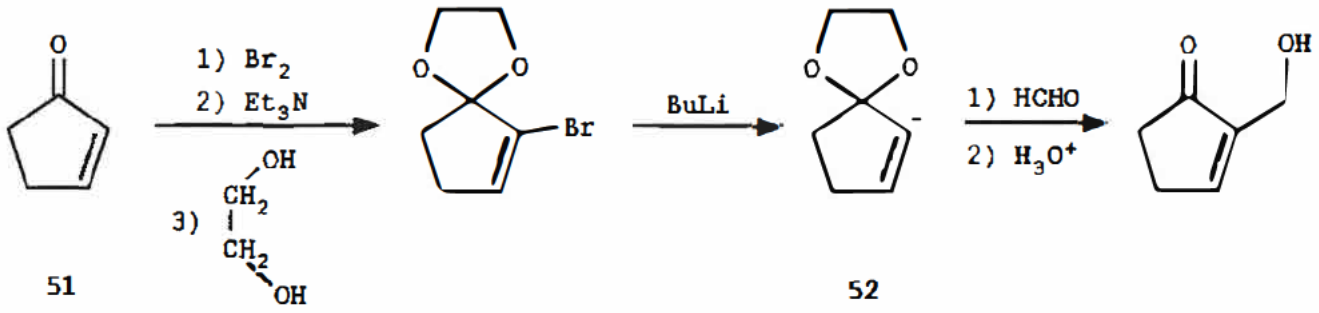
sp^2-hybridised α-position of the α,β-unsaturated ketone is an important operation, especially in carbon-carbon bond forming methodologies, a number of methods have been used to fulfil these requirements. Generally, these approaches involve a three-step procedure composed of **i)** Michael-type addition of M-Y to **47**, **ii)** attack of an electro- phile on **48**, and **iii)** elimination of Y-H from **49** to give the product **50** (**Scheme 18**).



M Y = $LiSiMe_2Ph$, R_2BSePh, $IMgSPh$, Me_2AlSPh, Bu_2BSPh, $Me_2SiSePh$

Scheme 18

Such a strategy requires the inevitable use of an equimolar amount of M-Y, which is either costly or diffcult to use. Another route used for effective electrophilic attack on the α-carbon of an α,β-unsaturated ketone is the preparation of an α-acylvinyl carbanion equivalent such as **52** (**Scheme 19**). However, many steps are required to complete the transformation from the α,β-enone **51**.

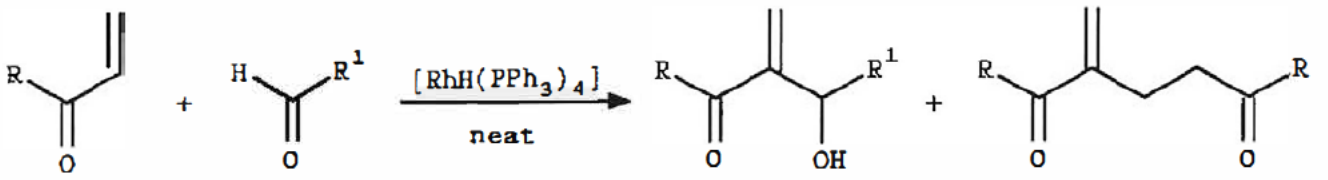


51 52

Scheme 19

Matsuda and co-workers had previously pointed out the possible intermediacy of a rhodium enolate formed by Michael-type addition of $[RhH(PPh_3)_4]$ to an α,β-enone in the synthesis of α-trimethylsilyl ketones.[72,73] They theorised that if this type of transition-metal enolate had sufficient nucleophilicity for an aldehyde, a direct transformation from **47** to **50** could be achieved through aldol-type carbon-carbon bond formation with the aid of transition-metal complexes such as $[RhH(PPh_3)_4]$ under neutral conditions.

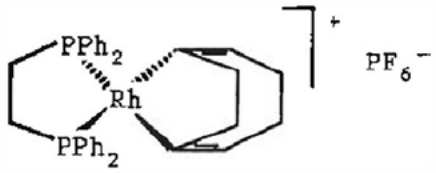
The Matsuda group did in fact achieve the catalytic aldol-type coupling of α,β-enones and aldehydes to give the desired product **53** (**Scheme 20**).[71]



53 54

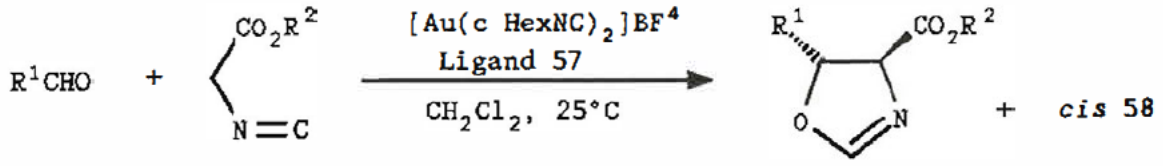
Scheme 20

Small amounts of self-condensed α,β-enone **54** were found as well. It was found that the catalysts $[Rh(COD)(Diphos)]^+PF_6^-$ **55**, when activated by H_2, and $[RuH_2(PPh_3)_4]$ were also able to catalyse the coupling reaction.[74,75] The ruthenium catalyst $[RuH_2(PPh_3)_4]$ gave greater yields of **53** than $[RhH(PPh_3)_4]$, and a better ratio of **53**:**54**. However, $[Rh(COD)(Diphos)]^+PF_6^-/H_2$ **55** gave no self-condensation product **54**.



55

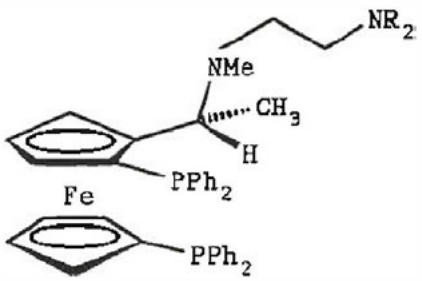
In 1986 Ito, Sawamura, and Hayashi reported the direct aldol type coupling of isocyanoacetate **56** and aldehydes by gold complexes containing chiral ferrocenylphosphine ligands **57** bearing a tertiary amino group at the terminal position of the pendant chain, giving optically active 5-alkyl-2-oxazoline-4 carboxylates **58** with high enantio- and diastereo-selectivity.[76] The *trans*-oxazolines thus obtained can be readily hydrolysed to the corresponding *threo*-β-hydroxy-α-amino acids **59** (**Scheme 21**). **Table** 3 summarises the results of coupling the isocyanate **56a** with various aldehydes.



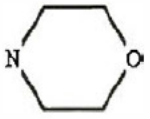
56a, R^2 = Me
b, R^2 = Et

trans-(4S,5R) 58

59

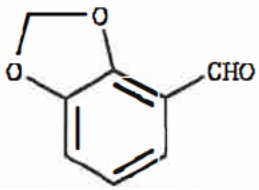


57a, NR_2 = NMe_2 c, NR_2 = 

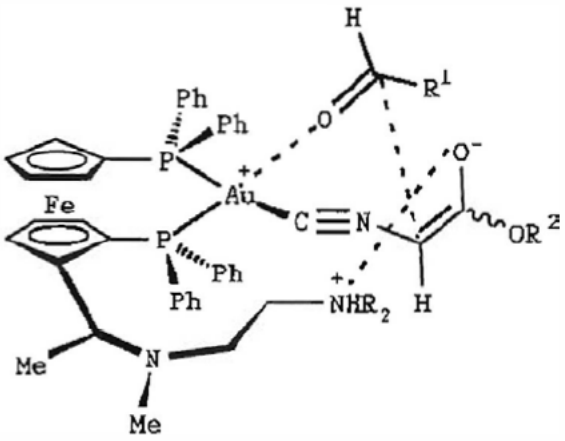
b, NR_2 = NEt_2 d, NR_2 = 

Scheme 21

Table 3

Entry	Aldehyde	Ligand	*cis/trans* ratio	%Ee of *trans* 48
1	PhCHO	57a	90/10	91
2	PhCHO	57b	89/11	93
3	PhCHO	57c	94/6	95
4	PhCHO	57d	95/5	95
5	MeCHO	57a	78/22	37
6	MeCHO	57b	84/16	72
7	MeCHO	57d	89/11	89
8	^{i}PrCHO	57a	99/1	94
9	^{t}BuCHO	57d	100/0	97
10		57d	95/5	96

The high enantio- and diastereoselectivities are remarkably dependent on the structure of the terminal amino-group of the ligand, indicating that it plays a key role in the stereo-selection. The catalyst is preprared *in situ* from a gold-isocyanate complex and the ligand, which chelates to the gold with the two phosphorous atoms, leaving the pendant chain with the two nitrogen atoms free. The terminal amino-group is thought to extract an α-methylene proton from the gold-coordinated isocyanoacetate, forming an ion-pair between enolate anion and ammonium cation. This attractive interaction permits a favourable arrangement of the enolate and aldehyde on the gold at the stereodifferentiating transition-state **60**.



60

The usefulness of the gold-catalysed aldol reaction has been illustrated by its application to the asymmetric synthesis of D-*erythro* and D-*threo*-sphingosine, an important membrane component.[77]

Recently, Hayashi *et al.* have shown that silver catalysts bearing ferrocenyl ligands **57** are also able to catalyse the same aymmetric aldol coupling, also with high enantio- and diatereoselectivity, with de's over 96% and ee's over 80%.[78] The results of the Hayashi group have shown that efficient and successful catalytic, asymmetric aldol reactions are feasible.

2 DISCUSSION

2.1 AIMS OF THIS INVESTIGATION

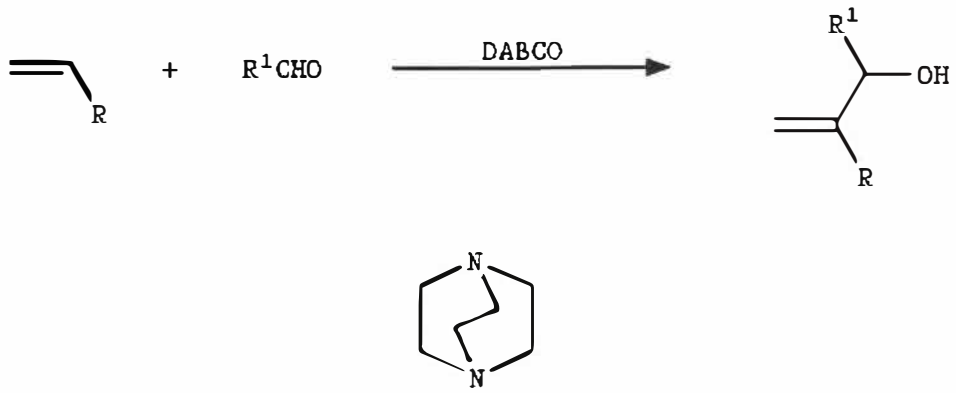
The importance of asymmetric aldol-type coupling reactions can be summarised thus: **i)** the products contain up to two new chiral centres, as well as two functional groups; **ii)** they provide a route to important natural products. The ability to perform the reaction catalytically offers major advantages over other stereoselective techniques, if significant stereoselection can be achieved. With these points in mind, the following considerations lead to the aims of the investigation which are set out on page 34.

Matsuda *et al.* pioneered the rhodium-catalysed coupling of preformed enolates (in the form of silyl enol ethers) with α,β-unsaturated ketones (**Scheme 13**).[64,65] Following the research of Heathcock and co-workers,[67] who proved the existence of oxygen-bound rhodium enolates, the Matsuda group developed a one-pot coupling of α,β-unsaturated ketones, aldehydes, and trialkylsilanes, proposing a rhodium-enolate intermediate **32** (**Scheme 14**).[68] The catalyst of choice for this coupling, Matsuda concluded, was $[Rh_4(CO)_{12}]$, and also that modification of this catalyst with monophosphines such as $MePh_2P$ improved its performance (yield and diastereoselectivity). The only enantioselective rhodium-catalysed coupling of preformed enolate and α,β-unsaturated ketone previously performed, is that of Reetz and Vougioukas[69], who achieved only modest ee's in this reaction. A logical approach to enantioselection in this type of aldol coupling reaction would be to modify the catalyst with chiral phosphine ligands.

Matsuda and co-workers also developed the direct aldol cross-coupling of α,β-unsaturated ketones and aldehydes, catalysed by

the complexes $[RhH(PPh_3)_4]$, $[(COD)Rh(Diphos)]^+PF_6^-$ **55**, and $[RuH_2(PPh_3)_4]$ (**Scheme 20**).[71,74,75] Because of the reasonably wide range of chiral diphosphine ligands available commercially, there is the possibility of preparing chiral rhodium catalysts, based on **54**, for asymmetric coupling of α,β-unsaturated ketones. Being expensive, it would be of advantage to dispense with chiral diphosphine ligands, and to use easily-derived dinitrogen ligands such as **8**, prepared by Corma *et al.* from proline.[37]

Whilst the Matsuda group performed the coupling on a variety of substrates, they did not attempt to couple α,β-unsaturated esters with aldehydes. This would give potentially very useful synthetic intermediates. Further, these coupling reactions parallel the Baylis-Hillman reaction which is the coupling of activated vinyls with aldehydes, catalysed by tertiary amines such as DABCO **61** (**Scheme 22**).[79]

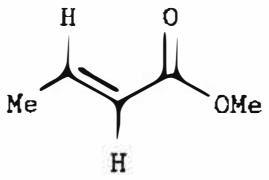


61

Scheme 22

A major area of research in our department is asymmetric Baylis-Hillman couplings using chiral auxiliaries either on the vinyl moiety or the aldehyde. It would be beneficial if the analagous rhodium-catalysed coupling reaction (of the Matsuda

type) could be performed in an enantioselective manner, using a chiral rhodium catalyst. Furthermore, the coupling of aldehydes with crotyl-type vinyl systems, such as methyl crotonate **62**, does not proceed with DABCO (except under high pressure),[80] although recent results have shown that Bu_3P (tributyl phosphine) may prove more successful in catalysis of the coupling.[81]



62

The aims of the investigation were thus:

(a) to investigate the possibility of enantioselective one-pot coupling of α,β-unsaturated ketones, aldehydes, and trialkylsilane by using a chiral $[Rh_4(CO)_{12}]$-based catalyst.

(b) to determine the scope of the direct coupling of α,β-unsaturated ketones and aldehydes by varying the vinyl component of the reaction to include systems such as crotonates, as well as varying the catalysts.

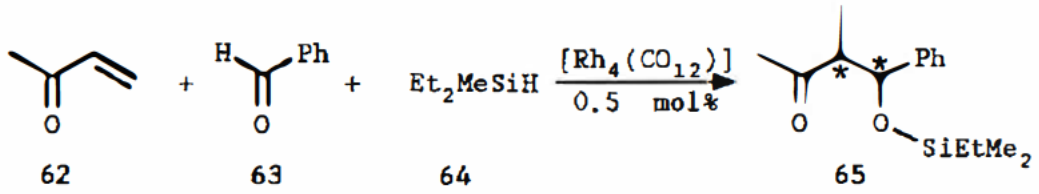
(c) to investigate the use of chiral rhodium catalysts based on $[(COD)Rh(Diphos)]^+PF_6^-$ in the enantioselective coupling of α,β-unsaturated ketones (or other activated vinyl systems) with aldehydes.

(d) to investigate the use of chiral rhodium catalysts bearing dinitrogen ligands similar to **8** in the direct coupling of α,β-unsaturated ketones and aldehydes.

