ENANTIOSELECTIVE HOMOGENEOUS CATALYSTS FOR
THE SYNTHESIS OF FLUORINATED ORGANIC
COMPOUNDS

Charlotte Ellen Susan Jones

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Enantioselective Homogeneous Catalysts for the Synthesis of Fluorinated Organic Compounds

A thesis presented for the degree of Doctor of Philosophy
In the Faculty of Science of the University of St. Andrews by Charlotte Ellen Susan Jones MChem (Hons)

Supervised by
Dr. Matthew L. Clarke

School of Chemistry
September 2010
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I, Charlotte Ellen Susan Jones hereby certify that this thesis, which is approximately 41000 words in length, has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree.

I was admitted as a research student in September 2005 and as a candidate for the degree of PhD in October 2006; the higher study for which this is a record was carried out in the University of St Andrews between 2005 and 2010.

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Abstract

This thesis is divided into three main results chapters that reflect the path my research took. In the first results chapter, the first organocatalyst for the carbonyl-ene reaction here was were discovered and found to give high conversion using 1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea. Various carbonyl and alkene precursors were examined in the ene reaction in both catalysed and uncatalysed reactions. It was found that ene reactions using fluoral and ethyl trifluoropyruvate give higher rates of reaction when compared to other carbonyl compounds. A novel enantiopure thiourea was synthesised and the ene reaction was catalysed enantioselectively to 33% e.e. In an attempt to catalyse the reaction to a further extent a new thiourea bonded to a P(=S)R₂ group was developed. However, the intramolecular hydrogen bonding of this catalyst was thought to be so strong that this it did not catalyse the reaction. The synthesis of a chiral phosphoric acid was achieved but this was an unsuccessful catalyst in the ene reaction. Two component achiral thiourea and chiral acids were also examined in the ene and Mannich-type reaction. The new easily synthesised thiourea for this reaction has an interesting intermolecular hydrogen bonding coordination in the solid state.

Asymmetric fluorination of ketoesters using palladium is a dynamic kinetic resolution. In the 2nd chapter cationic palladium complexes were synthesised and used to determine the optimum parameters for bidentate ligands in this reaction. Four carbon chain phosphines were found to give the highest conversion for this reaction among those ligands tested such as 1,4-bisdiphenylphosphinobutane (bite angle 99°). A new bis-phosphinous amide chiral ligand was developed with a bite angle of 96.7°. The dichloropalladium complex of this phosphine was isolated and structurally characterised. The use of the palladium complex in asymmetric fluorination was attempted however this was found to be unsuccessful. Mechanistic studies reveal that the formation of the desired cationic catalyst did not occur under conditions shown to work well for other palladium phosphate complexes. The ligand was investigated further in hydrogenation reactions.
The phosphinous amide was protected as its borane and was used in the rhodium catalysed hydrogenation of alkenes to give high conversion and up to 93% e.e. The borane protected phosphinous amide was also found to catalyse the hydrogenation of acetophenone using copper complexes with up to 84% e.e for the hydrogenation of acetophenone, although conversion was quite low.
Dedicated to my parents,

Kenneth and Cecilia,

without whom this thesis would definitely not be here.
Chemistry without catalysis would be a sword without a handle, a light without brilliance, a bell without sound.

- A lwin Mittasch
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Writing a few words on a piece of paper doesn’t really feel like enough to say thank you to everyone who has helped me during my PhD but I will always appreciate everything everyone has done to help me, especially those people I have forgotten to mention above.

September 2010

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January 2011
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µw- microwave
Ac- acetyl
Ar- aryl
atm- atmosphere 1.013 bar
BDPAB- 2,2-bis (dicyclohexylphosphinoamino)-1,1-binaphthyl
BDPP- bis(diphenylphosphino)pentane
BINAM- 1,1′-Bi(2-naphthylamine)
BINAP- 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINOL- 1,1′-bi-2-naphthol
Boc- t-Butyl carboxy
Bu- butyl
CPME- cyclopentyl methyl ether
COD- cis,cis-1,5-cyclooctadiene
CI- chemical ionisation
Cy- cyclohexyl
d.r.- diastereomeric ratio
DABCO- 1,4-diazabicyclo[2.2.2]octane
DCC- N,N′-Dicyclohexylcarbodiimide
DCM- dichloromethane
dcpp- dicyclohexylphosphinoethane
DET- diethyl tartrate
DIOPI- 4,5-Bis(diphenylphosphino-methyl)-2,2-dimethyl-1,3-dioxolane
dppf- 1,1′-bis(diisopropylphosphino)ferrocene
dppach- 1,2-bis(diphenylphosphinamino)cyclohexane
dppb- diphenylphosphinobutane
dppe- diphenylphosphinoethane
dppf- 1,1′-Bis(diphenylphosphino)ferrocene
dppp- diphenylphosphinopropane
dfppe- di( (para-fluorophenyl) phosphino)ethane
DMAP- dimethylaminopyridine
DMF- dimethylformamide
DMFU- 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO- dimethylsulfoxide
DPEN- 1,2-diphenyl-1,2-ethanediamine
e.e.- enantiomeric excess
EI- electronic ionisation
eq.- equivalents
ES- electrospray
Et- ethyl
Eu(hfc)3- europium (III) tris[3-(heptafluoropropylhydroxymethylene)-( +)- camphorat1.2
EWG- electron withdrawing group
Hexaphemp-1,1′,4,4′,5,5′,6,6′-hexamethyl[1,1′-biphenyl]-2,2′-diyl]bis[1,1-
diphenylphosphate
HFIP-1,1,1,1′,1′,1′-hexafluoroisopropanol
HOMO-highest occupied molecular orbital
hrs- hours
IPA- Isopropyl alcohol (propan-2-ol)
K_a-the acid dissociation constant
LDA- lithium diisopropylamide
LUMO- lowest unoccupied molecular orbital
Me- Methyl
Me-BPE- 1,2-Bis[2,5-dimethylphospholano]ethane
mol% - percentage molecular equivalents
MO- molecular orbital
MS- molecular sieves
NBS- nitrobromosuccinimide
NFSI- N-fluorobenzene sulfonimide
nHex- n-Hexyl
NMR- Nuclear Magnetic Resonance
Phanephos- 4,12-Bis(diphenylphosphino)-[2.2]-paracyclophe
Ph- phenyl
Ph-BPE- 1,2-Bis[2,5-diphenylphospholano]ethane
pK_a- -log K_a
PMHS- poly(methylhydrosiloxane)
PMP- p-methoxybenzilidene
Pr- propyl
PyBOX- 2,6-Bis[(4R)-isopropyl-2-oxazolin-2-yl] pyridine
Pyr- pyridine
rt- room temperature
S-PHOS- 2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
SEGPHOS- 5,5′-Bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole
Selectfluor- 1-Chloromethyl-4-fluoro-1,4-diaziobiacyclo[2.2.2]octane
TADDOL- 2,2-Dimethyl-α,α,α′,α′-tetraphenyldioxalene-4,5-dimethanol
TBS- tert-butyldimethylsilyl
Tf- trifluoromethylsulfonic
TFA- trifluoroacetic acid
THF- tetrahydrofuran
TMEDA- tetramethyleneendiamine
tol- tolyl
Ts-tosyl i.e. 4-toluene sulfonyl
TS- transition state
Chapter 1
1. INTRODUCTION

1.1. Preamble

A reaction proceeds by conversion of starting materials into products. This process occurs via an excited energy state, known as a transition state (‡) (Figure 1.1). A transition state is a high energy, excited configuration which permits bond formation and cleavage, leading to the products of the reaction.\textsuperscript{[1]}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{energy_states.png}
\caption{Representational diagram of energy states as a reaction proceeds}
\end{figure}
Catalysts are components of a reaction which are not themselves consumed during the reaction, but which affect the energy of the transition state relative to the reagents and the products.\[2\]

1.2. Asymmetric catalysis

Whereas a catalyst changes the overall rate of a reaction, an asymmetric catalyst changes the rate at which one enantiomer is formed to a greater degree than the other. This difference makes the asymmetric catalysis synthetically very attractive, as for example an asymmetric catalyst can take an achiral or prochiral feedstock and turn it into a chiral product. If it can do so selectively, efficiently and with little waste then it may be a very effective tool in the synthesis of compounds with stereogenic elements such as drug candidates, pesticides or other reagents used on biological systems.

Fundamentally, there are two differences between enantiomers. Firstly, one will rotate plane polarised light clockwise (known as the (+)-enantiomer) and the other will rotate the light anti-clockwise (known as the (–)-enantiomer). Secondly, although interactions with achiral substances will be the same, this cannot be said for the interaction between two chiral compounds. Many biological molecules are chiral, and the difference between enantiomers is important. Such importance is placed on the enantiopurity that in 1992 the US federal food and drugs authority (FDA) required that the pharmacokinetic properties of both enantiomers be studied, in recognition of the fact that both can have significantly different biological effects.\[3\] This difference can be illustrated with the two stereoisomers of methamphetamine (Figure 1.2). (R)-methamphetamine is a vasoconstrictor and can be used as a decongestant sold over the counter. (S)-methamphetamine is a psychostimulant and a Class A substance under the UK Misuse of Drugs Act 1971\[4\] when sold enantiopure or in racemic form.
There are many examples of asymmetric catalysts in the literature. Such catalysts can be sub-divided into three categories: biocatalysts, organocatalysts, and metal-based catalysts.

1.2.1. Biocatalysis

Biocatalysis uses enzymes to bind substrates into chiral catalytic pockets within the molecule, in which the chiral environment which promotes the formation of only one enantiomer in excess. An example of this is provided by the synthesis of 1,2-butanediol 1 (Scheme 1.1), which is a useful pharmaceutical intermediate for the synthesis of compounds such as azetidinone derivatives.\textsuperscript{[5]} The reduction of 4-hydroxy-2-butanone with enzymes was examined for use in industrial synthesis. The enzyme \textit{Kluveromyces lactis IFO 1267} was found to give high yield and enantioselectivity compared to others tested.\textsuperscript{[6]} The enzyme selectively hydrogenates the ketone to form the chiral alcohol although no specific mechanistic studies appear to have been carried out.

![Scheme 1.1 Use of enzyme to reduce ketone enantioselectively](image)

There are several successful examples of the use of this type of catalyst; however there can be drawbacks to enzyme catalysis. Often very specific conditions have to be used as enzymes are sensitive to solvent, pH and temperature. There are
also limits on which substrates can be used because the catalytic pockets have selective binding sites that depend on the electronic and steric properties of the substrate.

1.2.2. Metal based catalysts

Metal-based asymmetric catalysts use a metal with chiral ligands bound to the metal centre. The interaction between substrates and the metal catalyses the reaction whilst the chiral ligands promote enantioselectivity. Transition metal catalysed asymmetric synthesis has been and continues to be a vibrant area of research. There are a few examples of the use of asymmetric catalysts in industrial synthesis with two of these shown below. The use of Jacobsen hydrolytic kinetic resolution with (salen)Co(III)X catalysts (where X is a counterion) has been widely studied, particularly for epichlorohydrin 2, a useful chiral intermediate for the synthesis of biologically active compounds (Scheme 1.2). Another interesting example uses the Sharpless-Kagan oxidation method to form the anti-ulcer drug compound esomeprazole, which is chiral at sulfur. Esomeprazole 3 (Nexium®) is the S enantiomer of the racemic drug omeprazole (Losec®) and is the active stereoisomer. By using titanium and chiral diethyl tartrate ((S,S)-DET) in the presence of oxidising agent and base esomeprazole was formed in 74% isolated yield and 93% e.e. on a tonne scale (Scheme 1.3). The exact mechanism of this reaction is not known however it is thought to proceed via a transition state where the peroxide and DET are complexed to a dinuclear titanium system in a similar fashion to Sharpless epoxidation catalyst. Given that thousands of papers have been published on the subject, it is surprising that only a handful of reactions are used industrially, this reflects the need for further research in many areas.
1.2.3. Organocatalysis

The term organocatalysis describes an area of research which aims to develop purely organic compounds for catalysis. It has been defined by Dalko and Moisan as
"the acceleration of chemical reactions with a substoichiometric amount of an organic compound which does not contain a metal ion".[12] Organocatalysis is currently a growing field of research as evidenced by the increasing number of examples appearing in the chemical literature. There are several reasons for this popularity; organocatalysts can promote some reactions that are not suitable for metal based catalysis, and are not as toxic as some heavy metals. The field of organocatalysis has become dramatically more researched in the past decade.

Asymmetric organocatalysts bridge the gap between enzymes and metal-based catalysts, and might mimic the best properties of both. Organocatalysts often act in ways similar to enzymes, for example by binding a substrate through covalent or hydrogen bonding. Enzymes can change the orientation and environment of the substrates and can thus promote given reactions. However, enzymes are complicated proteins and therefore are difficult to synthesise. Organocatalysts are less specific to reactants than enzymes and are therefore easier to adapt through changing synthetic routes. They are often less air sensitive than their metal based equivalents, but are similarly versatile for use in several different reactions since they can be tuned to suit a range of substrates. Problems associated with organocatalysis include higher catalyst loadings and longer reaction times compared to transition metal catalysts.

Within organocatalysis, one of the most important areas of research is enamine catalysis. Research on enamine catalysis has been widely published in recent years,[12-13] with one of the simplest examples of an enamine catalyst being proline. Enamine catalysts can give extremely high enantioselectivity in reactions such as the aldol reaction[15] and many others. The organocatalysed Diels-Alder reaction[14] uses similar catalysts to proceed via an iminium ion intermediate. Also of interest are organocatalysts that hydrogen bond to substrates. Many chiral Brønsted-Lowry acids (Brønsted-Lowry acids are moieties which are able to donate a proton[16]) have been developed which catalyse several different reactions, often with low catalyst loadings. Many chiral alcohol based systems capable of donating protons, such as BINOL, have been developed to catalyse organic transformations including the aza-Diels-Alder reaction[17] and the Mannich reaction,[18] amongst others.[19]
The current work focuses on the chemistry based in two of these areas: organocatalysis and metal based catalysis. The following section reviews the area of organocatalysis, more specifically urea and Brønsted-Lowry acid based catalysis. The review covers these areas since this serves as a useful introduction to Chapter 2.

1.3. Hydrogen bonding and Brønsted acid Catalysis

A hydrogen bond can be considered as a proton transfer where the proton donor does not fully yield the hydrogen to the hydrogen bond acceptor. Thus hydrogen bond donors can also be classified as Brønsted acids,\[^{[20]}\] and may also be used in a variety of organocatalytic reactions. General acid catalysis in organocatalysis implies the substrate is activated by hydrogen bonding in the transition state, and specific acid catalysis a proton transfer from the Brønsted acid catalyst to the substrate with enantioselectivity resulting from the ion pair formed (Figure 1.3).\[^{[21]}\]

![Figure 1.3 General acid catalysis and specific acid catalysis with hydrogen bond donors](image)

1.3.1. Hydrogen Bonding Catalysis

An X-H…A interaction is described as a hydrogen bond provided it constitutes a local bond and X-H acts as a proton donor to A.\[^{[22]}\] Hydrogen bonding catalysts have become increasingly popular and have been the subject of several reviews.\[^{[23]}\] They are often used to catalyse reactions where Lewis acids have been used successfully. Ureas and thioureas are the most widely used examples of these catalysts although amides can also be utilised. Thiourea 5 (Figure 1.4) is one of the most intensively studied and the corresponding urea 4 first used in conjunction with...
metal reagents\textsuperscript{[24]} though it has also been proven to be effective for many reactions in the absence of metals. Jacobsen’s Schiff base catalysts 6 and 7 (Figure 1.4) were also developed as ligands and an example of their use without metals is shown in the Mannich reaction (Scheme 1.4).\textsuperscript{[25]} Such catalysts are usually assembled from the corresponding isocyanate or thiocyanate with an amine.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.4.png}
\caption{Hydrogen-bonding Catalysts}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme1.4.png}
\caption{Use of Thiourea 4 in an addition reaction}
\end{figure}

Thioureas tend to be used more often than ureas as organocatalysts for two reasons. Firstly there is poor orbital overlap between C 2p and S 3p orbitals forming the $\pi$ orbital of the C=S bond (Figure 1.5). Of the two resonance structures, the more ionic is favoured and the C=S bond is therefore better described with a slight positive charge on the carbon atom (Figure 1.6). This difference means thioureas are more acidic and therefore better hydrogen bond donors.\textsuperscript{[26]} $N,N'$-diphenylurea has a $pK_a$, (acid association constant) in DMSO of 19.5 and $N,N'$-diphenylthiourea has a $pK_a$ of 13.5.\textsuperscript{[27]} Secondly, sulfur is a poorer hydrogen-bond acceptor than oxygen and hence intermolecular forces are weaker in the catalyst, making thioureas generally more soluble than analogous ureas.
Such thiourea derived compounds have been used in place of Lewis acid catalysts in several reactions.\textsuperscript{[28]} They may be used in the place of Lewis acids since they bind to carbonyl or imine groups to withdraw electron density from the hydrogen bonded oxygen or nitrogen atom and therefore increase the electrophilicity of the corresponding carbonyl or imine group. They lower the energy of the LUMO allowing a nucleophile (Nu) to form a Nu-C bond with a C=X species.\textsuperscript{[29]} More recently they have also been used to bind to a counterion for catalysis.\textsuperscript{[30]}

An advantage of hydrogen-bonding organocatalysts over Lewis acids, especially in asymmetric catalysis, is that it is easier to understand through molecular modelling why certain catalysts are superior. Metal catalysts use many orbitals in coordinating substrates whereas, using MO theory, computer modelling need only consider the HOMO and LUMO of the catalyst and in this way stereoselectivity can be improved.\textsuperscript{[31]}

A study by Schreiner has shown\textsuperscript{[32]} that modifying the substituents has a significant effect on the catalytic activity of thioureas for the Diels-Alder reaction (Figure 1.7, Scheme 1.5). However, it should be noted that relatively electron-rich thioureas such as 6 are still good asymmetric catalysts for a range of reactions that have relatively low activation energy. Depending on the substrates in a given reaction the thiourea is electron-withdrawing enough to still catalyse a reaction, although in many of Jacobsen’s examples the reactions in question do proceed with
thermal heating; even at quite modest temperatures. In these successful asymmetric procedures reaction conditions are designed to minimise the background reaction. As you will read later this is not always possible.

Schreiner’s study found that various substituents gave an enhanced rate of reaction, and using a 3,5-bis(trifluoromethyl)phenyl group (5) gave a significant increase in rate. Surprisingly there was not much difference between substituents such as cyclohexyl and phenyl but adding electron-withdrawing substituents to the meta position of the aromatic ring gives enhanced activity. Schreiner suggests that this is due to entropic effects overcoming the effect of binding exothermicities since the binding of such compounds to the carbonyl is relatively strong. The authors suggest that compounds which are rotationally restricted such as 5 lose less entropy on binding than phenyl (10, Figure 1.7) or alkyl groups (8, 9, Figure 1.7) which can rotate more freely when unbound. This effect also means ortho substituted compounds, which were also examined in the study, are disfavoured since when bound to ketone the ortho groups can be in close proximity to each other (Figure 1.8) and to the sulfur atom, thus increasing the energy of binding. In contrast the weak acidity of the ortho protons on meta or para substituted catalysts such as 13 and 14 means they can form weak hydrogen bonds to the sulfur (Figure 1.9) and thus increase the stability of the bound state. The thiourea is more conformationally restricted and thus the hydrogen bonding is less entropically disfavoured.\textsuperscript{[23a]}

\begin{center}
\textbf{Scheme 1.5} Diels-Alder reaction catalysed by various thioureas (Figure 1.7)
\end{center}
Introduction

| Thiourea | 8 (−) | n-Octyl |
| 9 (+) | Cyclohexyl |
| 10 (−) | Phenyl |
| 11 (X) |
| 12 (×) |
| 13 (▲) | Phenyl CF₃ |
| 14 (●) | Phenyl CF₃ |
| 5 (●) | Phenyl CF₃ |

Figure 1.7 Comparison of Substituents on Thiourea for Catalysis of the Diels-Alder reaction

Figure 1.8 Steric repulsion between ortho substituents on phenyl ring

Figure 1.9 Favourable electrostatic interaction between ortho protons and thiourea EWG indicates electron-withdrawing group

Although the thiourea 5 is very active, it is not easily adapted to make chiral thioureas for use in catalysis. There have been interesting ideas for ways to adapt
these catalysts to achieve this, and several novel organocatalytic reactions have been developed as a result.

Research has also been focused on incorporating functionalities such as amines into the thiourea catalyst structure, which has been shown to improve activity in conjugate additions. Takemoto et al. developed one of the most effective catalysts, 15, in this area first used for the Michael addition of malonates to nitro olefins (Scheme 1.6), and also the aza-Henry reaction. Takemoto does not propose a mechanism for activation but other groups have conducted computational studies on similar systems with primary amines and it has been determined that they proceed via amine intermediates.

\[
\begin{align*}
R-\text{NO}_2 + \text{EtO}_2\text{C}-\text{CO}_2\text{Et} & \quad \text{toluene, rt} \\
2 \text{ eq} & \quad \text{12-72 hrs} \\
10 \text{ mol\%} & \quad \text{74-95\% Yield} \\
& \quad \text{81-93\% e.e.}
\end{align*}
\]

**Scheme 1.6** Catalysed Michael addition of diethylmalonate to nitro-olefins

15 has been used in further reactions such as kinetic resolution of azalactones and the racemic variant in ring opening polymerisation of a cyclic ester (Scheme 1.7). Further studies have also been conducted into the use of thioaminoindoles and thioamidobenzimidazoles for use in this reaction.
Modification of Takemoto’s catalyst to 16 led to the improved catalysis of a Petasis-type reaction using quinolines and vinyl boronic acids in the presence of aryl chloroformates (Scheme 1.8). Takemoto proposes this reaction may proceed via a transition state where the alcohol activates the boronic acid.

Some of the most effective thiourea catalysts have “privileged” based structures such as 1,1’-binaphthyl and cinchona alkaloids. A binaphthyl based thiourea tertiary amine catalyst has been used in the Baylis-Hillman reaction (Scheme 1.9) where the base tethered thiourea 17 has given some of the highest selectivity in this reaction to date. The reason for this success is most likely due to
the way it tethers the enolate formed in the reaction. The base adds to the alkene and the resulting enolate can bind to the thiourea. The bulky binaphthyl backbone blocks off the face of the ketone promoting the formation of one enantiomer.

\[ \text{Scheme 1.9 Binaphthalene-Based Catalyst of the Baylis-Hillman Reaction} \]

This thiourea has also been found to be an effective catalyst for Michael addition reactions\[^{42}\] however cinchona alkaloid based thioureas have been found to be effective in a wider variety of reactions.\[^{43}\] Cinchona alkaloid thioureas have been widely used as organocatalysts in a variety of reactions which have recently been reviewed by Connon.\[^{44}\] These chiral cinchona alkaloid amines are extracted from cinchona tree bark and thus readily accessible. The thioureas are synthesised by reaction with the 3,5-bis(trifluoromethyl)phenyl isothiocyanate. Chen and co-workers first published the use of thiourea cinchona alkaloid catalysts 18 and 19 for the Michael addition of thiophenols to unsaturated imides although this did not give significant enantioselectivity (Scheme 1.10).\[^{45}\] Greater selectivity than in the Michael addition has been seen in a variety of reactions such as in the Diels-Alder reaction where the catalyst can be varied to change the selectivity of the product (Scheme 1.11).\[^{46}\]
Scheme 1.10 Thiourea catalysed Michael addition of thiophenol to an unsaturated imide

Scheme 1.11 Thiourea catalysed Diels-Alder reaction
Ellman and co-workers have investigated the aza-Henry reaction\cite{47} and the addition of thioacetic acid to nitroalkenes using chiral N-sulfinyl urea catalysts 20 and 21 (Scheme 1.12).\cite{48} In the aza-Henry reaction the thioureas were found to give significantly lower yield than ureas. N-sulfinyl thioureas are innovative because the sulfinyl is chiral and electron-withdrawing, making these catalysts more acidic than with the 3,5-bis(trifluoromethyl)phenyl analogue (Figure 1.10). Ellman’s results obtained using thioacetic acid addition are promising, and it would be interesting to see the results of this catalyst in other addition reactions.

Scheme 1.12 N-sulfinyl urea catalysed addition of thioacetic acid to nitroalkenes

Figure 1.10 $pK_a$ for N-sulfinyl thiourea and compared to the equivalent 3,5-bis(trifluoromethyl)phenyl substituted urea and thiourea
Cheng and co-workers have examined the relationship between pK\textsubscript{a} with both the catalytic activity and the enantioselectivity of thiourea catalysts in the Michael addition reaction. The thioureas examined had the substituents of the aromatic rings varied on those shown below (Figure 1.11) and the initial rate (k) and the ratio of the R enantiomer to the S was determined. The study found that linear free energy relationships (LFER) were observed for pK\textsubscript{a} against –log(k) and pK\textsubscript{a} against -log(R/S) for meta- and/or para-substituted aromatic thioureas. This trend was not applicable to alkyl or ortho-substituted thioureas; however when an ethyl group was exchanged for a trifluoroethyl group the trend in activity between them is comparable. The para and meta aromatic substituted thioureas otherwise followed a trend in pK\textsubscript{a} and reactivity in agreement with σ values calculated from the Hammett equation.\textsuperscript{[49]} The σ values are calculated from the Hammett equation which relates the acid dissociation of benzoic acid in water to analogues with meta or para substituents on the aromatic ring. Higher values indicate more electron-withdrawing effects which give greater acidity.

This tendency was observed for all types of thiourea tested, indicating that in the Michael addition reaction structurally related thioureas which are more acidic give faster reaction rates and higher enantioselectivity. However, these catalyst backbones were already known to give high enantioselectivity for the Michael addition and various other organocatalytic. For a novel chiral catalyst decreasing the pK\textsubscript{a} should in theory improve the catalysis but there is a possible limit to how much the enantioselectivity can be improved. It also follows that this trend should be seen in other thiourea catalysed reactions.
1.3.1.1. Hydrogen Bonding Catalysts with Two Urea Groups

Sohtome and co-workers developed bisthiourea 22 for use in the Morita-Baylis-Hillman reaction (Scheme 1.13). Our interest in this area began with this research paper since the proposed transition state showed the intermediate bound to both thiourea sites (Figure 1.12), and we thought that the thioureas were positioned too closely together to both bind to the transition state. Based on this hypothesis we investigated synthesised n-hexyl and 3,5-bis(trifluoromethyl)phenyl substituted thioureas with diamine linkers with the idea that the structure activity relationship with the transition state could be improved. Once again the 3,5-bis(trifluoromethyl)phenyl substituted thioureas were significantly more catalytic than the n-hexyl substituted thiourea. The transition state was optimised using DFT calculations. The binding of the transition state to the catalyst was then found using semi-empirical basis sets to model the two moieties together. The thiourea 23 with a larger diamine linker was calculated to bind the transition state more effectively and thiourea 22 catalysed the reaction with a twofold acceleration in reaction rate. This result, whilst interesting, was not quite as dramatic a rate increase as we were hoping. Different strategies which have lower changes in entropy for the bound state are likely to be required for greater rate increases in the Morita-Baylis-Hillman reaction.
Scheme 1.13 Bisthiourea catalysed Morita-Baylis-Hillman reaction

![Scheme 1.13](image)

Figure 1.12 Transition state proposed by Sohtome and co-workers

![Figure 1.12](image)

Scheme 1.14 Baylis-Hillman reaction of p-fluorobenzaldehyde and cyclohexenone catalysed by bisthiourea and dimethylaminopyridine (DMAP)

![Scheme 1.14](image)
Smith et al. have developed another effective catalyst containing a urea and a thiourea (24) for the Mukiyama-Mannich reaction (Scheme 1.15).\textsuperscript{[51]} Rather than developing a system where the urea and thiourea are binding to the substrates, the system was designed so that the urea hydrogen bonded to the thiourea, which acts as a chiral catalyst, hydrogen bonding to the imine. This arrangement enhances the catalytic activity of the thiourea by lowering the entropy lost on binding the imine, and also increases the acidity of the thiourea. A thiourea (25) synthesised without the urea, but with a similar structure, showed a significantly lower conversion.
Each catalyst gives a different enantiomer for this reaction (Scheme 1.15). Using the same conditions but using 1 mol% of the each catalyst in a competition experiment the (S) enantiomer was formed in 93% e.e. and 97% yield which would be consistent with the urea/thiourea 24 binding significantly more strongly to the imine than the thiourea 25. One issue with such compounds is that solubility is poor in the less polar solvents such as toluene and dichloromethane required to allow these catalysts to bind to the substrates. However if the catalyst is so active that low loadings can be used this is not as much of an issue. Given the effectiveness of this strategy these significant results may be extended for use in other reactions and the catalyst modified to improve the intramolecular bonding.

There has also been significant interest in alternative catalysts with the aim being to improve upon the promising results seen for thiourea catalysts.

1.3.1.2. Alternative Hydrogen Bonding Catalysts

Shea et al. have recently examined the use of bridging atoms in N-H bonding to improve on the result seen for urea and thiourea catalysts. They developed the
hydrogen bond donors 26, 27 and 28 and compared their catalytic activity to 5 in Friedel-Crafts (Scheme 1.16, Table 1.1) and Morita-Baylis-Hillman reactions. The results are promising since 28 showed significantly higher catalytic activity than the thiourea and rate for the Friedel-Crafts reaction and all the new catalysts gave higher conversion and initial rates than the thiourea catalyst in the Morita-Baylis-Hillman reaction. Catalyst 28 exploits the high H-bond donor capacity of P-NH units and is a concept that was briefly investigated in Chapter 2.

![Scheme 1.16 Friedel-Crafts catalysed reaction with threefold excess of indole to observe pseudo-first order kinetics](image)

**Table 1.1 Results for Friedel-Crafts catalysed reaction with hydrogen bond donors**

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>$k_{\text{rel}}$</th>
<th>% conversion (24 hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>&lt;0.02</td>
<td>&lt;1</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>49</td>
</tr>
<tr>
<td>26</td>
<td>0.3</td>
<td>20</td>
</tr>
<tr>
<td>27</td>
<td>0.1</td>
<td>8</td>
</tr>
<tr>
<td>28</td>
<td>2.6</td>
<td>80</td>
</tr>
</tbody>
</table>

Amide and sulfonamide catalysts have also been shown to be effective organocatalysts. The use of chiral sulfinamides as organocatalysts was examined by Sun et al.. For the hydrosilylation of imines the chiral sulfinamide 29 hydrogen
bonds to the imine and promotes enantioselectivity, although with fairly high catalyst loadings (Scheme 1.17).\[53\]

![Scheme 1.17 Sulfinamide catalysed hydrosilylation](image)

Sun and co-workers also developed the bisformamide catalyst 30 for use in the same reaction although the enantioselectivities observed were not as high as those found for the sulfonimide (Scheme 1.18).\[54\] Shortly after Feng and co-workers independently developed this catalyst for a three component Strecker reaction in up to 99% yield and 86% e.e.\[54\]

![Scheme 1.18 Bisformamide catalysed hydrosilations](image)

Squareamides are planar hydrogen-bonding motifs used in molecular recognition as hydrogen bond donors. Rawal et al., have used these compounds as hydrogen bonding motifs appended with 3,5-bis(trifluoromethyl)benzyl and cinchona alkaloids substituents as catalysts for conjugate addition reactions.\[55\] Such compounds are readily synthesised from the dimethylsquarate and the corresponding amine in two steps. The catalyst 31 showed high enantioselectivity in the conjugate
addition for a variety of nitro-alkenes and ketones (Scheme 1.19). Xu and co-workers have developed a squareamide catalyst for the Michael addition of coumarins to keto esters.\textsuperscript{[56]}

![Scheme 1.19 Squareamide catalysed conjugate addition reaction](image)

Philp and co-workers have also developed an achiral system where an amide based catalyst 32 acts as a hydrogen bond accelerator for a variety of reactions. The system is designed such that the molecule 33 binds at two sites of the catalyst, at the amide and at the pyridine ring (Figure 1.14).\textsuperscript{[57]} Catalysis was carried out on a variety of reactions using the same achiral catalysts and substrate to examine the rate acceleration observed in the presence of 20 mol% 33 (Table 1.2). The study also examined charges on the transition states using computational methods. The rate acceleration was significantly greater for the conjugate addition reaction than for the cycloaddition reaction. From this and the transition state data it was concluded that a significant charge must be present within the transition state of a reaction in order for it to be accelerated by hydrogen bond donors and that for hydrogen bonding catalysts cycloaddition is significantly more difficult to catalyse than conjugate addition reactions.
Introduction

Figure 1.14 Catalyst and substrates used to determine rate acceleration for hydrogen bonding

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Starting Material</th>
<th>$k_{cat}/k_{uncat}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diels-Alder</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Cycloaddition with azide</td>
<td>BnN$_3$</td>
<td>1.5</td>
</tr>
<tr>
<td>Cycloaddition with nitrone</td>
<td>PhN$_2$O</td>
<td>1.8</td>
</tr>
<tr>
<td>Conjugate addition</td>
<td>PhSH</td>
<td>37</td>
</tr>
</tbody>
</table>

Table 1.2 Rate acceleration for reactions with 32 on addition of catalyst 33

Chiral diols have also been found to be effective organocatalysts. Interest in this area began with the use of TADDOL. TADDOL is another privileged ligand structure with a pK$_a$ of approximately 17. [58] Rawal et al. examined the use of TADDOL 34 in the hetero Diels-Alder reaction since this reaction is also accelerated by protic solvents [59] and it follows that hydrogen bonding catalysts should accelerate the reaction. The reaction gave high selectivity for reaction between 1-amino-3-siloxydiene and benzaldehyde (Scheme 1.20). [60] Mechanistic studies using computational methods have since been carried out on various starting materials and TADDOL based catalysts and have determined that the reaction proceeds via a transition state structure where the aldehyde is hydrogen bonded to the TADDOL O-H and the aromatic ring $\pi$-$\pi$ stacks with the aromatic rings of the TADDOL. [61] There has also been the suggestion from Berkessel et al. that one alcohol group binds
to the other alcohol group which is in turn hydrogen bonded to the aldehyde and this cooperative hydrogen bond improves the activity of the catalyst.\textsuperscript{[62]}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme120.png}
\caption{\textit{TADDOL Catalysed Cyclisation Reaction}}
\end{figure}

PHANOL\textsuperscript{[63]} and BINOL\textsuperscript{[64]} derivatives have also been found to organocatalyse reactions. BINOL has a pK\textsubscript{a} of 10.3 and thus is considerably more acidic than TADDOL\textsuperscript{[65]} but phosphoric acids with a BINOL backbone have been more widely investigated as organocatalysts (Section 1.3.2).

