IMPROVEMENTS IN THE CATALYTIC HYDROGENATION OF ALKENES

A thesis presented for the degree of Master of Science

in the Faculty of Science of the University of St. Andrews

by

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University of St. Andrews

To my Father for his invaluable help and encouragement.

DECLARATION

I, Sheila Ann Preston, hereby certify that this thesis has been composed by myself, that it is a record of my own work, and that it has not been accepted in partial or complete fulfilment of any other degree or professional qualification.

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ABSTRACT

This research is based upon earlier work by Wilkinson *et al.* showing that alkenes can be hydrogenated at ambient temperature and pressure in the presence of chlorotris (triphenylphosphine) rhodium(I).

Commercially there is great interest in high selectivity in the hydrogenation of unsaturated hydrocarbons. The current state of knowledge of asymmetric catalytic hydrogenation of alkenes is reported from an extensive literature survey and the potential of homogeneous transition metal catalysts to operate in a highly specific manner is highlighted. Guiding principles are given for the elaboration of a chiral catalyst, rationalizing earlier empirical approaches.

The preparations of phosphinite ester complexes of Rh(I) and Ru(II) are described, with experimental detail. Limitations, especially the slow rate of hydrogenation of highly substituted alkenes have been overcome and unusual selectivities for diene reduction observed. Suggestions are made for more research into modifications of the catalyst, $RhCl(PPh_3)_2Ph_2PO_2CCH{=}CMe_2$, replacing the triphenylphosphine groups by an asymmetric *bis*(phosphine) ligand. If successful, this should result in an unusual and valuable addition to asymmetric hydrogenation catalysts.

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INTRODUCTION

A catalyst is a compound which changes the rate of a chemical reaction and is recovered unchanged at the end of the reaction. In accordance with the second law of thermodynamics no chemical reaction can proceed unless the total Gibbs free energy (ΔG) of the products of the reaction is lower than that of the starting materials under reaction conditions. Even if this fundamental condition is obeyed a reaction may not proceed, this failure being due to a high kinetic barrier or free energy of activation (ΔG^*) for the reaction. Catalysts are employed in order to lower the activation energy of a reaction, achieving this by formation of one or more intermediates or transition states. Since the catalyst remains unchanged on conclusion of the reaction only small amounts need be used (typically ~ 0.1 mole %) and even complexes of the most expensive metals can find large scale industrial uses.

Homogeneous precious metal catalysts are becoming increasingly important in organic chemical synthesis. Although the hydrogenation of simple alkenes is not of industrial significance as alkanes are considerably more abundant, there are certain types of hydrogenation in which selectivity is of importance and the use of homogeneous catalysts desirable. These reactions can be divided into two types: asymmetric hydrogenations and selective hydrogenations. Other types of hydrogenation, for example that of C≡N and C=O in the

Fischer-Tropsch process, are of industrial significance. Transfer hydrogenations are also possible but have less importance.

Before discussing these in detail mention should be made of the early homogeneous hydrogenation catalysts, in particular Wilkinson's catalyst[1-3]. This compound has had a profound effect on many areas of chemistry and besides being a useful homogeneous hydrogenation catalyst it has also been found to catalyse transfer hydrogenation, hydrosilylation and isomerization. Its discovery was the starting point of modern homogeneous catalysis and many of the complexes now being investigated or employed for various types of hydrogenation reaction are modelled on the basic structure of Wilkinson's catalyst.

The complexes of the platinum group metals are of special interest for use as homogeneous catalysts due to their d^8 electron configurations. For transition metal ions, the stable inert gas structure is achieved with 18 electrons in the valence shell. However d^8 metal complexes, particularly of 2nd. and 3rd. row transition metals favour a square planar arrangement with 16 electrons in the outer shell. This enables the molecule to be activated by either simple coordination, normally for a neutral molecule by donating two electrons to the metal to form a bond, or by oxidative addition. Once activated, the reagents react together by insertion, and the product is then released usually by reductive elimination.

The substantial d-electron density on the metal centre allows for coordination of molecules such as alkenes to be stabilized through back donation. These do not bond to the metal end-on because there are no lone pair electrons; the bonding is a sideways, synergic interaction leading to a considerable weakening of the unsaturated linkage. This type of bonding, known as the Dewar, Chatt, Duncanson model, renders the coordinated alkene susceptible to nucleophilic attack and attack by small molecules such as H_2, unlike the more electronegative free alkene, (fig.1, page 7).

Due to this method of hydrogenation, Wilkinson's catalyst shows many advantages over conventional heterogeneous hydrogenation catalysts, which are usually finely divided late transition metals. One advantage is the elimination of problems associated with the reproducibility of uniform catalyst particle size and surface properties. Superficially, heterogeneous catalysts would appear to be the more desirable as separation of the product is simple. However, homogeneous catalysts, by their very nature, are inherently more selective, it being possible to engineer selectivity by modification of various ligands in the molecule.

Unlike heterogeneous hydrogenation catalysts, $RhCl(PPh_3)_3$ does not catalyse side reactions during the hydrogenation of C-C multiple bonds, nor does it usually suffer severely from poisoning by sulphur compounds. Its main limitation is the slow rate of hydrogenation shown by highly substituted alkenes.

By replacing one of the triphenylphosphine ligands with a chelating αβ-unsaturated phosphinite ester we have achieved greater rates of hydrogenation for highly substituted acrylic acid substrates. Asymmetric syntheses seem possible and reduction of dienes to monoenes has been achieved with selectivities towards the more substituted double bond.

CHAPTER I

HOMOGENEOUS CATALYTIC HYDROGENATION OF ALKENES

A LITERATURE SURVEY

1.1 Asymmetric hydrogenation

An asymmetric synthesis is a preferred transformation of an achiral substrate (or intermediate fragment) possessing enantiotopic groups, atoms, faces or centres into one enantiomer of the product. Substrates incorporating these features can loosely be called prochiral.

The need to resolve racemic mixtures whenever an asymmetric centre is produced has been a serious limitation to the synthetic chemist. Usually only one isomer is needed and resolution, involving many recycle loops and fractional crystallizations is an expensive and time consuming business. In the past, biochemical routes have been resorted to such as in the preparation of L-glutamate, L-lysine and L-menthol[4]. Enzymes are potentially available for converting an achiral substrate to a chiral product. However, the isolation, purification, identification and stabilization of enzymes remains an obstacle to their use.

The enantiomeric purity of a chiral compound is defined by its enantiomeric excess (% *ee*)

$$\frac{\text{(R)enantiomer - (S)enantiomer}}{\text{(R)enantiomer + (S)enantiomer}} \times 100\ \% = \%\ ee$$

To improve enantiomeric purity in a compound, three methods are available:-

(a) Resolution[6-7]

This technique involves the resolution of a racemate via diastereoisomers and requires 1/2 - 1 molar quantities of chiral resolving agent. To be economically viable this agent must be recoverable.

(b) Chiral template method[8-10]

The synthesis of vitamen C from D-glucose is an example of this method in which an inexpensive, readily available pure enantiomer is converted into a relatively expensive chiral product.

(c) Catalytic asymmetric synthesis

Until 1968 there was no single non-enzymatic catalytic asymmetric synthesis achieved with an enantiomeric excess above 50%. Now no fewer than seven reactions can be carried out in *ee* of 75% - 100%. In addition to catalytic hydrogenation[11-16], these include intramolecular aldol cyclizations, Michael additions, carbene additions, cycloadditions, thiol additions and epoxidations.

Of these, this dissertation is concerned with improvements in asymmetric catalytic hydrogenation.

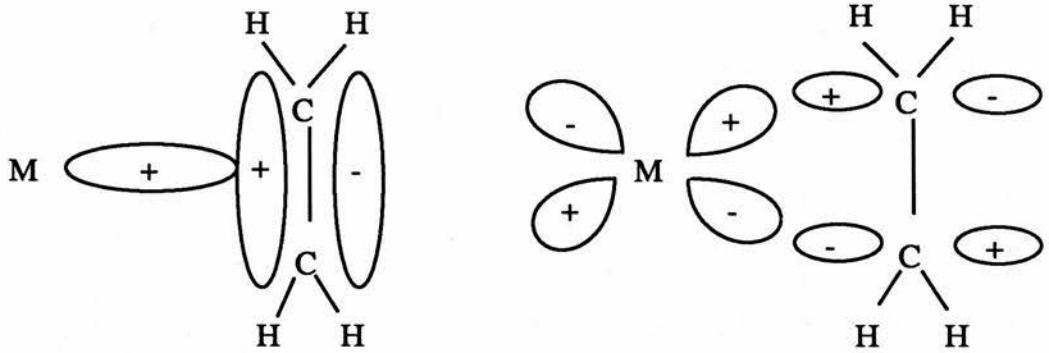


Fig. 1

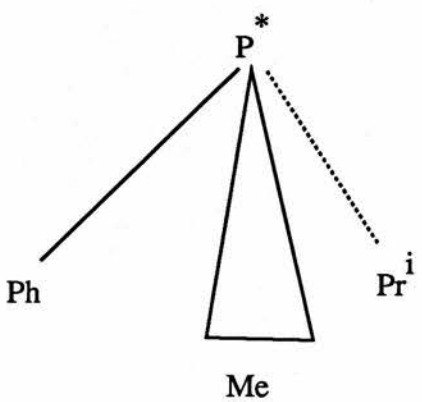
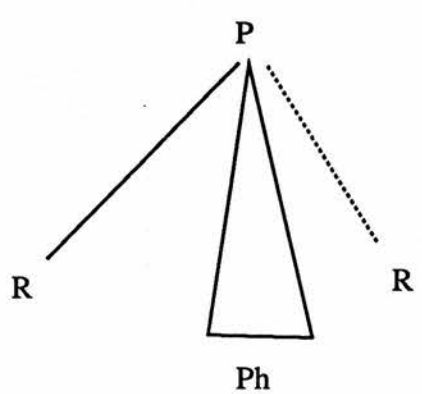


Fig. 2



$R = -CH_2C^*HEtMe$

Fig. 3

Asymmetric catalysis is fundamentally a kinetic phenomenon. A chiral auxiliary associated with the catalyst discriminates the prochiral features of the bound substrate by differences in the reaction rates associated with the production of one or other of the enantiomers of the product. The enantiomeric excess is determined by the two diastereomeric transition states formed during the asymmetric reaction. The greater this difference, the better is the enantioselection. The *ee* is determined in the first, irreversible step involving the diastereomeric transition states (the enantioselective step).

The difference in the diastereomeric transition state free energies is affected by extremely subtle interactions of the chiral auxiliary and the bound, prochiral substrate. Because a difference of only *ca* 12 KJ/mole is sufficient to give essentially an optically pure product, the task of predicting the magnitude and sense of the *ee* of the product is extremely difficult. Generally, however, it is necessary to have a fairly rigid orientation as well as close association of the chiral catalyst and the prochiral substrate.

Soon after the discovery by Wilkinson that $RhCl(PPh_3)_3$ was a homogeneous catalyst for hydrogenation of carbon-carbon double bonds, the search for an asymmetric analogue began.

It is not easy to design a chiral catalyst as very often the configuration determining step of the catalysis is not known. It is also difficult to predict from molecular models or X-ray crystallographic data how the chiral ligand will be orientated in the coordination sphere of the metal and what are the chances of a good chiral discrimination at the key steps of the catalysis. Further complications arise from the fact that during the reaction some intermediates with labile chiral metallic centres can be created[17]. The elaboration of a chiral catalyst was quite empirical at first but, from knowledge gained over the past twenty-five years, when a known achiral catalyst is to be modified by the introduction of chiral ligands[20], guiding principles can be given:-

i) the chiral ligand should not drastically decrease the catalytic activity;

ii) because of the structural modifications on the ligands, it should be expected that the reaction mechanism of the known achiral catalyst could be altered;

iii) the chiral ligand has to remain coordinated to the metal during the step in which the asymmetric centre is created on the substrate;

iv) the synthesis of the ligand should be easy and flexible, allowing a start from cheap, natural products. Thus a resolution step is avoided and many analogues and quasi-enantiomeric ligands become available;

v) predictions and rational approaches are expected from information on the reaction mechanism and the structure of the various catalytic species.

Additionally, other factors such as the nature of the catalyst and reaction conditions must be taken into account while designing a catalytic system.

1.1.1 Early work on development of non-enzymatic catalysts

Prior to 1968 only a few examples of non-enzymatic catalytic asymmetric hydrogenation had been reported[21]. In 1968 Knowles and Sabacky[11] described a method of asymmetric hydrogenation employing as catalyst precursor a soluble rhodium complex that contained optically active tertiary phosphine ligands, RhL_3Cl_3 where L=PPhMePr (1a) or $PhP(CH_2.CHMeEt)_2$ (1b), (figs.2,3, p.7) and the structure of the catalyst's ligands could be varied according to the particular unsaturated substrate. Hydrogenation of α-phenylacrylic acid, $CH_2=C(Ph)COOH$ at 60° C with (1(a)) above as the catalyst gave optically active hydratropic acid with 15% optical purity.

In the same year Horner *et al*[12] found that α-ethylstyrene and α-methoxystyrene were hydrogenated to (S)-(+)-2-phenylbutane

(7-8% optical yield) and (R)-(+)-1-methoxy-1-phenylethane (3-4% optical yield) respectively by use of a rhodium catalyst formed *in situ* from [Rh(1,5-hexadiene)Cl]$_2$ and (S)-(+)-methyl - phenyl-n-propylphosphene in benzene.

The majority of these initial studies were concentrated upon tertiary phosphines which were chiral at phosphorus. This seemed reasonable as there is an intuitive tendency to design a system with the asymmetry as close to the metal as possible in the hope of increasing the asymmetric bias. However, it follows from general symmetry principles that the only necessary condition for asymmetric synthesis is that the hydrido intermediate must be chiral, and complexes of ligands that are dissymmetric remote from phosphorus also fulfil this requirement.

In 1971 Morrison and Burnett[13] reported the preparation of a chiral rhodium complex with neomenthyldiphenylphosphine (NMDPP) by reaction with Rh(I) μ-complexes of ethene or dienes in ethanol-benzene. The catalytically active species thus produced is of the type RhL_3Cl where L=NMDPP. The reduction of (E)-β-methylcinnamic acid in the presence of this catalyst gave a 61% enantomeric excess of (S)-3-phenylbutanoic acid, α^{25}_D+34.5° (neat). Similarly, reduction of (E)-α-methylcinnamic and atropic acids gave (R)-2-methyl-3-phenylpropanoic (52% *ee*) and (S)-hydratropic (28% *ee*) acids.

A further improvement in optical yields was introduced in 1971 when Kagan and Dang[22] achieved enantionmeric excesses of

72% for the reduction of acetamidocinnamic acid to (R)-N-acylphenylalanine and 63% for the reduction of atropic acid to (S)-hydratropic acid. The catalyst in this case was a rhodium(I) compound of the type [Rh(DIOP)ClS] where S=solvent.

The bidentate phosphine ligand has its chirality centred on carbon rather than phosphorus and the high stereo selectivities were attributed to the conformational rigidity of the phosphine chelating to the Rh atom, together with the participation of the acid function of the substrate.

The Monsanto group of W.S. Knowles *et al.*[23] in 1972 realised asymmetric synthesis of α-amino acids from α-acylamidoacrylic acids.

$$RCH{=}C(NHCOCH_3)COOH \xrightarrow[Rh\ cat.]{H_2} RCH_2{*}CH(NHCOCH_3)COOH \longrightarrow RCH_2{*}CH(NH_2)COOH$$

The method provided a practical synthesis of α-amino acids.

Enantiomeric excesses of up to 90% were achieved by using a new family of phosphine ligands containing an o-anisyl group and asymmetric at the phosphorus atom. Considerable variations in optical yield were obtained illustrating the importance of matching the phosphine and substrate. The o-anisyl ligand plays a major role, especially in the case of the phosphine ligand CAMP, presumably by involving weak interactions with the metal.

Chiral phosphine ligands have a central place in much of this early work; subsequent work followed several routes mainly using ligands chiral at phosphorus or at carbon, the latter being derived from a number of sources. Also during these developments, phosphinite ligands in place of phosphine ligands were examined.

1.1.2 Chiral phosphine ligands for alkene hydrogenation

Chiral phosphines can be divided into two main classes: monodentate and bi-dentate phosphines.

i) Monodentate chiral phosphines: there are three ways to design a chiral phosphine; the chirality can be located on the phosphorus atom, on a side chain or on both.

ii) Bidentate chiral phosphines: the chelation of the ligand can occur through one phosphorus atom and another group (amine, nitrile, amide, etc.) or it can involve two P atoms. One important objective is to keep a suitable distance between the two chelating points, in order to obtain a 5- to 8-membered chelate ring. If the ring is too large, the ligand will have a tendency to complex in a monodentate fashion (or to form a bridge between two metal atoms).

Another useful way to classify these ligands is according to the location of the chirality.

a) Ligands chiral at phosphorus

Early work[11,12] using Rh(I) complexes of methylphenylpropylphosphine has been described previously. In 1972, various α-substituted styrenes were reduced using Rh-alkylmethylphenylphosphine complexes[24], the optical purities of the products varying between 2% and 19%. Prior to this, in 1970, other substrates had been examined, in particular the αβ-unsaturated carboxylic acids[25], using several new asymmetric phosphine catalysts.

In 1972, excellent results (*ee*'s 85-90%) were obtained for the reduction of α-acetamidoacrylic acids with a Rh(I)-CAMP catalyst[23], the products being L-amino acids with (+)-CAMP and D-amino acids with (-)-CAMP. The presence of the o-methoxyphenyl group provided an additional binding site for the substrate molecule and it was assumed that α-acetamidoacrylic substrates might act as a tridentate species binding to rhodium through the double bond and the carboxylate group and to the methoxy group of CAMP by hydrogen bonding.

Further investigations were made into the effect of the position of the methoxy group in acylmethylpropylphosphines[26]. For the hydrogenation of acetamidoacrylic acid and α-acetamidocinnamic acid a methoxy group in the para-position

had no influence on the optical yield, whereas an ortho-methoxy group caused significantly higher optical yields to be obtained. This can be explained by the weak interaction between the heteroatoms and rhodium. It is possible that, through this ortho- effect, a labile five membered ring is formed that hinders rotation around the metal-phosphorus bond, thus enabling a highly stereoselective interaction with the prochiral alkene.

Further studies with CAMP led to the synthesis of DiPAMP [1,2-*bis*[2-methoxyphenylphenylphosphino]ethane][22]. The Rh(I)-DiPAMP catalyst is not as sensitive to variations in reaction conditions as are many others, giving yields of over 80% for the reaction of α-acetamidoacrylic acid esters and over 90% for the reduction of α-enolethers, (fig.4, p.17).

b) Ligands chiral at carbon

i) Ligands derived from neomenthol

The first rhodium catalyst containing a chiral carbon atom was synthesised in 1971 using neomenthyldiphenylphosphine (NMDPP)[13]. αβ-unsaturated carboxylic acids such as (E)-β-methylcinnamic acid were reduced to products with higher optical yields than simple alkenes.

ii) Ligands derived from tartaric acid

In 1971, the chiral *bis*(phosphine) ligand (-)-2,3-isopropylidine-2,3-dihydroxy-1,4-*bis*[diphenylphosphino]-butane (DIOP) was prepared from (+)-tartaric acid[14,22]. By 1976, derivatives of phenylalanine were being prepared

catalytically[28] using a Rh(I)-(-)-DIOP catalyst in optical yields of up to 81%, all hydrogenations giving products in the (R)-conformation. Using Rh(I)-(+)-DIOP all products had the (S)-conformation. The high enantioselectivity of reduction of various substrates with DIOP arises from the high conformational rigidity of the *trans*-fused dioxolane within the chelate ring where diphosphine ligands are firmly bound to the metal.

Results obtained for the Rh(I)-DIOP and Ru-(PPh_3) systems for hydrogenation experiments were good , so it was attempted to combine the advantages into a single molecule by forming Ru-DIOP complexes[29-31]. The first catalytically active complex to be prepared was a binuclear complex with chiral tertiary phosphine ligands (fig.5, p.17), which efficiently catalysed mild-conditioned hydrogenations of carboxylic acids[30], the optical purity of the product being similar to that obtained using a 1:1 Rh-DIOP complex[14].

As with the Rh complexes the use of (+)-DIOP led to a predominance of the (S)-enantomer. In addition, the unsaturated dicarboxylic acids, itaconic, mesaconic and citraconic acids, (fig.6, p.17) have been reduced in the presence of $H_4Ru_4(CO)_8[(-)\text{-DIOP}]_2$ in toluene[29], the main product being methylsuccinic acid, 1.1% *ee* of the (S)-isomer from mesaconic acid and the racemic product from itaconic acid.

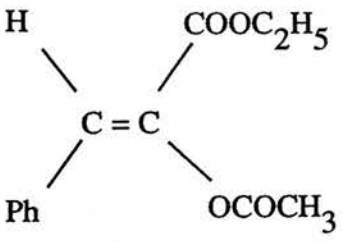


Fig.4

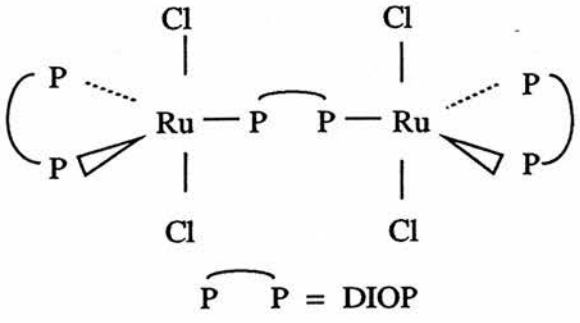
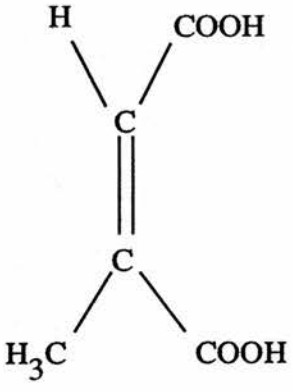
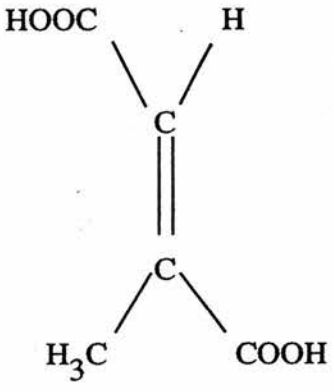


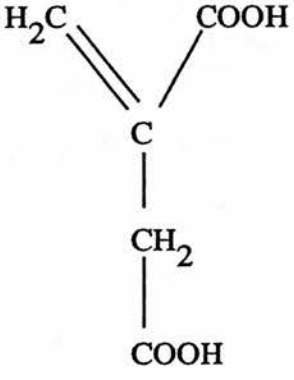
Fig.5



Itaconic acid

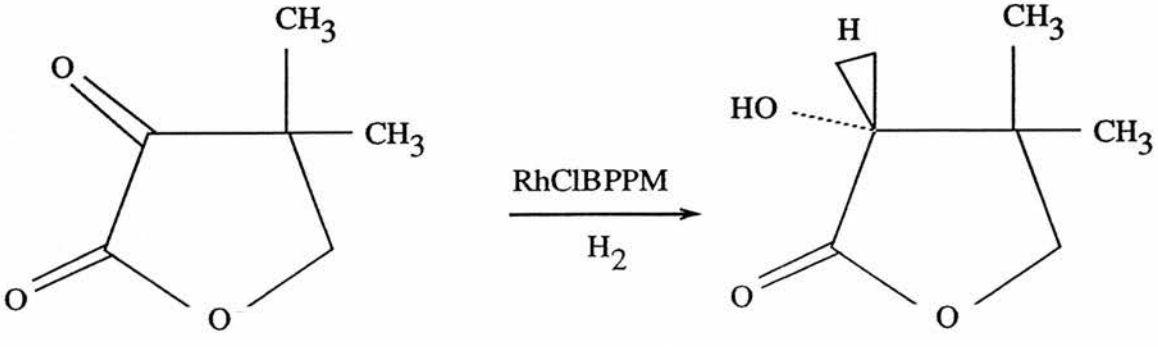


Mesaconic acid



Citraconic acid

Fig.6



Pantolactone synthesis

Eqn.1

iii) Ligands derived from hydroxyproline

The ligand (2R,4S)-N-t-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrridine (BPPM) was prepared in 1976 by Japanese workers[32]. It is a seven membered chelator with Rh(I) and Rh(I)-BPPM complexes have proved to be much more selective than those of Rh(I)-DIOP. An important intermediate in the synthesis of pantheine and coenzyme A, (R)-(-)-pantolactone, was synthesized using an asymmetric hydrogenation (87% optical purity) in the presence of a rhodium catalyst prepared from [Rh(1,5-cyclooctadiene)Cl]$_2$ and BPPM[33,34], (Eqn.1, p.17).

Mostly the unnatural (R)-amino acids are produced although varying the N-substituents of PPM strongly influences the optical yield and the steric course of the reaction, (Table 1).

Ligand	% *ee* and configuration of product
BPPM	84.8(R)
PPPM	59.2(R)
PPM	15.4(S)

Table 1: Ligand dependent optical yields in the pantolactone synthesis (50° C in benzene)

Various other N-substituents have been introduced; these include the N-cholesteryloxycarbonyl function to give CPPM[35] (giving 62%-67% optical yields of lactates) and the N-benzoyl function to give BZPPM[36]. PCPPM, NPPM and 1NPPM are more examples of a series of chiral, pyrrolidine-phosphines bearing various N-acyl substituents[37].

iv) Ligands derived from camphor

The ligand (+)-CAMPHOS, ((+)-(1R,3S)-1,2,2-trimethyl-1,3-*bis*[diphenylphosphinomethyl]cyclopentane) was prepared from (+)-camphoric acid[38]. Hydrogenations of αβ-unsaturated carboxylic acids in the presence of Rh(I)-CAMPHOS catalyst gave very poor optical yields (between 11% *ee*(R) and 6% *ee*(S)) whereas the related CRCPHOS gave slightly higher enantiomeric excesses, (15%(S))[39].

v) Ligands derived from butanediol

In 1977, Fryzuk and Bosnich[16] prepared the chiral phosphine (2S,3S)-*bis*(diphenylphosphino)butane, [(S,S)-CHIRAPHOS]. The very rigid conformation this adopts when coordinated to a metal leads to exceptionally high optical yields for the hydrogenation of (Z)-α-N-acetamidoacrylic acids, leucine and phenylalanine being produced in optically pure (R) form.

vi) Ligands derived from lactic acid

The ligand (R)-PROPHOS derived from (S)-lactic acid is contained in the chiral catalyst Rh-R-PROPHOS(norbornadiene)].ClO_4.0·5 CH_2Cl_2[40]. Asymmetric hydrogenations of (Z)-N-acetamidoacrylic acid derivatives gave the natural (S)-amino acids with *ee*'s of between 87% and 93%.

vii) Ligands derived from ferrocene

Chiral ferrocenylphosphine ligands possess two kinds of chirality, one on the side chain and the other on the 1,2-substituted cyclopentadiene ring. For this reason, ligands of this class such as (R)-(S)-BPPFA[41] and (R)-(S)-BPPFOH[42] exhibit a high degree of stereoselectivity in rhodium-complex catalysed hydrogenations. Hydrogenated products with lower optical purities and inverted (S)-configurations are obtained with BPPFA, an analogue of BPPFOH which lacks the hydroxyl group.

viii) Ligands derived from sugars

There has been considerable interest in utilizing the natural chiral pool in order to prepare ligands for asymmetric synthesis. The previous paragraphs have described various phosphines prepared from natural sources prior to 1978.