2.2 RHODIUM-CATALYSED ALDOL COUPLING OF α,β-UNSATURATED KETONES, ALDEHYDES, AND TRIALKYLSILANE

Matsuda and co-workers were the first researchers to investigate the one-pot coupling of α,β-unsaturated ketones, aldehydes, and trialkylsilanes.[65] Armed with the reported knowledge that rhodium-bound enolates **32** exist, and that rhodium(I) complexes are able to catalyse the hydrosilylation of α,β-unsaturated ketones **31**, these workers realised that amalgamation of the reactions **34** to **33**, and **31** to **34** could provide a direct synthesis of aldol-type compounds from α,β-unsaturated ketone, aldehyde, and trialkylsilane through intervention of the rhodium enolate **32** (**Scheme 14**).

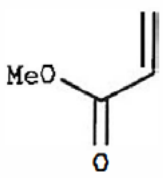
Matsuda and co-workers performed the one-pot coupling of methyl vinyl ketone **62**, benzaldehyde **63**, and diethylmethyl silane **64** to give the aldol type product **65** *syn*-selectively in the presence of a number of rhodium catalysts, but found $[Rh_4(CO_{12})]$ to be the most efficient (**Scheme 23**).



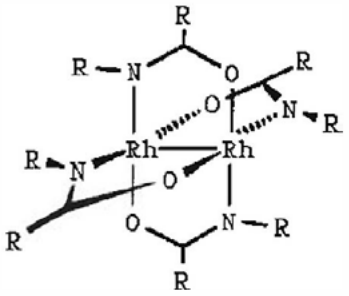
Scheme 23

We then repeated the same $[Rh_4(CO)_{12}]$-catalysed coupling as Matsuda (**Scheme 23**) in order to develop and optimise a coupling method. Although the yields that were obtained were slightly lower than those published by the Matsuda group (60% as oppose to 64%), the *syn:anti* ratios afforded for the same general reaction conditions were comparable. (Matsuda reported a *syn:anti* ratio of 81:19, whilst our result gave 78:22).

Although the Matsuda group reported the coupling of a number of α,β-unsaturated carbonyl compounds with aldehydes, there was no mention of reaction or attempted reaction with α,β-unsaturated esters. This type of coupling is of particular interest to researchers in our department. Coupling of methyl acrylate **66** with benzaldehyde and Et_2MeSiH in the presence of $[Rh_4(CO)_{12}]$ did not proceed, despite increasing reaction time and catalyst concentration. The first step of the coupling reaction involves formation of the silyl enolate by addition of hydride from Et_2MeSiH to the activated vinyl system of the methyl vinyl ketone. The vinyl system needs to be sufficiently electrophilic to accept the hydride. The electron-donating methoxy group deactivates the double bond relative to methyl vinyl ketone **71** so that no hydride addition can take place, and hence no formation of an enolate, without which reaction cannot proceed.



66

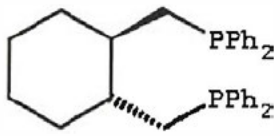


67

The range of catalysts which are able to catalyse the coupling is quite large, including $RhCl_3.H_2O$,[82] $[Co(DPM)_2]$,[83] $[RhH(PPh_3)_4]$, $[RhCl(PPh_3)_4]$, and $[(COD)Rh(DPPB)]X$ (X = PF_6 or ClO_4).[65] Because dirhodium acetates such as $[Rh_2(OCOCH_3)]_4$ are well characterised, and the use of similar chiral complexes well documented (particularly in carbene insertion reactions), it was decided to try this specific catalyst in the one pot coupling reaction above (**Scheme 23**). If successful, this would provide a promising route into an asymmetric catalysis of the coupling reaction, through the use of related chiral dirhodium complexes of the type **67**. However, no coupling product **65** was detectable at all in the presence of $[Rh_2(OCOCH_3)_4]$, even when

the concentration of the complex was increased from 0.5mol% to 2 mol%, and the temperature from 25° to 60°C.

Asymmetric catalysis was then attempted by its modification of the catalyst with a chiral diphosphine ligand. Matsuda *et al.* had previously reported improved yields of aldol-type products and *syn:anti* ratios when the $[Rh_4(CO)_{12}]$ catalyst was modified by monophosphines such as $MePh_2P$, Ph_3P, and Bu_3P; and diphosphines like DPPB and DCPE.[65] Strongly coordinating phosphines are able to substitute highly labile carbon monoxide from the rhodium metal cluster, leaving the tetra-nuclear metal framework intact.[84,85] In this investigation, the chiral diphosphine used was (1S,2S)-(+)-trans-1,2-bis(diphenylphosphinomethyl)cyclohexane (BDPMC) **68**.



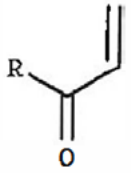
68

The modified catalyst was prepared *in situ*, and the reactants then added under the appropriate conditions. However, the results showed that the enantiomeric excess achieved was a mere 0.3%, which is negligible within experimental error. The *syn:anti* ratio was 81:19. The ratio for the $MePh_2P$ modified catalyst was 83:17 under the same conditions. A possible reason for the poor enantioselection may be in the manner of bonding of the diphosphine to the rhodium cluster. ^{31}P NMR data indicate that bonding of the phosphine did occur, with unbound **68** appearing as a sharp singlet at -20.96ppm and the $[Rh_4(CO)_{12}]$/**68** mixture giving a broad peak at 27ppm. A number of small peaks give the signal an upfield shoulder, making the interpretation more difficult. No free diphosphine signal was observable, indicating that reaction was complete. The broadness of the peak may be due to fluxionality of the

diphosphine ligand, which would not affect the activating function (chemical catalytic role) of the complex. This would, however, affect its enantioselectivity, which relies on a rigid and structurally stable chirotopic moiety to transfer chirality. Another possibility is that the usually bidentate ligand binds in a pendant fashion, in other words, through only one of the two phosphorus atoms. This would allow free rotation around the metal-phosphorus bond which might preclude a rigid structure capable of transferring chirality to the substrate. From a chemical point of view, the electron-rich phosphine is still able to enhance the catalyst function as long as it is coordinated to the cluster.

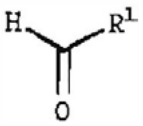
2.3 VARIATION OF THE SCOPE OF THE DIRECT COUPLING OF α,β-UNSATURATED KETONES AND ALDEHYDES

The direct coupling of α,β-unsaturated ketones and aldehydes catalysed by rhodium and ruthenium complexes was developed by the Matsuda group (**Scheme 20**).[71,74,75] The importance of the reaction is that it enables the addition of an electrophile to the sp^2 hybridised α-position of an α,β-unsaturated ketone in one step, under almost neutral conditions. This is normally a difficult procedure, other methodologies requiring more steps, which makes them more costly and/or troublesome to carry out (**Schemes 18** and **19**). Synthetically, the products **53** of these reactions are very useful, having three consecutive carbons functionalised differently. Such functional groups can be transformed into a variety of others by conventional means. The Matsuda group confined their range of α,β-unsaturated ketones **69** and aldehydes **70** to simple alkyl and aryl derivatives.



69

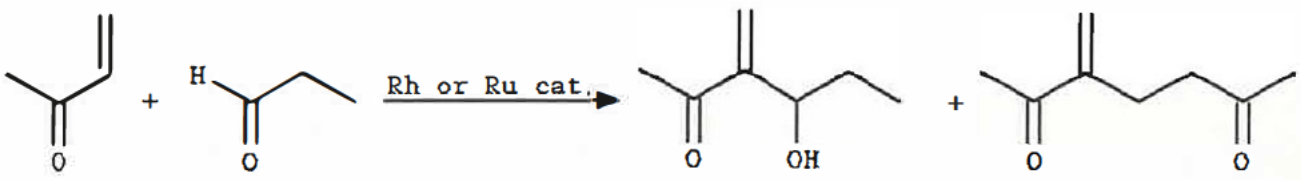
R = Me, Et, n-C_5H_{11}, n-C_8H_{17}, Ph, 2-Methylpropyl, 1-Ethylpentyl, Cyclohexyl, 2-Phenylethyl



70

R^1 = Et, n-C_3H_7, Ph, 2-Methylpropyl, 1-Methylethyl, 1-Ethylpentyl

Matsuda and co workers tested their catalysts under different conditions using the coupling of methyl vinyl ketone **71** and propanal **72** as the standard test reaction (**Scheme 24**). They found that the desired cross-coupling aldol product **73** was formed predominately, as opposed to the self-coupling product **74** of the α,β enone **71**. When the substrates **69** and **71** bore phenyl substituents, the yield of the cross-coupling product **53** was lowered (**Scheme 20**). In fact their results show that an increase in bulk of the aldehyde substituent increased the dimerisation of the vinyl ketone, giving **74** in greater yield.[75]

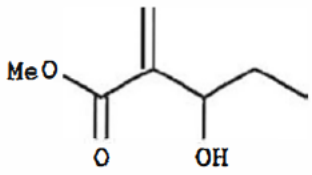


71 72 73 74

Scheme 24

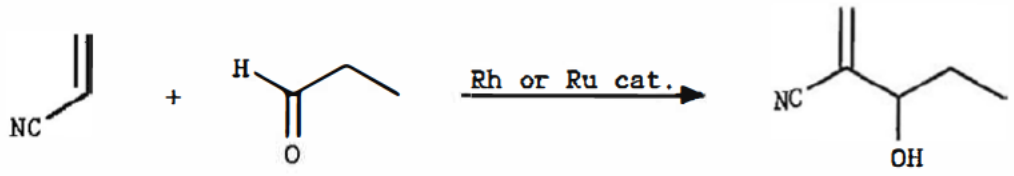
Having repeated the results of the coupling reaction in **Scheme 24** with [$RhH(PPh_3)_4$] **75** and [$RuH_2(PPh_3)_4$] **76**, an attempt was

then made to couple an α,β-unsaturated ester, methyl acrylate **66**, with propanal to give the product **77**. As stated before, this type of coupling has wider applicability in synthetic chemistry than **73**, having the more versatile ester as opposed to a ketone at the end of the carbon chain.



77

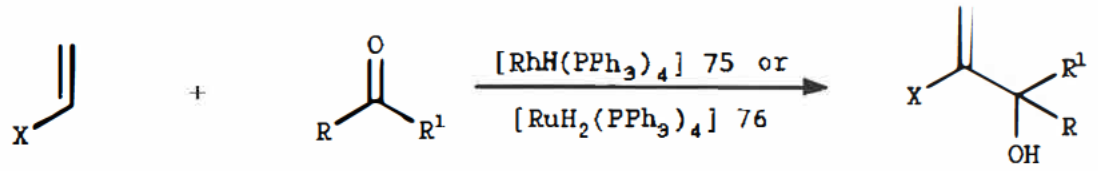
However, no coupling of methyl acrylate with aldehyde occurred at all despite the use of harsher reaction conditions. This then forced us to try a different route to obtain the same type of product. The method used was to couple acrylonitrile **78**, a more activated vinyl system than methyl acrylate, with propanal to give the product **79** (**Scheme 25**). The nitrile group is easily hydrolysed to the corresponding acid by treatment with base (for example aq. $NaOH/H_2O_2$),[86] from which the ester **77** or other derivatives may be formed.



78 **72** **79**

Scheme 25

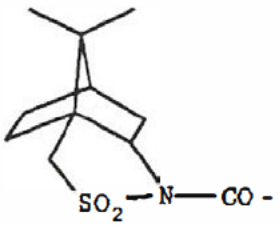
The coupling of various activated vinyl systems with carbonyl compounds by the catalysts $[RhH(PPh_3)_4]$ and $[RuH_2(PPh_3)_4]$ (**Scheme 26**) under various conditions is recorded in **Table 4**.



66, X = -COOMe
71, X = -COMe
78, X = -CN
80, X = 81

72, R = H, R^1 = Et
82, R = Me, R^1 = Me
83, R = H, R^1 = Ph

73a, X = -COMe, R = H, R^1 = Et
73b, X = -COMe, R = Me, R^1 = Me
77a, X = COOMe, R = H, R^1 = Et
77b, X = COOMe, R = Me, R^1 = Me
77c, X = -COOMe, R = H, R^1 = Ph
79, X = -CN, R = H, R^1 = Et
84, X = 81



81

Scheme 26

The results of the coupling of methyl vinyl ketone **71** with propanal **72** (Entries 1 to 3) show firstly the temperature dependence of the catalysis, with the higher temperature obviously being the more favourable; and secondly that the ruthenium catalyst is the more efficient at effecting the coupling.

The coupling of methyl acrylate **66** with propanal was attempted because, as explained previously, the aldol-type cross-coupling product **77** is more versatile than **73**. Despite using forcing conditions such as increased reaction times, temperatures, catalyst concentrations, and pressures, coupling would not proceed. The use of $[RuH_2(PPh_3)_4]$, which was found to be more efficient as a catalyst than $[RhH(PPh_3)_4]$ in the present work as well as in the research of Matsuda and co-workers,[75] did not effect the coupling reaction. Because water was found to be a

Table 4

Entry	Vinyl	Carbonyl	Catalyst(mol%)	Temp.(°C)	Time(h)	Pressure(atm)	Result(%yield)
1	71	72	75 (0.6)	40	40	1	73a (15)
2	71	72	75 (0.6)	105	2	1	73a (40)
3	71	72	76 (0.6)	105	4	1	73a (72)
4	71	73	75 (0.6)	105	4	1	73b (0)
5	66	72	75 (0.6)	105	2	1	77a (0)
6	66	72	75 (0.6)	40	68	1	77a (0)
7	66	72	75 (0.6)	105	5½	1	77a (0)
8	66	72	75 (0.6)	130	20	1	77a (0)
9	66	72	75 (2 9)	105	4	1	77a (0)
10	66	72	75 (4.3)	105	4	1	77a (0)
11	66	72	75 (0.6)	105	2	5	77a (0)
12	66	72	75 (0.6)	105	2	8	77a (0)
13	66	72	76 (0.6)	105	4	1	77a (0)
14	66	72	76 (2.5)	105	8	1	77a (0)
15	66	73	75 (0.6)	105	24	1	77b (0)
16	66	83	75 (0.6)	105	17	1	77c (0)
17	78	72	75 (0.6)	105	4	1	79 (24)
18	78	72	75 (5.3)	105	4	1	79 (45)
19	78	72	75 (0.6)	105	3	7	79 (30)
20	78	72	76 (0.6)	105	4	1	79 (55)
21	80	72	75 (1.0)	105	6	1	84 (0)