Guanidine based organocatalysts have also been developed.\textsuperscript{[66]} A recent example is that developed by Feng \textit{et al.} using the bisguanidine catalyst 35 for the retro-hetero-Diels-Alder reaction (Scheme 1.21).\textsuperscript{[67]} The group also propose a transition state; however they do not give any evidence for this and it is more likely that the conjugate ketone is hydrogen bonded to the second guanidine group as opposed to the amide as proposed.
Introduction

Scheme 1.21 Guanidine catalysed retro hetero-Diels-Alder reaction with proposed transition state

1.3.1.3. Quaternary Ammonium and Phosphonium Ion Catalysed reactions

Quaternary ammonium ions are well known as phase transfer catalysts in synthesis. These reactions have been widely researched and are reviewed elsewhere.\(^\text{[12, 13c, 68]}\) Quaternary ammonium ions can also be used as hydrogen bond donors for reactions in one phase. Johnston et al. developed the chiral 2-aminopyridinium ion 36 for use in catalysis of the aza-Henry reaction, albeit with long reaction times (Scheme 1.22).\(^\text{[69]}\) The helical pyridinium ion catalyst 37 is another interesting example of a hydrogen-bonding catalyst and Yu and co-workers found this catalyst was also active in the conjugate addition reaction (Scheme 1.23).\(^\text{[70]}\) These catalysts are interesting because they are significantly more acidic than thioureas and 2-aminopyridinium ions have a pK\(_a\) of approximately 6.\(^\text{[70]}\) Although it is to be assumed the both the catalysts shown below have similar pK\(_a\) values, Johnston concludes the reaction occurs via specific acid catalysis and Yu by hydrogen bonding, although neither has conducted a study to confirm their
Introduction

hypotheses. At this pKₐ they are not likely to be acidic enough to protonate the imine so hydrogen bonding catalysis is more likely.⁷¹

\[ \text{Scheme 1.22 Proton catalysed aza-Henry reaction} \]

\[ \text{Scheme 1.23 Helical pyridinium ion catalysed conjugate addition reaction} \]

Chiral arylaminophosphonium barfates can be used as catalysts in the aza-Michael reaction of aryl amines to nitro-olefins (Scheme 1.24).⁷² The binaphthyl based catalysts 38 were shown to give high enantioselectivity for aza-Michael reactions in toluene. The aryl substrates give higher enantioselectivity but for alkyl substrates the solvent can be changed to diisopropyl ether to retain high e.e. values.
Scheme 1.24 Chiral arylaminophosphonium barfates as catalysts in the conjugate addition of arylamines to nitro-olefins

Ooi and co-workers also recently discovered that when alkylaminophosphonium phenolate 40 is synthesised in the presence of excess phenol the catalyst forms a four component structure in the solid state which they hypothesise continues in equilibrium in solution (Scheme 1.25).\(^{73}\) The neutral phosphinous amide 39 alone does not catalyse this reaction to high enantioselectivity, but as this supramolecular ion complex greater selectivity is achieved. Addition of phenol to the phosphinous amide also gives similar enantioselectivity to the ionic complex. Based on this work they conclude that the phenols in the ion pair act as hydrogen bond donors and catalyse the reaction by pulling electron density away from the acyl benzotriazole (Scheme 1.26).\(^{74}\) The reaction was further optimised by changing the phenol in the ion pair to 3,5-dichlorophenol and increasing concentration to give 97% yield and 87% e.e. in 4 hours. Further mechanistic studies are required to determine if the reaction proceeds via the hydrogen bonded intermediate proposed or through an unknown mechanism.
Scheme 1.25 Alkylphosphonium catalysed conjugate addition of azlactones to unsaturated acyl benzotriazoles

Scheme 1.26 Proposed co-ordination of acyl benzotriazole to supramolecular structure

1.3.2. Brønsted Acid Organocatalysis

In the course of this study we will also encounter chiral Brønsted catalysts and some introduction of these is also useful. Brønsted acids are used as catalysts in many reactions, including the esterification of carboxylic acids. Brønsted acids catalyse reactions by protonating relatively inactive electrophiles to give a significantly more reactive species than the starting reagent as specific acid
catalysts. There are many strong Brønsted acids including trifluoromethylsulfonic acid, nitric acid, sulphuric acid and hydrochloric acid, however these are all achiral proton donors. Chiral Brønsted acids could also be used to catalyse reactions of these acids, and a chiral proton donor could make the reaction enantioselective. Several examples of this form of catalysis exist to date and phosphoric acid based catalysts have been found to be among the most successful.

1.3.2.1. Diol based Brønsted acids

BINOL based phosphoric acids have been synthesised for use in catalysis with various substituents on the 3, 3’ positions of the binaphthol. These reagents were first used by Akiyama in organocatalysis and have been found to be useful for reactions such as enantioselective reductive amination (Scheme 1.27) and transfer hydrogenation (Scheme 1.28). Such results are encouraging because transfer hydrogenations are typically conducted with metal catalysts. The use of Hantzch ester as stoichiometric reagent makes large scale use of these reactions impractical because of costs.

**Scheme 1.27 Enantioselective reductive amination using catalytic binaphthol phosphoric acid and Hantzch ester**
The mode of action of these catalysts is not yet understood in most reactions but it is likely that one of the steps involves protonation of the substrate and the formation of an ion pair in relatively close proximity to the bulky 3,3’ substituents. Variation of the substituent groups on the acid seems to make a significant difference to enantioselectivity.\textsuperscript{[76c]} It is to be inferred that this is related to the ion pair relationship between the substrate and the catalyst (Figure 1.15). Many different groups have been substituted onto the 3 positions of the phosphoric acids and this remains the most effective catalyst backbone for chiral Brønsted acid catalysts to date. Some of these catalysts are commercially available and they are generally more expensive than most precious metal based asymmetric catalysts, mostly because of the many steps often required to substitute the 3,3’ positions on the aromatic ring.
The syntheses of the 3,3' substituted (R)-1,1'-binaphthalene-2,2'-dial hydrogen phosphate are shown with substituting triphenylsilyl groups (41, Scheme 1.29)\cite{78, 80} and 3,5-bis(trifluoromethyl)phenyl (42, Scheme 1.30)\cite{81} groups which have overall yields of 52% over four steps and 40% over six steps respectively. In both cases the 3,3' position is initially functionalised using directed ortho-lithiation.
Scheme 1.30 Synthesis of (R)-3,3'-Bis[3,5-bis(trifluoromethyl)phenyl]1,1'-binaphthyl-2,2'-diyl hydrogen phosphate

A phosphoric acid anion with a pyridinium cation (45) has been used for catalysis of the aza-Diels-Alder reaction with Brassard’s diene[82] 43 and aldimines (Scheme 1.31). The reaction can be carried out with the phosphoric acid 44 but the use of the pyridinium cation improves reaction yield.[17] In wet d8-toluene a time-course NMR spectroscopy experiment was carried out to determine the decomposition of this diene with the phosphoric acid and the phosphate salt present. The diene showed significantly more decomposition over time in the presence of the acid when compared to the salt, which is thought to be due to the sensitivity of the diene to acid and also the higher pKₐ pyridinium ion which results in less decomposition.
TADDOL based phosphoric acids have also been synthesised and used in the catalysis of a Mannich-type reaction (Scheme 1.32).[18a] The aromatic groups were varied with phenyl, $p$-phenylbenzene, $p$-fluorobenzene and $p$-trifluoromethylbenzene giving yields of 0%, 31%, 34% and 97% respectively. A similar trend was seen in enantioselectivity. This paper remains the only example of TADDOL based phosphoric acids published.

There have recently been several studies into using slight variations on the phosphoric acid group. Chiral diols can also be used to make thiophosphoric acids for catalysts.[83] Blanchet et al. recently developed a methodology to synthesise H8-
BINOL thiophosphoric acids on the basis that the counterion of the acid would be more stable and thus the acidity would be greater (Figure 1.16). However it is known that thiophosphoric acids can be explosive so this may not be the case. The results obtained from the use of phosphorodithioic acid in Nazarov cyclisations were not promising (Scheme 1.33). However, the phosphorodithioic acid 46 was found to catalyse the \(N\)-acyliminium alkylation reaction, which is known to be also catalysed by strong Brønsted acids such as NHTf\(_2\), but is not catalysed by BINOL phosphoric acids. It is possible that these catalysts would be more effective in other reactions.

![Figure 1.16 Proposed relative stability of counterions](image)

![Scheme 1.33 Phosphorodithioic acid catalysed Nazarov reaction](image)

Chiral phosphoramides have been found to be more acidic substances for catalysis since the anion is more stable than for the phosphoric acids. Since phosphoric acid catalysts are thought to be specific acid catalysts, the more acidic catalyst should give a faster reaction rate based on the lower pK\(_a\). For the Diels-Alder reaction Nakashima and Yamamoto found these catalysts can give high enantioselectivity and yield, albeit with some isomerisation.\(^{[84]}\) The BINOL phosphoric acid 47 does not work as a catalyst in this reaction (Scheme 1.34).
These phosphoramidate-based catalysts were used in a Nazarov cyclisation reaction by Rueping and co-workers to give high yield and enantioselectivity (Scheme 1.35).\[^{[85]}\] The reaction with the N-triflyl phosphoramidate was found to be catalysed significantly faster since it can be conducted at 0 °C, with phosphoric acids heating to 60 °C was required. The reaction was further optimised for use with different substrates and catalyst loadings of 2 mol%.

**Scheme 1.34 Brønsted acid catalysed Diels-Alder reaction**

**Scheme 1.35 N-Triflylphosphoramidate catalysed Nazarov reaction**
Wenzel et al. have examined biphenyl-2,2'-diol based catalysts for hydrophosphonylation reactions and Friedel-Crafts alkylation.\cite{86} Although the enantioselectivities obtained were low to moderate in both cases it is worth noting that for this Friedel-Crafts reaction the best result for enantioselective catalysis to date is 56% e.e.\cite{87} It follows that there is scope for the improvement of enantioselectivity of these catalysts in other reactions.

![Scheme 1.36 Brønsted Acid Catalysed Friedel-Crafts alkylation of indole](attachment:image)

1.3.2.2. Diamine and Sulfonyl Based Brønsted Acids

Diamines have also been found to be effective chiral precursors for chiral Brønsted acid catalyst synthesis. The hetero-Diels-Alder reactions has been found to be catalysed by the relatively simple \(N,N'\)-dinonaflyl diamine 51 (Scheme 1.37) and it is to be assumed that the pKa is low enough that they act as Brønsted acids.\cite{88} Jørgensen and co-workers also screened a number of other fluoroalkylsulfonyl groups and other chiral diamines but 51 was found to be the most effective. Mikami
and Tonoi independently reported similar results for hetero Diels-Alder reactions with aldehydes.\textsuperscript{[89]}

\begin{scheme}{Scheme 1.37} \textit{Brønsted acid catalysed Diels-Alder reaction} \end{scheme}

Terada \textit{et al.} have developed the sulfonyl phosphorodiamidic acid for use in the Mannich reaction (\textbf{Scheme 1.38}).\textsuperscript{[90]} The groups on the sulfonyl substituent were varied but in all cases the reaction gives moderate yield and enantioselectivity. However, this structural motif is novel and thus more effective catalysts based on it may yet be developed.

\begin{scheme}{Scheme 1.38} \textit{Phosphorodiamidic acid catalysed Mannich reaction} \end{scheme}

The List,\textsuperscript{[91]} Giernoth,\textsuperscript{[92]} and Lee\textsuperscript{[93]} research groups have independently reported the synthesis of the chiral disulfonimide 54 (\textbf{Figure 1.17}). Giernoth states that the catalyst is very hydroscopic and must be handled under inert conditions. List and Lee have both developed the synthetic methodology to produce the 3,3’ substituted catalyst through different routes.
This catalyst has a pK$_a$ of 2.4 in DMSO$^{[94]}$ with 3,3’-substituted derivatives having been used by List in the Mukiyama aldol reaction, where phosphoric acid 55, sulfonic acid 57 and N-triflylphosphoramide 56 had been tested unsuccessfully (Scheme 1.39). The reaction was shown to work using 58 with a range of substrates to give up to 94% e.e and gave good enantioselectivity even when the catalyst loading was lowered to 0.01 mol%.

An interesting system using achiral amines and chiral sulfonyl acids has been developed by Ishihara and co-workers (Scheme 1.40)$^{[95]}$. They use a 1,1’-binaphthyl based system in a Mannich-type reaction in conjunction with 2 equivalents of achiral amine to the catalyst. It is thought the protonated amine acidifies the imine substrate and the association between the chiral sulfate and cationic imine intermediate promotes enantioselectivity. This presence of the amine significantly improves the selectivity.
A key area to assist understanding of hydrogen bonding and Brønsted acid catalysis in future years is the determination of the point at which general acid catalysis, observed with thioureas, becomes specific acid catalysis, seen using moieties such as phosphoric acids, and for which reaction conditions this distinction is important. Whilst inferences can be made about how reactions work from general chemical knowledge the only method of confirming this is to study the reactions mechanistically. There seems to be a relationship between $pK_a$ and activity of the catalyst, but this is also significantly affected by steric properties. Since much research in this area is still relatively recent it is likely that more catalytic reactions will be discovered with greater structural variation of catalysts and during these studies greater knowledge may be gained. One reaction which had not been studied at the beginning of this research is the ene reaction, and this was taken as our starting point.
References for Chapter 1


Introduction


Chapter 2

Organocatalysis of the Ene Reaction
2. ORGANOCATALYSIS OF THE ENE REACTION

2.1. The Ene reaction

The ene reaction is a reaction between an “ene”, an alkene, with an allylic hydrogen and an “enophile” which can be one of several unsaturated species (Scheme 2.1). The enophile can be a carbonyl, imine or alkene. This pericyclic reaction differs from the Diels-Alder reaction in that one of the diene bonds which transfers is replaced by the allylic C-H bond. As a result of this, the reaction tends to proceed at a much slower rate. A slight positive charge is thought to build up on the alkene and a slight negative charge on the Y atom in the enophile (Scheme 2.1). This weak polarisation means that 1,1-disubstituted enes with electron donating groups favour the reaction more than mono or unsubstituted, since the positive charge is better stabilised. It also follows that electron-poor enophiles are likely to be more reactive. Lewis acid catalysts have been found to catalyse imine and carbonyl-ene reactions because of their ability to bind to the nitrogen or oxygen atom (atom Y, Scheme 2.1) and thus stabilise the slight negative charge built up in the transition state. Some ene reactions can proceed thermally\textsuperscript{[1]} and/or at high pressure,\textsuperscript{[2]} but many substituents are not reactive enough to do so and require catalysis with Lewis acids.
Carbonyl-ene reactions have been widely studied and the use of chiral ligands coordinated to the Lewis acids has been shown to make these reactions stereoselective. An example of a carbonyl-ene Lewis acid catalysed reaction is that of the highly reactive alkene, 2-methoxy propene which was found to react with benzaldehyde analogues in the presence of the chromium catalyst 59 (Scheme 2.2).[3] A second example is a syn selective reaction developed by Evans and co-workers using scandium catalysts 60 (Scheme 2.3).[4] Both are thought to act as Lewis acids with a chiral ligand promoting stereoselectivity. In the carbonyl ene reaction most of the enophiles used are aldehydes since it is a pericyclic reaction and the $\pi^*$ orbital is of a lower energy and hence more reactive than ketones.
Organocatalysis of the Ene Reaction

There is only one example of an ene-type reaction based on organocatalysts using a binaphthol phosphoric acid \( \text{60} \) as the organocatalyst (Scheme 2.4) \(^5\) as shown below. However, in this example, the ene is not a simple alkene but a much more nucleophilic enamine. In any case the extremely low catalyst loading again illustrates the synthetic potential of these reagents and their use in enantioselective reactions.

**Scheme 2.3 Scandium Catalysed Syn Selective Ene Reaction**

\[
\begin{align*}
\text{Scheme 2.4 Phosphoric acid catalysed aza-ene-type reaction with proposed method of catalysis}
\end{align*}
\]
As Lewis acids have proven to be effective catalysts for the ene reaction it is feasible that thioureas may also act as a catalyst in this reaction (Figure 2.1). However to date, no organocatalyst has been found for the carbonyl-ene reaction. This section describes the attempt to find a suitable organocatalyst, and to subsequently design an asymmetric catalyst for ene type reactions. A suitable thiourea organocatalyst was sought for the ene reaction using a carbonyl “enophile”.

Mikami et al. recently demonstrated palladium catalysed ene reaction (Scheme 2.5) between various alkenes and ethyl trifluoropyruvate using 5,5′-Bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole (SEGPHOS) as ligand.[6] This reaction is unusual because it uses a ketone instead of an aldehyde as the enophile. It also proceeds relatively quickly going to completion in 15 minutes, using the palladium catalyst. It was therefore decided to use this pyruvate to test our organocatalyst.

![Figure 2.1 Lewis acid binding in the carbonyl-ene reaction opposed to proposed method of thiourea binding](image)

![Scheme 2.5 Enantioselective Catalysed Ene Reaction](image)
Doherty et al. have also conducted research into the metal catalysed carbonyl ene reaction of ethyl trifluoropyruvate with cationic complexes of platinum, nickel and palladium using BINAP as ligand (Scheme 2.6, Table 2.1) they have found that significant isomerisation is observed with these metals.[7]

![Scheme 2.6 Metal catalysed ene reaction of ethyl trifluoropyruvate and methylene cyclopentane.](image)

Reactions all gave >98% conversion to product

<table>
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<th>Metal</th>
<th>Ratio a:b:c:d</th>
<th>endo:exo ratio</th>
<th>e.e. (%)</th>
<th>d.e.(%)</th>
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Table 2.1 Ratios and selectivities for cationic metal BINAP catalysed reaction between methylene cyclopentene and ethyl trifluoropyruvate

2.2. Aims and Objectives

The carbonyl-ene reaction is a cyclisation reaction which is likely to require a strongly hydrogen bonding moiety to bind to its transition state and catalyse the reaction. The reaction of alkenes with ethyl trifluoropyruvate appears to give isomerisation when catalysed by metal salts. Therefore it was hypothesised that use of a hydrogen bonding catalyst could avoid this isomerisation. An active
organocatalyst could be adapted to create an asymmetric catalyst which could then be used to give chiral products for the reaction. We were also interested in forming novel hydrogen bonding catalysts which could be used in other reactions.

2.3. Synthesis of an Organocatalyst for the Ene Reaction

Microwave irradiation was initially used as a source of heating to form the ene product of ethyl trifluoropyruvate and \( \alpha \)-Methyl styrene for characterisation. \( \alpha \)-Methyl styrene was used for our initial studies as it forms a less volatile product and is consequently easier to work with than methylene cyclopentane and cyclohexanes. The microwave irradiation creates a high pressure and temperature environment and it has been found that many reactions proceed at an enhanced rate under these conditions (Scheme 2.7). In this case the dichloromethane is heated to approximately 100 °C above its boiling point. There was a small amount of impurity observed by \(^{19}\text{F}\) and \(^{1}\text{H}\) NMR spectroscopy and these were characterised by GCMS. Both HPLC and GCMS show three peaks, which E.I. mass spectrometry indicate to have the same ion fragments. This analysis suggests that the three peaks seen by \(^{19}\text{F}\) NMR spectra correspond to the E and Z products (62) of the isomerised ene product which would have the same mass as the desired ene product. It is possible that isomerisation occurs because of the electron withdrawing nature of the phenyl group of \( \alpha \)-Methyl styrene which decreases the energy required for isomerisation. The ratio of isomers was determined by integration of the GCMS trace assuming equal response estimated factors for these isomers.
Scheme 2.7 Microwave-Accelerated Ene Reaction.

Having isolated the products of the reaction thiourea 5 was added to see if the reaction was accelerated. This thiourea was readily synthesised from 3,5-bis(trifluoromethyl) phenyl isothiocyanate and 3,5-bis(trifluoromethyl)aniline in 76% isolated yield (Scheme 2.8).

Scheme 2.8 Synthesis of thiourea

The reaction was stirred over a period of two days using 20 mol% catalyst loading since the ene reaction often occurs at a very slow rate. After four days both the uncatalysed and catalysed reactions had gone to completion. This speed of reaction was unexpected since most aldehydes, including highly activated ethyl glyoxylate, do not react particularly efficiently without additives. It is thought this was due to the particularly electron-withdrawing effect of the trifluoromethyl group. Dichloromethane was used in further experiments to test percentage conversions since it dissolved catalyst 5 more readily than toluene or chloroform. Reactions were analysed by $^{19}$F NMR spectroscopy after four hours at 30 °C to investigate the rate of conversion.
Scheme 2.9 below shows the shifts of the fluorine NMR peaks in the spectrum. Two side products (63a and 63b) are formed in variable amounts when the ethyl trifluoropyruvate is exposed to atmospheric moisture. It is believed that one of these species is the hydrated ketone, on the basis of infra red spectra and mass spectrometry but the second is unknown.

\[
\begin{align*}
\text{Scheme 2.9} & \quad 19^F \text{ NMR spectra fluorine shifts for the reaction of ethyl trifluoropyruvate with } \alpha-\text{methyl styrene} \\
\end{align*}
\]

\[\delta_F -76.2 \quad \delta_F -79.16 \]

\[\delta_F -83.2 \quad \delta_F -83.9 \]

\[\text{63a} \quad \text{63b} \]

\[\text{19F NMR analysis showed no starting material remaining in the reaction mixture after four hours, indicating >99\% conversion to product 61 and the hydrated product of the pyruvate 63. It was therefore decided to investigate percentage conversion by isolating the product by chromatography after a reaction time of three hours. The difference in conversion of the uncatalysed reaction against catalysed reaction (Figure 2.2) shows conclusively that the reaction is organocatalysed. Pleasingly isomerisation seen in the microwave reaction was not observed in the uncatalysed or catalysed reactions.} \]
Figure 2.2 Isolated Yield of Ene Product 61 after 3 hours at room temperature with a 1:1.2 ratio of ethyl trifluoropyruvate: alpha-methyl styrene in dichloromethane

Further experiments measuring the catalytic effect of the thiourea were undertaken (Table 2.2). In order to explore the scope of this catalyst alternative substrates were selected. Mikami and co-workers use cyclohexene, 1-hexene and allyl benzene as substrates with the ethyl trifluoropyruvate[6a] although the $^{19}$F NMR spectroscopy data in this study with the shifts of around +99 ppm were inconsistent for trifluoromethyl groups which usually come around -50 to -90 ppm. Pure samples of these ene products were synthesised in the microwave or over long reaction times to confirm the structure of the products obtained. These mono-substituted enes have slower rates of reaction because the transition state is less well stabilised. Over long periods of time the starting material for these reactions decomposes to the hydrated side products so no further conversion is possible. The slow reaction rate of mono substituted alkenes in the presence of the thiourea suggests a low catalytic activity (Table 2.2, entries 2, 3 and 4). However, the reaction shows no or relatively little conversion to the product when the thiourea is absent, showing the reaction has a slow rate. In comparison, 1,1’-disubstituted alkenes methylenecyclopentane and 2-methoxypropene react to completion in less than an hour without the catalyst (Table 2.2). This difference in rate may be explained by the stabilisation of the positive charge in the transition state. In an attempt to prevent the decomposition of the starting material to hydrate 63, 4 Å molecular sieves were added to the reaction with 2-methoxypropene but the reaction proceeds to give a purer product in their absence yielding >95% pure product after removing the solvent and excess 2-methoxypropene in vacuo. The amide substrate was tested to see if bifunctional catalysis
could be undertaken in a manner similar to that in a previous project. The reaction is thought not to have occurred because of the steric hindrance of the ortho-amide substituent.

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**Table 2.2 Reactions of enes with ethyl trifluoropyruvate**

*Using a 1.2:1 ratio respectively in dichloromethane at 30°C under an inert atmosphere except the reaction using 2-methoxy propene where 2.5 eq. of the alkene was used. NR indicates no reaction \(^{[a]}\) based on \(^{19}F\) NMR spectroscopy.*

As 2-methoxypropene is such an activate substrate it was reacted with \(p\)-fluorobenzaldehyde and benzaldehyde in the presence of 20 mol% of the thiourea 5 in dichloromethane in an attempt to catalyst these reactions. No product was observed for these reactions after several days. Various other carbonyl compounds
have been tested for reactivity with \(\alpha\)-methyl styrene. These include \(\alpha,\alpha,\alpha\)−trifluoroacetophenone and ethyl glyoxylate. Ethyl glyoxylate is a widely used substrate in the ene reaction, and is commercially available as a polymer solution in toluene which is cracked before use in the ene reaction. With ethyl glyoxylate there is virtually no reaction and the glyoxylate begins to convert back to polymer on standing (Table 2.3). The product produced by the reaction of ethyl glyoxylate and \(\alpha\)-methyl styrene is potentially more useful than that shown above (61) and so it would be desirable for 5 to catalyse its reaction. However, it was found that although some product was observable after four days the reaction was not accelerated enough to be useful for synthesis. \(\alpha,\alpha,\alpha\)−trifluoroacetophenone was found to be unreactive when tested under the same microwave conditions as ethyl trifluoropyruvate in Scheme 2.7 and it was therefore assumed to be too unreactive except when used with strong promoters for the ene reaction such as stoichiometric \(\text{AlCl}_3\).\[^9\]

\(\alpha,\alpha,\alpha\)−trifluoroacetaldehyde (fluoral) and \(\alpha,\alpha,\alpha\)−trichloroacetaldehyde (chloral) were prepared by distillation of the corresponding hydrate from concentrated sulphuric acid. \(\alpha,\alpha,\alpha\)−trifluoroacetaldehyde is used in large excess due to its low boiling point of -18 °C. \(\alpha\)-methyl styrene was reacted with \(\alpha,\alpha,\alpha\)−trifluoroacetaldehyde, in large excess due to its low boiling point, in the presence of 20 mol\% thiourea 5 and compared to the reaction without thiourea in dichloromethane. However, both the catalysed and the uncatalysed reactions between \(\alpha\)-methyl styrene and \(\alpha,\alpha,\alpha\)−trifluoroacetaldehyde were found to go to completion within 15 minutes (Scheme 2.10, Table 2.3). \(\alpha,\alpha,\alpha\)−trichloroacetaldehyde was found not to give product in either the uncatalysed or catalysed reaction suggesting a better promoter, such as a Lewis acid, should be used. The findings with the extremely reactive alkenes and ethyl trifluoropyruvate and also highly active fluoral with most alkenes do not preclude catalysis of the reaction by the thiourea, but show that catalysis is not necessary to form racemic products. Fast background reactions are actually quite a common occurrence in organocatalysis literature,\[^{10}\] but good asymmetric processes can still result.
Organocatalysis of the Ene Reaction

Scheme 2.10 Thiourea catalysed reactions of aldehydes with ethyl trifluoropyruvate

<table>
<thead>
<tr>
<th>Substrate</th>
<th>mol% thiourea 5</th>
<th>Time (hrs)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>94</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0.25</td>
<td>&gt;99&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>0.25</td>
<td>&gt;99&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>16</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2.3 Results from reaction with α-methylstyrene in the presence of thiourea 5

<sup>a</sup> reaction carried out at -20 °C

2.4. Asymmetric Organocatalysis of the Ene Reaction

An enantiomerically pure thiourea 70 was synthesised by reacting two equivalents of 3,5-bis(trifluoromethyl)phenylisothiocyanate with (R)-2,2'-diamino-1,1'-binaphthalene (Scheme 2.11) The C<sub>2</sub> symmetry of the catalyst and the relative inaccessibility of the active site of this catalyst once a carbonyl compounds is associated could promote enantioselectivity. This compound was a new thiourea when we first carried out its synthesis but was then published by Connon <i>et al.</i> shortly after our work.  <sup>[11]</sup>
Organocatalysis of the Ene Reaction

Scheme 2.11 Synthesis of \( \text{N,N''-(1R)-2,2'}\text{-diylbis[N''-[3,5-bis(trifluoromethyl)phenyl] thiourea}} \)

The enantioselectivity of the catalyst in the ethyl trifluoropyruvate ene reaction was not found to be very high (Scheme 2.12), although this was the first example of an organocatalysed asymmetric carbonyl ene reaction of this type.

Scheme 2.12 Reaction of ethyl trifluoropyruvate with \( \alpha \)-methyl styrene in the presence of chiral \( \text{bis(thiourea)} \) catalyst.

* e.e determined using \( \text{Eu(hfc)}_3 \)

Further attempts were made to improve the enantioselectivity of this reaction (Scheme 2.13, Table 2.4). Varying temperature and catalyst concentration did not improve the enantioselectivity to an acceptable level, whilst using stoichiometric amounts of catalyst gave poor enantioselectivity, suggesting that the catalyst enantioselectivity cannot be improved above approximately 30% e.e.
Organocatalysis of the Ene Reaction

Scheme 2.13  Chiral thiourea reactions of carbonyl with alkenes

\[
\text{CH}_2\text{Cl}_2
\]

Table 2.4  Conditions for use of catalyst 70 in the ene reaction between ethyl trifluoropyruvate and \(\alpha\)-methylstyrene.

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>Alkene</th>
<th>Thiourea 70 (mol% loading)</th>
<th>Temp ((^\circ)C)</th>
<th>Time (hrs)</th>
<th>Isolated Yield (%)</th>
<th>e.e.(^{[a]}) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{Et}_2\text{C}=\text{CF}_3)</td>
<td>Ph</td>
<td>10</td>
<td>0</td>
<td>16</td>
<td>32(^1)</td>
</tr>
<tr>
<td>2</td>
<td>(\text{Et}_2\text{C}=\text{CF}_3)</td>
<td>Ph</td>
<td>10</td>
<td>-20</td>
<td>210</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>(\text{Et}_2\text{C}=\text{CF}_3)</td>
<td>Ph</td>
<td>25</td>
<td>-20</td>
<td>345</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>(\text{Et}_2\text{C}=\text{CF}_3)</td>
<td>Ph</td>
<td>25</td>
<td>0</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>(\text{Et}_2\text{C}=\text{CF}_3)</td>
<td>Ph</td>
<td>100</td>
<td>-20</td>
<td>46</td>
<td>67</td>
</tr>
<tr>
<td>6</td>
<td>(\text{Et}_2\text{C}=\text{CF}_3)</td>
<td>Ph</td>
<td>10</td>
<td>-20</td>
<td>3</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>(\text{F}_3\text{C}=\text{H})</td>
<td>Ph</td>
<td>10</td>
<td>-20</td>
<td>3</td>
<td>93</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Enantioselectivity determined by Eu(hfc)\(_3\) and \(^{19}\)F NMR spectroscopy

Attempts to use the catalyst on the reaction between methylene cyclohexene and ethyl trifluoropyruvate at -20 \(^{\circ}\)C showed 95% conversion but gave no enantioselectivity (Table 2.4). The reaction between \(\alpha,\alpha,\alpha\)-trifluoroacetaldehyde and
\(\alpha\)-methyl styrene at -20 °C also showed full conversion but no enantioselectivity, presumably because the background reaction produces the racemic product without the aid of the catalyst. Lower temperatures were not investigated.

### 2.5. Attempt to Increase Activity by Use of a Different Kind of Thiourea

Although we had discovered the first organocatalysts for the carbonyl-ene reaction, they are still not particularly efficient. In order to increase the rate of reaction, a catalyst was required which was both a more acidic thiourea and with a smaller difference between the entropy of the bound and unbound state. One obvious target would be the synthesis of thiourea 5 with a significantly more electron-withdrawing nitrile, nitro or methyl-sulfonyl groups instead of trifluoromethyl. These thioureas should be more conformationally restricted and therefore active in line with Schreiner’s experiments based on the Diels-Alder reaction. However, the aniline and isothiocyanate which would be required to make these thioureas are not commercially available, and it is unlikely that there would be a significant rate enhancement, since in the Diels-Alder reaction Changing the substituents of the thiourea from phenyl to 3,5-bis(trifluoromethyl)phenyl gave a three-fold rate improvement. Furthermore, Schreiner et al. are thought to have been unsuccessful in attempts to synthesise thioureas with these substituents.

