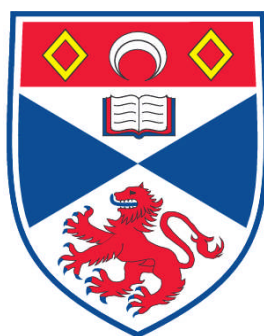


**EXPLORING AND EXPLOITING BENZYLIC REGIOSELECTIVITY IN
RHODIUM-CATALYSED HYDROFORMYLATION**

Nicola Martin

**A Thesis Submitted for the Degree of MPhil
at the
University of St. Andrews**



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Exploring and Exploiting Benzylic
Regioselectivity in Rhodium-Catalysed
Hydroformylation

MPhil Thesis

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Supervisor: Dr. Matthew L. Clarke
October 2010

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ABSTRACT

This project involves a study into the hydroformylation of substituted alkenes and ways to exploit “benzylic regioselectivity”. It was our aim to develop a clean, selective hydroformylation reaction which takes advantage of the tendency for benzylic regioselectivity in styrene-type molecules; in doing so, providing a potential route to important biologically active molecules.

In Chapter Two, hydroformylation of methyl cinnamate is explored since we envisaged that a regioselective hydroformylation of this substrate would serve as a step in an efficient route to γ -amino acids derivatives; which are important building blocks for the synthesis of important drug molecules. Most Rh-phosphine catalysts install the formyl group α - to the ester group however, we found that certain reaction conditions and appropriate choice of phosphorus containing ligands led to highly chemoselective and regioselective hydroformylation. Regioselectivities of up to 25 : 1 favouring the benzylic aldehyde were observed. However, as will be explained, this reaction is hindered by significant hydrogenation under hydroformylation conditions. Using a novel ligand this side reaction was lowered to 5% with reasonable regioselectivity, however overall conversion to the desired aldehyde was low. As a means to synthesise γ -amino acid derivatives, enamine formation using the aldehyde products was also attempted.

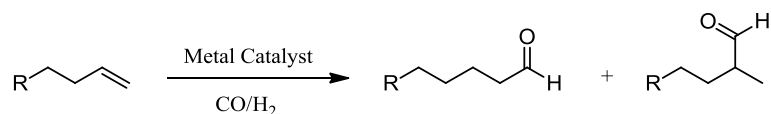
An alternative alkenyl arene substrate is studied in Chapter Three. High benzylic regioselectivity was observed using a variety of chiral and achiral ligands and again reaction conditions were optimised with the aim to develop an efficient process for the synthesis of γ -amino alcohol derivatives. It was found that PPh_3 , tris(3,4,5-trifluorophenyl)phosphine and a phosphadamantane cage phosphine ligand gave the most promising results with moderate to high regioselectivity observed. Asymmetric hydroformylation was not possible due to low activity using a variety of state-of-the-art chiral ligands.

CHAPTER ONE

Exploring and Exploiting Benzylic Regioselectivity

Introduction

1.1 Hydroformylation- General Background and Mechanism



The year 1938 saw the birth of hydroformylation, as German chemist Otto Roelen made a chance discovery while working on Fisher-Tropsch chemistry. Hydroformylation or “Oxo Synthesis” is a process in which an alkene reacts to give an aldehyde. Since its invention it has become one of the most notable examples of homogeneous catalysis and a widely used industrial process. In the bulk chemical industry millions of tonnes of “oxo products” are produced each year.¹ To date this industry has been mostly interested in producing linear aldehydes to be used in production of polymers, plastics etc. A lot of research has focussed on the attainment of very high linear to branched (L/B) ratios. In addition to the development of linear selective hydroformylation as a massive scale industrial process, it is now also seen as an effective general method to yield linear aldehydes from terminal olefins in organic synthesis. Studies of the transition metal used as a catalyst in hydroformylation have included platinum, cobalt and rhodium with the latter being by far the most effective. Both ligand-modified and unmodified rhodium catalyst systems have been researched.

The most industrially applied catalyst system is the rhodium-PPh₃ catalyst and its use in hydroformylation was initially reported by Wilkinson and co-workers². The chemistry of Rh-PPh₃ has been studied in great detail³ and literature from the late 1960s is still relevant today. Heck first proposed the mechanism⁴ shown in Figure 1.1 and it depicts Wilkinson’s “dissociative” mechanism. This mechanism will be described as a means to explain the hydroformylation reaction in a general sense.

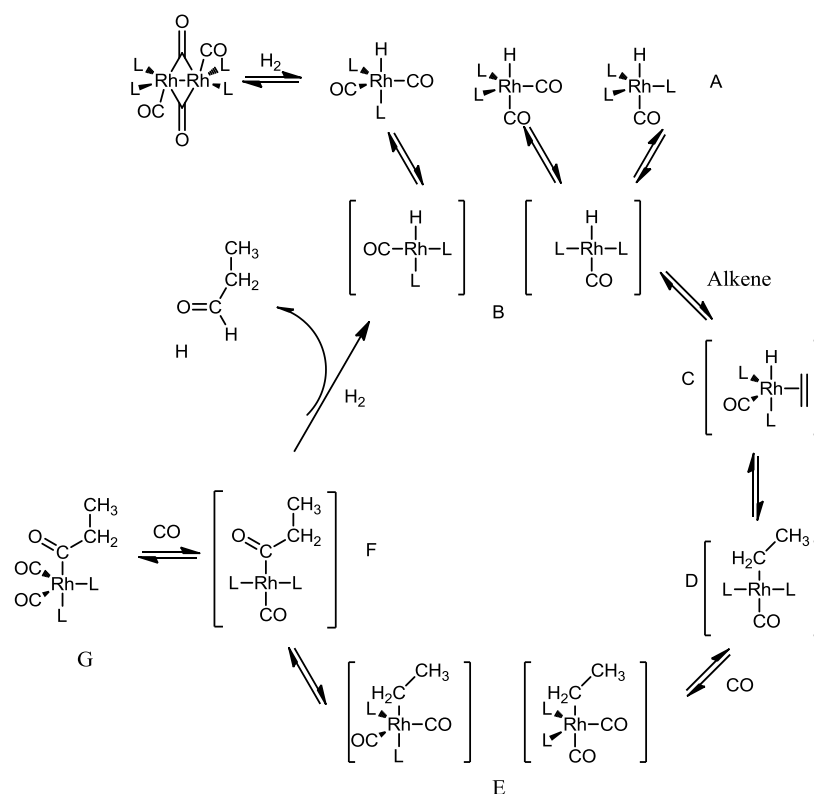


Figure 1.1- General Hydroformylation Mechanism

The starting point in the mechanism is the dissociation of either a phosphine ligand or carbonyl to form a square planar 4-coordinate rhodium hydride complex B. In general, preferential dissociation of equatorial ligands from trigonal bipyramidal complexes is seen. The next step is the association of alkene in an equatorial fashion and so the hydride sits in an apical position (C).

Following this step is migratory insertion of the hydride to the double bond of the alkene to give a square planar alkyl complex D. It is at this stage that β -hydride elimination may occur and lead to isomerisation of the alkene or carbon monoxide (CO) may associate to give a coordinatively saturated complex E.

Complexes E can then undergo migratory insertion of CO to give the acyl complex F and further reaction with CO leads to saturated acyl intermediates (G). Alternatively hydrogenolysis of complex F will give the aldehyde product and the unsaturated complex B. For this final step it is unclear whether it is reversible or not and the mechanism is unknown. An oxidative addition and reductive elimination are probably involved although for rhodium systems, trivalent intermediates have not been observed.³

1.2 Hydroformylation in Industry

Now more than ever, the importance of “green chemistry” is widely acknowledged. Scientists are now faced with the challenge of synthesising complex molecules with as little environmental impact as possible. The development of industrial processes must have the objective of clean, efficient and selective chemistry and the focus must be on minimising solvent use and developing tandem methods such that purification is reduced. Metal based homogeneous catalysis is one area in which efficient, selective technology has been developed. Hydroformylation of alkenes has the potential to be a 100% atom efficient reaction but thus far has only been industrially utilised to produce simple linear aldehydes e.g. *n*-butanal and *iso*-butanal from propene and 1-nonanal from octene (See Figure 1).

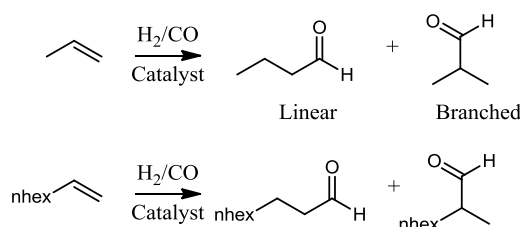


Figure 1.2- Propene and Simple Terminal Alkene Hydroformylation

Hydroformylation has huge potential for more widespread use with many advantages over more traditional methodologies. It shows impressive tolerance of relatively labile functional groups; for example ketones, aldehydes, esters, acetals, alcohols, tosylates, silyl ethers and many others⁵. Synthesis gas is cheap and essentially the only other reagent and sub-stoichiometric quantities of metal catalyst are required (typically <0.1 mol%). Environmental benefits include the relatively low temperature that can be used, and the potential for 100% atom economical reactions. Industrial chemical companies use a massive amount of energy and money to safely dispose of waste products and in particular solid waste poses a huge problem. Under optimum conditions, hydroformylation can produce aldehydes with no side products so it is clear that hydroformylation is very attractive for practical application.

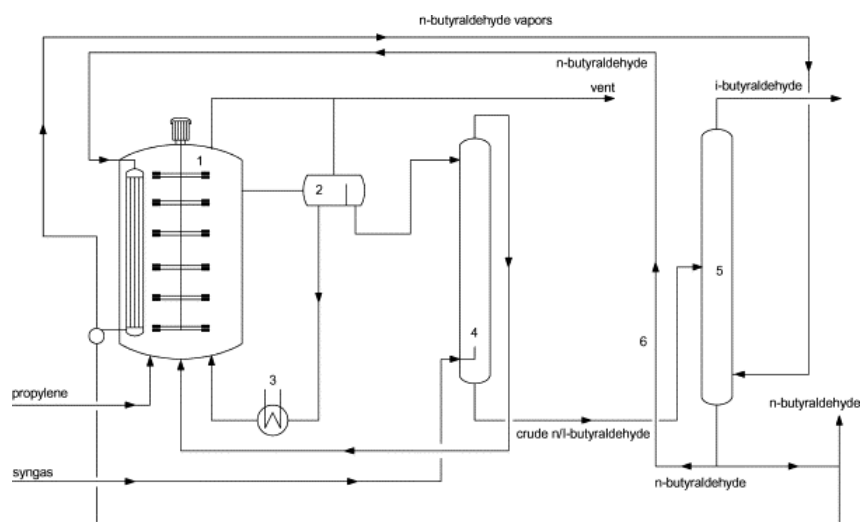


Figure 1.3- Schematic of Rhône-Poulenc Process⁶

The revolutionary Rhône-Poulenc process exemplifies the effective application of green chemistry in industry. The process is biphasic using a water soluble phosphine ligand (TPPTS) and involves a continuous feed of propene and synthesis gas while pure butanal is decanted off⁶ (See Figure 1.3). This process is entirely chemoselective with only aldehyde product formed and very regioselective with 98% linearity. The apparatus set up is very simple and the aqueous biphasic reaction media means easy catalyst recovery, excellent economics and a safe, environmentally friendly process.

1.3 Ligand Modified Rhodium Catalysis

For modified catalyst systems rhodium is the favoured metal, producing more active catalysts leading to high turn-over numbers (TON) and high turn-over frequency (TOF). Rhodium-based ligand modified catalysts also show better chemoselectivity and regioselectivity compared to cobalt for example. In the case of platinum based catalysts, poor chemoselectivity is often seen with alkane and alcohol side products being formed. The first rhodium based ligand modified processes used in industry were rolled out in 1974 by Celanese, 1976 by Union Carbide Corporation and in 1978 by Mitsubishi Chemical Corporation; all using PPh_3 as the modifying ligand. As well as triphenylphosphine, diphosphines and bulky phosphites have gathered much interest for research. For asymmetric hydroformylation BINAPHOS⁷ (Figure 1.4) has been the most interesting ligand to date.

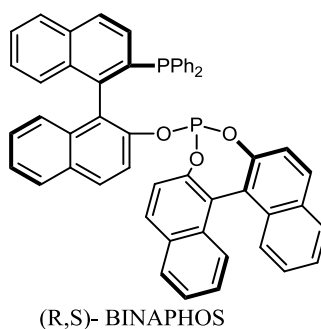


Figure 1.4- Structure of BINAPHOS Ligand

Despite the obvious advantages, hydroformylation has not yet been extensively utilised in organic synthesis. It has been found that substrate structure has great influence over regioselectivity and so impressive results reported can be entirely substrate specific. Generally hydroformylation favours the formation of the linear aldehyde and so substrate structure becomes even more important in asymmetric hydroformylation as the branched aldehyde is usually the desired product. The challenge for researchers is a matter of simultaneous control between regioselectivity, chemoselectivity and enantioselectivity while retaining high TOF. To widen the scope of hydroformylation i.e. to successfully develop methods for more substituted alkenes, it is necessary to intelligently design and test effective ligands.

1.4 Function of a Ligand and Ligand Parameters

Electronic and steric properties of a ligand can have a drastic effect on rate and selectivity in hydroformylation. Although the literature to date fails to provide a completely reliable, systematic study into ligand effects, a few rules of thumb can be postulated. Electron donating ligands e.g. alkylphosphines can give slow catalysts whereas, electron withdrawing ligands lead to a decrease in back donation to carbon monoxide and so weaker binding of the CO ligands.

More sterically bulky ligands will favour formation of species with fewer ligands thereby creating more “space” for CO ligands. High proportion of CO ligands also leads to electron poor rhodium species and so enhanced dissociation of CO.

For monodentate ligands there is a standard steric parameter, Tolman cone angle θ . This parameter can be even more important than electronic parameters and complex stability can be a dominant factor, using bulky ligands. The Tolman cone angle can be defined as the apex

angle of a cylindrical cone corresponding to the steric bulk imparted by the substituents on the phosphorus atom of a phosphine or phosphite ligand³. This θ -value is calculated using models or computationally by taking an average of the substituents on the phosphorus. The overall electron donating or withdrawing effect of a phosphorus ligand is defined by the electronic parameter χ . High χ -values correspond to strong π -acceptors and low χ -values correspond to σ -donor ligands.

For bidentate phosphorus ligands Tolman extended the cone angle parameter to include them, which takes an average of the cone angle for two substituents and the angle between the metal-phosphorus (M-P) bond and the bisector of the P-M-P angle. Casey and Whiteker⁹ described a method of predicting the “ligand preferred” P-M-P angle and introduced the concept of natural “bite angle” (β_n) and also a flexibility range for diphosphines. The bite angle affects both steric and electronic properties of the metal centre.

1.5 Monodentate Ligands

Monodentate ligands are extremely versatile ligands for rhodium catalysed hydroformylation. As mentioned previously triphenylphosphine, PPh_3 , has been by far the most widely used ligand in rhodium catalysed hydroformylation and as a result many of its derivatives have been studied. Arylphosphines containing electron-withdrawing substituents have been shown to give higher rates in hydroformylation than triphenylphosphine¹⁰. Studies by Abatjoglou¹¹, indicate that tppms (shown in Figure 1.5) has potential for hydroformylation of higher, terminal alkenes in a system in which catalyst recovery is aided by the addition of an aqueous phase after reaction.

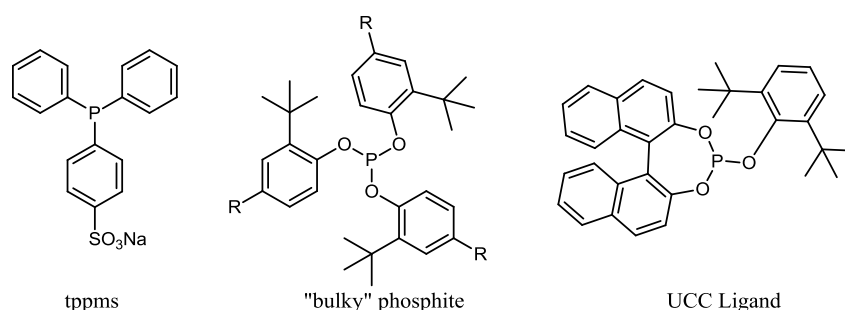


Figure 1.5 Successful Monodentate Ligands

Moser and co-workers²² used Cylindrical Internal Reflectance Infrared Spectroscopy (CIR-FTIR) to observe the “deactivation” of the $\text{RhH}(\text{CO})_2(\text{PR}_3)_2$ species to a dimeric species $[\text{Rh}(\text{CO})(\text{PR}_3)_2]_2$ and then to an inactive binuclear complex with a bridged phosphide ligand. It was found that deactivation was far greater when the substituents on the triphenylphosphine based ligands were strongly electron donating e.g. *p*-methoxy, *p*-dimethylamine.

Overall it has been seen that phosphites produce faster catalysts than phosphines (Figure 1.4) and this is down to the fact that they are better π -acceptors. As mentioned previously this has the effect of more facile CO dissociation and stronger alkene association. As with arylphosphines, studies have shown that increasing electron withdrawing properties of a phosphite, increases selectivity for the linear aldehyde¹³. It is also noteworthy that phosphites are easier to prepare than phosphines and are far less sensitive to sulfur compounds and oxidising agents.

In the 1980s there was renewed interest in phosphites when van Leeuwen and co-workers¹⁴ reported bulky monophosphites giving very high reaction rates. This work has been further expanded by Bryant and co-workers at Union Carbide Corporation¹⁵ who also used bulky monophosphites (Figure 1.5). Further work has led to utilising of diphosphines and diphosphites

1.6 Bidentate Ligands

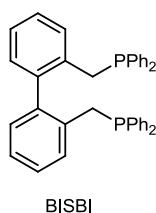


Figure 1.6- Eastman's BISBI Diphosphine Ligand

In the past, high selectivity for linear aldehyde products was achieved using high concentrations of PPh_3 , to ensure that the bis-ligated phosphine species was in excess with respect to the mono-ligated¹². Therefore the introduction of bidentate phosphine ligands seems logical and has the added advantage of metal geometry control and potentially efficient asymmetric induction. Since the early 1970s much research has been carried out into

diphosphines with many successful ligands being highlighted. For example, in 1987 Devon and co-workers²¹ reported the diphosphine ligand BISBI (Figure 1.6) that in propene hydroformylation showed very high regioselectivity for linear aldehyde products. The measured natural bite angle for BISBI was calculated to be 124°, which is much greater than 90° the most common bite angle for bidentate ligands. This result therefore led to speculation that wide bite angles may be advantageous for high linear/branched ratios.

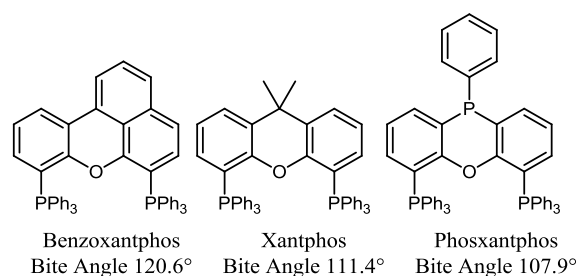
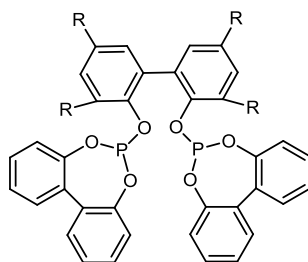


Figure 1.7- Xantphos Type Ligands and Their Calculated β_n Values

Diphosphines derived from the readily available xanthene backbone provided a variety of ligands with bite angles outside the common range of 75 to 99°. The oxygen ether bridge in this backbone is a key feature that prevents metalation and usually does not participate in coordination to the metal. Changing the fragment in the backbone means various bite angles can be created and so the xanthene based diphosphines are known as having “tunable” bite angles. Work by Kranenburg and co-workers¹⁶ on this family of ligands demonstrated that wider bite angles lead to high selectivity for linear aldehydes.

We know that bulky monophosphites have been shown to be very useful in rhodium catalysed hydroformylation due to the high reaction rates observed with respect to the reaction using triphenylphosphine. It must be noted however that selectivity was far less using these ligands.



Typical UCC Diphosphite

Figure 1.8- Typical Diphosphite Used by UCC

This problem was solved when Bryant and co-workers¹⁷ highlighted that changing to wide bite angle diphosphite catalyst systems showed promising results. Figure 1.8 exemplifies one typical bulky diphosphite patented by UCC after these results were reported. Using ligands with this biphenol linker moiety showed massive increase in the selectivity for linear products with only slight decrease in reaction rates, and still much higher than rates seen using triphenylphosphine.

1.7 Branched Selective Hydroformylation and Asymmetric Applications

Thus far industry has focussed on developing highly linear selective hydroformylation processes. However for enantioselective methodologies, which may be useful for the pharmaceutical industry, branched selective hydroformylation is necessary. Enantioselective hydroformylation is an active area of research both in academia and industry. However so far, only model substrates such as styrene, vinyl acetate and allyl cyanide have been thoroughly studied. These substrates are well suited to the enantioselective reaction since they display a high tendency towards the branched aldehyde since hydroformylation is likely to occur α to an electron-withdrawing group²⁵.