In 1978 Cullen and Sugi[43] reported the preparation of a *bis*(phosphinite), methyl- 2,3 -*bis*[o-diphenylphosphinol- 4,6 - o-benzylidine-α-D-glucopyranoside, synthesised from D-glucose, (fig.7, p.22). Complexed with Rh(I) this proved effective for the asymmetric hydrogenation of α-acetamidoacrylic acids and esters producing enantiomeric excesses of up to 80% of the natural (S)-amino acids, the reactions being fast and quantitative at low temperatures. Again, as for the chiral *bis*(phosphines) previously described, the high *ee*'s are probably due to the conformational rigidity of the ligand.

Various sugar derived monophosphines have been prepared by Descotes *et al.*[44] by the addition of lithium diphenylphosphide to the tosylates:
6-O-tosyl-1,2;3,4-di-o-isopropylidene-α-D-galactopyranose (a),
6-O-1,2;3,5-α-D-glucofuranose (b) and
5-O-tosyl-3-o-methyl-1,2-isopropylidine-α-D-xylofuranose (c).
That derived from (a) (fig.8,p.22) gave the highest enantiomeric excess for the reduction of α-acetamidoacrylic acids.

The *bis*(phosphines) erythritop and dioxop (figs.9,10, p.22) prepared by the degradation of the corresponding sugar, followed by reduction, tosylation and phosphination have been used for the catalytic hydrogenation of α-acetamidoacrylic acids giving *ee*'s as high as 86%.

Finally, the preparation of the chiral phosphinites *bis*(glucophinite) and *bis*((iodophinite), derived ultimately from glucose was reported by Johnson and Rangarajan in 1980[45].

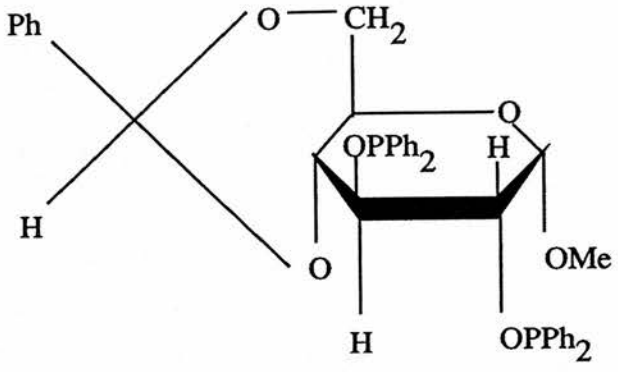


Fig. 7

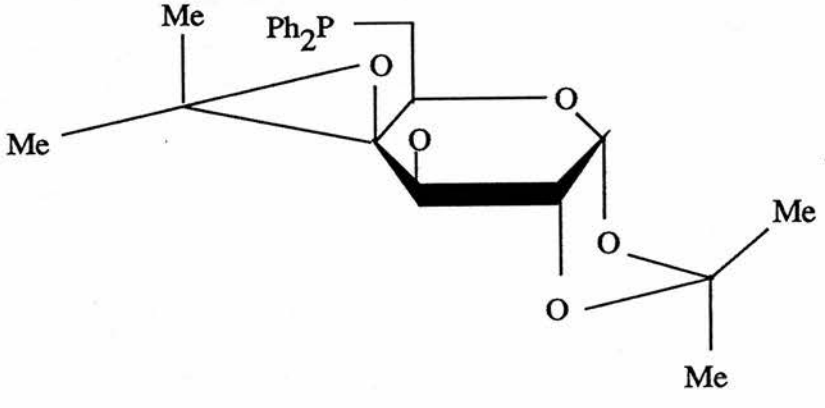
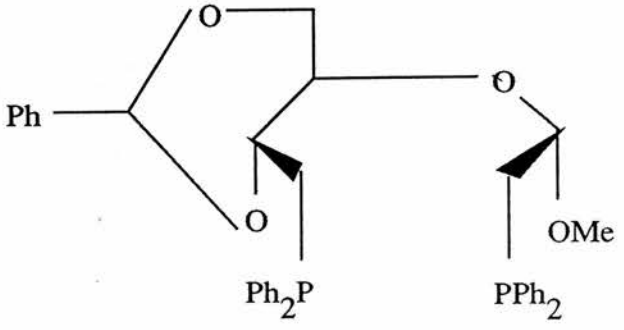
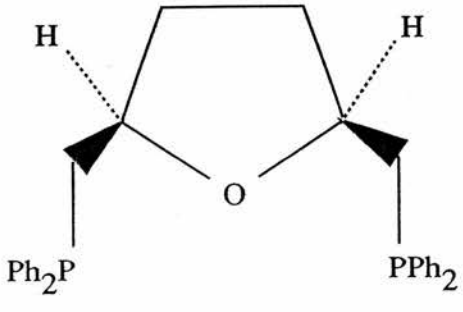


Fig. 8



Erythritop

Fig. 9



Dioxop

Fig.10

c) Ligands chiral at both phosphorus and carbon

In 1977 Fisher and Mosher[46] synthesised the first phosphine ligands chiral both at phosphorus and carbon, the 1-menthylmethylphenylphosphines (MMPP) that possessed opposite configurations at the phosphorus atoms. Reductions of (E)-β-methylcinnamic acid by Rh(I)-MMPP complexes of both epimers gave enantiomeric products. Thus, the stereo-chemistry at the phosphorus rather than at the carbon seems to control the product configuration.

1.1.3 Chiral phosphinite ligands for alkene hydrogenation

Most early studies into transition metal catalysed asymmetric hydrogenations concentrated on phosphine ligands of the types previously described. In 1975, Tanaka and Ogata[47] reported the preparation of the chiral *bis*(phosphinite), (+)-*trans*-BDPCH, ((+)-*trans*- 1,2 -*bis*(diphenylphosphinoxy)-cyclo -hexane) which, when complexed with rhodium exerted fairly effective stereochemical control, especially on the asymmetric hydrogenation of N-acetamidoacrylic acid derivatives. The optical yields obtained were in general higher than those in which DIOP is the asymmetry inducing ligand. Tanaka and Ogata attributed the good stereoselectivity to the chelating power and the greater distortion of the diphenylphosphinoxy group of the *bis*(phosphinite) compared with the diphenylphosphino group of DIOP.

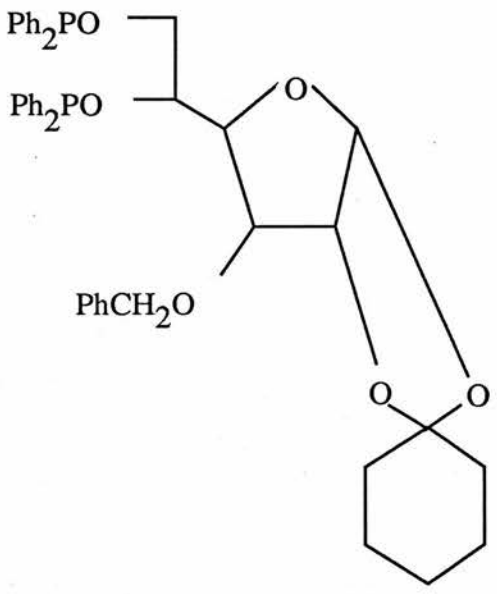
A further phosphinite, d-*trans*-BDPCP (d-*trans*-1,2-*bis*[diphenylphosphinoxy]cyclopentane)[48], improved on the general principle of (+)-*trans*-BDPCH by removing the conformational disadvantage of the flexible cyclohexane ring. The stereoselectivity for the asymmetric hydrogenation of N-acetamidoacrylic acids was considerably less than for (+)-*trans*-BDPCH. However it is interesting to note the very high optical yields obtained for simple substrates containing no polar functional groups such as carbonyl or amido groups. An *ee* of 60% (R) was obtained in the hydrogenation of α-ethylstyrene as opposed to 33% (R) with (+)-*trans*-BDPCH and 24.5% (S) with (-)-DIOP. The first example of a *bis*(phosphinite) prepared from a sugar was methyl- 2,3 - *bis*[o-diphenylphosphinol - 4,6 - o-benzylidene-α-D-glucopyranoside, as described previously[43].

From the work of Kagan[14,22] on DIOP and Hayashi[48] on d-*trans*-BDPCP it seemed that chiral phosphines may be better for the asymmetric reduction of alkenes containing a carboxylic acid moiety while chiral phosphinites may be more effective for alkenes not containing an acid or acetamido group. However, the two ligands, DIOP and BDPCP are too different in structure to relate this effect entirely to their differing phosphorus groups. Johnson *et al*[49] sought to determine whether a better asymmetric induction could be obtained by some substrates with chiral phosphines while the hydrogenation of other substrates may be influenced more by structurally similar phosphinites. The phosphinite analogue of CAMPHOS[38] was prepared and rhodium catalysed hydrogenations of unsaturated acids explored using

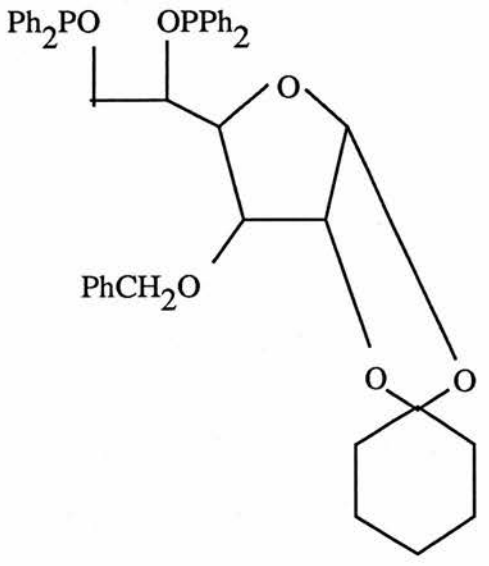
both CAMPHOS and CAMPHINITE. The results were consistent with extrapolations made from Hayashi's study, the phosphine proving an equal or better ligand when a carboxylic or acetamido group was present and the analogous phosphinite ligand giving the greater asymmetric induction in the presence of an ester group.

CAMPHINITE was not found to be very effective for inducing asymmetry in many substrates. In an attempt to find more effective phosphinites for asymmetric hydrogenation the *bis*(phosphinites) glucophinite and idophinite (fig.11,p.26) were prepared from α-D-glucofuranose and α-L-idofuranose[45]. The analogous phosphine ligands (fig.12,p.26) were prepared and the results of the hydrogenation experiments compared. Interestingly, idophinite was found to be competitive with idophos for inducing asymmetry in substrates containing an acetamido moiety, although previously phosphinites derived from glucopyranoses were ineffective in such a synthesis[43].

The developments described above have given an insight into the nature of the catalyst and substrate and this in turn has led to a better understanding of the mechanism of the reactions. Coupled with adjustment of the reaction conditions there is now more confidence in the design of new catalytic systems.

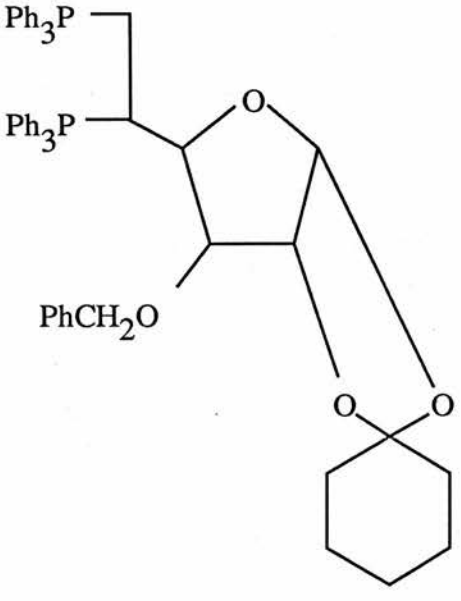


Glucophinite

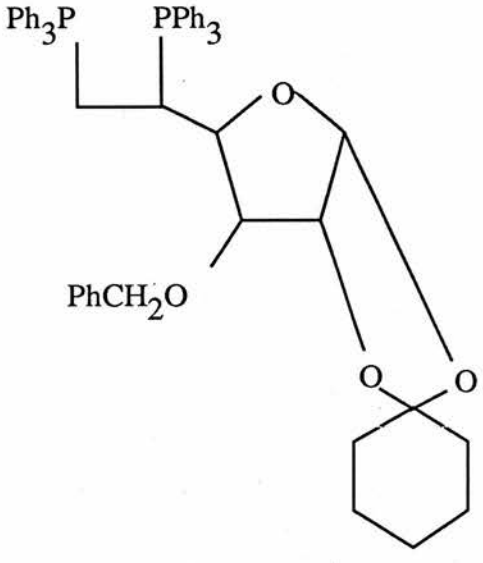


Idophinite

Fig.11



Glucophos



Idophos

Fig.12

1.1.4 Nature of catalyst and substrate and effect of reaction conditions

a) The nature of the catalyst

Early work carried out in the field of asymmetric hydrogenation (1968-72) utilised catalysts prepared *in situ* from $[RhCl(alkene)_2]_2$ and the appropriate phosphine, chelating dienes such as 1,5-cyclooctadiene (COD) and norbornadiene (NBD) giving more stable complexes than monoalkenes. More recently the catalysts have been prepared as isolated cationic complexes, the neutral rhodium precursor being treated with the phosphine and NH_4PF_6 or $NaBF_4$ in order to precipitate the cationic complex of the formula $[Rh(alkene)_2L_2]^+ X^-$, where generally $(alkene)_2$ stands for COD or NBD, L_2 being a chiral diphosphine.

In their paper on the chiral biphosphinites glucophinite and idophinite, Johnson and Rangarajan[45] compared the performance of a neutral catalyst prepared from $[Rh(COD) Cl]_2$ and the phosphinite and a cationic catalyst $[Rh(phosphinite)COD]^+ X^-$ in the hydrogenation of αβ-unsaturated acids and α-acetamidoacrylic acids. The conclusion that they drew from this study was that the cationic system is quite superior to the catalyst system prepared from the neutral complex and phosphinite. They did, however, point out that these differences in realized stereoselectivity are probably not manifested only in the differences between a cationic and neutral rhodium complex. They also found that the use of the cationic complex allowed for considerably lower pressures and

temperatures to be employed. A similar study by Descotes *et al.*[44] using monophosphine saccharides showed that enantiomeric excesses up to 54% were obtained for the hydrogenation of α-acetomidoacrylic acids in the presence of a cationic catalyst. However, when a neutral complex was used as the asymmetric inducer no reduction of the amino acid precursor was observed. The effect of various anions was also explored by Johnson and Rangarajan[45] and it is interesting to note that the order of greatest influence by an anion is not the same in different solvents. In tetrahydrofuran (thf) this order is $BF_4^{(-)} > ClO_4^{(-)} > PF_6^{(-)} > BPh_4^{(-)}$, whilst in EtOH it is $BPh_4^{(-)} > BF_4^{(-)} = PF_6^{(-)} > ClO_4^{(-)}$. Although the source of the effect is not known, it does seem real. However, in general, for cationic complexes containing chiral phosphine ligands the counterion is not important, although complexes with $PF_6^{(-)}$ tend to be most stable whilst those with $ClO_4^{(-)}$ are the least stable.

b) <u>The nature of the substrate</u>

Many unsaturated compounds are reduced in the presence of chiral rhodium catalysts. It now appears clear that two categories of alkenes have to be considered; one where there is an isolated prochiral double bond and the other where polar groups are close to the unsaturated linkage. With the exception of the reduction of 2-phenylbut-1-ene with a *bis*(phosphinite) Rh catalyst[46] (60% *ee*), optical yields are always low (less than 30% *ee*) in asymmetric reduction of simple alkenes whatever the chiral catalyst[46,50].

Generally when polar groups are located close to the double bond, alkenes in the Z-configuration give consistently higher optical purities and rates of reaction. This is particularly true with acyl substituents and poor results still hold for E-isomers in the aliphatic series for all the ligands except DiPAMP[81].

The category of alkenes which gives very high optical yields with many chiral catalysts is related to the α-N-acylamino-α-acrylic acids and their derivatives, so much so that the asymmetric synthesis of N-acetylalanine and N-acetylphenylalanine remains a classic test for new chiral ligands. In spite of the range of ligands that have been explored, the resulting catalysts all exhibit similar strengths and weaknesses. Because virtually every catalyst transfers chirality via a chiral array of aryl groups that are bound directly to the phosphine, the alkene must fulfil a set of requirements regardless of the catalyst used in order to exhibit good enantioselectivity. These appear to include:

i) a substituent such as NHCOR, OCOR or CH_2COOR containing a basic carbonyl group located β- to the double bond and

ii) an electronegative substituent such as COOR, CN or C_6H_5 on the α-carbon atom[82].

In order to illustrate these requirements in the best manner, the effect of replacing each of the 4 substituents of Z-α-acetamidocinnamic acid has been examined, (fig. 13).

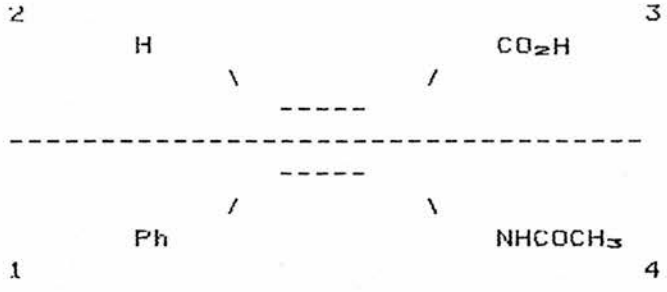


Fig. 13

First, the phenyl group at position 1 can be replaced by any functionality without significantly affecting the enantioselectivity, thus numerous α-amino acids can be produced in high enantiomeric excesses. In contrast the hydrogen (position 2), geminal to the phenyl, cannot be replaced by any other functionality due to the "face/edge" array of phenyl groups on the catalyst. Hence disubstituted dehydroalanines are not yet viable structures for asymmetric hydrogenations.

The role of the carboxylic acid functionality has been investigated[53,54] and the possible range of alternative substituents found to be much narrower than that found for the phenyl group in position 1, and it appears that any substituent geminal to the amide - carbonyl "tie down" must be electron withdrawing. In 1980 Koenig *et al*[55] reported the first example

of a chelating alkene with a fully saturated geminal substituent to hydrogenate rapidly with high *ee*. From their results they illustrated the importance for the geminal functionality to be strongly electron withdrawing. Several groups are at present studying the hydrogenation of alkenes with electron withdrawing amides that bridge to an α-amino acid and whether peptides can be efficiently produced from prochiral precursors[56].

Investigations into the effect of replacing the acetamido group with other functionalities have shown it to be by far the most important for this type of catalysis. Without it or a group that mimics its effect, e.g. a phosphinate[57], high *ee*'s cannot be obtained with any of the commonly used catalyst systems. The important requirement seems to be the presence of a coordinating group α- to the alkene[58] in order to allow the alkene to chelate to the rhodium creating a highly rigid, sterically demanding complex. Halpern[57] and Brown[40] confirmed this theory by low temperature nuclear magnetic resonance.

Chelation is important because it generates a low-energy complex in the transition state, which results in a fast reaction rate and because it produces a rigid complex which maximizes the substrate-ligand interactions and consequently the enantioface discriminating ability of the catalyst.

The effect of hydrogen bonding between substrate molecules and between the substrate and chiral ligands has been investigated. The most notable example of hydrogen bonds existing between substrate molecules is in the case of itaconic

acid which should form the type of chelate produced by other related substrates. However this has met with low asymmetric inductions when hydrogenated with most catalyst systems. This anomalous behaviour was investigated by Christopfel and Vineyard[58] and was explained in terms of intermolecular hydrogen bonding giving dimeric and/or polymeric species at higher concentrations. At 0.4 M. concentration in alcohol *ee*'s of 38% were obtained. However, at lower concentrations (0.002 M.) where intermolecular hydrogen bonding plays a minimal role *ee*'s of 77% were obtained.

The presence of a hydroxyl group on the chiral ligand such as that found in BPPFOH can cause very high asymmetric induction which can be ascribed to hydrogen bonding possibly between the substrate carbonyl group and ligand hydroxyl group. This may increase the conformational rigidity in the diasteriomeric transition states[42].

Finally it has become apparent that the matching of the substrate and ligand in a catalytic asymmetric reduction is of paramount importance. Different ligands have different sensitivities to the nature of N-acyl and β-vinylic substituents of the substrates. Of particular note are CHIRAPHOS with which the optical yield is very sensitive to these functionalities[16] and the closely related PROPHOS ((R)-1,2-*bis*(diphenylphosphine)-propane) which in practice is nearly an ideal ligand for producing optically active amino acids from Z-α-acetamidoacrylic acids, since the optical yields appear to be insensitive to the nature of the substituents[40]

c) Reaction conditions

i) Effect of temperature and pressure

In general, the reactions tend to give higher enantioselectivities at lower temperatures[43,45]. Indeed, with some cationic catalysts it is only possible to obtain high *ee*'s at 0° C where the reaction rate is impracticably slow[41]. In most cases the efficiency drops with increasing hydrogen pressure, this problem being particularly severe with flexible, seven-membered chelators and less so with five-membered chelators. Some phosphine ligands, e.g. DiPAMP[27], give excellent results at higher temperatures and pressures so making them more desirable for general use.

ii) Effect of added base

After considerations of the nature of the catalyst and of the substrate, the effect of added triethylamine is the next most important factor that affects the asymmetric induction. Most work that has been carried out has been in the presence of small amounts of Et_3N.

This has the effect of promoting hydride formation and it is probably the $C{=}C{-}COO^-$ chromophore that is hydrogenated. Generally, good asymmetric induction is not obtained without added triethylamine.

The role of Et_3N has been illustrated by Descotes *et al*[44] in the asymmetric hydrogenation of α-acetamidoacrylic acids by Rh catalysts containing the phosphine saccharide dioxop, (fig.10, p.22). The free acid coordinates to the complex via the double bond but hydrogen bonding of the carbonyl hydrogen to one of the oxygen atoms in the *bis*(phosphine) renders coordination of the enamide function very difficult through steric constraints. It is the enamide coordination that is important for enantioselection and as a result the *ee*'s obtained are low. Addition of Et_3N produces an ammonium salt so removing the possibility of COOH coordination through H-bonding. Thus the acetamido group can become coordinated to give a bidentate substrate species and improved *ee*'s.

Although all *bis*(phosphine)-Rh catalyst species give higher enantioselection in the presence of Et_3N, one ligand BPPM[32] shows a remarkable difference from others such as DIOP and CAMP. Addition of Et_3N causes a change in conformation of the chiral reagent-Rh complex and a much greater nucleophilicity of the carboxylate anion generated by the action of Et_3N on the carbonyl functionality. In the absence of Et_3N the efficiency of the reaction drops off drastically with pressure whereas in its presence the efficiency is non-variant up to 50 atmospheres.

iii) Solvent effects

Benzene, primary alcohols (EtOH and MeOH), mixtures of these, and thf are all commonly used solvents. However, the susceptibility of the catalyst to hydrolysis and

solvolysis must be taken into account and usually an inert medium is best used. Less protic solvents tend to make the interaction between triethylamine and the substrate more favourable. Many factors, such as the nature of the catalyst, the counter ion of anionic catalysts and the substrate, go towards deciding on the optimum solvent for a particular reaction. Although usually only small differences are observed between the *ee*'s produced in varying solvents, e.g. for CHIRAPHOS[18], they are large in free energy terms. PROPHOS[40] although related to CHIRAPHOS is particularly insensitive to solvent variation. Taken with its insensitivity to temperature and pressure and substrate nature it can be seen as an almost ideal ligand.

The most notable exception to the small differences usually found in *ee* is the observation by Kagan *et al.*[64] of a remarkable solvent effect during the asymmetric hydrogenation of prochiral enamides using [RhCl.DIOP] as the asymmetric inducer. Altering the solvent from pure benzene to 1:2 benzene/ethanol for the synthesis of N-acetyl-α-phenylethylamine they obtained both enantiomers (R, using benzene and S, using the benzene/ethanol mixture) in approximately 45% enantiomeric excess.

1.1.5 Mechanism of reaction[63]

The flourishing research work initiated by the success of asymmetric hydrogenations with chiral phosphines had as a consequence a parallel interest in the mechanism of this type of

catalysis. A better understanding of the reaction could help to devise rationally new catalytic systems for specific problems.

It soon appeared that high *ee*'s were often associated with bidentate coordination of both the chiral ligand (phosphine) and the substrate alkene, via the double bond and amide group. Steric interactions that mediate the chiral recognition can be expected to be higher than in the case where the metal is surrounded by monodentate ligands. Halpern[44] found the first experimental evidence for the special character of α-aminoacid precursors showing by X-ray crystallography that the oxygen of the amide group is coordinated to the Rh atom.

It is clear that some correlations must exist between the ligand conformation of chiral diphosphines and the absolute configuration of the products. The twist conformation of a five membered chelate tends to induce specific orientations of the P-Ph bonds and of the phenyl rings, and some correlations have been made by Knowles *et al.*[45] concerning the orientation of phenyl groups of many types of 1,2- and 1,4- diphosphines, as given by X-ray structures of various complexes.