There are several chiral thioureas developed by Jacobsen and co-workers that have been found to promote organocatalytic reactions. Nonetheless these are more electron-rich and so are likely to be less active than thiourea 5. The commercially available thiourea 71 was tested in the ene reaction and gave no enantioselectivity, even when repeated at lower temperatures (Scheme 2.14). This result when contrasted with the high yields and enantioselectivities reported by Jacobsen in a reaction with a lower activation barrier highlights the difficulties associated with the ene reaction.
Organocatalysis of the Ene Reaction

Scheme 2.14 Jacobsen thiourea catalysed ene reaction

A thiourea with different and more electron-withdrawing substituents was required to examine if an increase in activity could be achieved. Thiourea 72 (Figure 2.3) has been synthesised[^15] as a ligand for platinum. This thiourea has one obvious advantage over catalysts such as 5 in that the phosphorus atoms may be made asymmetric by having two different substituents replacing the phenyl groups. The synthesis is complicated in the first step and on analysis by 31P NMR spectroscopy several side products were observed. It has been proposed for this reaction Schmultz and co-workers[^16] that compounds 73, 74 and 75 are formed (Scheme 2.15). The trans and gauche isomers are likely to appear as an averaged signal on the NMR timescale.

Figure 2.3 Diphosphine derivative of thiourea
Initial attempts to synthesise the compound involved dropwise addition of a solution of chlorodiphenylphosphine to a suspension of the thiourea and triethylamine. This was left to stir overnight. An unknown species was formed with an NMR spectroscopy resonance +39 ppm in $^{31}$P NMR spectra which was unreactive when treated with sulfur. A second attempt at synthesis with a shorter reaction time led to the formation of a species with the expected shift (+31 ppm). Purification then reaction with $S_8$ led to the formation of a species with a shift of +53 ppm as a minor product. Efforts to improve the yield of this step were unsuccessful since it is difficult to avoid the formation of side-products in the first step according to the mechanism proposed.\[16\] Schmultzer et al. concluded that it was not possible to make the thiourea 72 after reacting for five hours at -30 °C. However, Woollins et al. synthesised\[15\] the compound at room temperature over a shorter time period though this approach was not successful in our hands. An alternative method was therefore
developed by modification of the synthesis of alkyl thioureas by Spence et al.\textsuperscript{[17]} We used 3,5-bis(trifluoromethyl)aniline as an amine with the intermediate isothiocyanate.

Chlorodiphenylphosphine was oxidised with elemental sulfur, followed by conversion to the isothiocyanate followed by conversion to the isothiocyanate (Scheme 2.16). This synthesis could then be adapted if the thiourea synthesised was highly active. The isothiocyanate synthesised was then used to make the novel thiourea 73 although due to the poor nucleophilicity of 3,5-bis(trifluoromethyl)aniline the reaction required a week to go to completion (Scheme 2.16). The thiourea was isolated and tested in the ene reaction of ethyl trifluoropyruvate and its reactivity was compared with other thioureas (Table 2.5).

![Scheme 2.16 Synthesis of unsymmetrical thioureas](image-url)
Organocatalysis of the Ene Reaction

<table>
<thead>
<tr>
<th>Thiourea</th>
<th>Time (hrs)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Thiourea" /></td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td><img src="image2" alt="Thiourea" /></td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td><img src="image3" alt="Thiourea" /></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><img src="image4" alt="Thiourea" /></td>
<td>1</td>
<td>95</td>
</tr>
</tbody>
</table>

Table 2.5 Percentage Conversion measured by $^{19}$F NMR spectroscopy and time in hours for the reaction of ethyl trifluoropyruvate and α-methylstyrene in the presence of 10 mol% thiourea at room temperature in CH$_2$Cl$_2$.

The results show that the synthesised thiourea 73 gives poor conversion to the product of the ene reaction. The thiourea was also tested in a Mannich-type reaction for which it showed similarly poor results. This poor reactivity, despite the Ph$_2$P(S) group being strongly electron withdrawing, could be due to straightforward steric effects impeding co-ordination of the substrate or inter- or intramolecular hydrogen bonding with the catalyst blocking off the thiourea. In order to determine whether this was the case the X-ray crystal structure of the thiourea was obtained (Figure 2.4). The crystals were obtained from acetone solution by slow vapour diffusion of hexane.
Figure 2.4 Single Crystal X-Ray structure of thiourea 73

Crystals obtained by slow vapour diffusion of hexane into acetone solution. Pink denotes fluorine, black denotes carbon, white denotes hydrogen, light blue denotes nitrogen, yellow denotes sulfur and orange denotes phosphorus. Selected properties: S(1)-H hydrogen interspatial distance 2.38(2) \( \text{Å} \), C(1)=S(2) bond 1.668(3) \( \text{Å} \), P(1)=S(1) bond 1.9488(12) \( \text{Å} \), P(1)-N(1) bond 1.707(2) \( \text{Å} \), P(1)-N(1)-C(1) angle 130.7(2)º, N(1)-C(1)-N(2) angle 114.4(3)º

The close S-HN distance suggests a hydrogen bonding relationship between the sulfur and the thiourea. The distance between them of just over 2.37 \( \text{Å} \) would indicate that hydrogen bonding is taking place in the solid state which, if occurring in solution, would explain the lack of catalytic activity. In solution there is also the possibility that this would occur between different thioureas. Acetone was chosen as a crystallisation solvent so that the molecule could show binding to the thiourea but this did not occur.

In order to determine if strong intramolecular or intermolecular hydrogen bonding was occurring in solution a dilution study was attempted. The two \(^1\text{H}\) NMR N-H resonances were assigned by use of \(^1\text{H}-^{31}\text{P}\) HMQC NMR data which confirmed that the upfield N-H proton signal was close to the phosphorus atom and thus the downfield N-H signal was connected to the aromatic ring. Using NMR spectroscopy, the movement of signals during dilution of a solution can indicate the association between them since the interaction between two species should weaken on dilution.
The resonances would be expected to shift when a separate species hydrogen bonded
weakens their association. Thus if there is intermolecular hydrogen bonding the N-H
resonances of the thiourea would be expected to move significantly. However, intramolecular hydrogen bonds are concentration independent.

In CDCl$_3$ a solution of 73 was diluted gradually from 0.1 M to 0.04 M and both
thiourea protons (Figure 2.5) showed a gradual shift upfield. However, one proton
signal moved 0.03 ppm and the other 0.21 ppm. A NMR spectroscopy study was also
conducted where acetone was added to the reaction mixture and gradually diluted
from 0.05 M to 0.0175 M to determine amount of disruption to hydrogen bonding
that acetone induces. This experiment with acetone should have a significant effect
on the shift of the protons in the spectra however once again little change (<0.02
ppm) was seen to the shift of the downfield thiourea proton. It can be concluded that
this is tentative evidence that the intramolecular hydrogen bond is retained in
solution. A less likely explanation that cannot be ruled out is that there is no
hydrogen bonding in solution.

![Figure 2.5](image)

*Figure 2.5 NMR spectra of thiourea 73 from 0.1 M to 0.04 M dilution. The first shows the small shift on one thiourea proton during dilution in solution. The second indicates the shift of the other thiourea proton in solution.*

If this strong intramolecular hydrogen bond is occurring, as the results of the
NMR dilution experiments would seem to indicate, the thiourea proton would not be
as available for intermolecular hydrogen bonding of the thiourea. Thus thiourea
would not catalyse reactions through hydrogen bonding effectively.
2.6. Chiral Binaphthol Phosphoric Acid Synthesis

Chiral binaphthol phosphoric acids have been shown to work as organocatalysts in a variety of reactions. It was hypothesised that the reaction could potentially be catalysed via two mechanisms. Either by acting as a proton shuffle (Figure 2.6a, similar to that proposed for the aza-Ene reaction in Scheme 2.4\cite{5}) or via a Prins type reaction mechanism (Figure 2.6b). The Prins reaction is a stepwise reaction involving protonation of the ketone followed by attack of the alkene on the carbocation and regeneration of the proton.

![Figure 2.6 Potential methods for Phosphoric acid catalysis for the ene reaction](image)

Chiral phosphoric acids are synthesised from the corresponding BINOL (Scheme 2.17) and the binaphthyl phosphoric acid 74 was prepared without incident\cite{18}.

![Scheme 2.17 Synthesis of (R)-1,1′-Binaphthyl-2,2′-diyl hydrogen phosphate](image)

To substitute the 3,3-positions of the acid, directed ortho-metalation is used. This procedure has proved invaluable in many reactions. An example of this is in the
synthesis of (R)-3,3'-Bis(triphenylsilyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate by MacMillan and co-workers 41 (Scheme 1.29).[18]

Synthesis of the acid requires protection using methoxymethyl chloride, which acts as a directing group for ortho-lithiation. This substituted species was deprotected using acid. In our hands it was found that during the deprotection of the MOM, one of the triphenylsilyl groups is removed by the use of acid (Scheme 2.18) and was detected by LCMS. Attempts to optimise this were unsuccessful and so an alternative method of producing a 3,3'-disubstituted analogue of 1,1’ binaphthol was sought. Snieckus and co-workers have been very active in the area of ortho-lithiation,[19], [20] and a method of producing atrialkylsilyl group on the 3,3’ positions is has been reported.[20] The Snieckus method was applied to make the novel 3,3’-bistrimethylsilyl substituted BINOL 75 in Scheme 2.19, produced in 84% yield. This substituted BINOL was reacted with POCl₃ to give the phosphoric acid 76 in 62% yield (Scheme 2.20).

![Scheme 2.18 Attempted synthesis of (R)-3,3’-Bis(triphenylsilyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate](image-url)
Organocatalysis of the Ene Reaction

Scheme 2.19 Synthesis and isolated yields of (R)-3,3′-Bis(trimethylsilyl)-1,1′-binaphthyl-2,2′-diol

Scheme 2.20 (R)-3,3′-Bis(trimethylsilyl)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate

Both chiral phosphoric acids 74 and 76 were tested in the ene reaction (Scheme 2.21). Both gave very low conversions that are consistent with the background reaction and no enantioselectivity. Hence it is thought that neither catalyse the reaction. Thus far phosphoric acids had only been found to activate imines that are more prone to protonation. We felt that stronger Brønsted acids would be needed to promote these reactions. This project was terminated at this early stage when Rueping and co-workers, having seen our initial report of thiourea catalysis,\(^{[21]}\)
published the use of strongly more acidic chiral N-triflylphosphoramides for the same asymmetric ene reactions giving excellent enantioselectivity.\textsuperscript{[22]}

\[
\begin{array}{c}
\text{F}_3\text{C}-\text{CO}_2\text{Et} + \text{CH}_2\text{Cl}_2, 1\text{ hr} \\
\text{20 mol% acid} \\
\text{74: 15\% conversion} \\
\text{76: 12\% conversion}
\end{array}
\]

\textbf{Scheme 2.21} Use of Chiral Phosphoric acids to catalyse the ene reaction

\textbf{2.7. Potential Self-Assembled Systems with an Achiral Thiourea and a Chiral Acid}

From the previous section (\textbf{Section 2.5}) it can be concluded that many thioureas catalyse the ene reaction, and that the chiral phosphoric acids synthesised do not. Achiral thioureas are easily synthesised, and many chiral acids are available. A high enantioselectivity might be achieved with an achiral thiourea associated with a chiral acid close enough to the active site to cause the reaction to be enantioselective but far enough away that it would not obscure the catalytic site. Our group recently introduced self-assembled organocatalysts into the field of enamine catalysis (\textbf{Figure 2.7, Scheme 2.22})\textsuperscript{[23]} and this is an area that is beginning to attract significant attention. The use of an achiral thiourea, self assembling with a chiral co-catalyst seemed an attractive concept to study.
Many chiral acids are commercially available and together with the synthesised chiral phosphoric acid 74, they could potentially be used to catalyse an ene reaction asymmetrically. It is also possible that this system could be used to catalyse several other reactions catalysed by thioureas. The novel thiourea 77 is readily synthesised from the 2-hydrazinopyridine and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (Scheme 2.23). This thiourea could hydrogen bond or associate as an ionic interaction to chiral acids (Figure 2.8). The ketone could then hydrogen bond to the thiourea and the self-assembled species would catalyse the reaction.
Scheme 2.23 Synthesis of thiourea from 2-hydrazinylpyridine and 3,5-bis(trifluoromethyl)phenyl isothiocyanate

A solid state structure was obtained of the thiourea 77 from crystals obtained from slow evaporation of a solution in acetonitrile (Figure 2.9). The structural refinement obtained is not of the same quality as the previous X-ray structure (Figure 2.4). The structure contained two molecules hydrogen bonded to each other through several contacts in a twisted conformation. The hydrogen bonds between the pyridyl nitrogen and thiourea are good with donor acceptor distances of N(4)...N(8) 2.981(12) Å and N(5)...N(1) 3.007(12) Å. There is also a hydrogen bond between the hydrazines of N(6)...N(3) 3.110(12) Å. Previously reported [24] N-pyridyl thioureas synthesised by other research groups form intramolecular hydrogen bonds where the N-pyridine atom hydrogen bond to the thiourea in the solid state, as opposed to 77 where the N-pyridyl atom forms intermolecular hydrogen bonds to the thiourea proton. Unfortunately attempts to co-crystallise thiourea 77 with a phosphoric acid were unsuccessful.
Crystals grown by slow evaporation of solution in acetonitrile. Black denotes carbon, pink fluorine, blue nitrogen and yellow sulfur. Selected bond lengths $C(1)=S(1)$ 1.698(10) Å, $C(2)=S(2)$ 1.704 (11) Å, $N(2)-N(3)$ 1.397(11) Å $N(6)-N(7)$ 1.433(11) Å Hydrogen bond donor-acceptor distances $N(4)...N(8)$ 2.981(12) Å, $N(5)...N(1)$ 3.007(12) Å, $N(6)...N(3)$ 3.110(12) Å

A variety of chiral acids were used in conjunction with the achiral thiourea (Scheme 2.24, Table 2.6). ($S$)-Mandelic acid (Table 2.6, Entry 3), ($S$)-camphanic acid (Entry 4), ($S$)-alanine (Entry 6) and ($S$)-valine (Entry 7) are all commercially available. The phosphoric acid 74 was prepared previously (Section 2.7) and 78 was supplied by Chirotech. All the acid additives gave good conversion but this is comparable to the background reaction and no enantioselectivity was obtained.
Table 2.6 Conversion and enantioselectivity for acid additives

<table>
<thead>
<tr>
<th>Acid</th>
<th>Conversion to product 3 hrs (%)(^a)</th>
<th>e.e. (%)(^b)</th>
<th>Conversion to product 16 hrs (%)(^a)</th>
<th>e.e. (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 None(^c)</td>
<td>13</td>
<td>-</td>
<td>90</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>0</td>
<td>91</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>-</td>
<td>87</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
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<td>0</td>
</tr>
<tr>
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<td>0</td>
<td>92</td>
<td>0</td>
</tr>
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<td>80</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>15</td>
<td>0</td>
<td>&gt;99</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2.6 Conversion and enantioselectivity for acid additives

\(^a\) Conversion determined by integration of NMR spectra  
\(^b\) Selectivity determined by HPLC with AS-H column  
\(^c\) Thiourea 77 only

Out of curiosity, we also investigated if this self-assembled catalyst could promote the Mannich reaction. This Mannich-type reaction has successfully been catalysed by thioureas\(^{[14a]}\) and so the use of the acid and thiourea was determined (Scheme 2.27, Table 2.7) in this reaction. The precursors are easily synthesised using literature methods (Scheme 2.25 and Scheme 2.26).\(^{[14a]}\)
Scheme 2.25 Synthesis of 1-(tert-butyldimethylsiloxy)-1-methoxyethylene

Scheme 2.26 Synthesis of benzaldehyde N-(t-butoxycarbonylimine)

Scheme 2.27 Mannich-type reaction catalysed by achiral thiourea and acid
Table 2.7 Acids used as additives in the Mannich-type reaction

\[a\] determined by \(^1\text{H} \text{NMR spectroscopy} \ [b] \text{Enantioselectivity measured using HPLC-with AD-H column} \ [c] \text{Thiourea only}

The enantioselectivity and conversions obtained were poor, and in order to determine whether this was due to poor binding of the thiourea to the chiral acid a \(^1\text{H} \text{NMR spectroscopy binding study was attempted. The } K_{\text{ass}} \text{ of two components in a solution can be calculated from the shift of a } ^1\text{H} \text{NMR resonance on gradual dilution of a solution of both of them to measured concentrations.}^{[23]}

A solution of thiourea 77 in deuterated chloroform gradually coagulates to form a gel, and so solubility studies were conducted to determine if another deuterated
solvent could be used. Acetonitrile fully dissolves the thiourea \textit{77}; however when phosphoric acid \textit{74} was added to the solution a solution of the thiourea in deuterated acetonitrile at 0.05 M the mixture again coagulated on standing. This may indicate the two species are forming a salt which becomes more insoluble in solution. The \( K_{\text{ass}} \) in acetonitrile of the thiourea in solution was calculated to be 13 through NMR spectroscopy, which indicates the thiourea is associating with itself even in this fairly polar solvent. This may preclude the use of this thiourea \textit{77} in self-assembled catalysis although studies have been conducted into its use in other organocatalytic reactions.

\textbf{2.8. Conclusions and Future Work}

The ene reaction between ethyl trifluoropyruvate and \( \alpha \)-methyl styrene has been found to be accelerated through microwave heating. Catalysis by thioureas is another method of catalysing this reaction and this is the first example of organocatalysis of the carbonyl-ene reaction. These ene reactions can be catalysed in low enantioselectivity with up to 33\% e.e. achieved using an enantiopure thiourea catalyst with a chiral BINAM backbone.

The novel chiral phosphoric acid \textit{76} has been synthesised and examined as a promoter in the carbonyl-ene reaction. Before our studies had the chance to move on to more acidic systems, the group of Rueping published an excellent demonstration that more acidic \( N \)-triflylphosphinamides were exceptional catalysts for these reactions (\textbf{Scheme 2.28}).\textsuperscript{[22]} Multicomponent catalysis was also examined, although the no enantioselectivity was observed.
There are several avenues of future work that could be pursued on the basis of this study. The ene reaction can be accelerated by microwave heating in dichloromethane. This reaction was not examined further but could potentially be optimised as a method of producing racemic ene products. It is possible that by using other solvents with dielectric constants more suited to microwave heating higher temperatures could be achieved and thus the reaction could be accelerated further. A new thiourea containing a hydrazino-pyridine hydrogen bonding tag had been synthesised and fully characterised. A conceptually new approach where this achiral thiourea was combined with chiral acids was investigated for enantioselective catalysis. Poor results were obtained and with hindsight, the observation of the solubility suggests that perhaps more soluble components would need to be designed. However, it should also be considered that part of the appeal of this approach is to combine readily available components and this could be lost if other systems were designed.

\(N\)-triflylphosphorylamides can be more acidic than the corresponding phosphoric acids\(^{[25]}\) and BINOL based \(N\)-triflylphosphorylamides are the principle catalysts of this type which have been investigated. \(N\)-triflylphosphorylamides can be synthesised from a chiral alcohol through reaction with \(\text{OPCl}_3\) and then addition of the amine (Scheme 2.29). By using a more readily available starting chiral diol a more effective and potentially cheaper \(N\)-triflylphosphorylamine catalyst could be developed. Many chiral diol precursors could also be synthesised from alkenes through asymmetric Sharpless dihydroxylation (Scheme 2.31).\(^{[26]}\) The main
challenge of such a system would be having enough steric bulk around the phosphoric moiety to transfer the chirality of the system well. A chiral alcohol with bulky groups close to the alcohol centre could be synthesised using this method. If PCl₃ is used instead of POCl₃ the resulting aminophosphites could potentially be useful chiral monodentate ligands (Scheme 2.30)

![Scheme 2.29 Potential synthetic route to chiral N-triflylphosphorylamides](image_url)

![Scheme 2.30 Potential synthetic route to chiral N-triflylphosphorylamines](image_url)

![Scheme 2.31 Sharpless asymmetric dihydroxylation of alkenes](image_url)

These new acidic reagents could also be used as complementary catalysts in multicomponent thiourea catalysed reactions. Another possibility is that amino acids such as proline could be used in conjunction with thiourea 77 in asymmetric catalysis. I did undertake some preliminary investigations in this area which are not included here, since meaningful data was precluded. These were limited by the
solubility of these zwitterionic amino acids in all but more polar solvents such as DMSO. A combination of amino acid amides and the thiourea 77 would be more soluble in less polar solvents such as dichloromethane and therefore more likely to form a hydrogen bonding pair for use in enamine catalysis.

![Potential hydrogen bonding pair of a proline based amide and thiourea for use in enamine catalysis](image)

**Figure 2.10** Potential hydrogen bonding pair of a proline based amide and thiourea for use in enamine catalysis
References for Chapter 2


Chapter 3

Lewis Acid Catalysis in Fluorination
3. **LEWIS ACID CATALYSIS IN FLUORINATION**

### 3.1. Fluorination of Organic Compounds

There are several methods for the introduction of fluorine into organic compounds, the most common of which are by use of free radicals, nucleophilic fluorination agents or electrophilic fluorination.\(^1\) Elemental fluorine is toxic and difficult to store, and hence is not ideal for use as a direct fluorinating agent, but it is also very reactive and can be used as a source of fluorine radicals. Radical reactions are difficult to control selectively, and since the formation of C-F bonds can be particularly exothermic, this method is only useful over other methods of fluorination in a handful of cases.\(^2\) Safer synthetic methods have been developed for the introduction of fluorine into organic compounds using fluorinating agents.

Nucleophilic fluorination can use inorganic species such as potassium fluoride, silver fluoride, antimony fluoride and cobalt fluoride.\(^2\) Fluoride is not a good nucleophile because of fluorine’s electronegativity, and these reagents are often used to fluorinate carbon atoms substituted with other functional groups such as hydroxy, chlorine or iodine groups. As a consequence this method is not as widely applicable as electrophilic fluorination for asymmetric catalysis since the chiral centre will have been formed prior to fluorination, adding an extra step to the synthesis. HF solution can also be used as a fluoride source but anhydrous HF is corrosive and very toxic.
due to fluorine’s affinity for calcium; once absorbed through the skin it proceeds to dissolve bones.\textsuperscript{[3]} Less corrosive reagents which deliver HF such as Et$_3$N·3HF and HF$_x$·Pyr are safer to use.\textsuperscript{[2]}

Electrophilic fluorination requires a very electronegative species bonded to fluorine in order to make it an “F$^+$” equivalent. Reagents such as FClO$_3$ and hypofluorites can be used but these have problems with oxidation and the necessity of generating them \textit{in situ} respectively.\textsuperscript{[4]} Recent interest in electrophilic fluorination can be attributed to the development of the relatively stable R$_2$N-F and R$_3$N$^+$-F reagents which are commercially available and easily prepared. They are also more readily soluble in common organic solvents. 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2] octane bis(tetrafluoroborate) (Selectfluor)\textsuperscript{[5]} and N-fluorobenzene sulfonimide (NFSI)\textsuperscript{[6]} are both widely used examples of fluorinating agents (\textbf{Figure 3.1}). The key to these reagents is the ease with which fluorine can be abstracted, but not so readily that they decompose easily, allowing these reagents to be stored for long periods of time. NFSI can be prepared from NH(SO$_2$Ph)$_2$ and F$_2$, and Selectfluor from 1,4-diazabicyclo[2.2.2] octane (DABCO), F$_2$ and a metal BF$_4^-$ salt in the presence of dichloromethane.\textsuperscript{[4]} The two reagents are dissimilar in that one is a salt and the other is a neutral compound. Selectfluor is generally more reactive because the loss of the fluorine reduces one of the quaternary ammonium ions. These reagents can be combined with Lewis acid catalysts to fluorinate organic compounds, with the enantioselectivity of these systems being dependant on the properties of the Lewis acid and the chiral ligands that bind to it.

\textbf{Figure 3.1} Electrophilic fluorinating reagents
3.2. Asymmetric Fluorination using Lewis Acid Catalysts

Fluorine can be introduced to a tertiary carbon centre using asymmetric electrophilic fluorination to form a new chiral compound with a quaternary carbon centre. Chiral fluorine compounds can be particularly useful for drug manufacture since fluorine can be used as a hydrogen isostere and the stability of the C-F bond means that they can improve properties of the drug compound such as the rate at which it is metabolised. In 2007 there were 44 fluorinated drugs in phase III trials and 151 in phase II drug trials,\(^7\) and 30% of leading blockbuster drugs contain fluorine.\(^8\)

Asymmetric electrophilic fluorination has been developed using Lewis acid catalysts. Scheme 3.1 illustrates the mode of action of these catalysts. The Lewis acid metal (M) coordinates to the ketone and another functional group such as an ester. The metal withdraws electron density from the ketone and allows the fluorinating agent (R"F, an F\(^+\) equivalent) to form a bond to the \(\alpha\)-carbon. Some systems use a base to promote the reaction. Labile ligands coordinated to the complex allow the ketoester to coordinate in their place.

\[
\begin{align*}
\text{R}^+\text{L}^+\text{M}^+\text{nX}^- & \quad \rightarrow \quad \text{R}^\alpha\text{F} \quad \text{OR}'
\end{align*}
\]

Scheme 3.1 Simplified mechanism of metal catalysed electrophilic fluorination via an enolate type intermediate

Togni and co-workers developed one of the first catalytic systems using this type of reagent to fluorinate a ketone.\(^9\) It was observed by other workers that fluorination of the ketone occurs at the \(\beta\) position with certain N-F reagents at room
temperature,[10] and it was therefore hypothesised that addition of a Lewis acid would catalyse the reaction further. In a screen of titanium, aluminium, boron, zinc, silicon, copper and ytterbium based compounds it was found that TiCl₄, AlCl₃ and [CpTiCl₃] were the most effective catalysts, with reactions giving high yields in under a day.[9]

In a further screen it was found that [TiCl₂(TADDOL)L₂] was particularly effective as a chiral catalyst, where the L ligands are labile permitting the coordination of the ketone. In the octahedral complex [TiCl₂(TADDOL)(NCMe)₂] 79 (Scheme 3.2) the two acetonitrile ligands are labile and easily displaced by the ketone. Computational mechanistic studies by the Togni et al. imply that the process occurs via a single electron transfer mechanism but not conclusively.[11] The fluorine is added to the titanium complexed enolate substrate from a transient [N-F⁻] radical.

![Scheme 3.2 Asymmetric fluorination of ketones using titanium TADDOL system](image)

One disadvantage of this catalyst is that in less active substrates chlorination can also occur. The chlorine atom in this reaction is obtained from the catalyst and so alternatives have been developed by Togni[12] and others.[13] An example using ruthenium catalyst 80 is shown (Scheme 3.3).[12] The ruthenium system also gives high enantioselectivity for a variety of substrates, though it can also give the enol as a side product, which reacts to with the NFSI to give a racemic fluorinated product. The extent of the formation of the enol is dependent on the solvent used. Further screening of this chiral catalyst can optimise the selectivity for specific substrates.
Chiral bisoxazoline copper complexes have also been found to give moderate enantioselectivity in asymmetric fluorination reactions (Scheme 3.4). Further catalytic fluorination reactions have been reviewed elsewhere.\textsuperscript{[4, 14]}

### 3.3. Palladium as a Lewis acid and its’ Use in Asymmetric Fluorination

Palladium is known for its ability to cross couple various organic substituents in transmetallation reactions, including alkynes with vinyl or aryl halides in a Sonagashira reaction and organoboronic acids to halides in a Suzuki coupling. There
are comparatively few examples of palladium acting as a Lewis acid, and asymmetric variants are rarer.\textsuperscript{[15]} Palladium is relatively electron rich and as a result is a poorer Lewis acid than other metals such as aluminium and titanium. There are however some reasons for using it over other metals. The ene reaction is one example in which palladium has been successfully used as a Lewis acid (Scheme 2.5).

One of the first examples of asymmetric fluorination using palladium based catalytic systems\textsuperscript{[13a]} uses BINAP to give an 88\% e.e.(Scheme 3.5). The system was further optimised for this reaction with tert-butoxycarbonyl lactones and lactams in ethanol to give up to 99\% e.e.\textsuperscript{[13h]} The bridged palladium catalyst 81 can also be used to catalyse the fluorination of oxindole in high enantioselectivity (Scheme 3.6).

![Scheme 3.5](image)

\textbf{Scheme 3.5} $\text{[Pd((R)-BINAP)(OH}_2)_2\text{][OTf]}_2$ catalysed fluorination of beta-ketosesters

![Scheme 3.6](image)

\textbf{Scheme 3.6} Fluorination of oxindole

The bite angle of the ligand used can be varied such that the coordination sphere of the complex favours a particular reaction. For bidentate ligands the bite
angle is often used as a descriptor, and is taken from the angle of the P-M-P bonds. The bite angle can be measured crystallographically or predicted using computational methods in which case it is called the natural bite angle.\textsuperscript{[16]} The bite angle can be varied such that for small ligands such as diphenylphosphinoethane the angle is 78°\textsuperscript{[17]} whereas the larger diphenylphosphinobutane has a bite angle of 99°\textsuperscript{[17]}. Four coordinate palladium complexes are usually square planar, and so chiral bidentate ligands can be used to bind to the palladium so only two labile ligands are required to stabilise the metal complex used for catalysis, which can then be displaced by the substrate. In fluorination this property is particularly useful since as there are many chiral bidentate ligands that can be screened and also the problem of chlorination seen in reactions with titanium complexes can potentially be avoided. Four coordinate nickel complexes have also been shown to catalyse asymmetric fluorinations.\textsuperscript{[13i]} In Lewis acid catalysis the metal acts as a Lewis acid and the chiral ligand and the substrates acts as Lewis bases.

3.4. Aims and Objectives

There has as yet been no comparison of the effect of changing the ligands in the asymmetric fluorination reaction. In other metal catalysed reactions such as the rhodium catalysed hydroformylation of styrene\textsuperscript{[17-18]} and the Lewis acid catalysed Diels-Alder reaction\textsuperscript{[19]} electronic effects and bite angles of the ligand have been shown to have a significant effect on the activity of the catalyst.

It was decided to see how varying the ligand on the palladium catalyst changes the reactivity of the system and to either use a known ligand complex which has not been used in the reaction before, or synthesise a new one which could give high activity and also enantiomeric excess.

3.5. Fluorination of ketoesters

The ketones required for the fluorination reaction are not commercially available but are readily accessible by the aldol reaction between benzaldehyde and
the corresponding alkyl propionate (Scheme 3.7). The substrate could also be easily changed by using two different starting materials, *i.e.* another aldehyde or ester, in order to study the limits of the catalysts developed. Oxidising the aldol product using Jones reagent gave a significantly higher yield than using Dess-Martin periodane and so this method was used.

![Scheme 3.7 Synthesis of ketone substrate](image)

Having synthesised the ketone, the palladium complexes to be used in catalytic tests were then prepared. A method of producing dichloropalladium salts of the ligands from sodium tetrachloropalladate in acetonitrile quickly and in high conversion using microwave heating was utilised (Scheme 3.8, Table 3.1, Table 3.2). The dichloropalladium complexes of dppf and dippf (Figure 3.2) had previously been synthesised within our group. The ligands chosen were selected because of their range of bite angles and steric properties.

It is thought microwave heating is more efficient in this case since the solvent reaches temperature quickly and the reaction is consequently faster. It also has the advantage of using the relatively cheap palladium salt Na$_2$PdCl$_4$. The product can be purified by separation between dichloromethane and water to extract sodium chloride and any excess ligand can be removed by filtration through a small plug of alumina. The dichloropalladium complexes are stable enough to be handled briefly in solution in air.