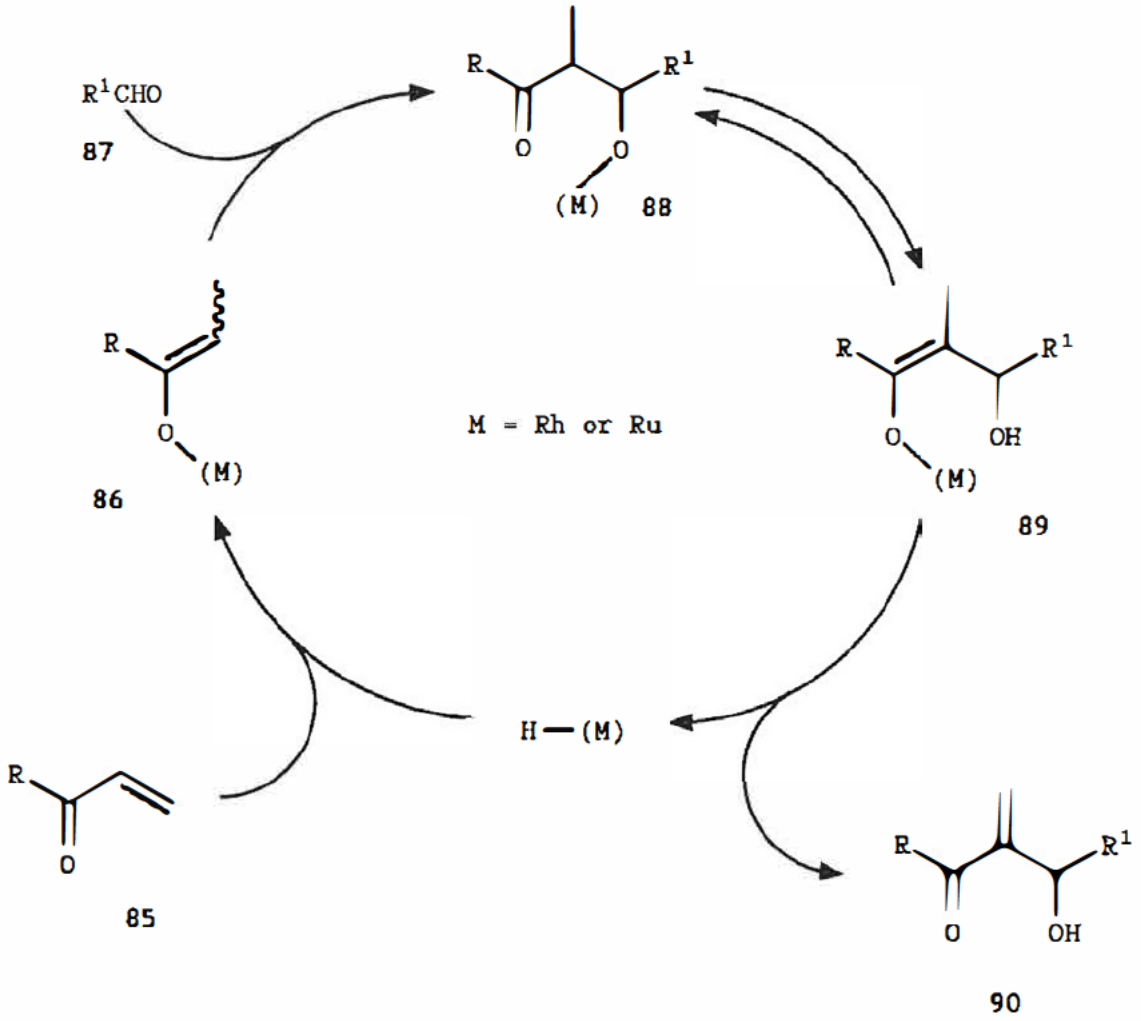
by-product after reaction of both **66** and **71** with propanal, it was suspected that self-coupling of the aldehyde was occurring. For this reason, propanal was replaced with a less reactive carbonyl compound, acetone **82** (Entries 4 and 15), or a non-enolizable aldehyde, benzaldehyde **83** (Entry 16). Presumably

acetone was not reactive enough to couple with propanal (Entry 4), whilst methyl acrylate was unable to couple with either carbonyl compound (Entries 15 and 16).

The coupling of acrylonitrile **78** with propanal was an attempt to circumvent the lack of reactivity of methyl acrylate. Although the procedure is longer, the same type of product can be obtained. Entries 17 to 20 show that the coupling reaction is sluggish at low catalyst concentrations (for $[RhH(PPh_3)_4]$), but the yield may be improved by performing the reaction under a pressure of nitrogen, or by increasing the proportion of catalyst. $[RuH_2(PPh_3)_4]$ proved once again to be more efficient than the rhodium catalyst. Low yields of the coupling product **79** may be due to insertion of the nitrile group into the metal hydride bond.

The N-acryloyl camphor sultam **81** was reacted with propanal purely on a one-off basis. This particular type of coupling is usually performed in our department under Baylis-Hillman conditions using DABCO as catalyst. Had the coupling proceeded, it would have provided an interesting and useful application for this type of catalyst.

The Matsuda group has proposed a mechanism for the coupling reaction. This involves a rhodium or ruthenium enolate as an intermediate.[75] The fact that rhodium enolates have been isolated by Heathcock and co-workers previously,[67] and that they have been proposed as intermediates in the rhodium-catalysed isomerization of β-trimethylsilylallyl alcohols[72,73,87,88] and cross-aldol reactions of enol trimethylsilyl ethers,[64,65,67,89] lends weight to this theory. The reaction mechanism proposed by Matsuda is shown in **Scheme 27**.



Scheme 27

The catalytic cycle is initiated by the Michael-type addition of metal hydride to an α,β-enone **85** to give the metal-bound enolate **86**, which undergoes aldol-type addition of aldehyde **87** to give the metal-bound aldolate **88**. Keto-enol tautomerism gives equilibration of **88** and **89**. Retro-Michael-type elimination regenerates the metal hydride and releases the aldol-type product **90**.

The formation of the self-coupling product of the α,β-enone, such as **74** (**Scheme 24**), can be explained by the 1,4-addition of **86** to **85**. Self-coupling products from the coupling of methyl

vinyl ketone **71** and acrylonitrile **78** with propanal were not isolated in this study, but Matsuda and co-workers report that the ratios of self-coupling to cross-coupling products (**53**:**54** in **Scheme 20**) are dependent on steric and electronic factors of the substrates.

The proposed mechanism of the catalytic cycle in **Scheme 27** is initiated by the addition of a hydride from the metal catalyst to the α,β-enone. Should the vinyl system not be sufficiently activated by an electron-withdrawing group, it may not be electrophilic enough to add the hydride at all. Hence no enolate would be formed and the cycle would not proceed. This may provide the reason for the inertness of methyl acrylate **66** under these reaction conditions. The electron-donating methoxy group possibly deactivates the vinyl system enough to prevent hydride addition. Methyl vinyl ketone **71**, on the other hand, is activated enough to react with the hydride. The nitrile group of acrylonitrile is less electron-withdrawing than the acetyl group of methyl vinyl ketone, and hence the former is less reactive towards the hydride. One would thus expect the yield of the acrylonitrile/propanal coupling product **79** to be lower than that of the methyl vinyl ketone/propanal product **73**, which was the case. The same trend in activity has been observed in the Baylis-Hillman couplings of activated vinyl systems with aldehydes, for example, the coupling of benzaldehyde **83** with methyl vinyl ketone **71** took thirty hours, with acrylonitrile **78** forty hours, and with methyl acrylate **66** seven days.[90,91]

In an attempt to explain the catalytic activitiy of the rhodium and ruthenium complexes, one has to bear in mind that the arguments used are based on the mechanism of catalysis proposed by Matsuda and co-workers, which has not been proved, and thus cannot always be supported by physical data.

The $[RhH(PPh_3)_4]$ and $[RuH_2(PPh_3)_4]$ catalysts are both coordinately saturated, yet the catalytic process requires a

vacant site on the metal for the substrate, in this case the α,β-enone, to coordinate. The ability of these two complexes to catalyse the coupling reaction arises from the their behaviour in solution. In both cases a single triphenylphosphine ligand dissociates from the complex, establishing an equilibrium between the resultant tri- and tetrakis(triphenylphosphine) complexes at ambient or relatively low temperatures (**Scheme 28**).[92,93] The loss of the ligand leaves a vacant coordination site, enabling the substrate to coordinate. This is presumably why Matsuda and co-workers found that the complex [RhH(Diphos)$_2$] exhibited only trace catalytic activity.[75] The chelate diphosphine ligand, to which it is bonded, is unable to dissociate, leaving the complex coordinately saturated which reduces its catalytic activity severely.

$$[RhH(PPh_3)_4] \rightleftharpoons [RhH(PPh_3)_3] + PPh_3$$

$$[RuH_2(PPh_3)_4] \rightleftharpoons [RuH_2(PPh_3)_3] + PPh_3$$

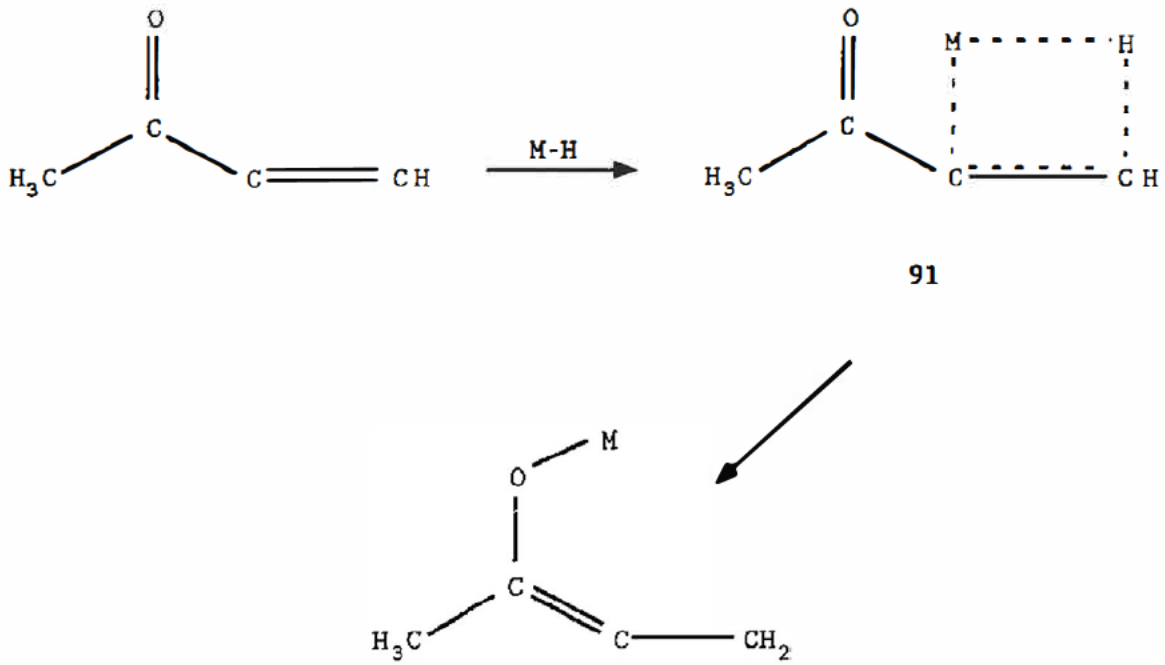
Scheme 28

Both this study and the work of the Matsuda group have shown that [RuH$_2$(PPh$_3$)$_4$] is usually more efficient than [RhH(PPh$_3$)$_4$] in catalysing coupling reactions of this type, giving greater yields of the aldol-type products. One can only speculate as to the reasons for this, as the mechanism for the catalysis has not been elucidated unambiguously. The difference in turnover of the two catalysts may simply be due to the fact that the ruthenium complex has two coordinated hydrides as opposed to the monohydridic rhodium catalyst. There is, in other words, twice the concentration of hydride present to initiate the reaction.

Another possible reason for the difference in catalytic activity of the rhodium and ruthenium complexes concerns the relative nucleophilicity of their hydrides. The more nucleophilic the metal hydride, the more reactive it is towards the double-bond of the activated vinyl compound, which is electrophilic in character. On this basis, one would expect to be able to find some evidence of the greater nucleophilicity of the ruthenium hydride. In theory, from a nuclear magnetic resonance point of view, the more nucleophilic the hydride, the more shielded it is and the further upfield its shift will appear in a ^{1}H NMR spectrum. Practically, however, this will be affected by the ligands bonded to the metal centre and the coordination geometry of the complex. Also, metal hydride resonances are difficult to observe even with modern NMR techniques. This may be as a result of limited solubility of the complexes, the ligand exchange exhibited by these catalysts, or weakness of the hydride resonances due to splitting of the signal by couplings with ligand or metal.[93,94] The hydride resonance for $[RhH(PPh_3)_4]$ has been determined using special NMR techniques,[93] but no researchers have as yet been able to carry out the same determination for $[RuH_2(PPh_3)_4]$. Comparisons of analagous rhodium and ruthenium complexes to ascertain trends in hydride resonance values seem to indicate that rhodium hydrides tend to resonate further upfield than the corresponding ruthenium hydrides.[93-95] This is consistent with the trend of increasing electronegativity across a period from left to right. This implies that metal hydrides should become less nucleophilic across the period as the metals become more electropositive. This information would seem to indicate that rhodium hydrides are more nucleophilic than ruthenium hydrides, but this is not reflected in the catalytic activities of the complexes.

A further factor is that increasing nucleophilicity of a hydride may make it more difficult for transfer from the metal to vinyl system to occur. Bearing in mind that the addition of

the hydride to the double-bond is a transfer process via a four-membered transition-state (such as **91**) rather than an independent metal hydrogen bond breaking and carbon-hydrogen bond forming one, this factor may or may not affect the catalytic efficiency of the complexes (**Scheme 29**).[96]



91

Scheme 29

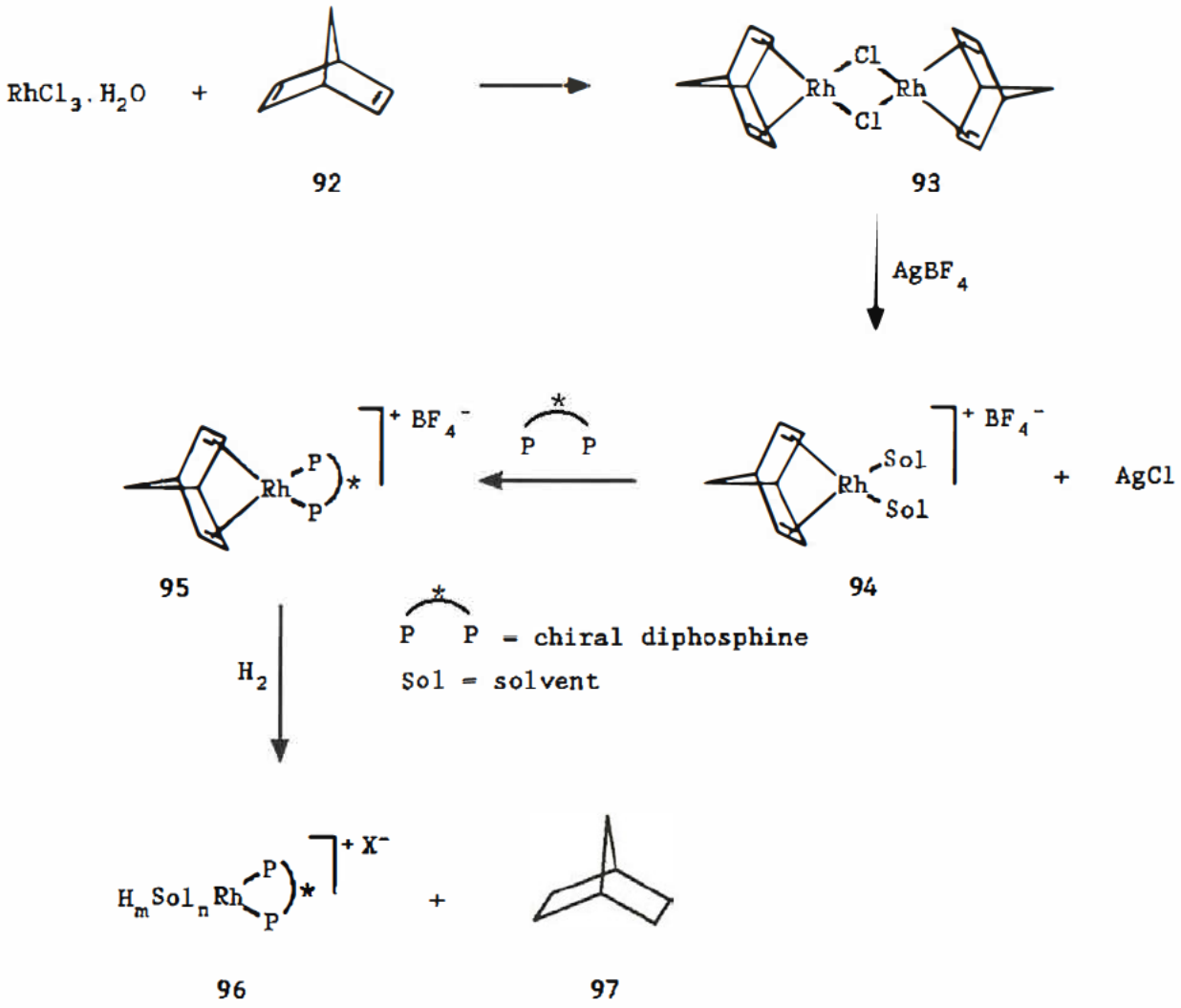
One can only conclude that there are more factors influencing the catalysis than we realise. These will only be elucidated when the reaction mechanism has been unequivocally established. Only then is a successful catalytic process likely to be established.