Despite literature available to date, asymmetric hydroformylation is still a severely underused reaction in organic synthesis and implementing hydroformylation of more complex substrates is now the target for many research groups. Clarke and co-workers^{18,19} reported an interesting example of branched selective hydroformylation of unsaturated esters using a phosphorus adamantyl cage ligand. Keulemans rule states that “in hydroformylation formyl groups are not produced at quaternary centres” and yet the work of Clarke and co-workers demonstrated

unsaturated esters can undergo hydroformylation to form quaternary aldehyde products in high chemo and regioselectivity, using active bulky ligands.

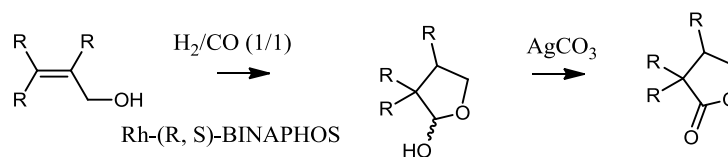


Figure 1.9- Synthesis of γ -Butyrolactones

In 1997 Nozaki and co-workers⁷ reported a method for the asymmetric synthesis of chiral γ -butyrolactones via an asymmetric hydroformylation followed by an oxidation step (Figure 1.9). These targets are sub-units of biologically important molecules including natural products and pro-drugs of bioactive substances such as GHB (γ -hydroxybutyric acid). The method used a Rh(I)-(R, S)- BINAPHOS catalyst and hydroformylation of substrates such as cinnamyl alcohol proved successful with conversions of >99% and 88% e.e. using low syngas pressure and a reaction temperature of 60 °C.

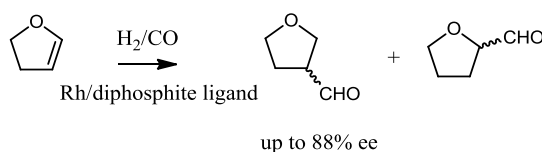


Figure 1.10- Asymmetric Hydroformylation of 2,3-Dihydrofuran

Claver and co-workers²⁸ recently hydroformylated 2,3-dihydrofuran and 2,5-dihydrofuran (Figure 1.9). Total chemo- and regioselectivity was achieved with e.e.'s up to 88% using Kelliphite and diphosphite/carbohydrate ligands.

1.8 Hydroformylation in Synthesis of Drugs/Biologically Active Compounds

The scope of hydroformylation with regards to drug synthesis is demonstrated in a review by P. Eilbracht²⁰. For example, stepwise hydroformylation/reductive amination is described in which Tolteridine, an important urological drug, is formed in good yields from 1-[(2-hydroxy-5-methyl)phenyl]-1-phenyl ethylene (Figure 1.11).

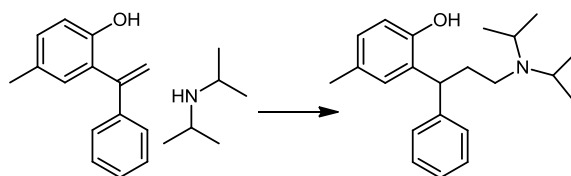


Figure 1.11- Synthesis of Tolteridine

A one-pot tandem procedure, a hydroaminomethylation, using a $\text{Rh}/\text{P}^n\text{Bu}_3$ catalyst was also developed using a diaryl ethene precursor giving 3,3-diarylpropylamine drugs. Hydroaminomethylation has also been utilised recently in the synthesis of dopamine-4-antagonists.

Major developments in the area of asymmetric hydroformylation (AHF) mean that it is rapidly becoming an attractive process for enantioselective aldehyde synthesis and these versatile products are of major interest to the fine chemical industry. Although the majority of reactions utilising asymmetric hydroformylation have been on “model” substrates, there are some examples in which other interesting substrates are used.

Figure 1.12 shows an example of asymmetric hydroformylation in the synthesis of a highly active carbapenem antibiotic precursor. For this reaction a modified BINAPHOS ligand, (*R*)-2-Nap-BIPNITE-*p*F gave 95% conversion, 75% branched aldehyde and the desired enantiomer was formed in a 92% enantiomeric excess⁵.

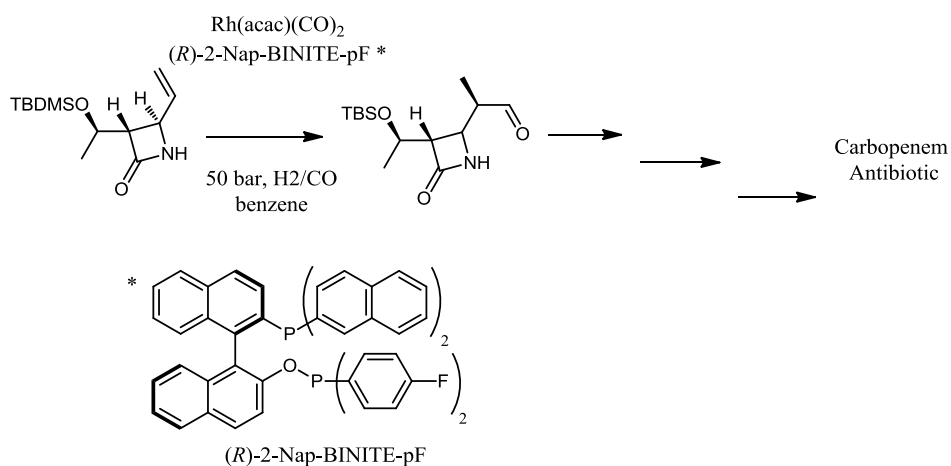


Figure 1.12- Asymmetric Hydroformylation in the Synthesis of Carbapenem Antibiotics

1.9 Benzylic Regioselectivity in Hydroformylation

In a review by Clarke¹ it is noted that terminal aryl alkenes tend to react to form the product with the formyl group on the carbon α to the aryl ring i.e. branched products. Typically regioselectivities are between 5-30 : 1 in favour of the branched products. It has been noted that lower temperatures and moderate pressures (~40 bar) lead to higher branched selectivity. The rationale behind this regioselectivity is the formation of a η^3 -benzyl complex (See Figure 1.13) which gives added stability to the rhodium alkyl intermediate. However since other quite electron poor alkenes show branched selectivity, it is worth noting that the electron withdrawing nature of the aryl ring stabilises the negative charge at the α -carbon and thus may enhance the preference for the branched rhodium alkyl intermediate. Ojima⁶ reports this phenomenon and states that the α -intermediate is energetically more stable than the alternative β -bonded complex. These stabilisation effects have been exploited for asymmetric hydroformylation of styrene e.g. Landis²⁷ uses (*S, S, S*)-Bisdiazaphos to enantioselectively form the branched aldehyde isomer in 71% e.e. and such aldehydes can be oxidised to their corresponding 2-arylpropionic acids; leading to biologically active analgesic drugs such as Naproxen.

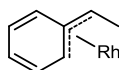


Figure 1.13- η^3 -benzyl complex

Regardless of the origin of this effect, a search of the literature reveals that a significant number of phosphorus ligand based rhodium catalysts will deliver α -aldehydes with good chemo and regioselectivity for many styrene derivatives. The diagram shown in Figure 1.14 is a small representation of the literature precedence for benzylic regioselectivity.

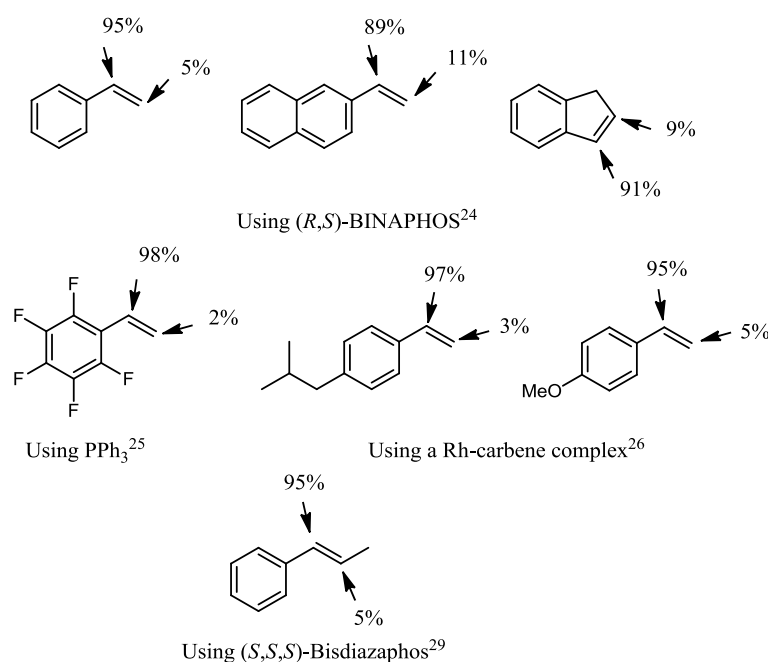


Figure 1.14- Examples of Benzylic Regioselectivity in Hydroformylation

The diagram shows a variety of benzylic substrates which have been successfully hydroformylated and the percentage values represent the ratio of aldehyde product at each position. It is clear that a wide variety of rhodium based catalysts can be used in hydroformylation to take advantage of this effect and the scope for diverse substrates is great. It is the opinion of the author that this benzylic regioselectivity is a powerful characteristic which has not yet been fully exploited.

With regard to the current study we were interested in results gained from Botteghi *et al*²³ who have demonstrated a hydroformylation with significant regioselectivity for the benzylic position of methyl cinnamate using a Rh₂O₃ catalyst. Despite the strongly electron withdrawing nature of the ester function, the reaction was reported as almost regiospecific for the benzylic aldehyde product. The drawback of the reported reaction was the need for high temperatures (120 °C) and hydrogenation side products (31.2%).

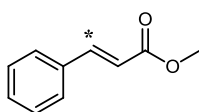


Figure 1.15- Methyl Cinnamate

1.11 Aims

The preparation of low molecular weight, highly functionalised aldehydes is an important goal for organic chemists. They serve as important building blocks for secondary and tertiary amine formation. Such amines are a common structural motif in agrochemicals and biologically-active molecules. Reductive amination is the route of choice for these target molecules as it creates C-N bonds with only water as a side product. The products from clean, selective hydroformylation of unsaturated esters should therefore prove to be extremely valuable precursors. The scope of possible useful products from such aldehydes is vast; including heterocycles, diols, amino acid derivatives, amino alcohols and 1,4-dicarboxylic acids (Figure 1.16).

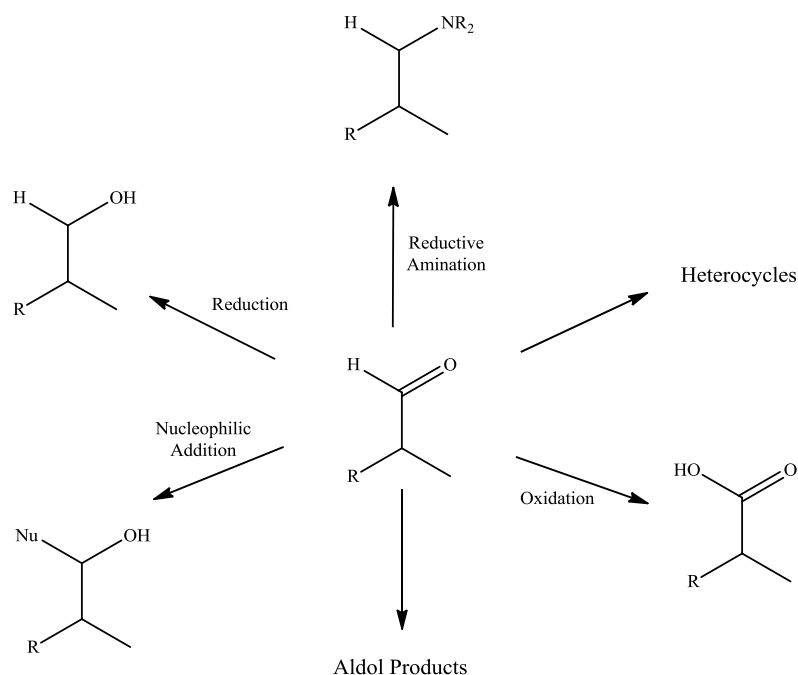


Figure 1.16 Potential Applications for Products of Hydroformylation

As will be discussed further in Chapter Two, we saw potential in the results reported by Botteghi and co-workers²³, to potentially develop a process for synthesising γ -amino acid esters. A selective hydroformylation of methyl cinnamate to give the β -aldehydes (β with respect to the ester function) opens up the possibility of further reductive amination or even one-pot hydroaminomethylation process in which the γ -amino acid derivatives are formed. We aimed to develop an optimised, ligand modified rhodium catalyst for the clean

hydroformylation of methyl cinnamate with a view to then forming valuable amine molecules.

In Chapter Three, we further explore hydroformylation of a substrate in which benzylic regioselectivity is expected to be favoured (Figure 1.17).

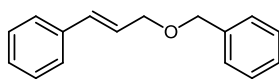


Figure 1.17- Benzyl Ether Substrate

Again, here we aimed to develop a ligand modified rhodium catalyst that would yield the benzylic aldehyde products with complete regioselectivity.

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CHAPTER TWO

Hydroformylation of α,β -Unsaturated Esters and Their Conversion to γ -Amino Acid Derivatives

2.1 Background- Hydroformylation of Unsaturated Esters and Aims

The success of a particular hydroformylation reaction can be extremely substrate dependant. Unsaturated esters are in relative terms unreactive substrates, being less reactive by 2 orders of magnitude than alkenes, allyl alcohols and styrene¹. The rationale behind this reduced reactivity is likely to be the formation of thermodynamically stable five or six membered rings in the intermediate σ -acyl complex, due to substrate carbonyl coordination to the metal centre (Figure 2.1).

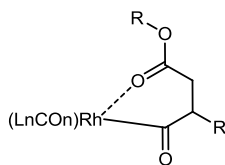


Figure 2.1- Intermediate Acyl-Species in Hydroformylation of Unsaturated Esters

However despite the inherent low reactivity, researchers have made effective progress in finding catalytic systems for some of these substrates. For example, work carried out previously in this research group², has shown a homogeneous rhodium based system with good activity and high selectivity for the α -aldehyde in substrates such as methyl crotonate (99% conversion, 100 : 1 (α : β)). In 2008, Xumu Zhang and co-workers³ reported a method for the hydroformylation of alkyl acrylates such as methyl acrylate using a tetraphosphorous ligand (See Figure 2.2) in which very high TOFs were observed as well as almost total linearity and reasonable conversion (up to 63%) with minor side products.

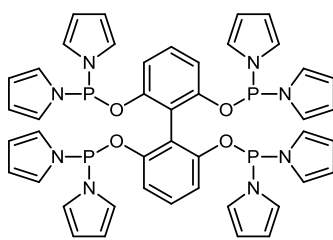


Figure 2.2 – Tetraphosphorous Ligand

Classically the literature has reported the hydroformylation of unsaturated esters to be α -selective, with respect to the ester function.

Hydroformylation of cinnamic acid esters with benzylic regioselectivity (rather than α -selectivity) would give some very valuable aldehyde precursors. For example, they could be converted to phenylsuccinic acids and so lead to the antiepileptic drug *N*-methyl-2-phenylsuccinimide⁷ (Figure 2.3). Another example of a drug whose synthesis could be improved via this method is (*R*)-Rolipram- a phosphodiesterase inhibitor used as an antidepressant (Figure 2.3).

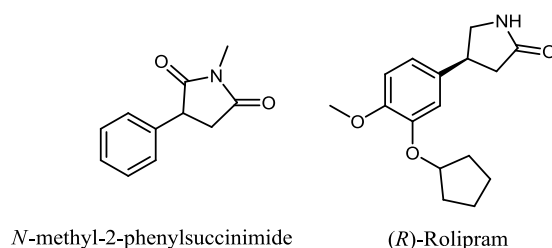


Figure 2.3- Hydroformylation of Cinnamate Esters Can Lead to Important Drug Products

Furthermore, reductive amination can convert the aldehydes to their corresponding γ -amino acids which are recognised as important pharmacophores. And so there is potential for these products to be used as “building blocks” in the synthesis of pharmaceutically useful molecules e.g derivatives of gamma-aminobutyric acid (GABA) (See Figure 2.4). Nitrogen containing molecules are of huge biological and industrial importance and much research has concentrated on the efficient synthesis of amines. Hydroaminoalkylation e.g. hydroaminomethylation is an especially promising reaction since it involves conversion from relatively simple alkene starting materials to more complex amines and is potentially 100% atom economical. However in particular high yielding, regioselective hydroformylation of such 1,2-disubstituted unsaturated esters is yet to be seen with β -selectivity in the literature.

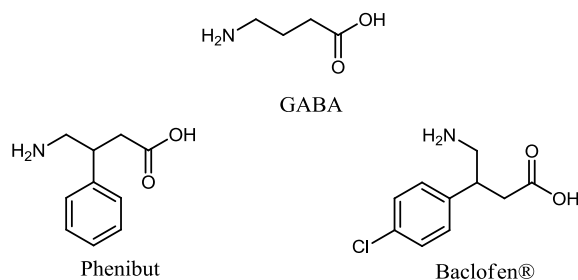


Figure 2.4- Structure of γ -Aminobutyric Acid and GABAergic Drugs

The development of hydroformylation of unsaturated esters has potential as an efficient alternative for the synthesis of novel or current pharmaceuticals such as β -(aminomethyl)-*p*-chlorohydrocinnamic acid (Baclofen®) a myorelaxant agent used to treat spasticity or Phenibut used to treat anxiety and insomnia (Figure 2.5).

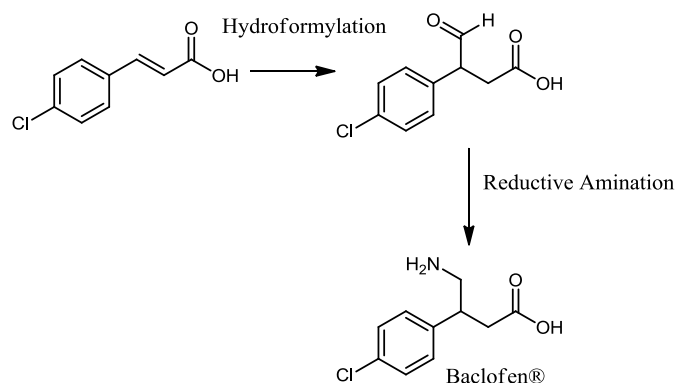


Figure 2.5- Proposed Alternative Route to Baclofen

An initial regioselective hydroformylation step could yield the required aldehyde with 100% atom efficiency and a further reductive amination step would lead to the amino acid derivative potentially with very high efficiency. If this is successful, enantioselective variants of the reaction could then be considered.

The substrate chosen for this study was methyl cinnamate. Hydroformylation of this compound can deliver either α -aldehydes (formyl group α to the ester) or β -aldehydes (formyl group in benzylic position); both of which are of potential interest (Figure 2.6). Highly β -selective hydroformylation of methyl cinnamate has already been demonstrated by Botteghi *et al*⁸, although over 30% conversion to hydrogenation product is reported. A Rh_2O_3 catalyst is used, which is possibly an example of soluble-metal-particle catalysis⁹ rather than of true homogeneous catalysis and we speculate that this system is not optimal. With soluble-

particle or “soluble heterogeneous” catalysis there is likely to be numerous active sites on the particle surface and more than one type of site and so selectivity may be impeded²⁸. Catalysis of this type may also be sensitive to change in particle size, synthetic procedures, catalytic conditions and display a heightened sensitivity to poisons. Another factor to consider may be stability with respect to agglomeration.

For methyl cinnamate hydroformylation using the ^{Me}CgPPh ligand, our group reported hydrogenation as low as 4%, high conversion (89%) and regioselectivity of 13.8/1 in favour of the α -aldehyde. We reasoned that further work with this substrate to attempt to reverse the selectivity to the β -aldehyde would be worthwhile.

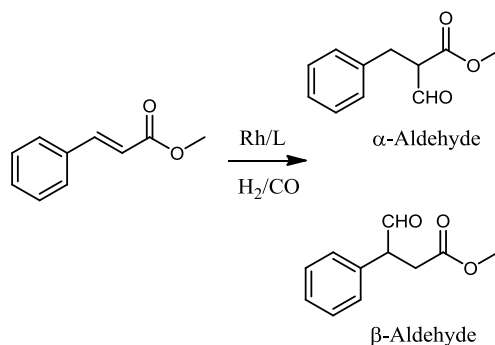


Figure 2.6- Hydroformylation of Methyl Cinnamate

Our ultimate goal was a domino type reaction in the presence of amines or a sequential process to deliver the γ -amino esters (Figure 2.7). We sought to selectively attain the β -aldehyde by screening a range of ligand modified rhodium complexes to moderate reactivity and selectivity.

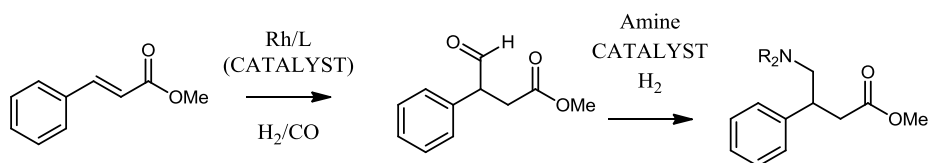


Figure 2.7- Proposed Domino Process to Yield Amino Esters

The hydroformylation reaction is extremely sensitive to experimental conditions and the catalytic cycle involved can be conceived as a web of equilibria. Altering the concentration of metal precursor, CO, H₂, alkene or ligand will distort a particular equilibrium in the system and so can have a dramatic effect on overall reaction rate. Optimisation of the reaction for a

particular substrate is quite complex and means striking a balance between all variables to achieve the desired product. With the aim to eventually convert methyl cinnamate to its γ -amino acid derivative, we needed to develop a clean, β -selective hydroformylation.