![Scheme 3.8 Synthesis of palladium dichloride complexes and their transformation into palladium cations](image)
Lewis Acid Catalysis in Fluorination

Figure 3.2 Structures of dppf and dippf dichloropalladium complexes

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Structure</th>
<th>Yield (%) [PdLCl₂]</th>
</tr>
</thead>
<tbody>
<tr>
<td>84</td>
<td>dppe</td>
<td>Ph₂P</td>
</tr>
<tr>
<td>85</td>
<td>dppp</td>
<td>PPh₂P</td>
</tr>
<tr>
<td>86</td>
<td>dppb</td>
<td>PPh₂P</td>
</tr>
<tr>
<td>87</td>
<td>dcpe</td>
<td>(Cy)₂P</td>
</tr>
<tr>
<td>88</td>
<td>dfppe</td>
<td>(FC₆H₄)₂P</td>
</tr>
<tr>
<td>89</td>
<td>(R, R)-Ph-BPE</td>
<td>Ph Ph Ph</td>
</tr>
<tr>
<td>90</td>
<td>(S, S)-Me-BPE</td>
<td>quant.</td>
</tr>
<tr>
<td>92</td>
<td>(S)-BINAP</td>
<td>PPh₂ PPh₂</td>
</tr>
</tbody>
</table>

Table 3.1 Synthesised palladium complexes and isolated yields
The formation of the cationic palladium salt is triggered by the precipitation of silver chloride after treatment of the dichloride with two equivalents silver triflate (Scheme 3.9, Table 3.3). Monitoring by $^{31}$P NMR spectroscopy shows clearly the formation of a new complex with a new phosphorus peak formed downfield from the starting material. AgBF$_4$ was initially used to precipitate the chloride, however AgOTf was found to produce the cationic salt more efficiently.

\[
\text{Scheme 3.9 Synthesis of palladium cation salts}
\]
Table 3.3 Yield for synthesis of $[{\text{PdL(OH}_2\text{)}}(\text{NCMe})]\text{[OTf]}_2$

<table>
<thead>
<tr>
<th>Complex</th>
<th>Ligand</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>96</td>
<td>dppe</td>
<td>73</td>
</tr>
<tr>
<td>97</td>
<td>dppp</td>
<td>78</td>
</tr>
<tr>
<td>98</td>
<td>dppb</td>
<td>49</td>
</tr>
<tr>
<td>99</td>
<td>dcpe</td>
<td>72</td>
</tr>
<tr>
<td>100</td>
<td>dfppe</td>
<td>67</td>
</tr>
<tr>
<td>101</td>
<td>$(R, R)$-Ph-BPE</td>
<td>79</td>
</tr>
<tr>
<td>102</td>
<td>$(S, S)$-Me-BPE</td>
<td>82</td>
</tr>
<tr>
<td>103</td>
<td>dppf</td>
<td>59</td>
</tr>
<tr>
<td>104</td>
<td>dippf</td>
<td>53</td>
</tr>
<tr>
<td>105</td>
<td>$(S)$-BINAP</td>
<td>71</td>
</tr>
<tr>
<td>106</td>
<td>$(R)$-phanephos</td>
<td>55</td>
</tr>
<tr>
<td>107</td>
<td>$(S)$-xylylphanephos</td>
<td>69</td>
</tr>
<tr>
<td>108</td>
<td></td>
<td>54</td>
</tr>
</tbody>
</table>

Having synthesised these complexes it was decided to investigate their use in the fluorination reaction. NFSI was used as fluorinating agent since this has previously been shown to be effective in palladium catalysed fluorinations by other research groups.$^{[13d]}$

\[
\begin{align*}
\text{Ph} & \quad \text{NH} & \quad \text{HN} & \quad \text{Ph} \\
\text{O} & \quad \text{O} & \quad \text{O} & \quad \text{Bu}
\end{align*}
\]

5 mol\% $[{\text{PdL(OH}_2\text{)}}(\text{NCMe})]\text{[OTf]}_2$

\[
\begin{align*}
&\text{1.5 eq. NFSI} \\
&\text{EtOH, rt} \\
&\rightarrow
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{F} & \quad \text{O} & \quad \text{O} & \quad \text{Bu}
\end{align*}
\]

Scheme 3.10 Palladium complex catalysed fluorination
Table 3.4 Conversion to product 109 (%)\textsuperscript{[a]}

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Conversion to product 109 (%)\textsuperscript{[a]}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>23 hrs</td>
</tr>
<tr>
<td>dppe</td>
<td>20</td>
</tr>
<tr>
<td>dppp</td>
<td>24</td>
</tr>
<tr>
<td>dppb</td>
<td>68</td>
</tr>
<tr>
<td>dcpe</td>
<td>18</td>
</tr>
<tr>
<td>dfppe</td>
<td>15</td>
</tr>
<tr>
<td>(S,S)-Me-BPE</td>
<td>&lt;5</td>
</tr>
<tr>
<td>(R,R)-Ph-BPE</td>
<td>&lt;5</td>
</tr>
<tr>
<td>dppf</td>
<td>38</td>
</tr>
<tr>
<td>dippf</td>
<td>&lt;5</td>
</tr>
<tr>
<td>(S)-BINAP</td>
<td>48</td>
</tr>
<tr>
<td>(R)-phanephos</td>
<td>&lt;5</td>
</tr>
<tr>
<td>(S)-xylphanephos</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]}Conversion measured by integration of \textsuperscript{19}F NMR
\textsuperscript{[b]}Enantioselectivity measured using HPLC with an AD-H column eluting with 200:1 hexanes:iPrOH 0.4ml/min

The results would seem to indicate that the catalyst activity decreases between 23 and 48 hours since conversions did not increased significantly, possibly indicating catalyst decomposition. From these results it also appears that ligands which form a four atom chain ligand such as dppb and BINAP give higher conversion. The higher rate of reaction obtained by using these ligands will be related to how the ligands stabilises the transition state. These fluorination reactions are thought to proceed via a palladium enolate complex (Figure 3.3). The reaction is likely to proceed via coordination of the ketone, then proton elimination to form the enolate, and fluorination of the carbon atom by electrophilic attack before elimination. As yet, no mechanistic studies have been carried out on this reaction using palladium but it is likely that the coordination sphere of these phosphines stabilise the transition state of the rate determining step.
From the knowledge gained from these experiments it was decided to investigate two approaches to the development of a new cationic palladium containing asymmetric fluorination catalyst. Firstly, BINAP is clearly a useful ligand for this reaction showing good conversion and it was used as a control system when developing the conditions. Secondly, ligands with the bite angle close to BINAP appear to favour fluorination, and thus there is scope for the development of new ligands with similar bite angles which may give better results for fluorination reactions.

3.6. Identifying conditions and substrates

In order to investigate the reaction a readily accessible substrate was required. In the literature phenylcyanoacetic acid ethyl ester 110 shown in Scheme 3.11 is commercially available and has been found to fluorinate readily.\[21\] A palladium complex with racemic BINAP was then used to catalyse the fluorination reaction with the cyano substrate. It was thought that since the cyano group is more electron-withdrawing it may give a faster rate of reaction, since the hydrogen atom removed in the course of the fluorination reaction would be more acidic. However, the reaction took three days to give 59% conversion in THF (Scheme 3.11) and 54% in ethanol. A similar ketone with another carbonyl, 3-cyano-3-phenylpyruvic acid ethyl ester showed no reaction in fluorination.
3.11 Catalysed fluorination of phenylcyanoacetic acid ethyl ester

Scheme 3.11 Catalysed fluorination of phenylcyanoacetic acid ethyl ester

The enantioselectivity was not determined as a method was not found to resolve the stereoisomers readily. Similar problems were encountered when the keto-ester 83 was synthesised with an ethyl group in the place of the t-butyl group. The fluorinated compounds run off the HPLC system even when using low polarity mixes such as 0.1:99.9 iPrOH: hexanes and so separation by HPLC becomes difficult. The original keto-ester 83 was therefore selected as the model substrate for use in further reactions.

3.7. Chiral Counterions in the Fluorination Reaction

As dppb gave significantly higher conversion to the product, and is not a particularly sterically bulky ligand it was decided to examine whether a chiral counterion could be used with this complex. Chiral counterions, synthesised from phosphoric acids such as 111, have been found by Hamilton et al. to catalyse asymmetric hydroalkoxylation with an achiral ligand and gold catalysts. In the hydroalkoxylation reaction they have been found to give higher enantioselectivity than BINAP or SEGPHOS complexes of gold (Scheme 3.12).
Synthesis of the chiral counterions was attempted *in situ* from phosphoric acids 74 and 76 reacted with AgCO$_3$ to give the silver salts and then stirred with [Pd(dppb)Cl$_2$] before filtration and addition to a fluorination reaction of 83. However, this reaction but found to give no product after several attempts (Scheme 3.13). The silver salts were not fully characterised due to their hygroscopic nature making them more convenient to use *in situ*.

Scheme 3.12 Gold catalysed hydroalkoxylation
3.8. Synthesis of a New Chiral Ligand

As the use of a chiral anion 76 with [Pd(dppb)Cl$_2$] was found to be catalytically inactive, it was decided to investigate the effect of a chiral ligand with a similar bite angle to dppb but a different structure. The cationic palladium complex of (4S, 5S)-\((+)-4,5\text{-bis(diphenylphosphinomethyl)}\)-2,2\text{-dimethyl\text{-1,3-dioxolane}} ((S,S)-DIOP) would also be synthesised since this privileged ligand, with a bite angle of 96º,\textsuperscript{[23]} has not been tested in asymmetric fluorinations.

\((R,R\)-9,10\text{-dihydro\text{-9,10-ethanoanthracene\text{-11,12-diamine}} has previously been synthesised within our group according to literature methods,\textsuperscript{[24]} which also isolate the (S,S) enantiomer of this diamine. In the previously unknown phosphinous amide of this diamine, the amines are substituted with a diphenylphosphine group to give a chiral ligand. It was thought this would have a similar bite angle to BINAP and dppb, but it may give better activity since the ligand has a significantly different steric and electronic structure. Addition of \textit{n}\text{-butyl lithium solution in hexanes to the amine in ether and then chlorodiphenylphosphine gave an unknown side product at +101 ppm as well as the phosphinous amide. A more successful method used triethylamine as a base added to a solution of the amine in ether and then chlorodiphenylphosphine before stirring for several hours (Scheme 3.14). A slight excess of the
chlorodiphenylphosphine and triethylamine is required for the reaction to reach completion. The isolated ligand was contaminated with a trace amount of triethylamine hydrochloride and phosphine oxide which could not be removed by recrystallisation and the ligand is unstable on silica and alumina. Use of methyl pyrrolidine in the place of triethylamine was attempted since the hydrochloride is less soluble than that of triethylamine, however use of this meant the reaction did not reach completion. The ligand is air and water sensitive and so the product was used in situ in an impure form in further syntheses with the palladium complexes and boranes derived purified and fully characterised.

\[
PPh_2Cl + Et_2O, \text{rt, 40 hrs} \rightarrow \text{Ph}_2PHN(NHPPh}_2\text{Cl}
\]

92% yield
95% purity

Scheme 3.14 Synthesis of chiral phosphinous amide

The phosphinous amide was used to synthesise the square planar dichloropalladium complex in the microwave (Scheme 3.15) which was easily purified by filtration through alumina. Crystals of the complex were obtained by vapour diffusion of hexane into a solution of the complex in acetone, and analysed by single crystal X-ray diffraction (Figure 3.4). The complex looked promising for catalysis in the solid state since the phenyl groups of the ligand block the face of either side of the palladium, and the ligand has a crystallographic bite angle of 97.6°.

\[
\text{Na}_2\text{PdCl}_4 + \text{MeCN, 120 °C microwave, 5 mins} \rightarrow \text{Cl}_2\text{PdCl}_2\text{Ph}_2PHN(NHPPh}_2\text{Cl}
\]

74% yield

Scheme 3.15 Synthesis of phosphinous amide palladium complex
Figure 3.4 Crystal structure for palladium complex 113
Black denotes carbon, pale grey palladium, orange phosphorus, blue nitrogen and green chlorine. A molecule of water and acetone have been omitted for clarity. Selected properties Pd-Cl bonds 2.3611(11) and 2.3722(11) Å Pd-P bonds 2.2628(11) and 2.2897(10) Å P-N bonds 1.675(3) and 1.667(3) Å P-Pd-P angle 97.58(4)° P-N-C angle 123.6(2) and 125.4(3)°

The dichloropalladium complex with (S,S)-DIOP 114 was synthesised in the microwave using the same method to give an orange solid in 96% yield (Scheme 3.16).

Scheme 3.16 Synthesis of [Pd(S,S-DIOP)Cl]₂

Both dichloropalladium complexes were treated with silver triflate to synthesise the cationic palladium salt, [Pd(L)(NCMe)(OH₂)](OTf)₂. The reaction of
Lewis Acid Catalysis in Fluorination

[Pd((S,S)-DIOP)Cl₂] with AgOTf gave only the cationic salt, [Pd((S,S)-DIOP)(OH₂)(NCMe)](OTf)₂. This salt gave 36% conversion and 9% e.e in the fluorination reaction (Scheme 3.17).

\[
\begin{align*}
\text{Scheme 3.17 } & [\text{Pd}(\text{S,S})\text{-DIOP}]^{2+} \text{ catalysed fluorination of ketone} \\
\end{align*}
\]

After repeated attempts the reaction of the phosphinous amide complex 113 with AgOTf did not give the cationic palladium complex. \(\text{\textsuperscript{31}}\text{P} \text{NMR spectroscopy} \) of the reaction mixture shows three resonances, the starting material and two peaks at +88 ppm and +16 ppm which are inconsistent with the palladium cationic complex. Adding excess AgOTf did not change the ratio of \(\text{\textsuperscript{31}}\text{P}\) NMR spectroscopy resonances. Addition of AgBF₄ to [Pd(112)Cl₂] also did not yield the cationic salt.

The reaction mixture was used as a crude mixture for the attempted fluorination of ketone 83 but gave no conversion. [Pd(112)Cl₂] was then used pre-stirred with AgOTf in ethanol but gave no reaction. [Pd(112)Cl₂] was also used pre-stirred with AgOTf in dichloromethane with filtration, and then added to the reaction in ethanol but this similarly gave poor results. It can be concluded that [Pd(112)Cl₂] is not a catalyst precursor for the reaction because it does not form the cationic palladium salt.

3.9. Conclusions and Future Work

Fluorination of ketones using palladium cationic salts was favoured by ligands with four atom chain backbones such as dppb and DIOP. The ideal ligand for palladium catalysed fluorination is a bulky ligand with a four carbon chain and a bite
angle of around 95° which is why BINAP has previously proven effective as an asymmetric catalyst in this reaction.

It has been determined that four atom chain ligands favour this reaction among those tested although it is not known why. Recent work by Mezzeti\cite{25} has looked at isolation of enolate and β-ketoesters of the ruthenium catalytic system shown in Scheme 3.3 and determining how addition of different reagents affects reaction rate. A similar study using palladium could help determine the mechanism for this reaction, and thus the factors which effect fluorination.

A chiral ligand was been synthesised which was previously unreported in the literature and so we were interested in the use of this in other reactions using other transition metals. Reactions using this chiral ligand are examined in Chapter 4. The cationic palladium complex of with this ligand was not formed and so this complex could not be used in fluorination. Since BINAP is an effective catalyst for this reaction, similar biaryl ligands would be expected to be fairly active. These should form the cationic palladium complex fairly readily since they are similar in structure to BINAP and should thus catalyse the reaction in a similar fashion.
References for Chapter 3


Chapter 4

Chiral Phosphinous Amides in Rh and Cu Catalysed Hydrogenations
4. CHIRAL PHOSPHININOUS AMIDE LIGANDS IN RHODIUM AND COPPER CATALYSED HYDROGENATIONS

4.1. Phosphinous Amides and their Uses

Phosphinous amides are substances containing $R_2P-NR_2$ bond where $R$ are carbon or hydrogen atoms.$^{[1]}$ In the previous section ligand $\text{112}$ was successfully synthesised. The cationic palladium salt of $\text{112}$ could not be formed and thus it was not successfully used in fluorination. $\text{112}$ is interesting because of its crystallographic bite angle of 97.6°. This bite angle is close to that of BINAP, a privileged ligand$^{[2]}$ which has been found to be successful in many reactions such as hydrogenation using ruthenium$^{[3]}$ and Lewis acid catalysed reactions such as the ene reaction.$^{[4]}$ The phosphinous amide $\text{112}$ could potentially be used in similar reactions and because of its different steric and electronic properties may be more active than existing catalysts or useful for different substrates.

Phosphinous amides have already been used as ligands in asymmetric hydrogenation. $\text{(S,S)-1,2-bis(diphenylphosphinamino)cyclohexane (}(S,S)\text{-dppach, 115)}$ has been found to give moderate enantioselectivity in the hydrogenation of $\alpha$-
acetoaminocinnamic acid (Scheme 4.1\textsuperscript{[5]} and hydrogenation of the methyl ester of this alkene has also been examined (Scheme 4.2).\textsuperscript{[6]} This ligand has been widely studied by several research groups for use in hydrogenation catalysis of alkenes,\textsuperscript{[6-7]} and there is one example of the hydrogenation of imines using (\textit{R}, \textit{R})-dppach and ruthenium complexes.\textsuperscript{[8]}

(S,S)-dppach is not commercially available however (\textit{R})-2,2-bis (dicyclohexylphosphinoamino)-1,1-binaphthyl ((\textit{R})-BDPAB, 118) is and has been found be a good ligand for hydrogenation of aryl enamides (Scheme 4.3).\textsuperscript{[9]}
4.2. Aims and Objectives

From the above examples using phosphinous amides it can be concluded that these are useful ligands for hydrogenation. The phosphinous amide 112 was synthesised as an enantiopure ligands in the previous chapter however initial attempts to isolate the metal complex of this ligand as both rhodium and ruthenium metal complexes for hydrogenation were unsuccessful.

Since ligand 115 ((S,S)-dppach) has previously been used in the hydrogenation of alkenes we were interested in using the borane protected phosphine in situ, and also the comparison between this ligand and the novel ligand 112. Rhodium is not the only metal which can be used in asymmetric hydrogenation, and we were also interested in the use of chiral phosphinous amides in other catalytic hydrogenations such as with ruthenium or copper.
4.3. Protection of the Novel Chiral Ligand with Borane

The phosphinous amide was resynthesised using (11\textit{R},12\textit{R})-9,10-dihydro-9,10-ethanoanthracene-11,12-diamine, and protected with borane to give a stable, more readily purified precursor 119 which was fully characterised and could be stored over longer periods (Scheme 4.4). The borane is formed as the main component of the reaction and can be purified by dissolving in toluene and filtering through alumina. The protection should be carried out on phosphinous amide of high purity since one of the decomposition products of the phosphine when protected with borane cannot be easily removed from the product. A pure chiral borane can be used as a ligand by cleaving the borane with DABCO \textit{in situ} in the presence of a metal salt.\[10\] There are several known examples of this to synthesise metal phosphine complexes either directly or \textit{in situ} for catalysis.\[11\]

![Scheme 4.4 Synthesis of borane protected phosphinous amide](image)

The borane complex of the known cyclohexadiamine-based ligand 115 was also synthesised for comparison in asymmetric catalysis (Scheme 4.5). The protection of this phosphine appears to take significantly longer than the previous amide and when monitored by $^{31}$P NMR spectroscopy the reaction appears to proceed via a mixture of boranes. These boranes are present in solution until one major peak is seen in the spectra and the reaction reaches completion. If isolated earlier the intermediate boranes appear to decompose to give an unknown protected phosphine with a resonance at 1 ppm in the $^{31}$P NMR spectrum.
4.4. Rhodium Complex Catalysed Hydrogenation; Application of phosphinous amide diboranes as ligands

Having synthesised these boranes we were interested in their use in rhodium catalysed hydrogenation of alkenes. The reaction was then carried out in toluene or partially evaporated in vacuo and methanol added. Both gave high conversions but addition of methanol lowered the enantioselectivity (Scheme 4.6, Table 4.1). Use of [Rh(COD)]OTf as a precursor was also attempted in both iso-propanol, toluene and ethyl acetate but this gave no conversion.

Scheme 4.6 Rhodium catalysed hydrogenation of dimethyl itaconate using ligand 51
Addition of methanol to α-acetaminocinnamic acid leads to the formation of the methyl ester product (Scheme 4.7, Table 4.2). The presence of DABCO may lead to the formation of this side product through nucleophilic catalysis of the esterification of hydrogenated product in the presence of methanol. The reaction does not proceed without heating and it is thought this is because increases the amount of acid in solution. Heating was also required to hydrogenate the α-acetaminocinnamic methyl ester which also showed full conversion to product (Scheme 4.8).

**Table 4.1** Yield and enantioselectivity for rhodium catalysed hydrogenation of dimethyl itaconate using ligand 51

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Conversion to product (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>e.e. (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>&gt;99</td>
<td>69</td>
</tr>
<tr>
<td>MeOH/toluene</td>
<td>&gt;99</td>
<td>46</td>
</tr>
</tbody>
</table>

<sup>a</sup> determined by <sup>H</sup> NMR spectroscopy  
<sup>b</sup> Determined by HPLC using an OD-H column eluting with 2.98 iPrOH: hexanes 0.8 ml/min

**Scheme 4.7** Rhodium catalysed hydrogenation of α-acetaminocinnamic acid

**Table 4.2** Results for rhodium catalysed hydrogenation of α-acetaminocinnamic acid

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Conversion to 116&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Conversion to 122&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>&gt;99</td>
<td>-</td>
</tr>
<tr>
<td>MeOH/toluene</td>
<td>36</td>
<td>64</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by <sup>H</sup> NMR spectroscopy
Scheme 4.8 Rhodium catalysed hydrogenation of α-acetaminocinnamic methyl ester

The rhodium catalysts were then compared to the less bulky protected borane ligand 119 to determine if they gave higher enantioselectivity and conversion.

4.5. Comparison of Borane Protected Phosphinous Amides in Hydrogenation

The reactions were repeated with borane protected ligand 120 for comparison for all three alkenes examined above and the results from above are tabulated for comparison below. For dimethyl itaconate the conversion and enantioselectivity obtained from the catalyst derived from the new ligand 119 was higher than that for ligand 120 (Scheme 4.9, Table 4.3).

Scheme 4.9 Hydrogenation of dimethyl itaconate
<table>
<thead>
<tr>
<th>Ligand</th>
<th>Conversion to product 121 (%)</th>
<th>% e.e.[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Chemical structure]</td>
<td>72</td>
<td>51</td>
</tr>
<tr>
<td>![Chemical structure]</td>
<td>&gt;99</td>
<td>69</td>
</tr>
</tbody>
</table>

Table 4.3 Conversion and enantioselectivity for catalysed reaction of dimethylitaconate

[a]Enantioselectivity determined by HPLC using an OD-H column eluting with 2:98 iPrOH:hexanes 0.8 ml/min

For α-acetaminocinnamic acid the conversion obtained from the catalyst derived from ligand 119 was higher than that for ligand 120 but the enantioselectivity was not as high (Scheme 4.10, Table 4.4).

Scheme 4.10 Rhodium catalysed hydrogenation of α-acetaminocinnamic acid
Ligand | Conversion to product (%)\textsuperscript{[a]} | % e.e.\textsuperscript{[b]}
\hline
|  | 20 | 90 |
|  | >99 | 30 |

Table 4.4 Results for hydrogenation of α-acetaminocinnamic acid

\textsuperscript{[a]} Determined by \textsuperscript{1}H NMR spectroscopy \textsuperscript{[b]} Determined using HPLC using AD-H eluting with 10:90 iPrOH:hexanes 0.8 ml/min on methyl ester

For α-acetaminocinnamic methyl ester the conversion obtained from the catalysed derived from ligand 119 was higher than that for ligand 120 (Scheme 4.11, Table 4.5).

\textbf{Scheme 4.11 Rhodium catalysed hydrogenation of α-acetaminocinnamic methyl ester}
Table 4.5 Results for hydrogenation of α-acetaminocinnamic methyl ester

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Conversion to product (%)(^{[a]})</th>
<th>% e.e.(^{[b]})</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Ligand Diagram" /></td>
<td>50</td>
<td>93</td>
</tr>
<tr>
<td><img src="image" alt="Ligand Diagram" /></td>
<td>&gt;99</td>
<td>94</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Determined using \(^1\)H NMR spectroscopy \(^{[b]}\) Determined using HPLC using AD-H eluting with 10:90 iPrOH:hexanes 0.8 ml/min

Very good enantioselectivity that surpasses the e.e.’s obtained using (S)-BDPAB, a ligand that has been patented by Johnson Matthey for this purpose, were recorded. The conversions obtained using protected ligand \((R,R)\)-dppach 115 were not as high as those obtained using the unprotected ligand in the literature. It is possible that the DABCO may not be deprotecting the ligand efficiently and so the ligand is not as effective. However, it is also possible that the new ligands described here are more enantioselective and active. This study demonstrates that borane protected ligand 51 is effective in hydrogenation and we were interested in using this with other catalytic systems in hydrogenation. Since the formation of ruthenium complexes such as \([\text{Ru}(L)((R,R)\text{-DPEN})\text{Cl}]\) proved unsuccessful the use of this ligand in copper catalysed hydrogenation was examined next.

4.6 Copper catalysed hydrogenation

In homogeneous asymmetric hydrogenation the majority of highly selective catalysts are ruthenium, rhodium and iridium based. Copper catalysts can be used for hydrogenation in heterogeneous systems using supports such as Al\(_2\)O\(_3\) to hydrogenate alkenes.\(^{[12]}\) Reduction using copper in homogeneous systems has not been widely examined; however there are several examples in the chemical literature.\(^{[13]}\) Copper has some distinct advantages over other metal for use in catalysis. Firstly, copper
ores are widely available and so are therefore more considerably more affordable. Secondly, copper is less toxic than metals such as rhodium, ruthenium and iridium.

The mechanism of copper catalysed reductions is not known but can use silanes (such as Ph₂SiH₂),[13d, 14] hydrogen gas,[13a] or Hantzsch esters[13g] as reducing agents for the hydrogenation of ketones or alkenes. An early example is that shown (Scheme 4.12) where DIOP is used in conjunction with copper tert-butoxide in the presence of diphenylsilane to give the product in 20% e.e. Stryker and co-workers have developed a system using copper(I) chloride and using poly(methylhydrosiloxane) (PMHS) (Scheme 4.13).[13d] They discovered Stryker’s reagent, [(PPh₃)CuH]₆, which can be used in hydrogenation but is air sensitive.[15] [(PPh₃)CuH]₆ is synthesised from copper chloride and sodium tert-butoxide in the presence of triphenylphosphine and silanes, and it can be assumed similar species are formed in situ for the hydrogenation of aryl ketones.[16] Copper(II) carbene salts have also been found to be effective precursors for reduction of ketones in the presence of silanes.[17

![Scheme 4.12 Copper catalysed hydrogenation of acetophenone](image)
There are few examples of homogeneous copper catalysed hydrogenation using hydrogen gas.\textsuperscript{[13a, 13c]} An exciting breakthrough was the discovery that (2\textit{S},3\textit{S})-bis(diphenylphosphino)pentane ((\textit{S},\textit{S})-BDPP) in conjunction with copper phosphine nitrate complexes and tris(3,5-xylyl)phosphine to catalyse the hydrogenation of ketones in high enantioselectivity using H\textsubscript{2} as reductant (Scheme 4.14).\textsuperscript{[13a]} It was found in this work that flexible ligands with three and four carbon chain linkers gave the highest conversion. More recently, after we had started work in this areas, SEGPHOS has also been found to catalyse these reactions in high enantioselectivity.\textsuperscript{[18]} None-the-less, there is considerable scope for improvement. If a copper catalyst gave similar performance to a ruthenium based Noyori system,\textsuperscript{[3]} it would most likely supercede the ruthenium systems.
Chiral Phosphinous Amide Ligands in Rhodium and Copper Catalysed Hydrogenations

The study using (S,S)-BDPP also screened further chiral ligands in the above reaction using triphenylphosphine in excess. The following results were obtained: (S,S)-CHIRAPHOS 2% conversion; (R)-BINAP 17% conversion, 24% e.e.; (R,R)-DIOP >99% conversion, 12% e.e.; (S,S)-BPPM >99% conversion, 27% e.e; (R)-(S)-Josiphos 99% conversion, 45% e.e. Schimizu and co-workers conclude this is that the reaction is strongly favoured when 3-4 atom chain phosphines are used.

4.7. Copper Catalysed Hydrogenation Using Phosphinous Amides

Hydrogenation of acetophenone was attempted in the presence of copper(II) triflate and protected phosphinous amide 119. It was hoped the ligand would be deprotected and the copper(II) reduced in the reaction mixture in order to catalyse the reaction in the presence of triphenylphosphine, but this did not occur. It was therefore necessary to use copper(I) salts as precursors. Copper(I) phosphine nitrate salts are readily synthesised by heating copper(II) nitrate in the presence of the phosphine. The reaction mixture undergoes a colour change from blue to green to then precipitate out the colourless complex (Scheme 4.15). The triphenylphosphine and diphenyl-o-tolylphosphine salts were synthesised and tested in the hydrogenation of acetophenone in situ with deprotected phosphine borane 119. The enantioselectivity of the product is very encouraging. The diphenyl-o-tolylphosphine complex was found to give significantly higher enantioselectivity (Scheme 4.16).

\[
\text{Cu(NO}_3\text{)}_2\text{.3H}_2\text{O + PAr}_3 \xrightarrow{\text{MeOH, reflux, 10 mins}} [\text{Cu(PAr}_3\text{)}_2\text{NO}_3]
\]

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>124 PPh₃</td>
<td>62%</td>
</tr>
<tr>
<td>125 PPh₂(o-tolyl)</td>
<td>70% yield</td>
</tr>
</tbody>
</table>

Scheme 4.15 Synthesis of cuprous phosphine nitrates

The phosphinous amide 119 was tested under various different conditions to determine if the deprotection of the borane was affected by the method of addition and to see if this increased conversion. The use of [Cu(PPh₃)₂NO₃] 124 gave lower yield and enantioselectivity than the use of [Cu(PPh₂(o-tolyl))NO₃] 125 (Scheme
4.16). The conversion to alcohol decreases when the ligand is deprotected and transferred as a solution. Fortunately there is little difference in conversion when deprotecting the ligand before the reaction or adding the DABCO, ligand, phosphine and copper salt together at the beginning and so this streamlined protocol was followed afterwards (Scheme 4.17, Table 4.6).

Scheme 4.16 The use of cuprous triarylphosphine nitrate salts in the hydrogenation of acetophenone

Scheme 4.17 Hydrogenation of acetophenone using copper catalysts
Chiral Phosphinous Amide Ligands in Rhodium and Copper Catalysed Hydrogenations

<table>
<thead>
<tr>
<th>Copper salt</th>
<th>Conversion to alcohol (%)&lt;sup&gt;[d]&lt;/sup&gt;</th>
<th>e.e. (%)&lt;sup&gt;[e]&lt;/sup&gt;</th>
<th>Isomer&lt;sup&gt;[e]&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [Cu$_2$(benzene)OTf$_2$]&lt;sup&gt;[a]&lt;/sup&gt;</td>
<td>22</td>
<td>57</td>
<td>$S$</td>
</tr>
<tr>
<td>2 [Cu(PPh$_2$(o-tolyl))$_2$NO$_3$]&lt;sup&gt;[a]&lt;/sup&gt;</td>
<td>22</td>
<td>62</td>
<td>$S$</td>
</tr>
<tr>
<td>3 [Cu$_2$(benzene)OTf$_2$]&lt;sup&gt;[b]&lt;/sup&gt;</td>
<td>13</td>
<td>71</td>
<td>$S$</td>
</tr>
<tr>
<td>4 [Cu(PPh$_2$(o-tolyl))$_2$NO$_3$]&lt;sup&gt;[b]&lt;/sup&gt;</td>
<td>14</td>
<td>31</td>
<td>$S$</td>
</tr>
<tr>
<td>5 [Cu$_2$(benzene)OTf$_2$]&lt;sup&gt;[c]&lt;/sup&gt;</td>
<td>18</td>
<td>68</td>
<td>$S$</td>
</tr>
<tr>
<td>6 [Cu(PPh$_2$(o-tolyl))$_2$NO$_3$]&lt;sup&gt;[c]&lt;/sup&gt;</td>
<td>21</td>
<td>56</td>
<td>$S$</td>
</tr>
</tbody>
</table>

Table 4.6 Conversion and enantioselectivity for ligand and copper salts under selected conditions.

[a] Ligand deprotected using DABCO and evaporated in the reaction vessel before addition of diphenyl(o-tolyl)phosphine and then base and acetophenone. [b] Ligand deprotected using DABCO and transferred as a solution in toluene to copper reaction vessel before addition of diphenyl(o-tolyl)phosphine and then base and acetophenone. [c] Copper, ligand and DABCO not stirred before addition of diphenyl(o-tolyl)phosphine and then base and acetophenone. [d] Conversion measured by $^1$H NMR. [e] Data determined using HPLC with OD-H column eluting with 95:5 hexanes:iPrOH 0.5 ml/min.

Reaction conditions were varied to determine if triphenylphosphine was required and if the catalytic activity was improved by varying triphenylphosphine and the amount of copper present (Scheme 4.18, Table 4.7). The reaction was still catalysed without triphenylphosphine present; however the conversion unexpectedly lowered when more catalyst was added. Although conversions were low, very encouraging enantioselectivity was observed.

![Scheme 4.18 Conditions for hydrogenation of ketone](image)

-137-
Chiral Phosphinous Amide Ligands in Rhodium and Copper Catalysed Hydrogenations

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Conversion to alcohol (%)[a]</th>
<th>e.e. (%)[b]</th>
<th>Isomer[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25 mol% [Cu₂(benzene)OTf₂]</td>
<td>0.5 mol% 119 + 1 mol% DABCO No PPh₃</td>
<td>25</td>
<td>42</td>
</tr>
<tr>
<td>0.25 mol% [Cu₂(benzene)OTf₂]</td>
<td>0.5 mol% 119 + 1 mol% DABCO 3 mol% PPh₃</td>
<td>23</td>
<td>84</td>
</tr>
<tr>
<td>1.25 mol% [Cu₂(benzene)OTf₂]</td>
<td>2.5 mol% 119 + 5 mol% DABCO 12 mol% PPh₃</td>
<td>10</td>
<td>74</td>
</tr>
</tbody>
</table>

Table 4.7 Conversion and enantioselectivity for ligand and [Cu₂(benzene)OTf₂]
[a] Conversion measured by ¹H NMR [b] Enantioselectivity determined using HPLC with OD-H column eluting with 95:5 hexanes:iPrOH 0.5 ml/min

The solvent was then varied to determine if the conversion or enantioselectivity could be improved by variation. It was found that all the solvents tested gave good enantioselectivity but poor conversion except for ethanol (Scheme 4.19, Table 4.8).

