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Development of catalysts for asymmetric hydrogenation

By

Katherine Emma Jolley

A thesis submitted in fulfillment of the degree of
Doctor of Philosophy in Chemistry

Department of Chemistry, University of Warwick
May 2013

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Acknowledgements.

I would like to thank Professor Martin Wills for giving me the opportunity to carry out the research discussed in this thesis and for all the guidance and support he has given me throughout my studies.

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Declaration.

This thesis is submitted to the University of Warwick in support of my application for the degree of Doctor of Philosophy. The work presented was carried out at the Department of Chemistry, University of Warwick between September 2009 and May 2013. It has been composed by myself and has not been submitted in any previous application for any degree.

The work presented in this thesis was carried out solely by myself unless otherwise stated. Collaborative work carried out with Johnson Matthey and colleague Dr. Rina Soni is included in this thesis however the results given are solely those obtained by myself unless otherwise stated.

Parts of this thesis have been published in the following scientific literature:

1. K. E. Jolley, A. Zanotti-Gerosa, F. Hancock, A. Dyke, D. M. Grainger, J. A. Medlock, H. G. Nedden, J. J. M. Le Paih, S. J. Roseblade, A. Seger, V. Sivakumar, D. J. Morris, I. Prokes and M. Wills, *Adv. Synth. Catal.* 2012, **354**, 2545-2555.

2. M. Wills, R. Soni and K. E. Jolley, Catalyst and Process for Synthesising the Same, Patent application, European Patent Office, 1219716.6, November 2012.

Abstract.

The application of tetradentate aminoalcohol ligands to the KO^{t}Bu-catalysed hydrogenation of benzophenone has been studied. Hydrogenation was found to proceed *via* a transfer hydrogenation process with the ligands acting as hydrogen donors.

A series of bidentate and tetradentate ligands containing a variety of coordinating groups including amino, hydroxy, silyl, phosphine and amido functionalities have been prepared and applied to the transition metal-catalysed asymmetric transfer hydrogenation of ketones using iron, ruthenium and rhodium metals although none were found to be enantioselective for the hydrogenation of acetophenone.

A series of asymmetric tethered ruthenium half sandwich complexes have been applied to the asymmetric pressure hydrogenation of ketones. Studies have investigated the effect of changing the sulfonamide group, halide and tether length on the activity of the catalysts. The application of an achiral tethered ruthenium half sandwich complex as a catalyst for the pressure hydrogenation of aldehydes is also reported.

A novel synthesis of tethered ruthenium complexes using aryl substitution methodology has been developed and applied to the preparation of a series of novel complexes which were found to be highly active for asymmetric pressure hydrogenation of ketones. The application of the synthesis to the preparation of poly(methyl methacrylate) supported complexes is also discussed. Application of the supported catalysts to asymmetric pressure and transfer hydrogenation of acetophenone has shown potential for the development of an active heterogeneous catalyst for transfer hydrogenation of ketones in aqueous media.

Abbreviations.

$[\alpha]_D$	Optical rotation (alpha D)
°C	Degrees celsius
δ_C	Carbon chemical shift
δ_H	Proton chemical shift
ν_{max}	Wavenumber (cm^{-1})
Å	Angstroms
Ad	Adamantane
aq.	Aqueous
APH	Asymmetric pressure hydrogenation
Ar	Aryl
ATH	Asymmetric transfer hydrogenation
atm.	Atmospheres
BH_3.DMS	Borane dimethylsulfide complex
BINAP	2,2'-Bis(diphenylphosphino)-1,1'binapthyl
Boc	*tert*-Butoxycarbonyl
Bu	Butyl
c	Concentration (g/100 cm^3)
CBS	Corey-Bakshi-Shibata
$CDCl_3$	Deuterated chloroform with 0.3% TMS
CI	Chemical ionization
cm^3	Centimetres cubed
^{13}C NMR	^{13}Carbon nuclear magnetic resonance
COD	Cyclooctadiene
Conv.	Conversion

Cy	Cyclohexyl
d	Doublet
D	Dextro
D_2O	Deuterium oxide
d$_6$-DMSO	Deuterated dimethyl sulfoxide
d$_4$-MeOD	Deuterated methanol
dd	Doublet of doublets
DCM	Dichloromethane
Ee	Enantiomeric excess
En	Ethylenediamine
Er	Enantiomeric ratio
ESI	Electrospray Ionisation
Et	Ethyl
FLP	Frustrated Lewis Pair
FT-IR	Fourier Transform-Infrared
g	Grams
GC	Gas chromatography
GC/MS	Gas Chromatography/Mass Spectrometry
^{1}H NMR	Proton nuclear magnetic resonance
hr	Hours
Hz	Hertz
I	Iso
J	Coupling constant (Hz)
J	Joules
kJ	Kilojoules

L	Levo
LC/MS	Liquid Chromatography/Mass spectrometry
Lit	Literature
Ln	Ligands
M	Mol dm^{-3}
M^+	Molecular ion
m	Multiplet
m-	Meta
Me	Methyl
mg	Milligrams
MHz	Mega Hertz
Min	Minutes
mmol	Millimoles
mol	Moles
Mp	Melting point
MS	Mass spectrometry
Ms	Mesyl
MSPV	Meerwein-Schmidt-Ponndorf-Verley
MTPA-Cl	α-Methoxy-α-trifluoromethylphenylacid chloride
m/z	Mass/charge ratio
ND	Not determined
NMR	Nuclear Magnetic Resonance
o-	Ortho
p-	Para
Pet ether	Petroleum ether

PH	Pressure Hydrogenation
Ppm	Parts per million
Pr	Propyl
Psi	Pounds per square inch
q	Quartet
quin	Quintet
R	Rectus
Rf	Retention factor
RT	Room temperature
s	Singlet
S	Sinister
t	Triplet
t or *tert*	Tertiary
TBAF	tetra-butyl ammonium fluoride
TBDMS	*tert*-Butyl dimethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TOF	Time Of Flight
Ts	*p*-Toluenesulfonyl
TsDPEN	1,2-Diphenyl-*N*-(*p*-toluenesulfonyl)ethylenediamine
TsEN	*N*-(*p*-Toluenesulfonyl)ethylenediamine
UV	Ultra Violet

1. Introduction.

1.1 Chirality.

Chirality, derived from the Greek word *cheir* meaning hand, is a form of stereoisomerism and is the structural characteristic of an object that can exist as one of two non-superimposable mirror images of itself. A molecule is said to be chiral if it can exist in a pair whereby both molecules have the same molecular formulae, but differ in their structural arrangement to the extent that the pair form mirror images of each other.[1] Each mirror image of the compound is called an enantiomer. Chirality arises in a molecule when a central atom has a different atom or functionality as each of its substituent groups. The central atom is referred to as the chiral centre.

It is particularly important within asymmetric synthesis to specify the absolute configuration of a chiral molecule at each of its chiral centres. Within a chiral compound each chiral centre has either '*R*', from the Latin *rectus* meaning right, or '*S*', from the Latin *sinister* meaning left, configuration.[2] These terms relate to the order in which substituent groups are arranged around the chiral centre and hence describe the configuration of the molecule at the chiral centre. An equal mixture of (*R*) and (*S*) enantiomers of the same compound is referred to as a racemate.

An example of a chiral molecule is bromochlorofluoromethane **1** shown in Figure 1. The carbon atom at the centre of the molecule is bound to four different atoms, bromine, chlorine, fluorine and hydrogen, and is thus a chiral centre. To determine the absolute configuration of each enantiomer it is necessary to use the Cahn-Ingold-Prelog system to assign priorities to each substituent group.[3]

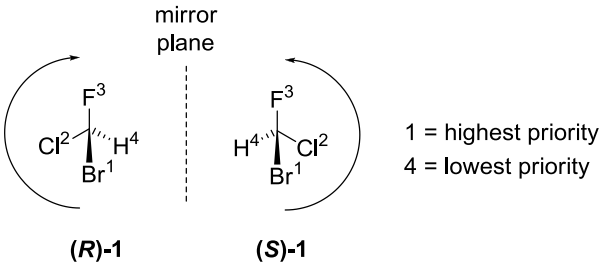


Figure 1. Assignment of absolute configuration of stereochemistry in enantiomers of bromochlorofluoromethane **1**.

The priorities relate to the atomic number of each atom bound to the chiral centre. The atom having the highest atomic number has the highest priority. Where two atoms bound to the chiral centre have the same atomic number, the atomic number of the next atom to each in sequence is considered. When priorities have been assigned, the molecule is oriented with the lowest priority group pointing backwards. If the priorities then decrease in a clockwise manner around the chiral centre the configuration is *R* and if in an anti-clockwise manner the configuration is *S*. The enantiomeric purity of an asymmetric product is reported either as an enantiomeric ratio (er.) of *R:S* or as a percentage enantiomeric excess (ee.) using the equation: ((proportion of most abundant enantiomer)-(proportion of least abundant enantiomer)/(*R* + *S*)) x 100.

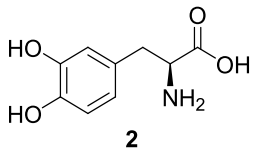
Enantiomers of a compound will have the same chemical and physical properties as each other, however they are optical isomers of each other. Each enantiomer will rotate the plane of polarised light in the opposite direction.[4] If the light is rotated to the left the enantiomer is *D*, the *dextro-rotatory enantiomer* (+) and if the light is rotated to the right the enantiomer is *L*, the *levo-rotatory enantiomer* (-). Polarimetry is an analytical technique which measures the rotation of polarised light when passed through a chiral sample and can be used to determine which enantiomer of the

compound is present. The $[\alpha]_D$ value obtained can be compared to literature measurements to confirm the *R* or *S* configuration of a compound.

Many naturally occurring compounds are chiral including amino acids, sugars and natural products and almost all will possess the (*L*)-configuration in their natural states.[5] Amino acids are the building blocks for proteins and enzymes within biological systems. Enzymes operate as biological catalysts, each exhibiting selectivity for a specific reaction or transformation within a biological system. The enzymes exhibit a preference for the reaction of one enantiomer of the starting material over the other to form an enantiopure product.[6]

1.1.1 Industrial importance of chiral compounds.

Proteins and biological compounds are built from (*L*)-amino acids meaning that biological organisms operate within a chiral environment of a single handedness. This has a major impact on the design of drugs which must be compatible with this environment in order to work successfully. An example of this is the use of (*L*)-3,4-dihydroxyphenylalanine **2** ((*L*)-DOPA) shown in Figure 2, which is used as a treatment for Parkinson's Disease.[7]



2

Figure 2. Structure of (*L*)-DOPA (**2**)

The active compound dopamine is not able to cross the blood-brain barrier to reach the site of action. Dopamine is thus administered as DOPA which undergoes enzyme-mediated decarboxylation in the body to form dopamine. Due to the enantiomerically pure nature of the amino acids it is built from, the dopamine

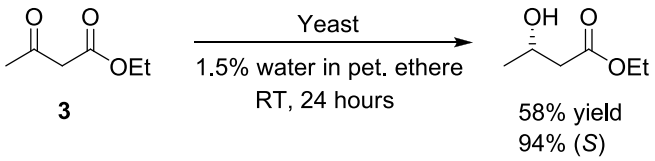
decarboxylase enzyme is only active for conversion of (*L*)-DOPA to dopamine. Administering racemic DOPA to patients would lead to a dangerous build up of (*D*)-DOPA in the body. It is thus important to synthesise and administer pure (*L*)-DOPA to patients.

1.1.2 Preparation of chiral compounds.

The need for enantiomerically pure compounds, particularly within the pharmaceutical industry, has made asymmetric and enantioselective synthesis an important area of chemical research. Many strategies discussed below have been used to achieve asymmetric synthesis.

1.1.2.1 Biosynthesis.

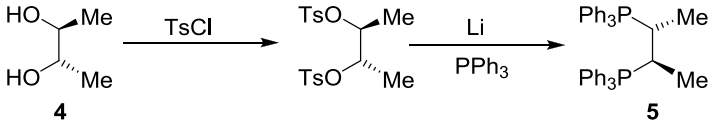
Biosynthesis involves the use of enzymes to perform chemical transformations. The enantioselectivity of enzymes leads to formation of enantiomerically pure products, either *via* kinetic resolution whereby the enzyme converts only one enantiomer of a racemic starting material to the product, or *via* a biocatalysed asymmetric synthesis where the stereochemistry of the enzyme allows formation of only one enantiomer of a product. An example of a biocatalysed asymmetric hydrogenation is the yeast mediated reduction of ethyl acetoacetate (**3**) reported by Smallridge *et al.* in 1993 shown in Scheme 1.[8]



Scheme 1. Yeast-catalysed asymmetric hydrogenation of ethyl acetoacetate.

1.1.2.2 Chiral pool synthesis.

Chiral pool synthesis is the use of enantiomerically pure starting materials in reactions to give enantiomerically pure products. Naturally occurring chiral compounds are almost always enantiomerically pure and can be used stoichiometrically to give enantiomerically pure products, as long as the chiral centre does not undergo racemisation during the reaction. An example of a successful approach is the preparation of Chiraphos (**5**) from naturally occurring (*L*)-tartaric acid (**4**) as shown in Scheme 2.[9]

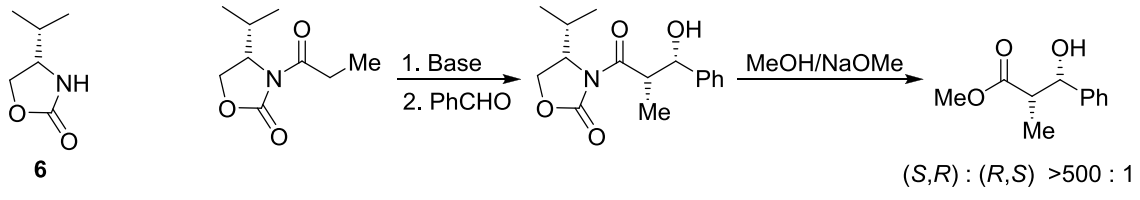


Scheme 2. Asymmetric synthesis of Chiraphos from (*L*)-tartaric acid.

1.1.2.3 Chiral auxiliaries.

A chiral auxiliary is an enantiomerically pure compound which is added to a reagent to create a chiral centre. Subsequent reaction at an additional chiral or pro-chiral centre in the molecule will give an enantiomerically enriched product at this centre due to the steric influence imposed by the auxiliary. After the reaction the auxiliary is removed to give the enantiomerically enriched product.

A particularly well known and widely used family of oxazolidinone auxiliaries such as **6** was developed by David Evans in the mid 1980s.[10] Initially the auxiliaries were used for asymmetric aldol reactions as shown in Scheme 3.[11]



Scheme 3. Use of Evans Auxiliary for asymmetric aldol reaction.

Evans auxiliaries have also been applied to the asymmetric synthesis of carboxylic acids,[12] asymmetric Diels-Alder cylcoadditions[13] and the synthesis of a range of antibiotics[14] and pharmaceutical products including Ezetimibe[15] and Lipitor[16] for treatment of high cholesterol and Tipranavir[17] a HIV protease inhibitor.

1.1.2.4 Asymmetric catalysis.

A catalyst increases the rate of a reaction by decreasing the activation energy of the transformation but is not itself consumed in the reaction. Catalysts may be homogeneous (in the same phase as the reaction mixture) or heterogeneous (in a different phase to the reaction mixture) and may be metallic, often based on transition metals, or organic comprising of small C, H, N, O, S based molecules. The variable oxidation states and incomplete *d*-orbitals of transition metals gives good scope for their use as catalysts allowing variable coordination numbers for interaction with ligands and substrate and elimination of products. Catalysts possessing chirality, for example with coordinated enantiomerically pure ligands, can impose enantioselectivity upon the reaction they are catalysing.

An achiral catalyst used in the reaction of a racemic or pro-chiral starting material to form a chiral product will give the product as a racemate. This is because the reaction pathway from either enantiomer of starting material to either enantiomer of product requires the same energy. Use of an asymmetric catalyst lowers the energy required for the formation of one enantiomer of product below that of the other enantiomer as shown in Figure 3. During the reaction this enantiomer of product is formed preferentially leading to an enantiomerically enriched product.[18] Development of a sufficiently active catalyst may decrease the activation energy to such an extent that an essentially enantiomerically pure product is formed.

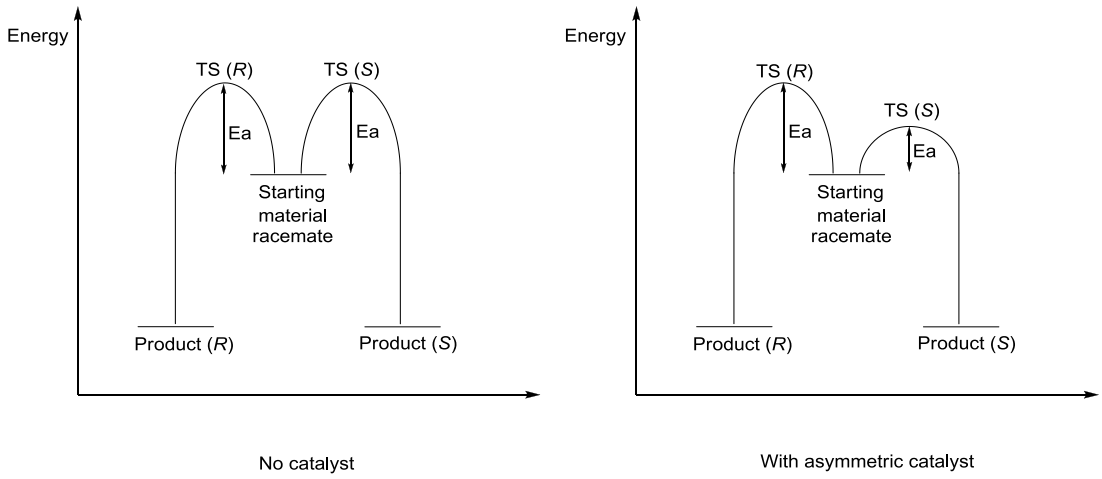


Figure 3. Activation energies for transition state formation with and without an asymmetric catalyst.

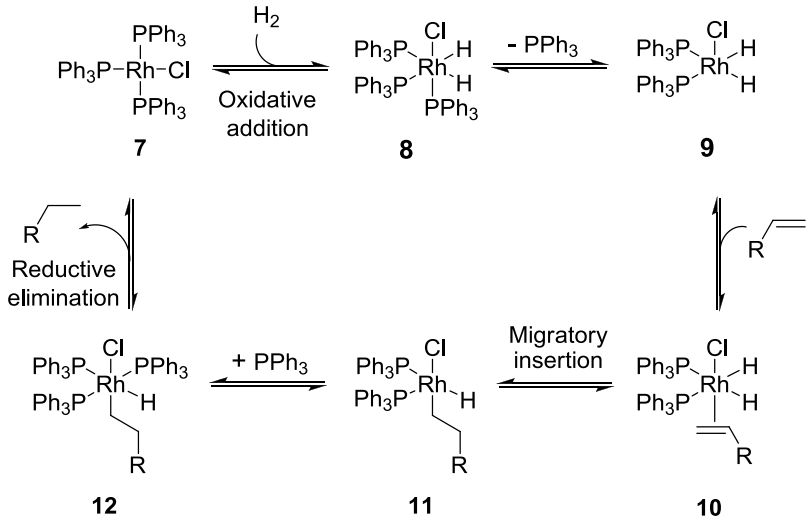
Asymmetric catalysis is advantageous as it allows both enantiomers of a starting material to react to give a single enantiomer of the product. Racemic starting materials can be used rather than expensive, less available, enantiomerically pure starting materials. It is also a more efficient process without the need for additional steps in the reaction for the addition and removal of an auxiliary for example. Some drawbacks of the process are that the metals used are often transition metals which may be toxic and not readily available leading to an increase in costs, thus catalysts need to be highly active to minimise the amount of them it is necessary to use.

1.2 Hydrogenation.

Hydrogenation is the addition of hydrogen to an unsaturated bond, often a C≡C, C=C, C=O or C=N bond. Transfer hydrogenation uses a hydrogen donor such as formic acid or 2-propanol to supply the substrate with hydrogen, whilst pressure hydrogenation uses pressurised hydrogen gas. A vast range of homogeneous and heterogeneous catalysts have been used for hydrogenation applications.[19]

1.2.1 Pressure hydrogenation with transition metal catalysts.

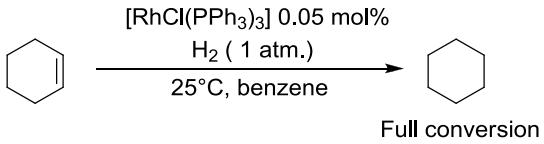
Pressure hydrogenation of unsaturated compounds is achieved with use of hydrogen gas. One of the earliest examples of a homogeneous transition metal catalyst for hydrogenation was reported by Wilkinson in 1966.[20] $[RhCl(PPh_3)_3]$ (**7**) as the catalyst precursor was used along with hydrogen gas under mild conditions for the hydrogenation of alkenes. The catalyst precursor **7** is formed from the reaction of $RhCl_3.3H_2O$ with excess triphenylphosphine. The catalytic cycle for the hydrogenation of alkenes is shown in Scheme 4.



Scheme 4. Mechanism of pressure hydrogenation of alkenes using Wilkinson's catalyst.

The mechanism of catalysis[20] proceeds with oxidative insertion of hydrogen to the 16-electron Rh^+ species **7** to give 18-electron dihydride Rh^{3+} complex **8**. Loss of a triphenylphosphine ligand allows η^2-coordination of the substrate to the rhodium to give complex **10**. Migratory insertion into a Rh-H bond followed by reductive elimination yields the hydrogenated product. Coordination of triphenylphosphine reforms the 16-electron Rh^+ species **7** for continuation of the catalytic cycle.

The system was found to show good selectivity for hydrogenation of alkene bonds with ketones, hydroxy, cyano, nitro, chloro, azo, ethers, esters and carboxylic acids each being stable to hydrogenation.[20] Scheme 5 shows the hydrogenation of cyclohexene using Wilkinson's catalyst **7**.



Scheme 5. Hydrogenation of cyclohexene using Wilkinson's catalyst.

The study also investigated the scope of the reaction, finding that terminal alkenes underwent hydrogenation more readily than internal alkenes; alkenes with *cis* geometry were hydrogenated more readily than *trans* and an increase in hydrogen pressure was required to bring about hydrogenation of conjugated alkenes.[20]

1.2.2 Asymmetric pressure hydrogenation with transition metal catalysts.

Asymmetric pressure hydrogenation (APH) is the addition of hydrogen to a pro-chiral unsaturated bond to give a specific enantiomer of the chiral saturated product. The enantioselectivity in the reaction originates from the use of asymmetric ligands such diphosphines and diamines as shown in Figure 4.

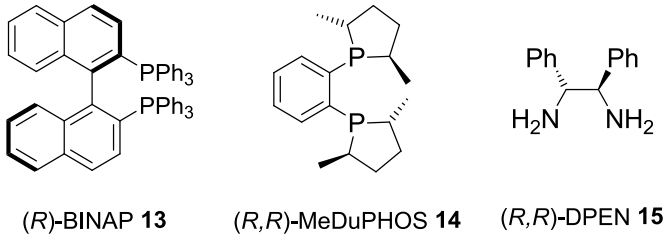
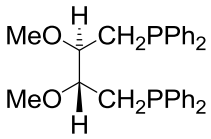


Figure 4. Examples of asymmetric ligands.

Early examples of APH took inspiration from Wilkinson's catalyst, using enantiopure chiral phosphine ligands and a rhodium catalyst. An early example was

reported by Knowles in 1968.[21] Reaction of (-)-methylpropylphenylphosphine (P) and $RhCl_3.3H_2O$ gave the catalyst precursor [$RhCl_3P_3$] which was applied to the hydrogenation of prochiral compounds. Use of 0.15 mol% catalyst with benzene:EtOH 1:1 with Et_3N (3.5 equiv. relative to Rh) at 60°C allowed the hydrogenation of phenylacrylic acid to phenylpropanoic acid with an optical purity of 15%. The reaction is believed to have proceeded *via* the same mechanism as Wilkinson's catalyst and established the potential for asymmetric hydrogenation using rhodium-phosphine catalysts.

Improvements to this system were reported by Kagan in 1971[22] for the asymmetric pressure hydrogenation of unsaturated prochiral acids with an *in situ* formed catalyst comprising of rhodium and an asymmetric diphosphine ligand **16** shown in Figure 5, derived from (+)-ethyl tartrate.



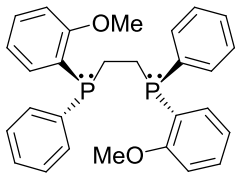
Ligand **16**

Figure 5. Structure of ligand **16** for use in the rhodium APH of unsaturated prochiral acids.

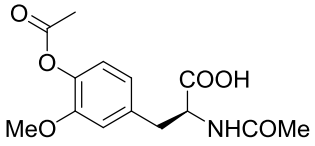
In combination with [Rh(cyclooctene)$_2$Cl]$_2$ and benzene:EtOH 1:2 at room temperature and with atmospheric hydrogen, ligand **16** was used in the asymmetric hydrogenation of atropic acid giving the product in quantitative yield with an optical purity of 63%. The system was found to be particularly active for the asymmetric hydrogenation of α-acetamidocinnamic acid giving a quantitative yield of product with 72% optical purity.[22]

Knowles reported further improvements to the asymmetric hydrogenation of alkenes in 1986 with use of rhodium and an asymmetric diphosphine ligand ethane-1,2-

diylbis[(2-methoxyphenyl)phenylphosphine] (DiPAMP) **17** shown in Figure 6, for the preparation of (*L*)-DOPA precursor **18** in 94% ee.[23]



(*R,R*)-DiPAMP **17**

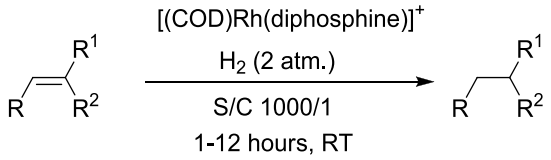


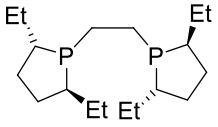
(*L*)-DOPA precursor **18**
94% ee

Figure 6. Structure of (*R,R*)-DiPAMP **17** and (*L*)-DOPA precursor **18**.

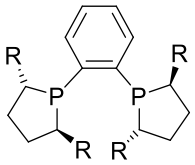
More recently the use of rhodium with asymmetric diphosphine ligands such as C_2-symmetric EtDuPHOS **19** has proved to be an effective system for APH of alkenes. Burk has reported the hydrogenation of prochiral acetamidoacrylates and enol acetates[24] at low temperature and hydrogen pressure and with short reaction times and low catalyst loadings to give high enantiomeric excesses as shown in Table 1.

Table 1. Enantiomeric excesses achieved for APH of acetamidoacrylates and enol acetates.

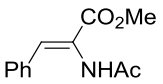
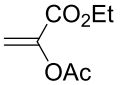
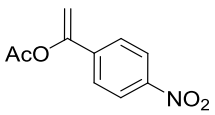
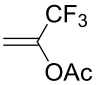




19

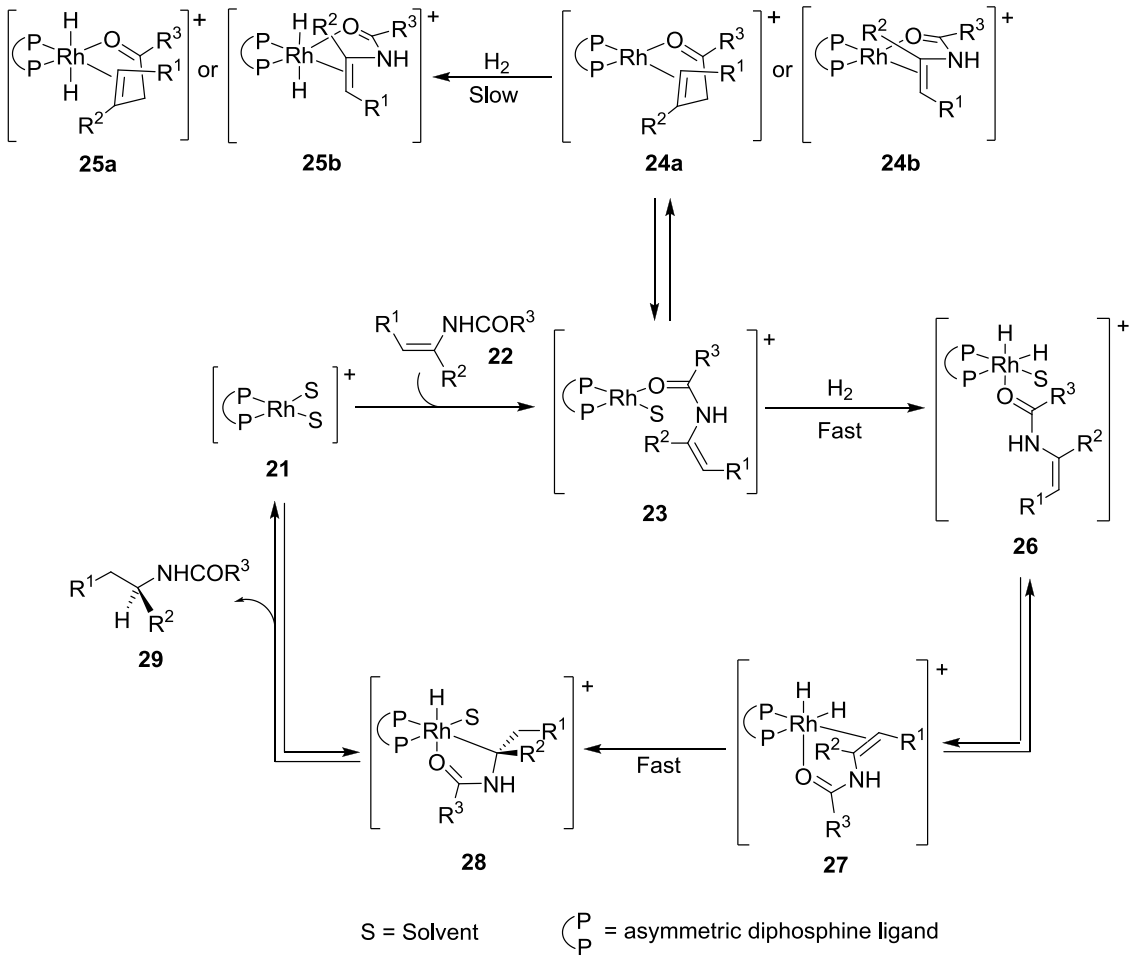


14 MeDuPHOS R = Me
20 EtDuPHOS R = Et

Entry	Diphosphine ligand	Substrate	Ee.[a] (%)
1a	(*S,S*)-**14**		98 (*S*)
1b	(*S,S*)-**20**		99 (*S*)
1c	(*S,S*)-**19**		93 (*S*)
2	(*S,S*)-**20**		99 (*S*)
3	(*S,S*)-**19**		90 (*R*)
4a	(*S,S*)-**14**		94 (*S*)
4b	(*S,S*)-**19**		>95 (*S*)

[a] Determined by chiral HPLC.

The reaction mechanism was reported by Gridnev and Imamoto[25] and is shown in Scheme 6.

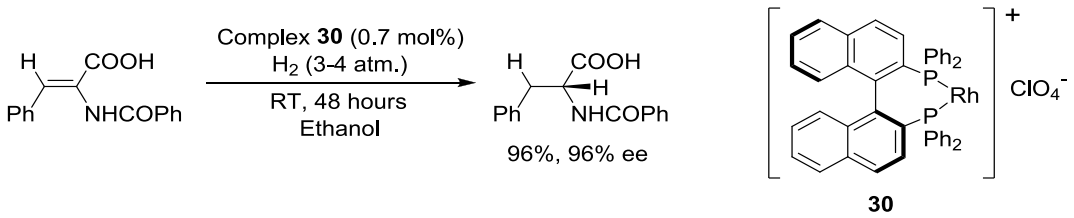


Scheme 6. Mechanism for rhodium-catalysed APH of acetamidoacrylates using asymmetric diphosphine ligands such as DuPHOS.

The reaction involves initial coordination of the substrate **22** to the rhodium precursor **21** to give complex **23** which exists at a low concentration in a fast equilibrium with the substrate chelate complexes **24a** and **b**. Complexes **24a** and **b** were found to react slowly with hydrogen to form the product *via* complexes **25a** and **b** whilst **23** reacts quickly with hydrogen. It was therefore proposed that once formed, complex **23** reacts quickly with hydrogen to give complex **26**. The rhodium in **23** is activated to oxidative addition of hydrogen by electron donation from the

carbonyl group and also the process is sterically favoured. After oxidative addition of hydrogen, the double bond of the substrate coordinates to the rhodium to give **27** which can exist as one of two diastereomers. Once the sterically favourable diastereomer of **27** forms, fast migratory insertion of the C=C bond into the Rh-H bond occurs fixing the stereochemistry of the product and giving complex **28**. The favoured conformation is that which minimises steric clash between the diphosphine ligand and the substrate. The product **29** is released by reductive elimination.

The use of rhodium and 2,2'-bis(diphenylphosphino)-1,1'-binapthyl (BINAP) as the asymmetric diphosphine has been reported by Noyori and co-workers however its scope is limited to the synthesis of amino acids as shown in Scheme 7.[26]



Scheme 7. Preparation of enantiomerically pure amino acids with rhodium BINAP complex **30**.

This system is reported to follow an analogous mechanism to that of the Rh-DuPHOS system shown in Scheme 6.[26] The system does not offer a significant improvement over the Rh-DuPHOS system, with Noyori reporting it as being relatively slow and the need for specific conditions to give a high degree of enantioselectivity.[27] For example, the pressure of hydrogen gas used in the reaction must be carefully selected as too high a pressure leads to a reduction in the enantiomeric excess of the product. This is due to the relative reactivities of the chelate complex diastereomers (analogous to **24a** and **24b** in Scheme 6). Halpern and Ashby report that under low hydrogen pressures the formation of the chelate complex is reversible.[28] The minor diastereomer is more reactive with hydrogen than

the major diastereomer. The reversibility of the reaction allows conversion of the less reactive major diastereomer to the highly reactive minor diastereomer which then determines the configuration of the product. Increasing the hydrogen pressure reduces the reversibility of the process and hence the degree of interconversion between diastereomers. With increased hydrogen pressure the amount of the major diastereomer present and its reactivity increases which causes a reduction in the enantiomeric purity of the product.[28]

The concentration of the reaction solution with respect to the substrate is also important in the reaction. Under high substrate concentrations, complexes containing two coordinated substrates each bound through their C=C bonds were observed[28] and the ee. of the products obtained from these complexes was found to be lower than that obtained *via* the conventional mechanism.

Improvements to this system were first reported by Noyori *et al.* in 1986 upon using ruthenium metal instead of rhodium.[29, 30] This system was found to be highly enantioselective and have broad scope and high activity for a range of substrate types. The use of [Ru(BINAP)(carboxylate)$_2$] complexes has been applied to the APH of allylic alcohols,[31] isoquinolines[29] and α,β-unsaturated carboxylic acids,[32] whilst use of [Ru(BINAP)(halide)$_2$] complexes have been applied to the APH of ketones[33] as illustrated in Figure 7.

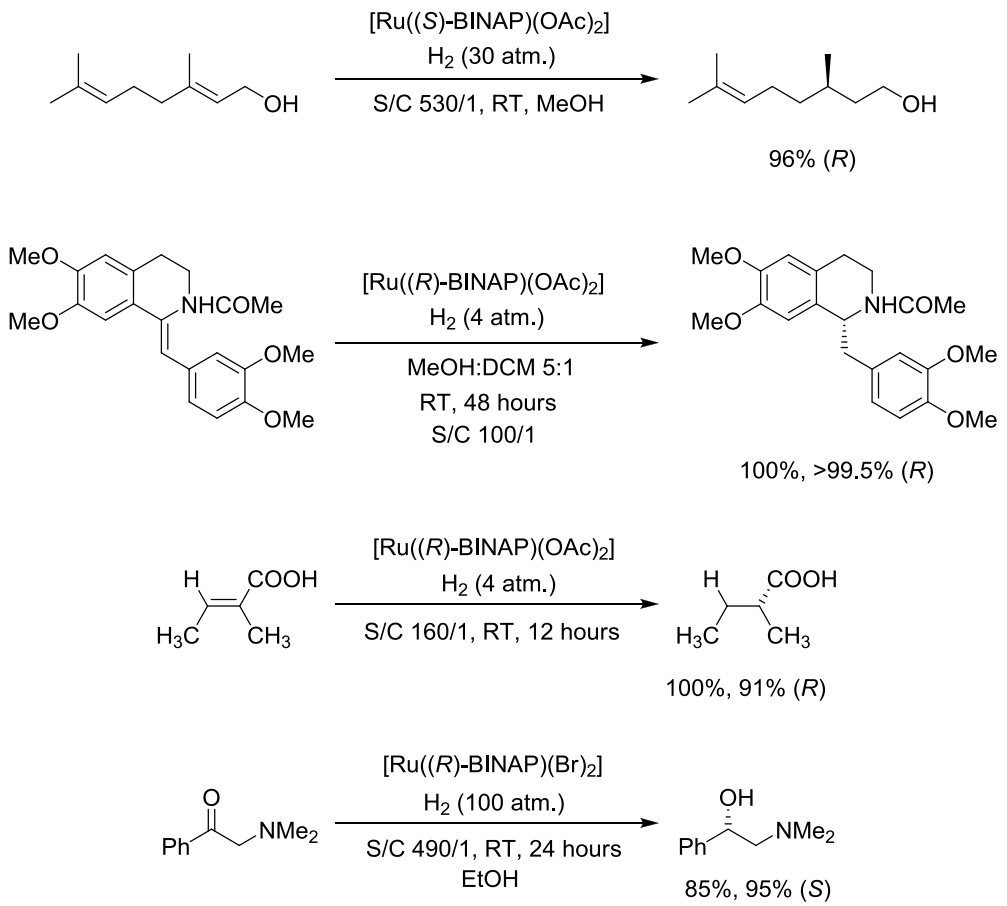
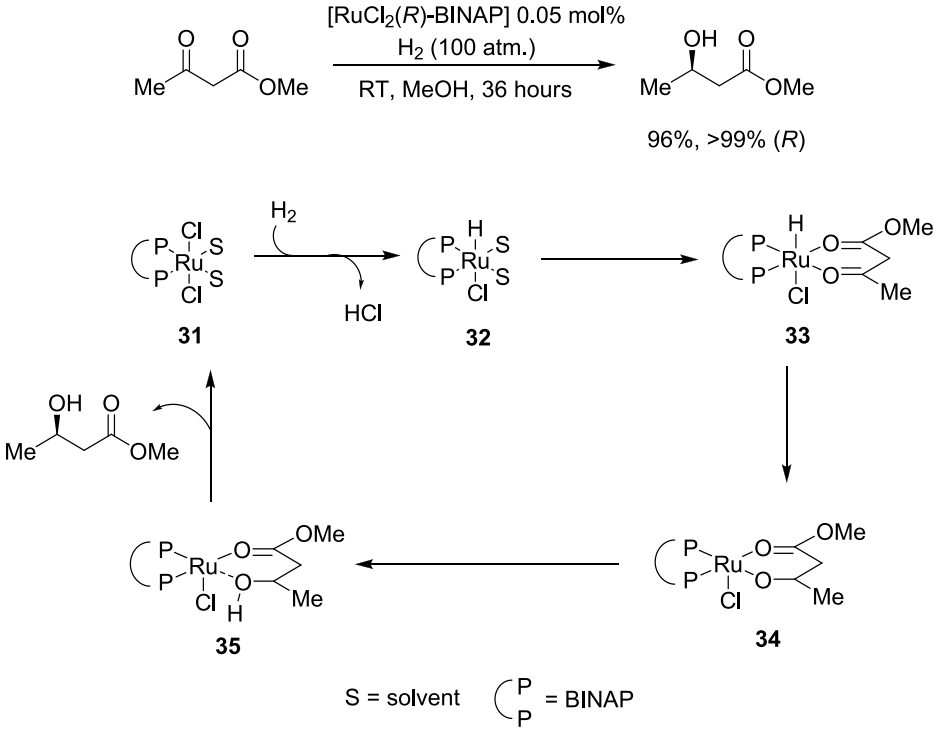


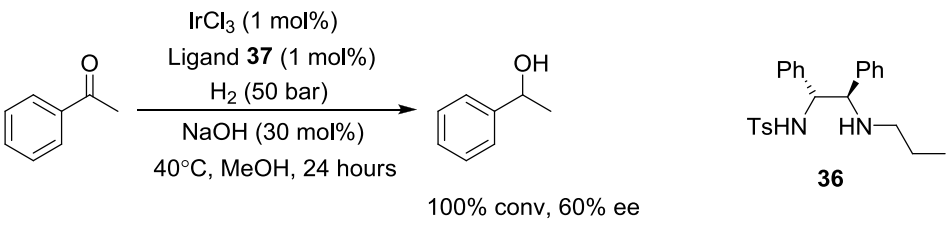
Figure 7. Ruthenium BINAP-catalysed APH of a range of unsaturated substrates.[30-33]

The mechanism for APH using the ruthenium BINAP catalyst is shown in Scheme 8. The mechanism differs to that of the rhodium BINAP catalyst in that it involves a ruthenium monohydride and that the ruthenium remains in its +2 oxidation state throughout the cycle. The mechanism for the APH of β-keto esters is shown below.[34,35] Heterolytic cleavage of hydrogen allows formation of a ruthenium hydride complex **32**. The C=O bonds of the β-keto ester substrate coordinate to the ruthenium to give complex **33**. The C=O of the ketone then inserts into the Ru-H bond to give complex **34** before protonation of the Ru-O bond (**35**) gives the product and reforms catalyst pre-cursor (**31**).



Scheme 8. Mechanism for Ru-BINAP-catalysed APH of β-keto esters.

More recently Wills and co-workers have reported an iridium-catalysed approach to the APH of ketones using $IrCl_3$ and asymmetric diamine ligands.[36] Of a range of metals tested, $IrCl_3$ was shown to give excellent selectivity for hydrogenation of the C=O bond of acetophenone over hydrogenation of the aromatic ring using *N*-alkylated TsDPEN ligands. A range of *N*-alkylated derivatives of TsDPEN were then employed as ligands with $IrCl_3$ for the APH of acetophenone with ligand **36** giving the highest ee. of 60% as shown in Scheme 9.[36]

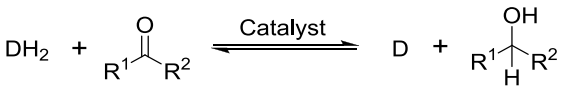


Scheme 9. Iridium-catalysed APH of ketones using alkylated TsDPEN ligand **36**.

The best performing ligands including **36** in Scheme 9 were successfully applied to the APH of a range of aromatic ketones. Further extension of this work was reported the synthesis and application of derivatives of ligand **36** with a variety of sulfonamide groups to iridium-catalysed APH of a range of ketones with the 2-napthalene sulfonyl derivative was found to be most successful allowing 100% conversion of a large range of ketones with up to 85% ee.[37]

1.2.3 Transfer hydrogenation of ketones with transition metal catalysts.

Catalytic transfer hydrogenation provides a mild process for reduction of saturated compounds, often carbonyl compounds. It is generally considered to be safer than pressure hydrogenation as the use of hydrogen donors to supply hydrogen to the substrate removes the need to use pressurised hydrogen gas. As shown in Scheme 10, hydrogen is donated from a donor molecule such as 2-propanol or formic acid, and is accepted by the substrate.



Scheme 10. Asymmetric transfer hydrogenation of ketones.

There are two general inner sphere mechanisms for transfer hydrogenation, a monohydride mechanism and dihydride mechanism as shown in Figure 8.[38]

The monohydride process involves substitution of the chloride in a metal chloride precursor for the hydrogen donor molecule. β-elimination generates a metal hydride complex and insertion of the unsaturated substrate into the metal hydride bond forms the saturated species. The product is displaced from the complex by a further hydrogen donor molecule which then allows continuation of the catalytic cycle.

The dihydride mechanism involves replacement of chloride in a metal dichloride complex with the hydrogen donor molecule and β-elimination to give a metal dihydride complex. Co-ordination of the substrate to the complex followed by insertion into the metal hydride bond forms the saturated compound which is displaced by reductive elimination to give the product. The hydrogen donor molecule re-coordinates to the metal complex *via* oxidative insertion forming a metal hydride complex. A further β-elimination then generates the second metal hydride bond with displacement of the now unsaturated donor molecule reforming the metal dihydride complex for further hydrogenation of the substrate molecule.

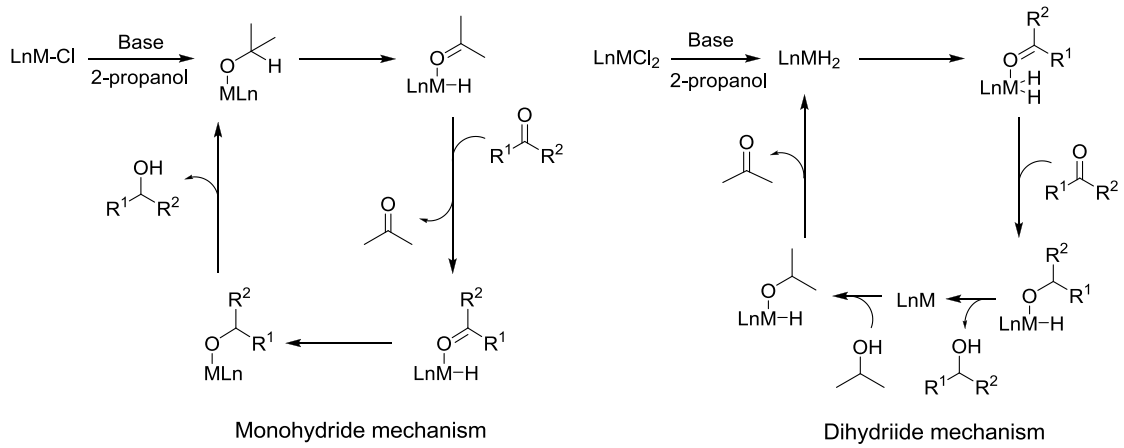
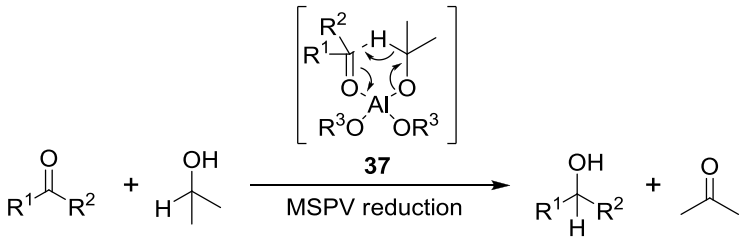


Figure 8. Mono- and Dihydride mechanisms for ATH of ketones.

An early example of transfer hydrogenation reported in the literature is the Meewein-Schmidt-Ponndorf-Verley (MSPV) reduction which was reported by Meerwein and Schmidt [39], Ponndorf[40] and Verley[41] independently in the 1920s. Each reported the use of a stoichiometric aluminium alkoxide reagent (**37**) in 2-propanol for the transfer of hydrogen to aldehydes and ketones shown in Scheme 11. The reverse of this process was later reported by Oppenauer[42] allowing the oxidation of alcohols.

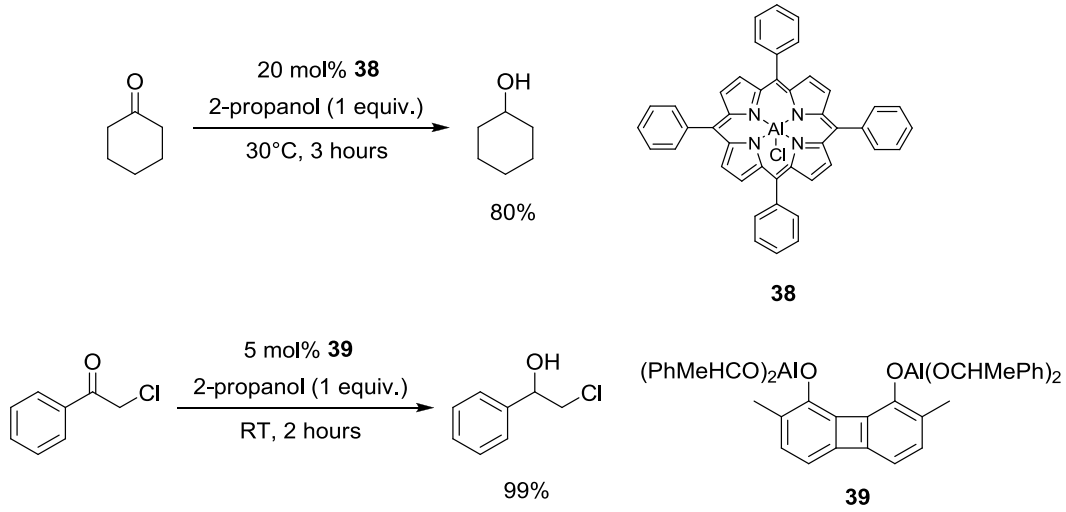


Scheme 11. MSPV reduction of ketones.

The ketone substrate and 2-propanol co-ordinate to the aluminium alkoxide and *via* a 6-membered cyclic transition state hydrogen is transferred from 2-propanol to the ketone in a concerted manner as shown in Scheme 11.[43]

Catalytic variations of the MSPV reaction have also been reported. The use of protic acids was first reported by Rathke in 1977[44] where use of 2.5 mol% trifluoroacetic acid with 5 mol% $Al(O^tBu)_3$ allowed the oxidation of cyclohexanol to cyclohexanone with 88% yield using benzaldehyde as the hydrogen acceptor. Akamanchi and Noorani later reported the reduction of a range of ketones and aldehydes using trifluoroacetic acid.[45] Using a ratio of substrate:aluminium isopropoxide:TFA of 1:0.08:0.003, benzaldehyde was reduced to benzyl alcohol with 93% conversion. Rathke proposed that use of the protic acid with oligomeric aluminium isopropoxide allows replacement of one or more bridging isopropoxy ligands with an anion, increasing the Lewis acidity of the aluminium which improves coordination with the carbonyl.

The use of ligands has also been found to improve the activity of the MSPV reduction of aldehydes and ketones as shown in Scheme 12. The use of tetraphenylporphyrin aluminium complex **38** was reported by Inoue[46] and the use of binuclear aluminium complex **39** was reported by Maruoka.[47]



Scheme 12. Catalytic MSPV reduction of ketones using aluminium complexes.

Kagan has reported the use of lanthanides as catalysts for the MSPV reduction of aldehydes. Use of 0.1 equiv. *t*-BuOSmI_2 at 65°C gave 94% conversion of *p*-nitrobenzaldehyde to *p*-nitrobenzyl alcohol with 2-propanol as the hydrogen donor.[48] In a later study, use of lanthanum and cerium *iso*-propoxides were also reported to be highly active for the MSPV reduction of 2-octanone with >98 and 95% yield respectively, however ytterbium *iso*-propoxide was less active.[49]

1.2.4 Asymmetric transfer hydrogenation with transition metal catalysts.

A broad range of asymmetric transition metal catalysts have been developed for use in transfer hydrogenation reactions.

1.2.4.1 Asymmetric MSPV transfer hydrogenation reactions.

The MSPV reduction methodology has been expanded in recent years to allow asymmetric reduction of carbonyl compounds.

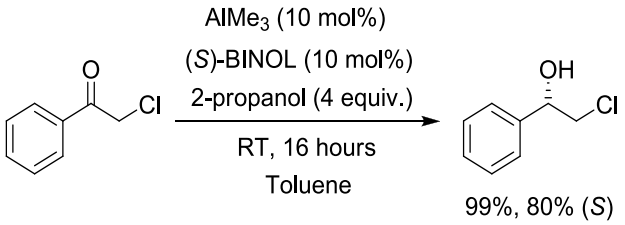
Evans and co-workers have reported the application of samarium complexes with asymmetric tridentate aminoalcohol ligands for the asymmetric MSPV reduction of a range of ketones.[50] *O*-chloroaxetophenone was reduced with full conversion and

97% (*R*) ee. in 24 hours at room temperature with 5 mol% catalyst using 2-propanol as the hydrogen donor.

Maruoka has reported the use of (*R*)-phenyl ethanol as a chiral hydrogen source for MSPV-type ATH of α-chloroacetophenone achieving 82% yield and an ee. of 54%. Use of sterically encumbered (*R*)-*o*-bromophenyl ethanol as the hydrogen source showed an improved ee. of 82% although the yield of product was reduced to 51% as a result of increased steric hindrance.[51]

In 2002, Nguyen reported the addition of enantiopure 2, 2'-dihydroxy-1, 1'binapthyl (BINOL) to the reduction of a range of ketones as shown in Table 2.[52]

Table 2. ATH of acetophenone derivatives using MSPV methodology.



Entry	BINOL	R	Yield[a] (%)	Ee.[a] (%)
1	(*S*)	CH_2Cl	99	80 (*S*)
2	(*R*)	CH_2Cl	99	80 (*R*)
3	(*S*)	CH_2Br	99	83 (*S*)
4	(*R*)	CH_2CH_3	30	50 (*R*)
5	(*R*)	CH_3	54	30 (*R*)
6	(*S*)	$CH(CH_3)_2$	20	61 (*S*)

[a] Determined by GC analysis.

Acetophenone was reduced with 54% yield and 30% ee. however this was seen to improve upon the reduction of α-chloroacetophenone achieving a yield of 99% and ee. of 80%.[52] Increasing the number of equivalents of 2-propanol used increased the yield of product however enantioselectivity was reduced.

1.2.4.2 Ruthenium-catalysed ATH reactions.

Ruthenium catalysts have also been applied to the ATH reactions. In 2006 Reetz and Li reported the use of BINOL derivatives as ligands for ruthenium-catalysed ATH of ketones. Ligand **40** (Figure 9) was found to be the most effective giving 91% conversion of acetophenone to (*R*)-phenyl ethanol with 97% ee. in 28 hours with 0.5 mol% ruthenium using 2-propanol and KOH at 40°C.[53]

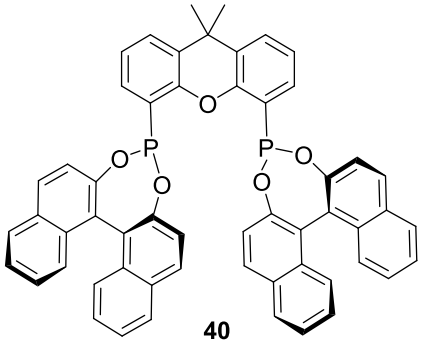
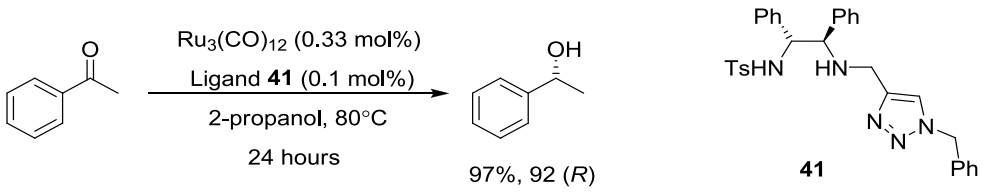


Figure 9. Structure of BINOL derived ligand **40** used for ATH of ketones.

Wills and co-workers have recently reported the first use of asymmetric tridentate triazole containing ligands, such as **41** in Scheme 13, with $Ru_3(CO)_{12}$ for the ATH of ketones.[54] The reaction was found to proceed well with use of the ruthenium dodecacarbonyl precursor, other ruthenium sources gave low conversion to product with low enantioselectivity. Use of formic acid as the hydrogen source was detrimental to the reaction with no reaction taking place, whereas use of 2-propanol lead to high yields and enantioselectivities of product.

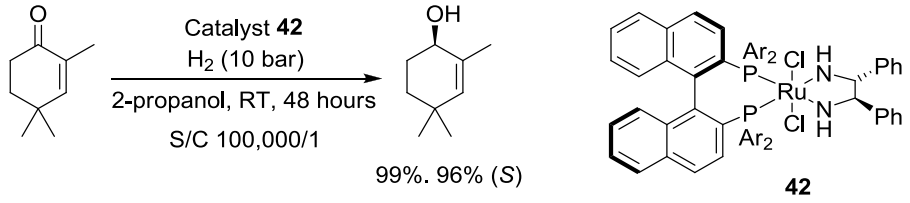


Scheme 13. ATH of acetophenone using tridentate ligand **41**.

1.3 Hydrogenation *via* metal ligand bifunctional catalysis.

The hydrogenation catalysts discussed thus far have primarily operated *via inner sphere* mechanisms involving interaction of the substrates with the metal centres themselves by co-ordination or insertion into metal hydride bonds. A development to this strategy was realised by Noyori who developed catalysts for pressure and transfer hydrogenation of ketones *via* an *outer sphere* mechanism in which the substrate does not bind directly to the metal centre and instead interacts with a metal coordinated hydride and protonated ligand on the catalyst.[55] This allows selective hydrogenation of polar bonds such as C=O as the mechanism delivers both a negatively charged hydride and positively charged proton to the substrate for interaction with the δ^+ C and δ^- O of the C=O bond respectively. The process is referred to as *metal ligand bifunctional catalysis* as both the metal and ligand participate in the catalytic cycle.

An example of this within the context of APH is the further development of the ruthenium-BINAP system (shown in Figure 7) by Noyori. The addition of a second asymmetric ligand in the form of an asymmetric diamine, to the ruthenium-BINAP to give complex **42** was reported by Noyori in 1998.[56] This system offered significant advantages over the earlier system using just a BINAP ligand by allowing selective hydrogenation of C=O bonds in the presence of C=C functionality as shown in Scheme 14.



Scheme 14. APH of 4,4-dimethyl-2-cyclohexen-1-one using ruthenium BINAP/DPEN catalyst **42**.

Catalyst **42** uses an (*S*)-BINAP and (*S*,*S*)-DPEN ligand to impose asymmetry on substrates. This system is tolerant to low catalyst loadings (S:C 50,000:1) and low hydrogen pressures. The mechanism of hydrogenation has been widely studied.[57, 58] The chloride ligands in **42** are replaced with hydride ligands and a 6-membered cyclic transition state is then formed between the metal hydride and protonated diamine ligand with the ketone substrate (Figure 10 A). A hydride is then transferred to the δ^+ carbon of the carbonyl group and the δ^- oxygen coordinates with the proton on the nitrogen of the amino ligand eliminating the product as a specific enantiomer. Potassium alkoxide is also used in the reaction and is reported by Chen and Hartmann[59] to act as a Lewis acid interacting with the nitrogen to properly position the alkoxide base to assist with cleavage hydrogen for formation of the active ruthenium dihydride complex as shown in Figure 10 B.

