THE UNIVERSITY OF CENTRAL LANCASHIRE

THE DEVELOPMENT OF NOVEL HETEROGENEOUS CATALYSTS FOR THE HYDROGENATION OF PROCHIRAL IMINES

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ABSTRACT

Catalysts have been studied for the enantioselective hydrogenation of prochiral imines. Work has centred on the support of homogeneous catalysts, with the intention of establishing a heterogeneous catalyst without loss of activity.

Initially, established heterogeneous systems were investigated. As the methyl pyruvate system of cinchona modified catalysts was to be used, this system was first investigated with a series of platinum catalysts. Although these results provided some interesting results they maintained that the 5% Pt/alumina catalyst was the best for this hydrogenation. Investigations using this system for prochiral imine hydrogenation resulted in the production of chiral amines. Hydrogenation of *N*-(1-methylbenzylidene)-2,3-dimethylbutylamine gave encouraging percentage conversions, but unfortunately, enantiomeric excesses were particularly low. These results led to investigations on supporting a suitable homogeneous catalyst.

Initial work involving Wilkinson's catalyst investigated different preparations, solvents and supports. Results achieved in this section of the study showed an increase in activity of clay and zeolite supported catalysts when run in 1,1,1-trichloroethane and ethanol, but a drop in activity when benzene was the reaction solvent.

Work with imines centred around two homogeneous catalysts. BINAP and DIOP ligands were used to create rhodium and iridium centred catalysts which were used to homogeneously hydrogenate two imines (*N*-(1,2-dimethylpropylidene)aniline and

N-(1methylbenzylidene)-2,3-dimethylbutylamine). These catalysts were then tethered to a Montmorillonite clay support and NaY zeolite, before repeated hydrogenations of the above imines. Results achieved were very encouraging , with an increase in activity being noted for some of the supported catalysts.

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Introduction

INTRODUCTION

1.1 Background

The initial rate of reaction can be increased with the use of a catalyst. A catalyst can be defined as 'any reagent that can increase the rate of a reaction while not being consumed by the reaction'.[1] A catalyst can increase the rate of reaction in a number of ways: by lowering the activation energy, making bond breaking or bond formation easier in the rate determining step; by improving the orientation of the reacting molecules which increases the effectiveness of collisions; and by altering the mechanism by opening up another pathway with a lower activation energy. Catalysts can also be used to increase the selectivity of chiral reactions, a catalyst being chosen due to its ability to increase the production of a particular enantiomer.

There are two main types of catalysts, homogeneous and heterogeneous. Homogeneous catalysts are in the same phase as the reactants, usually liquid with the catalyst dissolved in it. Heterogeneous catalysts are in a different phase to the reactants, usually with the catalyst as a solid and the reactants as liquid or gas. From an industrial point of view, heterogeneous catalysts have a distinct advantage over homogenous systems due to the easy separation of the products from the catalyst. However, a number of industrial processes using homogeneous catalysts are in use because they have much higher selectivity in reactions, operate under milder conditions of temperature and pressure, or have other technical advantages.[2] Attempts to overcome any technical disadvantages using homogeneous catalysts include; phase transfer reactions (e.g. where the catalyst is in the aqueous phase, but

is transferable to the organic phase, and the substrate and products are in an organic phase) and supporting the catalysts on surfaces.

This project is concerned with the use of both homogeneous and heterogeneous catalysts for the hydrogenation of prochiral imines. The aim is to establish a successful asymmetric catalyst for such reactions. Should the most active catalyst be homogeneous, it is hoped to support, or tether, this catalyst in order to produce a heterogeneous catalyst, without significant loss of activity.

Catalysis is one of the most important technologies in the world today. It plays a pivotal role in a wide range of applications, from production of materials, to the removal of unwanted ones. Approximately 90 % of all chemicals and materials are produced with the use of catalysts at some point.[3] There are essentially two areas of catalysis; homogeneous catalysis where the catalyst and reactants are in the same phase, and heterogeneous catalysis where the reactant and catalyst are in different phases. One of the major areas of growth within catalysis research and development is that of selective catalysis, particularly enantioselective catalysis.

The synthesis of optically pure chiral compounds has become one of the most important challenges in modern synthetic chemistry, particularly in the pharmaceutical and agrochemical industries. Research into the production of pure samples of each of the enantiomers or diastereomers of a compound has increased rapidly since the discovery that, in many cases, one of the enantiomers will have more desirable properties than the other. The 'wrong' enantiomer can, at best, show no effect on the resulting product and, at worst, act as pollutants with effects that

often outweigh the benefits of the 'right' enantiomer. This is particularly true of biologically active compounds. The most notorious example of the adverse effects of the 'wrong' enantiomer was thalidomide, released in the 1960's by the pharmaceutical industry to alleviate the symptoms of morning sickness in pregnant women. The drug was sold as a racemate, and tragically only the (*R*)-isomer of the drug showed these properties, the (*S*)-isomer was found to be a powerful teratogen. It is also unfortunate that when the pure (R)-isomer of the drug is taken it will racemise in the body, therefore still resulting in the tragic deformation of an unborn foetus. Legislation, beginning in the USA, is now aiming for only one enantiomer to be present in drugs, which are offered for licence.

Traditionally, the preferred route to an enantiomerically pure compound was to synthesise a racemic mixture of a compound and then to use classical methods to resolve the mixture. For example; reacting the racemic mixture with a single enantiomer of another compound to create a mixture of diastereoisomers which having different physical properties can be more easily separated, rarely a compound will for different crystals for each enantiomer (e.g. tartaric acid) allowing for them to be separated by hand. Other methods available included the use of readily available naturally occurring chiral compounds, such as amino acids, as chiral auxiliaries or building blocks in a synthesis, or the use of enzymes, cell cultures or microorganisms to carry out an asymmetric synthesis. All of these methods are used today; however, utilisation of asymmetric catalysis provides powerful and unique advantages. In most cases the use of a chiral catalyst in a reaction offers control of enantioselectvity, resulting in higher yields and faster rates. For industrial processes, catalysis has provided the ability to produce large quantities of product with a

relatively small amount of catalyst or promoter. Consequently there are a number of important industrial processes in existence using asymmetric catalysis, as well as achiral catalysis, to great effect in the synthesis of many important pharmaceutical and agrochemical compounds.[4] These processes employ homogeneous catalysts, heterogeneous catalysts, and biocatalysts. Although many of these kinds of processes are homogeneous, this involves costly operations to remove the catalyst from the product. Heterogeneous catalysts in this situation could be easily removed, making the process less costly and perhaps continuous. To this end there is a great drive at present to develop suitable asymmetric catalysts.

1.2 Enantioselective Catalysis Using Heterogeneous Catalysts

An enantioselective catalyst has two functions; firstly to act as a chemical catalyst (i.e. rate enhancing), and secondly to control the stereochemical outcome of the reaction (i.e. influencing the enantiomeric excess, the e.e.). In order to achieve enantioselectivity using a metal catalyst, the reaction must take place in a chiral environment. Since conventional metal catalysts do not contain any chiral sites, the use of modifiers must be employed. A modifier is a chiral substance, which is adsorbed onto the active phase of a conventional metal catalyst.

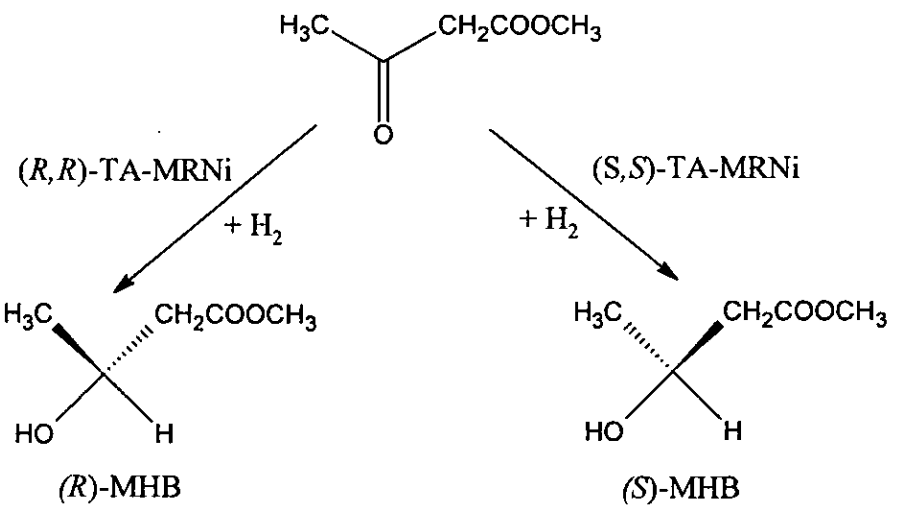
Initial research into the use of chiral solid catalysis for hydrogenation, hydrogenolysis and dehydrogenation reactions was carried out in the 1930's. The first technique was pioneered by Schwarb in 1932,[5] using Cu, Ni and Pt on quartz to dehydrogenate 2-butanol. Low enantiomeric excesses were recorded (<1%), it was however noted that the left- and right-handed quartz gave the opposite optical

rotation of the products. Quartz forms helices, so that enantiomorphic crystals occur which can be easily recognised and separated. [2] Lipkin and Stewart later developed the second more successful technique,[6] involving the use of Raney nickel modified with glucose, and platinum modified with cinchonine. Late, in 1956, Japanese workers used a catalyst based on palladium and silk which resulted in high optical yields for the hydrogenation of both C=C double bonds and C=N double bonds.[7]

Heterogeneously catalysed reactions tend to be very specific; few catalyst/modifier combinations give good optical yields. Research in this area has centred on; the hydrogenation of β-ketoesters and β-diketones, catalysed by nickel modified by optically active acids and amino acids, and the hydrogenation of α-ketoesters and α,β-diketones, catalysed by platinum catalysts modified with cinchona alkaloids. The development of these catalytic systems will be discussed in detail in the following sections.

1.2.1 Hydrogenation of β-ketoesters

The most systematically studied system for the hydrogenation of β-ketoesters has been that of Raney nickel (RNi) modified with optically active compounds. The use of an optically active modifier, with the catalyst, results in a catalyst suitable not only for hydrogenation, but also enantioselectivity. For example, RNi modified with an amino acid or hydroxy acid (e.g. tartaric acid, TA) hydrogenates methyl acetoacetate (MMA) to produce optically active methyl 3-hydroxybutyrate (MHB), Scheme 1.1[8]



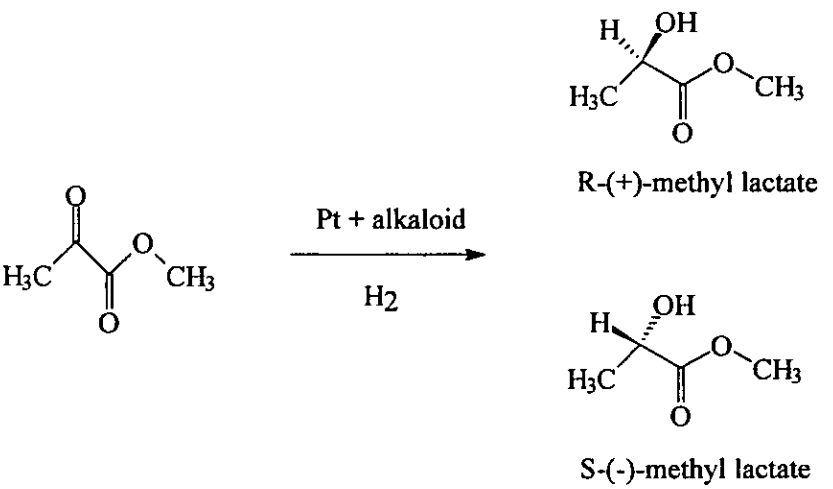
Scheme 1.1 Hydrogenation of MAA to MHB using RNi modified with tartaric acid.

The direction of enantioselective control is dependent upon the modifier used. In the case of Raney nickel, (*R*)-hydroxy or (*S*)-amino acids give an excess of the (*R*) product, whereas (*S*)-hydroxy or (*R*)-amino acids give an excess of the (*S*)-product.

The most suitable modifier for the Raney nickel system was determined to be optically active tartaric acid.[8] However, the enantio-differentiating ability (EDA) of the modified catalyst was found to be affected by trace amounts of organic acids, amines, and hydrogen acceptor compounds (NaOH).

1.2.2 Hydrogenation of α-ketoesters

The use of cinchona alkaloids to modify supported platinum to achieve hydrogenation of α-ketoesters was first reported in 1978 by Orito *et al.*[9] A platinum/carbon catalyst was modified with cinchonidine for the enantioselective hydrogenation of methyl pyruvate to methyl lactate.



Scheme1.2 Hydrogenation of methyl pyruvate to methyl lactate.

It was discovered that the use of cinchonidine or quinine as a modifier led to an excess of the (*R*)-enantiomer; whereas the use of cinchonine or quinidine led to an excess of the (*S*)-enantiomer.[9]

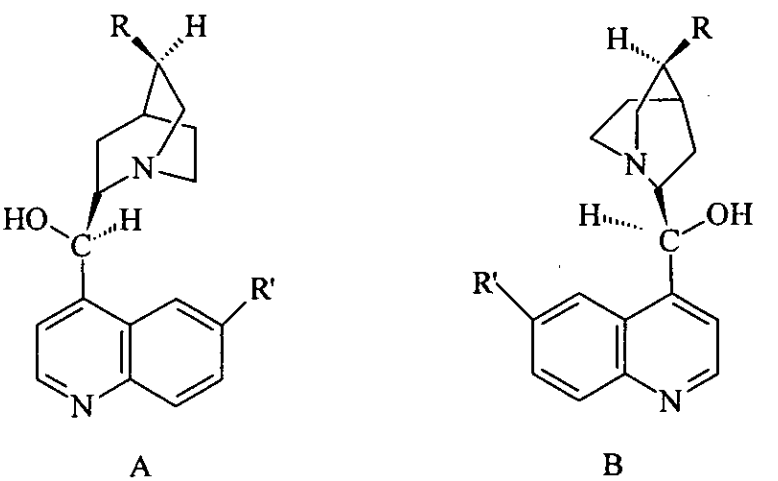


Figure 1.1 A, cinchonidine (R = C_2H_3, R' = H), quinine (R = C_2H_3, R' = MeO); B, cinchonine (R = C_2H_3, R' = H), quinidine (R = C_2H_3, R' = MeO).

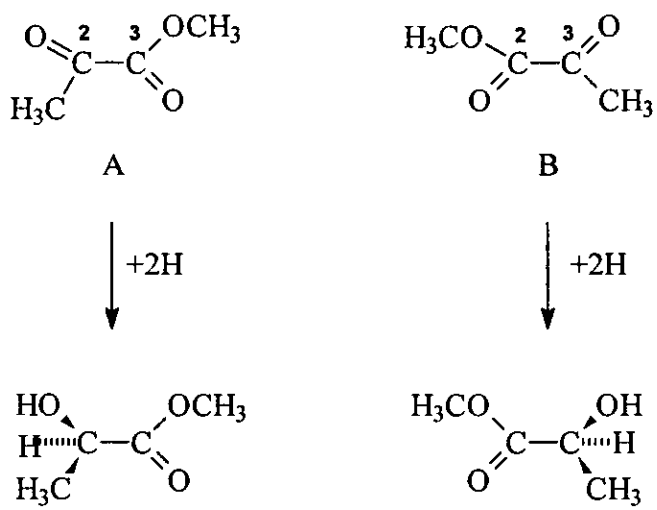
The catalyst was first reduced at an elevated temperature under a hydrogen atmosphere, before modification, to optimise the enantiomeric excess. The optical yield was shown to be sensitive to several variables such as, solvent, activation temperature and the presence of additional alkaloid in the reaction mixture. The highest recorded e.e. (78.7 % of (*R*)-methyl lactate [9]) was achieved by preheating the catalyst in a hydrogen atmosphere at 300°C, the catalyst was modified in a 1 % cinchonidine – ethanol solution at room temperature. Hydrogenation was then carried out in an ethanol solvent with cinchonidine as an additive.

Orito later reported an increase in optical yield (86.8 % of (*R*)-methyl lactate) with the use of a quinine modified platinum/alumina catalyst, operating with benzene as a solvent, with a small amount of quinine additive.[10]

Since the original work by Orito, three groups have concentrated on this area of research, Blaser, Baiker and Wells, and have been centred on the hydrogenation of methyl pyruvate and ethyl pyruvate over cinchona alkaloid modified, supported noble metal catalysts.[11] All have reported the remarkable effect of an alkaloid modifier on the optical yield for the hydrogenation of α-ketoesters. However, in addition to this, an increase in rate by a factor of at least 20 has also been reported.[11,12,13,14] In all cases it was noted that the presence of a cinchona alkaloid modifier increases the rate of hydrogenation of both ethyl and methyl pyruvate. This increase in rate has been attributed to several phenomenon; the action of the modifier as an alicyclic N-base, the ability of the modifier to enhance the surface coverage of adsorbed hydrogen and its affect as an aromatic adsorbate on the specific activity of platinum.[15]

Studies into new modifiers for the hydrogenation of ethyl pyruvate, such as chiral amino alcohols,[16] heterocyclic N-compounds and substituted amines,[17,18] have resulted in high enantiomeric excess (67-82 %).

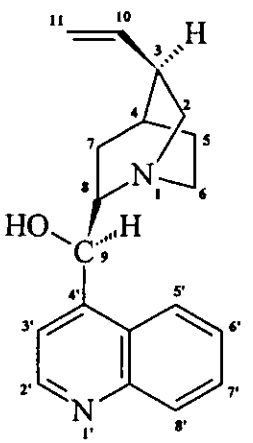
A model for these reactions is not so easily agreed upon. Methyl pyruvate (α-ketoester) is strongly adsorbed onto the surface platinum atoms. Before adsorption the pyruvate molecules can rotate freely in solution. However, the methyl pyruvate is adsorbed onto the platinum surface as either species A or species B (see below).



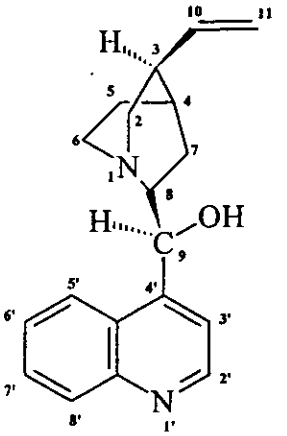
Scheme 3. Formation of (*R*)- and (*S*)-methyl lactate, assuming addition of hydrogen from the platinum surface, i.e. from below.

Enantioselectivity resulting from hydrogenation is induced by the modifier, the chirality produced depends upon the chirality of the modifier used; as mentioned above, cinchonidine used as a modifier for the hydrogenation of methyl pyruvate results in an excess of (*R*) lactate; whereas the modifier cinchonine (the enantiomer of cinchonidine) produces an excess of (*S*) lactate. There are two theories as to the cause of this effect. The theory proposed by Wells and co-workers suggests the production of the enantiomer is determined by the shape of the modifier.[19] The second theory proposed by Baiker [20] and Wells [15] suggests the pyruvate is transformed into a half hydrogenated state on interaction of the reactant and modifier. This occurs by hydrogen bonding between the protonated quinuclidine nitrogen of cinchonidine and the α-carbonyl of pyruvate. The complex which leads to the formation of (*R*)-methyl lactate is energetically more stable than the complex leading to the formation of (*S*)-methyl lactate. Thus cinchonidine as a modifier results in an excess of (*R*)-methyl lactate.

The model proposed by Wells and co-workers suggests that the L-shaped cinchonidine adsorbs onto the platinum surface as a non-close packed array, thus leaving shaped groups of Pt atoms exposed.[11] Cinchonine is also L-shaped, but in the opposite sense; therefore, the adsorption of cinchonine onto the platinum provides an environment for the production of (S)-methyl lactate, whilst cinchonidine provides an environment for the production of (R)-methyl lactate.



Cinchonidine



Cinchonine

Figure 1.2 Structures of cinchonidine (left) and cinchonine (right), showing numbered carbon atoms.

Wells reported that for low surface coverage of the modifier (i.e. very open arrays), pyruvate could adsorb onto the surface as either species A or B (See Scheme 1.2). For a high surface coverage of the modifier, the capacity of species A to adsorb remained, but that for species B was lost; for a very high surface coverage of modifier (i.e. a saturated surface) little to no pyruvate adsorbed was expected.

According to this template model the platinum atoms left exposed for pyruvate adsorption were surrounded by 2 or 3 cinchonidine molecules, (Figure 1.3). The modifier molecules were therefore acting as templates for the corresponding enantiomer.

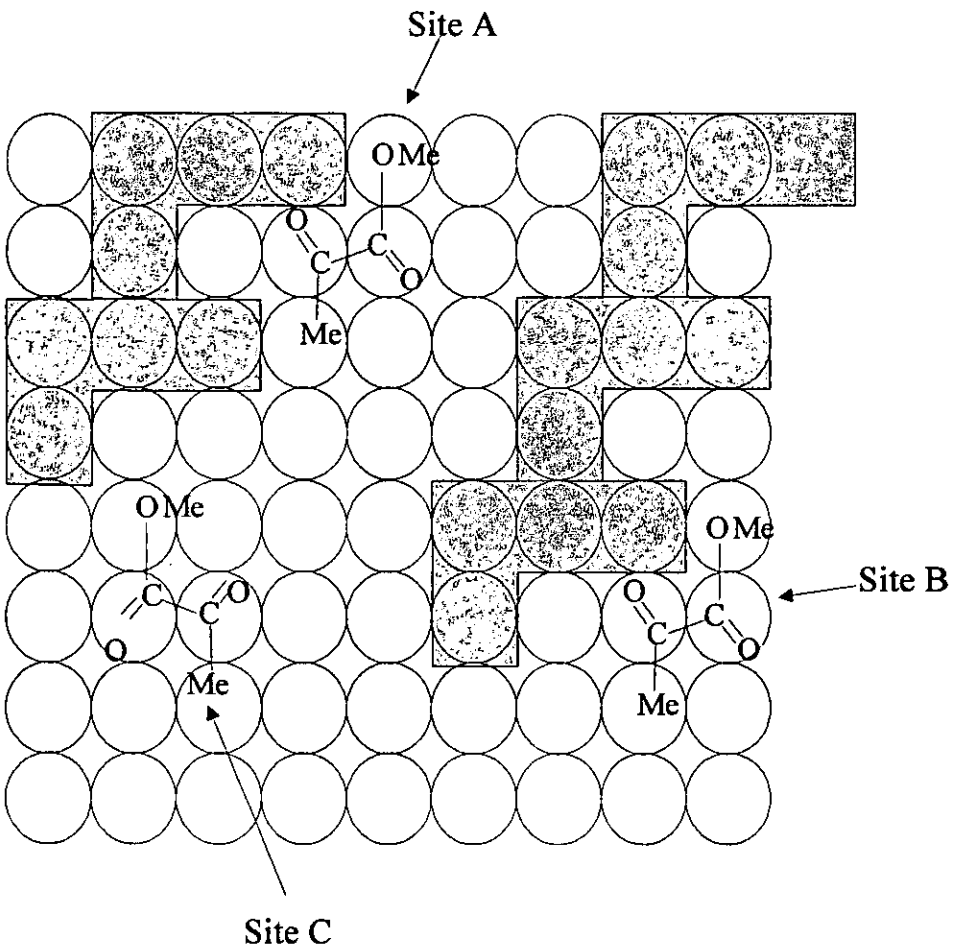


Figure 1.3 A representation of a non-close packed ordered array of cinchonidine molecules adsorbed onto Pt(100) together with two molecules of methyl pyruvate adsorbed as species A and species B. Site A represents an asymmetric hydrogenation site according to the template model. Site B is a 1:1 interaction site. Site C is a racemic hydrogenation site.[21]

Recent studies by Wells and co-workers [22] have looked into the relationship between conversion and enantioselectivity for the asymmetric hydrogenation of ethyl pyruvate. These studies also show that increased enantiomeric excess and conversion are related to the interaction between the modifier and the substrate. Other studies [23], also support the interaction between the quinuclidine of a

cinchonidine molecule and the methyl pyruvate molecule as a control of the stereoselectivity of the catalytic process.

1.2.3 Other Applications for Heterogeneous Catalysts

Despite the success of systems such as the hydrogenation of pyruvate esters using heterogeneous catalysis, there has been little success in other areas of heterogeneous hydrogenations.

However, work by Baiker and co-workers [24] involving the hydrolysis of the C=N double bond has had limited success. Pyruvic acid oxime has been hydrogenated to alanine, achieving both racemic and optically rich mixtures. High yields of racemic alanine have been reported; however, the highest reported e.e. was 26 %, using a palladium catalyst at 10 bar hydrogen pressure.[24]

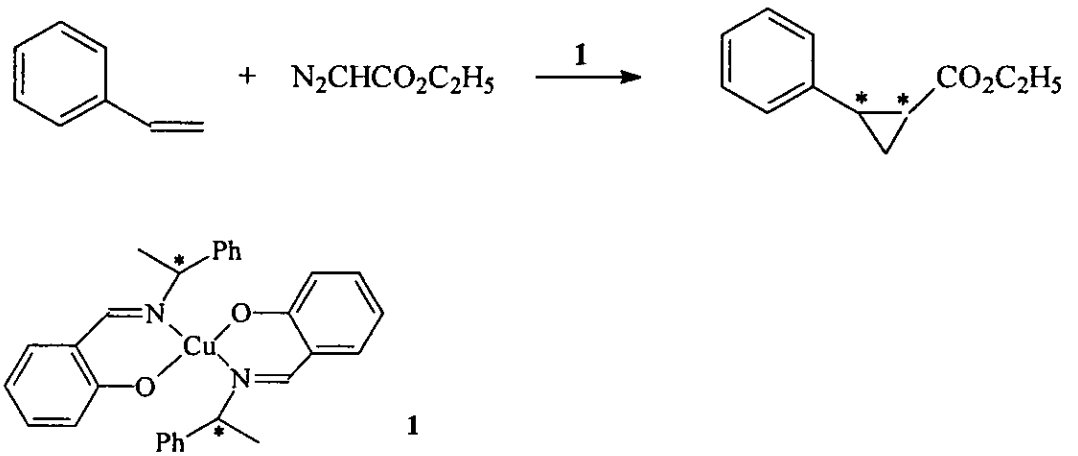
Despite obvious advantages of heterogeneous catalysts, the major research in the formation of chiral compounds has been carried out using homogeneous systems.

1.3 Enantioselective Catalysis Using Homogeneous Catalysts

The majority of homogeneous catalysts are organometallic compounds.[25] The first commercially viable homogeneous catalytic system was the cobalt-catalysed 'oxo' process developed by Roelen in 1938.[26] This was the beginning of a productive period in the development of new homogeneous catalysts and organometallic chemistry. Asymmetric catalysis did not appear in the literature until the late 1960's

with the report of the first asymmetric homogeneous catalytic process.[27] It was realised that a small amount of a chiral reagent could produce many times that amount of chiral molecules with a preference for only one enantiomer. The process studied was the decomposition of ethyl diazoacetate in styrene to give *cis*- and *trans*-2-phenylcyclopropanecarboxylates, Scheme 1.4. It was shown that the chiral Schiff base-Cu(II) complex, **1**, led to the active copper carbenoid species. In the years since this preliminary report, asymmetric catalysts have been developed for a wide variety of synthetic reactions.

In most cases the application of a catalyst to a reaction offers control of the enantioselectivity of the reaction, higher yields and faster rates. For industrial processes, catalysis has provided the ability to produce large quantities of product with a relatively small amount of catalyst or promoter. Consequently, there are a number of important industrial processes in existence using asymmetric catalysis (involving catalysts which are chiral), as well as achiral catalysis (involving catalysts which are superposable on their mirror image), to great effect in the synthesis of many important pharmaceutical and agrochemical compounds.[28]



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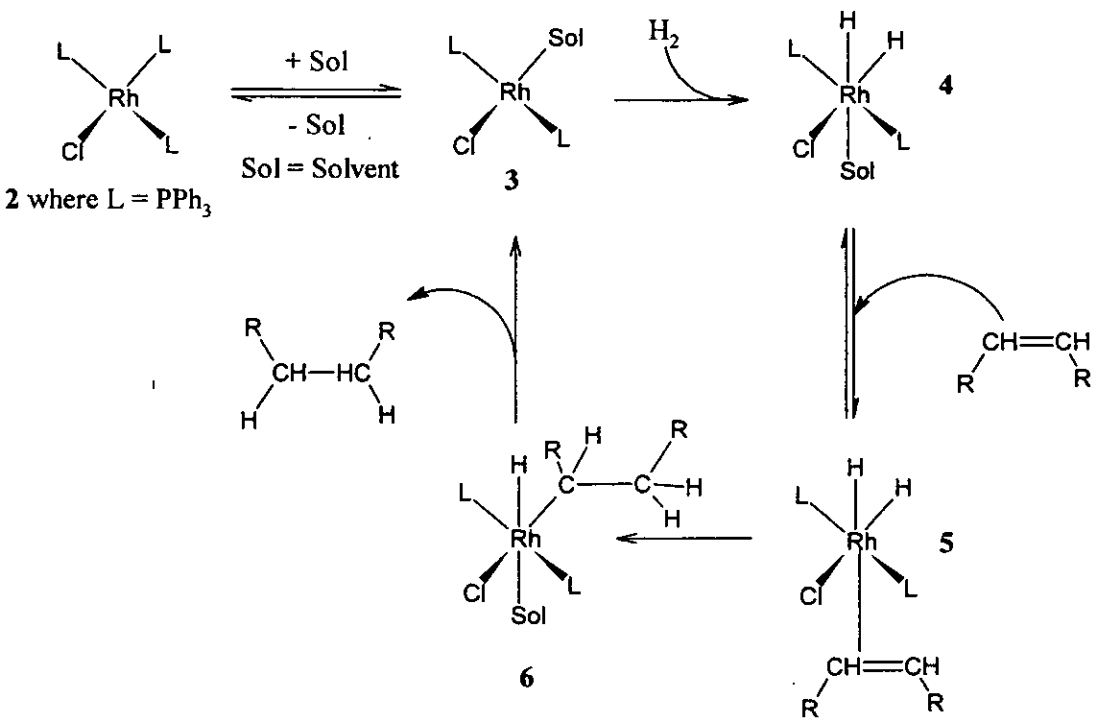
Scheme 1.4 The decomposition of diethyl diazoacetate in styrene, catalysed by complex **1**.

One of the most studied catalytic processes developed is the use of Wilkinson's catalyst, $RhCl(PPh_3)_3$ **2**, for the hydrogenation of a wide range of alkenes. This is not an asymmetric catalytic process, but is a homogeneous hydrogenation catalyst which has been much studied. This complex, $RhCl(PPh_3)_3$ **2,** has been used in many processes because it catalyses the hydrogenation at low pressures of hydrogen, 1 atm or less, unlike other systems which can require much higher pressures. The catalytic cycle for the hydrogenation is given in Scheme 1.5. The first step in the process is the substitution of one of the phosphine ligands in **2** for a molecule of solvent to give **3**. The species **3** has not been observed during spectroscopic analysis of the reaction but is believed to have the structure shown. The next step is the oxidative addition of hydrogen to **3** to give **4**. There is evidence to suggest that oxidative addition of hydrogen to **2** also occurs, but the kinetic evidence suggests that the complex **3** reacts with hydrogen 10^7 times faster than **2**. Substitution of the solvent for the alkene occurs to give **5** before the rate-determining migratory insertion reaction to

give the alkyl hydrido complex **6**. The reductive elimination of the alkane then gives complex **3** and the cycle is completed, furnishing **3** to continue the process once again.



Scheme 1.5 The catalytic cycle for the hydrogenation of alkenes by Wilkinson's catalyst (**2**), adapted from Shriver, Atkins and Langford.[29]

The catalysis is sensitive to the nature of the phosphine ligand and the alkene substrate. If the phosphine ligands are changed to trialkyl phosphines then the complex formed is inactive in the catalysis. For efficient hydrogenation the alkene must be of the right size, those that have high steric hindrance about the C=C double bond are not hydrogenated.

1.4 Homogeneous Catalysts for Imine Hydrogenation

The use of chiral amines in both the pharmaceutical and agrochemical industries is well established. Research in this area is centred on developing new routes to chiral amines. One of the main routes to chiral amines is the hydrogenation of a prochiral C=N centre. Thus far the majority of catalysts developed are homogeneous, there are, however, a few exceptions [30] (see Section 1.2.3). A variety of homogeneous catalysts have been found to be successful, many of them are based on rhodium and iridium centred catalysts, with some exceptions.

1.4.1 Rhodium Centred Catalysts

It has previously been reported that the use of a halide co-catalyst can have an advantageous affect on the optical yield during the hydrogenation of some imines.[31] Kang and co-workers found that the addition of an iodide co-catalyst had a beneficial effect on some of the imines hydrogenated, but in some cases the use of an iodide ion was found to inhibit the reduction.

Kang *et al.*,[32] used a rhodium based phosphine complex ($Rh^{(I)}/Ph_2CH(C_6H_{11})CH_2PPh_2$) successfully to hydrogenate a number of imines based on the structure below, (Figure 1.4), all resulting in high enantiomeric excess.

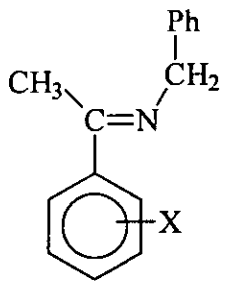


Figure 1.4 General structure of imines hydrogenated by Kang *et al.*

Zhou *et al.*[33] reported the use of a zwitterionic rhodium complex for the hydrogenation of imines. No enantiomeric excess was reported, but high yields of up to 98% were recorded. A large number of imines were hydrogenated successfully using the rhodium catalyst, $(\eta^6\text{-PhBPh}_3)^-\text{Rh}^+(1,5\text{-COD})$.

Many of the complexes reported as being successful for homogeneous hydrogenations are based on chiral phosphine ligands around a central atom. The majority of these have been hydrogenation of the C=C double bond, however, there has been some interest in the C=N double bond.

Riley and Shumate [34] used a new chiral bidentate phosphine ligand, coordinated to rhodium(I), for the asymmetric hydrogenation of α-amidoacrylic acids.

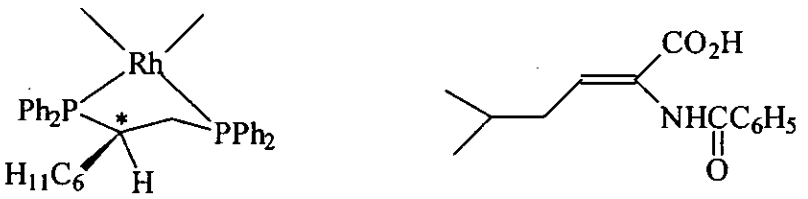


Figure 1.5 Rhodium based chiral bidentate phosphine ligand (left). Example of an α-amidoacrylic acid used by Riley *et al.* (right).

Reported optical yields were high, greater than 80% and generally above 90%, for the corresponding (*S*)-α-amino acid derivatives. Other structurally similar phosphines have not shown such high optical yields; the success of this bidentate phosphine ligand was attributed to the ethyl cyclohexyl substituent, allowing a more stereochemically rigid chelating phosphine.

Zang *et al.*[35] report a highly effective rhodium catalyst containing a chiral bisaminophosphine ligand for the synthesis of a variety of α-arylethylamine derivatives. High enantioselectives were achieved (99 %) along with high reactivities.

Work carried out by Morimoto *et al.*,[36] used modified DIOPs (Figure 1.6) as ligands for a number of rhodium catalysed asymmetric hydrogenations. From their results it was found that the most effective catalysts were ones bearing a diphenylphosphino or dicyclohexylphosphino group, using these catalysts they achieved high activities and high e.e.'s.

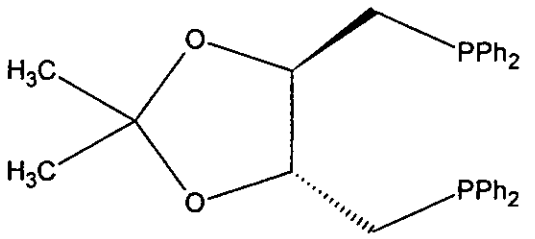


Figure 1.6 (- or +)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphine)-butane. DIOP ligand.

Many other groups[37,38] have reported success in the hydrogenation of prochiral imines, using both rhodium and iridium catalysts, but the above mentioned are the most successful reported to date.

Burial *et al.*,[39] reported the hydrogenation of imines using a rhodium based diphosphine complex in the presence of reverse AOT micelles, which were found to promote enantioselectivity.

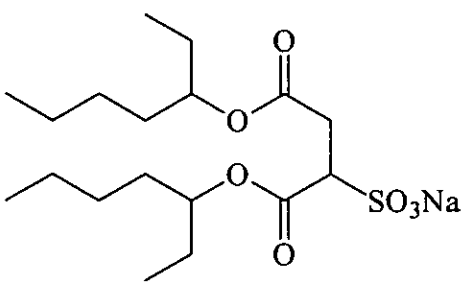


Figure 1.7 Representation of AOT.

Hydrogenations carried out in the absence of such micelles were found to give an enantiomeric excess of approximately 6 %; however, the presence of these micelles increased the e.e. to over 80 %. The excess was found to increase still further, to 92

%, when the reaction was carried out at 4 °C. Substitution of the water, present in the reverse micelles, with such solvents as anisole and methanol also increased the enantiomeric excess and yields.

Leucine and phenylanine were obtained successfully in nearly 100% enantiomeric excess using various phosphine based rhodium centred complexes, by Fryzuk *et al.*,[40] Other prochiral compounds were also hydrogenated successfully to give high optical yields of greater than 80%.

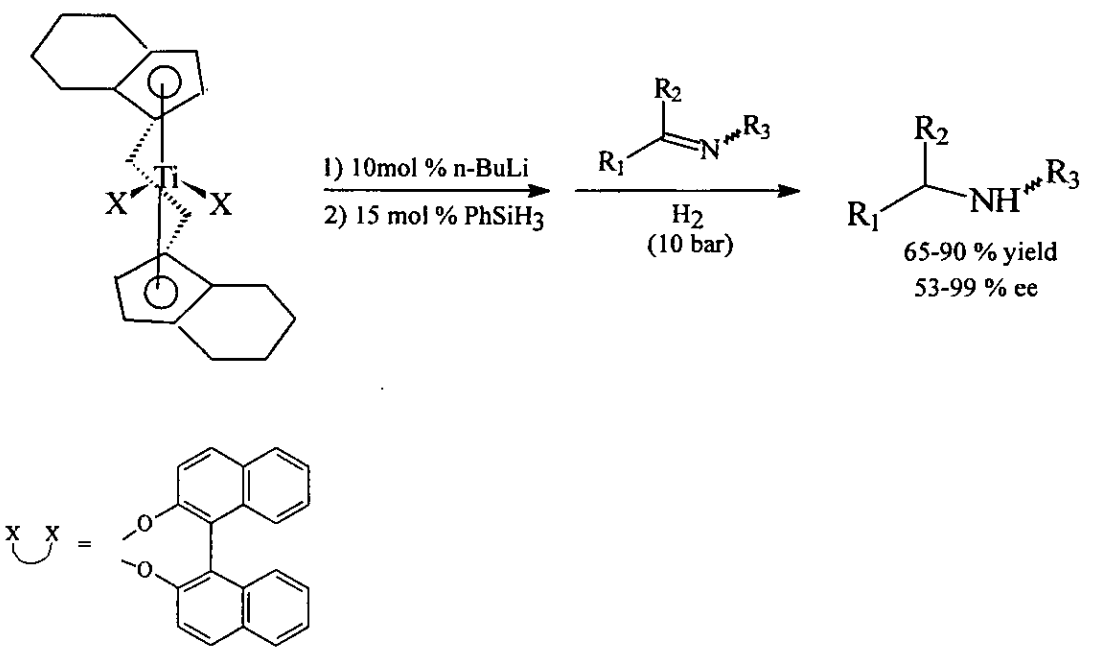
1.4.2 Iridium Centred Catalysts

The work of Osborn *et al.*,[41,42,43] made a significant contribution to the area of enantioselective catalysis using homogeneous iridium catalysts. A variety of different ligands, mainly phosphine based, all producing high enantioselectivity and high activities, have been used. Other similar work in this area has been carried out in Japan by Morimoto *et al.*,[44,45] The catalysts produced have been used successfully to hydrogenate, mainly cyclic imines, asymmetrically; again using iridium centred catalysts with biphosphine ligands.

Bedford *et al.*,[48] studied imine hydrogenation using di-orthometalated iridium complexes of triaryl phosphine. The emphasis of this paper was a study of the phosphine complexes used as catalysts. No enantiomeric excesses were recorded; however, some of the yields quoted were between 50% and 60%.

1.4.3 Other Metal Centred Catalysts

Exceptions to the use of rhodium or iridium centred catalysts include the work carried out by Willoughby *et al.*,[49] who developed a successful chiral titanocene catalyst, Scheme 1.6, which has been widely used to hydrogenate a number of prochiral ketimines to chiral amines. Enantiomeric excess varies between 58% and 98%; hydrogenation of all the ketimines studied resulted in relatively high yields (> 70%).



Scheme 1.6 Catalytic reduction of imines to corresponding amines.

Fogg *et al.*,[48] carried out imine hydrogenation using ruthenium ditertiary phosphine complexes. They reported increased difficulty in homogeneous hydrogenation of the C=N double bond, in comparison to the C=C double bond. In this report only two prochiral enamines, $PhCH_2N=C(R)Ph$ (R = H or Me), were hydrogenated using a

variety of different ruthenium complexes. High conversions with many of the complexes were noted, however, a maximum e.e. of only 27% was achieved using $Ru_2Cl_5(chiraphos)_2$ as a catalyst.

Other work involving the use of ruthenium complexes for homogeneous hydrogenation of imines has been carried out in recent years. The study of Araujo *et al.* [50] shows that the ruthenium (III) complexes used were air stable and showed a high activity for imine hydrogenation

1.5 Comparison of Homogeneous and Heterogeneous Catalysts

Greater emphasis is being placed on establishing heterogeneous systems for many of today's catalytic processes. A heterogeneous system allows for easy recovery of the catalyst, reducing the cost and complexity of the process. Heterogeneous systems are also thought to be cleaner, increasing the lifetime of the catalyst.

A comparison of homogeneous and heterogeneous catalysts for the enantioselective hydrogenation of α-ketoesters was carried out by Blaser *et al.*[51] Blaser and co-workers found that a homogeneous system, using Rh-diphosphine catalysts, showed superior selectivity; however, these optical yields were only achieved at low substrate/catalyst ratios (s/c = 50). Despite this higher selectivity, Blaser found in favour of a heterogeneous system, based on 5% platinum/alumina catalysts modified with cinchona alkaloids. This choice of system was based mainly on cost of the catalyst, including the metal, preparation cost, and cost of chiral auxiliaries.

1.6 Supported Catalysts

Recently there has been extensive interest in the support of homogeneous catalysts, to create effective heterogeneous catalysts, which are more easily recovered and reused. Work in this area involves a variety of different reactions and catalysts, all with little or no loss in activity. [52,53,54,55]

Thus far, research into this area has concentrated on polymers, clays and zeolites as supports [56,57,58,59,60,61]. However, Pugin [62] bound both rhodium and iridium catalysts to silica gel; the catalysts were then used successfully for the enantioselective hydrogenation of a C=C double bond.