Further insight into the mechanism of asymmetric hydrogenation was obtained by nuclear magnetic resonance (nmr) investigations of the reaction intermediates, useful information being obtained from ^{31}P nmr and substrate labelling. Diasterioisomeric complexes have been detected at low temperatures (-45°C) that differ by the face complexation[46,47], the ratio of these complexes depending on

the nature of the diphosphine and alkene. Some correlation was found between this ratio and the optical yield of the reduction leading to the assumption that the stereoselectivity of the asymmetric reduction was directly related to the stereoselectivity of the complexation of the prochiral alkene. However, further studies did not support this hypothesis.

On the basis of nmr and kinetic studies, Halpern[66] proposed a new interpretation of asymmetric catalytic hydrogenation. At room temperature the equilibrium between the diasterioisomeric complexes (A or A') is not important for the final R/S stereoselectivity. Oxidative addition of hydrogen is followed by alkene insertion into a Rh-H bond. The rate determining step is probably the oxidative addition of hydrogen; the reductive elimination is the fast irreversible step leading to the product. At low temperatures the final reductive elimination becomes rate determining and the less abundant enantiomer of the Rh-alkene intermediate disappears faster to give rise to the major product enantiomer, the stereoselectivity being closely related to the relative energy of the two diasteriomeric transition states. A change in the rate determining step also occurs with increasing pressure, the oxidative addition of H_2 becoming fast, thus the total stereoselectivity of the process can be altered as found experimentally. The suppression of the rate with increasing H_2 pressure by catalytic amounts of Et_3N is explained by salt formation of the conjugate acid which then behaves as a strong bidentate ligand[67].

The proposed mechanism is in agreement with observations dealing with a Rh/DiPAMP complex[70] at low temperatures it being possible to detect by nmr two diastereomeric complexes. The minor isomer disappeared more rapidly on introduction of H_2. However nmr investigations have revealed the enormous complexity of many systems. For example, it has been established by ^{13}C techniques that Z-isomers are bound to Rh by the double bond and the amide group whereas for E-isomers bonding is through double bond and the carbonyl function[67]. The steroechemistry of hydrogen addition is the same in both cases but much slower for E-isomers. So it has become apparent that stereochemical generalizations are rendered very difficult and each case must be carefully considered on its own merits.

1.2 Selective hydrogenation using rhodium and ruthenium catalysts

The ability of homogeneous transition metal catalysts to effect selective transformations of functional groups has led to a recognition of the potential for such catalysts to operate on organic molecules in a highly specific manner.

The number of really new catalysts for the addition of hydrogen to carbon-carbon double and triple bonds (excluding chiral ligand systems) following the proliferation during the 1960's has been relatively small . Notable advances have been made in the reduction of aromatic compounds[71,72] which could be of importance in oil based chemical processes.

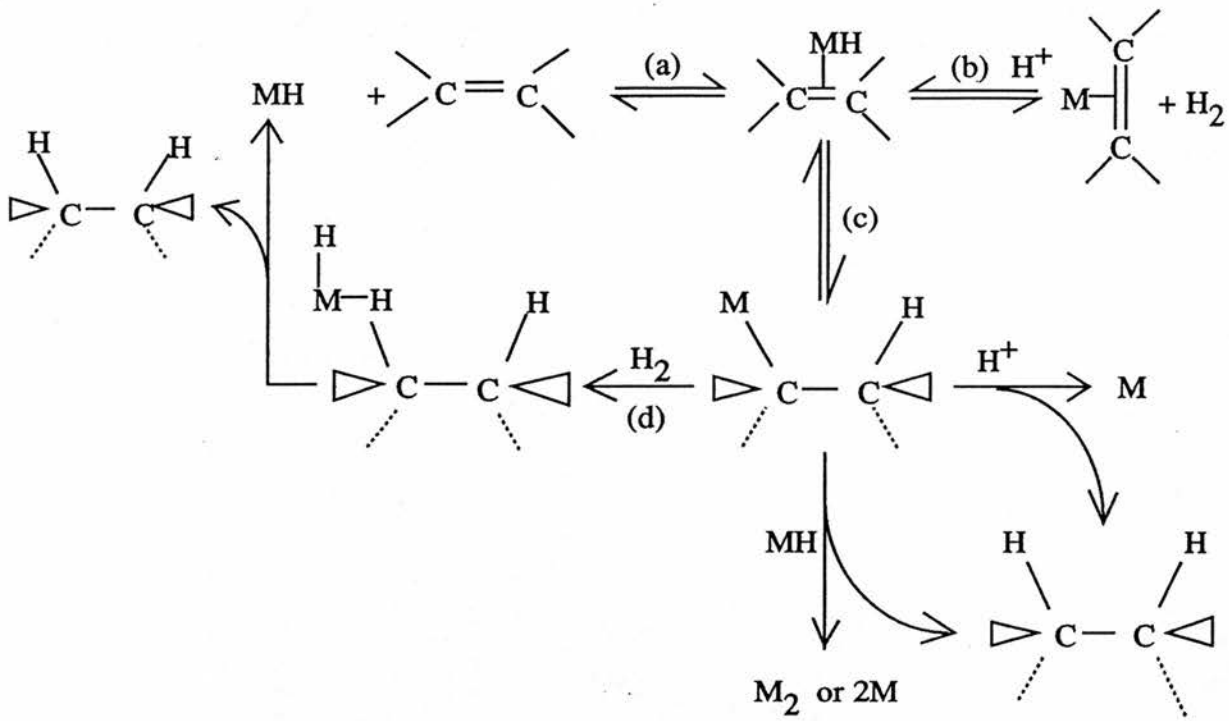
Interest in the hydrogenation of aromatic substrates and in metal cluster and dimer systems is likely to continue, mainly as a result of renewed attention into the utilization of coal. With aromatic compounds, selective hydrogenation of benzene to cyclohexene (a precursor of adipic acid used in the synthetic fibre industry) would be a worth-while goal.

Catalysts for the selective reduction of monoenes, polyenes to monoenes and alkynes to monoenes are abundant[73]. Although the field is reaching the stage where one can almost use the transition metal of one's choice, only monohydride and dihydride catalysts of rhodium and ruthenium will be discussed in this dissertation.

It must be pointed out that individual reaction rates can be the wrong criteria for predicting which substrates in a mixture will hydrogenate first. For example, although alkenes are reduced by $RhCl(PPh_3)_3$ more rapidly than are alkynes, the favoured binding to alkynes over alkenes allows for the initial reduction of the triple bonded species with a high degree of specificity.

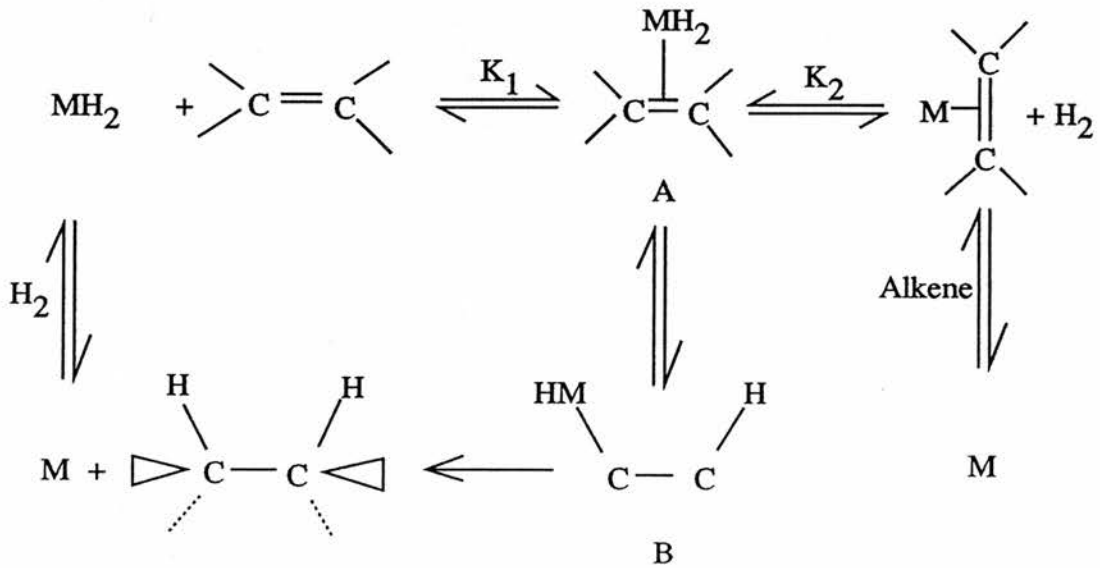
1.2.1 Monohydride catalysts

Proposed mechanistic pathways for monohydride catalysts are summarized in Scheme 1, (p.40) for the hydrogenation of monoalkenes, step (a) defining the 'hydride' and step (b) the 'unsaturate' routes.



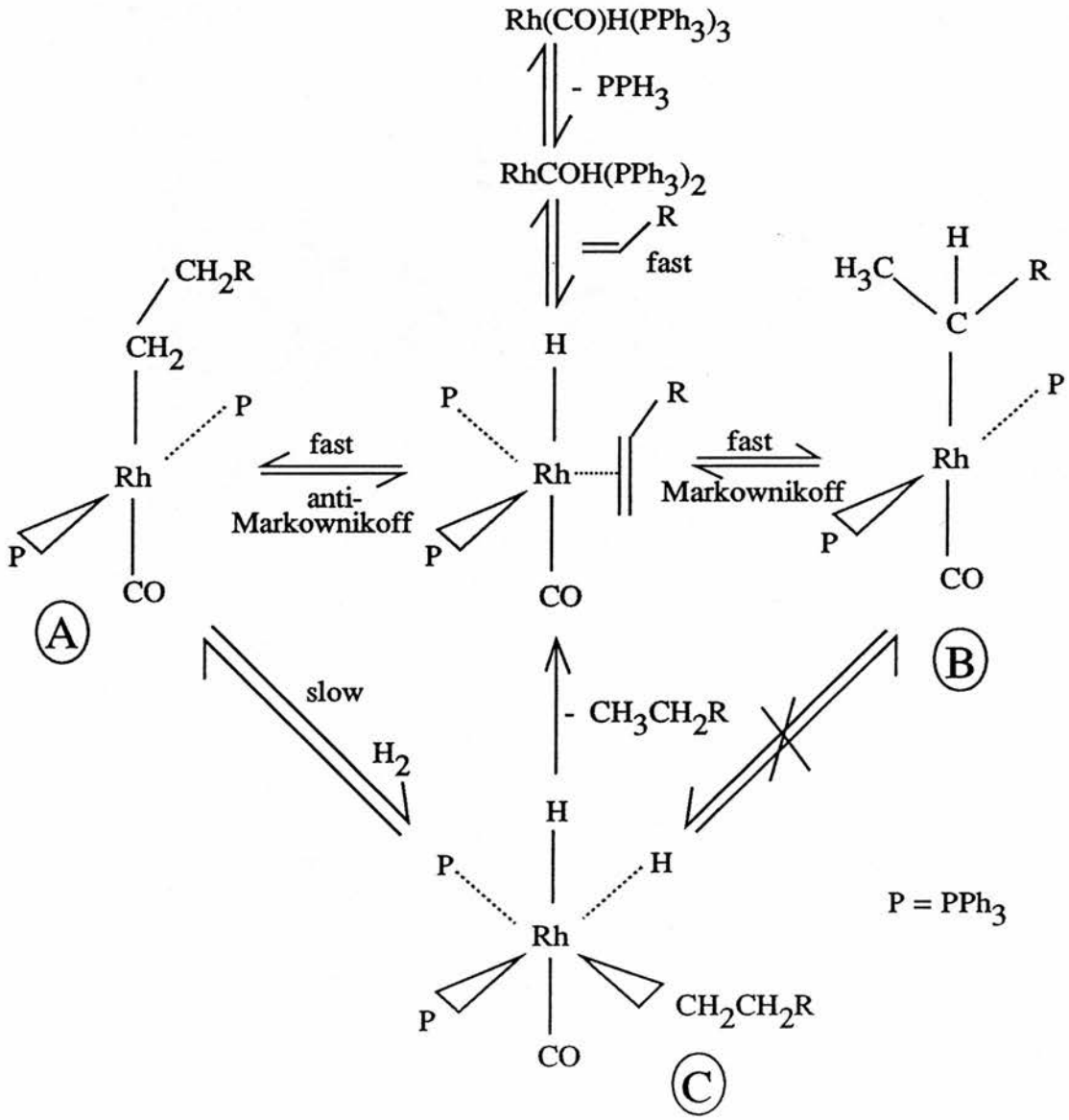
Scheme 1

Mechanistic pathways for monohydride catalysis



Scheme 2

Mechanistic pathways for dihydride catalysis



Scheme 3

Catalytic cycle of hydrogenation
and isomerization of terminal alkenes
by $RhH(CO)(PPh_3)_3$

Monohydride catalysts such as $RuHCl(PPh_3)_3$[74], $Rh(CO)H(PPh_3)_3$[75], $RuH(OCOR)(PPh_3)_3$[76,77,78] and $Ru(OCOR)_2(PPh_3)_2$[77] show very high sensitivities towards terminal alkenes arising from the difficulty in step (c) for non-terminal alkenes, steric interaction of the phosphine groups preventing effective hydride transfer to the coordinated alkene. Terminal alkenes can react with a metal-hydrogen bond in either a Markownikoff or an *anti*-Markownikoff fashion to give, respectively, a secondary branched or a primary straight-chain alkyl. Internal alkenes can give only a branched-chain alkyl. The selectivity has been explained as follows[80].

In the square species A and B of Scheme 3, (p.41), the bulky triphenyl phosphine groups are in *trans*-positions, and the result is that a primary alkyl (i.e. $Rh-CH_2CH_2R$) will experience much less steric interaction than will a more bulky alkyl (e.g. $Rh-CH(CH_3)CH_2R$). The lowered stability of a secondary alkyl complex means that such a species would undergo the reverse β-hydrogen transfer reaction to give an alkene more easily; hence the alkyl would have a shorter lifetime in solution - so short, in fact, that it would not live long enough to undergo the slow rate-determining oxidative addition of hydrogen to give species C. That the secondary alkyl complex is formed simultaneously with the primary alkyl complex from terminal alkenes is shown by comparability of the rates of isomerization (terminal and 2-alkenes) and hydrogenation.

Protonation of methanolic solutions of the carboxylate complexes of Ru by a strong acid having a non-coordination anion

leads, in the presence of triphenylphosphine, to efficient catalysts with acid ratios ($H^+/COOR^-$) of 1:1 giving the highest rates of reduction for terminal alkenes[77].

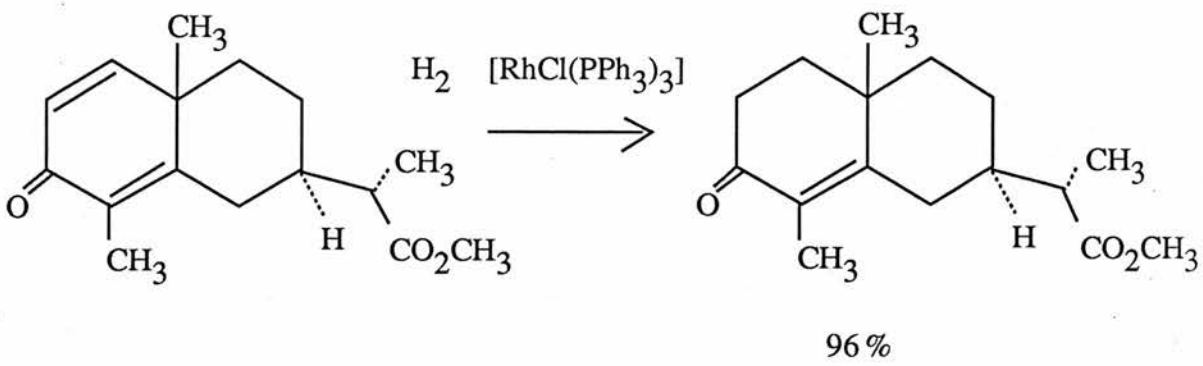
The order of selectivities is generally as follows for monohydride catalysts: terminal alkenes and non-conjugated dienes are reduced rapidly, cyclic alkenes and conjugated dienes are reduced fairly slowly and internal alkenes undergo isomerization only. With $RuH(OCOR)(PPh_3)_3$ internal alkenes remain unchanged, no isomerization occurring due to prohibitive steric inhibition of hydride transfer to bulky alkenes.

Few exceptions to these selectivities have been observed. However in 1973 Ugo *et al*[81] reported hydrogenation of 1,3-dienes to give terminal alkenes with selectivities of 80% - 95% in the presence of $RhH(PPh_3)_4$ and $[Rh(CO)_2(PPh_3)]_2.2C_6H_6$. The use of high temperatures and pressures was necessary, rendering this type of catalyst unattractive. The complex $RuCl_2(CO)_2(PPh_3)_2$[82,83] also exhibits unusual selectivities. These are in the order: conjugated dienes > non-conjugated terminal dienes > non-conjugated internal dienes > terminal alkenes > internal alkenes. The order of rates parallels the relative stabilities of the π-bonded Ru-alkene intermediates towards alkene dissociation and also the predicted stabilities of the alkyl-Ru intermediates towards RuH elimination. Selectivities of up to 98.5% for the reduction of 1,5,9-cyclododecatriene to cyclododecene were obtained using this complex in the presence of an added Lewis base.

1.2.2 Dihydride catalysts

Scheme 2, (p.40) shows reaction pathways available for hydrogenation of alkenes using dihydride catalysts. The K1 step defines the 'hydride' route and K2 the 'unsaturate' route via oxidative addition of H_2 to a metal-alkene complex. Both lead to the same key dihydride-alkene intermediate which decomposes through two successive fast hydrogen atom transfers. As for monohydride catalysts an overall *cis* addition of hydrogen results. The first evidence for the intermediates A and B was obtained by Halpern *et al* for Rh systems[66]. Complexes that give isolable dihydrides are generally considered to operate via the hydride route.

Of all the dihydride catalysts the most intensively studied is Wilkinson's catalyst[1,3,64,66]. Whilst the coordination of reducible substrates to naked transition metal surfaces is most unselective, the active intermediate $RhH_2Cl(PPh_3)_2$ generated from Wilkinson's catalyst coordinates the least sterically hindered unsaturated C-C linkage of polyenes. Due to selective coordination to the vacant sixth site, substrates containing other reducible groups are hydrogenated specifically at the C-C multiple bond. These trends in selectivity are illustrated by the catalytic hydrogenation below, (Eqn.2,p.45)[66].



96 %

Eqn.2

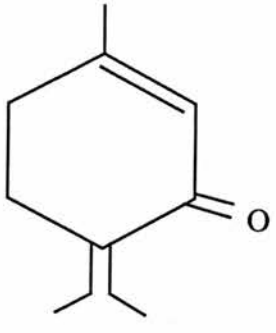
The selective reduction of the di-substituted 1,2-double bond was achieved without attack of the trisubstituted 4,5-double bond or the ketonic bond.

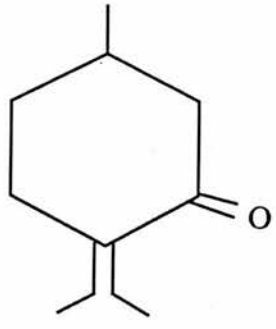
Although terminal alkenes are hydrogenated at a faster rate than internal cycloalkenes, the action of Wilkinson's catalyst is by no means specific. The differences in rate arise primarily through the effect of alkene stereochemistry on the formation of the dihydride-alkene intermediate. The addition of polar solvents also affects the selectivity achieved[67].

In 1969, a group of catalysts of the type $RhH_2L_2S_2^+$, where L = PPh_3 or $PPhMe_2$ and S = solvent, were prepared from $Rh(diene)L_2^+$[68]. Relative rates of reaction for various alkenes proved to be similar to those obtained with Wilkinson's catalyst except that alkynes were reduced more rapidly than alkenes.

Again, unsaturated ketones and esters were hydrogenated without reduction of the carbonyl functionality. This work was expanded by Schrock and Osborn[87] who, using $L=PPhMe_2$ obtained selectivities of 99% for the reduction of 2-hexyne to *cis*-hexene.

In 1978, Solodar[90] prepared a similar group of complexes where L=asymmetric phosphine ligand. Thus the effects of selective and asymmetric hydrogenation catalysts were combined. The action of these catalysts on piperitenone, (fig.14), a prochiral compound containing two different alkenic bonds and one ketonic bond, was investigated. As found by Schrock and Osborn the ketonic bond was not reduced, whereas in all but a few instances the least substituted carbon-carbon double bond was hydrogenated with selectivities of 85%-92%. At the same time, optical yields of 27%-33% were obtained for the major product pulegone, (fig.14).



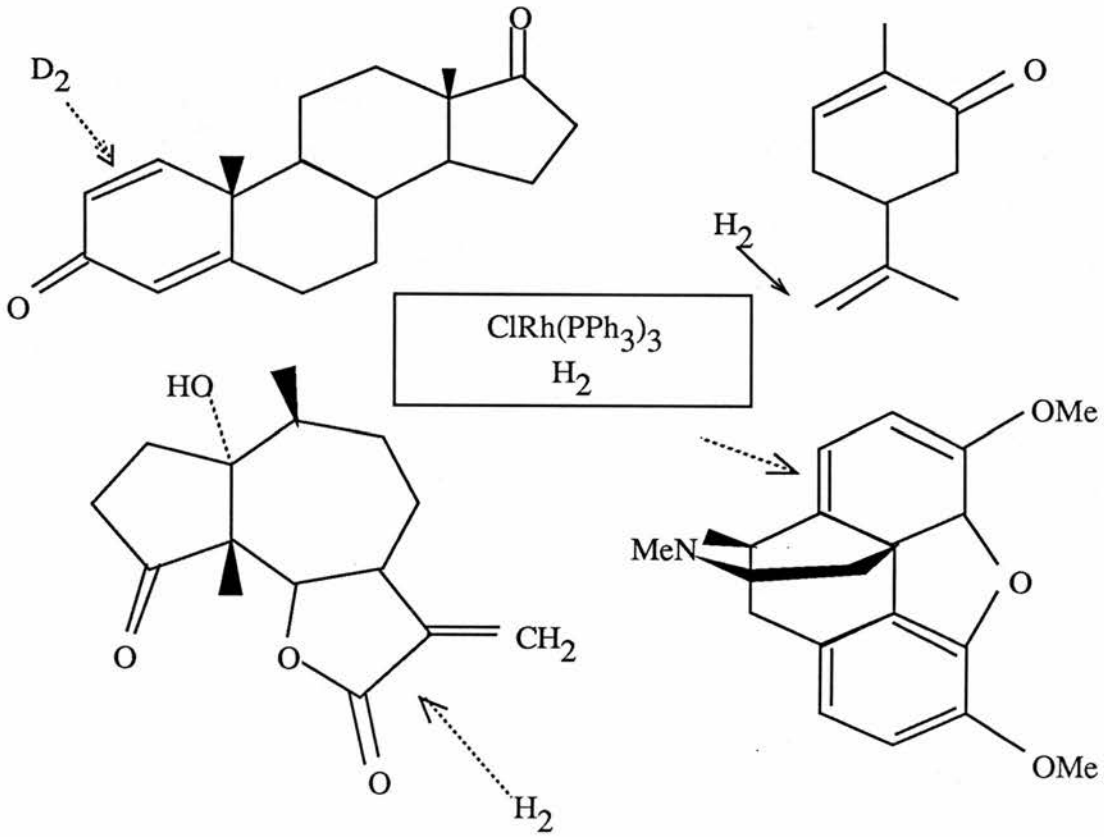


Piperitenone Pulegone

Fig.14

Scheme 4 illustrates some examples of selective homogeneous hydrogenation of natural products catalysed by $RhCl(PPh_3)_3$, arrows denoting the stereoselectivity of reduction.

Other examples of dihydride catalysts that exhibit similar selectivities are $RuH_2(PPh_3)_4$, $RuH_4(PPh_3)_3$[21] and $Rh(OCOR)(PPh_3)_3$[22], (c.f. the monohydride catalyst $RuH(OCOR)(PPh_3)_3$).



Scheme 4

1.3 Concluding remarks to Chapter 1

Intense interest continues in the hydrogenation reactions catalysed by transition metal complexes, with the general aim of developing catalysts for selective processes under mild conditions. Hydrogenations of unsaturated hydrocarbons are important commercially within photochemical, pharmaceutical and food industries, and selectivity is critical to the success of industrially based processes. Greater product selectivity has an important impact on energy and resource utilization in terms of low-value by-products.

The development of chiral catalysts for commercial production of optically active amino acids is an outstanding example of the application of well understood principles of H_2 activation and its subsequent addition to alkenic bonds.

CHAPTER II

PREPARATION OF SOME PHOSPHINITE ESTER COMPLEXES OF RHODIUM(I) AND RUTHENIUM(II)

2.1 Introduction

It is apparent from Chapter I that the literature on homogeneous hydrogenations catalysed by rhodium and ruthenium is extensive. From this work it has emerged that, for coordination of highly functionalised alkenes where complexation constants are low, chelate binding is essential in order that a stable metal-alkene interaction is achieved; such an interaction is necessary for high asymmetric induction. In addition to the Rh-α-acetamidoacrylic acid interaction previously discussed (section 1.1.4), chelated unsaturated phosphine derivatives[72] and several complexes of the general type shown in fig. 15, prepared from substantially labile d8 Rh complexes[73,74,75], have been reported.