2.2 Ligand Screening

As discussed in Chapter One, electronic and steric properties of a ligand can have a drastic effect on rate and selectivity in hydroformylation. We decided to test a variety of different monodentate and bidentate phosphorus ligands for the hydroformylation of methyl cinnamate as the first step of the proposed route to γ -amino esters.

Monodentate Ligands

The ligands chosen for initial testing are shown in Figure 2.8. Triphenylphosphine (**2**) being one of the most widely used phosphine ligands in organometallic catalysis¹² provided us with a benchmark for comparison in activity.

Bulky triarylphosphite ligands have been shown to be even more active and selective in hydroformylation than the industrial workhorse ligand triphenylphosphine¹⁰. Bulky ligands have larger cone angles and so when coordinated to a metal centre tend to prevent coordination of a second bulky phosphite. Since only one ligand is bound to the catalyst the overall steric hindrance is greatly reduced and so this means the site is more accessible for substrate complexation. Additionally because the metal is bound to the π acceptor phosphite and three strongly π -accepting carbonyls, the centre itself becomes electron poor. This in turn means the CO ligands are more loosely bound and so their dissociation is more facile and alkene addition is faster and high reaction rates are observed. Phosphite ligands however are susceptible to hydrolysis and also tend to react with product aldehydes. Doverphos was chosen as a useful phosphite ligand (Figure 2.8).

Fluoroaryl phosphines are an attractive alternative as they are seemingly similar donors to phosphites. It is known that electron withdrawing substituents on arylphosphines increase activity of the rhodium hydroformylation catalyst e.g. Moser and co-workers¹¹ used $P(C_6H_4X-4)_3$ ($X = H, Cl, F, CF_3$) phosphine ligands for the hydroformylation of 1-hexene,

showing that electron-withdrawing functions led to higher catalytic activity. Again, this is down to forming a more electron poor metal centre.

Fluorous arylphosphines are effective due to their electron withdrawing effect on the metal centre e.g. a fluoroaryl analogue of the bidentate ligand BISBI was synthesised by Casey and co-workers¹³ and proved to be even more regioselective and five times more active than the original ligand. Tris(3,4,5-trifluorophenyl)phosphine (**1**) and tris(3,5-bis(trifluoromethyl)phenyl)phosphine (**3**) have been shown to be stable under hydroformylation conditions and have given quite good results; slightly better than triphenylphosphine when used as ligands in 1-hexene and 4-methoxystyrene hydroformylation¹⁴. Ligand **3** has shown good activity in the hydroformylation of methyl acrylate¹⁵ as well as proving useful in hydroformylation of 1-octene in supercritical CO₂¹⁶ thus making them a worthwhile candidate in our ligand screen.

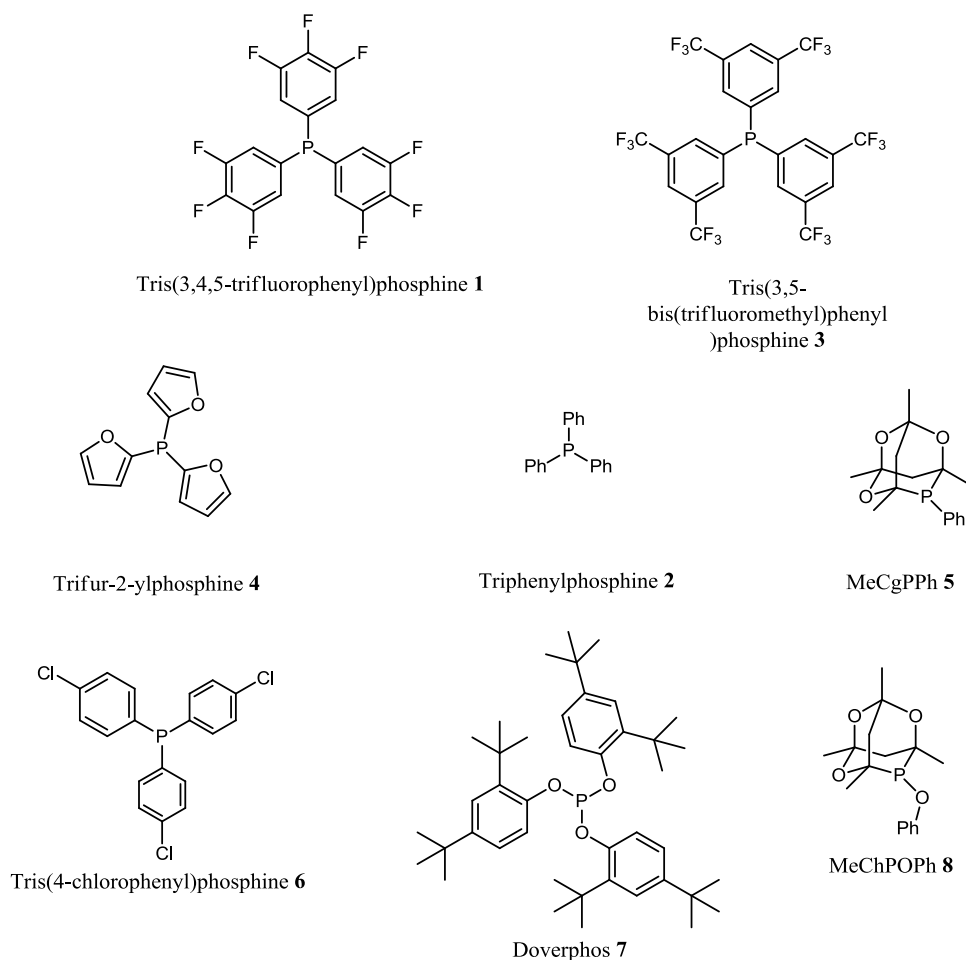


Figure 2.8- Monodentate Phosphine Ligands

In general tertiary aryl-phosphine rhodium complexes have proved successful in hydroformylation of various substrates. Tris(4-chlorophenyl)phosphine has been tested in the hydroformylation of acrolein acetal¹⁸ and proved to be one of the most active ligands tested and was also used here.

The bulky, electron poor phenylphosphaadamantane ligands have been used to form rhodium(I) catalysts with impressive activity and selectivity^{2,15,17} and have the added advantage of high stability. Cage phosphonite **8** was kindly donated by Pringle and co-workers. Table 2.1 represents results from our initial ligand screen.

Ligand	$\beta : \alpha$	Aldehyde (%)	Alkene (%)	Alkane (%)
1	1.43 : 1	56	14	33
3	0.96 : 1	23	44	33
2	0.29 : 1	61	12	26
4	-	1	96	3.5
5	0.1 : 1	52	38	7.5
6	0.35 : 1	62	18	20
7	0.22 : 1	50	45	5
Mixed 1 and 3*	1.2 : 1	20	33	47
8	0.35 : 1	27	58	15

Reaction Conditions- Solvent Toluene, Pressure 50 bar, Temperature 50 °C, Time 16 hours, Substrate Concentration 0.99 molL⁻¹, L/Rh = 5:1, Catalyst Loading 0.2%, *Each L/Rh = 2.5:1.

Table 2.1- Hydroformylation of Methyl Cinnamate Using a Variety of Monodentate Phosphine Ligands

In this initial screen 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane (^{Me}CgPPh) **5**, tris(4-chlorophenyl)phosphine **6**, tris(3,4,5-trifluorophenyl)phosphine **1** and triphenylphosphine **2** showed the highest activity. However, regioselectivity for the β -aldehyde was poor and still a reasonably large amount of hydrogenation was seen. However

with conversions around 80-90% these three ligands performed reasonably well at 50 °C in terms of activity. The electron withdrawing substituents on tris(4-chlorophenyl)phosphine seem to have no positive effect on activity and in fact this ligand proves to give less overall conversion than triphenylphosphine.

The phosphine cage ligand, ^{Me}CgPPh, has previously been studied with respect to the hydroformylation of 1-hexene²⁰ and has been shown to form a far more active rhodium catalyst than triphenylphosphine. Kinetic studies have revealed that turnover frequencies using a ^{Me}CgPPh containing catalyst resemble that of a phosphite based catalyst system. However this activity does not seem to transfer to methyl cinnamate. Relatively poor conversion (52%) to aldehyde product shows that the ^{Me}CgPPh ligand struggles to match the catalytic activity of triphenylphosphine in our system. Due to the inadequate $\beta : \alpha$ ratio, we would not take this ligand on for further study.

Under the initial conditions Doverphos showed mediocre activity with 50% conversion to aldehyde product and was selective for the α -aldehyde. Disappointingly tris(2-furyl)phosphine produced almost no activity in hydroformylation. Tris(3,4,5-trifluorophenyl)phosphine **1** and tris(3,5-bis(trifluoromethyl)phenyl)phosphine **3** have shown reasonable activity and the most promising $\beta : \alpha$ ratio which is of most interest to us. In the case of ligand **1** we have the only example where β -selectivity is favoured. At this stage it was decided to use these two ligands for further optimisation. We attempted to improve on these results by using a catalytic system in which both ligands were used²⁷. Combining ligands **1** and **3** in the same reaction however did not give the results we were hoping for. Moderate regioselectivity for the β -aldehyde was still observed however there was a drop in activity and a dramatic increase in hydrogenation.

Bidentate Ligands

Bidentate, diphosphine ligands have been successfully utilised for many selective hydroformylation processes e.g. in the 1980s it was reported that rhodium catalysts derived from BISBI and xantphos ligands give high regioselectivity for linear aldehydes²¹. Benefits of such ligands include greater control of metal geometry and more stable complexes due to a chelation effect. We decided to test three diphosphine ligands (as shown in Figure 2.9).

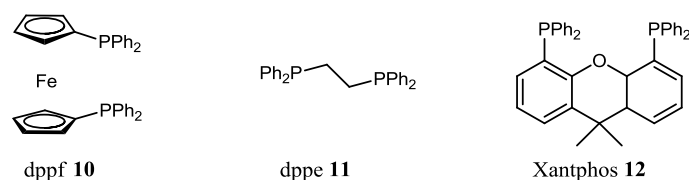


Figure 2.9- Bidentate Phosphine Ligands

The diphosphine ligand Xantphos **12** and related xanthene compounds are interesting for catalysis due to their “tunable” bite angle. We speculated that if Xantphos proved to be active in the case of methyl cinnamate hydroformylation, analogues with various bite angles could be tested for optimisation.

1,1'-Bis(diphenylphosphino)ferrocene, dppf **10**, is another diphosphine ligand widely used in hydroformylation. The ferrocene backbone of the structure means it is a flexible ligand through rotation of the cyclopentadienyl fragments. Unruh and Christenson²² first studied dppf and modified catalysts in 1982. They showed that by increasing the accepting ability of the ligand i.e. making a better π -acceptor by adding Cl, F and $-\text{CF}_3$ substituents to the phenyl groups, the rate of the reaction increases. This trend corresponds to easier CO dissociation from the metal due to decreased π -back donation. Consequently electron withdrawing functionality on the aryl groups of dppf increases rate of hydroformylation. Altering the steric bulk on the phosphine also has the potential to improve catalytic activity. We believe the ferrocene backbone to be interesting and could be further explored, and so dppf was chosen in our screen.

In the case of both dppf and Xantphos, the relatively large bite angles are known to be beneficial to activity and to have distinctive effects on selectivity¹². At this stage, some preliminary solvents studies had shown Me-THF to be an interesting alternative to toluene as the solvent in our reaction (see Section **2.6 Solvent Screening**). In some cases it seemed that Me-THF may have a beneficial effect of lowering occurrence of the hydrogenation side reaction. Thus for the bidentate ligands we decided to run reactions in both toluene and Me-THF for comparison (Table 2.2).

Ligand	$\beta : \alpha$	Aldehyde (%)	Alkene (%)	Alkane (%)	Solvent
dppf	-	<1	99	-	Me-THF
dppe	-	~1	97	~1	Me-THF
xantphos	-	<1	83	9	Me-THF
dppf	-	5	95	-	toluene
dppe	0.15 : 1	14	84	1	toluene
xantphos	0.25 : 1	5	95	-	toluene

Reaction Conditions- Pressure 50 bar, Temperature 50 °C, Time 16 hours, Substrate Concentration 0.99 molL⁻¹, L/Rh = 1.2 : 1, Catalyst Loading 0.2%.

Table 2.2- Hydroformylation of Methyl Cinnamate Using Various Bidentate Ligands

At 50 °C and high syngas pressure, using Me-THF as the solvent, it is clear that none of the diphosphine catalysts show good activity in our reaction. Likewise when toluene was used conversion was extremely poor and the reaction was regioselective for the α -aldehyde.

Ligand	$\beta : \alpha$	Aldehyde (%)	Alkene (%)	Alkane (%)	Solvent
dppf	5.4 : 1	25.5	62	12.5	Me-THF
dppe	8 : 1	22.5	57	20.5	Me-THF
xantphos	0.74 : 1	24	51	25	Me-THF
dppf	0.47 : 1	53	37	10	toluene
dppe	0.41 : 1	55.5	8	36.5	toluene
xantphos	0.06 : 1	60.5	21	18	toluene

Reaction Conditions- Pressure 10 bar, Temperature 90 °C, Time 16 hours, Substrate Concentration 0.99 molL⁻¹, L/Rh = 1.2 : 1, Catalyst Loading 0.2%.

Table 2.3- Hydroformylation of Methyl Cinnamate Using Various Bidentate Ligands

It is possible that more energy was required to form the active catalytic species so we decided that increasing the reaction temperature to 90 °C may yield better results (Table 2.3). Additionally we lowered syngas pressure to 10 bar hoping to increase β -selectivity. With Me-THF as the solvent we saw an improvement in activity with conversions around 40% and in the case of dppf and dppe, promising β : α ratios were seen. However, yet again the level of hydrogenation side reaction was unacceptable. Using toluene as the solvent under these conditions saw a vast improvement in activity with conversions up to 92% and in the case of xantphos conversion to aldehyde was 60.5%. Here, however, all three ligands prove to be regioselective for the α -aldehyde and hydrogenation was still a considerable problem.

1,2-Dicarba-*closo*-dodecaboranes are interesting novel backbones for bis-phosphane ligands. Hey-Hawkins and co-workers²³ synthesised novel ligands 1,2-bis[bis(4-*tert*-butylphenoxy)phosphanyl]-*closo*-dicarbaborane (**13**) and 1,2-bis[bis(2-*tert*-butylphenoxy)phosphanyl]-*closo*-dicarbaborane (**14**) (See Figure 2.10) and demonstrated the potential of **13** as a ligand for homogeneous hydroformylation catalysis. The efficacy of its rhodium complex was tested in the hydroformylation of dimethyl itaconate; a 1,1-disubstituted alkene. At 100 °C ligand **13** gave good regioselectivity for the linear product and full conversion. Various other 1,1-disubstituted alkene substrates were tested including methyl cinnamate which reacted to completion at 100 °C and gave 25 : 1 regioselectivity for the β -aldehyde although 21% of hydrogenation product was also seen. The rationale behind this good regioselectivity is down to the orientation of the 4-*tert*butyl groups; which shield one coordination side at the metal centre. Despite the problem of hydrogenation, we envisaged that testing this type of ligand and further optimisation could have been fruitful.

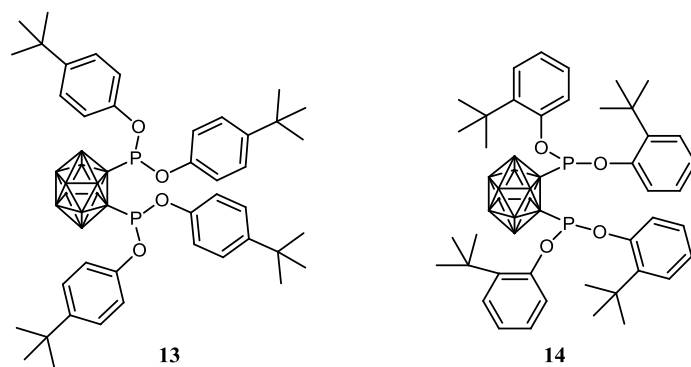


Figure 2.10- 1,2-Dicarba-*closo*-dodecaborane Ligands

A sample of ligand **14** was kindly donated to our group by Hey-Hawkins and co-workers and Table 2.4 shows the result, using the optimised conditions as stated in the publication, in hydroformylation of methyl cinnamate.

Ligand	Temperature (°C)	$\beta : \alpha$	Aldehyde (%)	Alkene (%)	Alkane (%)
14	80	1.75 : 1	22	72	14.5
14	100	5.5 : 1	59	-	34.5

Reaction Conditions- Solvent Toluene, Pressure 50 bar, Time 24 hours, Substrate Concentration 0.99 molL⁻¹, L/Rh = 5:1, Catalyst Loading 0.2%.

Table 2.4- Hydroformylation of Methyl Cinnamate using 1,2-bis[bis(2-tert-butyl phenoxy)phosphanyl]-closo-dicarbaborane Ligand.

At 100 °C, the dicarbaborane ligand is active for methyl cinnamate hydroformylation, with 100% overall conversion and regioselectivity for the β -aldehyde product is favoured here with ratios among the highest we observed in toluene. However hydrogenation is still a significant issue and so we tried the reaction again at a lower temperature. At 80 °C the catalytic activity is very poor with only 22% conversion to aldehyde and the β -selectivity also suffers.

2.3 Solvent Screening

When developing a new process, solvent is an important consideration and several factors must be addressed. Solubility being the most obvious and fundamental aspect and the optimum solubility for catalyst, substrate and reagents must be achieved. An additional consideration is formation of side-products in different solvents e.g. in this case hydrogenation or aldol products. If possible it is useful at this stage to also consider the application in an industrial sense; an ideal solvent for industry would be environmentally benign, sustainable, cheap, non-toxic, safe, have low volatility and would enable easy catalyst/product recovery.

The effect of solvent in hydroformylation varies widely according to the alkene used. Therefore it seems sensible to optimise the reaction of any new substrate by screening a

variety of solvents. All other variables in this screen were kept constant and tris(3,4,5-trifluorophenyl)phosphine **1** and tris(3,5-bis(trifluoromethyl)phenyl)phosphine **3** were the chosen ligands as they had shown fairly promising results in the ligand screen.

Ligand	Solvent	$\beta : \alpha$	Aldehyde (%)	Alkene (%)	Alkane (%)
1	toluene	2.7 : 1	48	3	49
1	Me-THF	8.2 : 1	55	6	30
1	DCM	2 : 1	50	4	40
1	H ₂ O/acetone	2 : 1	21.7	30	48
1	hexane	4.4 : 1	44	1	55
3	toluene	1 : 0	16	14	63.5
3	Me-THF	15 : 1	16	63	19
3	DCM	3.5 : 1	18	27	51
3	H ₂ O/acetone	3.8 : 1	57	41	2
3	hexane	4 : 1	4	80	15
Mixed 1 and 3	Me-THF	10.5 : 1	7	67	23

Reaction Conditions- Pressure 10 bar, Temperature 60 °C, Time 65 hours, Substrate Concentration 0.99 molL⁻¹, L/Rh = 5:1, Catalyst Loading 0.2%.

Table 2.5- Hydroformylation of Methyl Cinnamate Using Different Solvents

As noted in Table 2.5, altering reaction solvent can have a marked effect on regioselectivity, conversion and side product formation. Using toluene for reaction with both ligands resulted in substantial hydrogenation side product. The runs using dichloromethane showed a decreased amount of alkane side-product and the reactions were selective for the β -aldehyde but were not the most selective we had seen. The amount of hydrogenation product formed is still far from ideal and conversions were unsatisfactory. Dichloromethane is unsuitable for industry due its high volatility and health hazards and so we confirmed that we would not use it for our optimisation. Likewise, using hexane had no advantage over other solvents.

Stanley and co-workers²⁴ reported that using 30% water by volume to acetone as the solvent in the hydroformylation of 1-hexene with mono-rhodium phosphine catalysts gave 30-115% rate enhancements compared to using acetone alone. The addition of water creates a simple polar phase solvent system and higher alkenes such as 1-hexene can dissolve sufficiently. Whereas in the water soluble Rh-TPPTS industrial process a limitations lies in the solubility of the substrate in water and only small chain alkenes can be used e.g. propene. We were interested to test this solvent system with our reaction. For the experiment using ligand **1**, the results were unimpressive with almost half the reaction going to alkane side-product and only 70% total conversion. However when tested in the reaction using ligand **3** we observed reasonable β -selectivity ratios, almost 60% conversion to aldehyde and very little hydrogenation (2%).

Ligand	Temperature (°C)	Time (hours)	$\beta : \alpha$	Aldehyde (%)	Alkene (%)	Alkane (%)
3	60	65	3.8 : 1	57	41	2
3	70	24	-	2	98	0
3	80	24	-	1	99	0

Reaction Conditions- Pressure 10 bar, Substrate Concentration 0.99 molL⁻¹, L/Rh = 5:1, Solvent H₂O/acetone, Catalyst Loading 0.2%, Ligand **3**, *tris(3,5-bis(trifluoromethyl)phenyl)phosphine*.

Table 2.6- Hydroformylation of Methyl Cinnamate Using Acetone/H₂O as Solvent.