![Scheme 4.19 Conditions for variation of solvent in hydrogenation reaction](image)

Table 4.8 Results for variation of solvent in copper hydrogenation in the presence of ligand 119
[a] Conversion determined using ¹H NMR [b] Enantioselectivity determined using HPLC with OD-H column eluting with 95:5 hexanes:iPrOH 0.5 ml/min

<table>
<thead>
<tr>
<th>Solvent</th>
<th>% Conversion to product[^a]</th>
<th>% e.e.[^b]</th>
<th>Isomer[^b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dichloromethane</td>
<td>4</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Ethanol</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isopropyl alcohol</td>
<td>8</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Toluene</td>
<td>16</td>
<td>83</td>
<td></td>
</tr>
</tbody>
</table>

It is possible the conversion could be improved by changing the phosphine and various other conditions. The amount of base and the phosphine varied (Scheme 4.20, Table 4.8). Schimizu found DIOP gave full conversion overnight but only 11% e.e using [Cu(PPh₃)₂NO₃].[^13a] Tri(3,5-xylyl)phosphine was found to give the highest

[^a]: Conversion determined using ¹H NMR
[^b]: Enantioselectivity determined using HPLC with OD-H column eluting with 95:5 hexanes:iPrOH 0.5 ml/min
conversion, and the results would seem to indicate that more electron donating monophosphines promote the reaction.

![Scheme 4.20 Conditions variation of phosphines and base](image)

**Table 4.9 Variation of phosphine and chiral phosphine in using conditions shown in Scheme 4.20**  
<table>
<thead>
<tr>
<th>x mol% 119</th>
<th>PAr₃</th>
<th>Conversion to product[a]</th>
<th>e.e.[b]</th>
<th>Isomer[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mol% 119</td>
<td>PPh₃</td>
<td>25</td>
<td>84</td>
<td>S</td>
</tr>
<tr>
<td>0.5 mol% 119[c]</td>
<td>PPh₃</td>
<td>28</td>
<td>72</td>
<td>S</td>
</tr>
<tr>
<td>0.87 mol% 119</td>
<td>PPh₃</td>
<td>18</td>
<td>76</td>
<td>S</td>
</tr>
<tr>
<td>0.5 mol% 119</td>
<td>-</td>
<td>20</td>
<td>75</td>
<td>S</td>
</tr>
<tr>
<td>0.5 mol% 119</td>
<td>PPh₃(o-tolyl)</td>
<td>18</td>
<td>68</td>
<td>S</td>
</tr>
<tr>
<td>0.5 mol% 119</td>
<td>P(4-MeOC₆H₄)₃</td>
<td>20</td>
<td>62</td>
<td>S</td>
</tr>
<tr>
<td>0.5 mol% 119</td>
<td>P(C₆H₃(CF₃)₃)</td>
<td>7</td>
<td>88</td>
<td>S</td>
</tr>
<tr>
<td>0.5 mol% 119</td>
<td>P(C₆F₅)₃</td>
<td>-</td>
<td>-</td>
<td>S</td>
</tr>
<tr>
<td>0.5 mol% 119</td>
<td>P(xylyl)₃</td>
<td>30</td>
<td>85</td>
<td>S</td>
</tr>
</tbody>
</table>

An attempt was made to improve the yield by optimising conditions using the DIOP ligand since Shimizu had found DIOP to give full conversion albeit with 11% e.e.. However, in our hands the DIOP ligand also gave low conversions (Scheme 4.21, Table 4.10). Lower conversions using DIOP were seen although this might be because the reaction was more dilute than using my ligand. In order to copy the literature conditions more closely, the DIOP reaction used solution of tBuOH in isopropanol (instead of tBuOH in table Table 4.9). We found the base must be fully
dissolved in the reaction solvent otherwise a copper mirror can be formed in the reaction vessel (Figure 4.2).

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{Ph} & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
0.25 \text{ mol}\% \text{[Cu}(\text{benzene})(\text{OTf})_2] & \quad 0.5 \text{ mol}\% \text{(S,S)-DIOP, 3 mol}\% \text{P(\text{xylyl})}_3 \\
5 \text{ mol}\% \text{KOtBu, x} \, {}^\circ\text{C} & \quad 16 \text{ hrs} \\
\text{solvent, 50 bar H}_2
\end{align*}
\]

**Scheme 4.21** Conditions used to optimise copper catalysed hydrogenation reaction using DIOP

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>% Conversion to product(^{[a]})</th>
<th>% e.e.(^{[b]})</th>
<th>Isomer(^{[b]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPrOH</td>
<td>30</td>
<td>10</td>
<td>11</td>
<td>R</td>
</tr>
<tr>
<td>iPrOH</td>
<td>50</td>
<td>15</td>
<td>9</td>
<td>R</td>
</tr>
<tr>
<td>iPrOH</td>
<td>70</td>
<td>10</td>
<td>6</td>
<td>R</td>
</tr>
<tr>
<td>toluene</td>
<td>50</td>
<td>30</td>
<td>5</td>
<td>R</td>
</tr>
<tr>
<td>toluene</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>tBuOH</td>
<td>30</td>
<td>21</td>
<td>7</td>
<td>R</td>
</tr>
<tr>
<td>dichloromethane</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 4.10** Conditions used and conversion for copper catalysed hydrogenation of acetophenone

\(^{[a]}\) Determined using 1H NMR \(^{[b]}\) Enantioselectivity determined using HPLC with OD-H column eluting with 95:5 hexanes:iPrOH 0.5 ml/min

**Figure 4.2** Copper mirror formed in reaction vessel

Other copper(I) salts were then tested as precursors but this again gave low conversion (Scheme 4.22, Table 4.11).

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{Ph} & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
0.5 \text{ mol}\% \text{Cu(I) salt} & \quad 0.5 \text{ mol}\% \text{(S,S)-DIOP, 3 mol}\% \text{P(\text{xylyl})}_3 \\
5 \text{ mol}\% \text{KOtBu, 30} \, {}^\circ\text{C} & \quad 16 \text{ hrs} \\
i\text{PrOH, 50 bar H}_2
\end{align*}
\]

**Scheme 4.22** Copper catalysed hydrogenation of acetophenone

-140-
Chiral Phosphinous Amide Ligands in Rhodium and Copper Catalysed Hydrogenations

<table>
<thead>
<tr>
<th>Copper salt</th>
<th>% Conversion to product&lt;sup&gt;[a]&lt;/sup&gt;</th>
<th>e.e.&lt;sup&gt;[b]&lt;/sup&gt;</th>
<th>Isomer&lt;sup&gt;[b]&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Cu(MeCN)&lt;sub&gt;4&lt;/sub&gt;OTf]</td>
<td>5</td>
<td>4</td>
<td>R</td>
</tr>
<tr>
<td>[Cu&lt;sub&gt;2&lt;/sub&gt;(toluene)(OTf)&lt;sub&gt;2&lt;/sub&gt;]</td>
<td>15</td>
<td>15</td>
<td>R</td>
</tr>
<tr>
<td>[Cu&lt;sub&gt;2&lt;/sub&gt;(benzene)(OTf)&lt;sub&gt;2&lt;/sub&gt;]</td>
<td>15</td>
<td>12</td>
<td>R</td>
</tr>
</tbody>
</table>

Table 4.11 Conversion and enantioselectivity of copper catalysed hydrogenation

<sup>[a]</sup> Determined using 1H NMR  
<sup>[b]</sup> Enantioselectivity determined using HPLC with OD-H column eluting with 95:5 hexanes:iPrOH 0.5 ml/min

The reason for the low conversion seen is not known. The reaction vessels were purged with argon before addition of solvent and base in the sealed autoclave through an injection port and solvents were dried and degassed before addition. Given the sensitivity of the copper hydride species it is possible that one of the reagents is poisoning the catalyst.<sup>[13a]</sup> Hydrogenation of α,α,α-trifluoroacetophenone was also attempted since this is often found to react at a faster rate than acetophenone but under these conditions this ketone did not convert to alcohol. A small amount (>5%) of other species were observed by 19F NMR spectroscopy but it was thought these were side products which are reversibly formed in the presence of base and an alcohol. Hydrosilylation using the phosphinous amide was also attempted using PMHS but this gave no conversion to product.

High enantioselectivities for this reaction are seen, which is promising but low conversions mean this reaction is not yet useful for further synthesis. It is possible that a variant of this copper catalysed reduction would also give high enantioselectivities and also higher conversion, and therefore be of considerable utility.

**4.8. Conclusions and Future Work**

Phosphinous amides can be used successfully as ligands for the rhodium catalysed hydrogenation of dimethyl itaconate, α-acetaminocinnamic acid and α-acetaminocinnamic methyl ester. Good conversions and hydrogenations were
obtained which clearly indicates that these are useful ligands for alkene hydrogenation.

Copper catalysts were also found to be good for enantioselective hydrogenation although high conversion was not achieved. The low conversion was also shown using DIOP which indicates that a component of the reaction mixture could be poisoning the catalyst. None-the-less the high enantioselectivity is very encouraging; we felt we have examined all the obvious routes to increasing catalytic activity leaving us tantalisingly close to an effective copper catalysed ketone hydrogenation procedure.

The chiral phosphinous amide ligand 119 is clearly a useful ligand for asymmetric catalysis; however it does not give high conversion with copper catalysed hydrogenation of ketones. It is possible Noyori type [Ru(L)(R,R-DPEN)Cl₂] complexes of this phosphinous amide would be reactive in catalysis. By protecting the nitrogen on the phosphinous amide with a triflate or alkyl group (Figure 4.3) the ligand could be made more stable and thus the complexes more readily synthesised. It could also make the synthesis of other metal complexes for hydrogenation such as [Rh(L)(COD)]OTf more feasible since it may hinder decomposition of the catalyst. Since major decomposition of the ligand was seen in previous attempts to synthesise these complexes these new ligands may retain the high enantioselectivity of this ligand in hydrogenation but make it less sensitive to reaction conditions and thus more stable. In examples using (R,R)-dppach substituting the nitrogen with a methyl has made the ligands more enantioselective for the hydrogenation of alkenes.[5, 7a]

![Figure 4.3 Triflate or alkyl substituted ligands of 119](image-url)
References for Chapter 4


5. EXPERIMENTAL

5.1. General information

All commodity chemicals and solvents were standard laboratory grade, obtained from commercial sources and were used as received with the exceptions of chlorodiphenylphosphine, triethylamine, Jones reagent, trichloroacetaldehyde, trifluoroacetaldehyde and ethyl glyoxylate. The methods of preparation for Jones reagent, trichloroacetaldehyde, trifluoroacetaldehyde and ethyl glyoxylate are described below. Chlorodiphenylphosphine was distilled under reduced pressure (b.p. 126 °C ~2 Torr) and triethylamine over potassium hydroxide at atmospheric pressure (b.p. 90 °C). An inert atmosphere of N₂ or Argon and Schlenk line techniques were used throughout preparative procedures. Solvents were removed in vacuo by rotary evaporation on a Heidolph labrota 4000 or under vacuum on a Schlenk line. Dry, degassed solvents were used for reactions unless otherwise indicated. Solvents were degassed by several freeze thaw cycles before use or by bubbling argon or nitrogen gas through the solvents. Dry solvents were purified via alumina columns in a Grubbs system Braun MSB 8000 still, purchased in sure-seal bottle from Aldrich or distilled from 4 Å molecular sieves (dimethylformamide). Thin layer chromatography was conducted using Macheray-Nagel plastic TLC plates coated with fluorescents silica UV₂₅₄ to 0.200 mm. The components were observed under UV light and/or using permanganate or vanillin stains. Flash column chromatography was performed using Davisil silica gel Fluorochem 60 Å, particle size 35-70 micron with normal grade solvents.
5.1.1. Preparation of starting materials

Preparation of Jones reagent

Jones reagent prepared by dissolving chromium trioxide (25 g) into concentrated sulphuric acid (>95%, 25 ml). The solution was added slowly to stirred water (75 ml) cooled to 0°C.

Preparation of trichloroacetaldehyde

Conventional laboratory distillation equipment was set up[1] with a 5 cm Vigreux column with a Schlenk flask attached as a collecting flask. The equipment was flame dried under vacuum. After cooling to room temperature concentrated sulfuric acid (>95%) was poured into the distillation flask containing a stirrer bar with the system under a flow of inert gas. Chloral hydrate was cautiously added to the acid. The system was sealed with a vent to the nitrogen line. The mixture was heated to ~140 ºC until the hydrate dissolved and two layers were formed in the vessel. The top layer of the two phases began to boil and the distillate was collected and stored under argon at 5 ºC before use.

Preparation of trifluoroacetaldehyde

The procedure was followed as above but with anhydrous CaSO₄ packed between two small plugs of glass wool into the top of the condenser, cotton wool lagged around the still receiver joint soaked in dichloromethane and the vent to the nitrogen line being through the Schlenk flask. Trifluoroacetaldehyde hydrate solution in water was added to the sulphuric acid solution with the collecting Schlenk flask cooled to -40 ºC. The distillate was used immediately.
Procedure for cracking of 50% ethyl glyoxylate polymer solution in toluene.

Conventional laboratory distillation equipment was set up\textsuperscript{[1]} with a 5 cm Vigreux column and a pig collection adapter attached to three flasks. The mixture was heated to 120-150 °C. The first fraction was collected whilst the flask was heated to temperature. The second fraction was used directly, and the third was collected whilst the apparatus was cooling down. Once the ene reaction with the ethyl glyoxylate was set up, the remaining distillate was analysed in CDCl\textsubscript{3} by $^1$H NMR spectroscopy to determine the proportion of ethyl pyruvate to toluene with the average ratio being 95:5 pyruvate: toluene.

5.1.2. Microwave reactions

Microwave reactions were carried out in a Biotage® Initiator using 10 ml heavy-walled reactor vials equipped with an air tight seal. The temperature is measured by an infra red temperature probe that measures the temperature on the surface of the vial. The pressure is measured by direct reading of the deflection of the septa on the vial using a load cell behind the inner part of the cavity lid.

5.1.3. Autoclave reactions

Hydrogenations were carried out in stainless steel autoclaves. The reactions were carried out within a glass vial equipped with a stirrer bar. The vial was placed in the autoclave which was then sealed and put under an inert atmosphere. The autoclave was then purged with hydrogen three times and then filled at the required pressure before checking the vessel screw seal for leaks. Heating was carried out in a steel heating jacket attached to a thermocouple or in an oil bath. After the specified time reactions were cooled and then vented before analysis.
5.2. Analysis

5.2.1. NMR Spectroscopy

All NMR spectra were recorded on Bruker Avance 300 or Bruker Avance 400 instruments as specified in the analysis data. All $^{13}$C, $^{31}$P and $^{19}$F NMR spectroscopy values quoted in ppm to the nearest 1 decimal place and $^1$H NMR spectroscopy values quoted in ppm to the nearest 2 decimal places. $^1$H and $^{13}$C NMR spectra were referenced to the residual solvent peak in deuterated solvent with respect to TMS at $\delta=0$. $^{19}$F and $^{31}$P NMR spectra were referenced externally to CFCl$_3$ and 85% H$_3$PO$_4$ solution respectively. Coupling constants ($J$) are quoted in Hertz to the nearest 1 decimal place. {X} indicates X atom decoupled spectra. The symbols s, d, t, q and br are used to denote singlet, doublet, triplet, quartet and broad respectively.

5.2.2. HPLC data

High pressure liquid chromatography was conducted on a Varian HPLC with an autosampler using analytical chiral columns with HPLC grade solvents. In cases where the ratio of solvent was less than 1:99 $^3$PrOH: hexanes the HPLC solvent was pre-mixed to provide consistency with the running time of the separated peaks. Where running times for products in reaction mixtures were inconsistent to those previously observed the HPLC sample was doped with pure racemic sample to ensure the peaks corresponded to the product.

Compounds 61$^{[2]}$ methyl 3-((tert-butoxycarbonyl)amino)-3-phenylpropanoate (Mannich reaction product),$^{[3]}$109,$^{[4]}$117,$^{[5]}$121$^{[6]}$ and 123$^{[7]}$ were analysed according to literature HPLC methods. Data for 116 determined by reaction of the acid with SOCl$_2$ in methanol cooled to 0 °C to complete conversion to the methyl ester and the mixture was then extracted between dichloromethane and water before concentration of the organic layer in vacuo. The methyl ester was then analysed by HPLC. Other HPLC methods were used as described in experimental data.
5.2.3. **Chiral Lanthanide shift reagents**

The method was optimised using a racemic sample of the ene product 61. Europium tris[3-(heptafluoropropylhydroxymethylene)-d-camphorate] (Eu(hfc)_3, 0.8 eq) was added to a solution of the product in CDCl$_3$ and then the ratio of enantiomers measured from the integration of the two $^{19}$F NMR spectra peaks of the ene product.

5.2.4. **Calculation of $K_{ass}$ for 77**

![Chemical structure](image)

Binding constant determination- NMR dilution from solutions in CD$_3$CN were analysed at 298 K using a 400 MHz spectrometer. The solution was made up using standard volumetric flask (accuracy ± 0.02 ml). The solution was left to equilibrate at 298 K before initial analysis. Data from these experiments were entered into an Excel spreadsheet programmed by Prof. D. Philp to calculate $K_a$ values for intermolecular interactions. The data was entered and optimised as below based on the doublet for the pyridyl aromatic ring. The $\delta_{obs}$ of the unbound state was determined from a very weak solution of the thiourea in solution. Solutions were prepared to a concentration of 50 mM which was gradually diluted to 15 mM and the chemical shift changes were noted. The variation in chemical shift with respect to the thiourea concentration was used to calculate the dissociation constant by fit to the equation below using the spreadsheet which utilised a non-linear curve fitting program.

$$
\delta_{obs} = \delta_G + \Delta\delta \left[ 1 + \frac{K_d}{2C_0} - \sqrt{\left( \frac{K_d}{2C_0} \right)^2 + \left( \frac{K_d}{C_0} \right)} \right]
$$

**Figure 5.1 Equation for the calculation of the dissociation constant, $K_{diss}$**

$\delta_{obs}$ is the chemical shift at concentration $C_0$ of the molecule, and $\Delta\delta$ is the maximum chemical shift.
The dissociation constant can be used to calculate the $K_{\text{ass}}$ from the relationship $K_{\text{diss}} = 1/K_{\text{ass}}$. Below is shown the plotted saturation curve and residuals.

Figure 5.2 Saturation curve, plot of residuals and observed δ for a given concentration
5.2.5. *Single x-ray crystallography*

Single x-ray crystallography was carried out in the University of St Andrews by Prof. A.M.Z. Slawin. Structural data were collected at 93 K by using a Rigaku MM007 High brilliance RA generator and Mercury CCD system. Intensities were corrected for Lorentz-polarisation and for absorption. The structures were solved by direct methods. Hydrogen atoms bound to carbon were idealised. Structural refinements were obtained with full-matrix least-squares based on $F^2$ by using the program SHELXTL.

5.2.6. *Further analytical techniques*

Mass spectra were recorded on Water Micromass GCT (Time of flight) fitted with lockspray for accurate mass (ES) or GCT (CI) instruments by the University of St Andrews service. Microanalyses (CHN) were carried out by the University of St. Andrews service on a Carlo Erba 1110 CHNS analyser and are quoted to 2 d.p. Infra-red (IR) spectra were recorded on NaCl plates using a Perkin-Elmer Spectrum GX spectrometer.

$74^{[8]}$, tert-butyl((1-methoxyvinyl)oxy)dimethylsilane$^{[3]}$ and tert-butyl benzylidene carbamate$^{[3]}$ were prepared using literature methods and analysis corresponded with the literature data. Analysis of $116^{[9]}$, $117^{[5]}$, $121^{[6]}$ and $123^{[7]}$ corresponded to literature values. Where new synthetic routes are followed to synthesise a known compound the paper containing analytical data is cited after the data given.
5.3. Synthesis and General Procedures

Synthesis of 1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea 5

3,5-bis(trifluoromethyl)phenylisothiocyanate (1.83 ml, 10 mmol) was added to a solution of 3,5-bis(trifluoromethyl)aniline (1.63 ml, 10.5 mmol) in dichloromethane (5 ml) at 0 °C under nitrogen. The mixture was left to stir for 10 minutes then a further 18 hours at room temperature. The solvent was removed under reduced pressure and the residue washed with cold dichloromethane to give a colourless solid (3.6g, 72%).

$\nu_{\text{max}}$(film)/cm$^{-1}$ 3170, 2920, 1555, 3207, 1467, 1376, 1179, 1139, 929, 890

$^1$H NMR: (300MHz, d6-DMSO) $\delta$H 7.86 (2 H, s, Ar-H), 8.19 (4 H, s, Ar-H), 10.64 (2 H, s, NH)

$^{19}$F NMR (282 MHz, d6-DMSO) $\delta$F -61.94

$^{13}$C NMR (75.4 MHz, CDCl$_3$) $\delta$C 117.5, 123.0 (J$_{CF}$ 272.7), 124.0, 130.3 (J$_{CF}$ 33.0), 141.1, 180.5

$m/z$ (ES -ve) 499.96 (29%, M-H), 498.88 (100%). [Data consistent with literature values][10]
Experimental

Synthesis of N,N''-(1R)-[1,1'-binaphthalene]-2,2'-diylbis[N'-[3,5-bis(trifluoromethyl)phenyl]-thiourea 70

(R)-2,2'-diamino-1,1'-binapthalene (127 mg, 0.44 mmol) was transferred to a Schlenk flask under an argon blanket, the Schlenk sealed with a suba-seal and the amine dissolved in dry THF (2 ml). 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.16 ml, 0.89 mmol) was added and the mixture was left to stir for 16 hours at room temperature. Dichloromethane was added (10 ml) and the solvent was removed under reduced pressure. The reaction mixture was further purified by column chromatography eluting with 9:1→5:1 hexanes: ethyl acetate to give a pale yellow solid (122 mg, 52%).

υ_{max} (KBr)/cm^{-1} 3156, 2930, 1701, 1619, 1177, 886

$^1$H NMR (300 MHz; CDCl$_3$) δ$_H$ 7.04 (2 H, d, $J$ 9.2, Ar-$H$), 7.22 (2 H, t, $J$ 8.2, Ar-$H$), 7.43 (2 H, t, $J$ 6.9, Ar-$H$), 7.50 (2 H, s, NH), 7.54 (2 H, s, NH), 7.63 (4 H, s, Ar-$H$), 7.80 (2 H, d, $J$ 9.0, Ar-$H$), 7.89 (2 H, d, $J$ 8.2, Ar-$H$), 7.94 (2 H, s, Ar-$H$), 8.07 (2 H, d, $J$ 8.7, Ar-$H$)

$^{19}$F NMR (282 MHz, CDCl$_3$) δ$_F$ -63.5

$^{13}$C NMR (75.4 MHz, CDCl$_3$) δ$_C$ 122.7 (J$_{CF}$ 272.9), 124.2, 124.8, 125.4, 127.1, 127.5, 128.1, 128.8, 130.7, 131.9 (J$_{CF}$ 33.8), 132.4, 132.7, 133.5, 138.7, 180.1

m/z (ES) 849 (100%, M+Na) [Data consistent with literature values][11]
**Example of ene reaction in microwave: Synthesis of ethyl 2-hydroxy-4-phenyl-2-(trifluoromethyl)pent-4-enoate and its isomers**

Ethyl trifluoropyruvate (0.098 ml, 0.75 mmol) was added to a solution of the olefin (0.9 mmol, ~1.2 eq) in dichloromethane (2 ml) under an inert atmosphere. The mixture was heated to 140 ºC for 30 minutes. The solvent was removed *in vacuo* and the crude product purified by chromatography eluting with 6:1 hexane to give the product as a colourless oils. The isomers 61, 62 and 63 were not separable and characterised by NMR and GCMS.

63% isolated yield of three products from reaction, GC-EIMS values

61 13.78 mins (288, M+), 19F NMR (282 MHz, CDCl3) δF -79.7

62 14.08 mins (288, M+), 19F NMR (282 MHz, CDCl3) δF -79.5

62 14.96 mins (288, M+), 19F NMR (282 MHz, CDCl3) δF -79.5.

**General Procedure for testing of thioureas in ene reaction ethyl trifluoropyruvate with alkene**

Ethyl trifluoropyruvate (0.098 ml, 0.75 mmol) was added to a solution of the thiourea and the alkene (0.9 mmol, ~1.2 eq) in dichloromethane (2 ml). The mixture was left to stir until analysis by 19F NMR spectroscopy at which point it was transferred to an NMR tube under nitrogen with a d6-benzene filled capillary for analysis. The percentage conversion was taken from the integration of the product over the total integration of fluorine peaks within the starting material and product region of the spectra. Product peaks were confirmed by spiking experiments with authentic samples. Pure products were isolated by column chromatography and characterised as described below.
Characterisation data of Ethyl 2-hydroxy-4-phenyl-2-(trifluoromethyl)pent-4-enoate 61

![Structural formula](image)

$^{1}$H NMR (300 MHz, CDCl$_3$) $\delta$H 1.08 (3 H, t, $J$ 7.2, CH$_3$), 2.96 (1 H, d, $J$ 14.0, C=CCH$_2$), 3.21 (1 H, d, $J$ 14.0 1H, s, CHH'), 3.48-3.61 (1 H, m, CHH'), 3.70 (1 H, s, OH), 3.90-4.02 (1 H, m), 5.21 (1 H, s, C=CCHH'), 5.31 (1H, s, CHH'), 7.19-7.32 (5 H, m, Ar-H)

$^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$F -78.9

$^{13}$C NMR (75.4 MHz, CDCl$_3$) $\delta$C 22.1, 37.0, 63.5, 77.1 (q, $J_{CF}$ 28.9), 119.4, 123.4 (q, $J_{CF}$ 286.3), 126.8, 127.7, 128.2, 141.1, 168.9

$m/z$ (EI) 280 (M$^+$ 100%).

Characterisation data of (E)-ethyl 2-hydroxy-2-(trifluoromethyl)oct-4-enoate 65

![Structural formula](image)

$^{1}$H NMR (300 MHz, CDCl$_3$) $\delta$H 0.78 (3 H, t, $J$ 7.1, CH$_3$), 1.22-1.35 (5 H, m) 1.90 (2 H, q, $J$ 7.1, CH$_2$), 2.49-2.65 (2 H, m, CH$_2$), 3.72 (1 H, s, OH), 4.26 (2 H, q, $J$ 6.7, CH$_2$), 5.19-5.30 (1 H, m, C=CH), 5.57-5.59 (1 H, m, C=CH)

$^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$F -78.9

$^{13}$C NMR (75.4 MHz, CDCl$_3$) $\delta$C 12.9, 13.5, 20.4, 29.9, 36.2, 62.1, 77.8 (q, $J_{CF}$ 28.4), 121.3, 123.4 (q, $J_{CF}$ 286.2), 136.5, 169.4

$m/z$ (EI) 254 (M$^+$ 100%). [Known Compound][12]
Experimental

Characterisation data of (E)-ethyl 2-hydroxy-5-phenyl-2-(trifluoromethyl)pent-4-enoate 64

![Chemical structure image]

$^1$H NMR (300 MHz, CDCl$_3$) δ$_H$ 1.26 (3 H, t, $J$ 7.1, CH$_3$), 2.79 (2 H, m, CH$_2$), 4.27 (2 H, m, CH$_2$), 6.00 (1 H, m, C=CH), 6.46 (1 H, d, $J$ 16.6, C=CH), 7.20-7.27 (5 H, m, Ar-H)

$^{19}$F NMR (282 MHz, CDCl$_3$) δ$_F$ -78.8

$^{13}$C NMR (75.4 MHz, CDCl$_3$) δ$_C$ 14.1, 35.4, 63.9, 77.4 (q, J$_{CF}$ 35.3), 120.4, 123.4 (q, J$_{CF}$ 286.4), 126.3, 127.8, 128.6, 135.5, 136.6, 169.3

$m/z$ (EI) 280 (M$^+$ 100 %).[Known Compound]$^{[12]}$

Characterisation data of Ethyl 2-(cyclopentenylmethyl)-3,3,3-trifluoro-2-hydroxypropanoate 67

![Chemical structure image]

$^1$H NMR (300 MHz, CDCl$_3$) δ$_H$ 1.26 (3 H, t, $J$ 7.1, CH$_3$); 1.76 (2 H, quintet, $J$ 7.3, CH$_2$), 2.06-2.34 (4 H, m, CH$_2$), 2.60 (1 H, d, $J$ 4.4, CHH’), 2.79 (1 H, d, $J$ 4.4, CHH’), 3.72 (1 H, s, OH), 4.21-4.32 (2 H, m, CH$_2$), 5.46 (1 H, s, C=CH)

$^{19}$F NMR (282 MHz, CDCl$_3$) δ$_F$ -79.2

$^{13}$C NMR (75.4 MHz, CDCl$_3$) δ$_C$ 13.9, 23.6, 32.5, 33.0, 36.0, 63.7, 77.8 (q, J$_{CF}$ 29.0), 123.3 (q, J$_{CF}$ 286.4), 130.1, 136.4, 169.8

$m/z$ (EI) 252 (M$^+$ 100 %).[Data consistent with literature values]$^{[13]}$
**Characterisation data of ethyl 2-hydroxy-4-methoxy-2-(trifluoromethyl)pent-4-enoate 66**

![Chemical structure](image)

$\nu_{\text{max}}$(film)/cm$^{-1}$ 3476, 2895, 1751, 1370, 1231, 1190, 1146, 863, 701

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$H 1.25 (3 H, t, $J$ 14.1, CH$_3$), 2.58 (1 H, d, $J$ 14.1, CHH’), 2.86 (1 H, d, $J$ 14.1, CHH’), 3.40 (3 H, s, CH$_3$), 3.89 (1 H, s, C=CH), 4.00 (2 H, m, OH), 4.26 (2 H, q, $J$ 7.1), CH$_2$

$^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$F -79.0

$^{13}$C NMR (75.4 MHz, CDCl$_3$) $\delta$C 13.8, 37.7, 54., 63.4, 77.8 (q, J$_{CF}$ 32.4), 86.0, 123.3 (q, J$_{CF}$ 286.1), 156.0, 169.0

$m/z$ (CI) 243.0863 (MH$^+$ C$_9$H$_{14}$O$_4$F$_3$ requires 243.0844)

**Synthesis of N-Acetyl Isopropenyl Aniline 68**

![Chemical structure](image)

Acetic anhydride (0.2 ml, 2.1 mmol) was added to a solution of 2-isopropenylaniline (0.27 ml, 2 mmol) in anhydrous dichloromethane (2 ml) under nitrogen at 0 °C. The mixture was left to stir for 10 minutes and quenched with aqueous sodium bicarbonate solution (20 ml). The product was extracted with dichloromethane (2 x 30 ml). The organic phases were combined and washed with aqueous saturated brine solution (20 ml). The organic phase was dried over magnesium sulfate and the solvent removed under reduced pressure to give colourless solid (201 mg, 57%).
Experimental

$\nu_{\text{max}}$(KBr)/cm$^{-1}$ 3176, 2990, 2221, 1710, 1605, 1518, 1459, 1376, 1159, 971, 902

$^1$H NMR (300 MHz; CDCl$_3$) $\delta$H 2.00 (3 H, s, CH$_3$), 2.08 (3 H, s, CH$_3$) 4.95 (1 H, s, C=CH), 5.32 (1 H, s, C=CH), 6.98-7.09 (2 H, m, Ar-H), 7.16-7.22 (1 H, m, Ar-H), 7.45 (1 H, br s, NH), 8.17 (1 H, d, $J$ 8.2, Ar-H)

$^{13}$C NMR (75 MHz; CDCl$_3$) $\delta$C 24.8, 25.1, 117.1, 121.6, 124.3, 128.1, 128.3, 134.0, 134.3, 143.4, 168.6

$m/z$ (ES) 198 (100%, M+Na) [Data consistent with literature values][14]

Note: Leaving the above reaction mixture for longer periods of time results in isomerisation to an unknown product of the same mass.

Synthesis of diphenylphosphinothioyl chloride

Sulfur (1.78 g, 55 mmol) was added to a solution of chlorodiphenylphosphine (2.6 ml, 13.9 mmol) in dry degassed toluene (7 ml). The mixture was heated under nitrogen at 105$^\circ$C for 4.5 hours. The mixture was cooled to room temperature and filtered. The solvent was removed under reduced pressure and the residue redissolved in dry degassed ether (8ml). The mixture was cooled to 0$^\circ$C overnight, filtered and the solvent removed under reduced pressure to give a pale yellow oil (3.48 g, 91%).