2.4 ENANTIOSELECTIVE COUPLING OF α,β-UNSATURATED KETONES AND ALDEHYDES BY CHIRAL RHODIUM CATALYSTS

Rhodium Wilkinson-type catalysts **5** bearing chiral diphosphine ligands have been extensively used in asymmetric hydrogenation reactions.[30] Similar catalysts **40-42** were used by Reetz and Vougioukas for the coupling of preformed enolates with aldehydes.[69] This was the first reported example of an asymmetric aldol-type reaction. Subsequently, Matsuda and co-workers reported the direct coupling of α,β-unsaturated ketones and aldehydes catalysed by the Wilkinson-type catalyst [Rh(COD)(Diphos)]$^{+}PF_6^{-}$ **55** when activated by hydrogen.[75] This proved to be the most selective of all the catalysts tested in the reaction of methyl vinyl ketone **71** with propanal **72** (**Scheme 24**), giving none of the α,β-unsaturated ketone self-coupling product **74**. The success of catalyst **55** in this reaction makes it a logical precursor to analogous chiral diphosphine catalysts for asymmetric aldol-type coupling. Although quite costly, a wide range of chiral chelating diphosphines have been developed, particularly for hydrogenation purposes. The synthetic chemist thus has a large choice of ligands at his disposal for the synthesis of catalysts for aldol coupling reactions.

2.4.1 THE CATALYTIC SYSTEM

A series of chiral catalysts analagous to **55** were thus synthesised in order to test their enantioselectivity in the coupling of methyl vinyl ketone **71** and propanal **72** (**Scheme 24**). The general method of preparation of these rhodium(I) catalysts is illustrated in **Scheme 30**.



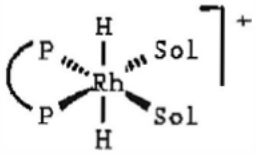
Scheme 30

Stirring of hydrated rhodium trichloride with norbornadiene **92** reduces the metal to the norbornadienerhodium(I) chloride dimer **93**.[97] A silver salt cleaves the dimer affording the norbornadienerhodium(I) solvento-species **94** as well as silver chloride precipitate.[98] Being extremely labile, the coordinated solvent molecules are easliy displaced by a stongly coordinating chiral diphosphine ligand, giving the catalyst precursor **95**.[99] The active catalytic species **96** is generated by bubbling hydrogen through a solution of **95** at atmospheric pressure.[100] This

serves firstly to hydrogenate the coordinated norbornadiene to release norbornane **97** leaving vacant coordination sites, and secondly to hydrogenate the rhodium metal by oxidative addition of hydride to the metal centre.

The exact form of the activated catalytic species **96** has been a topic of debate for a number of years. The preparation and structure of these catalysts, including catalyst precursor **95** and activated catalytic species **96**, are exactly the same as those used in catalytic hydrogenation of alkenes. Thus much of the discussion that follows is based on research undertaken on catalytic hydrogenation systems and their reaction mechanisms, which have been studied in detail. It also assumes that the catalytic cycle for the aldol-type coupling of α,β unsaturated ketones and aldehydes is initiated by a metal hydride as proposed by Matsuda and co-workers (**Scheme 27**).[75]

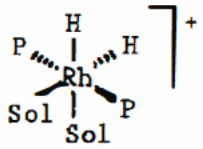
Schrock and Osborne, working on catalytic hydrogenation systems, assumed that **96** was a rhodium(III) complex $[RhH_2(Sol)_2(P\text{-}P)]$ **98**, formed by oxidative addition of hydrogen to the rhodium centre once the norbornadiene has been hydrogenated .[100]



98

Halpern *et al.*,[101,102] Slack *et al.*[103], as well as Brown and Chaloner[104,105] found no physical evidence at all to support the hydride structure proposed by Schrock and Osborne. These workers undertook what is probably the most detailed mechanistic study of a catalytic cycle to date in an attempt to elucidate the structure of the catalytic species **96** and other

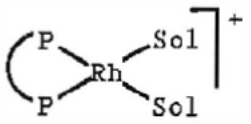
reaction intermediates in the catalytic hydrogenation of alkenes by catalysts of the type **96**. In ^{1}H NMR studies, these workers could find no hydride resonances, which in analagous monophopsphine compounds of the type $[RhH_2(Sol)_2P_2]^+$ **99** (P = monophosphine) are relatively easily determined.[101,102]



99

Furthermore, when the volume of hydrogen consumed in the catalyst activation process (**95** to **96**) was measured, only two equivalents were found to have been consumed. These correspond to the hydrogenation of coordinated norbornadiene in **95** to norbornane **97**, and not the formation of a metal hydride. No further uptake of hydrogen was measured. Unequivocally, the evidence indicates that no detectable rhodium hydride is formed. However, it is possible that a small percentage of rhodium hydride **98**, such as that described by Schrock and Osborne,[100] is formed. Hypothetically, if a mole ($6x10^{23}$ atoms) of precursor **95** is hydrogenated, and only 1% forms the rhodium hydride $[RhH_2(Sol)_2(P\text{-}P)]^+$ **99** (in other words $6x10^{21}$ atoms), the hydride resonance and hydrogen uptake may not be detectable, but the amount of rhodium hydride formed is appreciable. We cannot guess at the quantity of **98** formed, but this "small" amount of rhodium hydride is enough to catalyse the desired coupling reaction (**71** + **72**), as indicated by the results of Matsuda and co-workers who have had success with these catalysts.[75] It is thus possible for the catalysis of the coupling reaction to be performed by an undetectably small amount of catalyst which has a high turnover. The major species produced by the hydrogenation of **95** is the only detectable one, that is $[Rh(Sol)_2(P\text{-}P)]^+$ **100**. This is the complex which Halpern

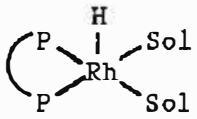
and co workers found to be the active catalytic species in the hydrogenation of alkenes.[101,102]



100

In the catalytic hydrogenation of alkenes, the hydride required for the hydrogenation process is obtained from the atmosphere of hydrogen gas under which the reaction is performed. By comparison, the catalytic coupling of α,β unsaturated ketones and aldehydes requires regeneration of metal hydride as the reaction does not consume hydrogen, and is performed in an inert atmosphere (**Scheme 27**).

It is also possible that a third rhodium species is formed on hydrogenation of the catalyst precursor **95**. Deprotonation of the rhodium(III) complex **98** is possible under appropriate conditions (not only by base abstraction of a proton, but also by ligand or solvent interaction)[106] to give the neutral rhodium(I) complex **101**.[100] This is likely to be a very small constituent of the catalytic system as the reaction conditions are almost neutral. This type of complex was found to be an efficient alkene hydrogenation and isomerization catalyst.[100] It is likely that this catalyst is able to catalyse the coupling of α,β-unsaturated ketones and aldehydes, but its presence in the catalytic system is purely speculative.

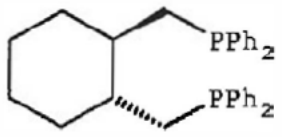


101

In summary, hydrogenation of the catalyst precursor probably results in three complexes being formed, that is **100**, **98**, and **101**. The complex **100** is the major product, and **98** the minor, while **101** is formed in negligibly small quantities. The rhodium(III) complex **98** is the active catalytic species for the aldol-type coupling reaction.

2.4.2 ENANTIOSELECTIVE COUPLING

The chiral phosphine ligands chosen for the preparation of the asymmetric rhodium catalysts were selected for specific structural properties, and also for the proximity of their chiral centres to the metal atom when coordinated, as the metal centre is the locus at which the substrate binds and around which reaction occurs. By the sequence outlined in **Scheme 30**, catalyst precursors of the general type **95** were prepared using the chiral diphosphine ligands (+) BDPMC **102**, (+)-Chiraphos **103**, (-) DIOP **104**, and (-)-BINAP **105**.



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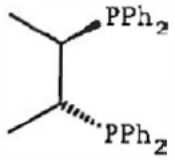
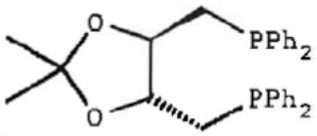
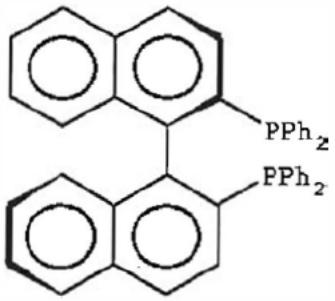


103



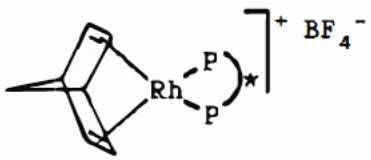
104



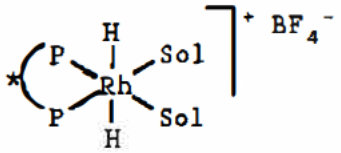
105

In (+)-BDPMC **102** and (-)-DIOP **104**, the chiral centres are two atoms away from the phosphorus and thus three away from the rhodium when coordinated. In (+)-Chiraphos **103** the chiral centres are two atoms away from the metal centre. (-)-BINAP **105** was selected because of its atropisomeric chirality which arises from restricted rotation around the bond joining the binaphthyl rings. The polar oxygen atoms of the isopropylidene ring in (-)-DIOP could provide secondary interaction with incoming substrate molecules, thus affecting the stereo-selectivity of the step.

Hydrogenation of the catalyst precursors **95a-d**, bearing ligands (**102-105**), resulted in formation of the corresponding active catalytic species **98a-d**. Coupling of methyl vinyl ketone **71** and propanal **72** to form **73** (**Scheme 24**) was performed under the same conditions with these complexes as the $[RhH(PPh_3)_4]$ and $[RuH_2(PPh_3)_4]$ catalysts. The results of the couplings performed with chiral catalysts 98a-d are shown in **Table 5**.



95a, P P = 102
95b, " = 103
95c, " = 104
95d, " = 105



98a, P P = 102
98b, " = 103
98c, " = 104
98d, " = 105

Table 5

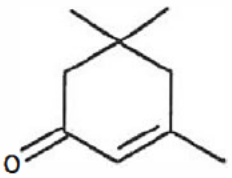
Entry	Catalyst (mol%)	Time (h)	$[\alpha]_D$	Ee (%)
1	**98a** (1)	5	+5.39	15.7
2	**98a** (1)	7	+5.85	17.0
3	**98a** (3)	5	+6.30	18.3
4	**98b** (1)	5	+5.40	15.7
5	**98c** (1)	5.5	-7.82	22.7
6	**98d** (1)	5	0	0
7	**98d** (2)	14	0	0

From the above results (Entry 5), it was evident that ( ) DIOP was the most effective of the ligands tested, giving the greatest enantioselectivity. (+)-BDPMC and (+)-Chiraphos performed similarly under exactly the same reaction conditions (Entries 1 and 4), whilst the ( )-BINAP complex **98d** failed to catayse the coupling reaction at all, even though reaction time and catalyst concentration were increased. Entries 1 and 3 indicate that increasing catalyst concentration is an effective means of elevating the optical yield. Reaction time was also found to effect the enantiomeric purity of the product **73** (Entries 1 and 2).

Interestingly, (+)-Chiraphos **103**, in which the chiral centres are closest to the rhodium when coordinated, performed no better than (+)-BDPMC **102** with its chiral centres one atom further away. Better asymmetric induction was expected with the former catalyst for this very reason. In ( )-DIOP **104**, the most successful ligand, the chiral centres are nevertheless three atoms away from the rhodium. All four catalyst systems (obtained by hydrogenation of **95a-d**) have been used as hydrogenation catalysts as well. In Koenig's excellent review of asymmetric catalytic hydrogenation,[35] his findings show that (+)-Chiraphos and (-)-BINAP are generally more successful ligands than (-)-DIOP. The relative success of the more functionalised (-)-DIOP ligand over the other unfunctionalised ligands in the coupling reaction is possibly due to interaction of the oxygen atoms in the isopropylidene ring with incoming polar substrate molecules (in this case aldehydes). The reason for the lack of activity of the (-)-BINAP **98d** catalyst is probably that the nature of the ligand prevents the rhodium(III) hydride **98d** from forming at all, or if it forms it reduces the hydride reactivity so that no reaction can occur.

It has also been noted by number a number of researchers studying hydrogenation catalysts, that the larger the size of the chelate ring formed in coordination of the diphosphine ligand to the rhodium centre, the greater the catalytic activity of the complex for a series of structurally similar ligands.[35,107] These workers concluded that the enhanced activity may reflect the increasing flexibility associated with increasing chelate ring size, resulting in more facile attainment of the favoured transition state geometries of the various reaction steps. Because of the similarities in the catalyst systems of the catalytic hydrogenation and aldol-type coupling reactions, one might expect the same trend to apply to the latter. However, based on results obtained by Koenig[35], differences in structural features have far greater effect than chelate size.

In an attempt to broaden the scope of this type of chiral catalyst, **98a** was used in the coupling of a variety of α,β-unsaturated ketones (isophoron **106**, mesityl oxide **107**, 2 cyclohexen-1-one **108**, and 1-acetyl-1-cyclohexene **109**) with propanal **73** at a standard catalyst concentration of 2 mol%, for seven hours at 105°C.