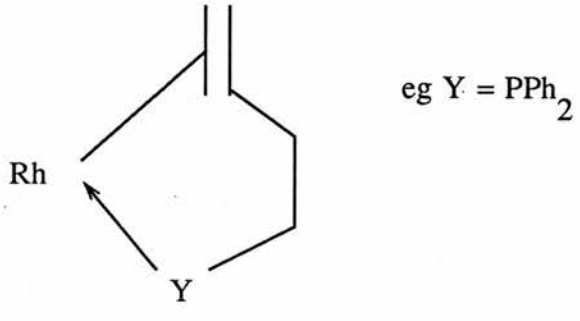


Fig.15

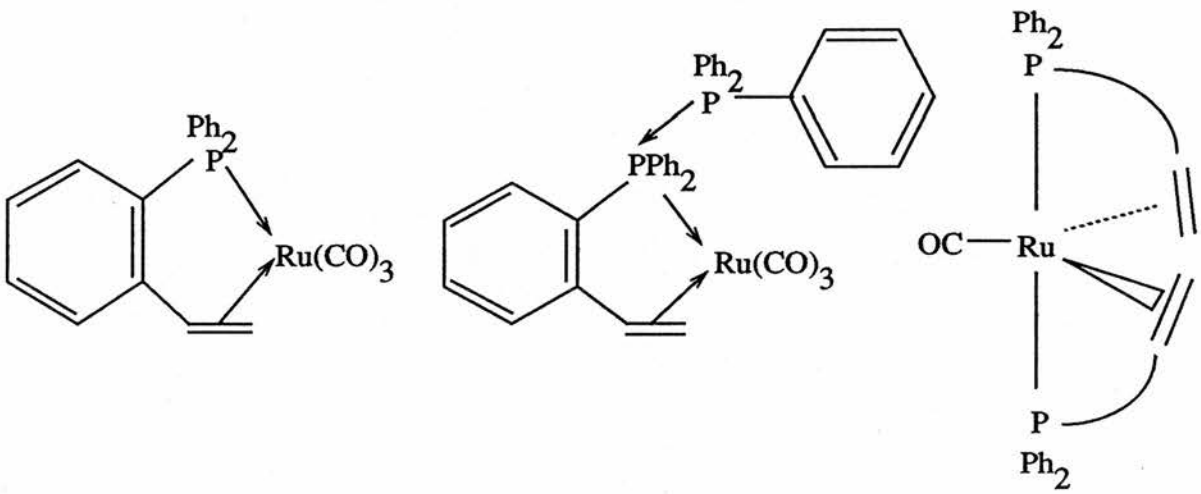
The binding of an alkene to the metal centre is of fundamental importance in homogeneous alkene hydrogenation reactions catalysed by transition metal complexes.

It is therefore of interest to review briefly the results that have been published on Rh and Ru complexes containing bound alkenes that are part of a chelate ring.

2.1.1 Complexes of ruthenium and rhodium containing multidentate monoalkene ligands.

a) Ruthenium

Refluxing solutions of $Ru_3(CO)_{12}$ in n-octane with o-styryldiphenylphosphine (SP)[74] affords cyclometalled π-complexes containing a 5.5-membered ring[72,77], (fig. 16(1,2)).



1 2 3

Fig.16

With refluxing n-nonane as solvent the trigonal bipyramidal species (fig.16(3)) is obtained. Reaction of $Ru_3(CO)_{12}$ with excess SP in refluxing n-nonane followed by addition of two equivalents of HX (X=Cl,Br) leads to an octahedral

Ru(II) complex containing the ligand *bis* -1,4- [o-(diphenyl phosphino)phenyl]-*cis*-2-butene, (1-BDPB), which has been structurally characterised by single crystal X-ray diffraction analysis[97].

b) Rhodium

In section 1.1.4 the interaction of a carbonyl oxygen atom, remote from the carbon-carbon double bond, with the Rh atom of a complex has been discussed. Chelate binding of $Me_2C=CHCMe_2OH$(L) in the complex $[RhL(CO)Cl]_2$ (fig.17) has been reported by Atkinson and Smith[98] where coordination of L is through the alkene and the oxygen of the hydroxyl function. The large chemical shift downfield of the hydroxyl proton to 6.24 ppm from 2.42 ppm is in accordance with the existence of a strong metal-oxygen interaction.

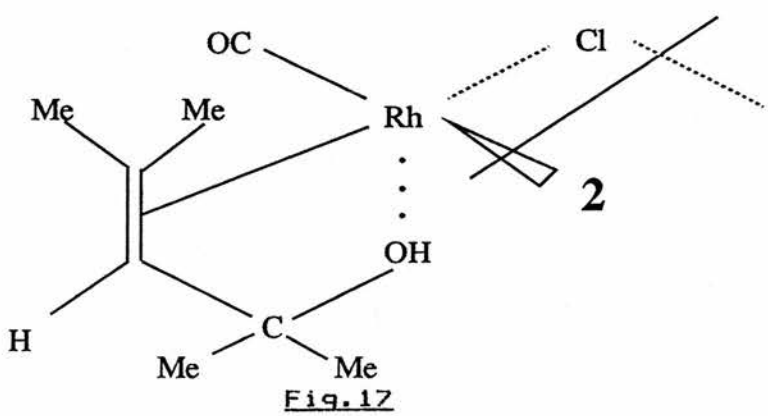


Fig.17

Many of the chelate bound alkene-rhodium complexes reported are of the type shown in fig. 15 . The five coordinate species $RhX(MBP)_2$, (X=Cl or Br, MBP = $Ph_2P(CH_2)_2CH=CH_2$) ; $RhCl(MAP)_2$, (MAP = $Ph_2POCH_2CH=CH_2$); and $RhCl(TBP)$, (TBP = $P(CH_2CH_2CH=CH_2)_3$)

have been prepared[72,73] as have the Rh(I) complexes of the bidentate ligands diphenyl(prop-2-enyloxo)phosphine, (DPPP) and (But-3-enyl)diphenylphosphine, (BDPP)[74].

Dehydrogenation of 1,6-*bis*(diphenylphosphino)hexane in the presence of $[RhCl(COD)]_2$ affords a Rh complex containing the tridentate ligand 1,6-*bis*(diphenylphosphino)hex-3-ene. This complex $RhCl(O\text{-}Ph_2PC_6H_4CH{=}CHC_6H_4PPh_2\text{-}O)$ has been fully characterised by X-ray crystallography[14,77-102]. Oxidative addition of Cl_2 to this complex affords an octahedral Rh(III) species[101,103], (fig.18).

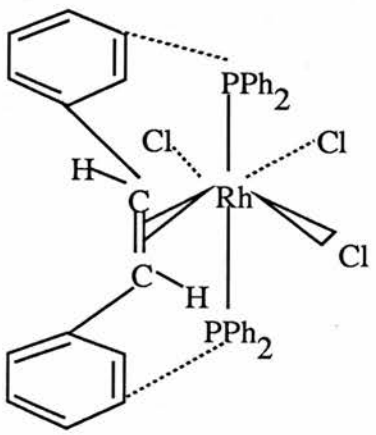


Fig.18

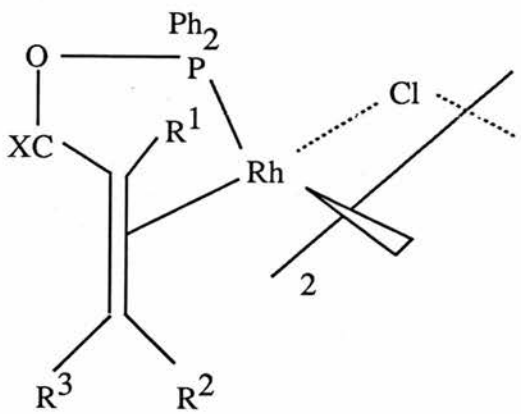


Fig.19

Similar dehydrogenation reactions, in which the reaction sequence is the reverse of the mechanism involved in catalytic hydrogenation of alkenes have been reported when $[RhCl(COD)]_2$ is refluxed in mesitylene with $Ph_2E(CH_2)_4EPh_2$, (E = As,P)[101,102] or in toluene with PCy_3[104,105].

Recently, the phosphinite esters of αβ-unsaturated acids and βγ-unsaturated alcohols of the type $Ph_2POXCR^1=CR^2R^3$ (see footnote) have been reacted with $[RhClL_2]_2$ ($L=C_2H_4$,cyclooctene) to give the structurally characterised complexes $[Rh(Ph_2POXCR^1=CR^2R^3)Cl]_2$[106], (fig.19).

2.2 Phosphinite esters of αβ-unsaturated acids and reaction of these with chlorotris(triphenylphosphine)Rh(I)

As a result of the oxygen, moisture and thermal labilities of unsaturated phosphinite esters[107 - 109] the conversion of αβ-unsaturated acids to the corresponding phosphinite esters (Eqn.3) is generally quite difficult[110].

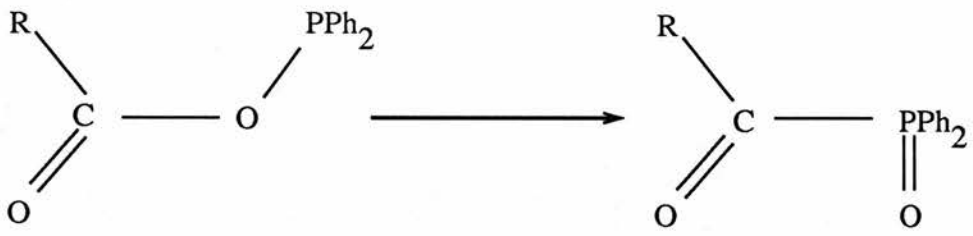
$$R\text{-}X\text{-}OH \longrightarrow R\text{-}X\text{-}OPPh_2 \text{: (X=CO or } CH_2 \text{)}$$

Eqn.3

Footnote

R^1 = H;	R^2 = H;	R^3 = Me;	X = CO
R^1 = H;	R^2 = Me;	R^3 = Me;	X = CO
R^1 = H;	R^2 = Me;	R^3 = Me;	X = CH_2
R^1 = H;	R^2 = H;	R^3 = MeCH=CH;	X = CO
R^1 = Me;	R^2 = Ph;	R^3 = H;	X = CO

In 1981, the synthesis of [Ph_2PO_2CR]; (R=Me, CF_3, C_2F_5 or C_3H_7), was reported[111] although these were found to be unstable at room temperature (except for R=Me) readily rearranging to the oxide (Eqn.4).



Eqn.4

Phosphinite esters of the type $Ph_2POXCR^1=CR^2R^3$ have since been prepared on a large scale using standard Schlenk line techniques[106]. The preparation of Rh(I) and Ru(II) complexes with these ligands is reported here.

2.2.1 Reaction of $RhCl(PPh_3)_3$ with $Ph_2PO_2CCR^1=CR^2R^3$

Addition of $Ph_2PO_2CCH=CMe_2$ (1 equivalent) to a solution of $RhCl(PPh_3)_3$ in tetrahydrofuran (thf) results in a lightening of the deep red-brown solution to red-orange. Evaporation of the solution followed by careful addition of light petroleum spirit yields a bright orange micro-crystalline solid that analyses for $RhCl(PPh_3)_2Ph_2PO_2CCH=CMe_2$[106]. Nmr analysis (^1H and ^{31}P) indicates that the phosphinite ester

ligand is bound in a monodentate fashion through the phosphorus atom only. The presence of absorptions, assigned to $\nu_{C=C}$ and $\nu_{C=O}$ in the 1600-1700 cm^{-1} region of the spectrum confirms this.

Attempts were made to prepare the $Ph_2PO_2CCMe=CHPh$ analogue of Wilkinson's catayst in the same way. Initial investigations by infra-red spectroscopy indicate that binding of the phosphinite ester is monodentate through the phosphorus atom, as was found for $RhCl(PPh_3)_2Ph_2PO_2CCH=CMe_2$

2.2.2 Spectroscopic details of phosphinite ester complexes

a) Infra red spectra

The relevant infra-red details of the ester complexes are given in Table 2, (p.59). The IR spectrum of $RhCl(PPh_3)_2Ph_2PO_2CCH=CMe_2$ shows $\nu_{C=O}$ and $\nu_{C=C}$ at 1705 cm^{-1} and 1635 cm^{-1} respectively. These are virtually the same as for the free ligand leading to the conclusion that the dimethylacrylate group is remote from the rhodium atom as the π-electron density has been disturbed little on bonding. The M-Cl bond stretch appears at ν_{M-Cl} 290 cm^{-1}.

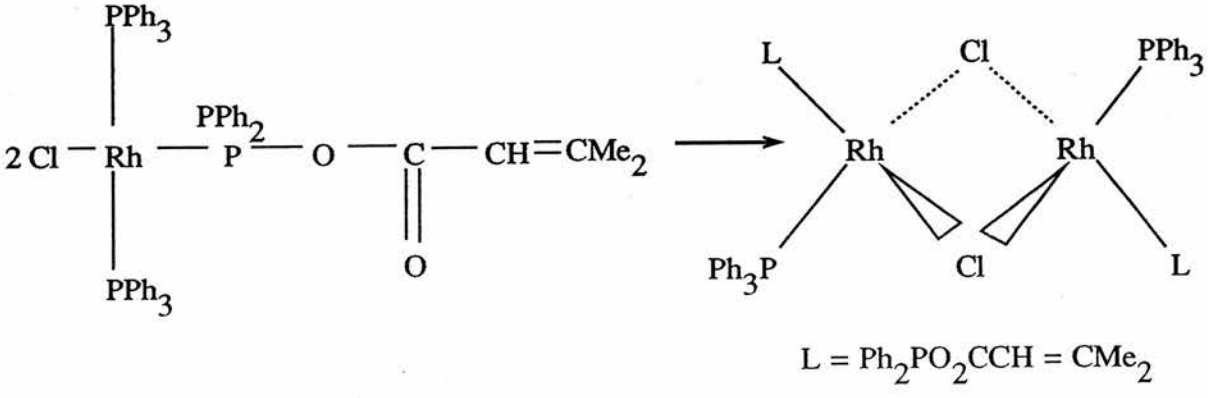
For the $RhCl(PPh_3)_2Ph_2PO_2CCMe=CHPh$ complex, $\nu_{C=O}$ and $\nu_{C=C}$ at 1695 cm^{-1} and 1615 cm^{-1} respectively are again virtually unchanged compared with the free ligand. Thus it would appear the binding is also of a non-chelate, monodentate nature. ν_{M-Cl} is observed as a broad weak feature at 290 cm^{-1}.

b) Nuclear magnetic resonance spectra

The relevant nmr details of the rhodium dimethylacrylate ester complexes are given in Table 3, (p.59).

The ^1H nmr spectrum of $RhCl(PPh_3)_2Ph_2PO_2CCH{=}CMe_2$ clearly shows the presence of an vinylic proton at δ 4.92 which is essentially unchanged from that observed for the free ligand. The two methyl groups of the dimethyl acrylate group are observed at δ 1.9 and δ 1.65 and are again virtually unchanged from those in the free ligand.

After a period of time, another set of signals appeared in the ^1H nmr spectrum. These signals consisted of two doublets at δ 1.85 and δ 2.10 and a multiplet at δ 5.68 and were interpreted in terms of the dimerization reaction of the compound, presumably via dissociation of a PPh_3 group and combination of two Rh moieties, (Eqn.5).



Eqn.5

The doublet signals were assigned to the methyl protons ($^4J_{M-H}$= 1.0 Hz) and the multiplet to the vinylic proton.

The ^{31}P nmr spectrum of a fresh solution shows an essentially first order AMX_2 spin system. The resonance from the two *trans*-PPh_3 phosphorus atoms appears at δ 32.4 as a doublet of doublets with coupling to rhodium ($^1J_{RhP}$ 143 Hz) and also to the ester phosphorus to which they are *cis* ($^2J_{PP}$ 38.1 Hz). The ester phosphorus atom signal appears as a doublet of triplets at δ 49.1 on account of coupling to the two *cis* PPh_3 phosphorus atoms and to the rhodium ($^1J_{RhP}$ 190.7 Hz). After a long period of time, another set of signals corresponding to the chloride bridged dimer appear in the ^{31}P nmr spectrum[106]. The doublet at δ 52.5 was assigned to the ester phosphorus which shows coupling to rhodium ($^1J_{RhP}$ 195.4 Hz), whilst the signal at δ 25.8 was attributed to free PPh_3 which is rapidly exchanging (on the nmr timescale) with the PPh_3 group of the dimer. The dimerization reaction was found to be accelerated by addition of benzene to solutions of the PPh_3-rhodium complex[106].

2.3 Preparation of cationic metal-alkene bonded species

2.3.1 Reaction of $RhCl(PPh_3)_2Ph_2PO_2CCH{=}CMe_2$ with $TlPF_6$

Addition of $TlPF_6$ (1 equivalent) to a solution of $RhCl(PPh_3)_2Ph_2PO_2CCH{=}CMe_2$ in thf resulted in the precipitation of yellow/white TlCl whilst the orange-red solution paled to a yellow-orange colour. The solvent volume was reduced under vacuum and subsequent recrystallization using petroleum spirit/diethyl ether (1:1) yielded brittle flattened

needle-shaped yellow crytals. The product analysed for $[Rh(PPh_3)_2Ph_2PO_2CCH{=}CMe_2]PF_6$. This complex cation may also be prepared by reaction of $RhCl(PPh_3)_2Ph_2PO_2CCH{=}CMe_2$ with AgX, ($X=SbF_6$ or BF_4).

2.3.2 Spectroscopic details of $[Rh(PPh_3)_2Ph_2PO_2CCH{=}CMe_2]^+$

Table 4, (p.60) shows the relevant spectroscopic details obtained for $[Rh(PPh_3)_2Ph_2PO_2CCH{=}CMe_2]^+$

a) Infra red

The spectrum of $[Rh(PPh_3)_2Ph_2PO_2CCH{=}CMe_2]^+$ clearly shows $\nu_{C=C}$ and $\nu_{C=O}$ at 1620 cm^{-1} and 1580 cm^{-1} respectively whilst no ν_{M-Cl} is detected. A strong absorption, ν_{P-F}, is observed at 830 cm^{-1}.

The large shift in $\nu_{C=O}$ from 1705 cm^{-1} in the neutral species, to 1580 cm^{-1} in the cation implies that chelate binding has occurred through the ester carbonyl oxygen atom rather than through the alkene. This contrasts with results obtained for the dimeric species $[RHL_2Cl]_2$, ($L=Ph_2PO_2CCH{=}CMe_2$), in which binding to the rhodium is through the phosphorus atom and the double bond, (fig.19,p.52).

Table 2: Infra-red data for phosphinite ester-rhodium complexes

Compound	$\nu_{C=O}$ cm^{-1}	$\nu_{C=C}$ cm^{-1}	ν_{Rh-Cl} cm^{-1}
$RhCl(PPh_3)_2Ph_2PO_2CCH=CMe_2$	1705 sst (1692)	1635 m (1640)	290
$RhCl(PPh_3)_2Ph_2PO_2CCMe=CHPh$	1695 s (1685)	1615 w (1620)	290

(Figures in brackets are for free ligands)

Table 3: Nmr data for $RhCl(PPh_3)_2Ph_2PO_2CCH=CMe_2$
(Selected resonances)

^1H (a) ppm	^{31}P (b) ppm
δMe 1.9d, 1.65d	δP 32.4 dd ($^1J_{RhP}$ 143 Hz, $^2J_{PP}$ 38.1 Hz)
δH 4.92 m ($^4J_{MeH}$ 1 Hz)	δP 49.1 dt ($^1J_{RhP}$ 190.7 Hz)

a) ppm with respect to CH_2Cl_2 reference at 5.2 ppm

b) ppm to high frequency of 85 % H_3PO_4 in CH_2Cl_2 at 298 K

Table 4: Spectroscopic data for $[Rh(PPh_3)_2Ph_2PO_2CCH{=}CMe_2]^+PF_6^-$
(Selected resonances)

Infra-red cm^{-1}	$\nu_{C=O}$ 1580			
	$\nu_{C=C}$ 1620			
^1H nmr (a)	δMe	1.17, 1.84		
	δH	5.80		
^{31}P nmr (b)	δP	170.3	$^1J_{RhP\ /P}$	320.4 Hz
	δP	26.0	$^1J_{RhP}$	185.5 Hz
	δP	37.7	$^2J_{PP}$	37.7 Hz
			$^2J_{PP}$	199.3 Hz
			$^2J_{PP}$	37.1 Hz

(a) ppm with respect to CH_2Cl_2 reference at 5.2 ppm

(b) ppm to high frequency of 85 % H_3PO_4 in CH_2Cl_2 at 298 K

b) Nmr

In the ^1H nmr spectrum, methyl resonances at δ 1.17(3H) and δ 1.84(3H) were observed. The vinylic proton resonance at δ 5.80 is fully consistent with there being no metal alkene interaction. The ^{31}P nmr consists of two doublet of doublets signals at δ 170.3 and δ 26.0 and a doublet of triplets signal at δ 37.7. The low field doublet of doublets signal at δ 170.3 is consistent with a 5-membered chelate ring structure in which the carbonyl oxygen is bound to the metal centre. The phosphorus atom is coupled strongly to rhodium ($^1J_{RhP}$ 320.4 Hz), and couplings to one *cis* PPh_3 group ($^2J_{PP}$ 37.7 Hz) and one *trans* PPh_3 group ($^2J_{PP}$ 199.3 Hz) are observed. The high field signal at δ 26.0 has the same splitting pattern as the phosphorus atom resonance at δ 170.3, coupling to one *cis* and one *trans* PPh_3 group and strongly to rhodium. The medium field signal at δ 37.7 arises from the PPh_3 group *trans* to the bound oxygen atom. A coupling to rhodium is observed ($^1J_{RhP}$ 185.5 Hz) and near equal couplings to the *cis* phosphorus atoms ($^2J_{PP}$ 37.1 Hz) give rise to a doublet of triplets splitting pattern. Thus, the spectroscopic data obtained for this cationic species implies that the phosphinite ester ligand is bound in a chelate manner to the metal through a phosphorus atom and the carbonyl oxygen atom, (fig.20, p.62).

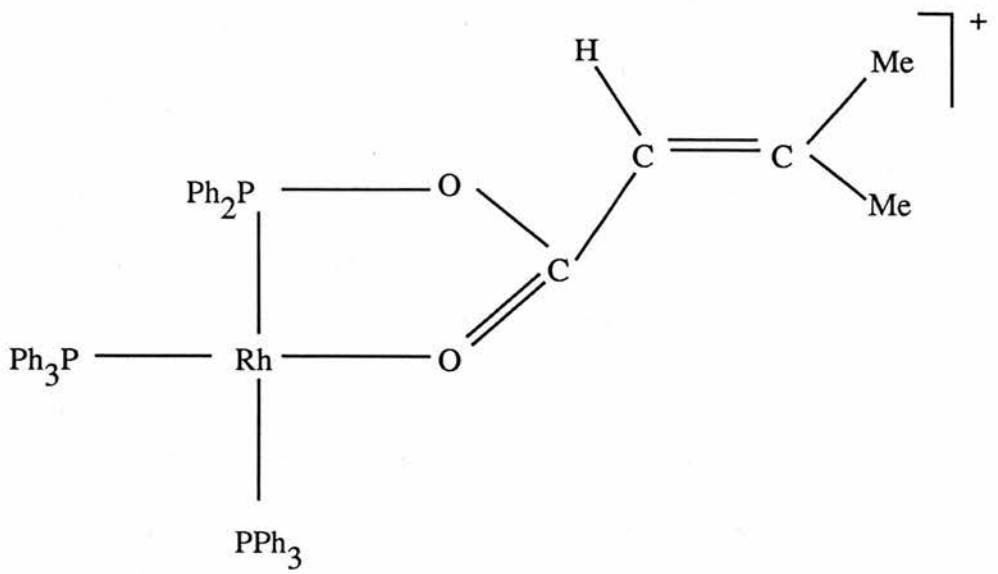


Fig.20

2.4 Preparation and spectral details of some ruthenium complexes of unsaturated phosphinite esters.

Reaction of $RuCl_2(PPh_3)_2Ph_2POCH_2CH=CMe_2$ with carbon monoxide and hydrogen.

2.4.1 Reaction of $RuCl_2(PPh_3)_4$ with $Ph_2POXCR^1=CR^2R^3$

a) $Ph_2PO_2CCH=CMe_2$

Addition of two equivalents of $Ph_2PO_2CCH=CMe_2$ to a brown-black solution of $RuCl_2(PPh_3)_4$ in dichloromethane caused the solution to become bright red. Evaporation of the solvent under reduced pressure and subsequent recrystallization afforded a bright red microcrystalline material that analysed for $RuCl_2(Ph_2PO_2CCH=CMe_2)_2$.

b) $Ph_2PO_2CCMe{=}CHPh$

A similar reaction was conducted between $RuCl_2(PPh_3)_4$ and the phosphinite ester of α-methlycinnamic acid. Addition of two equivalents gave rise to a bright red microcrystalline material, $RuCl_2(Ph_2PO_2CCMe{=}CHPh)_2$.

c) $Ph_2POCH_2CH{=}CMe_2$

Reaction between two equivalents of $Ph_2POCH_2CH{=}CMe_2$ and $RuCl_2(PPh_3)_4$ in dichloromethane caused the solution to become olive green. Recrystallization using a light petroleum/diethyl ether mixture (1:1) yielded a dark green crystalline material. The green colour suggested that the compound may be a 5-coordinate complex and microanalysis showed the formula to be $RuCl_2(PPh_3)_2Ph_2POCH_2CH{=}CMe_2$.

2.4.2 Spectroscopic details of ruthenium-phosphinite ester complexes

a) Infra-red

Relevant infra-red data for these complexes are given in Table 5,(p.65). The low values of the $\nu_{C=O}$ obtained for products of the reactions described in section 2.4.1 (a) and (b) suggest that the unsaturated phosphinite ester is bound to the ruthenium atom in a chelate manner through phosphorus and the oxygen atom of the ester carbonyl. The disruption of the

π-electron density of the system on coordination causes a weakening of the bond and hence a lowering of the stretching frequency. In the IR spectrum of $RuCl_2(PPh_3)_2Ph_2POCH_2CH{=}CMe_2$, a weak feature at 1670 cm^{-1} was ascribed to $\nu_{C=C}$ suggesting that the phosphinite ester ligand is not bound in a chelate fashion through the double bond. All spectra gave rise to single strong ν_{M-Cl} absorptions in the 330-350 cm^{-1} region of the spectrum indicating that the Cl atoms present are always *trans* to one another.

b) Nmr

Table 6 (p.65) shows relevant nmr data for the ruthenium-phosphinite ester complexes. The ^1H nmr(fig.21,p.66) of $RuCl_2(Ph_2PO_2CCH{=}CMe_2)_2$ clearly shows the presence of a vinylic proton at δ 6.19; this is in accordance with there being no metal-alkene interaction. The methyl protons appear as doublet resonances at δ 1.98 and δ 2.30, ($^4J_{M-H}$ 1.0 Hz). The low field signal at δ 185.6 in the ^{31}P nmr spectrum is indicative of the presence of an oxygen bound chelated phosphine ester ligand.