$^1$H NMR (300MHz, CDCl$_3$) $\delta$H 7.39-7.49 (8H, m), 7.83-7.92 (2H, m)

$^{31}$P NMR (121.4 MHz, CDCl$_3$) $\delta$P 81.3. [Data consistent with literature values][15]
Experimental

**Synthesis of diphenylphosphinothioyl isothiocyanate**

![Chemical Structure]

Potassium isothiocyanate (4.12 g, 42.3 mmol) was added to a solution of diphenylphosphinothioyl chloride (3.46 g, 13.7 mmol) in degassed acetonitrile (30 ml). The mixture was heated to 95ºC for 1.5 hours under nitrogen and then filtered. The solvent was removed from the filtrate under reduced pressure to give a yellow solid. This was further purified by dissolving the residue in dry pentane and filtering the mixture. The filtrate was again concentrated to give the product, a pale yellow solid (2.86g, 76%).

$^1$H NMR (300MHz, CDCl$_3$) 7.38-7.53 (3H, m), 7.74-7.86 (2H, m)

$^{31}$P NMR (121.4 MHz, CDCl$_3$) $\delta_p$ 57.5

$^{13}$C NMR (75.4 MHz, CDCl$_3$) $\delta_C$ 127.8 (J$_{CP}$ 14.3), 129.6 (J$_{CP}$ 12.3), 131.6 (J$_{CP}$ 3.2), 132.5 (J$_{CP}$ 77.7), 149.3[Data consistent with literature values][15]

**Synthesis of 1-(3,5-bis(trifluoromethyl)phenyl)-3-(diphenylphosphorothioyl)thiourea 73**

![Chemical Structure]

3,5-bis(trifluoromethyl)aniline (0.61 ml, 3.94 mmol) was added to a solution of diphenylphosphinothioyl isothiocyanate (1.0 g, 3.67 mmol) in tetrahydrofuran (7 ml). The mixture was left to stir under nitrogen for a week until the reaction had gone to completion by $^{31}$P NMR. The solvent was removed in vacuo and the residue recrystallised in dichloromethane to give a colourless solid (1.11g, 62%).
Experimental

mp 120-122ºC

$\nu_{\text{max}}$(CDCl$_3$/cm$^{-1}$) 2920, 1734, 1629, 1583, 1461, 1140, 997, 680, 635

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$H 7.03 (1 H, br s, Ph$_2$P(S)NH), 7.46-7.61 (6 H, m, Ar-H), 7.82 (4 H, d, J 7.0, Ar-H), 7.89 (1 H, s, Ar-H), 10.89 (1 H, br s, (CF$_3$)$_2$C$_6$H$_4$-NH)

$^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$F -64.2

$^{31}$P NMR (121.4 MHz, CDCl$_3$) $\delta$P 54.2

$^{13}$C NMR (75.4 MHz, d6-DMSO) $\delta$C 107.4, 113.0, 123.6 (q, $J_{CF}$ 272.4), 128.4 (d, $J_{CP}$ 12.5), 130.8 (q, $J_{CF}$ 32.1), 130.8 (d, $J_{CP}$ 9.9), 131.4 (d, $J_{CP}$ 2.4), 134.8 (d, $J_{CP}$ 134.7), 150.0

m/z (ES) 536.2 (52%, M+MeOH)

(Found: C, 50.15; H, 2.75; N, 5.45. C$_{21}$H$_{15}$N$_2$PS$_2$ requires C, 50.00; H, 3.00; N 5.55%).

Single crystal X-ray data given in Appendix 2-Structure 1

**Synthesis of phosphoric acid catalyst 76**

The 3,3’-disubstituted BINOL starting material 75 was synthesised according to literature methods and characterisation was in agreement with literature data.$^{[16]}$

Phosphoryl chloride (0.1 ml, 0.50 mmol) was added to a solution of the substituted BINOL (200 mg, 0.46 mmol) in pyridine (2 ml). The mixture was heated to 50 ºC for 16 hours and then allowed to cool to room temperature. Water (0.2 ml) was added dropwise and the mixture heated for 7 hours to 70 ºC before cooling and extracting between HCl (1 M) and dichloromethane. The aqueous phase was washed with dichloromethane and the organic phased combined and dried over Na$_2$SO$_4$. The mixture was concentrated *in vacuo* and further purified by column chromatography eluting with 2:98 methanol: dichloromethane to give the product as a yellow gum (140 mg, 62%).
\[
\text{[\(\alpha\)]}_{\text{D}}^{20} = -40.95 \text{ (c=0.2, CHCl}_3\text{)}
\]

\(\nu_{\text{max}}\text{(film)/cm}^{-1} = 3064, 2589, 2137, 1587, 1486, 1250, 953, 751\)

\(\text{\(^1H\ NMR (300 MHz, CDCl}_3\text{)}\delta_H 0.42 \text{ (18 H, s, } CH_3\text{), 7.09} \text{ (2 H, m, Ar-}\text{H}, \text{7.18} \text{ (2 H, m, Ar-}\text{H}, \text{7.27-7.44} \text{ (4 H, m, Ar-}\text{H}, \text{7.86} \text{ (2 H, t, J 7.8, Ar-}\text{H}, \text{8.08} \text{ (2 H, d, J 10.2, Ar-}\text{H})}\)

\(\text{\(^{31}P\ NMR (121.5 MHz; CDCl}_3\text{) } \delta_P +7.6\)

\(\text{\(^{13}C\ NMR (75 MHz; CDCl}_3\text{) } \delta_C 0.3, 106.6, 121.4, 125.5, 126.8, 127.5, 128.4, 129.9, 130.0, 133.5, 160.8\)

\(\text{HRMS } \text{m/z (ES) 468.1259 (C}_{24}\text{H}_{29}\text{O}_{4}\text{PSi}_2 \text{ requires 468.1342)}\)

**Synthesis of N-(3,5-bis(trifluoromethyl)phenyl)-2-(pyridin-2-yl)hydrazinecarbothioamide 77**

![](image)

3,5-bis(trifluoromethyl)phenylisothiocyanate (1.67 ml, 9.2 mmol) was added to a solution of 2-hydrazinopyridine (1.0 g, 9.2 mmol) in dichloromethane (10 ml) at 0 °C. The mixture was gradually allowed to warm to room temperature and left to stir for 2 hours. Cooled dichloromethane was added to the pale brown suspension and the mixture was filtered and washed with dichloromethane to give the thiourea as an off white solid (2.64 g, 76%).
m.p. 134-136 °C

$\nu_{\text{max}}$(film)/cm$^{-1}$ 3099, 1552, 1514, 1274, 1248, 1194, 1127, 678

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ H 6.65 (1 H, d, $J$ 8.4, Ar-H), 6.82 (1 H, t, $J$ 5.9, Ar-H), 7.64 (1 H, t, $J$ 7.1, Ar-H), 7.79 (1 H, s, NH-NH), 8.15 (1 H, d, $J$ 4.2, Ar-H), 8.49 (2 H, s, Ar-H), 8.66 (1 H, s, Ar-H) 10.16 (1 H, s, NH-NH), 10.41 (1 H, s, NH-C$_6$H$_4$(CF$_3$)$_2$)

$^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ F -63.2

$^{13}$C NMR (75 MHz; CDCl$_3$) $\delta$ C 107.8, 116.4, 117.5, 123.7 (q, $J_{CF}$ 273.5), 124.6, 129.9 (q, $J_{CF}$ 43.9), 138.2, 141.7, 148.1, 159.3, 181.4

m/z (ES) 260 (M$^+$ 100%)

(Found: C, 44.42; H, 2.66; N, 14.52. C$_{14}$H$_{10}$F$_6$N$_6$S requires C, 44.21; H, 2.65; N 14.73%).

Single crystal X-ray data given in Appendix 2-Structure 2

**General Procedure for the use of thiourea combined with acid in the ene reaction**

The acid (0.038 mmol) and thiourea 77 (14 mg, 0.038 mmol) were added to oven-dried tubes in an atlas orbit carousel. The reaction vessels were sealed under an inert atmosphere and dichloromethane (1 ml) was added. The reactions were left to stir for 30 minutes after which ethyl trifluoropyruvate (0.1 ml, 0.75 mmol) was added followed by $\alpha$-methyl styrene (0.11 ml, 0.78 mmol). The reaction mixture was left to proceed before analysis by $^{19}$F NMR spectroscopy.

**Synthesis of t-butyl (phenyl(phenylsulfonyl)methyl)carbamate**

\[
\begin{align*}
\text{NH} & \text{Boc} \\
\text{SO}_2\text{Ph}
\end{align*}
\]

t-butyl carbamate (10.0 g, 85.5 mmol) was suspended in a solution of aqueous methanol (250 ml, 2:1 H$_2$O:MeOH) with sodium benzenesulfinate (28 g, 2 eq.). Benzaldehyde (13 ml, 1.5 eq.) and then formic acid were added (6.4 ml, 98%). The
reaction was left to stir for 72 hrs. The solid was isolated by filtration and then triturated with water and ether to give the product, a white solid (26.2 g, 88%).

\(^1\)H NMR (300MHz, CDCl\(_3\)) \(\delta_H \) 7.84 (2 H, d, J 7.5, Ar-\(H\)), 7.56 (1 H, t, J 7.3, Ar-\(H\)), 7.45 (2 H, t, J 5.8, Ar-\(H\)), 7.36 (5 H, m, Ar-\(H\)), 5.79 (1 H, br d, J 10.8, Ar-\(H\)), 1.18 (1 H, s)

\(^{13}\)C NMR (75 MHz; CDCl\(_3\)) \(\delta_C \) 153.5, 136.9, 134.0, 129.9, 129.9, 129.1, 129.0, 128.8, 81.3, 73.9, 28.0

\(m/z\) (ES) 260.12 (M\(^+\))

**Synthesis of t-Butyl (phenylmethylene)carbamate\(^{[3]}\)**

Anhydrous potassium carbonate (4.13 g, 30 mmol) and sodium sulfate (5 g) were flame dried under vacuum. Once cool \(\text{t-butyl (phenyl(phenylsulfonyl)methyl)carbamate (1.73 g, 5 mmol) was carefully added the flask under a positive stream of nitrogen. THF was added and the mixture heated to reflux for 24 hours. The mixture was cooled, filtered under nitrogen and the supernatant concentrated in vacuo to give a pale yellow oil as the product (1.02 g, quantitative).}

\(^1\)H NMR (300 MHz; CDCl\(_3\)) \(\delta_H \) 8.79 (1 H, s, CHN), 7.86-7.80 (2 H, m, Ar-\(H\)), 7.52-7.44 (1 H, m, Ar-\(H\)), 7.42-7.35 (2 H, m, Ar-\(H\)), 1.51 (9 H, s, CH\(_3\))

\(^{13}\)C NMR (75 MHz; CDCl\(_3\)) \(\delta_C \) 28.0, 82.3, 128.9, 130.2, 133.5, 162.5, 169.7.

\(m/z\) (ES) 205
**Experimental**

**Synthesis of t-butyl((1-methoxyvinyl)oxy)dimethylsilane**\(^{[3]}\)

\[
\begin{align*}
\text{O} & \quad \text{Si} \\
\text{OMe} &
\end{align*}
\]

*n*-Butyl lithium solution in hexanes (6.7 ml, 2.5 M) was added to a solution of anhydrous diisopropylamine (2.5 ml) in THF (30 ml) at 0 °C. The reaction was left to stir for 40 mins and then cooled to -78 °C. Methyl acetate (1.19 ml, 15 mmol) was added dropwise and left to stir for 1 hr. To this was then added DMPU (3 ml) and then t-BuMe\(_2\)SiCl (2.5 g, 16.5 mmol) solution in THF (7 ml). The reaction was left to stir for another hour and then left to warm to room temperature and stirred for another hour. The solvent was removed *in vacuo* and the residue redissolved in pentane and separated with water, then saturated CuSO\(_4\) solution, saturated sodium bicarbonate solution and brine successively. The organic layer was dried over Na\(_2\)SO\(_4\) and concentrated *in vacuo* to give the product, a pale yellow oil (1.26 g, 86%).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta_H 3.36 (3 \text{ H, s, OCH}_3\)), 3.05 (1H, d, J 2.6, C=CHH'), 2.92 (1 H, d, 2.6, C=CHH'), 0.76 (9 H, s, t-Bu), 0.00 (6 H, s, SiCH\(_3\))

\(^{13}\)C NMR (75 MHz; CDCl\(_3\)) \(\delta_C 162.3, 60.0, 55.0, 25.7, 18.10, -4.7\).

**General procedure for the use of thiourea combined with acid in the Mannich-type reaction**

The acid (0.038 mmol) and thiourea \(77\) (14 mg, 0.038 mmol) were added to oven dried tubes microwave tubes. The reaction vessels were sealed under an inert atmosphere and toluene (1 ml) was added. The reactions were left to stir for 30 minutes after which \(N\)-Boc imine (150 mg, 0.75 mmol) was added in toluene (0.5 ml) and then the silyl ketene acetal (0.375 ml, 1.5 mmol) added and then 1-methyl napthalene (0.036 ml). The reactions were then cooled to -28 °C and left for 46 hours.
after which TFA (0.05 ml) was added and left to stir for 2 minutes. The reaction mixtures were then partitioned between sodium carbonate solution and dichloromethane. The phases were partitioned and the aqueous phase washed with dichloromethane and then dried over sodium sulfate. The solvent was removed under reduced pressure and the mixtures analysed by integration of the $^1$H NMR spectra and HPLC.

**Methyl 3-((tert-butoxycarbonyl)amino)-3-phenylproanoate .**

![Chemical Structure](image)

$^1$H NMR (300MHz, CDCl$_3$) $\delta$H 1.45 (9 H, s, Boc), 2.82 (2 H, br s, CH$_2$), 3.59 (3 H, m, CH$_3$), 5.10 (1 H, br s, CH), 5.50 (1 H, br s, NH), 7.24-7.36 (5 H, m, Ar-H)

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$C 28.2, 40.5, 51.3, 79.5, 125.9, 127.6, 128.5, 141.0, 155.3, 171.8 [Data consistent with literature values$^{[3]}$]

**General procedure synthesis of alkyl 3-hydroxy-2-methyl-3-phenylpropanoates**

$n$-Butyl lithium (11.0 ml, 27.5 mmol, 2.5 M in hexanes) was added to a solution of diisopropylamine (4.1 ml, 29.6 mmol) in THF (100 ml) at 0 °C. The mixture was left to stir for 40 minutes before cooling to -78 °C and addition of the alkyl propanoate (27.5 mmol). The reaction mixture was left to stir for 45 minutes before dropwise addition of benzaldehyde (2.77 ml, 27.5 mmol). The mixture was left to stir for 2 hours before addition of aqueous saturated ammonium chloride solution (100 ml). The reaction was allowed to warm to room temperature before extraction with ethyl acetate (x3). The organic phases were combined, dried over magnesium sulfate and concentrated in vacuo. The residue was further purified by silica chromatography eluting with 1:10 to 1:5 ether to hexanes. Diastereomers were recombined for oxidation.


**Experimental**

*t-butyl 3-hydroxy-2-methyl-3-phenylpropanoate 82*

![Chemical structure](image)

The procedure was followed as above using *t*-butyl propionate (4.1 ml, 27.5) to give a yellow oil (5.19 g, 80%).

61:39 syn: anti (determined by $^1$H NMR spectroscopy)

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.94 (3 H, d, $J$ 7.2, anti, CH$_3$), 1.02 (3 H, d, $J$ 7.2 syn, CH$_3$), 1.32 (9 H, s, anti, C(CH$_3$)$_3$), 1.36 (9 H, s, syn, C(CH$_3$)$_3$), 2.62 (1 H, m, syn and anti, OH), 3.04 (1 H, d, $J$ 2.91, anti, CH-OH), 3.14 (1 H, d, $J$ 4.3, syn, CH-OH), 4.62 (1 H, q, $J$ 3.3 anti, CH-CH$_3$), 4.95 (1 H, q, $J$ 1.8 syn, CH-CH$_3$), 7.15-7.29 (5 H, m, Ar-H, syn and anti)

$^{13}$C NMR (75.4 MHz, CDCl$_3$) $\delta$C 10.0, 13.6, 26.9, 27.0, 46.0, 46.7, 72.8, 75.3, 75.6, 76.0, 76.4, 80.0, 80.2, 125.1, 125.6, 126.4, 126.8, 127.1, 127.3, 140.5, 140.8, 174.3 m/z (ES) 259 (M+Na, 100%) [Data consistent with literature values] [17]

**Ethyl 3-hydroxy-2-methyl-3-phenylpropanoate**

![Chemical structure](image)

The procedure was followed as above using ethyl propionate (3.1 ml, 27.5 mmol) to give a yellow oil (4.48 g, 78%).

55:45 syn: anti (determined by $^1$H NMR spectroscopy)
Experimental

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$H 1.03 (3 H, d, $J$ 7.1, anti, CH-CH$_3$), 1.12 (3 H, d, $J$ 7.1, syn, CH-CH$_3$), 1.19 (3 H, t, $J$ 7.1 syn, CH$_2$CH$_3$), 1.25 (3 H, t, $J$ 7.0, anti, CH$_2$CH$_3$), 2.64-2.73 (1 H, m, anti CHCH$_3$), 2.76 (1 H, m, syn, CHCH$_3$), 2.95 (1 H, s, syn, OH), 4.10 (2 H, q, $J$ 7.1, syn, CH$_2$CH$_3$), 4.16 (2 H, q, $J$ 7.1, anti, CH$_2$CH$_3$), 4.73 (1 H, d, $J$ 8.2, anti, CHO), 5.10 (1 H, d, $J$ 4.1, syn, CHO), 7.23-7.34 (5 H, m, syn and anti, Ar-H)

$^{13}$C NMR (75.4 MHz, CDCl$_3$) $\delta$C 10.7, 13.7, 14.0, 14.3, 46.7, 47.2, 60.5, 73.8, 75.9, 125.4, 125.8, 127.4, 127.8, 1278.0, 128.3, 141.6, 141.7, 175.4, 175.8

$m/z$ (ES) 231 (M+Na, 100%) [Data consistent with literature values]$^{[18]}$

**General procedure for the synthesis of alkyl 2-methyl-3-oxo-3-phenylpropanoates**

Jones reagent (3 ml) was added to a cooled solution of alkyl 3-hydroxy-2-methyl-3-phenylpropanoate (0.84 mmol) in acetone (10 ml) at 0 °C. The mixture was left to stir gradually warming to room temperature for 4 hours after which it was concentrated in vacuo. The mixture was extracted between dichloromethane and HCl solution (1 M). The aqueous phase was washed with dichloromethane then the organic phases combined and dried over magnesium sulfate. The solvent was removed in vacuo and resulting yellow oil was found to be the product.

**t-butyl 2-methyl-3-oxo-3-phenylpropanoate 83**

![Structure](image)

Procedure followed as above using t-butyl 3-hydroxy-2-methyl-3-phenylpropanoate (198 mg, 0.84 mmol) to give the product (147 mg, 75%).
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$H 1.27 (9 H, s, C(CH$_3$)$_3$), 1.38 (3 H, d, $J$ 7.1 CH$_3$), 4.18 (1 H, q, $J$ 7.1, CH-CH$_3$), 7.36-7.43 (2 H, m, Ar-H), 7.47-7.53 (1 H, m, Ar-H), 7.87-7.92 (2 H, m, Ar-H)

$^{13}$C NMR (75.4 MHz, CDCl$_3$) $\delta$C 13.5, 28.0, 49.6, 81.8, 128.5, 128.6, 133.2, 136.8, 170.4, 196.5.

m/z (ES) 257 (M+Na, 100%) [Data consistent with literature values][19]

Ethyl 2-methyl-3-oxo-3-phenylpropanoate

Procedure followed as above using ethyl 3-hydroxy-2-methyl-3-phenylpropanoate (173 mg, 0.84 mmol) to give the product (123 mg, 72%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$H 1.09 (3 H, t, $J$ 7.1, CH$_2$C), 1.42 (3 H, d, $J$ 7.1, CH$_3$), 4.07 (2 H, q, $J$ 7.2, CH$_2$C), 4.30 (1 H, q, $J$ 7.1, CH-CH$_2$), 7.48 (2 H, t, $J$ 7.2, Ar-H), 7.51 (1 H, m, Ar-H), 7.88-7.94 (2 H, m, Ar-H)

$^{13}$C NMR (75.4 MHz, CDCl$_3$) $\delta$C 14.0, 48.4, 61.4, 128.6, 130.4, 133.5, 173.4, 196.0.

m/z (ES) 229 (M+Na, 100%) [Data consistent with literature values][20]

General procedure for the synthesis of palladium complexes- Example procedure:

[(rac)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]dichloropalladium(II)

Acetonitrile (3 ml) was added to sodium tetrachloropalladate (100 mg, 0.34 mmol) and rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (211 mg, 0.34 mmol) in a sealed
microwave vial under nitrogen. The mixture was heated in the microwave to 120 °C for 5 minutes and the yellow solution extracted between dichloromethane and water. The solvent was removed from the organic phase under reduced pressure to give a yellow solid, the complex (151 mg, 56%).

$^1$H NMR (300 MHz, CDCl$_3$) δ$_H$ 6.67 (2 H, t, $J$ 6.2, Ar-H), 6.72 (2 H, d, $J$ 8.6, Ar-H), 6.80 (2 H, t, $J$ 7.4, Ar-H), 7.15-7.60 (20 H, m, Ar-H), 7.77 (6 H, m, Ar-H)

$^{31}$P NMR (121.5 MHz; CDCl$_3$) $\delta_p$ +29.9

m/z (CI) 361 (22% M-(Cl$_2$)$_2$), 262 (31%), 185 (87%), 113 (100%) [Data consistent with literature values][21]

[1,2-bis(diphenyl)phosphinoethane]dichloropalladium(II) 84

![Diagram of 1,2-bis(diphenyl)phosphinoethane]dichloropalladium(II)

Procedure followed as above using sodium tetrachloropalladate (100 mg, 0.34 mmol) and 1,2-bis(diphenyl)phosphinoethane (135 mg, 0.34 mmol) to give a pale yellow solid (178 mg, 92%).

$^1$H NMR (300 MHz, CDCl$_3$) δ$_H$ 2.38 (4 H, br s, CH$_2$), 7.38-7.54 (12 H, m, Ar-H), 7.81 (8H, d, $J$ 6.9, Ar-H)

$^{31}$P { $^1$H} NMR (121.4 MHz, CDCl$_3$) $\delta_p$ +64.9 [Data consistent with literature values][22]

[1,3-bis(diphenylphosphino)propane]dichloropalladium(II) 85

![Diagram of 1,3-bis(diphenylphosphino)propane]dichloropalladium(II)
Experimental

Procedure followed as above using sodium tetrachloropalladate (100 mg, 0.34 mmol) and 1,3-bis(diphenylphosphino)propane (140 mg, 0.34 mmol) to give a yellow solid (187 mg, 94%).

$^1$H NMR (300 MHz, CDCl$_3$) δ$_H$ 2.12 (2 H, m, CH$_2$), 3.39 (4 H, m, CH$_2$), 6.82-7.15 (4 H, m, Ar-$H$), 7.21-7.78 (16 H, m, Ar-$H$)

$^{31}$P NMR (121 MHz; CDCl$_3$) δ$_P$ +11.3 [Data consistent with literature values$^{[23]}$]

[1,3-Bis(diphenylphosphino)butane]dichloropalladium(II) 86

![Structure of [1,3-Bis(diphenylphosphino)butane]dichloropalladium(II) 86]

Procedure followed as above using sodium tetrachloropalladate (100 mg, 0.34 mmol) and 1,3-bis(diphenylphosphino)butane (145 mg, 0.34 mmol) to give a yellow solid (126 mg, 62%).

$^1$H NMR (300 MHz; CDCl$_3$) δ$_H$ 1.51 (4 H, br s, CH$_2$), 2.13 (4 H, br s, CH$_2$), 7.64 (8 H, m, Ar-$H$), 7.08-7.49 (12 H, m, Ar-$H$)

$^{31}$P NMR (121.5 MHz; CDCl$_3$) δ$_P$ +29.3. [Data consistent with literature values$^{[24]}$]

[1,2-di(cyclohexyl)phosphinoethane]dichloropalladium(II) 87

![Structure of [1,2-di(cyclohexyl)phosphinoethane]dichloropalladium(II) 87]

Procedure followed as above using sodium tetrachloropalladate (50 mg, 0.17 mmol) and 1,2-di(cyclohexyl)phosphinoethane (71 mg, 0.17 mmol) to give a yellow solid (80 mg, 79%).
**Experimental**

$^1$H NMR (300MHz, CDCl$_3$) $\delta$H 1.15-1.52 (20 H, m, CH$_2$), 1.64-2.42 (28 H, m, CH$_2$)

$^{31}$P{$^1$H} NMR (121.4 MHz, CDCl$_3$) $\delta_p$ +94.5 [Data consistent with literature values]$^{[25]}$

**[1,2-di(p-fluorophenyl)phosphinoethane]dichloropalladium(II)88**

![Chemical Structure]

Procedure followed as above using sodium tetrachloropalladate (50 mg, 0.17 mmol) and 1,2-di(p-fluorophenyl)phosphinoethane (77 mg, 0.17 mmol) to give a yellow solid (94 mg, 86%).

m.p. 242 ºC (decomposed)

$\nu_{\text{max}}$(CDCl$_3$)/cm$^{-1}$ 3740, 1053, 970

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$H 2.43 (4 H, m, CH$_2$), 7.46 (4 H, m, Ar-H), 7.68 (4 H, dd, J 4.3, 11.9, Ar-H)

$^{31}$P NMR (121.4 MHz, CDCl$_3$) $\delta_p$ +63.4

$^{19}$F NMR (282.3 MHz, CDCl$_3$) $\delta_F$ -109.3

m/z (ES) 672.8 (M$^+$+Na, 12%), 670.8 (M$^+$+Na, 100%), 668.8 (M$^+$+Na, 57%),

HRMS m/z (ES) 670.9279 (C$_{26}$H$_{20}$F$_4$Na$^{35}$Cl$^{37}$ClPdP$_2$ requires 670.9256, 100%) 668.9297 (C$_{26}$H$_{20}$F$_4$Na$^{35}$Cl$_2$PdP$_2$ requires 668.9286, 70%)
Experimental

\[1,2\text{-}\text{Bis((2S,5S)-2,5-dimethylphospholano)ethane}]\text{dichloropalladium(II)} \, 90

![Chemical structure of [1,2-Bis((2S,5S)-2,5-dimethylphospholano)ethane]dichloropalladium(II)]

Procedure followed as above using sodium tetrachloropalladate (50 mg, 0.17 mmol) and 1,2-bis((2S,5S)-2,5-dimethylphospholano)ethane (44 mg, 0.17 mmol) to give a yellow powder (74 mg, quant).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) H 1.20 (12 H, br s, CH\(_3\)), 1.38-2.31 (12 H, m, CH\(_2\)), 3.42 (4 H, br s, CH)

\(^{31}\)P NMR (121.5 MHz; CDCl\(_3\)) \(\delta\) P +101.6

\(m/z\) (ES) 399 (M\(^+\)-Cl, 100%)

(Found: C, 38.95; H, 6.38; N, 0.00. C\(_{21}\)H\(_{15}\)N\(_2\)PS\(_2\) requires C, 38.42; H, 6.91; N 0.00%) [Data consistent with literature values]\(^{[26]}\)

\[1,2\text{-}\text{bis((2R,5R)-2,5-diphenylphospholano)ethane}]\text{dichloropalladium(II)} \, 89

![Chemical structure of [1,2-bis((2R,5R)-2,5-diphenylphospholano)ethane]dichloropalladium(II)]

Procedure followed as above to using sodium tetrachloropalladate (50 mg, 0.17 mmol) and 1,2-bis((2R,5R)-2,5-diphenylphospholano)ethane (86 mg, 0.17 mmol) to give a brown solid (107 mg, 92%).

m.p. 281-283 °C (decomposed)

\(\nu_{\text{max}}\) (film) cm\(^{-1}\) 2910, 2894, 1293, 1147, 913, 458, 699, 503
Experimental

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$H 0.88 (2 H, m, CH$_2$), 1.42 (2 H, m, CH$_2$), 1.92-2.32 (4 H, m, CH$_2$), 2.46 (2 H, m, CH$_2$), 2.72 (2 H, m, CH$_2$), 3.03 (2 H, m, CH), 4.78 (2 H, m, CH), 6.73 (4 H, br d, J 7.1, Ar-H), 7.08 (6 H, m, Ar-H), 7.21 (6 H, m, Ar-H), 7.48 (4 H, br d, J 7.4, Ar-H)

$^{31}$P{$^1$H} NMR (121.46 MHz, CDCl$_3$) $\delta$P +99.0

$^{13}$C NMR (75.4 MHz, CDCl$_3$) $\delta$C 27.1 (t, $J_{CP}$ 18.7), 33.0, 35.3, 45.5(m), 54.4 (m), 126.9, 127.8, 127.9, 128.9 (m), 129.2, 135.5 (m), 137.3.

(Found C, 59.45; H, 6.41; N, 0.35; C$_{34}$H$_{36}$Cl$_2$P$_2$Pd requires C, 59.70; H, 6.30; N, 0.00)

[(S)- 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]dichloropalladium(II) 92

![Diagram of [(S)- 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]dichloropalladium(II)]

Procedure followed as above using sodium tetrachloropalladate (50 mg, 0.17 mmol) and (S)- 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (105 mg, 0.17 mmol) to give a yellow solid (102 mg, 76%)

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$H 6.68 (2 H, t, J 6.1, Ar-H), 6.71 (2 H, d, J 8.5, Ar-H), 6.79 (2 H, t, J 7.3, Ar-H), 7.12- 7.58 (20 H, m, Ar-H), 7.76-7.83 (6 H, m, Ar-H)

$^{31}$P NMR (121.5 MHz; CDCl$_3$) $\delta$P +29.7. [Data consistent with literature values]$^{[27]}$

[(R)- 4,12-Bis[diphenylphosphino]-[2.2]-paracyclophane]dichloropalladium(II) 93

![Diagram of [(R)- 4,12-Bis[diphenylphosphino]-[2.2]-paracyclophane]dichloropalladium(II)]]
Procedure followed as above using sodium tetrachloropalladate (50 mg, 0.17 mmol) and \((R)-4,12\text{-Bis[diphenylphosphino]-[2.2]-paracyclophane}\) (98 mg, 0.17 mmol) to give a yellow solid (79 mg, 62%).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 2.13-2.17 (2 H, m, CH\(_2\)), 2.40 (2 H, m, CH\(_2\)), 2.43-2.56 (4 H, m, CH\(_2\)), 6.34 (1 H, J 6.1, Ar-\(H\)) 6.42 (2 H, m, Ar-\(H\)), 7.08-7.14 (3 H, m, Ar-\(H\)), 7.26-7.35 (6 H, m, Ar-\(H\)), 7.39-7.44 (5 H, m, Ar-\(H\)), 7.47-7.52 (4 H, m, Ar-\(H\)), 7.60 (1 H, d, Ar-\(H\)), 7.98-8.04 (4 H, m, Ar-\(H\))

\(^{31}\)P NMR (121.5 MHz; CDCl\(_3\)) \(\delta\) +43.8. [Known Compound][28]

\((S)-4,12\text{-Bis[di(3,5-xylyl)phosphino]-[2.2]-paracyclophane]dichloropalladium(II)}\)

Procedure followed as above using sodium tetrachloropalladate (50 mg, 0.17 mmol) and \((S)-4,12\text{-Bis[di(3,5-xylyl)phosphino]-[2.2]-paracyclophane}\) (108 mg, 0.17 mmol) to obtain an orange solid (124 mg, 90%).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 2.01 (2 H, m, CH\(_2\)), 2.19 (12 H, s, CH\(_3\)) 2.26 (12 H, s, CH\(_3\)), 2.33-2.57 (6 H, m, CH\(_2\)), 6.27 (1 H, d, J 7.9), 6.30 (1 H, d, J 7.9, Ar-\(H\)), 6.37 (1 H, s, Ar-\(H\)), 6.39 (1H, s, Ar-\(H\)), 6.94 (2 H, s, Ar-\(H\)), 7.10 (2 H, s, Ar-\(H\)), 7.21-7.26 (6 H, m, Ar-\(H\)), 7.53 (4 H, d, J 10.0, Ar-\(H\))

\(^{31}\)P NMR (161 MHz; CDCl\(_3\)) \(\delta\) +43.7

HRMS \(m/z\) (ES) 831.2110 (M-Cl\(^+\) C\(_{48}\)H\(_{50}\)P\(_2\)ClPd requires 829.2111) [Data consistent with literature values][29]
Experimental

\[(1R,2R,4R,5R)-4,5\text{-dimethyl-}N^{1},N^{2}\text{-bis((S)-1-phenylethyl)cyclohexane-1,2-diamine}]\text{dichloropalladium(II)} 95

\[
\begin{array}{c}
\text{Ph} \\
\text{Pd} \\
\text{Cl} \\
\text{Cl} \\
\end{array} \\
\begin{array}{c}
\text{NH} \\
\text{NH} \\
\text{Ph} \\
\end{array}
\]

Procedure followed as above using sodium tetrachloropalladate (100 mg, 0.34 mmol) and \((1R,2R,4R,5R)-4,5\text{-dimethyl-}N^{1},N^{2}\text{-bis((S)-1-phenylethyl)cyclohexane-1,2-diamine} (119 mg, 0.34 mmol) to give a brown solid (132 mg, 74%).

m.p. 234 °C (decomposed)

\([\alpha]_D^{20} = -16.0 \text{ (c 0.2, CHCl}_3\text{)}

\(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2952, 1214, 1153, 915, 574, 638, 564, 503

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta_H\) 0.58 (3 H, d, \(J 7.2, \text{CH}_3\)), 0.68-0.87 (8 H, m, \text{CH, CH}_3), 1.01-1.28 (3 H, m, \text{CH}_3), 2.02 (2 H, d, \(J 6.7, \text{CH}_2\)), 2.27 (2 H, d, \(J 7.0, \text{CH}_2\)), 3.06 (1 H, m, \text{CH}), 3.44 (1 H, m, \text{CH}), 4.11 (1 H, m, \text{CH}), 4.30 (1 H, m, \text{CH}), 6.45 (1 H, m, \text{NH}), 6.57 (1 H, m, \text{NH}), 7.10-7.27 (4 H, m, Ar-H), 7.44 (4 H, m, Ar-H), 7.29 (2 H, d, \(J 7.3, \text{Ar-H}\))

\(m/\text{z} \) (ES) 457 (MH\(^+\)-Cl\(_2\)), 455 (MH\(^+\)-Cl\(_2\))

HRMS \(m/\text{z} \) (ES) 455.1686 (C\(_{24}\)H\(_{33}\)N\(_2\)Pd requires 455.1678)

\[\text{[(S)-2,2-Dimethyl-4,5-} \\
\text{((diphenylphosphino)dimethyl)dioxolane]dichloropalladium(II)} 114
\]

\[
\begin{array}{c}
\text{Ph}_2 \\
\end{array} \\
\begin{array}{c}
\text{Pd} \\
\text{Cl} \\
\text{Cl} \\
\end{array}
\]

\(-176-\)
Procedure followed as above using sodium tetrachloropalladate (100 mg, 0.34 mmol) and (S)-2,2-Dimethyl-4,5-((diphenylphosphino)dimethyl)dioxolane (169 mg, 0.34 mmol) to give a yellow solid (204 mg, 89%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$H 1.08 (6 H, br s, C(CH$_3$)$_2$), 2.47 (2 H, br s, CH$_2$), 2.70 (2 H, br s, CH$_2$), 3.82 (2 H, s, CH), 7.23-7.93 (20 H, m, Ar-H)

$^{31}$P NMR (121.46 MHz; CDCl$_3$) $\delta$P +16.1

HRMS m/z (ES) 639.0605 ([M-Cl]$^+$ C$_{31}$H$_{32}$O$_2$P$_2$ClPd requires 639.0601). [Data consistent with literature values$^{[30]}$]

**Synthesis of (acetonitrile)(aqua)(rac)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]palladium(II) tetrafluoroborate**

A solution of silver tetrafluoroborate (36 mg, 0.188 mmol) in acetonitrile (1 ml) was added to a solution of the palladium complex (150 mg, 0.188 mmol) in dichloromethane (2 ml) and left to stir for 3 hours. The solution was filtered through celite to give an orange solution which was concentrated *in vacuo* to give an orange solid (82%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$H 1.94 (3H, s), 6.62 (3 H, m, Ar-H), 6.70 (2 H, d, J 8.1), 6.81 (3 H, m, Ar-H), 7.07 (2 H, t, J 7.4, Ar-H), 7.26 (3 H, m, Ar-H), 7.31-7.50 (13 H, m, Ar-H), 7.51 (2 H, d, J 8.1, Ar-H), 7.72-7.81 (4 H, m, Ar-H)

$^{31}$P $^1$H NMR (121.5 MHz; CDCl$_3$) $\delta$P 34.7

$^{19}$F NMR (282.3 MHz, CDCl$_3$) $\delta$F -152.4 [Data consistent with literature values$^{[31]}$]
General Procedure for the synthesis of \([\text{PdL(OH}_2\text{)(NCMe)}](\text{OTf})_2\).