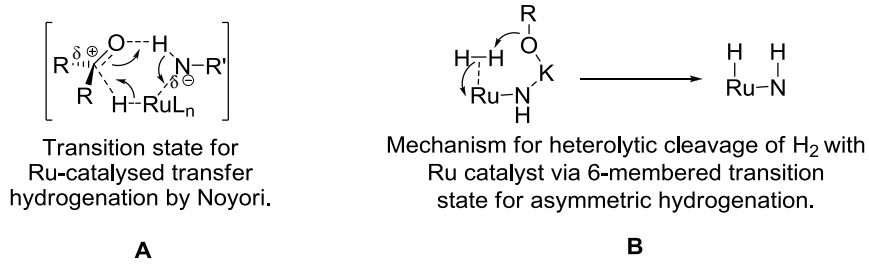
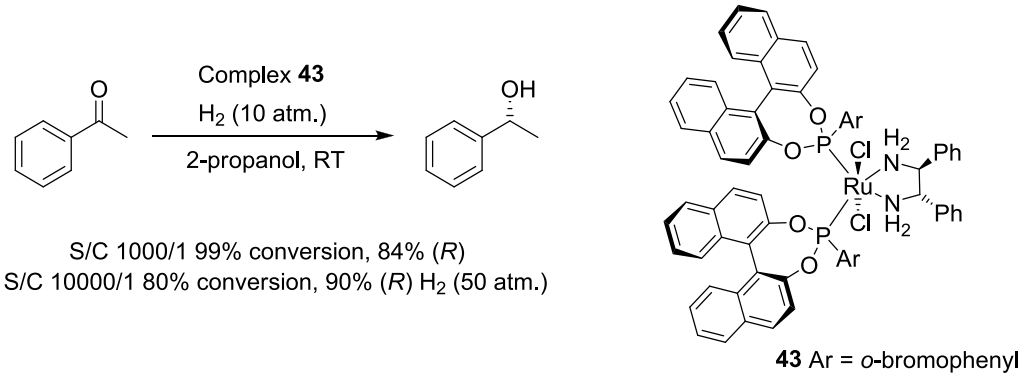


Figure 10. Transition states for hydrogenation of ketones with catalyst **42**.

Wills has also reported the use of phosphine-diamine ruthenium complexes for the APH of ketones as shown in Scheme 15. Use of BINOL with DPEN to give complex **43** was found to be the most effective complex.[60]



Scheme 15. APH of acetophenone using ruthenium complex 43**.**

The reaction is believed to proceed *via* the same transition state as with the BINAP/DPEN complex **42** reported by Noyori (Figure 10).[56]

Transition metal complexes have also been used for ATH of ketones *via* metal ligand bifunctional catalysis methodology. Noyori and Gao have reported the use of diimino/diaminodiphosphine ligands such as **44** and **45** below with ruthenium, rhodium and iridium metals.[61-64] In 1996 and 2000, Noyori and Gao reported the use of ruthenium with ligand **45** to afford highly enantioselective hydrogenation of ketones.[61, 62] Ligands **44** and **45** were also combined with $[RuCl_2(DMSO)_4]$ and refluxed in toluene to form complexes **46** and **47** (Figure 11).

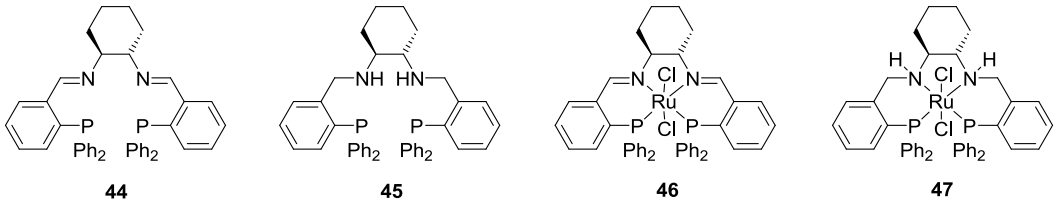
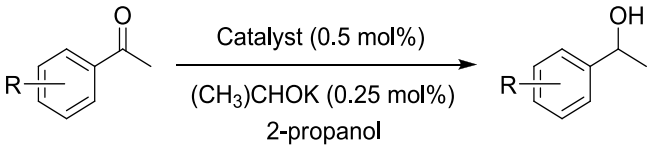


Figure 11. Diimino/diaminodiphosphine ligands and ruthenium complexes used for ATH of ketones.

The complexes were then applied to the ATH of a series of ketones with the results summarised in Table 3.

Table 3. Use of diimino/diaminodiphosphine ruthenium complexes for ATH of ketones.

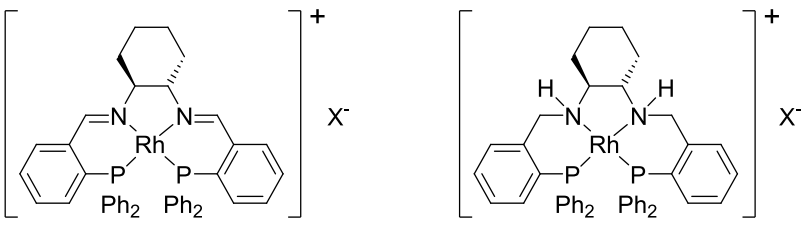


Entry	R	Catalyst	Temp (°C)	Time (hours)	Yield[a] (%)	Ee.[a] (%)
1	H	(*S*,*S*)-**46**	23	48	3	18 (*R*)
2	H	(*S*,*S*)-**46**	82	4	7	5 (*R*)
3	H	(*R*,*R*)-**47**	23	25	91	97 (*S*)
4	H	(*S*,*S*)-**47**	45	7	93	97 (*R*)
5	*o*-Cl	(*S*,*S*)-**47**	45	5	15	91 (*R*)
6	*m*-Cl	(*S*,*S*)-**47**	45	6	99	95 (*R*)
7	*p*-Cl	(*S*,*S*)-**47**	45	5	95	94 (*R*)
8	*p*-CN	(*S*,*S*)-**47**	45	6	99	89 (*R*)
9	*p*-F	(*S*,*S*)-**47**	45	6	97	80 (*R*)
10	*m*-OCH_3	(*S*,*S*)-**47**	45	6	74	95 (*R*)
11	*p*-OCH_3	(*S*,*S*)-**47**	45	6	67	58 (*R*)

[a] Determined by GLC analysis.

The diiminodiphosphine complex **46** was found to be relatively inactive to transfer hydrogenation conditions (Table 3, entries 1 and 2), whilst the amine derivative (complex **47**) was found to be highly active demonstrating the importance of the NH functionality in the reaction. The reaction is reported to proceed under kinetic control with a low level of reversibility and high level of differentiation between enantiomeric transition states leading to the high enantioselectivities observed. An increase in the concentration of base within the reaction was found to increase the rate of reaction but reduce the enantioselectivity, presumably by increasing the rate of reaction of the unfavoured enantiomeric transition state increasing the amount of the unwanted enantiomer present in the product.

These findings were mirrored in the application of the rhodium derivatives of complexes **46** and **47** to APH of ketones.[62, 63] Ligands **44** and **45** were combined with $[Rh(COD)Cl_2]_2$ and an appropriate anion to give complexes **48**-**51** (Figure 12). These were then applied to the ATH of ketones and the results are shown in Table 4.[63]

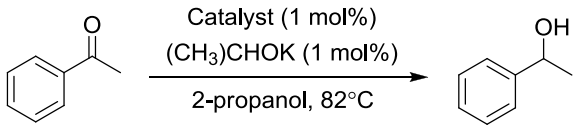


48 X=PF_6

49 X=PF_6
50 X=BF_4
51 X=ClO_4

Figure 12. Diaminodiphosphine rhodium complexes for ATH of ketones.

Table 4. Application of rhodium complexes for ATH of ketones.

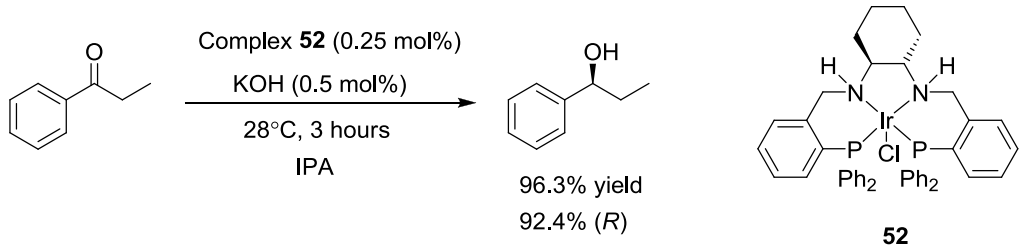


Entry	Catalyst	Time (hours)	Yield[a] (%)	Ee.[a] (%)
1	$[Rh(COD)Cl]_2$ + (*R*,*R*)-**44**	9	56	36 (*S*)
2	(*R*,*R*)-**48**	7	40	40 (*S*)
3	(*R*,*R*)-**49**	7	97	91 (*R*)
4	(*R*,*R*)-**49**[b]	24	85	89 (*R*)
5	(*R*,*R*)-**50**	7	98	80 (*R*)
6	(*R*,*R*)-**51**	9	87	86 (*S*)

[a] Determined by GC. [b]Substrate/catalyst 400/1

Again the imine complex (**48**) was found to be less active to ATH than the amine complexes. Use of PF_6 as the anion with the amine complex gave the best enantiomeric excess of product (complex **49**).

In more recent studies, Gao has also applied iridium derivatives of the complexes to ATH of ketones shown in Scheme 16.[64]

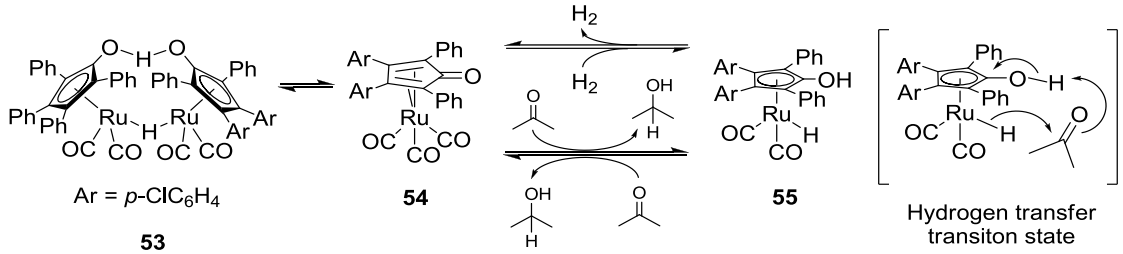


Scheme 16. Application of iridium diaminodiphospine complex **52** to APH of propiophenone.

Other examples of iridium catalysts for ATH applications include the use of $[Ir(COD)Cl]_2$ with TsDPEN reported by Lamaire for the hydrogenation of β-keto esters, however yields and conversions obtained were low.[65]

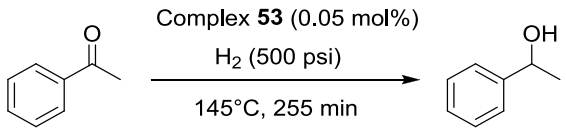
1.3.1 Metal ligand bifunctional catalysis with phosphine free catalysts.

In the mid 1980s Shvo reported the use of a tetraphenylcylcopentadienyl ruthenium carbonyl dimer for hydrogenation and dehydrogenative applications.[66] Initially the structure of the complex was assigned as $[(\eta^4\text{-}Ph_4C_4CO)(CO)_2Ru]_2$ however ^1H NMR analysis of the compound indicated the presence of a hydride with a signal at -17.75 ppm.[67] Replacing two of the phenyl groups with *p*-Cl-(C_6H_4) groups allowed an X-ray structure to be obtained showing the dimer to have the structure shown below with a bridging hydride between the two ruthenium centres and a bridging proton between the two oxygen atoms. Use of complex **53** in the dehydrogenation of an alcohol gave two complexes **54** and **55** which were presumed to form *via* fragmentation of the bridging hydrogen atoms. A catalytic cycle was proposed for complex involving interaction with hydrogen and hydrogen transfer between alcohols and ketones as shown in Scheme 17.[67]



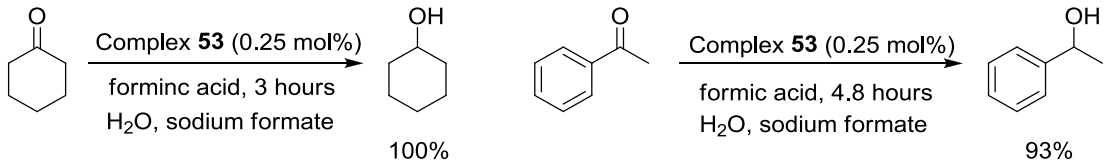
Scheme 17. Interaction of Shvo catalyst **53** with hydrogen and transition state for transfer hydrogenation of ketones.

In 1985 Shvo reported the application of complex **53** to the pressure hydrogenation of ketones however high pressures and temperatures were required.[68] The hydrogenation of acetophenone is shown in Scheme 18.



Scheme 18. Pressure hydrogenation of acetophenone with complex **53.**

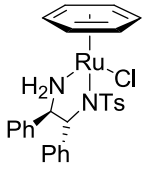
Shvo also reported the application of the complex to transfer hydrogenation with formic acid as the hydrogen source as in Scheme 19. Addition of a small amount of water and sodium formate prevented formation of the formate adduct of the desired alcohol product.[69]



Scheme 19. Transfer hydrogenation of ketones with complex **53.**

1.3.1.1 Ruthenium half sandwich complexes.

In 1995, Noyori reported the preparation and application to ATH of ketones of a new type of ruthenium half sandwich catalyst such as **54** shown in Figure 13.[70]

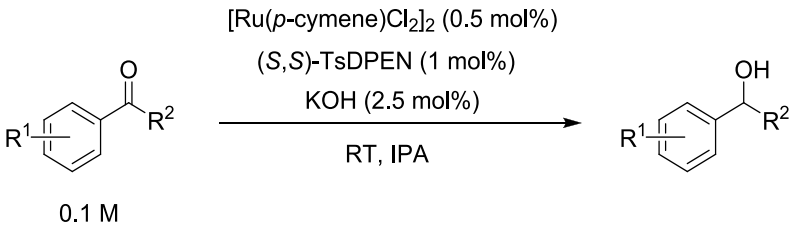


54

Figure 13. Ruthenium half sandwich complex **54** developed by Noyori.

The catalyst consists of an η-6 bound arene, an asymmetric diamine (TsDPEN) and a chlorine ligand and is prepared from the reaction of $[Ru(benzene)Cl_2]_2$ dimer and TsDPEN with either 1 equivalent of KOH in DCM or with 2 equivalents of Et_3N in 2-propanol at 80°C. The catalyst can also be prepared *in situ* and in this manner was applied to the ATH of a range of ketones and the results are shown in Table 5.[70]

Table 5. *In situ* formation of ruthenium half sandwich complexes and application to ATH of ketones with 2-propanol as the hydrogen donor.



Entry	R^1	R^2	Time (hours)	Yield[a] (%)	Ee.[b] (%)
1	H	Me	15	95	97 (*S*)
2	H	Et	14	94	97 (*S*)
3	*o*-Me	Me	24	53	91 (*S*)
4	*m*-Cl	Me	2.5	98	98 (*S*)
5	*p*-Cl	Me	19	95	93 (*S*)
6	*m*-OMe	Me	16	96	96 (*S*)
7	*p*-OMe	Me	20	53	72 (*S*)
	Substrate				
8	Tetralone		27	65	97 (*S*)
9	1'-acetonapthone		62	92	93 (*S*)
10	2'-acetonapthone		16	93	98 (*S*)

[a] Determined by GLC or ^{1}H NMR. [b] Determined by GLC or HPLC.

The use of 2-propanol as a hydrogen donor however has its drawbacks. It allows reversibility within the ATH reaction, as both the IPA and product are similar, both being secondary alcohols. The desired alcohol product can act as the hydrogen donor to the catalyst reforming the ketone substrate.[71] This reverse reaction is detrimental to both the yield of product and its enantiopurity. It is therefore important to use the right concentration of substrate within an ATH reaction and also control the time of the reaction in order to limit the exposure of the reaction mixture to the catalyst.

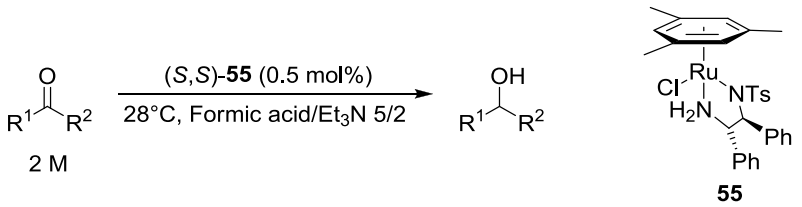
Noyori reported that the use of a 1 M substrate concentration in the reaction mixture showed an initial enantiomeric ratio for the product of (*S*):(*R*) 99:1 however at a conversion of 75% this had reduced to 97:3.[70] The reverse reaction of the dehydrogenation of phenyl ethanol was found to be ~2 orders of magnitude faster for (*S*)-phenyl ethanol than for the (*R*) enantiomer with use of (*S*,*S*)-TsDPEN in the catalyst. This therefore means that as well as reducing the product yield the reverse reaction also reduces the enantiomeric excess of the remaining product. The reaction is enantioselective in both the forward and reverse direction and over time there is a tendency towards racemisation. The equilibrium composition of the reaction mixture with a 1 M concentration of acetophenone was found to be 80:20 phenyl ethanol:acetophenone thus under sufficient reaction time, full conversion is not theoretically possible in this system.[70]

In order to maximise the conversion and enantioselectivity of ATH with hydrogen donation by 2-propanol it is necessary to use low concentrations of substrate, typically ~ 0.1 M.

The use of formic acid as the hydrogen donor offers a solution to the problem of reversibility in ATH reactions. Dehydrogenation of formic acid is irreversible thus

increased reaction concentrations, conversions and enantioselectivities are possible. Noyori reported the use of an azeotropic mixture of formic acid:triethylamine 5:2 for the ATH of a range of ketones and the results are shown in Table 6.[71]

Table 6. Application of complex **55** to ATH of ketones with formic acid as the hydrogen donor.

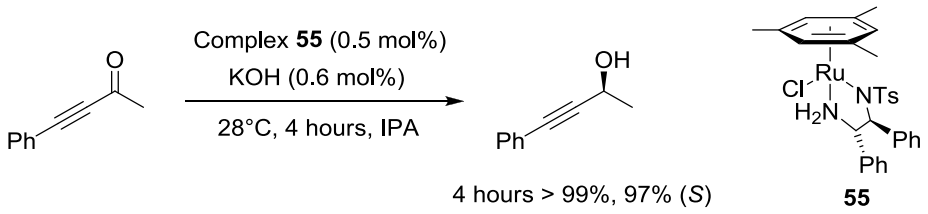


55

Entry	R^1	R^2	Time (hours)	Yield (%)	Ee.[a] (%)
1	Ph	Me	20	>99	98 (*S*)
2[c]	Ph	Me	1.5	>99	96 (*S*)
3	*m*-Cl	Me	21	>99	98 (*S*)
4	*p*-Cl	Me	24	>99	95 (*S*)
5	*p*-CN	Me	14	>99	90 (*S*)
6	*m*-OMe	Me	50	>99	98 (*S*)
7	*p*-OMe	Me	60	>99	97 (*S*)
8	H	Et	60	96	97 (*S*)
9	H	$(CH_2)_3CO_2Et$	90	99	95 (*S*)
	Substrate				
10	Tetralone		48	>99	99 (*S*)
11[b]	Tetralone		6	>99	98 (*S*)
12	1'-acetonapthone		60	93	83 (*S*)
13	2'acetonapthone		22	>99	96 (*S*)

[a]Determined by GC [b]Reaction carried out at 60°C.

The ATH of a range of acetylenic ketones has also been reported by Noyori. For example, the ATH of 4-phenyl-3-butyn-2-one proceeded with >99% conversion and 97% (*S*) ee. as shown in Scheme 20.[72]



Scheme 20. ATH of 4-phenyl-3-butyn-2-one using complex **55**.

The ATH of acetylenic ketones proceeds well with 2-propanol as the hydrogen donor. Although the reverse reaction is still possible, the product is favoured more at equilibrium than with aromatic ketones, therefore higher substrate concentrations can be used without the racemisation observed with aromatic ketones. Noyori reports the ATH of a 1 M solution of 4-phenyl-3-butyn-2-one using the 16 electron complex **56** to give a 94% yield and 95% ee. of product and use of a 5 M solution was found to give an ee. of 94% although the yield was reduced to 58% in 41 hours (Figure 14).[72]

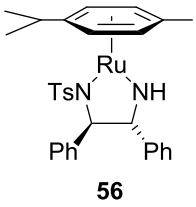


Figure 14. Structure of 16 electron complex **56**.

Use of formic acid as a hydrogen donor was reported to give low conversions for the ATH of acetylenic ketones as shown in Figure 15. The *p*-cymene catalyst **57a** was found to deactivate under the reaction conditions with irreversible coordination of the C≡C bond to the ruthenium to form complex **57b** in Figure 15. This prevents interaction of the complex with hydrogen.[72]

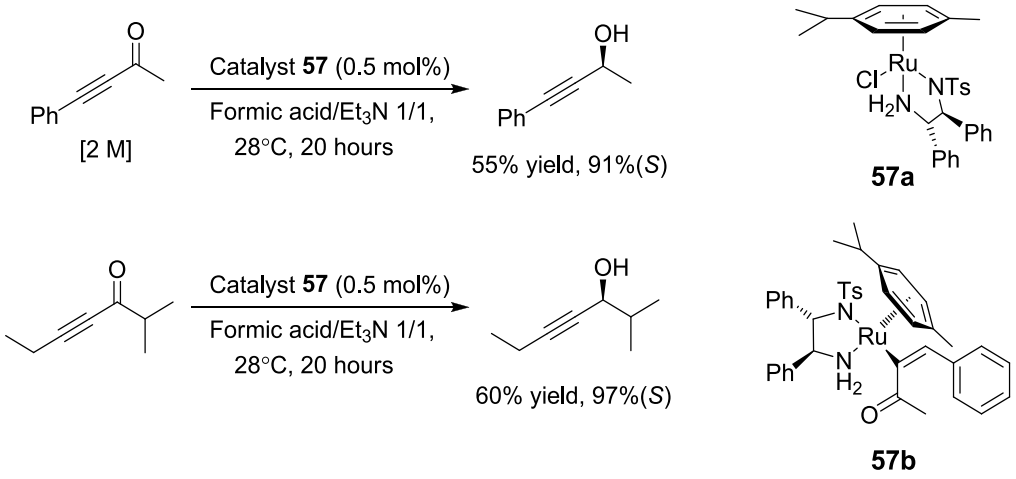
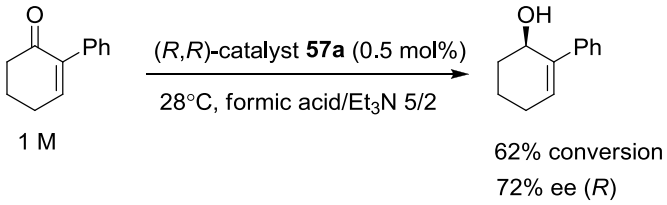


Figure 15. Deactivation of catalyst by irreversible coordination to alkyne bonds.

Wills has also reported the use of Noyori-type ruthenium half-sandwich complexes as catalysts for ATH of α, β-unsaturated ketones such as shown in Scheme 21.[73]



Scheme 21. ATH of 2-phenyl-2-cyclohexen-1-one using complex **57a**.

1.3.1.2 Structure of ruthenium half sandwich complexes.

Noyori has reported X-ray structures for the catalyst the series of reaction intermediates[74] – the catalyst precursor, the active catalyst and the ruthenium hydride complex shown in Figure 16.

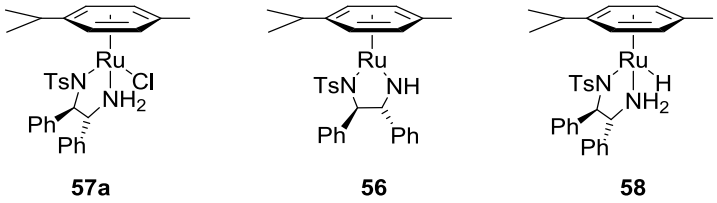


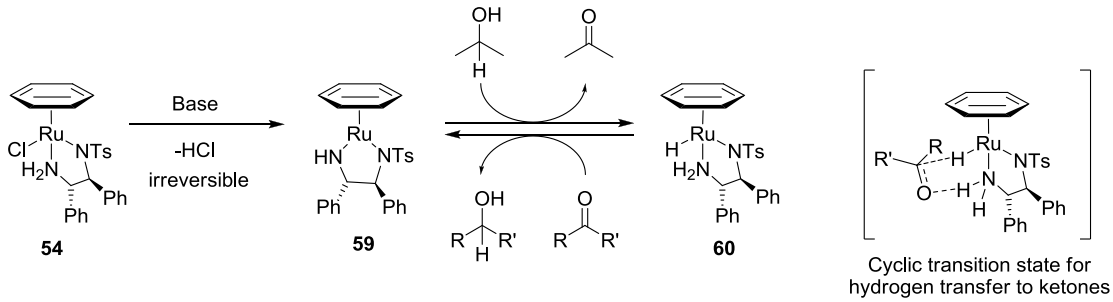
Figure 16. Ruthenium half sandwich catalyst pre-cursor (**57a**), 16 electron (**56**) and hydride (**58**) complexes.

The catalyst precursor **57a** has 18 electrons and is reported to have a distorted octahedral structure with three chiral centres, two within the diamine and the third being the ruthenium. The coordination of the diamine to the ruthenium forms a 5-membered ring and it is this that determines the configuration of the catalyst at the ruthenium. Use of (*S*,*S*)-TsDPEN gives an (*R*) configuration at the ruthenium. ^{1}H NMR analysis found the complex to exist as a single diastereomer in $CDCl_3$.[74]

The 16 electron complex **56** is formed from **57a** *via* elimination of HCl by a base such as KOH. The length of the HN-Ru bond shown in the X-ray structure suggested a degree of double bond character making the nitrogen lone pair less available than in the 18 electron complex. The complex was found to dehydrogenate methanol, ethanol and 2-propanol to give complex **58** with a Ru-H bond and protonated amine.[73] Complexes **56** and **58** were found to catalyse the ATH of acetophenone in IPA without the need for KOH, showing that the presence of KOH in the reaction mixture is necessary only for generation of the 16 electron complex **56**.[74]

1.3.1.3 Mechanism of asymmetric transfer hydrogenation using ruthenium half sandwich catalysts.

The ATH mechanism is shown in Scheme 22.[75] As mentioned previously, under ATH conditions with the presence of base, the 18 electron catalyst precursor (**54** in Scheme 22) undergoes loss of HCl to form a 16 electron species (**59** in Scheme 22). The 16 electron species then interacts with the hydrogen donor (2-propanol in Scheme 22) forming a 6-membered pericyclic transition state whereby hydrogen is transferred to the 16 electron species to again form an 18 electron species with a ruthenium hydride and protonated amine (**60**). The hydride and proton are transferred to the substrate *via* a further cyclic transition state to afford the desired product and reform the 16 electron species.

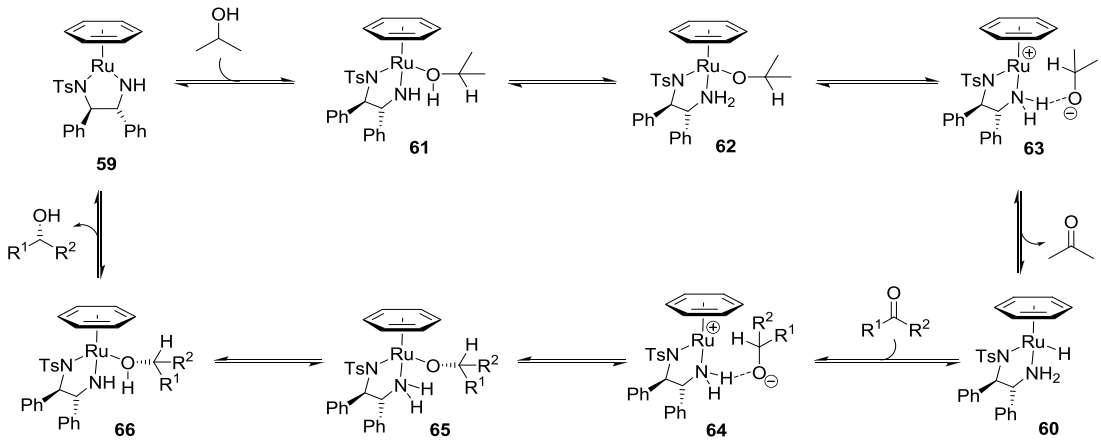


Scheme 22. Mechanism for ATH of ketones using ruthenium half sandwich complexes.

Much evidence has been reported that supports this ATH mechanism[74,76,77] however there are also reports that suggest an alternative mechanism. For example Xiao reported that the rate of the reaction increased with use of water and a co-solvent with the degree of acceleration of the reaction increasing with the polarity of the cosolvent.[78] This suggests that transition states within the reaction must be polar and possess a dipole. The pericyclic mechanism proposed by Noyori would not show a solvent effect as both the catalyst and reactants possess a similar charge distribution. Meijer studied the molecular dynamics of the reaction and found that the concerted mechanism was predicted in a gas phase reaction, however in solution phase the reaction mechanism became sequential.[79,80] In water, the hydride was found to transfer to the substrate with the proton being transferred by water at a later stage.

Recently, Ikariya has published the results of further studies into the reaction mechanism and proposed a non-concerted mechanism shown in Scheme 23.[81] After formation of the 16 electron species **59**, the ruthenium initially coordinates with the 2-propanol solvent and a proton is transferred to the amino nitrogen to form a ruthenium-alkoxide complex **62**. The alkoxide is then displaced and the hydride is transferred to the ruthenium to form complex **60** and acetone. The hydride is then transferred to the substrate forming an alkoxide which first hydrogen bonds with the proton on the amino group of the ligand (**64**) and is then transferred to the ruthenium

to give complex **65**. The substrate is then displaced with addition of a proton from the nitrogen (**66**) to again form the 16 electron species (**59**).

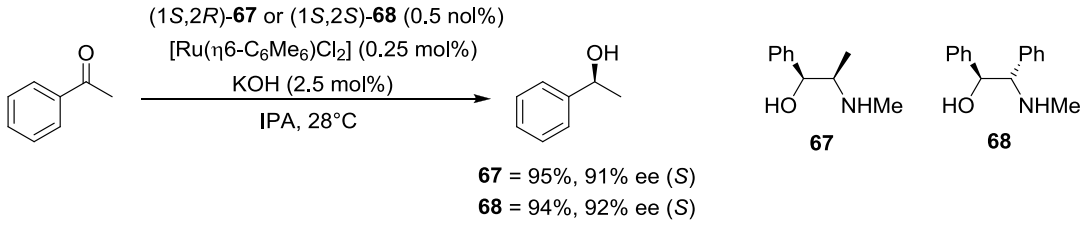


Scheme 23. Mechanism of ATH using ruthenium half sandwich complex **59** proposed by Ikariya.

In 2004 Ikariya reported insights into the mechanism of ATH of ketones using formic acid as the hydrogen with Noyori-type catalysts.[82] The reaction of the 16 electron complex **59** with formic acid first gave a formate complex which underwent decarboxylation to give ruthenium hydride complex **61** and CO_2. This can then react with CO_2 to reform the formate complex. The catalyst also promotes hydrogenation of CO_2 to form formic acid and it is therefore important to remove CO_2 from ATH reactions.

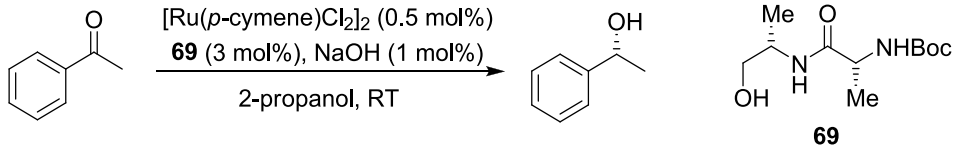
1.3.1.4 Further derivatives of half sandwich complexes for ATH applications.

The use of asymmetric amino alcohols as ligands in place of the TsDPEN in ruthenium half sandwich complexes has also been investigated. Noyori first reported the use of this type of catalyst in 1996[83] showing high activity for the ATH of ketones as shown in Scheme 24.



Scheme 24. ATH of acetophenone using asymmetric amino alcohol ligands **67** and **68**.

More recently, Wills and co-workers have used asymmetric amino alcohol ligands with $[Ru(p\text{-cymene})Cl_2]_2$ for the ATH of ketones as shown in Scheme 25.[84]

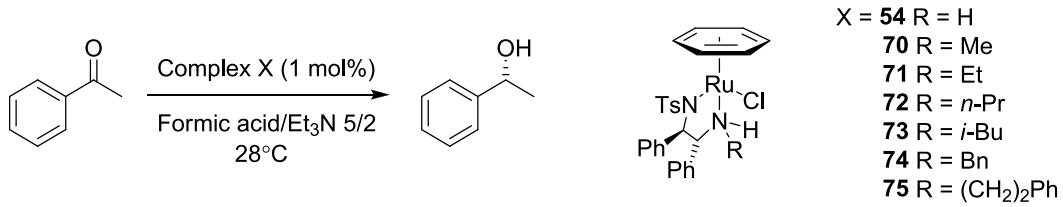


Scheme 25. Application of amino acid ligand **69** to ruthenium-catalysed ATH of acetophenone.

Puntener and co-workers have since reported the use of a range of amino alcohol ligands demonstrating excellent activity for selective ATH of C=O bonds in the presence of C=C bonds.[85]

Wills has reported results of investigations into the effects of *N*-substituents on the TsDPEN ligand of Noyori-type complexes.[87,88] The use of *N*-benzyl-*N'*-tosyl-DPEN was reported to give an ineffective catalyst when *p*-cymene was used as the aryl ligand, however when benzene was used the activity of the system was increased achieving 97% conversion of acetophenone to (*R*)-phenyl ethanol with 95% ee. in 7 days.[87] Other *N*-substituted derivatives of TsDPEN were prepared and used with $[Ru(benzene)Cl_2]_2$ dimer to give complexes **54** and **70**-**75** which were applied to the ATH of acetophenone as shown in Table 7.[86]

Table 7. ATH of acetophenone using *N*-alkylated ruthenium complexes.



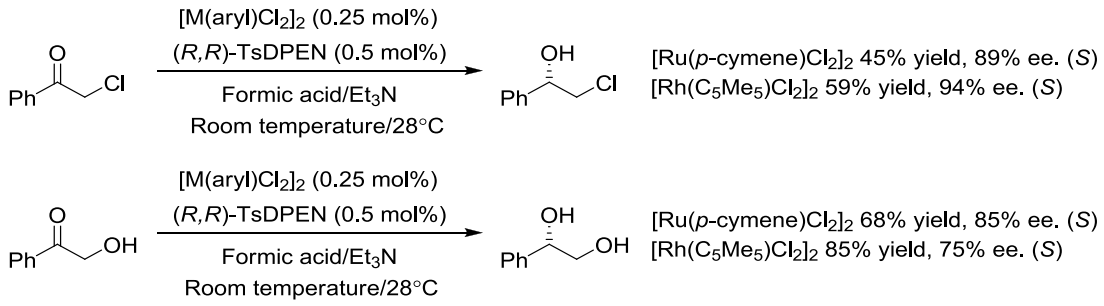
Entry	Complex	Time	Yield (%)	Ee.[a] (%)
1	**54**	26 hours	99	95 (*R*)
2	**70**	11 hours	99	96 (*R*)
3	**71**	3 days	99	96 (*R*)
4	**72**	3 days	99	96 (*R*)
5	**73**	7 days	88	98 (*R*)
6	**74**	7 days	97	95 (*R*)
7	**75**	7 days	97	96 (*R*)

[a] Determined by GC.

All *N*-substituted complexes showed excellent activity and enantioselectivity for the hydrogenation of acetophenone, with complex **70** giving the best results. A decrease in activity was seen for complexes **71-75** with increasing steric bulk of the substituent group. The complexes were also applied to the ATH of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline giving full conversion and high enantiomeric excesses with complexes **54** and **70** providing the highest rate of reaction. Complex **74** with increased steric hindrance gave the highest enantioselectivity of 85% ee. Further work looked at the effect of the degree of substitution on the aryl ligand of *N*-benzyl substituted complexes. Reactivity and enantioselectivity was found to decrease upon aryl substitution.[87]

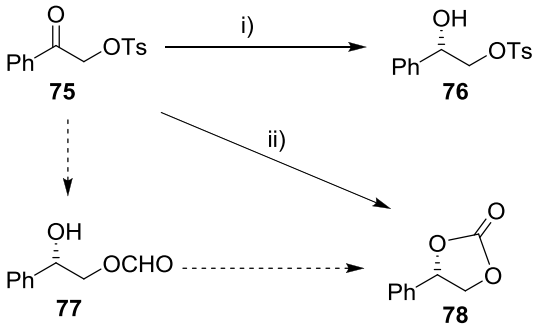
Wills *et al.* has also reported the use of a rhodium derivative of Noyori-type catalysts for the ATH of ketones. Use of $[Rh(C_5Me_5)Cl_2]_2$ with (*R*,*R*)-TsDPEN gave

contrasting results to use of [Ru(*p*-cymene)Cl_2]$_2$ for the ATH of chloro and hydroxy substituted acetophenone as shown in Scheme 26.[88]



Scheme 26. Application of ruthenium and rhodium half-sandwich catalysts to ATH of α-chloro and α-hydroxy acetophenone.

Interestingly, it was also reported that upon subjection of α-tosyloxyacetophenone **75** to ATH conditions, the use of [Rh(C_5Me_5)Cl_2]$_2$ and (*R,R*)-TsDPEN gave (*R*)-2-tosyloxy-1-phenylethanol **76** with 93% ee. whilst use of [Ru(*p*-cymene)Cl_2]$_2$ and (*R,R*)-TsDPEN gave a cyclic carbonate product **78** with 94% (*S*) ee.[88] It was proposed that the carbonate formed *via* hydrogenation of the C=O bond followed by formation of phenacylformate **77** which cyclises to give **78** as shown in Scheme 27.



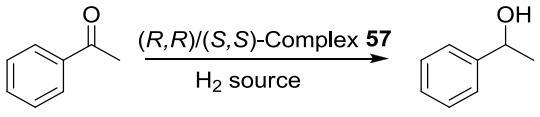
i) [Rh(C_5Me_5)Cl_2]$_2$ (0.25 mol%), (*R,R*)-TsDPEN (0.5 mol%), formic acid/Et_3N 5/2.
ii) [Ru(*p*-cymene)Cl_2]$_2$ (0.25 mol%), (*R,R*)-TsDPEN (0.5 mol%), formic acid/Et_3N 5/2.

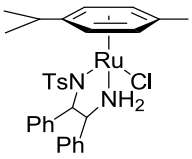
Scheme 27. Reaction of -tosylacetophenone with rhodium and ruthenium catalysts under ATH conditions.

1.3.1.5 Aqueous ATH of ketones with ruthenium half sandwich complexes.

The use of water as a solvent for ATH of ketones using Noyori-type complexes has also been investigated as a more economical and environmentally solvent than the 2-propanol or formic acid/Et_3N that has conventionally been used. The first report of this was by Xiao and co-workers in 2005.[89] Initial attempts looked at the addition of water to the use of formic acid/Et_3N azeotrope as the hydrogen source.[90] Improvements to the activity of the system were seen with use of aqueous formic acid/Et_3N with the pH of the reaction solution maintained at 5-8 by addition of Et_3N.[89] Further studies were made using sodium formate as a water soluble alternative hydrogen source to formic acid/Et_3N.[90] Table 8 shows a comparison of the results for the ATH of acetophenone with a range of hydrogen sources.[70-71, 89-90]

Table 8. Comparison of the ATH of acetophenone in formic acid, 2-propanol and water solvents.





57a

Entry	H_2 source	S/C	Solvent	Temp (°C)	Time (hr)	Conv. (%)	Ee.[a] (%)
1	2-propanol/KOH	200/1	2-propanol	RT	15	95	97 (*S*)
2	Formic acid/Et_3N 5/2	200/1	-	28	20	>99	98 (*S*)
3	Formic acid/Et_3N 5/2	100/1	Water	40	12	98	97 (*R*)
4	Formic acid/Et_3N 1.2/1	100/1	Water[b]	40	1.5	100	97 (*R*)
5	Sodium formate	100/1	Water	40	0.5	76	95 (*R*)

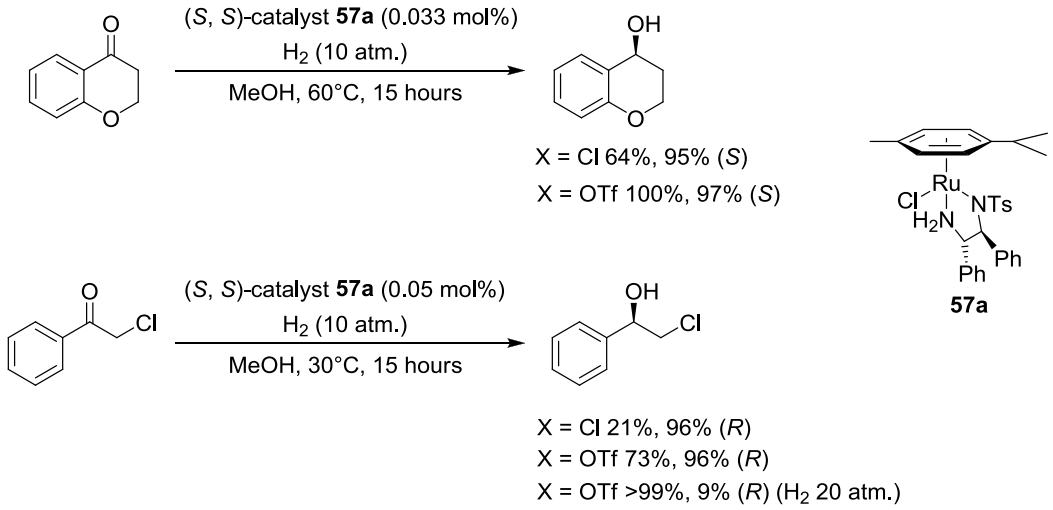
[a]Determined by GC. [b]pH of reaction maintained at pH5-8 with addition of Et_3N.

Complex **57** showed a relatively slow rate of reaction for the ATH of acetophenone in 2-propanol[70] and formic acid/Et_3N[71] compared to the reaction carried out in water (entry 3)[90]; in water with pH 5-8 (entry 4)[89] and that carried out with sodium formate

and water (entry 5).[90] To further understand the mechanism of the ATH reaction carried out in water, Xiao investigated the effect of pH on the reaction, and proposed two competing catalytic cycles.[89] At low pH, the tosylamine of the diamine ligand is protonated leading to its partial dissociation from the ruthenium centre. This dissociation will reduce the rigidity and hence enantioselectivity of the complex, thus the pH of the reaction should be maintained at 5-8 for the duration of the reaction to achieve maximum activity and enantioselectivity.

1.3.1.6 Asymmetric pressure hydrogenation of ketones with Noyori catalysts.

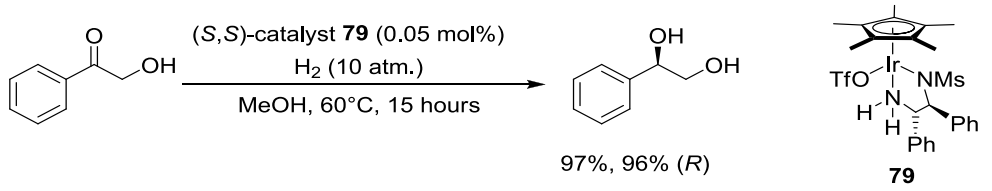
Noyori has also reported the application of catalyst **57a** to asymmetric pressure hydrogenation achieving high conversions and enantioselectivities of chromanones and α-chloro aromatic ketones as shown in Scheme 28.[75, 91]



Scheme 28. APH of chromanone and α-chloroacetophenone with complex **57a**.

Use of the triflate form of the catalyst was found to give improved results over the chloride, and indeed Ohkuma developed a related catalyst based on an iridium triflate and it too was found to allow effective hydrogenation of ketones with

hydrogen gas.[92] The application of the catalyst to the APH of α-hydroxyacetophenone is shown in Scheme 29.

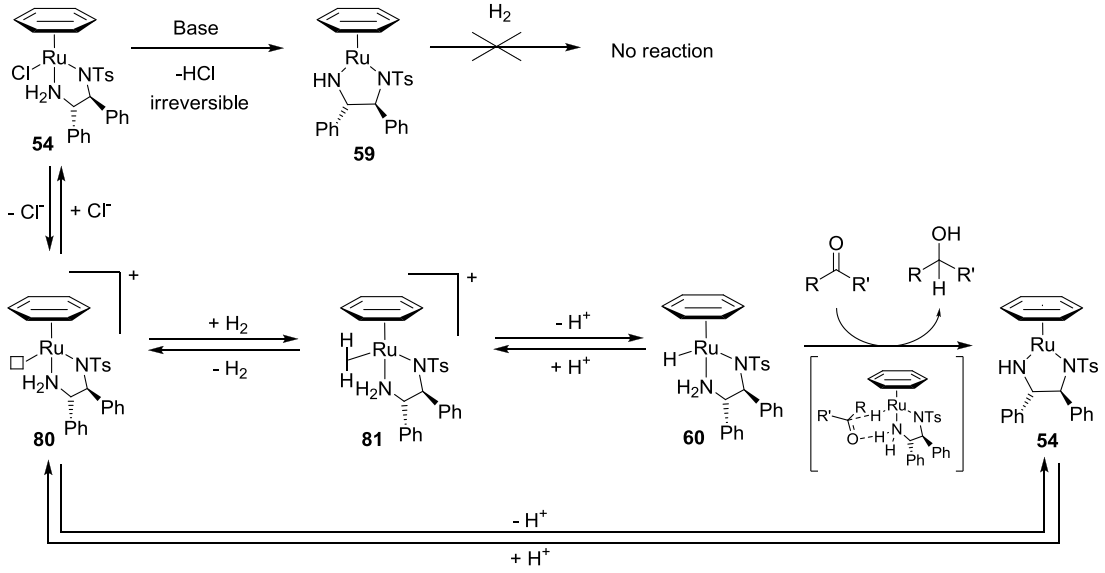


Scheme 29. APH of α-hydroxyacetophenone using iridium catalyst **79**.

The enhanced activity of the triflate catalyst over its chloro derivative for APH of ketones is explained when the reaction mechanism for APH is considered.

1.3.1.7 Mechanism of asymmetric pressure hydrogenation using ruthenium half sandwich catalysts.

The mechanism of APH with ruthenium half-sandwich complexes is shown in Scheme 30. Under APH conditions the catalyst precursor undergoes loss of chloride by ionisation to give cationic complex **80** which possesses a vacant co-ordination site for interaction with molecular hydrogen. Heterolytic cleavage of the H-H bond then allows formation of the ruthenium hydride species **60** as with ATH. The hydrogenation of the substrate proceeds *via* a cyclic transition state as for ATH.[75, 93]

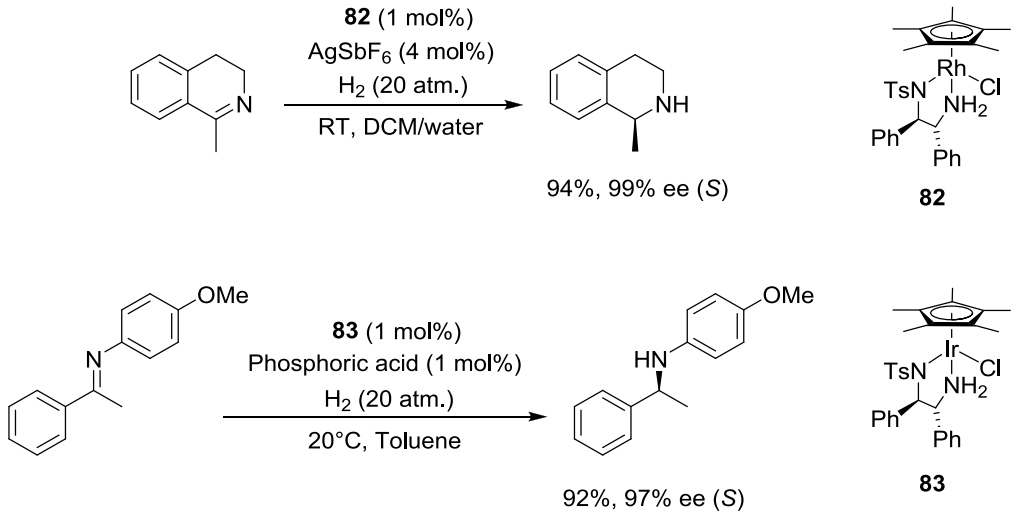


Scheme 30. Mechanism of APH of ketones using ruthenium half sandwich complexes.

The use of ruthenium triflate complexes as shown in Schemes 28 and 29 is believed to lead to an increased rate of ionisation in the first step of the mechanism and indeed an increased rate of catalyst activation. Silver salts, known to readily interact with halides, have also been used to improve the rate of ionisation and activation of the catalyst.[94]

1.3.1.8 Derivatives of half-sandwich metal complexes for APH applications.

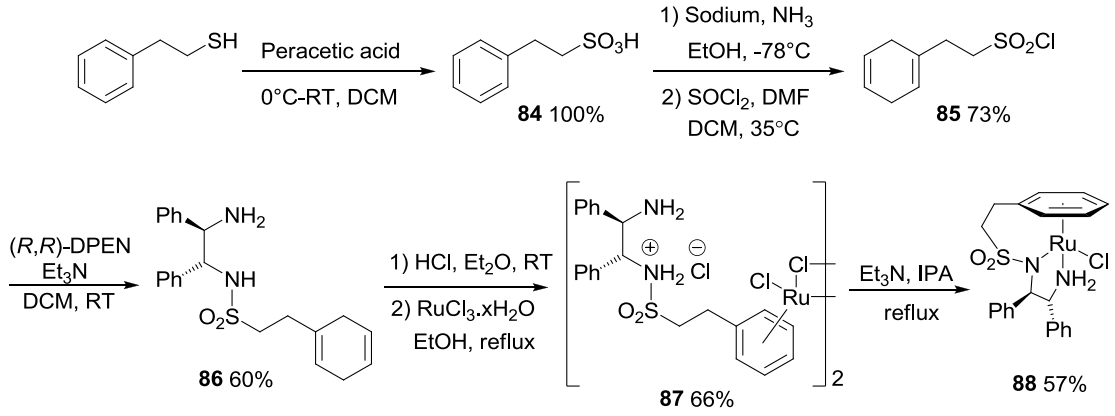
Xiao has reported the use of rhodium and iridium derivatives of Noyori-type catalysts for the APH of imines as shown in Scheme 31.[94, 95]



Scheme 31. Application of rhodium and iridium complexes to APH of imines.

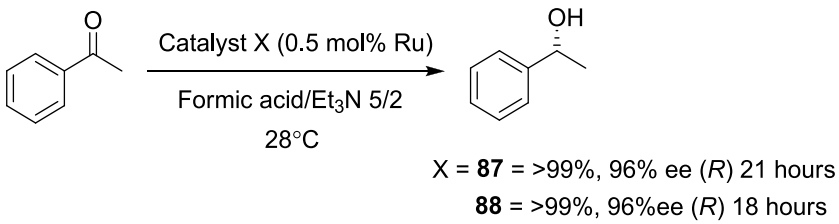
1.3.2 Tethered ruthenium complexes for ATH and APH of ketones.

In 2004, Wills and co-workers reported the synthesis and application of a new class of half-sandwich ruthenium complex to the hydrogenation of ketones incorporating a tether between the aryl and diamine ligand as shown in Scheme 32.[96]



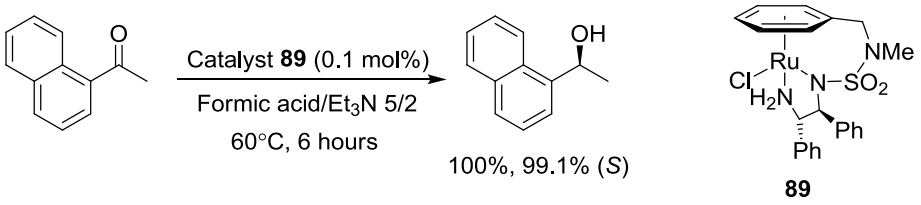
Scheme 32. Synthesis of tethered ruthenium complex **88.**

Ruthenium complexes **87** and **88** were applied to the ATH of acetophenone as shown in Scheme 33.



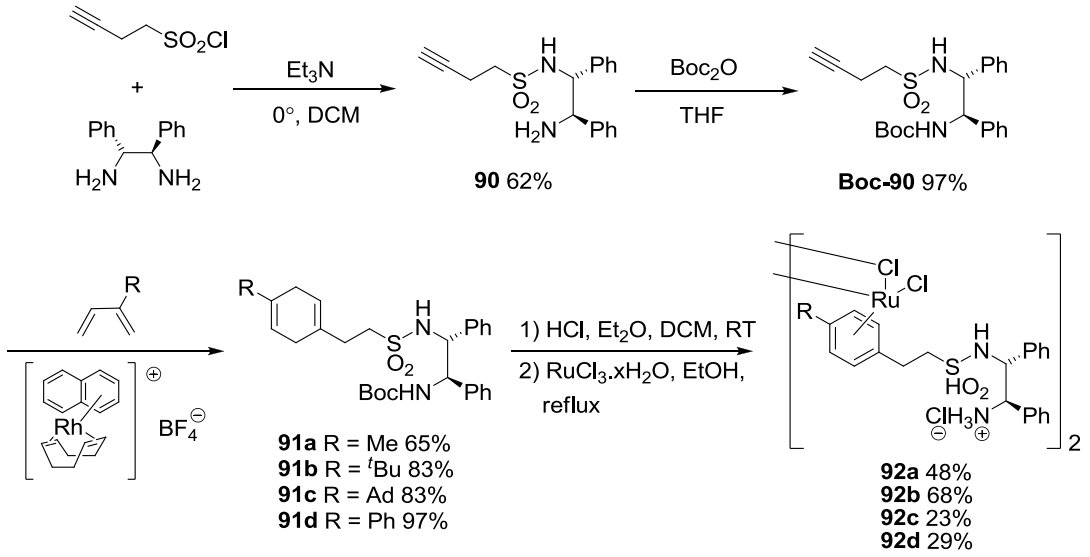
Scheme 33. Application of tethered ruthenium monomer **88** and dimer **87** to ATH of acetophenone.

The dimeric (**87**) and monomeric (**88**) forms of the catalyst were found to be highly active for the ATH of acetophenone and a series of aromatic ketones.[96] Recently Mohar has reported the preparation of a similar tethered catalyst and found excellent activity and enantioselectivity for the ATH of 1-napthyl ketones (Scheme 34).[97]



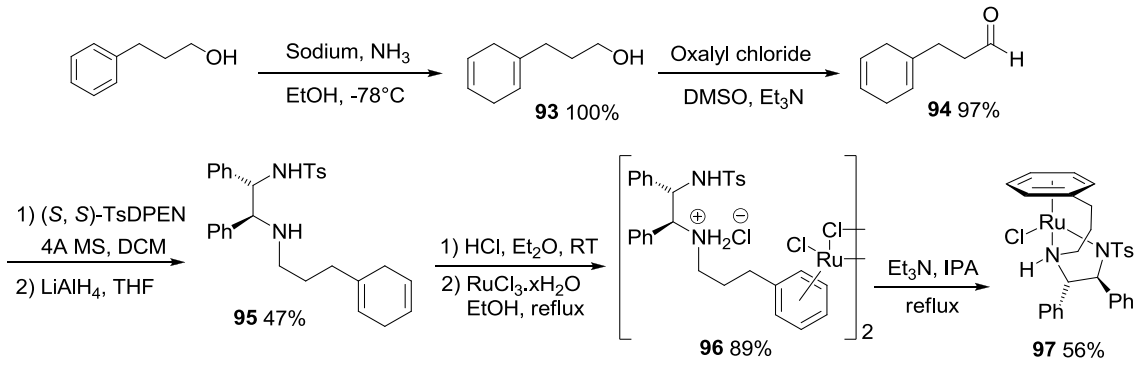
Scheme 34. ATH of 1-acetonapthone with catalyst **89**.

Wills and co-workers have reported an alternative synthesis for catalysts of type **88** which avoids the hazardous Birch reduction for formation of the diene *via* a [4+2] cycloaddition.[98] The synthesis of the analogous complexes (**92a-d**) is shown in Scheme 35.



Scheme 35. Synthesis of tethered ruthenium catalysts **92a-d** by an initial [4+2] cyclisation.

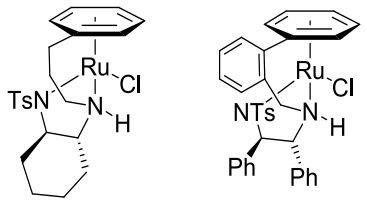
The catalysts prepared were subjected to the ATH of acetophenone however each was less active than catalyst **88**, with the best being **92a** achieving 88% conversion, 63% ee. in 96 hours with 0.25 mol% dimer in formic acid/Et_3N 5/2 at 40°C.[98] Further investigations into the position of the tether within the complex by the Wills group found that tethering the aryl ligand to the amino rather than sulfonamide nitrogen gave a significantly more active catalyst as shown in Scheme 36.[99.]



Scheme 36. Synthesis of 'reverse tethered' ruthenium complex **97.**

Catalyst **97** was found to show high activity for ATH of ketones allowing the formation of (*S*)-phenyl ethanol with 100% conversion and 96% ee. in 3 hours at 28°C with 0.5 mol% catalyst.

Further tethered catalysts, including the use of cyclochexadiamine (**98**) and the incorporation of a benzene ring into the tether (**99**) as shown in Figure 17, were found to be less active than **97**.[100]



98 **99**

Figure 17. Further derivatives of tethered catalysts.

At 28°C with a catalyst loading of 0.5 mol% catalyst **98** gave only 43% conversion to (*R*)-phenyl ethanol in 66 hours however the ee. was high at 97%. Catalyst **99** was more active giving 100% conversion in 12 hours however the ee. was reduced slightly to 92% under the same conditions. The activity of catalyst **98** was improved with an increase in temperature to 40°C giving (*R*)-phenyl ethanol in 100% conversion and 95% ee.[100]

The incorporation of a tether within the aryl/diamine half sandwich ruthenium complexes has been found to give a more stable structure. Catalyst **88** gave full conversion of acetophenone to phenyl ethanol within 24 hours, upon which more acetophenone and formic acid/Et_3N 5/2 was added and full conversion was achieved in 73 hours and upon further addition again full conversion was reached in 176 hours each time without a reduction in the ee.[99]

1.3.2.1 Structural and mechanistic insights for application of tethered ruthenium catalysts to ATH of ketones.

The preparation of a range of catalysts with different tether lengths and a range of aryl substituent groups allowed for further insights into the structure and mechanism of action of the catalysts.[101,102] The catalysts prepared are shown in Figure 18 and results of their application to the ATH of acetophenone are given in Table 9.

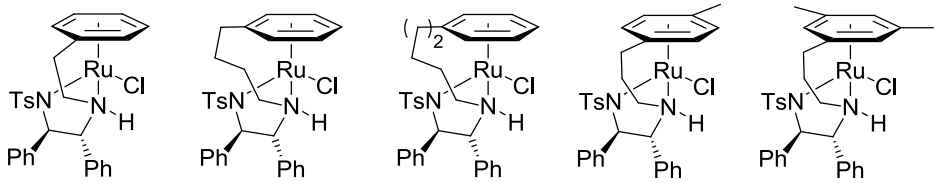
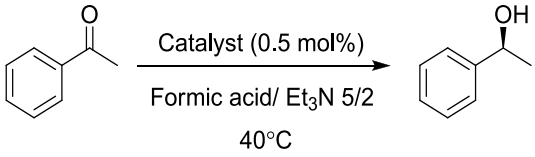


Figure 18. Structures of tethered catalysts with a variety of tether lengths and aryl substituents.