We therefore decided to increase temperature in a bid to increase conversion to product. As shown in Table 2.6, increasing temperature to 70 °C and 80 °C killed almost all catalytic activity. We reasoned that perhaps in this solvent system the catalyst complex was unstable at higher temperatures and this coincided with a black precipitate observed in the reactions- i.e. possibly degraded catalyst releasing rhodium metal.

Me-THF proved to be interesting in our solvent screen. In general, lower hydrogenation was observed which was particularly significant when compared to toluene and the highest β -regioselectivity ratios in the comparison were seen. Hydrogenation is a significant side reaction in hydroformylation of this substrate and it was vitally important to be able to reduce this as much as possible. When using tris(3,5-(trifluoromethyl)phenyl)phosphine ligand **3**

conversion to aldehyde was low but hydrogenation was also low relative to the other solvents. In the case of the tri(3,4,5-trifluorophenyl)phosphine ligand **1**, the highest conversion to aldehyde product was observed using Me-THF.

2-Me-THF has the huge advantage of being derived from 2-furaldehyde which is in turn obtained from renewable sources such as corncobs and sugar beet²⁵. 2-Me-THF is beyond doubt a green alternative to tetrahydrofuran and dichloromethane. It is an aprotic polar solvent with similar physical properties to toluene. It is less volatile than THF, is easier to dry and has limited miscibility with water and so is a particularly well suited solvent for industrial processes. When using ligands **1** and **3** we now ran reactions in Me-THF and as discussed previously we tested the bidentate ligands in both Me-THF and toluene.

2.4 Pressure, Syngas and Temperature Effects

In hydroformylation, conversion, rate, regioselectivity and enantioselectivity can all be affected by syngas pressure. In this study we first tested the effect of changing overall syngas pressure i.e. always using a 1:1 mixture of CO to H₂. It is known that in general high CO pressures slow the rate of hydroformylation¹². In the catalytic cycle, there is potential for various isomeric alkyl-rhodium species and so effects seen when changing parameters can be complex. Previous work in the group² found that higher pressures and lower temperatures favoured the α -aldehyde product in the hydroformylation of methyl cinnamate. Lower pressures and higher temperatures were seen to produce higher conversion to the β -aldehyde.

Keeping this in mind we set out to further determine the effects of changing pressure and temperature in the hydroformylation of methyl cinnamate. To do so our most effective ligands **1** and **3** were used.

Pressure (bar)	$\beta : \alpha$	Temperature (°C)	Aldehyde (%)	Alkene (%)	Alkane (%)	Solvent
3	-	60	2	79	-	Me-THF
6	20 : 1	60	21	38	38	Me-THF
10	8.2 : 1	60	55	6	30	Me-THF
6	9.3 : 1	70	41	2	49	toluene
10	5.5 : 1	70	19	29	52	toluene

Reaction Conditions- Time 65 hours, Substrate Concentration 0.99 molL⁻¹, L/Rh = 5:1, Catalyst Loading 0.2%, Ligand **1**, *tris(3,4,5-(trifluorophenyl)phosphine)*.

Table 2.7- Hydroformylation of Methyl Cinnamate Using Varying Syngas Pressure and Temperatures

Ligand **1** was used in several experiments in both toluene and Me-THF and the results are displayed in Table 2.7. At lower pressures the regioselectivity is far more promising e.g. 20 : 1 when 6 bar pressure is used with Me-THF as the solvent. However the activity of the catalyst dwindles as pressure is lowered to 3 bar. At 3 bar pressure it is possible that the reaction is hindered by mass transfer limitations of the reagents. With both solvents, it can be seen that increasing syngas pressure leads to a decrease in regioselectivity. At both 6 bar and 10 bar, increasing the temperature by 10 °C leads to a significant increase in alkane side-product. In Me-THF, syngas pressure of 10 bar and a reaction temperature of 60 °C demonstrates the most favourable reactivity and least hydrogenation with moderate regioselectivity.

Pressure (bar)	$\beta : \alpha$	Aldehyde (%)	Alkene (%)	Alkane (%)
3	-	0.5	97	2.5
6	-	6	85	8
10	15 : 1	16	63	19

Reaction Conditions- Time 65 hours, Temperature 60 °C, Substrate Concentration 0.99 molL⁻¹, L/Rh = 5:1, Solvent Me-THF, Catalyst Loading 0.2%, Ligand **3**, *tris(3,5-bis(trifluoromethyl)phenyl)phosphine*.

Table 2.8- Hydroformylation of Methyl Cinnamate Using Varying Syngas Pressure

Ligand **3** proved to form a much less active catalyst than ligand **1** under these low pressure conditions (Table 2.8). In Me-THF, at 3 bar and 6 bar syngas pressure, almost no catalytic activity was detected with extremely low conversion to product. At 10 bar syngas pressure, the reaction gave good regioselectivity but extremely poor conversion and more alkane side-product than aldehyde.

Since phosphine and CO concentration play an important role in the kinetics of the hydroformylation reaction we wanted to test varying the CO and H₂ ratio. The results using our arylphosphine ligands and syngas of the ratio 80/20, CO/H₂ can be seen in Table 2.9.

Ligand	$\beta : \alpha$	Aldehyde (%)	Alkene (%)	Alkane (%)
3	-	3	81	15.5
1	-	5	51	48.5

Reaction Conditions- Pressure 10bar, CO/H₂ (80/20), Temperature 60 °C, Time 16 hours, Substrate Concentration 0.99 molL⁻¹, L/Rh = 5:1, Solvent Toluene, L/Rh 5:1, Catalyst Loading 0.2%, Ligand **1**, *tris(3,4,5-(trifluorophenyl)-phosphine)*.

Table 2.9- Hydroformylation of Methyl Cinnamate Using 80/20 CO/H₂ Syngas.

Unfortunately conversion using this syngas ratio was very low. This is potentially due to less facile CO dissociation and so slower formation of the active rhodium hydride species'. For aryl phosphines it has been determined that the dissociation and association of CO ligands is reversible and faster than hydroformylation¹². So our result agrees with an inverse order in CO pressure; at high CO concentration carbonyl dissociation is the rate determining process. Again we noted that ligand **1** is more active than ligand **3** although most of the observed conversion was to alkane product.

2.5 Ligand/Metal Ratio

Another vital aspect for study was phosphine to rhodium ratio. It is possibly more logical to think in terms of concentration, and in this project, substrate and rhodium concentration was always kept constant and so this section really deals with phosphine ligand concentration. As mentioned in chapter one, the catalytic cycle involves a series of reversible processes which

are each in equilibrium. For hydroformylation of 1-hexene and 1-octene it has been determined¹² that at high PPh₃ ligand concentration the catalyst resting state is (PPh₃)₃Rh(CO)H and a PPh₃ ligand must dissociate for the reaction to proceed. This dissociation process is inhibited by increasing the concentration of PPh₃ and so the concentration of the active rhodium species is reduced. In situ studies have shown that at lower PPh₃ concentration the principal resting state species is (PPh₃)₂Rh(CO)₂H and CO dissociation must occur before the reaction can proceed. We wanted to test the effect of changing phosphine concentrations i.e. ligand to metal ratio (L/Rh), on our reaction and the results can be seen in Table 2.10.

Ligand : Metal	$\beta : \alpha$	Aldehyde (%)	Alkene (%)	Alkane (%)
1 : 1	-	1	97	1.5
2 : 1	25 : 1	26	65	11
5 : 1	15 : 1	16	63	19
8 : 1	18 : 1	29	31	38.5

Reaction Conditions- Pressure 10 bar, Temperature 60 °C, Time 65 hours, Substrate Concentration 0.99 molL⁻¹, Solvent Me-THF, Catalyst Loading 0.2%, Ligand **3**, *tris(3,5-bis(trifluoromethyl)phenyl)phosphine*.

Table 2.10- Hydroformylation of Methyl Cinnamate with Varying L3/Rh Ratios

Using ligand **3** and Me-THF had shown good results in our solvent screen and it can be seen that increasing L/Rh from 5 : 1 to 8 : 1 has a slightly positive effect on β -selectivity and marked effect on overall conversion. Although conversion to aldehyde increases slightly from 16% to 29%, the main issue is the large increase in hydrogenation product to 38.5%. Lowering L/Rh to 2 : 1 gave our best regioselectivity of 25 : 1 in favour of the desired β -aldehyde. Again conversion to aldehyde is low and significant alkane is formed. Dropping the phosphine concentration further saw an almost complete loss of catalytic activity.

Ligand : Metal	$\beta : \alpha$	Aldehyde (%)	Alkene (%)	Alkane (%)
1 : 1	-	~3	88	3
2 : 1	22 : 1	23	32	47
5 : 1	8.2 : 1	55	6	30
8 : 1	7.8 : 1	53	1	40

Reaction Conditions- Pressure 10 bar, Temperature 60 °C, Time 65 hours, Substrate Concentration 0.99 molL⁻¹, Solvent Me-THF, Catalyst Loading 0.2%, Ligand **1**, *tris(3,4,5-(trifluorophenyl)phosphine)*.

Table 2.11- - Hydroformylation of Methyl Cinnamate With Varying L/Rh Ratios

As seen in Table 2.11, using ligand **1**, reducing L/Rh from 5 : 1 had a detrimental effect on activity with almost no conversion for L/Rh of 4 : 1, 3 : 1 and 1 : 1. An anomalous result was seen when L/Rh of 2 : 1 was used where the conversion was more reasonable at 68% and an impressive β -selectivity of 22 : 1 was seen. Unfortunately mostly alkane side product was formed. Increasing phosphine ligand concentration with a L/Rh ratio of 8 : 1 only served to increase the amount of hydrogenation product.

Ligand : Metal	$\beta : \alpha$	Aldehyde (%)	Alkene (%)	Alkane (%)
1 : 1	8 : 1	35	57	11.5
2 : 1	5.6 : 1	46	31	23
5 : 1	2.7 : 1	48	3	49
8 : 1	4.6 : 1	39	9	50

Reaction Conditions- Pressure 10 bar, Temperature 60 °C, Time 65 hours, Substrate Concentration 0.99 molL⁻¹, Solvent Toluene, Catalyst Loading 0.2%, Ligand **1**, *tris(3,4,5-(trifluorophenyl)phosphine)*.

Table 2.12- Hydroformylation of Methyl Cinnamate with Varying L/Rh Ratios.

Overall conversion was surprisingly low and so it was decided that experiments with toluene as the solvent would be of interest (Table 2.12). Conversion to aldehyde did improve in general; but, hydrogenation became a more significant problem. The most promising results were given from a L/Rh ratio of 2 : 1 and 1 : 1 with reasonably good β -selectivity and less hydrogenation than other runs.

We can make a few conclusions from these comparison experiments. Firstly a relatively low phosphine concentration e.g. L/Rh ratio of 2 : 1 in our reaction gives high regioselectivity for the desired isomer. Additionally an obvious trend can be seen in that increasing phosphine concentration in our system leads to an increase in catalytic activity. However this increase in activity, unfortunately, did not mean an increase in conversion to aldehyde and again the problem of hydrogenation side product still hinders our study.

Substrate Concentration (molL ⁻¹)	$\beta : \alpha$	Aldehyde (%)	Alkene (%)	Alkane (%)
0.99	8.3 : 1	56	6	27.5
Min. solvent	1 : 1	57	15	16
0.5	5.8 : 1	30.5	50	19.5

Reaction Conditions- Pressure 10 bar, Temperature 50 °C, Time 65 hours, Substrate Concentration 0.99 molL⁻¹, Solvent Me-THF, Catalyst Loading 0.2%, Ligand **3**, *tris(3,5-bis(trifluoromethyl)phenyl)phosphine*.

Table 2.13- Hydroformylation of Methyl Cinnamate with Varying Substrate Concentration.

Another consideration is the overall amount of solvent in the reaction i.e. the substrate concentration. In all our studies to this point a constant substrate concentration of 0.99 molL⁻¹ was used. We tried a hydroformylation reaction where substrate concentration was diluted to 0.5 molLmolL⁻¹ (See Table 2.13). A drop in our desired regioselectivity was observed as well as a dramatic drop in activity. There is little literature precedent for minimum solvent or solvent free hydroformylation methodologies but the idea is extremely attractive. Matt and co-workers²⁶ reported a solvent free hydroformylation of 1-octene and styrene using hemispherical diphosphites. We attempted a reaction using a minimum amount of solvent i.e. the minimum volume of solvent to dissolve starting material was used. We observed no negative effect with conversion to aldehyde comparable to our previous runs with a substrate concentration of 0.99 molL⁻¹. Hydrogenation side reaction was still present in similar levels to that observed previously and the reaction was not selective for either aldehyde isomer with a regioisomeric ratio of 1 : 1 ($\beta : \alpha$).

2.6 Testing a Novel Ligand

We envisaged that combining aspects of both ligands **1** and **3** into one novel phosphine might provide a “best of both” situation. Hence bis(3,5-trifluoro-phenyl)(3,4,5-fluoro-

phenyl)phosphine (Figure 10) was synthesised from commercially available starting materials. A Grignard reagent was prepared by adding an ether solution of 1-bromo-3,4,5-trifluorobenzene to a cooled suspension of magnesium at a 1:1 molar ratio. Warming the solution and adding 0.3 equivalent of bis(3,5-bis(3,5-trifluoromethyl)phenyl)chlorophosphine, and stirring overnight yielded the crude product, bis(3,5-trifluoromethyl-phenyl)(3,4,5-fluoro-phenyl)phosphine. After a work up, the product was obtained in high purity (0.36 g, 0.7 mmol, 70%).

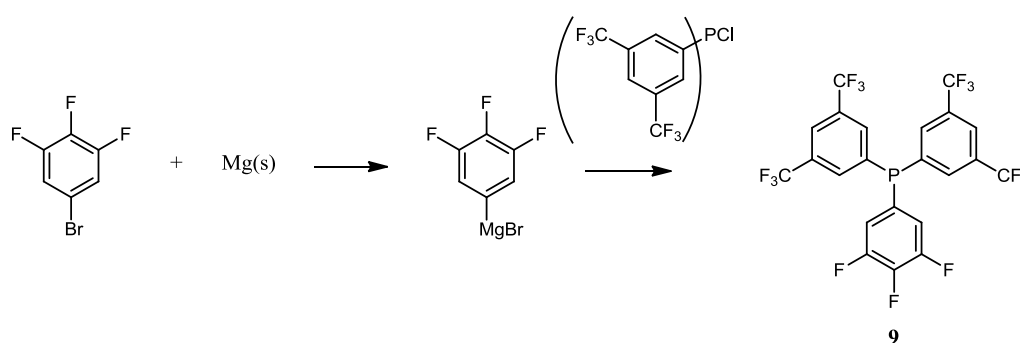


Figure 2.11- Synthesis of Bis(3,5-trifluoromethyl-phenyl)(3,4,5-fluoro-phenyl)phosphine

This novel ligand **9** was tested under the initial conditions used for the other monodentate ligands (Table 2.14).

Ligand	$\beta : \alpha$	Aldehyde (%)	Alkene (%)	Alkane (%)
9	1.15 : 1	29	70	1

Reaction Conditions- Solvent Toluene, Pressure 50 bar, Temperature 60 °C, Time 65 hours, Substrate Concentration 0.99 molL⁻¹, L/Rh = 5:1, Catalyst Loading 0.2%.

Table 2.14- Hydroformylation of Methyl Cinnamate Using Bis(3,5-trifluoromethyl-phenyl)(3,4,5-fluoro-phenyl)phosphine.

The results from this initial reaction using novel ligand **9** were disappointing as neither regioselectivity nor activity were matched to that of ligand **1** and catalytic activity was far less than that of triphenylphosphine **2**. This outcome was at first a little surprising as it is expected that triarylphosphines with electron withdrawing substituents will give faster hydroformylation than triphenylphosphine. However the slight selectivity for β -aldehyde and the very low level of hydrogenation warranted further investigation.

Using the information we had gained throughout the study we set up further experiments under what we found to be “optimal” conditions. To that end we used 10 bar syngas pressure, a temperature of 50 °C and a ligand/rhodium ratio of 2 : 1.

Entry	Solvent	L/Rh	Catalyst Loading (%)	$\beta : \alpha$	Aldehyde (%)	Alkene (%)	Alkane (%)
1	toluene	2 : 1	0.2	5.8 : 1	34	61	5
2	toluene	2 : 1	1	3.6 : 1	52.5	39	7.5
3	Me-THF	2 : 1	1	4.2 : 1	53	26	21

Reaction Conditions- Pressure 10 bar, Temperature 50 °C, Time 65 hours, Substrate Concentration 0.99 molL⁻¹, Solvent Toluene, Ligand **9**.

Table 2.15- Hydroformylation of Methyl Cinnamate Using Bis(3,5-trifluoromethyl-phenyl)(3,4,5-fluoro-phenyl)phosphine.

As can be seen from Table 2.15, under these conditions novel ligand **9** performs far better. Regioselectivity for the desired β -aldehyde is far more promising at almost 6 : 1. Again we observed very low levels of hydrogenation side reaction but unfortunately the overall conversion to product was poor. The reaction was allowed to run for 65 hours and so to improve the catalytic activity we thought an increase in temperature would be effective. However based on previous results, we suspected that increasing the temperature could also produce increased levels of alkane side product.

One variable that had not been studied in this project thus far was catalyst loading and so we decided to test ligand **9** using an increased catalyst loading of 1 mol%. Table 2.15 shows that, as expected, this increase leads to higher conversion (Entries 2 and 3). Hydrogenation is still fairly low in comparison to previous results however regioselectivity suffers slightly.

Since Me-THF has proved to be a suitable solvent for the hydroformylation of our substrate, and in some cases we observed far less hydrogenation using it, we decided to repeat the experiment shown as Entry 2 above, using Me-THF (Entry 3).

Disappointingly the use of Me-THF (Table 2.15) did not eradicate the hydrogenation problem but in fact increased it almost three-fold. Conversion to aldehyde and regioselectivity were almost the same as the reaction using toluene. And so although this novel ligand showed some promisingly results, the hydroformylation of methyl cinnamate suffers from high instances of hydrogenation side reaction. We observed that the level of alkane side product can vary dramatically depending on reaction conditions and ligand used but we were not able to eradicate the problem entirely.

2.7 Alternative Substrates

At this stage we considered some other unsaturated ester substrates in an effort to modulate the selectivity and widen the scope of the reaction. Using the ligand **1**, gave the most active catalyst, we tested three more esters (Table 2.16).

Substrate	Pressure (bar)	Temperature (°C)	$\beta : \alpha$	Aldehyde (%)	Alkene (%)	Hydrog. (%)
^t butyl cinnamate	10	50	99 : 1	10	45	45
^t butyl cinnamate	10	60	11 : 1	23.5	70	7
^t butyl cinnamate	10	70	99 : 1	47	7	46
ethyl cinnamate	10	60	-	-	93	-
methyl crotonate	10	60	3 : 1	<4	81	<1
methyl crotonate	10	90	4 : 1	15	63	5
methyl cinnamate	10	60	8.2 : 1	55	6	30

Reaction Conditions-, Time 65 hours, Substrate Concentration 0.99 molL⁻¹, L/Rh = 5:1, Ligand **1**. Solvent Me-THF, Catalyst Loading 0.2%.

Table 2.16- Hydroformylation of Various Unsaturated Ester Substrates

Methyl cinnamate, ethyl cinnamate, ^tbutyl cinnamate and methyl crotonate were initially reacted at 10 bar syngas pressure at 60 °C. Our catalyst is much less active when the substrate ^tBu-cinnamate is used, with only around 30% overall conversion but regioselectivity observed is good. We tried a hydroformylation with this substrate at a higher temperature (70

°C) in an attempt to increase conversion to product. This led to almost complete selectivity for the β -aldehyde; but, half of the overall conversion was to alkane side product. The *t*-butyl group on this molecule adds significant steric bulk and so perhaps the substrate struggles to bind to the active catalyst complex. Surprisingly no conversion was detected in the reaction of ethyl cinnamate although this reaction was only run once.

We also chose to test methyl crotonate which differs from the cinnamate substrates in that it lacks a phenyl group. Conversion to product and side product were fairly low and so removing the phenyl function showed no advantage, although it is interesting that some β -selectivity is possible even without the “benzylic” directing effect.

2.8 Enamine Formation

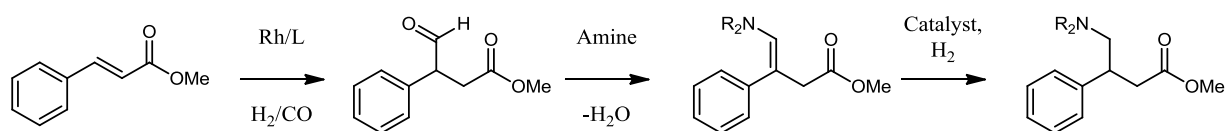


Figure 2.12- Proposed Route to γ -Amino Acid Derivatives

Our investigation into the regioselective hydroformylation of methyl cinnamate did not produce a completely clean, selective process. The overall goal was to develop a process in which methyl cinnamate is converted to its γ -amino acid derivative and so there was further work to be done. Using the method described by Botteghi and co-workers⁸, using Rh_2O_3 , a temperature of 120 °C and 50 bar syngas pressure, we were able to convert the substrate to the corresponding β -aldehyde with a $\beta : \alpha$ ratio of 22 : 1 and 43% conversion and 13% hydrogenation product. The aldehyde was isolated in 33% yield. We then sought to form the corresponding enamine with a view to then hydrogenate to give the γ -amino acid derivative (Figure 2.12).