Polymer bound catalysts were investigated by Pittman *et al.*[56] They found that by binding transition metal homogeneous catalysts to polymers it was possible to use the catalyst and separate it from the products by simply decanting off. Using a variety of techniques chromium, molybdenum, tungsten and iron complexes were bound successfully to polymers. Most of the catalysts were then used successfully, mainly for hydroformylations.

Work by Corma *et al.*[57] involved anchoring rhodium complexes on zeolites. It was found that rhodium complexes, such as $[RhCl(COD)]_2$, once anchored to modified USY zeolites, when used for the hydrogenation of prochiral alkenes, produced an increase in enantioselectivity (>95%). The enantioselectivity of similar complexes supported on silica were found to be lower (as low as 58% e.e. for some hydrogenations). This work was expanded and Corma *et al.*[63] report the success in

heterogenising dioxomolybdenum complexes, using USY-zeolites, for the selective epoxidation of allylic alcohols.

There has been a significant amount of research into the support of Wilkinson's catalysts.[64,65,66,67] These studies have supported Wilkinson's catalyst on a range of different supports, including silica, carbon, phosphorous and alumina. Results in all cases were very positive, in some cases an increase in activity [64,65] and yield [66] of the compounds hydrogenated was reported. All reported little or no deactivation of the catalysts, quick and easy recovery of the catalyst for re-use and resistance to sulphur poisoning.[64]

In recent years, work has begun on the support of homogeneous catalysts, for imine hydrogenation, using a range of different supports.

Claver *et al.*, [68] looked at the rhodium and iridium homogeneous catalysts for imine hydrogenation being supported on clay. A range of supports were studied and the supported catalysts used for imine hydrogenation. Results showed that for the first run catalytic activity was comparable to that of the catalyst run homogeneously. However, in subsequent runs a reduction in rate was noticed, with the exception of supported $[Ir(COD)(PPh_3)_2]BF_4$ which maintained its activity over several runs. Studies also showed that the structural characteristics of the clay support could affect the stability of the catalyst.

Similar work was carried out using a range of mesoporous silica and zeolite supports.[69] This study showed that there was a boost in activity of some of the

supported catalysts when used for imine hydrogenation. There was no deactivation of the catalysts but enantioselectivity was reported to be low.

Recent work using iridium diphosphine catalysts for imine hydrogenation [70] has concentrated on the problem of deactivation. This study showed that immobilisation of the catalyst on silica gel enhanced the stability of the catalysts tested. Some affect to the initial rates and enantiomeric excess was noted, but this slight change was outweighed by the significant increase in the stability of the supported catalysts.

Chapter 2
Experimental

EXPERIMENTAL

2.1 Autoclave Reactor Design

An automated steel autoclave was designed for the hydrogenation of prochiral molecules (Figures 2.1 and 2.2). The autoclave (Baskerville and Lindsay), capable of pressure up to 250 atmospheres, was 17.5 cm deep with a diameter of 4 cm. For all hydrogenations the reaction mixture was contained in a Teflon liner (outer diameter 40 mm, inner diameter 30 mm, height 140 mm). The reaction mixture was stirred by means of a twin bar magnetic stirrer (Radleys), which was placed at the bottom of the autoclave vessel and controlled by a hot-plate/stirrer. Hydrogen introduction was computer controlled, allowing the hydrogen pressure to be maintained throughout the experiment. Hydrogen could also be introduced manually. A thermocouple encompassed into the autoclave allowed temperature to be monitored, in the event that elevated temperatures were required.

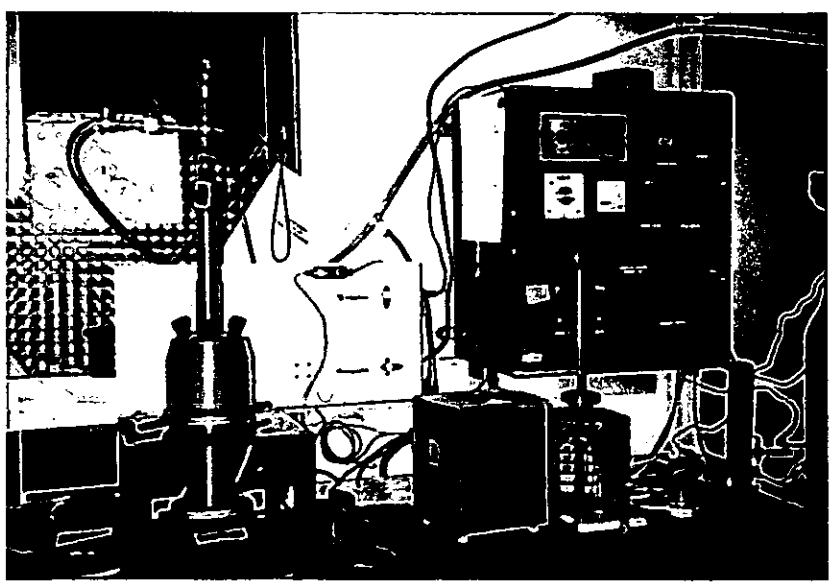


Figure 2.1 Baskerville and Lindsay Autoclave reactor

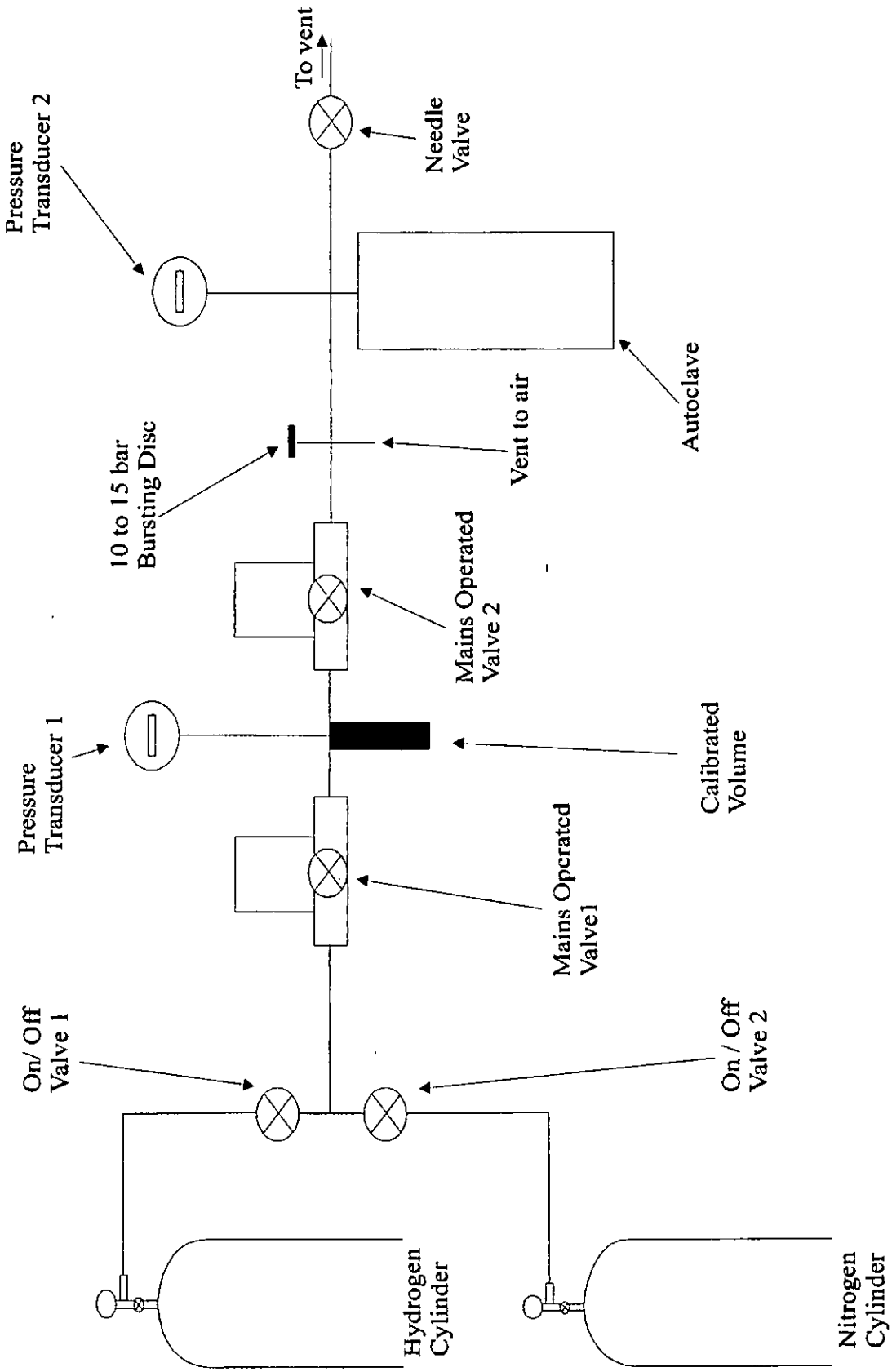


Figure 2.2 Schematic of Autoclave Reactor

2.2 Operational Procedure for Autoclave Reactor

For all hydrogenations the autoclave was initially flushed with nitrogen (BOC gases), to remove air from the system. Hydrogen (99.95%, BOC gases) was then introduced to a standard operating pressure (10 bar hydrogen). All hydrogenations were carried out at room temperature, unless otherwise stated. Stirring of the reaction mixture began upon commencement of the reaction, and continued throughout. The hydrogen pressure was monitored by pressure transducer. As hydrogen was consumed by the reaction computer controlled solenoid valves were opened to allow a known volume of gas to enter the reactor. Thus the hydrogen pressure was maintained constant throughout the course of the experiment. The hydrogen consumption was recorded as a function of time. The data was saved to disc in a format that allowed it to be manipulated and displayed in Microsoft Excel.

2.3 Product Analysis

The products of reactions were analysed by gas chromatography, with the use of a chiral capillary column (Chiraldex, γ-cyclodextrin, propionyl, 20 m × 0.25 mm). The gas chromatograph used was a Pye Unicam PU4550 fitted with a flame ionisation detector. The output signal was recorded and the peak area integrated using an integrator. Pyruvate esters were analysed using an isothermal oven temperature of 40°C (injector 250°C, detector 250°C). Amine analysis was carried out using a temperature programme (50°C held for 3 minutes, increased to 150°C at a rate of 3°C/minute to a maximum temperature of 150°C) the detector and injector

temperatures remained the same. From these analyses the percentage conversion and enantiomeric excess was obtained (Appendix A).

The initial reaction rate of all reactions (expressed in mmol h^{-1} g^{-1}) was calculated from the hydrogen uptake curve, which was acquired from computer analysis of the reaction. This was acquired from linear regression performed over the first 3 minutes of the hydrogen uptake curve.

2.4 Molecular Modelling

In order to help interpret some of the results attained a molecular modelling program using 3D imagery was used to visualise some of the compounds. ACD Labs 3D viewer, version 8.04, was used for this modelling.

In this modelling program, the 3D optimization algorithm rapidly transforms the planar (2D) structure from ACD Labs ChemSketch, version 8.17, into a realistic 3-dimensional structure. It is based on modified molecular mechanics which take into account bond stretching, angle bending, internal rotation and Van der Waals non-bonded interactions. Modifications include minor simplification of potential functions and enforcement of the minimization scheme by additional heuristic algorithms for dealing with "bad" starting conformations.

Chapter 3
Pyruvate Esters

PYRUVATE ESTERS

The aim of this study was at the outset to use the hydrogenation of methyl pyruvate, using 5 % Pt/alumina, as a model for the hydrogenation of similar imines. In order to create a comparison for the intended imine hydrogenations this system was initially investigated.

As part of an industrial project a series of commercial platinum catalysts were screened for their efficacy as enantioselective hydrogenation catalysts. The test reaction chosen was the hydrogenation of methyl pyruvate to methyl lactate using cinchona alkaloid modifiers. These results could then be used as a comparison for prochiral imine hydrogenations.

3.1 Enantioselective Hydrogenation of Pyruvate Esters

The hydrogenation of methyl pyruvate has been investigated using a number of different heterogeneous catalysts, all platinum based, (Table 3.1). These catalysts differ in their support, loading and preparation, their activity in comparison to that of the standard catalytic system for this reaction (5%Pt/alumina/cinchona alkaloid) was investigated. All catalysts were used both un-modified and modified with cinchona alkaloids (cinchonidine and cinchonine). In order to establish the effectiveness of the catalysts, they were assessed on their initial reaction rate, the enantiomeric excess of the product, and the percentage conversion of the reaction.

All catalysts used were supplied by BNFL, with the exception of 5% platinum/alumina, supplied by Johnson Matthey. Catalysts A and B are commercially produced platinum/silica catalysts, mesoporous platinum. [86] Table 3.1 shows all catalysts used, along with their know composition.

Table 3.1 Catalyst Identification

Catalyst	Composition	Referred to as:
Platinum / alumina	5% Platinum supported on alumina	Pt/alumina
Catalyst A	Pt supported on SiO_2, reduced under hydrogen	Catalyst A
Catalyst B	Pt supported on SiO_2 reduced under air	Catalyst B
D313	CATAL Int. Ltd. D313 (Platinum catalyst)	D313
Mesoporous Platinum	Mesoporous Platinum	Meso Pt
Pt / Mg :ZrO2	Platinum supported on Mg:ZrO2	$Pt/MgZrO_2$

3.2 Catalyst Pre-treatment

0.05 g samples of the catalyst were reduced (523 K) under flowing hydrogen at ambient pressure for 1 h. Once cooled to room temperature, a solution of 0.5 g cinchona alkaloid in 25 ml of ethanol was injected onto the reduced catalyst, prior to exposure to air. This suspension was then stirred in an open container for 1 h, the alkaloid solution decanted off and the modified catalyst transferred to the autoclave liner. To this were added approximately 25 mmol of methyl pyruvate (accurately weighed) and 25 ml of the solvent, absolute ethanol. In hydrogenation experiments using no modifier, the catalyst was treated identically, with the exception of being stirred in an open container for 1 h with the solvent, instead of an alkaloid solution.

Hydrogenation of the reaction mixture was then carried out as described in Section 2.1, hydrogen uptake being measured as detailed in Section 2.2. Each catalyst was evaluated in the un-modified, modified with cinchonidine and modified with cinchonine states. Analysis of the products was carried out as described in Chapter two, (Section 2.3).

3.3 Hydrogenation of Methyl Pyruvate

The activity of each catalyst was assessed by means of a comparison of the initial rate of reaction, enantiomeric excess (e.e.) and percentage conversion after 10 hours, Table 3.2. Although each catalyst was used once for the hydrogenation of methyl pyruvate, the experiments were repeated several times, errors are approximately 0.5%. All catalysts were compared to the modified and un-modified 5% Pt/alumina system, the standard catalyst for this reaction.

Table 3.2 Hydrogenation of methyl pyruvate with all catalysts and modifiers

Catalyst	Modifier	Initial Rate / mmol h^{-1}	e.e. / %	Conversion / %
5% Pt/alumina	CD	58.2	74.3	92.9
5% Pt/alumina	CN	44.6	68.8	100
5% Pt/alumina	None	46.5	0	74.5
Catalyst A	CD	50.4	44.9	45.6
Catalyst A	CN	34.8	7.9	7.2
Catalyst A	None	42.0	0	27.7
Catalyst B	CD	17.3	21.7	10.2
Catalyst B	CN	12.5	7.3	4.7
Catalyst B	None	34.4	0	4.7
D313	CD	50.6	19.5	19.7
D313	CN	50.4	15.6	13.4
D313	None	45.6	0	8.7
Mesoporous Pt	CD	33.6	1.1	31.0
Mesoporous Pt	CN	39.6	34.0	32.0
Mesoporous Pt	None	38.0	0	35.3
Pt/Mg:ZrO_2	CD	31.2	3.1	27.1
Pt/Mg:ZrO_2	CN	38.0	1.1	73.5
Pt/Mg:ZrO_2	None	42.0	0	3.4

CD = catalyst modified with Cinchonidine

CN = catalyst modified with Cinchonine

None = un-modified catalyst

3.4 Results and Discussion

In order to compare the catalysts more effectively, several graphs showing the hydrogen uptake of the reactions have been complied. Figures 3.1 to 3.6 show the activity of each separate catalyst when modified with cinchona alkaloid and unmodified. This allowed an evaluation of the initial and overall rate for each separate catalyst to be determined.

3.4.1 Hydrogenation of Methyl Pyruvate with 5% Pt / Alumina

Table 3.3 Hydrogenation of methyl pyruvate with 5% Pt/alumina

Catalyst	Modifier	Initial Rate / mmol h^{-1}	e.e. / %	Conversion / %
5% Pt/alumina	CD	58.2	74.3	92.9
5% Pt/alumina	CN	44.6	68.8	100
5% Pt/alumina	None	46.5	0	74.5

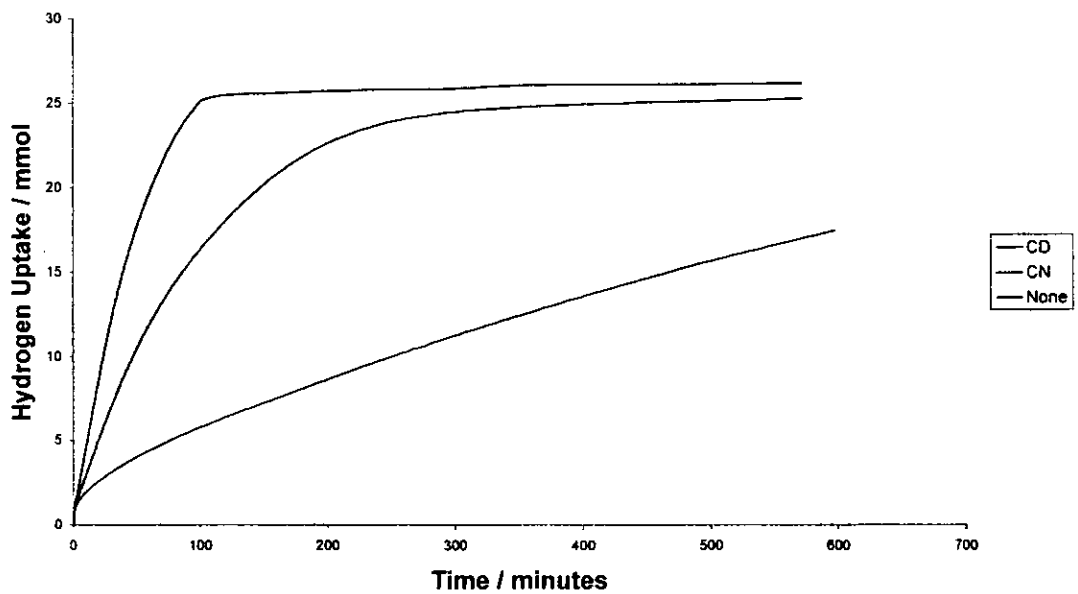


Figure 3.1 Hydrogenation of Methyl Pyruvate with 5% Pt/alumina

The standard catalyst / modifier combination quoted in the literature is either Euro-Pt (Meheux *et al.*[13]) or 5% Pt / Al2O3 (Margitfalvi *et al.*[14]). As can be seen from Figure 3.1 cinchonidine shows the greatest initial rate of hydrogen uptake and both modified catalysts take the reaction to completion. However, the un-modified catalyst shows a slow initial rate with the 25 mmol of reactant not being completely hydrogenated after 10 hours, i.e. 100% conversion of methyl pyruvate to methyl lactate. Enantiomeric excess achieved (74.5%) was comparable to previously reported results.

3.4.2 Hydrogenation of Methyl Pyruvate with Catalyst A

Table 3.4 Hydrogenation of Methyl Pyruvate with Catalyst A

Catalyst	Modifier	Initial Rate / mmol h^{-1}	e.e. / %	Conversion / %
Catalyst A	CD	50.4	44.9	45.6
Catalyst A	CN	34.8	7.9	7.2
Catalyst A	None	42.0	0	27.7

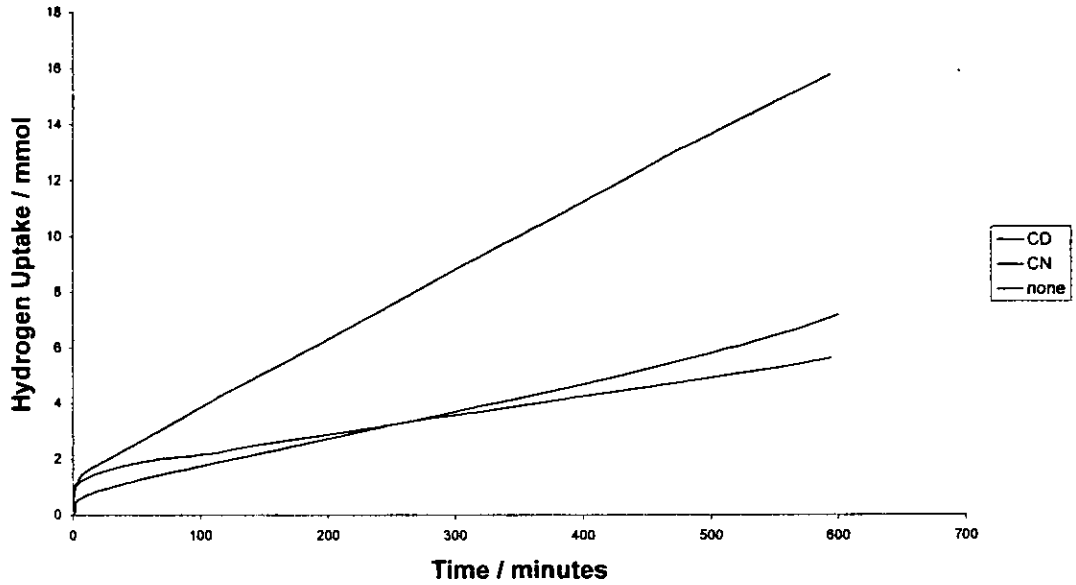


Figure 3.2 Hydrogenation of Methyl Pyruvate with Catalyst A

The hydrogen uptake curve for the hydrogenation of methyl pyruvate over Catalyst A shows some interesting trends. The catalyst appears to operate best when modified with cinchonidine but surprisingly performed very poorly when modified with cinchonine. In the initial stages the cinchonine modified was even out performed by the un-modified catalyst. One possible explanation for this could be the position the modifier is absorbed onto the catalyst surface. In the case of cinchonine the modifier may be absorbed onto the catalyst surface in such as way as to hinder the formation of methyl lactate.

3.4.3 Hydrogenation of Methyl Pyruvate with Catalyst B

Table 3.5 Hydrogenation of Methyl Pyruvate with Catalyst B

Catalyst	Modifier	Initial Rate / mmol h^{-1}	e.e. / %	Conversion / %
Catalyst B	CD	17.3	21.7	10.2
Catalyst B	CN	12.5	7.3	4.7
Catalyst B	None	34.4	0	4.7

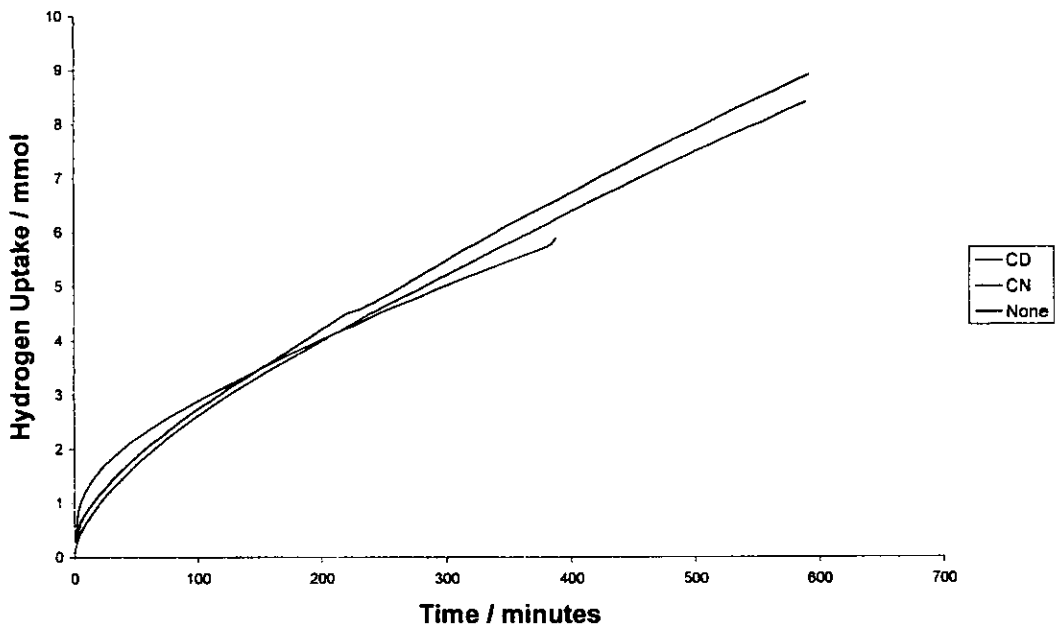


Figure 3.3 Hydrogenation of Methyl Pyruvate with Catalyst B

The performance of Catalyst B was disappointing in comparison to the 5% Pt/alumina catalyst. The initial rate and overall conversion for both the modified and un-modified catalysts were low in comparison to all the other catalysts tested. The enantiomeric excess in the case of the modified catalysts is also much lower the standard operating system used as a reference (5 % Pt/alumina). There was little

difference between Catalyst B modified with cinchonidine and cinchonine. Again the enantiomeric excess was greater for the cinchonidine-modified catalyst but not comparable to the established 5% Pt/alumina system.

Catalysts A and B are unique in that they display a significant reduction in enantioselectivity when modified with cinchonine compared with cinchonidine. This reduction in enatioselectivity is mirrored in a reduction in the rate of reaction, this relationship between rate and selectivity has previously been observed by other authors and is a contradiction to Dowden's Rule; which states that if the activity of a chiral catalyst is high then the selectivity of that catalyst will be low. However, such a difference in selectivity between catalysts modified with cinchonine and cinchonidine has not previously been reported. Had there not been confidentiality clauses which prevented characterisation of the catalysts then these materials could have provided a useful insight into how catalytic structure can modify the adsorption geometry of the modifier. Such information could have provided further insight into the working mechanism of these systems.

3.4.4 Hydrogenation of Methyl Pyruvate with D313

Table 3.6 Hydrogenation of Methyl Pyruvate with D313

Catalyst	Modifier	Initial Rate / mmol h^{-1}	e.e. / %	Conversion / %
D313	CD	50.6	19.5	19.7
D313	CN	50.4	15.6	13.4
D313	None	45.6	0	8.7

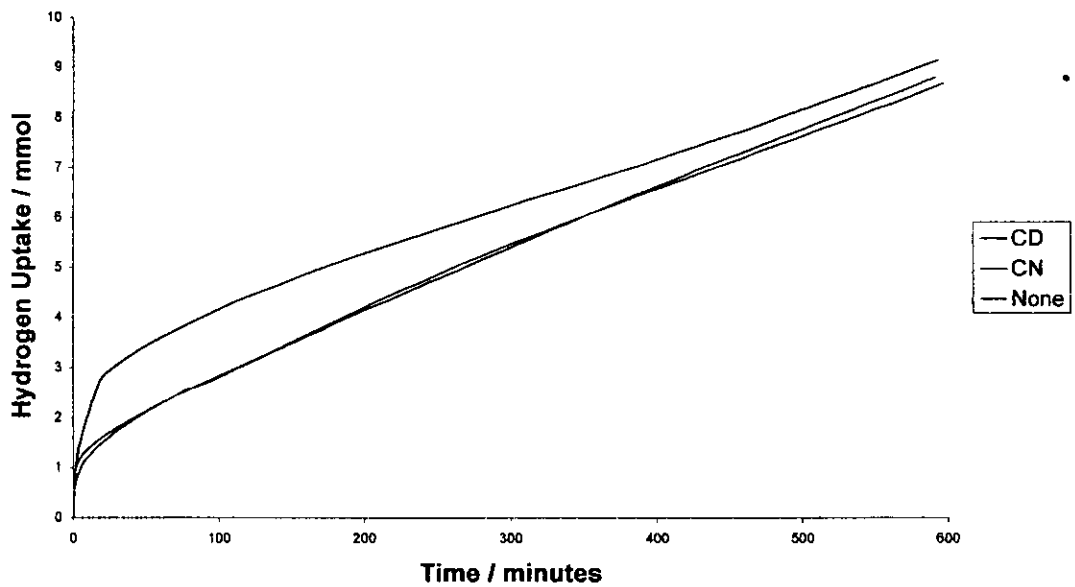


Figure 3.4. Hydrogenation of Methyl Pyruvate with D313

Hydrogenation with the D313 catalyst was initially promising, showing very good initial rates of reaction, which was maintained for some time when D313 was modified with cinchonidine. However, both modified and un-modified catalysts showed a low percentage conversion of the methyl pyruvate; the modified catalysts also showed low enantiomeric excess in comparison to the standard 5% Pt/alumina.

3.4.5 Hydrogenation of Methyl Pyruvate with Mesoporous Platinum

Table 3.7 Hydrogenation of Methyl Pyruvate with Mesoporous Platinum

Catalyst	Modifier	Initial Rate / mmol h^{-1}	e.e. / %	Conversion / %
Mesoporous Pt	CD	33.6	1.1	31.0
Mesoporous Pt	CN	39.6	34.0	32.0
Mesoporous Pt	None	38.0	0	35.3

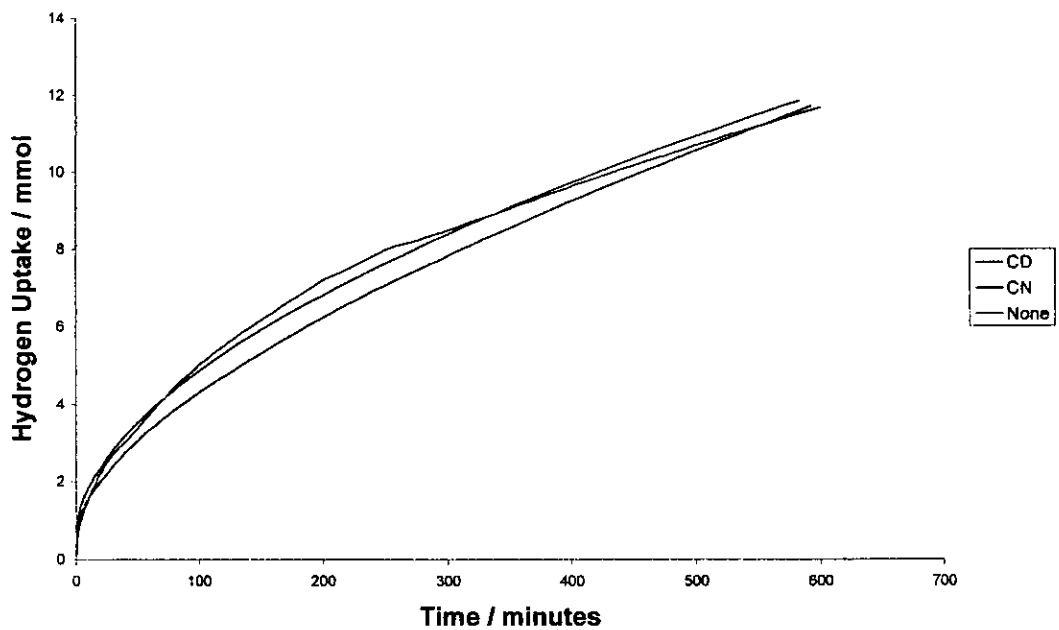
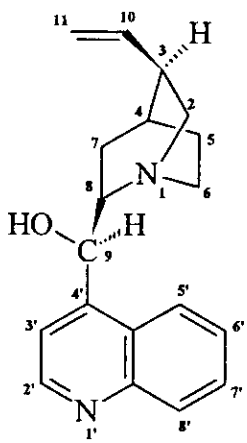


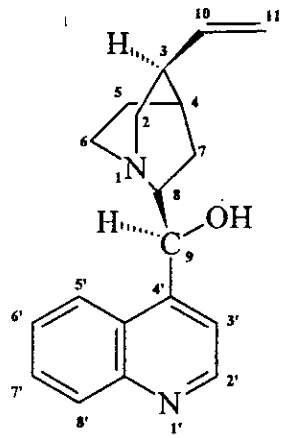
Figure 3.5 Hydrogenation of Methyl Pyruvate with Mesoporous Platinum

There is little difference between the rate of reaction and percentage conversion of methyl pyruvate using the mesoporous platinum catalyst when modified (with both cinchonidine and cinchonine) and un-modified. Enantiomeric excess was very disappointing for the cinchonidine modifier. However, the catalyst showed a good e.e. when modified with cinchonine; although this was low when compared to the

5% Pt/alumina. This difference in the two modified systems could be explained by the ability of the modifier to cover the mesoporous platinum, entering the pores, and allowing for full surface coverage. Since the cinchonidine modifier shows a very low enantiomeric excess (1.1 %), very close to the un-modified system, it is thought that the cinchonidine modifier was unable to adsorb fully onto the catalyst surface. Whereas the cinchonine catalyst has been able to enter the pores; allowing for a greater surface area to be covered. Molecular modelling carried out shows this difference in size between the two molecules (Figures 3.6 to 3.8).



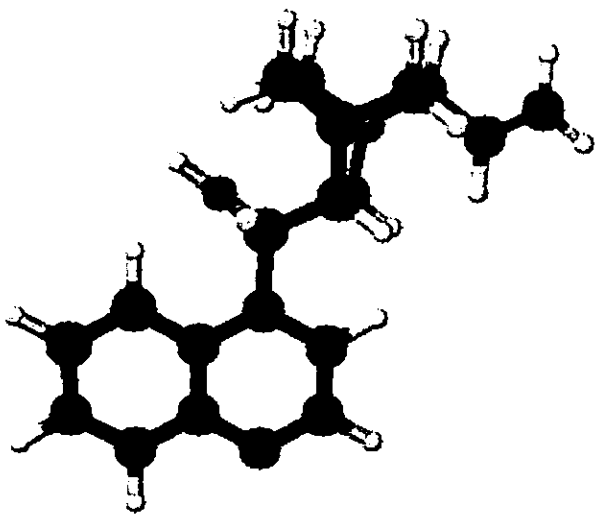
Cinchonidine



Cinchonine

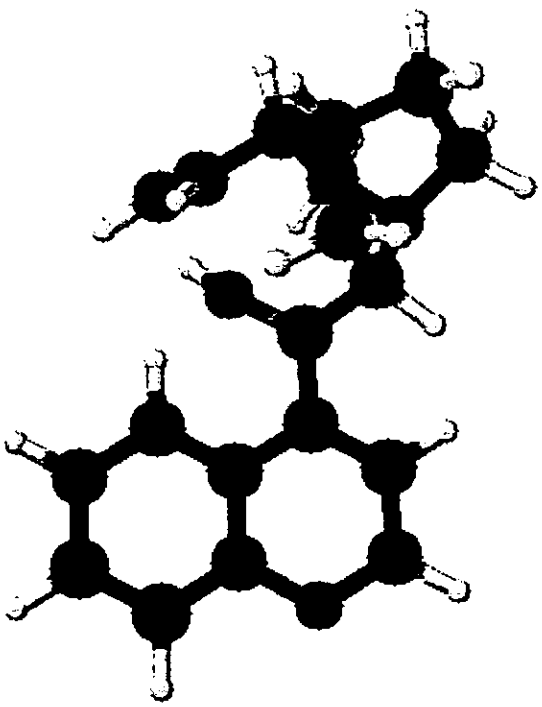
Figure 3.6 Cinchonidine and Cinchonine with carbon and nitrogen atoms numbered.

The compounds were drawn using a molecular modelling programme, including stereochemistry. The distance between carbon atoms on the ring (carbon 7') and on the ethane group (carbon 11) were measured.



Red = nitrogen
Pale blue = carbon
Blue = oxygen
White = hydrogen

Figure 3.7 3D representation of Cinchonidine with carbon 7' and carbon 11 highlighted in green.



Red = nitrogen
Pale blue = carbon
Blue = oxygen
White = hydrogen

Figure 3.8 3D representation of Cinchonine with carbon 7' and carbon 11 highlighted in green.

As can be seen from figures 3.7 and 3.8, due to the stereochemistry of the two compounds the cinchonine is a smaller molecule, allowing it to fit into the pores of the mesoporous platinum. To ensure that the largest distance across the cinchonine was measured, both molecules were also measured between carbon 7' and carbon 2. All distances are recorded in Table 8, where it can be seen that the cinchonine molecule is much more compact (6.423 Å between carbon 7' and carbon 11) than the cinchonidine, supporting the belief that the cinchonine has been able to enter the pores on the mesoporous platinum.

Table 3.8 Distances between carbon atoms in Cinchonidine and Cinchonine

Carbon atoms	**Distance in Cinchonidine**	**Distance in Cinchonine**
Carbon 7' to Carbon 11	11.212 Å	6.423 Å
Carbon 7' to Carbon 2	8.983 Å	8.918 Å

3.4.6 Hydrogenation of Methyl Pyruvate with Pt/Mg:ZrO_2

Table 3.9 Hydrogenation of Methyl Pyruvate with Pt/Mg:ZrO_2

Catalyst	**Modifier**	**Initial Rate / mmol h^{-1}**	**e.e. / %**	**Conversion / %**
Pt/Mg:ZrO_2	CD	31.2	3.1	27.1
Pt/Mg:ZrO_2	CN	38.0	1.1	73.5
Pt/Mg:ZrO_2	None	42.0	0	3.4

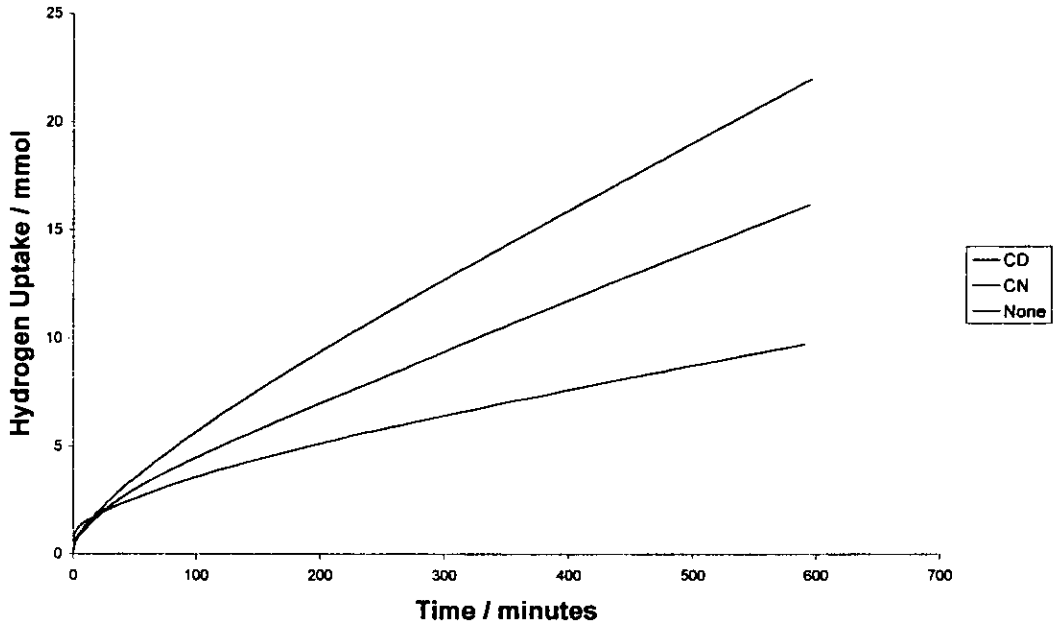


Figure 3.9 Hydrogenation of Methyl Pyruvate with Pt/Mg:ZrO_2

In this reaction, using Pt/Mg:ZrO_2 the cinchonine modified catalyst shows the greatest hydrogen uptake and overall rate of reaction. Initial reaction rates are very similar with both the un-modified and cinchonidine modified catalyst showing a drop in rate of reaction after approximately 50 minutes. Enantiomeric excess was very poor for this catalyst with e.e.'s below 5% for both modifiers and despite its high percentage conversion, the cinchonine modifier results in an e.e. of 1.1% (very near 0%, and the un-modified system).

It is thought that in the case of Pt/Mg:ZrO_2, the adsorption of the modifier onto the catalyst surface is enhancing the activity with respect to rate of reaction and conversion; however, the selectivity of the modified catalyst is very low. Since there is such a marked difference between the percentage conversions of the modified catalyst, it is assumed that the modifier has adsorbed onto the catalyst surface and improved the conversion to methyl lactate, but not the selectivity of the catalyst. As

no further analysis of the used catalysts were carried out, it is difficult to suggest theories as to why the conversion has improved with the use of a modifier, but not the selectivity. Perhaps the modifier in this case is acting as a promoter for the reaction.

3.5 Hydrogenation of Methyl Pyruvate with Platinum Catalysts

The hydrogenation of methyl pyruvate with this series of platinum catalysts has shown that the established 5 % Pt/alumina catalyst modified with cinchona alkaloids remains the best overall system. However, several interesting issues have been raised which would require both further study and further information about the catalysts.

Catalysts A and B have raised questions about the reduction in rate and enantioselectivity. Further information about these catalysts from the industrial sponsors and investigations into the characterisation of the catalysts before and after the reactions may help to answer these questions.

Other catalyst tested showed little difference between modified and unmodified catalyst raising questions as to whether the modifier has been adsorbed onto the catalyst. Again catalyst characterisation to establish if the modifier has been adsorbed onto the catalyst surface, or in the case of the mesoporous catalyst into the pores, may establish reasons for the results obtained.

Chapter 4

Synthesis and Heterogeneous Hydrogenation of Prochiral Imines

SYNTHESIS AND HETEROGENEOUS HYDROGENATION OF PROCHIRAL IMINES

4.1 Preparation of Imines

The initial aim for this study was that the system used in the hydrogenation of methyl pyruvate, involving hydrogenation with platinum catalysts modified with cinchona alkaloids, could be used to hydrogenate pro-chiral imines with a similar molecular structure. Since the imines in question were not stable (but their corresponding amines were) it was hoped that the pro-chiral imines could be prepared in the laboratory and then immediately hydrogenated to form the stable, chiral amine.

This chapter deals with the preparation of imines. Initial attempts to reproduce imines which corresponded to methyl pyruvate; thus, hopefully, enabling a comparison with pyruvate system previously studied (see Chapter 3). It also details preparation of further imines which were attempted, noting the success of such attempts, including the final imines and preparation methods used for the remainder of the project; i.e. hydrogenation of prochiral imines to chiral amines.

Several problems producing suitable imines for hydrogenation were initially experienced. Therefore some time was spent preparing different imines and optimising the synthesis method. Where more than one preparation method was available the most successful method, considering percentage yield and reproducibility was used. Also, since high yields were difficult to achieve, the

'cleanness' of the reaction was taken into account, limiting by-products to a minimum.