Although no satisfactory ^1H nmr data has yet been obtained for $RuCl_2(Ph_2PO_2CCMe{=}CHPh)_2$ the ^{31}P nmr spectrum consists of a single resonance at δ 186.6. This again suggests that both phosphinite ester ligands are coordinated in a chelate manner through phosphorus and oxygen.

Table 5: Infra-red data for ruthenium complexes of unsaturated phosphinite esters

Compound	$\nu_{C=C}$ cm^{-1}	$\nu_{C=O}$ cm^{-1}	ν_{M-Cl} cm^{-1}
$RuCl_2(Ph_2PO_2CCH=CMe_2)_2$	1630	1600 st	347
$RuCl_2(Ph_2PO_2CCMe=CHPh)_2$	1620	1590 sst	340
$RuCl_2(PPh_3)_2Ph_2POCH_2CH=CMe_2$	1670 w	-	330

Table 6: Nmr data for the ruthenium complexes of unsaturated phosphinite esters
(Selected resonances)

Compound	^1H ppm(a)	^{31}P ppm(b)
$RuCl_2(Ph_2PO_2CCH=CMe_2)_2$	δMe 1.98d, 2.30d δH 6.19 ($^4J_{MeH}$ 1.0 Hz)	δP 185.6
$RuCl_2(Ph_2PO_2CCMe=CHPh)_2$	-	δP 186.6
$RuCl_2(PPh_3)_2Ph_2POCH_2CH=CMe_2$	δMe 1.10d, 1.41d δCH_2 3.5 δH 4.58	δP 219.47 δP 163.8 ($^2J_{PP}$ 30.3 Hz)

(a) ppm with respect to CH_2Cl_2 reference at 5.2 ppm

(b) ppm to high frequency of 85% H_3PO_4 in CH_2Cl_2 at 298 K

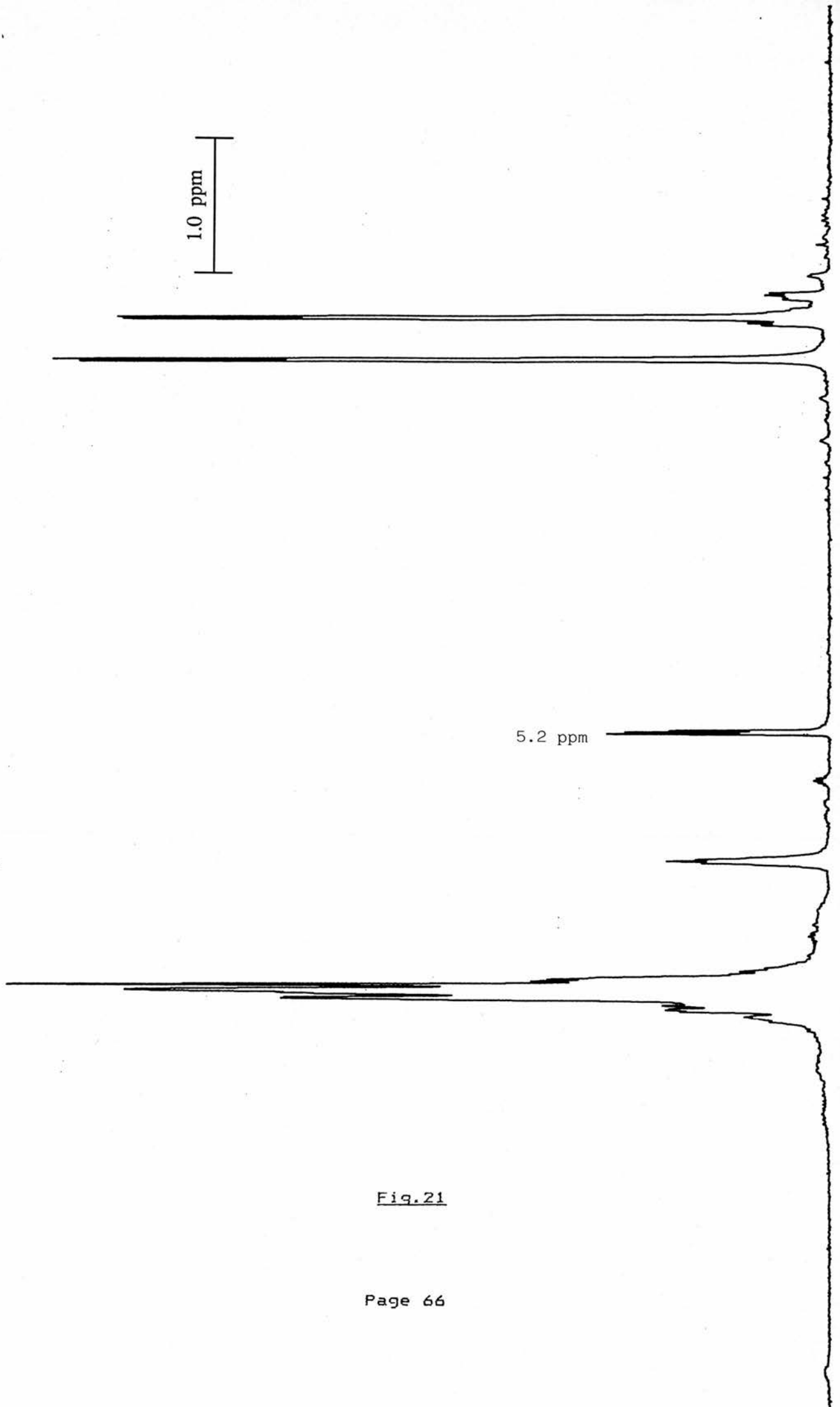
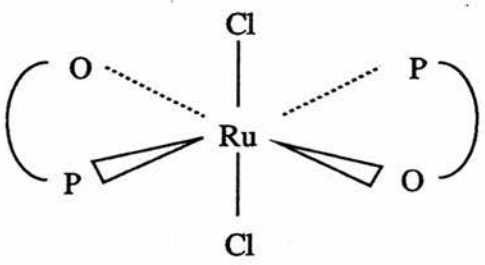


Fig.21

The ^1H nmr of $RuCl_2(PPh_3)_2Ph_2POCH_2CH{=}CMe_2$ shows resonances from the vinylic proton at δ 4.58 and the methylene protons at δ 3.5 in addition to methyl resonances at δ 1.10 and δ 1.41. The ^{31}P nmr consists of two signals, a triplet resonance at δ 163.8 arising from the ester phosphorus atom and a doublet resonance at δ 29.47 from the *trans* triphenylphosphine phosphorus atoms ($^2J_{PP}$, 30.3 Hz).

On the basis of infra-red and nmr data for the first two complexes the following structure has been assigned, (fig.22).



$P\frown O = Ph_2PO_2CCH = CMe_2$

or $Ph_2PO_2CCMe = CHPh$

Fig.22

Similar complexes have been prepared recently by Braunstein *et al* in which P O=$Ph_2PCH_2CO_2Et$ (see section 3.2.4).

The spectroscopic data for the $RuCl_2(PPh_3)_2Ph_2POCH_2CH{=}CMe_2$ complex are slightly ambiguous, necessitating further investigation. The weak feature at 1670 cm^{-1} ascribed to $\nu_{C=C}$ in the infra-red spectrum suggests that the phosphinite ligand is monodentate. However, the triplet resonance at δ 163.8 arising from this ligand in the ^{31}P nmr spectrum is higher than is generally observed for monodentate binding of this kind. Even so, the dark green colour of the complex does suggest that it is

5-coordinate and the following structure has been tentatively assigned, (fig.23), although the infra-red spectrum shows only a broad ν_{M-Cl} feature rather than two absorptions.

2.4.3 Reaction of $RuCl_2(PPh_3)_2Ph_2POCH_2CH=CMe_2$ with CO and H_2

a) With CO

Passing carbon monoxide gas through dichloromethane solutions of $RuCl_2(PPh_3)_2Ph_2POCH_2CH=CMe_2$ results in an immediate change of colour from olive green to red. Recrystallization using petroleum ether results in a yellow-red solid that analyses for $RuCl_2(PPh_3)_2(CO)_2$. Neither the ^1H nor the ^{31}P nmr spectra show any evidence for the presence of a phosphinite ester linkage and the infra red spectrum, with ν_{C-O} at 2000 cm^{-1} and ν_{M-Cl} at 330 cm^{-1} indicates that the product is an octahedral *trans,trans,trans* complex, (fig.24).

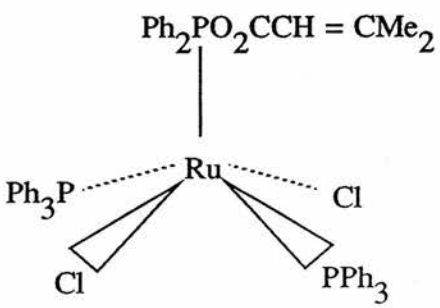


Fig.23

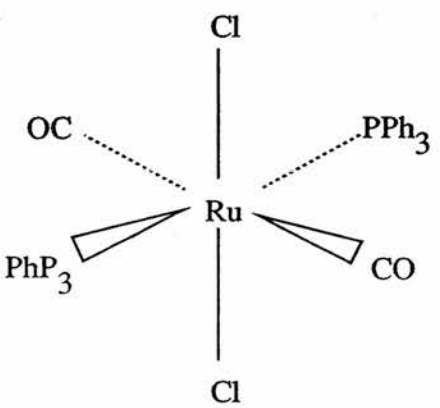


Fig.24

This displacement of the phosphinite ester ligand in preference to PPh_3 by CO is unusual as generally PPh_3 is the more labile ligand and this requires further investigation. It is possible that the ester is undergoing some sort of rearrangement reaction which causes it to become labile.

b) With H_2

Nmr data indicated that no change occurs on passing H_2 gas through dichloromethane solutions of $RuCl_2(PPh_3)_2Ph_2POCH_2CH{=}CMe_2$ implying that it would be inactive as a hydrogenation catalyst. However further work with higher hydrogen pressures would be of interest.

2.5 Conclusions from Chapter II

The effects of steric constraints introduced by bulky triphenylphosphine groups in the complexes discussed in this chapter seem to be important in determining the coordination of the phosphinite ester ligand. In the Wilkinson's catalyst analogues $RhCl(PPh_3)_2Ph_2PO_2CCR^1{=}CR^2R^3$ and in $RuCl_2(PPh_3)_2Ph_2POCH_2CH{=}CMe_2$ the triphenylphosphine groups are located *trans* to one another and *cis* to the ester ligand. The steric constraints introduced by this stereochemistry effectively inhibits the chelation of the ester either through the double bond or the carbonyl oxygen.

Experiments involving the addition of one equivalent of $Ph_2PO_2CCH=CMe_2$ to $RuCl_2(PPh_3)_4$ yield black crystalline $RuCl_2(PPh_3)_2Ph_2PO_2CCH=CMe_2$, preliminary results suggesting that the phosphinite ester is bound in a monodentate fashion. This lends weight to the suggestion that the presence of bulky *trans* PPh_3 groups prevents chelate coordination.

Although phosphinite ester ligands of the type described have been shown to chelate to rhodium through the double bond and phosphorus[106], this has not been found to be the case for either the cationic rhodium or the neutral ruthenium species described.

The most probable explanation for the oxygen bound chelation exhibited by the Rh species is that steric constraints caused by the interaction of bulky PPh_3 groups with the functional groups of the acrylate moiety inhibit the coordination of the unsaturated linkage.

Although considerations of steric constraints introduced by triphenylphosphine groups are not appropriate for ruthenium complexes of the type $RuCl_2(Ph_2PO_2CCR^1=CR^2R^3)_2$ the phosphinite ester ligand is again chelated through the carbonyl oxygen atom. The obvious implication of this is that, although steric hinderance is of importance, electronic effects exist that favour the coordination of the carbonyl functionality rather than the carbon-carbon double bond.

2.6 Experimental detail of preparations

Phosphinite esters of αβ-unsaturated acids and βɣ-unsaturated alcohols were prepared by standard literature methods. Infra-red spectra were recorded on a Perkin Elmer Type 1330 spectrometer, and nmr spectra on Brucker WP80 ^{1}H and Varian CFT20 ^{31}P spectrometers. Standard Schlenk line techniques and dried distilled solvents were used throughout.

2.6.1 Rh(I) complexes

(i) $RhCl(PPh_3)_2Ph_2PO_2CCH{=}CMe_2$

To a suspension of $RhCl(PPh_3)_3$ (0.5g, 0.54 mmol) in tetrahydrofuran (20 cm^3) was added a solution of $Ph_2PO_2CCH{=}CMe_2$ (0.15g, 0.54 mmol) in tetrahydrofuran (10 cm^3). On addition, an immediate reaction occurred, the solution paled to red-orange and the $RhCl(PPh_3)_3$ dissolved to give a homogeneous solution. After rapid stirring (5 mins) and filtration the solvent was evaporated to approximately 5 cm^3 and a bright orange crystalline solid was precipitated by addition of light petroleum spirit. The solid was collected, washed with petroleum (2x10 cm^3) and dried *in vacuo*. The complex was slightly air-sensitive and became dull orange in colour when exposed to air over a few days.

Yield 0.43 g, (85%).

Found: C, 66.95%; H, 4.98%.

$C_{53}H_{47}ClO_2P_3Rh$ requires: C, 67.0%; H, 5.0%

(ii) $RhCl(PPh_3)_2Ph_2PO_2CCMe{=}CHPh$

The complex was prepared as in (i) but using $RhCl(PPh_3)_3$ (0.27g, 0.29 mmol) and $Ph_2PO_2CCMe{=}CHPh$ (0.1g, 0.29 mmol) in tetrahydrofuran solution. The complex was isolated to give a bright orange solid.

Yield 0.23g (80%).

No analysis was obtained for this complex.

(iii) $[Rh(PPh_3)_2Ph_2PO_2CCH{=}CMe_2]^+PF_6^-$

To a solution of $RhCl(PPh_3)_2Ph_2PO_2CCH{=}CMe_2$ (0.44g, 0.46 mmol) in tetrahydrofuran (20 cm^3) was added a solution of $TlPF_6$ (0.16g, 0.46 mmol) in thf (10 cm^3). The solution was stirred for 30 minutes during which time the precipitation of yellow-white TlCl occurred. The solid was allowed to settle and the resulting yellow-orange solution filtered. The solvent was removed by evaporation under reduced pressure to a volume of approximately 5 cm^3 and the yellow crystalline solid isolated by addition of a mixture of light petroleum/diethyl ether (1:1).

No yield was recorded for this complex.

Found: C, 58.83%; H, 4.38%.

$C_{53}H_{47}O_2P_4F_6Rh$ requires : C, 60.24%; H, 4.48%.

2.6.2 Ruthenium(II) complexes

(i) $RuCl_2(Ph_2PO_2CCH{=}CMe_2)_2$

To a solution of $RuCl_2(PPh_3)_4$ (0.43g, 0.35 mmol) in dichloromethane (20 cm^3) was added $Ph_2PO_2CCH{=}CMe_2$ (0.20g, 0.70 mmol) in dichloromethane (10 cm^3). An immediate reaction occurred and the brown-black solution became bright red. The solution was filtered, the solvent reduced by evaporation to approximately 5 cm^3 and a bright red crystalline solid precipitated by careful addition of a mixture of petroleum spirit and diethyl ether (1:1). The solid was collected and washed with petroleum (2x10 cm^3) and dried *in vacuo*. Yield 0.21g. (80%).

Found: C, 55.58%; H, 4.61%.

$C_{34}H_{34}O_4P_2Cl_2Ru$ requires : C, 55.14%; H, 4.63%.

(ii) $RuCl_2(Ph_2PO_2CCMe{=}CHPh)_2$

The complex was prepared the same way as in (i) but using $RuCl_2(PPh_3)_4$ (0.43g, 0.35 mmol) and $Ph_2PO_2CCMe{=}CHPh$ (0.25g, 0.72 mmol) in dichloromethane solution. The complex was isolated to give a bright red microcrsytalline solid. Yield 0.26g.(85%).

Found: C, 60.94%; H, 4.46%.

$C_{44}H_{38}O_4P_2Cl_2Ru$ requires: C, 61.11%; H, 4.43%.

(iii) $RuCl_2(PPh_3)_2Ph_2POCH_2CH{=}CMe_2$

To a stirred solution of $RuCl_2(PPh_3)_4$ (0.63g, 0.52 mmol) in dichloromethane (20 cm^3) was added $Ph_2POCH_2CH{=}CMe_2$ (0.28g, 1.04 mmol) in dichloromethane (10 cm^3). A rapid reaction occurred and the brown-black solution became olive-green. the solution was stirred for 5 minutes before filtering. The solvent was then reduced by evaporation to approximately 5 cm^3 and the dark green crsytalline product precipitated by a careful addition of a 1:1 mixture of light petroleum spirit/diethyl ether.The product was washed with petroleum (2x10 cm^3) and dried *in vacuo*.

Yield 0.43g. (83%).

Found: C, 65.47%; H, 4.99%.

$C_{55}H_{49}OP_3Cl_2Ru$ requires: C, 65.84%; H, 5.07%.

CHAPTER III

HYDROGENATION REACTIONS CATALYSED BY Rh(I) and Ru(II) COMPLEXES

ATTEMPTED PREPARATION OF A BIS(PHOSPHINE) PHOSPHINITE ESTER COMPLEX OF Rh(I)

3.1 Introduction

The importance of chelate binding in the hydrogenation reactions of highly substituted alkenes has been discussed in Chapter I (Section 1.1.4). Previous work, involving rhodium complexes of $Ph_2POXCR^1=CR^2R^3$ has led to the preparation of stable dimeric Rh(I) complexes containing a chelating phosphine ester ligand[106]. It appeared that this family of compounds may offer a new route for the hydrogenation of highly functionalised alkenes (which includes many unsaturated substrates containing prochiral centres). This conclusion was drawn since the phosphinite ester ligands in question possess the following properties:

a) the phosphinite is a good coordinating group;

b) alkene coordination is favoured by chelate ring formation;

c) the phosphinite group can be removed by hydrolysis or transesterification after reaction.

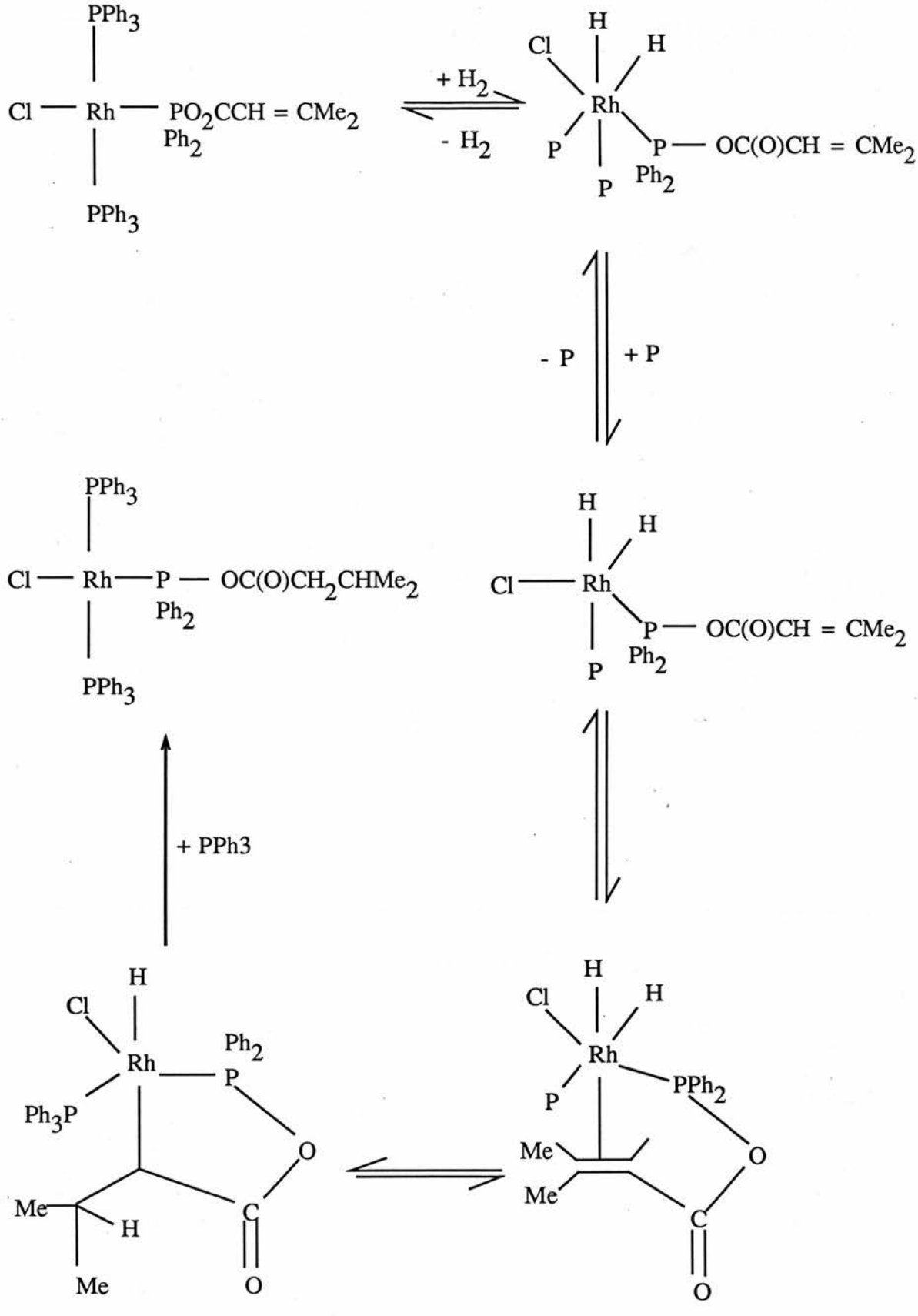
These observations led to the preparation of analogues of Wilkinson-type systems as described in Chapter II. The results of hydrogenation reactions using $RhCl(PPh_3)_2Ph_2PO_2CCH=CMe_2$ obtained prior to the start of this work are outlined below.

The stoichiometric hydrogenation reaction of $RhCl(PPh_3)_2Ph_2PO_2CCH=CMe_2$, (Eqn.6) has been established to occur via an intra-molecular mechanism rather than an inter-molecular one where the "dangling" alkene is hydrogenated by a second molecule which is acting in a similar manner to Wilkinson's catalyst. The proposed mechanism is given in Scheme 5,p.(77), and is very similar to that observed for Wilkinson-type catalysis except that the important step is the formation of the chelate bound alkene intermediate, which stabilizes the metal alkene interaction, thus favouring hydrogenation of the double bond.

$$RhCl(PPh_3)_2Ph_2PO_2CCH=CMe_2 \xrightarrow{H_2} RhCl(PPh_3)_2Ph_2PO_2CCH_2CHMe_2$$

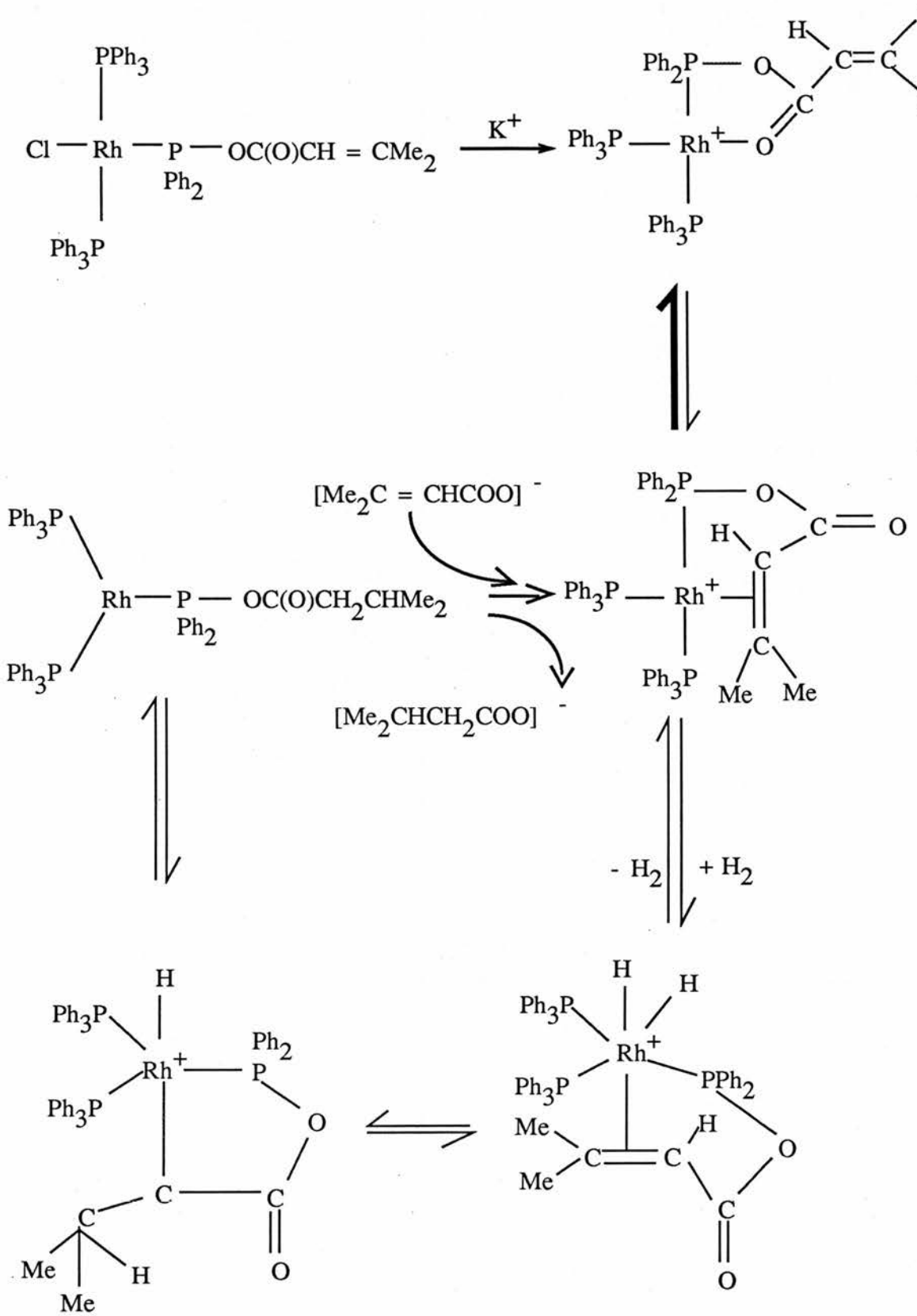
Eqn.6

This hydrogenation reaction was found to be catalytic under certain conditions, namely with acetone solutions in the presence of a potassium salt. Reductions of $[Me_2C=CHCOO]K$ to $[Me_2CHCH_2COO]K$ were observed with greater than 50 % conversion , and a reaction mechanism has been proposed, (Scheme 6.p.78). Although the equilibrium between alkene coordination and chelation through the carbonyl oxygen atom is not favourable, alkene coordination and hence hydrogenation does occur. The important step was presumed to be a transesterification reaction of the $Me_2CHCH_2CO_2PPh_2$ moiety that occurs via nucleophilic attack on the coordinated phosphorus by $Me_2C=CHCOO^-$, (Eqn.7).