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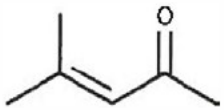

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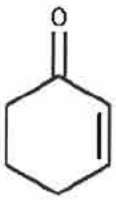

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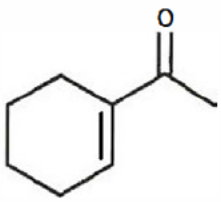


109

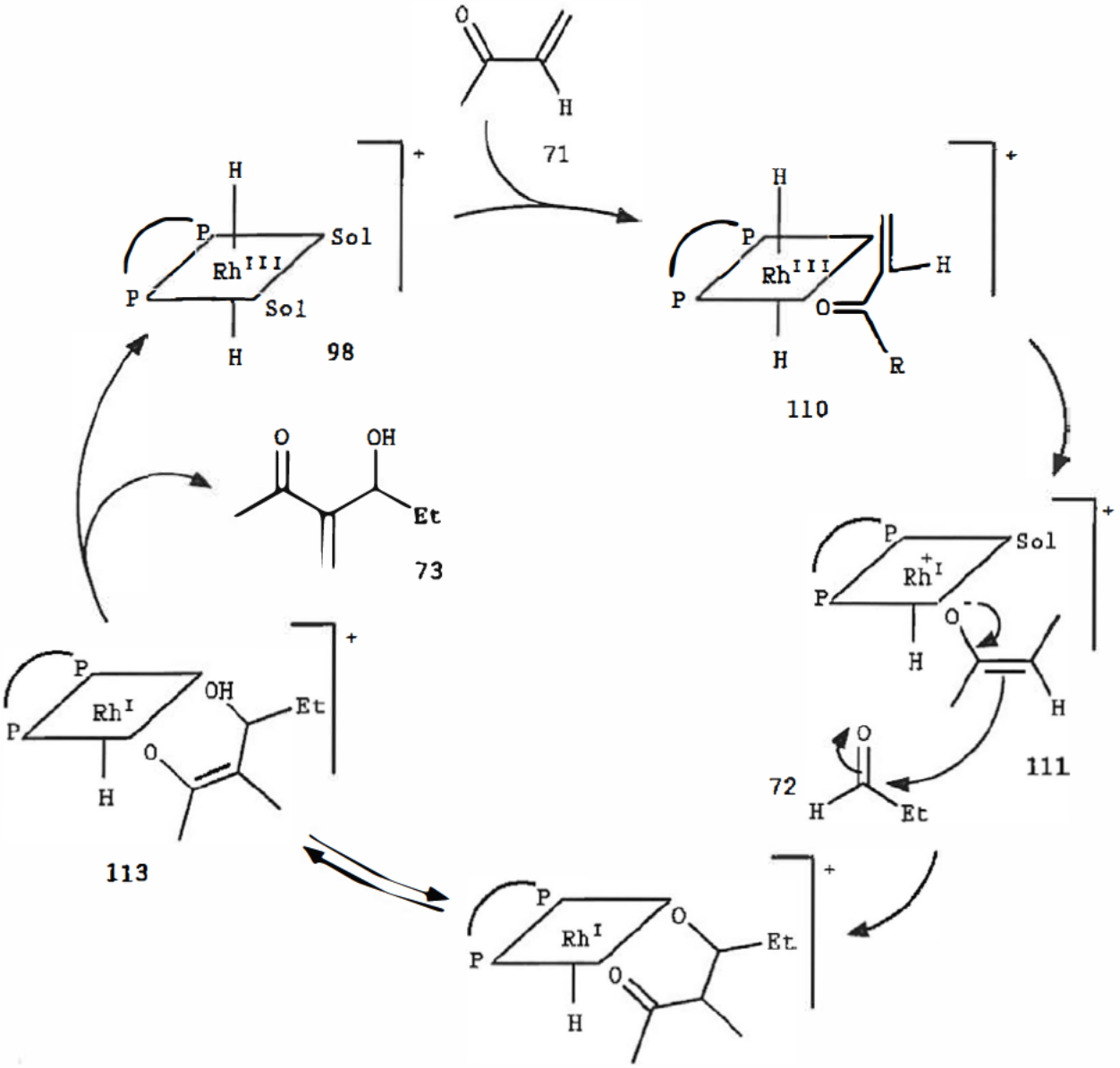
However, none of these α,β-enones coupled with propanal at all. The explanation of this is again that the vinyl systems are too deactivated by electron-donating substituents to undergo nucleophilic attack by a hydride, and hence the catalytic cycle cannot be initiated.

2.4.3 MECHANISM OF CATALYSIS AND ORIGIN OF STEREOSELECTIVITY

The mechanism of the catalytic cycle for the rhodium-catalysed coupling of α,β-unsaturated ketones and aldehydes is based on that proposed by Matsuda and co-workers,[73-75] involving an

initial nucleophilic attack of rhodium hydride on the activated vinyl system of the ketone (**Scheme 27**). A modified mechanism can be based on a comparison with the mechanism for the catalytic hydrogenation of alkenes in which most of the intermediates have been isolated and structurally characterised by X-ray studies.[35] The majority of alkenes which are hydrogenated are vinyl functionalised with either carbonyls, amides, or both. These polar groups allow the substrate to chelate to the metal centre, and this is the first step in the mechanism of catalytic hydrogenation. The proposed mechanism for the coupling of methyl vinyl ketone **71** and propanal **72** is illustrated in **Scheme 31**.

Assuming that the active catalytic species for the aldol-type coupling reaction is the coordinately-saturated rhodium(III) complex **98**, the first step is likely to be the substitution of coordinated solvent by the α,β-unsaturated ketone via an associated mechanism, affording intermediate **110**. This would be followed by transfer of hydride from the rhodium to the vinyl system via a four-member cyclic transition state, which reduces the metal to rhodium(I), and forms an enolate to give a complex such as **111**. According to Koenig,[35] the electrophilicity of the vinyl system is increased by coordination to the positive rhodium species, as opposed to a neutral one. Electrophilic attack of the incoming aldehyde occurs at the enolate, to yield the corresponding aldolate, which is likely to chelate to the rhodium centre, probably to give intermediate **112**, which in turn would be in equilibrium with **113**. With oxidative transfer of hydride from the β-position of the aldolate to the rhodium centre, the catalyst **98** is regenerated, and the aldol-type product **73** released.



Scheme 31

As mentioned above, this reaction mechanism is based on that theorised by Matsuda and co-workers[73-75] and also on Koenig's mechanism for catalytic hydrogenation.[35] It should be seen as no more than a proposal, as none of the intermediates has been isolated or characterised. For the purpose of demonstrating the origin of stereoselectivity, it is not sufficient to deduce a "kinetic mechanism" (i.e., a mechanistic scheme that fits the

kinetic behaviour) or merely to characterise them spectroscopically. Absolute configurations of the intermediates involved in the enantiodetermining step(s) must be correlated with those of the reactants and products. This requires actual interception and structural characterisation of the pertinent reaction intermediates.

From a stereoselective point of view, a thermodynamic mechanism in which the ratio of products depends on their free energies, is undesirable as it allows for equilibration of the stereoisomeric products. A kinetic mechanism is infinitely more desirable as the product which is formed fastest is formed in the largest amount, because the free energy of its transition state is lower. If, however, the step is reversible, the product formed fastest may in time be converted partly or completely to the more stable stereoisomer (lower in free energy). Not only is kinetic control desirable, but the stereoselective step should preferably be irreversible.

Heathcock and co-workers[67] elucidated the mechanism of the rhodium catalysed coupling of preformed enolates with aldehydes (**Scheme 15**). These workers deduced that if chiral phosphine ligands were used, the enantioselective step would be the silyl-transfer step (reaction of rhodium aldolate **37** with enol silane **38**) (Step 2) which is irreversible, and not the aldehyde addition step (Step 1). They concluded that the difference in energy of the silyl-transfer intermediates would not be enough for effective asymmetric induction. However, if a set of ligands could be found that rendered Step 1 irreversible, the stereoselectivity of the products would be established in this step as the transition state energies are sufficiently different.

In the rhodium catalysed direct coupling of methyl vinyl ketone **71** and propanal **72**, the low enantioselectivities (**Table 5**) may be due purely to the very small quantity of active catalyst **98**

present, because of the behaviour of the catalyst precursor on hydrogenation. In this case the catalyst is an effective one, with a high turnover if a small concentration is able to produce detectable amounts of coupling product.

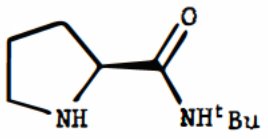
On the other hand, the catalytic system may be a poor one if the enantioselective step is one in which the diastereomeric transition states do not differ sufficiently in energy, for instance the aldol elimination step (**113-98** in **Scheme 31**). The enantioselection in this case would be low. Ideally, the enantioselective step needs to be irreversible and with substantial energy differences in the transition state, such as the aldehyde addition step (**111-112**).

The actual source of induction in asymmetric hydrogenation catalysts is thought to be the array of phenyl rings (bonded to the phosphorus atoms of the chiral ligand) around the metal centre.[35,36] If the poor asymmetric induction is due to inefficient transfer of chirality, ferrocenyl-type ligand **23** has a chain with a polar chirotopic group which is able to influence incoming molecules by means of secondary interactions. This type of ligand design has greatly enhanced stereoselectivity in gold and silver catalysed aldol-type couplings.[29]

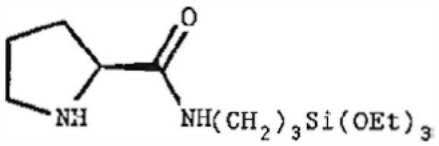
Without intensive study into the catalytic cycle, isolation and structural characterisation of the reaction intermediates, the reasons for the empirically poor asymmetric induction can only be surmised. Nevertheless, the results are novel, and should be viewed in this light.

2.5 ENANTIOSELECTIVE COUPLING OF α,β UNSATURATED KETONES AND ALDEHYDES BY RHODIUM CATALYSTS WITH CHIRAL DINITROGEN LIGANDS

In the previous section of the discussion (**2.4**) we have seen that the catalysts used for enantioselective aldol type couplings are exactly the same as those used for asymmetric hydrogenation except for the final catalytic species. Corma *et al.*[37] recently reported using new ligands for asymmetric hydrogenation. These ligands were proline-based dinitrogen compounds **114** and **115**, the latter being modified enabling it to be anchored on a silica or modified zeolite USY support.

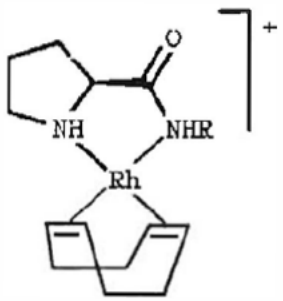


114



115

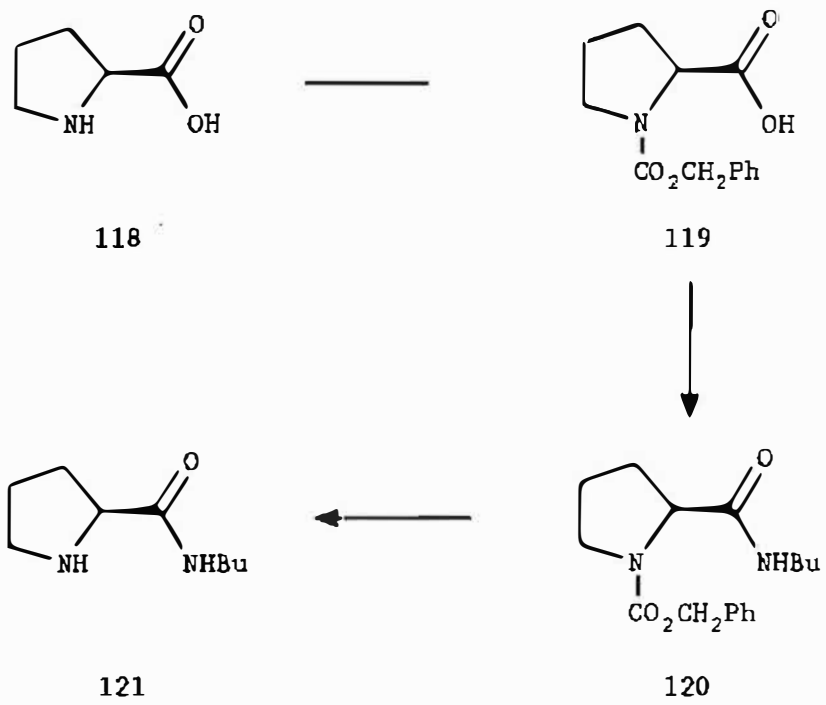
The advantage of dinitrogen ligands over diphosphine ligands is that they are more cheaply and easily produced from readily available starting materials such as amino-acids. Corma *et al.* coordinated these ligands to [Rh(COD)Cl]$_2$ to yield catalyst precursors **116** and **117**.[37] This is analogous to the preparation of the corresponding diphosphine complexes (**Scheme 30**).



116, R = ^{t}Bu
117, R = (CH$_2$)$_3$Si(OEt)$_3$

As with the diphosphine complexes, hydrogenation of the precursor leads to the activated catalytic species.

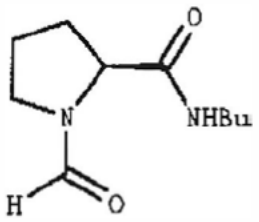
The similarity of this type of catalyst to the diphosphine complexes used to catalyse asymmetric aldol-type couplings in the previous section (2.4), and their relative cheapness, lead to their use in this study for the same purpose. For this reason dinitrogen ligand **121** was synthesised from L-proline **118** by the route shown in **Scheme 32**.



Scheme 32

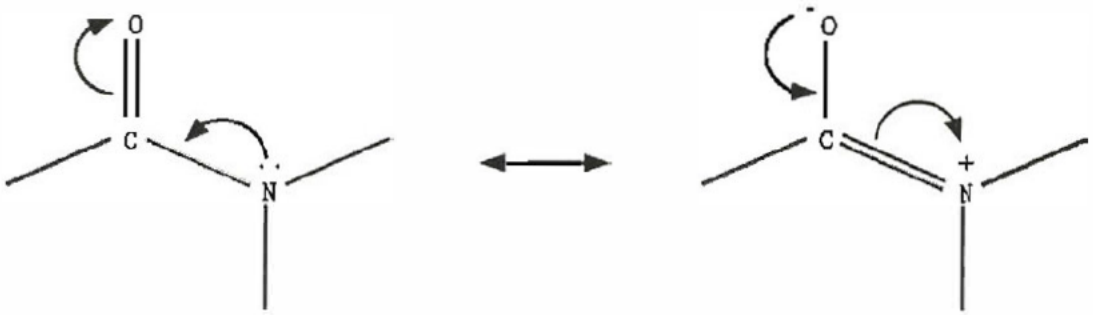
The synthesis of **121** is a three-step one, involving initial protection of nitrogen in L-proline **118** with the Cbz (carbobenzoxy) protecting group to give **119**.[108] Electrophilic attack of n-butylamine on the carbonyl carbon of **119** results in the amide **120**,[109] deprotection of which gives the desired product **121**.[110,111] All of these steps are literature

procedures, yet the final deprotection step, using the well-known method of hydrogenation by palladium on carbon with cyclohexene as the hydrogen source[110] did not give **121** cleanly, even though the activity of the Pd/C catalyst had been confirmed. Another method, that of ElAmin *et al.*,[111] using palladium black in 4.4% formic acid-methanol was tried. This protocol gave only two spots when analysed by TLC (many were present when Pd/C with cyclohexene was used), a first spot on the baseline and a second one just off it. These two compounds were duly separated and purified by column chromatography. Mass spectroscopic analysis of the second spot (off the baseline) gave a molecular ion peak of 198 as opposed to the expected value of 170. Analysis of the same sample by ^{1}H and ^{13}C NMR gave very interesting results. Although the sample was clean (gas-chromatograph), the ^{13}C spectrum showed far too many peaks (±18) for a compound of mass 198. 18 carbons on their own have a molar mass of 216! The ^{1}H NMR spectrum showed a distinct doubling-up of peaks. The compound could not possibly be diastereomeric, so the only plausible conclusion was that there were two conformational isomers (see **Spectra 1** and **2** in the **Appendix**). Infra-red spectra of the isolated second spot showed two carbonyl stretches, implying that two carbonyls were present. The compound was obviously not unreacted **120**, which has a molar mass of 306. A second carbonyl could have been introduced in the deprotection step from the solvent, 4.4% formic acid-methanol. In fact, N-formylation of **121** gives compound **122** with two carbonyl groups and a mass of 198. Mass spectroscopy confirmed the baseline spot to be that of the desired product with a molecular ion peak of 170.



122

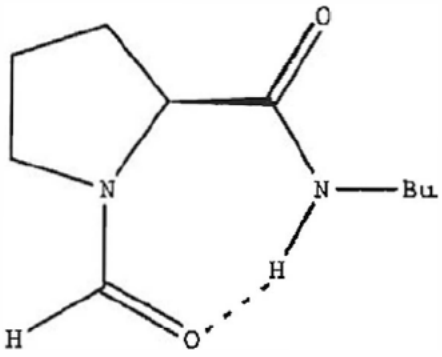
Elemental analysis confirmed the structure of the compound isolated from the second spot to be **122**. Conformational isomerism arises from restricted rotation around the carbon-nitrogen bond of the n-butylamide side-chain. This type of conformational isomerism is well-known,[112-114] and arises from delocalization of the nitrogen lone-pair electrons to the carbon-nitrogen bond. This is known as "resonance" and is illustrated in **Scheme 33**. Restricted rotation is as a result of the fluxional double-bond between the carbon and nitrogen atoms.