4.1.1 Preparation of Ethyl 2-iminopropanoate and Methyl 2-iminopropanoate

As mentioned above, initial work started with attempts to prepare 2 pro-chiral imines with similar structures to methyl and ethyl pyruvate were made, Figures 4.1 and 4.2.

A B

Figure 4.1 Ethyl 2-iminopropanoate (A) and Ethyl Pyruvate (B)

A B

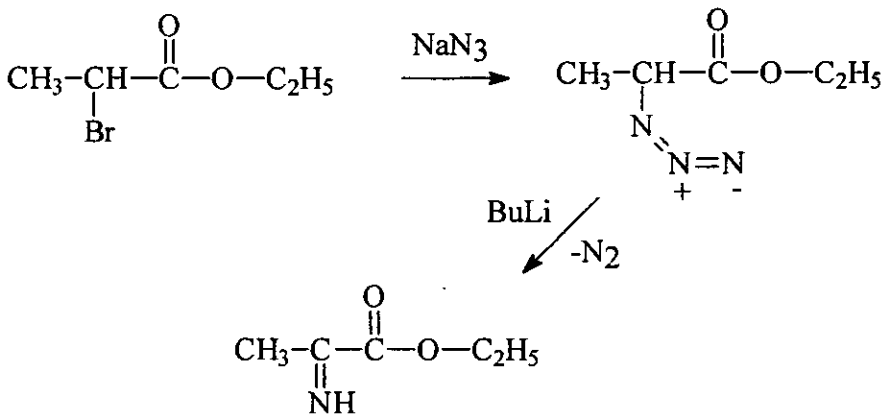
Figure 4.2 Methyl 2-iminoporpanoate (A) and Methyl Pyruvate (B)

4.1.1.1 Preparation of Ethyl 2-iminopropanoate

The general method of Manis *et al.* [71] was adopted, as shown in Scheme 1.1. To a suspension of sodium azide (49 g, Aldrich) in 50 ml of dimethylformamide (Lancaster), ethyl 2-bromopropionate (65 ml, Aldrich) was added; the mixture was stirred for 2.5 h at room temperature. After this time 200 ml of distilled water was

added, and the solution extracted with two 50 ml portions of dichloromethane (BDH). The combined organic layers were washed with a further 200 ml of distilled water, dried with calcium sulphate (anhydrous) (BDH), and the solvent removed *in vacuo*. Reduced pressure distillation gave ethyl 2-azidopropanoate as a colourless oil.

Ethanol (0.5 ml, BDH) was added to *n*-butyl lithium (3.2 ml, Aldrich) in hexane, and the mixture dissolved in 50 ml of carbon tetrachloride (BDH). Ethyl 2-azidopropanoate (7.15 g) was added drop wise with stirring to yield ethyl 2-iminopropanoate as an orange solid.



Scheme 4.1 Preparation of Ethyl 2-Iminopropanoate

4.1.1.2 Preparation of Methyl 2-iminopropanoate

This imine was prepared as above (Section 4.1.1.1), using methyl 2-bromopropanoate (Aldrich) to prepare the azide. 6.45 g of methyl 2-azidopropanoate was used to prepare methyl 2-iminopropanoate which formed as an

orange suspension, which was separated from the carbon tetrachloride solvent before hydrogenation.

4.1.1.3 Success of Preparation of Ethyl 2-iminopropanoate and Methyl 2-iminopropanoate

NMR analysis was carried out at all stages of the preparation of the above imine. The intermediate stage of the azide was analysed, NMR showing that the azide was reasonably pure; however, some DMF (solvent) from its preparation was still present. Unfortunately the NMR for the final product (Figure 4.3) was inconclusive. The sample had been masked by solvents, and it was difficult to identify the peaks corresponding to ethyl 2-iminopropanoate. The modelling program used does not allow predicted NMR to be obtained from drawn structures, perhaps the use of a different modelling program with this facility may aid analysis.

Further attempts to produce the imine were also unsuccessful; purification was attempted but did not improve the final product. It was suspected that the imine degraded quickly, preventing its analysis, purification and ultimately use for hydrogenation.

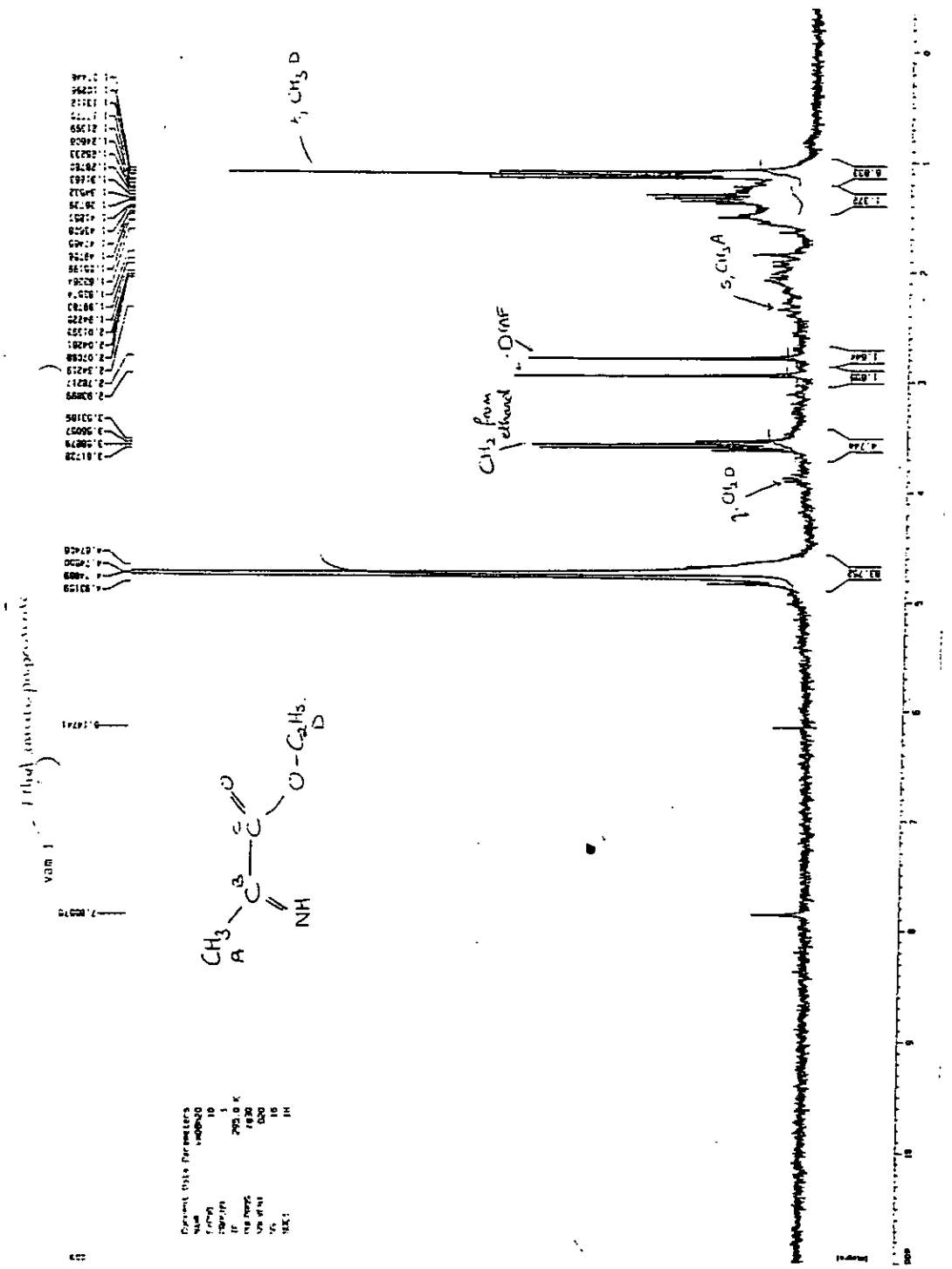


Figure 4.3 NMR analysis of Ethyl 2-iminopropanoate

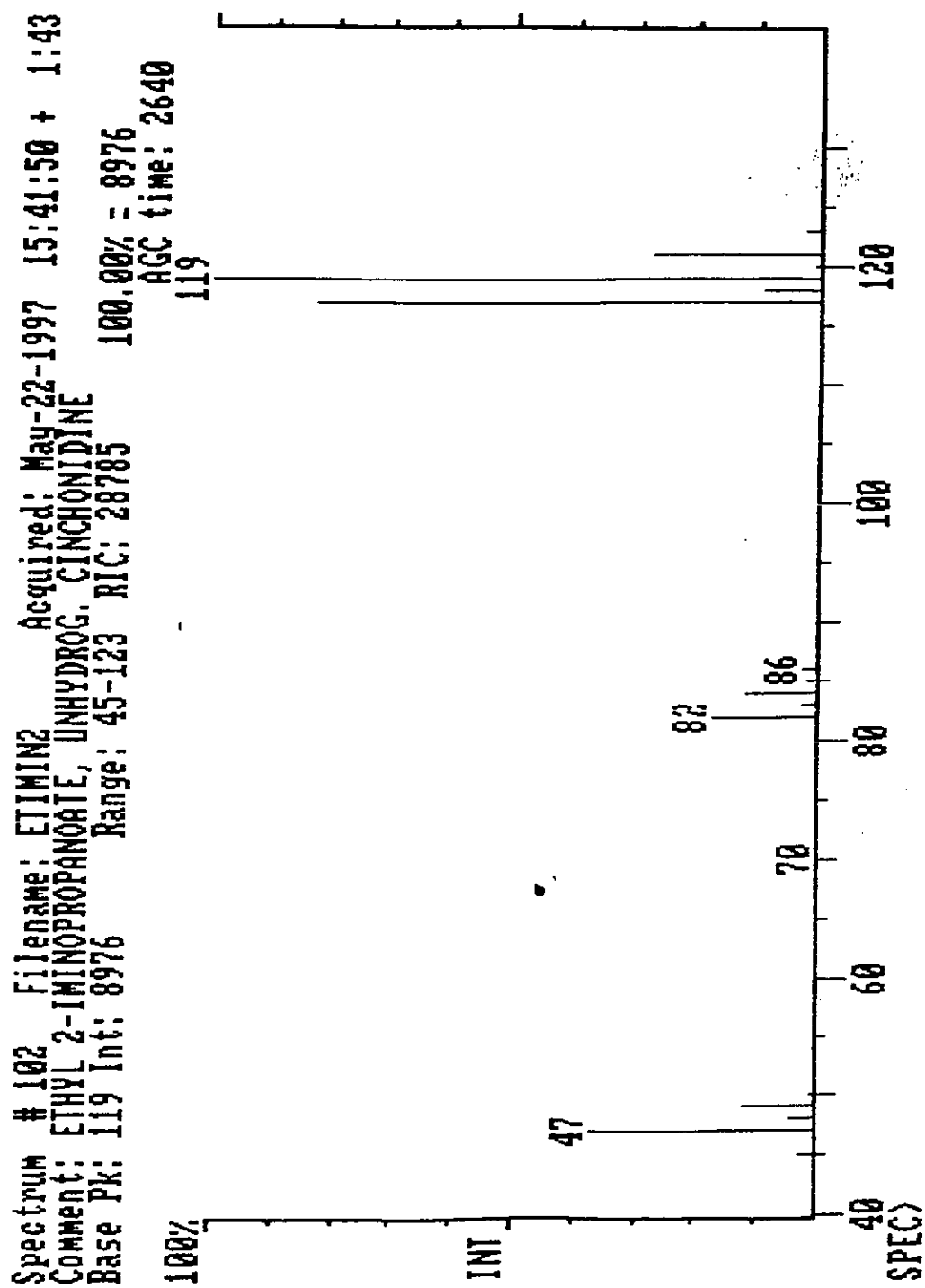


Figure 4.4 GCMS analysis of Ethyl 2-iminpropanoate

GC/MS was carried out on freshly prepared ethyl 2-iminopropanoate (Figure 4.4). It is thought that the compound fragmented to give m/z = 70, m/z = 86. Peaks at approximately m/z = 117, m/z = 119 and m/z = 82 were identified as imine which may have decomposed on standing, Figure 4.5.

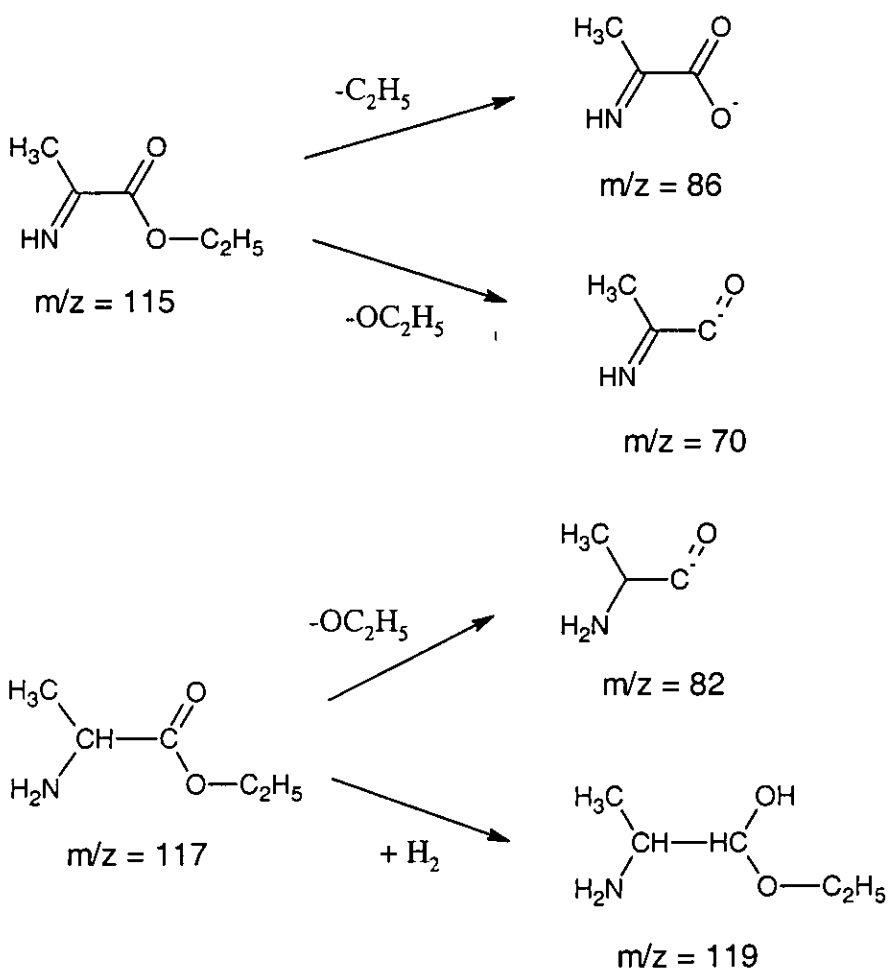


Figure 4.5 Fragmentation of imine, analysed using GCMS.

The preparation process was repeated several times with no further improvement on producing ethyl 2-iminopropanoate. It was however, decided to hydrogenate the compound produced in case the imine was decomposing during analysis, thus preventing definite identification. It was, therefore, hoped that keeping the imine

under argon until hydrogenation would allow the corresponding amine to form and be positively identified, thus enabling positive identification of the starting imine.

Unfortunately, attempts to hydrogenate the product produced in this preparation were unsuccessful. Despite a small hydrogen uptake curve difficulties were experienced in analysing the results of the hydrogenation. It was decided that the preparation of the imine was not a clean process, and some impurities existed, which upon analysis, using chiral GC, appeared to mask the actual imine, and the chiral amine produced. It was therefore impossible to achieve an enantiomeric excess and percentage conversion for this hydrogenation.

In an attempt to identify the amine produced from the hydrogenation of ethyl 2-iminopropanoate, and resolve the GC traces, different methods of producing the chiral amine (analine ethyl ester, Figure 4.6) were tried.

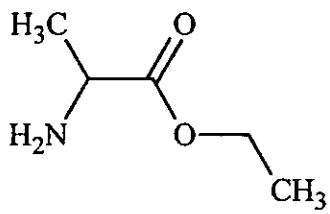


Figure 4.6 Analine Ethyl Ester

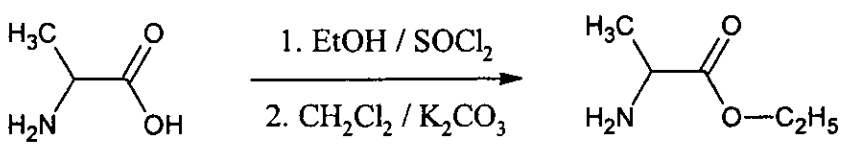
4.1.1.4 Esterification of Alanine

Alanine was esterified using the method of Mazur *et al.* [72] producing the same amine obtained from the above mentioned hydrogenation, see Scheme 4.2, aiding analysis of the hydrogenation.

Ethanol (300 ml) was cooled to -20°C and 10.9 ml of thionyl chloride (Aldrich) was added drop wise with stirring, followed by 11.1 g of D,L-alanine (Aldrich). The solution was refluxed for 24 h, and most of the solvent removed under vacuum. The residue was dissolved in 200 ml of diethyl ether (BDH). Upon standing the hydrochloride of the ester was formed.

18.4 g of D,L-alanine hydrochloride was suspended in 25 ml of dichloromethane, and shaken with 10 ml of 5M K_2CO_3 (Aldrich). The CH_2Cl_2 was decanted off, and the aqueous slush shaken with 25 ml of fresh CH_2Cl_2. The organic layers were combined and dried over $CaSO_4$ and stripped to dryness to form the amino ester.

The above procedure was repeated with L-alanine (Aldrich) to help determine if the enantiomeric excess was (R) or (S).



Scheme 4.2 Esterification of alanine

4.1.1.5 Analine Ethyl Ester Hydrochloride

In a further attempt to analyse the product from the hydrogenation of ethyl 2-iminopropanaote, the HCl was removed from analine ethyl ester hydrochloride. A small amount of the ester was dissolved in ethanol and a small amount of 10M K_2CO_3 was added. The solid formed was filtered off, and the solution analysed using both chiral GC and GC/MS methods. This was repeated using triethylamine, and butylamine.

Unfortunately, the production of the amine via other methods than hydrogenation of the imine, proved unsuccessful in helping to identify the parent imine from the hydrogenated product.

Further attempts to produce a cleaner form of this imine and to hydrogenate it, to produce a chiral amine, were unsuccessful. It was thought that the azide, produced as an intermediate product had similar retention time to the imine and amine. Therefore any excess azide masked the products (imine and amine). However, all attempts to improve the purity of the reaction were unsuccessful.

Similar problems were experienced when attempting to produce methyl 2-iminopropanoate. Analysis of the compound showed the azide was again being produced, but analysis of the imine was difficult. Hydrogenation did not show the amine, therefore it could not be said that the imine had been formed. Attempts to improve the imine preparation were again unsuccessful and further imines were investigated, see subsequent sections.

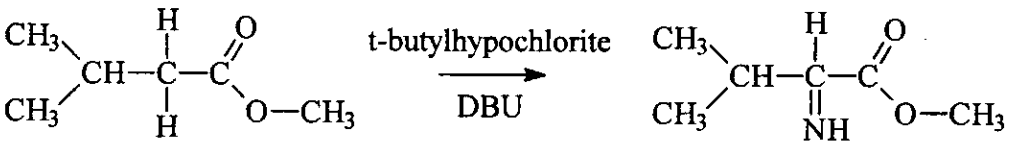
4.1.2 Preparation of Methyl 2-imino-3-methylbuterate

The method employed by H. Poisel *et al.* (Scheme 4.3) was used to prepare this imine. [73] In order to carry out this preparation *t*-butyl hypochlorite was first prepared. [74] A solution of 4.8 g of sodium hydroxide in 30 ml of water was prepared, and cooled to 15-20°C. 4.44 g of *tert*-butyl alcohol (BDH) was added together with enough water (approximately 30 ml) to form a homogeneous solution. Chlorine gas (Aldrich) was passed through the solution, with stirring, at approximately 1 l/min for 30 minutes, then for a further 30 minutes at a rate of 0.5 l/min. The upper oily layer was washed with 10 ml portions of 10% sodium carbonate (BDH) solution until the washings were no longer acidic to Congo red. The oily layer was washed a further four times with an equal quantity of water, and dried over calcium sulphate (anhydrous).

Valin methyl ester hydrochloride (Aldrich) was used. Therefore, the hydrochloride had first to be converted to the free ester. This was achieved by adding a 10 g of valin methyl ester hydrochloride to sodium methoxide; the precipitate (sodium chloride) formed was filtered through Celite, and the methanol removed by rotary evaporation.

To a solution of 2.62 g of valin methyl ester in 20 ml of ether, *t*-butyl hypochlorite was added drop wise with stirring. The solvent was removed *in vacuo*, leaving a colourless oil. The oil was dissolved in 60 ml of dry ethyl ether (BDH), 3.04 g of 1,5-diazabicyclo[5.4.0]undec-7-ene (DBU) (Aldrich) was added drop wise with vigorous stirring, continuing for 10 minutes after the addition of the DBU. The solid

formed was removed by filtration and the solution partially evaporated down in vacuum. Reduced pressure distillation yielded the product as a colourless oil.



Scheme 4.3 Preparation of methyl 2-imino-3-methyl buterate

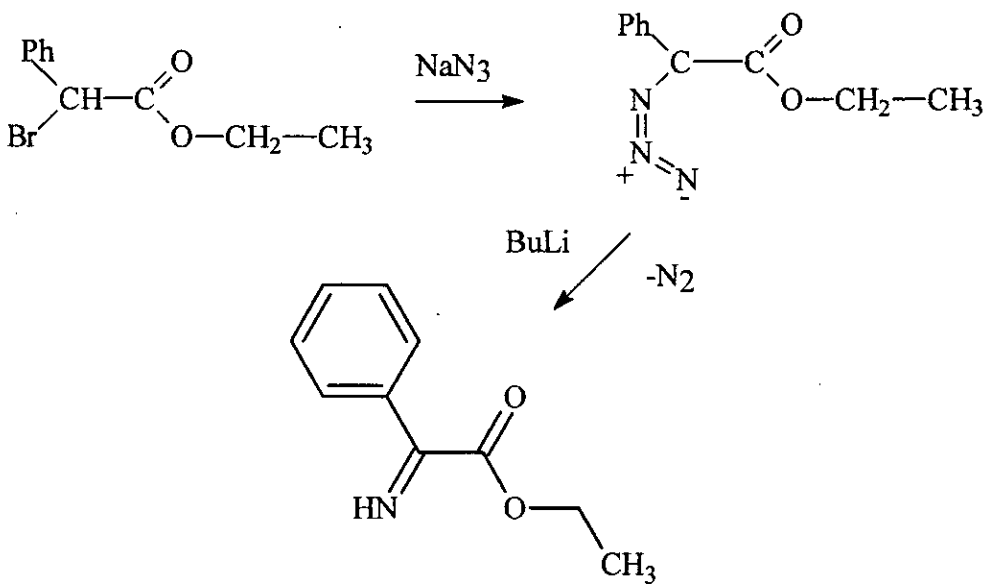
4.1.2.1 Success of Preparation of Methyl 2-imino-3-methyl buterate

It was hoped that this imine, still similar to the above imines discussed, would be more stable and could be prepared and hydrogenated successfully. Unfortunately the preparation of this imine was unsuccessful.

Reduced pressure distillation of the final solid formed after addition of the DBU should have yielded the product as a colourless oil. However, this final step was unsuccessful. Repetition of the experiment proved fruitless. It was thought that the imine was being produced in such small quantities that it was not being detected; unfortunately scaling up the quantities did not yield the imine.

4.1.3 Preparation of Ethyl 2-imino-3-phenylpropanoate

This was prepared using the adapted method of Manis *et al.* [71] Scheme 2.3. Benzyl 2-bromoacetate (13 ml, Aldrich) was added to a suspension of sodium azide (9.8 g), in 10 ml of DMF and stirred for 2.5 h. 40 ml of water was added, and the solution extracted with two 10 ml portions of dichloromethane. The combined organic layers were combined, washed with 40 ml of water, dried ($MgSO_4$) and concentrated in vacuo. Vacuum distillation afforded the azide, methyl 2-azido-3-phenylpropanoate. The following procedure was carried out under argon. Ethanol (0.5 ml) was added to *n*-butyl lithium in hexane (3.2 ml). The mixture was dissolved in 50 ml of carbon tetrachloride. The previously prepared azide (1.5 g) was added drop wise, and the mixture stirred until 50 mmol of N_2 was evolved.



Scheme 4.4 Preparation of ethyl 2-imino-3-phenylpropanoate

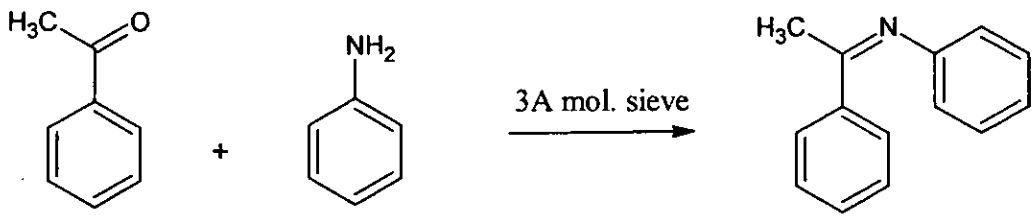
4.1.3.1 Success of Preparation of Ethyl 2-imino-3-phenylpropanoate

It was thought that preparation of this imine was successful and the larger molecular mass would make the compound slightly more stable. Initial analysis using GCMS was promising. However, initial yields had been disappointing and attempts to produce the imine in greater quantities, suitable for hydrogenation, were unsuccessful and the product obtained, even in low quantities, was impure.

4.1.4 Preparation of *N*-(1-phenylethylidene)aniline

It was decided that to produce a more stable imine, which would allow detailed analysis and catalytic hydrogenation, to investigate larger molecules. The preparation of this imine was attempted as it was thought the presence of the aromatic rings would stabilise the structure, literature also reported the successfully preparation of *N*-(1-phenylethylidene)aniline.

The general procedure of Schnider *et al.* was followed, [75] Scheme 4.5. To a solution of acetophenone (12.0 g, 100 mmol, Aldrich) and aniline (11.2 g, 120 mmol, Aldrich) in benzene (40 ml) were added 50 g 3 Å molecular sieve which had been activated using microwave irradiation. The mixture was stirred for 2 h at room temperature, before being filtered. The solvent was evaporated, distillation under vacuum afforded the imine as a yellow solid.



Scheme 4.5 Preparation of *N*-(1-phenylethylidene)aniline, using the procedure of Schnider *et al.*

An adaptation of the method of Gutherie *et al.* [76] using acetophenone and aniline was also carried out in an attempt to yield the above imine.

A mixture of acetophenone (24.2 g, Aldrich), aniline (21.4 g, Aldrich), and benzene (100 ml, May and Baker) was refluxed past a Dean-Stark trap for 12 h, in the presence of a catalyst. The catalyst was prepared by adding benzylamine (0.5 ml) to a mixture of 4 g of saturated aqueous zinc chloride and 2 ml of ethanol. The white precipitate formed was filtered and washed with ethanol.

After refluxing the mixture was filtered through Celite (Aldrich) and the benzene removed *in vacuo* to give a yellow oil. Pentane was added to yield imine, *N*-(1-phenylethylidene)aniline.

4.1.4.1 Success of Preparation of *N*-(1-phenylethylidene)aniline

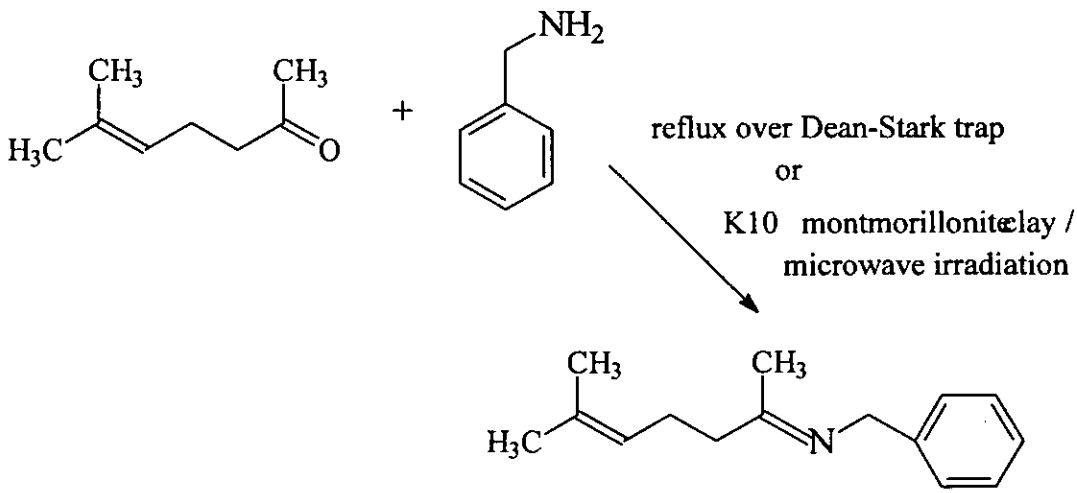
The method of Schnider *et al.* [75] was the more successful of the two methods attempted and the imine was yielded as a yellow oil (11 %). Analysis showed the imine to have been successfully prepared, but the reaction was not as 'clean' and many by-products had been produced.

An adaptation of the method of Gutherie *et al.* [76], which was also attempted for the production of this imine, with the hope of producing a 'cleaner' product, was unsuccessful. In this case the imine was not produced at all.

4.1.5 Preparation of *N*-(1,5-dimethylhex-5-enylidene)benzylamine

Preparation of this imine was again attempted using the above mentioned techniques, Scheme 4.6. Using the Willoughby method [47], 2.18 ml of benzylamine and 20 ml of 6-methyl-5-hepten-2-one were dissolved in dry THF (75 ml), and refluxed over a Dean-Stark trap (under nitrogen) for 72 hours. The solvent was removed *in vacuo*, and the imine purified by reduced pressure distillation.

An alternative approach for the synthesis of *N*-(1,5-dimethylhex-5-enylidene)benzylamine was used which involved the use of microwave radiation. Using the procedure of Varma *et al.* [77], 0.2 g of K10 Montmorillonite clay was added to benzylamine (1.07 g) and 6- methyl-5-hepten-2-one (1.26 g) the mixture was then irradiated in a microwave oven for 25 minutes. The imine was extracted using CH_2Cl_2 (3 x 50 ml), the solvent was then removed to yield the imine.



Scheme 4.6 Preparation of *N*-(1,5-dimethylhex-5-enylidene)benzylamine [47, 77]

4.1.5.1 Success of Preparation of *N*-(1,5-dimethylhex-5-enylidene) benzylamine

The second of the above methods attempted, Varma [77], was the more successful of the two. Neither method produced the imine at high percentage yields, but the Varma method involving microwave irradiation was the slightly more successful of the two methods (9.6 % yield opposed to 3.2 %), was much quicker to carry out and was the cleaner of the two reactions.

4.1.6 Preparation of *N*-(1-methylpentylidene)benzylamine

Using the general procedure of Willoughby and Buchwald [47], this imine was prepared. Benzylamine (3.25 ml) and 2-hexanone (3.7 ml) was refluxed in toluene over a Dean-Stark trap (under nitrogen) for 3 days. After this time, the solvent was removed, and the imine purified using reduced pressure distillation.

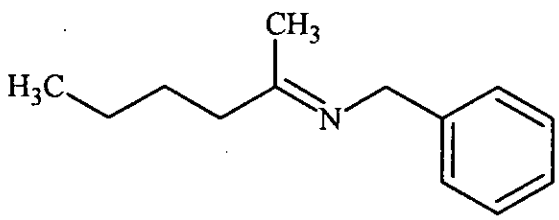


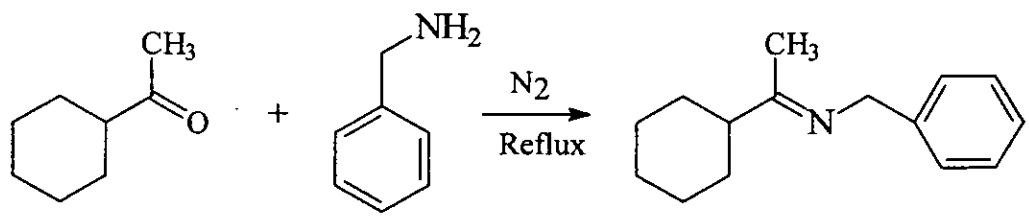
Figure 4.8 *N*-(1-methylpentylidene)benzylamine

4.1.6.1 Success of Preparation of *N*-(1-methylpentylidene)benzylamine

Unfortunately this preparation, again using the Willoughby method, was unsuccessful; the final step not yielding the purified imine. Repetition of the procedure did not yield the imine. It is thought the initial stage of refluxing under nitrogen for 3 days was unsuccessful and the imine was not produced in that stage.

4.1.7 Preparation of *N*-(1-cyclohexylethylidene)benzylamine

Preparation of this imine was attempted using the method of Riley *et al.* [34] Benzylamine (2.18 ml) and acetylcyclohexanone (2.76 ml) was dissolved in toluene, and refluxed over a Dean-Stark trap (under nitrogen) for 3 days. Removal of the solvent and purification of the product gave the desired imine, Scheme 4.7.



Scheme 4.7 Preparation of *N*-(1-cyclohexylethylidene)benzylamine

4.1.7.1 Success of Preparation of *N*-(1-cyclohexylethylidene)benzylamine

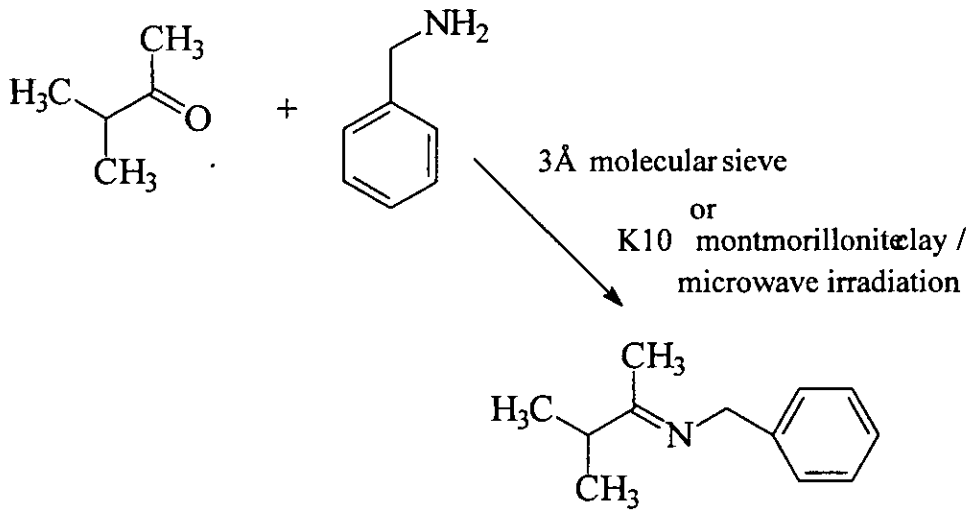
This imine was successfully prepared, as detailed above. Removal of the solvent and purification of the product gave the desired imine (identified with GCMS), Scheme 4.7. Unfortunately, the yield was very low (3.4 %), and despite several attempts it could not be improved upon and approximately 15 % of the imine was needed to permit hydrogenation.

4.1.8 Preparation of *N*-(1,2-dimethylpropylidene)benzylamine and *N*-(1,2-dimethylproplyidene)aniline

4.1.8.1 Preparation of *N*-(1,2-Dimethylpropylidene)benzylamine

Preparation of this imine was prepared using two different methods, (Scheme 4.8). Initially the method of Willoughby and Buchwald [47] was used. Benzylamine (Aldrich, 2.18 ml) and 3-methyl-2-butanone (Lancaster, 2.1 ml) was dissolved in 100 ml of benzene. The solution was stirred overnight with 10 g of activated 3Å molecular sieve (Lancaster). After this time the solvent was removed and the imine purified using low-pressure distillation techniques.

The second, and more successful preparation, was a variation on the method of Varma *et al.* [77] In an open glass container Montmorillonite K10 clay (0.2 g) was added to a mixture of benzylidene (Aldrich, 1.07 g) and 3-methyl-2-butanone (Lancaster, 0.86 g). The mixture was then irradiated in a microwave oven for 25 minutes, upon cooling; the product was extracted into dichloromethane (3 x 50 ml). The solvent was removed by rotary evaporation to yield the imine (21.4 %).

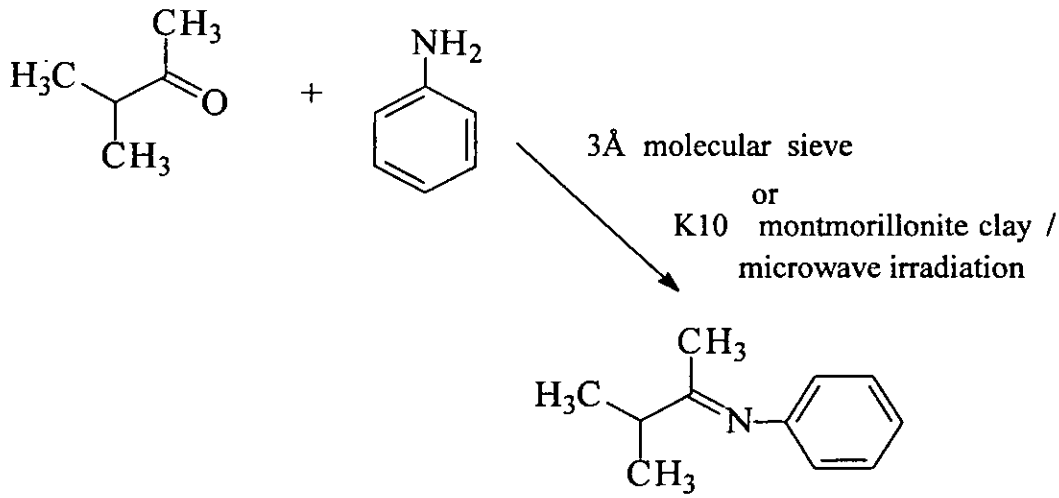


Scheme 4.8 Preparation of *N*-(1,2-Dimethylpropylidene)benzylamine

4.1.8.2 Preparation of *N*-(1,2-Dimethylpropylidene)aniline

This imine was prepared in the same way as above, using both the Willoughby [47] and Varma [77] methods, again the Varma proved the more successful and was used for subsequent syntheses.

In an open glass container Montmorillonite K10 clay (0.2 g) was added to a mixture of aniline (Aldrich, 0.93 g) and 3-methyl-2-butanone (0.86 g). The mixture was then irradiated in a microwave oven for 25 minutes, the product was extracted into dichloromethane (3 x 50 ml). The solvent was removed by rotary evaporation to yield the imine (21.4 %), Scheme 4.9



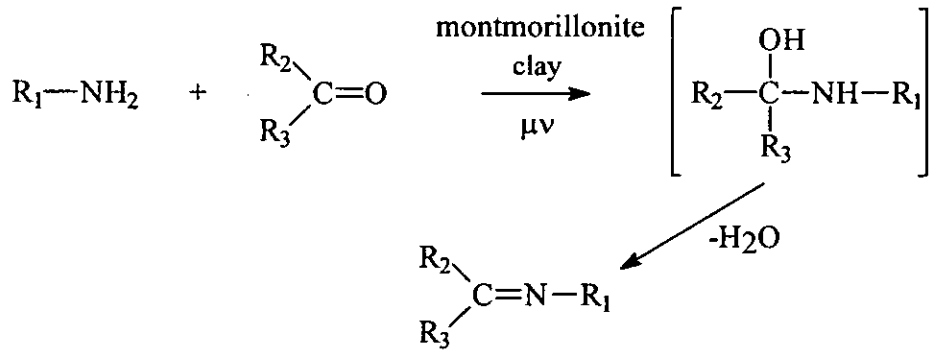
Scheme 4.9 Preparation of *N*-(1,2-Dimethylpropylidene)aniline

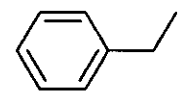
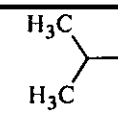
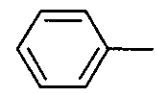
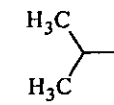
4.1.8.3 Success of Preparation of *N*-(1,2-dimethylpropylidene)benzylamine and *N*-(1,2-dimethylproplyidene)aniline

The preparation of these imines was successful, the preparation of *N*-(1,2-dimethylproplyidene)aniline being the more successful of the two and the imine chosen to study in greatest detail.

The Varma method produced the largest percentage conversion of the starting products to the required imine (21.4 % for *N*-(1,2-dimethylpropylidene)aniline and 17.6 % for *N*-(1,2-dimethylproplyidene)benzylamine). This method was also found to be the quickest and cleanest method.

The Varma synthesis, involving the condensation reaction of aldehydes with primary amines, (Scheme 4.10) was therefore used to prepare the above imines for hydrogenation



Imine	R_1	R_2	R_3
N-(1,2-dimethylpropylidene)benzylamine		$-CH_3$	
N-(1,2-dimethylproplyidene)aniline (B).		$-CH_3$	

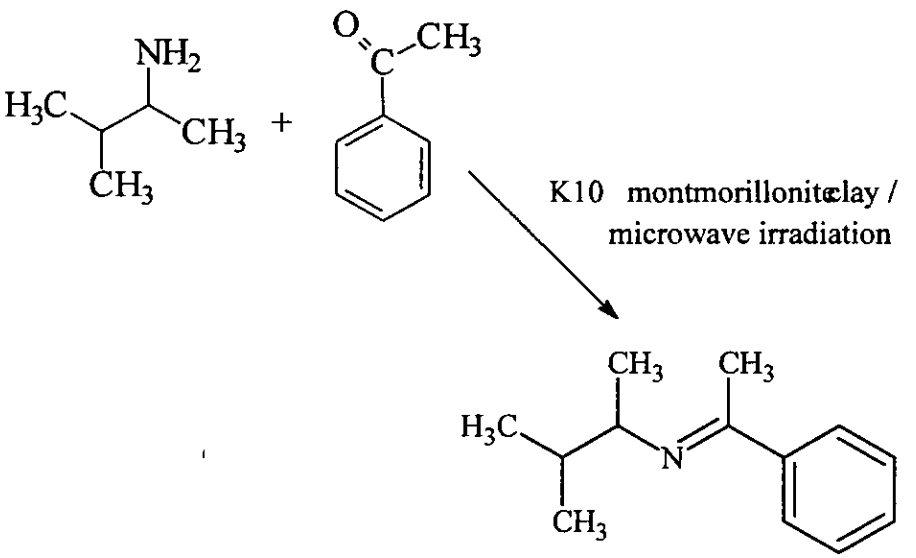
Scheme 4.10 Imine synthesis using method of Varma *et al.* [77]

4.1.9 Preparation of *N*-(1-methylbenzylidene)-2,3-dimethylbutylamine

This imine was prepared as a comparison to *N*-(1,2-dimethylpropylidene)aniline; the aromatic group being next to the carbon and the alkyl next to the nitrogen in this imine (the opposite to *N*-(1,2-dimethylpropylidene)aniline). It was synthesised using an adaptation of the Varma [77] method mentioned above.