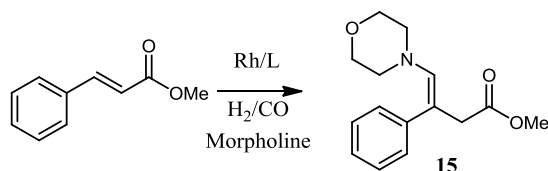


Figure 2.13- In-Situ Hydroformylation-Enamine Formation Using Morpholine

We attempted an “in situ” enamine formation (Figure 2.13) in which the amine morpholine was added to the standard hydroformylation reaction mixture using Rh_2O_3 as the catalyst. The reaction was allowed to proceed for 24 hours under the conditions used previously for methyl cinnamate hydroformylation; 50 bar syngas pressure, 120 °C and toluene as the solvent. Unfortunately this method failed even to yield any aldehyde or enamine products. We observed 50% conversion to hydrogenation and other side products were present, so we speculate that the presence of morpholine is a retardant for the hydroformylation of methyl cinnamate.

It therefore seemed logical to try adding morpholine to the reaction mixture after allowing hydroformylation to take place. An autoclave with an injection port was used and after allowing the reaction to proceed for 24 hours under the conditions stated above, 1.3 eq of morpholine was injected into the depressurised autoclave and heated to 100 °C. Again this method proved to be unsuccessful with no enamine formed at all as observed by ^1H NMR spectroscopy.

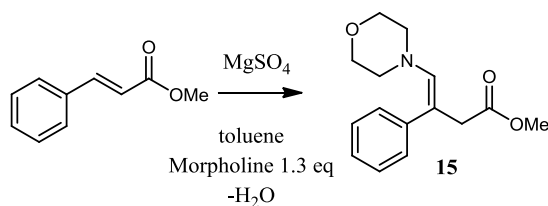


Figure 2.14- Enamine Formation Using Magnesium Sulphate

Removing water from the reaction should pull the equilibrium over to the enamine product and we used magnesium sulphate for this reason (Figure 2.14). The reaction was allowed to run for 24 hours under reflux. We observed around 60% conversion to the enamine by ^1H NMR spectroscopy; peaks at 6 and 5.8 ppm which we attribute to the olefinic CH peaks of the *E* and *Z* isomers of the desired enamine. Previous work in the group has established a work-up method for the analogous styrene enamine in which an extraction using acetonitrile and hexane should see the enamine product go to the hexane layer. This method was used here; however enamine **15** showed no preference for either solvent and in every case aldehyde starting material was present.

A further purification attempt was made via flash column chromatography on silica; initially using an eluent system of hexane/ethyl acetate (2/1). We discovered that enamine **15** could

not be purified using column chromatography. The product eluted from the column in only very small quantities and by ^1H NMR spectroscopy was shown to be impure as significant aldehyde product was observed. Increasing polarity of the eluent system, washing with pure ethyl acetate or a mixture of ethyl acetate/methanol (90/10) and using an alumina stationary phase did not aid purification. Further attempts were made in which the solvent system had 5% triethylamine added to stop the enamine “sticking to” the stationary phase but this was unsuccessful. Finally we tried changing the stationary phase from silica to alumina with no success in isolating our desired product.

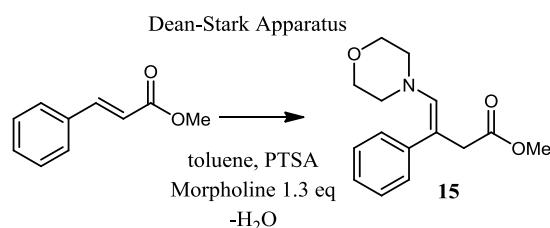


Figure 2.15- Enamine Formation Using Dean-Stark Apparatus

Since purification of the enamine proved to be problematic, a reaction showing full conversion to product was necessary. In a bid to increase conversion to enamine product we removed water from the reaction via Dean-Stark apparatus (Figure 2.15). The reaction was allowed to run for 24 hours and we observed that the calculated volume of water was seen in the collection trap. However the samples taken for analysis by NMR spectroscopy showed to have only around 88% enamine relative to starting material aldehyde. We suspected that the presence of trace water in the CDCl_3 NMR solvent may be enough to tip the equilibrium and convert some product to aldehyde. Using dried C_6D_6 as the solvent for NMR spectroscopy also saw significant aldehyde peaks in the spectra. We concluded that this enamine was particularly unstable and difficult to purify and so would not be ideal for our study. ^1H NMR spectroscopy indicated the presence of a mixture of E/Z isomers.

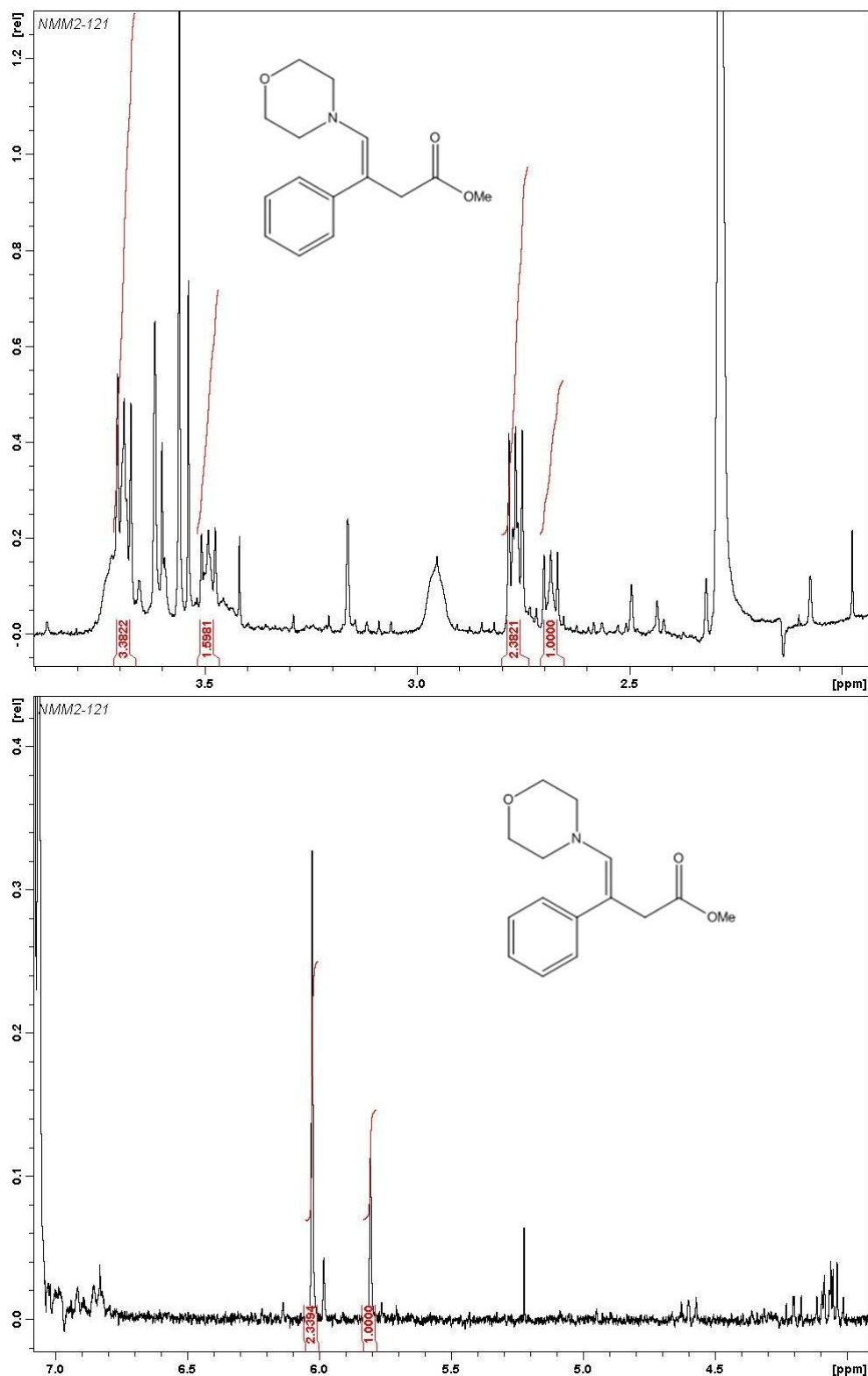


Figure 2.16- ^1H NMR Spectrum for (Z)-methyl 4-morpholino-3-phenylbut-3-enoate **15**

Peaks consistent with morpholino shifts were observed at 2.68 and 3.49 ppm for one isomer and at 2.77 and 3.69 ppm for the other. These two sets of peaks were in a ratio of 2.4 : 1. In addition two peaks were observed in the olefinic region at 5.8 and 6.03 ppm in the same ratio.

By integration, the olefinic peaks are in agreement with the morpholino peaks indicating the presence of the desired enamine in a mixture of E/Z isomers.

An alternative enamine formation was attempted using (*S*)-*N*-benzyl-1-phenylethanamine and similar stability and purification problems were encountered. Similarly an enamine formation using diisopropylamine was attempted and ^1H NMR spectroscopy suggested 51% conversion to a mixture of E/Z isomers. As above, purification was not possible. Although for all enamine formations, we observed that the calculated volume of water was collected in the Dean-Stark trap, NMR spectroscopy in dry solvent showed significant aldehyde peaks. We reasoned that either the enamine products formed are unstable and very water sensitive or that the reaction was not going to full conversion in any case.

2.9 Conclusions

In this section of the project we aimed to optimise the hydroformylation of methyl cinnamate to give a clean, efficient, β -selective reaction which could be utilised in the synthesis of important biologically active molecules. We made steps towards this optimisation by screening many variables. After our initial monodentate ligand screen ligand **1** and ligand **3** looked to be the most promising in terms of activity and regioselectivity. In general the bidentate ligands we tested were less active although dppe and dppe gave good β -selectivity at low pressure and high temperature. We also determined that in some cases Me-THF was a more beneficial solvent than toluene, with hydrogenation being less of an issue. We noted that syngas pressure lower than 50 bar improved regioselectivity but reactions with pressure lower than 10 bar suffered from low activity and/or large amounts of hydrogenation side product.

H₂O/acetone was an interesting solvent at 60 °C, giving a reasonable β : α ratio of 3.5 : 1 and more intriguingly a very low amount of hydrogenation. However at higher temperatures catalytic activity dwindled- possibly due to instability of the catalyst in this system. The highest regioselectivity was observed when a Rh/L ratio of 2 : 1 was used e.g. hydroformylation using ligand **3** gave a β : α ratio of 25 : 1. The problem with this result is the presence of substantial alkane side product and low activity. Increasing the temperature

here from 60 °C would only have increased the amount of hydrogenation. We determined there was no benefit from using other analogous cinnamate substrates.

And so our attempts to optimise this reaction did not lead to an ideal situation and we did not develop a hydroformylation methodology that would be suitable for our proposed route to γ -amino acid derivatives. By obtaining the β -aldehyde via the method described by Botteghi *et al.*, we attempted to form the corresponding enamine. Various methods were tried; all of which suffered problems with product stability and purification.

At this stage of the project, and in light of the time restrictions of MPhil research, it was decided to tackle a new substrate for hydroformylation. We wanted to further explore benzylic regioselectivity and aimed to develop a new method of selective hydroformylation using unsaturated ether substrates.

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CHAPTER THREE

Hydroformylation of an Unsaturated Benzyl Ether Substrate

3.1 Hydroformylation of Allyl Alcohols

Hydroformylation of unsaturated esters has the inherent problem of hydrogenation as a side reaction as well as the electron withdrawing ester group making α -selectivity more likely which is undesirable in our case. With the task of developing a synthesis of γ -amino acids derivatives and γ -amino alcohols, we sought to find an alternative route (See Figure 3.1).

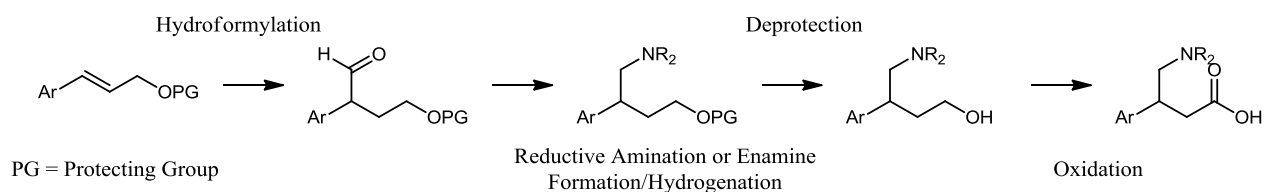


Figure 3.1- Proposed Route to γ -Amino Acids

Hydroformylation of allyl alcohols is an active area of research with many recent advances. Breit and co-workers¹ have recently reported a method for highly regioselective hydroformylation of homo-allylic alcohols to give γ -lactols in high yields using catalytic amounts of a diphenylphosphite directing group (See Figure 3.2) The directing group binds covalently but reversibly to the substrate molecule meaning no extra deprotection step in the synthesis is required, as is the case for directing protecting-groups. The diphenylphosphite forms a cyclic transition state between the substrate and metal forming species with 1, 3 (**A**) or 1, 4 (**B**) relations to the reacting alkene function with the same directing effect, which for the latter is very unusual.

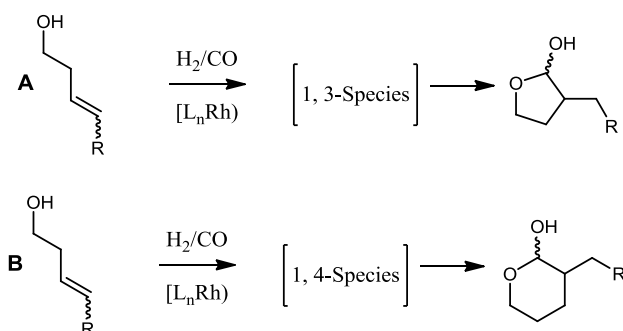


Figure 3.2- Linear Selective Hydroformylation of Allylic Alcohols

In 2008, B. M. Bhanage and co-workers² developed a method in which a linear selective hydroformylation of allylic alcohols was achieved using a Rh/PPh₃ liquid phase catalyst. The hydroformylation was followed by hydrogenation to give 1, 4-butanediol; an important feedstock for polymer synthesis as well as THF and γ -butyrolactones.

One could envisage an unsaturated alcohol starting material for the hydroformylation step might be advantageous (See Figure 3.3). By choosing a substrate that does not contain the ester functionality, the strong electron withdrawing effect it imparts is removed, and so formation of α -aldehyde product is less likely. Additionally the stabilising effect of the ester carbonyl in the α -rhodium alkyl intermediate is eliminated and so the preference for benzylic regioselectivity for substrates such as styrene should be operative for cinnamyl alcohol derivatives.

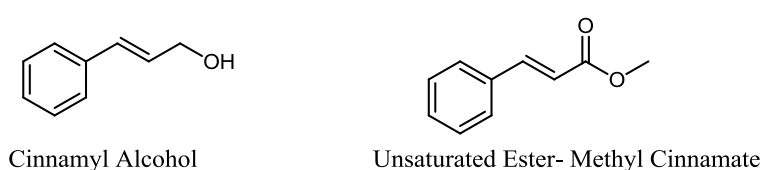


Figure 3.3

Cinnamyl alcohol type substrates have previously been utilised e.g.a synthesis for tetrahydrofuro[2,3*b*]furans was developed by Eilbracht and co-workers⁴ via hydroformylation of *o*-hydroxyl cinnamyl alcohols (See Figure 3.4).

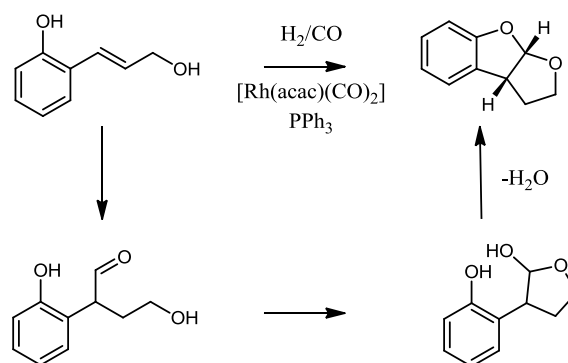


Figure 3.4- Hydroformylation of Hydroxyl Cinnamyl Alcohols

Substituents at the double bond or aliphatic alcohol were tolerated under hydroformylation conditions and give the corresponding substituted tetrahydrofuro-benzofurans. This methodology results in the synthesis of interesting heterocyclic building blocks and demonstrates the potential for hydroformylation of cinnamyl substrates. However the bicyclic structure of the products here are in fact down to hemi-acetal formation which is a feature that makes using the allyl alcohol above not ideal for our purposes.

3.2 Hydroformylation of Allyl Ethers

In the hydroformylation of allyl alcohols, the hydroxyl group in the product has the potential to react with the aldehydic carbonyl to form a hemi-acetal (See Figure 3.5).

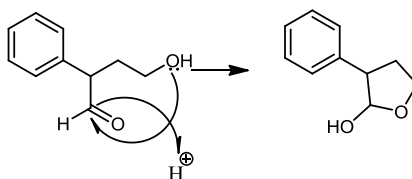


Figure 3.5- Hemi-Acetal Formation

This characteristic has proven to be useful for researchers such as B. Breit² since the products shown in Figure 3.2 can be easily oxidised to the corresponding γ -lactones. In fact Nozaki⁵ uses cinnamyl alcohol as the substrate for exactly that purpose. If hemi-acetal formation needs to be avoided, it is logical to use a substrate in which the alcohol moiety is protected. In this next part of our investigation we chose a benzyl ether protected substrate shown in Figure 3.6.

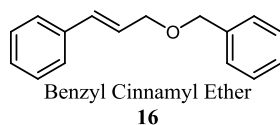
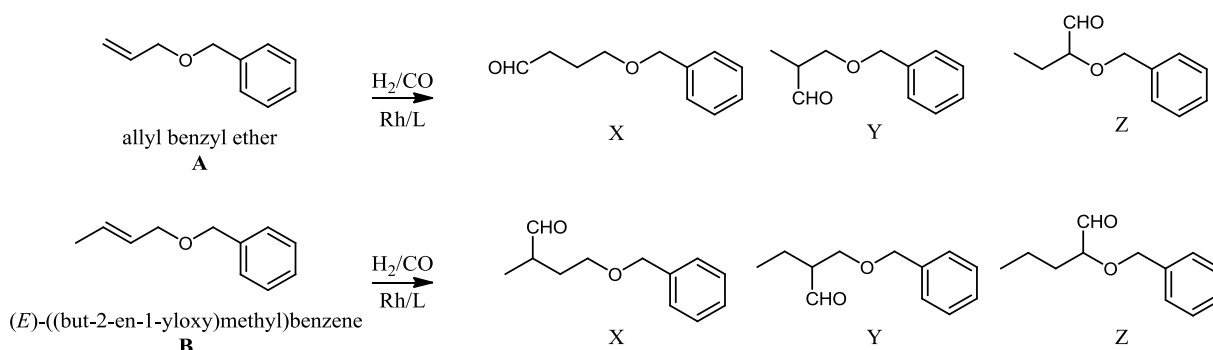


Figure 3.6- Benzyl Ether Protected Substrate

As with the alcohol discussed previously, the benzyl ether can be considered as electron donating and selectivity for the carbon nearest the oxygen is not favoured. By changing from an ester to an ether substrate, the most electron withdrawing group in the molecule is now the phenyl group. This has a directing effect and means that the benzylic regioselectivity is more likely and this is well documented in the case of styrene.

An advantage of using a benzyl ether protecting group for our route is the ease of deprotection; a palladium catalysed hydrogenation could be used to form the alcohol after reductive amination chemistry. This is favourable in terms of developing a process for large scale fine chemical synthesis since catalytic hydrogen methods are welcomed.

There is some precedence for benzyl ether hydroformylation in the literature e.g. Claver and co-workers⁷ report the hydroformylation of various allyl ether substrates (See Figure 3.8). Using $[\text{Rh}(\mu\text{-S}(\text{CH}_2)_3\text{NMe}_2)(\text{cod})]_2$ and PPh_3 , hydroformylation of allyl benzyl ether (A) occurred with fairly good activity at 5 bar syngas pressure and 80 °C giving an X/Y/Z ratio of 59/40/1 (See Figure 3.7). Using tris-(*o*-*tert*-butylphenyl)phosphite as the ligand, ((but-2-en-1-yloxy)methyl)benzene (B) reacted at 120 °C and 80 bar syngas pressure to give an X/Y/Z ratio of 2.44/0.56/1. These results illustrate the issue of the competing isomerisation reaction with these substrates.



Sémeril and co-workers⁸ have more recently described a novel approach to the regioselective hydroformylation of allyl benzyl ether using a hemi-spherical diphosphite chelator ligand and $[\text{Rh}(\text{acac})(\text{CO})_2]$. Using 10 bar syngas pressure and a reaction temperature of 120 °C; 100% conversion to aldehyde was observed with a linear : branched ratio of 20 : 1. The regioselectivity here is said to be down to the unique “three-dimensional” metal environment defined by the ligand-metal complex resulting in a “reaction pocket” of the correct structural constraint for the incoming alkene.