Scheme 33

This type of conformational isomerism is normally only a small effect, but in this case it is affected greatly by the amide group of the pyrrolidine ring. The formyl group of this amide functionality makes it very electron-withdrawing, so that the acidity of the amide proton of the n-butylamide side-chain is increased by a positive inductive effect. This allows hydrogen-bonding between this proton and the oxygen of the pyrrolidine

amide functionality to occur (**Scheme 34**).



Scheme 34

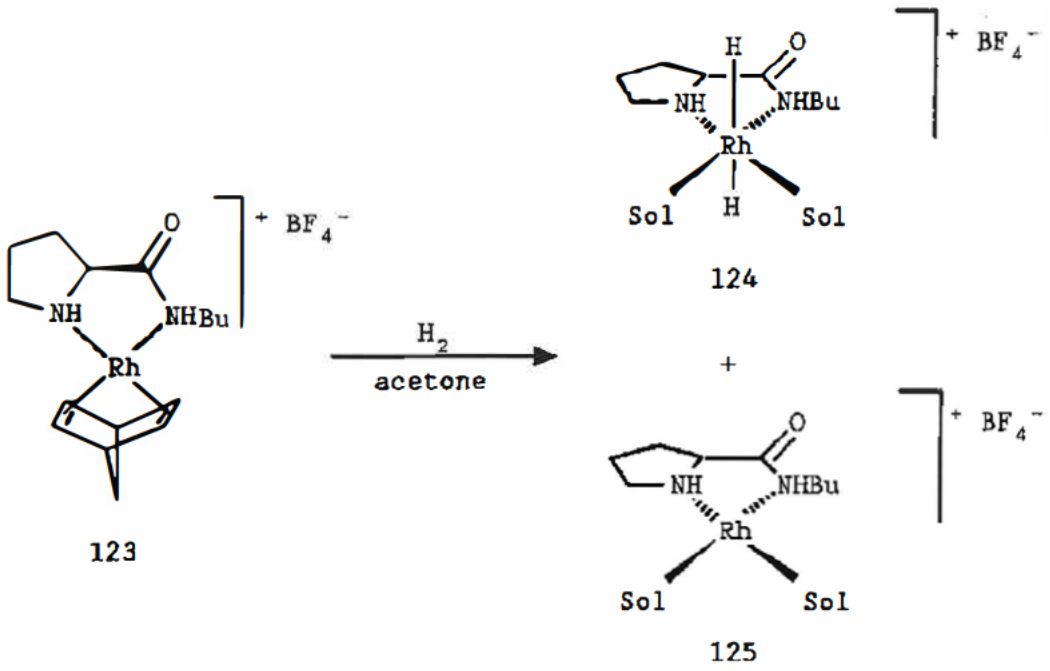
The resultant seven-membered ring further decreases rotation around the carbon-nitrogen bond of the side-chain amide group, giving rise to the distinct doubling-up of peaks in the ^{1}H and ^{13}C NMR spectra. The NMR signals most affected by the conformational isomerism are those closest to the carbon-nitrogen bond (see **Spectra 3** and **4** in the **Appendix**).

A very small doubling-up effect is seen in the desired product **121** as the conformational isomerism of the amide group is not enhanced by any other effects such as hydrogen-bonding. No effect is observed in **120** either, despite the presence of a pyrrolidine amide functionality. This group is not electron-withdrawing enough to allow hydrogen-bonding to occur as in **122**.

The formation of **122** whilst using the method of ElAmin *et al.*[111] was overcome by monitoring the reaction by means of TLC, so that the reaction was quenched before it had formed in appreciable quantities.

After synthesis, the ligand **121** was coordinated to the rhodium centre by reaction with $[Rh(NBD)Cl]_2$ **93** in the presence of the

silver salt $AgBF_4$ to form the catalyst precursor **123**. As is the case with the analagous rhodium-diphosphine precursors **95**, hydrogenation of **123** probably produces a "catalyst soup" containing only a small amount of the corresponding catalytically-active rhodium(III) dihydride **124**, and a relatively large amount of the rhodium(I) solvento-species **125** (**Scheme 35**).



Scheme 35

The resultant "catalyst soup" was used to catalyse the coupling of methyl vinyl ketone **71** and propanal **72** using the same reaction conditions as with the diphosphine systems.

The result was that the desired coupling product **73** was formed with an enantiomeric excess of 12.3%. This is not a particularly large asymmetric induction, but is nevertheless the first reported asymmetric aldol-type coupling catalysed by a rhodium complex with a chiral dinitrogen ligand.

2.6 CONCLUSION

This investigation has shown that enantioselective rhodium catalysed aldol-type coupling reactions are not at the level of being synthetically useful. The low enantioselectivities achieved with all types of chiral rhodium catalysts are probably as a result of a shortcoming inherent in the type of catalyst system used, rather than inefficient asymmetric induction by the ligands.

The drawback of the enantioselective catalysts is that the concentrations of active catalytic species, rhodium hydrides **98a-d** and **124**, are so small that they cannot be detected, that is if they exist at all. Their existence is based on the mechanism proposed by Matsuda *et al.*,[75] which requires a metal hydride to initiate the catalysis. It may be that another catalytic species in the "catalyst soup" is actually the active species. In order to increase the optical yield of the reaction, one has to understand the mechanism of the reaction to be able to design rationally a catalyst capable of high turnover as well as high enantioselectivity. In order to accomplish this, intermediates in the catalytic cycle have to be isolated and structurally characterised. This would be a major research undertaking, requiring some prior indication that the study would be worth the effort.

If it were proved that the mechanism of catalysis was initiated by a metal hydride, then it is possible that a chiral metal hydride complex could be found that is present in sufficiently large concentrations, and is reactive enough to perform the catalysis. Furthermore, the catalyst, if it is to be of value to the synthetic chemist should be stable enough to be handled easily.

In catalyst design, it is important to pinpoint which of the catalytic steps is the enantioselective one. Heathcock and co-workers[67] isolated the intermediates in a catalytic aldol reaction, and found that the enantioselective step was not the addition of aldehyde to the enolate (which theoretically would give the greatest energy differences between the diastereomeric transition states), but the final silyl-transfer step, in which the difference in diastereomeric transition states is small (**Scheme 15**). The energy difference between these transition states needs to be as large as possible for efficient asymmetric induction to be achieved. A specific step can only be the enantioselective one if it is irreversible, in other words kinetic conditions prevail. In the catalytic cycle investigated by the Heathcock group,[67] the aldehyde addition step is fast and reversible, precluding it from being the enantioselective step. In future catalytic asymmetric aldol couplings, the catalysts should be designed so that the enantioselective (irreversible) step is the aldehyde addition one, or any in which the diastereomeric transition states differ in energy by more than 3 kcal mol^{-1}.[67]

The forefront of catalysis in the future may be in designing ligands that are able to interact with the substrate not only sterically, but by means of chemical bonding. Examples of these are the ferrocenyl ligands **23** developed by the Hayashi group[29] which have chirotopic polar groups on a side chain, which are then able to hydrogen-bond to incoming substrate molecules.[78] If the ligand is able to bond in more than one place, the asymmetric induction and selectivity are likely to tend towards those of enzymes. This might be an answer to increasing asymmetric inductions in aldol couplings of this type, since the substrate molecules often lack functional groups through which they may coordinate to the metal centre.[24]

For a catalyst to be synthetically useful, however, it should have a broad range of selectivity. This was the purpose behind

the coupling of a variety of α,β-unsaturated ketones and aldehydes by the catalysts $[RhH(PPh_3)_4]$ **75** and $[RuH_2(PPh_3)_4]$ **76**. The scope of reaction of these catalysts proved to be small, however (**Table 4**), whilst that of the chiral diphosphine catalysts proved to be smaller still.

Recently, chiral ruthenium catalysts have given a new impetus to asymmetric hydrogenation, with catalysts similar in design to the current rhodium hydrogenation catalysts. Just as $[RuH_2(PPh_3)_4]$ **76** proved to be a better catalyst than $[Rh(PPh_3)_4]$ **75** in the coupling of methyl vinyl ketone **71** and propanal **72** (**Table 4**),[75] chiral ruthenium catalysts may prove better than their rhodium counterparts.

The future of catalytic asymmetric aldol-type coupling reactions may lie in finding a completely new catalytic system through elucidation of the reaction mechanism.

3 EXPERIMENTAL

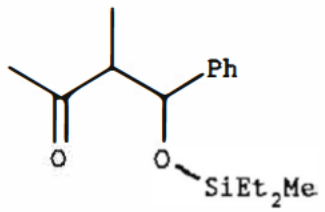
3.1 INSTRUMENTATION AND CHEMICALS

Melting-points were measured on a Kofler hot-stage apparatus and are uncorrected. Elemental analyses were determined using Perkin-Elmer 240B and 2400 elemental analysers. NMR spectra (^{1}H 200MHz and ^{13}C 50MHz) were recorded on a Gemini 200, ^{1}H 60MHz spectra on a Varian T 60 and ^{31}P 32MHz on a Varian FT 80A instrument. For ^{1}H and ^{13}C NMR, $CDCl_3$ was used as solvent and TMS as the internal standard, unless specified to the contrary. For ^{31}P NMR, $P(OMe)_3$ was used as the internal standard. Mass spectra were recorded on a Hewlett-Packard gas chromatographic-mass spectrometer (HP5988A) and a Varian high resolution mass spectrometer Optical rotations were determined on a Perkin-Elmer 241 polarimeter. Infra-red spectra were recorded on a Shimadzu FTIR-4300 spectrophotometer using KBr discs unless otherwise stated. Precoated Kieselgel 60 F_{254} Merck plastic sheets were used for thin-layer chromatography. Preparative column chromatography was performed using the technique of Still *et al.*[115] on Merck silica gel 60 (230 - 400 mesh). Solvents were dried using standard techniques[116] and distilled prior to use. When neccessary, solvents were degassed by performing five successive freeze-thaw cycles under vacuum. Low temperatures were maintained using dry ice-solvent baths or ice-salt mixtures according to the procedures of Phipps and Hume.[117] Diastereomeric and enantiomeric excesses were determined by ^{1}H NMR spectroscopy, the latter using [Eu(hfc)$_3$] as chiral shift reagent. Chemical shifts for NMR spectroscopy denote those of the major diastereomer. Shifts of minor diastereomers are denoted in curly ({}) brackets. Procedures carried out under argon or nitrogen were performed using standard Schlenk and vacuum-line techniques.[118]

3.2 PREPARATIONS

3.2.1 ONE-POT COUPLING OF α,β-UNSATURATED KETONES, ALDEHYDES AND TRIALKYLSILANES

3.2.1.1 Preparation of *4-(±) (Diethylmethylsilyloxy)-3-methyl-4-phenylbutan 2 one* 65[68]



$C_{16}H_{26}O_2Si$

MW = 278.46

65

Benzene (1ml), methyl vinyl ketone **62** (0.561g, 8mmol), benzaldehyde **63** (0.212g, 2mmol), and diethylmethylsilane (Et_2MeSiH) **64** (0.409g, 4mmol) were placed in a Schlenk-tube with stirrer-bar under nitrogen. The contents were frozen in liquid nitrogen, and flushed with nitrogen three times before adding tetrarhodium dodecacarbonyl (0.0374g, 0.5mol%, $5x10^{-5}$mol) in benzene (2ml). (The reason for cooling is that the addition of $[Rh_4(CO)_{12}]$ is exothermic). The mixture was allowed to warm to room temperature, with stirring. Stirring at room temperature (26-27°C) was continued for 4 hours. The catalyst was then filtered off on a celite pad. Concentration of the filtrate at reduced pressure removed the excess of benzene, methyl vinyl ketone and Et_2MeSiH. The concentrate was purified by flash chromatography on silica gel with 10% EtOAc-hexane, yielding **65** as a pale yellow oil (0.334g, 60%); δ_H -0.05 {-0.12} (3H, s, $-SiCH_3$), 0.49 {0.45} (4H, q, $SiCH_2CH_3$), 0.83 {0.88} (6H, t, $-SiCH_2CH_3$), 1,16 {0.90} (3H, d, $-CHCH_3$), 1.90 {2.28} (3H, s, $-COCH_3$), 2.82 {2.93} (1H, m,

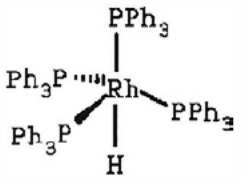
-C*H*CH$_3$), 4.83 {4.64} (1H, d, -C*H*Ph), 7.28 {7.31} (5H, s, -CH*Ph*).

3.2.1.2 Attempted enantioselective synthesis of **65** with a modified chiral catalyst[68]

(1S,2S)-(+)-*trans*-1,2-Bis(diphenylphosphinomethyl)cyclohexane (0.024g, 0.5mol%, $5x10^{-5}$mol) was stirred with tetrarhodium dodecacarbonyl (0.037g, 0.5mol% $5x10^{-5}$mol) in toluene (1ml) in a Schlenk tube for 20 minutes under argon. This allows the diphosphine to displace carbonyl from the metal cluster. Methyl vinyl ketone **62** (0.561g, 8mmol), benzaldehyde **63** (0.212g, 2mmol), Et_2MeSiH **64** (0.409g, 4mmol), and toluene (2ml) were stirred in a Schlenk-tube under argon. The stirred mixture was cooled to -5 to -10°C and the prepared catalyst solution then added. The reaction mixture was stirred for a further 2½ hours before being allowed to reach room temperature. The product was worked up and characterised as above (Section **3**.2.1.1.). NMR spectroscopy was used to determine diastereomeric and enantiomeric excesses. For modified catalyst, δ_P 27 (broad signal).

3.2.2 VARIATION OF THE SCOPE OF THE DIRECT COUPLING OF α,β-UNSATURATED KETONES AND ALDEHYDES

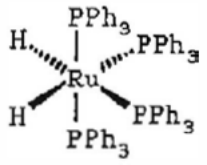
3.2.2.1 Preparation of Hydrotetrakis(triphenylphosphine) rhodium(I)[119]



$C_{72}H_{61}P_4Rh$
MW = 1153.07

Solutions of hydrated rhodium trichloride (0.26g, 1.0mmol) in warm, degassed ethanol (20ml) and potassium hydroxide (0.4g) in warm ethanol (20ml) were added in rapid succession to a vigourously stirred solution of triphenylphosphine (2.62g, 10mmol) in boiling ethanol (80ml) under nitrogen. The mixture was heated under reflux for 10 minutes, cooled to 30°C, filtered, and the precipitate washed with ethanol, water, ethanol, and finally n-hexane. It was then dried *in vacuo* to give the required product as yellow microcrystals (0.76g, 66.5%), m.p. 142°C in air; ν_{RhH} 2150cm^{-1} (Found: C, 74.5; H, 5.5. $C_{72}H_{61}P_4Rh$ requires C, 75.0; H, 5.3%); δ_H (Rh-*H*, unfound), 7.48 7.75, (60H, m, Rh P*Ph*$_3$).(Lit.[119] for all data).