In an open glass container Montmorillonite K10 clay (0.2 g) was added to a mixture of 1,2 dimethylpropylamine (Lancaster, 0.87 g) and acetophenone (Aldrich, 1.20 g). The mixture was then irradiated in a microwave oven for 25 minutes, the product

was extracted into dichloromethane (3 x 50 ml). The solvent was removed by rotary evaporation to yield the imine, Scheme 4.11



Scheme 4.11 Preparation of *N*-(1-methylbenzylidene)-2,3-dimethylbutylamine

4.1.9.1 Success of Preparation of *N*-(1-methylbenzylidene)-2,3-dimethyl-butylamine

Preparation of this imine using the Varma method, was again successful. Yields were lower than those for *N*-(1,2-dimethylproplyidene)aniline, being only 15.6 % and although this imine was hydrogenated, studies with this imine were limited, due to time constraints.

4.1.10 Preparation of *N*-(α-methylbenzylidene)benzylamine

Several methods of synthesising the imine, *N*-(α-methylbenzylidene)benzylamine were investigated. [76,78,79] The most successful method was found to be that of Gutherie *et al.* [76] (Scheme 4.12). This method has been used as the standard method of synthesising this imine.

A mixture of acetophenone (24.2 g, Aldrich), benzylamine (21.4 g, Aldrich), and benzene (100 ml, May and Baker) was refluxed past a Dean-Stark trap for 12 h, in the presence of a catalyst. The catalyst was prepared by adding benzylamine (0.5 ml) to a mixture of 4 g of saturated aqueous zinc chloride and 2 ml of ethanol. The white precipitate formed was filtered and washed with ethanol.

After refluxing the mixture was filtered through Celite (Aldrich) and the benzene removed *in vacuo* to give a yellow oil. Pentane was added to yield white crystals, recrystallisation in pentane gave *N*-(α-Methylbenylidene)benzylamine.

Scheme 4.12 Preparation of *N*-(α-Methylbenzylidene)benzylamine

4.1.10.1 Success of Preparation of *N*-(α-Methylbenzylidene)benzylamine

Preparation of this imine was the most successful of all those attempted. The method of Gutherie *et al.* [76] being the most successful, giving high yields of 86.7 %. NMR analysis (Figure 4.9) of the imine showed the compound to be pure and we were able to keep the imine for several days in the fridge before decomposition occurred.

Other methods attempted either gave very low yields in comparison or did not produce the imine; the Varma method [77], so successful in preparing other imines attempted, did produce the imine but the reaction was very 'unclean' and yields were low (4.7 %).

Unfortunately, problems were encountered during the analysis of the produced amine. Attempts were made using both chiral GC columns and chiral HPLC columns, but the enantiomers could not be separated and as a result this imine was not studied in any detail.

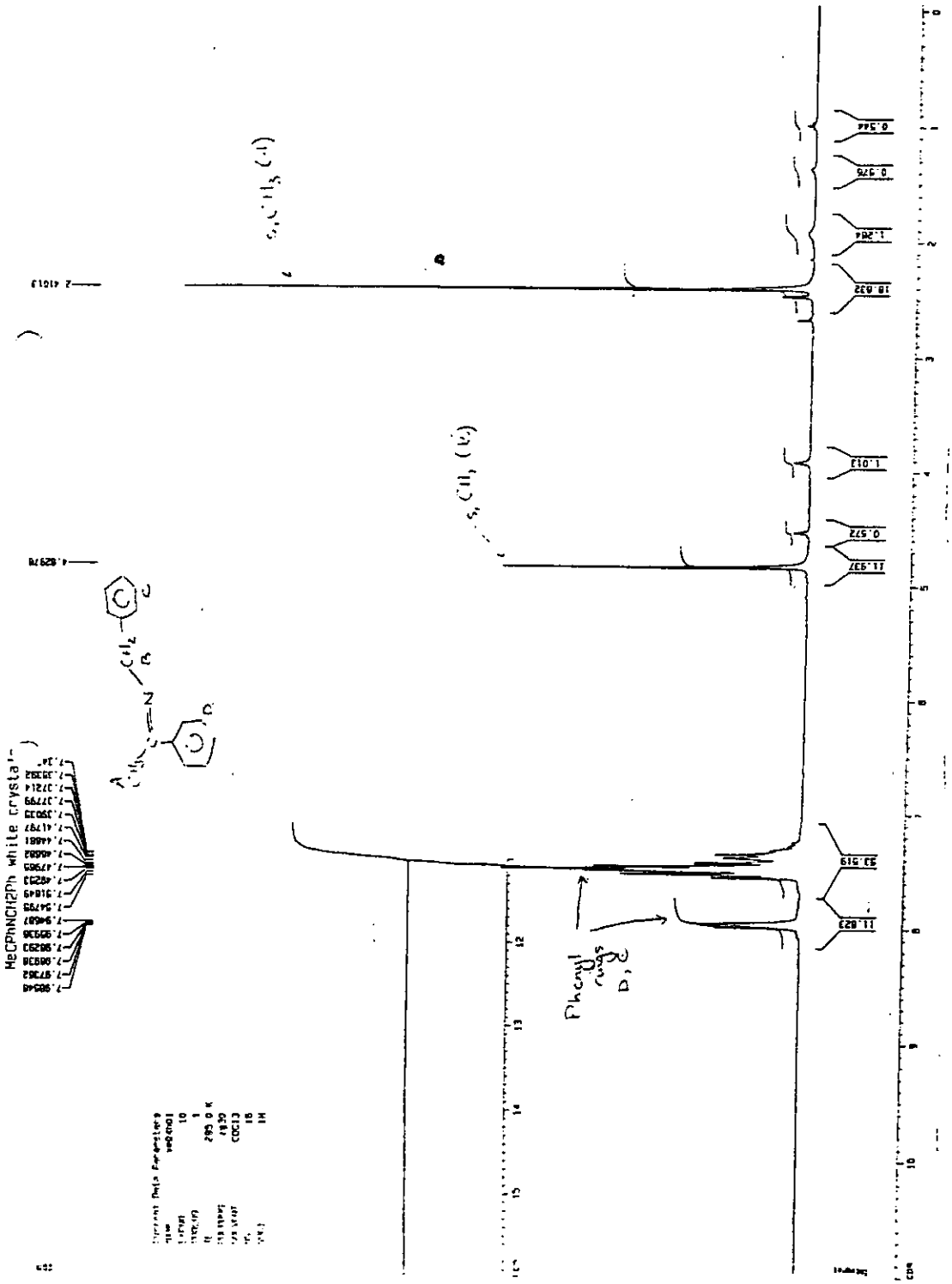


Figure 4.9 NMR analysis of *N*-(α-methylbenzylidene)benzylamine

4.2 Heterogeneous Hydrogenation of Prochiral Imines

The main aim of this study was to investigate the enantioselective hydrogenation of prochiral imines. It was initial hoped that imines with similar structures to those of methyl and ethyl pyruvate could be hydrogenated using the 5 % Pt/alumina system. However, several problems were encountered in the preparation of these imines (Section 4.1). It was therefore decided to investigate the hydrogenation of imines which could be synthesised successfully. Those which were successful were hydrogenated with a series of catalysts, both homogeneous and heterogeneous, the selected imines were prepared as detailed in Section 4.1.

This section deals with the hydrogenation with heterogeneous catalysts, homogeneous and supported homogeneous catalysts tested will be discussed in later chapters.

4.2.1 Catalyst Pre-treatment

Heterogeneous catalysts (supplied by Johnson Mathey) were used both un-modified and modified with cinchona alkaloids. In the case of modified catalysts the following procedure was used; 0.05 g samples of the catalyst were reduced (523 K) under flowing hydrogen at ambient pressure for 1 h. Once cooled to room temperature, a solution of 0.5 g cinchona alkaloid in 25 ml of ethanol was injected onto the reduced catalyst, prior to exposure to air. This suspension was then stirred in an open container for 1 h, the alkaloid solution decanted off and the modified catalyst transferred to the autoclave liner. To this were added approximately 5 mmol

of imine (accurately weighed) and 25 ml of the solvent, absolute ethanol. In hydrogenation experiments using no modifier, the catalyst was treated identically, with the exception of being stirred in an open container for 1 h with the solvent, instead of an alkaloid solution.

The initial rate of the reaction, the percentage conversion and the enantiomeric excess (where applicable) were used to determine the effectiveness of each catalyst for the different imines. Enantiomeric excess and percentage conversion were determined using a gas chromatograph fitted with a chiral capillary column, see Section 2.2.

4.2.2 Hydrogenation of *N*-(1,2-Dimethylpropylidene)aniline

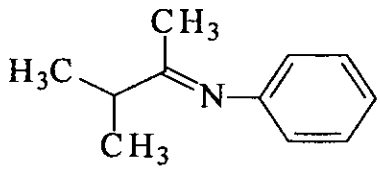


Figure 4.10 *N*-(1,2-Dimethylpropylidene)aniline

This imine was comprehensively investigated using heterogeneous, homogeneous and supported homogeneous catalysts. Three modified heterogeneous catalysts were chosen for hydrogenation with the imine: 5% Pt/alumina modified with cinchona alkaloids was chosen as a comparison to the methyl pyruvate system already tested and discussed (Chapter 3), 5% Rh/alumina and 5% Ir/alumina, both modified with cinchona alkaloids, were chosen as heterogeneous catalysts with the same metal ions as homogeneous catalysts tested. The use of 5% catalysts in the case of the rhodium

and iridium heterogeneous catalysts enabled comparison with the 5% Pt/alumina system studied. All supported metal catalysts were commercially produced (Johnson Mathey).

In each case approximately 10 mmol of imine was used in the reaction.

Homogenous and supported homogeneous catalysts tested for their effectiveness with this imine are discussed in Chapter 6.

Table 4.1 Heterogeneous catalyst identification for the hydrogenation of *N*-(1,2-Dimethylpropylidene)aniline

Catalyst	Composition
5%Pt/alumina	5% platinum catalyst supported on alumina, no modifier
5%Pt/alumina/CD	5% platinum catalyst supported on alumina, cinchonidine modifier
5%Pt/alumina/CN	5% platinum catalyst supported on alumina, cinchonine modifier
5%Rh/alumina	5% rhodium catalyst supported on alumina, no modifier
5%Rh/alumina/CD	5% rhodium catalyst supported on alumina, cinchonidine modifier
5%Rh/alumina/CN	5% rhodium catalyst supported on alumina, cinchonine modifier
5%Ir/alumina	5% iridium catalyst supported on alumina, no modifier
5%Ir/alumina/CD	5% iridium catalyst supported on alumina, cinchonidine modifier
5%Ir/alumina/CN	5% iridium catalyst supported on alumina, cinchonine modifier

4.2.2.1 Hydrogenation Results

Table 4.2 Hydrogenation of *N*-(1,2-Dimethylpropylidene)aniline with all catalysts and modifiers

Catalyst	Modifier	Initial Rate / mmol h^{-1}	e.e. / %	Conversion / %
5% Pt/alumina	CD	44.0	2.3	27.0
5% Pt/alumina	CN	56.0	1.0	11.6
5% Pt/alumina	None	52.3	0	7.3
5% Rh/alumina	CD	37.5	0.4	30.2
5% Rh/alumina	CN	56.7	6.7	27.9
5% Rh/alumina	None	51.0	0	29.8
5% Ir/alumina	CD	49.5	1.4	44.8
5% Ir/alumina	CN	52.0	0.2	55.0
5% Ir/alumina	None	43.5	0	62.2

CD = catalyst modified with Cinchonidine
CN = catalyst modified with Cinchonine
None = un-modified catalyst

As can be seen from the above table, all the initial rates of reaction are similar to the pyruvate system. However, the enantiomeric excess in all the reactions studied were very disappointing with all the modified catalyst having an e.e. of close to zero. The most promising of the catalyst was 5% Rh/alumina modified with cinchonine which showed the highest enantiomeric excess and initial rate. However, this e.e. is still very low (6.7 %) and but the initial rate is comparable to that seen in the pyruvate system.

The graphs below show the rate of reaction of each catalyst when modified with cinchona alkaloid and when unmodified. The activity of each catalyst was assessed by means of comparing the initial rate of reaction, enantiomeric excess (e.e.) and conversion, Table 4.2

4.2.2.2 Hydrogenation of *N*-(1,2-Dimethylpropylidene)aniline with 5% Pt/Alumina

Table 4.3 Hydrogenation of *N*-(1,2-Dimethylpropylidene)aniline with 5% Pt/Alumina

Catalyst	Modifier	Initial Rate / mmol h^{-1}	e.e. / %	Conversion / %
5% Pt/alumina	CD	44.0	2.3	27.0
5% Pt/alumina	CN	56.0	1.0	11.6
5% Pt/alumina	None	52.3	0	7.3

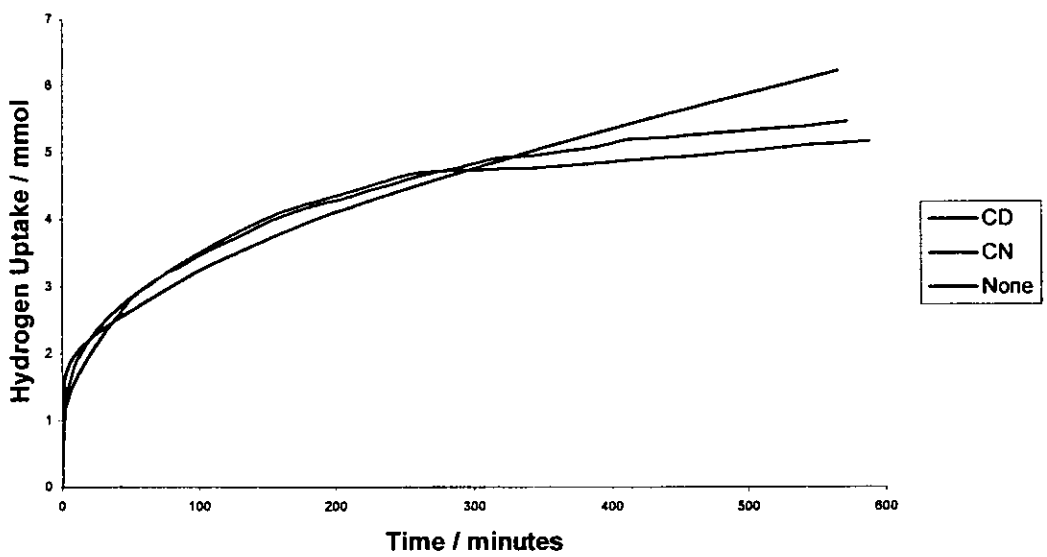


Figure 4.11 Hydrogenation of *N*-(1,2-Dimethylpropylidene)aniline with 5% Pt/alumina

The initial rate of reaction in all cases was very encouraging, with rates of reaction similar to those seen with 5% Pt/alumina for the methyl pyruvate system. However, these rates quickly ease off and on analysis the enantiomeric excess and the percentage conversion were very disappointing.

The cinchonidine modified catalyst showed the greatest e.e. (2.3 %) and percentage conversion (27.0 %) but these were still very low. The enantiomeric excess for both modifiers was practically zero, making the product racemic.

4.2.2.3 Hydrogenation of *N*-(1,2-Dimethylpropylidene)aniline with 5% Rh/Alumina

Table 4.4 Hydrogenation of *N*-(1,2-Dimethylpropylidene)aniline with 5% Rh/Alumina

Catalyst	Modifier	Initial Rate / mmol h^{-1}	e.e. / %	Conversion / %
5% Rh/alumina	CD	37.5	0.4	30.2
5% Rh/alumina	CN	56.7	6.7	27.9
5% Rh/alumina	None	51.0	0	29.8

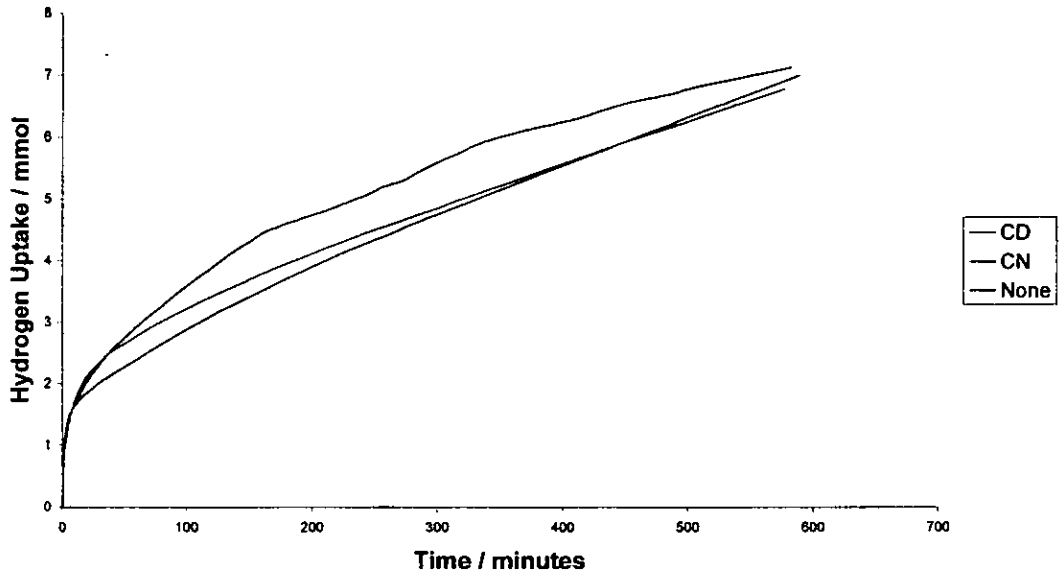


Figure 4.12 Hydrogenation of *N*-(1,2-Dimethylpropylidene)aniline with 5% Rh/Alumina

Again the initial reaction rate was promising, but the enantiomeric excess and percentage conversion were very disappointing. The 5% Rh/alumina catalyst modified with cinchonine did, however, show the highest e.e. for this set of reactions (6.7 %); it is still not comparable to the enantiomeric excesses accomplished with the pyruvate system. Percentage conversion was also low, despite being greater than that for the 5% Pt/alumina catalysts.

These low enantiomeric excesses and percentage conversions have also been attributed to the reasons explained above. The size and shape of the imine molecule makes absorption onto the catalysts surface, when modified very difficult. The propyl group blocking the pro-chiral centre also hinders the hydrogenation reaction, Figure 4.13.

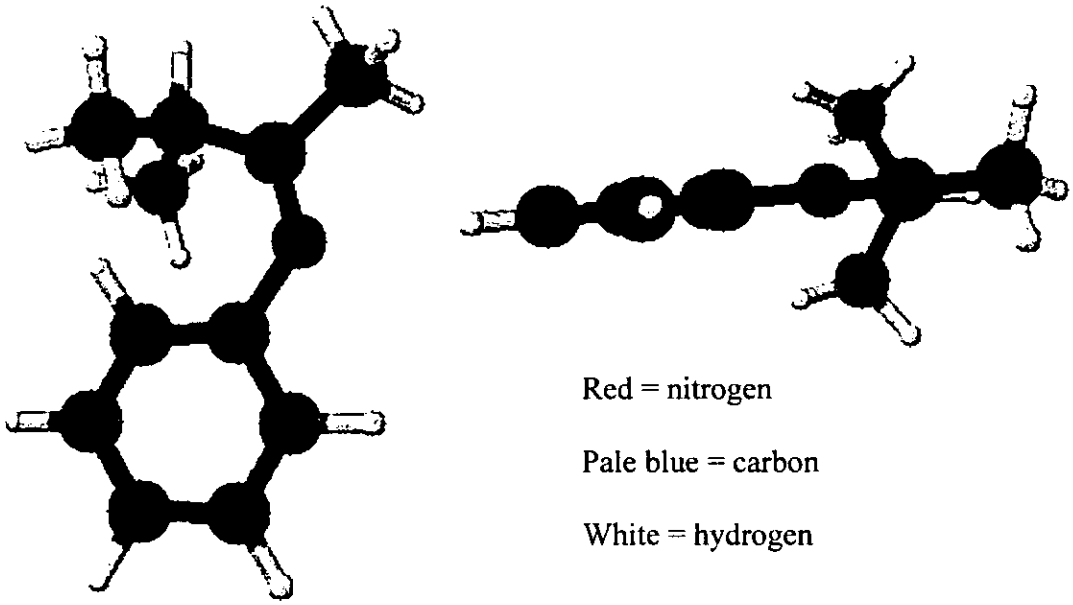


Figure 4.13 3D image of *N*-(1,2-Dimethylpropylidene)aniline, from different perspectives.

4.2.2.4 Hydrogenation of *N*-(1,2-Dimethylpropylidene)aniline with 5% Ir/Alumina

Table 4.5 Hydrogenation of *N*-(1,2-Dimethylpropylidene)aniline with 5% Ir/Alumina

Catalyst	Modifier	Initial Rate / mmol h^{-1}	e.e. / %	Conversion / %
5% Ir/alumina	CD	49.5	1.4	44.8
5% Ir/alumina	CN	52.0	0.2	55.0
5% Ir/alumina	None	43.5	0	62.2

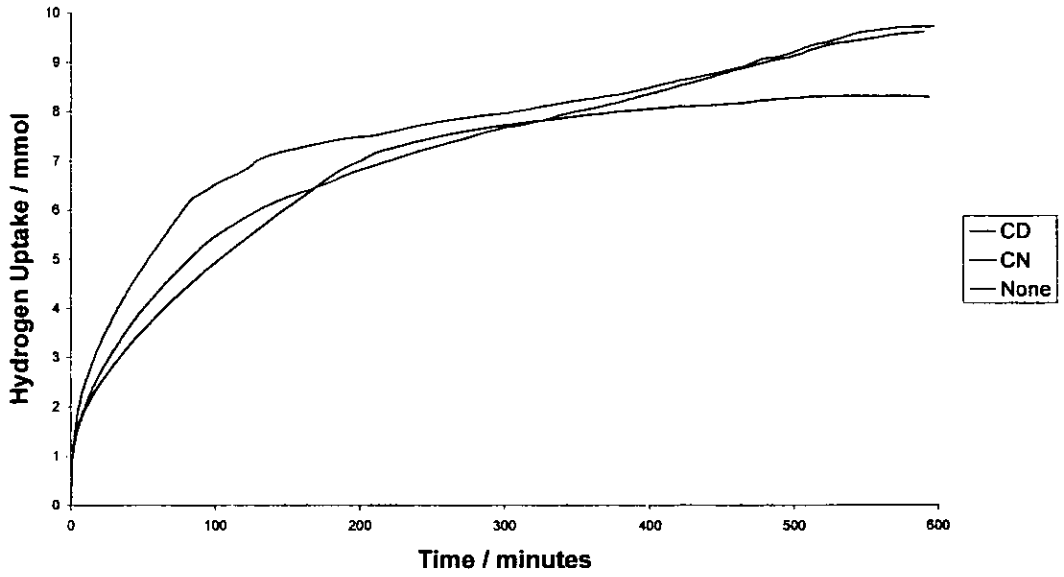


Figure 4.14 Hydrogenation of *N*-(1,2-Dimethylpropylidene)aniline with 5% Ir/Alumina

The 5% Ir/alumina showed good initial reaction rates which were comparable to the other catalysts tested. However, the percentage conversion for this catalyst was the greatest, despite having a very low enantiomeric excess; 1.4 % for cinchonidine being the highest recorded.

4.2.2.5 Discussion

For all the heterogeneous catalysts tested with this imine, it is thought that the size and shape of the reactant hindered the ability of the modifier to promote the production of any one enantiomer, resulting in the production of a racemic mixture each time.

Using the template model suggested by Wells and co-workers [11,21] the size of the pro-chiral imine in this case inhibits its absorption onto the platinum surface, but it is further hindered by its stereochemistry, Figures 4.15 and 4.16

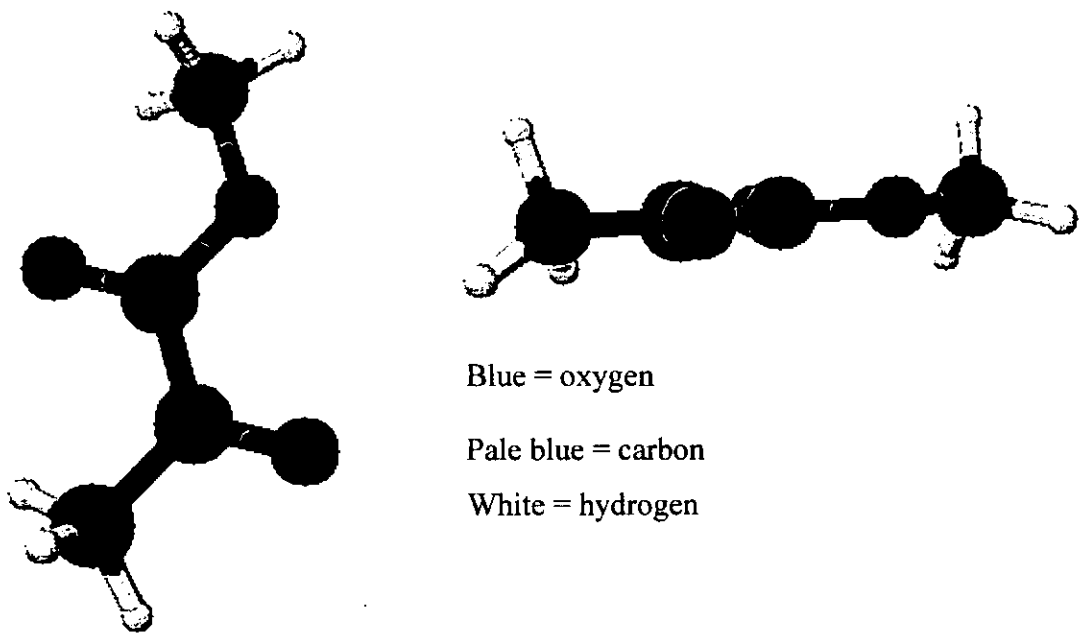


Figure 4.15 3D representation of Methyl Pyruvate, shown from above and on the level as it would absorb onto the platinum surface of the catalyst.

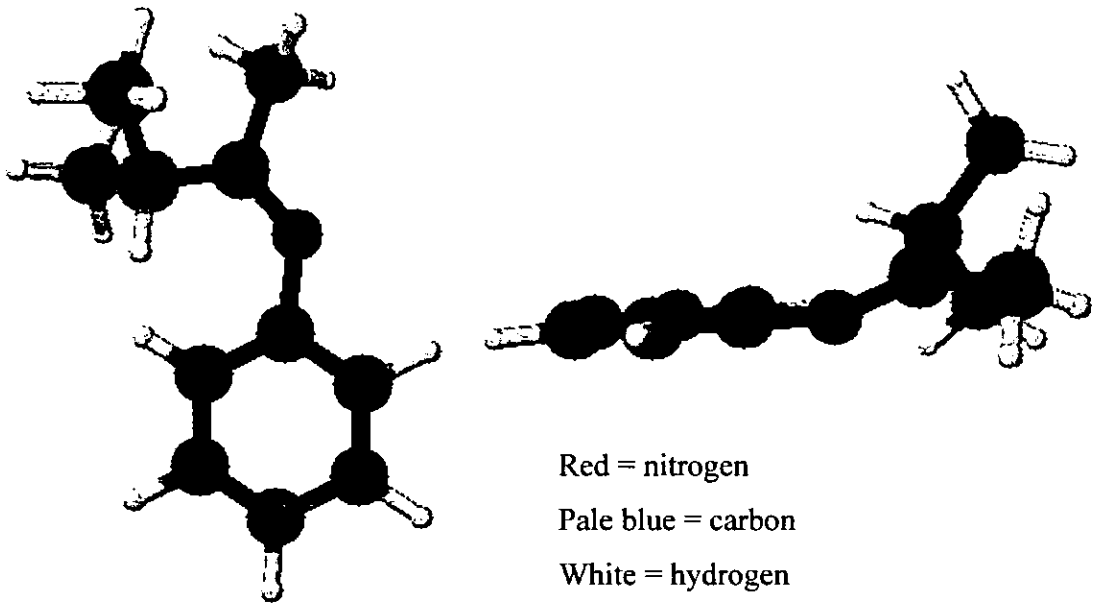


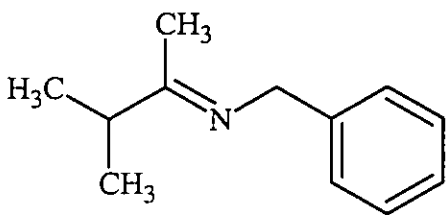
Figure 4.16 3D representation of *N*-(1,2-Dimethylpropylidene)aniline shown from above and on level as it would absorb onto the platinum surface.

As can be seen from the above representations of the reactant the presence of the benzene ring means the size of the molecule is much bigger than that of methyl pyruvate and as such absorption onto the modified platinum surface would be very difficult. The hydrogenation site (the nitrogen atom in red) is also blocked to some extent by the propyl group if the compound is absorbed onto the platinum surface in this way. This will also hinder the conversion from the imine to the amine, explaining the low conversion in the case of an un-modified catalyst.

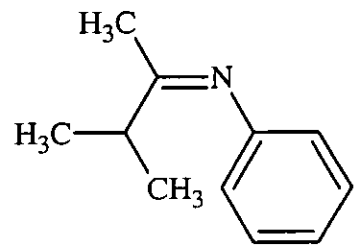
It is thought that this will also be the case for the rhodium and iridium heterogeneous catalysts, as the metal will not significantly alter how the modifier and imine absorb onto it.

4.2.3 Hydrogenation of *N*-(1,2-Dimethylpropylidene)benzylamine

The hydrogenation studies on *N*-(1,2-dimethylpropylidene)benzylamine were very limited, since the yield from the reaction to produce the imine was lower than that for other imines (17.6 %) and time constraints were an issue. This imine was only hydrogenated heterogeneously with one catalyst; the imine was hydrogenated with an un-modified 5% Pt/alumina catalyst, to provide a comparison to *N*-(1,2-dimethylpropylidene)aniline.



A



B

Figure 4.17 *N*-(1,2-dimethylpropylidene)benzylamine (A) and *N*-(1,2-dimethyl propylidene)aniline (B).

Table 4.6 Hydrogenation of *N*-(1,2-dimethylpropylidene)benzylamine, compared to *N*-(1,2-dimethylpropylidene)aniline, hydrogenated with un-modified 5% Pt/alumina.

Imine	Initial Rate / mmol h^{-1}	e.e. / %	Conversion / %
Aniline imine	52.3	0	7.3
Benzylamine imine	56.5	0	5.8

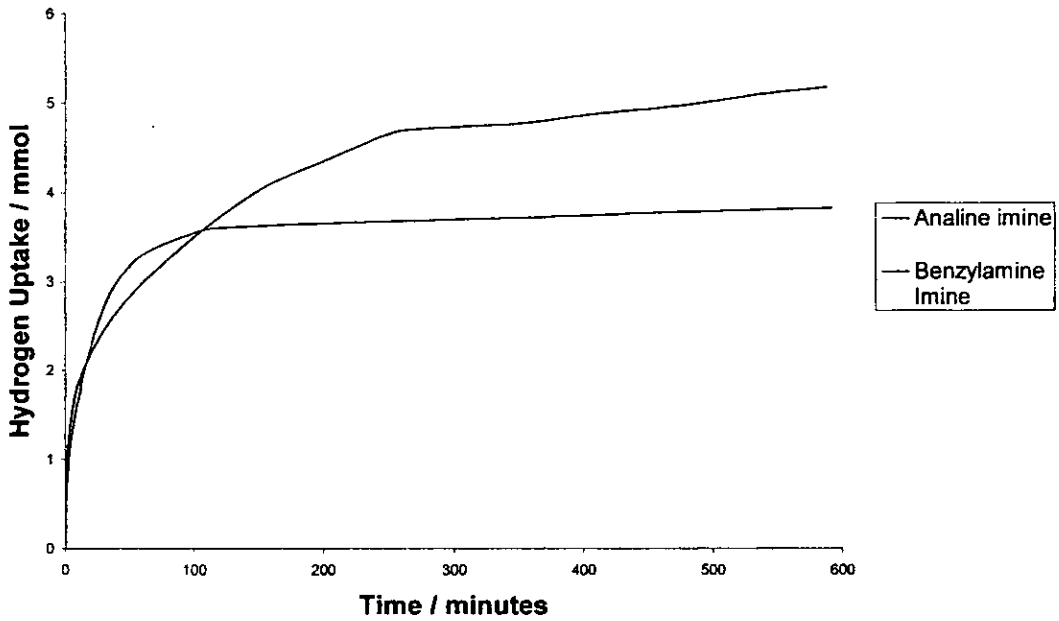


Figure 4.18 Comparison of hydrogenation of *N*-(1,2 dimethylpropylidene) benzylamine and *N*-(1,2-dimethylpropylidene)aniline, with un-modified 5% Pt/alumina.

Analine Imine = *N*-(1,2-dimethylpropylidene)aniline
Benzylamine imine = *N*-(1,2-dimethylpropylidene)benzylamine

As can be seen from Table 4.6 and Figure 4.18, the results from this hydrogenation were very disappointing. Despite having a slightly higher initial rate (56.5 mmol h^{-1}) the benzylamine imine did not have as high a conversion to that of the analine imine. However, the difference in the conversions is small, suggesting that this imine give similar results to those of the *N*-(1,2-dimethylpropylidene)aniline with the different heterogeneous catalysts tested.

The presence of the CH_2 group between the ring and the C=N suggests that the propyl group, which was thought to hinder the hydrogenation of the C=N in *N*-(1,2-dimethylpropylidene)aniline (Section 4.2.2), may not hinder the hydrogenation of the

double bond in the case of *N*-(1,2-dimethylpropylidene)benzylamine. 3D modelling (Figure 4.19) also shows that the molecule may adsorb onto the metal surface in such a way as the molecule would lie 'flat'. Using the template model of Wells [21] this would suggest that the hydrogenation of the double may be easier and that selectivity may be higher than that seen with *N*-(1,2-dimethylpropylidene)aniline.

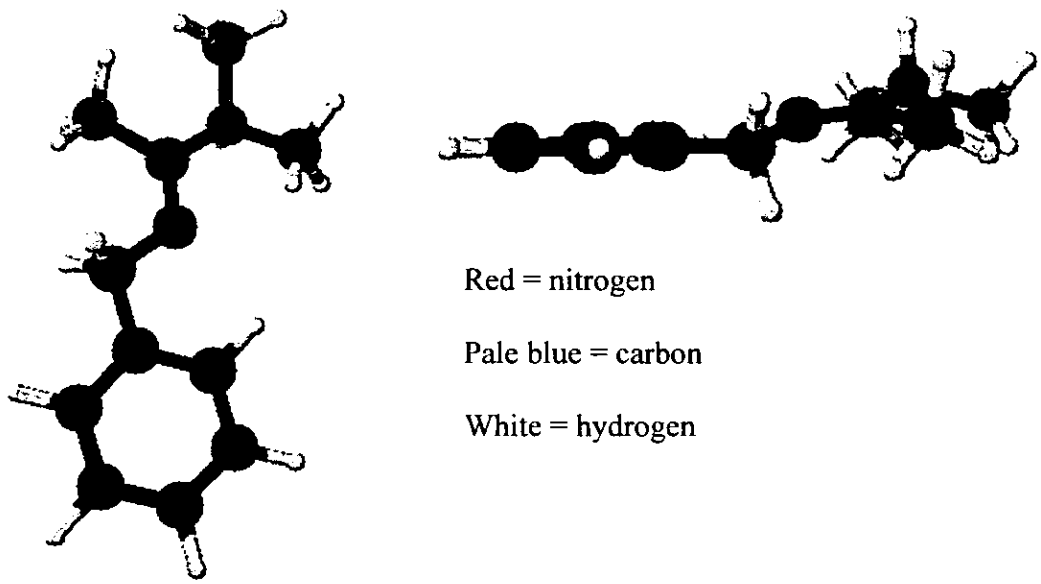


Figure 4.19 3D modelling of *N*-(1,2-dimethylpropylidene)benzylamine

Time limitations meant that this imine was studied no further with heterogeneous catalysts. Further studies involving this imine should start with a continuation of its hydrogenation in the presence of a modified 5 % platinum catalyst, before hydrogenation with the other heterogeneous catalysts investigated for *N*-(1,2-Dimethylpropylidene)aniline.

4.2.4 Hydrogenation of *N*-(1-methylbenzylidene)-2,3-dimethylbutylamine

As previously mentioned (Section 4.1.9), this imine was made as a comparison to *N*-(1-methylbenzylidene)aniline; the alkyl and aromatic ring being on different sides of the nitrogen. Although it was not studied as comprehensively as its partner imine it was heterogeneously hydrogenated with 5% Pt/alumina, 5% Rh/alumina and 5% Ir/alumina modified with cinchonidine and in the unmodified state.

Since the yield for this imine was low, the preparation was scaled up to increase the imine present in the hydrogenation reaction. As a result, in this set of reactions approximately 30 mmol of imine was used for each reaction.

Table 5.7 Catalyst identification for the hydrogenation of *N*-(1methylbenzylidene)-2,3-dimethylbutylamine

Catalyst	Composition
5%Pt/alumina	5% platinum catalyst supported on alumina, no modifier
5%Pt/alumina/CD	5% platinum catalyst supported on alumina, cinchonidine modifier
5%Rh/alumina	5% rhodium catalyst supported on alumina, no modifier
5%Rh/alumina/CD	5% rhodium catalyst supported on alumina, cinchonidine modifier
5%Ir/alumina	5% iridium catalyst supported on alumina, no modifier
5%Ir/alumina/CD	5% iridium catalyst supported on alumina, cinchonidine modifier

4.2.4.1 Results and Discussion

Table 5.8 Hydrogenation of *N*-(1methylbenzylidene)-2,3-dimethylbutylamine with all catalysts and modifiers

Catalyst	Modifier	Initial Rate / mmol h^{-1}	e.e. / %	Conversion / %
5% Pt/alumina	CD	60.7	1.1	79.6
5% Pt/alumina	None	56.7	0	81.0
5% Rh/alumina	CD	50.0	2.0	73.7
5% Rh/alumina	None	60.0	0	76.4
5% Ir/alumina	CD	60.0	0.4	48.9
5% Ir/alumina	None	64.9	0	56.4

As can be seen from Table 4.8 the initial rates and percentage conversions for this catalyst were very good indeed. However, the enantiomeric excesses were very low, near 0 %, almost racemic. The un-modified catalysts seem to show the better rates of conversion for those catalysts tested.

4.2.4.2 Hydrogenation of *N*-(1methylbenzylidene)-2,3-dimethylbutylamine with 5% Pt/alumina

Table 4.9 Hydrogenation of *N*-(1methylbenzylidene)-2,3-dimethylbutylamine with 5% Pt/alumina

Catalyst	Modifier	Initial Rate / mmol h^{-1}	e.e. / %	Conversion / %
5% Pt/alumina	CD	60.7	1.1	79.6
5% Pt/alumina	None	56.7	0	81.0

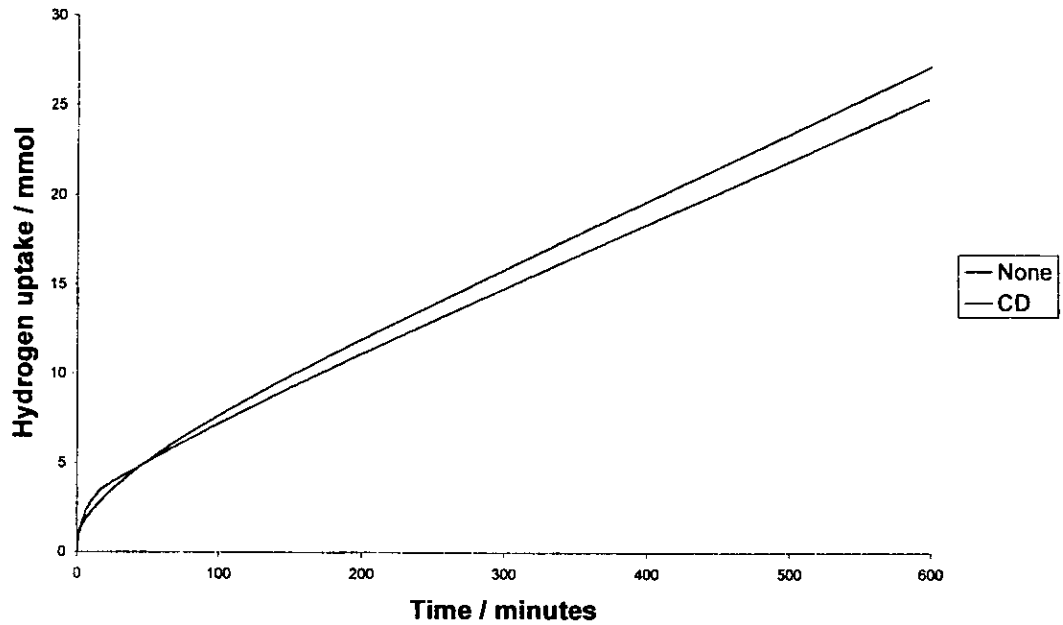


Figure 4.20 Hydrogenation of *N*-(1methylbenzylidene)-2,3-dimethylbutylamine with 5% Pt/alumina

As can be seen from Table 4.9 and Figure 4.20 the high initial rate of reaction with the modified catalyst is not maintained for as long as that for the un-modified catalyst. Both reactions lead to similar high yields, but in the case of the modified reaction, very low enantiomeric excess.

4.2.4.3 Hydrogenation of *N*-(1methylbenzylidene)-2,3-dimethylbutylamine with 5% Rh/alumina

Table 4.10 Hydrogenation of *N*-(1methylbenzylidene)-2,3-dimethylbutylamine with 5% Rh/alumina

Catalyst	Modifier	Initial Rate / mmol h^{-1}	e.e. / %	Conversion / %
5% Rh/alumina	CD	50.0	2.0	73.7
5% Rh/alumina	None	60.0	0	76.4

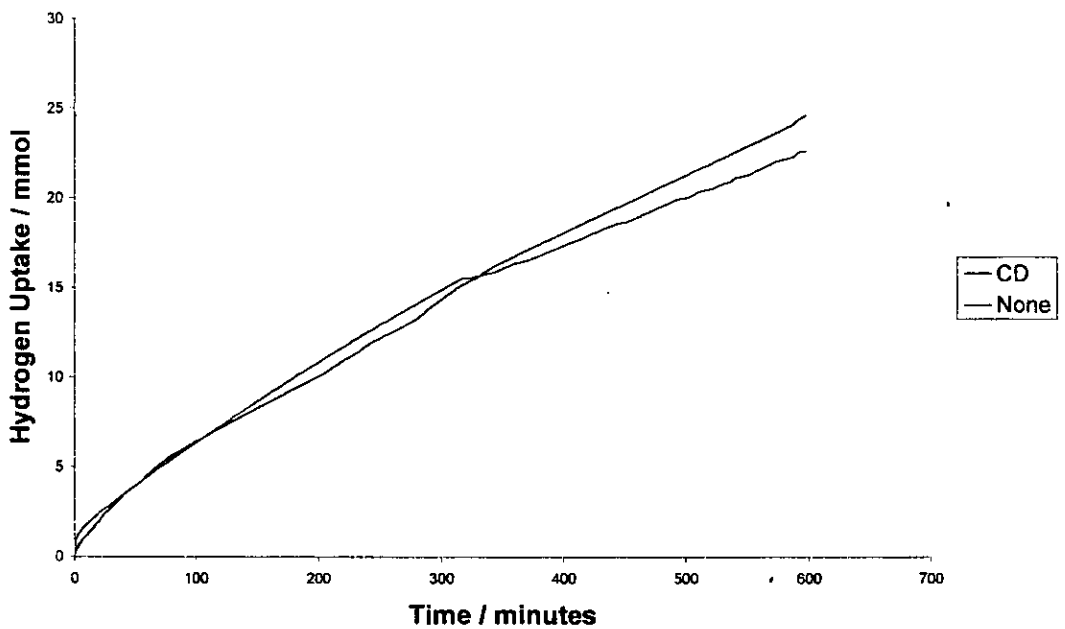


Figure 4.21 Hydrogenation of *N*-(1methylbenzylidene)-2,3-dimethylbutylamine with 5% Rh/alumina

As with the platinum catalysts we are seeing good initial rates of reaction and relatively high percentage conversion of the pro-chiral imine to chiral amine. Again, unfortunately, the mixture of enantiomers for the modified reaction is almost racemic.