Example: (acetonitrile)(aqua)[ (rac)- 2,2'-bis(diphenylphosphino)-1,1'-
binaphthyl]palladium(II) trifluoromethylsulfonate

\[
\begin{align*}
\text{Pd} & \quad \text{Ph}_2\text{OH}_2 \\
& \quad \text{Ph}_2\text{NCMe} \\
\end{align*}
\]

\([\text{Pd(rac-BINAP)}\text{Cl}_2]\) in dichloromethane (36 mg, 0.19 mmol) in acetonitrile (1 ml)
was added to a solution of the palladium complex (150 mg, 0.19 mmol) in
dichloromethane (2 ml) and left to stir for 5 hours. The solution was filtered through
celite to give an orange solution which was concentrated \textit{in vacuo} to give an impure
orange solid which was further purified by recrystallisation in dichloromethane to
give the product, an orange solid (158 mg, 74%).

\(^1\text{H NMR (400 MHz, CDCl}_3\) \(\delta H \) 1.97 (3H, s, NCC\(\text{H}_3\)), 6.63 (2 H, d, \(J 8.6\), Ar-\(H\)), 7.95
(2 H, m, Ar-\(H\)), 7.13 (2 H, m, Ar-\(H\)), 7.40-7.64 (6 H, m, Ar-\(H\))
\(^{31}\text{P \{^1\text{H}\} NMR (121.5 MHz; CDCl}_3\) \(\delta \) +32.1
\(^{19}\text{F NMR (376 MHz, CDCl}_3\) -78.3 [Data consistent with literature values\(^{[32]}\)]

(acetonitrile)(aqua)[1,2-bis(diphenyl)phosphinoethane]palladium(II)
trifluoromethylsulfonate 96

\[
\begin{align*}
\text{Pd} & \quad \text{Ph}_2\text{OH}_2 \\
& \quad \text{Ph}_2\text{NCMe} \\
\end{align*}
\]

Procedure followed as above to give a dark yellow solid (73%).
Experimental

$^1$H NMR (300 MHz, CDCl$_3$) $\delta_H$ 1.94 (3 H, s, NCC$_H$3), 2.91 (4 H, m, CH$_2$), 7.50-7.79 (20 H, m, Ar-$H$)

$^{31}$P { $^1$H} NMR (121.4 MHz, CDCl$_3$) $\delta_p$ +75.5 (br s)

$^{19}$F NMR (282.3 MHz, CDCl$_3$) $\delta_F$ -78.0

(acetonitrile)(aqua)[1,2-bis(diphenyl)phosphinopropane]palladium(II)

trifluoromethylsulfonate 97

Procedure followed as above to give a yellow solid (78%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta_H$ 1.92 (3 H, s, CH$_2$), 2.07-2.18 (2H, m, CH$_2$), 3.26 (4 H, br s, CH$_2$), 7.29-7.47 (12 H, m, Ar-$H$), 7.58 (8 H, dd, $J$ 7.7, 12.2, Ar-$H$)

$^{31}$P NMR (121 MHz; CDCl$_3$) $\delta_p$ +13.6

$^{19}$F NMR (100 MHz; CDCl$_3$) $\delta_F$ -78.6 [Data consistent with literature values$^{[32]}$]

(acetonitrile)(aqua)[1,2-bis(diphenyl)phosphinobutane]palladium(II)

trifluoromethylsulfonate 98

Procedure followed as above to give a yellow solid (49%).

$^1$H { $^{31}$P} NMR (300 MHz, CDCl$_3$) $\delta_H$ 1.96 (3 H, s, NCC$_H$3), 2.12 (4 H, br s, CH$_2$), 2.55 (4 H, br s, CH$_2$), 7.36-7.52 (12 H, m, Ar-$H$), 7.56-7.62 (8 H, m, Ar-$H$)

$^{31}$P NMR (121.5 MHz; CDCl$_3$) $\delta_p$ +37.3

$^{19}$F NMR (75 MHz; CDCl$_3$) $\delta_F$ -78.6
Experimental

(acetonitrile)(aqua)[1,2-bis(dicyclohexyl)phosphinoethane]palladium(II) trifluoromethylsulfonate 99

\[
\text{[Cy}_2\text{Pd(OH}_2\text{)}\text{NCMe} \text{2OTf}^+]^{2+}
\]

Procedure followed as above to give yellow solid (72%).

\(^1\text{H NMR (300MHz, CDCl}_3\text{)} \delta_{\text{H}} 1.12-1.52 (20 \text{ H, m, CH}_2\text{, CH}_3\text{, NCCH}_3\text{),}
\]

\(^{31}\text{P \{}^{1}\text{H}\text{\} NMR (121.4 MHz, CDCl}_3\text{)} \delta_{\text{p}} +110.5
\]

\(^{19}\text{F NMR (282.3 MHz, CDCl}_3\text{)} \delta_{\text{F}} -78.2 \text{ [Data consistent with literature values]}^{[33]}

(acetonitrile)(aqua)[1,2-di(p-fluorophenyl)phosphinoethane]palladium(II) trifluoromethylsulfonate 100

\[
\text{[F}_3\text{C}_3\text{Pd(OH}_2\text{)}\text{NCMe} \text{2OTf}^+]^{2+}
\]

Procedure followed as above to give yellow solid (67%).

\(^1\text{H NMR (300 MHz, CDCl}_3\text{)} \delta_{\text{H}} 1.97 (3 \text{ H, s, NCCH}_3\text{), 3.02 (4 \text{ H, br m, CH}_2\text{, CH}_3\text{, NCCH}_3\text{), 7.05-}
\]

7.17 (8 \text{ H, br s, Ar-H), 7.52-7.70 (8 \text{ H, br s, Ar-H)}
\]

\(^{31}\text{P \{}^{1}\text{H}\text{\} NMR (121.4 MHz, CDCl}_3\text{)} \delta_{\text{p}} +76.3
\]
\[ ^{19}F \text{NMR (282.3 MHz, CDCl}_3 \] \delta F -78.7, -108.2

(acetonitrile)(aqua) \[ 1,2-\text{Bis((2R,5R)-2,5-dimethylphospholano)ethane}\]palladium(II) trifluoromethylsulfonate 102

Procedure followed as above to give a pale brown solid (82%)

\[ ^{1}H \text{NMR (400 MHz, CDCl}_3 \] \delta H 1.14-1.73 (12 H, m, CH\textsubscript{3}), 1.96 (3 H, s, NCC\textsubscript{H}} \text{3}), 1.97-2.25 (12 H, m, CH\textsubscript{2}), 3.38 (4 H, br s, CH)
\[ ^{19}F \text{NMR (376 MHz; CDCl}_3 \] -78.2
\[ ^{31}P \{ ^{1}H \} \text{NMR (162.0 MHz; CDCl}_3 \] \delta P +104.2.

(acetonitrile)(aqua) \[ 1,2-\text{bis((2R,5R)-2,5-diphenylphospholano)ethane}\]palladium(II) trifluoromethylsulfonate 101

Procedure followed as above to give a brown solid (79%).
Experimental

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 0.80 (2 H, m, CH$_2$), 1.37 (2 H, m, CH$_2$), 1.96-2.51 (11 H, m, CH$_2$ and NCCH$_3$), 3.59 (2 H, m, CH), 4.05 (2 H, m, CH), 6.89 (4 H, br s, Ar-H), 7.20-7.23 (6 H, m, Ar-H), 7.24-7.30 (10 H, Ar-H)

$^{31}$P {1H} NMR (162.0 MHz, CDCl$_3$) $\delta$P +118.5

$^{19}$F NMR (282.3 MHz, CDCl$_3$) $\delta$F -78.1.

(acetonitrile)(aqua)[1,1'-Bis(di-i-propylphosphino)ferrocene]palladium(II)
trifluoromethylsulfonate 104

![Chemical Structure]

Procedure followed as above to give a purple solid (53%)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 1.29 (12 H, dd, J 6.2, 16.8, CH(CH$_3$_)$_2$), 1.59 (12 H, dd, J 6.3, 16.9, CH(CH$_3$_)$_2$), 2.00 (3 H, br s, NCCH$_3$), 2.60 (4 H, br s, CH(CH$_3$_)$_2$), 4.79 (4 H, s, CpH), 5.23 (4 H, s, CpH)

$^{31}$P {1H} NMR (162.0 MHz; CDCl$_3$) $\delta$P +93.6

$^{19}$F NMR (376 MHz, CDCl$_3$) -78.1 [Data consistent with literature values$^{[32]}$]

(acetonitrile)(aqua)[1,1'-bis(diphenylphosphino)ferrocene]palladium(II)
trifluoromethylsulfonate 103

![Chemical Structure]
Procedure followed as above to give a purple solid (59%).

\[^1\text{H} \text{NMR (300 MHz, CDCl}_3 \] \( \delta_\text{H} 1.94 \) (3 H, s, NCC\( \text{H}_3 \)), 4.56 (4 H, s, Cp-H), 5.23 (4 H, s, Cp-H), 7.39-7.61 (12 H, m, Ar-H), 7.78 (8 H, q, J 5.0, Ar-H)

\[^{31}\text{P NMR (121.4 MHz; CDCl}_3 \] \( \delta_\text{P} +43.8 \)

\[^{19}\text{F NMR (282.7 MHz; CDCl}_3 \] -78.6 [Data consistent with literature values][32]

\((\text{acetonitrile})(\text{aqua})[(S)-2,2'-\text{bis(diphenylphosphino)}-1,1'-\text{binaphthyl}]\text{palladium(II)} \text{ trifluoromethylsulfonate 105}\)

\[
\text{Pd} \quad \begin{array}{c} \text{Ph}_2 \text{NMe} \\ \text{Ph}_2 \text{OH}_2 \end{array} \quad \begin{array}{c} \text{2OT}^+ \\ \text{2PPh}_2 \text{OH}_2 \end{array}
\]

Procedure followed as above to give a yellow powder (71%).

\[^1\text{H} \text{NMR (400 MHz, CDCl}_3 \] \( \delta_\text{H} 1.96 \) (3 H, s, NCC\( \text{H}_3 \)), 6.63 (2 H, d, J 8.6, Ar-H), 7.95 (2 H, m, Ar-H), 7.13 (2 H, m, Ar-H), 7.40-7.64 (6 H, m, Ar-H)

\[^{31}\text{P }\{[^1\text{H}] \text{NMR (121.5 MHz; CDCl}_3 \] \( \delta_\text{P} +31.9 \)

\[^{19}\text{F NMR (376 MHz, CDCl}_3 \] -78.2 [Data consistent with literature values][32]

\((\text{acetonitrile})(\text{aqua})[(R)-4,12-\text{Bis[diphenylphosphino]-}[2.2]-\text{paracyclophane}]\text{palladium(II)} \text{ trifluoromethylsulfonate 106}\)

\[
\text{Pd} \quad \begin{array}{c} \text{Ph}_2 \\ \text{Ph}_2 \text{NMe} \end{array} \quad \begin{array}{c} \text{2TFO}^- \\ \text{2PPh}_2 \text{OH}_2 \end{array}
\]
Experimental

Procedure followed as above to give a yellow solid (55%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$H 1.93 (3 H, s, NCC$_3$H$_3$), 2.44-2.70 (8 H, m, CH$_2$), 6.45 (2 H, br s, Ar-H), 6.59 (2 H, d, J 7.9, Ar-H), 7.15-7.73 (18 H, m, Ar-H), 7.86-8.00 (4 H, m, Ar-H)

$^{31}$P NMR (121.5 MHz; CDCl$_3$) $\delta$P +47.6. [Data consistent with literature values]$^{[19]}$

(acetonitrile)(aqua)((S)- 4,12-Bis[di(3,5-xylyl)phosphino]-[2.2]-paracyclophane)palladium(II) trifluoromethylsulfonate 107

Procedure followed as above to give a yellow solid (69%).

m.p. 201 °C

$[\alpha]_D^{20}=-0.61$ (c=0.4, CHCl$_3$

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$H 1.95 (3 H, s, NCC$_3$H$_3$), 2.19 (2 H, m, CH$_2$), 2.28 (24 H, s, CH$_3$), 2.39-2.61 (6 H, m, CH$_2$), 6.46 (2 H, m, Ar-H), 6.62 (2 H, m, Ar-H), 6.93-7.31 (12 H, m, Ar-H), 7.38 (2 H, m, Ar-H)

$^{31}$P NMR (161 MHz; CDCl$_3$) $\delta$P +49.2

$^{19}$F NMR (282.3 MHz; CDCl$_3$) -78.1
Experimental

(acetonitrile)(aqua)([(1R,2R,4R,5R)-4,5-dimethyl-N\(^1\),N\(^2\)-bis((S)-1-phenylethyl)cyclohexane-1,2-diamine]palladium(II) trifluoromethylsulfonate 108

\[
\begin{array}{c}
\text{Ph} \\
\text{NH} \\
\text{NH} \\
\text{MeCN} \\
\text{OH}_2 \\
\text{Pd} \\
\text{2OT}^- \\
\end{array}
\]

Procedure followed as above to give a dark yellow solid (54%).

\([\alpha]_D^{\text{20}}= -15.2 \text{ (c}=0.20, \text{ CHCl}_3\) \]

\(^1\text{H NMR} \ (300 \text{ MHz, CDCl}_3) \ \delta_H \ 0.70 \ (3 \text{ H, d, J} 7.2, \text{ CH}_3), \ 0.68-0.82 \ (5 \text{ H, m, CH, CH}_3), \ 0.92 \ (3 \text{ H, d, J} 7.2, \text{ CH}_3), \ 1.31 \ (3 \text{ H, d, J} 6.9, \text{ CH}_3), \ 1.63 \ (2 \text{ H, d, J} 6.9, \text{ CH}_2), \ 1.94 \ (3 \text{ H, s, NCH}_3), \ 2.35-2.71 \ (2 \text{ H, m, CH}_2), \ 3.01 \ (1 \text{ H, m, CH}), \ 3.49 \ (1 \text{ H, m, CH}), \ 3.64 \ (1 \text{ H, m, CH}) \ 4.51 \ (1\text{H, m, CH}), \ 6.01 \ (1 \text{ H, m, NH}), \ 6.52 \ (1 \text{ H, m, NH}), \ 7.48-7.72 \ (\text{H, m, Ar-H}) \ 7.92 \ (\text{H, m, Ar-H}),7.52 \ (2 \text{ H, t, J} 8.9, \text{ Ar-H}) \ 7.66 \ (2\text{H, t, J} 7.1, \text{ Ar-H}) \ 8.10 \ (2 \text{ H, J} 7.1, \text{ Ar-H})

\(^1\text{H NMR} \ (282 \text{ MHz, CDCl}_3) \ \delta_F \ -78.4

(acetonitrile)(aqua(S)-2,2-Dimethyl-4,5-((diphenylphosphino)dimethyl)dioxolane]palladium(II) trifluoromethylsulfonate

\[
\begin{array}{c}
\text{Ph}_2 \\
\text{P} \\
\text{Ph}_2 \\
\text{O} \\
\text{Pd} \\
\text{OH}_2 \\
\text{NCMe} \\
\text{2OT}^- \\
\end{array}
\]

Procedure followed as above to give a yellow solid (52%).
Experimental

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 1.28 (6 H, s, C(CH$_3$)$_2$), 1.96 (3 H, s, NCCH$_3$), 2.76-3.00 (2 H, m, CH$_2$), 3.83 (2 H, br s, CH$_2$), 4.19 (2 H, m, CH), 7.26-7.69 (20 H, m, Ar-H)

$^{31}$P NMR (162.0 MHz; CDCl$_3$) $\delta$P +19.0

$^{19}$F NMR (282.3 MHz, CDCl$_3$) $\delta$F -78.5

**General procedure for fluorination reactions using [PdL(OH$_2$)(NCMe)](OTf)$_2$**

The palladium salt (0.0064 mmol, 0.05 eq.), ketone (0.128 mmol), trifluorotoluene (5 µl, 0.042 mmol) and NFSI (60 mg, 0.19 mmol) were placed in a Schlenk flask under inert gas and then ethanol was added (2 ml). The mixture was left to stir vigorously until sampled and analysed by integration of $^{19}$F NMR spectra.

**Synthesis of (R,R)-N$_{11}$,N$_{12}$-bis(diphenylphosphino)-9,10-dihydro-9,10-ethanoanthracene-11,12-diamine 112**

![Chemical structure](image)

Triethylamine (0.14 ml, 1.05 mmol) was added to a solution of (11R,12R)-9,10-dihydro-9,10-ethanoanthracene-11,12-diamine (100 mg, 0.42 mmol, triturated in toluene and left under high vacuum o/n) in ether (7 ml) cooled to 0 ºC. To this was added chlorodiphenylphosphine (0.18 ml, 0.87 mmol). The mixture was left to stir overnight for 19 hours gradually warming to room temperature. Analysis by $^{31}$P NMR spectroscopy showed full conversion of the chlorodiphenylphosphine to the phosphinous amide product and a small amount of the oxide decomposition product of chlorodiphenylphosphine. The product appeared to be $>$95% pure by $^{31}$P NMR. The mixture was then filtered under an inert atmosphere and the filter cake washed with further ether (2x 5 ml). The supernatant was concentrated *in vacuo* to give the phosphinous amide as a yellow solid (234 mg, ~92% pure estimated by uncalibrated
The product was contaminated with a small amount of triethylamine hydrochloride and phosphinous oxide.

\[ ^{31}P \text{ NMR} \] (161 MHz; CDCl\textsubscript{3}) \( \delta \) +43.6

**Synthesis of [(R,R)-\(N^{11},N^{12}\)-bis(diphenylphosphino)-9,10-dihydro-9,10-ethanoanthracene-11,12-diamine]dichloropalladium(II) 113**

![Chemical Structure Image]

The impure ligand 49 (100 mg, >90% pure) and Na\textsubscript{2}PdCl\textsubscript{4} (50 mg, 0.17 mmol) were loaded into a microwave vial which was sealed and then acetonitrile (2 ml) added. The reaction mixture was heated to 120 °C for 5 minutes in the microwave. The mixture was then separated between water and dichloromethane. The organic phase was concentrated \textit{in vacuo} and analysed by \(^{31}\text{P} \text{ NMR} \) spectroscopy. The residue was redissolved in dichloromethane. The mixture was then filtered through an alumina plug and then concentrated \textit{in vacuo} to give the product (98 mg, 74%).

m.p. 257 °C (decomposed)

\( \nu_{\text{max}} \text{(CDCl}_3)/\text{cm}^{-1} \) 3140, 1429, 1210, 1162, 914, 753, 513

\(^1\text{H NMR} \) (400 MHz, CDCl\textsubscript{3}) \( \delta \)H 3.20 (2 H, br s, CH), 4.00 (2 H, br s, CH), 7.06-7.45 (28 H, m, Ar-H)

\(^{31}\text{P NMR} \) (161 MHz; CDCl\textsubscript{3}) \( \delta \)P +69.0

\(^{13}\text{C NMR} \) (100 MHz; CDCl\textsubscript{3}) \( \delta \)C 50.3, 60.2, 124.3, 125.6, 126.9, 127.9, 128.2, 128.5, 131.1, 132.1, 132.8

HRMS m/z (ES) 745.0926 (M-Cl\textsuperscript+ \( \text{C}_{40}\text{H}_{34}\text{ClN}_2\text{P}_2\text{Pd} \) gives 745.0921)

(Found: C, 60.28; H, 5.07; N, 3.26. \( \text{C}_{40}\text{H}_{34}\text{ClN}_2\text{P}_2\text{Pd.C}_3\text{H}_6\text{O.H}_2\text{O} \) (solvents observed in X-ray structure) requires C, 60.19; H, 4.93; N 3.26%)

Single crystal X-ray data given in Appendix 2-Structure 3
Experimental

**Synthesis of borane protected \((11R,12R)-N^{11},N^{12}\text{-bis(diphenylphosphino)}-9,10\text{-dihydro}-9,10\text{-ethanoanthracene-11,12-diamine} 119**

\[(11R,12R)-9,10\text{-dihydro}-9,10\text{-ethanoanthracene-11,12-diamine} (300 \text{ mg, 1.26 mmol, tritutated in toluene and left under high vacuum o/n}) \text{ was dissolved in ether (7 ml)}\] and then triethylamine (0.42 ml, 3.15 mmol) and chlorodiphenylphosphine were added (0.54 ml, 2.61 mmol). The mixture was left to stir for 4 days and analysed for completion using \(^{31}\text{P}\) NMR spectroscopy. It was then filtered, under an inert atmosphere. The filter cake was washed with ether (3 x 10 ml) and the supernatant concentrated in vacuo. The residue was re-dissolved in THF (4 ml) and cooled to 0 °C. Borane solution (5.1 ml, 5.1 mmol, 1 M in THF) was then added dropwise. The mixture was then left to stir overnight gradually warming to room temperature before concentrating in vacuo to give a yellow residue. The residue was further purified by dissolving in toluene and filtering through an alumina plug to give the product, an off white powder (613 mg, 77%).

m.p. 182-183 °C

\([\alpha]_{D}^{20} = +28.85 \text{ (c=0.35, CHCl}_3\text{)}\)

\(\nu_{\text{max}}(\text{CDCl}_3)/\text{cm}^{-1} = 3145, 2450, 1435, 1210, 1153, 913, 743, 507\)

\(^1\text{H NMR} \text{ (300 MHz, CDCl}_3)\)

\(\delta_H = 1.91 \text{ (2 H, d, J 11.8, CH)},\ 3.49 \text{ (2 H, t, J 8.2, CH)},\ 3.92 \text{ (2 H, s, CH)},\ 6.67 \text{ (2 H, d, J 6.8, Ar-H)},\ 6.93 \text{ (2 H, td, J 6.9, 1.3, Ar-H)},\ 7.02 \text{ (2 H, td, J 7.4, 1.3, Ar-H)},\ 7.07-7.53 \text{ (18 H, m, Ar-H)},\ 7.65 \text{ (4 H, m, Ar-H)}\)

\(^{31}\text{P NMR} \text{ (121 MHz; CDCl}_3)\)

\(\delta_P = +55.0 \text{ (br)}\)

\(^{13}\text{C NMR} \text{ (100 MHz; CDCl}_3)\)

\(\delta_C = 52.1, 63.7 \text{ (CH, dd, J}_{CP} 3.3, 8.5),\ 124.6, 126.1, 126.8, 131.6 \text{ (m)},\ 128.7 \text{ (m)},\ 133.0, 137.9, 141.4\)

\(m/z \text{ (ES) 654 (100%, M+Na)}\)

(Found C, 76.14; H, 6.39; N, 4.01; C\(_{40}\)H\(_{40}\)N\(_2\)B\(_2\)P\(_2\) requires C, 75.98; H, 6.38; N, 4.43)
Experimental

Synthesis of (R,R)-1,2-bis(diphenylphosphinamino)cyclohexane 116

Chlorodiphenylphosphine (0.80 ml, 4.44 mmol) was added to a solution of (1R, 2R)-cyclohexadiamine (250 mg, 2.17 mmol triturated in toluene and left under high vacuum o/n) and triethylamine (0.77 ml, 5.47 mmol) in ether (5 ml) at 0 °C under an inert atmosphere. The solution was left to stir for 24 hours and then additional ether was added (3 ml). The mixture was left to stir for a further 41 hours and further ether added (10 ml). The solution was filtered under an inert atmosphere and concentrated in vacuo for several hours to give a pale yellow solid, the pure phosphinous amide (457 mg, 90%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta \) 0.77-2.82 (12 H, m, CH, CH\(_2\), NH) 7.08-7.30(20 H, m, Ar-H)

\(^{31}\)P \(^1\)H NMR (162.0 MHz, CDCl\(_3\)) \(\delta \) +32.9 [Data consistent with literature values][34]

Synthesis of borane protected (R,R)-1,2-bis(diphenylphosphinamino)cyclohexane 120

(1R,2R)-diaminocyclohexane (143 mg, 1.26 mmol, triturated in toluene and left under high vacuum o/n) was dissolved in ether (10 ml) and then triethylamine (0.42 ml, 3.15 mmol) and chlorodiphenylphosphine were added (0.54 ml, 2.61 mmol). The mixture was left to stir for 24 hours monitoring by \(^{31}\)P NMR spectroscopy and then filtered under an inert atmosphere. The filter cake was washed with ether (3 x 10 ml) and the supernatant concentrated in vacuo. The residue was re-dissolved in THF (4
ml) and cooled to 0 °C. Borane solution (5.1 ml, 5.1 mmol, 1 M in THF) was then added dropwise. The mixture was then left to stir 3 days after gradually warming to room temperature before concentrating in vacuo to give a yellow residue. The residue was further purified by dissolving in toluene and filtering through an alumina plug to give the product, a yellow gum (613 mg, 77%).

m.p. 175-177 °C
$\alpha_{D}^{20} = +27.2$ (c 0.2, CHCl$_3$

$\nu_{\text{max}}$(CDCl$_3$/cm$^{-1}$) 3140, 1442, 1216, 1162, 917, 749, 501

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 0.44-2.61 (20 H, m, CH, CH$_2$, NH), 7.16 (4 H, m, Ar-H), 7.37 (8 H, m, Ar-H), 7.65 (8 H, m, Ar-H)

$^{31}$P {$^1$H} NMR (121.6 MHz, CDCl$_3$) 53.7 (br)

$^{13}$C NMR (100 MHz, CDCl$_3$) 27.8, 34.3, 37.0, 129.4, 129.9, 130.2, 134.3, 134.6, 134.9, 135.1, 135.2, 135.6

$m/z$ (ES) 533 (100%, M+Na)

(Found C, 71.05; H, 7.0; N, 6.01; C$_{30}$H$_{38}$N$_2$B$_2$P$_2$ requires C, 70.62; H, 7.51; N, 5.49)

**Synthesis of (Z)-Methyl 2-acetylamino-3-phenylacrylate 120**

DCC (651 mg, 3.15 mmol) was dissolved in dimethylformamide (1 ml) and then dichloromethane (4 ml) added. The mixture was cooled to ~10 °C and to this added a solution of $\alpha$-acetaminocinnamic acid (502 mg, 2.44 mmol) in dichloromethane (4 ml), methanol (3 ml) and dimethylformamide (1 ml). The reaction was left to stir for 16 hours. The mixture was then filtered and washed with dichloromethane. The supernatant was washed with HCl solution (1 M) and dried over magnesium sulfate. The solution was filtered and concentrated in vacuo to give a yellow solid. This was re-dissolved in dimethylformamide and left to stand for 3 days. The precipitate was filtered and the supernatant concentrated in vacuo. It was then purified three times in the following manner: the residue was dissolved in the minimum amount of
methanol and the same volume of ether. The mixture was then frozen and the precipitate filtered to give a colourless powder, the product (182 mg, 34%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$H 2.13 (3 H, s, CH$_3$), 3.86 (3 H, s, CH$_3$), 7.17 (1 H, br s, NH), 7.31-7.43 (3 H, m, Ar-H), 7.38 (2 H, d, $J$ 6.9, Ar-H), 7.61 (1H, br s, C=CH)

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$C 23.38, 52.71, 124.3, 128.6, 129.5, 129.7, 132.3, 133.7, 165.7, 168.9

$m/z$ (ES) 219 (M$^+$). [Data consistent with literature values$^{[35]}$]

A typical procedure for rhodium catalysed hydrogenations.

[Rh(COD)Cl$_2$ (5 mg, 0.010 mmol), DABCO (5 mg, 0.04 mmol) and the borane protected ligand (0.02 mmol) were loaded into a Schlenk and toluene (1 ml) added. The mixture was heated to 50 ºC for 30 minutes. The solution was then added to a mixture of the substrate (4 mmol) in toluene (1 ml) in a sealed vial under nitrogen. The vial was then transferred to an autoclave and the autoclave filled using the standard procedure to 8 bar hydrogen pressure and heated for a set time, after which the mixture was analysed.

Synthesis of copper nitrate salts

Copper(II) nitrate trihydrate (139 mg, 0.057 mmol) and the triarylphosphine (0.14 mmol) were heated to reflux in methanol (3 ml) under nitrogen for 20 minutes during which time a colour change from blue to green to colourless was observed and a white powder precipitated. The suspension was cooled to ~0 ºC then the powder was filtered and washed with cold methanol to give the product.