Other than these reports, relatively little is known about the hydroformylation of cinnamyl compounds and ether protected cinnamyl alcohol has not been investigated.

3.3 Synthesis of Benzyl Cinnamyl Ether

Initially we attempted to synthesise the benzyl cinnamyl ether using a general method for the synthesis of aryl-benzyl ethers⁹ (See Figure 3.8).

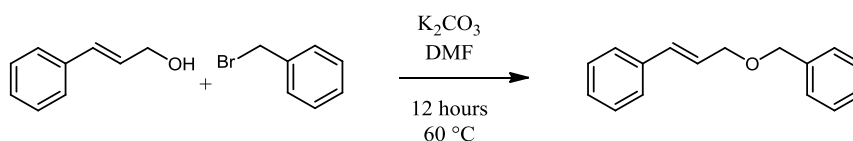


Figure 3.8- Synthesis of Cinnamyl Benzyl Ether

However ^1H NMR and ^{13}C NMR spectra of the resulting product showed peaks which do not match the literature data and an unexpected peak at 8.2 ppm which by integration corresponded to one hydrogen. The ^{13}C NMR spectra of the product showed an extra carbon resonance at 161 ppm and so we speculate that a cinnamyl formate may have been formed (See Figure 3.9).

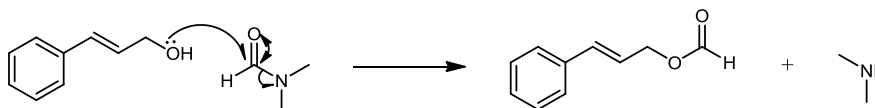


Figure 3.9- Proposed Formate Formation

These peaks in the NMR spectra correspond to formate groups and GCMS data is fully consistent with the formate above being formed. The desired ether was obtained via an alternative synthesis¹⁰ (See Figure 3.10).

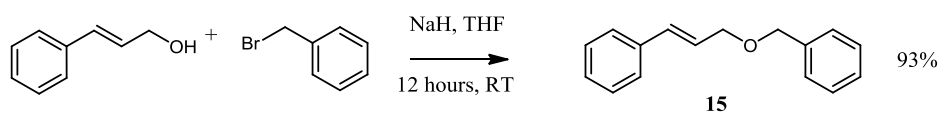


Figure 3.10- Synthesis of Cinnamyl Benzyl Ether

The crude product was purified via column chromatography to give 93% isolated yield of product. A problem arose when, after around 7 days, ^1H NMR spectra showed that the substrate was degrading to isomeric olefin and other unknown degradation products. A very simple experiment was set up to determine the possible cause of this degradation. To five vials was added 1 ml of benzyl cinnamyl ether and each vial was exposed to different variables (as shown in Figure 3.11).

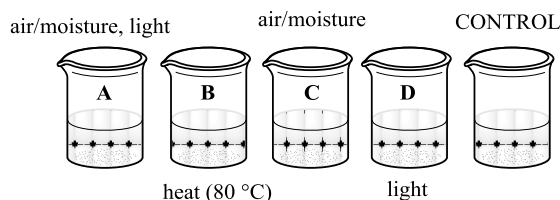


Figure 3.11- Vials Containing Benzyl Cinnamyl Ether Exposed to Different Variables

A sample was taken from each vial after 10 days and a ^1H NMR spectrum recorded.

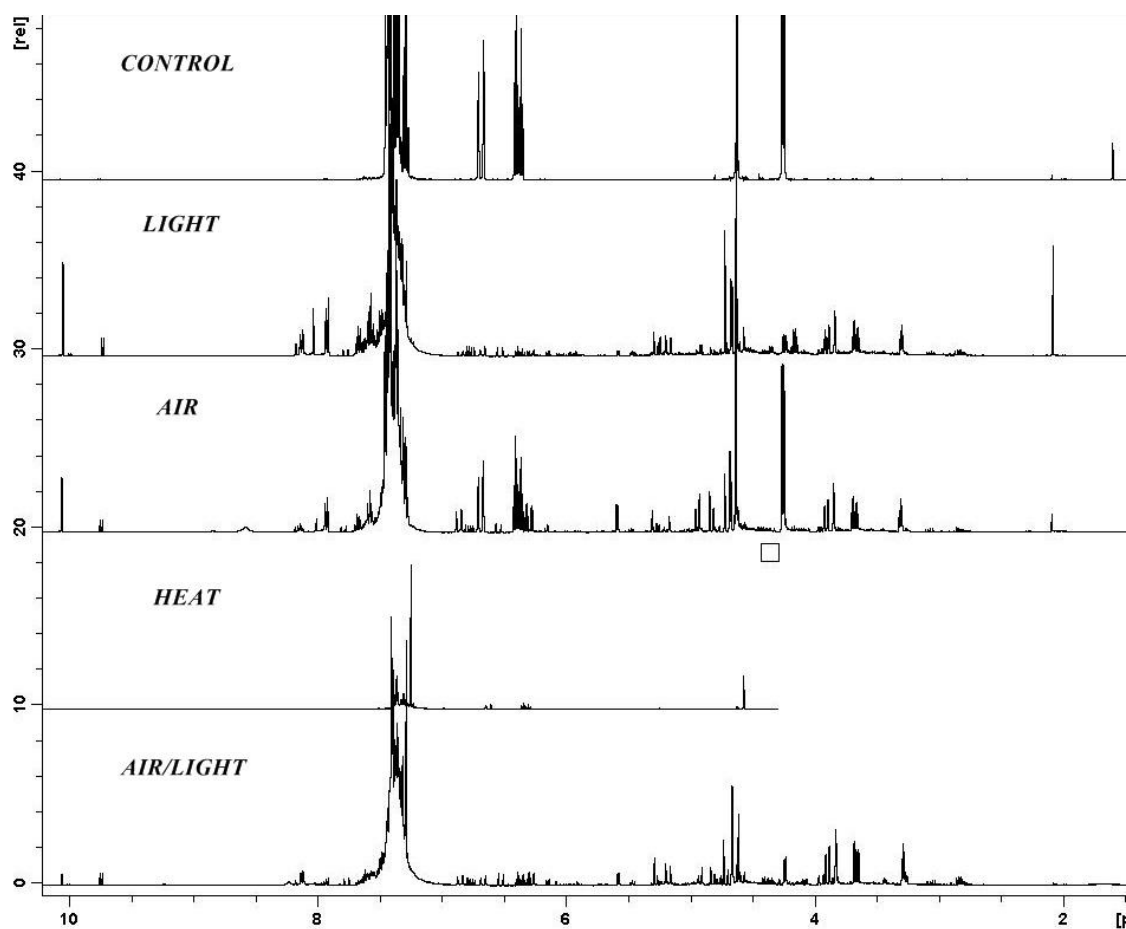


Figure 3.12- Stacked NMR Spectra

From the NMR spectra we can see that after 10 days the control which was covered in foil and kept in a freezer under an atmosphere of argon did not degrade in any way. The most prominent decomposition was seen in the vials exposed to air and light and so it was decided that our benzyl ether substrate would be stored under an inert atmosphere, with no exposure to light and kept in a freezer. During catalytic runs an internal standard was added and a $t=0$ ^1H NMR spectrum was recorded and so purity of the starting material was always checked before reaction.

3.4 Achiral Ligand Screening

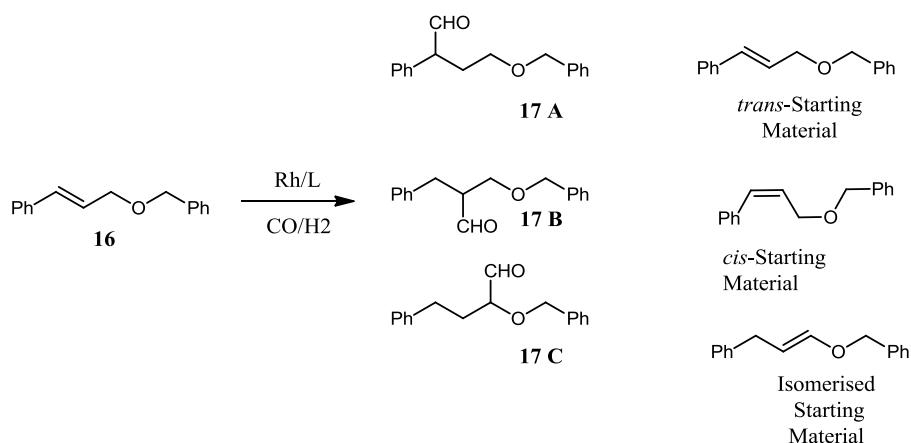


Figure 3.13- Hydroformylation of Benzyl Cinnamyl Ether and Possible Aldehyde Products

In ¹H NMR spectra of crude reaction mixtures, we sometimes observed the presence of two isomeric alkenes as well as starting material. The *trans*-starting material was observed (indicated by: δ_H= 6.6 (1H, dt, ³*J* 15.9 Hz, ⁴*J* 1.5 Hz) and 6.3 (1H, dt, ³*J* 15.9 Hz, ⁴*J* 6.0 Hz). A *cis*-alkene was also sometimes observed and we speculate that this is *cis*-allylic ether rather than the *cis*-alkenyl ether since the alkene peak is close to that of the corresponding starting material proton peak (indicated by: δ_H= 6.1 (1H, dt, ³*J* 6.2 Hz, ⁴*J* 1.5 Hz)) and there is no indication of the expected upfield signal. The *trans*-alkenyl ether was also observed (indicated by: δ_H= 6.4 (1H, dt, ³*J* 12.6 Hz, ⁴*J* 1.2 Hz) and 5.1 (1H, dt, ³*J* 12.6 Hz, ⁴*J* 7.4 Hz)). (See Figure 3.13).

Hydroformylation of the allyl ether substrate **16** has three possible aldehyde products- **17 A**, **17 B** and **17 C** (Figure 3.13); the latter of which would result from olefin isomerisation during the reaction. The identity of aldehyde isomers **17 A** and **17 B** was assigned unambiguously using 2D NMR spectroscopy (COSY, HSQC and HMBC) of the corresponding purified alcohols obtained after NaBH₄ reduction. Conversion to aldehyde **17 C** was usually very low and so this isomer was not isolated but was assigned from the ¹H NMR spectra of the crude reaction mixtures. Considering we observed significant isomeric alkene after catalytic runs, it is reasonable to speculate that **17 C** has the structure as shown above (Figure 3.13).

We aimed to develop a ligand modified rhodium catalysed hydroformylation so that aldehyde **17 A** is the major product.

Using $\text{Rh}(\text{acac})(\text{CO})_2$ as a catalyst precursor we screened a variety of monodentate and bidentate phosphorus containing ligands (Figure 3.14). As discussed in Chapter Two, rhodium complexes of triphenylphosphine, PPh_3 **1**, are the most used hydroformylation catalysts.

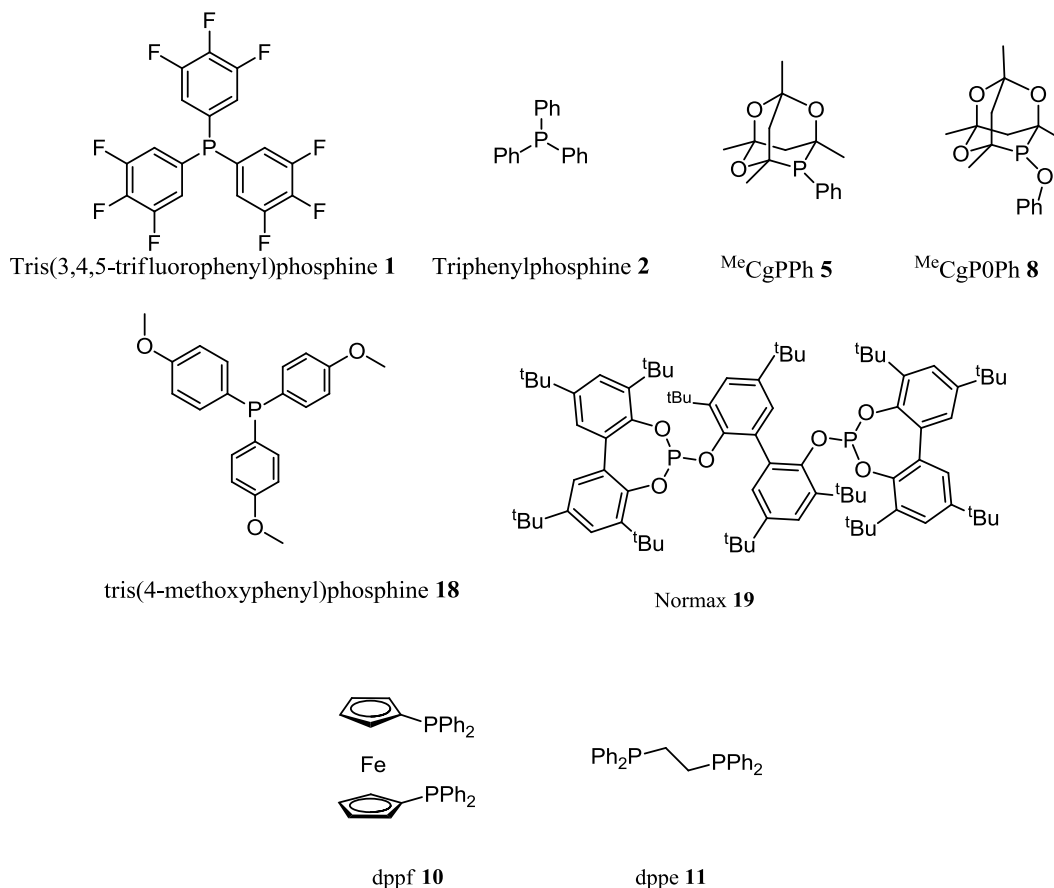


Figure 3.14- Monodentate and Bidentate Phosphorus Containing Ligands

Tris(3,4,5-fluorophenyl)phosphine **1** proved to be one of the most promising ligands in Chapter Two for the hydroformylation of methyl cinnamate. We envisaged that we might see improved activity and regioselectivity using this ligand in the hydroformylation of benzyl ether substrate **16** and possibly little or no hydrogenation as a side reaction. As in Chapter Two, the flexible ferrocene backbone of dppf **10** makes it an appealing ligand with potential for optimisation should it prove to be effective. We also decided to test MeCgPPh **5** and the analogous MeCgPOPPh **8** ligand for the hydroformylation of this substrate. (MeCgPOPPh was kindly donated by Paul Pringle and co-workers).

We know that bulky phosphite ligands give extremely high reactions rates and so are suitable for hydroformylation of less reactive functionalised alkenes but they also suffer from lower

selectivity. In 1987 Bryant and co-workers¹³ highlighted diphosphite catalyst systems as a means of improving this selectivity issue and since then extensive research has been carried out in academia and industry resulting in several patents. Bulky diphosphites with a bisphenol “linker” have proven to give exceptional increase in linearity in rhodium catalysed hydroformylation of 1-alkenes¹⁴ with rates still higher than those when triphenylphosphine is used. The bidentate phosphite ligand NORMAX™ **19** is used commercially in the hydroformylation of propene to give the highest known selectivity for normal butyraldehyde. Selectivity depends on structural variation in this type of ligand and so we wanted to investigate whether NORMAX™ was beneficial for the regioselectivity in our reaction.

After each reaction, a crude ¹H NMR spectrum was recorded and conversion to products was calculated by integration with relation to an internal standard. As well as the expected aldehyde products **17 A** and **17 B** (and **17 C**) we also sometimes observed a peak at 9.98 ppm (aldehydic region). This aldehyde, **17 D**, was usually a very minor product and was not isolated. The structure of **17 D** is unknown.

As seen in Table 3.1, the most successful ligand for hydroformylation of our substrate, at 50 °C and 15 bar syngas pressure, proved to be PPh₃ which also shows the highest regioselectivity for aldehyde product **A** and no isomeric alkene was observed. ^{Me}CgPOPh **8** competes with PPh₃ by almost matching the overall conversion to aldehyde and provided the only reaction to go fully to completion. Ligand **8** also comes very close to PPh₃ in terms of regioselectivity which is in agreement with the findings of Pringle and co-workers¹² showing that phosphadamantane type ligands display better activity than PPh₃ with little loss in selectivity. For ligands **1**, **5**, **10**, **11** and **19**, isomerisation is a significant side reaction showing conversion to aldehyde **17 C** as well as free isomeric alkene which isn't surprising since we know that this substrate is prone to isomerisation.

NORMAX™ **19** and dppf **10** show the poorest catalytic activity which is particularly surprising for the former. It was expected that this diphosphite ligand would show far greater reactivity than the phosphine ligands; however it is likely that the steric bulk of this ligand made coordination of the fairly bulky substrate more hindered

Ligand	Conversion to Aldehyde (%)	A / B / C / D (%)	Isomer Alkenes (%)	Alkene (%)
2	87	83 / 14 / 3 / 0	0	6
5	59	59 / 20 / 14 / 7	28	13
8	83	76 / 15 / 9 / 0	0	0
1	64	71 / 17 / 12 / 0	25	11
18	72	79 / 16 / 5 / 0	12	16
19	44	56 / 31 / 5 / 8	21	35
10	39	64 / 21 / 5 / 10	21	40
11	43	61 / 21 / 9 / 9	31.5	25.5

Reaction Conditions- Solvent Toluene, Pressure 15 bar, Temperature 50 °C, Time 16 hours, Substrate Concentration 0.23 molL⁻¹, L/Rh = 5:1, Catalyst Loading 0.2%.

Table 3.1- Hydroformylation of Substrate 16 Using Mono and Bidentate Phosphine Ligands

3.5 Pressure Effects

Syngas pressure can have a great effect on the hydroformylation reaction and so we wanted to explore hydroformylation of this substrate using the above ligands at various reaction pressures.

Monodentate Ligands

The monodentate phosphine ligands mentioned previously were used in reactions at 5, 15 and 50 bar syngas pressures (Table 3.2). The results for reactions run at the lower pressure of 5 bar show a clear trend in that a slight improvement in regioselectivity is seen as there is no aldehyde **C** or **D** formed. The ratio between aldehyde **A** and **B** generally does not suffer and in the case of ligand **1** and **18** actually increases.

Ligand	Pressure (bar)	Conversion to Aldehyde (%)	A / B / C / D (%)	Isomer Alkenes (%)	Starting Material (%)
2	5	14	85 / 15 / 0 / 0	0	77
2	15	87	83 / 14 / 4 / 0	0	6
2	50	16.5	90 / 10 / 0 / 0	0	83.5
5	5	10	69 / 31 / 0 / 0	0	90
5	15	59	59 / 20 / 14 / 7	28	13
5	50	18	90 / 10 / 0 / 0	0	77
8	5	29	78 / 22 / 0 / 0	0	74
8	15	83	76 / 15 / 9 / 0	0	0
8	50	18	80 / 20 / 0 / 0	0	82
1	5	3	85 / 15 / 0 / 0	0	90
1	15	64	71 / 17 / 12 / 0	25	11
1	50	47	88 / 12 / 0 / 0	0	53
18	5	5	84 / 16 / 0 / 0	0	91
18	15	72	79 / 16 / 5 / 0	12	16
18	50	15	87 / 13 / 0 / 0	0	85

Reaction Conditions- Solvent Toluene, Pressure 15 bar, Temperature 50 °C, Time 16 hours, Substrate Concentration 0.23 molL⁻¹, L/Rh = 5:1, Catalyst Loading 0.2%.

Table 3.2- Hydroformylation Pressure Study Using Monodentate Phosphine Ligands

However dropping syngas pressure from 15 to 5 bar has a hugely negative effect on catalyst activity and we reason that 5 bar syngas pressure was not sufficient for the active catalyst species to form. When syngas pressure was increased to 50 bar a similar effect was seen; a large drop in catalytic activity. We postulate that there are two distinct deactivation mechanisms involved and in the case at high pressure; reduced dissociation of CO means less of the active four-coordinate rhodium species is formed. At 50 bar pressure it is also clear that regioselectivity for the desired aldehyde **17 A** increases, however at such low conversion to product this is not of practical use. It is worth noting that using the electron deficient ligand **1**, this activity drop is mitigated.

It is interesting that at 5 bar and 50 bar pressure no isomerisation is seen i.e. there is no conversion to aldehyde **17 C** or formation of free isomer alkene. At 15 bar pressure “t= 0” NMR spectra show there is no isomer alkene in the starting material as an impurity and yet we see formation of isomer alkene up to 17% and a significant amount of aldehyde **17 C** in the case of ligand **5**, ^{Me}CgPPh. β-Hydride elimination from an intermediate Rh-alkyl species

is necessary for isomerisation. It is possible that at 15 bar we have an optimal situation for this to occur.

Bidentate Ligands

As above the bidentate phosphine and phosphite ligands were tested at various pressures (Table 3.3).

Ligand	Pressure (bar)	Conversion to Aldehyde (%)	A / B / C / D (%)	Isomer Alkenes (%)	Starting Material (%)
19	5	4	92 / 3 / 0 / 6	0	96
19	15	44	56 / 31 / 5 / 8	21	35
19	50	2	100 / 0 / 0 / 0	0	87
10	5	1	100 / 0 / 0 / 0	0	90
10	15	39	64 / 21 / 5 / 10	25.5	40
10	50	0	-	0	86
11	5	0	-	0	89
11	15	43	61 / 21 / 9 / 9	31.5	25.5
11	50	0	-	0	99

Reaction Conditions- Solvent Toluene, Pressure 15 bar, Temperature 50 °C, Time 16 hours, Substrate Concentration 0.23 molL⁻¹, L/Rh = 5:1, Catalyst Loading 0.2%.