Scheme 5

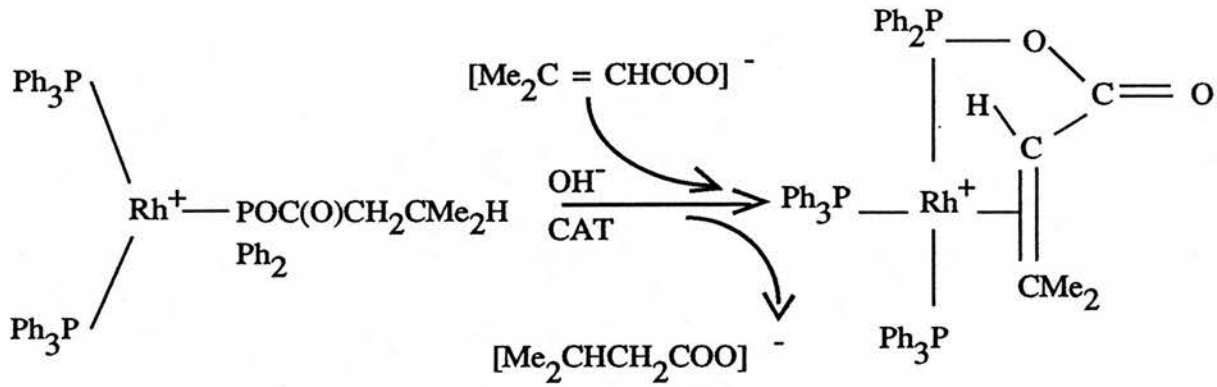
Stoichiometric reduction of $RhCl(PPh_3)_2Ph_2PO_2CCH=CMe_2$



Scheme 6

Catalytic hydrogenation of $[Me_2C=CHCOO]K$ using

$RhCl(PPh_3)_2Ph_2PO_2CCH=CMe_2$



Eqn.7

A transesterification reaction between $Ph_2PO_2CCH=CMe_2$ and HO_2CMe has been observed[112]. Base catalysed transesterifications have been reported for aromatic and αβ-unsaturated methyl esters with primary, secondary and tertiary alcohols[113]. A similar reaction occurs for the substitution of the pyridinyloxy group of $Mo(CO)_4(2\text{-}Me_2POC_5H_4N)$ by $LiOCH_2CR^1=CR^2R^3$[114].

In this work the activities of $RhCl(PPh_3)_2Ph_2PO_2CCH=CMe_2$ and $RhCl(PPh_3)_2Ph_2PO_2CCMe=CHPh$ have been investigated and further hydrogenation reactions involving a variety of αβ-unsaturated acid substrates will be described. An attempt has also been made to prepare analogous catalysts suitable for the asymmetric hydrogenation of a prochiral carbon centre.

3.2 Catalytic hydrogenation reactions: Results and discussion

3.2.1 Catalytic hydrogenation of α-methylcinnamic acid by $RhCl(PPh_3)_2Ph_2PO_2CCMe=CHPh$

An acetone solution of $RhCl(PPh_3)_2Ph_2PO_2CCMe=CHPh$, $HO_2CCMe=CHPh$ (20 equivalents) and KOH was stirred under H_2 (3 atmospheres) for 23 hours. On addition of hydrogen the red solution became yellow. The ^1H nmr of the product showed resonances at δ 1.75 d ($^2J_{M-H}$ 2 Hz) and at δ 7.80 m corresponding to the methyl group and vinylic proton respectively of the starting material, and at δ 0.78 d ($^2J_{M-H}$ 6 Hz) from the methyl group and a complex multiplet at δ 2-3 from the CH_2 and CH groups of the product. Comparisons of the doublet resonances at δ 0.78 and δ 1.75 showed that hydrogenation of α-methylcinnamic acid had occurred with 62.5 % conversion to 2-methyl-3-phenylpropionic acid.

The product of this reaction is a chiral molecule (fig.25) and the generation of large enantiomeric excesses is potentially possible in the presence of an asymmetric catalyst.

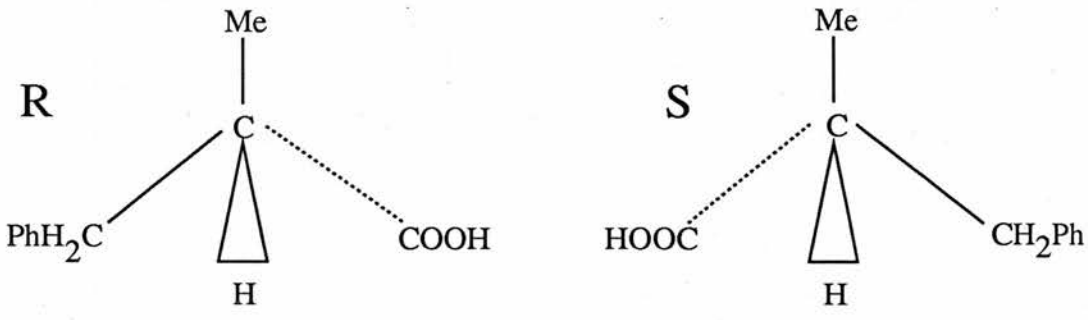
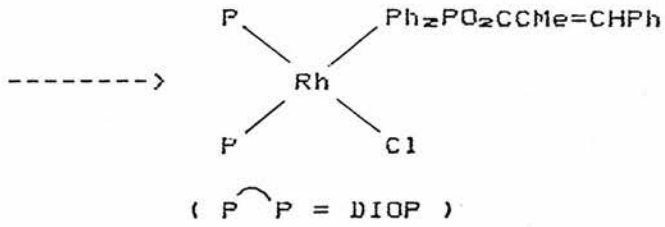


Fig.25

An attempt was made to generate such a catalyst *in situ* (Eqn. 8) by stirring $RhCl(PPh_3)_2Ph_2PO_2CCMe{=}CHPh$ and DIOP (1 equivalent) together in acetone. $HO_2CCMe{=}CHPh$ (20 equivalents) and KOH were added to the resulting solution and the reaction mixture was stirred under H_2 (3 atmospheres) for 16 hours.

$RhCl(PPh_3)_2Ph_2PO_2CCMe{=}CHPh$ + DIOP



Eqn.8

The proton spectrum, however, indicated that no hydrogenation had occurred, the most likely explanation for this being that the reaction is inhibited by the presence of free triphenylphosphine generated during the preparation of the asymmetric catalyst. This type of inhibition is common in hydrogenation reactions catalysed by Wilkinson's catalyst[3]. Thus, it would seem necessary to prepare and isolate the asymmetric catalyst before hydrogenation experiments of this type are conducted. Attempts to do so are described in section 3.3.

3.2.2 Catalytic hydrogenation of αβ-unsaturated acids with $RhCl(PPh_3)_3$ and $RhCl(PPh_3)_2Ph_2PO_2CCH=CMe_2$

The results of catalytic hydrogenation reactions for a range of αβ-unsaturated acids with $RhCl(PPh_3)_3$ and $RhCl(PPh_3)_2Ph_2PO_2CCH=CMe_2$ are shown in Table 7 . In all cases higher activity is observed with the $RhCl(PPh_3)_2Ph_2PO_2CCH=CMe_2$ catalyst than with Wilkinson's catalyst and the fact that the same catalyst precursor can be employed for a range of catalytic reactions is further evidence that a transesterification occurs during the hydrogenation.

Substrate	% conversion (a)	
	$RhCl(PPh_3)_3$	$RhCl(PPh_3)_2Ph_2PO_2CCH=CMe_2$
$HO_2CCH=CMe_2$	26.7	80.0
$HO_2CCMe=CHPh$	57.6 (8%,b)	68.2 (13%,b)
$HO_2CCH=CMeH$	75.8 (31%,b)	100.0 (76%,b)
$HO_2CCH=CHCH=CHMe$	10.6 (c)	64.7 (d)

a) Conditions: [catalyst] $=3\times10^{-3}$ mol dm^{-3},

[substrate] $=6\times10^{-2}$ mol dm^{-3}

[KOH] $=4\times10^{-2}$ mol dm^{-3}, in acetone ($5cm^3$), 17 hr.,22°C, $p(H_2)$= 3 atm.

b) Conditions as for (a) but T=2 hr.

c) Hexanoic acid

d) Hex-4-enoic acid (52.3%), hexanoic acid (47.7%).

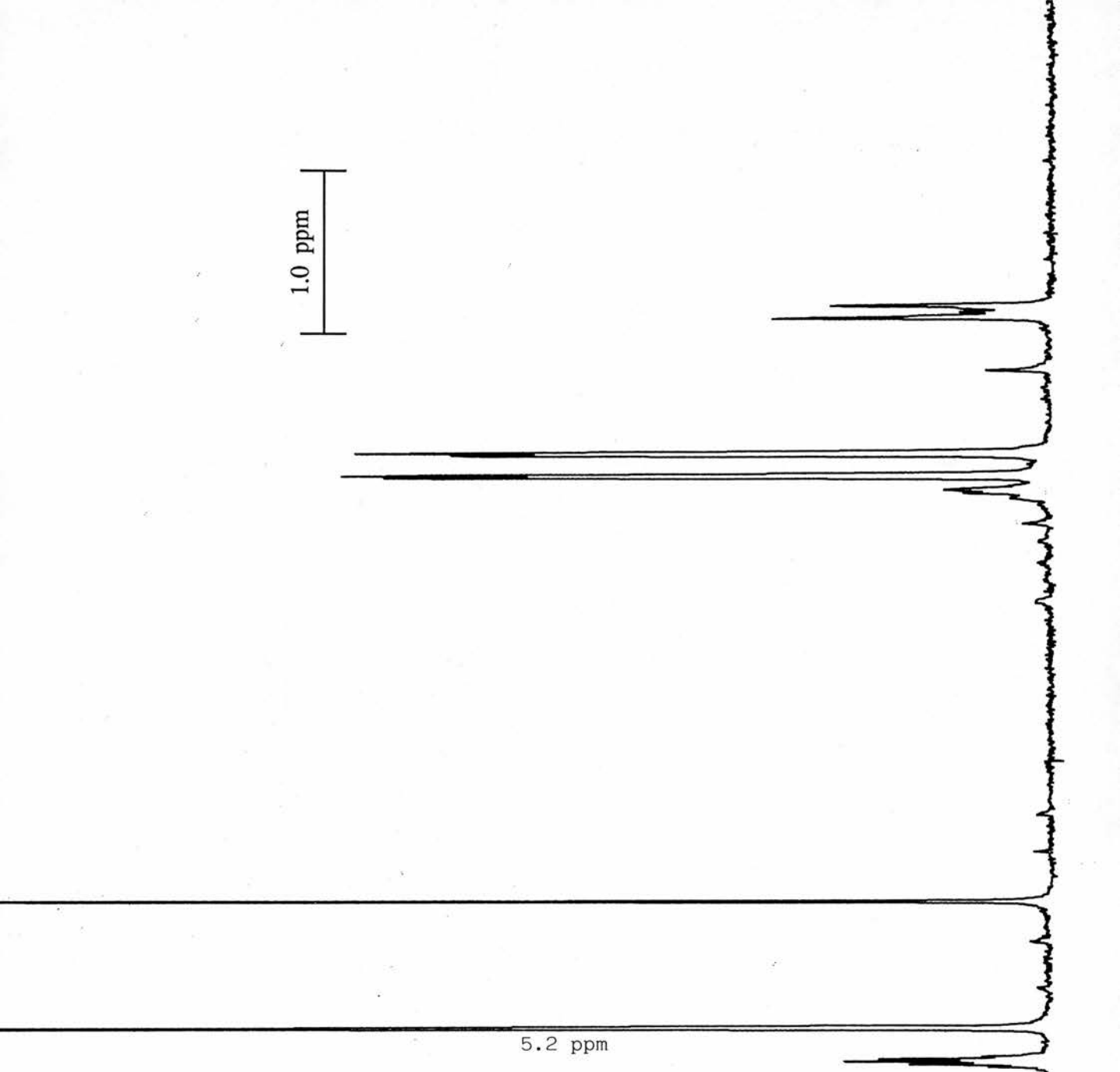
Table 7

^{1}H nmr data (a)

$Me_2C=CHCOOH$	δ_{Me} 1.53 d, 1.68 d	($^4J_{MeH}$ 1 Hz)
	δ_H 5.40 m	
Me_2CHCH_2COOH	δ_{Me} 0.64 d	($^2J_{MeH}$ 6 Hz)
	δ_{CH} 1.78 d	
	δ_{CH} small multiplet, not seen.	
$MeCH=CHCOOH$	δ_{Me} 1.55 d.d	($^4J_{MeH}$ 2 Hz) ($^2J_{MeH}$ 6 Hz)
	δ_H 5.47 m, 5.65 m	
$MeCH_2CH_2COOH$	δ_{Me} 0.63 t	($^2J_{MeH}$ 7 Hz)
	δ_{CH} 1.28, 1.94	($^2J_{MeH}$ 7 Hz)
$PhCH=CMeCOOH$	δ_{Me} 1.75 d	($^2J_{MeH}$ 2 Hz)
	δ_H 7.80 m	
$PhCH_2CH_2MeCOOH$	δ_{Me} 0.78 d	($^2J_{MeH}$ 6 Hz)
	δ_{CH} ,$_{CH}$ 2-3 complex multiplet	
sorbic acid	δ_{Me} 1.85 t	
	δ_{CH} 5.65 s, 5.85 s	
	δ_{CH} 7 m, 6-6.3 m	
Hex-4-enoic acid	δ_{Me} 1.65 d.d	($^2J_{MeH}$ 4 Hz) ($^4J_{MeH}$ 1 Hz)
	δ_H 5.55 m	
Hexanoic acid	δ_{Me} 0.92 t,	
	δ_{CH} 1.32 m,	
	δ_{CH} 2.22 m,	

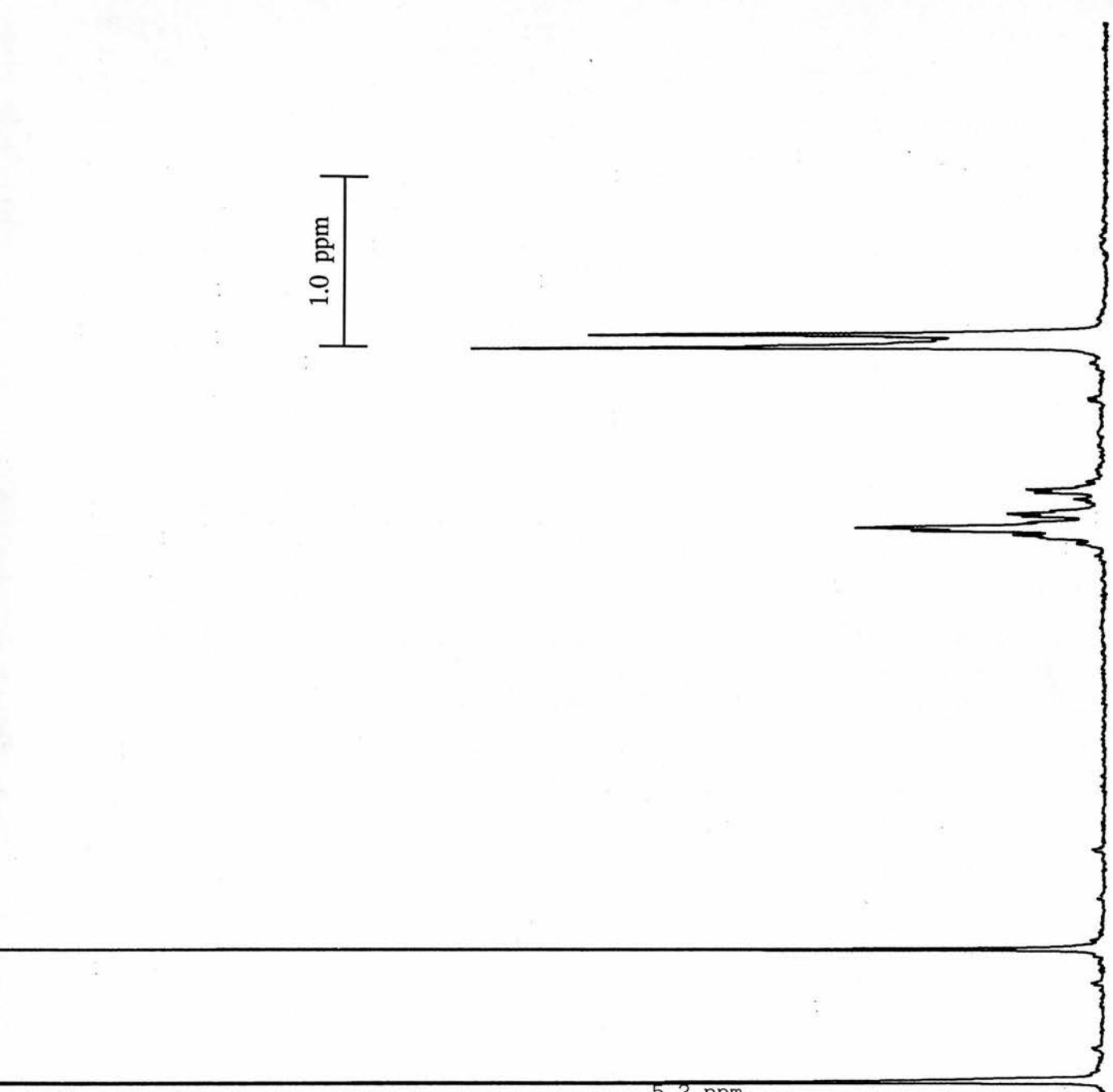
(a) ppm with respect to CH_2Cl_2 in D_2O at 298 K