4.2.4.4 Hydrogenation of *N*-(1methylbenzylidene)-2,3-dimethylbutylamine with 5% Ir/alumina

Table 4.11 Hydrogenation of *N*-(1methylbenzylidene)-2,3-dimethylbutylamine with 5% Ir/alumina

Catalyst	Modifier	Initial Rate / mmol h^{-1}	e.e. / %	Conversion / %
5% Ir/alumina	CD	60.0	0.4	48.9
5% Ir/alumina	None	64.9	0	56.4

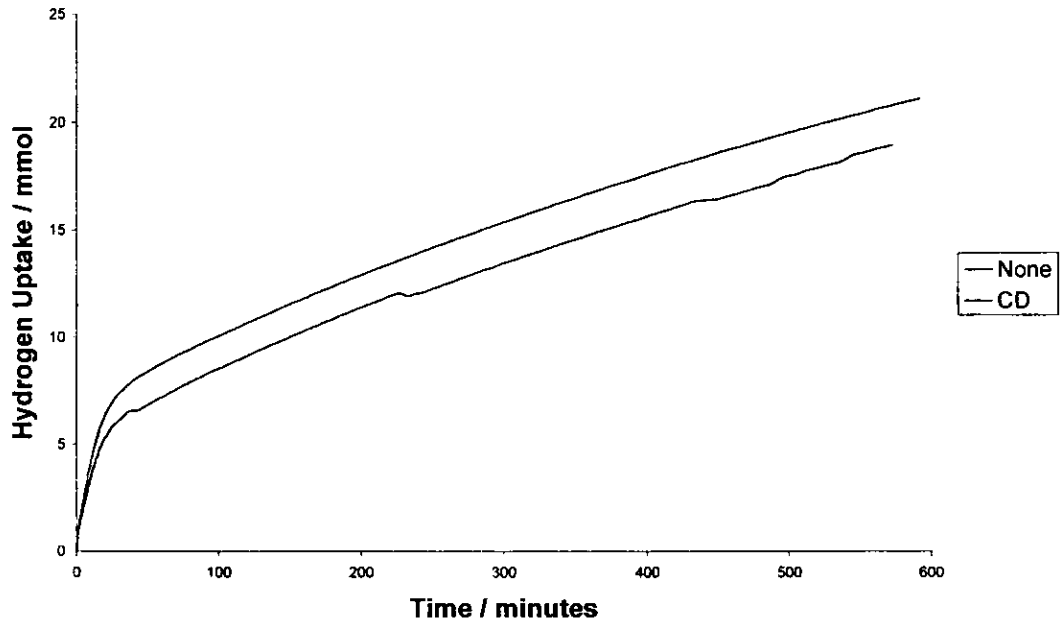


Figure 4.22 Hydrogenation of *N*-(1methylbenzylidene)-2,3-dimethylbutylamine with 5% Ir/alumina

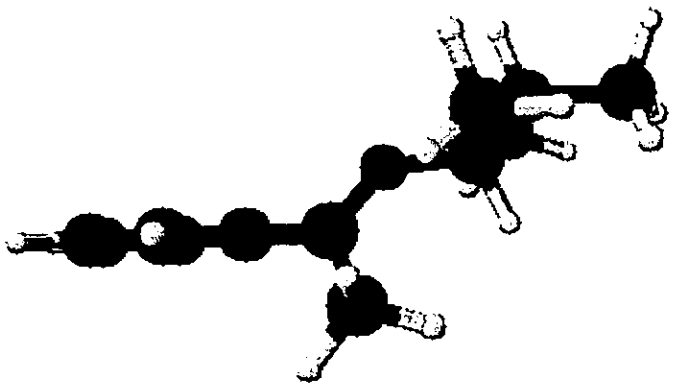
Again with the modified Ir/alumina catalyst there is very little enantiomeric excess. The initial rates of reaction are good, and are maintained for some time, but the final percentage conversion is much lower than those for the platinum and rhodium catalysts. It is thought that this low rate of conversion is due to the iridium metal and its ability to catalyse this imine. For the analine imine the iridium catalyst showed the best rates of conversion and was more suited to that particular imine.

4.2.4.5 Discussion

It is thought that the high percentage conversion for these hydrogenations could be attributed to the shape of the molecule. As can be seen from Figures 4.23 and 4.24, the analine imine (*N*-(1-methylbenzylidene)aniline) will lie flat on the catalyst surface, resulting in the hydrogen atoms having limited access to the C=N. However, using the template model of Wells as a guide, it is thought that the hydrogen passes through the catalyst in order to hydrogenate the double bond. This would suggest that the aniline imine lying flat on the surface would fit with the template model and result in good conversions and high enantiomeric excess. In the case of *N*-(1methylbenzylidene)-2,3-dimethylbutylamine (butyl imine) it would be difficult for the molecule to lie on the catalyst surface, as the C=N bond is raised by the $(CH_3)_2CH\text{-}CCH_3$ group. Although this would result in the double bond being 'accessible' to the hydrogen for all angles it may result in low enantiomeric excess being achieved.

In order to ascertain the reason for the difference in behaviour of the two imines with heterogeneous catalysts further studies need to be carried out into the mechanistic process and further hydrogenations carried out with *N*-(1methylbenzylidene)-2,3-dimethylbutylamine using cinchonine as a modifier.

Figure 4.23 3D representation of *N*-(1-methylbenzylidene)aniline



Red = nitrogen

Pale blue = carbon

White = hydrogen

Figure 4.24 3D representation of *N*-(1methylbenzylidene)-2,3-dimethylbutylamine

4.2.5 Hydrogenation of *N*-(α-methylbenzylidene)benzylamine

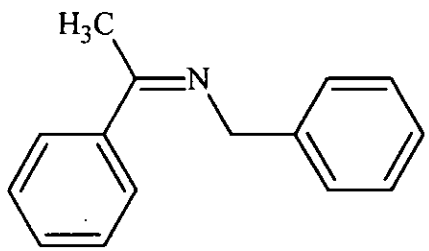


Figure 4.25 *N*-(α-methylbenzylidene)benzylamine

This imine (Figure 4.25) was hydrogenated with one catalyst, 5% platinum supported on alumina. As can be seen from Figure 4.26, the hydrogen uptake curve for the reaction was very promising.

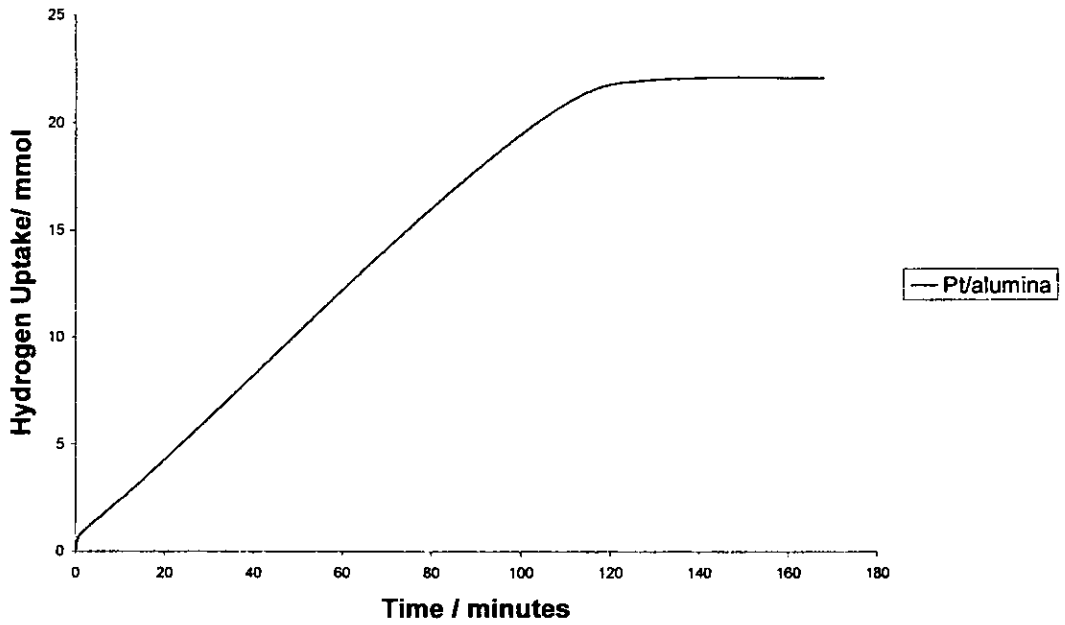


Figure 4.26 Hydrogenation of *N*-(α-methylbenzylidene)benzylamine with un-modified 5% Pt/alumina.

Unfortunately, as mentioned in Section 4.1.10, there were problems with the analysis of the chiral amine produced. Several different methods were used (GCMS, chiral GCMS, chiral GC, GC, chiral HPLC and HPLC) in an attempt to resolve the final products of the reaction, all of which were unsuccessful.

Figure 4.27 shows an analysis trace achieved from chiral GC analysis of *N*-(α-methylbenzylidene)benzylamine once hydrogenated with 5% Pt/alumina in its un-modified state. Such a reaction should result in the production of a racemic mixture, with equal quantities of the two amine enantiomers. To assist in the identification of the imine and amine, the reaction was not allowed to continue to completion in this case. The solvent (ethanol) was identified as peak number 1, (1.392 minutes), the prochiral imine was identified as peak number 2, (18.78 minutes) and the resulting amine as peak number 3, (27.13 minutes). It is thought that the two enantiomers of

the chiral amine were not being separated by the chiral column, resulting in one amine peak. Unfortunately this peak could not be separated further to allow identification of the two enantiomers.

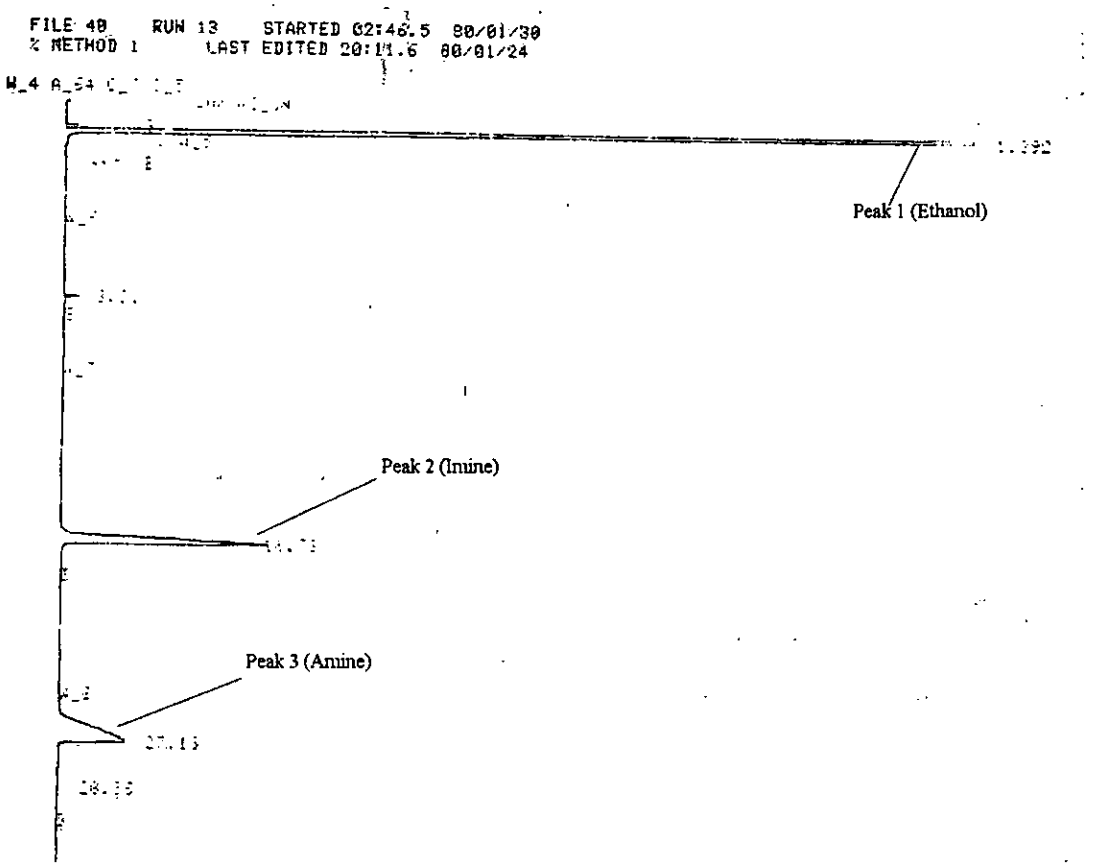


Figure 4.27 Chiral GC analysis of hydrogenated *N*-(α-methylbenzylidene) benzylamine.

The reaction was repeated several times, and as previously mentioned several different attempts to analyse the chiral amine produced were attempted, but the chiral amine could not be separated into its enantiomers. As a result, it was impossible to determine percentage conversion and enantiomeric excess.

Modeling of this imine (Figure 4.28, 4.29) suggested that the position it would lay on the metal surface would be with one of the aromatic rings flat against the platinum surface. This would easily enable the C=N to be hydrogenated, since the double bond would be proud of the metal surface and un-hindered by the second aromatic group.

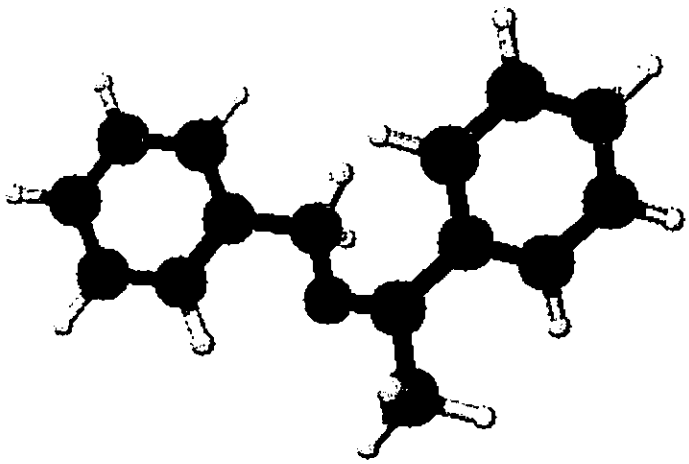
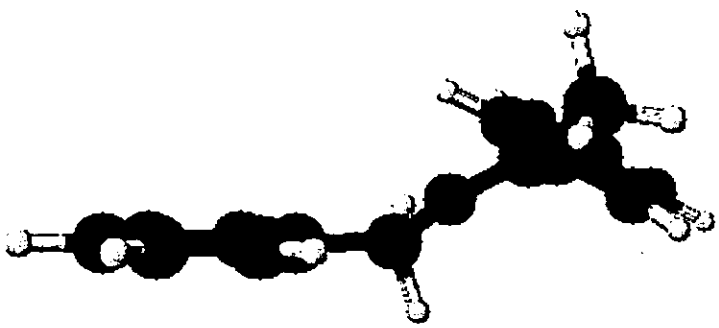


Figure 4.28 *N*-(α-methylbenzylidene) benzylamine, viewed from above, as it would position on the platinum surface.



Red = nitrogen
Pale blue = carbon
White = hydrogen

Figure 4.29 *N*-(α-methylbenzylidene) benzylamine, viewed from the side, with the aromatic ring lying flat against the platinum surface.

It was therefore hoped that, despite the difference in size between *N*-(α-methylbenzylidene) benzylamine (9.414 Å x 5.014 Å) and methyl pyruvate (5.158 Å x 3.518 Å), that this imine would be able to fit in with the cinchona alkaloid

modifier, assuming the template model proposed by Wells and co-workers. [21] This would be the case since the 'bulky' aromatic group would be raised from the catalytic surface, allowing the rest of the imine to be 'locked' in place by the modifier. Thus the C=N could be readily hydrogenated with cinchona modified alkaloid Pt/alumina; to yield a chiral amine.

Unfortunately, consideration of time was an issue and due to the difficulty in identifying the chiral amines yielded, this imine was left unresolved. However, *N*-(α-methylbenzylidene) benzylamine was produced in its pure form (see Section 4.1.10).

When hydrogenated with un-modified 5% Pt/alumina it showed very promising initial rates of reaction. The hydrogen uptake curves suggested that the imine had been completely hydrogenated to its corresponding amines, which should have been chiral. Figure 4.26 shows an example of a hydrogen uptake curve for *N*-(α-methylbenzylidene) benzylamine, in which approximately 25 mmol of imine was used for the hydrogenation. Initial rate of reaction was calculated as 59.8 $mmolh^{-1}$, which, when compared to those achieved for the methyl pyruvate study, is very promising.

Chapter 5
Hydrogenation of Cyclohexene

HYDROGENATION OF CYCLOHEXENE

As discussed in Sections 1.4 and 1.5 the number and diversity of homogeneous catalytic systems capable of inducing enantioselectivity far exceeds their heterogeneous counterparts. As previously stated one possibility for developing enantioselective heterogeneous systems is through supporting homogeneous catalysts on heterogeneous supports.

In order that suitable procedures could be developed initial studies focused on a much simpler and more robust system, namely, the hydrogenation of cyclohexene with chlorotris(triphenylphosphine)rhodium (Wilkinson's Catalyst). The catalyst was used both un-supported and supported on clay and NaY zeolite for the hydrogenation of cyclohexene, in different solvents. Any change in activity as assessed by rate or conversion was monitored via the use of hydrogen uptake curves, and product analysis using G.C.

Some work in this area (supporting Wilkinson's catalyst) had already been published there was, at the time of the study. However, no references were available which investigated the use of different solvents for supporting Wilkinson's on Montmorillonite clay, or for the support of Wilkinson's on NaY zeolite, the chosen supports for this heterogenisation.

5.1 Preparation of Chlorotris(triphenylphosphine)rhodium

The following procedure was carried out under an inert atmosphere. Chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst $RhCl(PPh_3)_3$) was prepared using the method of Osborn *et al.*[80] To a solution of freshly recrystallised triphenylphosphine (6.0 g, BDH), in hot ethanol (175 ml) was added a solution of rhodium trichloride (1 g, Johnson Matthey) in hot ethanol (35 ml). The resulting solution was heated under reflux for 30 min, and the hot solution filtered to yield the air stable catalyst.

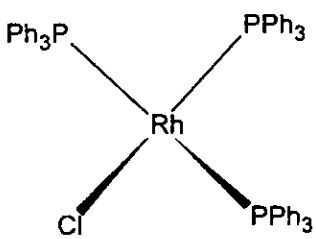


Figure 5.1 Chlorotris(triphenylphosphine) rhodium (Wilkinson's catalyst).

Wilkinson's catalyst was successfully made, pure chlorotris(triphenylphosphine)rhodium being precipitated from the hot reflux solution.

5.2 Support of Chlorotris(triphenylphosphine)rhodium

The catalyst was produced as detailed above, before being tethered to two different supports, Montmorillonite clay (BDH) and NaY zeolite (BNFL).

Montmorillonite clay was chosen due to its layered structure which can be used to intercalate molecules and ions. Clays also have ion exchange properties, often with high selectivity. [81] Three different solvents were used for tethering the catalyst to the support, ethanol, benzene and 1,1,1-trichloroethane.

These solvents were chosen since they are common solvents for hydrogenations using chlorotris(triphenylphosphine)rhodium and enable the layers of the clay to be swelled by different amounts. It was hoped that by investigating the different solvents, a suitable solvent would be determine which allowed the clay layers to swell enough for the catalyst to enter. Once the catalyst was established between the layers, the solvent could be removed, the distance between the layers of clay would then contract, trapping the catalyst in place. Therefore the three solvents, which expanded the layers of clay to different amounts were used.

1,1,1- Trichloroethane should give the greatest swelling of the clays layers, as the bulky molecule and the negative charges on the layers of the clay being repelled by those of the Chloride forces the layers apart; thus allowing larger molecules to enter the layers. Benzene would provide the least amount swelling, as the flat ring does not force the clay layers apart; therefore only enabling small molecules to be sandwiched between the layers. Ethanol would expand the layers to a distance in

between that of 1,1,1-trichloroethane and benzene, providing a comparison for the other two solvents.

1,1,1- Trichloroethane is often used in the preparation of clay supported catalysts to separate the layers within the clay enabling the catalyst to be introduced. [82,83] Once the catalyst was in the clay, the solvent was removed by two different methods (filtration and evaporation), to determine the most efficient, allowing the layers of the Montmorillonite clay to 'sandwich' the catalyst.

In contrast to clays zeolites have a framework structure enclosing cavities occupied by large ions and water molecules, which have freedom of movement allowing ion exchange and reversible dehydration. [81] In the anhydrous form the zeolite cavities can be occupied by molecules brought into contact with it. Once within the cavities the molecules are held in place by attractive forces (electrostatic and van der Waals), the zeolite absorbing and strongly retaining those molecules which just enter the cavities.

With NaY zeolite, the catalyst was supported by trapping it within the structure of the zeolite cage. This was attempted with two different methods, stirring the catalyst in slurry with the zeolite and preparing the catalyst in situ with the zeolite, to enable the catalyst to form with the zeolite cage. To allow comparison between the clay and zeolite, the same solvents were used to support the catalyst within the zeolite cage before removing the solvent by filtration or evaporation.

5.2.1 Preparation of Supported Wilkinson's Catalysts on Montmorillonite Clay

2.0 g of montmorillonite clay was first stirred with the required solvent (50 ml) for 30 minutes. After this time 0.02 g of the catalyst (prepared as detailed in Section 5.1), was added. This slurry was then stirred for a further 30 minutes before the solvent was removed. Removal of the solvent was carried out by two different methods, rotary evaporation and filtration.

Assuming all catalyst present was entrapped by the support, this method gave a 1 % loading of the catalyst on the support for all solvents. This supported catalyst was prepared in 1,1,1- trichloroethane, benzene and ethanol.

5.2.2 Preparation of Supported Wilkinson's Catalyst with NaY Zeolite

As results from the clay work will show, the catalyst prepared using filtration to remove the solvent showed a slightly higher activity than those where the solvent was removed by evaporation (Section 5.4.5). It was therefore decided to use this method of solvent removal for the zeolite catalysts.

2.0g of NaY Zeolite was stirred in the required solvent (50 ml) for 30 minutes. After this time 0.02 g of the catalyst was added. The slurry was stirred for a further 30 minutes before the solvent was removed by filtration.

To allow for the molecule entering the zeolite pore, the catalyst was also prepared in the presence of the zeolite.

The following procedure was carried out under an inert atmosphere. 10 g of NaY zeolite was stirred for 30 minutes in ethanol (50 ml). To this was added a solution of freshly recrystallised triphenylphosphine (0.3 g, BDH), in hot ethanol (10 ml). A solution of rhodium trichloride (0.05 g, Johnson Matthey) in hot ethanol (2 ml) was then added. The resulting solution was heated under reflux for 30 min, and the hot solution filtered to yield the air stable, supported, catalyst.

5.3 Hydrogenation of Cyclohexene

Hydrogenation of cyclohexene was carried using the supported catalysts (prepared as detailed above) and the un-supported catalyst normally used for the hydrogenation of cyclohexene (Wilkinson's Catalyst, Section 2.4.1). Catalysts tested are detailed in Table 5.1. Hydrogenation was carried out using the procedure detailed in Section 2.1, for each reaction approximately 5 mmol of cyclohexene was used. Each heterogeneous catalyst tested was used for the hydrogenation of cyclohexene three times, to establish if any drop in reactivity was noticed.

The hydrogenation mixture at the end of each reaction was also tested using atomic absorption spectroscopy analysis, to determine if any rhodium had leached from the catalyst. Using a calibration graph (Appendix B) the concentration of rhodium in each solution was determined, allowing the percentage of rhodium leached from the catalyst to be determined.

Table 5.1. Catalyst Identification for hydrogenation of cyclohexene

Catalyst	Composition
$Rh(PPh_3)_3$	unsupported Wilkinson's catalyst, run in all 3 solvents tested
Benzene(filtered)	Wilkinson's catalysts supported on Montmorillonite clay using a benzene solvent (removed by filtration)
Benzene(evaporated)	Wilkinson's catalysts supported on Montmorillonite clay using a benzene solvent (removed by rotary evaporation)
TCE(filtered)	Wilkinson's catalysts supported on Montmorillonite clay using a 1,1,1- trichloroethane solvent (removed by filtration)
TCE(evaporated)	Wilkinson's catalysts supported on Montmorillonite clay using a 1,1,1- trichloroethane solvent (removed by rotary evaporation)
EtOH(filtered)	Wilkinson's catalysts supported on Montmorillonite clay using an ethanol solvent (removed by filtration)
EtOH(evaporated)	Wilkinson's catalysts supported on Montmorillonite clay using an ethanol solvent (removed by rotary evaporation)
TCE(evaporated)EtOH	Wilkinson's catalysts supported on Montmorillonite clay using a 1,1,1- trichloroethane solvent (removed by rotary evaporation). Reaction run in an ethanol solvent
NaY Zeolite/benzene	Wilkinson's catalyst supported on NaY zeolite using a benzene solvent (removed by rotary evaporation)
NaY Zeolite/TCE	Wilkinson's catalyst supported on NaY zeolite using a 1,1,1- trichloroethane solvent (removed by rotary evaporation)
NaY Zeolite/EtOH	Wilkinson's catalyst supported on NaY zeolite using an ethanol solvent (removed by rotary evaporation)
NaY Zeolite/caged	Wilkinson's catalyst prepared in the presence of NaY zeolite.

5.4 Results and Discussion for Clay Supported Catalysts

5.4.1 Hydrogenation of Cyclohexene with a Homogeneous Catalyst

As a comparison to the supported catalysts, Wilkinson's catalyst was used homogeneously (un-supported) to hydrogenate cyclohexene, in all three solvents: ethanol (EtOH), 1,1,1- trichloroethane (TCE) and benzene (Benz)

Table 5.2. Hydrogenation of cyclohexene with homogeneous catalyst

Catalyst	Solvent	Initial Rate / mmol h^{-1}	Conversion / %
Homogeneous Wilkinson's	EtOH	34.0	100.0
Homogeneous Wilkinson's	TCE	4.6	31.9
Homogeneous Wilkinson's	Benz	10.1	55.8

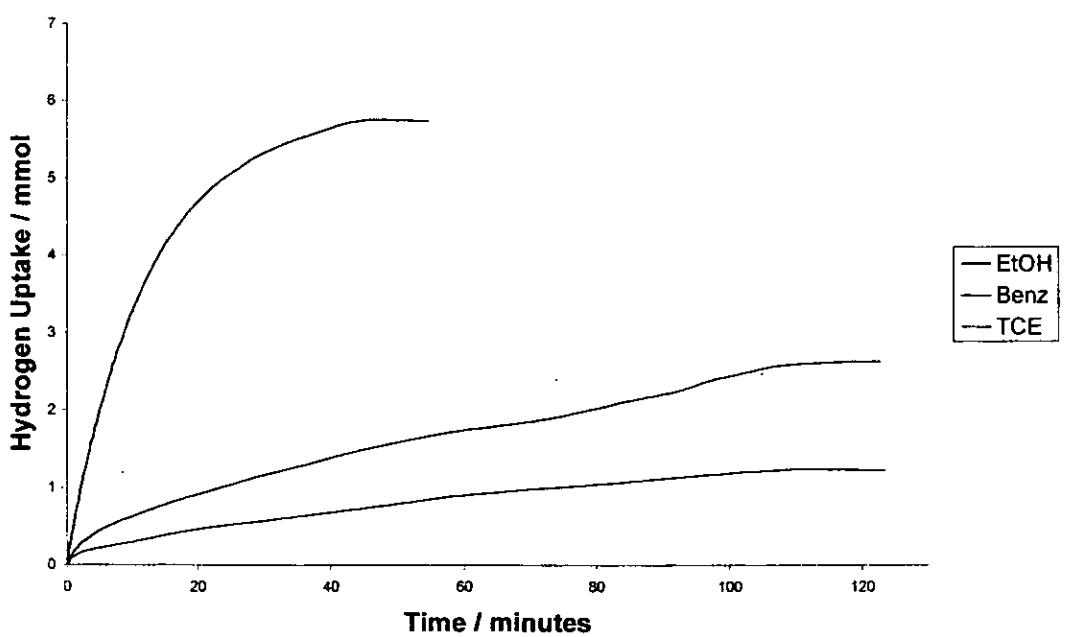
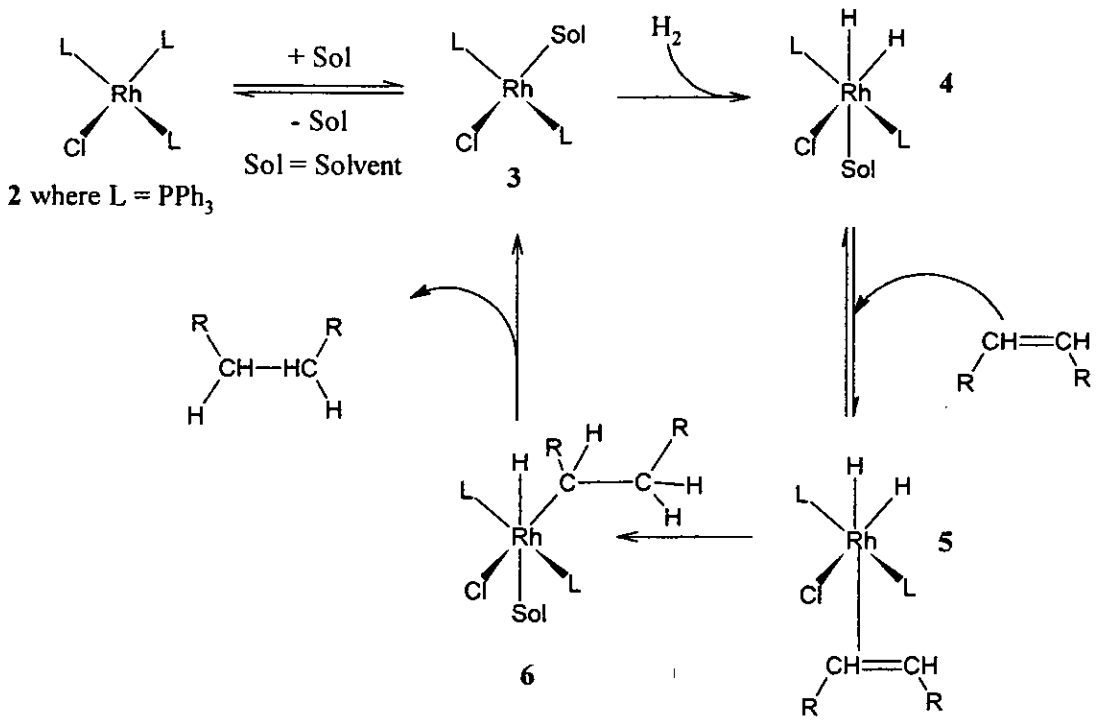


Figure 5.2 Hydrogenation of cyclohexene with homogeneous catalyst

As can be seen from Table 5.2 and Figure 5.2, the best solvent for this hydrogenation is ethanol, giving 100 % conversion, and a high initial reaction rate of 42.8 mmol h^{-1}. In comparison to the ethanol, the standard solvent for this reaction, the other solvents used are very disappointing, with conversion rates below 50 % and poor initial rates of reaction. As discussed in Section 1.3, the solvent is thought to replace one of the phosphine ligands during the catalytic cycle. [2,29] It is therefore suggested that the alternative solvents used for this reaction (1,1,1- trichloroethane and benzene) affect the formation of this complex, hindering the catalytic cycle and preventing the reaction going to completion.

It is thought that the use of benzene as a solvent allowed the formation of complex **3** (Scheme 5.1) with electrons being withdrawn on to the delocalised π-system of the benzene ring. The complex formed in this way, when using benzene as a solvent, is not thought to be as stable as that formed with ethanol. Further studies in this area would be needed to confirm this.

In the case of the trichloroethane as a solvent, it is thought that the presence of the lone pairs of electrons on the chlorine hinders the formation of complex **3**, potentially deactivating the complex. This may not allow the formation of a 16 electron complex (complex **3**, Scheme 5.1) which would prevent the formation an 18 electron complex (complex **4**); thus thwarting the catalytic cycle. Again, further studies in this area would be needed to confirm this.



Scheme 5.1 The catalytic cycle for the hydrogenation of alkenes by Wilkinson's catalyst (**2**). [29]

5.4.2 Hydrogenation of Cyclohexene with Montmorillonite/Wilkinson Catalysts (Solvent Removed by Filtration)

5.4.2.1 Hydrogenation of Cyclohexene with EtOH (filtered) Catalyst

Table 5.3. Hydrogenation of Cyclohexene with EtOH(filtered) Catalyst

Catalyst	Solvent	Run Number	Initial Rate / mmol h^{-1}	Conversion / %	Rhodium leached / %
Montmorillonite/ Wilkinson/filtered	EtOH	1	22.0	100	0
Montmorillonite/ Wilkinson/filtered	EtOH	2	38.0	99.7	0
Montmorillonite/ Wilkinson/filtered	EtOH	3	38.6	99.1	0
Homogeneous Wilkinson's	EtOH	-	34.0	100	-

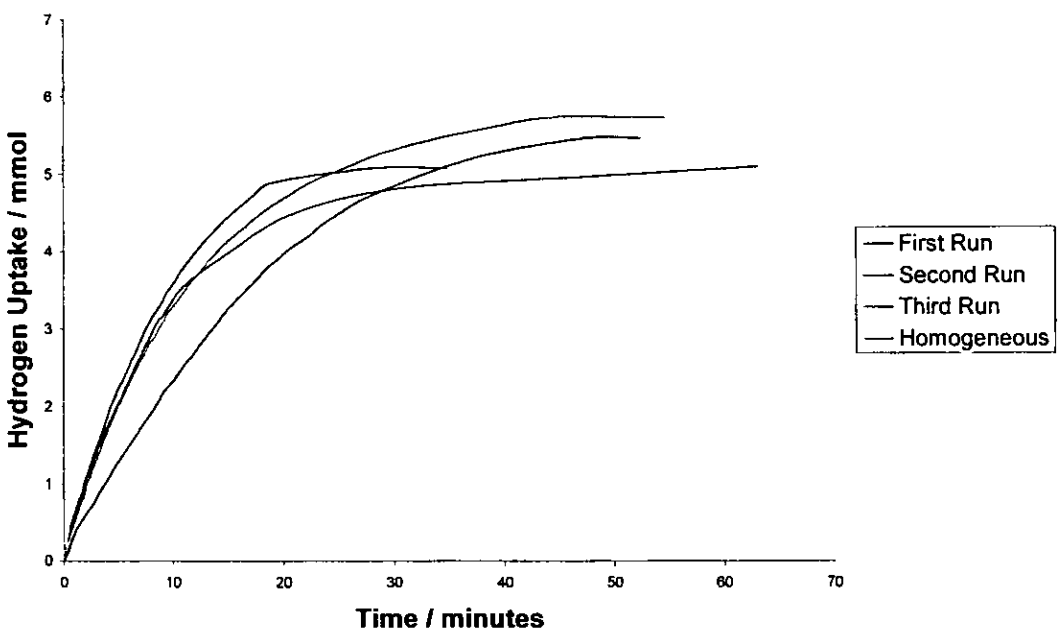


Figure 5.3. Hydrogenation of Cyclohexene with EtOH(filtered) Catalyst

As previously mentioned (Section 5.3) each supported catalyst was used for the hydrogenation of cyclohexene three times, to determine if there was any loss of activity. As can be seen from Figure 5.3, there was very little deactivation in this catalyst over the three runs, a conversion rate of almost 100 % being achieved every time. There is, however, a change in initial reaction rate; after the first run of the catalyst, the reaction rate increases dramatically (22.0 mmol h^{-1} to 38.0 mmol h^{-1}). The rate in each case, with the heterogeneous catalyst is slightly higher than that for the homogeneous reaction in the same solvent.

Atomic absorption showed there was no leaching of the catalyst from the support, maintaining a 1% loading of rhodium centred catalyst for all reactions. Therefore any change in rate of reaction was not due to a change in loading of the catalyst.

The results, for this catalyst, are very encouraging and the small reduction in rate and percentage conversion was acceptable to change the system into a heterogeneous system. Especially if over repeated testing there was no further leaching.

5.4.2.2 Hydrogenation of Cyclohexene with TCE (filtered) Catalyst

Table 5.4. Hydrogenation of Cyclohexene with TCE (filtered) Catalyst

Catalyst	Solvent	Run Number	Initial Rate / mmol h^{-1}	Conversion / %	Rhodium leached/%
Montmorillonite/ Wilkinson/filtered	TCE	1	25.3	43.9	0.003
Montmorillonite/ Wilkinson/filtered	TCE	2	24.0	32.4	0.003
Montmorillonite/ Wilkinson/filtered	TCE	3	23.7	45.8	0
Homogeneous Wilkinson's	TCE	-	4.6	31.9	-

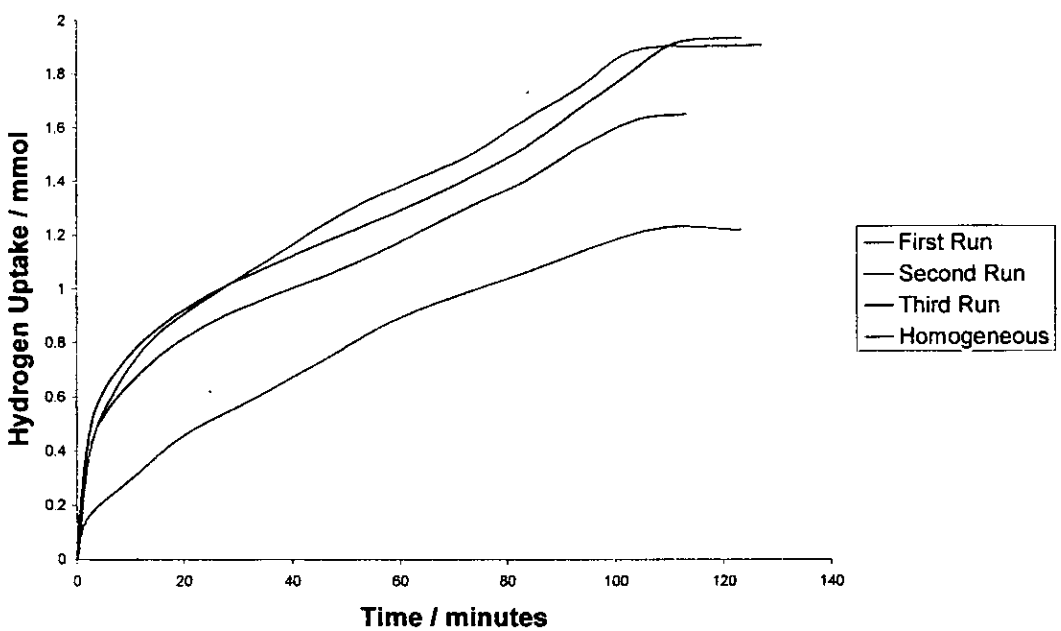


Figure 5.4 Hydrogenation of Cyclohexene with TCE(filtered) Catalyst

This supported catalyst showed a marked improvement in the initial rate of reaction and percentage conversion to that of the homogeneous catalyst. Although there was some improvement in the percentage conversion, it was not the three fold change noted with the rate of reaction.

Some separation of the rhodium catalyst from the support was noted for this catalyst, however, the percentage of rhodium leached was so small (0.003 %) as to be deemed inconsequential.

5.4.2.3 Hydrogenation of Cyclohexene with Benzene (filtered) Catalyst

Table 5.5. Hydrogenation of Cyclohexene with Benzene (filtered) Catalyst

Catalyst	Solvent	Run Number	Initial Rate / mmol h^{-1}	Conversion / %	Rhodium leached/%
Montmorillonite/ Wilkinson/filtered	Benz	1	8.1	26.7	0.003
Montmorillonite/ Wilkinson/filtered	Benz	2	18.7	35.4	0
Montmorillonite/ Wilkinson/filtered	Benz	3	26.0	34.5	0
Homogeneous Wilkinson's	Benz	-	10.1	55.8	-

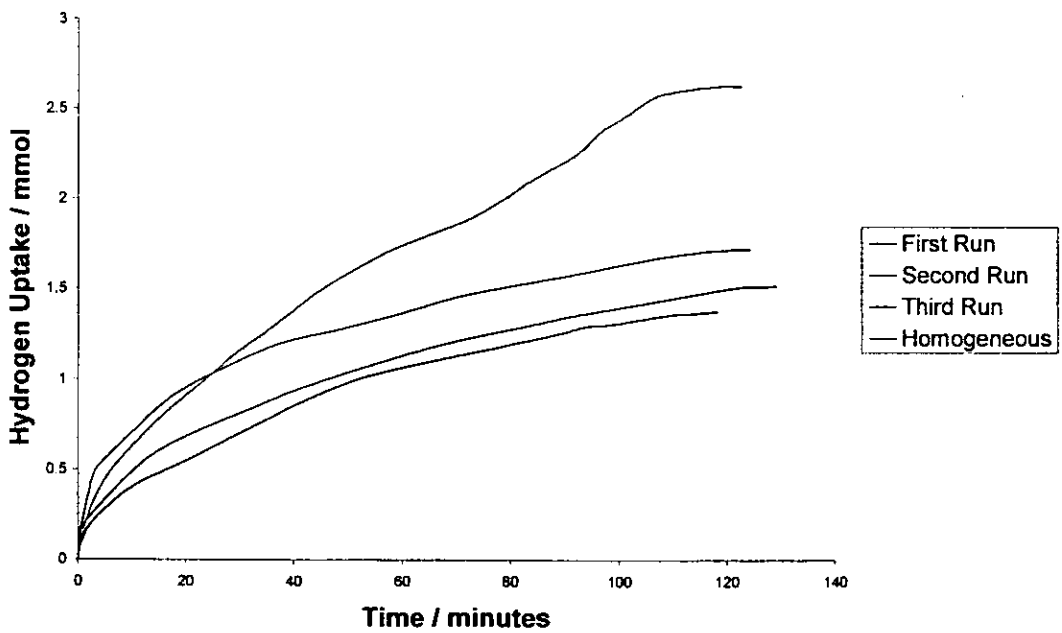


Figure 5.5. Hydrogenation of Cyclohexene with Benzene (filtered) Catalyst

Again an increase in the initial rate of reaction is noted on the second and third run of the catalyst, in comparison to the homogeneous system. Despite this slight increase in the initial rate of reaction, for the second and third use for the catalyst, when Figure 5.5 is studied it can be seen that this rate is not maintained. When looking at the complete reaction, the homogeneous catalyst appears to be better than the supported version this is upheld by the percentage conversion of cyclohexene to cyclohexane.