Table 9. Application of catalysts 9**7** and **100**-**104** to the APH of acetophenone.



Entry	Catalyst	Time (hours)	Conv. (%)	Ee.[a] (%)
1	**100**	15	19	92 (*R*)
2	**97**	2	100	96 (*R*)
3	**101**	1.25	100	96 (*R*)
4	**102**	6	38	94 (*R*)
5	**103**	4	100	96 (*R*)
6	**104**	5	100	93 (*R*)

[a]Determined by GC.

Complex **101** was the most active of the catalysts both as the monomer shown above and also in its dimeric form. Kinetic studies revealed this increase in activity to be due to an increased rate of ruthenium hydride formation and ketone reduction. For

the other catalysts tested, the overall rate of the reaction was limited by their rate of hydride formation.

Andersson has reported that the H-Ru-NH angle in Noyori-type catalysts is important for the catalytic process with a smaller angle giving an increase in reaction rate.[103] It is thought that the smaller angle gives a catalyst that is better pre-organised for efficient hydrogen transfer. In catalyst **101** with a four-carbon tether, although an X-ray structure of the ruthenium-hydride complex has not been reported, inspection of the X-ray for the chloride complexes shows **101** to have the smallest Cl-Ru-N-H angle of 3.04° compared to 4.59° in the parent three carbon tethered catalyst **97**. If this pattern is retained upon formation of the ruthenium hydride complexes then this would explain the high reactivity of catalyst **101**.

In addition to providing a more stable structure for the catalysts, the tether also prevents rotation of the aromatic ring. The addition of substituent groups to the aromatic ring could therefore be used to affect the selectivity or activity of the catalyst as their position within the catalyst would be fixed rather than existing in an equilibrium environment as in Noyori's untethered catalysts due to rapid rotation of the aromatic ring. Reaction of the complexes with cyclohexyl methyl ketone showed complex **104** to give the highest ee. of 90%.[101] It is believed that the additional methyl groups on the aromatic ring, fixed in position with the addition of the tether to the catalyst enhance the preference for the substrate to adopt the favoured transition state shown in Figure 19, in order to minimise steric clash between the cyclohexyl ring and the methyl groups.

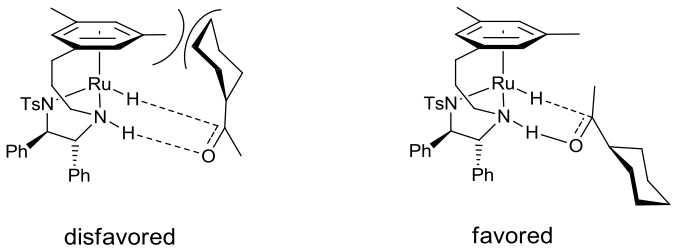
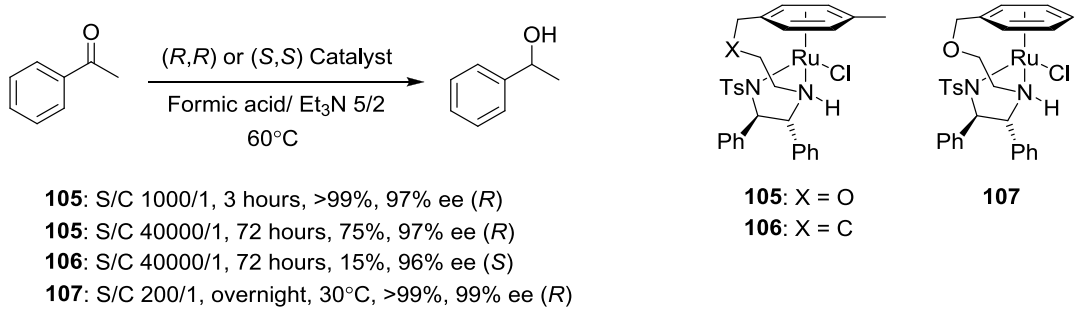


Figure 19. Cyclic transition states for ATH of cyclohexylmethyl ketone with catalyst **104**.

1.3.2.2 *O*-Tethered ruthenium catalysts.

In late 2011 and early 2012 both Ikariya [104] and Wills[105] independently reported the synthesis and use of four atom ether tethered catalysts **105**-**107** as shown in Scheme 37. The catalyst showed improved activity for ATH of ketones over the conventional carbon tethered catalysts. Another benefit offered by this catalyst is that its preparation is achieved by use of a [4+2] cycloaddition to afford the required diene as reported by Wills[98] rather than the hazardous Birch reduction.



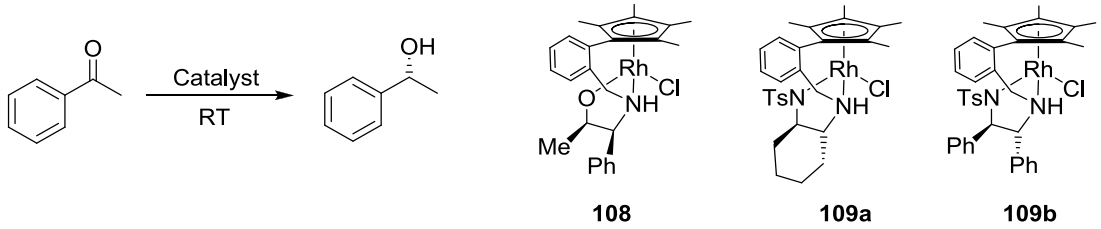
105: S/C 1000/1, 3 hours, >99%, 97% ee (*R*)
105: S/C 40000/1, 72 hours, 75%, 97% ee (*R*)
106: S/C 40000/1, 72 hours, 15%, 96% ee (*S*)
107: S/C 200/1, overnight, 30°C, >99%, 99% ee (*R*)

Scheme 37. Application of ether tethered ruthenium catalysts to the APH of acetophenone.

1.3.2.3 Tethered rhodium catalysts.

In 2004, Wills and co-workers reported the use of a tethered rhodium catalyst for the ATH of ketones.[106] Initially asymmetric amino alcohol ligands were used however later reports showed the use of asymmetric *N*-(*p*-tosyl)-1,2-cyclohexanediamine or TsDPEN as ligands gave improved enantioselectivity for product formation.[107, 108] The results are shown in Table 10.

Table 10. ATH of acetophenone with tethered rhodium catalysts **108, 109a** and **109b**.



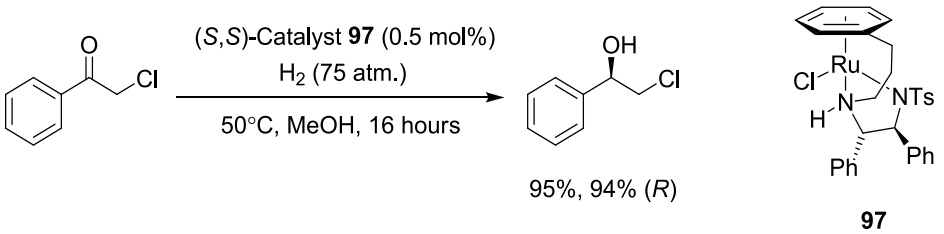
108 **109a** **109b**

Entry	Catalyst	Base	Solvent	Time (hours)	Conv.[a] (%)	Ee.[b] (%)
1	**108** (5 mol%)	KO^{t}Bu	2-propanol	10 min.	95	68 (*R*)
2	**109a** (0.5 mol%)	-	Formic acid/Et_3N 5/2	2	100	96 (*R*)
3	**109a** (0.5 mol%)	-	Water/sodium formate	3	100	96 (*R*)
4	**109b** (0.5 mol%)	-	Formic acid/Et_3N 5/2	10	100	98 (*R*)

[a]Determined by ^{1}H NMR. [b]Determined by chiral HPLC.

1.3.2.4 APH with tethered catalysts.

Although Noyori-type untethered ruthenium catalysts have successfully been applied to the APH of ketones, there is little precedent in the literature for the application of tethered ruthenium catalysts to the APH of ketones. In 2007 Wills and Morris reported the application of the three carbon tethered catalyst **97** to the APH of α-chloro acetophenone as shown in Scheme 38.[109]



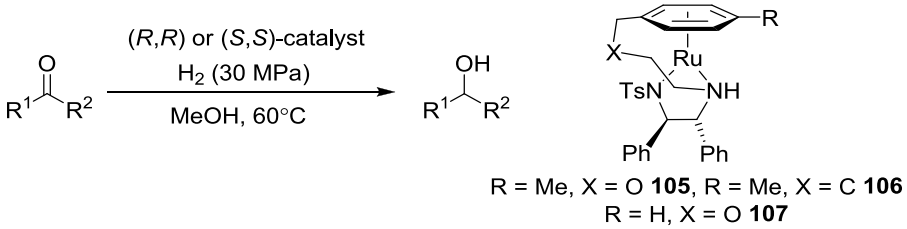
97

Scheme 38. Application of catalyst **76** to APH of α-chloroacetophenone.

In the more recent publication, Ikariya reported the application of the *O*-tethered catalyst **105** and the 4C tethered catalyst **106** to the APH of a range of ketones,

revealing **105** to be highly active for this application.[104] Compared to *O*-tethered catalyst **105**, the four carbon tethered catalyst **106** was found to be less active for APH at very low loadings. The results are summarised in Table 11.

Table 11. Application of catalysts **105**, **106** and **108** to APH of ketones.



Entry	R^1	R^2	Catalyst	S/C	Time (hours)	Yield (%)	Ee.[a] (%)
1	Ph	CH_3	(*R*,*R*)-**105**	500/1	20	58	90 (*R*)
2	Ph	CH_3	(*R*,*R*)-**107**	500/1	20	99	95 (*R*)
3	Ph	CH_2OH	(*R*,*R*)-**105**	5000/1	18	99	93 (*S*)
4	Ph	CH_2OH	(*S*,*S*)-**106**	5000/1	18	35	89 (*R*)
	Substrate						
5	4-Chromanone		(*R*,*R*)-**105**	1000/1	20	99	99 (*R*)
6	4-Chromanone		(*R*,*R*)-**107**	1000/1	20	99	97 (*R*)
7	1-Indanone		(*R*,*R*)-**105**	1000/1	18	59	98 (*R*)
8	1-Indanone		(*R*,*R*)-**107**	1000/1	18	97	98 (*R*)
9	1-Tetralone		(*R*,*R*)-**105**	1000/1	18	52	>99 (*R*)
10	1-Tetralone		(*R*,*R*)-**107**	1000/1	18	85	>99 (*R*)

[a]Determined by GC or HPLC.

1.3.3 Polymer supported catalysts for hydrogenation of ketones.

Supporting a catalyst on a polymer offers several advantages to a reaction, in particular the opportunity for facile and efficient recovery of the catalyst after the reaction. This not only reduces the costs involved in purifying reaction products to ensure residual catalyst is removed but also allows for the catalysts to be recycled and used in subsequent reactions.

The use of poly(ethylene glycol) (PEG) as a soluble polymer support for hydrogenation catalysts has been widely studied due to its solubility in a range of solvents, low toxicity and high stability. [110, 111]

The first reported use of PEG-2000 as a support for a TsDPEN based hydrogenation catalyst was developed by Xiao in 2004.[112] The PEG is linked to the TsDPEN *via* an ether linkage at the *meta* position of each of the phenyl substituents to give PTsDPEN **109** shown in Figure 20.

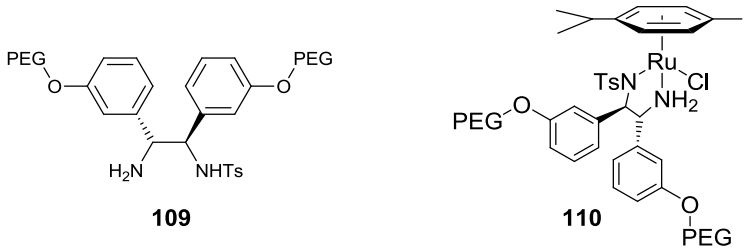
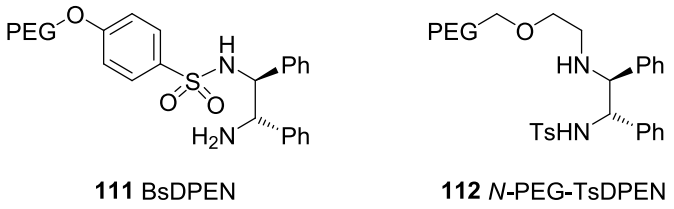


Figure 20. Structure of PEG supported ligands and complexes.

The reaction of $[Ru(p\text{-cymene})Cl_2]_2$ with the supported ligand **109** in water at 40°C allowed the formation of polymer supported Noyori-type complex **110**. Previous application of supported catalyst **110** to the ATH of acetophenone in formic acid gave good conversion and enantioselectivity however attempts to recycle the catalyst were unsuccessful.[113] Use of catalyst **110** in water with five equivalents of sodium formate gave 99% conversion to (*R*)-phenyl ethanol with 92% ee. in only 1 hour (40°C, 1 mol% catalyst). The catalyst was successfully recycled and used in subsequent reactions with the no significant reduction in activity until after the fourteenth cycle of the reaction where a conversion of 87% was achieved.

Chan and Li reported the synthesis and application of other PEG supported TsDPEN ligands, firstly with an ether link at the *para*-position of the benzenesulfonamide

group (PEG-BsDPEN **111**)[114] and secondly linked *via* the free amine (*N*-PEG-TsDPEN **112**).[115] The structures of both supported ligands are shown in Figure 21.



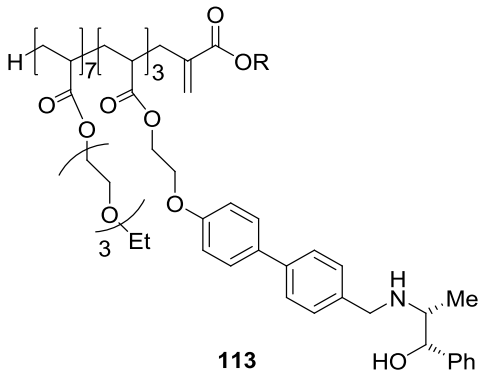
111 BsDPEN **112** *N*-PEG-TsDPEN

Figure 21. Structures of MsDPEN (**111**) and *N*-PEG-TsDPEN (**112**).

When **111** (PEG-750) was combined with $[Ru(p\text{-cymene})Cl_2]_2$ at a catalyst loading of 1 mol% in water with 5 equivalents of sodium formate, acetophenone was reduced to (*S*) phenyl ethanol with >99% conversion and 96% ee. in 2 hours at room temperature. The system was also found to give higher enantioselectivities than **110** (PTsDPEN) for the ATH of a range of ketones.[114] Use of ligand **112** (with PEG200-PEG2000) under the same conditions as for **111** but at 40°C gave the reduction of acetophenone to (*S*)-phenyl ethanol with >99% conversion and 94-94.8% ee. in 15 hours. Use of *N*-PEG2000-TsDPEN maintained high conversions and enantioselectivity for nine catalytic cycles. Lower molecular weight *N*-PEG200-TsDPEN was found to be more soluble than *N*-PEG2000-TsDPEN and when used in hydrogenation reactions a decrease in activity was seen after three cycles possibly due to the ligand being too soluble causing leaching of the catalyst.[115]

The use of pendant groups on a polymer chain as ligands for ruthenium-catalysed ATH has also been reported in the literature. Wills has reported the use of pendant chiral β-amino alcohols with a copolymer of PEG ethylether methacrylate and hydroxyethyl methacrylate (HEMA) for use in catalytic ATH of ketones.[116] (1*S*, 2*R*)-*N*-(4-bromobenzyl)norephedrine was coupled with the *O*-*p*-bromobenzene derivative

of the hydroxyethyl component of HEMA by Suzuki coupling to form a biphenyl spacer group and give polymer supported ligand **113** (Figure 22). The best result achieved for the ATH of acetophenone to phenyl ethanol was 85% conversion and 81% ee. in 20 hours with a 0.5 mol% catalyst loading in 2-propanol/KOH.[116]

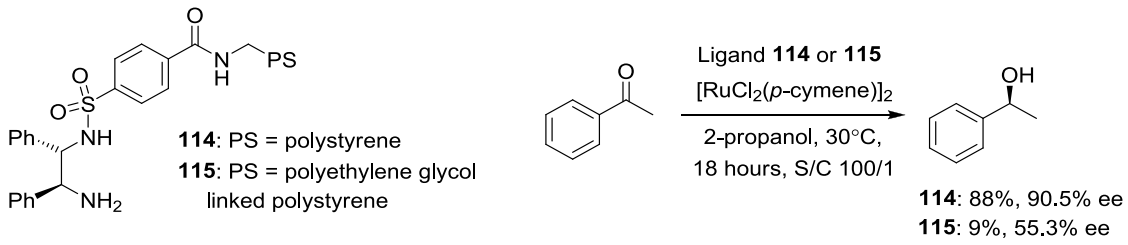


113

Figure 22. Structure of PEG ethylether methacrylate and hydroxyethyl methacrylate copolymer supported TsDPEN ligand **113**.

The use of insoluble polymers as supports for ligands has also been applied to the ATH of ketones offering convenient recovery of the catalyst from the reaction solution by filtration for regeneration and reuse and also allowing removal of traces of transition metals from reaction products. Polystyrene has commonly been used in this application due to its stability to a range of reaction conditions and wide scope for functionalisation.

Polywka *et al.* reported the use of two polystyrene bound diamines (**114** and **115**) for the ATH of ketones using ruthenium.[117] The ligands are bound to the polymer by an amide linkage at the *para* position of the aryl sulfonamide group. The application of the ligands to the ATH of acetophenone as shown in Scheme 39 showed ligand **114** to be the more reactive of the two giving significantly higher conversions and enantioselectivities than **115**.



Scheme 39. Application of polystyrene supported TsDPEN ligand to ATH of acetophenone.

Use of formic acid/Et_3N 5/2 increased the activity of ligand **115** to give 95% conversion, 96.7% ee. for the ATH of acetophenone although the activity of **114** was decreased. The enantioselectivity of the reaction with ligand **115** was unchanged over two reaction cycles.

Itsuno has reported the first application of polystyrene supported TsDPEN in aqueous ATH of ketones using polymer supported ligands.[118] Use of ligand **116** (Figure 23) with $[RuCl_2(p\text{-cymene})]_2$ gave a conversion and enantiomeric excess for the ATH of acetophenone of 100% and 97% (*R*) ee. respectively in only three hours using 1 mol% catalyst at 40°C with water and sodium formate. The catalyst was recycled five times with conservation of the enantiomeric excess.

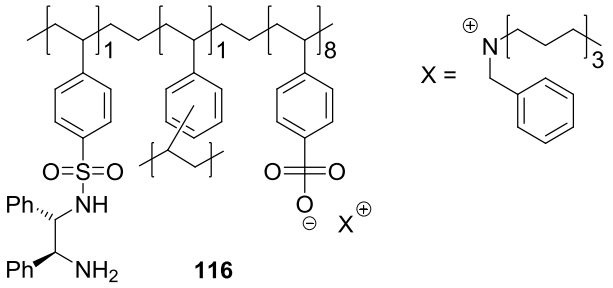


Figure 23. Structure of polystyrene supported TsDPEN ligand **116**.

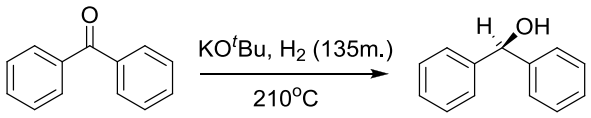
1.4 Non-Precious metal catalysts for asymmetric hydrogenation.

Within synthetic chemistry, particularly on an industrial scale, there is an ever growing need to develop more viable preparations of desirable products in order to

develop a more environmentally friendly approach, to reduce costs or increase efficiency. Of particular interest is the development of non-precious metal catalysts for key transformations. Although highly active as catalysts, many transition metals are a limited resource making them expensive and many are also toxic making expensive and stringent purification methods to ensure their removal from reaction products essential. Much research has and is therefore being carried out in this field.

1.4.1 Base-catalysed hydrogenation of ketones using potassium *tert*-butoxide.

One of the earliest reports of non-transition metal-catalysed pressure hydrogenation of ketones was reported by Walling and Bollyky in 1964 using KO^{t}Bu to catalyse the hydrogenation of benzophenone to benzhydrol as shown in Scheme 40.[119]



Scheme 40. Hydrogenation of benzophenone to benzhydrol using KO^{t}Bu catalyst.

The reaction required high temperatures of up to 210°C and hydrogen pressures of up to 135 atm. to generate high product yields as shown in Table 12. With low loadings of KO^{t}Bu the rate of reduction was slow with reactions requiring up to 25 hours to form high product yields. Using an excess of KO^{t}Bu improved this allowing slightly reduced temperatures, pressures and time to give an almost quantitative yield of product (Table 12, entry 2).[119]

Table 12. Base-catalysed reduction of benzophenone. (0.43-0.46 M benzophenone).

Entry	Solvent	Catalyst	Moles catalyst	H_2 (atm.)	Temp (°C)	Time (hours)	Benzhydrol (%)
1	^{t}BuOH	None	-	102	170	28	0
2	^{t}BuOH	^{t}BuOK	0.086	102	170	18	63
3	^{t}BuOH	^{t}BuOK	0.093	102	153	50.5	47
4	^{t}BuOH	^{t}BuOK	0.093	135	210	25	98
5[a]	^{t}BuOH	^{t}BuOK	0.333	96	150	14.5	98
6	Benzene	^{t}BuOK	0.093	125	204	23	98
7	Diglyme	^{t}BuOK	0.093	100	170	18	52
8[b]	Diglyme	^{t}BuOK	0.283	78	130	5	98
9	^{t}BuOH	^{t}BuOLi	0.086	102	170	18	32
10	Benzene	^{t}BuONa	0.464	95	100	5	0
11	H_2O	KOH	8.9	125	200	28	1
12	Diglyme	$(i\text{-PrO})_2$Al	0.093	123	210	34	Trace

[a] 0.111 M benzophenone used. [b] 0.094 M benzophenone used.

Walling and Bollyky also investigated the use of different solvents and catalysts in the reaction and the results are summarised in Table 12 above. Diglyme, the dimethyl ether of diethylene glycol, was reported as the most effective solvent allowing higher yields at lower temperatures and pressures than with *tert*-butanol or benzene. Indeed, with excess catalyst, the reaction was complete in only 5 hours at the reduced temperature of 78°C and hydrogen pressure of 130 atm. Using LiO^{t}Bu generated a yield of 32%, but NaO^{t}Bu, KOH and $(^i\text{PrO})_3$Al gave little or no product.

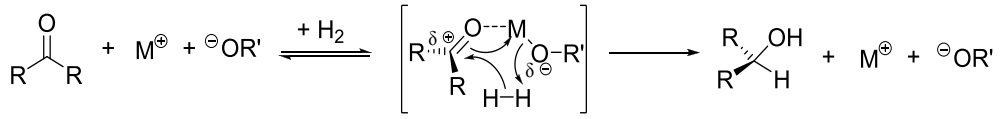
The reduction of a range of substrates using KO^{t}Bu was investigated and it was found that the reaction was most effective with aromatic ketones.[119] Aliphatic substrates (acetone and cyclohexene) generated no reduced product. Nitrobenzene

was effectively reduced to aniline demonstrating the application of the conditions to the reduction of NO_2 groups in addition to carbonyl.[119]

In 2002 Berkessel reported further studies into the KO^{t}Bu-catalysed hydrogenation of ketones.[120] After initial repetition of the findings reported by Waling and Bollyky investigations were carried out to establish a mechanism of the reaction. The reaction was found to be irreversible as the reaction of benzhydrol with KO^{t}Bu under 45 bar hydrogen pressure did not form benzophenone. Increasing the pressure and temperature of the reaction was found to increase the rate of reaction. At 100°C the conversion to product was found to plateau after a short time at only 15% however at 210°C quantitative conversion to product was achieved. The reaction was found to be first order with respect to benzophenone, hydrogen and KO^{t}Bu.[120]

The nature of the alkali metal used as the catalyst was also found to have an effect on the reaction.[120] Use of lithium, sodium, potassium, rubidium and cesium benzhydrolates at 135 bar hydrogen and 210°C showed the rate of reaction to decrease in the order Cs › Rb ≈ K » Na » Li. This follows the trend of increasing covalency of the metal-oxygen bonds, and hence reducing partial charge on the metal. A lower charge on the metal makes it less effective at activating the ketone towards nucleophilic attack from the hydride of the hydrogen molecule.

A mechanism for the reaction was proposed as shown in Scheme 41.[120]

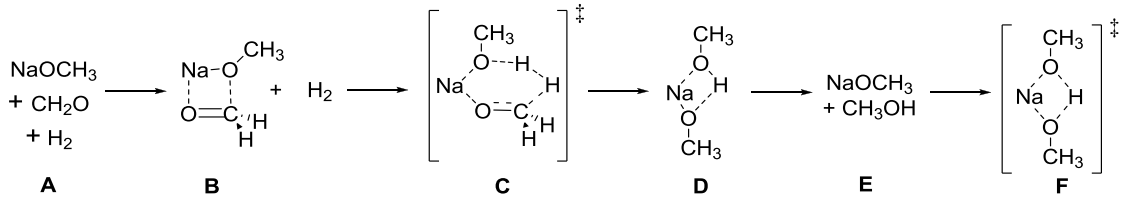


Scheme 41. Mechanism for base-catalysed hydrogenation of ketones.

The mechanism was proposed to proceed *via* a 6-membered cyclic transition state within which both the ketone substrate and alkoxide base are bound to the alkali metal. Heterolytic cleavage of the hydrogen molecule occurs to form the final product *via* hydride attack at the carbon centre of the carbonyl group and protonation of the alkoxide. Proton transfer to the substrate gives the final product. The cleavage of the hydrogen molecule is not thought to be the rate-determining step of the reaction and instead it was thought that the formation of the ordered transition state was the main factor limiting the reaction rate.[120]

In 2005 Chan and Radom reported further insight into the base-catalysed hydrogenation of ketones using computational molecular orbital theory.[121]

Initially the group looked at the thermodynamics of the reaction and elected to model the sodium methoxide-catalysed reduction of formaldehyde at 0°K. The mechanism for the reaction was divided into 6 key steps (A-F) as shown in Scheme 42.[121]



Scheme 42. Proposed mechanism for sodium methoside-catalysed hydrogenation of formaldehyde.

Sodium methoxide and formaldehyde initially form a strong adduct with both oxygen atoms strongly associated to sodium (**B**). Interaction of the methoxide and carbonyl with hydrogen leads to the formation of transition state **C** which was found to have a near linear arrangement of the methoxy oxygen and hydrogen and a highly angular arrangement of the carbonyl group and hydrogen. The overall formation of **C** from **A** was found to have a $\Delta H_{A\text{-}C}$ of -4 kJ mol^{-1} and thus there is effectively no

barrier to the hydrogenation process. From **C**, a strong complex is formed between what will become the alcohol product and the sodium methoxide (**D**) which then dissociates to give the product as a sodium alkoxide (**E**) before proton exchange *via* a second transition state affords the final alcohol product (**F**).[121]

Further work looked at the enthalpy and free energy of the reaction at 483.15 K (210°C). Findings showed the enthalpy and free energy profiles at 483.15 K to differ significantly, for example formation of **B** has a free energy change of -51 $kJmol^{-1}$ at 483.15 K whilst at 0 K the change is -109 $kJmol^{-1}$. Formation of **C** from **A** has an overall free energy change of 65 $kJmol^{-1}$ at 483.15 K and -4 $kJmol^{-1}$ at 0 K. The differences are attributed to a significant entropic effect on the reaction which supports the theory presented by Berkessel and Walling and Bollyky that the formation of an ordered transition state, an entropic effect, is a limiting factor in the reaction affecting the size of the energy barrier for the formation of transitions states and heterolysis of hydrogen.[121]

Studies into the effect of variables on the reaction were also carried out.[121] In the solution phase, use of group I metals caused the rate of the reaction to increase down the group and use of group II metals caused the rate of reaction to decrease down the group. Overall group II metals allowed the reaction to proceed with lower energy barriers than with group I metals. The effect of the anionic base used in the reaction was also investigated. Use of *tert*-butoxide showed similar catalytic activity to the methoxide species showing that the size of the base has little effect on the reaction. When benzyloxide analogues were used however, the energy barriers calculated were higher than for the methoxides and *tert*-butoxides, suggesting that aromatic alkoxides are less reactive than aliphatic alkoxides. Non-polar solvents gave lower

energy barriers for the reaction than polar solvents, however, in practice the metal cation in the catalyst is likely to be insoluble in a non-polar solvent and therefore a polar solvent would most likely be the solvent of choice for the reaction. It was observed that solvents with lower dielectric constants allowed for lower energy barriers and hence the most suitable solvent for the reaction was deemed to be a polar solvent with a low dielectric constant.

Different substrates were also investigated, with work focussing on comparing aliphatic and aromatic ketones. Previous observations by Walling and Bollyky[119] and also Berkessel[120] suggested that aromatic ketones were more susceptible to hydrogenation than aliphatic ketones. Chan and Radom's investigations agreed with these previous findings with the hydrogenation of acetophenone occurring with a lower energy barrier than that of acetone. It was thought that the aromatic ketones were more reactive due to the electron-withdrawing phenyl substituent helping to activate the carbonyl carbon towards nucleophilic attack from the hydride. Resonance effects of the phenyl ring, as shown in Figure 24, can also help stabilise an oxygen anion.[121]

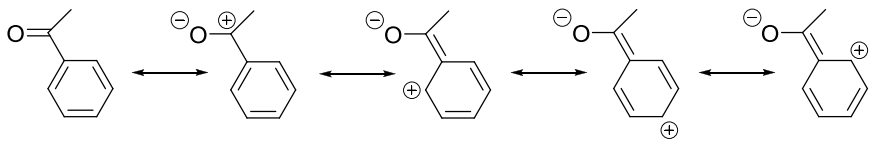


Figure 24. Resonance stabilisation of charge separated structures of acetophenone.

1.4.1.1 Asymmetric KO^{t}Bu-catalysed hydrogenation of ketones.

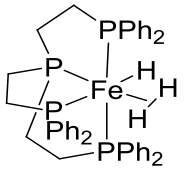
Berkessel also investigated the scope for asymmetric hydrogenation using a chiral catalyst and prochiral ketone.[120] The reduction of prochiral ketone pivalophenone with potassium *R*-1-phenylethanoate catalyst was found to give a 50% yield of the

desired alcohol product with an ee. of 12%, the major enantiomer being the *R* enantiomer of the product. In order to ensure that the low ee. was not due to racemization of the chiral base used in the catalyst, the alcohol analogue of the base was obtained after the reaction and was found to have essentially the same ee. as the starting chiral base. The low ee. was therefore attributed to a lack of discrimination between the diastereomeric transition states that lead to the final products.

1.4.2 Iron catalysts for asymmetric hydrogenation of ketones.

The use of iron catalysts has also been reported for both ATH and APH of ketones as well as many other reactions.[122]

An early example of iron-catalysed transfer hydrogenation was reported by Bianchini in 1993.[123] Isostructural trihydride complexes of iron(II), ruthenium(II) and osmium(II) were compared for the selective transfer hydrogenation of α, β-unsaturated ketones. The complexes were of the form $[MH(H_2)(P(CH_2CH_2PPh_2)_3)]BPh_4$ as shown with **117** in Figure 25, and used *iso*-propanol or cyclopentanol as the hydrogen source.



117

Figure 25. Structure of Bianchini's catalysts.

The use of iron trihydride complex **117** showed limited success for selective hydrogenation of the C=O bond over the C=C bond as illustrated in Figure 26.[123]

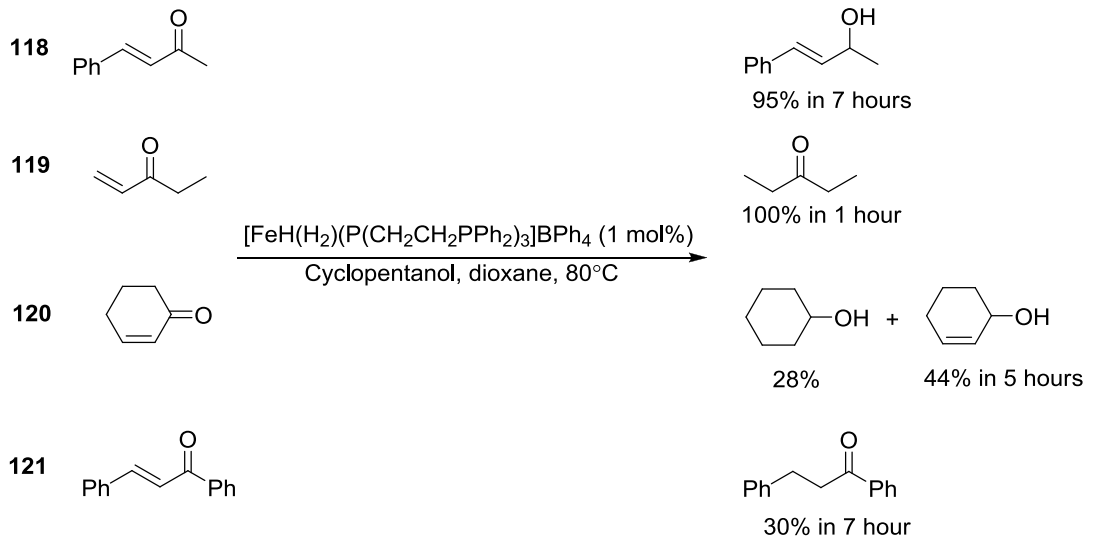
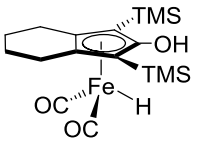


Figure 26. Hydrogenation results using catalyst **117**.

Hydrogenation of benzylideneacetone (**118**) was achieved with excellent selectivity for hydrogenation of the C=O bond however ketones with terminal or cyclic C=C bonds or indeed more hindered C=O bonds as in example **119-121** showed little or no selectivity for hydrogenation of the C=O bond over the C=C bond.[123] When applied to the hydrogenation of saturated ketones such as acetophenone, the catalyst was highly successful achieving 96% conversion to the racemic alcohol. The use of ruthenium and osmium metals with the same ligand system did not offer significant improvement to the selectivity for C=O hydrogenation over C=C hydrogenation in unsaturated ketones.[123]

An *inner sphere* mechanism is proposed for the C=O hydrogenation using this catalyst. The metal initially loses hydrogen and the ketone co-ordinates to the vacant site *via* the C=O. The hydride is transferred from the metal to the carbon of the carbonyl group. The second hydrogen is taken from the solvent alcohol to give the desired alcohol product which is then eliminated, and the remaining alkoxide solvent co-ordinates to the metal before being eliminated as the carbonyl form.[123]

More recently, Casey has reported the use of catalyst **122** below for both transfer and pressure hydrogenation of ketones.[124] The catalyst shown in Figure 27, is based on the ruthenium Shvo catalyst[66-69] and also Knölker's iron complex.[125]



122

Figure 27. Structure of Knölker's iron catalyst (**122**), used by Casey for hydrogenation applications.

Using *iso*-propanol as the hydrogen source and a 1 mol% loading of complex **122** at 75°C, acetophenone was successfully converted to racemic 1-phenylethanol with a yield of 87%.[124] This result compared well with the application of the complex to pressure hydrogenation achieving 83% yield of phenyl ethanol from acetophenone with hydrogen gas. The catalytic cycle is analogous to that of the Shvo catalyst as shown in Figure 28.

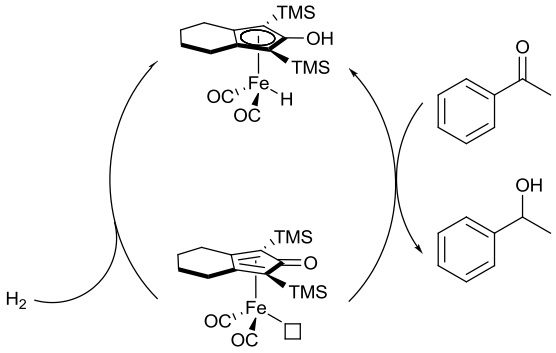
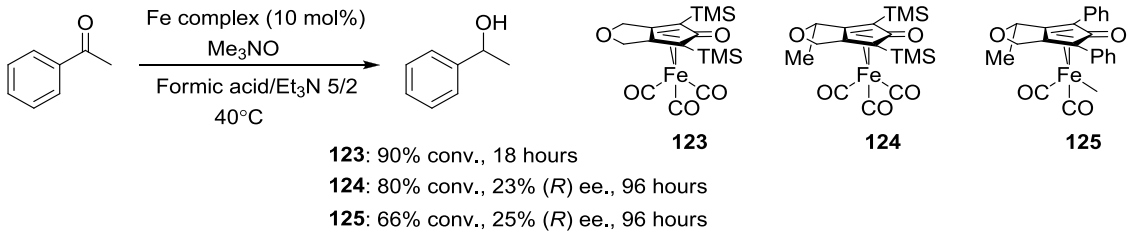


Figure 28. Catalytic cycle for reduction by catalyst **122**.

The use of cyclopentadienyl iron carbonyl complexes has also been reported by Wills for oxidation of alcohols[126] and reduction of ketones.[127] Scheme 43 shows the application of asymmetric iron complexes to the ATH of ketones. The tricarbonyl complexes are converted into the active iron hydride complexes *in situ* with use of

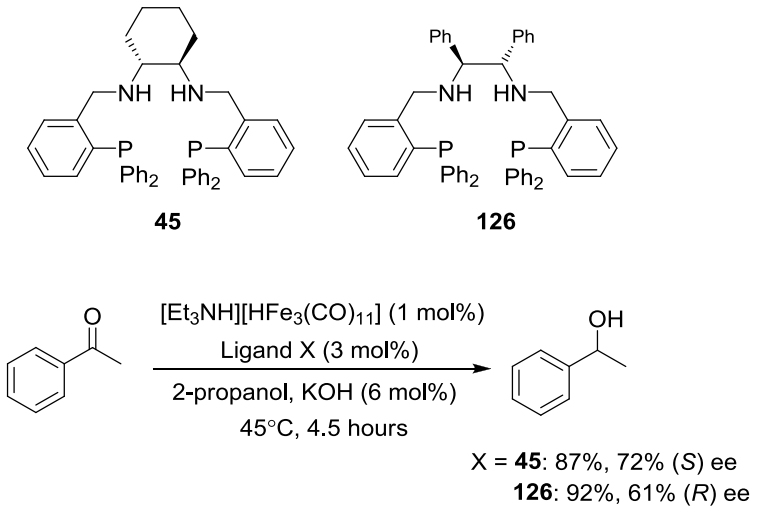
trimethyl-*N*-oxide to remove a carbonyl ligand. The complexes show some enantioselectivity although enantiomeric excesses were low.[127]



Scheme 43. Racemic and asymmetric hydrogenation of acetophenone with achiral and asymmetric iron complexes **123-125**.

1.4.2.1 Iron-catalysed asymmetric hydrogenation of ketones with diaminodiphosphine ligands.

Gao and Noyori have previously reported the use of diaminodiphosphine ligands with ruthenium, rhodium and iridium for ATH of ketones.[61-64] In 2004, Gao reported the application of the ligands to iron-catalysed ATH using $[Et_3NH][Fe_3H(CO)_{11}]$ as shown in Scheme 44.[128,129]



Scheme 44. ATH of acetophenone using *in situ* formed iron diaminodiphosphine catalysts.

The ligands proved most successful with aryl alkyl ketones such as acetophenone and both complexes in conjunction with 2-propanol as the hydrogen source gave a

promising yield and ee. of 92% and 61% respectively for the DPEN based complex and 87% and 72% respectively for the cyclohexadiamine based complex in only 4.5 hours at 45°C.[128,129]

In recent years, Morris and co-workers have reported the use of similar catalysts for ATH and APH of ketones.[129] Work began with preparation of cyclohexadiamine-diphosphino iron complexes as shown in Figure 29. [130]

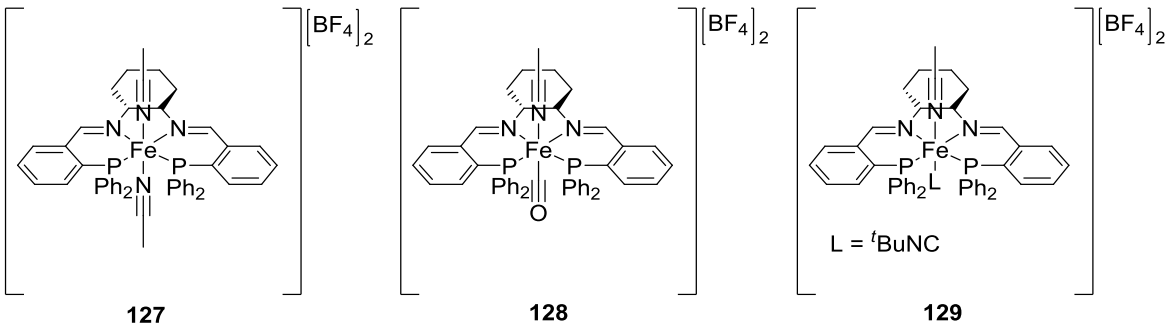
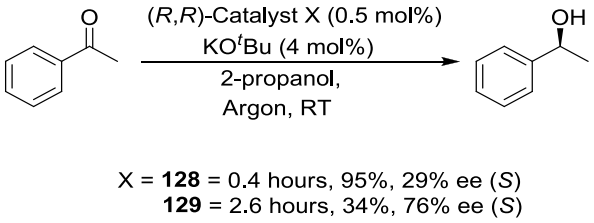


Figure 29. Structure of complexes used by Morris.

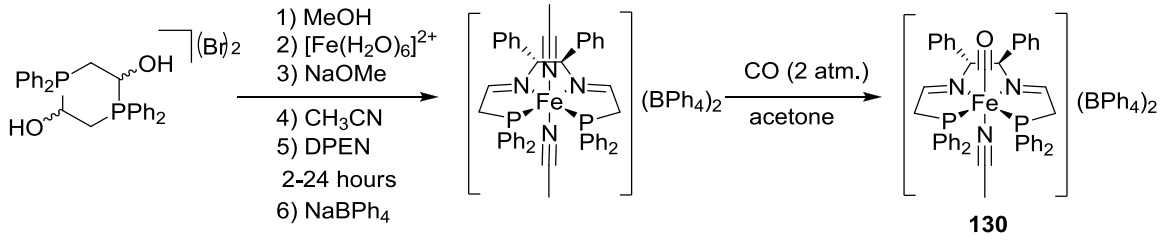
Complex **127** showed some activity for hydrogenation using hydrogen gas achieving 40% conversion of acetophenone to phenyl ethanol in 27% ee. using substrate/catalyst 225/1 and 25 atm. hydrogen at 50°C, however no activity for transfer hydrogenation was seen. In contrast, complex **128** was inactive for hydrogenation with hydrogen gas, but gave high conversions for the hydrogenation of a series of ketones, aldehydes and imines under transfer hydrogenation conditions, although the enantioselectivities obtained were low.[130] Complex **129** was also active for transfer hydrogenation, giving higher ee.'s than for complex **128** but low conversions as shown in Scheme 45.



Scheme 45. ATH of acetophenone using iron complexes **128** and **129**.

It was proposed that during the reaction the imine ligand may be hydrogenated to its amine form allowing transfer of a hydride from the iron and proton from the amine to the unsaturated substrate.[130]

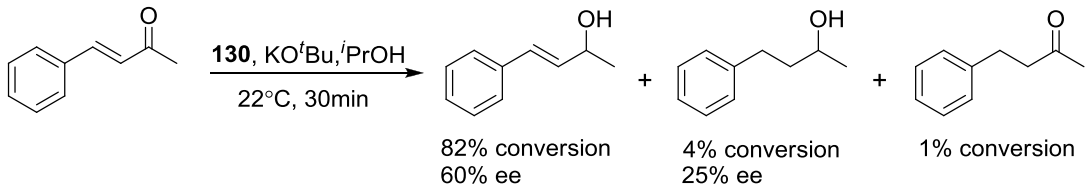
Morris has also reported a template synthesis for the preparation of diaminodiphosphine iron complexes as shown in Scheme 46.[131]



Scheme 46. Preparation of iron complexes using the template method.

It is thought that initially the phosphonium compound is deprotonated to give an unstable diphenylphosphinoacetaldehyde which is then trapped by the iron precursor. Elimination of water then gives the desired imine form of the co-ordinated ligand. Substitution of an acetonitrile ligand with carbon monoxide leads to the desired complex.[131] Complex **130** shown above was applied to the transfer hydrogenation of ketones and was found to have greater activity for transfer hydrogenation of ketones than the cyclohexadiamine complexes in Figure 29. With a substrate:catalyst:base ratio of 2000:1:8 and at room temperature, acetophenone was converted to 1-phenylethanol with a conversion of 90% and an ee. of 82% in only 30 minutes.[132]

The complex was also found to exhibit high levels of chemoselectivity when applied to the transfer hydrogenation of an α,β-unsaturated ketone as shown in Scheme 47, with the major product of the reaction being the unsaturated alcohol with only trace amounts of the saturated alcohol and ketone being formed.[132]



Scheme 47. Reduction of *trans*-4-phenyl-3-buten-2-one using complex **130**.

This demonstrates a high selectivity of the catalyst for C=O bonds rather than non-polar C=C bonds complying with an outer-sphere mechanism for the reaction with a metal hydride and amino proton interacting with the polar C=O bond.

The use of further iron complexes shown in Figure 30 for APH of acetophenone as shown in Scheme 48 was also investigated by Morris.[133]

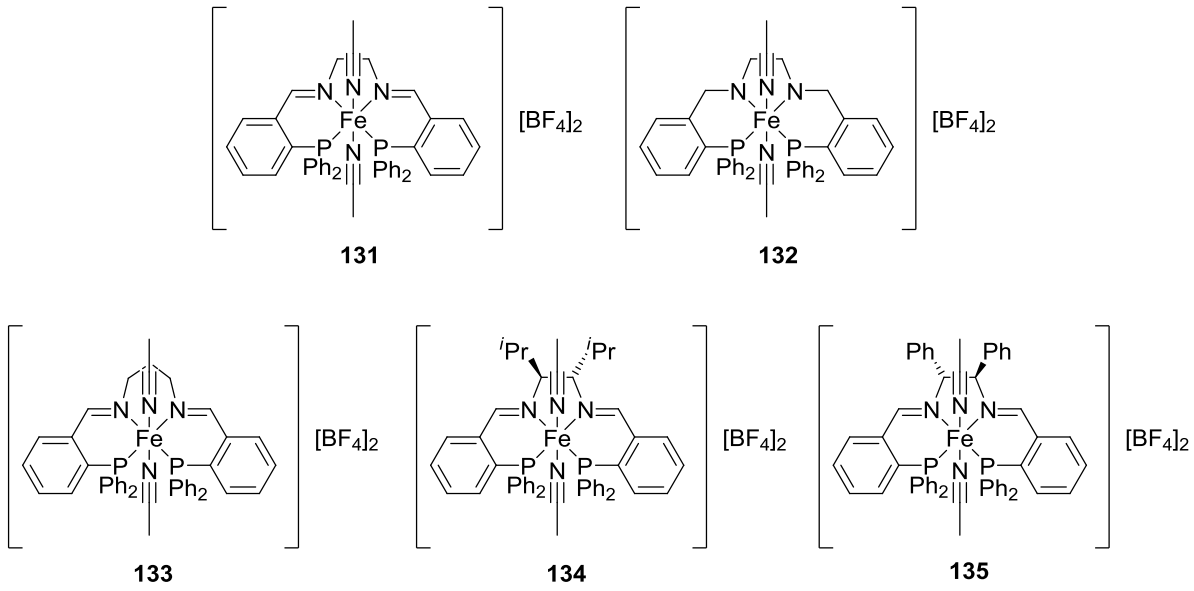
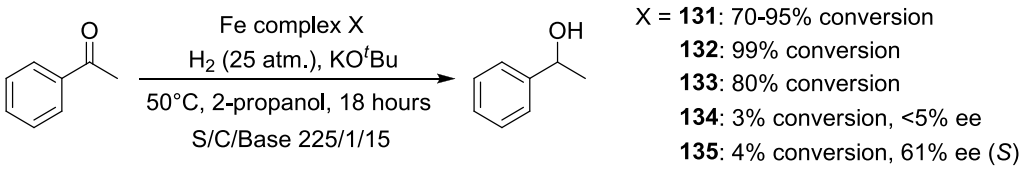


Figure 30. Structures of iron complexes used for APH of ketones.



Scheme 48. Application of complexes **131-135** to APH of acetophenone.

Complexes **131-135** were most active for pressure hydrogenation of acetophenone. It was proposed that ligand **131** may convert to the same active species as that formed by **132** *via* conversion from the imine in **131** to an amine due to the slightly enhanced activity of **132** over **131**. These findings also indicate an importance for the presence of the NH functionality in the ligand which again is evidence for an outer-sphere mechanism as discussed previously. Complexes **134** and **135** show little activity and it was proposed that this was due to the bulky amine substituent groups blocking the access of the substrate to the iron.[133]

Morris has also reported a series of investigations into the effects of steric hindrance and electronics within the ligand by preparation of a range of complexes shown in Figure 31 and their application to the ATH of acetophenone shown in Scheme 49.[134]

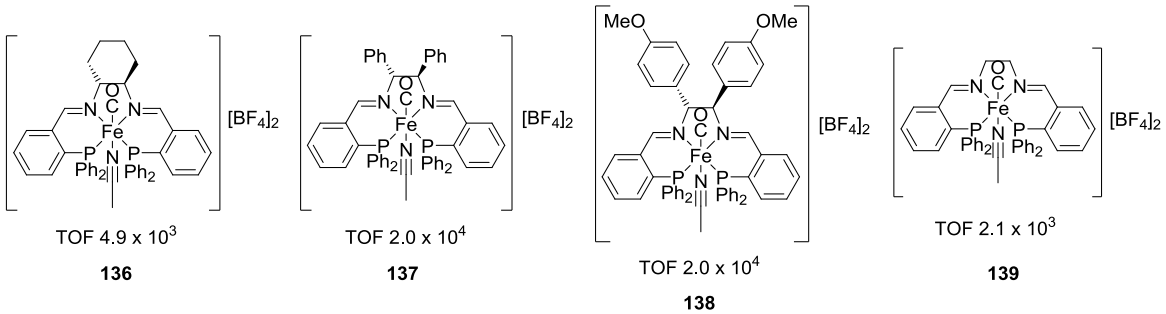
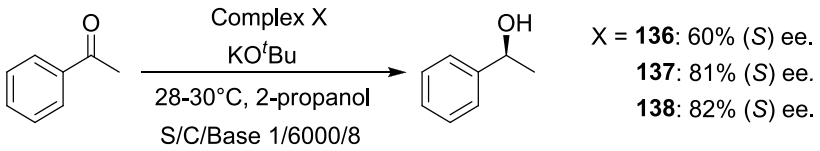


Figure 31. Asymmetric iron complexes prepared from a variety of diamines.



Scheme 49. Effect of the diamine structure on the enantiomeric excess of the reduction product.

The more bulky diamine ligands in complexes **137** and **138** was found to increase the catalytic activity of the complex with higher turnover frequencies and also increase the enantioselectivity of the reaction. Morris has also looked at the effect of changing the phosphorus substituents from phenyl to alkyl groups.[135] Variations of both the ethyldiamine and DPEN derived tetradentate imine ligands with cyclohexyl, isopropyl and ethyl groups on the phosphorus as shown in Figure 32 were prepared using the previously discussed template method.[135]

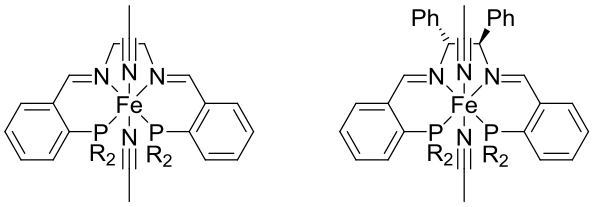
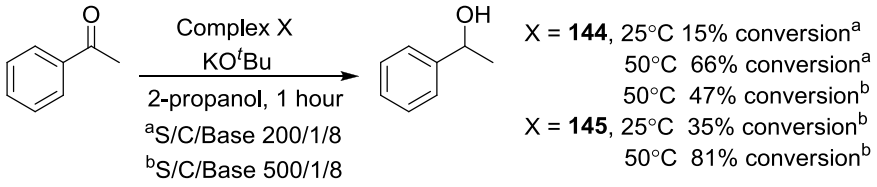


Figure 32. Complexes used to investigate the effect of the phosphine groups of the ligands on the reaction.

Complexes **140**-**143** with tricyclohexyl and triisopropyl phosphine groups were found to be inactive to transfer hydrogenation of acetophenone at room temperature and 50°C. The complexes with triethylphosphine groups showed some activity at room temperature and improved activity at 50°C although complex **145** with DPEN was more active than complex **144** as illustrated in Scheme 50. The enantioselectivity was lower than with the initial DPEN derived PPh_3 complex **137**.[135]

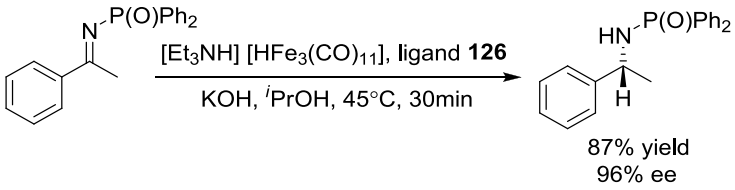


Scheme 50. Hydrogenation of acetophenone using catalysts **144** and **145**.

It was proposed that dissociation of the phosphine species from the ligand may be necessary for the required catalysis to occur. The more electron-donating cyclohexyl and *iso*-propyl groups would make the phosphorus more basic than with the ethyl substituent groups and so dissociation of the phosphorus would be less likely.[135]

1.4.2.2 Iron-catalysed transfer hydrogenation of imines.

Beller and co-workers have recently investigated the application of Iron systems such as those discussed above for the asymmetric hydrogenation of *N*-(diphenylphosphinyl)-imines.[136] The reactions use the iron carbonyl hydride cluster complex $[Et_3NH][HFe_3(CO)_{11}]$ as the catalyst precursor and utilise a KOH base and 2-propanol as the hydrogen donor. The asymmetric nature of the reaction is provided by an asymmetric tetradentate ligand such as the diaminodiphosphine ligands used initially by Gao[61-64, 128] and also Morris[129-135] discussed above. The cyclohexadiamine based ligand was found to be most effective, achieving product yields of 85-95% and ee.'s of 94-96% in only 30 min at 45°C (Scheme 51).



Scheme 51. Iron-catalysed ATH of diphenylphosphinyl imine.

The nature of the base used in the reaction is reported as having no effect on the reaction, with the use of KOH, NaO^{i}Pr and NaO^{t}Bu giving comparable yield and ee. values. In an absence of base the ee. of the reaction product was found to decrease significantly to 45%. Control experiments containing no iron source and no ligand gave no amine product.[136]

2. Results and Discussion.

2.1 Potassium-catalysed APH of ketones.

Although highly active, conventional ruthenium, iridium and rhodium-based hydrogenation catalysts are expensive and toxic which, particularly on an industrial scale, leads to increased costs and the need for extensive purification processes. The development of a transition metal free catalytic system for hydrogenation of ketones is therefore of great interest. Inspired by work of Walling and Bollyky in 1964[119] work began to develop a potassium-based catalyst for ketone hydrogenation.

Walling and Bollyky reported the KO^{t}Bu-catalysed hydrogenation of ketones under high temperatures and hydrogen pressures.[119] It was necessary to use ketones that did not contain protons at the α-position in order to prevent enolate formation which would inhibit formation of the alcohol product. We proposed that the use of ligands may increase the catalytic activity of the system by providing a well defined transition state for the reaction (Figure 33), allowing it to proceed under mild conditions. The importance of such a transition state in the reaction was reported by Berkessel[120] and Chan and Radom.[121]

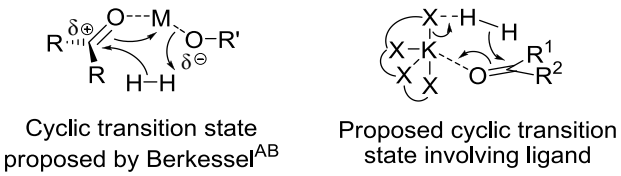
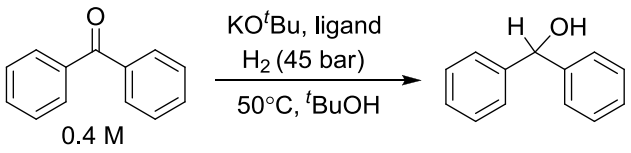


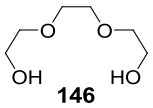
Figure 33. Proposed cyclic transition states for KOtBu-catalysed hydrogenation of ketones.

Initial work focused on identifying appropriate conditions for the KO^{t}Bu-catalysed hydrogenation of benzophenone that would give sufficient conversion to products to allow analysis by GC, but would also still allow scope for the observation of improvements to conversion when using more effective ligands or catalysts.

Secondly, conditions should comply with the need to develop a favourable hydrogenation process operating under mild conditions. Initial investigations into temperature, pressure and KO^{t}Bu loading were therefore carried out (Tables 13 and 14). Triethylene glycol **146** was used as a model for a potential tetradentate ligand.

Table 13. APH of benzophenone using KOtBu as a catalyst and triethylene glycol **146** as an example ligand structure.

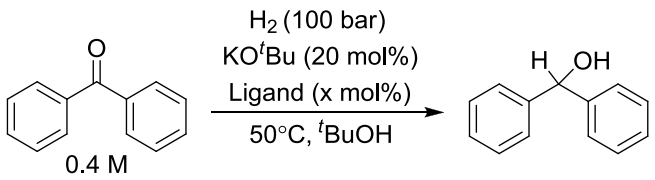


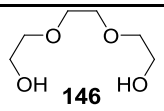
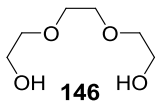
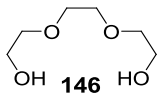
Entry	Solvent	Mol% KO^{t}Bu	Mol% ligand	Ligand	Benzhydrol [%][a]	Time [hours]
1	^{t}BuOH	5	0	None	None	113
2	^{t}BuOH	20	0	None	5.2%	113
3	^{t}BuOH	40	0	None	6.8%	113
4	^{t}BuOH	20	20	 **146**	7.3%	113

[a] Determined by GC analysis.

Entries 1 to 3 in Table 13 show the effect on conversion of increasing the catalyst loading in the absence of ligand. With 5 mol% KO^{t}Bu no product was obtained, however with 20 and 40 mol% KO^{t}Bu a small conversion to product was seen. Entry 4 shows a slight improvement to conversion upon the addition of triethylene glycol as a potential tetradentate ligand. Increasing the temperature and hydrogen pressure to 100°C and 60 bar hydrogen gave a significant increase in conversion, allowing the effect of the presence of ligand to be investigated. The results are summarised in Table 14.