Table 8: ^{1}H nmr data for hydrogenation experiments



^1H nmr - Hydrogenation of $Me_2C=CHCOOH$ by $RhCl(PPh_3)_3$

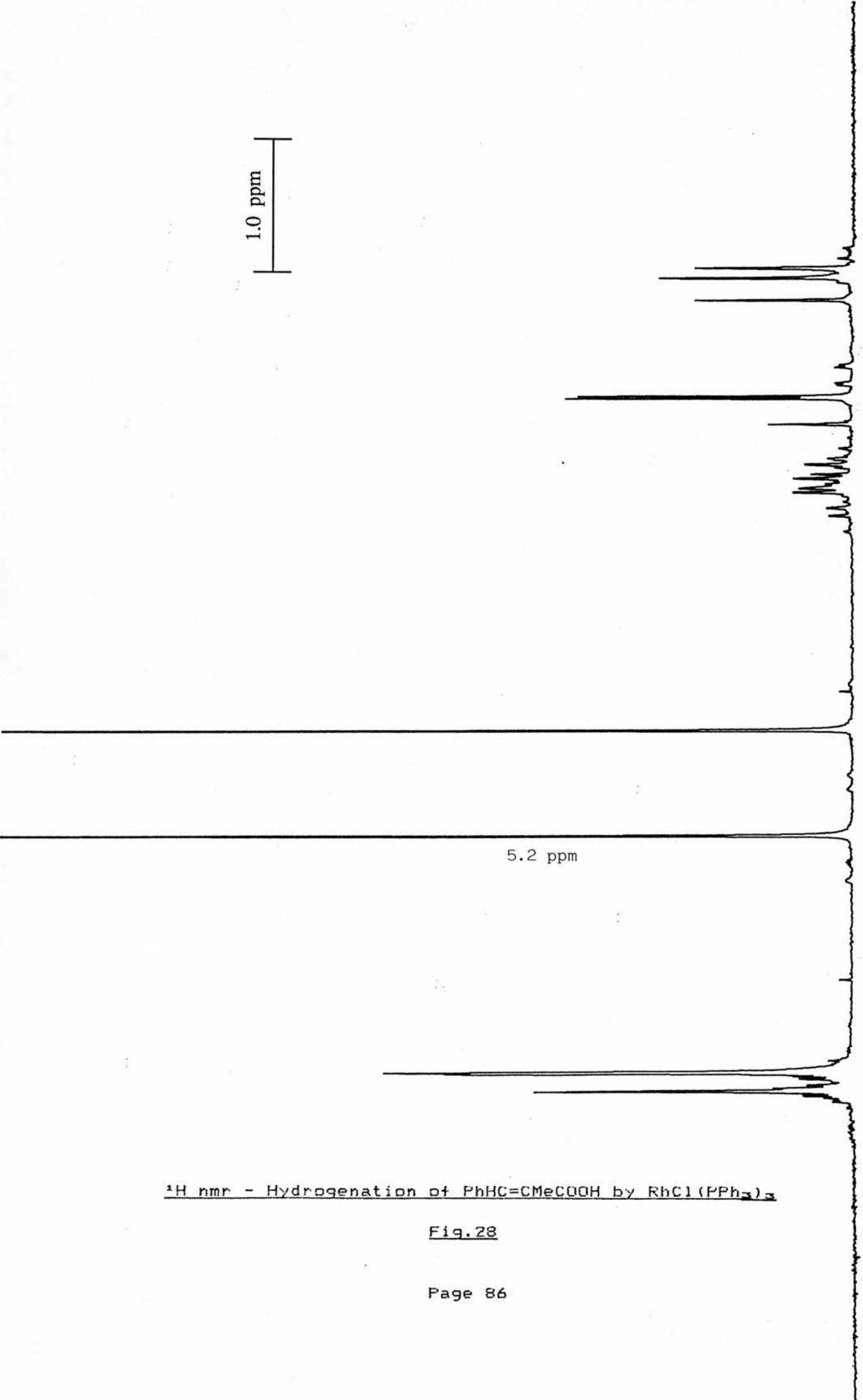
Fig.26



^{1}H nmr - Hydrogenation of $Me_2C=CHCOOH$ by

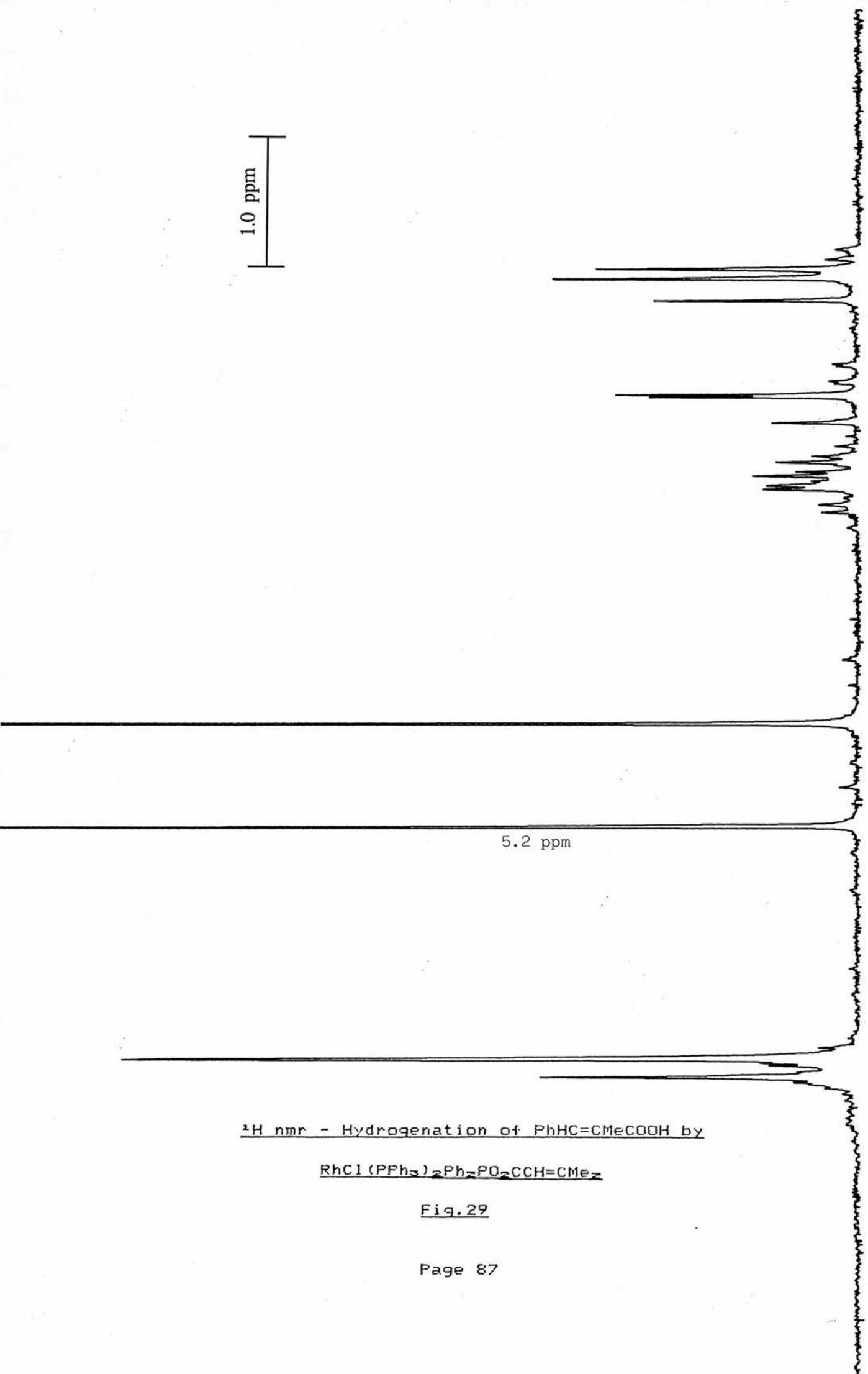
$RhCl(PPh_3)_2Ph_2PO_2CCH=CMe_2$

Fig.27



^{1}H nmr - Hydrogenation of PhHC=CMeCOOH by $RhCl(PPh_3)_3$

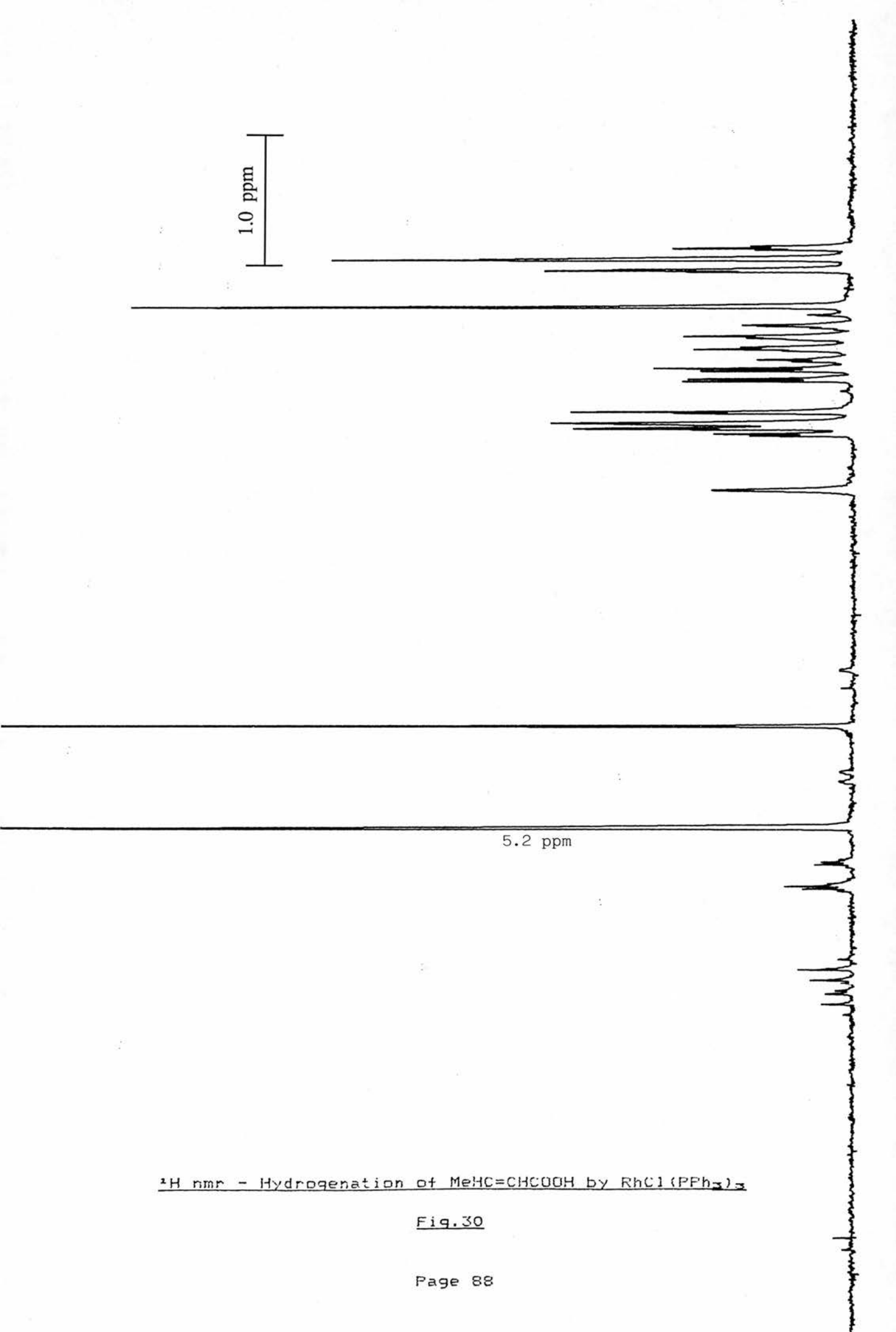
Fig.28



^{1}H nmr - Hydrogenation of PhHC=CMeCOOH by

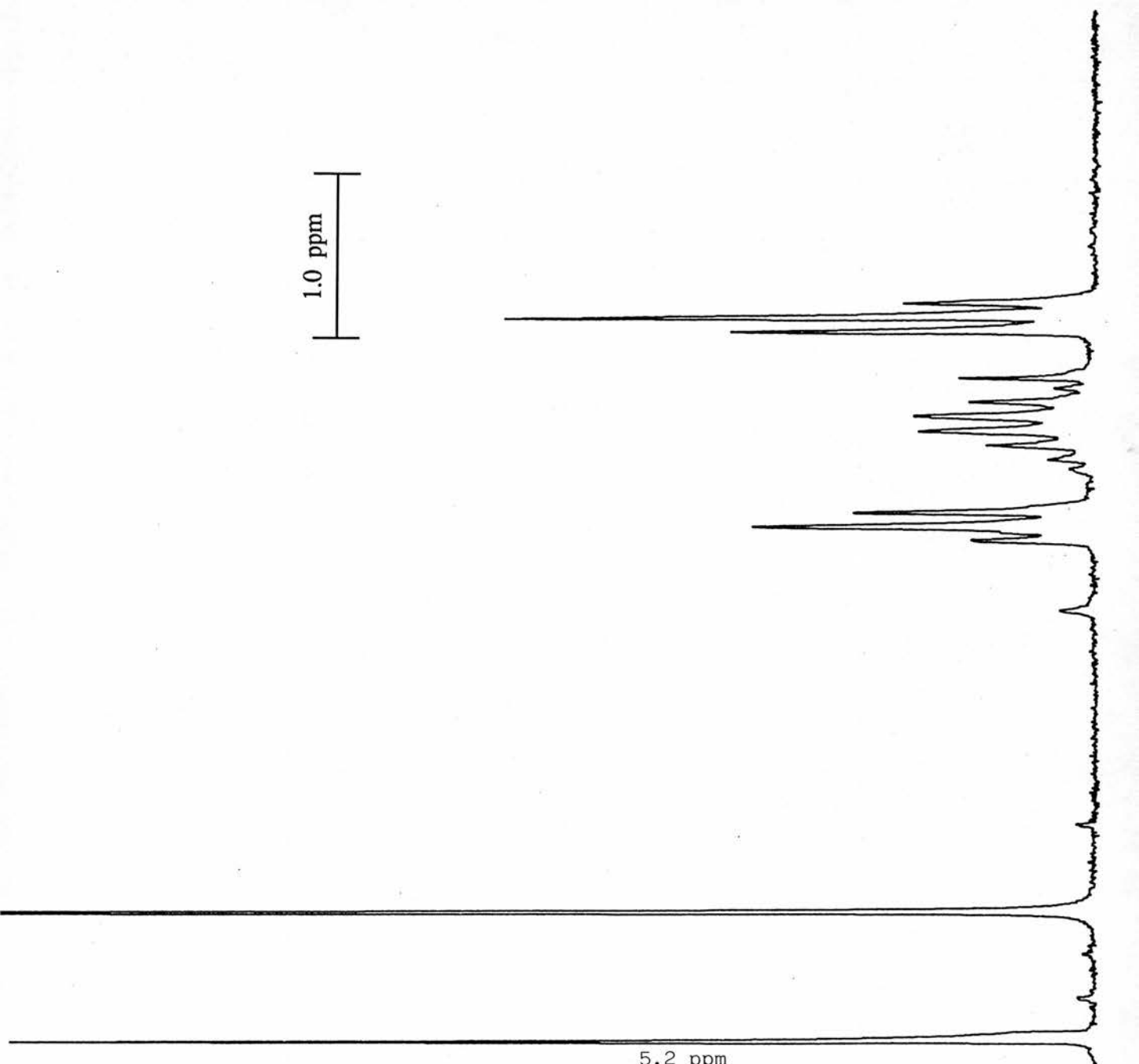
$RhCl(PPh_3)_2Ph_2PO_2CCH=CMe_2$

Fig.29



^1H nmr - Hydrogenation of MeHC=CHCOOH by $RhCl(PPh_3)_3$

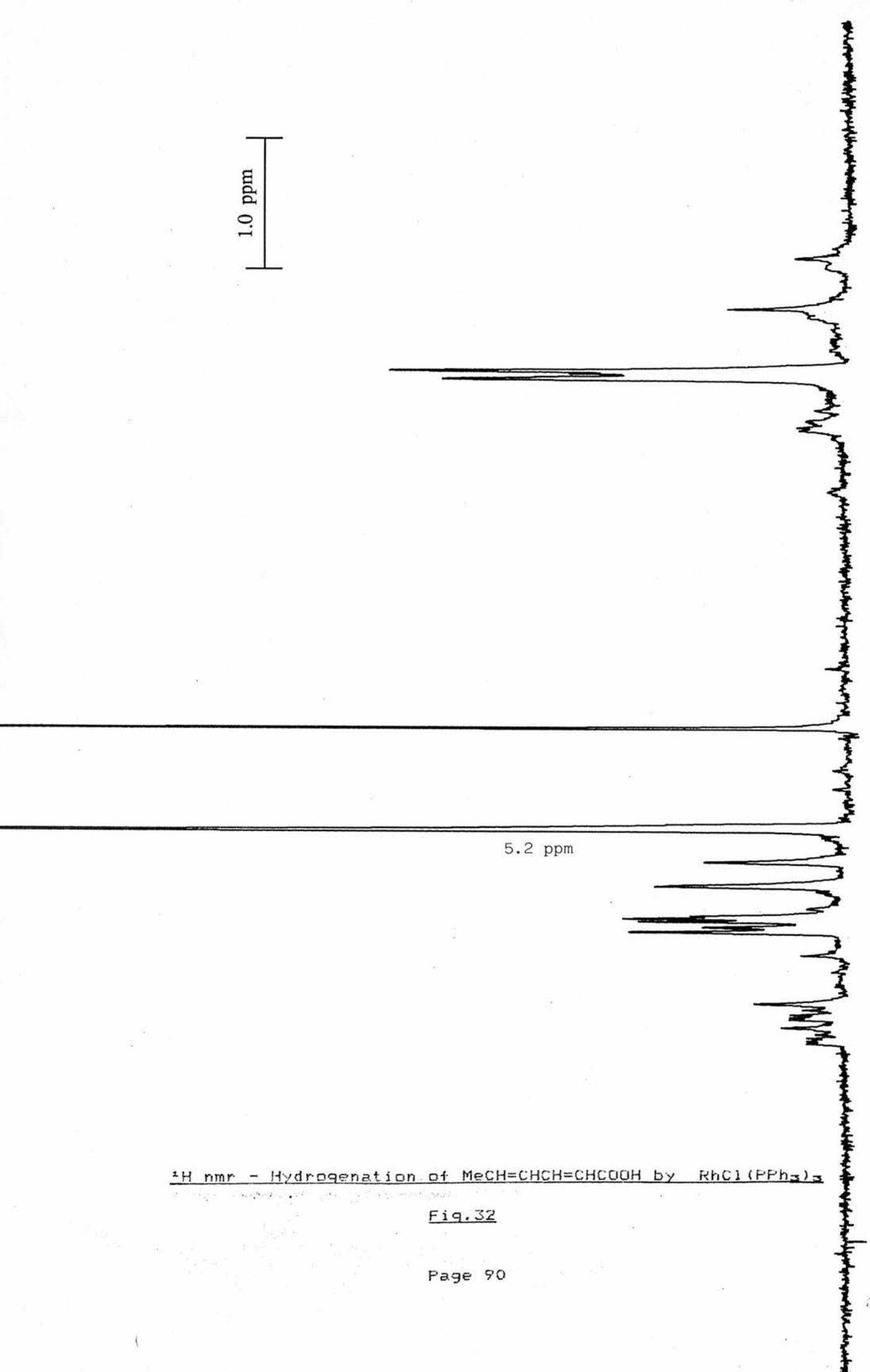
Fig.30



^{1}H nmr - Hydrogenation of MeHC=CHCOOH by

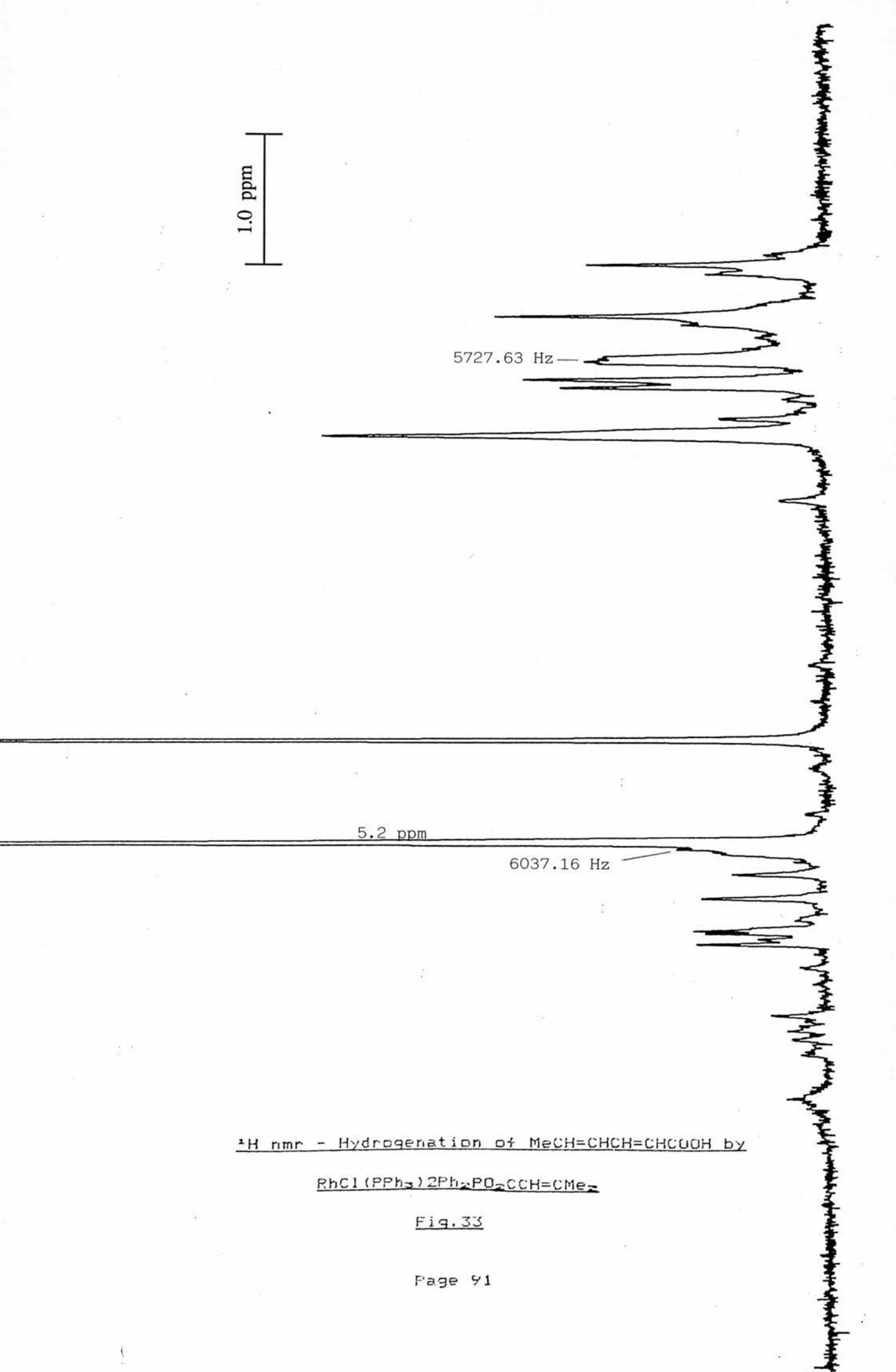
$RhCl(PPh_3)_2Ph_2PO_2CCH=CMe_2$

Fig.31



^1H nmr - Hydrogenation of MeCH=CHCH=CHCOOH by $RhCl(PPh_3)_3$

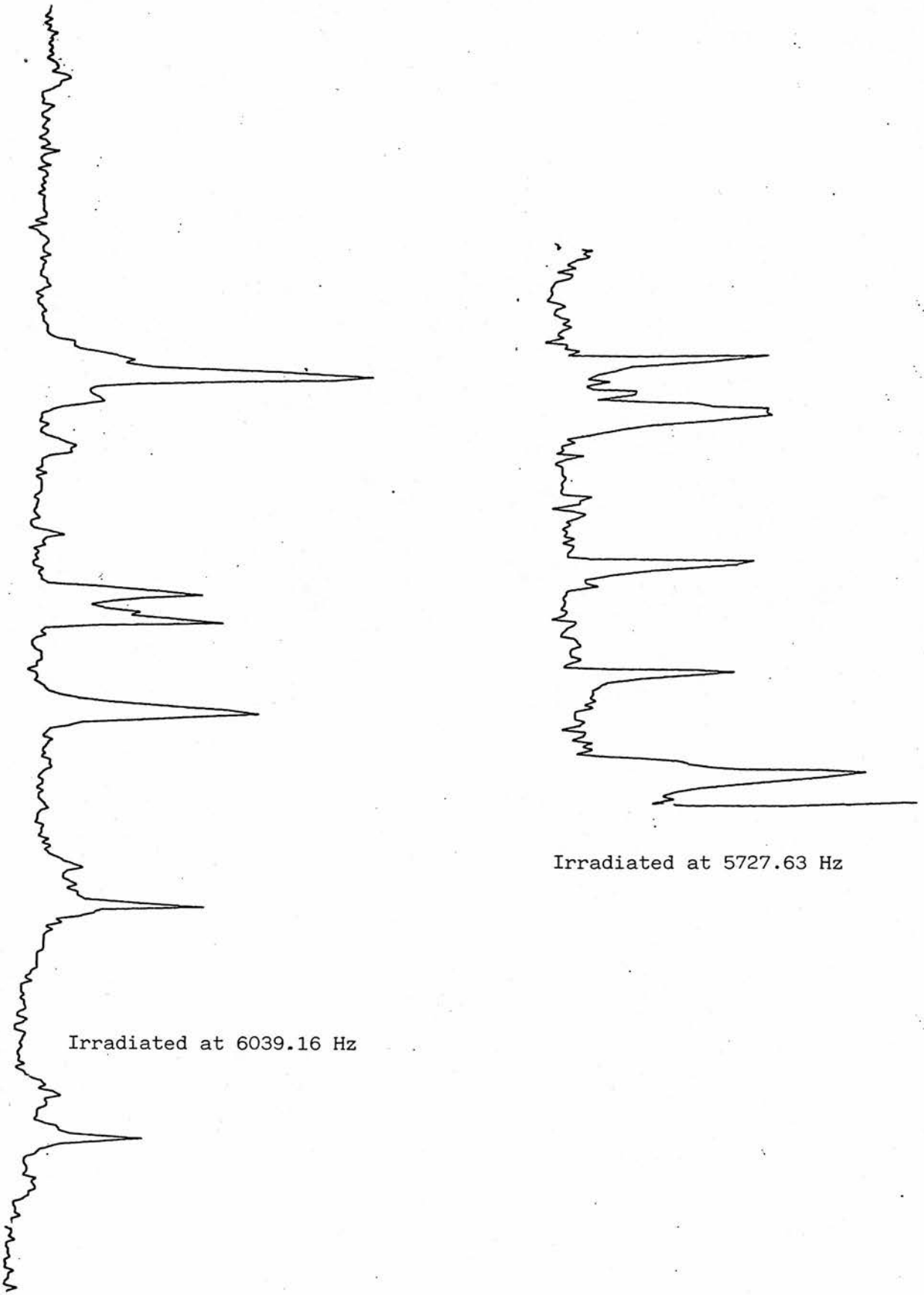
Fig.32



^{1}H nmr - Hydrogenation of MeCH=CHCH=CHCOOH by

$RhCl(PPh_3)2Ph_2PO_2CCH=CMe_2$

Fig.33



Irradiated at 5727.63 Hz

Irradiated at 6039.16 Hz

Decoupling experiments on ^2H nmr, Fig.33

Fig.34

The unusual selectivity in the hydrogenation of hexa-2,4-dienoic acid is of particular interest as it lends strong support to the mechanism proposed in scheme (6),(p.78). Normally this acid is fully hydrogenated to hexanoic acid[115] or alternatively hydrogen adds across the diene to give hex-3-enoic acid or across the C-4 double bond to give hex-2-enoic acid[116,117]. The former case is true with $RhCl(PPh_3)_3$ giving low conversions to hexanoic acid, the triplet methyl resonance appearing in the ^1H nmr spectrum (fig.32,p.90) at δ 0.9 and multiplet resonances at δ 1.32 andδ 2.22 corresponding to $-(CH_2)_3-$ and $-CH_2COOH$ respectively. The spectrum of the hydrogenation product of hexa-2,4-dienoic acid catalysed by $RhCl(PPh_3)_2Ph_2PO_2CCH=CMe_2$ presents a somewhat more complicated picture (fig.33,p.91). In addition to resonances from hexanoic acid there is a major product giving rise to doublet of doublets methyl resonance at δ 1.65 ($^2J_{Me-H}$ 4 Hz) and ($^4J_{Me-H}$ 1 Hz) and a vinylic resonance at δ 5.55. Decoupling experiments were carried out (fig.34,p.92) in which irradiation of the methyl resonance at δ 1.65 caused breakdown of the vinylic proton signal at δ 5.55 to a broad singlet and irradiation of the vinylic resonance collapsed the methyl resonance in a similar way. As a result of these experiments the product was assigned as hex-4-enoic acid.

This acid arises from hydrogen addition across the C-2 double bond and supports the suggestion of chelate binding of $Ph_2PO_2CCH=CHCH=CHMe$ by the phosphorus atom and the C-2 double bond during the catalytic cycle. Such binding has already been

demonstrated in the crystallographically characterised $[RhCl(Ph_2PO_2CCH{=}CHCH{=}CHMe)]_2$[112]. The other product, hexanoic acid, may arise from isomerization of hex-4-enoic acid to hex-2-enoic acid, followed by hydrogenation. Such isomerizations have been reported, e.g. for $RhCl(CO)(Ph_2P(CH_2)_nCH{=}CH_2)_2$, (n = 2 or 3)[116], although they are generally rather slower than hydrogenation. A series of hydrogenation experiments in which the reaction time is varied is necessary in order to elucidate whether this isomerization occurs and if it proceeds at an appreciable rate.

3.2.3 Catalytic hydrogenation of HOOCCH=CHMe with $RhCl(PPh_3)_3$ and $RhCl(PPh_3)_2Ph_2PO_2CCH{=}CMe_2$

A comparison of initial reaction rates.

The hydrogenation experiments described in section 3.2.2 were run for 17 hrs. During this time 75.8 % and 100 % conversions of HOOCCH=CHMe to $HOOCCH_2CH_2Me$ were observed with $RhCl(PPh_3)_3$ and $RhCl(PPh_3)_2Ph_2PO_2CCH{=}CMe_2$ respectively. At these high conversions it is not possible to draw any conclusions about the relative initial hydrogenation rates obtained with the two catalysts. Consequently an additional series of experiments was undertaken in which the reaction time varied from 0.5 to 2.0 hrs. at 15 minute intervals, the results of which are shown in Table 9, (p.95).

Fig.35, (p.95) illustrates the initial % conversion gained with $RhCl(PPh_3)_3$ compared with that obtained with $RhCl(PPh_3)_2Ph_2PO_2CCH{=}CMe_2$. It is apparent that, although high conversions are obtained for both catalysts (section 3.2.2),

the initial hydrogenation rate is considerably higher (approximately 4 times) in the case of the $RhCl(PPh_3)_2Ph_2PO_2CCH{=}CMe_2$ catalysed reaction. This is further support for the proposed mechanism (Scheme 6,p.78) as initial rates of hydrogenation for non-chelate bound substituted alkenes using Wilkinson's catalyst are slow.

Time/min	% conversion (a)	
	$RhCl(PPh_3)_3$	$RhCl(PPh_3)_2Ph_2PO_2CCH{=}CMe_2$
30	8.1	39.8
45	14.0	50.0
60	12.8(b)	48.8(b)
75	19.5	74.5
90	27.9	82.1
105	25.0(b)	85.8
120	31.0	75.6(b)

a) Conditions: [catalyst] $=3\times10^{-3}$ mol dm^{-3},
[HOOCCH=CHMe] $=6\times10^{-2}$ mol dm^{-3}
[KOH] $=4\times10^{-2}$ mol dm^{-3}, in acetone ($5cm^3$),
22^oC, $p(H_2)$= 3 atm.

b) From initial studies; further experiments are required to gain more accurate figures.

Table 9

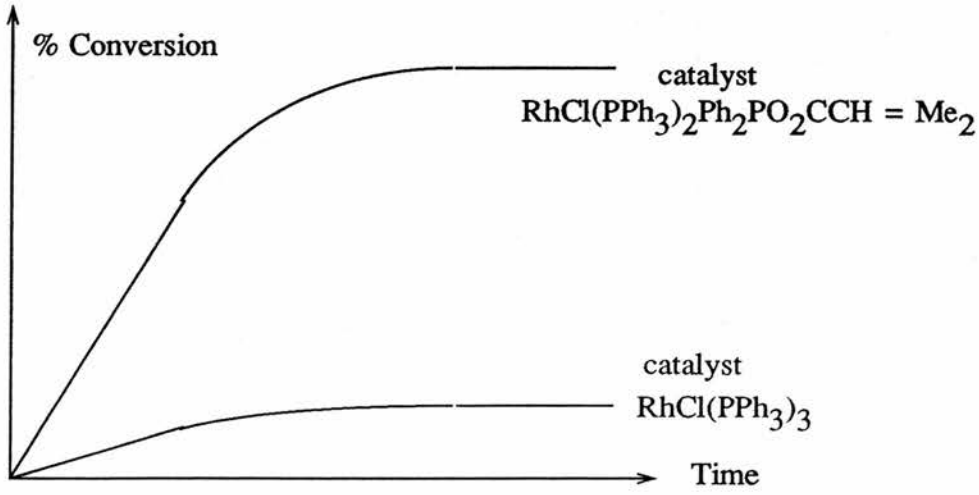


Fig.35

3.2.4 Attempted catalytic hydrogenation of $HOOCCH=CMe_2$ with $RuCl_2(PPh_3)_2Ph_2PO_2CCH=CMe_2$

An acetone solution of $RuCl_2(PPh_3)_2Ph_2PO_2CCH=CMe_2$, $HOOCCH=CMe_2$ (20 equivalents) and KOH was stirred under H_2 (3 atmospheres) for 2 hrs. The ^1H nmr of the product consisted of 2 doublet methyl resonances at δ 1.50 and δ 1.78 and a vinylic resonance at δ 5.90 from $HOOCCH=CMe_2$. No resonances from $HOOCCH_2CHMe_2$ were detected.