There is some leaching of rhodium from the support during the first run, which is not noted in further uses. But this small percentage of leaching, (0.003 %) can have little, if no, effect on the reaction rate.

5.4.3 Hydrogenation of Cyclohexene with Montmorillonite/Wilkinson Catalysts (Solvent Removed by Evaporation)

5.4.3.1 Hydrogenation of Cyclohexene with Montmorillonite / Wilkinson's EtOH (evaporated) Catalyst

Table 5.6 Hydrogenation of Cyclohexene with EtOH (evaporated) Catalyst

Catalyst	Solvent	Run Number	Initial Rate / mmol h^{-1}	Conversion / %	Rhodium leached/%
Montmorillonite/ Wilkinson/ evaporated	EtOH	1	29.3	100	0.017
Montmorillonite/ Wilkinson/ evaporated	EtOH	2	35.5	100	0
Montmorillonite/ Wilkinson/ evaporated	EtOH	3	36.4	100	0
Homogeneous Wilkinson's	EtOH	-	34.0	100	-

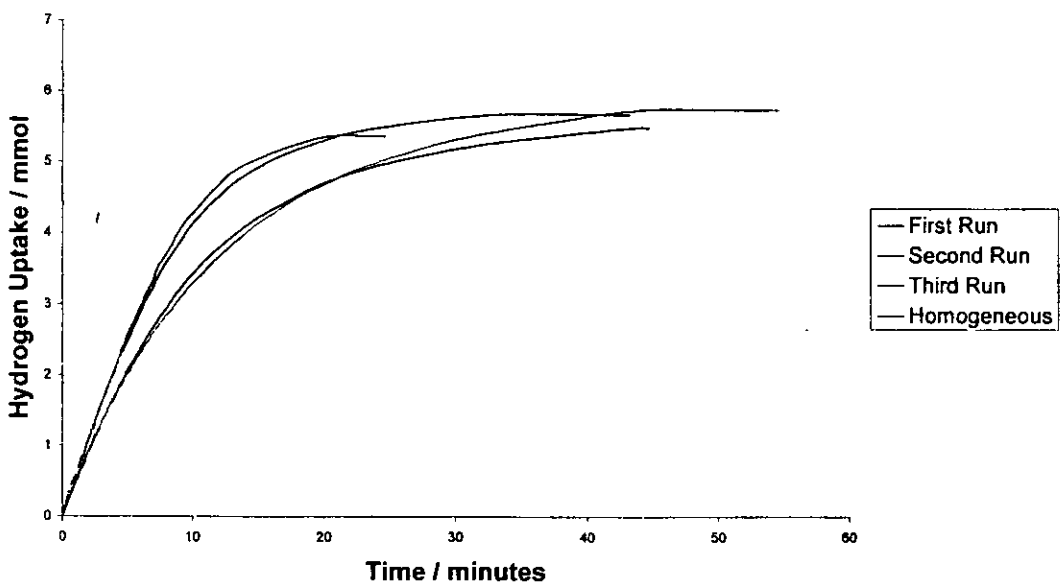


Figure 5.6 Hydrogenation of Cyclohexene with EtOH (evaporated) Catalyst

As with the catalyst produced using filtration to remove the solvent, this catalyst shows no loss of reaction with respect to conversion; each run of the catalyst resulting in 100 % conversion to cyclohexane. There is very little difference in the initial rates of reaction for all the catalysts tested in this series. The first run of the supported catalyst shows little difference to the homogeneous system. From Figure 5.6, it can be seen that the initial rate of reaction for the second and third run is maintained for longer than for the first use of the supported catalyst, or the homogeneous catalyst.

A very small amount of leaching is noticed after the first run, but in subsequent runs there is no further leaching, it is therefore assumed that there would be little deactivation of the catalyst in this respect.

5.4.3.2 Hydrogenation of Cyclohexene with TCE(evaporated) Catalyst

Table 5.7. Hydrogenation of Cyclohexene with TCE(evaporated) Catalyst

Catalyst	Solvent	Run Number	Initial Rate / mmol h^{-1}	Conversion / %	Rhodium leached/%
Montmorillonite/ Wilkinson/ evaporated	TCE	1	8.9	62.8	0
Montmorillonite/ Wilkinson/ evaporated	TCE	2	8.9	48.4	0
Montmorillonite/ Wilkinson/ evaporated	TCE	3	8.2	66.2	0
Homogeneous Wilkinson's	TCE	-	4.6	31.9	-

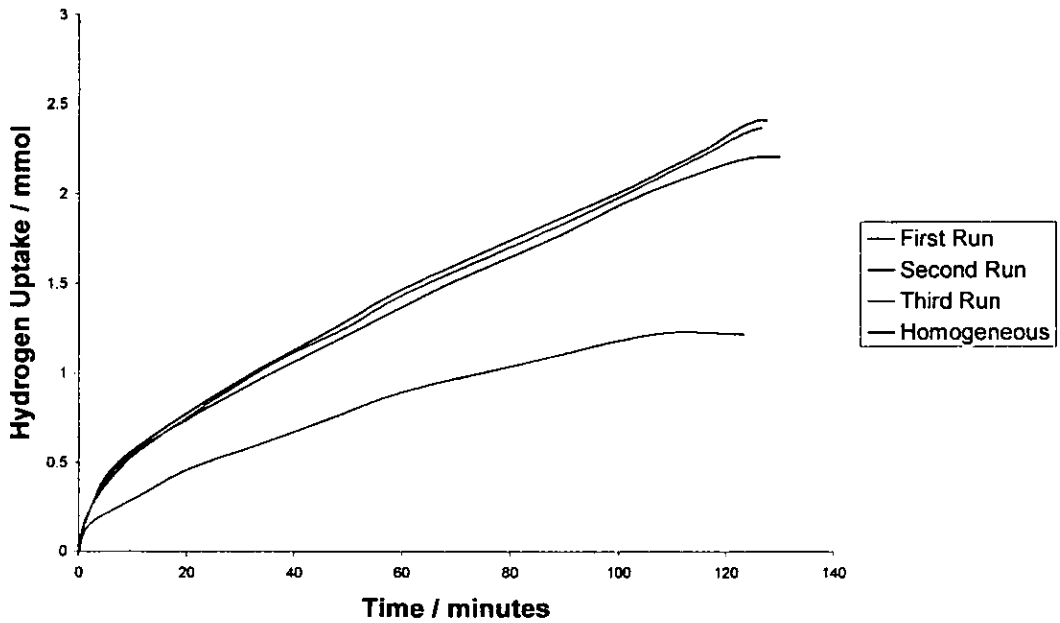


Figure 5.7 Hydrogenation of Cyclohexene with TCE(evaporated) Catalyst

As with the catalyst prepared by filtration and run in this solvent, there is an increase in rate of reaction. Although, this is not as dramatic as with the previous catalyst run with this solvent, there is no change in the rate of reaction. The increase in rate of reaction for this catalyst is accompanied by an increase in the yield of cyclohexane, when compared to the filtered catalyst.

5.4.3.3 Hydrogenation of Cyclohexene with Benzene (evaporated) Catalyst

Table 5.8. Hydrogenation of Cyclohexene with Benzene (evaporated) Catalyst

Catalyst	Solvent	Run Number	Initial Rate / mmol h^{-1}	Conversion / %	Rhodium leached/%
Montmorillonite/ Wilkinson/ evaporated	Benz	1	8.8	42.6	0.003
Montmorillonite/ Wilkinson/ evaporated	Benz	2	7.6	23.5	0.003
Montmorillonite/ Wilkinson/ evaporated	Benz	3	8.0	46.5	0
Homogeneous Wilkinson's	Benz	-	10.1	55.8	-

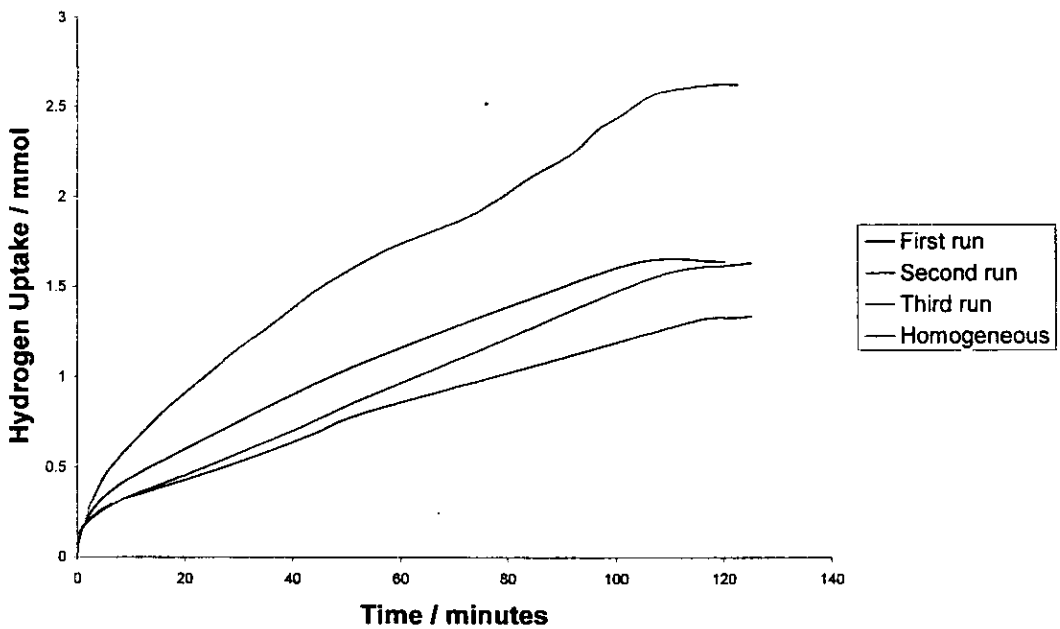


Figure 5.8 Hydrogenation of Cyclohexene with Benzene(evaporated) Catalyst

Again Wilkinson's catalyst, run in a benzene solvent, shows a decrease in activity when supported. In this case the initial rate is similar to that of the homogeneous system, but very quickly, this rate decreases (Figure 5.7) resulting in the overall reaction for the supported catalysts being lower than the homogeneous catalyst.

As with all the clay supported catalysts, there is very little leaching of rhodium, and therefore catalyst, from the support; suggesting there would be little deactivation of the catalyst over time.

5.4.4 Hydrogenation of Cyclohexene with Montmorillonite/Wilkinson Catalysts (TCE(evaporated)EtOH)

As described in Section 5.2, this catalyst was prepared by stirring the homogeneous catalyst with Montmorillonite clay in slurry with 1,1,1- trichloroethane. The solvent was then removed by evaporation and the catalyst used to hydrogenate cyclohexene with ethanol as a reaction solvent.

This catalyst was attempted as the best solvent for expanding the layers of clay, to introduce the catalyst, is 1,1,1- trichloroethane, but the best solvent to run the reaction in is ethanol. The above experiments showed better percentage conversion to cyclohexane was achieved when using a supported catalyst where the solvent had been removed with evaporation. Therefore the supported catalyst was made using 1,1,1- trichloroethane, removed with evaporation, and the hydrogenation was carried out in the presence of ethanol.

Table 5.9 Hydrogenation of Cyclohexene with TCE(evaporated)EtOH Catalyst

Catalyst	Solvent	Run Number	Initial Rate / mmol h^{-1}	Conversion / %	Rhodium leached/%
Montmorillonite/ Wilkinson/ evaporated prepared in TCE	EtOH	1	35.4	100	0.017
Montmorillonite/ Wilkinson/ evaporated prepared in TCE	EtOH	2	32.8	100	0
Montmorillonite/ Wilkinson/ evaporated prepared in TCE	EtOH	3	29.7	100	0
Homogeneous Wilkinson's	EtOH	-	34.0	100	-

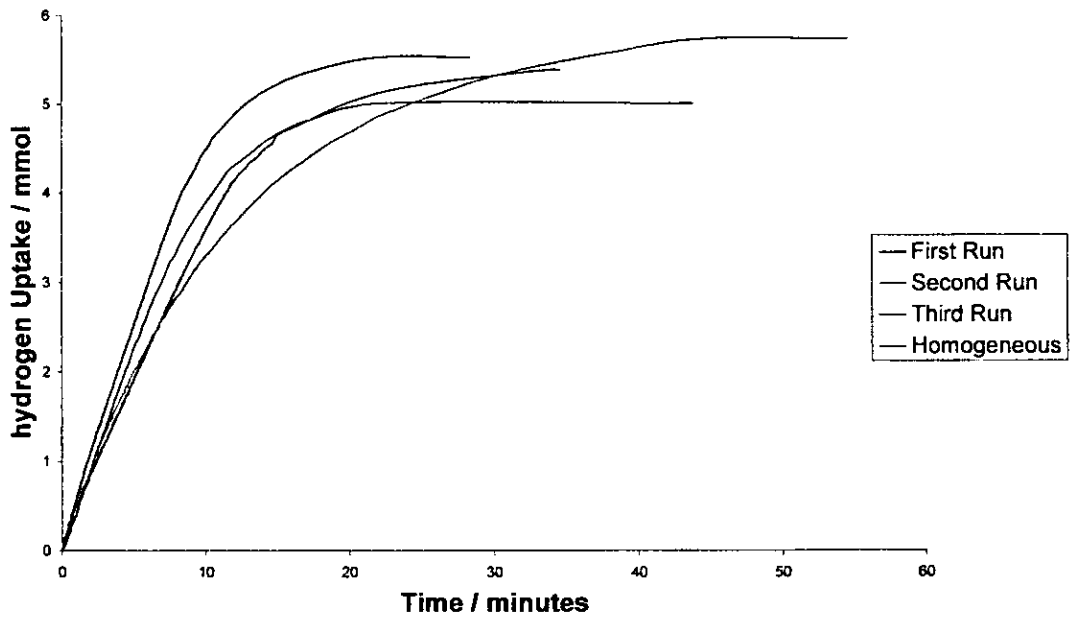


Figure 5.9 Hydrogenation of Cyclohexene with TCE(evaporated)EtOH Catalyst

Initial rates of reaction for this catalyst are comparable to those of the similar catalysts prepared using ethanol solvent, when the solvent is evaporated and filtered during preparation. The initial rate of reaction for the supported catalysts is slightly higher than the homogeneous catalysts, and as can be seen from Figure 5.8, the rate of reaction for the supported system is maintained for longer than the homogeneous reaction, with little loss of activity when the supported catalyst is reused.

There is some loss of rhodium during the first run of the catalyst (0.017 %) this is deemed to be so small as to be insignificant, especially as there is no loss seen in subsequent runs.

Overall there seems to be no advantage to preparing the catalyst in 1,1,1-trichloroethane before carrying out the hydrogenation of cyclohexene with an ethanol solvent.

5.4.5 Discussion

5.4.5.1 Preparation of Catalysts

As previously mentioned (Section 5.2) two different methods for removal of the solvent were investigated. From these results it can be seen that with both methods of solvent removal there is little or no leaching of the catalyst; showing no difference of the catalysts in this respect. However, when comparing the initial rate of reaction and the percentage conversion to cyclohexane, a difference is noted. Slightly higher rates of reaction are seen for the filtered catalysts, although in some cases there is

very little difference. However, when comparing the percentage conversion, the evaporated solvent shows the higher yield of cyclohexane.

A possible theory for this small difference could be a difference in the catalyst surface, created by the solvent evacuation process. Research shows that the structural characteristics of the support can affect the stability and activity of the catalyst. [68] Figures 5.10, 5.11 and 5.12, show X-ray diffraction of each catalyst, compared to Montmorillonite clay and Montmorillonite clay in the relevant solvent. As can be seen from this analysis there is a difference in the catalysts d-spacing when the solvent is removed by filtration, as opposed to evaporation. Although this difference is only slight, it could explain the slight difference in activity of the two types of catalysts.

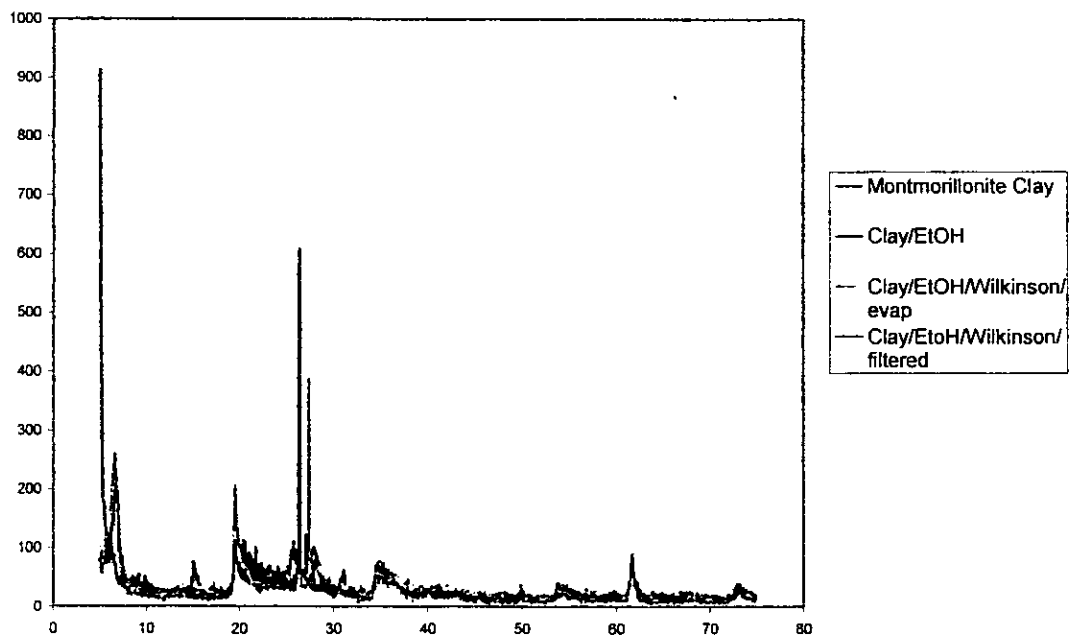


Figure 5.10 X-Ray Diffraction of clay catalysts prepared in ethanol

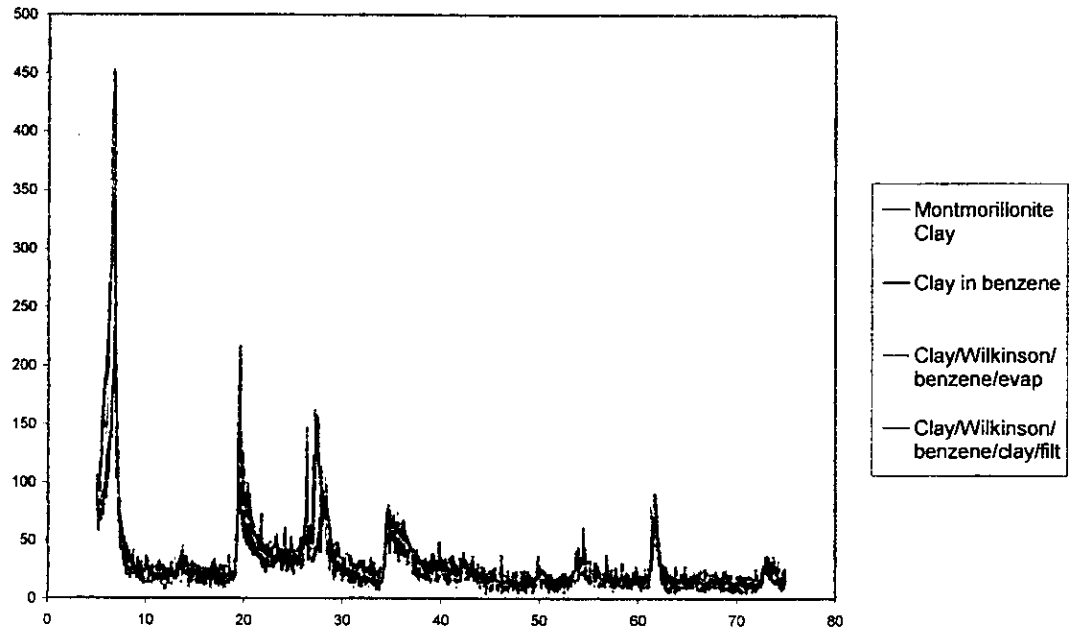


Figure 5.11 X-Ray Diffraction of clay catalysts prepared in benzene

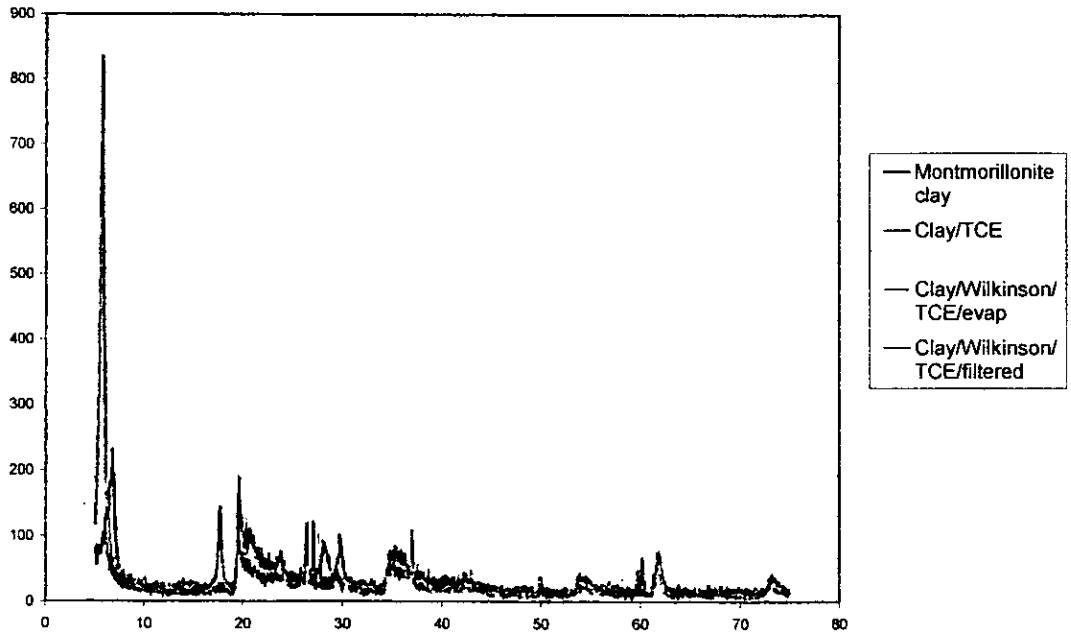


Figure 5.12 X-Ray Diffraction of clay catalysts prepared in 1,1,1- trichloroethane

There is little or no advantage to preparing the catalyst in 1,1,1- trichloroethane before using it in an ethanol solvent. Although, the percentage conversion to cyclohexane is a little higher than the catalyst prepared in ethanol using filtration to remove the solvent, it is no different to the catalyst where the solvent was removed by evaporation. Again, when comparing the rate of reaction, the catalyst prepared through filtration of the solvent, shows slightly higher rates, due to the difference in the catalyst d-spacing.

5.4.5.2 Preferred Solvent

The high rates and yields of cyclohexane in the homogeneous system, saw only a small increase in activity when the catalyst was supported in ethanol. With the supported catalysts prepared in benzene and run in benzene, there was a drop in activity, lower rates and percentage conversions being noted. However, with the catalysts prepared in 1,1,1- trichloroethane there was an improvement in activity. This improvement was more significant in the filtered catalysts where a six-fold increase was noted in the initial rate of reaction. It is possible that this is due to electronic effects of the lone pairs of electrons on the chlorine. However, further studies would be needed in order to confirm this.

From the information available, this gives an order of activity of the catalysts as that prepared in trichloroethane > ethanol > benzene. Since this is the order of swelling of the clay layers that each solvent invokes, it is thought that the swelling of the layers is related to this increase in activity. One possible suggestion for this is that once the catalyst has been sandwiched between the layers during preparation, the

layers again swell during reaction, through the presence of the trichloroethane solvent. This swelling during hydrogenation could allow more contact with the supported catalysts, thus increasing the activity of that catalyst.

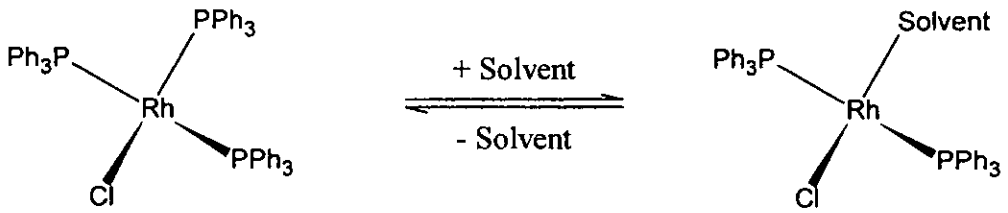
In order to confirm this theory, further studies need to be carried out. For example, investigations involving the catalysts prepared in a benzene solvent and run in the presence of an ethanol solvent will provide a comparison for other catalysts used with an ethanol solvent. Further XRD analysis may also help confirm the structure of each catalyst prepared.

5.4.5.3 Support of Catalyst

As mentioned in Section 5.4.5.2, an increase in activity was noted with the supported catalysts prepared and run in 1,1,1- trichloroethane and ethanol. Other similar studies [64,65], supporting Wilkinson's catalyst on γ-Al_2O_3, also show an increase in the activity when the catalyst is supported. One possible theory for this improved activity is the role of the solvent in the catalytic process.

As discussed in Section 1.3, it is thought that a molecule of the solvent is substituted for one of the phosphine ligands (Scheme 5.2). This substitution of the phosphine ligand could be made easier through the support of the catalyst. Once entrapped in the support, this initial substitution step could be more easily carried out, thus allowing completion of the catalytic cycle to be quicker and more efficient. In the case of the trichloroethane, the support of the complex on the clay could help the

formation of the 16 electron complex needed for the catalytic cycle to continue, Section 5.4.1.



Scheme 5.2 Initial step in catalytic cycle for the hydrogenation of alkenes by Wilkinson's Catalyst

It is thought that this increase in activity is not seen with the supported catalyst run in benzene due to the shape and size of the molecule. There may be difficulty in the benzene ring substituting for a phosphine ligand, due to its shape or due how the molecule bonds to the rhodium; potentially inhibiting the catalytic cycle, Section 5.4.

Other research into supported homogeneous catalysts [69] suggests that a slight acidity in the support increases the catalytic activity. Further research in this area would be needed to determine if this was the case with the Wilkinson's catalysts prepared.

It thought with Montmorillonite clay, that the catalyst is tethered to the support by swelling the layers of clay (using a solvent) and 'sandwiching' the catalyst between the layers (by removing the solvent). Further studies need to be carried out in order to determine if this is the case for the supported Wilkinson's catalyst. Such studies would also help determine the exact percentage loading of the catalyst on the support.

5.5 Results and Discussion for Zeolite Supported Catalysts

5.5.1 Hydrogenation of Cyclohexene with NaY Zeolite/Wilkinson Catalyst (Solvent Removed by Filtration)

5.5.1.1 Hydrogenation of Cyclohexene with NaY Zeolite / EtOH Catalyst

Table 5.10. Hydrogenation of Cyclohexene with NaY Zeolite/ EtOH Catalyst

Catalyst	Solvent	Run Number	Initial Rate / mmol h^{-1}	Conversion / %	Rhodium leached/%
NaY Zeolite/ Wilkinson/filtered	EtOH	1	19.1	100	0.006
NaY Zeolite/ Wilkinson/filtered	EtOH	2	20.9	100	0
NaY Zeolite/ Wilkinson/filtered	EtOH	3	28.4	100	0.007
Homogeneous Wilkinson's	EtOH	-	34.0	100	-

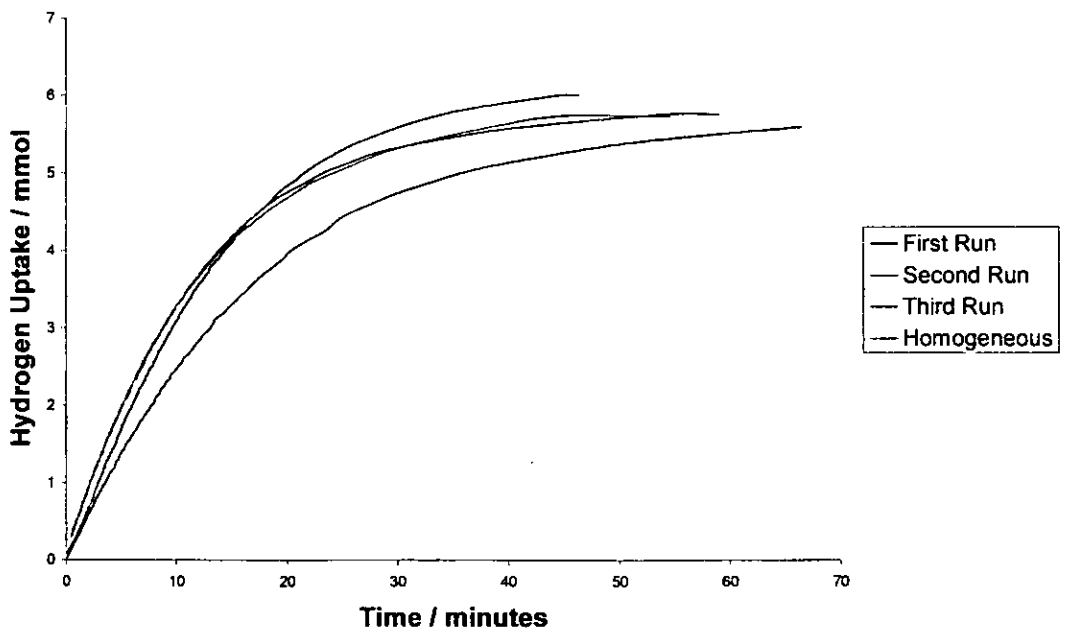


Figure 5.13. Hydrogenation of Cyclohexene with NaY Zeolite / EtOH Catalyst

The use of zeolite in this case shows no improvement on that of the hydrogenation of cyclohexene using a clay supported catalyst. Despite an increase in the initial rate of reaction being seen after the first use of the supported catalysts, the rates are lower than those for similar clay catalysts. When compared to the homogeneous system, there is little difference, conversion in all cases being 100 %.

As with the clay supported Wilkinson's catalysts, there is some leaching, however, this was so low as to be negligible.

5.5.1.2 Hydrogenation of Cyclohexene with NaY Zeolite / TCE Catalyst

Table 5.11. Hydrogenation of Cyclohexene with NaY Zeolite / TCE Catalyst

Catalyst	Solvent	Run Number	Initial Rate / mmol h^{-1}	Conversion / %	Rhodium leached/%
NaY Zeolite/ Wilkinson/filtered	TCE	1	5.8	28.4	0.003
NaY Zeolite/ Wilkinson/filtered	TCE	2	18.0	49.6	0.003
NaY Zeolite/ Wilkinson/filtered	TCE	3	17.1	50.5	0.003
Homogeneous Wilkinson's	TCE	-	7.0	31.9	-

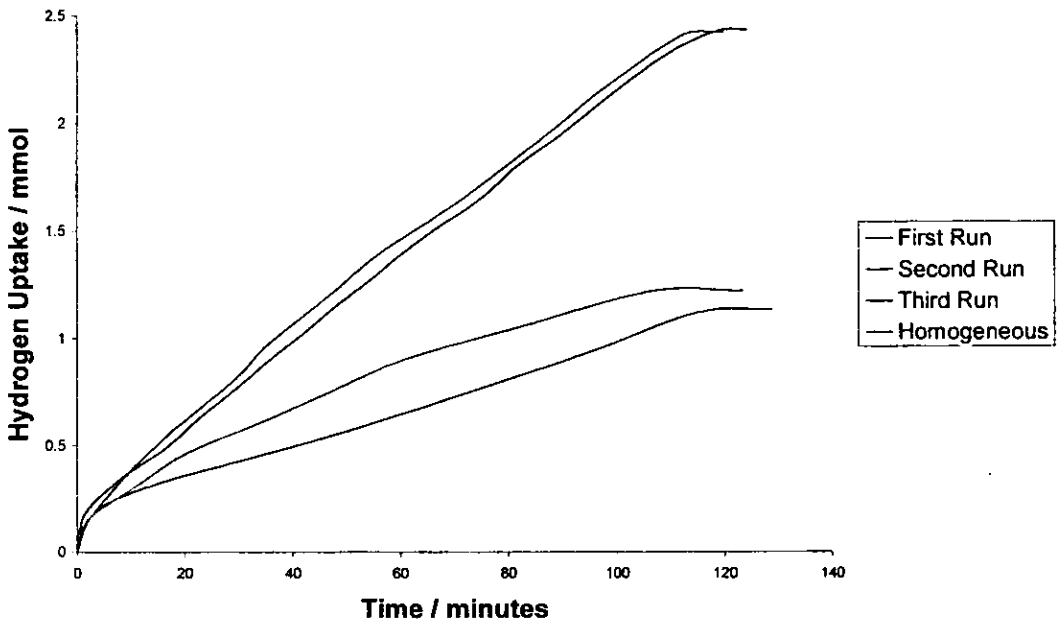


Figure 5.14. Hydrogenation of Cyclohexene with NaY Zeolite / TCE Catalyst

This zeolite supported catalyst proved to give lower initial rates of reaction than the clay supported catalysts. Percentage conversion is comparable to the TCE (filtered) catalyst, but lower than that for the TCE (evaporated) catalyst. As can be seen from Figure 5.14, the rate of reaction for the second and third use of the catalyst is maintained for a longer period of time to that of the first use and the homogeneous catalyst.

An increase in the activity of the catalyst is again noted after the first use of the support catalyst. There is some leaching of the catalyst from the support, this is thought to be insignificant as far as the rate of reaction is concerned. However, as this leaching is maintain through subsequent runs of the catalyst, over a long period of time, this small amount of leaching could become a consideration in deactivation of the catalyst.

5.5.1.3 Hydrogenation of Cyclohexene with NaY Zeolite / Benzene Catalyst

Table 5.12. Hydrogenation of Cyclohexene with NaY Zeolite / Benzene Catalyst

Catalyst	Solvent	Run Number	Initial Rate / mmol h^{-1}	Conversion / %	Rhodium leached/%
NaY Zeolite/ Wilkinson/filtered	Benz	1	12.4	44.6	0
NaY Zeolite/ Wilkinson/filtered	Benz	2	15.7	35.0	0
NaY Zeolite/ Wilkinson/filtered	Benz	3	20.2	60.2	0.003
Homogeneous Wilkinson's	Benz	-	5.9	55.8	-

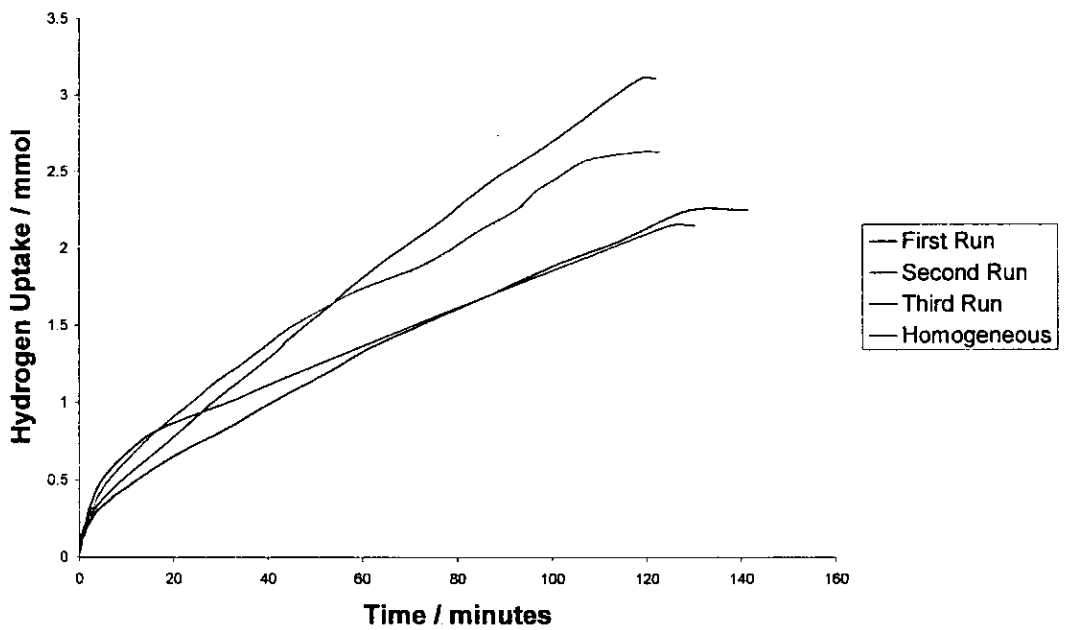


Figure 5.15. Hydrogenation of Cyclohexene with NaY Zeolite / Benzene Catalyst

When compared to other supported catalyst run with benzene, the initial rates of reaction are comparable to the benzene (evaporated) catalyst, with slightly higher percentage conversions. As with the aforementioned clay catalyst there is a dip in activity seen during the second use of the catalyst, which improves in the third use.

Leaching is insignificant, although a very small quantity of rhodium was detected after the third run; further tests would needed to be carried out to establish if this leaching was maintained or increased.

As with other supported catalysts run with a benzene solvent, the reactivity of the supported catalysts does not seem to be as great as for the homogeneous catalyst. However, in the case of the zeolite catalyst this difference in activity does not seem to be as great, the third run of the catalyst showing a slightly higher rate of reaction and percentage conversion. This is thought to be as a result of the support. The interaction between the catalyst and support may not inhibit the substitution of a benzene molecule with a phosphine ligand, as suggested in Section 5.4.5.3.

5.5.2 Hydrogenation of Cyclohexene with NaY Zeolite / Caged Catalyst

Table 5.13. Hydrogenation of Cyclohexene with NaY Zeolite/ Caged Catalyst

Catalyst	Solvent	Run Number	Initial Rate / mmol h^{-1}	Conversion / %	Rhodium leached/%
NaY Zeolite / Wilkinson / caged	EtOH	1	24.0	100	0.2
NaY Zeolite / Wilkinson / caged	EtOH	2	43.9	100	0.017
NaY Zeolite / Wilkinson / caged	EtOH	3	41.7	100	0.003
Homogeneous Wilkinson's	EtOH	-	42.8	100	-

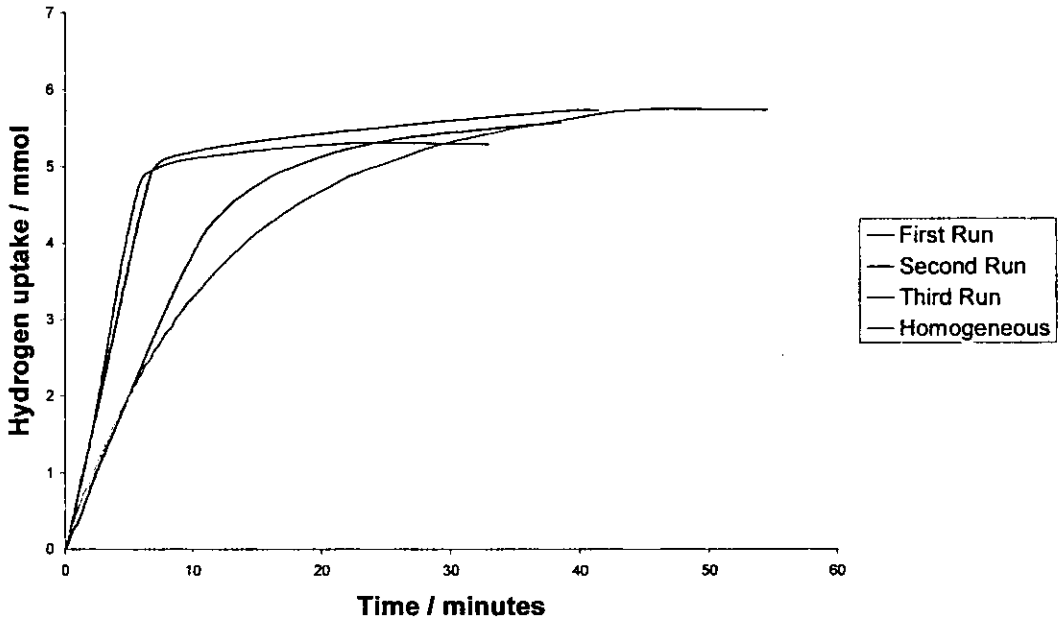


Figure 5.16. Hydrogenation of Cyclohexene with NaY Zeolite/ Caged Catalyst

This catalyst shows the best activity of the supported catalyst with an initial rate very similar to that of the homogeneous catalysts. However, this high rate of reaction is maintained for longer and the hydrogenation of cyclohexene reaches completion quicker than the homogeneous. Again the activity of the catalyst improves after the initial use, one possibility in this case could be leaching from the zeolite. There is some leaching of the catalyst in the first run (0.2 %), this is the greatest amount seen in any of the catalyst tested. The increase in activity in this case could be the result of catalyst molecules being formed within the zeolite cage, but access to the cage being blocked by excess catalyst. The leaching of this excess, which decreases with use, could allow access of the cyclohexene into the zeolite cage and the catalyst 'trapped' there. Thus as the cyclohexene has more contact with the catalyst, the reaction rate improves.