Table 3.3- Hydroformylation Pressure Study Using Bidentate Ligands

The bidentate ligands proved to be far less active and regioselective in hydroformylation of this substrate in comparison to the monodentate phosphine ligands. In agreement with results from the monodentate ligands, at 15 bar syngas pressure, significant isomerisation is present as well as formation of aldehyde **17 D**. We observed that changing to 5 and 50 bar pressure in these runs resulted in very low conversion and with ligand **11** we see no conversion at all. And so from the data for both monodentate and bidentate ligands we can conclude that for optimum catalytic activity we need to use pressures in the region of 15 bar but an improvement to regioselectivity and a reduction in isomerisation is needed for us to develop an ideal reaction.

3.6 Effect of Temperature

To improve regioselectivity and also conversion to aldehyde product it was necessary to further optimise reaction conditions. We investigated the effect of changing temperature on the hydroformylation of our substrate using the monodentate phosphine ligands (Table 3.4).

Ligand	Temperature	Conversion to Aldehyde (%)	A / B / C / D (%)	Isomer Alkenes (%)	Starting Material (%)
2	40	16.4	85 / 12 / 2 / 0	0	79
2	50	87	83 / 14 / 4 / 0	0	6
2	70	4	90 / 10 / 0 / 0	0	95
8	40	21	76 / 24 / 0 / 0	0	68
8	50	83	76 / 15 / 9 / 0	0	0
8	70	14	77 / 23 / 0 / 0	0	86
1	40	70	90 / 10 / 0 / 0	0	30
1	50	64	71 / 17 / 12 / 0	25	11
1	70	9	93 / 6 / 0 / 1	0	89
18	40	23	91 / 9 / 0 / 0	0	66
18	50	72	79 / 16 / 5 / 0	12	16
18	70	3	69 / 24 / 0 / 7	0	97

Reaction Conditions- Solvent Toluene, Pressure 15 bar, Time 16 hours, Substrate Concentration 0.23 molL⁻¹, L/Rh = 5:1, Catalyst Loading 0.2%.

Table 3.4- Effect of Temperature on Hydroformylation of Allyl Benzyl Ether

In general, by lowering reaction temperature from 50 °C to 40 °C conversion to product showed a dramatic decrease although in reactions using ligands **1** and **18** there is a substantial improvement in regioselectivity. In fact ligand **1** is the only case in which there is improved conversion. Lower conversion to product at lower temperature is unsurprising in the case of ligand **18**.

Disappointingly at 70 °C we see an even more prominent dip in catalytic activity with conversions between 3- 14%. We reason that this higher temperature must result in some of the catalyst breaking down i.e. the active catalyst species is unstable at higher temperatures.

3.7 Varying Catalyst Loading

So at this stage it seemed that syngas pressure of 15 bar and a reaction temperature of 50 °C were most suited to our reaction. However our results were still not ideal and so we tried reactions at a higher catalyst loading of 1.7% with the hope of improving activity and potentially regioselectivity.

Ligand	Catalyst Loading (%)	Conversion to Aldehyde (%)	A / B / C / D (%)	Isomer Alkenes (%)	Starting Material (%)
2	1.7	89	86 / 14 / 0 / 0	0	<1
8	1.7	94	78 / 22 / 0 / 0	0	0
1	1.7	99	80 / 16 / 4 / 0	0	0
18	1.7	79	84 / 16 / 0 / 0	0	21

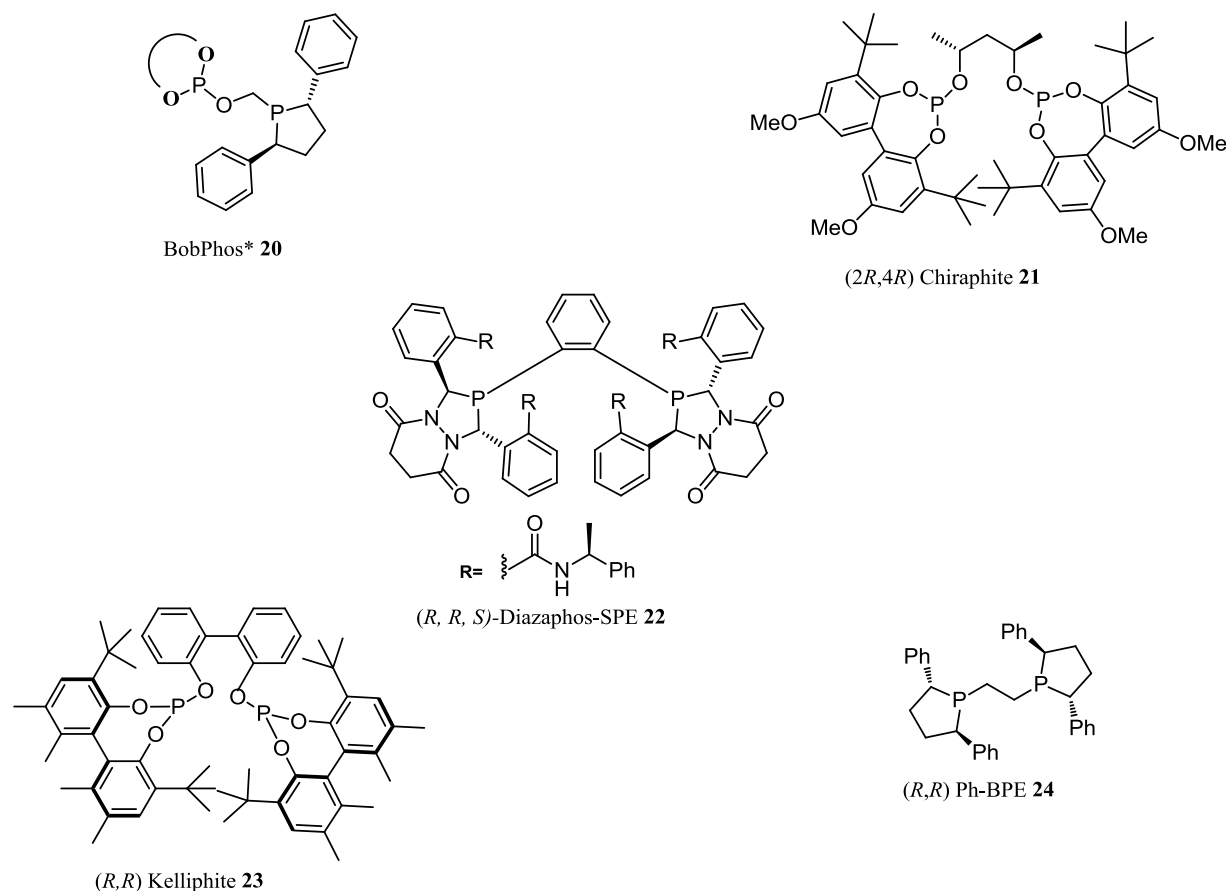
Reaction Conditions- Solvent Toluene, Temperature 50 °C, Pressure 15 bar, Time 16 hours, Substrate Concentration 0.23 molL⁻¹, L/Rh = 5:1.

Table 3.5- Effect of Increased Catalyst Loading on Hydroformylation of Allyl Benzyl Ether

It is clear than in comparison to previous catalytic runs at 50 °C, the higher catalyst loading give much improved reactivity. This effect can be seen especially for ligand **1** with an improvement from 63 % to 99% total conversion to aldehyde products. Additionally there is a slight improvement in regioselectivity for aldehyde **A** at this higher catalyst loading. Hydroformylation using ligand **18** also showed a significant increase in selectivity and no conversion to isomeric products was observed.

At this higher catalyst loading it would seem that the phosphorus ligands ^{Me}CgPOPh **8** and tris(3,4,5-trifluorophenyl)phosphine **1**, yield the most promising results. With almost complete conversion to aldehyde and around 5 : 1 selectivity for the desired aldehyde **A** and no isomerisation side reaction.

3.8 Chiral Ligand Screening



*Structure of diol not shown due to commercial reasons.

Figure 3.15- Some of the Most Successful Ligands for Asymmetric Rhodium Catalysed Hydroformylation

For the synthesis of drug molecules it is highly desirable to form products as single enantiomers. Highly enantioselective asymmetric hydroformylation using chiral phosphorus ligands is becoming an important method and further research on the asymmetric hydroformylation of functionalised substrates is needed. We tested a range of state of the art chiral ligands for the hydroformylation of the benzyl ether substrate **15** (Figure 3.15).

Previous work in the group has shown that in general; due to the unreactive nature of di-substituted alkenes, higher reaction temperatures are required and so for these chiral ligands we used a reaction temperature of 80 °C. The results are shown in Table 3.6.

Ligand	Total Conversion Aldehyde (%)	A : B : C : D (%)	Isomer Alkenes (%)	Starting Material (%)
24	30	40 / 25 / 31 / 4	50	20
22	4.5	73 / 21 / 0 / 6	18	77.5
23	26	35 / 30 / 30 / 5	54	20
21	32	35 / 37 / 26 / 2	50	18
20	36	32 / 39 / 26 / 3	48	16

Reaction Conditions- Solvent Toluene, Temperature 80 °C, Pressure 10 bar, Time 16 hours, Substrate Concentration 0.23 molL⁻¹, L/Rh = 1.25:1, Catalyst Loading 0.2%.

Table 3.6- Hydroformylation of Allyl Ether Substrate Using Chiral Ligands

Unfortunately very low activity was observed for all of the chiral ligands with conversion no higher than 32%. Additionally poor regioselectivity was seen for reactions using all ligands with significant amounts of aldehyde **C** and isomer alkene. Due to such poor aldehyde conversion, e.e. was not calculated for these runs.

In the runs using PhenylBPE (*R,R*) and (*R,R*)-Kelliphite, the amount of observed isomerisation was significant at around 50%. We therefore wanted to see if the rhodium complex of these ligands were in fact a good isomerisation catalysts. An autoclave containing catalyst precursor (Rh(acac)(CO)₂), PhenylBPE (*R,R*) and toluene was pressurised with syngas to 15 bar, heated to 80 °C and allowed to stir for 15 minutes to allow catalyst formation. The autoclave was then depressurised and a solution of substrate was added and the mixture then allowed to stir at 80 °C for 24 hours. After this time however no isomer alkene was observed in the ¹H NMR spectrum of the crude reaction mixture.

Ligand	Ligand/Rhodium	Temperature (°C)	Total Conversion to Aldehyde (%)	A / B / C / D	Isomer Alkene (%)	Starting Material (%)	e.e. (%) α^*	e.e. (%) β^*
PhenylBPE	2.5/1	80	83	80 / 16 / 4 / 0	0	3	2.5	14.6
PhenylBPE	1.25/1	60	4.5	59 / 0 / 15 / 26	0	86	-	-

Reaction Conditions- Solvent Toluene, Temperature 80 °C, Pressure 10 bar, Time 16 hours, Substrate Concentration 0.23 molL⁻¹, L/Rh = 1.25:1, Catalyst Loading 0.2%. * e.e. calculated by HPLC analysis of reduced reaction products i.e. alcohols.

Table 3.7- Hydroformylation of Allyl Benzyl Ether Using PhenylBPE

An attempt to improve results using PhenylBPE was made by first increasing the ligand/rhodium ratio from 1.25/1 to 2.5/1. This increase saw a great increase in catalytic activity with conversion to aldehydes going from 32% to 83%. However regioselectivity and enantioselectivity was quite poor. Then a lower reaction temperature of 60 °C was used in a final run with the ligand PhenylBPE. Very low conversion to aldehyde was observed and also poor regioselectivity.

3.9 Conclusions

In synthesising this alternative substrate for hydroformylation, it was observed that it is fairly sensitive to air/light degradation. Precautions were taken to avoid this degradation and it is worth noting that the hydroformylation reaction itself in some cases was effected by a competing isomerisation reaction. The hydroformylation of this substrate has the potential to form three distinct aldehyde isomers (Figure 3.13), and the structures of two of these were determined absolutely by 2D NMR spectroscopy.

In testing various experimental conditions it was found that 15 bar syngas pressure produced by far the most active catalysts and likewise a reaction temperature of 50 °C was most suitable. Overall the ligands that formed the most active catalyst complexes were PPh₃ and ^{Me}CgPOPh and the former gave the best regioselectivity in this study. Unfortunately an asymmetric process was not developed as all chiral ligands tested proved to be insufficiently active for this substrate.

References Chapter Three

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Conclusions and Future Work

In Chapter Two, we aimed to develop a selective and efficient hydroformylation of methyl cinnamate. By testing various reaction conditions and phosphorus ligands, steps towards optimisation were made. We observed that generally bidentate ligands produced less active catalysts than monodentates; however dppe and dppf gave good regioselectivity using low syngas pressure and high temperature. We saw that in some cases using Me-THF as solvent was favourable in terms of decreased hydrogenation side reaction. Syngas pressure of 10 bar seemed to be optimal for high regioselectivity. Using a Rh/L ratio of 2 : 1 with ligand **3** (tris(3,5-trifluoromethyl(phenyl))phosphine), gave our highest β/α ratio of 25 : 1. However this reaction suffered from high levels of hydrogenation side reaction and low conversion to product. Thus we were unable to develop an effective hydroformylation in terms of our proposed route to γ -amino acid derivatives. An enamine formation using the β -aldehyde also proved problematic.

The hydroformylation of a benzyl ether protected substrate was studied in Chapter Three. We tested various chiral and achiral phosphorus ligands as well as various reaction conditions with the aim to selectively produce aldehydes with benzylic regioselectivity. Using 15 bar syngas pressure and a reaction temperature of 50 °C, gave the highest catalytic activity and so more conversion to products. Overall, PPh_3 and $^{\text{Me}}\text{CgPOPh}$ ligands produced the most active catalyst at 50 °C. However the catalyst of tris(3,4,5-trifluorophenyl)phosphine ligand operates best at 40 °C and 50 bar pressure. Bidentate chiral ligands tested showed low activity for this substrate. Isomerisation of the alkene proved to be a competing reaction but appropriate choice of ligand eradicated this problem. Using PPh_3 , a hydroformylation reaction showing high conversion and high benzylic regioselectivity was observed.

Future work would possibly concentrate on producing γ -amino acid derivatives from the substrate studied in Chapter Three. The aldehydes formed in this reaction could then be taken on to produce enamines which in turn could be reduced via catalytic hydrogenation while simultaneously deprotecting the alcohol moiety. Alternatively, a reductive amination reaction could be developed. Additionally, research into the hydroformylation of more complex substrates could be fruitful. Bergdahl and co-workers* describe a highly efficient Wittig reaction performed using water as the solvent. Various heterocyclic unsaturated esters are formed in high yield with short reaction times.

Using this method we envisage that many new interesting substrates for hydroformylation could be synthesised and so potentially provide many pharmaceutically valuable molecules.

* M. Bergdahl, A. El-Batta, C. Jiang, W. Zhao, R. Anness and A. L. Cooksy, *J. Org. Chem.*, 2007, **72**, 5244-5259.

CHAPTER FOUR

Experimental

4.1. General Procedures

Reagents, starting materials and solvents that were not synthesised and described here were purchased from commercial suppliers and used as received. Syngas was purchased from BOC. Dry solvents (toluene, tetrahydrofuran, diethyl ether, and dichloromethane) were used directly from Grubbs system Braun MSB 8000 still without degassing. Degassing of solvent where necessary was carried out using the freeze-pump-thaw method. All chiral ligands were donated by Chirotech Technology Ltd.

IR-Spectroscopy

Infra-red spectra were recorded on a Perkin-Elmer Paragon spectrometer.

Thin Layer Chromatography

TLC was carried out on Polygram Sil G/UV₂₅₄ silica plates. Developed plates were viewed under a UV lamp and stained with standard potassium permanganate or ninhydrin dip were appropriate.

NMR Spectroscopy

¹H, ¹³C and ³¹P nuclear magnetic resonance spectra attained using a Bruker Avance 400 spectrometer and a Bruker Avance 300 spectrometer. Chemical shift information (δ_H and δ_C) for each signal is given in units of parts per million (ppm) relative to 1-methylnaphthalene where δ_H and δ_C TMS = 0.00ppm. All coupling constants are quoted to the nearest 0.1 Hz. The symbols s, d, t, q, m and br used in the assignment of the ¹H NMR spectra refer to singlet, doublet, triplet, multiplet and broad respectively. The number of protons (n) for a reported signal is indicated by nH calculated from the integral value. Multiplicity is reported with their coupling constants (J) quoted in Hz. In the assignment of ¹³C NMR spectra, the abbreviations CH, CH₂, CH₃, and quat. are used to denote primary, secondary, tertiary and quaternary carbon centres respectively. In the assignment of all NMR spectra the symbol Ar

denotes aromatic. Coupling constants and integral values determines by analysis using Topspin[®].

Mass Spectrometry

MS and GCMS refer to mass spectrometry and gas-chromatography mass spectrometry. Electrospray Mass Spectrometry (ESMS) and high-resolution mass spectrometry were carried out on a Micromass LCT orthogonal acceleration time of flight (TOF) mass spectrometer .

Enantiomeric Excess

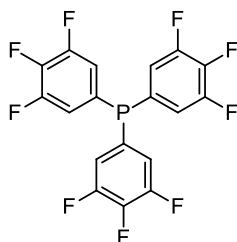
e.e. values were measured using chiral HPLC, using a Varian Prostar and Galaxie Workstation PC software. An ODH chiral column was used. Flow rate used 0.5 ml/min.

Flash Chromatography

Column chromatography was carried out using Silicycle-P Flash Silica Gel 40-63 μm and Brockman I standard grade ~ 150 mesh, 58 Å neutral alumina were appropriate. Eluent systems were selected with referral to TLC and supplied under a positive pressure of air.

4.2 Hydroformylation of Cinnamate Esters

Synthesis of tris(3,4,5-trifluorophenyl)phosphine



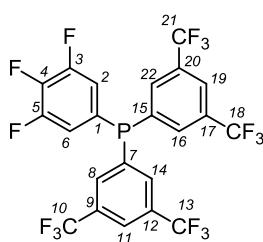
The Grignard reagent 3,4,5- $\text{C}_6\text{H}_2\text{F}_3\text{MgBr}$ was prepared by gradually adding a solution of 1-bromo-3,4,5-trifluorobenzene (3.50 g, 16.8 mmol) in Et_2O (10 ml) into a cooled suspension of magnesium (0.40 g, 16.8 mmol) in Et_2O (10 ml). The mixture was warmed to room temperature before the addition of a solution of PCl_3 (0.77 g, 5.6 mmol). After stirring overnight, the solvents were removed *in vacuo* and the residue dissolved in toluene and filtered through a sinter stick. The toluene solution was washed with brine solution, dried with sodium sulfate and the solvent was removed *in vacuo* to give tris(3,4,5-

trifluorophenyl)phosphine as a white solid (1.74 g, 73%). This is an unoptimised yield as some product was lost during the filtration stage.

(Found: C, 50.90; H, 1.31. C₁₈H₆F₉P requires C, 50.96; H, 1.43%); ³¹P NMR δ_P (121.4 MHz, C₆D₆) 1.11 (s); ¹⁹F{¹H} NMR δ_F(282 MHz, C₆D₆) -131.75 (6F, d, ³J 20.74 Hz) and -156.35 (3F, td, ³J 20.80 Hz); ¹H NMR δ_H(300 MHz, C₆D₆) 6.34 (6H, q, *J* 6.62 Hz). MS (ES+) *m/z*: 462.65 ([M + K⁺]).

This is in agreement with the literature¹.

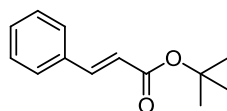
Synthesis of bis(3,5-bis(trifluoromethyl)phenyl)(3,4,5-trifluorophenyl)phosphine



The Grignard reagent (3,4,5-trifluorophenyl)magnesium bromide was prepared by adding a solution of 1-bromo-3,4,5-trifluorobenzene (0.36 ml, 3.0 mmol) in diethylether (4 ml) to a cooled suspension of magnesium turnings (0.072 g, 3.0 mmol) in diethylether (4 ml). The mixture was allowed to warm to room temperature before addition of bis(3,5-bis(trifluoromethyl)phenyl)phosphine (0.49 g, 1.0 mmol) in diethylether. After stirring overnight, the solvents were removed *in vacuo* and the residue dissolved in toluene and filtered through a sinterstick. The toluene solution was washed with brine solution, dried with sodium sulfate and the solvent was removed *in vacuo* to give bis(3,5-bis(trifluoromethyl)phenyl)(3,4,5-trifluorophenyl)phosphine (0.36 g, 0.70 mmol, 70%) in high purity (>99% by NMR spectroscopy). This is an unoptimised yield as some product was lost during the filtration stage.

³¹P NMR δ_P (121.4 MHz, CDCl₃) -3.42 (s); ¹⁹F{¹H} NMR δ_F(282 MHz, C₆D₆) -63.42 (12F, m, C¹⁰F₃, C¹³F₃, C¹⁸F₃, C²¹F₃), -130.80 (2F, d, C⁵F, C³F) and -155.30 (1F, td, ³J_{F-F} 20.6 Hz, ⁴J_{F-H} 1.8 Hz, C⁴F); ¹H NMR δ_H (300 MHz, C₆D₆), 7.90 (2H, b.s., C¹¹H, C¹⁹H), 7.63 (4H, d, *J* 7.0 Hz, C⁸H, C¹⁴H, C¹⁶H, C²²H) and 6.87 (2H, dd, *J*_{P-H} 14.4 Hz, *J*_{F-H} 7.1 Hz, C⁶H, C²H). MS (ES+) *m/z*: 626.50 ([M + O⁺]). HRMS (ES+) *m/z*: Found 626.9974; [C₂₂H₈OF₁₅P] +Na which requires 626.9971.