Table 14. APH of benzophenone using KO^{t}Bu and triethylene glycol ligand **146** at increased temperature and hydrogen pressure.



Entry	Solvent	Mol% KO^{t}Bu	Mol% ligand	Ligand	Benzhydrol [%][a]	Time [hours]
1	^{t}BuOH	20	5	 **146**	28	136
2	^{t}BuOH	20	10	 **146**	27	136
3	^{t}BuOH	20	20	 **146**	39	136

[a] Conversions to benzhydrol determined by GC.

The greatest conversion was achieved with 20 mol% ligand, showing increased conversion to benzhydrol compared to the use of 5 and 10 mol% ligand, however a significant degree of solvent evaporation occurred during the reaction making results unreliable. Future reactions were carried out at the lower temperature of 60°C and with 60 bar H_2 pressure.

2.1.1 Further ligands for KOtBu-catalysed APH of ketones.

The addition of a ligand was shown to benefit the reaction and improve conversion. Attention turned to investigating the effectiveness of other ligands in the reaction. A variety of ligands comprised of different co-coordinating groups were used for hydrogenation of benzophenone with KO^{t}Bu. The results are shown in Figure 34.

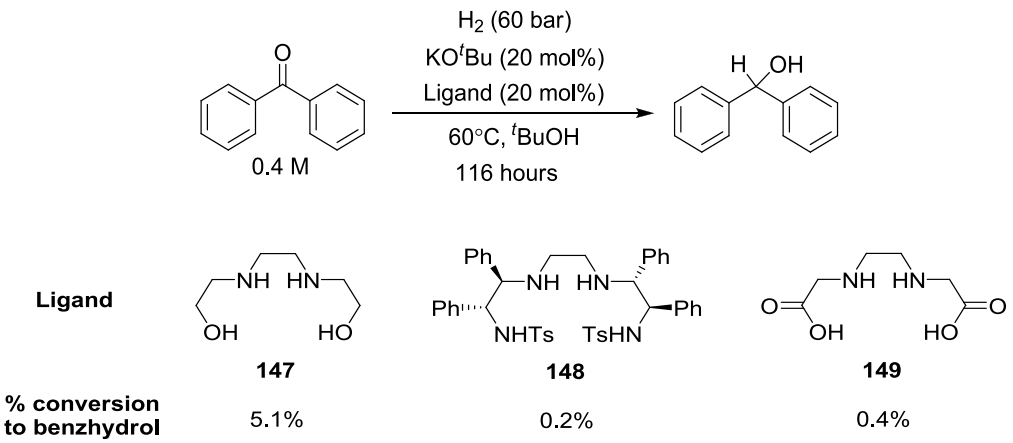
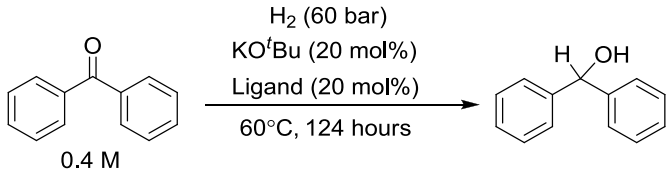


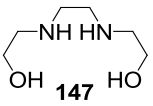
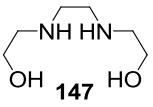
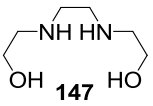
Figure 34. Investigations into the effectiveness of different ligand structures for the KO^{t}Bu-catalysed APH of benzophenone.

Equal aliquots of a bulk solution of KO^{t}Bu, ^{t}BuOH and benzophenone were used for all reactions in order to eliminate error and allow consistency between reactions with the ligand used being the only variable. Bis-(2-hydroxyethyl)ethylenediamine (**147**) was the most effective giving 5.1% conversion of benzophenone to benzhydrol. Ligand **149** may react with KO^{t}Bu to form the potassium salt of the ligand, meaning the potassium may not be available to catalyse the hydrogenation reaction. The ligands may also either co-ordinate too strongly to the potassium and hinder the approach of the ketone or restrict movement and rotation of the system hindering the transfer of hydrogen to the ketone, or may not co-ordinate strongly enough, if at all, removing any benefit they may otherwise have brought to the reaction.

It was noted that the evaporation of the solvent seen with the reactions carried out at 100°C was still occurring at 60°C. An investigation into the use of solvents with higher boiling points was therefore carried out as summarised in Table 15.

Table 15. Effect of different solvents on the APH of benzophenone.



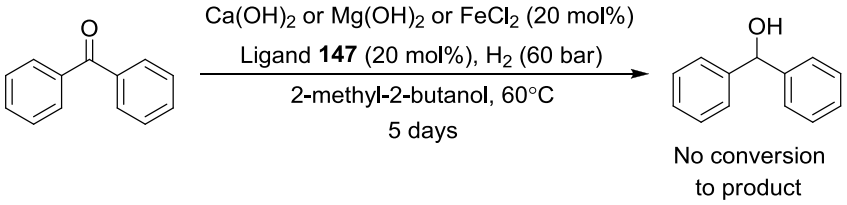
Entry	Solvent	Boiling point [°C]	Mol% KO^{t}Bu	Mol% ligand	Ligand	Benzhydrol[a] (%)	Time (hours)
1	^{t}BuOH	83	20	-	None	1.9	124
2	^{t}BuOH	83	20	20	 **147**	7.4	124
3	2-methyl-2-butanol	102	20	-	None	0.8	124
4	2-methyl-2-butanol	102	20	20	 **147**	6	124
5	Triethylene glycol	125-127	20	-	None	0	124
6	Triethylene glycol	125-127	20	20	 **147**	0	124

[a]Determined by GC analysis.

Ligand **147** was used as this was one of the most effective ligands at this point, showing comparable conversion in Table 15, entry 2 to use of triethylene glycol in Table 13, entry 4. Each solvent was used in the reaction both with and without ligand and for ^{t}BuOH and in 2-methyl-2-butanol the conversion was increased upon the addition of ligand. Use of 2-methyl-2-butanol in place of ^{t}BuOH showed only a minor reduction in conversion and significantly less solvent evaporation taking place. The use of triethylene glycol seemed to prevent the reaction entirely. Tables 13 and 14 suggest that triethylene glycol does have some activity as a ligand thus,

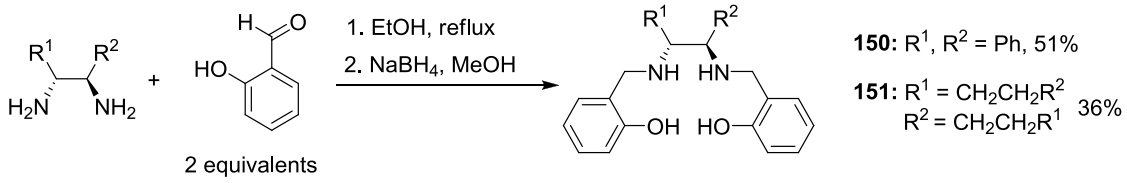
when used as the solvent triethylene glycol may fully saturate the potassium and block co-ordination sites preventing the hydrogenation reaction from taking place.

The effectiveness of other metals as catalysts in the reaction was investigated as shown in Scheme 52, however no conversion to benzhydrol was observed.



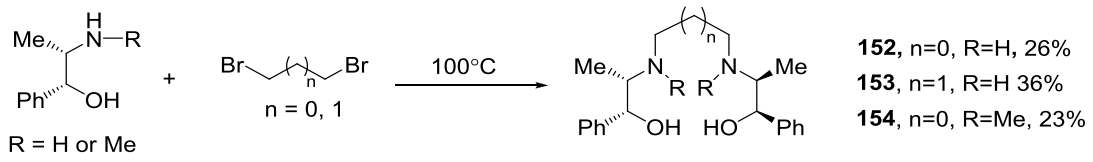
Scheme 52. Application of Metal(II) salts to the hydrogenation of benzophenone with ligand **147**.

Further investigations into the use ligands containing the bis-(2-hydroxyethyl)ethylenediamine (**147**) backbone were carried out. The potential for asymmetric hydrogenation was also to be investigated so a variety of tetradentate asymmetric ligands were prepared. Initial syntheses gave ligands **150** and **151** from reaction of DPEN with salicylaldehyde as shown in Scheme 53.[137-139] In this case the terminal hydroxy groups are provided by phenols rather than primary alcohol groups.



Scheme 53. Preparation of tetradentate ligands **161** and **162**.

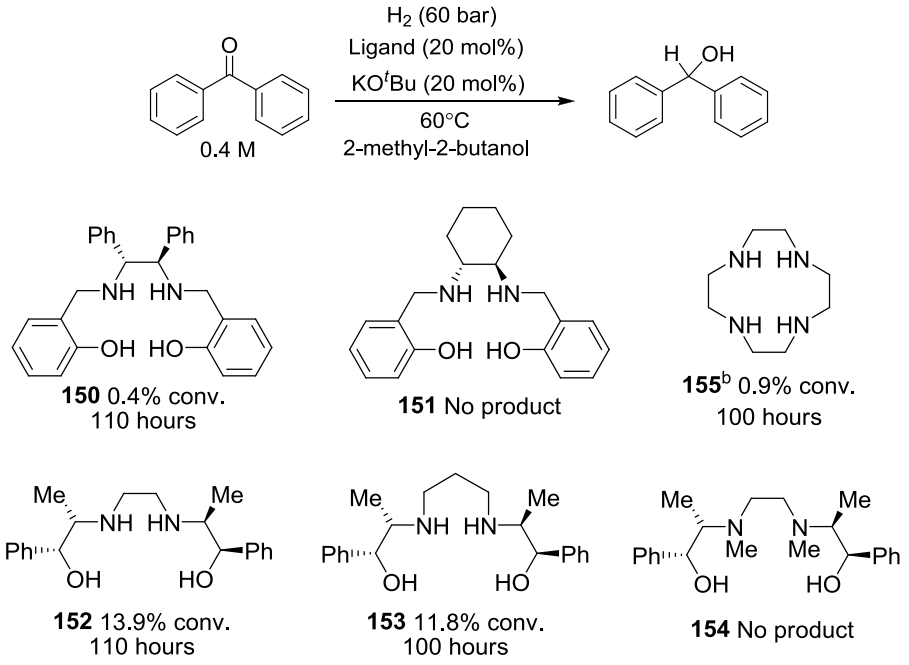
Ligands **152-154** were prepared by the coupling of 2 equivalents of norephedrine with dibromoethane (**152**) and dibromopropane (**153**), and also the coupling of ephedrine with dibromoethane (**154**) as shown in Scheme 54.



Scheme 54. Synthesis of tetradentate ligands **152-154**.

The reaction is carried out at 100°C in the absence of solvent with the norephedrine or ephedrine melting to give a liquid reaction mixture. As the reaction proceeds however, the reaction mixture rapidly solidifies causing stirring and thus the mixing of unreacted starting materials to cease. ^{1}H NMR analysis of crude reaction mixtures showed incomplete conversion to product showing approximately 50:50 product:unreacted amino alcohol. The unreacted amino alcohol starting material and product were both highly polar and separation was difficult. Various alterations were made to the reaction: changing the number of equivalents of amino alcohol used, adding a solvent to prevent solidification of the reaction mixture and also employing different purification strategies, however yields were not improved.

A sufficient amount of each ligand was obtained for application to the hydrogenation of benzophenone. The results are summarised in Figure 35.



[a]Ligand obtained from Aldrich. [b]Ligand obtained from Acros Organics. % conversions to benzhydrol.

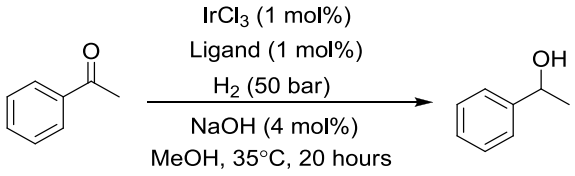
Figure 35. Percentage conversions for APH of benzophenone using a range of tetradentate diaminodihydroxy ligands.

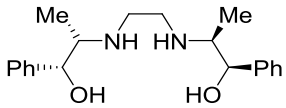
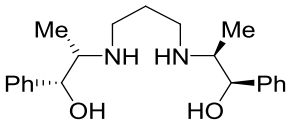
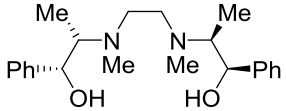
The previous use of the unsubstituted ligand **147** gave a conversion of 7.4% (Table 15, entry 2). Ligands **150** and **151** both gave low conversions, indicating that the ligands are less effective, possibly because the phenol groups do not co-ordinate to the potassium as well as free hydroxyl groups. This may be due to the delocalised aromatic system drawing electron density away from the oxygen. Also the structure and rigidity of the aromatic ring may hinder effective co-ordination to the potassium ion. It may also be the case that the phenol groups react with the KO^{t}Bu to form the potassium salt which prevents the catalysis of the hydrogenation reaction. Ligand **152** was found to be the most effective ligand giving a conversion of almost 14%. Ligand **154** with methyl substituted nitrogen atoms gave no conversion to benzhydrol. This is assumed to be because the methyl substituted nitrogen does not co-ordinate to the potassium. Use of ligand **153** allowed the importance of the chain length of the alkyl 'bridge' between the two norephedrine components to be

investigated, and gave a conversion of 12%, comparing well with **152**. Finally the use of cyclic crown-type ligands was investigated with the use of cyclen (ligand **155**) however this was shown to be ineffective as a ligand for APH of ketones.

In order to establish the potential for APH of ketones, ligands **152-154** were applied to the asymmetric hydrogenation of pro-chiral acetophenone. As conversions of benzophenone to benzhydrol with KO^{t}Bu as the catalyst remained low and also as acetophenone would be likely to enolise in the presence of KO^{t}Bu, $IrCl_3$ was used as the catalyst. $IrCl_3$ is known to be active and selective for APH of ketones[37] and the system was expected to be more active than with KO^{t}Bu allowing greater conversion and hence accurate ee. determination. The results are shown in Table 16.

Table 16. APH of acetophenone using ligands **152-154** and $IrCl_3$.



Entry	Ligand	Conv.[a] (%)	Ee[a] (%)
1	 **152**	98.6	25.5 (*R*)
2	 **153**	37.5	19.9 (*R*)
3	 **154**	15.5	2.7 (*R*)

[a]Determined by GC analysis.

Ligand **152** shows excellent conversion to the desired alcohol product, however the enantiomeric excess of the product obtained is low. Conversion is reduced significantly with use of ligand **153** suggesting that the ethylenediamine structure is advantageous to the reaction over the propylenediamine structure, allowing enhanced co-ordination to the metal centre. The enantioselectivity achieved with ligand **153** is also lower than with **152**. Use of the *N*-methyl ligand **154** gave the lowest conversion and essentially racemic product. This confirms the need for the presence of NH groups within the ligand for effective complex formation. The results show that the prepared ligands do not have potential for use in the asymmetric hydrogenation of ketones under these reaction conditions.

2.1.2 Reaction mechanism for KO^{t}Bu catalysed hydrogenation of ketones.

With more effective ligands (**152** and **153**) beginning to emerge for KO^{t}Bu-catalysed hydrogenation of benzophenone, investigations were made to identify the reaction mechanism. The reaction solution from Figure 35 using ligand **153** was analysed by mass spectroscopy after the reaction had taken place and both mono and fully oxidised derivatives of the ligand as shown in Figure 36 were found to be present.

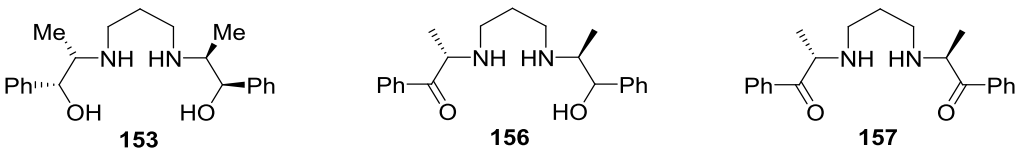
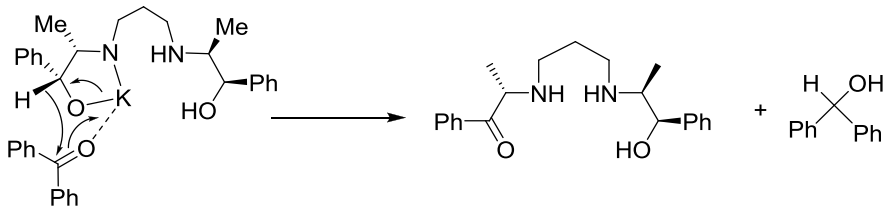


Figure 36. Ligand species identified in reaction solution by mass spectrometry.

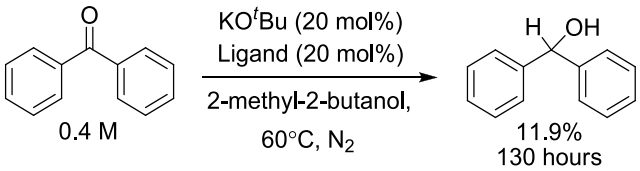
The presence of oxidised ligand may be evidence of a transfer hydrogenation process rather than interaction of the ketone with hydrogen gas. The ligands may transfer

hydrogen from their terminal hydroxyl groups to benzophenone resulting in oxidation of the ligand and reduction of benzophenone. The presence of the phenyl groups adjacent to the terminal hydroxyl group may help this process with delocalisation of the oxygen's electron density into the aromatic ring weakening the O-H bond. Also the resulting carbonyl group in the ligand would provide increased conjugation and hence stability making the oxidation process favourable. A proposed mechanism for the transfer hydrogenation process is shown in Scheme 55.



Scheme 55. Proposed mechanism for the transfer of hydrogen from ligand **153** to benzophenone.

The mass spectrometry results, showing the presence of the oxidised derivatives of the ligand, are not conclusive as ionisation and fragmentation processes occurring in the mass spectrometer could also be the reason for the oxidised species being seen. In order to obtain conclusive evidence for or against the hydrogen transfer process, the hydrogenation of benzophenone with KO^{t}Bu and ligand **153** was carried out under atmospheric nitrogen rather than pressurised hydrogen (Scheme 56). If molecular hydrogen is not involved in the reaction, and it is indeed the ligands that are transferring the hydrogen, conversion to benzhydrol should occur to a similar extent as under pressurised hydrogen reported in Figure 35.

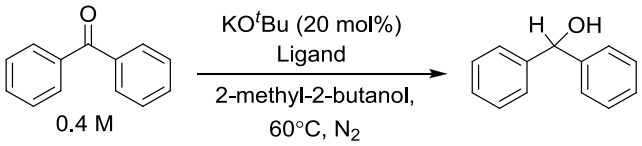


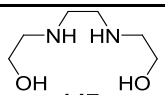
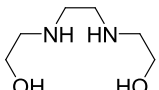
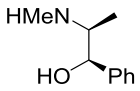
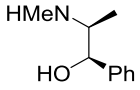
Scheme 56. Hydrogenation of benzophenone with KOtBu and ligand **153 i**n the absence of hydrogen.

As shown in Scheme 56, the reaction did proceed under nitrogen and a similar conversion to that seen in Figure 35 was obtained. This implies that molecular hydrogen is not involved in the process and the ligands are transferring the hydrogen to the benzophenone. Further evidence for the transfer hydrogenation process can be seen when looking back to results obtained in Figure 35. Where the transfer hydrogenation process from ligand to ketone is not possible, no conversion to benzhydrol was achieved. For example with ligands **150** and **151**, where the hydroxyl component of the ligand is provided by a phenol, it is not possible to oxidise the C-O bond and transfer hydrogen to the benzophenone, possibly due to the formation of the potassium phenoxide salt of the ligand. Also with ligand **155** possessing no hydroxyl groups, no conversion to benzhydrol was achieved.

The hydrogen transfer process would be stoichiometric with respect to the ligand and thus the reaction was therefore repeated with 20 and 100 mol% ligand. In order to investigate the importance of the presence of a phenyl group adjacent to the terminal hydroxy groups, bis-(2-hydroxyethyl)ethylenediamine (**147**) was used. To investigate the importance of the tetradentate nature of the ligand, the reaction was also carried out using 20 and 100 mol% ephedrine **158**. The results are summarised in Table 17.

Table 17. Conversion to benzhydrol using 20 and 100 mol% ligand for transfer hydrogenation.



Entry	Solvent	Mol% KO^{t}Bu	Mol% ligand	Ligand	Benzhydrol (%)[a]	Time (hours)
1[b]	2-methyl-2-butanol	20	20	 **147**	2.1	116
2	2-methyl-2-butanol	20	100	 **147**	0.2	116
3[c]	2-methyl-2-butanol	20	20	 **158**	0.8	116
4	2-methyl-2-butanol	20	100	 **158**	2.4	116

[a]Determined by GC analysis. [b] Ligand obtained from Aldrich. [c]Ephedrine obtained from Aldrich.

The conversions obtained for Table 17, entry 1 with 20 mol% of the unsubstituted ligand **147** are significantly lower under the absence of hydrogen than previously seen for the same ligand (Table 15) suggesting that the absence of the phenyl groups reduces the preference for the transfer hydrogenation process relative to reaction with hydrogen gas. When the ligand loading was increased to 100 mol%, the conversion to benzhydrol was significantly reduced. It is thought that this may be due to the increased amount of ligand saturating the potassium, thereby preventing co-ordination of the benzophenone and thus the hydrogenation process. Entries 3 and 4 of Table 17 investigate the importance of the tetradentate nature of the ligand. Use of ephedrine at 20 and 100 mol% loadings of ephedrine gave low conversions

suggesting tetradentate ligands are more active for the transfer hydrogenation process, possibly exhibiting improved co-ordination to the metal centre.

Our aim in this work was to develop convenient conditions for highly active catalytic APH of ketones using transition metal-free catalysts. The transfer hydrogenation process found to be taking place is not deemed appropriate for further development as a viable transition metal-free process for catalytic asymmetric ketone hydrogenation. The process is not efficient both in terms of the synthesis of the ligands and also because at best, half an equivalent of ligand relative to the substrate would be required to achieve full conversion to the alcohol product. The ligands were also found to offer no advantage to the reaction in terms of enantioselectivity. Indeed, processes involving active non-precious metal catalysts for transfer hydrogenation and asymmetric transfer hydrogenation such as the MSPV reduction[43] are already prominent in the literature and thus further development of the KO^{t}Bu system was not investigated.

2.2 Transition metal-catalysed ATH of ketones.

The use of iron as a catalyst for hydrogenation is appealing due to its high availability and low cost and toxicity. In the past Gao has applied the use of iron carbonyl complexes and asymmetric diamine-diphosphine ligands to the ATH of ketones.[128] More recently, Morris has used pre-formed iron-diaminodiphosphine complexes for ATH and APH of ketones[129-135, 143] and in 2006 Beller reported the use of iron carbonyl complexes and diaminodiphosphine ligands for the asymmetric hydrogenation of *N*-(diphenylphosphinyl)-imines.[136] Each approach used ligands

such as **45** and **126** shown in Figure 37 and their derivatives, achieving excellent conversions and enantioselectivities for the conversion of ketones to alcohols.

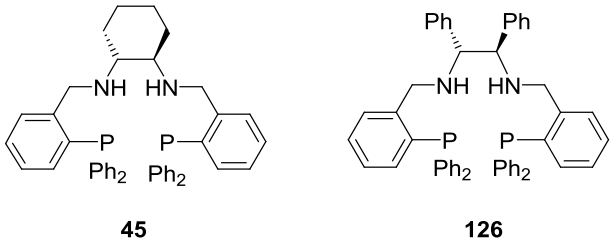
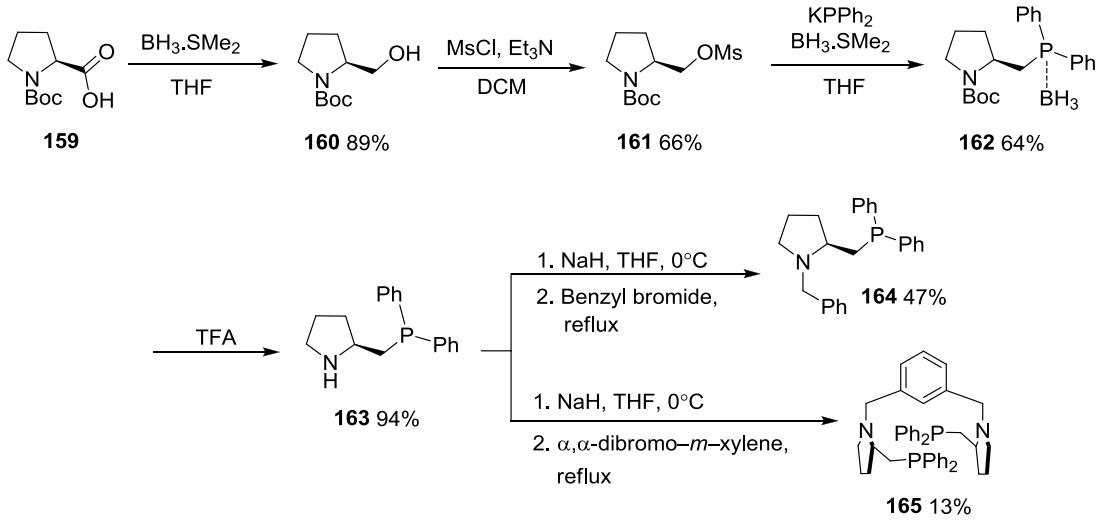


Figure 37. Examples of diaminodiphosphine ligands used for iron-catalysed hydrogenation of ketones.

2.2.1 Iron-catalysed ATH of ketones with aminophosphine ligands.

We proposed the development of new asymmetric diaminodiphosphine ligands for application to the iron-catalysed ATH of ketones. Initially diaminodiphosphine ligands derived from proline **159** were prepared as shown in Scheme 57 in order to determine the importance of the NH functionality and also determine the effect on the enantioselectivity of the reaction of moving the asymmetry from the diamine component of the ligand to the phosphine component.



Scheme 57. Synthesis of proline-based aminophosphine ligands.

Preparation of mesylate **161** from Boc prolinol **160** allowed substitution with diphenyl phosphine followed by addition of borane to give **162**. Formation of borane complex **162** stabilises the phosphorus to oxidation allowing purification of the compound by column chromatography. Removal of the Boc group and borane with TFA gave aminophosphine ligand **163** which could then undergo alkylation with benzyl bromide or α,α-dibromo-*m*-xylene to give ligands **164** and **165** respectively. The synthesis of **163** proceeded with good yields, however upon alkylation of the amine to give **164** and **165**, the yields of product were depleted, primarily due to isolation and purification of the compounds. Ligand **45** used by Gao was also prepared for use in ATH reactions in order to repeat published results and as a comparison for the activity of ligands **163-165**.

Preparation of triethylammonium undecacarbonylhydridotriferrate **166** as used by Gao[128] and Beller[136] was carried out as reported in the literature[144] and is shown in Figure 38. Previous work within our group has found iron hydrides to be unstable in air and moisture and thus full characterisation is difficult however ^{1}H NMR analysis in degassed deuterated benzene compared well with that reported in the literature by Beller[136] and showed the desired complex to have been formed with presence of the Fe-H signal at -15.25 ppm. The ^{1}H NMR spectrum obtained is shown in Figure 38.

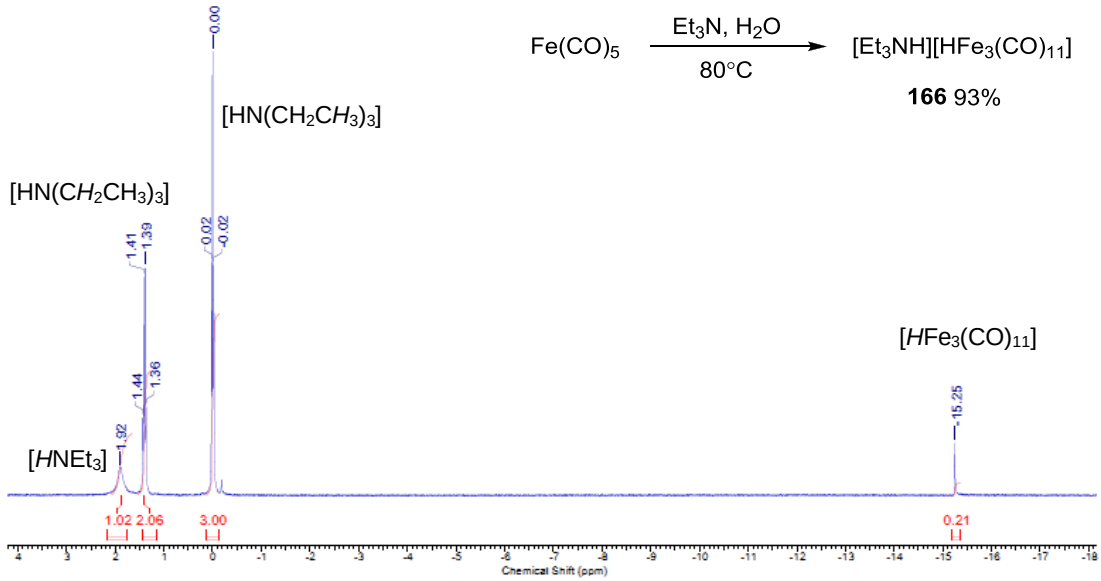
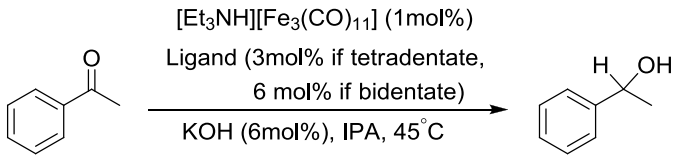
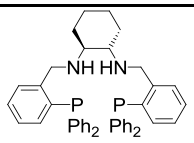
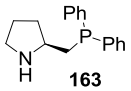
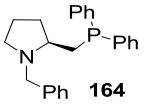
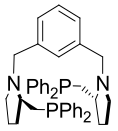


Figure 38. ^{1}H NMR spectrum of $[Et_3NH][HFe_3(CO)_{11}]$ **166** (300 MHz, d_6-benzene).

Ligands **45** and **163-165** were applied to the ATH of acetophenone (Table 18).

Table 18. Application of proline based aminophosphine ligands to iron-catalysed ATH of acetophenone.



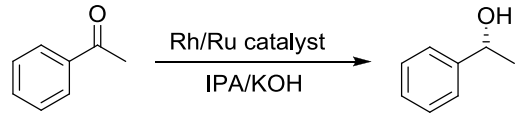
Entry	Ligand	Time (hours)	Conversion[a] (%)	Ee.[a] (%)
1	 **45**	41	76	32 (*R*)
2	 **163**	87	2	5 (*R*)
3	 **164**	87	4	6 (*R*)
4	 **165**	90	0.3	4 (*R*)

[a]Determined by GC analysis.

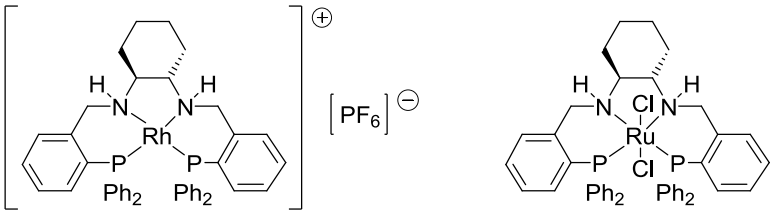
Ligands **163-165** did not promote hydrogenation with the iron complex. Ligand **45** which has been used by Gao did show some conversion and enantioselectivity, although these did not compare to the literature results where a conversion of 87% and an ee. of 72% for ATH of acetophenone was achieved in 4.5 hours under the same conditions.[128, 129] Analysis of the ^{1}H NMR spectrum for the iron complex (Figure 38) shows only 0.2:1 iron hydride:Et_3NH suggesting that the desired iron hydride complex is not forming as readily as expected thus reducing the loading of iron hydride present in the ATH reactions affecting the activity of the system.

2.2.2 Ruthenium and rhodium-catalysed ATH of ketones.

Gao has also used ligand **45** for the rhodium and ruthenium-catalysed ATH of ketones.[61] The use of ligand **45**, $[Rh(COD)Cl]_2$ and IPA/KOH gave some conversion and enantioselectivity for ATH of acetophenone[63] however improved results were achieved when the pre-formed rhodium complex **49** was used.[62] A pre-formed Ru complex **47** prepared by the reaction of ligand **45** and $[RuCl_2(DMSO)_4]$ was also successfully used for the ATH of ketones.[61] the results are summarised in Figure 39.



Ligand **45** with $[Rh(COD)Cl]_2$=56%yield, 36% (*S*) ee., 9 hours, 82°C, 100/1/1/1 S/Rh/**45**/^{i}PrOK
Pre-formed Rh complex **49**=97% yield, 91 (*R*) ee., 7 hours, 82°C, 100/1/1 S/**49**/^{i}PrOK
Pre-formed Ru complex **47**=93% yield, 97% (*R*) ee., 7 hours, 45°C, 200/1/0.5 S/**47**/^{i}PrOK

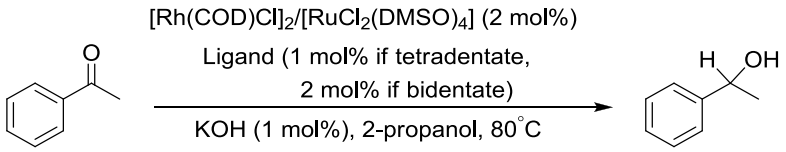


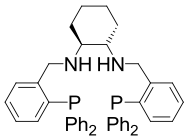
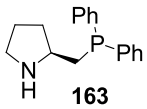
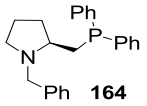
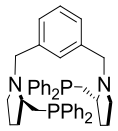
49 **47**

Figure 39. ATH of acetophenone using diamino-diphosphine Rh and Ru complexes.

In a similar manner, ligands **163-165** were also applied to rhodium and ruthenium-catalysed ATH reactions to see if a more active ligand/catalyst precursor combination could be developed (Table 19). The ligands and metal precursors were used rather than pre-formed complexes in both cases. Reactions were carried out for 24 hours to allow time for *in situ* complex formation.

Table 19. Application of proline-based aminophosphine ligands with rhodium and ruthenium catalysts.



Entry	Ligand	Time (hours)	Conversion[a] (%)	Ee.[a] (%)
1	 **45**	24	Rh: 66	72 (*R*)
2			Ru: None	-
3	 **163**	24	Rh: <0.5	ND
4			Ru: 0.6	ND
5	 **164**	24	Rh: 79	0.9 (*R*)
6			Ru: None	-
7	 **165**	24	Rh: 13	3.0 (*R*)
8			Ru: 5.6	63.7 (*R*)
9	No ligand	24	Rh: 10	Racemic
10			Ru: None	-

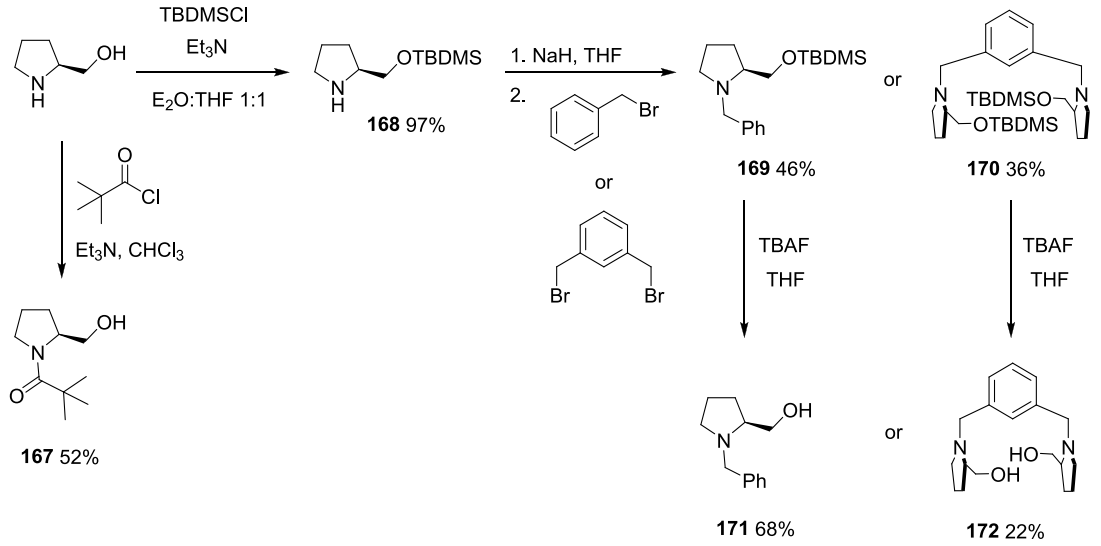
[a]Determined by GC analysis.

Table 19, entries 1 and 2 show repeats of the reactions reported by Gao shown in Figure 39. Table 19, entry 1 compares well with results reported by Gao,[61-63]

achieving improved conversion and enantioselectivity to that reported for the ATH of acetophenone with ligand **45** and $[Rh(COD)Cl]_2$, although the reaction time was longer than reported by Gao.[63] Entry 2 also compares well with the literature results, with Gao reporting the use of only pre-formed complexes as achieving high yields and enantioselectivities.[61] Use of ligands **163-165** showed no improvement to the reported results. Ligands **163** and **165** gave low conversions and enantioselectivity and although ligand **165** gave 79% conversion the enantioselectivity was low.

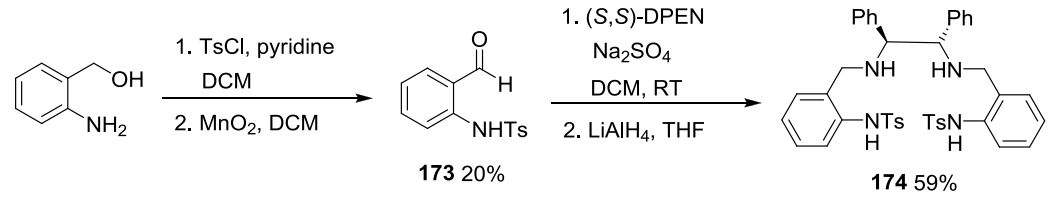
With ligands **163-165** proving to be inactive to ATH conditions, further ligands were prepared including silyl, hydroxy and amide derivatives of ligands **163-165** (Scheme 58) and also the *N*-toluenesulfonamide derivative of ligand **159** (Scheme 59) in order to investigate the effect of different co-ordination groups on the activity of the ligands towards *in situ* complex formation and the ATH of ketones.

Reaction of (*L*)-prolinol with trimethylacetyl chloride gave amide **167** whilst protection of the alcohol in (*L*)-prolinol with TBDMSCl and alkylation if necessary gave silyl ligands **168-170**. Removal of the silyl group gave aminohydroxy ligands **171** and **172** (Scheme 58).



Scheme 58. Synthesis of proline-based hydroxyamide, aminosilyl and aminohydroxy ligands.

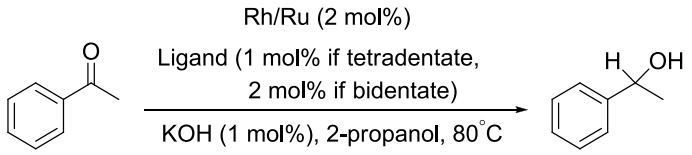
Initial formation of the *p*-toluenesulfonamide from 2-aminobenzyl alcohol followed by oxidation with MnO_2 gave aldehyde **173**. The desired tetradentate ligand **174** was obtained after reductive amination with (*S*,*S*)-DPEN (Scheme 59).

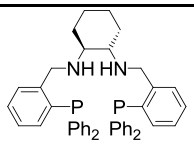
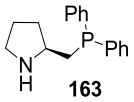
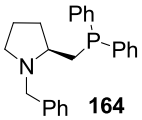
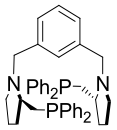
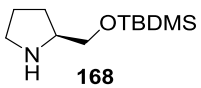
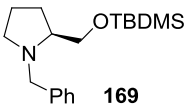
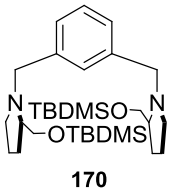
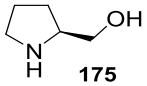


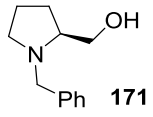
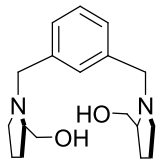
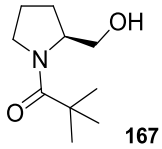
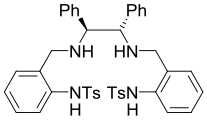
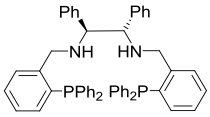
Scheme 59. Synthesis of *N*-tosyl substituted derivative of ligand **174**.

The ligands were applied to the ATH of acetophenone using a variety of metal complexes (Table 20).

Table 20. Application of ligands with a range of co-ordination groups to rhodium and ruthenium-catalysed ATH of acetophenone.



Entry	Ligand	Complex	Time (hours)	Conversion[a] (%)	Ee.[a] (%)
1	 **45**	$[Ru(benzene)Cl_2]_2$	24	11	8.9 (*R*)
2	 **163**	$[Ru(benzene)Cl_2]_2$	24	1.1	ND
3	 **164**	$[Ru(benzene)Cl_2]_2$	24	1.7	ND
4	 **165**	$[Ru(benzene)Cl_2]_2$	24	56.3	1.5 (*R*)
5	 **168**	$[Ru(benzene)Cl_2]_2$	24	67.4	Racemic
6		$[Rh(COD)Cl]_2$		21.1	Racemic
7		$[RuCl_2(DMSO)_4]$		1.3	ND
8	 **169**	$[Ru(benzene)Cl_2]_2$	24	65.8	Racemic
9		$[Rh(COD)Cl]_2$		42.3	Racemic
10		$[RuCl_2(DMSO)_4]$		0.79	Racemic
11	 **170**	$[Ru(benzene)Cl_2]_2$	24	97.0	Racemic
12		$[Rh(COD)Cl]_2$		41.5	Racemic
13		$[RuCl_2(DMSO)_4]$		0.54	Racemic
14	 **175**	$[Ru(benzene)Cl_2]_2$	24	5.4	26.9 (*R*)
15		$[Rh(COD)Cl]_2$		2.1	13.9 (*S*)
16		$[RuCl_2(DMSO)_4]$		6.5	46.0 (*R*)

17		$[Ru(benzene)Cl_2]_2$		96.4	Racemic
18		$[Rh(COD)Cl]_2$	24	1.5	ND
19	**171**	$[RuCl_2(DMSO)_4]$		None	-
20		$[Ru(benzene)Cl_2]_2$		94.3	Racemic
21		$[Rh(COD)Cl]_2$	24	1.2	ND
22	**172**	$[RuCl_2(DMSO)_4]$		1.7	ND
23		$[Ru(benzene)Cl_2]_2$		26.8	6.1 (*S*)
24		$[Rh(COD)Cl]_2$	24	None	-
25	**167**	$[RuCl_2(DMSO)_4]$		1.4	ND
26		$[Ru(benzene)Cl_2]_2$		2.8	ND
27		$[Rh(COD)Cl]_2$	24	0.7	ND
28	**174**	$[RuCl_2(DMSO)_4]$		1.7	ND
29		$[Ru(benzene)Cl_2]_2$	24	54.5	Racemic
30	**159**	$[Rh(COD)Cl]_2$		48.3	4.2 (*R*)
31	No ligand	$[Ru(benzene)Cl_2]_2$	24	98	Racemic

[a]Determined by GC analysis.

In some cases the addition of a ligand improved the conversion of acetophenone to phenyl ethanol, however none of the ligands were found to induce high enantioselectivity in the reaction. In the case of Table 20, entries 11, 17 and 20 >90% conversion was achieved, however $[Ru(benzene)Cl_2]_2$ itself was shown to be highly active for ketone hydrogenation (Table 20, entry 31). It is likely that use of ligands **170-172** allows such high conversions to be retained because the ligands are not co-coordinating to the ruthenium complex and thus $[Ru(benzene)Cl_2]_2$ remains available to carry out the transfer hydrogenation process itself. In other cases where less or indeed no conversion is achieved with the same ruthenium source, it is likely

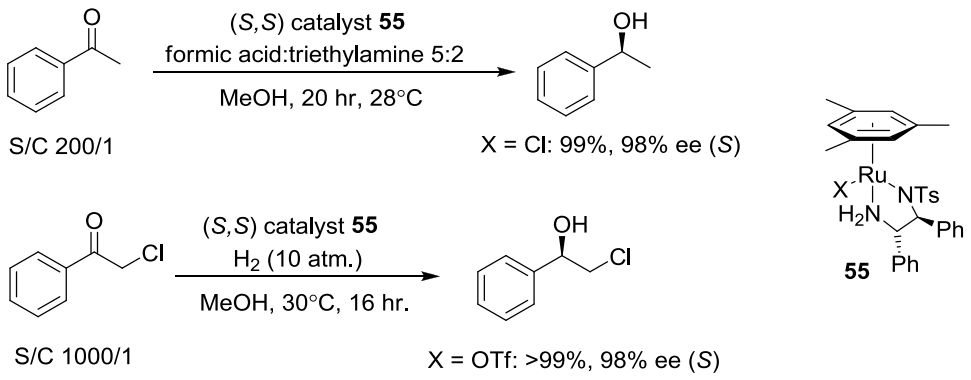
that the ligands are able to co-ordinate to the ruthenium and in doing so inhibit the transfer hydrogenation reaction, possibly blocking all co-ordination sites on the metal centre.

Entries 6, 9 and 12 in Table 20 also show improved conversion of acetophenone to phenyl ethanol with $[Rh(COD)Cl]_2$ compared to the absence of ligand (Table 19, entry 9), although again no enantioselectivity was achieved. The use of $[RuCl_2(DMSO)_4]$ gave low conversions of acetophenone to phenyl ethanol with all ligands. Ligands **167** and **174** with amide and sulfonamide co-coordinating groups respectively showed no significant activity with either of the metal precursors used.

Due to the lack of enantioselectivity achieved with the ligands tested and a variety of metal precursors, further studies into their application to ATH of ketones was not pursued.

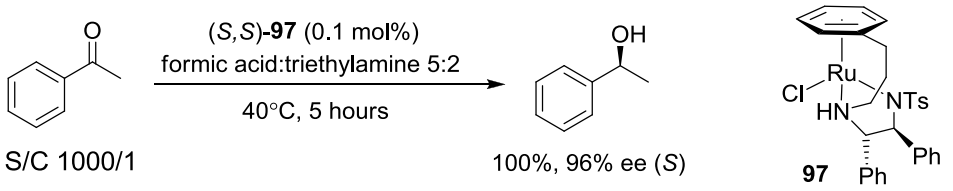
2.3 Application of tethered ruthenium catalysts to APH of carbonyl compounds.

A successful series of catalysts for both ATH and APH of ketones are half-sandwich ruthenium complexes such as **55** in Scheme 60 developed by Noyori, incorporating an aromatic ligand and asymmetric TsDPEN ligand.[71, 92]



Scheme 60. Reported ATH[70] and APH[89] of acetophenone using Noyori's catalyst **55**.

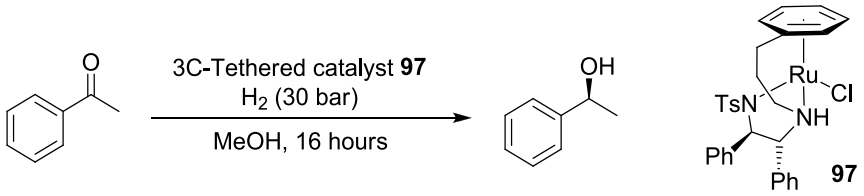
A variation of this catalyst was developed by Wills *et al.* in 2005 incorporating a three carbon tether between the aromatic and diamine ligand to give **97** shown in Scheme 61.[99]



Scheme 61. (*S,S***)**-TsDPEN-3C-tethered ruthenium catalyst **97** for ATH of acetophenone.

The application of complex **97** to the ATH of ketones has been extensively studied[99,101,102] however limited precedent exists for its application to APH of ketones,[109] a process that would be of particular interest to industry. In collaboration with Johnson Matthey, work began to assess the scope of **97** for APH of ketones. Initially Johnson Matthey had screened a range of reaction conditions to identify appropriate catalyst loadings, reaction concentrations and temperatures for the APH of acetophenone. They found that concentrations of 0.5 - 1 M and substrate/catalyst loadings of 100-1000/1 allowed for full conversion to phenyl ethanol with high enantioselectivity in 16 hours at 40-60°C, with the lower catalyst loadings requiring the higher temperature.[145] Initial studies began with repetition of these findings to establish appropriate reaction conditions for our reaction set-up prior to assessing the catalyst's scope for APH of a range of ketones. Results of this investigation are shown in Table 21.

Table 21. Results for APH of acetophenone using (*R*,*R*)-TsDPEN-3C-tethered catalyst **97**.

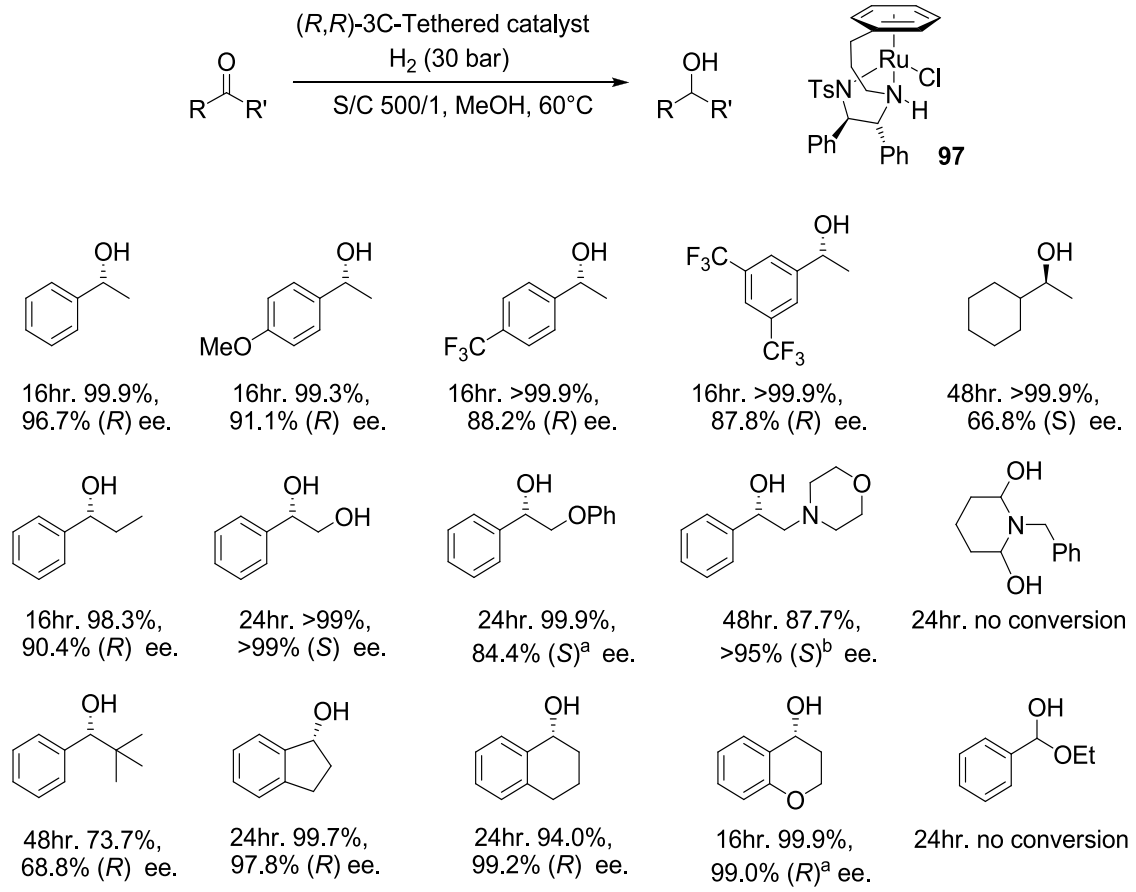


Entry	Catalyst	Substrate/ catalyst	[Substrate]	Temp. (°C)	Conv.[a] (%)	Ee[a] (%)
1	none	-	-	40	0.31	N/A
2	(*R*,*R*)-**97**	100/1	1 mmol [0.5 M]	40	99.9	92.2 (*R*)
3	(*S*,*S*)-**97**	100/1	1 mmol [0.5 M]	40	99.9	94.4 (*S*)
4	(*R*,*R*)-**97**	500/1	1 mmol [0.5 M]	60	50.4	91.4 (*R*)
5	(*S*,*S*)-**97**	500/1	1 mmol [0.5 M]	60	38.0	87.1 (*S*)
6[b]	(*R*,*R*)-**97**	500/1	1 mmol [0.5 M]	60	99.9	91.7 (*R*)
7[b]	(*S*,*S*)-**97**	500/1	1 mmol [0.5 M]	60	92.3	93.0 (*S*)
8[c]	(*R*,*R*)-**97**	500/1	1 mmol [0.5 M]	60	65.8	92.8 (*R*)
9[b]	(*R*,*R*)-**97**	1000/1	1 mmol [0.5 M]	60	34.7	86.9 (*R*)
10[b]	(*S*,*S*)-**97**	1000/1	1 mmol [0.5 M]	60	39.2	88.3 (*S*)

[a]Determined by chiral GC. [b]Acetophenone purified by kugelrohr distillation. [c]Reaction carried out for 8 hours.

Full conversion was achieved at a substrate/catalyst (S/C) ratio of 100/1 (1 mol% catalyst) at 30 bar H_2 and 40°C. With a reduction in catalyst loading to S/C 500/1 (0.2 mol%) however, even with an increase in temperature to 60°C full conversion was not achieved (Table 21, entries 3 and 4). Purification of the acetophenone by kugelrohr distillation was found to improve this allowing full conversion to phenyl ethanol at S/C 500/1 (Table 21, entry 5 and 6). A reduction in reaction time to 8 hours at S/C 500/1 showed a significant reduction in conversion to 65.8% demonstrating the need for a 16 hour reaction time at this loading. At S/C 1000/1, even with distilled acetophenone, full conversion to phenyl ethanol was not achieved in contrast to results obtained by Johnson Matthey. Trace impurities remaining in the acetophenone or present in the solvent or catalyst itself, may be the cause of this. At such low S/C loadings, even trace impurities could poison a sufficient proportion of

the catalyst present to reduce conversion. Conditions as in Table 21, entry 3 were used to assess the scope of the catalyst for APH of a range of ketones (Figure 40).[145]



All conversions and enantiomeric excesses determined by chiral GC unless otherwise stated.
[a]Determined by chiral HPLC. [b]Determined by Mosher's method.[156]

Figure 40. APH of carbonyl compounds using (*R*,*R*)-3C-tethered ruthenium catalyst **97**.

The ketones tested demonstrated good catalyst scope for APH with tethered ruthenium catalysts achieving high conversions and enantioselectivities. The results also show good tolerance of the catalyst and reaction conditions to a range of substituent groups.

For more sterically encumbered ketones such as 2,2-dimethyl-1-phenyl propanone however, a reduction in the conversion and ee. were observed, even with longer

reaction times. 1-phenyl propanone however was reduced well along with its α-hydroxy and α-phenoxy derivatives.

Both electron donating OMe and electron withdrawing CF_3 *p*-substituent groups were tolerated on the aromatic ring of the ketone, however a small reduction in ee. was observed with CF_3 substituents. This may be due to a loss of electron density in the phenyl ring of the ketone due to the electron withdrawing nature of the CF_3 group. This would reduce the favourable π/CH-attraction between catalyst and substrate shown in Figure 43 and hence reduce the ee. APH of bicyclic ketones was found to give the highest conversions and enantioselectivities.

Aliphatic ketones such as cyclohexylmethyl ketone performed less well under APH conditions with catalyst **97**, achieving only 66.8% ee. (*S*), although this is consistent with ATH results.[99] The low ee. is due to there being only a small energy difference between transition states for each enantiomer of product. It should also be noted that reduction of cyclohexylmethyl ketone gives the opposite enantiomer of product compared to the other substrates tested. This is due to the absence of π/CH-interactions between the catalyst and the substrate, hence steric factors determine the most favourable geometry of the transition state. The ketone is oriented with the large cyclohexyl substituent away from the catalyst giving the (*S*) enantiomer of product (Figure 41).

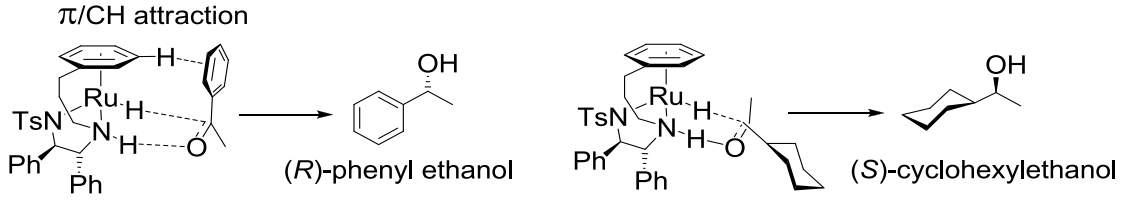


Figure 41. Transition state geometry for APH of aromatic and non-aromatic ketones by the 3C-tethered ruthenium catalyst **97**.

Ethyl benzoate and 1-benzylpiperidine-2,6-diene were also subjected to the APH conditions however no conversion was seen after 24 hours.

Determination of the enantiomeric excess and assignment of the stereochemistry of 2-(morpholin-4-yl)-1-phenylethanol from the APH of 2-morpholino-1-phenylethanone was achieved using Mosher's method.[146] This technique involves the reaction of the obtained alcohol product with (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride to give the resulting ester. The ester now has two chiral centres, the first resulting from the acetyl chloride which is enantiomerically pure and a second from the initial alcohol APH product which may or may not be enantiomerically pure. The resulting ester is therefore present as a mixture of diastereomers depending on the enantiomeric purity of the APH product. Analysis of the ester by ^{1}H NMR allows determination of both the enantiomeric excess and configuration of the alcohol product by use of the model shown in Figure 42 and comparison to ^{1}H NMR data obtained for the ester formed from a racemic sample of the alcohol product. Further details of the analysis carried out is given in the Experimental section of this thesis.

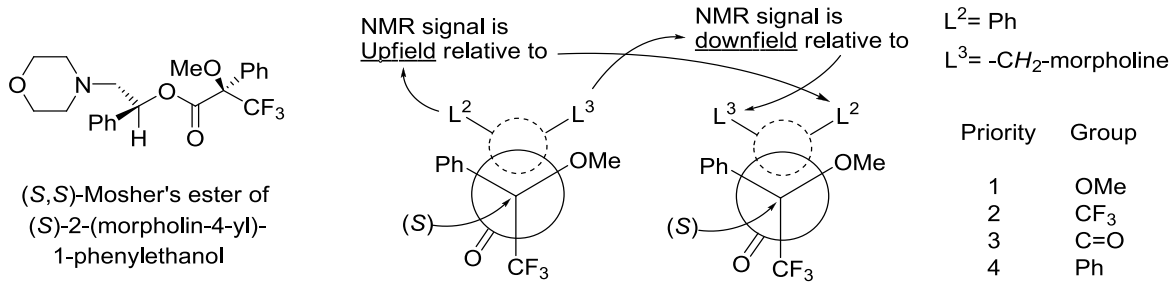
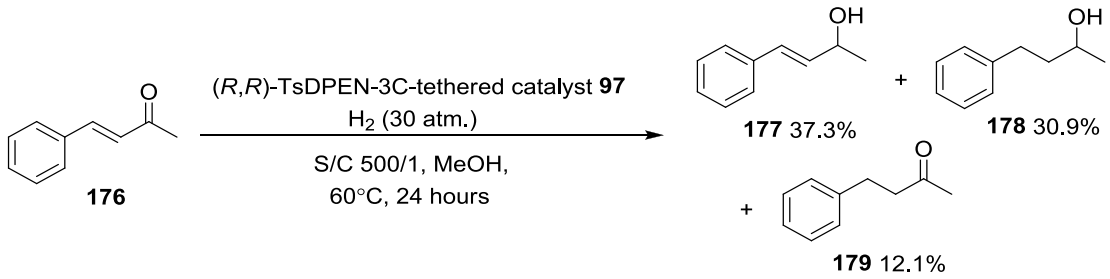


Figure 42. Model for assignment of enantiomeric excess and configuration of 2-(morpholin-4-yl)-1-phenylethanol.