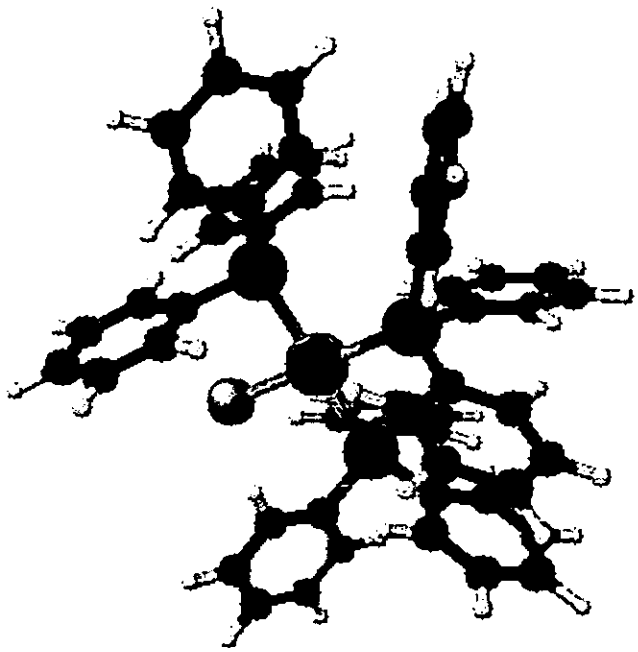
5.5.3 Discussion

5.5.3.1 Increase in Rate After Initial Catalyst Use

All the catalysts tested showed an increased rate after the first use of the catalyst. This increase is particularly significant in the NaY Zeolite / TCE Catalyst, which shows a 2.5 fold increase. One theory for this is the reaction are carried out under high pressures of hydrogen (5 bar Hydrogen). It is speculated that this higher pressure (an increase on atmospheric pressure) in the initial run, favourably alters the active site to increase the reactivity of the catalyst in subsequent runs. Further work would need to be carried out in this area to ascertain if this increase in activity is noted in different conditions. For example, if the hydrogen pressure was reduced, or if the catalyst was subjected to a high pressure atmosphere before its initial use.

5.5.3.2 Increase in activity with NaY Zeolite/ Caged Catalyst

The pore size of NaY zeolite is reported to be 7.4 Å [58, 59], molecular modelling of Wilkinson's Catalysts showed the diameter of the molecule to be 11.833 Å, see Figure 5.17. This would mean that when the catalyst is prepared, before introduction to the support, that it cannot enter the zeolite pore, but must decorate. This could mean that distribution of the catalyst is not uniform over the support, but could form clusters on the zeolite surface. Thus the reactant has limited access to the catalyst and the rate, although increased due to the interaction suggested in Section 5.4.5.3, is not increased as it may do if distribution of the catalyst were more uniform.



Carbon = pale blue
Hydrogen = white
Phosphorus = pink
Chlorine = yellow
Rhodium = grey

Figure 5.17 3D representation of Wilkinson's catalysts, distance of 11.833 Å measured from highlighted carbon atoms (green).

The separate constituents use to prepared Wilkinson's catalyst would fit into the zeolite pore. Therefore, preparing the catalyst *insitu* with the zeolite would allow a 'ship in a bottle' effect, when a large molecule is caged within the zeolite pore. This could allow a more uniform distribution of the catalyst, with some of the molecules forming within the cage, whilst others cover the surface. This more uniform distribution could allow easier interaction between the catalyst and reactant, thus increasing the rate of reaction.

Chapter 6

Homogeneous and Heterogenised Catalysts for the Hydrogenation of Prochiral Imines

HOMOGENEOUS AND HETEROGENISED CATALYSTS FOR THE HYDROGENATION OF PROCHIRAL IMINES

The aim of this study was to investigate the enantioselective hydrogenation of prochiral imines, with a heterogeneous catalyst. The study was to involve the investigation of established heterogeneous systems and the possibility of creating a heterogeneous catalyst through the support of an effective homogeneous catalyst. As described in previous chapters, studies were carried out into the use of commercial heterogeneous catalysts for these hydrogenations and investigations into techniques for supporting a homogeneous catalyst. The work centred on techniques for supporting a homogeneous catalyst was carried out using Wilkinson's catalyst for the hydrogenation of hexenes. The techniques developed in this section of the study were then adapted for the support of catalysts reported as suitable for the enantioselective hydrogenation of the chosen prochiral imines.

Further investigations could be carried out using the successfully supported Wilkinson's catalyst for the hydrogenation of the imines investigated.

6.1 Preparation of Homogeneous Catalysts

As well as the preparation of tris(triphenylphosphine)chlororhodium (Wilkinson's catalyst), used for the hydrogenation of cyclohexene, several homogeneous catalysts were attempted for the hydrogenation of prochiral imines.

Very few problems were encountered with the synthesis of the homogeneous catalysts. Work was able to be carried out on two different homogeneous catalysts with both iridium and rhodium metal centres. These catalysts, synthesis below, were chosen for their reported success in the homogeneous hydrogenation of similar imines. [38, 44]

6.1.1 Preparation of di-μ-chloro-bis(1,5-cyclooctadiene)diiridium(I). $[Ir(COD)Cl]_2$

This complex was made using a general preparation from "Inorganic Syntheses" [84]. 2.0 g of iridium trichloride hydrate (Johnson Matthey) was dissolved in ethanol (34 ml) and water (17 ml). 6.0 ml of 1,5-cyclooctadiene was added, and the solution, refluxed under nitrogen, for 24 hours. The mixture was allowed to cool to room temperature and the $[Ir (COD) Cl]_2$ was collected by filtration and washed with ice-cold methanol to remove any remaining 1,5-cyclooctadiene. The complex was dried in vacuo for 8 hours.

6.1.2 Preparation of di-μ-chloro-bis(1,5-cyclooctadiene)dirhodium. $[Rh(COD)Cl]_2$

This complex was made using an adapted preparation from "Inorganic Syntheses" [84]. 2.0 g of rhodium trichloride hydrate (Johnson Matthey) was dissolved in ethanol (34 ml) and water (17 ml). 6.0 ml of 1,5-cyclooctadiene was added, and the solution, refluxed under nitrogen, for 24 hours. The mixture was allowed to cool to room temperature and the $[Rh (COD) Cl]_2$ was collected by filtration and washed with ice-

cold methanol to remove any remaining 1,5-cyclooctadiene. The complex was dried in vacuo for 8 hours.

Both di-μ-chloro-bis (1,5-cyclooctadiene)diiridium(I) ,$[Ir(COD)Cl]_2$, and di-μ-chloro-bis (1,5-cyclooctadiene)dirhodium(I), $[Rh(COD)Cl]_2$, were successfully prepared as precursors to the rhodium and iridium catalysts used for hydrogenation.

6.1.3 Preparation of Iridium and Rhodium Complex of (4R,5R)-DIOP. Ir-DIOP and Rh-DIOP

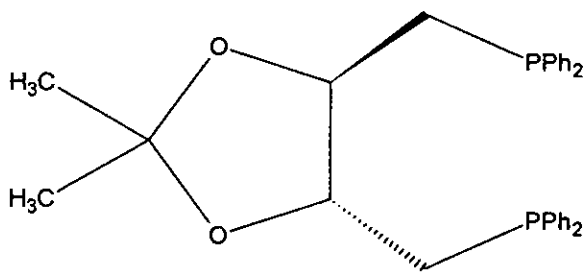


Figure 6.1 (- or +)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphine) -butane. DIOP ligand.

This homogeneous catalyst was prepared *insitu* with the prochiral imine, Morimoto *et al.* [44]. The substrate (5 mmol) was placed in the autoclave liner along with $[Ir(COD)Cl]_2$ (0.16 g), 4R,5R-DIOP (0.299 g, Aldrich), tetrabutylammonium iodide (0.369 g, Aldrich) and 2.5 ml of solvent (ethanol). The mixture was stirred under nitrogen (in the sealed autoclave) for 1 hour, after this time hydrogen was introduced to the reaction mixture and the hydrogenation was carried out at 10-bar hydrogen for up to 10 hours.

For the corresponding rhodium complex, the equivalent procedure was used with $[Rh(COD)Cl]_2$ replacing $[Ir(COD)Cl]_2$.

6.1.4 Preparation of Iridium and Rhodium Complex of (S)-BINAP. Ir-BINAP and Rh-BINAP

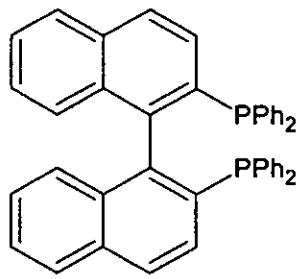


Figure 6.2 BINAP [2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]

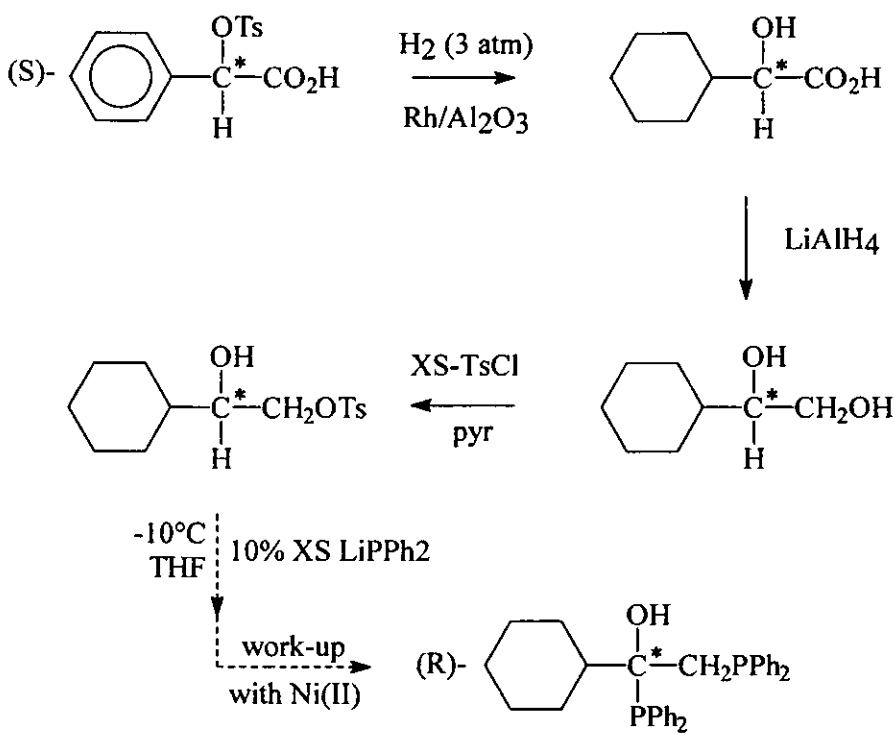
This catalyst was again prepared *insitu* with the imine, Tani *et al.* [38]. The hydrogenation vessel was charged with 5 mmol of the imine to be hydrogenated, $[Ir(COD)Cl]_2$ (9.3 mg), (S)-tol-BINAP (Aldrich, 19.4 mg) and a solution of benzylamine (15 mg) in methanol (2.2 ml). The reaction mixture was stirred under nitrogen for 1 hour, needed to attain a high and reproducible enantioselectivity. After this time, the autoclave was flushed with hydrogen. The hydrogen pressure within the reactor was increased to 6 bar and the hydrogenation was allowed to proceed for up to 10 hours.

For the corresponding rhodium complex, the equivalent procedure was used with $[Rh(COD)Cl]_2$ replacing $[Ir(COD)Cl]_2$.

For each hydrogenation where the catalysts were used, Ir-DIOP, Rh-DIOP, Ir-BINAP and Rh-BINAP were successfully produced in the hydrogenation vessel, in situ, with the imine immediately before hydrogenation.

6.1.5 Preparation of (R)-1,2-bis(diphenylphosphino)cyclohexylethane ((R)-Cycphos)

This ligand was designed for a rhodium centred homogeneous catalyst, for the hydrogenation of imines, Scheme 6.1. This preparation was a multi-step reaction, using the general method of D. P. Riley *et al.* [34] The individual steps are detailed below, Sections 6.1.5.1 to 6.1.5.3.



Scheme 6.1 Preparation of (R)-1,2-bis(diphenylphosphino)cyclohexylethane

6.1.5.1 Preparation of (S)-(+)-Hexahydromandelic acid [34]

(S)-(+)-Mandelic acid (7.6 g, Aldrich) was dissolved in methanol (40 ml) containing glacial acetic acid (5 ml, Aldrich), before being hydrogenated in the presence of 0.05 g of a 5% Rh/alumina catalyst (Johnson Matthey), at 7 bar hydrogen pressure, for a minimum of 10 h. The solution was filtered through Celite, and the methanol removed via rotary evaporation. The white solid formed was dissolved in 100 ml of hot diethyl ether and filtered whilst hot. The volume was reduced to approximately 40 ml, and 25 ml of cyclohexane (BDH) was added. The remaining ether was removed, upon standing in the refrigerator the product ((S)-(+)-hexahydromandelic acid) was formed as white crystals.

6.1.5.2 Preparation of (S)-Cyclohexyl-1,2-ethanediol [34]

5.85 g of (S)-(+)-hexahydromandelic acid was used in this step to prepare (S)-cyclohexyl-1,2 ethandiol. The acid was dissolved in 30 ml of THF (BDH) before being added drop wise to a suspension of lithium aluminium hydroxide (3.21 g, Aldrich) in 60 ml of dry THF at 0°C. Upon complete addition the solution was warmed to 25°C and refluxed for 2 h. The solution was allowed to cool to room temperature, and the excess $LiAlH_4$ quenched by drop wise addition of 5.25 ml of water, followed by 0.7 ml of 4 N NaOH (Aldrich) and finally a further 12 ml of water. The mixture was then refluxed for 1 hour and filtered. The alumina cake remaining was washed five times with 24 ml portions of boiling THF. The combined filtrates were reduced to dryness to give a yellow oil. The oil was

decolourised and dried over calcium sulphate (anhydrous). The solution was filtered and reduced to dryness to yield the desired diol.

6.1.5.3 Preparation of (S)-Cyclohexyl-1,2-bis(*p*-toluenesufonyloxy)ethane [34]

The diol (1.76 g) was dissolved in dry pyridiene (1.25 ml) , and the solution was added drop wise over 0.5 h to an ice cold solution of *p*-toluene-sulfonyl chloride (5.3 g) in dry pyridine. The solution was maintained at 0°C and stirred for 6 hours, forming pyridene hydrochloride as a white precipitate. The reaction was then warmed to 25°C and stirred for an additional 18 hours. Several portions of ice were added with vigorous shaking, destroying an excess TsCl. The product was then poured onto 250 ml of ice, 5.2 ml of concentrated HCl was added, and the mixture stirred for 1 h. A solid was formed, which was collected and washed with water. Dichloromethane was used to redissolve the solid, this solution was then washed twice with 4 ml of HCl (5N), and once with water (6 ml). The organic layer was dried over HgSO4 with activated charcoal, the solution filtered through Celite and its volume reduced by half. While hot 10 ml of cyclohexane was added, the solution was slowly cooled, and stored at 0°C overnight. The product was then collected by filtration.

6.1.5.4 Success of Preparation of (R)-1,2-bis (diphenylphosphino) cyclohexylethane ((R)-Cycphos)

Unfortunately, preparation of this catalyst was unsuccessful; problems were encountered in the final stages of preparation. (S)-(+)-hexahydromandelic acid and (S)-cyclohexyl-1,2-ethanediol, the first two stages in the catalyst's production, were successfully synthesised. Problems were experienced with the final stage of the catalysts production (described in detail in Section 6.1.5.3) when filtration failed to yield the product. Further attempts to synthesise this catalyst were also unsuccessful.

6.1.6 Preparation of Chiral Titanocene catalyst

This titanium centred catalyst (Figure 6.3) had been previously reported as effective in imine hydrogenations. [47] The preparation was a multi-step reaction, all steps were carried out under an argon atmosphere.

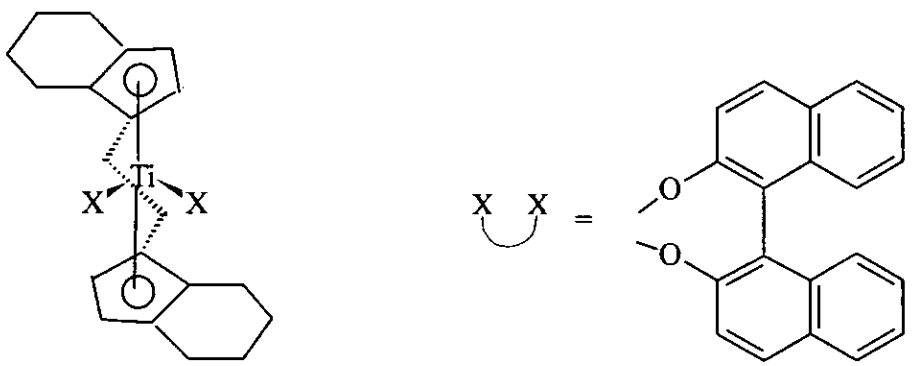


Figure 6.3 *rac*-Ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)titanium Dichloride

6.1.6.1 Preparation of *rac*- and *meso*-Ethylene-1,2-bis(η^5-3-indenyl)titanium Dichloride [47]

1,2-Bis(3-indenyl)ethane (12.92 g) (Aldrich) was dissolved in 500 ml of dry THF. The solution was cooled to 0°C, and a solution of *n*-butyl lithium (2.5M in hexane) was added. The mixture was then allowed to warm to room temperature and stirred for 30 minutes. After this time it was transferred drop wise to a solution of $TiCl_3$ in toluene (50 mmol) (Aldrich), in dry THF (500 ml) over a period of 2 hours. The resulting green-brown solution was stirred for an further four hours before the addition of $CHCl_3$ (50 ml), this solution was left to stir overnight. The dark green solution obtained was reduced *in vacuo* to yield a brown air-stable solid - a mixture of the *meso* and *rac* isomers.

6.1.6.2 Preparation of *rac*-Ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)titanium Dichloride [85]

The complex prepared above was hydrogenated with 10% Pd/charcoal catalyst (Johnson Matthey) in 30 ml of dry dimethoxyethane, under 10 bar hydrogen for 8 hours. After this time the catalyst was removed by filtration, and the solvent evaporated to give a red solid. At this point there is still a mixture of the two isomers.

A chromatic separation, using 0.28 g of product was carried out using reverse phase silica, and cooled solvents. Elution of the column was carried out using

toluene/petroleum ether (1:2), leading to two separated fractions. Evaporation of the solvent should have yielded the required isomer.

6.1.6.3 Success of Preparation of Chiral Titanocene Catalyst

Again problems were experienced with the synthesis of this catalyst in the final stages of the reaction. The preparation of the racemic mixture of isomers was successful, but with low yields (23.5 %). Attempts to separate *rac*-ethylene-1,2-bis(η5-4,5,6,7-tetrahydro-1-indenyl)titanium dichloride from this mixture were unsuccessful.

6.2 Homogeneous Hydrogenation of Prochiral Imines

As discuss in Chapter 4, the hydrogenation of prochiral imines concentrated on small number which were successfully prepared, their preparation being reproducible. Heterogeneous hydrogenation was carried out on four imines, successfully.

Homogeneous hydrogenation was carried out on two of those imines, the more successful of those heterogeneously hydrogenised, using catalysts successfully prepared, detailed above (Section 6.1). Imines hydrogenation with chiral homogenous catalysts were also hydrogenated with the none chiral basis for those catalysts, $[Rh(COD)Cl]_2$ and $[Ir(COD)Cl]_2$.

6.2.1 Hydrogenation of *N*-(1,2-Dimethylpropylidene)aniline

This prochiral imine (Figure 6.4), was comprehensively hydrogenated with heterogeneous catalysts (Chapter 4) and homogeneous catalysts: $[Rh(COD)Cl]_2$, Rh-DIOP, Rh-BINAP, $[Ir(COD)Cl]_2$, Ir-DIOP and Ir-BINAP. To allow comparison with heterogeneous catalysts used, approximately 10 mmol of imine was again used. The catalysts were prepared *insitu* with the imine and hydrogenation carried out as detailed in Section 6.1.4.

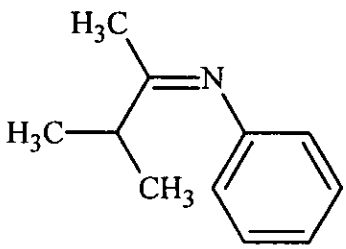


Figure 6.4 *N*-(1,2-Dimethylpropylidene)aniline

Table 6.1 Homogeneous catalyst identification for the hydrogenation of *N*-(1,2-Dimethylpropylidene)aniline

Catalyst	Composition
Rh-COD	Di-μ-chloro-bis (1,5-cyclooctadiene)Dirhodium(I), $[Rh(COD)Cl]_2$. None chiral catalyst.
Rh-DIOP	Rh-COD with chiral ligand, (4R,5R)-DIOP
Rh-BINAP	Rh-COD with chiral ligand, (S)-BINAP
Ir-COD	Di-μ-chloro-bis (1,5-cyclooctadiene)Diiridium(I), $[Rh(COD)Cl]_2$. None chiral catalyst.
Ir-DIOP	Ir-COD with chiral ligand, (4R,5R)-DIOP
Ir-BINAP	Ir-COD with chiral ligand, (S)-BINAP

6.2.1.1 Results and Discussion

Table 6.2 Hydrogenation of *N*-(1,2-Dimethylpropylidene)aniline with all catalysts.

Catalyst	Initial Rate / mmol h^{-1}	e.e. / %	Conversion / %
Rh-COD	40.8	0	65.2
Rh-DIOP	46.8	17.3	15.0
Rh-BINAP	45.6	8.4	18.8
Ir-COD	48.0	0	91.0
Ir-DIOP	42.0	16.5	43.3
Ir-BINAP	40.0	4.0	95.6

The initial rates and enantiomeric excess for these catalysts was much more promising than that for the heterogeneous catalysts based on the methyl pyruvate system. The percentage conversion for the iridium catalysts is greater than for the rhodium, with only slightly lower e.e.'s.

6.2.1.2 Hydrogenation of *N*-(1,2-Dimethylpropylidene)aniline with rhodium homogeneous catalysts.

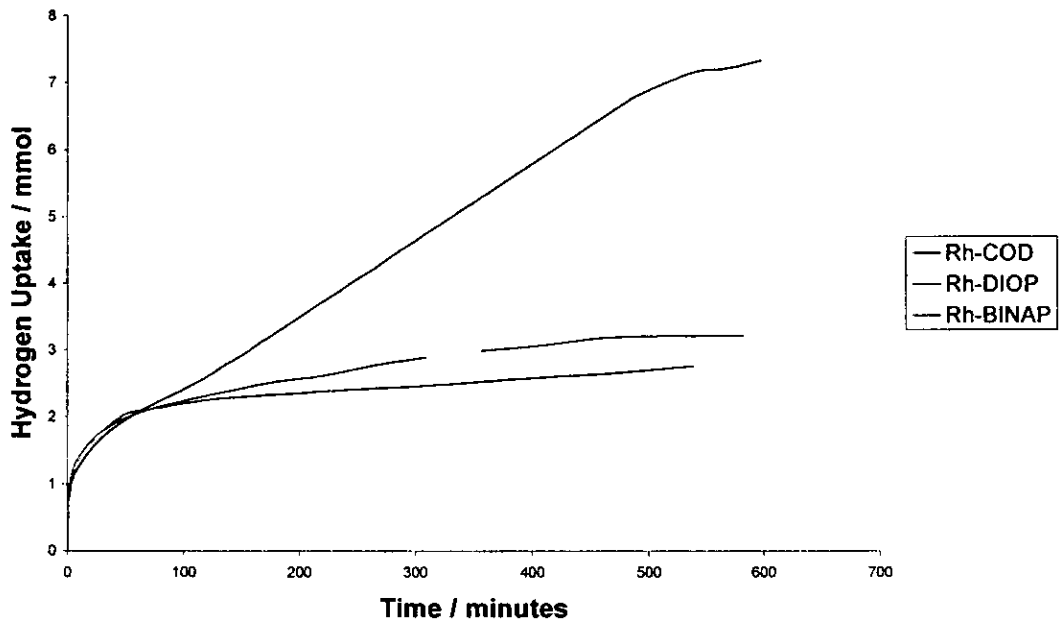


Figure 6.5 Hydrogenation of *N*-(1,2-Dimethylpropylidene)aniline with rhodium homogeneous catalysts.

As can be seen from Table 6.2 and Figure 6.4, the Rh-COD catalyst has the higher conversion, with only a slightly lower initial rate. However, this ligand is none chiral and the resulting amine mixture was racemic. The e.e.'s for the rhodium centred catalysts, despite being low in comparison to the pyruvate studies carried out, were significantly higher than for the rhodium based heterogeneous catalyst. Unfortunately the percentage conversion for the chiral catalysts was very low and disappointing.

6.2.1.3 Hydrogenation of *N*-(1,2-Dimethylpropylidene)aniline with iridium homogeneous catalysts.

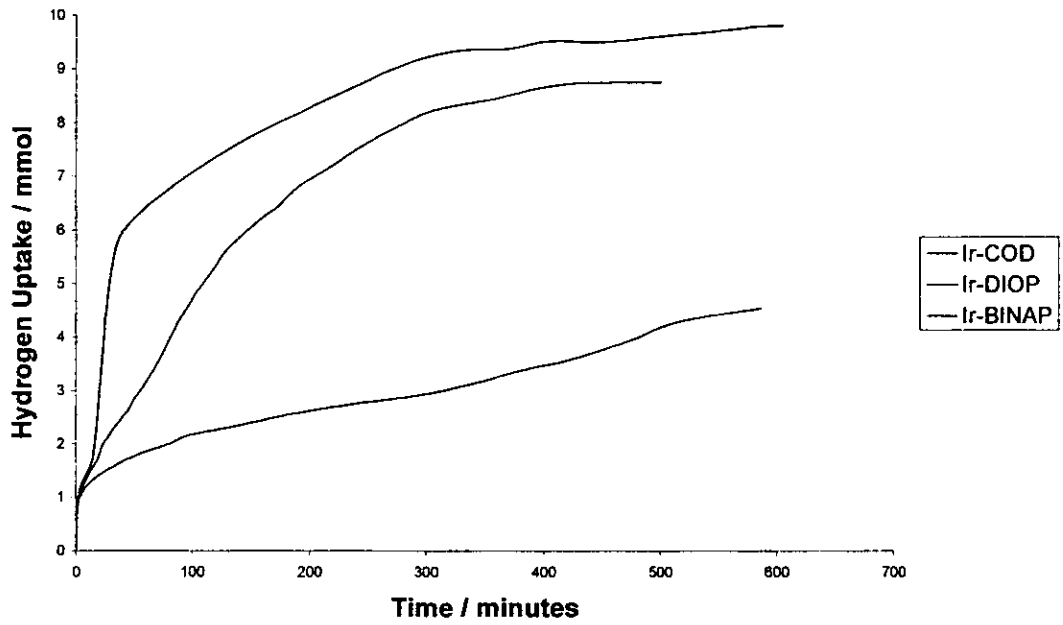


Figure 6.6 Hydrogenation of *N*-(1,2-Dimethylpropylidene)aniline with iridium homogeneous catalysts.

Again the non-chiral catalyst shows a greater percentage conversion. However, in the case of the iridium centred catalysts, the chiral catalyst also shows good rates of conversion; Ir-BINAP showing a higher rate of conversion than Ir-DIOP. The enantiomeric excess is comparable to the rhodium centred catalysts, but is again greater than that noted for the heterogeneous catalysts (1.4 %).

Overall, the homogeneous catalysts showed better activity towards the hydrogenation of *N*-(1,2-dimethylpropylidene)aniline, the iridium centred catalysts being preferred to the rhodium centred catalysts, mainly due to the percentage

conversion achieved. In the case of the iridium catalysts, the Ir-BINAP showed the better conversion, but the Ir-DIOP the better enantiomeric excess.

6.2.2 Hydrogenation of *N*-(1-methylbenzylidene)-2,3-dimethylbutylamine

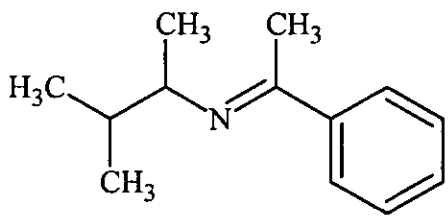


Figure 6.7 *N*-(1methylbenzylidene)-2,3-dimethylbutylamine

The above imine was also hydrogenated using the iridium and rhodium centre chiral catalysts; the non-chiral starting compound (Rh-COD and Ir-COD) was again used as a comparison to the chiral ligands. Approximately 30 mmol of this imine was used for each hydrogenation. The catalysts were again prepared *insitu* with the imine and hydrogenation carried out as detailed in Section 6.1.4.

Table 6.3 Hydrogenation of *N*-(1-methylbenzylidene)-2,3-dimethylbutylamine with all catalysts.

Catalyst	Initial Rate / mmol h^{-1}	e.e. / %	Conversion / %
Rh-COD	66.0	0	19.5
Rh-DIOP	48.0	0.31	43.7
Rh-BINAP	46.8	1.4	61.1
Ir-COD	55.60	0	97.0
Ir-DIOP	52.0	1.5	48.3
Ir-BINAP	45.6	8.4	59.9

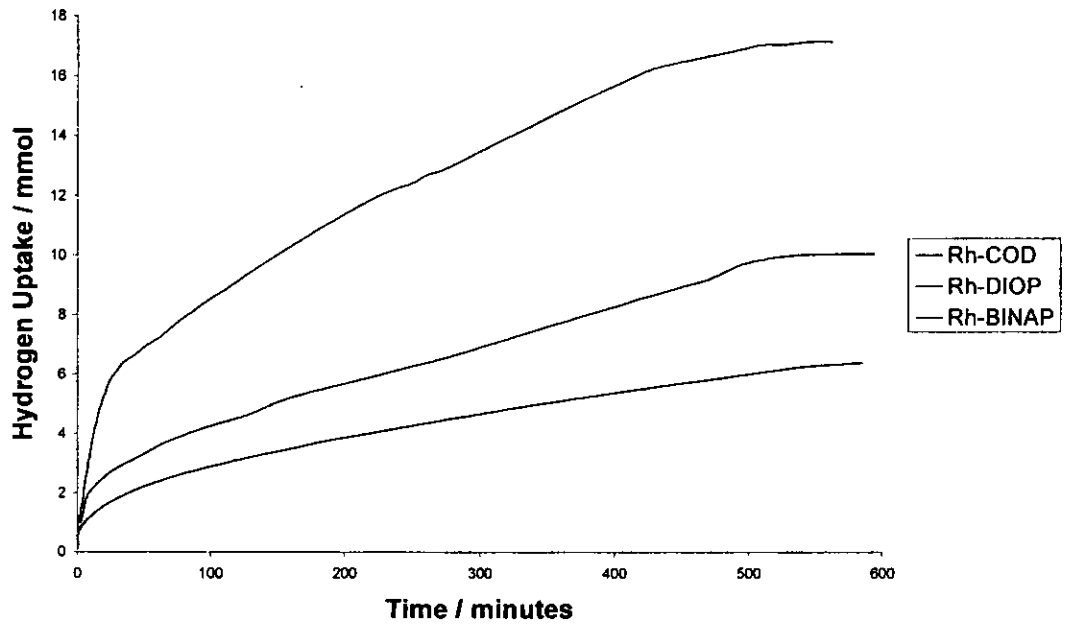


Figure 6.8 Hydrogenation of *N*-(1-methylbenzylidene)-2,3-dimethylbutylamine with rhodium centred catalysts.

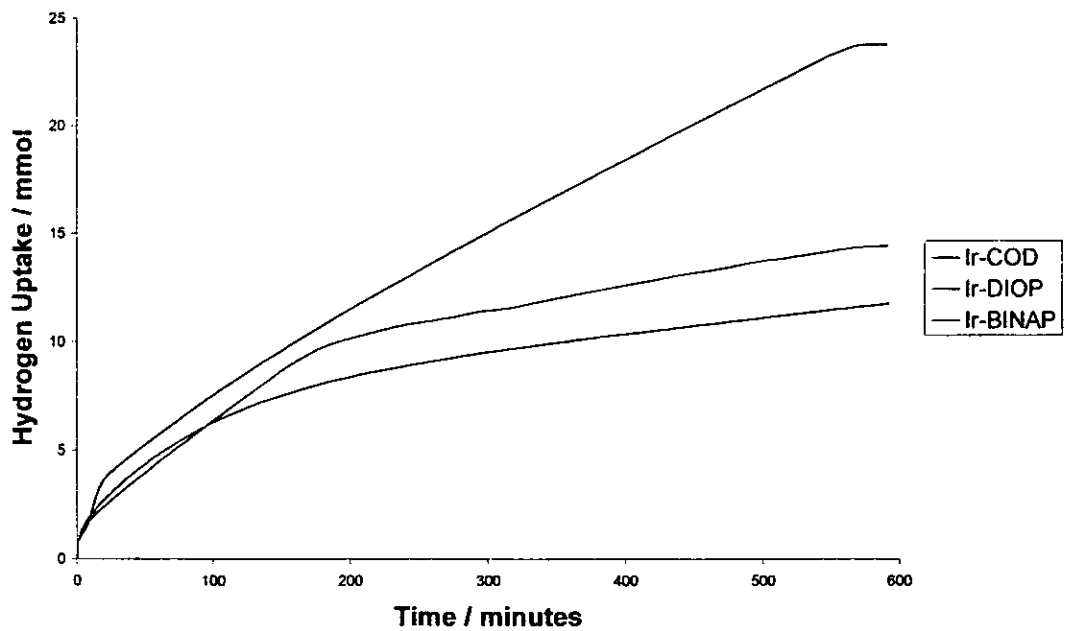


Figure 6.9 Hydrogenation of *N*-(1methylbenzylidene)-2,3-dimethylbutylamine with iridium centred catalysts.

The initial rates of reaction for this imine were very promising, Table 6.3 and Figure 6.8 and 6.9. However, the enantiomeric excesses achieved were not as good as those for *N*-(1,2-Dimethylpropylidene)aniline, Ir-BINAP showing the highest e.e. (8.4 %).

The percentage conversions for the chiral, rhodium centred catalysts are much improved on the first imine and the modified heterogeneous catalyst, but the e.e., as mentioned, was very disappointing, being nearly zero in each case.

Conversions for the Ir-COD and Ir-DIOP are comparable in both imines, the Ir-BINAP shows a lower percentage conversion, but higher enantiomeric excess for *N*-(1-methylbenzylidene)-2,3-dimethylbutylamine.

6.3 Support of Homogeneous Catalyst

Since time was a limiting factor, only one catalyst was chosen to be supported. Rh-BINAP catalyst was tethered using both Montmorillonite clay and NaY zeolite as support. This rhodium centred catalysts was chosen to be a comparison to the rhodium centred Wilkinson's catalyst, on which initial studies were carried out. The BINAP ligand was chosen since higher enantiomeric excesses (1.4 % opposed to 0.31 % for DIOP) and percentage conversion rates were recorded for *N*-(1-methylbenzylidene)-2,3-dimethylbutylamine. Whilst the Rh-DIOP showed better enantiomeric excess for *N*-(1,2-dimethylpropylidene)aniline, it was thought that, as only one catalyst would be supported, to select the most appropriate catalyst for *N*-(1-methylbenzylidene)-2,3-dimethylbutylamine. This imine showed lower enantiomeric excess and percentage conversion than *N*-(1,2-

Dimethylpropylidene)aniline to the rhodium catalysts, so the most suitable catalyst for this imine was chosen.

6.3.1 Support of Rh-BINAP

A 1% loading of catalyst was prepared, tethered to each support. The catalyst was prepared *insitu* with the chosen support, Montmorillonite clay and NaY zeolite, under a nitrogen atmosphere. The clay support was stirred in a solution of 1,1,1-trichloroethane for 30 minutes before addition of the catalyst components, Section 6.1.4. The zeolite support was stirred in a slurry of ethanol for 30 minutes before addition of the catalyst components. The solvent was removed by evaporation before being used for the hydrogenation of *N*-(1,2-Dimethylpropylidene)aniline and *N*-(1methylbenzylidene)-2,3-dimethylbutylamine.

Each supported catalyst was used three times for imine hydrogenation, A.A analysis again being carried out to determine any leaching of the catalyst from the support.

6.3.2 Results and Discussion

6.3.2.1 Hydrogenation of *N*-(1,2-dimethylpropylidene)aniline with supported Rh-BINAP.

Table 6.4 Hydrogenation of *N*-(1,2-dimethylpropylidene)aniline with supported Rh-BINAP.

Catalyst	Run number	Initial Rate / mmol h^{-1}	e.e. / %	Conversion / %	Rhodium leached / %
Rh-BINAP / Montmorillonite	1	30.0	9.7	16.1	0.07
Rh-BINAP / Montmorillonite	2	9.0	8.5	20.9	0.074
Rh-BINAP / Montmorillonite	3	42.0	9.4	46.1	0.07
Rh-BINAP / NaY Zeolite	1	48.0	7.0	29.3	0.034
Rh-BINAP / NaY Zeolite	2	53.5	3.1	28.4	0.034
Rh-BINAP / NaY Zeolite	3	60.0	4.1	38.1	0.034

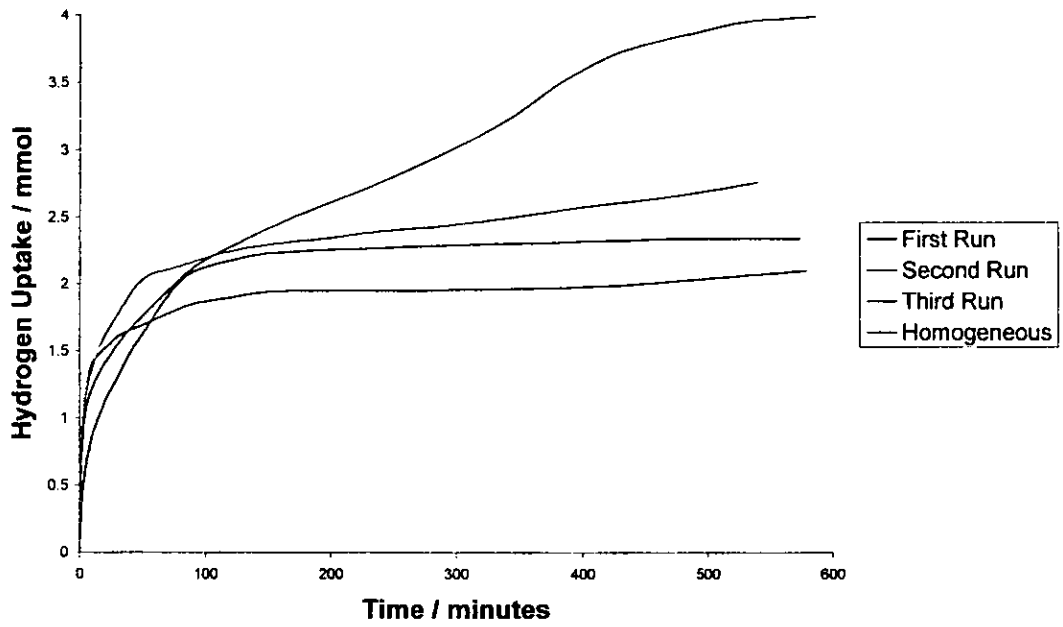


Figure 6.10 Hydrogenation of *N*-(1,2-Dimethylpropylidene)aniline with supported Rh-BINAP / Montmorillonite

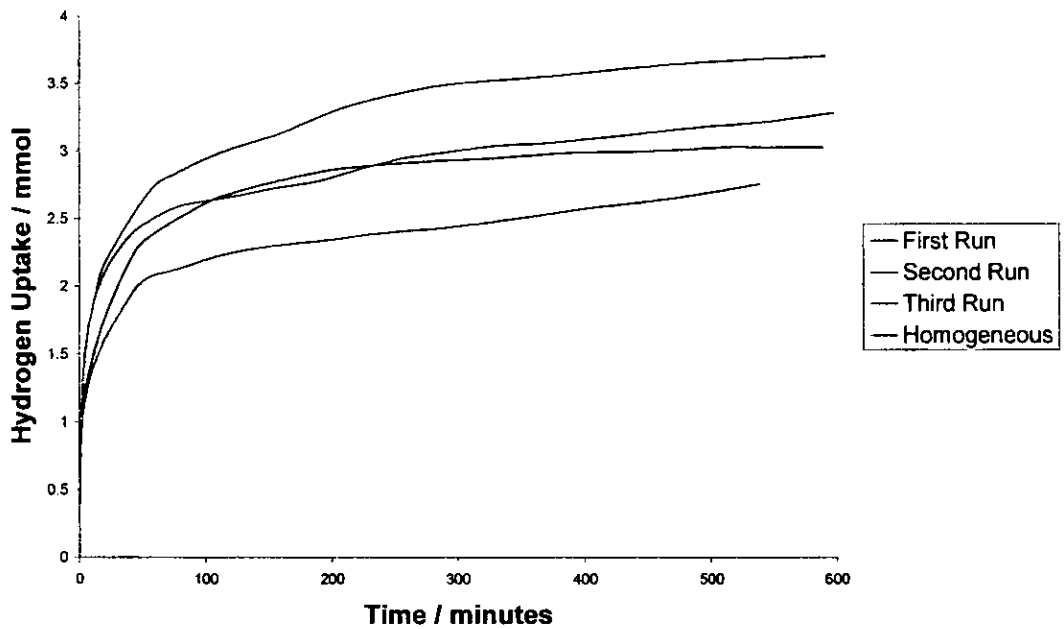


Figure 6.11 Hydrogenation of *N*-(1,2-Dimethylpropylidene)aniline with supported Rh-BINAP / NaY Zeolite

From Table 6.4, it can be seen that the rates of conversion are comparable to those for 5% Rh/alumina from the heterogeneous catalysts (Chapter 4). However, the enantiomeric excess is much improved and is comparable to the homogeneous catalyst, of the same type, in the case of the catalyst support on Montmorillonite clay. For the catalysts supported on the NaY Zeolite, there is a small drop in e.e. when comparing the homogenous catalyst.

Initial rates of reaction for the clay supported catalysts are promising. However, when comparing the overall rate to that of the homogenous system (Figure 6.10), it can be seen that the first and second run show poorer rates to the homogeneous system, despite an increase in rate between the first and second run. The third use of the supported catalyst shows an increase in rate when compared to the homogeneous system. The catalyst appears to be improving with use; further studies would help determine if this trend continued.

The zeolite supported catalyst shows good initial reaction rates, which are shown to increase with use, as noted with the clay catalyst. All runs with the supported catalyst show a higher rate of reaction than for the homogeneous system for this imine.

The atomic adsorption analysis for both supported catalysts showed leaching of rhodium from the support. Although this is in very small amounts, it is greater than that seen with the Wilkinson's supported catalysts and the leaching does not appear to decrease significantly. This leaching, although small, and seeming not to affect

the activity, could be significant over the life time of a catalyst and result in deactivation of the catalyst.

6.3.2.2 Hydrogenation of *N*-(1-methylbenzylidene)-2,3-dimethyl butylamine.with supported Rh-BINAP.

Table 6.5 Hydrogenation of *N*-(1-methylbenzylidene)-2,3-dimethyl butylamine.with supported Rh-BINAP.