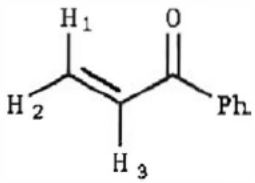
3.2.2.2 Preparation of Dihydrotetrakis(triphenylphosphine) ruthenium(II)[120]



$C_{72}H_{62}P_4Ru$
MW = 1152.25

Hydrated ruthenium trichloride (0.53g, 2.0mmol) in hot, degassed ethanol (20ml) was added to a vigourously stirred solution of triphenylphosphine (3.14g, 12.0mmol) in boiling ethanol (120ml) under argon. Subsequent, rapid, portionwise addition of of sodium borohydride (0.38g, 10.0mmol) in hot ethanol (20ml) gave a yellow precipitate which was filtered off, washed with ethanol, water and ethanol again before being dried *in vacuo* to give the product as mustard yellow microcrystals (2.02g, 87.5%), ν_{RuH} 2075cm^{-1}; (Found: C, 74.5; H, 5.9. $C_{72}H_{62}P_4Ru$ requires C, 75.05; H, 5.45%); δ_H (Ru-*H*, unfound), 6.72-7.85 (60H, m, Ru-P*Ph*$_3$). (Lit.[120] for all data except ^{1}H NMR).

3.2.2.3 Preparation of Phenyl Vinyl Ketone 83[121]



C_9H_8O
MM = 132.15

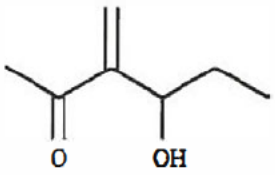
83

β-Dimethylaminopropiophenone hydrochloride (20.00g, 0.13mol) was steam distilled until the distillate coming over no longer appeared cloudy (≈ 4 - 8 hours). The distillate was then extracted with methylene chloride (3 x 50ml)and the combined extracts dried over anhydrous magnesium sulphate. Quinol was added to prevent polymerisation of the phenyl vinyl ketone during the distillation and extraction processes. Filtration and removal of the solvent *in vacuo* gave phenyl vinyl ketone **83** as a pale yellow oil (10.04g, 59%) δ_H 5.87 (1H, dd, H_2), 6.40 (1H, dd, H_1), 7.30 (1H, dd, H_3), 7.3 - 8.3 (5H, m, -*Ph*). (Lit.[121]).

3.2.2.3 General Procedure 1: The Coupling of Vinyl Compound and Aldehyde to Prepare Aldol-Type Products[75]

Vinyl compound (5mmol) and propanal **72** (0.581g 10mmol) were sealed in a pyrex tube under argon with $[RhH(PPh_3)_4]$ **75** or $[RuH_2(PPh_3)_4]$ **76** catalyst (0.6-5.3mol%). The tube was then heated by placing it in an oven at the correct temperature for a set time. After cooling, the catalyst was filtered off on a silica gel plug with 20% EtOAc-hexane. Solvent and the excess of propanal were removed *in vacuo*, and the sample was then purified by means of column chromatography.

3-Hydroxy-2-methylenehexan-2-one **73**

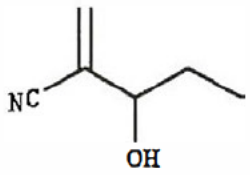


$C_7H_{12}O_2$
MW = 128.17

73

Methyl vinyl ketone **71** (0.351g, 5mmol) was treated according to General Procedure 1 using reaction conditions and catalyst concentrations indicated in Entries 1 to 3 of **Table 4** (Chapter 2). Column chromatography with 5% EtOAc-hexane and 1 drop MeOH per 250ml solvent yielded pure **73** (0.096-0.46g, 15-72%) δ_H 0.90 (3H, t, CH_2CH_3), 1.60 (2H, m, $-CH_2CH_3$), 2.33 (3H, s, $-COCH_3$), 3.32 (1H, s, -OH), 4.40 (1H, t, -CHOH), 6.03 - 6.13 (2H, dd, $-C=CH_2$). (Lit. [122]).

3-hydroxy-2-methylenepentanenitrile **79**



C_5H_9NO
MW = 111.14

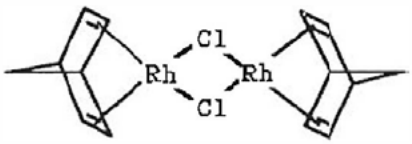
79

Acrylonitrile **78** (0.795g, 5mmol) was treated according to General Procedure 1 using the reaction conditions and catalyst concentrations indicated in Entries 17 to 20 in Table 4 of Chapter 2. Where the reaction was performed under pressure, the reactants were placed in an autoclave which was flushed with

nitrogen three times before being subjected to the indicated pressure (of nitrogen). Column chromatography with 5% EtOAc hexane yielded pure **79** (0.133-0.306g, 24-55%) δ_H 1.12 (3H, t, -C*H*$_3$), 2.49 (2H, m, -CH$_2$C*H*$_3$), 3.28 (1H, s, -O*H*), 4.30 (1H, t, -C*H*OH), 6.01 (2H, d, -C=C*H*$_2$). (Lit.[123])

3.2.3 ENANTIOSELECTIVE COUPLING OF α,β-UNSATURATED KETONES AND ALDEHYDES BY CHIRAL RHODIUM CATALYSTS

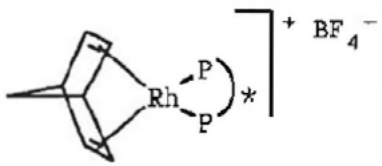
3.2.3.1 Preparation of Bis[(2,3,5,6-η)-bicyclo[2.2.1]hepta-2,5-diene]di-μ-chlorodirhodium(I) **93**[97]



$C_{14}H_{16}Cl_2Rh_2$
MM = 461.00

Hydrated rhodium trichloride (0.7g, 2.7mmol) and norbornadiene (2ml, 18.5mmol) in 95% ethanol (10ml) were shaken together for 2 days under argon. The yellow powder was filtered off and then recrystallised from hot chloroform-light petroleum, to give pure norbornadienerhodium(I) chloride 93 as fine yellow crystals (0.65g, 52%) δ_H 1.20 (2H, s, -C*H*$_2$), 3.88 (6H, m, -C*H*, -C*H*=C*H*); (Found: C, 37.2; H, 3.7. $C_{14}H_{16}Cl_2Rh_2$ requires C, 36.5; H, 3.5%). (Lit.[97]).

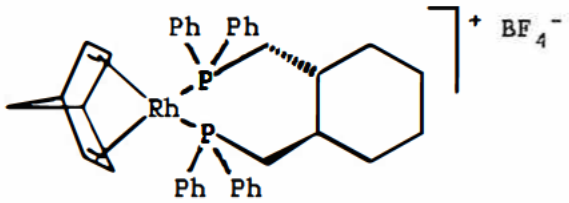
3.2.3.2 General Procedure 2: The Preparation of Catalyst Precursors 95a-d[98] (See **Scheme 30** in Chapter 2)



95a-d

$[Rh(NBD)Cl]_2$ **93** (0.100g, $2.79x10^{-4}$mol) was stirred in degassed acetone (8.0ml) under argon, while $AgBF_4$ (0.109g, $5.59x10^{-4}$mol) in acetone (8.0ml) was added dropwise at room temperature with stirring. After 2 hours, AgCl precipitate was filtered off with microfibre filter. The reaction mixture was cooled to 15°C in an ice/salt bath. Chiral diphosphine **102-105** ($4.7x10^{-4}$mol) in solvent (20ml) was then added cold, dropwise over 30 minutes with vigorous stirring. The mixture was allowed to warm to room temperature over 2 hours. Removal of solvent *in vacuo* yielded **95a-d**.

***(2,3,5,6 η)-Bicyclo[2.2.1]hepta-2,5-diene][((1S,2S)-(+) cyclohexane-1,2 dimethyleneyl)bis[diphenylphosphine]-P,P´]rhodium(I) tetrafluoroborate* 95a**



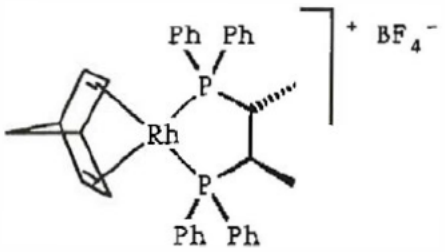
$C_{39}H_{42}P_2BF_4Rh$
MM = 762.39

95a

(+) BDPMC **102** was treated according to General Procedure 2 using degassed acetone as solvent, to yield **95a** (0.162g, 76%)

δ_P doublet at 21.64 and 26.39 ppm (J_{Rh-P} = 153.06 Hz); (Found: C, 60.9; H, 6.0. $C_{39}H_{42}P_2BF_4Rh$ requires C, 61.44; H, 5.55%).

[(2,3,5,6,-η)-Bicyclo[2.2.1]hepta-2,5,-diene][((2R,3R,)-(+)-(1,2-dimethyl-1,2-ethanediyl)bis[diphenylphosphino]-P,P']rhodium(I) tetrafluoroborate **95b**



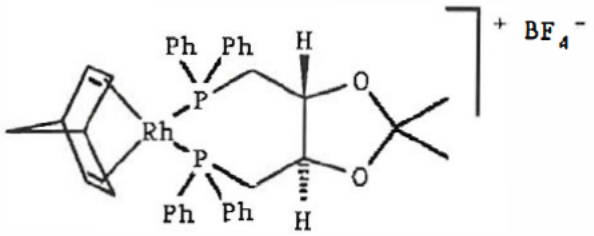
$C_{35}H_{36}P_2BF_4Rh$

MM = 708.30

95b

(+)-Chiraphos **103** was treated according to General Procedure 2 using degassed acetone as solvent, to yield **95b** (0.140g, 71%) δ_P doublet at 53.94 and 58.71ppm (J_{Rh-P} = 153.62 Hz); (Found: C, 60.0; H, 5.4. $C_{35}H_{36}P_2BF_4Rh$ requires C, 59.35; H, 5.12%). (Lit.[103,124,125]).

[2,3,5,6-η)-Bicyclo[2.2.1]hepta-2,5-diene][((4R,5R)-(-)-(2,2-dimethyl-1,3-dioxalane-4,5-diyl)bis(methylene)]bis[(diphenylphosphino)-P,P']rhodium(I) tetrafluoroborate **95c**

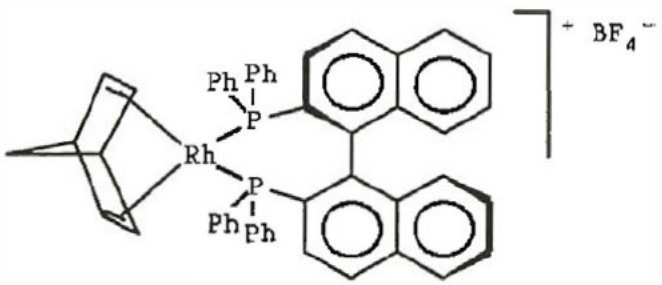


$C_{38}H_{40}O_2P_2BF_4Rh$
MM = 780.38

95c

(-)-DIOP **104** was treated according to General Procedure 2 using degassed acetone as solvent, to yield **95c** (0.176g, 81%) δ_P doublet at 12.73 and 17.49ppm (J_{Rh-P} = 153.49 Hz); (Found: C, 58.8; H, 5.5. $C_{38}H_{40}O_2P_2BF_4Rh$ requires C, 58.48; H, 5.17%). (Lit.[103]).

[(2,3,5,6-η)-Bicyclo[2.2.1]hepta-2,5-diene][1,1'-binaphthalene]-2,2'-diylbis[diphenylphosphino]-P,P']rhodium(I) tetrafluoroborate **95d**



$C_{51}H_{40}P_2BF_4Rh$
MM = 904.54

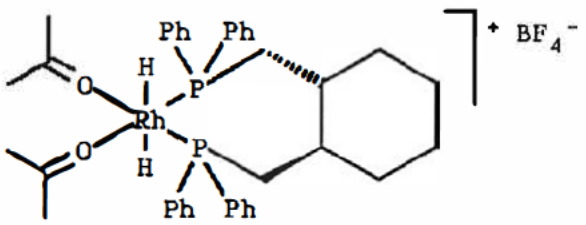
95d

( ) BINAP **105** was treated according to General Procedure 2 using degassed THF as solvent, to yield **95d** (0.197g, 78%) δ_P doublet at 22.32 and 27.18ppm (J_{Rh-P} = 156.44 Hz); (Found: C, 68.1; H, 4.8. $C_{51}H_{40}P_2BF_4Rh$ requires C, 67.72; H, 4.46%). (Lit.[126]).

3.2.3.3 General Procedure 3: Preparation of Activated Catalyst Species **98a-d**[99]

Catalyst precursor **95a-d** ($5x10^{-5}$mol) was dissolved in degassed acetone (10ml) under argon. Oxygen free hydrogen was then bubbled through at the rate of ±2 bubbles per second for 20 minutes. Solvent was then removed *in vacuo*, leaving the "catalyst soup" as a yellow brown powder, containing **98a-d** in small percentage. ^{31}P NMR doublet signals are probably due to the predominant species of the type $[Rh(Sol)_2(P\text{-}P)]^+$ **100** in the mixture.[101,102]

***Bis(acetone)[((1S,2S) (+) cyclohexane 1,2 dimethyleneyl)bis [diphenylphosphine]-P,P´]dihydrorhodium(III) tetrafluoroborate* 98a**

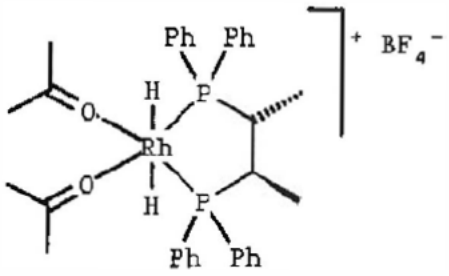


$C_{38}H_{48}O_2P_2BF_4Rh$
MM = 788.42

98a

[(NBD)Rh((+) BDPMC)]$^+BF_4^-$ **95a** (0.039g, $5x10^{-5}$mol) was treated according to General Procedure 3, yielding a mixture of catalyst species. δ_P("catalyst soup") doublet at 44.27 and 50.24ppm (J_{Rh-P} 192.02 Hz).

Bis(acetone)dihydro[((2R,3R,)-(+)-(1,2-dimethyl-1,2-ethanediyl)bis[diphenylphosphino]-P,P']rhodium(III) tetrafluoroborate **98b**

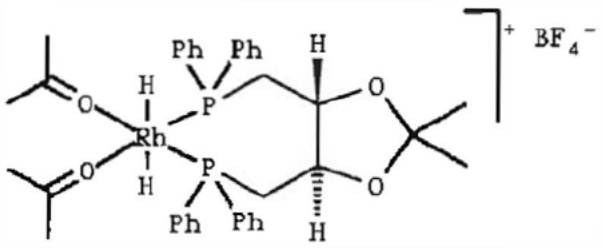


$C_{34}H_{42}O_2P_2BF_4Rh$
MM = 734.34

98b

[(NBD)Rh((+)-Chiraphos)]$^+BF_4^-$ **95b** (0.037g, 5x10^{-5}mol) was treated according to General Procedure 3, yielding a mixture of products. δ_P("catalyst soup") doublet at 77.03 and 83.08ppm (J_{Rh-P} = 194.72 Hz). (Lit.[103,124,125]).

Bis(acetone)dihydro[((4R,5R)-(-)-(2,2- dimethyl-1,3-dioxalane-4,5-diyl)bis(methylene)]bis[(diphenylphosphino)-P,P']rhodium(III) tetrafluoroborate **98c**

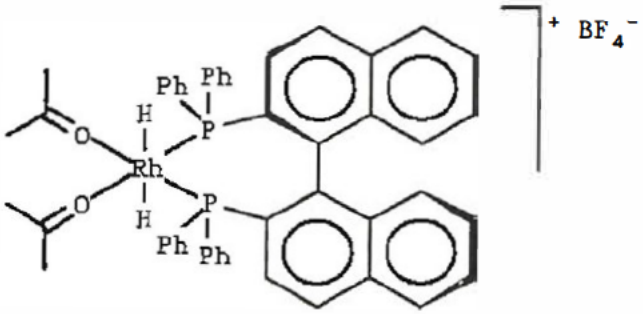


$C_{37}H_{46}O_4P_2BF_4Rh$
MM = 806.42

98c

[(NBD)Rh((-)-DIOP)]$^+BF_4^-$ **95c** (0.040g, 5x10^{-5}mol) was treated according to General Procedure 3, yielding a mixture of products. δ_P ("catalyst soup") doublet at 34.54 and 40.63ppm (J_{Rh-P} = 194.87 Hz). (Lit.[103]).