Synthesis of ^tbutyl cinnamate



At 0 °C under nitrogen, a solution of methyl cinnamate (2.5 g, 15.5 mmol) in diethylether (15 ml) was added to ^tBuOK (4.15 g, 37 mmol) in diethylether (60 ml). The mixture was stirred for 30 minutes at 20 °C before adding cold water until the white precipitate (MeOK) had completely dissolved. The organic layer was removed, dried using magnesium sulfate and then solvent was removed *in vacuo*. The residue was then purified using Kugelrohr distillation apparatus (bp 65 °C/ 1 mmHg) to yield the desired product (2.51 g, 79.4 %) as a colourless oil.

¹H NMR δ_H (300 MHz, CDCl₃) 7.51 (1H, d, *J* 16.0 Hz, C=CH), 7.46-7.40 (2H, m, Ar-CH), 7.32-7.26 (3H, m, Ar-CH), 6.29 (1H, *J* 16 Hz, C=CH) and 1.46 (9H, s, CH₃).

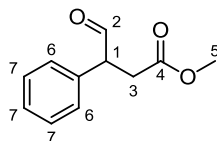
This is in agreement with literature data².

General Procedure for Hydroformylation of Cinnamate Esters

A maximum of four reactions were carried out in “batches” in high pressure autoclaves. The ligand was weighed out to give desired the ligand/metal ratio and added to a microwave vial before the vial was sealed and put under an inert atmosphere. Metallic catalyst precursor Rh(acac)(CO)₂ stock solutions were made up in dry vials under nitrogen with a known volume of toluene. This solution was added to the microwave vials to give 3.9×10^{-3} mmol of Rh(acac)(CO)₂ per reaction (concentration of 0.002 molL⁻¹)* and stirred for approximately 15 minutes. In general, substrate stock solutions were made up in the same way to give an overall substrate concentration of 1.97 molL⁻¹ per reaction*. 1-methyl naphthene was used as an internal standard in the substrate stock solution and a “t= 0” sample was taken before reaction for NMR analysis. Substrate stock solution was added to each microwave vial. To each sealed microwave vial, two needles were placed through the septum to allow exchange of gases. After each autoclave was pressurised, it was either heated using an electronic heating jacket or an oil bath. NMR analysis of each crude reaction was performed immediately after depressurisation.

*Except in dilution experiment.

Synthesis of methyl 4-oxo-3-phenyl butanoate



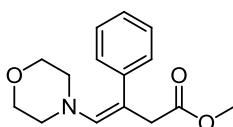
Under an atmosphere of syngas, a solution of methyl cinnamate (1.99 g, 12.3 mmol) in toluene (~20 ml) was added to an autoclave containing Rh_2O_3 (3.10 mg, 0.0123 mmol). 1-methylnaphthalene was added as an internal standard and the autoclave was pressurised with CO/H_2 (50/50) to 50 bar and then heated to 120 °C. The reaction was mechanically stirred for 24 hours. The solvent was then removed *en vacuo* to give a grey oil. This mixture was found to contain 45% aldehyde products, 13% hydrogenation products and a β : α aldehyde ratio of 22 : 1. The crude residue was then purified via flash column chromatography on silica eluted with hexane/ethyl acetate (95/5), giving the product as a colourless oil (0.78 g, 33.4% yield).

^1H NMR δ_{H} (300 MHz, CDCl_3) 9.63 (1H, s, C^2H), 7.35-7.22 (3H, m, $\text{C}^7\text{-H}$), 7.16-7.10 (2H, m, $\text{C}^6\text{-H}$), 4.05 (2H, q, J 7.23 Hz, C^1H), 3.60 (3H, s, C^5H_3), 3.75 (1H, dd, J 8.3 Hz, $\text{C}^3\text{H}'$) and 2.54 (1H, dd, J 6.1 Hz, $\text{C}^3\text{H}''$).

This is in agreement with literature data³.

4.3 Enamine Formation

Synthesis of (Z)-methyl 4-morpholino-3-phenylbut-3-enoate

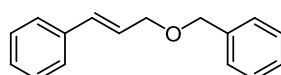


A two neck round bottom flask was fitted with a Dean-Stark apparatus and condenser and the set up was then flame dried. To the flask was added 4-oxo-3-phenyl butanoate (2.52 g, 13.1 mmol), *p*-toluenesulfonic acid (0.12 g, 0.65 mmol, 5 mol%), distilled morpholine (1.47 ml, 17 mmol, 1.3 eq) and toluene (~50 ml). The reaction mixture was stirred under reflux for 24 hours. Solvent was then removed *en vacuo* and hexane and acetonitrile were added and the product extracted from hexane. Product observed in 87 % conversion to a mixture of E/Z isomers with respect to the starting material in the crude ^1H NMR spectrum and minimal side

product seen. A purification of the resulting residue was then attempted via flash column chromatography using silica eluted with hexane/ethyl acetate (2:1) and 5% triethylamine. The NMR data and difficulties during purification are discussed in Chapter Two.

4.4- Regioselective Hydroformylation of Benzyl Ether Substrates

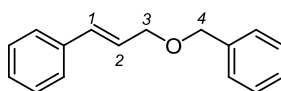
Initial method for synthesis of (*E*)-(3-(benzyloxy)prop-1-en-1-yl)benzene⁴



Under an atmosphere of argon, anhydrous potassium carbonate (10.30 g, 74.6 mmol) was added to a solution of cinnamyl alcohol (5.0 g, 37.3 mmol) in DMF (100 ml) and the mixture stirred for 2 hours. Then benzyl bromide (6.60 ml, 56 mmol) was added drop wise over a period of 45 minutes and the reaction was stirred for 12 hours at 60 °C. The mixture was then poured over ice and water (~100 ml) and this was extracted with ethyl acetate (5 x 50 ml). The combined organic fractions were combined and washed with a saturated solution of sodium chloride (100 ml) and dried over anhydrous magnesium sulfate. The solvent was removed *en vacuo*.

¹H NMR spectroscopy of the crude product revealed that peaks did not match that of the spectra reported in the literature for this compound. It was clear that more than one product had formed and an extra peak at 8.2 ppm corresponded to the formate species discussed in Chapter Two. ¹³C NMR spectroscopy also showed an extra CH peak at 161 ppm which also correlates with this formate formation. GCMS data revealed five peaks in addition to the desired product and so since this reaction was not selective we sought an alternative.

Second Synthesis of (*E*)-(3-(benzyloxy)prop-1-en-1-yl)benzene



To a solution of cinnamyl alcohol (5 g, 37.3 mmol) in dry THF (40 ml) was added sodium hydride (1.93 g, 60% dispersion in mineral oil, 48.5 mmol, 1.3 eq.) in dry THF (20 ml) and

benzyl bromide (5.29 ml, 44.76 mmol, 1.2 eq.) at 0 °C. The reaction was stirred for 5 hours at room temperature before quenching with H₂O (20 ml). This aqueous solution was then extracted with ethyl acetate and the organic layer was washed with H₂O and brine and then dried with magnesium sulfate. The solvent was then removed *en vacuo*. The residue was purified via flash column chromatography using hexane/ethyl acetate (30:1) as the eluent to afford the pure product (7.8 g, 93 %) as a colourless oil.

¹H NMR δ_H (300 MHz, CDCl₃) 7.47-7.23 (10H, m, Ar-H), 6.67 (1H, dt, *J*³ 15.9 Hz, *J*⁴ 1.5 Hz, C¹H), 6.35 (1H, dt, *J*³ 16.0 Hz, *J*⁴ 5.9 Hz C²H), 4.61 (2H, s, C⁵H₂) and 4.24 (2H, dd, *J*² 1.4 Hz, *J*³ 6.1 Hz, C³H₂). MS (ES+) *m/z*: 262.97 ([M + K⁺]).

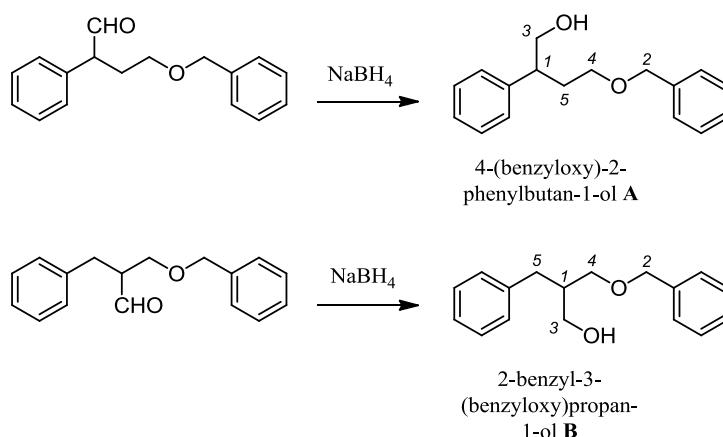
General Procedure for Hydroformylation of Benzyl Ether Substrates

A maximum of four reactions were carried out in “batches” in high pressure autoclaves. Ligand was weighed out to give desired the ligand/metal ratio and added to a microwave vial before the vial was sealed and put under an inert atmosphere. Metallic catalyst precursor Rh(acac)(CO)₂ stock solutions were made up in dry vials under nitrogen with a known volume of toluene. This solution was added to the microwave vials to give 3.9 x 10⁻³ mmol of Rh(acac)(CO)₂ per reaction (concentration of 0.002 molL⁻¹) and stirred for approximately 15 minutes. In general, substrate stock solutions were made up in the same way to give an overall substrate concentration of 0.22 molL⁻¹ per reaction. 1-methyl naphthalene was used as an internal standard in the substrate stock solution and a “t= 0” sample was taken before reaction for NMR analysis. Substrate stock solution was added to each microwave vial. To each sealed microwave vial, two needles were placed through the septum to allow exchange of gases. After each autoclave was pressurised it was either heated using an electronic heating jacket or an oil bath. NMR analysis of each crude reaction was performed immediately after depressurisation.

Characterisation of Benzyl Ether Aldehydes

In order to be able to report aldehyde isomer ratios for the above catalytic runs with complete certainty it was necessary to isolate and characterise them. Aldehydes can undergo atmospheric oxidation and also form aldol products so to ease isolation, the crude products from one hydroformylation run were reduced to the corresponding alcohols using sodium

borohydride (1 eq). Purification/separation of alcohols was then carried out via flash column chromatography using an eluent system of hexane/ethyl acetate (95/5).



Alcohol 17 A

Obtained (90.60 mg, 0.35 mmol, 38.8% w.r.t. starting alkene).

¹H NMR δ_H (300 MHz, CDCl₃) 7.41-7.19 (10H, m, Ar-H), 4.54-4.44 (2H, m, C²H₂), 3.79 (2H, d, *J* 6.43 Hz, C³H₂), 3.58-3.37 (2H, m, C⁴H₂), 3.02 (1H, m, C¹H), 2.23-1.86 (2H, m, C⁵H₂) and 2.02 (1H, m, OH) overlap with previous. HRMS (ES⁺) Found *m/z*: 279.1357 [M + Na⁺] requires 279.1361.

¹H NMR COSY shows- C¹H has cross-peaks with C⁵H₂ and C³H₂. C³H has cross-peaks with C¹H and OH. C⁵H₂ has cross-peaks with C¹H and C⁴H₂. C⁴H₂ has cross-peaks with C⁵H₂. C²H₂ has cross-peaks only with Ar-H. HSQC NMR confirms presence of 4 CH₂s, 1 CH plus aromatic peaks. HMBC shows *J*³ coupling between C² and the protons of C⁴.

Alcohol 17 B

Obtained (3.40 mg, 0.013 mmol, 1.4% w.r.t. starting alkene).

¹H NMR δ_H (300 MHz, CDCl₃) 7.33-7.04 (10H, m, Ar-H), 4.48-4.37 (2H, m, C²H₂), 3.73-3.56 (2H, m, C³H₂), 3.57-3.38 (2H, m, C⁵H₂), 2.62-2.56 (2H, m, C⁵H₂), 2.35 (1H, t, *J* 5.58 Hz, OH) and 2.14-2.01 (1H, m, C¹H). HRMS (ES⁺) Found *m/z*: 279.1364 [M + Na⁺] requires 279.1361.

¹H COSY NMR shows- C²H₂ has cross-peaks only with Ar-H. C³H has cross-peaks with C¹H and OH. C⁴H₂ has cross-peaks with C¹H. C⁵H₂ has cross-peaks with C¹H and Ar-H. OH has cross-peaks with C³H₂. C¹H has cross-peaks with C⁵H₂, C⁴H₂ and C³H₂.

References Chapter Four

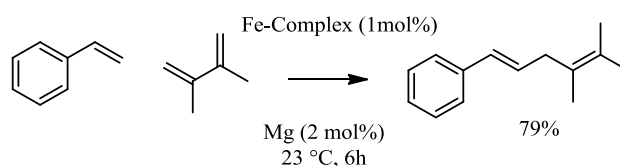
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APPENDIX

Attempted 1,4-Addition of α -Olefins to Dienes

Part One

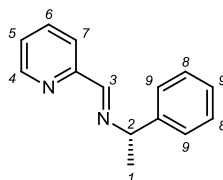
With the aim to synthesise a new interesting substrate for hydroformylation the following procedure described by T. Ritter *et al.*¹ was carried out.



It is reported that an iminopyridine-ligated iron complex, which is reduced in-situ using activated magnesium metal, catalyses carbon-carbon bond formation.

Experimental

Synthesis of (*S,E*)-1-phenyl-N-(pyridine-2-ylmethylene)ethanamine

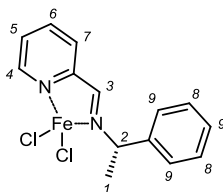


(*S*)- α -phenylethylamine (1.0 g, 1.06 ml, 8.25 mmol, 1 eq.) was added to pyridine-2-carboxaldehyde (0.88 g, 0.78 ml, 8.25 mmol, 1 eq.) in dichloromethane. The mixture was heated under reflux for 4 hours in the presence of Mg_2SO_4 . The solid was then removed by filtration and the reaction mixture concentrated *en vacuo*. The residue was distilled under reduced pressure (b.p.= 117 °C, 180 mTorr) to give a pale yellow oil (1.35 g, 78%).

^1H NMR δ_{H} (300 MHz, CDCl_3) 8.58-8.51 (1H, m, C^4H), 8.38 (1H, s, C^3H), 8.0 (1H, dt, J^3 7.91 Hz, J^4 1.04 Hz, C^7H), 7.64 (1H, td, J^3 7.71 Hz, J^4 1.63 Hz, C^6H), 7.38-7.32 (2H, m, C^8H), 7.30-7.13 (3H, m, C^9H), 4.55 (1H, q, J 6.6 Hz, C^2H) and 1.53 (3H, d, J 6.58 Hz, C^1H_3).

This corresponds to reported data¹.

Synthesis of (*S,E*)-1-phenyl-*N*-(pyridine-2-ylmethylene)ethanamine iron dichloride



Iron(II)chloride (0.7 g, 5.56 mmol, 1 eq.) was added to a flask under nitrogen. Dry, degassed dichloromethane (20 ml) was added to the flask, followed by (*S,E*)-1-phenyl-*N*-(pyridine-2-ylmethylene)ethanamine (1 ml, 5.56 mmol, 1 eq.). The reaction mixture was stirred at 23 °C for 28 hours. The reaction mixture was concentrated under reduced pressure. The solid was washed with ether, and then dried giving a bright purple solid (1.72 g, 92%). As reported in the literature the solid is not sufficiently soluble in ether, tetrahydrofuran, benzene, toluene or dichloromethane to take a ^{13}C NMR spectrum.

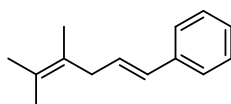
^1H NMR δ_{H} (300 MHz, CDCl_3) 8.45 (1H, d, J 4.88 Hz, C^4H), 8.38 (1H, s, C^3H), 8.0 (1H, d, J 7.88, C^7H), 7.62 (1H, t, J 7.49 Hz, C^6H), 7.38-7.31 (2H, m, C^8H), 7.29-7.11 (3H, m, C^9H), 4.55 (1H, q, J 6.6 Hz, C^2H) and 1.53 (3H, d, J 6.68 Hz, C^1H_3). Melting Point: 165-167 °C. ^1H NMR δ_{H} (300 MHz, CD_2Cl_2) IR: ν_{max} (film)/ cm^{-1} , 3449, 1614, 1444, 1310, 1240, 1070, 1009, 865, 760 and 703.

This corresponds with the literature data¹.

Preparation of Activated Magnesium¹

Magnesium turnings (2.8 g, 115 mmol, 1.5 eq.) were added to a two-neck flask equipped with a condenser and then the glassware was flame dried. A solution of 1,2-dibromoethane (14.4 g, 76.5 mmol, 1 eq.) in ether (45 ml) and toluene (15 ml) was added drop wise over 45 minutes, so that gentle reflux was achieved. To a separate argon purged two neck flask, lithium (1.06 g, 153 mmol, 2 eq.) and naphthalene (19.9 g, 155 mmol, 2.03 eq.) were added and cooled to 0 °C using an ice bath. THF (75 ml) was then added. The lithium/naphthalene mixture was stirred at 0 °C for 3 hours. The magnesium bromide solution was cooled to 23 °C and slowly added to the lithium/naphthalene solution at room temperature, via cannula. Once the addition was complete, the mixture was filtered by cannula filtration and the solid washed with THF. The solid was then placed under high vacuum to remove solvent, affording a grey solid (1.43 g).

Attempted Synthesis of (*E*)-(4,5-dimethylhexa-1,4-dienyl)benzene (A)

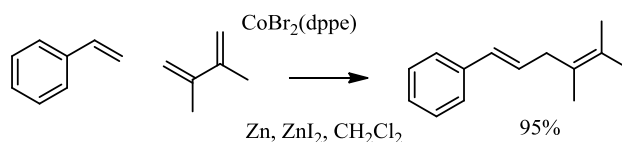


Complex; (*S,E*)-1-phenyl-*N*-(pyridine-2-ylmethylene)ethanamine iron dichloride (34 mg, 0.1 mmol, 1 mol%) was added to a dry vial under argon. To this was added diethyl ether (10 ml) and distilled 2,3-dimethyl-1,3-butadiene (905 mg, 11 mmol, 1.1 eq.) and distilled styrene (1040 mg, 1.14 ml, 10 mmol, 1 eq.). Magnesium (48.6 mg, 0.2 mmol, 2 mol%) was then added and the reaction mixture was stirred for 6 hours at room temperature. The reaction was quenched with water and extracted with diethyl ether. The combined organics were filtered over silica and solvent removed *en vacuo*. In repeated attempts no or little conversion was observed via ^1H NMR spectroscopy.

Various reducing agents tested in place of activated magnesium; $\text{BH}_3\cdot\text{THF}$, SuperHydride (LiEt_3BH), EtMgBr , Li/Napthalene in THF, $\text{MgBr}_2\cdot\text{Et}_2\text{O}$ and Na/toluene . No significant conversion to product was observed in all cases.

Part Two

Since the above preparation yielded none of the desired product, we sought an alternative route to this substrate. Hilt and co-workers² describe a synthesis using various cobalt complexes.

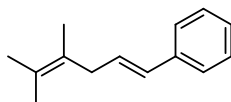


Synthesis of six cobalt complexes

Reactions were carried out in a six-reaction carousel under an atmosphere of argon. To a solution of anhydrous cobalt(II)dibromide (60.2 mg, 0.275 mmol, 1 eq.) in THF (1 ml) was added a solution of bidentate phosphine ligand e.g. dppe (99.6 mg, 0.25 mmol) in THF (1 ml). The resulting solution was stirred overnight. Solvent was then removed under reduced pressure. Diethyl ether was added (~5 ml) and the suspension stirred and filtered via cannula. The remaining volatiles were removed under reduced pressure to yield; Co(dppe)Br_2 - lime green powder, Co(dppp)Br_2 - dark green crystalline solid, Co(dppb)Br_2 bright turquoise

powder, Co(dpphex)Br₂- bright turquoise powder, Co(dppcype)Br₂- blue crystalline solid and Co(dppbenz)Br₂- olive green powder.

Attempted Synthesis of (*E*)-(4,5-dimethylhexa-1,4-dienyl)benzene (B)



To a dry flask was added anhydrous zinc iodide (0.03 g, 20 mol%), zinc dust (0.006 g, 20 mol%), Co(dppe)Br₂ (0.03 g, 10 mol%) and dichloromethane (3 ml) under an atmosphere of argon. Distilled styrene (0.06 ml, 0.48 mmol) and 2,3-dimethyl-1,3-butadiene (0.05 ml, 0.48 mmol) were added to the mixture with stirring at room temperature for 3 days. Crude ¹H NMR spectra show no conversion to product.

All cobalt complexes above were tested in this procedure with no conversion to product after 6 days in any case. Modified procedures using zinc dust and iodine instead of zinc dust and zinc iodide, and 3,4-dimethoxystyrene instead of styrene both proved unsuccessful.

References Appendix

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