A mechanism for hydrogenation of $HOOCCH=CMe_2$ with a $RuCl_2(PPh_3)_2Ph_2PO_2CCH=CMe_2$ catalyst may be expected to include the 18 electron intermediate $RuHCl(PPh_3)_2Ph_2PO_2CCH=CMe_2$ in which the phosphinite ester ligand is bound through phosphorus only. Although an equilibrium analogous to the one proposed for the catalytic intermediate $[RhH_2(PPh_3)_2Ph_2PO_2CCH=CMe_2]^+$ (Scheme 6, p.78) would generate a coordinated alkene, preliminary results suggest that no hydrogenation of $HOOCCH=CMe_2$ occurs.

Addition of hydrogen to 5-coordinate $RuCl_2(PPh_3)_3$ to give the catalytically active species $RuClH(PPh_3)_3$, is a well known reaction[11*], (Eqn.9). It would seem reasonable to assume that the same reaction would occur for $RuCl_2(PPh_3)_2Ph_2PO_2CCH=CMe_2$ to give $RuClH(PPh_3)_2Ph_2PO_2CCH=CMe_2$.

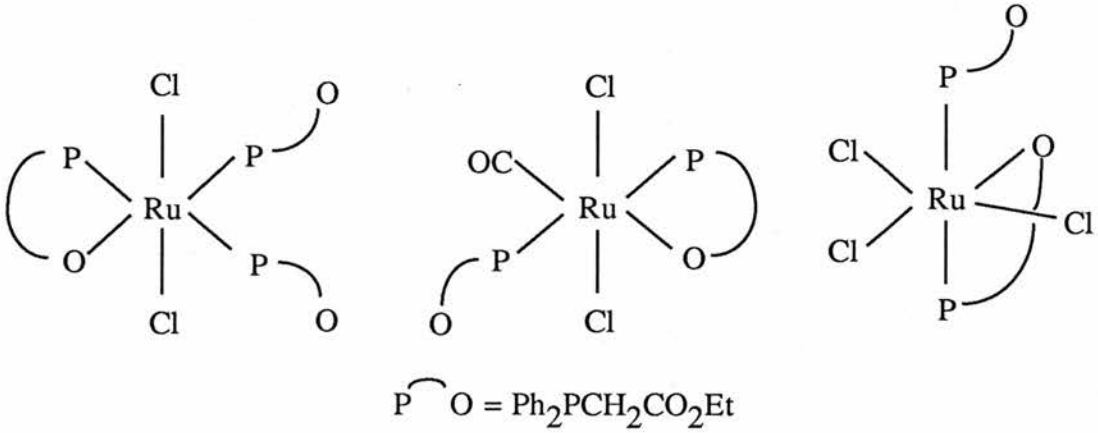
$$RuCl_2(PPh_3)_3 \xrightarrow{H_2/base} RuClH(PPh_3)_3 + HCl$$

Eqn.9

The lack of activity shown by $RuCl_2(PPh_3)_2Ph_2PO_2CCH{=}CMe_2$ would appear to result from the inability of the alkene linkage to coordinate to the metal centre.

Although the presence of triphenylphosphine groups in the molecule introduces steric constraints, this would not necessarily imply that the alkene cannot coordinate to ruthenium; in the $RhCl_2(PPh_3)_2Ph_2PO_2CCH{=}CMe_2$ system similar constraints are present but the alkene does coordinate at least long enough for hydrogen transfer to occur.

In complexes containing two phosphinite ester ligands they have been shown to chelate to Ru through the phosphorus and carbonyl oxygen atoms (fig.22,p.67). Although there is no great steric hinderance in this complex owing to the absence of large triphenylphosphine groups, the carbonyl oxygen is bonded to Ru in preference to the alkene. This is somewhat surprising in the light of results reported by Braunstein *et al*[120] for ruthenium complexes of $Ph_2PCH_2CO_2Et$ (fig.36) in which the Ru-O bond has been shown to be weak, (2.23A, ΔG^{*}= 55.6 $kJmol^{-1}$) and implies that the Ru-alkene interaction is weaker still.



P⌒O = $Ph_2PCH_2CO_2Et$

Fig.36

Thus it would appear that coordination of the alkene to ruthenium in $RuClH(PPh_3)_2Ph_2PO_2CCH=CMe2$ is unfavourable both electronically and sterically and for this reason the complex is catalytically inactive towards alkene hydrogenation.

3.3 Attempted preparation of $[Rh(DIPHOS)Ph_2PO_2CCH=CMe_2]^+$ and $Rh(DIPHOS)ClPh_2PO_2CCH=CMe_2$

For reasons discussed in section 3.2.1 attempts were made to isolate complexes of Rh containing both phosphinite ester and chiral *bis*(phosphine) ligands. Although unsuccessful these are worth mentioning as the desired complexes are potential catalysts for both asymmetric and regioselective hydrogenations of αβ-unsaturated acids and their derivatives. In the experiments described in this section DIPHOS was used in place of the more expensive asymmetric *bis*(phosphine) DIOP.

3.3.1 Reaction of $[RhClPh_2PO_2CCH=CMe_2]_2$ with DIPHOS

Addition of DIPHOS (2 equivalents) to an acetone solution of $[RhClPh_2PO_2CCH=CMe_2]_2$ results in a reaction in which the dark orange solution pales to yellow-orange. The infra-red spectrum of the recrystallised solid shows no absorption for $\nu_{C=O}$ or $\nu_{C=C}$ and it would appear that the phosphinite ester ligand has been replaced to give the chloride bridged DIPHOS dimer, (fig.37).

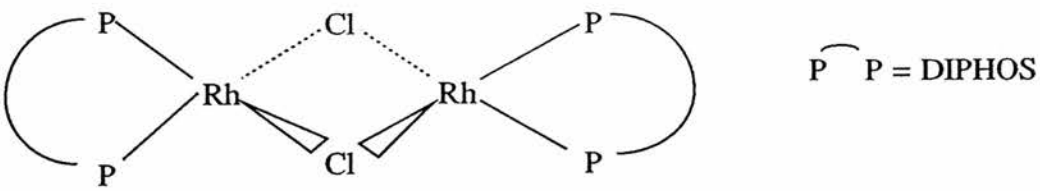


Fig.37

3.3.2 Reaction of $[RhClPh_2PO_2CCH{=}CMe_2]_2$ with $AgSbF_6$ followed by addition of DIPHOS

To a solution of $[RhClPh_2PO_2CCH{=}CMe_2]_2$ in thf was added $AgSbF_6$ (2 equivalents) in thf. Precipitation of AgCl occured over a period of 30 minutes. Addition of DIPHOS (2 equivalents) in thf to the filtered solution and subsequent recrystallisation using light petroleum spirit resulted in a yellow-orange microcrystalline solid, the IR spectrum of which showed no evidence for $Ph_2PO_2CCH{=}CMe_2$.

3.3.3 Reaction of $[RhCl(DIPHOS)]_2$ with $AgSbF_6$ followed by addition of $Ph_2PO_2CCH{=}CMe_2$

The presence of Ag^+ in solution in the previous experiment may result in reaction between it and the unsaturated linkage of the coordinated phosphinite ester. In order to avoid this possibility $AgSbF_6$ (2 equivalents) was added to a dichloromethane solution of $[RhCl(DIPHOS)]_2$. Although precipitation of AgCl occurred, addition of $Ph_2PO_2CCH{=}CMe_2$ (2 equivalents) to the filtered solution resulted in no visible change and the presence of $\nu_{C=C}$ or $\nu_{C=O}$ in the infra-red spectrum was not detected.

3.3.4 Reaction of $RhCl(PPh_3)_2Ph_2PO_2CCH{=}CMe_2$ with DIPHOS

To a solution of $RhCl(PPh_3)_2Ph_2PO_2CCH{=}CMe_2$ in thf was added DIPHOS (1 equivalent). The red-orange solution became yellow and recrystallisation using a mixture of light petroleum/diethyl ether (1:1) yielded fine needle-shaped yellow crystals. The

infra-red spectrum showed no evidence for the presence of $Ph_2PO_2CCH=CMe_2$. The ^{31}P nmr consisted of a doublet resonance at δ 58.5 ($^2J_{RhP}$, 132.3Hz) in accordance with the dimeric structure shown in fig.37.(p.98)

3.4 Experimental detail of preparations

All acetone was dried over Na_2SO_4 and distilled under N_2.

3.4.1 Catalytic hydrogenation of αβ-unsaturated acrylic acids

a) Hydrogenation of α-methylcinnamic acid with $RhCl(PPh_3)_2Ph_2PO_2CCMe=CHPh$

$RhCl(PPh_3)_2Ph_2PO_2CCMe=CHPh$ (0.0155g, 1.53×10^{-5}mol), $HOOCCMe=CHPh$ (0.1059g, 3.06×10^{-4}mol) and KOH (0.0119g, 2.12×10^{-4}mol) were stirred in acetone (5 cm^3) under H_2 (3 atms.) in a Fisher-Porter tube, the orange red solution becoming yellow on addition of H_2. After 23 hours the pressure was released and the product solution evaporated to dryness under reduced pressure. Residual acetone was removed by adding CH_2Cl_2 to the resulting solid and evaporating to dryness in the same way. The nmr sample was prepared by extracting the potassium salt of the product acid from CH_2Cl_2 (1 cm^3) into D_2O (1 cm^3).

b) Attempted hydrogenation of α-methylcinnamic acid with $RhCl(PPh_3)_2Ph_2PO_2CCMe{=}CHPh$ and DIOP.

$RhCl(PPh_3)_2Ph_2PO_2CCMe{=}CHPh$ (0.0156g, 1.55×10^{-5}mol), and DIOP (0.0078g, 1.56×10^{-5}mol) were stirred in acetone (5 cm^3) under N_2, for 15 minutes prior to addition of $HOOCCMe{=}CHPh$ (0.1073g, 3.10×10^{-4}mol) and KOH (0.0120g, 2.14×10^{-4}mol) . The resulting solution was stirred for 16 hrs. under hydrogen (3 atm.) in a Fisher-Porter tube and the nmr sample was prepared as before.

c) Hydrogenation of αβ-unsaturated acids with $RhCl(PPh_3)_3$ and $RhCl(PPh_3)_2Ph_2PO_2CCH{=}CMe_2$

Acetone solutions (5 cm^3) of catalyst (1.50×10^{-5}mol) were stirred with αβ-unsaturated acid substrates (3×10^{-4}mol) and KOH (0.0120g, 2.14×10^{-4}mol) under hydrogen (3 atms.) in a Fisher-Porter tube for 17 hrs. at 22°C. Nmr samples were prepared as before.

d) Hydrogenation of $HOOCCH{=}CHMe$ with $RhCl(PPh_3)_3$ and $RhCl(PPh_3)_2Ph_2PO_2CCH{=}CMe_2$

Method as for (c) except that the reaction times ranged from 0.5 - 2.0 hrs. at 15 min. intervals.

e) Attempted hydrogenation of $HOOCCH{=}CMe_2$ with $RuCl_2(PPh_3)_2Ph_2PO_2CCH{=}CMe_2$

Method as for (c) except that reaction time = 2.5 hrs.

3.4.2 Attempted preparation of $[Rh(DIPHOS)Ph_2PO_2CCH{=}CMe_2]^+$ and $Rh(DIPHOS)ClPh_2PO_2CCH{=}CMe_2$

a) Preparation of $[RhClPh_2PO_2CCH{=}CMe_2]_2$[106]

To a suspension of $[RhCl(C_8H_{14})]_2$ (0.3g, 0.42 mmol) in dichloromethane (15 cm^3) was added a solution of $Ph_2PO_2CCH{=}CMe_2$ (0.24g, 0.85 mmol) in dichloromethane (15 cm^3). An immediate reaction was observed and the $[RhCl(C_8H_{14})]_2$ rapidly dissolved to give a red-orange solution. The solution was filtered and the solvent was removed by evaporation under reduced pressure to approximately 5 cm^3. Petroleum spirit was added quickly to afford an orange solid. Yield: 0.30g (85%).

b) Preparation of $[RhClDIPHOS]_2$[106]

As for preparation of $[RhClPh_2PO_2CCH{=}CMe_2]_2$. On addition of DIPHOS an immediate reaction occurred to afford a yellow-orange solution. Recrystallisation using diethylether gave a yellow crystalline solid. Yield: 75%.

c) Reaction of $[RhClPh_2PO_2CCH{=}CMe_2]_2$ with DIPHOS

To a stirred solution of $[RhClPh_2PO_2CCH{=}CMe_2]_2$ (0.35g, 0.41 mmol) in acetone (15 cm^3) was added DIPHOS (0.33g, 0.82 mmol) in acetone (10 cm^3). An immediate

reaction occurred and the red-orange solution paled to yellow-orange. The solution was filtered and the solvent volume reduced by evaporation to approximately 5 cm^3. A yellow microcrystalline solid was isolated by addition of light petroleum spirit and washed (2x10 cm^3). No yield or analysis was recorded for this product.

d) Reaction between $[RhClPh_2PO_2CCH{=}CMe_2]_2$ and $AgSbF_6$ followed by addition of DIPHOS

To a solution of $[RhClPh_2PO_2CCH{=}CMe_2]_2$ (0.32g, 0.38 mmol) in thf (20 cm^3) was added $AgSbF_6$ (0.27g, 0.78 mmol) in thf (10 cm^3). The solution was stirred for 30 mins. during which time precipitation of off-white AgCl occurred. Addition of DIPHOS (0.30g, 0.75 mmol) to the filtered solution resulted in an immediate reaction causing the red-orange solution to become yellow-orange. The solvent volume was reduced by evaporation to approximately 5 cm^3 and subsequent recrystallisation using petroleum spirit afforded an orange powder, which was washed with petroleum spirit (2x10 cm^3) and dried *in vacuo*. No yield or analysis was recorded for this compound

e) Reaction between $RhCl(DIPHOS)]_2$ and $AgSbF_6$ followed by addition of $Ph_2PO_2CCH{=}CMe_2$

The method is the same as for (c) above and the weights as follows; [RhClDIPHOS] = 0.2g, 0.19 mmol , $AgSbF_6$ = 0.125g, 0.36 mmol , and $Ph_2PO_2CCH{=}CMe_2$ = 0.11g, 0.38 mmol.

f) Reaction between $RhCl(PPh_3)_2Ph_2PO_2CCH{=}CMe_2$ and DIPHOS

To a solution of $RhCl(PPh_3)_2Ph_2PO_2CCH{=}CMe_2$ (0.5g, 0.53 mmol) in thf (20 cm^3) was added DIPHOS (0.21g, 0.53 mmol) in thf (10 cm^3). An immediate reaction was observed and the deep red-orange solution paled to yellow. The resulting solution was filtered and reduced by evaporation to approximately 5 cm^3. The yellow microcrystalline product was isolated by addition of a mixture of petroleum spirit/diethyl ether (1:1), washed with petroleum spirit (2x10 cm^3) and dried *in vacuo*. No yield or analysis was recorded for this product.

CONCLUSIONS

From the previous discussions it has become apparent that although at first the elaboration of a chiral catalyst was quite empirical, some rationalizations are now possible. The following guiding principles are useful when a known achiral catalyst is modified by the introduction of a chiral group.

1) The chiral group should not drastically decrease the catalytic activity;

2) Because of the structural modifications on the ligands, it should be expected that the reaction mechanism of the known achiral catalyst could be altered;

3) The chiral ligand has to remain coordinated to the metal during the step in which the asymmetric centre is created on the substrate;

4) The synthesis of the ligand should be easy and flexible, allowing a start from cheap natural products. Thus a resolution step is avoided and many analogues and quasi-enantiomeric ligands become available;

5) Predictions and rational approaches are expected from information on the reaction mechanism and the structure of the various catalytic species.

Previous research has indicated that the most effective stereoselective hydrogenation catalysts are prepared using the *bis*(phosphine) group of ligands that bind to a metal centre in a rigid chelate ring. The presence of a chiral ligand facilitates the preferential hydrogenation of prochiral substrates to give an excess of one enantiomeric product. The tendency is for a particular catalyst to show a high specificity towards a small group of closely related substrates.

The greatest success achieved to date in asymmetric hydrogenation has been with α-amidoacrylic acid substrates using a variety of *bis*(phosphine) ligands. Simpler prochiral αβ-unsaturated carboxylic acids have also been hydrogenated to give high enantiomeric excesses using *bis*(phosphine) ligands. The fundamental substrate requirement appears to be the presence of polar substituents β to a Z-unsaturated linkage, allowing the metal-alkene interaction to be stabilized by chelate binding.

Most asymmetric catalysts differ only in the *bis*(phosphine) ligands in the molecule. Catalysts that effect regioselective alkene hydrogenation are far more diverse. Due to steric reasons the selectivity shown by these catalysts is almost without exception for the hydrogenation of terminal alkenes. This allows the selective reduction of monoenes, and polyenes and alkynes to monoenes.

From the hydrogenation experiments discussed in Chapter III it is apparent that $RhCl(PPh_3)_2Ph_2PO_2CCH{=}CMe_2$ is a more efficient catalyst than $RhCl(PPh_3)_3$ for the hydrogenation of

highly substituted αβ-unsaturated acids. The higher reaction rates can be attributed firstly to stabilization of the metal-alkene interaction through chelation of the phosphinite ester and secondly to the proposed cationic nature of the catalyst (see Section 1.1.4 (a)). Although evidence for various transesterification reactions has been reported in this case it is only circumstantial, supported by the fact that many different substrates are hydrogenated by the same catalyst. Additional evidence is that hydrogenation of the free acid does not occur and the presence of a base such as KOH seems to be necessary.

In contrast to more commonly used selective hydrogenation catalysts, $RhCl(PPh_3)_2Ph_2PO_2CCH{=}CMe_2$ has exhibited unusual regioselectivity in the hydrogenation of hexa-2,4-dienoic acid to hex-4-enoic acid. The chelate stabilization of the internal alkene-metal interaction is the important factor in this. Although there would seem to be potential for the development of an asymmetric catalyst containing αβ-unsaturated phosphinite ester ligands this has not been realised. Of the phosphine ligands present, the ester has the highest basicity and as a result it would be expected to remain coordinated to rhodium during the reaction described in Section 3.3. Thus it would appear some type of rearrangement or degradation occurs during the reaction. Alternatively, DIPHOS, being a sterically demanding ligand may prevent the coordination of another large ligand. The ester may simply be displaced during reactions in which DIPHOS is added or not coordinate when DIPHOS is already present in the coordination sphere.

Even though little success has been achieved to date in adapting these catalysts to effect asymmetric hydrogenations further work is worthwhile. It has been seen that they have a higher activity towards highly substituted alkenes than do more simple complexes such as Wilkinson's catalyst. In addition unusual selectivities, notably the reduction of hexa-2,4-dienoic acid to hex-4-enoic acid, have been observed.

If the triphenylphosphine groups can be replaced by an asymmetric *bis*(phosphine) ligand whilst the above features are retained, the resulting complex would be an unusual and valuable addition to asymmetric hydrogenation catalysts.

----------oOo----------

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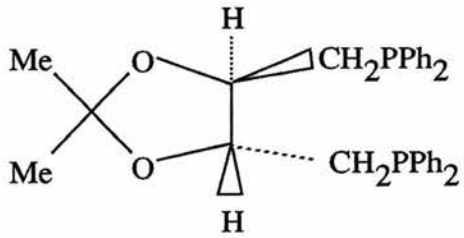
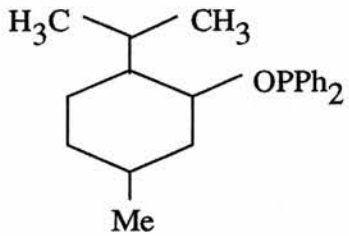
I am grateful for help and advice from my colleagues and the staff of the Chemistry Department at the University. Especially I must thank Professor D.J. Cole-Hamilton for his guidance, encouragement and critical supervision throughout the research.

Sheila Ann Preston, B.Sc.,(Liverpool)

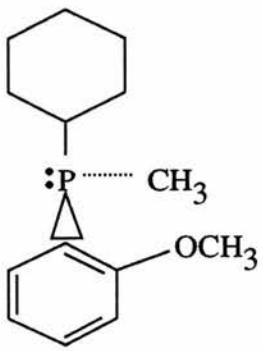
DIOP



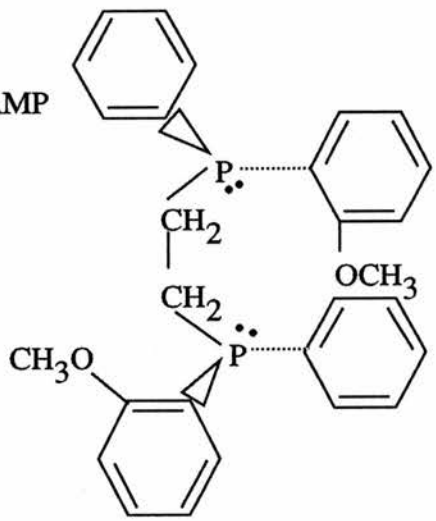
NMDPP



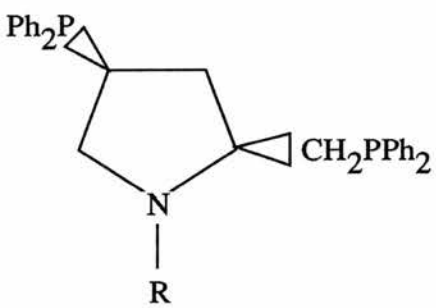
(R) - CAMP



(R, R) - DiPAMP



RPPM



BPPM, R = $CO_2C_4H_9^t$

PPPM, R = $COBu^t$

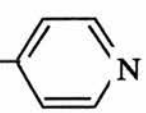
PPM, R = H

CPPM, R = $CO_2C_{27}H_{45}$

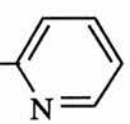
BZPPM, R = COPh

NPPM, R = CO

INPPM, R = CO

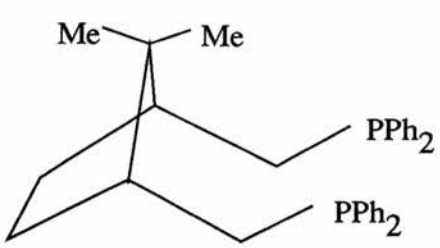


PCPPM, R =CO

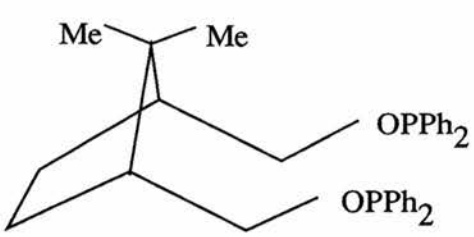


FPPM, R = COH

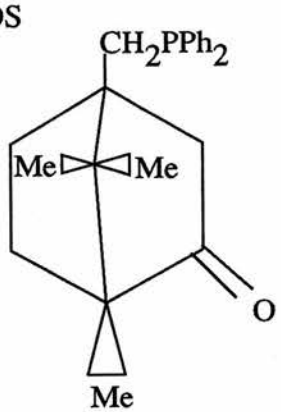
(+) - CAMPHOS



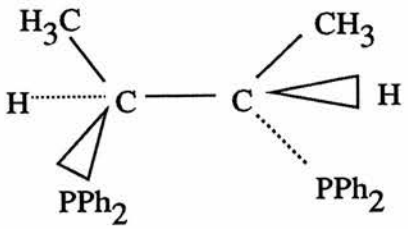
(+) - CAMPHINITE



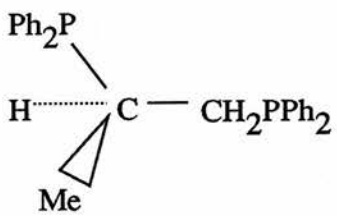
CRCPHOS



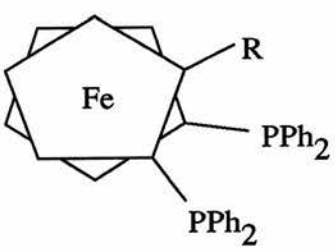
(S, S) - CHIRAPHOS



(R) - PROPHOS



(R) - (S) - BPPFR



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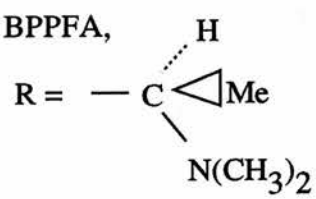

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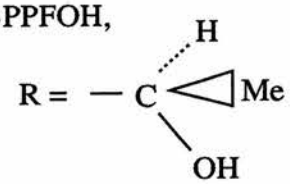
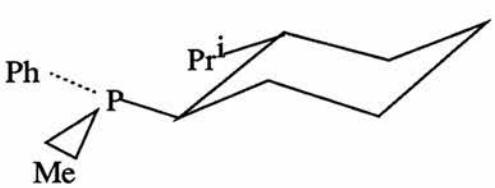
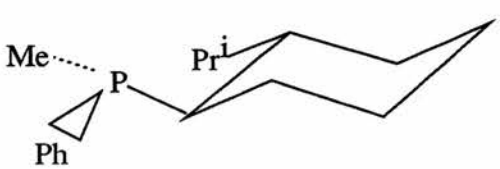


MMPP





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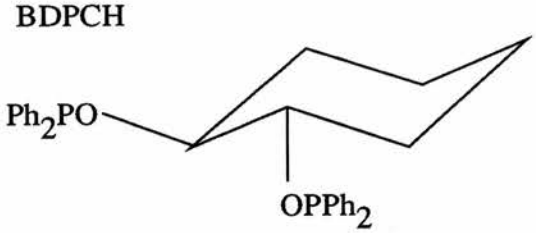

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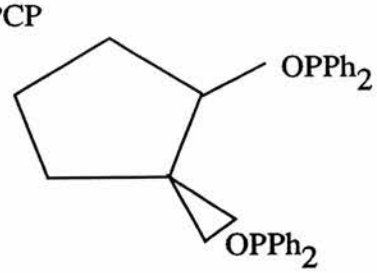

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