[1,1'-binaphthalene-2,2'-diylbis[diphenylphosphino] P,P']bis (acetone)dihydrorhodium(III) tetrafluoroborate **98d**



$C_{50}H_{46}O_2P_2BF_4Rh$
MM = 930.58

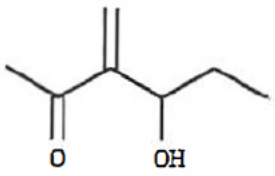
98d

[(NBD)Rh((-)-BINAP)]$^+BF_4^-$ **95d** (0.047g, 5x10 $^{-5}$mol) was treated according to General Procedure 3, to yield a mixture of products. δ_P ("catalyst soup") doublet at 47.76 and 54.01ppm (J_{Rh-P} = 201.24 Hz). (Lit.[126]).

3.2.3.4 General Procedure 4: The Coupling of α,β-Unsaturated Ketones and Aldehyde by Catalysts **98a-d**[75]

Activated "catalytic soup" containing **98a-d** (1-3mol%) in degassed acetone (± 2ml) was transferred under argon to a pyrex reaction vial. The solvent was removed *in vacuo* leaving the catalyst as a yellow-brown powder. To this was added α,β-unsaturated ketone **71,106-109** (5mmol) and propanal **72** (0.581g, 10mmol). The reaction vial was then sealed under argon, and heated to 105°C for 5-14 hours. After cooling, the vial was opened and the catalyst removed by eluting the reaction mixture through a silica gel plug with 20% EtOAc-hexane. Solvent and excess propanal were removed *in vacuo*, and the crude product was purified by means of column chromatography with 5% EtOAc-hexane and 1 drop of MeOH per 250ml of solvent.

3-Hydroxy-2-methylenehexan-2-one **73**



$C_7H_{12}O_2$
MW = 128.17

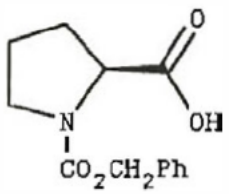
73

Methyl vinyl ketone 73 was treated according to General Procedure 4 using reaction times and catalyst concentrations as shown in **Table 5** (Chapter 2). Column chromatography yielded pure **73**. δ_H 0.90 (3H, t, $-CH_2CH_3$), 1.60 (2H, m, CH_2CH_3), 2.33 (3H, s, $-COCH_3$), 3.32 (1H, s, OH), 4.40 (1H, t, -CHOH), 6.03 6.13 (2H, dd, $-C=CH_2$). (Lit. [122]).

3.2.4 COUPLING OF α,β-UNSATURATED KETONE AND ALDEHYDE BY A RHODIUM CATALYST WITH A CHIRAL DINITROGEN LIGAND

3.2.4.1 Preparation of (S) 2 n Butylaminocarbonylpyrrolidine **122** as Ligand (See **Scheme 32** in Chapter 2)

(S)-1-Benzyloxycarbonylproline **119**[108]

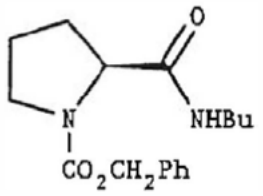


$C_{13}H_{15}NO_4$
MM = 251.28

119

L-Proline (20g, 0.174mol) was dissolved in 2N NaOH (250ml) and then cooled in an ice-bath to 0°C. Benzyl chloroformate (50% in toluene) (30ml, 0.18mol) was added with stirring. 4N NaOH (70ml) was then added. The solution was allowed to reach room temperature and then stirred overnight. The aqueous solution was acidified with cooling in an ice-bath to pH2 with 6M HCl. The resultant mixture was saturated with Na_2SO_4, and extracted with EtOAc (3x100ml). The extracts were combined, dried over anhydrous Na_2SO_4 twice and concentrated down to give a colourless oil, which was recrystallised from EtOAc-hexane. Filtration of the crystals yielded pure **119** (27.3g, 62.4%) δ_H 2.02 (4H, m, $-CH_2CH_2CH_2CH$), 3.52 (2H, t, $-CH_2N$), 4.38 (1H, t, $-CHCOOH$), 5.22 (2H, s, $-CH_2Ph$), 7.35 (5H, s, $-Ph$), 10.80 (1H, s, $-COOH$).

***(S)-1-Benzyloxycarbonyl 2 n butylaminocarbonylpyrrolidine* 120**[109]



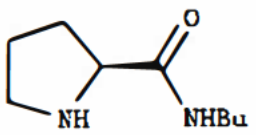
$C_{17}H_{24}N_2O_3$
MM = 306.40

120

A solution of (S)-1-Benzyloxycarbonylproline **119** (3.125g, 12.54mmol) was dissolved in EtOAc (20ml) at 0°C under argon. Triethylamine (1.269g, 12.54mmol) in EtOAc (10ml) was added. Ethyl chloroformate (1.361g, 12.54mmol) in EtOAc (10ml) was added slowly over 5 minutes at 15° to -20°C (using an isopropyl alcohol-liquid nitrogen bath). n-Butylamine (0.917g, 12.54mmol) in EtOAc (10ml) was added at -15°C. The mixture was kept at -15°C for 1 hour and at 0°C for another hour. The temperature was gradually raised to room temperature and

allowed to stir overnight. The mixture was quenched by the addition of water and more EtOAc. The organic layer was washed with each of 4% $NaHCO_3$ solution, brine, 2% HCl and brine again. The organic layer was dried over anhydrous magnesium sulphate and concentrated to give crude **120**. Recrystallisation from EtOAc-cyclohexane gave pure **120** (3.074g, 80%) δ_H 0.95 (3H, t, CH_2CH_3), 1.42 (4H, m, $-CH_2CH_2CH_3$), 2.03 (4H, m, $-CH_2CH_2CH_2CH$), 3.28 (2H, q, $-CONHCH_2$), 3.60 (2H, t, $-CH_2N$), 4.34 (1H, t, $-CHCONH$), 5.21 (2H, s, $-CH_2Ph$), 7.33 (5H, s, $-Ph$).

(S)-2-n-butylaminocarbonylpyrrolidine **121**[111]



$C_9H_{18}N_2O$
MM = 170.25

121

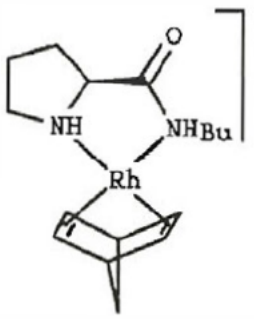
(S)-1-Benzyloxycarbonyl-2-n-butylaminocarbonylpyrrolidine **120** (0.200g, 1.17mmol) was dissolved in 4.4% HCOOH-MeOH (10ml) and placed in a 25ml round-bottom flask containing freshly prepared palladium-black (0.200g) and 4.4% HCOOH-MeOH (10ml). The mixture was stirred for ±5 minutes under argon until TLC indicated that reaction was complete and no N-formylated product **122** was present. The palladium black was filtered off and washed with MeOH (10ml) and then water (10ml). The combined filtrates were dried *in vacuo*. Column chromatography with 50% EtOAc-hexane yielded pure **121** (0.141g, 71%), IR(cm^{-1}) $\nu_{C=O}$ 1668; δ_H 0.91 (3H, t, $-CH_2CH_3$), 1.36 (2H, m, $-CH_2CH_3$), 1.49 (2H, m, $-CH_2CH_2CH_3$), 1.98 (4H, m, $-CH_2CH_2CH_2CH$), 2.32 (2H, $-CONHCH_2$), 3.25 (2H, t, $-CH_2N$), 4.36 (1H, $-CHCONH$), 7.68 (2H, s, $NH,NHCO$); δ_C 13.75 ($-CH_3$), 20.08 ($-CH_2CH_3$), 24.93 ($-CH_2CH_2CH_3$), 30.58 (ring $-CH_2CH_2NH$), 31.36 ($-CH_2CH$), 39.47 ($-CONHCH_2$), 46.28 ($-CH_2NH$), 59.34 ($-CHCO$), 170.25 ($-CO$); m/z(EI) 170(M^+, 1%), 70(100).

Palladium black[127]

Palladium chloride (5g) was dissolved in concentrated hydrochloric acid (30ml) and diluted with water (80ml). This solution was cooled in an ice-salt bath before addition of 40% formaldehyde (35ml). To this was added dropwise over 30 minutes a cold solution of potassium hydroxide (35g) in water (35ml) with vigorous stirring. The mixture was then warmed to 60°C for 30 minutes, allowed to cool, and the palladium precipitate washed with water 6 times by decantation. The precipitate was filtered on a sintered crucible, washed with water (1l), sucked dry, and transferred to a desiccator. Yield is ±3g.

3.2.4.2 Preparation of Catalyst, [(S) 2-n-Butylaminocarbonyl-pyrrolidine]diacetonedihydrorhodium(III) tetrafluoro borate **124**

[(S)-2-n-Butylaminocarbonylpyrrolidine]norbornadienerhodium(I) tetrafluoroborate **123**[128]



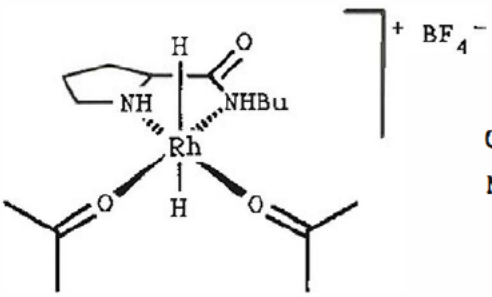
$C_{16}H_{26}N_2OBF_4Rh$
MM = 452.11

123

To a solution of $[Rh(NBD)Cl]_2$ (0.461g, 1mmol) in CH_2Cl_2 (10ml) under argon was added a solution of (S)-2-n-butylaminocarbonyl-

pyrrolidine **121** (0.255g, 1.5mmol) in CH_2Cl_2 (10ml) and a solution of $AgBF_4$ (0.389g, 2mmol) in CH_2Cl_2 (10ml). The reaction mixture was stirred for 3 hours at room temperature before the AgCl precipitate was filtered off. Removal of solvent *in vacuo* left a yellow-orange oil, which was washed several times with diethyl ether to leave **123**. (Found: C, 42.9; H, 5.6; N, 6.0. $C_{16}H_{26}N_2OBF_4Rh$ requires C, 42.50; H, 5.80; N, 6.20%).

***[(S)-2-n-Butylaminocarbonylpyrrolidine]diacetonedihydro-rhodium(III) tetrafluoroborate* 124**

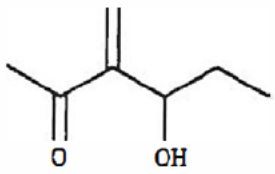


$C_{15}H_{32}N_2O_3BF_4Rh$
MM = 472.10

124

[(S)-2-n-Butylaminocarbonylpyrrolidine]norbornadienerhodium(I) tetrafluoroborate **123** (0.452g, 1mmol) was dissolved in degassed acetone (10ml) and oxygen-free hydrogen then bubbled through for ±20 minutes, upon which the yellow-orange solution turned brown. Removal of solvent *in vacuo* left an activated "catalyst soup" as an orange-brown oil, containing a small quantity of **124**.

3.2.4.3 Coupling of methyl vinyl ketone 71 and propanal 72 by catalyst 124 to form 3-Hydroxy 2 methylenehexan-2-one 73[75]



$C_7H_{12}O_2$
MW = 128.17

73

Activated "catalyst soup" containing **124** (0.024g, $5x10^{-5}$mol) in acetone (1ml) was transferred to a pyrex reaction vial under argon. The solvent was removed *in vacuo*, and methyl vinyl ketone **71** (0.350g, 5mmol) and propanal **72** (0.581g, 10mmol) added. The reaction vial was sealed under argon, and then heated to 105°C for 7 hours in an oven. After cooling, the vial was opened and the catalyst removed by eluting the reaction mixture through a silica gel plug with 20% EtOAc-hexane. Solvent and excess propanal were removed *in vacuo*, and the crude product was purified by means of column chromatography with 5% EtOAc-hexane and 1 drop of MeOH per 250ml of solvent, yielding pure **73**. δ_H 0.90 (3H, t, $-CH_2CH_3$), 1.60 (2H, m, $-CH_2CH_3$), 2.33 (3H, s, $-COCH_3$), 3.32 (1H, s, -OH), 4.40 (1H, t, -CHOH), 6.03 - 6.13 (2H, dd, $-C=CH_2$). (Lit. [122]).

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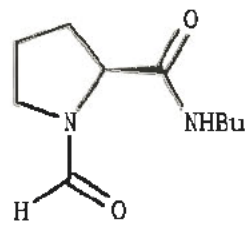
APPENDIX

^{1}H and ^{13}C Nuclear Magnetic Resonance Spectra

Spectrum 1

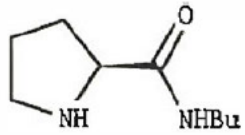
122

Spectrum 2

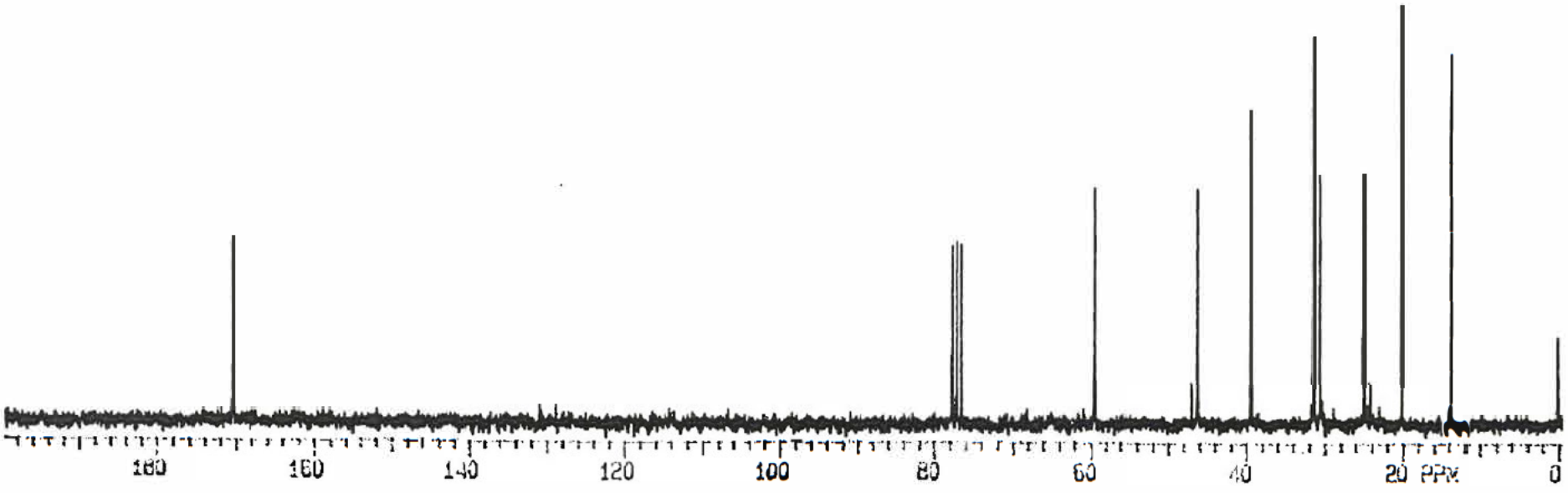


122

Spectrum 3



121



Spectrum 4

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