In the case of the hydrogenation of 2-morpholino-1-phenylethanone to 2-(morpholin-4-yl)-1-phenylethanol, comparison of the Mosher's ester of the asymmetric product to the racemic shows the morpholine peaks to be upfield in the ^{1}H NMR spectrum confirming the presence of the *S*-enantiomer of the product. Only one set of peaks was present in the ^{1}H NMR indicating a high enantioselectivity of >95%.

In order to investigate chemoselectivity for the APH of C=O bond over C=C bonds the APH of 4-phenyl-3-buten-2-one **176** was carried out as shown in Scheme 62.



Scheme 62. APH of 4-phenyl-3-buten-2-one with (*R*,*R*)-TsDPEN-3C-tethered catalyst **97**.

The reaction gave an overall conversion of 79% conversion but poor chemoselectivity for reduction of the carbonyl group with 43% conversion to products with hydrogenated C=C bonds. This is in contrast to the results achieved under ATH conditions with untethered catalyst **57a** reported by Wills[73] where the same ketone was reduced with complete conversion, the product comprising of 75% of the unsaturated alcohol **177** and 25% saturated alcohol **178**.

The low selectivity between hydrogenation of the C=C and C=O bond in APH is likely to be due to there being only a small energy difference between the energy of the transition states for each process meaning that there is little discrimination between the occurrence of both processes. In the APH reaction reported in Scheme 62, it was not possible to separate the two alcohol products formed by column

chromatography. The alcohol mixture was therefore subjected to hydrogenation with Pd/C and atmospheric hydrogen to give only the saturated alcohol which was then analysed by chiral HPLC and showed an ee. of only 4.7% (*R*). Both APH and ATH conditions gave low enantioselectivities for the reduction products.

2.4 Application of further tethered ruthenium catalysts to the APH of ketones.

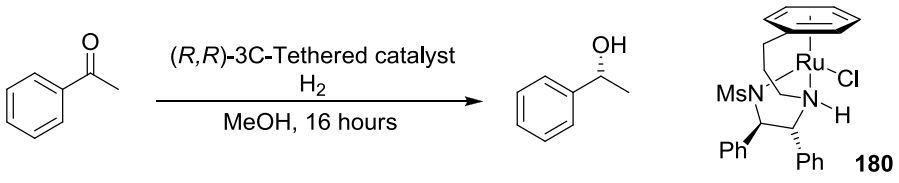
With the 3C-tethered ruthenium catalyst **97** demonstrating good activity for APH of ketones investigations were carried out into the scope of other catalysts for this reaction in order to identify a more active catalyst. Three aspects of the catalyst were chosen for further study:

1) The sulfonamide group
2) The halide ligand
3) The length of the aryl-diamine tether.

2.4.1 3C-tethered MsDPEN ruthenium catalyst.

Initially the (*R*,*R*)-3C-tethered-MsDPEN-RuCl catalyst **180**, supplied by Johnson Matthey, was applied to the APH of acetophenone as shown in Table 22.

Table 22. Results for APH of acetophenone using (*R*,*R*)-MsDPEN-3C-tethered catalyst **180**.

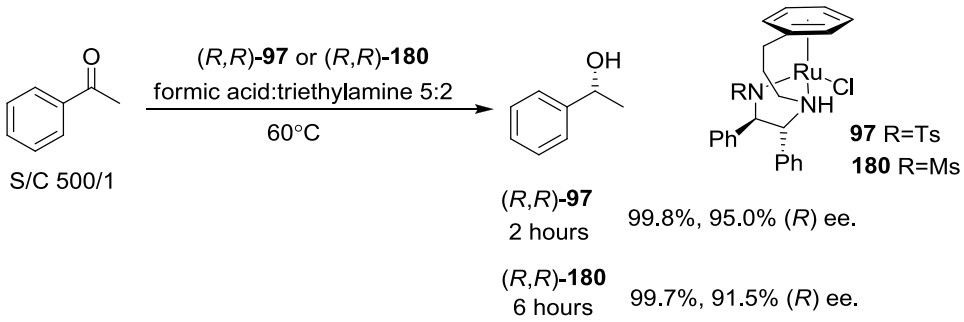


180

Entry	H_2 Pressure (bar)	Substrate/ catalyst	[Substrate][a]	Temp. (°C)	Conv.[b] (%)	Ee[b] (%)
1	30	500/1	1 mmol [0.5 M]	60	47.3	89.8 (*R*)
2	30	1000/1	1 mmol [0.5 M]	60	25.7	83.8 (*R*)
3	50	500/1	1 mmol [0.5 M]	60	99.9	91.1 (*R*)
4	50	1000/1	1 mmol [0.5 M]	60	60.4	87.8 (*R*)

[a]Distilled acetophenone used. [b]Determined by chiral GC.

The MsDPEN catalyst was found to be a less active catalyst than the TsDPEN catalyst, requiring an increase in pressure to achieve full conversion at S/C 500/1. These findings are mirrored in ATH reactions using the MsDPEN catalyst **180**. The ATH of acetophenone using catalyst **180** as shown in Scheme 63 required 6 hours to achieve full conversion, whilst use of TsDPEN catalyst **97** under the same conditions required only 2 hours for full conversion.



Scheme 63. ATH of acetophenone using TsDPEN[99] (**97**) and MsDPEN (**180**) tethered catalysts.

The reduction in the activity of the MsDPEN catalyst **180** may be due to a loss of steric bulk at the sulfonamide group, or indeed a reduction in the electron withdrawing nature of the sulfonamide group with a methyl rather than tolyl substituent affecting the electronic nature of the ruthenium and hence the Ru-H bond. The use of increased H_2 pressure was applied to the APH of a range of ketones using MsDPEN catalyst **180** (Figure 43).

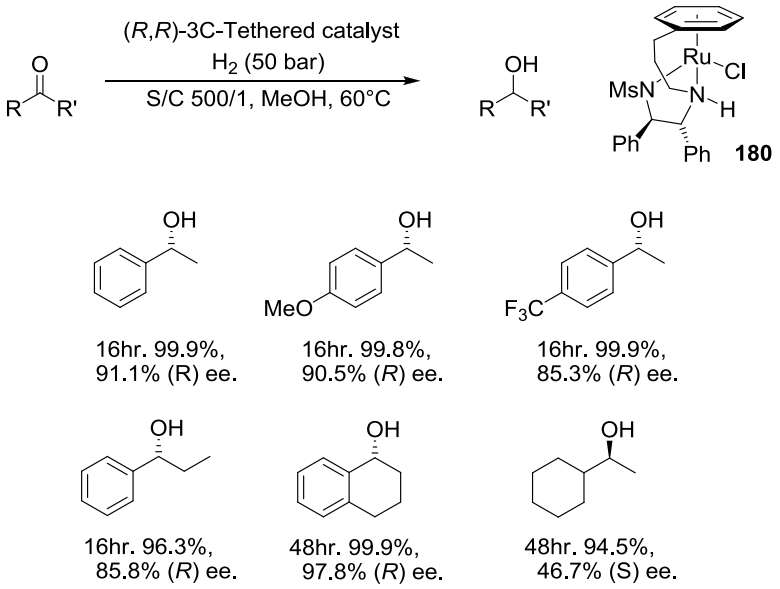


Figure 43. APH of ketones using (*R*,*R*)-MsDPEN-3C-tethered ruthenium catalyst **180**.

High conversions and ee.'s were achieved for ATH of the ketones using 50 bar H_2 pressure.

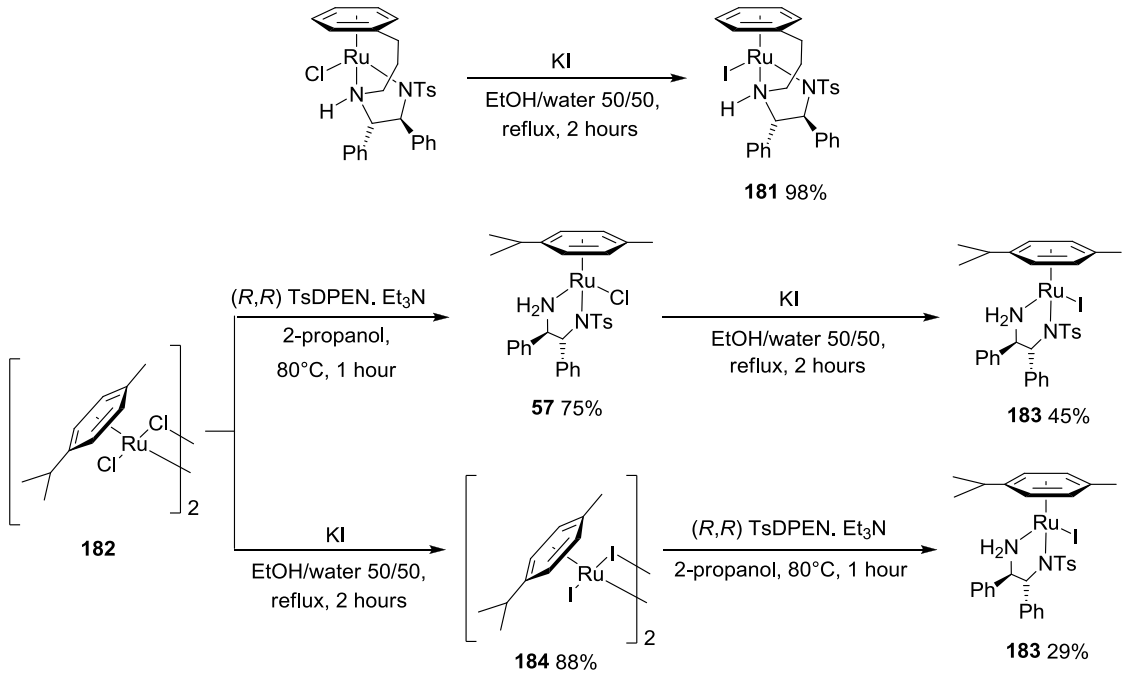
2.4.2 3C-tethered TsDPEN ruthenium iodo catalyst.

The second alteration made to the catalyst was to prepare the iodo derivative of catalyst **97**. Williams, Blacker and co-workers have shown iodo catalysts such as $[Cp^*IrI_2]_2$ to be highly active for hydrogen transfer processes for the alkylation of amines[147] and also dynamic kinetic resolution of chiral amines.[148]

Noyori has previously reported a proposed mechanism for APH using untethered ruthenium catalysts.[75] As described in Scheme 30, APH occurs under non-basic conditions with loss of chloride by ionisation to form a cationic Ru complex. The cationic complex then interacts with hydrogen to form an 18 electron ruthenium hydride complex. Hydrogenation of the ketone then occurs *via* a 6-membered pericyclic transition state with transfer of a hydride and proton to the C=O bond.

Protonation of the resulting ruthenium complex reforms the cation which then continues the catalytic process.

The ionisation step in the APH mechanism is a significant step in the mechanism, the faster the cationic species can be formed, the sooner the catalytic cycle and hence hydrogenation of substrate can begin. It has been found that Ru triflate complexes show improved activity for APH[75,76,93] due to rapid and facile ionisation in methanol solvent.[93] The literature also reports the use of silver salts within APH reactions to assist with the removal of the chloride[94,149] however studies carried out by Johnson Matthey found the addition of a variety of silver salts was detrimental the APH of acetophenone with the tethered catalyst **97** reducing conversions to phenyl ethanol to <10% and in some cases <1%.[145] In order to investigate whether iodide may be a better leaving group than chloride in the tethered catalyst improving the rate of activation of the catalyst, the tethered (**181**) and untethered (**183**) ruthenium iodide catalysts were prepared as shown in Scheme 64. X-ray crystallographic structures were also obtained for each complex (Figure 44).



Scheme 64. Preparation of tethered and non-tethered ruthenium iodide catalysts **181** and **183**.

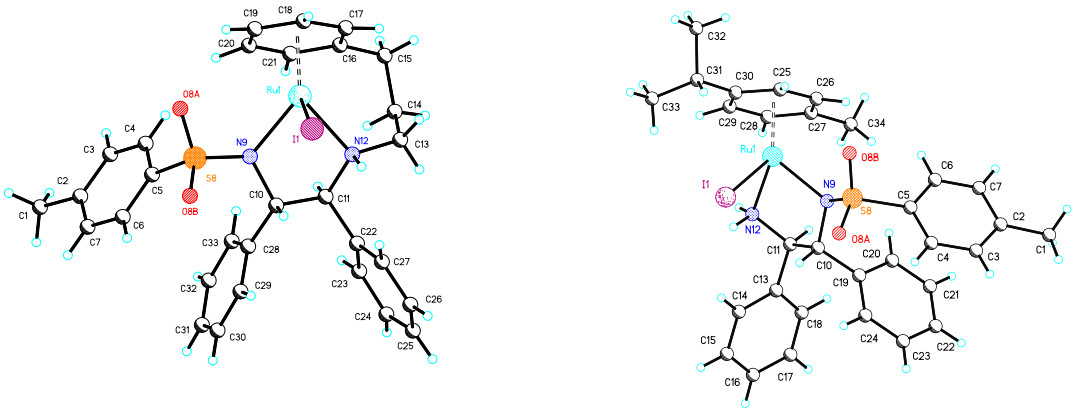


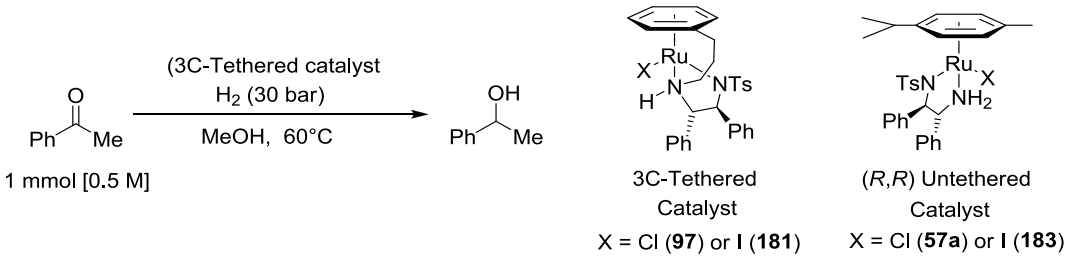
Figure 44. Solid state X-ray crystallographic structures of (*R*,*R*)-3C-tethered-RuI catalysts **181 (**left) and **183 (**right) with atom labelling.

The X-ray structures are consistent with those reported for the analogous RuCl complexes[74, 102]. Each complex was present as a single diastereomer, with the tosyl group oriented away from the chloride ligand and π/π-stacking between the tosyl group and neighbouring phenyl ring of TsDPEN observed. The Ru-I bond lengths were 2.77 and 2.78Å respectively for the tethered (**181**) and untethered (**183**)

complexes, longer in each case than the analogous RuCl complexes (Ru-Cl 2.43 and 2.44 Å for the tethered[102] (**97**) and untethered[74] (**57a**) complexes).

Conversion of the tethered RuCl catalyst (**97**) to its iodo derivative (**181**) proceeded with excellent product yield and without the need for purification. Formation of the untethered iodo catalyst proved to be less trivial with lower yields obtained due to the high solubility of both the monomer and its dimer precursor making isolation of the complexes more difficult. Conversion of the pre-formed untethered ruthenium chloride catalyst **57a** into its iodo derivative (**183**) gave a significantly higher yield than formation of the iodo dimer **184** followed by monomer formation. With both iodo catalysts in hand a series of APH reactions were carried out with acetophenone as the substrate (Table 23).

Table 23. APH of acetophenone using tethered and untethered ruthenium chloride and iodide catalysts **97, 181, 57a** and **183**.



Entry	Catalyst	S[a]/C	Temp. (°C)	Time (hr.)	Conv.[b] (%)	Ee[b] (%)
1	(*R*,*R*)-untethered RuCl catalyst **57a**	100/1	40	16	94.6	94.3 (*R*)
2	(*R*,*R*)-untethered RuI catalyst **183**	100/1	40	16	67.0	92.7 (*R*)
3	(*R*,*R*)-untethered RuCl catalyst **57a**	500/1	60	16	9.1	87.3 (*R*)
4	(*R*,*R*)-untethered RuI catalyst **183**	500/1	60	16	4.4	61.0 (*R*)

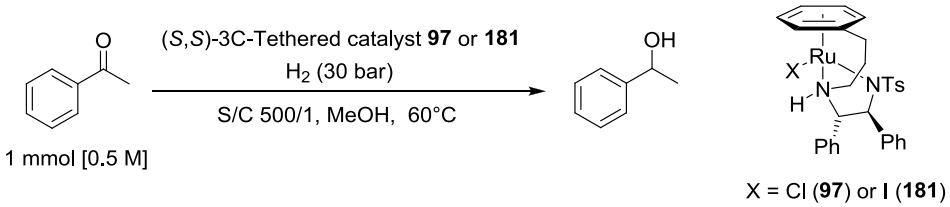
5	(*S*,*S*)-tethered RuCl catalyst **97**	500/1	60	16	99.8	93.2 (*S*)
6	(*S*,*S*)-tethered RuCl catalyst **97**	1000/1	60	16	21.0	86.6 (*S*)
7	(*S*,*S*)-tethered RuI catalyst **181**	500/1	60	16	56.5	92.7 (*S*)
8	(*S*,*S*)-tethered RuI catalyst **181**	1000/1	60	16	4.6	75.3 (*S*)
9	(*S*,*S*)-tethered RuCl catalyst **97**	2000/1	60	64.5	39.8	86.3 (*S*)
10	(*S*,*S*)-tethered RuI catalyst **181**	2000/1	60	64.5	45.2	86.7 (*S*)

[a]Distilled acetophenone used. [b]Determined by chiral GC.

The tethered iodo catalyst **181** was found to be more active than the untethered iodo catalyst **182**, however both iodo catalysts were less active than their chloro counterparts. Interestingly however, with a low catalyst loading and long reaction time (Table 23, entries 9 and 10) the activity of the tethered chloro and iodo catalysts was comparable in terms of conversion and ee. This suggests that although less active than the chloro catalyst, the iodo derivative **181** may exhibit increased stability over the chloro catalyst remaining active for longer allowing greater conversion over long reaction times than the chloro catalyst **97**. The results suggests that the ionisation process is not improved with an Ru-I rather than Ru-Cl bond as was originally proposed.

The reaction profile over time for both the tethered chloro and iodo catalyst offers further insight into the relative reactivities of the two complexes. Unlike the ATH reactions however, when using the sealed Parr reactor for APH reactions it was not possible to sample the same reaction at various time points for conversion analysis. Sampling APH reactions required cooling and depressurising the reaction before opening the reactor to extract a sample and once open, the reaction and all active

catalytic intermediates are exposed to air and moisture which may deactivate the catalyst. Indeed when initial reactions were sampled this way conversion was found to stop after the first sample was taken. Instead several reactions were carried out for different lengths of time and the conversion analysed. Each reaction was carried out in duplicate to confirm the results and identify anomalous results due to inaccurate weighing of catalyst or acetophenone. The same batch of catalyst, acetophenone and MeOH was used throughout. The results are shown in Figure 45.



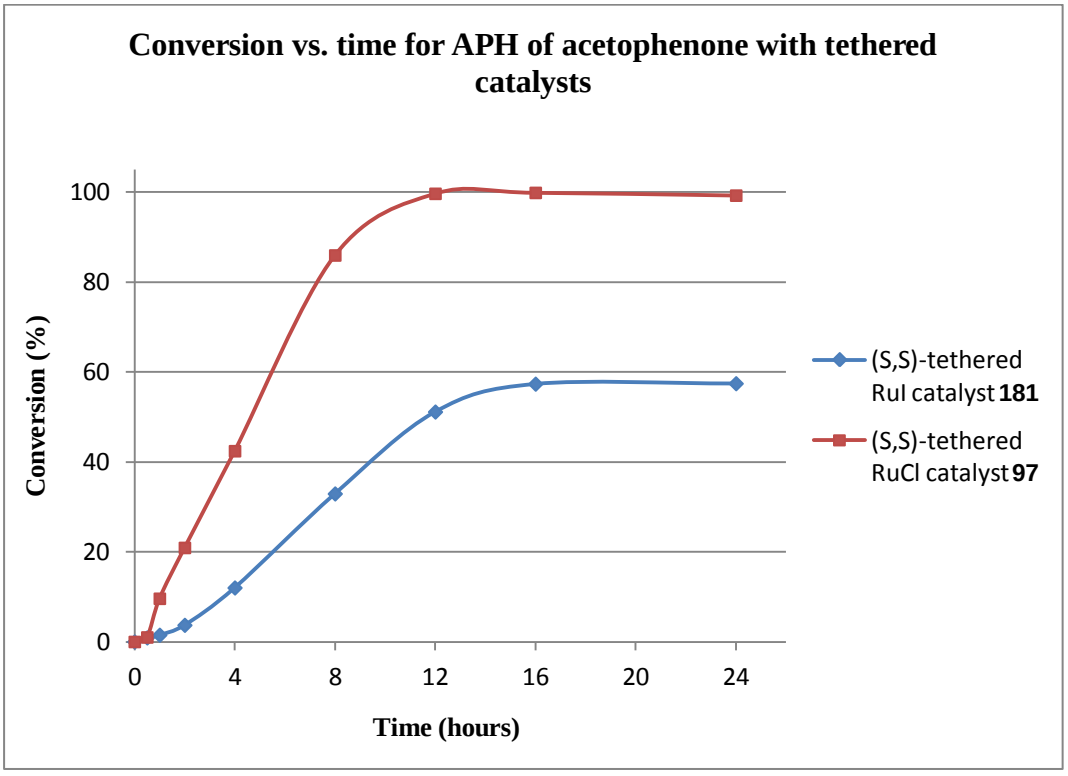


Figure 45. Analysis of conversion over time for APH of acetophenone using chloro (**97**) and iodo (**181**) tethered catalysts.

The conversion vs. time graph shows that the ruthenium iodide catalyst **181** is less active than the chloro derivative throughout the reaction process. A close up view of the first 4 hours of the reaction shown in Figure 46 shows that the initial activation period for the catalysts, is much longer for the iodo catalyst than the chloro catalyst.

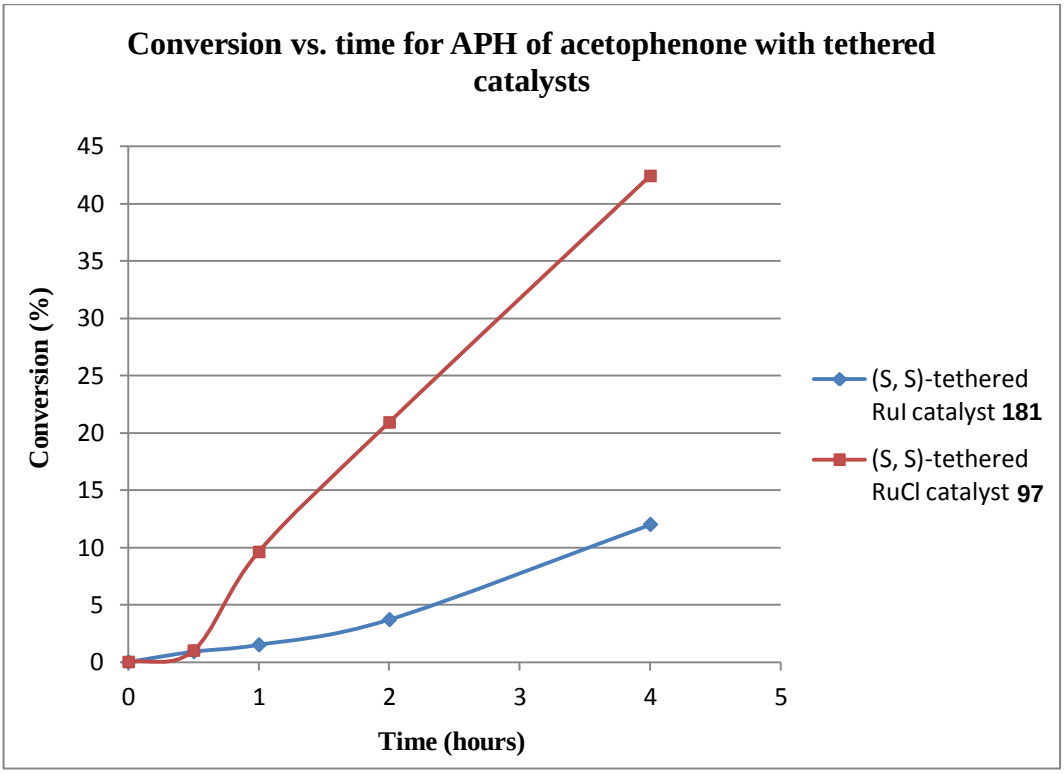


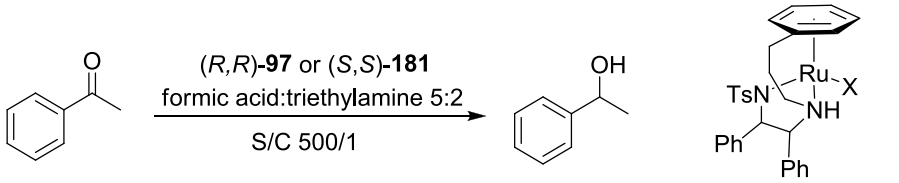
Figure 46. Analysis of conversion over time for hours 1-4 of the APH of acetophenone using chloro (**97**) and iodo (**181**) tethered ruthenium complexes.

The chloro catalyst (**97**) shows an activation period of 30 min before a significant increase in reaction rate is seen, however the iodo catalyst (**181**) requires 1.5-2 hours before the reaction rate increases, however it is a much more subtle increase in reaction rate than with the chloro catalyst. This reduction in the rate of activation again suggests that the ionisation process is slower for the iodo catalyst, rather than faster as was proposed. Contrary to expectations the larger iodide ion may not be a better leaving group allowing an improved rate of ionisation compared to the chloro

catalyst. Also the formation of HI during the reaction with the iodo catalyst **181** compared to HCl with the chloro catalyst may be detrimental to the reaction.

The tethered iodo catalyst **181** was also applied to the ATH of acetophenone. Under these conditions, where ionisation of the catalyst is not necessary for formation of the active species due to the presence of base, the iodo catalyst **181** performed equally to the chloro catalyst **97** (Table 24).

Table 24. ATH of acetophenone using tethered ruthenium chloride (**97**) and iodide (**181**) catalysts.



X = Cl (**97**) or I (**181**)

Entry	Catalyst	Temp. (°C)	Time (hours)	Conv.[a] (%)	Ee.[a] (%)
1	(*R*,*R*)-**97** RuCl	28	34	92.8	96.5 (*R*)
2	(*S*,*S*)-**181** RuI	28	34	99.6	95.9 (*S*)
3	(*R*,*R*)-**97** RuCl	60	2	99.8	95.0 (*R*)
4	(*S*,*S*)-**181** RuI	60	2	99.4	95.3 (*S*)

[a]Determined by chiral GC analysis.

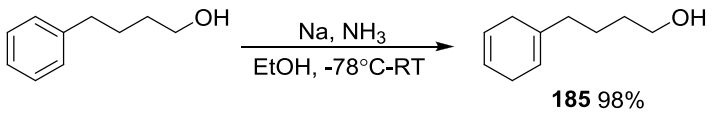
For the ATH conditions investigated, both catalysts gave comparable results showing no difference in activity upon substitution of the chloride for an iodide in the catalyst. The mode of activation for catalysts in ATH processes is loss of the halide ligand brought about by the presence of a base such as Et_3N or KOH. The loss of both chloride and iodide in this way should proceed at equal rates allowing equal

formation of the active Ru-hydride species and hence and equal rate of hydrogenation taking place.

2.4.3 4C-tethered ruthenium catalyst.

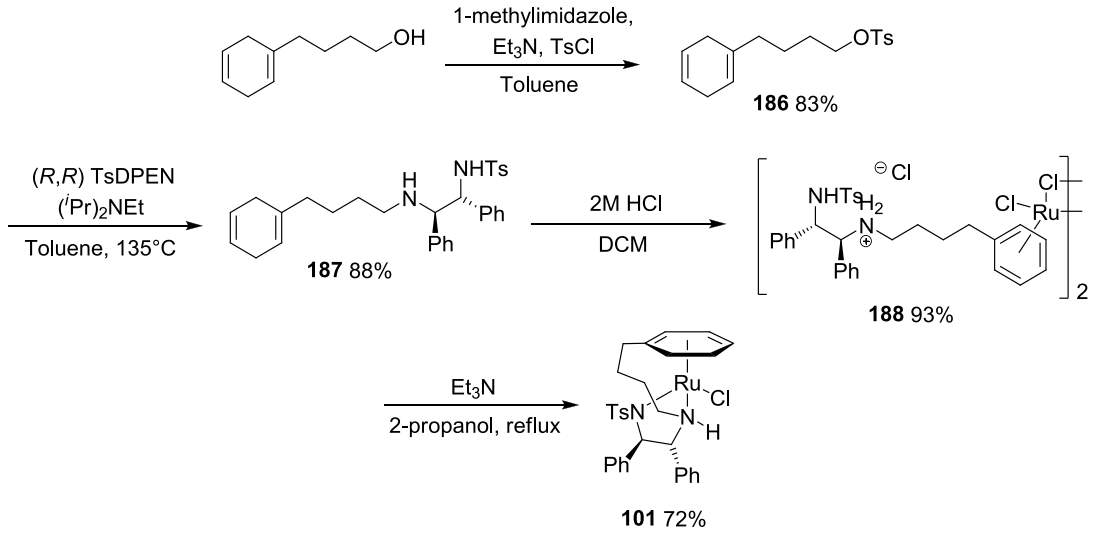
The third alteration made to the catalyst was to increase the length of the tether to a 4 carbon chain. This complex is known and has been reported to give improved results for ATH of ketones over the 3 carbon tethered catalyst.[101,102]

The initial preparation of the catalyst began according to literature procedures[101,102] with preparation of the 4-cyclohex-1,4-dienyl)butan-1-ol (**185**) starting material *via* Birch reduction of 4-phenyl-1-butanol as in Scheme 65.



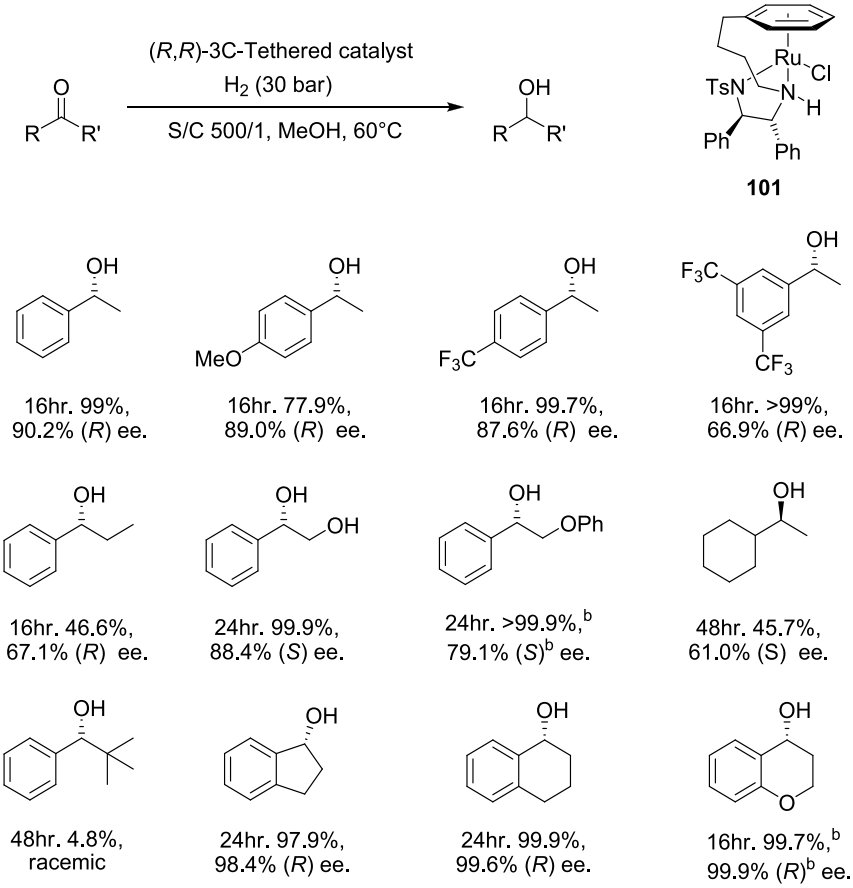
Scheme 65. Preparation of 4-cyclohex-1,4-dienyl)butano-1-ol **185**.

The next step in the synthesis is to couple the diene to the asymmetric diamine ligand, in this case (*R*,*R*)-TsDPEN. In the first reported synthesis of this catalyst this was achieved *via* Swern oxidation to afford the aldehyde and then reductive amination with TsDPEN to afford the coupled ligand.[99] Ikariya has published an alternative procedure for preparation of tethered diene ligands with conversion of the alcohol to a tosylate followed by nucleophilic substitution with the TsDPEN to afford the desired diene product.[104] This process was thus employed for preparation of the 4C-tethered ligand **187** as shown in Scheme 66. The ruthenium complex was then prepared from ligand **187** according to the reported method.[101,102]



Scheme 66. Synthesis of (*R*,*R*)-TsDPEN-4C-tethered ruthenium catalyst **101**.

With the catalyst in hand it was applied to APH of a range of ketones as with the 3C-tethered catalyst previously. Results are shown in Figure 47.



[a]Conversion and ee. determined by chiral GC unless otherwise stated. [b]Determined by chiral HPLC.

Figure 47. Application of (*R*,*R*)-4C-tethered TsDPEN ruthenium catalyst **101** to APH of ketones.

APH of ketones with the 4 carbon tethered catalyst **101** proceeded well with high activity and enantioselectivity. In most cases however, the 3 carbon catalyst gave the best results in terms of conversion, enantioselectivity or both. Only in some cases, namely APH of *p*-trifluoromethylacetophenone, indanone, tetralone and chromanone, did the results with **101** match those obtained with **97** in terms of conversion and enantioselectivity.

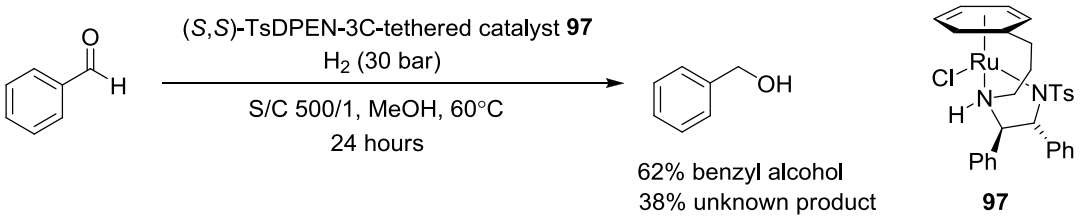
Under ATH conditions, the improved activity of the 4C-tethered catalyst **101** compared to its 3C counterpart **97** is reported to be due to the catalyst having a higher rate for formation and regeneration of the Ru-H species than **97**.[101,102] The results obtained for APH however show the 4C-tethered catalyst **101** to be less active than its 3C counterpart.

This may be due to the different mechanisms for ATH and APH as reported by Noyori[75] and discussed in Schemes 22 and 30. Although in both processes the reduction of the ketone occurs *via* the same cyclic transition state, the formation of the Ru-H species occurs by a different pathway for each process. In ATH, the presence of base allows the elimination of HCl to give the 16 electron complex (Scheme 22), in APH however, the chloride is lost through ionisation generating a cationic complex with interacts with molecular hydrogen to form the ruthenium hydride species (Scheme 30). In the 4C tethered catalyst **101**, the tether is reported to be oriented towards the chloride which increases the sterics in this region of the catalyst.[102] The increase in sterics may be a disadvantage under APH conditions, inhibiting either the ionisation of the chloride ligand, or the initial co-ordination of molecular hydrogen prior to Ru-H formation. Such inhibition would increase the

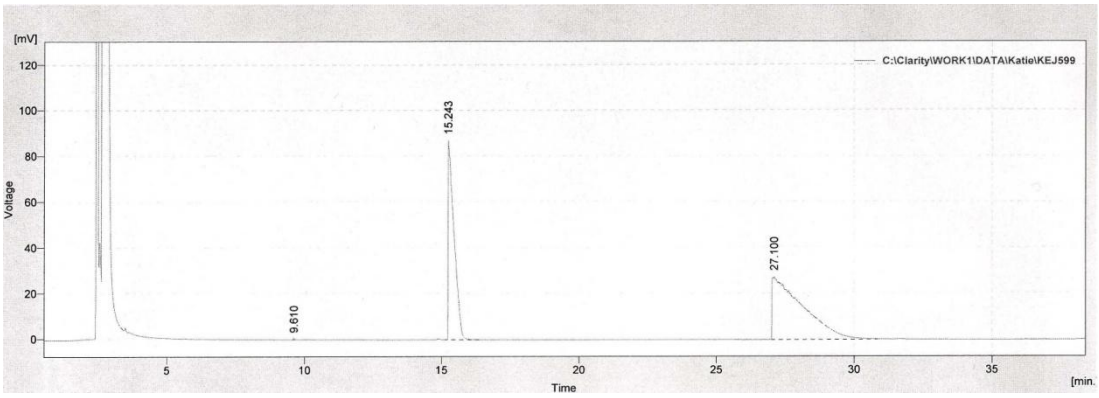
time required for Ru-H formation and regeneration in turn reducing the rate of turnover and hence activity of the catalyst.

2.5 Hydrogenation of aldehydes with tethered ruthenium catalysts.

The tethered catalysts, particularly the 3C tethered catalyst **97** have shown good activity and enantioselectivity for the APH of ketones, however the hydrogenation of aldehydes to prepare primary alcohols was also of interest. Initial attempts at the hydrogenation of benzaldehyde shown in Scheme 67 gave formation of a second product in addition to the desired benzyl alcohol (Figure 48).



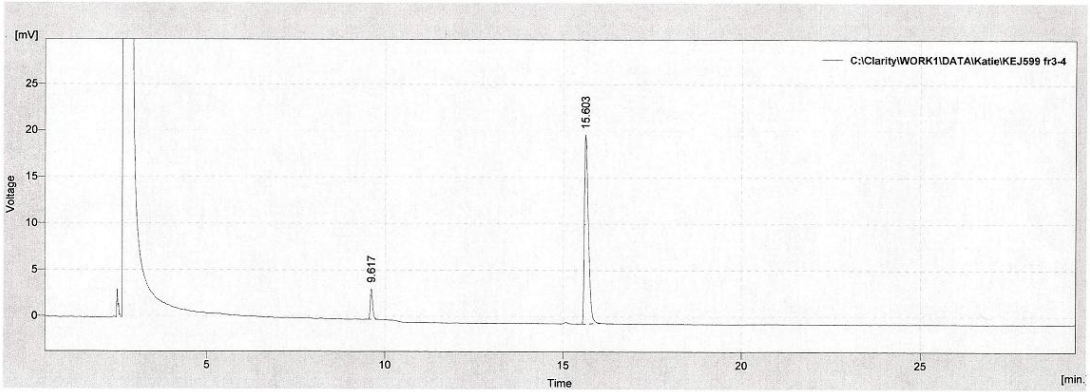
Scheme 67. APH of benzaldehyde using tethered ruthenium catalyst (*S*,*S*)-**97**.



GC conditions: Chrompac cyclodextrin-β-236M-19 50m x 0.25 mm x 0.25 μm, T = 100°C, P = 15psi H_2, det = FID 220°C, inj = 220°C, benzaldehyde 9.6 min., benzyl alcohol 27.1 min.

Figure 48. Example chrial GC chromatogram of the APH of benzaldehyde as shown in Scheme 67.

Isolation of the unknown compound at 15.6 min. was achieved by column chromatography. ^{1}H NMR analysis identified the compound as (dimethoxymethyl)benzene (Figures 49 and 50).



GC conditions: Chrompac cyclodextrin-β-236M-19 50m x 0.25 mm x 0.25 µm, T = 100°C, P = 15psi H_2, det = FID 220°C, inj = 220°C, (dimethoxymethyl)benzene 15.6 min.

Figure 49. Chiral GC chromatogram showing isolated unidentified compound at RT 15.6 min.

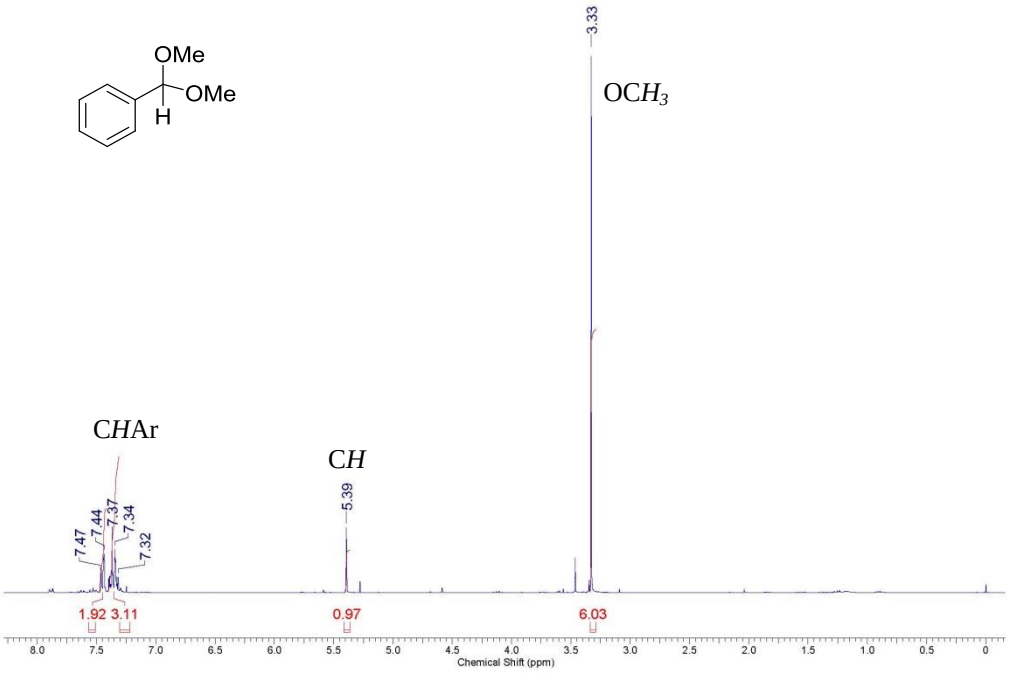
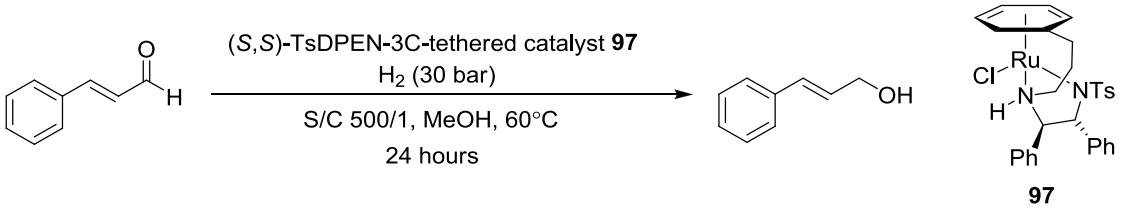


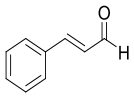
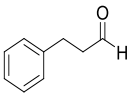
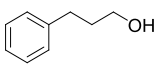
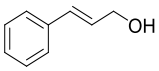
Figure 50. ^{1}H NMR of isolated unidentified compound at RT 15.6 min. ($CDCl_3$, 300 MHz).

In order to determine if the formation of the dimethoxy product was characteristic of aldehydes in general or was simply isolated to the case of benzaldehyde, cinnamaldehyde was also subjected to pressure hydrogenation (PH) conditions as shown in Table 25, and Figure 51.

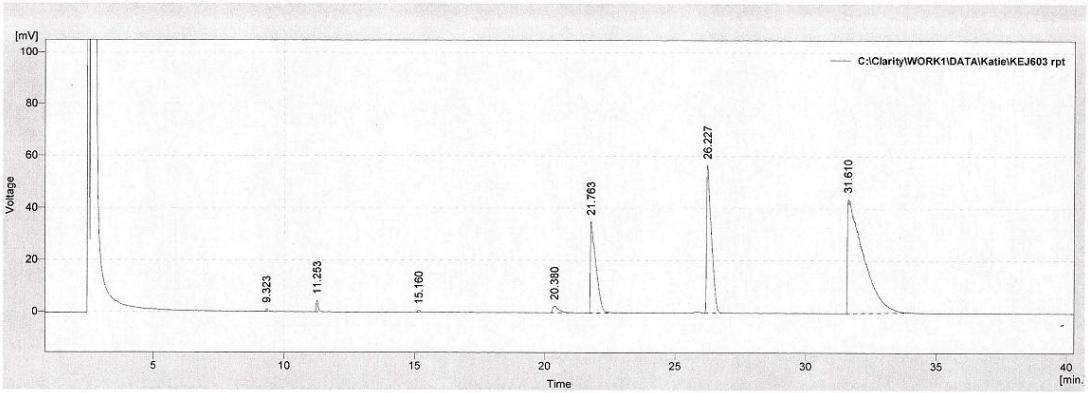
Table 25. APH of cinnamaldehyde using catalyst (*S*,*S*)-**97**.



97

Entry	Temp (°C)	Conversion to products[a] (%)				
						Unknown at 26 min.
1	60	0.3	0.3	7	78.4	13.9
2	40	16	0.9	1.2	59.2	22.7

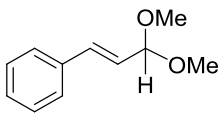
[a]Determined by GC.



GC Conditions: Chrompac cyclodextrin-β-236M-19 50m x 0.25 mm x 0.25 μm, T = 130°C, P = 15psi H_2, det = FID 220°C, inj = 220°C, 3-phenylprop-2-enal 11.2 min., 3-phenylpropan-1-ol 20.4 min., cinnamaldehyde 21.8 min., unknown product 26.2 min., 3-phenylprop-2-en-1-ol 31.6 min.

Figure 51. Example GC chromatogram for the APH of cinamaldehyde.

Again an unknown compound was found to form in the reaction (RT = 26.2 min.), isolation of this compound and analysis by ^{1}H NMR identified it as (3,3-dimethoxyprop-1-en-1-yl)benzene **189** (Figure 52).

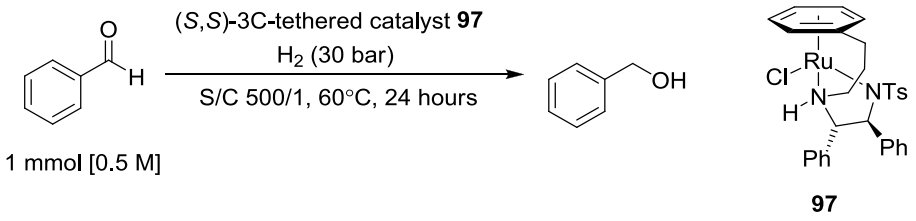


189

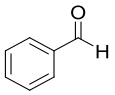
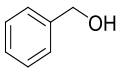
Figure 52. (3,3-dimethoxyprop-1-en-1-yl)benzene **189.**

It was thought that by altering the solvent to a more sterically encumbered alcohol or a non alcoholic solvent may prevent formation of such adducts (Table 26).

Table 26. Investigation into the use of different solvents for the APH of benzaldehyde.



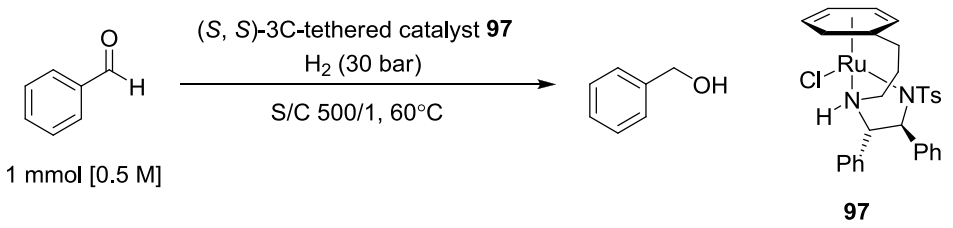
97

Entry	Solvent	Conversion to products[a] (%)		
			Other products	
1	IPA	91.8	0.3	7.9
2	DCM	98.1	-	1.9
3	Toluene	96.6	-	3.4
4	Cyclo-hexanol	95	-	5.0
5	Dioxane	97.4	0.6	2.0
6	DMF	93.8	-	6.2
7	H_2O	73.8	-	26.2

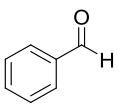
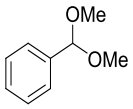
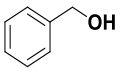
[a]Determined by GC analysis.

Of the solvents tested all gave low conversion to benzyl alcohol but the use of water as the solvent gave the highest of these conversions demonstrating a degree of tolerance to water for the catalyst. A systematic study was carried out to identify the effect of different MeOH/H_2O mixtures as the reaction solvent on the conversion of benzaldehyde to benzyl alcohol and (dimethoxymethyl)benzene under pressure hydrogenation (PH) conditions. The results are shown in Table 27.

Table 27. Use of aqueous solvent for the APH of benzaldehyde using (*S*,*S*)-**97**.



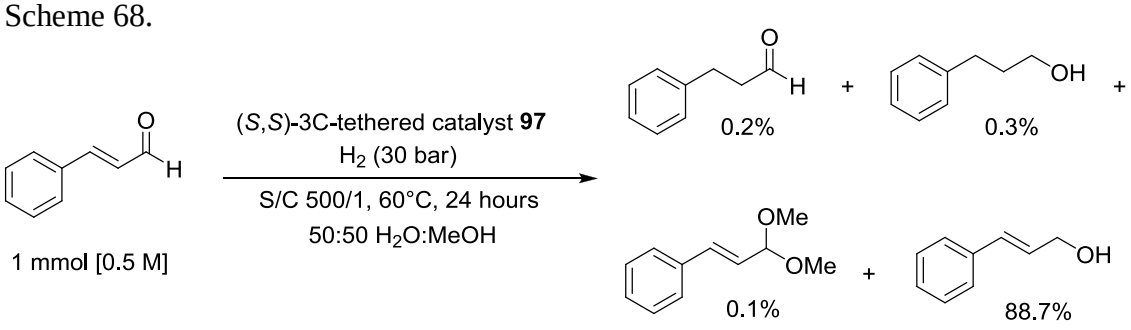
97

Entry	Solvent	Time (hours)	Conversion to products[a] (%)		
					
1	H_2O	24	73.8	-	26.2
2	MeOH + 0.2 mol% H_2O	24	5.7	39.5	54.8
3	MeOH + 2μL H_2O	24	<0.01	38.4	61.6
4	75:25 MeOH:H_2O	24	0.2	<0.01	99.8
5	50:50 MeOH:H_2O	24	0.2	<0.01	99.8
6	25:75 MeOH:H_2O	24	27.8	0.4	71.8

[a]Determined by GC analysis.

Initially catalytic amounts of water were added to the reaction however no improvement to the conversion to benzyl alcohol was seen. With larger amounts of water, (Table 27, entries 4 and 5) the formation of (dimethoxymethyl)benzene was inhibited and the reaction proceeded with full conversion to benzyl alcohol. Table 27. entry 6, with 75% water in MeOH shows the water to inhibit the hydrogenation reaction with incomplete conversion of benzaldehyde to products in 24 hours, although the amount of (dimethoxymethyl)benzene formed remained low. The PH of cinnamaldehyde was carried out using conditions as for Table 27, entry 5.

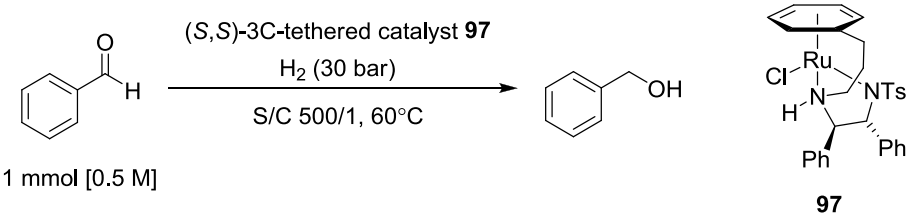
Cinnamaldehyde was found to be a more hindered substrate in the initial reductions carried out (Table 25) exhibiting lower overall conversion to product than the benzaldehyde reduction (Scheme 67) so it was deemed a good substrate to investigate the efficacy of the new reaction conditions. The results are shown in Scheme 68.



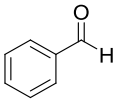
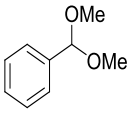
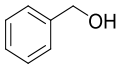
Scheme 68. APH of cinamaldehyde using (*S*,*S*)-**97**.

Although the reaction showed minimal formation of (dimethoxymethyl)benzene, the overall conversion to products for the reaction was 89.3% leaving 10.7% unreacted starting material, even with the long reaction time of 24 hours. This shows that the addition of water to the MeOH solvent will need to be minimised in order for the reaction to remain effective for the PH of more difficult substrates. A further study was therefore carried out to determine the minimum amount of water required to prevent formation of (dimethoxymethyl)benzene. The results are shown in Table 28.

Table 28. APH of benzaldehyde using (*S*,*S*)-**97** and aqueous solvent.



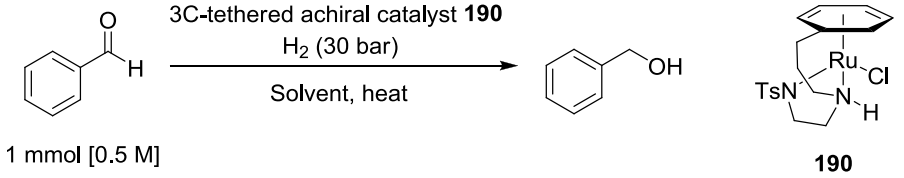
97

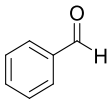
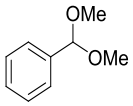
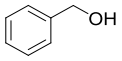
Entry	Solvent	Time (hours)	Conversion to products[a] (%)		
					
1	75:25 MeOH:H_2O	16	19.8	4.6	75.6
2	90:10 MeOH: H_2O	16	<0.01	<0.01	99.9
3	95:5 MeOH:H_2O	16	0.2	-	99.8
4	95:5 MeOH:H_2O	8	0.03	0.03	99.9

[a]Determined by GC analysis.

The reaction conditions used in Table, 28, entry 4 were deemed to be the best conditions for the PH reaction, with short reaction times, minimal amount of water and high conversion to the desired alcohol product. With appropriate reaction conditions in hand, a sample of 3C-tethered achiral catalyst **190** provided by Johnson Matthey was applied to PH of benzaldehyde (Table 29). Use of the achiral catalyst is desirable as the hydrogenation of aldehydes does not give chiral products. Thus, the presence of expensive enantiomerically pure diamine ligands in the catalyst is not required. The achiral catalyst is therefore more cost effective and appropriate to use than the asymmetric catalyst **97**.

Table 29. APH of benzaldehyde with achiral tethered ruthenium catalyst **190** and aqueous solvents.



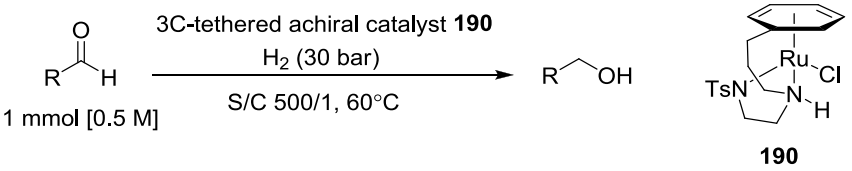
Entry	Solvent	Substrate/ catalyst	Temp (°C)	Time (hours)	Conversion to products[a] (%)		
							
1	95:5 MeOH:H_2O	500/1	60	8	10.6	13.4	76.0
2	95:5 MeOH:H_2O	500/1	60	4	44.6	32.3	12.3
3	95:5 MeOH:H_2O	1000/1	60	8	48.6	47.2	2.7
4	95:5 MeOH:H_2O	500/1	40	16	40.9	51.7	7.4
5	90:10 MeOH:H_2O	500/1	60	8	17.9	9.2	72.9
6	90:10 MeOH:H_2O	500/1	60	16	0.4	0.1	99.5

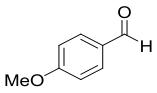
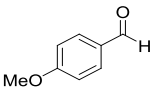
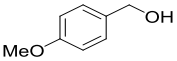
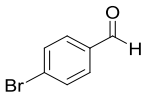
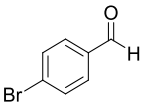
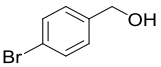
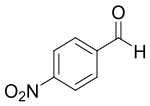
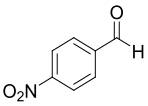
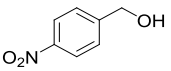
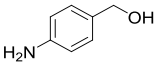
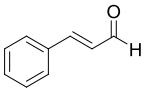
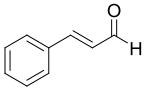
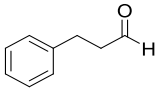
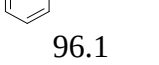
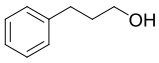
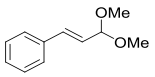
[a]Determined by GC analysis.

Initially the achiral catalyst showed reduced activity compared to the (*S*,*S*) catalyst. Comparison of Table 28, entry 4 and Table 29, entry 1, shows that under the same reaction conditions the achiral catalyst gave less conversion to benzyl alcohol and also allowed formation of (dimethoxymethyl)benzene. Investigations into reducing the reaction time, catalyst loading and temperature were further detrimental to the reaction, drastically reducing conversion to the desired product and increasing conversion to (dimethoxymethyl)benzene. Increasing the amount of water in the solvent and the reaction time was found to correct this achieving almost full

conversion to the desired alcohol product (Table 29, entry 6). A range of aldehydes were then subjected to APH under these conditions (Table 30).

Table 30. APH of aldehydes using achiral ruthenium catalyst **190** and aquesous solvent.



Entry	Substrate	Solvent	Time (hours)	Conversion to products[a] (%)		
1		90:10 MeOH: H_2O	16	 0.4	 99.6	-
2		90:10 MeOH: H_2O	16	 0.1	 99.8	Other 0.1
3		90:10 MeOH: H_2O	16	 0.8	 94.8	 2.8 Other 1.6
4		90:10 MeOH: H_2O	24	 0.05  0.06	 96.1	 3.5  0.3

[a]Determined by GC analysis.