Catalyst	Run number	Initial Rate / mmol h^{-1}	e.e. / %	Conversion / %	Rhodium leached / %
Rh-BINAP / Montmorillonite	1	56.0	13.9	28.7	0.08
Rh-BINAP / Montmorillonite	2	26.0	2.3	27.6	0.08
Rh-BINAP / Montmorillonite	3	52.5	5.5	11.6	0.033
Rh-BINAP / NaY Zeolite	1	68.6	2.2	2.0	0.041
Rh-BINAP / NaY Zeolite	2	68.4	6.9	78.5	0.044
Rh-BINAP / NaY Zeolite	3	60.0	1.9	36.4	0.044

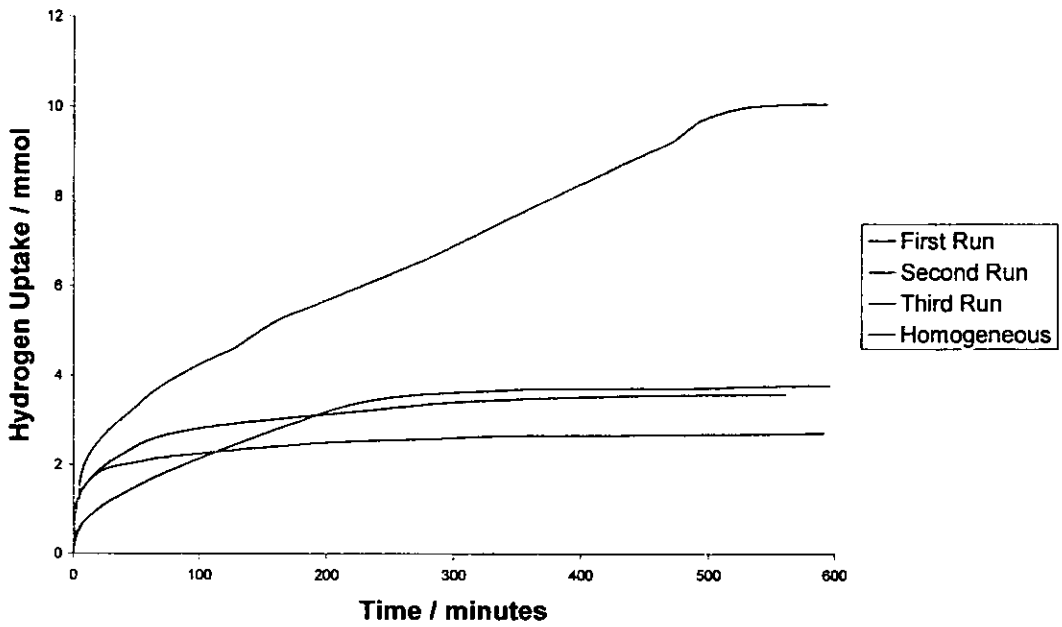


Figure 6.12 Hydrogenation of *N*-(1-methylbenzylidene)- 2,3-dimethyl butylamine with supported Rh-BINAP / Montmorillonite

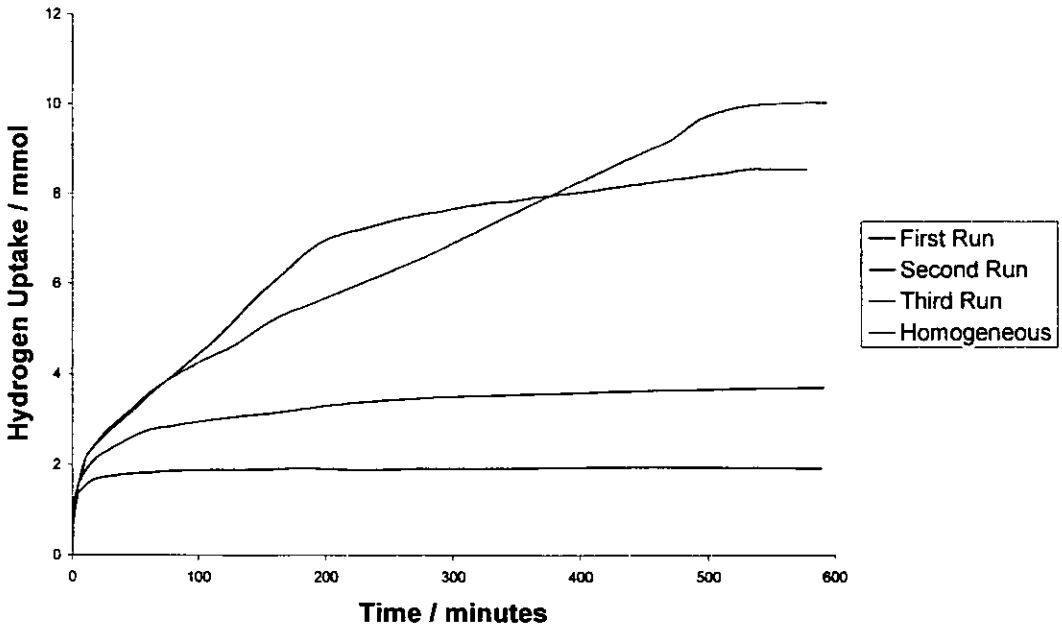


Figure 6.13 Hydrogenation of *N*-(1-methylbenzylidene)- 2,3-dimethyl butylamine with supported Rh-BINAP / NaY Zeolite

As can be seen from Table 6.5, the percentage conversion is much lower than for the homogeneous and heterogeneous catalysts previously attempted. There is, however, an increase in the enantiomeric excess compared to previous rhodium catalysts used.

For the clay-supported catalyst the reaction rate is much lower than for the homogeneous system. There is also a drop in the rate of reaction after the first use, and a drop in e.e. and percentage conversion is also noted. Despite an increase in the e.e. between run 2 and 3, this seems to suggest some deactivation in the catalyst, further studies would show if this trend continued with repeated use. There is a small amount of rhodium leaching from the catalyst after each run, decreasing in the final use. This could show that the deterioration in the catalyst is reducing, only further tests could establish if this deterioration had stopped.

The zeolite-supported catalyst also shows a lower rate than for the homogeneous system for the first and last runs. However, it also shows the increase in activity after the first use, as marked upon for the series of supported Wilkinson's catalysts tested (Chapter 5). Unfortunately this activity is seen to drop again for the third run. Although, for the third run, the percentage conversion does not drop to that of the first run, it is still significantly lower than the second use of the zeolite catalyst. There is very little leaching of rhodium from the support, but it is maintained, suggesting that over time deactivation would be inevitable.

6.3.2.3 XRD Analysis

As with the supported Wilkinson's catalysts, XRD analysis was carried out to establish if the distance between the clay layers was altered by the presence of the catalyst. For comparison analysis was also carried out on the clay and the clay in the solvent used for preparation (1,1,1-trichloroethane).

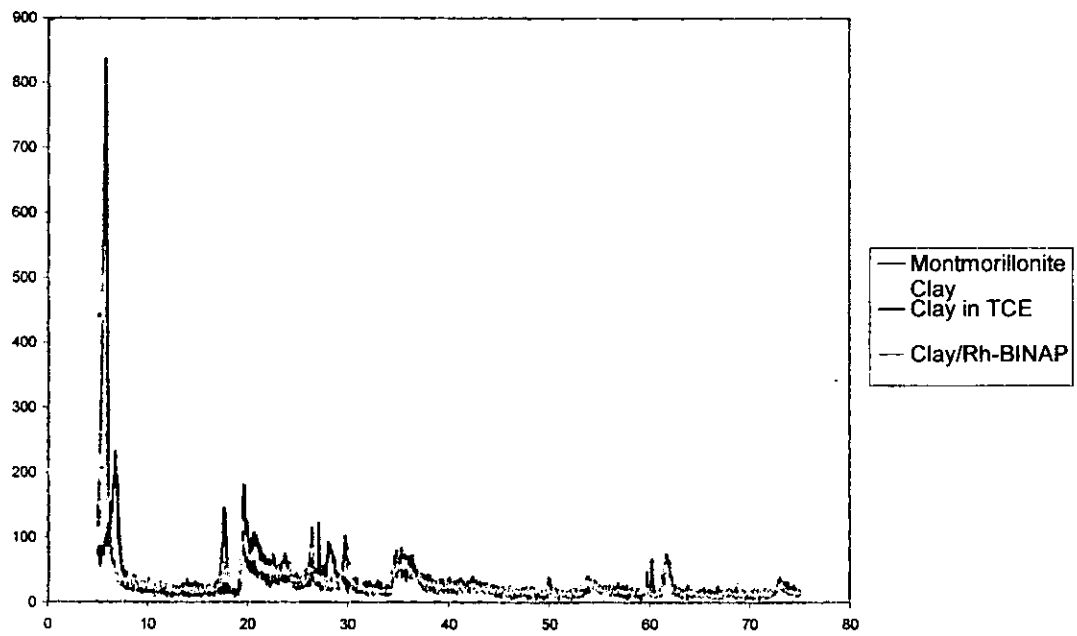


Figure 6.14 XRD Analysis of Montmorillonite clay supported Rh-BINAP.

Figure 6.14 has been given a darker background to enable easier identification of the different series.

As can be seen from Figure 6.14 there is a difference in the layers when the clay is in solution with 1,1,1-trichloroethane. This difference has decreased on analysis with the catalyst present, but not returned to the untreated clay, suggesting that the

catalyst has indeed been sandwiched between the layers. Therefore supporting and heterogenising the catalyst.

6.3.3 Discussion

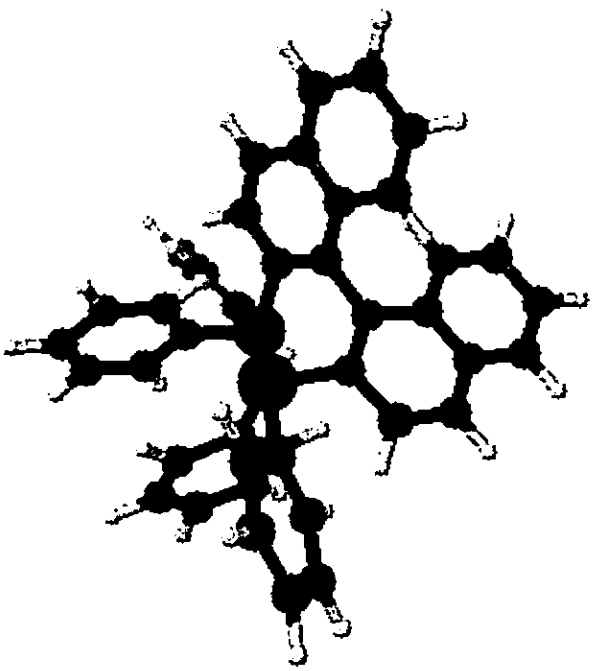
6.3.3.1 Clay Supported Catalysts

For both the imines hydrogenated with Rh-BINAP supported on Montmorillonite clay, there is a drop in activity, when comparing initial rate and percentage conversion. Similar research in this area [68] suggest that the acidity and the structural properties of the clay used to support the catalyst play an important role in the stability of each catalyst. Since this drop in activity was not noted for the worked carried out with supported Wilkinson's catalyst for the hydrogenation of cyclohexene, it is suggested that this clay was not suitable for this homogeneous catalyst and perhaps the catalyst has been affected by the acidity of the clay. Further studies in this area would help to resolve this question, the use of the supported Wilkinson's catalyst for the hydrogenation of these imines may also help resolve this issue.

6.3.3.2 Zeolite Supported Catalysts

Molecular modelling of this catalyst shows that it would only decorate the surface, despite the catalyst being made in situ with the zeolite. The pore size of NaY Zeolite is quoted as being 7.4 Å. [58,59] The distance across the BINAP ligand molecule, according to molecular modelling is 11.244 Å (Figure 6.15), therefore it would be

difficult for the ligand to enter the zeolite pore and for the catalyst to enter. Studies were still carried out using this zeolite, in order to provide a comparison to the clay supported catalyst; and to ascertain if it was necessary for the catalyst to be encapsulated within the pore in order to create a successful heterogenised catalyst. It was also thought that the ligand may enter the pore by 'rotating', thus allowing the catalyst to be prepared in the zeolite cage. Further characterisation of the supported catalyst would determine if this were in fact the case.



Carbon = pale blue

Hydrogen = white

Phosphorous = pink

Figure 6.15 3D representation of BINAP ligand, distance measured between carbon atoms highlighted in green.

Further studies involving the support of catalysts containing the DIOP ligand may prove more successful at creating a supported catalyst. Molecular modelling shows the ligand is smaller and may more easily enter the zeolite pore. Figure 6.16 shows 3D representations of the ligand. The distance between selected carbon atoms, highlighted in green, was measured at 7.724 Å and 7.719 Å respectively.

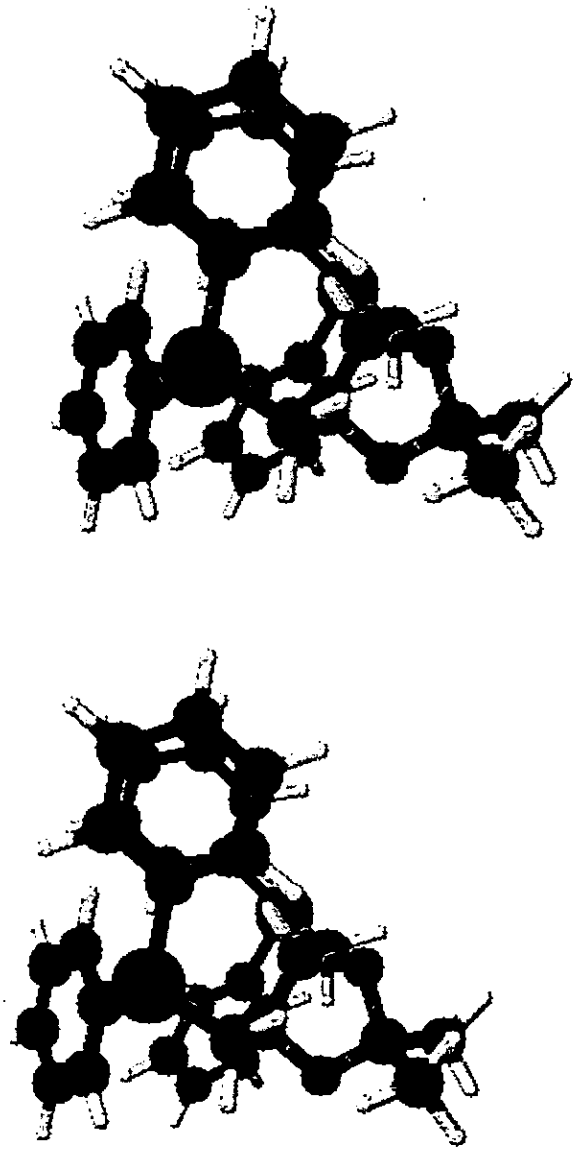


Figure 6.16 3D representation of DIOP ligand, distance measured between carbon atoms highlighted in green.

For *N*-(1,2-dimethylpropylidene)aniline an increase in rate of reaction is seen for the zeolite supported catalyst. The activity of the catalyst, as far as rate of reaction is concerned seems to improve with each run. It is thought that since the catalyst merely decorates the surface of the zeolite, and that a small amount of leaching is noted after each run, that the catalyst is not uniformly distributed over the surface. The small amount of leaching improves the uniformity of distribution and the catalyst is more active. Further studies would need to be carried out to ascertain if this was the case, and if repeated use of the catalyst continued to increase its activity.

For *N*-(1-methylbenzylidene)- 2,3-dimethyl butylamine, the order of activity is first run < third run < second run < homogeneous. This suggests, combined with the leaching noted, that the distribution of the catalyst reaches its optimum on the second run with this imine, before deactivation begins with the third use. Again further studies, involving extended use of the catalyst would help to ascertain if this were indeed the case.

Chapter 7
Conclusions and Future Work

CONCLUSIONS AND FURTHER WORK

7.1 Methyl Pyruvate Hydrogenations

The investigation into the hydrogenation of methyl pyruvate was intended as a lead in to the investigations with imines. As well as looking at the catalysts for industry, the initial aim was that a heterogeneous imine hydrogenation catalyst could be modelled on the pyruvate system.

The series of catalysts tested showed no improvement, or match, for the established platinum catalyst modified with cinchona alkaloids. However, in some respects the results were very interesting, especially those for Catalyst A and Catalyst B. These catalysts showed a reduction in the reaction rate and enatioselectivity when modified with cinchonine (Section 3.4.3). As discussed this was unexpected, but due to the confidentiality clauses and time limitations for this part of the study, no further investigations were carried out.

7.2 Synthesis of Prochiral Imines

Several problems were encountered when attempting to prepare imines for hydrogenation. Imines tend to have a short shelf life and therefore needed to be prepared and hydrogenated quickly.

Work initially concentrated on the synthesis of imines which would mirror the methyl pyruvate system (ethyl 2-iminpropanoate and methyl 2-iminopropanoate,

Section 4.1.1). This would then enable catalysts established for the hydrogenation of methyl pyruvate to be used for the hydrogenation of the prochiral imines. However, attempts to make such imines in a pure enough form to hydrogenate and analyse the results were unsuccessful.

Imines were successfully prepared, using a synthesis which involved microwave irradiation [77], (Section 4.1.8 and Section 4.1.9). Using this method three different imines were prepared; *N*-(1,2-dimethylpropylidene)aniline, *N*-(1,2-dimethylpropylidene)benzylamine and *N*-(1methylbenzylidene)-2,3-dimethyl butylamine. The yields from this synthesis were between 15 % and 22 %, but they were easily synthesised and purified to be successfully hydrogenated with both homogeneous and heterogeneous catalysts.

A further imine was prepared, (Section 4.1.10 - *N*-(α-methylbenzylidene) benzylamine) in high yields (86.7 %). Hydrogenation with a heterogeneous catalyst was carried out and initial results were very promising, but due to analysis difficulties hydrogenation of this imine was limited.

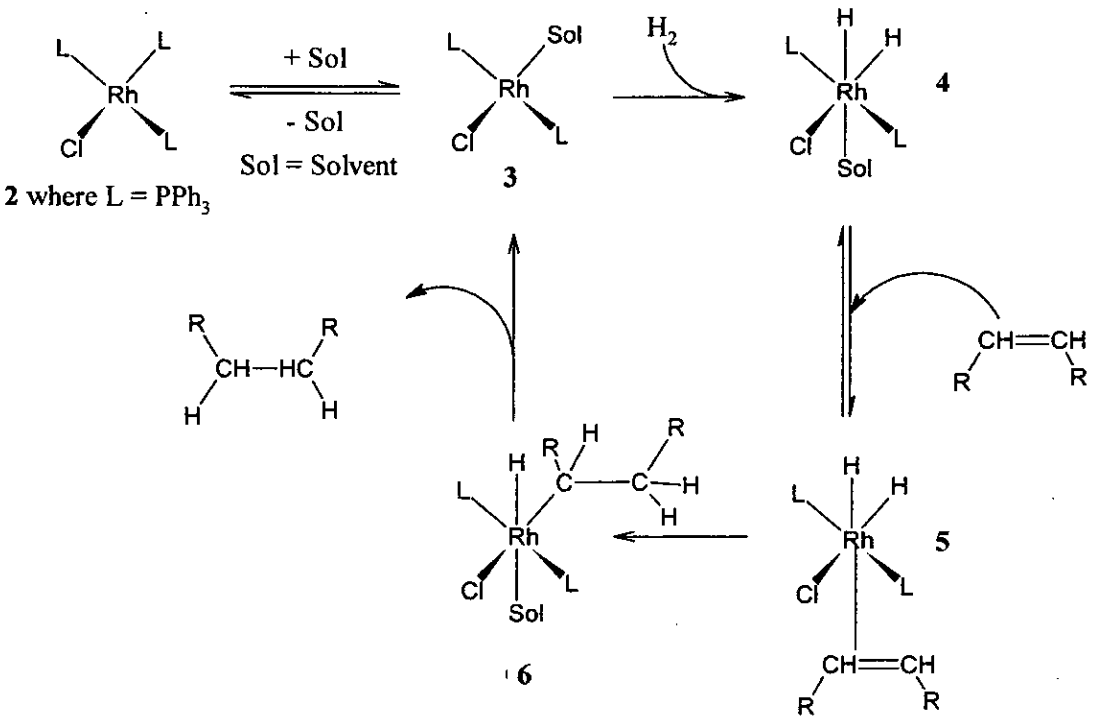
7.3 Wilkinson's Catalyst

The work carried out, initially to investigate methods of support for the imine catalysts, proved to be very successful. When the hydrogenation of cyclohexene was carried out homogeneously an ethanol solvent proved to give the highest yields. Although this was still the case with the supported catalysts, there was an increase in activity for supported catalysts run in ethanol and, more significantly, 1,1,1

trichloroethane. This increase in activity for clay supported catalysts showed an order of activity related to the swelling properties of the solvent on the clay (1,1,1, trichloroethane > ethanol > benzene) with benzene showing a drop in activity when supported. It is also thought that the role of the solvent in the catalytic process may result in a difference in activity. The catalytic cycle for Wilkinson's catalyst (Section 1.3) suggests that the solvent substitutes for one of the phosphine ligands in the initial stages of the cycle. It is suggested that this substitution of a solvent molecule is affected, depending upon the solvent used, possibly hindering or inhibiting this stage of the cycle, (Section 5.4.1).

It is thought that the use of benzene as a solvent allowed the formation of complex **3** (Scheme 7.1) with electrons being withdrawn on to the delocalised π-system of the benzene ring. The complex formed in this way is not thought to be as stable as that formed with ethanol.

When using trichloroethane as a solvent, it is thought that the lone pairs of electrons on the chlorine hinder the formation of complex **3**, potentially deactivating the complex, thus thwarting the catalytic cycle.



Scheme 7.1 The catalytic cycle for the hydrogenation of alkenes by Wilkinson's catalyst (**2**). [29]

Two methods of removing the solvent were attempted, filtration and evaporation. This showed that removing the solvent via filtration resulted in slightly higher initial rates and removing the solvent via evaporation resulted in slightly higher percentage conversions. This difference in activity has been attributed to a difference in the catalyst surface as a result of the removal of the preparation solvent. Similar work in this area suggests that small differences in the catalyst surface can result in an altered activity.[68]

Catalysts supported on zeolite showed an increase in activity after the initial run. It is thought that the higher pressure the reaction is run at favourably alters the active site of the catalyst, resulting in subsequent runs showing a higher activity.

Zeolite supported catalysts also showed a much greater activity when the catalyst was prepared in situ with the support. This is due to a more uniform distribution of the catalyst, since the catalyst constituents are able to enter the zeolite pore, the catalyst forms within the pore, allowing for more even distribution of the catalyst.

7.4 Hydrogenation of Imines

7.4.1 Hydrogenation of *N*-(1,2-Dimethylpropylidene)aniline

Hydrogenation of this imine was the most comprehensive. Studies showed that with heterogeneous catalysts, modified with cinchona alkaloids, this imine gave very poor enantiomeric excess, 6.7 % being the highest achieved with 5% Rh / alumina / CN. It is thought that the size and shape of the molecule hindered its interaction with the modifier, preventing high e.e.'s and disappointing conversions. A contribution to the low percentage yield of the chiral amines was attributed to the position of the molecule on the catalyst surface, which prevented the C=N double bond being easily hydrogenated.

Work carried out with homogeneous and supported homogeneous catalysts showed much more promise. High conversions (95.6 %) were achieved with the iridium catalysts used, but rhodium catalysts showed better enantioselectivity (Rh-DIOP giving 17.3 %).

Enantiomeric excess with the supported catalysts was disappointing, Montmorillonite clay supported catalysts showing the highest e.e. (9.7 %), a drop in

percentage conversion was also noted for both the clay and zeolite support. It is thought that the acidity and clay structure could be affecting the activity of the catalysts, as suggested by other groups. The zeolite support showed more promise as there was an increase in reaction rate with each use of the catalyst. Since this was accompanied by a small amount of leaching, it is thought that the catalyst was unable to enter the zeolite pore and was non-uniformly distributed over the surface; the leaching after each use allowing a more uniform and more active catalyst.

7.4.2 Hydrogenation of *N*-(1,2-Dimethylpropylidene)benzylamine

Due to time limitations and low imine yields from its synthesis, this imine was only hydrogenated with a heterogeneous catalyst (un-modified 5% Pt/alumina). Despite showing a good initial rate of reaction the conversions were poor and were lower than those achieved for *N*-(1,2-dimethylpropylidene)aniline with the same catalyst.

7.4.3 Hydrogenation of *N*-(1methylbenzylidene)-2,3-dimethylbutylamine

This imine was chosen since it was the 'reverse' of *N*-(1,2-dimethylpropylidene)aniline, in that the aromatic group was on the other side of the C=N bond; it was hydrogenated both homogeneously and heterogeneously.

When hydrogenated with heterogeneous catalysts, this imine showed much higher yield of its corresponding amine, than noted for heterogeneous hydrogenation of *N*-(1,2-dimethylpropylidene)aniline. However, the enantioselectivity was quite low, in all cases. The high percentage conversion of imine to amine has been attributed to

the position the imine would lie on the catalyst surface, its bulky structure meaning the C=N double bond was raised from the metal surface and more easily hydrogenated than *N*-(1,2-dimethylpropylidene)aniline.

Homogeneous hydrogenation showed that a BINAP ligand gave the best yield of amine (61.1 %), with Ir-BINAP giving the highest enantiomeric excess (8.4 %). Support of Rh-BINAP showed that a clay support reduced the activity of the catalyst. It is thought that the clay surface structure and its acidity affected the activity of the catalyst, which decreased over subsequent hydrogenations.

As previously mentioned the catalyst Rh-BINAP could not enter the pores of the zeolite and it is supposed decorated the zeolite surface non-uniformly. This imine showed a similar trend to that seen with *N*-(1,2-dimethylpropylidene)aniline, in that the activity increased with the second run, however, the third run showed a lower activity. It is thought that a small amount of leaching lead to the catalyst being more uniformly distributed, but further leaching lead to deactivation of the catalyst beginning to occur.

7.4.4 Hydrogenation of *N*-(α-methylbenzylidene) benzylamine

This was initially the most promising of the imines hydrogenated heterogeneously. Unfortunately only initial rates with an un-modified 5% Pt/alumina catalyst were recorded (59.8 mmol h^{-1}), since analysis of the chiral amines produced proved difficult. Resolution of the chiral amines was not achieved.

7.5 Future Work

7.5.1 Pyruvate Esters

There are several interesting phenomena that have been observed during the course in this study which would benefit from further work. First, the methyl pyruvate hydrogenations carried out over the alkaloid modified catalysts A and B displayed very unusual behaviour. Traditionally, supported platinum catalyst modified with cinchonidine display a proximately 5% greater enantiomeric excess than catalysts modified by cinchonine. This result from the cinchonidine and cinchonine not being exact enantiomers of each other and consequently have slightly differing adsorption geometries.. Catalyst A and B both display a 3-fold difference in enantioselectivity when modified with cinchonidine compared to that observed with cinchonine. Therefore we must conclude on these catalysts the adsorption geometry between the two chiral modifiers must differ substantially. In depth characterisation of these catalysts in terms of the platinum particle size and shape the pore size and pores size distribution and elemental analysis to determine the presence of any catalyst promoters would give an insight into factors that govern the adsorption of the alkaloid to the catalyst surface.

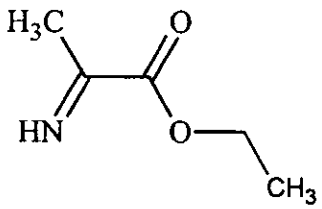
In-situ spectroscopic (infra red or Raman) studies of the modified catalysts could provide information concerning the adsorption of the cinchona alkaloid onto the surface has occurred. Such analysis could also help to establish the reason for the reduction in enantioselectivity and rate of reaction, discussed above.

In the course of this work, it was noted that there was a difference between the hydrogen uptake of the reaction and the percentage conversion. Suggesting that more hydrogen was taken up by the reaction than would account for the conversion calculated. This implies that there must be secondary processes occurring which could provide interesting results and further insight into the different catalysts used.

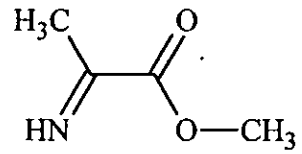
When using the Pt/Mg:ZrO_2 catalyst it was noted that when the catalyst was used with a modifier present an increase in the percentage conversion was noted, this was not reflected by an increase in enantiomeric excess. This could suggest that the modifier was acting as a promoter for the reaction. Further studies would be needed to establish if this was indeed the case.

7.5.2 Synthesis and Heterogeneous Hydrogenation of Prochiral Imines

Several problems were encountered in the synthesis of the imines. To establish if the heterogeneous catalysts used for imine hydrogenations could be successfully used for imines, similar to methyl and ethyl pyruvate, further attempts to synthesise these imines and hydrogenate them should be attempted. The reaction mechanism for the hydrogenation of methyl and ethyl pyruvate with 5% Pt/alumina, modified with cinchona alkaloids, has been well researched. [21] The proposed template model suggests that if such catalysts were to be used for imine hydrogenation, their structure should be similar to that of the pyruvate, ethyl 2-iminopropanoate and methyl 2-iminopropanoate (Figure 7.1).



A



B

Figure 7.1 Ethyl 2-iminopropanoate (A) and Methyl 2-iminoporpanoate (B)

The preparation of *N*-(α-methylbenzylidene)benzylamine (Figure 7.2) was the most successful, resulting in a product which could be prepared easily, in large quantities and stored for short periods of time (approximately 7 days, refrigerated) without degrading. However, problems were experienced with the resolution of the two enantiomers produced when the prochiral imine was hydrogenated. Further attempts and investigations to resolve the chiral amines produced may prove more successful.

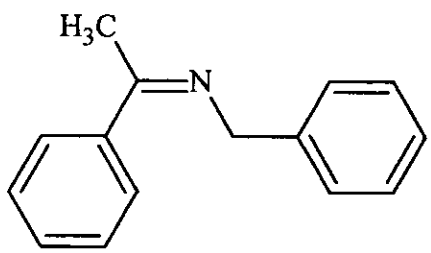
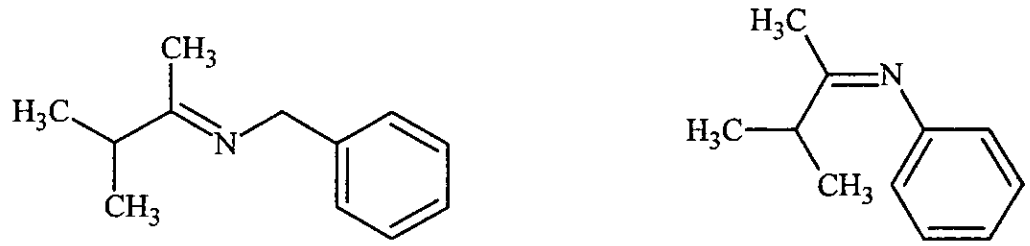


Figure 7.2 *N*-(α-methylbenzylidene)benzylamine

Investigations into the hydrogenation of this imine (*N*-(α-methylbenzylidene) benzylamine) with heterogeneous catalysts showed very interesting resulting with respect to rate of reaction. However, as the chiral amines were not resolved, further work is needed to ascertain if any enantiomeric excess were possible. This would involve hydrogenation with heterogeneous, homogeneous and supported chiral catalysts.

The successfully prepared imines which were then hydrogenated, *N*-(1,2-dimethylpropylidene)aniline, *N*-(1,2-dimethylpropylidene)benzylamine (Figure 7.3), were not investigated as fully as they might have been, due to time constraints. In particular the hydrogenation of *N*-(1,2-dimethylpropylidene)benzylamine with cinchona alkaloid modified heterogeneous catalysts used to hydrogenate *N*-(1,2-dimethylpropylidene)aniline; i.e. 5% Pt/alumina, 5% Ir/alumina, 5% Rh/alumina modified with cinchonidine and cinchonine.



A B

Figure 7.3 *N*-(1,2-dimethylpropylidene)benzylamine (A) and *N*-(1-methyl benzylidene)aniline (B).

No investigations into possible hydrogenation reaction mechanisms were carried out for the imines hydrogenated. Such investigations may help resolve some of the issues noted on examination of the results. For example, low enantiomeric excess, large differences in conversions noted for the different metals used; 5% Ir/alumina showing much higher conversions than those achieved for platinum or rhodium metal catalysts.

Hydrogenation of Cyclohexene

Work carried out supporting homogeneous catalysts, including Wilkinson's catalysts, has raised a number of questions as to the interaction of the catalyst with the support and the effect the clay surface and acidity of the clay has on the rate of reaction. Zeolite supported Wilkinson's catalysts showed an increase in activity after the initial use. Work needs to be carried out to ascertain if this is a result of the pressure in which the of the first catalyst run is carried out, i.e. above atmospheric pressure, as for all uses of the catalysts. Further investigation also needs to be carried out into the life time of supported catalysts and whether trends noted over the three uses of the catalyst were representative of the lifetime of the catalyst.

Again studies into possible reactions mechanisms for the supported Wilkinson's catalysts may provide valuable insight into the interaction of the catalyst and support and the effectiveness of different solvents. Such research would perhaps identify the cause for an increase in rate of reaction which was noted for Wilkinson's catalyst supported on clay and used in a 1,1,1-trichloroethane solvent.

Ethanol is the preferred solvent for hydrogenating cyclohexene with Wilkinson's catalyst. This research looked at the use of clay supported catalysts prepared in ethanol and used in ethanol, it also looked at catalysts supported in 1,1,1-trichloroethane and run in ethanol. However, the use of a supported catalyst prepared in benzene and run in an ethanol solvent was not investigated. Such studies may allow further understanding of, not only the solvent, but also how the catalyst is tethered to the support and any affects the solvent may have on the catalytic cycle.

When comparing the affect of different solvents on the hydrogenation of cyclohexene it was suggested that the solvent used may hinder or inhibit the completion of the catalytic cycle, resulting in low yields of cyclohexene. Low conversions of cyclohexene to cyclohexane were particularly noticeable with 1,1,1-trichloroethane. Further investigations into the role and influence of different solvents on the catalytic cycle need to be carried out in order to ascertain if the catalytic cycle is indeed impinged on by the solvent used.

When considering the interaction between the catalyst and the support it was not possible to state how the catalyst was tethered to the support; i.e. was the catalyst sandwiched between the layers of clay and entrapped within the zeolite pore. Further analysis of the supported catalysts may help to define the supported catalyst more accurately. This analysis would also help to determine the percentage loading of the catalyst onto the support. In this study it was assumed that, during the synthesis of the supported catalyst, all the catalyst was 'taken up' by the support; this may not be the case, especially where different solvents were used in the preparation.

7.5.3 Homogeneous and Heterogenised Catalysts for the Hydrogenation of Prochiral Imines

Imine hydrogenation with supported homogeneous catalysts has raised a number of issues which need further study. The BINAP ligand, chosen to be supported for imine hydrogenation is thought not to be able to enter the zeolite pore, allowing encapsulation, catalyst characterisation would resolve this issue. If the ligand could not enter the pore of the NaY zeolite, creating an encapsulated chiral catalyst,

perhaps a different zeolite with a larger pore size would create a more effective catalyst.

Molecular modelling shows that the DIOP ligand is more likely to be able to enter the NaY zeolite pore. This may create a more effective zeolite supported catalyst than the Rh-BINAP investigated. Studies carried out in this area should include catalyst characterisation and, as with the BINAP ligand the possible use of different zeolites as supports.

Due to time limitations the use and application of heterogenised versions all the homogeneous catalyst investigated was not possible. Therefore, a study involving the support and use as chiral hydrogenation catalysts of Ir-BINAP, Rh-BINAP and Rh-DIOP would provide a valuable insight into the enantioselective hydrogenation of prochiral imines.

Again, no research was carried out into possible reaction mechanisms for the hydrogenation of these imines. Such analysis may help understand the results achieved and produce a more effective catalyst for enantioselective hydrogenation.

The use of a supported Wilkinson's catalyst for the hydrogenation of cyclohexene showed some very interesting results. However, this section of the research was used mainly as a basis for developing techniques to support a homogeneous catalyst. It may provide an interesting comparison to use the different supported Wilkinson's catalysts for the hydrogenation of the different imines studied.

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Appendix A

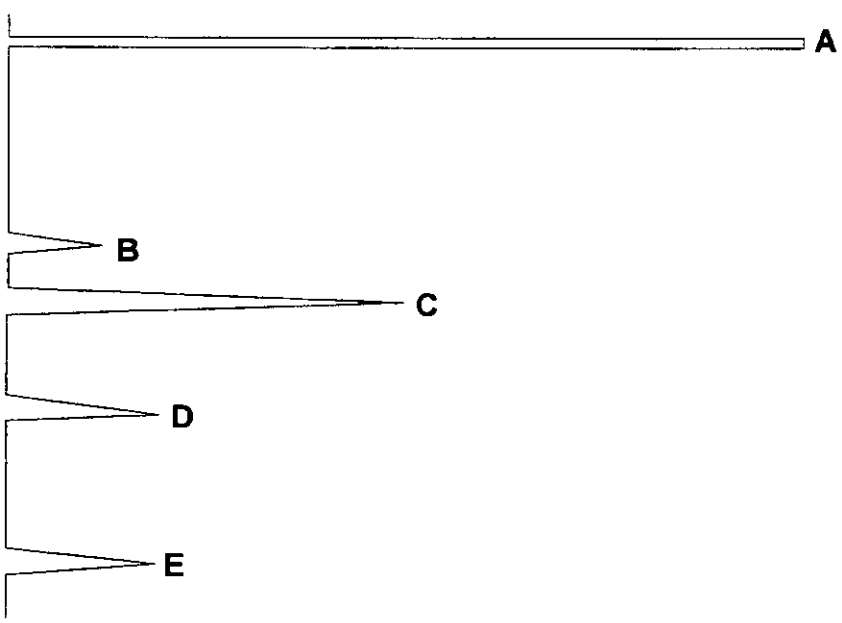
APPENDIX A

GC PROTOCOLS

Products were analysed by chiral GC (Chiraldex, γ-cyclodextrin, propionyl, 20 m × 0.25 mm). Analysis of pyruvate esters was carried out isothermally (40°C). Amine analysis was carried out using a temperature programme (50°C held for 3 minutes, increased at a rate of 3°C/minute to a maximum temperature of 150°C). Injector and detector temperatures were the same in each case (250°C). The analysis of cyclohexane was carried out using a temperature program (50°C held for 2 minutes, increased to 150°C at a rate 10°C per minute and then held at 150°C for 2 minutes.

The use of an internal standard (octan-2-one) in the analysis enabled the conversion and enantiomeric excess (e.e.) to be determined.

Calculation of Enantiomeric Excess



The sketch graph above shows a sample GC trace. Peak A being the solvent peak, peaks B and C the product peaks (each one representing an enantiomer). Peaks D and E represent the internal standard and the unreacted starting product resepectively. From this the enantiomeric excess and conversion can be calculated as percentages.

$$e.e = \frac{(peak\ area\ C - peak\ area\ B)}{(peak\ area\ C + peak\ area\ B)} \times 100$$

Giving the enantiomeric excess of C, if B were the bigger peak its e.e. would be calculated by deducting peak area of C from that of B, before dividing by the sum of the two peaks.

In order to ensure the results are uniform, a correction factor is calculated for each catalytic system using an unmodified catalyst. This should result in a racemic mixture of the compound.

The correction factor (C_f) is calculated using the following equation:

$$B \times C_f = C \qquad \text{so} \qquad C_f = \frac{C}{B}$$

Once a correction factor has been determined for a racemic mixture a corrected enantiomeric excess can be determined.

$$Corrected\ e.e = \frac{(peak\ area\ C - (peak\ area\ B \times C_f))}{(peak\ area\ C + (peak\ area\ B \times C_f))} \times 100$$

If B is the bigger peak the correction factor is calculated using: $C_f = \frac{B}{C}$, the C_f if then applied tot the peak area of C to calculate the corrected enantiomeric excess.

Calculation of Conversion

Before the conversion can be calculated, a response factor (R_f) for each compound needs to be determined. A calibration mixture containing a know mass of the internal standard (I.S.), starting material and end products is first analysed by GC, the R_f for each substrate can then be determined using the equation below.

$$R_f = \frac{peak\ area\ I.S.}{peak\ area\ substrate} \times \frac{mass\ substrate}{mass\ I.S.}$$

Once a response factor has been determined, the equation can be rearranged to determine the mass of starting product remaining (x) in subsequent analyses. Using x and the known mass of starting product upon commencement of the reaction (y), the percentage conversion can be calculated.

$$moles\ starting\ product\ remaining = \frac{R_f \times peak\ area\ starting\ product \times moles\ I.S.}{peak\ area\ I.S.}$$

$$\%\ conversion = \frac{(y-x)}{y} \times 100$$

APPENDIX B

ATOMIC ADSORPTION ANALYSIS

The final reaction mixture for each run of the supported Wilkinson's catalysts and for Rh-BINAP supported catalysts was analysed for leaching of the catalyst from the support. This was carried out using atomic adsorption spectroscopy to determine the amount of rhodium present in the mixture, and therefore the amount of catalyst, if any, which had leached from the support during hydrogenation.

A range of concentrations of rhodium chloride was used to obtain a calibration graph, from which the percentage of rhodium leached from the support, during the reaction, could be calculated.

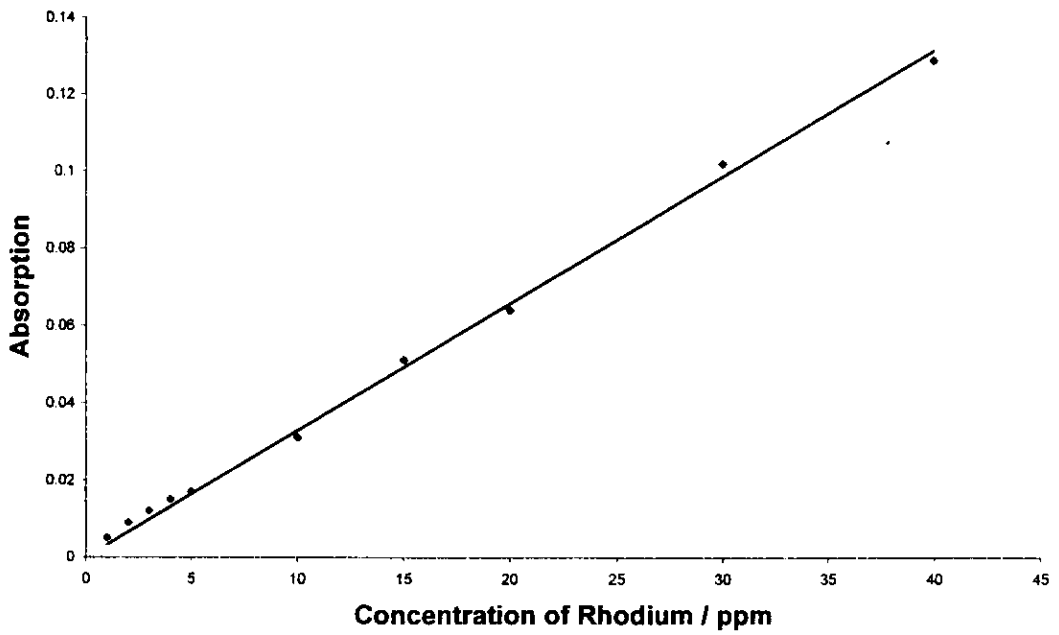


Figure App 1.1 Calibration graph for leaching of rhodium.

Appendix B

Thus, from the adsorption analysis the amount of rhodium in each sample could be determined using Figure App 1.1. This amount of rhodium (in parts per million) was converted into a mass, using the known volume of reaction mixture. The mass of rhodium was then taken as a percentage of the original mass of rhodium used to prepare the supported catalyst. Allowing the percentage of rhodium leached from the catalyst to be calculated.