[Bis(triphenylphosphine)]cuprous nitrate 124

Procedure followed as above to give a colourless powder (23 mg, 62%).
Experimental

$^{1}$H NMR (400 MHz, CDCl$_3$) $\delta$H 7.16-7.23 (18 H, m, Ar-H), 7.26-7.32 (12 H, m, Ar-H)

$^{31}$P NMR (161.9 MHz, CDCl$_3$) $\delta$P -0.7

HRMS $m/z$ (ES) 587.1106 ([Cu(PPh$_3$)$_2$]$^+$ C$_{36}$H$_{30}$P$_2$Cu requires 587.1119) [Data consistent with literature values$^{[36]}$]

[Bis(diphenyl-o-tolylphosphine)]cuprous nitrate 125

Procedure followed as above to give a colourless powder (27 mg, 70%)

m.p. 188-189 °C (decomposed)

$\nu_{\text{max}}$(CDCl$_3$)/cm$^{-1}$ 3055, 1650, 1597, 515

$^{1}$H NMR (400 MHz, CDCl$_3$) $\delta$H 2.34 (3H, s, CH$_3$), 6.76 (2 H, d, J 6.9, Ar-H), 7.10-7.53 (26 H, m, Ar-H)

$^{31}$P NMR (161.9 MHz, CDCl$_3$) $\delta$P +7.3

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$C 21.9, 126.2, 128.5 ($J_{CP}$ 13.1), 129.0, 130.3 ($J_{CP}$ 14.0), 131.3, 131.9, 132.0, 132.6, 134.0, 142.1

HRMS $m/z$ (ES) 615.1419 (M$^+$-NO$_3$ C$_{38}$H$_{34}$P$_2$Cu requires 615.1432)

General procedure for hydrogenation using copper catalysts using potassium tert-butoxide as a base in tert-butanol

The borane protected ligand (119, 8 mg, 0.012 mmol), triarylphosphine (0.060 mmol), copper salt (0.010 mmol eq. Cu) and DABCO (3 mg, 0.024 mmol) were sealed in a vial as specified in the reaction schemes. The potassium t-butoxide solution in t-butyl alcohol (1M) was added and the solution left to stir under nitrogen as specified in the reaction schemes. Acetophenone (0.23 ml, 2 mmol) was then added. Then 1-methyl naphthalene (0.094 ml, 0.66 mmol) or tetraethyilsilane (0.124 ml, 0.66 mmol) were added. The vial was then transferred to an autoclave filled with hydrogen before sealing the vessel at required hydrogen pressure and heating, after which it was vented and the mixture analysed.
General procedure for hydrogenation using copper catalysts for catalysis using sodium tert-butoxide as a base

NatOtBu (72 mg, 0.77 mmol) was fully dissolved in the reaction solvent (10 ml) by stirring at 50 ºC for 30 minutes (30 ºC in the case of CH₂Cl₂) to prepare a stock solution (0.077M).

The NaOtBu solution (2.6 ml, 0.2 mmol) was then injected through a port into an autoclave under nitrogen with the copper salt (0.02 mmol), (S)-DIOP (10 mg, 0.02 mmol), and tritylphosphine (41 mg, 0.12 mmol) loaded into a glass insert in the vessel. Acetophenone (0.46 ml, 4 mmol) was then injected and the autoclave filled using standard procedure at 50 bar hydrogen pressure and heated for 16 hours, after which it was vented and the mixture analysed.
References for Experimental


The Hydrogenation of 9-(trifluoroacetyl)anthracene
6. **APPENDIX 1:**

**THE HYDROGENATION OF 9-(TRIFLUOROACETYL)anthracene**

6.1. Asymmetric hydrogenation of fluorinated ketones

Trifluoromethyl groups can often significantly enhance the rate of reactions. This effect is in evidence in the ene reaction where ethyl trifluoropyruvate reacts with α-methylstyrene at room temperature whereas ethyl glyoxylate does not (Section 2.3). In asymmetric hydrogenation the activation barrier difference between the catalysed reactions forming either enantiomer of substrates with a trifluoromethyl group (such as α,α,α-trifluoroacetophenone) differs to such an extent that under the same conditions as the methyl group the reaction gives significantly lower enantioselectivity. There are a few recent examples where hydrogenation to form these trifluoromethyl alcohols has specifically been researched which are as follows.

Kuroki and co-workers used a rhodium complex, [Rh((S)-Cy,Cy-oxoProNOP)OCOCF$_3$)$_2$, to synthesise a range of chiral trifluoromethyl alcohols (Scheme 6.1, Table 6.1). This catalyst has previously been used to enantioselectively catalyse the hydrogenation of 2,2-difluoro-3-hydroxycarboxylates in a screen of
Appendix 1: The Hydrogenation of 9-(trifluoroacetyl)anthracene

chiral ligands.\textsuperscript{[1]} The catalyst gives high enantioselectivity for a range of substrates.\textsuperscript{[2]} Sterk and co-workers also devised a highly enantioselective system for the transfer hydrogenation of fluorinated ketones (Scheme 6.2, Table 6.2).\textsuperscript{[3]}

Scheme 6.1 Asymmetric hydrogenation of ketones using $[\text{Rh((S)-Cy,Cy-oxoProNOP)OCOCF}_3]_2$

![Scheme 6.1](image)

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
<th>e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C$_6$H$_5$</td>
<td>98</td>
<td>97</td>
</tr>
<tr>
<td>c-C$<em>6$H$</em>{11}$</td>
<td>90</td>
<td>97</td>
</tr>
<tr>
<td>c-C$_6$H$_5$CH$_2$</td>
<td>97</td>
<td>98</td>
</tr>
<tr>
<td>PhCH$_2$</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>PhCH$_2$CH$_2$</td>
<td>90</td>
<td>96</td>
</tr>
<tr>
<td>PhCH$_2$OCH$_2$</td>
<td>100</td>
<td>86</td>
</tr>
<tr>
<td>p-ClPh</td>
<td>8</td>
<td>38</td>
</tr>
<tr>
<td>p-CH$_3$OPh</td>
<td>100</td>
<td>83</td>
</tr>
</tbody>
</table>

Table 6.1 Catalytic results for asymmetric hydrogenation of ketones using $[\text{Rh((S)-Cy,Cy-oxoProNOP)OCOCF}_3]_2$

Scheme 6.2 Transfer hydrogenation of trifluoromethyl ketones
Table 6.2 Conversion and enantioselectivity for transfer hydrogenation of fluorinated ketones

Thus far no studies have examined the hydrogenation of Pirkle’s alcohol precursor 9-(trifluoroacetyl)anthracene, one of the most useful trifluoromethyl alcohols. Pirkle’s alcohol, (126, optically pure 1-(9-Anthryl)-2,2,2-trifluoroethanol) is a commercially available chiral solvating agent.

The chiral alcohol associates with a chiral substrate in the deuterated solvent and associates with either enantiomer to give diastereotopic signals in the NMR spectra (Figure 6.2). The difference in ratio of these signals allows the enantioselectivity of the mixture to be measured.
Appendix 1: The Hydrogenation of 9-(trifluoroacetyl)anthracene

Figure 6.2 (S)-1-(9-Anthryl)-2,2,2-trifluoroethanol forming diastereotopic species with S and R ≠ Valerolactone.

Pirkle suggests this is how the two species associate

6.2. The Synthesis of Pirkle’s Alcohol

Pirkle’s alcohol can also be prepared by resolving the protected racemic alcohol by using an enzyme[4] or a chiral alcohol in conjunction with LiAlH₄ (Scheme 6.3).[5] Other methods have been developed in the literature but none use chiral catalysts. Currently the R enantiomer of Pirkle’s alcohol is priced at £46 for 100 mg[6] thus a cheaper method of production would be desirable.

Scheme 6.3 Simplified version of synthetic route’s to Pirkle’s alcohol

Pirkle originally demonstrated the alcohol as a chiral NMR shift reagent on lactones,[7] but it has also been shown to resolve structures as diverse as pyrrolidinones,[8] oxaziridines[9] and axially chiral allenes (through derivitisation with mercuric acetate-methanol)[10] (Figure 6.3).
Appendix 1: The Hydrogenation of 9-(trifluoroacetyl)anthracene

Both transfer hydrogenation and pressure hydrogenation have been shown to give high enantioselectivity for conversion of trifluoromethyl ketones. It was therefore decided to study the application of both methods in the asymmetric catalytic hydrogenation of 1-(anthracen-9-yl)-2,2,2-trifluoroethanone.

Previous studies by Clarke et al. into hydrogenation have found that a tridentate ligand on ruthenium complex 128 gives both high conversion and high enantioselectivity for bulky ketones such as t-butylacetophenone.\cite{11} It was found that the ruthenium catalyst 128 gave moderate conversion and selectivity (Scheme 6.4) for the hydrogenation of 9-(trifluoroacetyl)anthracene.\cite{11c}

![Figure 6.3](image)

**Figure 6.3** Substances which have been shown to chirally resolve in the presence of Pirkle's alcohol

**Scheme 6.4** Hydrogenation of 9-(trifluoroacetyl)anthracene using a ruthenium complex with a tridentate ligand

### 6.3. Transfer Hydrogenation of 9-(trifluoroacetyl)anthracene

Many catalysts have been developed for transfer hydrogenation. Previous work has found that chiral amines can give high enantioselectivities when used in
conjunction with ruthenium and iridium precursors.\textsuperscript{[12]} There are many chiral amines that are available but since BINAP has proved a particularly effective ligand the related ligand $1,1'$-Bi(2-naphthylamine) (129, BINAM) could prove particularly effective in hydrogenation reactions. BINAM has not been used in transfer hydrogenations before and so its use was examined with $[\text{Ru}(\text{PPh}_3)_3\text{Cl}_2]$ and $[\text{IrCODCl}]_2$ at 1 mol\% metal loading (Scheme 6.5, Table 6.3). The ligand and metal precursor were pre-stirred in order to allow the BINAM to coordinate to the metal. $[\text{Ru}(\text{PPh}_3)_3\text{Cl}_2]$ gave the highest conversion but $[\text{IrCODCl}]_2$ gave the highest e.e.

Preliminary studies found that heating of the reaction was required in order for it to proceed at a reasonable rate. This slow reactivity is likely to be due to steric bulk of the 9-(trifluoroacetyl)anthracene.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
Metal salt & Conversion to product (19 hrs)$^{[a]}$ & Conversion to product (43 hrs)$^{[a]}$ & e.e. product (43 hrs)$^{[b]}$ \\
\hline
$[\text{IrCODCl}]_2$ & 81 & 79 & 6 \\
$\text{Ru}(\text{PPh}_3)_3\text{Cl}_2$ & 52 & 50 & 50 \\
\hline
\end{tabular}
\caption{Table 6.3 Results for Catalysed transfer hydrogenation of 9-(trifluoroacetyl)anthracene. $^{[a]}$Conversion determined using $^{19}$F NMR spectroscopy. $^{[b]}$e.e. determined using OJ column eluting with 95:5 hexanes: $^t$PrOH 1 ml/min}
\end{table}
The enantioselectivity obtained from these reactions was very modest so it was decided to use a different chiral amine in conjunction with [IrCODCl]₂ (Scheme 6.6, Table 6.4) and [Ru(PPh₃)₃Cl₂] (Scheme 6.7, Table 6.4) BINAM is an aromatic amine and thus may not be strongly coordinating to the metal centres. A chiral aliphatic amine that has been scarcely investigated in catalysis is (11R,12R)-9,10-Dihydro-9,10-ethanoanthracene-11,12-diamine 130. This diamine was also found to give poor enantioselectivity and with both metal precursors gave low enantiomeric excess.

![Scheme 6.6](image)

**Scheme 6.6** Use of chiral amine in transfer hydrogenation of 9-(trifluoroacetyl)anthracene

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Conversion to alcohol (%)</th>
<th>e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>20</td>
<td>26</td>
<td>9</td>
</tr>
<tr>
<td>54</td>
<td>27</td>
<td>7</td>
</tr>
</tbody>
</table>

**Table 6.4** Conversion to product and enantioselectivity for iridium and chiral amine catalysed hydrogenation shown in Scheme 6.6

[a]Conversion determined using ¹⁹F NMR spectroscopy. [b]e.e. determined using OJ column eluting with 95:5 hexanes: iPrOH 1 ml/min

-204-
Appendix 1: The Hydrogenation of 9-(trifluoroacetyl)anthracene

Scheme 6.7 Use of chiral amine in transfer hydrogenation 9-(trifluoroacetyl)anthracene

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Conversion to alcohol (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>e.e. (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td>54</td>
<td>54</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 6.5 Conversion to product and enantioselectivity for ruthenium and chiral amine catalysed hydrogenation

<sup>a</sup>Conversion determined using <sup>19</sup>F NMR spectroscopy. <sup>b</sup>e.e. determined using OJ column eluting with 95:5 hexanes: ¹PrOH 1 ml/min

6.4 Pressure hydrogenation of 9-(trifluoroacetyl)anthracene

Pressure hydrogenation uses hydrogen gas as a hydrogen source. Since BINAM gave some enantioselectivity in the previous reactions it was again used in pressure hydrogenations since it is possible that the enantioselectivity improves under different conditions. Ruthenium was found to give the highest enantioselectivity so two different methods were used to prepare the ruthenium-amine catalyst. The first was to mix (R)-BINAM with [Ru(COD)Cl<sub>2</sub>] polymer for one hour under nitrogen in isopropanol at 85 ºC. Triphenylphosphine was then added to this heated reaction mixture. The second was to pre-stir the (R)-BINAM with [Ru(PPh<sub>3</sub>)<sub>3</sub>Cl<sub>2</sub>]. The product of these reactions was then added to the solid 9-(trifluoroacetyl)naphthalene and the mixture heated to reflux and then used in the reaction. It was found that low enantioselectivities and conversions were obtained overnight (Scheme 6.8, Table 6.6). The catalyst mixture was also found to be air sensitive in solution since transfer via syringe to another reaction vessel containing the solid substrate lowers the yield. Increasing the catalyst loading significantly improved the yield but not the enantioselectivity.
Appendix 1: The Hydrogenation of 9-(trifluoroacetyl)anthracene

Scheme 6.8 Ruthenium catalysed hydrogenation of 9-(trifluoroacetyl)anthracene

\[
\begin{array}{c}
\text{Scheme 6.8 Ruthenium catalysed hydrogenation of 9-(trifluoroacetyl)anthracene} \\
\text{Catalyst precursor} & \text{Conversion to product (%)\textsuperscript{[a]}} & \text{e.e. (%)}\textsuperscript{[b]} \\
[\text{Ru(COD)Cl\textsubscript{2}}]_0 & 47 & 0 \\
[\text{Ru(PPh\textsubscript{3})\textsubscript{3}Cl\textsubscript{2}}] & 44 & 9
\end{array}
\]

Table 6.6 Results for ruthenium catalysed hydrogenation

\textsuperscript{[a]} Conversion determined using \textsuperscript{19}F NMR spectroscopy. \textsuperscript{[b]} e.e. determined using OJ column eluting with 95:5 hexanes: \textsuperscript{1}PrOH 1 ml/min

Scheme 6.9 Ruthenium catalysed hydrogenation of 9-(trifluoroacetyl)anthracene

\[
\begin{array}{c}
\text{Scheme 6.9 Ruthenium catalysed hydrogenation of 9-(trifluoroacetyl)anthracene} \\
\text{Catalyst precursor} & \text{Conversion to product (%)\textsuperscript{[a]}} & \text{e.e. (%)}\textsuperscript{[b]} \\
[\text{Ru(COD)Cl\textsubscript{2}}]_0 & >95\% & 0 \\
[\text{Ru(PPh\textsubscript{3})\textsubscript{3}Cl\textsubscript{2}}] & >95\% & 4
\end{array}
\]

Table 6.7 Results for ruthenium catalysed hydrogenation of 9-(trifluoroacetyl)anthracene

\textsuperscript{[a]} Conversion determined using \textsuperscript{19}F NMR spectroscopy. \textsuperscript{[b]} e.e. determined using OJ column eluting with 95:5 hexanes: \textsuperscript{1}PrOH 1 ml/min

[Ru(chiral bisphosphine)((R,R)-DPEN)Cl\textsubscript{2}] type complexes are the most successful asymmetric hydrogenation catalysts for ketones. Since they give such high activity and enantioselectivity the catalytic activity of these catalysts was tested for 9-(trifluoroacetyl)anthracene in pressure hydrogenation. [Ru((R)-BINAP((R,R)-DPEN)Cl\textsubscript{2}] was prepared in a microwave accelerated reaction (Scheme 6.10). Moderate enantioselectivity was found at the relatively low pressure of 10 bar using [Ru((S)-xyllylphanephos)((R,R)-DPEN)Cl\textsubscript{2}],  [Ru((S)-phanephos)((R,R)-DPEN)Cl\textsubscript{2}],  [Ru((R)-BINAP)((R,R)-DPEN)Cl\textsubscript{2}] but especially with [Ru((R)-hexahemp)((R,R)-DPEN)Cl\textsubscript{2}] which gave 93\% conversion and 61\% e.e (Scheme 6.11, Table 6.8).
When the reaction time was reduced to 6 hours from 16 the enantioselectivity was at a similar level but it was determined that longer reaction time were required to give high conversion.

![Scheme 6.10 Microwave accelerated synthesis of [Ru((R)-BINAP)((R,R)-DPEN)Cl$_2$](image)]

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Reaction time (hrs)</th>
<th>Conversion to product (%)$^{[a]}$</th>
<th>e.e. (%)$^{[b]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Ru((S)-xyllylphanephos)((R,R)-DPEN)Cl$_2$]</td>
<td>16</td>
<td>53</td>
<td>46</td>
</tr>
<tr>
<td>[Ru((S)-phanehos)((R,R)-DPEN)Cl$_2$]</td>
<td>16</td>
<td>41</td>
<td>40</td>
</tr>
<tr>
<td>[Ru((R)-BINAP)((R,R)-DPEN)Cl$_2$]</td>
<td>16</td>
<td>50</td>
<td>52</td>
</tr>
<tr>
<td>[Ru((R)-hexaphemp)((R,R)-DPEN)Cl$_2$]</td>
<td>16</td>
<td>93 (89%)$^{[c]}$</td>
<td>61</td>
</tr>
<tr>
<td>[Ru((R)-hexaphemp)((R,R)-DPEN)Cl$_2$]</td>
<td>6</td>
<td>34</td>
<td>57</td>
</tr>
</tbody>
</table>

**Table 6.8 Results for [Ru(L)((R,R)-DPEN)Cl$_2$] catalysed hydrogenation of 9-(trifluoromethyl)anthracene.**

$^{[a]}$Conversion determined using $^{19}$F NMR spectroscopy. $^{[b]}$e.e. determined using OJ column eluting with 95:5 hexanes: PrOH 1 ml/min. $^{[c]}$Isolated yield

It was thought that a new tridentate ligand could give high enantioselectivity; however when ruthenium catalyst 131 was tested (Scheme 6.12, Table 6.9) it gave
poor enantioselectivity, although better conversion under the same conditions. The structurally similar catalyst 132 also gave poor enantioselectivity (Scheme 6.13).

![Scheme 6.12 Hydrogenation of 9-(trifluoroacetyl)anthracene using catalyst 131]

<table>
<thead>
<tr>
<th>131 x mol%</th>
<th>Reaction Time (hrs)</th>
<th>Conversion to product (%)(^{[a]})</th>
<th>e.e. (%)(^{[b]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>16</td>
<td>&gt;95</td>
<td>6</td>
</tr>
<tr>
<td>1</td>
<td>16</td>
<td>&gt;95</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>46</td>
<td>&gt;95</td>
<td>3</td>
</tr>
</tbody>
</table>

**Table 6.9 Conversion and enantioselectivity of 131 catalysed hydrogenation of 9-(trifluoroacetyl)anthracene**

\(^{[a]}\)Conversion determined using \(^{19}\)F NMR spectroscopy. \(^{[b]}\)e.e. determined using OJ column eluting with 95:5 hexanes: \(^{1}PrOH\) 1 ml/min
Appendix 1: The Hydrogenation of 9-(trifluoroacetyl)anthracene

Scheme 6.13 Hydrogenation of 9-(trifluoroacetyl)anthracene using catalyst 132

Conversion determined using \(^{19}\)F NMR spectroscopy. e.e. determined using OJ column eluting with 95:5 hexanes: \(^{1}\)PrOH 1 ml/min

6.5. Conclusions and Future Work

9-(trifluoroacetyl)anthracene is a bulky ketone which can be hydrogenated with a range of catalysts. The difficulty lies with making this reaction enantioselective. Promising results were obtained with the transfer hydrogenation using [Ru(PPh\(_3\))\(_3\)Cl\(_2\)] with BINAM (Scheme 6.5, Table 6.3, 50% conversion, 50% e.e.), and with pressure hydrogenation using [Ru((R)-hexaphemp)(R,R-DPEN)Cl\(_2\)] (Scheme 6.11, Table 6.8, 93% conversion, 61% e.e.). However, these are not enantioselective enough to make the synthesis of enantiomerically pure 1-(9-anthryl)-2,2,2-trifluoroethanol viable without further resolution steps.

[Ru((R)-hexaphemp)(R,R-DPEN)Cl\(_2\)] gave the highest enantioselectivity and conversion for this reaction. It is possible that optimisation of this catalyst would give higher enantioselectivity. By using ligands such as MeO-BIPHEP or SEGPHOS (Figure 6.4) which have a similar dihedral angle to hexaphemp and therefore may be promising structurally related ligands that might give high enantiomeric excess.
Other diamine DPEN ligands such as N-p-Tosyl-1,2-diphenylethylenediamine (Ts-DPEN) the derived ruthenium catalyst could also be used. This catalyst could then be applied to other ketones with trifluoromethyl groups such as \( \alpha,\alpha,\alpha \)-trifluoroacetophenone to give (trifluoromethyl)benzyl alcohols that could also be used as chiral solvating agents. Other NMR spectroscopy derivitisation methods have been found using these alcohols. Williamson and co-workers have found that pure (\( R \))-\( \alpha \)-(trifluoromethyl)benzyl alcohol can be used to synthesise silyl ether reagents \textit{in situ} (Scheme 6.14) to determine chiral purity of chiral alcohols in NMR spectroscopy through the difference in diastereotopic peaks.\(^{13}\) The advantage if this method over other derivitising agents such as Mosher’s acid is that the silyl can be easily cleaved using TBAF and then purified by washing through silica. The development of this methodology could therefore proved useful for synthesis of chiral auxiliaries and agents used in the determination of enantiomeric excess using NMR spectroscopy.

\[ \text{Scheme 6.14 NMR spectroscopy derivitisation method for alcohols using chiral trifluoromethyl alcohol} \]
6.6. Experimental

**General procedure for transfer hydrogenation**

The catalyst reaction mixture was prepared as described in the reaction scheme in sealed glass vial equipped with a stirrer bar under inert gas in *iso*-propanol (1 ml). KOtBu solution (1 M in *tert*-BuOH) was added and then 9-(trifluoroacetyl)anthracene (274 mg, 1 mmol) as a solution dissolved in the minimum amount of *iso*-propanol. The mixture was then heated under inert gas for the specified time before analysis by $^{19}$F NMR spectroscopy and HPLC. The $^{19}$F NMR spectroscopy and HPLC data were obtained for comparison from the racemic sample synthesised using NaBH$_4$. The HPLC retention times were occasionally variable by ~2 minutes in which case the HPLC sample was re-run doped with racemic sample to confirm the presence of the product and no side products.

**(rac)-1,1,1-trifluoro-2-anthracene ethanol 126**

![Chemical structure](image)

9-(trifluoroacetyl)anthracene (100 mg, 0.36 mmol) was gradually added to a solution of NaBH$_4$ (37 mg, 1 mmol) in ethanol (3 ml) cooled to 0 °C. The mixture was left to stir for 16 hours gradually warming to room temperature. The mixture was quenched by slow addition to cooled aqueous HCl solution (2 M, 10 ml) and then extracted by repeatedly washing with dichloromethane. The solvent was removed in vacuo to give a yellow gum as the product (61 mg, 62%).
Appendix 1: The Hydrogenation of 9-(trifluoroacetyl)anthracene

$^1$H NMR (400MHz, CDCl$_3$) $\delta$H 2.92 (1H, s, O-H), 6.60 (1H, q, J 8.2, CH), 7.40-7.54 (4 H, m, Ar-H), 7.97 (2 H, d, J 8.4, Ar-H), 8.49 (1 H, s, Ar-H), 8.90 (2H, m, Ar-H)

$^{19}$F $\{^1$H$\}$ NMR (376.4 MHz, CDCl$_3$) $\delta$F -74.5; [Data consistent with literature values][14]

Chiral HPLC (Chiralcel OJ, 5:95 iPrOH: hexanes, 1 ml/min) $t_R$ 29.4 mins, $t_R$ 34.6 mins.

**General procedure for pressure hydrogenation of ketone**

9-(trifluoroacetyl)anthracene (274 mg, 1 mmol), KO$^t$Bu solution (1 M in tert-BuOH) and the catalyst were placed in a glass vial and sealed. The vial was purged with nitrogen and iso-propanol added (3 ml). The substrate was added as a solution in the minimum volume of iso-propanol. The reaction was put under hydrogen pressure at the required pressure and left to stir for the specified time before venting the autoclave and analysis by $^{19}$F NMR spectroscopy and HPLC.

**General procedure for pressure hydrogenation of ketone where the catalyst was prepared in situ**

The catalyst reaction mixture was prepared as described in the reaction scheme in iso-propanol (1 ml). KO$^t$Bu solution (1 M in tert-BuOH) was added and then 9-(trifluoroacetyl)anthracene (274 mg, 1 mmol) as a solution dissolved in the minimum amount of iso-propanol. The reaction was then pressurised, left to stir and analysed as above.

**Synthesis of Dichloro[(R)-bis(diphenylphosphino)-1,1-binaphthyl][(1R,2R)-1,2-diphenylethylenediamine]ruthenium(II)**

Modified from a group procedure for the synthesis of ruthenium complexes in the microwave$^{[11c]}$
Appendix 1: The Hydrogenation of 9-(trifluoroacetyl)anthracene

[Ru(C₆H₆)Cl₂]₂ (15 mg, 0.03 mmol) and (R)-BINAP (37 mg, 0.06 mmol) were loaded into a microwave vial which was sealed and tetrahydrofuran (2.5 ml) was added under inert gas. The mixture was heated to 120 °C for 15 minutes. (R,R)-DPEN (12 mg, 0.06 mmol) was then added as a solution in tetrahydrofuran (2 ml) and the mixture heated to 120 °C for 15 minutes. The solvent was removed in vacuo and recrystallised from 4:1 dichloromethane: ether to give the ruthenium complex as a brown solid (36 mg, 60%).

1H NMR (300 MHz, CDCl₃) δH 2.84 (2 H, m, NH), 3.15 (2 H, m, NH), 4.13 (2 H, m, CH), 6.07 (2 H, d, J 8.7, Ar-H), 6.42 (6 H, m, Ar-H), 6.57 (2 H, m, Ar-H), 6.68 (2 H, m, Ar-H), 6.95-7.29 (16 H, m, Ar-H), 7.50 (2 H, d, J 8.0, Ar-H), 7.59 (4 H, m, Ar-H), 7.72 (2 H, d, J 8.6, Ar-H), 7.88 (4 H, m, Ar-H), 8.23 (2 H, m, Ar-H)

31P {1H} NMR (121.5 MHz, CDCl₃) δP 45.5 [Data consistent with literature values][¹⁵]
Appendix 1: The Hydrogenation of 9-(trifluoroacetyl)anthracene

References for Appendix 1

Appendix 2

X-ray crystallography data
APPENDIX 2

X-RAY CRYSTALLOGRAPHY DATA

X-ray Crystal Structure 1

Empirical formula C_{21}H_{15}F_{6}N_{2}P S_{2}
Formula weight 504.44
Temperature 93(2) K
Wavelength 0.71073 Å
Crystal system Triclinic
Space group P-1
Unit cell dimensions a = 7.417(3) Å
              b = 11.813(4) Å
              c = 12.958(5) Å
              α = 92.781(13)°.
              β = 96.446(8)°.
              γ = 105.727(10)°.
Volume 1082.2(7) Å³
Z 2
Density (calculated) 1.548 Mg/m³
Absorption coefficient 0.383 mm⁻¹
F(000) 512
Crystal size 0.30 x 0.30 x 0.30 mm³
Theta range for data collection 1.59 to 25.35°.
Index ranges -8<=h<=8, -14<=k<=13, -11<=l<=15
Reflections collected 7030
Independent reflections 3815 [R(int) = 0.0274]
Completeness to theta = 25.00° 96.7 %
Absorption correction Multiscan
Max. and min. transmission 1.000 and 0.827
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 3815 / 44 / 325
Goodness-of-fit on F² 0.630
Final R indices [I>2sigma(I)] R1 = 0.0483, wR2 = 0.1236
R indices (all data) R1 = 0.0547, wR2 = 0.1315
Largest diff. peak and hole 1.109 and -0.754 e.Å⁻³
Appendix 2: X-ray crystallography

X-ray crystal structure 2

<table>
<thead>
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<th>Property</th>
<th>Value</th>
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</tr>
<tr>
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<td>93(2) K</td>
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<tr>
<td>Wavelength</td>
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<tr>
<td>Crystal system</td>
<td>Triclinic</td>
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<tr>
<td>Space group</td>
<td>P-1</td>
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<tr>
<td>b</td>
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<tr>
<td>c</td>
<td>15.824(9) Å</td>
</tr>
<tr>
<td>Volume</td>
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<tr>
<td>Z</td>
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<tr>
<td>Density (calculated)</td>
<td>1.529 Mg/m^3</td>
</tr>
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<tr>
<td>F(000)</td>
<td>768</td>
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<tr>
<td>Crystal size</td>
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</tr>
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<td>Theta range for data collection</td>
<td>2.23 to 25.35°</td>
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<td>Independent reflections</td>
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<td>Completens to theta = 25.00°</td>
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<tr>
<td>Absorption correction</td>
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<tr>
<td>Max. and min. transmission</td>
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<tr>
<td>Refinement method</td>
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<tr>
<td>Data / restraints / parameters</td>
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<td>Goodness-of-fit on F^2</td>
<td>1.362</td>
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<td>Final R indices [F&gt;2sigma(I)]</td>
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<tr>
<td>R indices (all data)</td>
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</tr>
<tr>
<td>Extinction coefficient</td>
<td>0.018(7)</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>1.006 and -0.792 e.Å^-3</td>
</tr>
</tbody>
</table>
Empirical formula: $\text{C}_{43}\text{H}_{42}\text{Cl}_2\text{N}_2\text{O}_2\text{P}_2\text{Pd}$
Formula weight: 858.03
Temperature: 93(2) K
Wavelength: 0.71073 Å
Crystal system: Orthorhombic
Space group: $P2_12_12_1$
Unit cell dimensions:
- $a = 10.543(2)$ Å, $\alpha = 90^\circ$
- $b = 17.439(4)$ Å, $\beta = 90^\circ$
- $c = 20.988(4)$ Å, $\gamma = 90^\circ$
Volume: 3858.7(14) Å$^3$
Z: 4
Density (calculated): 1.477 Mg/m$^3$
Absorption coefficient: 0.742 mm$^{-1}$
F(000): 1760
Crystal size: 0.2000 x 0.2000 x 0.2000 mm$^3$
Theta range for data collection: 2.16 to 25.32°
Index ranges: $-12 \leq h \leq 12$, $-16 \leq k \leq 20$, $-25 \leq l \leq 23$
Reflections collected: 24564
Independent reflections: 7018 [R(int) = 0.0682]
Completeness to theta = 25.00°: 99.9 %
Absorption correction: Multiscan
Max. and min. transmission: 1.0000 and 0.7699
Refinement method: Full-matrix least-squares on F$^2$
Data / restraints / parameters: 7018 / 4 / 488
Goodness-of-fit on F$^2$: 0.988
Final R indices [I>2sigma(I)]: $R1 = 0.0399$, $wR2 = 0.0666$
R indices (all data): $R1 = 0.0500$, $wR2 = 0.0710$
Absolute structure parameter: 0.01(2)
Largest diff. peak and hole: 0.777 and -0.676 e Å$^{-3}$
APPENDIX 3

COURSES AND CONFERENCES ATTENDED

Courses attended
The following courses were attended within EaSTChem as part of the compulsory requirement for PhD study within the School of Chemistry

**Hot Topics in Catalysis**- Prof. D.J. Cole Hamilton and Dr. P.A. Wright

**Supramolecular Chemistry**- 2 day symposium

**Organosilicon Chemistry**- Prof. I. Fleming

**NMR Spectroscopy**- Dr. T. Lebl

Conferences attended

December 2005 **Scottish Regional Meeting of the RSC Organic Division** (Edinburgh)

July 2006 **International Symposium on Organocatalysis in Organic Synthesis** (Glasgow)

September 2006 **USIC 2006** (St Andrews)

December 2006 **Scottish Regional Meeting of the RSC Organic Division** (Heriot-Watt)

March 2007 **Young Chemists 2007** (Imperial College)

June 2007 **International Symposium of Main Group Chemistry** (St Andrews)

June 2007 **Homogeneous Catalysis International Symposium** (St Andrews)

December 2007 **Scottish Regional Meeting of the RSC Organic Division** (Glasgow)

July 2008 **ISHC XVI International Symposium of Homogeneous Catalysis** (Florence, Italy)

September 2008 **Homogeneous Catalysis International Symposium** (Bristol)
APPENDIX 4

COMMUNICATIONS ARISING FROM THIS WORK

New Directions for Organocatalysis (presentation)
University of St Andrews Organic Research Seminar, 17th April 2006

The first organocatalytic carbonyl-ene reaction: isomerisation-free C-C bond formations catalysed by H-bonding thio-ureas (journal publication)

Chiral thioureas and Bronsted acids in catalysis (presentation)
University of St Andrews Organic Postgraduate symposium, 21st May 2008

An Organocatalytic Carbonyl-Ene Reaction (poster)

International Symposium on Homogeneous Catalysis XVI, Florence, 6-11th July 2008

Further publications on work reported in Chapter 4 and on the hydrazine thiourea are planned in the near future.