Good conversion to the desired product was achieved with each aldehyde demonstrating tolerance of a variety of aromatic substituents and also good chemoselectivity for hydrogenation of the carbonyl group over nitro and alkene groups. The hydrogenation of cinnamaldehyde proceeded with greater selectivity for

hydrogenation of the C=O bond over the C=C bond than with hydrogenation of 4-phenyl-3-buten-2-one (Scheme 70). The reduced steric environment of the C=O bond in cinnamaldehyde due to the presence of a proton rather than methyl group bonded to the carbonyl is thought to give a greater energy difference between transition states for C=O and C=C hydrogenation than for 4-phenyl-3-buten-2-one. Thus there is a greater preference for hydrogenation of the C=O bond in cinnamaldehyde over the C=C bond than in 4-phenyl-3-buten-2-one.

2.6 Synthesis of tethered ruthenium complexes by aryl substitution methodology and application to asymmetric hydrogenation of ketones.

In the previous section, tethered catalysts were successfully applied to the APH of ketones and aldehydes demonstrating high activity, enantioselectivity and chemoselectivity. Of all the catalysts investigated, the 3C-tethered TsDPEN RuCl catalyst **97** proved to be the most active. Although highly active for APH of ketones, and also aldehydes in both its chiral and achiral states, the preparation of the catalyst is far from ideal requiring a Birch reduction and also a two step ruthenium complexation process with formation of the dimer prior to formation of the monomer which is used in hydrogenation reactions.[96,97,101,102] The necessity of the Birch reduction also restricts the structure of the tethered catalysts it is possible to form using this existing synthesis, limiting substitution on the aryl ring of the catalyst to those which can be prepared through the Birch reduction. Reported tethered catalysts with aryl substituents have, as a result, been restricted to those containing one or two methyl groups (Figure 55).[101,102,104]

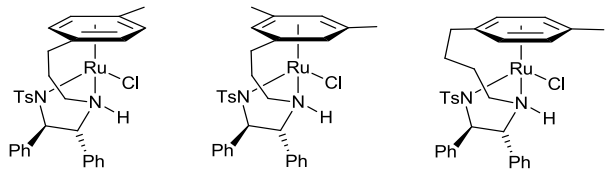
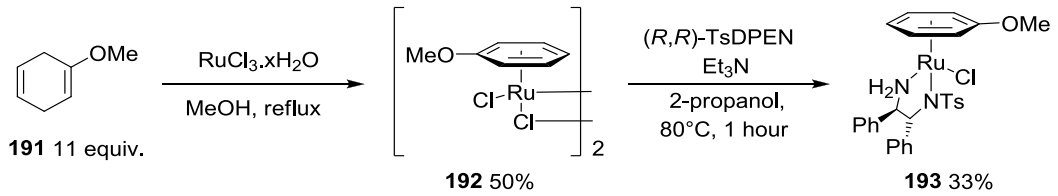


Figure 53. Examples of alkyl substituted tethered ruthenium catalysts.

Substituent groups on the aryl ring need to be stable to the Birch reduction conditions without hindering the reduction of the aromatic ring. The presence of electron donating groups such as alkoxy groups may encourage oxidation of the diene formed in the Birch reduction. This would lead to re-aromatisation of the ring preventing complexation with ruthenium. Bennett has reported the successful preparation of a series of arene ruthenium(II) complexes from a variety of substituted dienes including methyl, dimethyl and halogen substituted cyclohexadienes.[150] In a separate report however he reports that attempts to prepare the hexamethylbenzene ruthenium chloride dimer were unsuccessful due to the resistance of hexamethyl benzene to reduction in order to form its diene derivative for coordination with ruthenium.[151]This resistance to reduction suggests that hexamethylbenzene may exhibit a strong preference for oxidation due to the electron donation from the six methyl substituent groups.

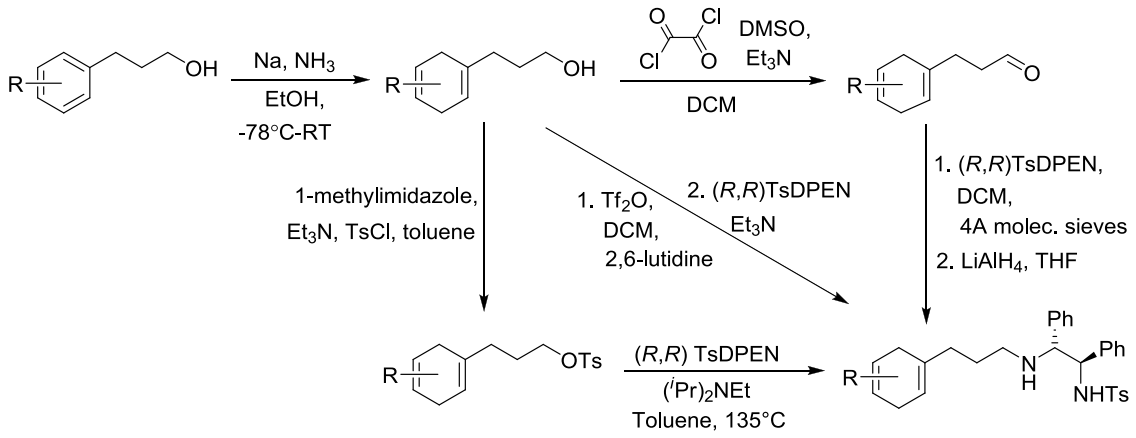
A further example of this is the reported synthesis of OMe-substituted Noyori type complex **193** which requires an 8-9 fold excess of 1-methoxycyclohexa-1,4-diene **191** in combination with $RuCl_3$ to form the OMe substituted dimer for monomer formation with TsDPEN. This reaction is reported in the literature[152, 153] and further confirmed with our own attempts at its synthesis shown in Scheme 69. Initial use of 1.2 equivalents of diene **191**, as used in the reported syntheses of tethered catalysts,

gave no formation of the desired dimer **192**. Use of 11 equivalents of diene **191** however gave dimer **192** in a 50% yield (Scheme 69) which was then converted to monomer **193**. Use of complex **193** for the hydrogenation of acetophenone gave >99.9% conversion to phenyl ethanol with an ee. of 94.5% (*R*) under ATH conditions (formic acid:triethylamine 5:2, S/C 100/1, 28°C for 24 hours), but only 11.8% conversion and 80.2% (*R*) under APH conditions (30 bar H_2 in MeOH, S/C 500/1 at 60°C for 24 hours).



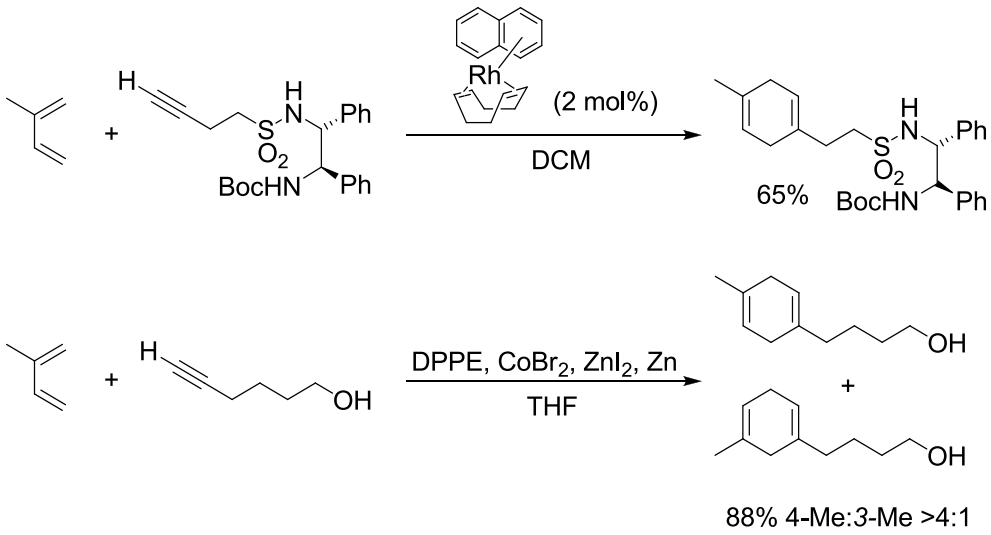
Scheme 69. Preparation of Noyori-type OMe substituted untethered ruthenium catalyst **204**.

Such a large excess of the diene is presumably required due to the electron-rich nature of the cyclohexadiene ring, with electron donation from the OMe encouraging oxidation to methoxybenzene. Employing a large excess of the diene is therefore necessary to ensure that enough diene remains present for complexation with the Ru. Whilst this process can be considered far from ideal but acceptable for complexes such as **193** which require simple and available diene starting materials, when considering the preparation of tethered complexes *via* a similar route it becomes significantly less viable. The use of such large excesses of enantiopure, TsDPEN containing diene ligands is not appropriate regarding the cost of such compounds and their preparation which involves multiple steps including a Birch reduction as shown in Scheme 70.



Scheme 70. Example preparations of TsDPEN tethered diene ligand.

The Birch reduction can be avoided, with both Wills[98] and Ikariya[104] reporting the [4+2] cycloadditions for diene formation as shown in Scheme 71.

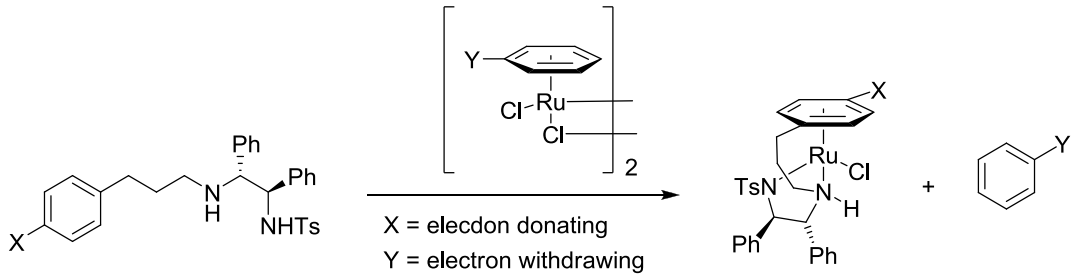


Scheme 71. [4+2] cycloadditions for preparation of dienes.

Precedent also exists for [4+2] cylcoadditions involving methoxy substituted 1,3-butadiene.[154] However, even with avoidance of the Birch reduction, the issue remains with complexing the formed diene ligand with ruthenium.

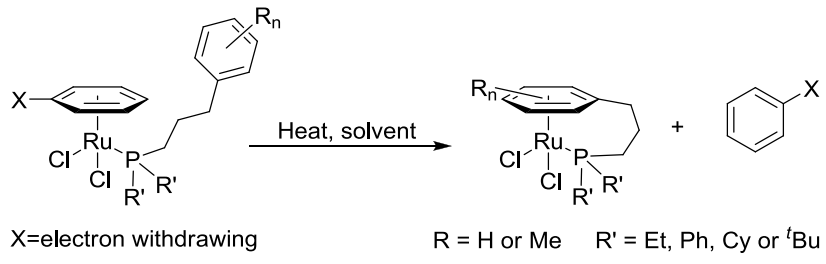
Despite the difficulties with the synthesis of such complexes, the preparation and use of tethered catalysts possessing aryl substituents remains of significant interest,

offering the potential to enhance the interaction between the catalyst and substrates in order to improve conversion and enantioselectivity. However, for such potential to be investigated, an effective synthesis of such complexes allowing diverse substitution of the aryl ring is required. Of particular interest to ourselves was preparation of the catalyst *via* an aryl substitution process, with an electron-poor aryl group on a preformed ruthenium dimer being displaced by a more electron-rich aryl group of a ligand (Scheme 72).



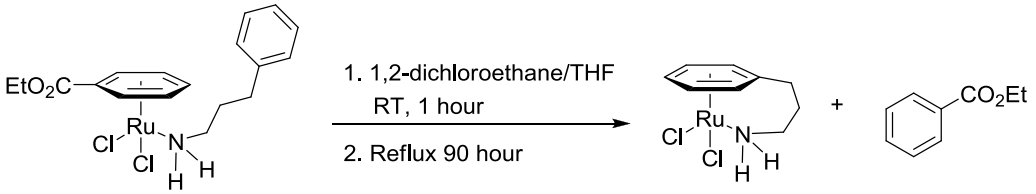
Scheme 72. Proposed synthesis of tethered ruthenium catalysts by an aryl substitution approach.

This type of reaction is known in the literature however it has not previously been applied to the preparation of catalysts with a structure synonymous to the 3C-tethered TsDPEN RuCl catalyst. There are many reports in the literature of the use of aryl substitution in the preparation of complexes involving phosphine ligands as shown in Scheme 73.[155]



Scheme 73. Preparation of *P*-tethered ruthenium complexes by aryl substitution.

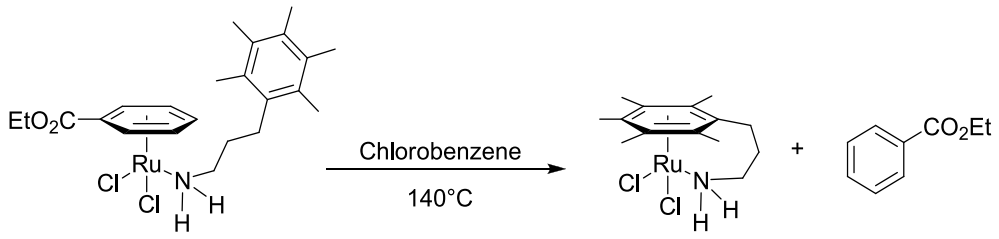
A review of the literature reveals only two examples of complexes formed *via* an aryl substitution involving nitrogen containing ligands. In 2007 Sadler reported the following reaction with tether lengths of 2 and 3 carbons long (Scheme 74).[156]



Complex formed *in situ* from Ethylbenzoate ruthenium(II)chloride dimer and 3-phenylpropylamine ligand.

Scheme 74. Preparation of *N*-tethered ruthenium complexes by aryl substitutions.

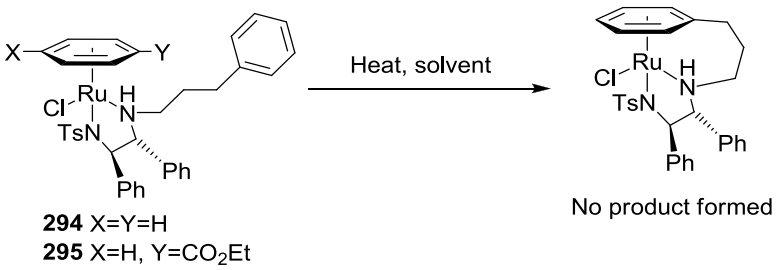
In 2009 Ikariya reported the following reaction with tether lengths of 3 and 4 carbons long (Scheme 75).[157]



Complex formed *in situ* from Ethylbenzoate ruthenium(II)chloride dimer and 3-phenypropylamine ligand.

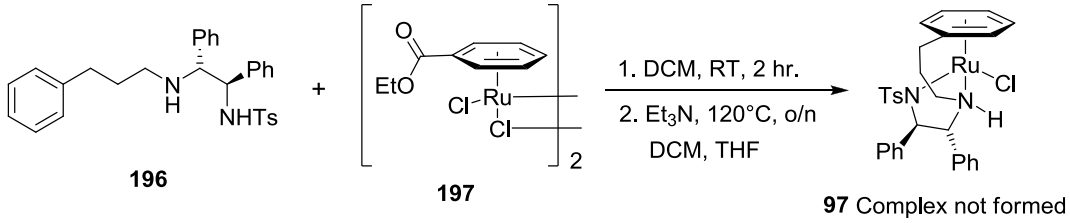
Scheme 75. Preparation of *N*-tethered ruthenium complexes by aryl substitution.

Initially it was thought that 3C-tethered TsDPEN ruthenium chloride complexes such as **97** could be prepared in a similar way however past attempts to achieve this within our group (carried out by Dr. Silvia Gosiewska) were unsuccessful, either with no reaction taking place or with decomposition occurring at higher temperatures (Scheme 76).



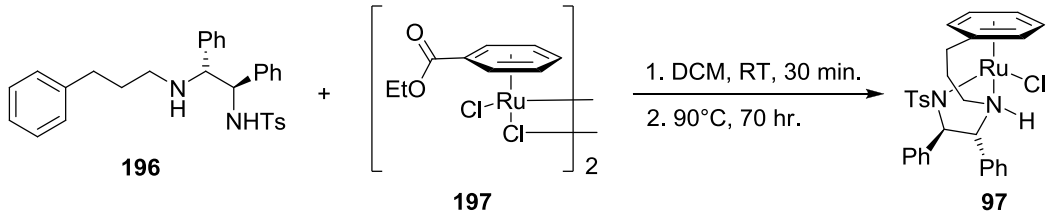
Scheme 76. Previous attempted formations of tethered complexes by aryl substitution in our group. Carried out by Dr. Silvia Gosiewska (unpublished result).

These findings showed that unlike the work of Sadler and Ikariya, whereby with a ligand containing a single nitrogen atom the nitrogen is first co-ordinated to the ruthenium *in situ* to give an initial complex prior to aryl substitution, in our case with a diamine containing ligand, initial co-ordination of both nitrogens to the ruthenium inhibits the substitution reaction. It is thought that with both nitrogens co-ordinated to the ruthenium the geometry and degree of flexibility of the complex, in particular the tethered aryl component, is not of the correct orientation to allow aryl substitution to occur. We propose that with only one point of co-ordination between the tethered aryl ligand and ruthenium prior to aryl substitution as reported by Sadler[156] and Ikariya[157], the complex retains flexibility allowing a more favourable orientation for aryl substitution to be adopted. An alternative strategy was therefore adopted within our group shown in Scheme 77, whereby the ligand **196** and electron poor dimer **197** were combined directly rather than attempting the aryl substitution on a pre-formed complex.



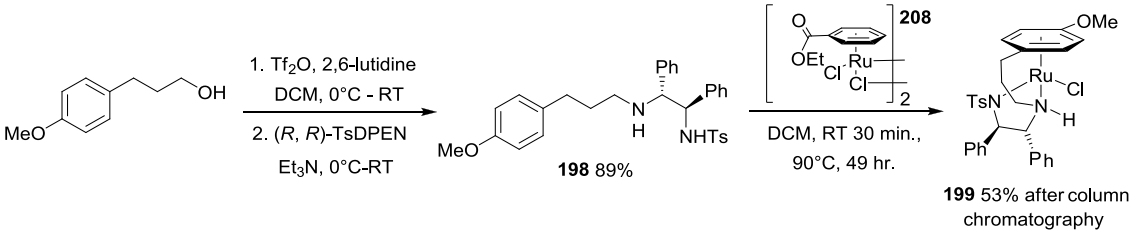
Scheme 77. Previous attempted synthesis of complex **97** by aryl substitution carried out by Dr. Silvia Gosiewska (unpublished result).

Under these conditions however, the desired complex was not formed. It was thought that the presence of Et_3N and a long reaction time at room temperature prior to heating may be encouraging formation of the unreactive complex **195** shown in Scheme 76, through deprotonation of the tosylated nitrogen which then co-ordinates to the ruthenium. Therefore, recent studies in our group carried out by Dr. Soni again looked at reacting ligand **196** and dimer **197** directly, however this time the Et_3N was omitted and the time spent at room temperature before heating was reduced to 30 min. as shown in Scheme 78.



Scheme 78. Further attempts at synthesis of complex **97** by aryl substitution (carried out by Dr. Soni).

On this occasion a small amount of product **97** was formed, although by mass spectrometry the major component of the reaction mixture was unreacted ligand **196** rather than complex **195**. The absence of base, along with the reduced time at room temperature shows inhibition of the formation of complex **195**, allowing aryl substitution to occur when the reaction was heated. In order to further improve conversion to the desired complex, the methoxybenzene derivative of the ligand was prepared for use in the aryl substitution reaction as it was felt that the electron rich nature of the aromatic ring may bias the system towards displacement of the electron poor ethylbenzoate ring and complexation of the methoxybenzene ring to ruthenium (Scheme 79). Conversion to complex was improved allowing isolation and characterisation of the obtained product.



Scheme 79. Synthesis of *p*-OMe substituted tethered catalyst **199** by aryl substitution (carried out by Dr. Soni).

Additional purification by further column chromatography and recrystallisation of the isolated complex was required to give product of sufficient purity for an X-ray crystallographic structure to be obtained (Figure 54) and initial ATH reactions to be carried out.

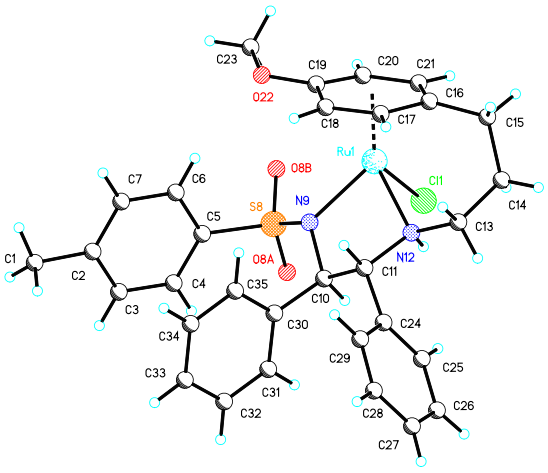


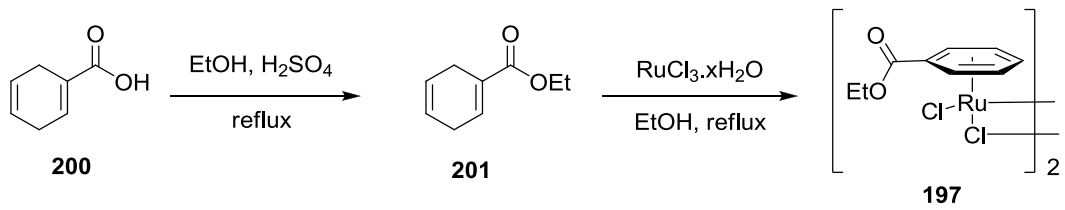
Figure 54. X-ray Crystal structure of catalyst **199** obtained by Dr. Soni.

The X-ray structure compares with that previously reported for complex **97**.[99] The complex is a single diastereomer with the tosyl group away from the chloride ligand and exhibiting π/π-stacking with the neighbouring phenyl group of TsDPEN. The methoxy arene substituent shows a degree of planarity with the aryl ring.

In an initial screening reaction, Dr. Soni found the catalyst **199** to give >99% conversion, 97.9% (*R*) for ATH of acetophenone using 1 mol% catalyst in formic acid triethylamine at 28°C. With the catalyst showing excellent activity for transfer

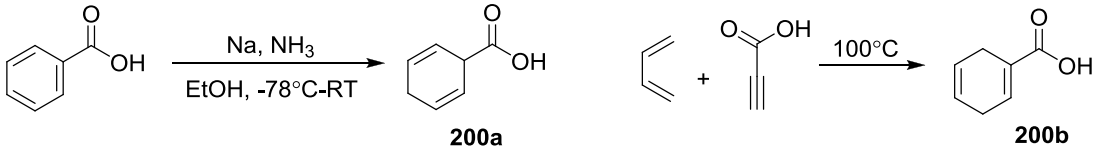
hydrogenation of ketones, it was felt necessary to further optimise its formation. Although the product was obtained under reaction conditions shown in Scheme 79, high levels of impurities were also formed observed by TLC analysis of the reaction product. To purify the product sufficiently for use in catalytic reactions, it was necessary to carry out column chromatography followed by multiple recrystallisations, a process which was detrimental to the yield of catalyst. It was thought that the long reaction time may be contributing to the high levels of impurities seen and that a higher temperature may improve this. Dr. Soni repeated the synthesis of **199** using chlorobenzene, with its higher boiling point, at 140°C. Formation of the complex with no ligand present by TLC was achieved after only 2 hours, however impurities were still present. Further optimisation of the method was required as well as investigations into the application of the methodology to the preparation of other tethered ruthenium complexes and their use in APH reactions. This work was carried out by myself.

My initial studies began with identifying the most appropriate synthesis for production of ethylbenzoate ruthenium(II)chloride dimer with initial formation of cyclohexa-1,4-dienecarboxylic acid, followed by formation of the ethyl ester. The ester then undergoes complexation with $RuCl_3$ to give the desired dimer product as shown in Scheme 80.



Scheme 80. Synthesis of electron poor Ethylbenzoate ruthenium(II)chloride dimer **197**.

There are two main methods reported for the production of cyclohexa-1, 4-dienecarboxylic acid: Birch reduction of benzoic acid[158] and cycloaddition of butadiene with propiolic acid[159]as shown in Scheme 81.

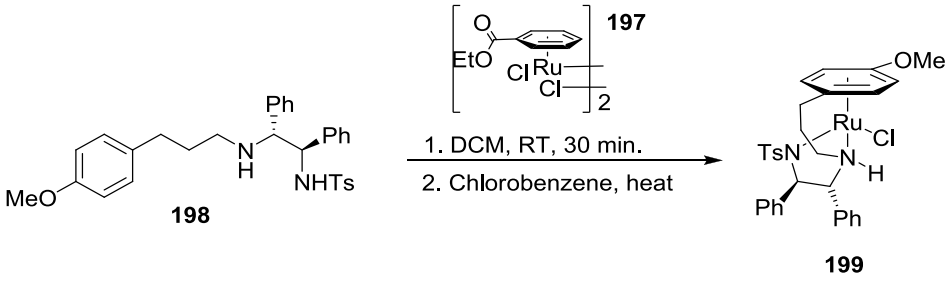


Scheme 81. Synthesis of cyclohexadienecarboxylic acids **200a** and **b**.

Birch reduction of benzoic acid proceeded well on a reasonable scale (8 g benzoic acid) giving 75% yield of product **200a**. However, along with the associated hazards of using sodium metal and ammonia, the reaction was found to be inconsistent with different isomers of diene product being formed on different occasions and ^{1}H NMR analysis showing evidence of decomposition and over reduction of the aromatic ring (see Experimental section of this thesis). Formation of **200b** by [4+2] cycloaddition of 1,3-butadiene and propiolic acid was found to be highly effective forming a single isomer of product in an 82% yield. Attempts to carry out the reaction using sulfone, which readily decomposes to 1,3-butadiene on heating, instead of 1,3-butadiene itself were unsuccessful giving only a 24% yield of the desired product.

2.6.1 Optimisation of aryl substitution methodology for the preparation of tethered ruthenium complexes.

With a robust synthesis of the dimer **197** in hand, work began to optimise the chlorobenzene method for preparation of catalyst **199**, as by TLC this method gave slightly cleaner product than that obtained from DCM at 90°C, and also was a significantly shorter method. Firstly different reaction temperatures were investigated (Scheme 82).



Scheme 82. Synthesis of *p*-OMe substituted tethered ruthenium catalyst **210** by aryl substitution.

The reaction was carried out at 90, 120 and 140°C in chlorobenzene for 2 hours after the initial 30 min. in DCM at room temperature. The reaction solutions were then analysed by TLC and mass spectrometry and the results are described in Figure 55.

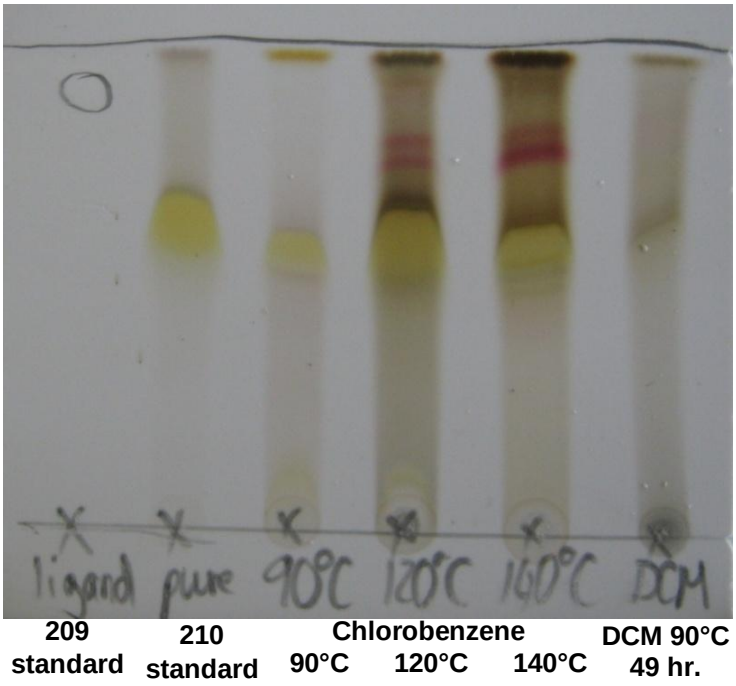


Figure 55. TLC analysis of complex **199** formation at different temperatures.

For comparison, the 49 hr., 90°C, DCM reaction was also carried out and analysed by TLC along with a sample of the purified catalyst. After 2 hours ligand **209**, seen by UV light, was present in the 90°C reaction, however none was visible in the 120 or 140°C reaction. Notably the reaction at 90°C gave significantly cleaner reaction product by TLC than the reactions carried out at higher temperatures. In addition,

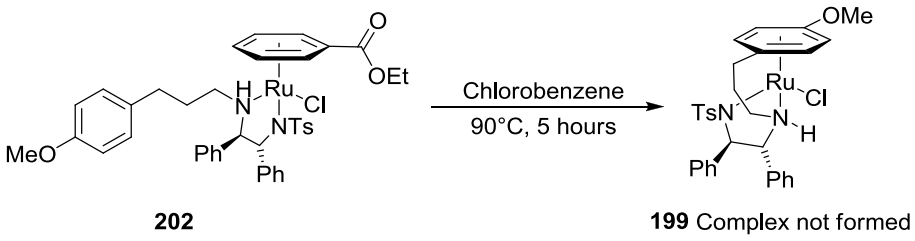
significantly more of the desired complex **199** seemed to be visible by TLC in the chlorobenzene reactions than in the DCM reaction. Mass spectrometry confirmed the presence of the desired complex in all reactions with a signal at *m/z* 615.1 $[M+H-Cl]^+$. In order to confirm the most appropriate temperature and reaction time for complex formation, further reactions were carried out at 75, 90 and 100°C. At 100°C the reaction was found to be complete with no ligand visible by UV after 3 hours, at 90°C, 5 hours was required for consumption of the ligand by TLC, however at 75°C ligand was still present by TLC after 5 hours. TLC showed more impurities present at 100°C than at 75 or 90°C and thus 90°C was deemed to be the most appropriate temperature for the reaction giving a good compromise between purity of the product obtained and reaction time.

Further investigations were conducted using different solvents for the reaction including chloroform, water, THF, ^{i}PrOH, MeCN and xylene at 90°C. After 2 hours, TLC and mass spectrometry showed the desired complex to only form in xylene, however there were many impurities present thus, chlorobenzene at 90°C was deemed the most appropriate conditions for preparation of the methoxy substituted catalyst **199**.

2.6.2 Mechanistic insights into the formation of ruthenium complexes by aryl substitution.

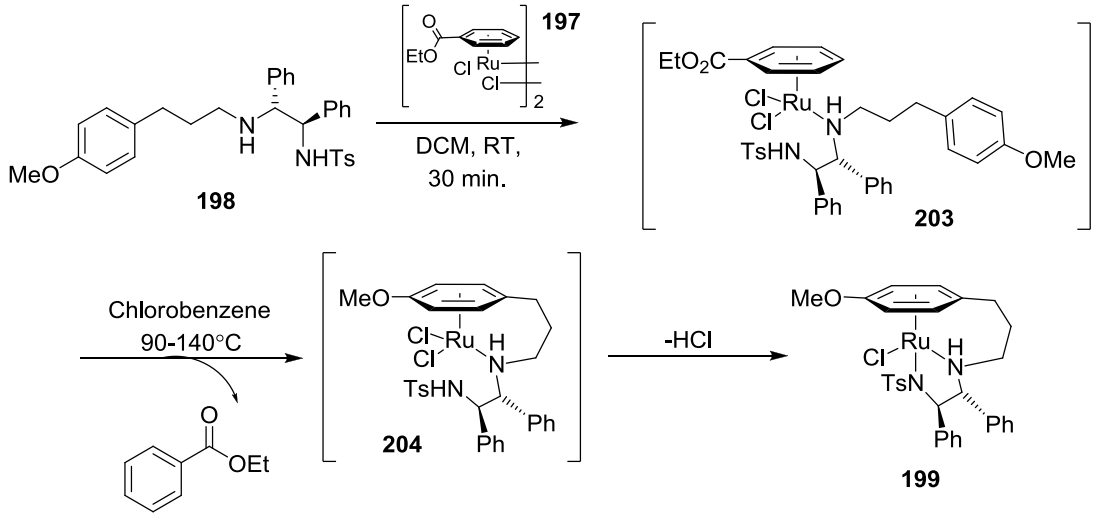
With an optimised synthesis of OMe-substituted tethered catalyst **199** *via* aryl substitution in hand, further work was carried out to understand the mechanism of formation for the catalyst. It is known from previous studies that the preformed, diamine co-ordinated complex **195** does not undergo aryl substitution to the desired complex. This was also the case with **202** and its application to the synthesis of **199**

by aryl substitution as shown in Scheme 83. Reaction of **202** in chlorobenzene at 90°C showed no evidence of formation of **199** by mass spectrometry after 5 hours.



Scheme 83. Attempted preparation of tethered catalyst **199** from **202.**

Dr Soni had also found that the absence of base is important for the aryl substitution to occur (Schemes 77 and 78). It was therefore possible to propose a mechanism for the formation of tethered catalysts *via* aryl substitution (Scheme 84).



Scheme 84. Proposed mechanism for complexation by aryl substitution.

It is thought that the initial stirring in DCM at room temperature in the absence of base allows formation of a coordinative bond between the amino nitrogen of the ligand and ruthenium to form complex **203**. Upon heating the aryl substitution takes place giving intermediate **204**, prior to loss of HCl allowing formation of the Ru-NTs bond to give complex **199**. The proposed intermediate **203** is analogous to the *in*

situ formed complexes reported by Sadler[156] and Ikariya[157] which are known to undergo aryl substitution for complexation with ruthenium.

An NMR study was carried out whereby the ligand and dimer were combined with $CDCl_3$ in an NMR tube and a ^1H NMR spectrum obtained at various time points. The spectra obtained were compared with each other and also with the ^1H NMR spectra of standards of the ligand **198**, dimer **197**, tethered complex **199**, unreactive complex **202** and also a sample of the complexation reaction taken after 30 min stirring in DCM at RT of dimer **197** and ligand **198**. The ^1HNMR spectra are shown in Figure 56.

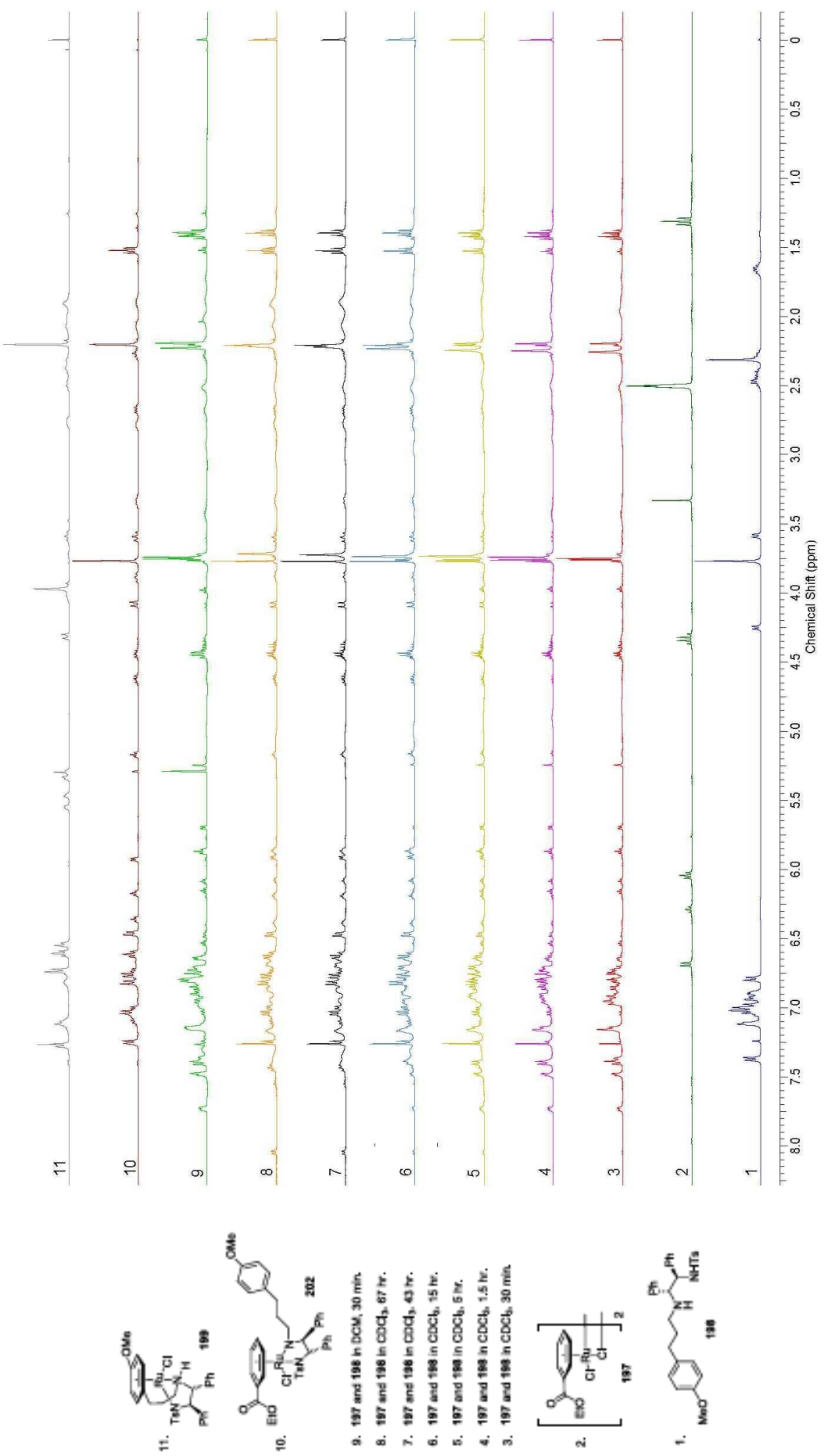


Figure 56. ^{1}H NMR spectra showing formation of complex *p*-OMe-**206** and **210** over time.

The NMR spectra show rapid consumption of dimer **197** and formation of two species upon the mixing of the ligand and dimer in $CDCl_3$ at room temperature (spectra 3-9). The formation of the two species is seen most easily by the appearance of two peaks at 1.4 and 1.5 ppm in spectra 3-9. These peaks relate to the CH_3 group in the ethyl ester of species related to dimer **197**. Comparison to spectrum 10 shows the peak at 1.5 ppm is due to formation of complex **202**. Spectra 3-8 show that initially the amount of complex **202** present is minimal with the species exhibiting a peak at 1.4 ppm present in a greater amount. It is thought that the species generating the peak at 1.4 ppm is intermediate **203** (Scheme 84). In spectra 3-5 there is evidence of another species under the 1.4 ppm peak, by spectra 7 and 8 the peak has resolved to a clean triplet assumed to be the CH_3 group in the ethyl ester of intermediate **203**.

Figure 56, spectra 3-8 show that over time, the ratio of complex **202** and the presumed intermediate **203** increases, reaching 1:1 in 15 hours, showing increased formation of complex **202** which is known to not undergo aryl substitution. Spectrum 9 shows the ^1H NMR spectrum obtained after 30 min. of stirring the ligand **198** and dimer **197** in DCM at room temperature as in a typical preparation of complex **199**. The spectrum achieved compares well with spectrum 3 and 4 showing minimal formation of complex **202** with a larger amount of **203** present. This confirms the importance of a short time frame for the initial stirring of the ligand and dimer at room temperature in a complexation reaction to prevent a large amount of the unreactive complex **202** forming and allow sufficient reactive material to undergo the aryl substitution process. In the case of initial reactions carried out by Dr. Gosiewska (Scheme 77) it is likely that in the initial 2 hour stirring period at room temperature, a large quantity of the dimer and ligand initially added to the

reaction had already formed the unreactive complex **202** leaving less available to form the desired tethered complex. Also the use of triethylamine in this earlier reaction is likely to have encouraged complex **202** to form more readily through deprotonation of the tosylated nitrogen and subsequent co-ordination of the nitrogen to ruthenium.

Within all aryl substitution reactions carried out for preparation of the OMe substituted tethered catalyst **199**, analysis of the reaction product by mass spectrometry shows the presence of ligand **198** (*m/z* 515 $[M+H]^+$) as well as the desired complex **199** (*m/z* 615 $[M+H-Cl]^+$), even when TLC showed no ligand to be present. An example mass spectrum is shown in Figure 57.

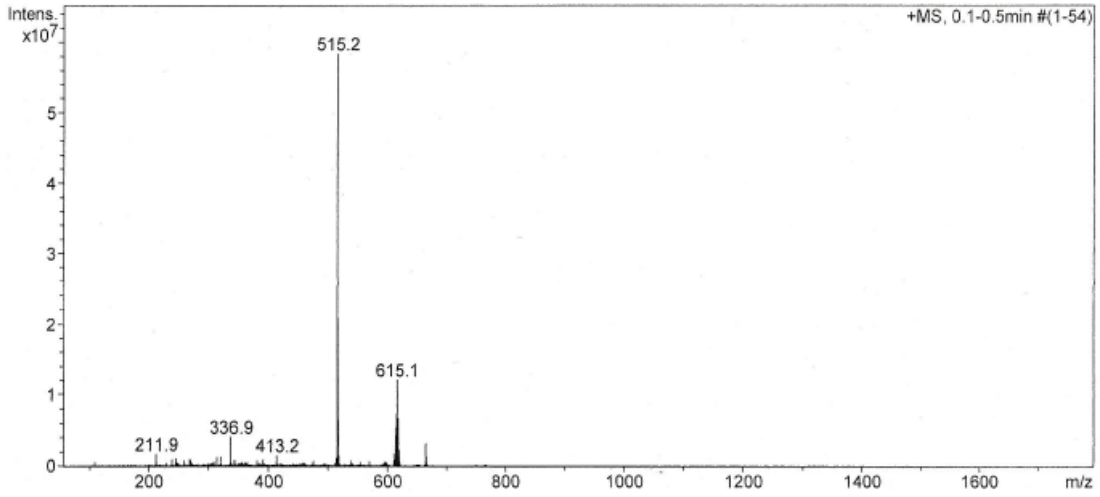


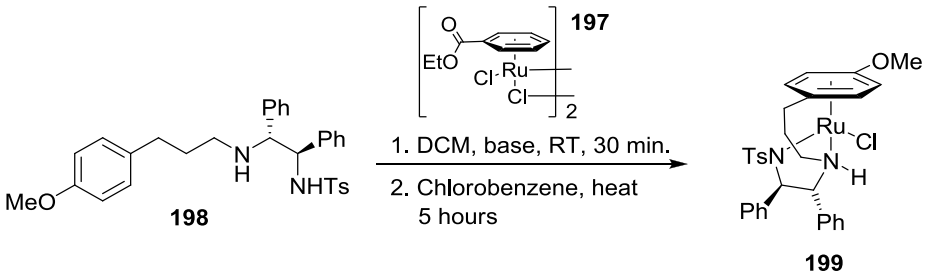
Figure 57. Mass Spectrum of reaction product for formation of complex **199**.

It is thought that HCl generated by reaction of the ruthenium dimer **197** with the ligand **198** allows formation of the HCl salt of unreacted ligand. The HCl salt (M) of the ligand would give the same *m/z* 515 $[M-Cl]^+$ signal in the mass spectrum as the free ligand (*m/z* 515 $[M+H^+]$), but would not be observed at the expected Rf of the ligand by TLC. Thus TLC analysis would suggest complete consumption of the

ligand whilst mass spectrometry would indicate the presence of ligand in its HCl salt form. In a separate experiment, (carried out by Dr. Soni), it was found that the HCl salt of the ligand does not undergo aryl substitution to form the desired complex **199** and its presence is hence detrimental to the yield of the desired complex.

The use of triethylamine is known to be detrimental to the reaction, promoting formation of complex **202** (Scheme 77). Use of a weaker base however, may help prevent formation of the HCl salt of the ligand but not be strong enough to deprotonate the tosylated nitrogen leading to formation of complex **202**. A base screen was carried out with addition of a range of weak inorganic bases to the formation of methoxy substituted tethered complex **199** by aryl substitution. NaOH was also screened as a strong base for comparison. The reactions were analysed by mass spectrometry after 5 hours and ratios of ligand:complex recorded (Table 31).

Table 31. Addition of inorganic base to the aryl substitution reaction.



Base	None	$Ca(OH)_2$	$Ca(OH)_2$	$NaHCO_3$	K_2CO_3	$Mg(OH)_2$	NaOH
Equiv. wrt. 209	-	1	2	1	1	1	1
Ratio 209:210	4:1	3:2	3:1	4:1	4:1	6:1	3:1
Complex 202 formed	No	No	No	No	No	No	Yes

Ratio refers to relative heights of peaks in mass spectrum.

Although mass spectrometry analysis is not quantitative and in this case the ligand is known to give a stronger signal than the complex, the spectra obtained provide a qualitative measure of amounts of ligand and complex present. Indeed multiple preparations of complex **199** using the procedure detailed in Scheme 82 at 90°C each achieve a consistent ratio of 4:1 ligand:complex after 5 hours at 90°C. It was also possible to observe whether complex **202** formed under each set of conditions with presence of a signal at *m/z* 765.2 for $[M+H-Cl]^+$. The results show that the use of 1 equivalent of $Ca(OH)_2$ was the most beneficial to the reaction, allowing increased formation of the desired complex with a ligand:complex ratio of 3:2 (Figure 58) which is an improvement on the ratio achieved in the absence of base.

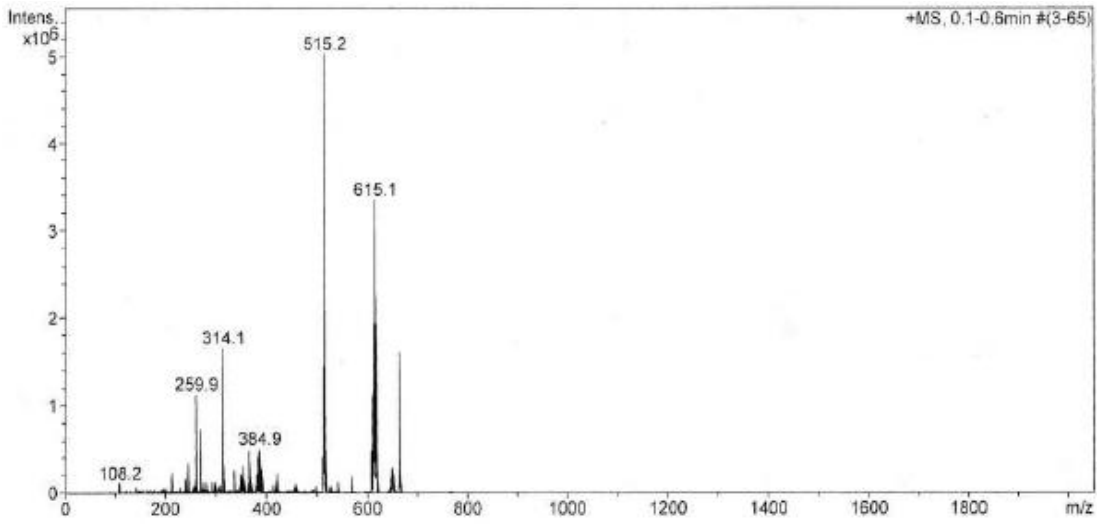


Figure 58. Mass spectrum for addition of 1 equiv. $Ca(OH)_2$ to formation of **199** by aryl substitution.

The use of two equivalents of $Ca(OH)_2$ relative to ligand however gave a ratio of only 3:1, an improvement upon the absence of base, but a reduction in conversion compared to the use of 1 equivalent. It is likely that the extra equivalent of $Ca(OH)_2$ is encouraging formation of the unreactive **202** complex or formation of the calcium salt of the ligand. The addition of $NaHCO_3$, K_2CO_3 and $Mg(OH)_2$ was either

detrimental to the amount of complex present or had no effect, possibly these bases were too strong allowing formation of complex **202**, too weak to prevent formation of the salt of the ligand or were allowing formation of metal salts of the ligand. The use of NaOH, a strong base, showed some improvement to the conversion to complex, however significant levels of complex **202** were formed with a large signal at *m/z* 765.2 $[M+H-Cl]^+$ (Figure 59).

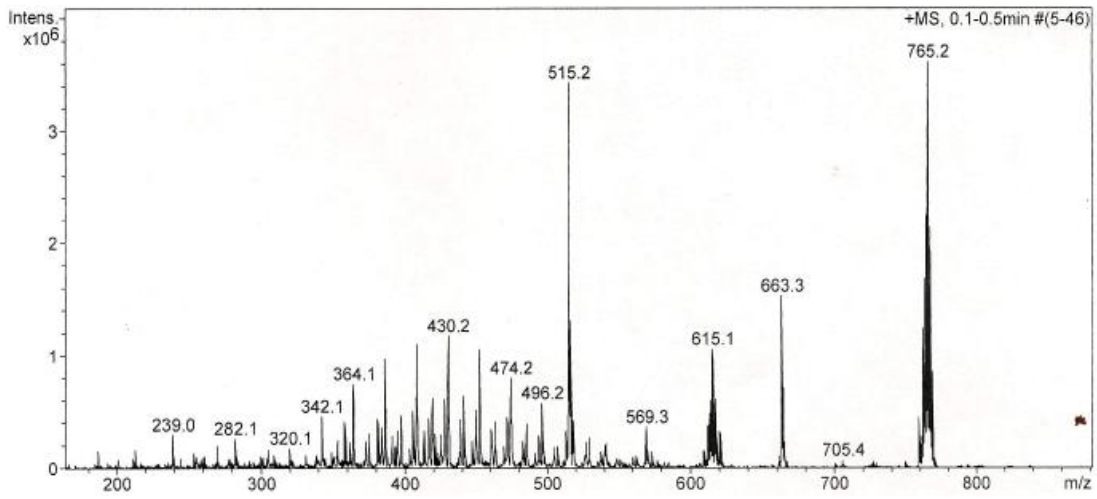


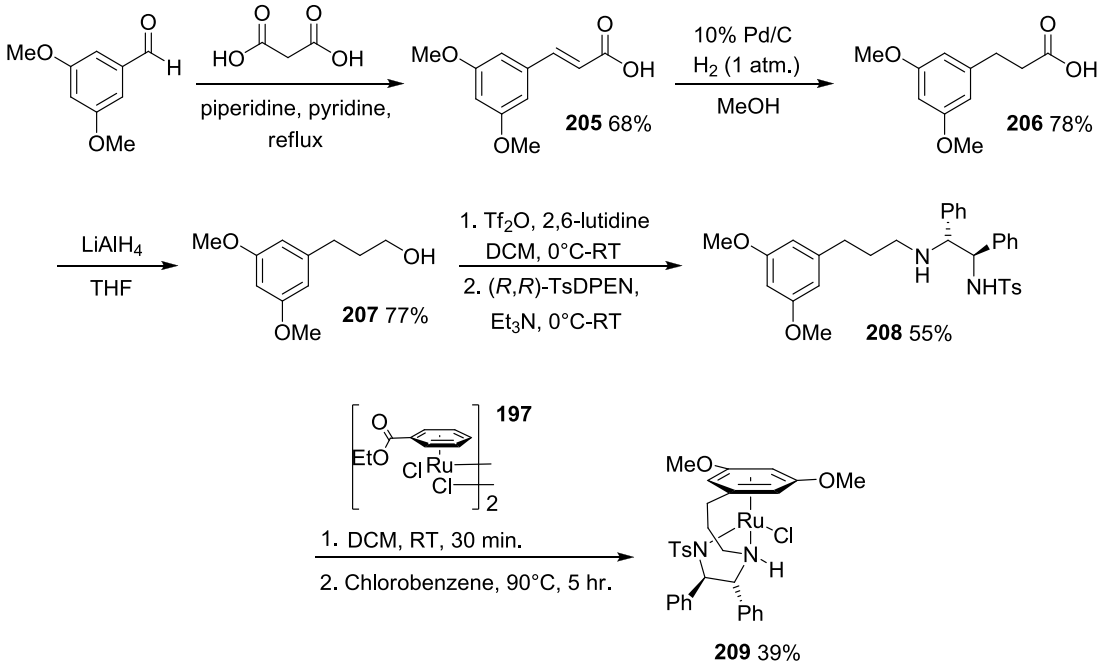
Figure 59. Mass spectrum for addition of NaOH to formation of **199** by aryl substitution.

2.6.3 Application of aryl substitution methodology to the preparation of novel tethered ruthenium complexes and their application to the hydrogenation of ketones.

Through optimisation of the synthesis and mechanistic studies, the preparation of *p*-methoxy substituted complex **199** was now well understood. The preparation of further methoxy substituted catalysts by aryl substitution methodology was investigated with the catalysts prepared being applied to the APH of ketones.

Initially the *meta*-substituted 3,5-dimethoxy catalyst **209** shown in scheme 85 was prepared. In the case of this catalyst, unlike with the *p*-methoxy catalyst, the required

alcohol for the TsDPEN coupling reaction is not commercially available and so it was synthesised in three steps prior to complex formation as shown in Scheme 85.



Scheme 85. Preparation of 3,5-dimethoxy substituted catalyst **209** by aryl substitution.

Purification of complex **209** by column chromatography and recrystallisation gave material of sufficient purity for use in hydrogenation reactions and also for an X-ray crystallographic structure to be obtained (Figure 60).

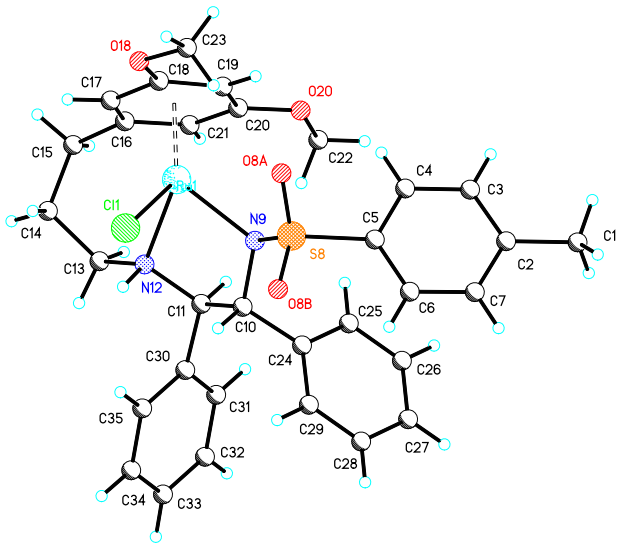
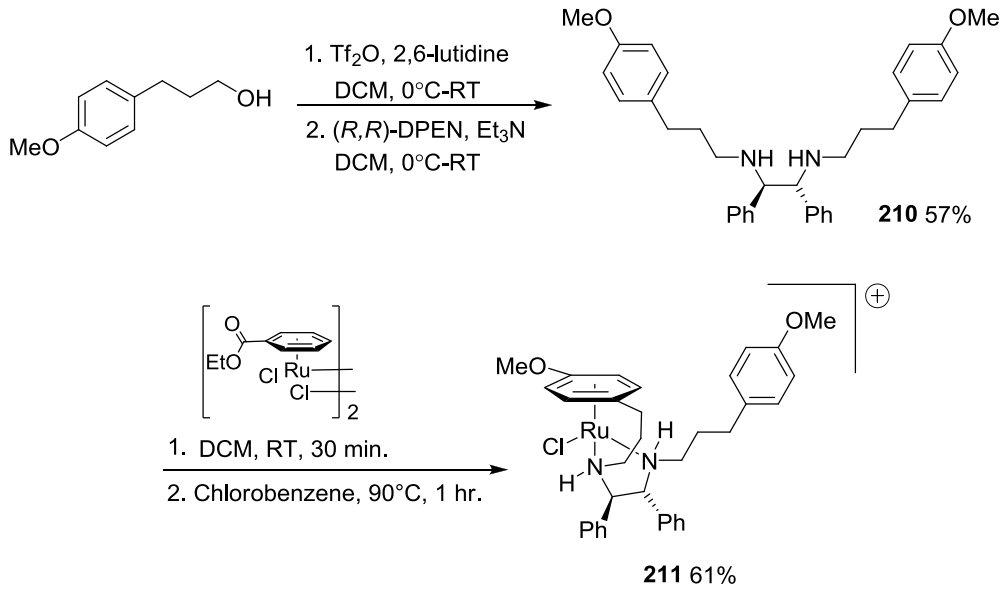


Figure 60. X-ray crystallographic structure of catalyst **209**.

The X-ray structure of **209** is consistent with that reported for complex **97**.[99] The X-ray structure shows **209** to have formed as a single diastereomer with π/π-stacking between the tosyl group and neighbouring phenyl ring on TsDPEN. The tosyl group is also shown to be oriented away from the chloride ligand. The methoxy arene substituent groups show a degree of planarity with the aryl ring.

Further studies focused on the preparation of an alternative tethered *p*-methoxy substituted catalyst derived from a DPEN-based rather than TsDPEN-based ligand to establish the effect of the absence of a sulfonamide substituted diamine on the aryl substitution process. It has been shown that with an alkylated amine, such as the alkylated TsDPEN ligand used in preparation of the conventional tethered catalyst **97**, the NH functionality is retained upon complexation to the ruthenium, forming a coordinative HN-Ru bond.[74] The tosylated nitrogen however loses the proton upon complexation to ruthenium forming a covalent N-Ru bond.[74]

The reaction of (*R*,*R*)-DPEN with excess 3-(4'-methoxyphenyl)-propan-1-ol *via* the triflate gave di-substituted ligand **210** which readily underwent complexation by aryl substitution in only 1 hour at 90°C in chlorobenzene to give **211** (Scheme 86).



Scheme 86. Synthesis of cationic methoxy substituted tethered catalyst **211**.

Complex **211** was obtained as a cationic complex. As expected, in the absence of an electron withdrawing sulfonamide group on the diamine the N-H bond is less acidic and the proton is retained by the nitrogen during complexation. In complex **211** the ruthenium is in its 2+ oxidation state and is thus bound to both nitrogens *via* coordinative bonds leaving the chloride as the only negative ligand in the complex giving an overall positive charge for the complex.

Mass spectrometry analysis of the reaction after 1 hour at 90°C in chlorobenzene shows retention of both NH functionalities and the chloride by the complex with a $[M^+ + H]$ peak at *m*/*z* 645.2 and no ligand present at *m*/*z* 509.3 $[M^+ + H]$ (Figure 61).

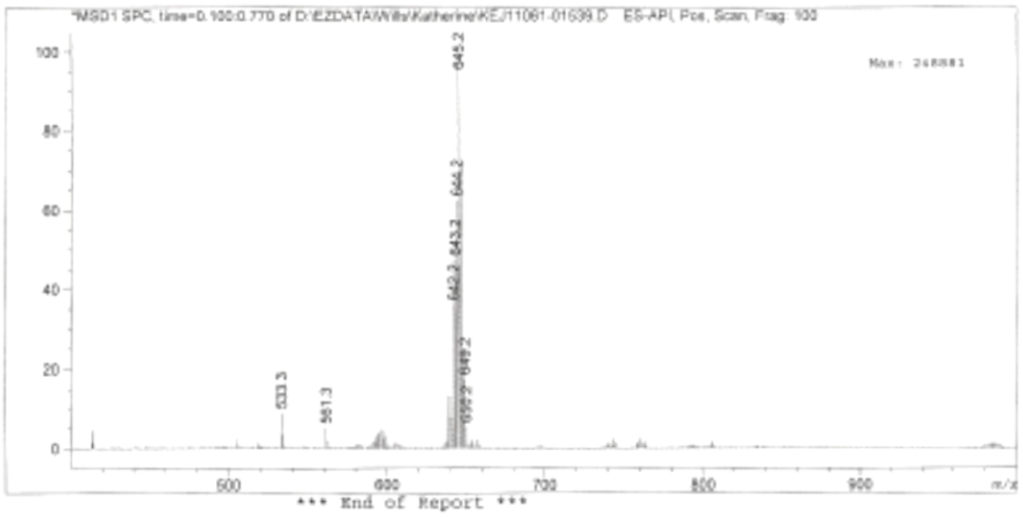
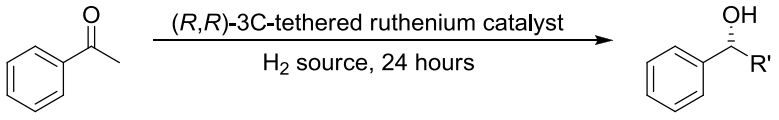


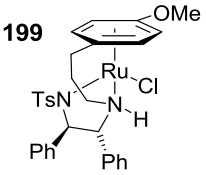
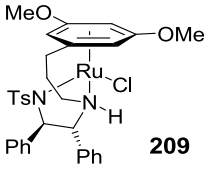
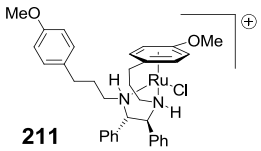
Figure 61. Mass spectrum of formation of complex **211**.

Purification of complex **211** was achieved by column chromatography although silica gel was required rather than florisil which was used for the purification of **199** and **209** as complex **211** was found to decompose on florisil. The complex was isolated as an orange/yellow solid with a silica column, but with use of florisil the orange/yellow band for complex **211** rapidly become red in colour as it moved through the column. Mass spectrometric analysis of the obtained red product showed no evidence of the complex.

With three methoxy substituted tethered catalysts in hand, (**199**, **209** and **211**), each was applied to the APH of acetophenone (Table 32).

Table 32. Application of complexes **199**, **209** and **211** to APH and ATH of acetophenone.



Conditions	**199** 		**209** 		**211** 	
	Conv.[a] (%)	Ee.[a] (%)	Conv.[a] (%)	Ee.[a] (%)	Conv.[a] (%)	Ee.[a] (%)
H_2 (30 atm.), MeOH, 60°C, S/C 500/1, 16 hours	99.9[b]	94.0 (*R*)[b]	99.8[b]	83.5 (*R*)[b]	0.4	ND
H_2 (30 atm.), MeOH, 60°C, S/C 100/1, 16 hours	Not attempted		Not attempted		2	17% (*R*)
Formic acid/Et_3N 60°C, S/C 1000/1, 4 hours	99.8	96.3 (*R*)	99.9	88.8 (*R*)	Not attempted	
Formic acid/Et_3N 60°C, S/C 100/1, 24 hours	Not attempted		Not attempted		1.6	13% (*R*)

[a]Determined by GC analysis. [b] Reactions carried out by Dr. Soni.

Complexes **199** and **209** were found to show high activity for ATH by Dr. Soni and also for APH by myself with both complexes achieving excellent conversions and high enantioselectivities. The enantioselectivity of complex **209** was found to be lower than that of **199** and it is thought that this may be due to the increased sterics of the arene ring reducing the ability of the ketone to co-ordinate in a favourable manner as shown below in Figure 62.

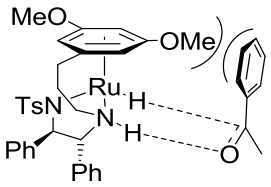


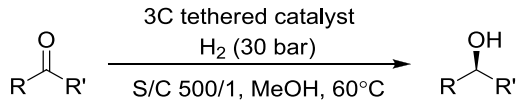
Figure 62. Model for the interaction of acetophenone with catalyst **209** showing the effect of steric hindrance on enantioselectivity.

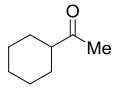
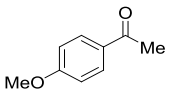
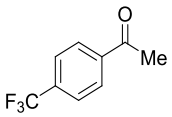
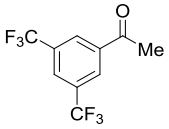
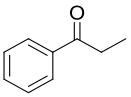
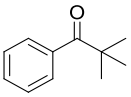
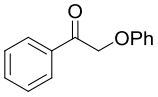
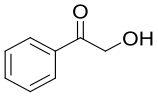
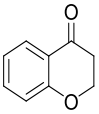
The cationic complex **211** was found to be inactive to hydrogenation both under ATH and APH conditions with high catalyst loadings and temperatures. As a cationic complex, it may be that substitution of the chloride ligand for a hydride to give the active catalytic species is not possible due to the strong retention of the chloride by the ruthenium. Indeed in mass spectrometry analysis (Figure 61) the chloride was not lost during the ionisation of the complex and it is known that for APH to occur the chloride must be lost through an ionisation process to allow the complex to interact with hydrogen.

Cationic half-sandwich ruthenium complexes are known to have biological applications, particularly in the area of cancer treatments. Indeed Sadler *et al.* have recently reported photoactivatable cationic pyridyl ruthenium(II) arene complexes to be active against cancer cell lines and also the ability of similar complexes to bind to DNA.[160] Work continues within our group to establish the scope for biological applications of complex **211** and complexes analogous to it.

With complexes **199** and **209** demonstrating high activity for APH of acetophenone, their application to the APH of a range of ketones was investigated and results are shown in Table 33.

,Table 33. Application of catalysts **199** and **209** to APH of a range of ketones.



Ketone	Time (hr.)	199		209	
		Conv.[a] (%)	E.e.[a] (%)	Conv.[a] (%)	E.e.[a] (%)
	48	99.3	37.1 (S)	40.0	81.4 (*S*)
	16	99.9	93.7 (R)	99.9	79.5 (R)
	16	98.2	92.4 (*R*)	99.2	73.5 (*R*)
	24	>99	81.8 (*R*)	>99.9	53.6 (*R*)
	16	69.6	84.3 (*R*)	18.8	72.8 (*R*)
	48	36.4	83.3 (*R*)	26.8	77.6 (*R*)
	24	99.6[b]	94.5[b] (*S*)	>99.9[b]	81.4[b] (*S*)
	24	99.7	90.7 (*S*)	94.2	87.8(*S*)
	48	95.0	97.7 (*R*)	71.7	95.2 (*R*)
	48	99.6	98.6 (R)	59.7	98.6 (R)
	24	97.6**[b]**	99.6[b] (*R*)	99.9[b]	>98.8[b] (*R*)

[a]Determined by GC analysis. [b]Determined by HPLC analysis.

In most cases the *p*-OMe substituted catalyst **199** performed equally to the unsubstituted catalyst **97** both in terms of conversion and ee. With more sterically demanding substrates such as cyclcohexylmethyl ketone and 2,2-dimethylpropiophenone however conversions and or ee.'s were lower than with the unsubstituted catalyst. This may be due to the increased steric hindrance of the aromatic ring of the complex disfavouring co-ordination of the complex to the ketone for hydrogen transfer as shown in Figure 63.

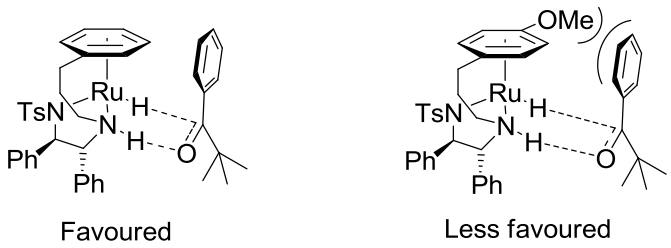


Figure 63. Favoured transition states for APH of acetophenone with catalyst **97** (left) and **199** (right).

With the 3,5-di-OMe substituted complex **209**, conversions and ee.'s were reduced compared to the unsubstituted complex **97** and *p*-OMe complex **199** in most cases. The main exception to this is with hydrogenation of cyclohexylmethyl ketone for which complex **209** gave a significantly higher ee. than complexes **97** and **199**. This is likely to be due to the increased steric effect of the aromatic ring on the complex generating a greater energy difference between transition states for formation of the possible enantiomers of product than the unsubstituted catalyst (Figure 64).

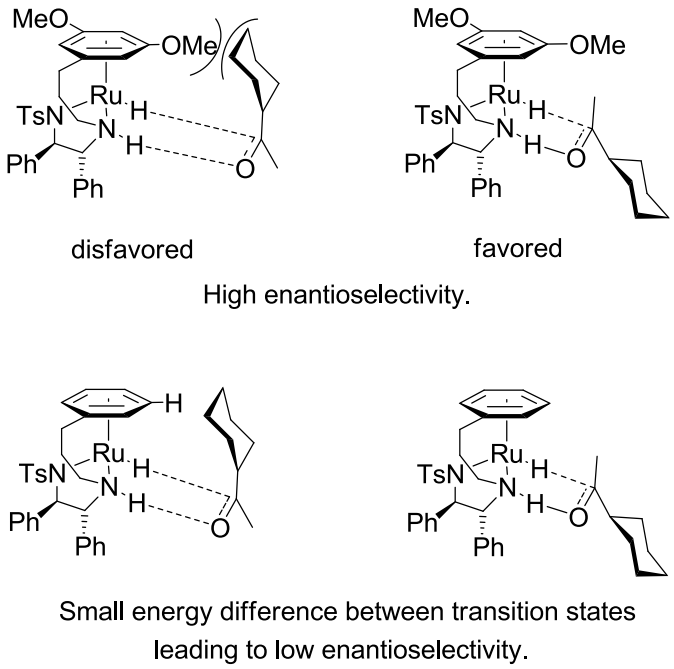
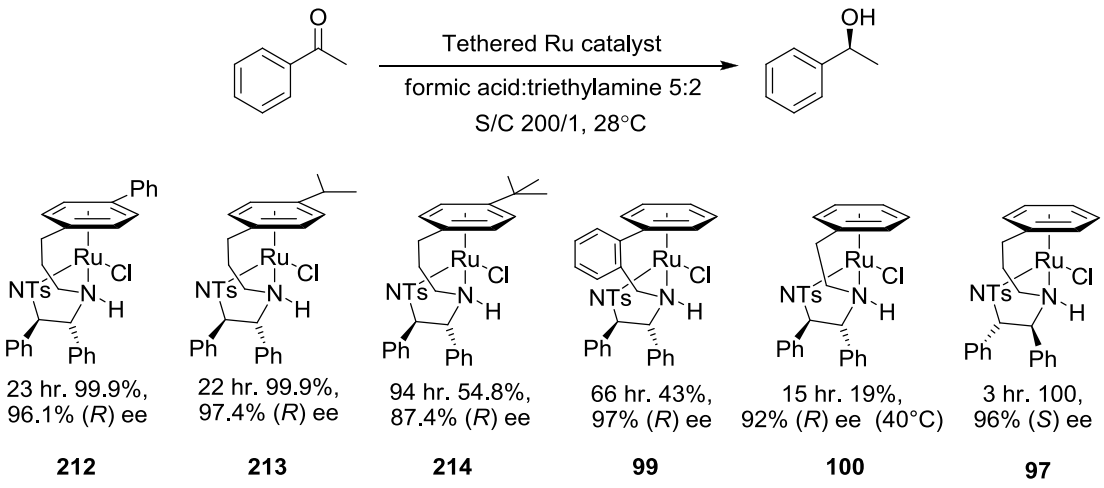


Figure 64. Transition states for APH of cyclohexylmethyl ketone with catalyst **209** (top) and **97**.

2.6.4 Attempted synthesis of further tethered ruthenium complexes by aryl substitution methodology.

In order to assess the scope of the aryl substitution method for the synthesis of tethered complexes, the synthesis of a range of further complexes was attempted.

Dr. Soni achieved the synthesis of the following complexes **212-214**, **99** and **100** using the developed aryl substitution methodology and applied them to the ATH of acetophenone as shown in Figure 65.

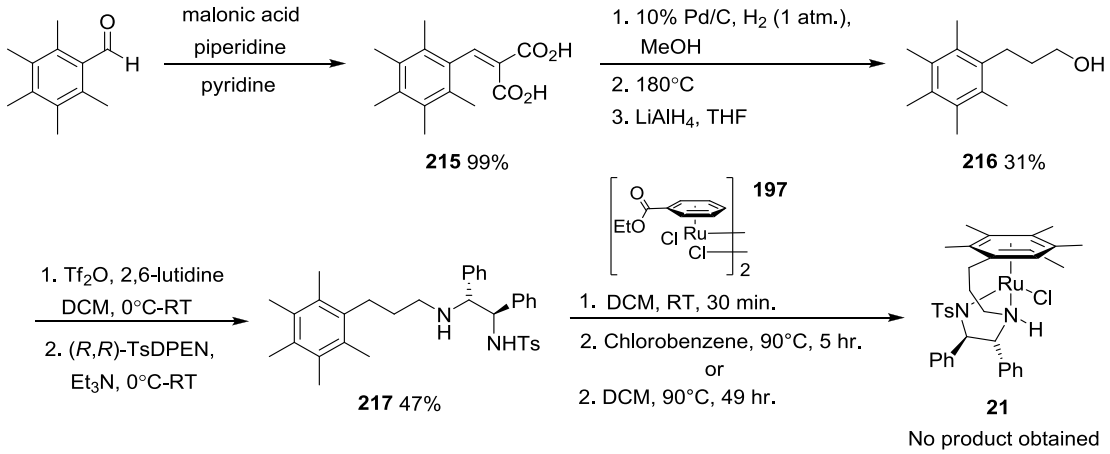


% refers to % conversion to phenyl ethanol and % ee. obtained.

Figure 65. Application of further catalysts prepared by aryl substitution to ATH of acetophenone.

Compounds **212-214** are novel, but were found to be less active to hydrogenation than the unsubstituted 3C tethered TsDPEN RuCl complex **97**.[99] Complexes **99** and **100** are known and are reported to be less active than complex **97**.[100-102]

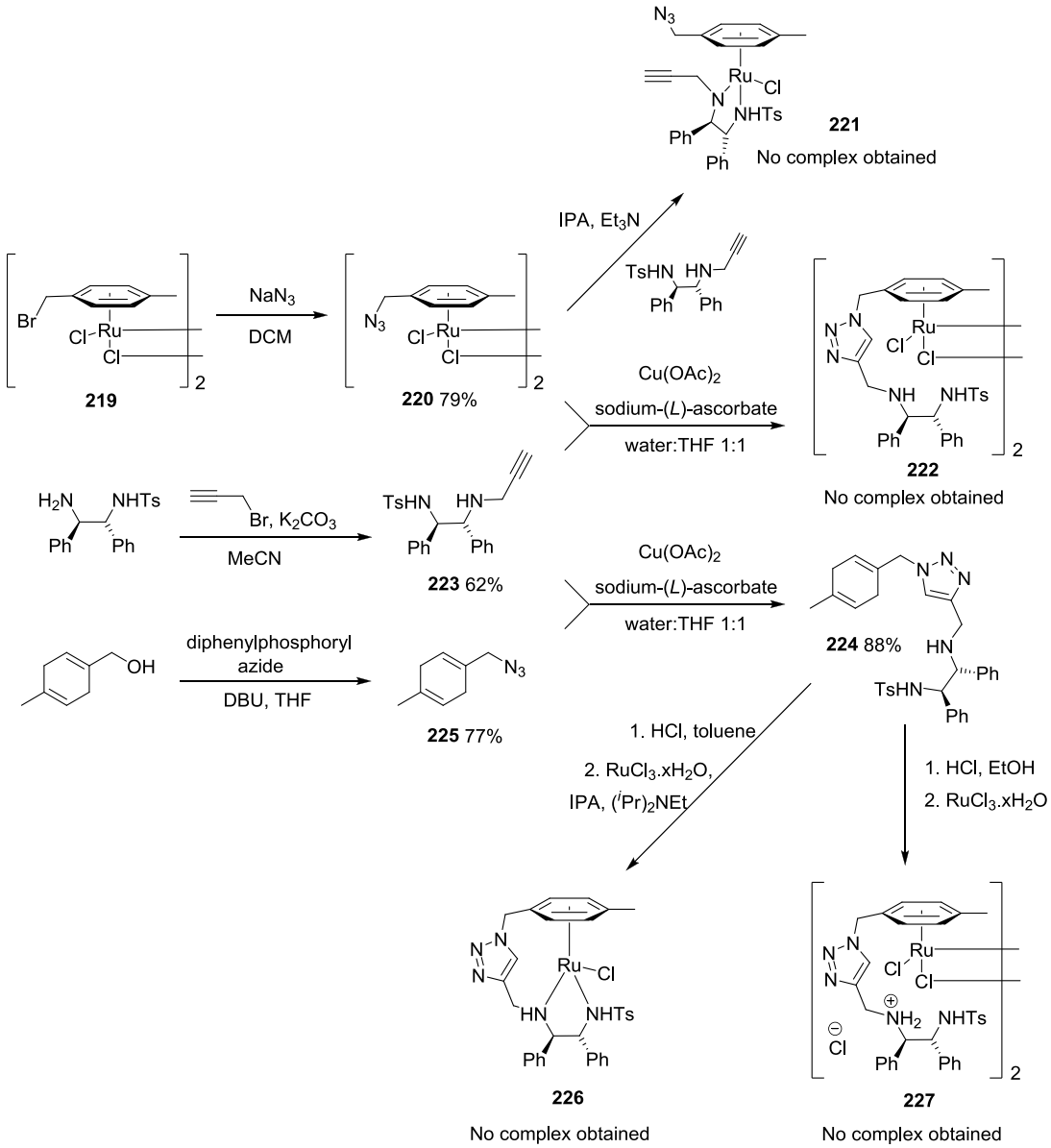
My own studies into the scope of the aryl substitution methodology are outlined below. Initially the preparation of the pentamethyl substituted 3C tethered complex was attempted, as previous attempts within our group to prepare similarly highly substituted tethered catalysts *via* the conventional synthesis akin to that in Scheme 20 were unsuccessful as formation of the required diene ligand was not achieved. With the aryl substitution process formation of a diene is not necessary, hence this alternative synthesis of the pentamethyl substituted complex was attempted as shown in Scheme 87



Scheme 87. Attempted synthesis of pentamethyl substituted tethered catalyst **218** by aryl substitution.

The desired ligand **217** was prepared, however attempts to prepare the desired complex **218** *via* an aryl substitution process were unsuccessful, both using the original 90°C 49 hr. DCM method and also the shorter process using chlorobenzene. Mass spectrometry showed only ligand and no evidence of the desired complex or pentamethyl derivative of complex **195** was seen. Presumably the high degree of substitution on the aryl ring is detrimental to the aryl substitution process.

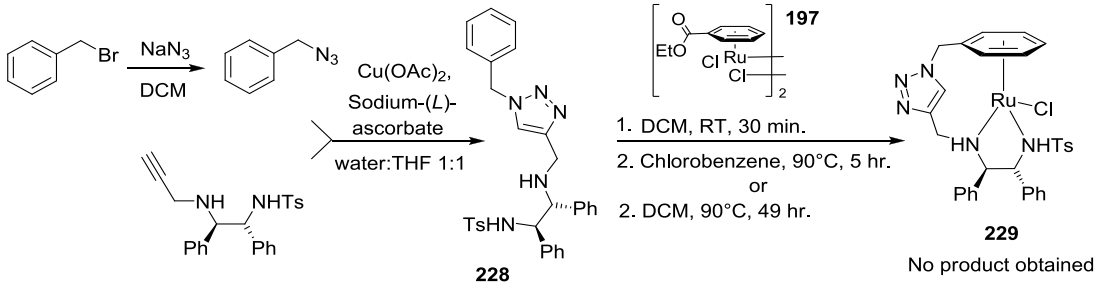
We were also interested in the scope for preparation of complexes containing alternative tethering motifs *via* the aryl substitution process. Previously I had attempted the synthesis of a complex containing a triazole tether using variations of the conventional syntheses of tethered complexes from dienes and ruthenium dimers, however no product was obtained (Scheme 88).



Scheme 88. Attempted syntheses of triazole tethered catalysts using conventional complexation procedures.

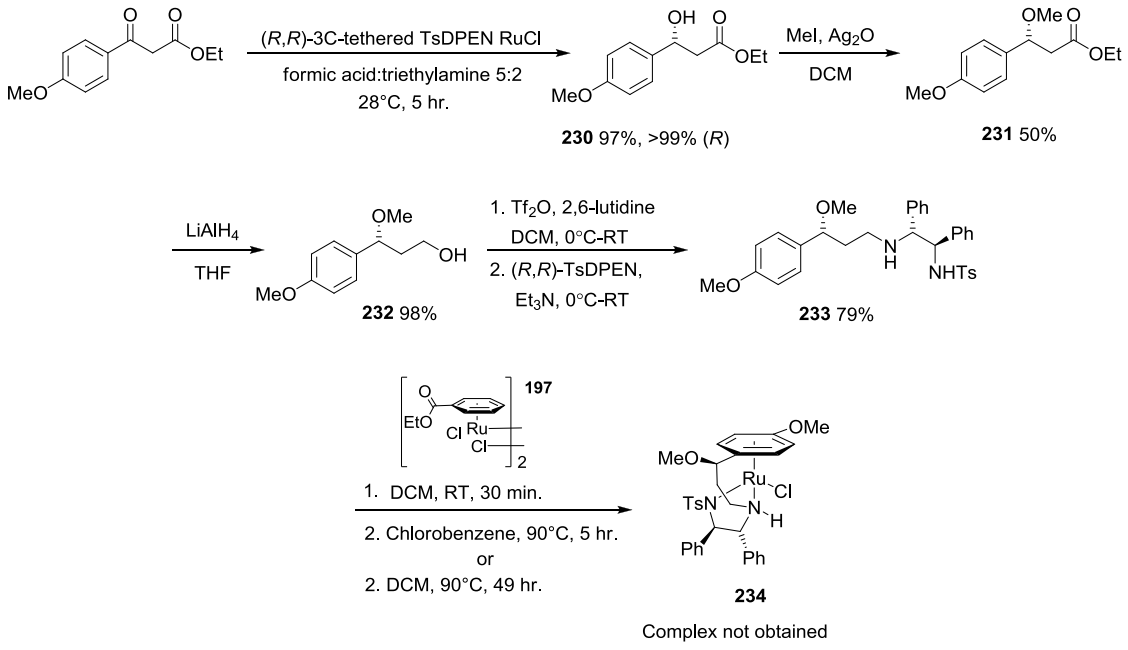
The prepared triazole containing diene ligand **224** was found not to undergo complexation with $RuCl_3.xH_2O$ to form dimer **227** or monomer **226** through *in situ* dimer formation. Preparation of an azide-containing Ru dimer **220** was also found not to undergo complexation with *N*-alkyne substituted TsDPEN **223** to form a Noyori type complex **221** which could then have undergone Click coupling to form the desired complex **226**. We therefore applied the optimised aryl substitution

methodology to the synthesis of the related complex **229** to see if it could be formed in this way, however again the desired complex was not obtained (Scheme 89).



Scheme 89. Attempted synthesis of triazole tethered catalyst **229** by aryl substitution.

Also of interest to us was the incorporation of substituent groups on the tether of the complex to create an additional chiral centre within the complex as shown in Scheme 90, however again, the desired complex **234** was not formed.



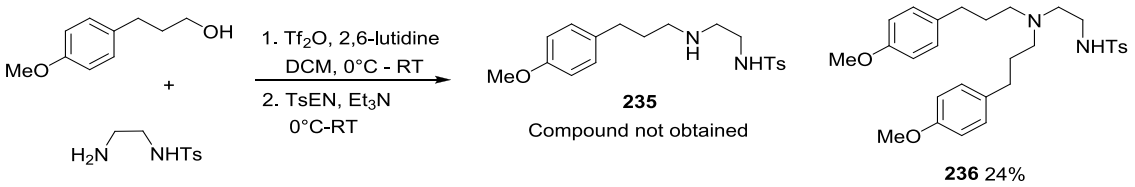
Scheme 90. Attempted synthesis of OMe substituted tethered catalyst **234** by aryl substitution.

In both cases with an alternative tether (complexes **229** and **234**), the aryl substitution methodology was unable to generate the desired complex. It is thought that the geometry of the tether may be important for the substitution to occur.

Previous studies published within our group have found differences in the geometry between the 3C and 4C tethered catalyst.[102] Both complexes exhibit similar geometry around the ruthenium centre, however with the 4C tethered catalyst **101**, the tether is oriented towards the chlorine increasing the sterics. With the 3C tethered catalyst **97** the tether is oriented away from the chlorine reducing the steric constraints. The increased sterics within 4C complex **101** may not be compatible with its formation *via* aryl substitution. This would also suggest why preparation of the OMe and triazole containing tethered complexes was also unsuccessful *via* the aryl substitution process, with both tethering motifs giving an increase in steric hindrance.

2.6.5 Preparation of achiral tethered ruthenium catalysts by aryl substitution.

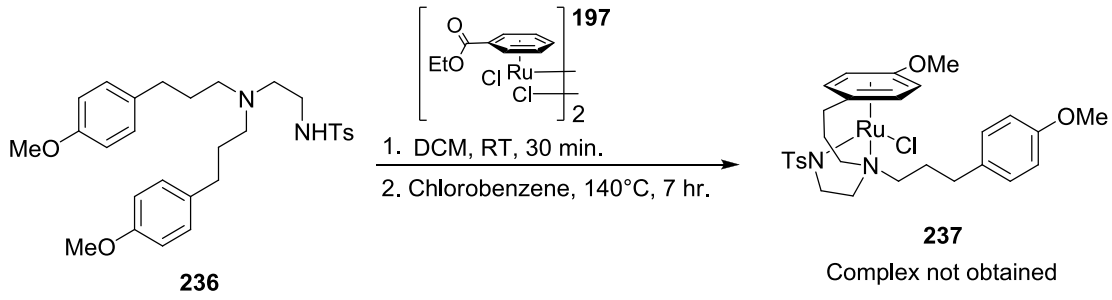
Also of interest to us was the use of the aryl substitution methodology to make an achiral tethered catalyst. Initial attempts to form the *p*-OMe-substituted achiral tethered ligand **235** from *N*-tosylethylenediamine were unsuccessful with double alkylation taking place to give **236** as shown in Scheme 91.



Scheme 91. Attempted synthesis of *p*-OMe substituted achiral tosylated diamine ligand **235**.

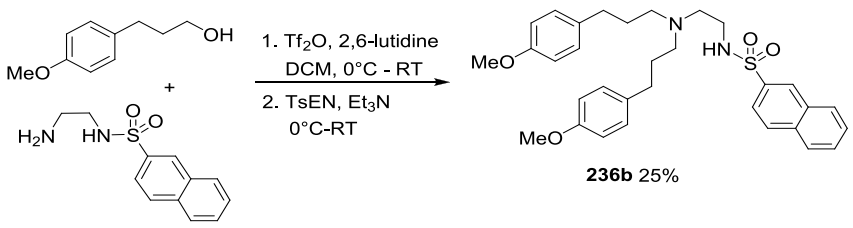
Even with the use of reduced equivalents of 3-(4-methoxybenzene)propanol, only the di-alkylated diamine and un-alkylated diamine were obtained. The lack of aromatic substituent groups on the ethyl chain enhances the nucleophilicity of the nitrogen towards reaction with the *in situ* formed triflate of the starting alcohol. It is also likely that once the first alkylation has taken place, the nitrogen becomes more

active towards an additional alkylation, this would explain why even with 1:1 triflate:diamine the product obtained is a 1:1 mixture of unalkylated diamine **235** and di-alkylated diamine **236**; the mono alkylated diamine being more reactive towards a second alkylation than the unalkylated diamine to initial alkylation. Subsequent reactions found the di-alkylated diamine **236** ligand not to undergo the aryl substitution to give the desired tethered complex **237** as shown in Scheme 92.



Scheme 92. Attempted synthesis of achiral complex **237** by aryl substitution.

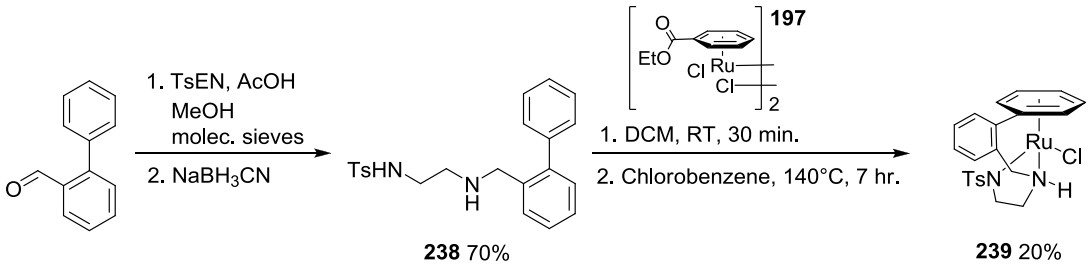
The preparation of *N*-((naphthalene-2-ylsulfonyl)methyl)ethane-1,2-diamine was also attempted (Scheme 93) as it was thought that the presence of a large aromatic group and hence increased steric hindrance may improve isolation of the ligand and complexes derived from it. However, again only di-alkylated product **236b** was obtained.



Scheme 93. Attempted synthesis of N-((napthalene-2-ylsulfonyl)methyl)ethane-1,2-diamine.

Further attempts to prepare an achiral ligand continued with preparation of *N*-(2-(biphenyl-2-yl)methylamino)ethyl)-4-methylbenzenesulfonamide **238** as shown below. A reductive amination synthesis would give only the mono-alkylated product

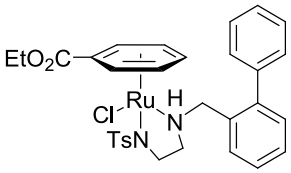
and also the additional aromatic ring as part of the tether should help with isolation of the ligand and complex by reducing the polarity of the compound. The asymmetric 3C tethered catalyst containing an aromatic ring within the tether (**99**) has previously been reported by our group as an active catalyst for ATH of ketones.[100] It was therefore felt that the achiral derivative **239** would also be a good candidate as a hydrogenation catalyst (Scheme 94).



238 70% **239** 20%

Scheme 94. Synthesis of achiral catalyst **239** by aryl substitution.

An increased temperature of 140°C was required to allow complex formation. Initial attempts at 90°C showed only complex **240** (Figure 66) by mass spectrometry.



240

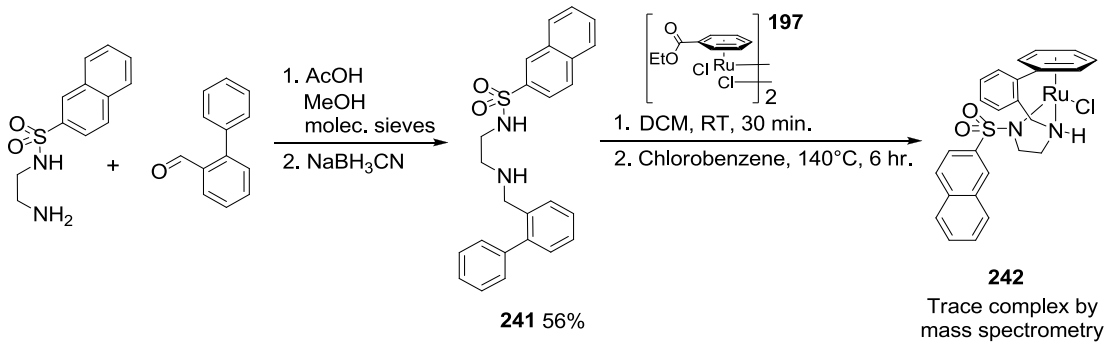
m/z 631.1 $[M\text{-}Cl+H]^+$

Figure 66. Structure of complex 240.

Increasing the temperature to 120°C showed only a trace amount of complex by mass spectrometry after 3 hours and little improvement after leaving the reaction at this temperature overnight. Stirring in DCM at 90°C for 49 hours showed only a trace amount of complex by mass spectrometry. At 140°C in chlorobenzene, mass spectrometry showed a 1:1 ratio of **239**:**240** after 5 hours and no improvement to this after 7 hours so the reaction was cooled and the crude product purified by column

chromatography using florisil. The isolated compound was shown to contain the desired complex but also impurities by mass spectrometry. Upon recrystallisation from hot MeOH and DCM, the small amount of solid obtained was not the desired product, with mass spectrometry and TLC analysis showing the product to be in the filtrate along with impurities. Further attempts at purification and recrystallisation did not show any improvement to the purity of the compound. It is thought that the complex remains too polar to allow effective isolation and purification.

In order to reduce the polarity of the complex, again by incorporating more aromaticity and steric bulk to the ligand, the *N*-((naphthalene-2-ylsulfonyl)methyl)ethane-1,2-diamine derivative **241** was prepared and complexation attempted as shown in Scheme 95. In this case only a trace amount of complex **242** was seen to have formed by mass spectrometry.

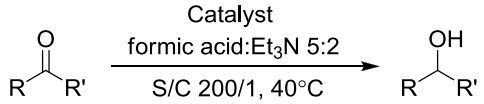


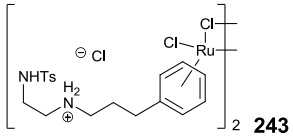
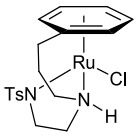
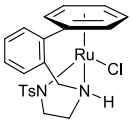
Scheme 95. Synthesis of achiral complex **242** by aryl substitution.

Despite still containing impurities, complex **239** was applied to the ATH of acetophenone. Previous work shows that tethered complexes are slightly less active to APH of ketones than ATH. For example, comparison of Table 22, entry 3 with Scheme 63 shows that APH required a longer reaction time to achieve full conversion than ATH at the same temperature and catalyst loading. We have also

found that the purity level of catalyst required for APH is higher than for ATH. With some impurities still present in the isolated complex **239** by TLC, ATH of acetophenone was carried out to assess its potential activity. For comparison the achiral 3C tethered ruthenium monomer **190** (supplied by Johnson Matthey) and dimer **243** (prepared according to the synthesis detailed in Scheme 66) were also used. The conversion of acetophenone to phenyl ethanol was monitored by GC with the results shown in Table 34. The 3C-tethered achiral dimer **243** was stirred at 40°C for 3 hours prior to addition of acetophenone to allow *in situ* monomer formation.

Table 34. ATH results using achiral dimer **243** and catalysts **190** and **239**.



Entry	Time (hr.)	 243	 190	 239
		Conv. (%)[a]	Conv. (%)[a]	Conv. (%)[a]
1	1	12.1	7.5	0.2
2	2	31.2	18.3	0.6
3	3	44.7	-	-
4	3.5	-	77.0	0.8
5	5	83.2	98.3	-
6	6	-	99.9	-
7	7	98.0	-	-
8	20	99.9	99.9	-
9	24	-	-	7.6

[a]Determined by GC analysis.

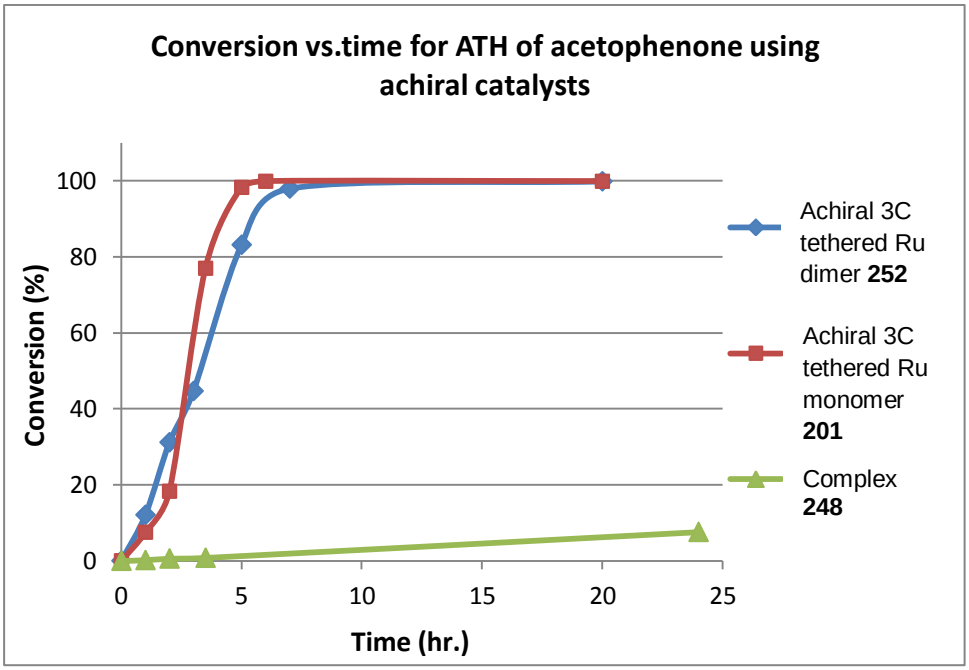


Figure 67. Conversion over time for ATH of acetophenone using achiral catalysts.

Table 34 and Figure 67 show the difference in activity between the conventional achiral 3C tethered monomer **190** and monomer **239**, showing the latter to be inactive to hydrogenation. Figure 67 also shows the similarity in activity of the conventional achiral dimer **243** and monomer **190**, both achieving full conversion to the racemic alcohol in 7 hours, with the reaction proceeding at comparable rates.

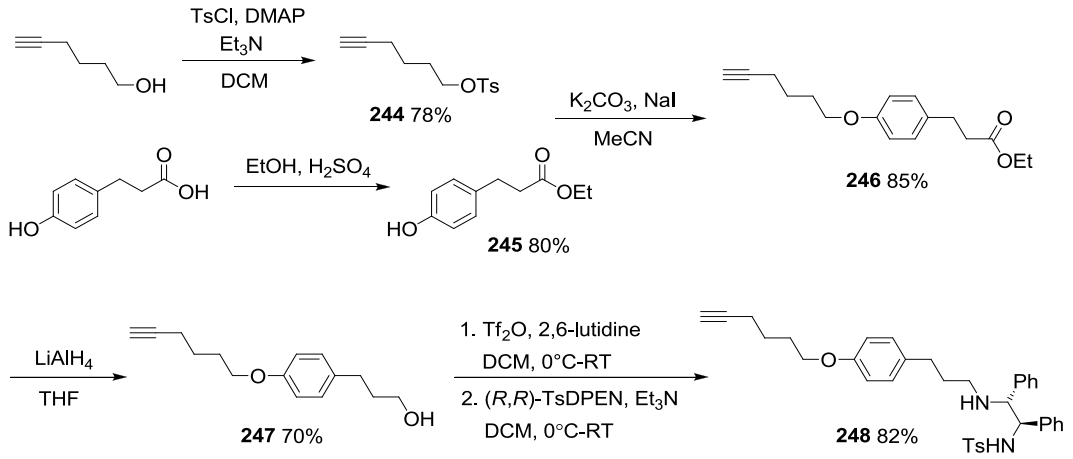
Work continues within the Wills group to develop novel achiral tethered ruthenium catalysts that are highly active for ATH and APH processes and are advantageous over complex **190** through improved accessibility by use of convenient aryl substitution methodology in their preparation.

2.6.6 Preparation of polymer supported ruthenium catalysts by aryl substitution and application to asymmetric hydrogenation of ketones.

Within the Wills group there have been many studies into the development of polymer supports for tethered ruthenium catalysts in order to establish a catalytic system that would allow for improved recovery of the catalyst after reactions and allow for recycling of the catalyst, as well as the potential to carry out hydrogenations in water through the use of water-soluble polymers. Previously work within our group has looked at linking the catalyst to methacrylate based polymer *via* a Click coupling with an alkyne substituted TsDPEN ligand.[161] With the development of the aryl substitution process for tethered catalyst preparation it was thought that the catalysts could be linked to the polymer through the aromatic ring, again with a Click coupling approach being most appealing due to its robust nature.

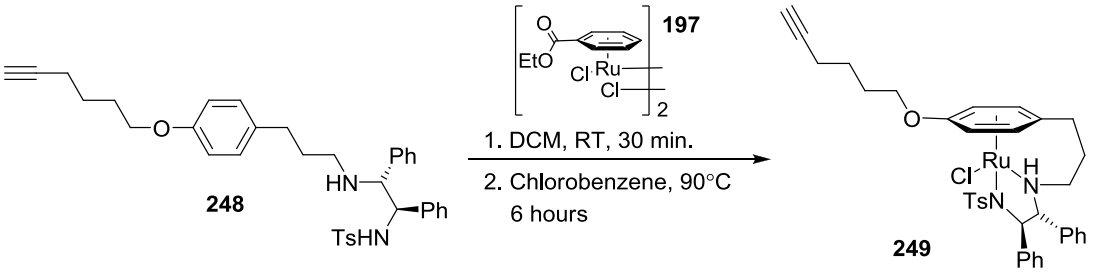
Poly(glycidyl methacrylate), as a well studied and readily available polymer, was selected as a basis for further studies. The epoxide functionality could easily be converted to an azide group through ring opening of the epoxide with an azide nucleophile giving a polymeric substrate for Click coupling to a ligand prior to complexation by aryl substitution.[162, 163]

A potential ligand with TsDPEN coupled to an aromatic ring with a 3C tether was prepared, with the aromatic ring containing an alkoxy substituent with a terminal alkyne for Click coupling (**248** in Scheme 96).



Scheme 96. Preparation of asymmetric ligand **248** as a substrate for Click coupling.

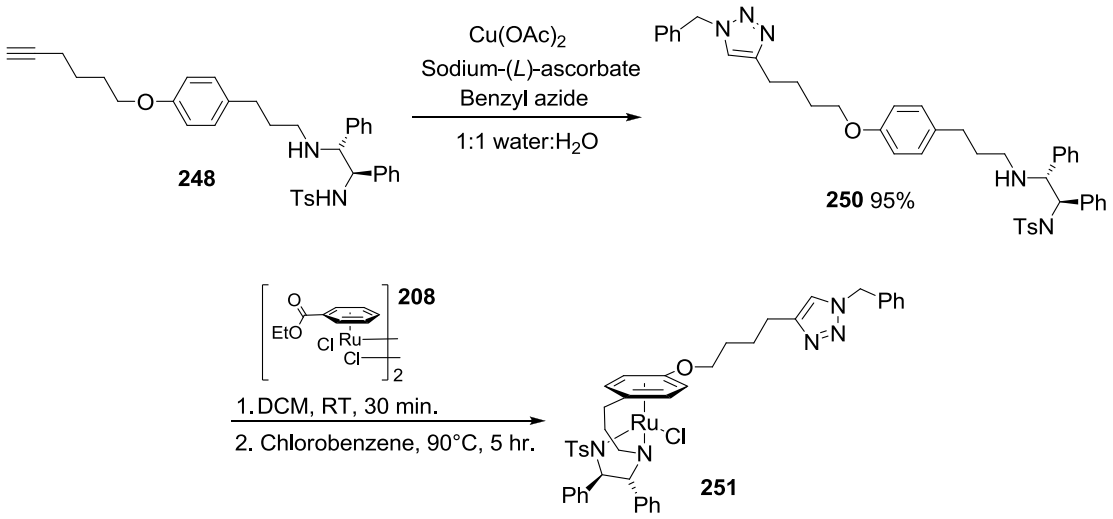
Initial small scale scouting reactions found the ligand to undergo complexation by aryl substitution to give a tethered complex **249** as shown in Scheme 97.



Scheme 97. Formation of complex **249** by aryl substitution as a model for polymer supported complexation.

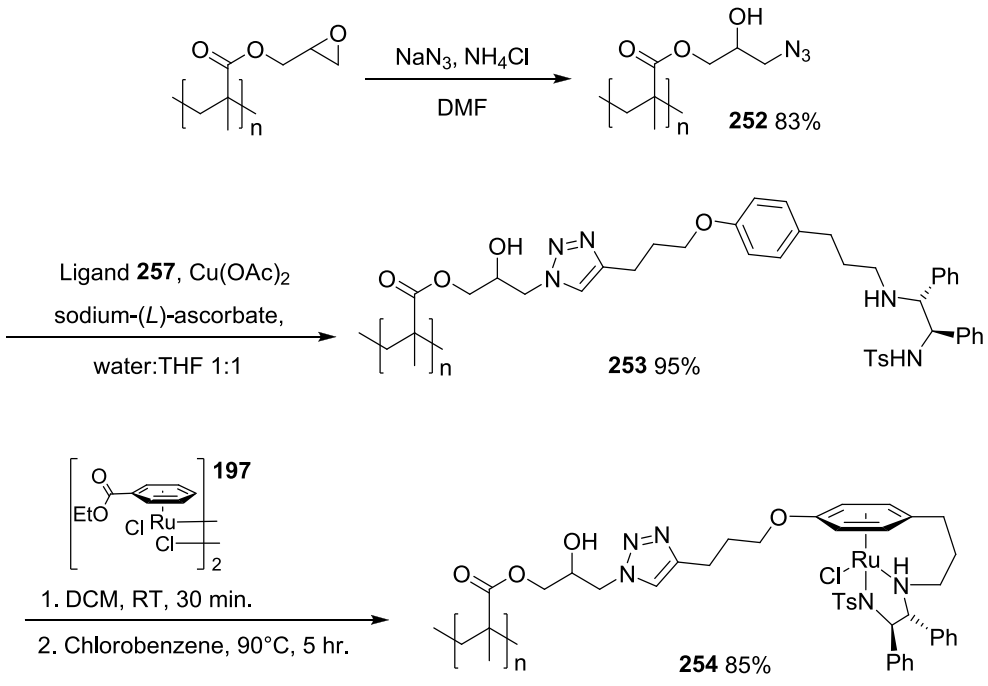
The crude complex **249** was found to show some activity for the ATH of acetophenone giving 21.5% conversion to phenyl ethanol with a high ee. of 97.1% (*R*) at a catalyst loading of 1 mol% in formic acid/Et_3N at room temperature for 24 hours.

Studies also found ligand **248** to undergo successful Click coupling with benzyl azide. Further small scale scouting reactions found this product to successfully undergo complexation by aryl substitution as shown in Scheme 98.



Scheme 98. Formation of complex **251** by aryl substitution as a model for polymer supported complexation.

The long alkyl chain between the aromatic ring and alkyne should allow the triazole group to be far enough from the complex after Click coupling to not affect the activity of the complex. A polymer supported ligand and complex was then prepared as shown in Scheme 99.



Scheme 99. Preparation of polymer supported tethered ruthenium catalyst **254**.

Compound **252** was soluble in THF and DMSO allowing characterisation data to be obtained. However compounds **253** and **254** were found to be insoluble in a range of solvents tested including THF, DMF, DCM, $CHCl_3$, MeOH, hexane, EtOAc and DMSO. Full characterisation data therefore could not be obtained for **253** and **234**. These compounds were analysed by Infrared Spectroscopy. The azide in **252** gives a characteristic absorbance at 2096 cm^{-1} shown in Figure 68, and reduction of this signal was taken as an indication of a successful Click coupling having occurred (Figure 69).

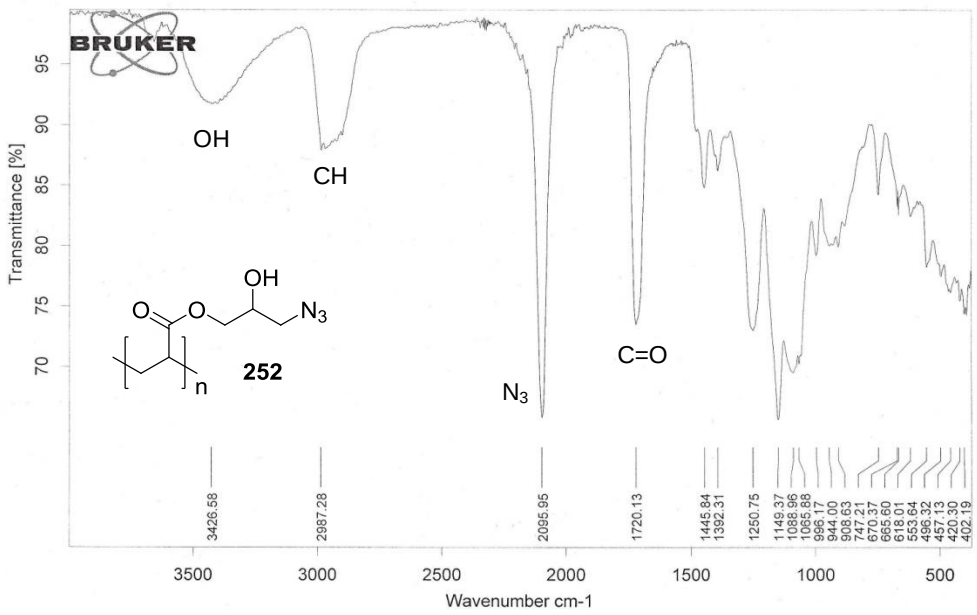


Figure 68. IR spectrum of azide opened polymer **252**.

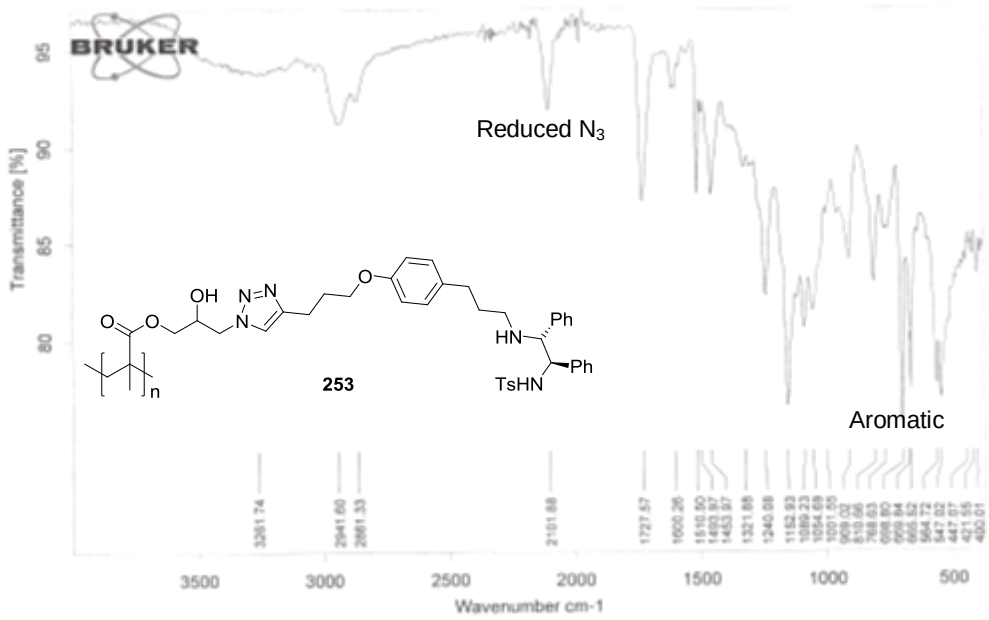
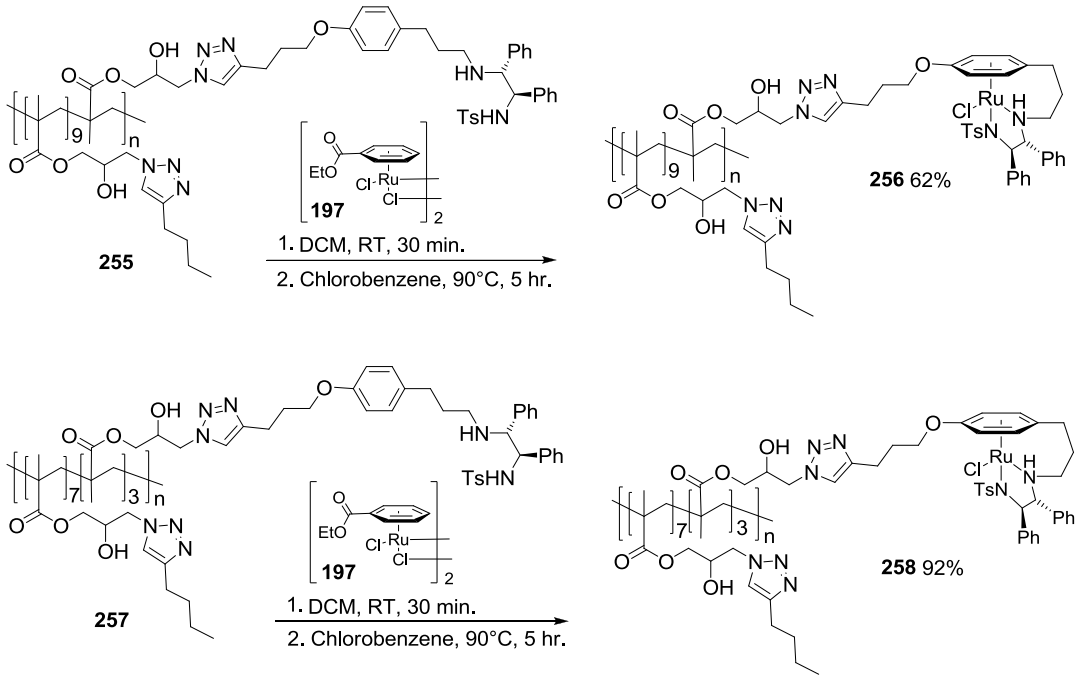


Figure 69. IR spectrum of polymer supported triazole-linked ligand **253**.

After complexation, the reaction mixture was washed with DCM to remove any unreacted dimer and this left an orange/brown insoluble solid which was later used in hydrogenation reactions to test for catalytic activity (Table 35 and 36).

The clicked ligand **253** prior to complexation, and indeed the product obtained after complexation, were insoluble. In order to reduce the catalyst loading on the polymer and increase the solubility and flexibility of the polymer, a 10 mol% loading of ligand **248** was used in an initial click reaction followed by a sequential reaction with 90 mol% hexyne to give complex **256**. A second complex (**258**) was also prepared using 30 mol% ligand and 70 mol% hexyne. An even distribution of hexyne and ligand is assumed along the polymer backbone (Scheme 100).

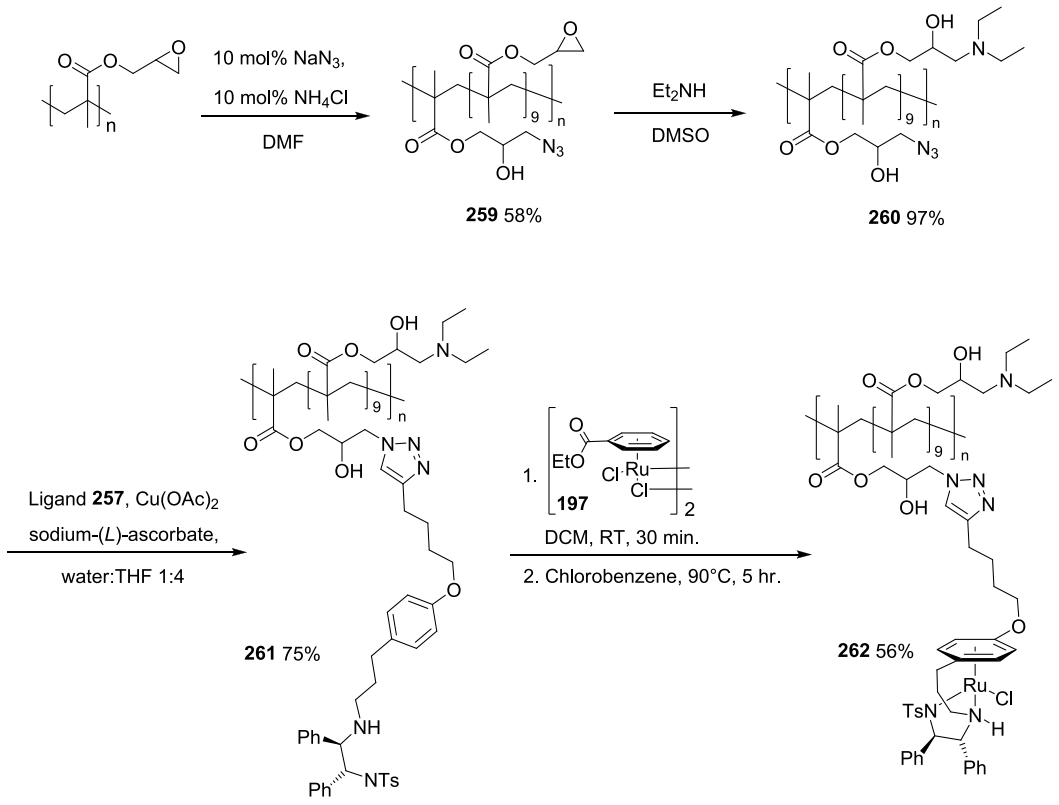


Scheme 100. Synthesis of polymer supported tethered ruthenium catalysts **256** and **258**.

The solubility of the polymer supported ligands and complexes was not improved so again, infrared spectroscopy was used to confirm successful Click coupling of the ligand and polymer.

Alternative functionalities were explored for ring opening of the epoxide. It was hoped that the epoxide could be opened with the *p*-OH derivative of the prepared ligand, however initial attempts to ring open the epoxide with phenol proved unsuccessful. A further survey of the literature showed that epoxides on analogous polymer chains had been ring opened with amines.[164] This approach was therefore applied to the preparation of our polymer supported complexes. Hence 90% of the epoxide was first opened with diethylamine whilst 10% was opened with sodium azide as before to give **260** which was then converted to polymer supported complex **262** as shown in Scheme 101. It is hoped that the use of diethylamine instead of an

additional 90% of clicked alkane chain will help improve the solubility of the supported ligands and hence complexes. Diethylamine was chosen as a small and available secondary amine that would mean there was no NH functionality in the polymer supported ligand to compete with the TsDPEN for complexation to ruthenium (Scheme 101).



Scheme 101. Preparation of diethylamine functionalised polymer supported ruthenium tethered catalyst **262**.

The addition of diethylamine and reduction in the loading of azide on the polymer did not improve the solubility of the polymer supported complex. Compounds **260-262** remained insoluble allowing only minimal characterization data to be obtained for each. The 10% azide functionality of **259** was confirmed by ^{1}HNMR analysis as shown in Figure 70.

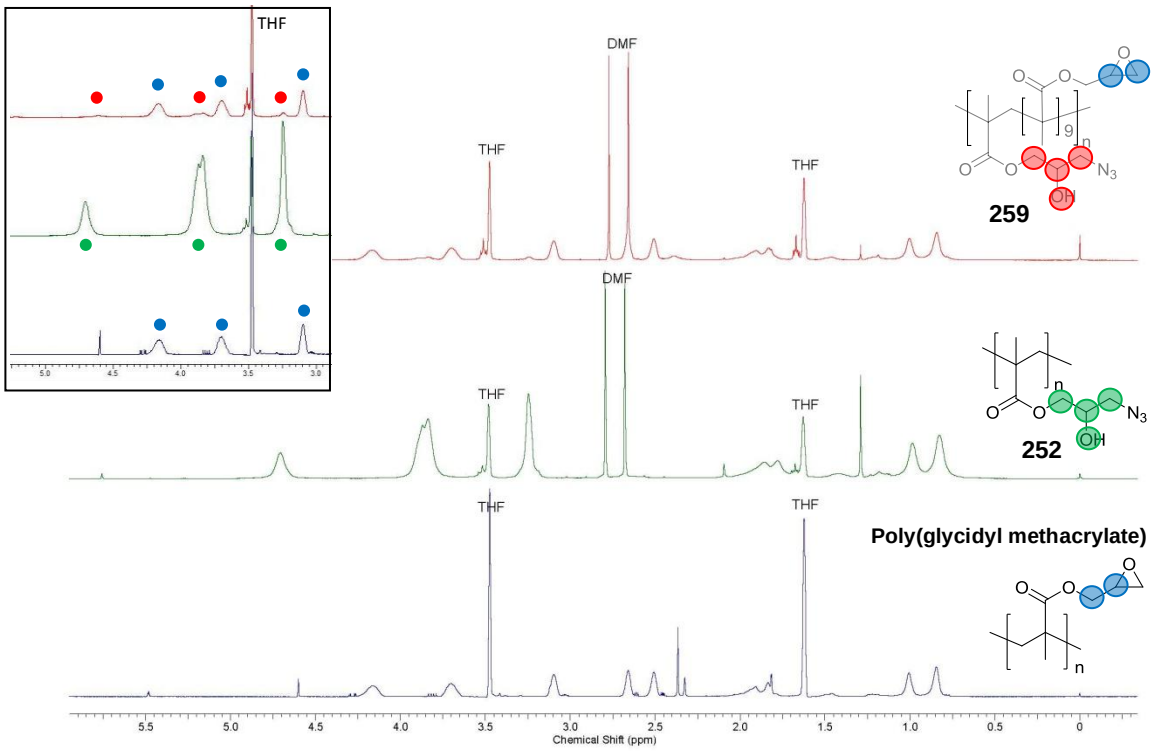


Figure 70. ^{1}H NMR analysis of **259 (**300 MHz, d_8-THF).

Comparison of the ^{1}H NMR of **259** to poly(glycidyl methacrylate) and **252** confirmed the presence of a 10% loading of azide. The major peaks in the spectrum compare well with the spectrum of poly(glycidyl methacrylate) and the smaller set of peaks match well with **252**. Analysis of the integration of the peaks shows a ratio of epoxide:azide of 9:1 as expected.

The ^{1}H NMR spectrum confirms the 10% opening of the epoxide with N_3 in compound **259**. Comparison to the ^{1}H NMR spectra for the starting material and fully ring opened product shows a 1:9 ratio of epoxide:azide peaks in compound **259**. Infrared spectroscopy also helped confirm the formation of **259** (Figure 71) and also **260** (Figure 72).

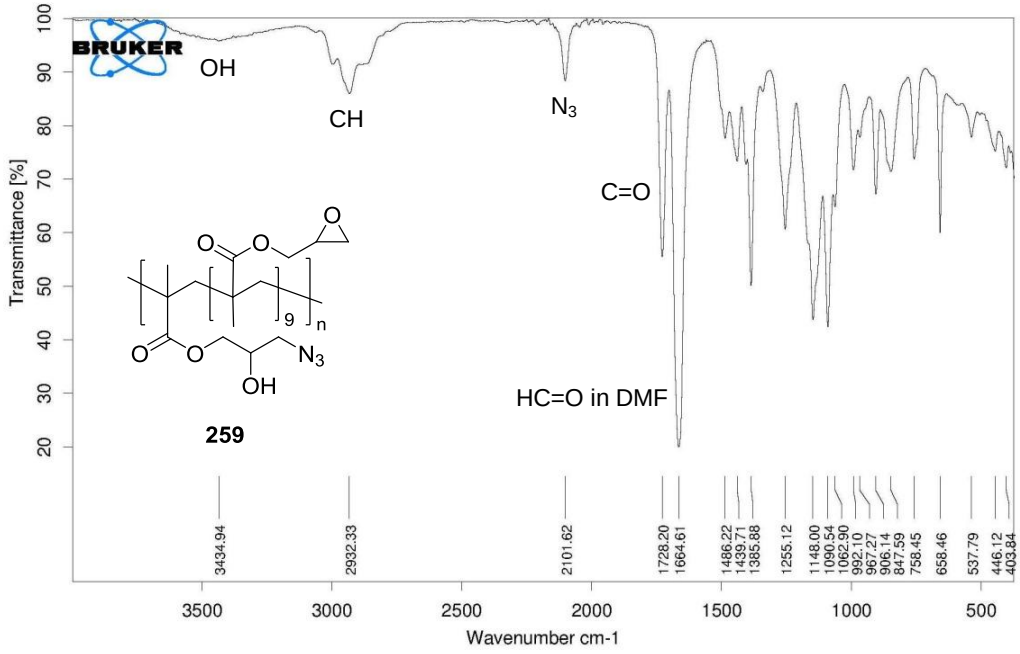


Figure 71. Infrared spectrum of **259**.

The small OH and N_3 absorbance at 3435 and 2102 cm^{-1} respectively show the presence of a small amount of azide opened epoxide in the compound. The weakness of the absorbances comply with the expected 10% loading of azide.

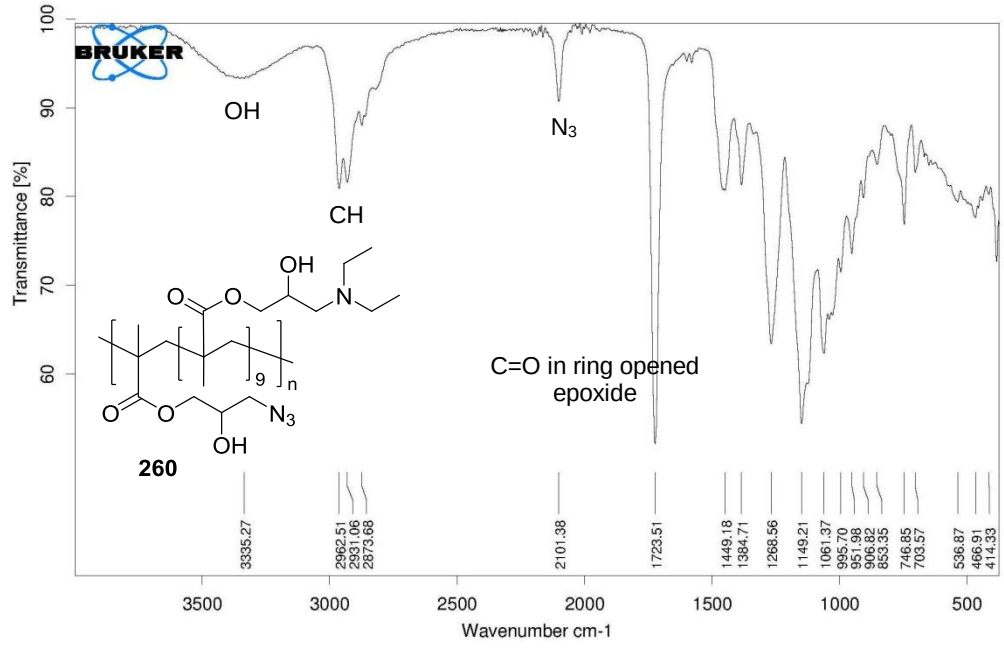
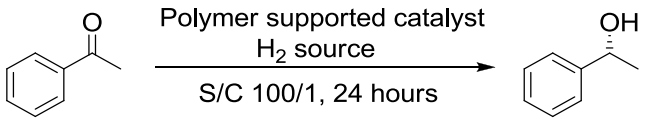


Figure 72. Infrared spectrum of **260**.

After ring opening the remainder of the epoxide with diethylamine to give **260** the size of the OH absorbance relative to that of the N_3 has increased suggesting the presence of more alcohol in **260** than in **259**. The CH signals at 2963-2874 cm^{-1} have also increased in intensity, presumably due to the presence of the diethylamine.

With a variety of polymer supported tethered ruthenium complexes having been prepared, a series of hydrogenations of acetophenone were carried out to establish the activity of the compounds. ATH and APH conditions were investigated and the results are shown in Table 35.

Table 35. ATH and APH of acetophenone using polymer supported tethered catalysts.



Entry	Catalyst	H_2 source	Temp. (°C)	Conv. (%)[a]	Ee. (%)[a,b]
1	**254**	Formic acid:Et_3N 5:2	28°C	1.3	ND
2	**254**	IPA/KOH	28°C	0.4	ND
3	**254**	Water/sodium formate	60°C	6.5	68.3 (*R*)
4	**256**	Formic acid:Et_3N 5:2	28°C	0.61	ND
5	**256**	IPA/KOH	28°C	0.71	ND
6	**256**	Water/sodium formate	60°C	32.0	92.7 (*R*)
7	Recovered **256** from entry 6	Water/sodium formate	60°C	4.3	Only 1 enantiomer seen by GC
8	**256**	H_2 , MeOH	60°C	13.1	Racemic

9	**258**	Water/sodium formate	60°C	16.2	50.2 (*R*)
10	**258**	H_2, MeOH	60°C	34.5	Racemic
11	**262**	Formic acid:Et_3N 5:2	28°C	6.9	93.0 (*R*)
12	**262**	IPA/KOH	28°C	0.45	ND
13	**262**	Water/sodium formate	60°C	26.3	37.9 (*R*)
14	**262**	H_2, MeOH	60°C	79.4	2.7 (*R*)

[a]Determined by GC analysis. [b]For conversions less than 2% the ee. was not determined.

Use of polymer supported ligand **261** and dimer **197** in place of the catalyst under all reaction conditions investigated gave no conversion to product. It was also found that use of formic acid/Et_3N as the hydrogen source caused leaching of the ruthenium from the polymer support in all cases with strong colouration of the reaction solution occurring. This explains the low activity of all complexes with use of formic acid as the hydrogen source.

Initial reactions using polymer supported complex **254** showed low conversion. Improvements to conversion were seen with use of water/sodium formate when polymer supported catalyst **256** was used giving 32% conversion, and an ee. of 92.7 (*R*) (Table 35, entry 6). Polymer **256** has only a 10% loading of ruthenium complex and it is thought that the reduced level of complexation leads to a more flexible polymer and also a reduction in steric hindrance allowing for improved conversion. The reaction solution was removed from the reaction for Table 35, entry 6 and further acetophenone and water/sodium formate mixture added in order to determine whether the polymer supported catalyst could undergo reaction cycles. In the second

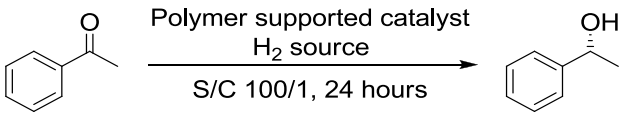
reaction however, only 4.3% conversion to product was obtained over 24 hours showing a loss of activity of the catalyst (Table 35, entry 7). Catalyst **256** also demonstrated activity for APH of acetophenone (Table 35, entry 8) however to a lesser extent than in ATH with water/sodium formate and with no enantioselectivity.

Polymer supported catalyst **258** was applied to ATH with water/sodium formate and APH as these conditions seemed most conducive to hydrogenation occurring. The results obtained showed a reduction in conversion with the water/formic acid system, but an increase in conversion for APH of acetophenone with hydrogen, although the product obtained was racemic.

Use of polymer supported catalyst **262** showed conversion to product with ATH in water/sodium formate and achieved the highest conversion of all at 79.4% with APH conditions although again the product obtained was racemic.

Further ATH reactions were carried out using formic acid/triethylamine and IPA/KOH at increased temperatures with those polymer supported catalysts found to be most active (**256, 258** and **262**) (Table 36).

Table 36. ATH of acetophenone using polymer supported ruthenium complexes.



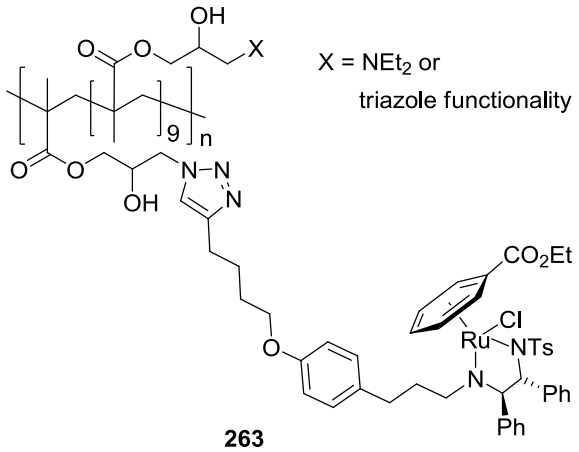
Entry	Catalyst	H_2 source	Temp. (°C)	Conv. (%)[a]	Ee. (%)[a]
1	**256**	Formic acid:Et_3N 5:2	60°C	10.8	87.0 (*R*)
2	**256**	IPA/KOH	80°C	11.3	2.8 (*R*)
3	**258**	Formic acid:Et_3N 5:2	60°C	17.9	82.7 (*R*)
4	**258**	IPA/KOH	80°C	35.2	Racemic
5	**262**	Formic acid:Et_3N 5:2	60°C	5.6	82.8 (*R*)
6	**262**	IPA/KOH	80°C	4.6	14.4 (*R*)

[a]Determined by GC analysis.

The conversions and enantioselectivities achieved were improved compared to the equivalent reactions at room temperature reported in Table 35, however the use of **256** with water/sodium formate (Table 35, entry 6) remains the best ATH result when both conversion and the enantiomeric excess of the product obtained are considered.

No conversion was achieved with use of only ruthenium dimer **197** or ligand **261** under each of the reaction conditions investigated. This confirms that the polymer supported catalysts themselves are the source of the hydrogenation taking place and that active complexes have successfully been linked to the polymer.

Due to the low solubility of all the prepared polymer supported catalysts, characterisation was difficult. It therefore cannot be determined whether the desired complexes were being formed. It may be the case that the desired complexation of ruthenium to the supported ligand by aryl substitution is not occurring in its entirety. For example it may be that the nitrogens of the TsDPEN coordinate to the ruthenium to give a derivative of complex **195** with aryl substitution and displacement of the ethylbenzoate not occurring to give complexes such as **263** in Figure 73 which may not be highly active or enantioselective for the hydrogenation of ketones.



263

Figure 73. Potential polymer supported complex obtained from incomplete aryl substitution process.

Work continues within the Wills group to establish more effective polymer supported catalysts for ATH and APH applications using aryl substitution methodology to achieve complexation.

3. Conclusions.

The application of tetradentate bis-hydroxydiamine ligands derived from norephedrine to the KO^{t}Bu-catalysed hydrogenation of benzophenone has been investigated. Hydrogenation was found to occur *via* a transfer hydrogenation process rather than *via* interaction of the catalyst and substrate with hydrogen gas. The ligands were found to act as hydrogen donors to afford the alcohol product. Although hydrogenation of benzophenone was achieved, the transfer hydrogenation process is not appropriate for further development due to the low conversions of ketone to alcohol achieved and the necessary synthesis of the ligands.

A series of aminophosphine ligands derived from proline have been prepared and applied to the iron-catalysed ATH of acetophenone using $[Et_3NH][HFe_3(CO)_{11}]$ as the catalyst precursor, however no conversion to phenyl ethanol was achieved. This was attributed to a lack of Fe-H functionality in the catalyst precursor. The ligands were also applied to rhodium and ruthenium-catalysed ATH of acetophenone using $[Rh(COD)Cl]_2$, $[RuCl_2(DMSO)_4]$ and $[Ru(benzene)Cl_2]_2$ precursors as well as a series of proline based aminoalcohol, aminosilyl and amido ligands. Use of *N*-Benzyl-(*S*)-2-((diphenylphosphino) methylpyrrolidine (**163**) with $[Rh(COD)Cl]_2$ gave the most active system giving 79% conversion to phenyl alcohol although the reaction was not enantioselective. Dimainodiphosphine ligands reported by Gao[61-64, 128] and Morris [129-135] with NH functionality and exhibiting asymmetry in their diamine components rather than the phosphine exhibit superior activity and enantioselectivity for iron, ruthenium and rhodium-catalysed ATH of ketones.

A series of tethered ruthenium complexes consisting of a tethered aryl-asymmetric diamine ligand have been applied to the APH of a range of ketones.[145] The 3C-

tethered TsDEPN RuCl catalyst **97** was found to be more active and enantioselective than the MsDEPN, iodo and 4C derivatives **180**, **181** and **101** respectively.

The achiral 3C-tethered RuCl catalyst **190** was applied to the hydrogenation of aldehydes.[145] Addition of 10% water to the MeOH reaction solvent was required to prevent formation of di-methoxy adducts of the desired alcohol products. The hydrogenation was found to proceed with excellent chemoselectivity for hydrogenation of the C=O bond over C=C and NO_2 functionalities.

The development and optimisation of a novel synthesis of *p*-methoxy substituted tethered ruthenium catalysts using aryl substitution methodology has been discussed. Reaction of *N*-((1*R*,2*R*)-2-(3-(4-methoxyphenyl)propylamino)-1,2-diphenylethyl) toluenesulfonamide (**198**) or *N*-((1*R*,2*R*)-2-(3-(3.5-dimethoxyphenyl)propylamino)-1,2-(diphenylethyl)toluenesulfonamide (**208**) with ethylbenzoate ruthenium(II) chloride dimer (**197**) gave the resulting tethered complexes **199** and **209**. Application of **199** and **209** to the APH of a range of ketones gave excellent conversions to the alcohol products with high enantioselectivities.

A series of poly(methyl methacrylate) supported tethered ruthenium complexes have been prepared with a triazole link between the ligand and polymer and using aryl substitution methodology for complexation. The activity for ATH and APH of acetophenone of such catalysts was generally found to be low. The highest conversion (79.4%) was achieved for APH with supported complex **262** although the product was racemic (Table 35). The highest ee. of 92.7% (*R*) was achieved with a conversion of 32% for ATH with supported complex **256** (Table 35). The results demonstrate potential for the preparation of more active and enantioselective supported catalysts for APH and ATH of ketones by the same methodology.

4. Future Work.

The use of aryl substitution methodology has been show to be applicable to the synthesis of a range of three carbon tethered ruthenium catalysts, however attempts carried out by Dr. Soni and myself to prepare catalysts with four carbon (**101**), triazole (**229**) and methoxy substituted (**234**) tethers were unsuccessful. The further development of the aryl substitution reaction conditions to allow synthesis of such complexes is of interest in order to identify and develop catalysts with improved activity for hydrogenation reactions. The 4C tethered catalyst **101** for example is known to be more active for ATH of ketones than the 3C catalyst **199**.[101, 102, 104]

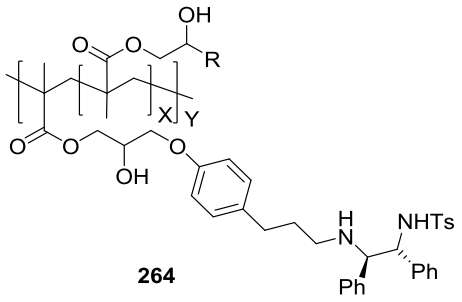
Also of interest is the development of the aryl substitution methodology to allow the synthesis of a range of achiral tethered ruthenium catalysts. Further studies into the aryl substitution reaction conditions, such as the use of weak inorganic bases to promote complexation may allow access to such achiral complexes. Further investigations to fine tune the electronics of both the ruthenium dimer and coordinating ligand may also allow more efficient complexation.

Although the polymer supported ruthenium complexes reported in this thesis have shown limited activity for ATH and APH of ketones, their convenient preparation using aryl substitution methodology demonstrates potential for the synthesis of further derivatives that may show increased activity and recyclability.

Modifications that could be made to improve the activity and recyclability of polymer supported catalysts include varying the polymer support used. For example, the use of co-polymers such as poly(glycidyl methacrylate)/hydroxyethyl

methacrylate, which has been shown to be form active supported hydrogenation catalysts[116] could be investigated.

The use of a range nucleophiles to ring open the epoxide could also be investigated and expanded beyond triazole and diamine functionalities as discussed in this thesis. Of particular interest is the development of methodology whereby the epoxide can be opened with an alcohol such as phenol thus allowing a different mode of attachment for the tethered ligand of the catalyst as shown in Figure 74. Studies reported in this thesis have shown methoxy substituted tethered catalysts (**199** and **209**) to be highly active for APH of ketones, thus it is proposed that an ether linked supported ligand such as **264** may also demonstrate activity for asymmetric hydrogenation of ketones.



264

Figure 74. Example of potential polymer supported ligand using a phenol link.

The ability to ring-open the epoxide of poly(gylcidyl methacrylate) with an amine offers potential for the formation of supported Noyori-type complexes such as that shown in Figure 75, through reaction of the epoxide with TsDPEN. During the course of my studies, the *in situ* formation of a polymer supported untethered ruthenium catalyst from reaction of supported ligand **261** with [Ru(benzene)Cl_2] showed potential for ATH of ketones achieving 18.8% conversion with 93.5% ee. (*R*) in 24 hours as shown in Figure 75.

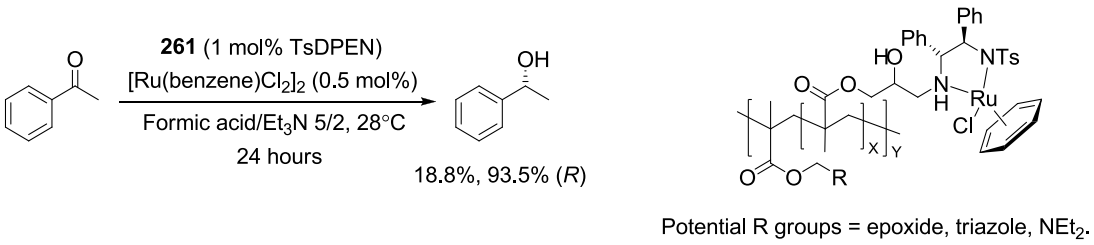


Figure 75. Example reaction showing potential for application of such complexes to ATH of ketones (right) and proposed structure of supported Noyori-type ruthenium complexes (right).

The successful preparation of cationic tethered ruthenium complex **211** by aryl substitution methodology offers potential for investigation into the use of such complexes in biological applications. In recent publications, Sadler has reported the application of cationic untethered ruthenium complexes to show anti-cancer and other biological activities.[160, 165] The chloride ligand of the complex can be substituted for OH_2 to allow further substitution for pyridine or a nucleo-base to allow interaction with cancer cell lines and DNA.[160, 166] Ru-OH_2 cationic complexes have also been shown to be active for reduction of NAD^+ in the NAD/NADH enzymatic pathway.[167] The use of aryl substitution methodology could allow access to a greater range of cationic ruthenium half sandwich complexes for further investigations into the development of these biological applications.

5. Experimental.

5.1 Chemicals.

All chemicals used in this project were obtained from Sigma Aldrich, Acros Organics, Alfa Aesar, TCI and Fischer Scientific.

5.2 Instrumentation.

NMR analysis: NMR analysis was carried out on a DPX-300 (300 MHz), DPX-400 (400 MHz), DRX-500 (500 MHz), AV III-600 (600 MHz) or AV II-700 (700 MHz) instrument using deuterated solvents including $CDCl_3$, d_6-DMSO, d_4-MeOD, d_8-THF, d_2-DCM or d_6-benzene.

Mass Spectrometry: All low resolution mass spectrometry data was acquired using a Bruker Esquire 2000 (ESI) spectrometer or Bruker HCT + (Ultra) (ESI) spectrometer coupled to an Agilent 1100 HPLC system for sample injection, or an Agilent 6130B ESI (quad) mass spectrometer coupled to an Agilent Technologies 1260 Infinity HPLC system. GC/MS analysis was carried out on a Varian 4000 GC/MS with chemical ionisation. All high resolution mass spectrometry data was obtained using a Bruker micro TOF spectrometer. Methanol was used as the solvent for LC/MS and high resolution mass spectrometry, and chloroform for GC/MS.

Infrared: Infrared spectroscopy data was acquired using a Perkin Elmer Spectrum One, Nicolet Avatar 320 or a Bruker ALPHA FT-IR spectrometer.

Gas Chromatography: All gas chromatography analysis was carried out using a Hewlett Packard 5890 Gas Chromatograph or a Perkin-Elmer 8500 Gas Chromatograph. Integration was carried out with a Hewlett Packard HP3396A Integrator or a PC running DataApex Clarity software.

High Pressure Liquid Chromatography: All HPLC analysis was carried out using a Hewlett Packard 1050 Series with a quaternary pump, autosampler and variable wavelength detector with integration carried out on a PC running DataApex Clarity software or a Gilson HPLC with 805 manometric module, 811b dynamic mixer, 305/306 pump modules and a Merck Hitachi L-4000 UV detector with integration carried out on a Hewlett Packard HP3396A Integrator.

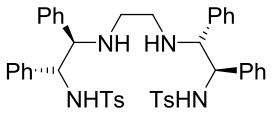
Polarimetry: All polarimetry was carried out using an Optical Activity Ltd. AA-1000 Polarimeter with a 2 dm cell using spectrophotemetric grade solvent.

Melting point analysis: Melting point analysis was carried out on Stuart Melting Point SMP10 apparatus.

5.3 Synthetic and catalytic procedures.

5.3.1 Synthetic procedures for section 2.1.

_N,N_-[1,2-Ethanediylbis[imino[(1_R_, 2_R_)-1,2-diphenyl-2,1-ethanediyl]]]bis[4-methylbenzenesulfonamide] (148).

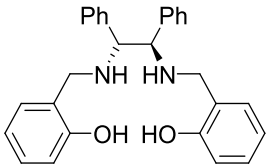


This compound is known in literature and has previously been fully characterised.[36]

To a nitrogen purged, 2-necked round bottom flask containing (*1R,2R*)-(-)-N-*p*-tosyl-1,2-diphenylethylenediamine ((*1R*,2R)-(-)-TsDPEN) (1.5 g, 4.1 mmol) was added 1,2-dibromoethane (0.17 cm^3, 2.0 mmol). The resulting mixture was then stirred at 130°C for 6 hours (monitored by TLC: 1:3 hexane:ethylacetate, visualisation by UV). The reaction mixture was dissolved in chloroform (30 cm^3) and washed with 1M sodium hydroxide solution (20 cm^3). The product was extracted with chloroform

(3 x 40 cm^3). The chloroform phases were collected and combined, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give the crude product as a white solid. The crude was purified by column chromatography (silica gel, 0-100% EtOAc in hexane, TLC: silica plates, 75% EtOAc in hexane, visualisation by UV and ninhydrin, product Rf = 0.89) to give the product as a white solid (753 mg, 0.996 mmol, 49%). Mp 169-171°C; $[\alpha]_D^{27}$ +18.4° (*c* 0.5, $CHCl_3$) (*R*,*R*) (lit.[36] $[\alpha]_D^{20}$ +22 (*c* 0.5 in $CHCl_3$) (*R*,*R*)); found (ESI) $[M+H]^+$, 759.3055. $C_{44}H_{47}N_4O_4S_2$ requires M, 759.3033; υ_{max} 3271, 3029, 15.98, 14.94, 1453, 1329, 1149, 1055, 937, 809, 696, 670 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 7.24-6.83 (28H, m, C*H*Ar); 4.38 (2H, d, *J* 8.6 Hz, C*H*NHSO$_2$); 3.71 (2H, d *J* 8.6 Hz, C*H*NH); 2.59-2.31 (10H, dd and s overlapping, 2 x CH_2 and 2 x CH_3 overlapping); δ_C (75 MHz, $CDCl_3$) 142.05 (2 *C*Ar), 138.81 (2 *C*Ar), 137.43 (2 *C*Ar), 136.87 (2 *C*Ar), 128.45 (2 *C*HAr), 127.63 (2 *C*HAr 127.29 (2 *C*HAr), 127.20 (2 *C*HAr), 126.84 (2 *C*HAr), 126.53 (2 *C*HAr), 126.35 (2 *C*HAr), 125.91 (2 *C*HAr), 67.40 (2 *C*H), 63.11 (2 *C*H), 45.74 (2 *C*H_2), 20.79 (2 *C*H_3); *m/z* (ESI) 759.2 (M^+ + 1). Data matches that previously reported for this compound.[36]

(1*R*,2*R*)-*N*, *N*'-Bissalicyl-1,2-diamino-1,2-diphenylethane (150).

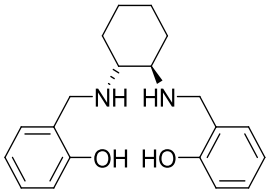


This compound is known in the literature but has not previously been fully characterised.[137, 138]

A solution of (*1R*,*2R*)-diphenylethylenediamine (250 mg, 1.17 mmol) dissolved in ethanol (1 cm^3) was slowly added to a stirred solution of salicylaldehyde (440 mg,

3.60 mmol) in ethanol (2 cm^3) in a nitrogen purged, 2-necked round bottom flask. The resulting solution was stirred under reflux for 3 hours. After this the solution was allowed to cool to room temperature and a yellow precipitate formed which was then collected by filtration. The precipitate was dissolved in methanol (3 cm^3) and sodium borohydride (95 mg, 2.5 mmol) was added. The solution was stirred for 2 hours at room temperature. The solvent was then removed under reduced pressure to leave a yellow solid. This was dissolved in dichloromethane (10 cm^3) and washed with saturated sodium carbonate solution (3 x 10 cm^3). The organic phases were collected and combined, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give the crude product as a yellow solid. The crude was purified by column chromatography (silica gel, 1:1 EtOAc:hexane, TLC: silica plate, 1:1 EtOAc:hexane, visualisation by UV, product Rf = 0.49) to give the product as a white solid (260 mg, 0.613 mmol, 52%). Mp 160-163°C; $[\alpha]_D^{22}$ + 10.2° (*c* 0.5, CH_2Cl_2) (*R*,*R*) (lit.[138] $[\alpha]_D^{25}$ +48.6 (*c* 0.01 in CH_2Cl_2) (*R*,*R*)); found (ESI) $[M+H]^+$, 425.2216. $C_{28}H_{29}N_2O_2$ requires M, 425.2224; υ_{max} 3250, 3026, 2851, 1587, 1489, 1454, 1249, 1101, 753, 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.27-7.23 (6H, m, C*H*Ar),7.20-7.14 (2H, m, C*H*Ar) 6.95-6.92 (4H, m, C*H*Ar), 6.89-6.86 (2H, m, C*H*Ar), 6.79-6.70 (4H, m, C*H*Ar), 4.02 (2H, s, 2 x C*H*), 3.85 (2H, d, *J* 13.5 Hz, 2 x CH^aH^b), 3.59 (2H, d, *J* 13.5 Hz, 2 x CH^aH^b); δ_C (75 MHz, $CDCl_3$) 157.20 (2 *C*Ar), 136.71 (2 *C*Ar), 128.37 (2 *C*HAr), 128.01 (2 *C*HAr), 127.93 (4 *C*HAr), 127.49 (4 *C*HAr), 127.46 (2 *C*HAr), 121.56 (2 *C*HAr), 118.69 (2 *C*HAr), 115.84 (2 *C*HAr), 65.74 (2 *C*H), 49.54 (2 *C*H_2); *m/z* (ESI) 425.2 (M^+ + 1). Data matches that previously reported for this compound.[137, 138]

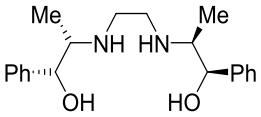
(1*R*,2*R*)-*N*,*N*'-Bissalicyl-1,2-diaminocyclohexane (151).



This compound is known in the literature but has not previously been fully characterised.[138, 139]

This compound was prepared as for compound **150** using (*1R*,*2R*)-cyclohexanediamine (250 mg, 2.19 mmol), salicylaldehyde (806 mg, 6.60 mmol), ethanol (5 cm^3), sodium borohydride (91 mg, 2.4 mmol) and methanol (3 cm^3). The crude was purified by column chromatography (silica gel, 0-100% EtOAc in hexane, TLC: silica plate, 75% EtOAc in hexane, visualisation by UV, product Rf = 0.46) to give the product as an orange solid (255 mg, 0.782 mmol, 36%). Mp 94-96°C; $[\alpha]_D^{22}$ – 37.3° (*c* 0.5, CH_2Cl_2) (*R*,*R*) (lit.[138] $[\alpha]_D^{25}$-26.6 (*c* 0.01 in CH_2Cl_2) (*R*,*R*)); found (ESI) $[M+H]^+$, 327.2069, $C_{20}H_{26}N_2O_2$ requires M, 327.2067; υ_{max} 3302, 3147, 2929, 2852, 1592, 1447, 1403, 1254, 1096, 854, 750, 725 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.63–7.57 (2H, m, C*H*Ar), 7.42-7.40 (2H, m, C*H*Ar), 7.26-7.19 (4H, m, C*H*Ar), 4.41 (4H, dd, *J,* 13.9 and 23.1 Hz, 2 x CH^aH^b), 2.89 – 2.86 (2H, m, C_6H_{10}), 2.60-2.56 (2H, m, C_6H_{10}), 2.16-2.12 (2H, m, C_4H_{10}), 1.71-1.57 (4H, m, C_6H_{10}); δ_C (75 MHz, $CDCl_3$) 157.34 (2 *C*Ar), 128.22 (2 *C*HAr), 127.69 (2 *C*HA), 122.28 (2 *C*Ar) 118.62 (2 *C*HAr), 115.82 (2 *C*HA), 59.09 (2 *C*H), 49.06 (2 CH_2), 29.82 (2 CH_2), 23.54 (2 CH_2); *m/z* (ESI) 327.2 (M^+ + 1). Data matches that previously reported for this compound.[138, 139]

***N,N'*-Bis[(*1R*,*2S*)-2-hydroxy-1-methyl-2-phenylethyl]-1,2-diaminoethane (152)**.

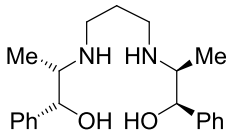


This compound is known in the literature but has not previously been fully characterised.[140, 141]

(1*R*,2*S*)-Norephedrine (1.0 g, 6.6 mmol) in a nitrogen purged 2-necked round bottom flask was stirred at 100°C until it had completely melted. To this was then added 1,2-dibromoethane (413 mg, 2.20 mmol) and the resulting mixture was connected to a condenser and stirred at 100°C overnight. It should be noted that the reaction mixture solidified within approx. 15 mins. After 2 hours, the reaction was cooled to room temperature and the reaction solid was dissolved in water (10 cm^3) with heating. The aqueous solution was washed with chloroform (15 cm^3), and then the aqueous phase was basified with the addition of 2M sodium hydroxide solution. The product was then extracted with chloroform (4 x 15 cm^3). The organic phases were collected, combined and dried over $MgSO_4$ before being filtered and then the solvent removed under reduced pressure to give the crude product as an off white solid. ^1H NMR ($CDCl_3$, 300MHz) analysis showed the desired product to be present at a conversion of 55%. Further purification was achieved by dissolving the crude in dichloromethane and adding 5 cm^3 1M hydrochloric acid. The product was extracted into the aqueous layer (3 x 15 cm^3 1M hydrochloric acid). The aqueous layer phases were combined and basified with saturated $NaHCO_3$ solution. The product was then extracted into DCM (3 x 15 cm^3). The organic phases were combined, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give the product as a white solid (186 mg, 0.567 mmol, 26%). Mp 108-110°C; $[\alpha]_D^{36}$ +10° (*c* 0.7, EtOH) (1*R*,2*S*) (lit.[141] $[\alpha]_D^{25}$ +6.9 (*c* 0.72 in EtOH) (1*R*,2*S*)); found (ESI) $[M+H]^+$,

329.2221, $C_{20}H_{29}N_2O_2$ requires M, 329.2224; υ_{max} 3266, 3081, 2963, 2920, 2828, 1447, 1284, 1120, 1005, 739, 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.29-7.15 (12H, m, C*H*Ar and 2 x N*H* overlapping), 4.64 (2H, d, *J* 3.9 Hz, 2 x C*H*(C_6H_5)), 2.82-2.78 (4H, m, 2 x C*H*CH_3 and 2 x O*H* overlapping), 2.66-2.60 (4H, m, 2 x C*H*$_2$NH), 0.79 (6H, d, *J* 6.5 Hz, 2 x C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 141.53 (2 *C*Ar), 128.12 (4 *C*HAr), 127.15 (2 *C*HAr), 126.18 (4 *C*HAr), 73.88 (2 *C*H), 58.53 (2 *C*H), 46.90 (4 *C*H_2), 14.74 (2 *C*H_3); *m/z* (ESI) 329.2 (M^+ + 1). Data matches that previously reported for this compound.[140, 141]

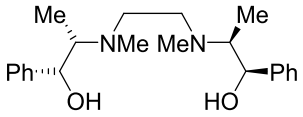
_N,N'_-Bis[(_1R,2S_)-2-hydroxy-1-methyl-2-phenylethyl]-1,2-diaminopropane (153).



This compound is novel.

Prepared as for ligand **152** using (1*R*,2*S*)-Norephedrine (1.0 g, 6.6 mmol) and 1,3-dibromopropane (666 mg, 3.30 mmol) instead of 1,2- dibromoethane. The purified product was obtained as a white solid (404 mg, 1.18 mmol, 36%). Mp 98- 100°C; $[\alpha]_D^{36}$ + 5.0 (*c* 0.5, EtOH); found (ESI) $[M+H]^+$, 343.2379, $C_{21}H_{31}N_2O_2$ requires M, 343.2380; υ_{max} 3065, 2969, 2871, 1488, 1449, 1200, 1144, 1102, 1089, 996, 897, 748, 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.24-7.14 (10H, m, C*H*Ar), 4.86 (2H, d, *J* 3.4 Hz, 2 x C*H*OH), 3.43 (4H, br s, 2 x N*H* and 2 x O*H* overlapping), 2.89-2.72 (6H, m, 2 x C*H*$_2$CH$_2$ and 2 x C*H*NH overlapping), 1.68 (2H, quin, *J* 6.3 Hz, CH$_2$C*H*$_2$CH$_2$), 0.78 (6H, d, *J* 6.5 Hz, 2 x C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 140.72 (2 *C*Ar), 127.49 (4 *C*HAr), 126.44 (2 *C*HAr), 125.44 (4 *C*HAr), 72.45 (2 *C*H), 58.24 (2 *C*H), 45.36 (2 *C*H$_2$), 28.59 (2 *C*H$_2$), 12.83 (2 *C*H$_3$); *m/z* (ESI) 343.2 (M^+ + 1).

***N,N'*-Bis[(*1R*,*2S*)-2-hydroxy-1-methyl-2-phenylethyl]-1,2-dimethylaminoethane (154).**



This compound is known in the literature but has not previously been fully characterised.[142]

This was prepared as for ligand **152** (1*R*,2*S*)-ephedrine (1.0 g, 6.1 mmol) instead of (1*R*,2*S*)-norephedrine and 1, 2-dibromoethane (564 mg, 3.00 mmol).. The purified product was achieved as a white solid (247 mg, 0.694 mmol, 23%). Mp 68-71°C; $[\alpha]_D^{34}$ +59.4 (*c* 1, $CHCl_3$) (1*R*,2*S*) (lit.[142] $[\alpha]_D^{34}$ +16.9 (*c* 1.0 in $CHCl_3$) (1*R*,2*S*)); found (ESI) $[M+H]^+$, 357.2541, $C_{22}H_{33}N_2O_2$ requires M, 357.2537; υ_{max} 2965, 2856, 2806, 1448, 1335, 1194, 1047, 758, 701, 638 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.26-7.19 (8H, m, C*H*Ar), 7.13-7.08 (2H, m, C*H*Ar), 5.12 (2H, d, *J* 3.1 Hz, 2 x C*H*OH), 3.20 (2H, d, *J* 11.3, 2 x C*H*^{a}H^b), 2.81-2.73 (2H, m, 2 x C*H*NCH_3), 2.38 (6H, s, 2 x CH_3N), 2.07 (2H, d, *J* 11.3, 2 x CH^a*H*^{b}), 0.68 (6H, d, *J* 6.7 Hz, 2 x CH_3); δ_C (75 MHz, $CDCl_3$) 141.87 (2 *C*Ar), 128.03 (4 *C*HAr), 126.67 (2 *C*HAr), 125.81 (4 *C*HAr), 76.72 (2 *C*H), 64.17 (2 *C*H), 51.43 (4 *C*H_2), 43.83 (2 *C*H_3), 6.04 (2 *C*H_3); *m/z* (ESI) 357.2 (M^+ + 1). Data matches that previously reported for this compound.[142]

General procedure 1: hydrogenation of benzophenone using 20 mol% KO^{t}Bu and 20 mol% ligand and hydrogen gas.

To benzophenone (164 mg, 0.901 mmol) in a small pyrex test tube was added KO^{t}Bu (20 mg, 0.18 mmol), ligand (0.18 mmol) and solvent (either ^{t}BuOH or 2-methyl-2-butanol) (2.25 cm^3). A micro stirrer was added to the test tube which was then placed inside the Parr Reactor. The reactor was purged with hydrogen gas and

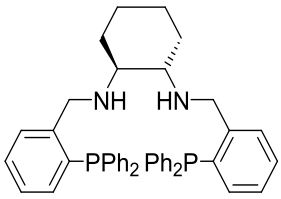
then charged to the desired pressure. The reaction was then stirred at the required temperature for the required time (approx. 5 days).

When multiple ligands were tested in the same experiment, a bulk solution of benzophenone, KO*t*Bu and solvent was prepared and divided into equal aliquots (2.25 cm^3) in separate pyrex test tubes and 1 ligand (0.18 mmol) was added to each.

The reaction solution was filtered through silica with EtOAc and the filtrate analysed by GC.

5.3.2 Synthetic procedures for section 2.2.

(1*S*,2*S*)-*N*,*N*-Bis(2-(diphenylphosphino)benzyl)cyclohexane-1,2-diamine (45).

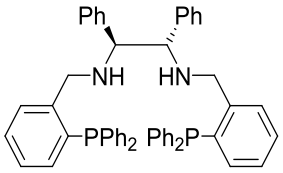


This compound is known in the literature but has not previously been fully characterised.[63]

To (*S*,*S*)-1,2-diaminocyclohexane (19 mg, 0.17 mmol) and Na_2SO_4 (142 mg, 1.00 mmol) was added anhydrous DCM (1.5cm^3). To the resulting solution was then added σ-(diphenylphosphino)benzaldehyde (100 mg, 0.344 mmol). The solution was then stirred at room temperature for 24 hours. After this the reaction was filtered and the solvent removed under reduced pressure to leave an orange solid. To this was then added anhydrous THF (2 cm^3) and the solution cooled to 0°C. To the cooled solution was then added 2M $LiAlH_4$ solution in THF (1.0 mmol, 0.50 cm^3). The reaction was stirred overnight. After this, water was slowly added to the reaction and

the THF was removed under reduced pressure. The product was then extracted with Et_2O (3 x 15 cm^3). The Et_2O phases were combined, dried over Na_2SO_4 and filtered. The solvent was then removed under reduced pressure to leave the crude product as a yellow oil (59 mg, 0.08 mmol, 47%). Further purification was not necessary. $[\alpha]_D^{32}$ + 6.4° (*c* 0.25 in $CHCl_3$) (*S*,*S*); (found (EI): $M^+ + H + O_2$, 695.2959 $C_{44}H_{45}N_2O_2P_2$ requires M,695.2951); υ_{max} 3051, 2925, 2853, 1710, 1433, 1357, 1180, 1090, 1026, 878, 741. 694 cm^1; δ_H (300 MHz, $CDCl_3$) 7.52-7.48 (2H, m, C*H*Ar), 7.33-7.18 (24H, m, C*H*Ar), 6.91-6.81 (2H, m, C*H*Ar), 4.02 (2H, dd, *J* 1.5 and 13.4 Hz, C*H*^{a}H^{b}N), 3.83 (2H, dd, *J* 1.5 and 13.4 Hz, CH^a*H*^{b}N), 2.29 (2H, br s, N*H*), 2.15-2.12 (2H, m, C*H*), 2.02-1.96 (2H, m, CH_2), 1.62-1.57 (2H, m, CH_2), 1.11-1.04 (2H, m, CH_2), 0.92-0.85 (2H, m, CH_2); δ_C (75 MHz, $CDCl_3$) 136.30 (2 *C*Ar, d, J_{CP} 4.6 Hz), 136.17 (2 *C*Ar, d, J_{CP} 4.6 Hz), 135.49 (2 *C*Ar), 134.85 (2 *C*Ar, d, J_{CP} 13.4 Hz), 133.42 (4 *C*HAr), 133.15 (4 *C*HAr), 132.75 (2 *C*HAr), 128.65 (*C*HAr), 128.41 (2 *C*HAr), 128.33 (2 *C*Ar), 128.10 (2 *C*HAr), 128.03 (4 *C*HAr), 127.98 (4 *C*HAr), 127.88 (2 *C*HAr), 126.41 (2 *C*HAr), 60.35 (2 *C*H), 48.26 (2 *C*H_2), 30.65 (2 *C*H_2), 24.29 (2 *C*H_2); δ_p (300MHz, $CDCl_3$) -17.0; *m/z* (ESI) 663.2 (M^+ + 1). Data matches that previously reported for this compound.[63]

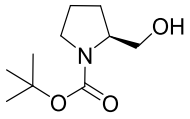
(1*S*,2*S*)-*N*,*N*-Bis(2-(diphenylphosphino)benzyl)-1,2-diphenylethane-1,2-diamine (159).



This compound is known in the literature but has not previously been fully characterised.[62]

This compound was prepared as for compound **45** using (*S*,*S*)-DPEN (53 mg, 0.25 mmol), Na_2SO_4 (213 mg, 1.50 mmol), anhydrous DCM (2 cm^3), σ-(diphenylphosphino)benzaldehyde (145 mg, 0.500 mmol), anhydrous THF (3 cm^3) and 2M $LiAlH_4$ solution in THF (0.75 cm^3, 1.5 mmol). Purification of the crude product by recrystallisation was attempted but gave no improvement to the purity of the products. $[\alpha]_D^{32}$ + 0.9 (*c* 0.5 in $CHCl_3$) (*S*,*S*); HRMS not obtained due to purity of product achieved; υ_{max} 3053, 2905, 1708, 1586, 1434, 1179, 1118, 1027, 742, 693 cm^1; δ_H (300MHz, $CDCl_3$) 7.48-7.44 (2H, m, C*H*Ar), 7.30-7.13 (34H, m, C*H*Ar), 6.85-6.79 (2H, m, C*H*Ar), 4.00 (2H, s, C*H*), 3.67-3.66 (2H, m, C*H*^{a}H^b), 3.59-3.57 (2H, m, CH^a*H*^{b}), 2.09 (2H, br s, N*H*); δ_C (75MHz, $CDCl_3$) 144.15 (2 *C*Ar), 139.78 (2 *C*Ar), 136.28 (2 *C*Ar), 136.04 (2 *C*Ar), 135.19 (2 *C*Ar), 133.41 (4 *C*HAr), 133.29 (2 *C*HAr, s), 133.14 (4 *C*HAr), 131.74 (2 *C*HAr), 131.40 (4 *C*HAr), 131.26 (4 *C*HAr), 128.27 (2 *C*HAr), 128.15 (2 *C*Ar), 127.94 (4 *C*HAr), 127.85 (4 *C*HAr), 127.53 (2 *C*HAr), 126.48 (2 *C*HAr), 66.89 (2 *C*H), 52.64 (2 *C*H_2); δ_p (300MHz, $CDCl_3$) -16.6; *m/z* (ESI) 777.1 (M^+ + 17). (For procedure see reference 155). Data matches that previously reported for this compound.[62]

Boc-(*L*)-prolinol (160).

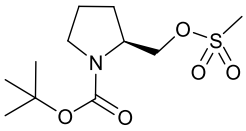


This compound is known in the literature and has previously been fully characterised.[168, 169]

A solution of *N*-Boc-(*L*)-proline (900 mg, 4.18 mmol) in anhydrous THF (8 cm^3) was cooled to 0°C with an ice bath. To the cooled solution was then added dropwise borane dimethyl sulfide complex 2M in THF (4.2 cm^3, 8.4 mmol). The solution was

stirred at 0°C for 5 hours and then at room temperature overnight. The reaction was followed by TLC (1:1 EtOAc:petroleum ether, visualisation by $KMnO_4$, product Rf 0.59). After this, water was slowly added to the reaction followed by EtOAc (15 cm^3). The organic phase was separated and the aqueous phase washed with further EtOAc (2 x 15 cm^3). The organic phases were combined and washed with brine, saturated Na_2HCO_3 solution and finally water. The organic phase was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to leave the product as a white solid (756 mg, 3.76 mmol, 90%). Further purification was not necessary. Mp 61-63°C, $[\alpha]_D^{25}$ -67.5 (*c* 0.5 in $CHCl_3$) (*S*) (lit.[168] $[\alpha]_D^{26}$ -52.7 (*c* 1.05 in $CHCl_3$) (*S*)); (found (EI): M^++Na, 224.1261 $C_{10}H_{19}NNaO_3$ requires M, 224.1257); υ_{max} 3432, 2979, 2932, 2872, 1656, 1392, 1478, 1455, 1392, 1365, 1161, 1127, 1054, 907, 864, 775 cm^{-1} ; δ_H (300MHz, $CDCl_3$) 4.78 (1H, br s, O*H*), 3.91 (1H, br s, C*H*N), 3.60-3.48 (2H, br m, CH_2OH), 3.42-3.34 (1H, br m, NCH^aH^b), 3.28-3.20 (1H, br m, NCH^aH^b), 1.97-1.88 (1H, m, CH_2), 1.80-1.71 (2H, m, CH_2), 1.53-1.46 (1H, m, CH_2), 1.42 (9H, s, (CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 164.16 (1 *C*=O), 79.57 (1 *C*), 67.03 (1 *C*H_2), 59.54 (1 *C*H), 46.91 (1 *C*H_2), 28.06 (1 *C*H_2), 27.82 (3 *C*H_3), 23.42 (1 *C*H_2); *m/z* (ESI) 224.1 (M^+ + 23) and 425.0 (M_2^+ + 1). Data matches that previously reported for this compound.[168, 169]

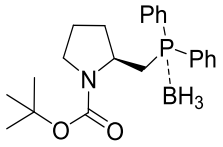
Boc-(*S*)-2-Methylsulfonyloxymethylpyrrolidine (161).



This compound is known in the literature but has not previously been fully characterised.[170, 171] For procedure see reference 172.

To a solution of *N*-Boc-(*L*)-prolinol **160** (756 mg, 3.76 mmol) was added anhydrous DCM (19 cm^3) and triethylamine (577 mg, 5.70 mmol). The resulting solution was stirred and to it was slowly added methanesulfonyl chloride (653 mg, 5.70 mmol). The reaction was stirred at room temperature and monitored by TLC (silica gel plates, 1:1 EtOAc:petroleum ether, visualisation by $KMnO_4$, product Rf 0.65). Once complete, the solvent was removed under reduced pressure. To the residue was added EtOAc (15 cm^3) and water (10 cm^3). The organic phase was separated and the aqueous phase washed with further EtOAc (2 x 15 cm^3). The organic phases were combined and then washed with brine and saturated $NaHCO_3$ solution. The organic phases was then dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to leave the crude product as a pale yellow oil (703 mg, 2.52 mmol, 67%). Further purification was not necessary. $[\alpha]_D^{25}$ -47.1 (*c* 0.5 in $CHCl_3$) (*S*); (found (EI): M^+ - $C_5H_8O_2$ + H, 180.0688 $C_{16}H_{14}NO_3S$ requires M, 180.0689); υ_{max} 2973, 1752, 1686, 1391, 1353, 1167, 1109, 956, 907, 814, 772 cm^{-1} ; δ_H (100 MHz, $CDCl_3$) 4.29-4.20 (1H, br m, C*H*N), 4.18-4.03 (2H, br s, CH_2N), 3.36 (2H, br s, CH_2OSO_2), 3.01 (3H, s, CH_3SO_2), 2.10-1.77 (4H, m, CH_2), 1.47 (9H, s, (CH_3)$_3$); δ_C (400MHz, $CDCl_3$) 164.10 (1 *C*=O), 79.15 (0.5 *C*), 79.56 (0.5 *C*), 68.93 (0.5 *C*H_2), 68.88 (0.5 *C*H_2), 55.09 (1 *C*H_3), 46.36 (1 *C*H_2), 46.02 (0.5 *C*H_2), 36.75 (0.5 *C*H), 36.31 (0.5 *C*H) 27.80 (3 *C*H_3), 27.14 (0.5 *C*H_2), 23.10 (0.5 *C*H_2), 22.23 (0.5 *C*H_2); *m/z* (ESI) 180.1 (M^+ - 100, + 1) and 302.1 (M^+ + 23). Data matches that previously reported for this compound.[170, 171]

Boc-(*S*)-2-((diphenylphosphino)methyl)pyrrolidine borane complex (162).

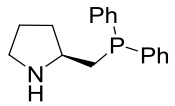


This compound is novel.

To Boc-(*S*)-2-Methylsulfonyloxymethylpyrrolidine **161** (2.31 g, 8.27 mmol) was added anhydrous, degassed THF (40 cm^3). The resulting solution was cooled to -25°C with an ice/NaCl bath and stirred. Potassium diphenylphosphide solution 0.5M in THF (33.2 cm^3, 16.6 mmol) was added to the solution dropwise. To the resulting vivid orange solution was then added borane dimethyl sulfide complex 2M in THF (8.3 cm^3, 16.6 mmol). The reaction was allowed to warm to room temperature and stirred overnight. After this the reaction solution was filtered through celite and the solvent removed under reduced pressure to leave the crude as a cloudy oil. The crude was purified by column chromatography (silica gel, 0-50% EtOAc in petroleum ether, TLC: silica plate, 20% EtOAc in petroleum ether, visualisation by $KMnO_4$, Rf product = 0.55) to give the pure product as a white solid (2.03 g, 5.30 mmol, 64%). Mp 83-84°C; $[\alpha]_D^{26}$ -19.8 (*c* 0.5 in $CHCl_3$) (*S*); (found (EI): M^+ +Na, 406.2084 $C_{22}H_{31}BNNaO_2P$ requires M, 406.2082); υ_{max} 2973, 2378, 1679, 1393, 1363, 1170, 1107, 1061, 734, 692 cm^{-1} ; δ_H (500 MHz, $CDCl_3$) mixture of rotomers 7.98-7.88 (1H, m, C*H*Ar), 7.77-7.73 (1H, m, C*H*Ar), 7.69-7.63 (2H, m, C*H*Ar), 7.51-7.37 (6H, m, C*H*Ar), 4.18 (0.5H, br s, C*H*N), 4.03 (0.5H, br s, C*H*N), 3.42-3.37 (0.5H, m, C$H_2$$PPh_2$), 3.34-3.19 (2H, m, C$H_2$N), 2.88-2.82 (0.5H, m, C$H_2$$PPh_2$), 2.35-2.25 (0.5H, m, C$H_2$$PPh_2$), 2.12-2.06 (0.5H, m, C$H_2$$PPh_2$), 1.96-1.87 (1H, m, C$H_2$), 1.85-1.81 (1H, m, C$H_2$), 1.77-1.68 (1.5H, m, C$H_2$), 1.60 (0.5H, br s, C$H_2$), 1.48-1.42 (9H, m, C(C$H_3$)$_3$), 1.24-0.72 (3H, br s, BH_3); δ_C (75 MHz, $CDCl_3$) 153.58 (1 *C*=O),

132.24 (*C*HAr), 131.99 (*C*HAr), 131.51 (*C*HAr), 131.27 (*C*HAr), 130.62 (*C*HAr), 130.32 (*C*HAr), 128.91 (2 CAr), 128.33 (2 *C*HAr), 128.20 (2 *C*HAr), 53.15 (*C*H), 45.65 (*C*H_2, d J_{CP}, 42 Hz), 30.52 (*C*), 30.20 (*C*H_2), 29.16 (*C*H_2, d, J_{CP}, 31 Hz), 28.00 (3 *C*H_3), 23.71 (*C*H_2, d, J_{CP}, 65 Hz); δ_p 10.6 (br s); *m/z* (ESI) 406.2 (M^+ + 23). (For procedure see reference 173)

(*S*)-2-((Diphenylphosphino)methyl)pyrrolidine (163).

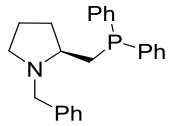


This compound is known in the literature and has not previously been fully characterised.[169, 174, 175]

To Boc-(*S*)-2-((diphenylphosphino)methyl)pyrrolidine borane complex **162** (600 mg, 1.57 mmol) at 0°C was added degassed TFA (19 cm^3, 250 mmol). The resulting clear, brown solution was stirred at 0°C for 2 hours. After this, the reaction was quenched at 0°C by the slow addition of saturated K_2CO_3 solution until effervescence ceased. After this the solution was brought to pH 7 by addition of 1M HCl solution. The product was then extracted with DCM (3 x 20 cm^3) to give the crude product as a pale yellow viscous oil (416 mg, 1.54 mmol, 98%). Further purification was not necessary. $[\alpha]_D^{26}$ - 5.4 (*c* 0.5 in $CHCl_3$) (lit.[175] $[\alpha]_D^{25}$ -13.0 (*c* 1.0 in $CHCl_3$) (*S*)); (found (EI): M^+ +H, 270.1402 $C_{17}H_{21}NP$ requires M, 270.1406); υ_{max} 2974, 2760, 1670, 1434, 1173, 1124, 831, 798, 740, 720 694 cm^{-1}; δ_H (300MHz, $CDCl_3$) 8.17 (1H, br s, N*H*), 7.36-7.21 (10H, m, CHAr), 3.33-3.06 (3H, m, CH_2N and C*H*N overlapping), 2.67 (1H, dd, *J* 13.5 and 6.1 Hz, CH^aH^b), 2.34 (1H, dd, *J* 13.5 and 9.0 Hz, CH^aH^b), 2.13-2.04 (1H, m, CH_2), 2.01-1.92 (1H, m, CH_2), 1.86-1.62 (2H, m, CH_2); δ_C (100MHz, $CDCl_3$) 136.79 (*C*Ar, d, J_{CP} 11.3 Hz), 136.11

(*C*Ar, d, J_{CP} 11.3 Hz), 132.87 (2 *C*HAr, d, J_{CP} 19.3 Hz), 132.51 (2 *C*HAr, d, J_{CP} 19.3Hz), 130.99 (*C*HAr, d, J_{CP} 9.7 Hz), 130.55 (*C*HAr, d J_{CP} 9.7 Hz), 129.22 (2 *C*HAr, d, J_{CP} 9.5 Hz), 128.75 (2 *C*HAr, t, J_{CP} 6.3 Hz), 116.64 (*C*H_2, d, J_{CP} 293.9 Hz), 58.32 (*C*H, d, J_{CP} 20.3 Hz), 44.71 (*C*H_2), 31.27 (*C*H_2) 23.67 (*C*H_2); δ_p (121 MHz, $CDCl_3$) -22.40 (s); *m/z* (ESI) 270.1 (M^+ + 1). Data matches that previously reported for this compound.[169, 174, 175]

_N_-Benzyl-(_S_)-2-((diphenylphosphino)methylpyrrolidine (164).

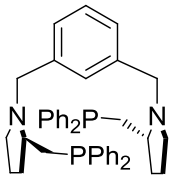


This compound is known in the literature[176, 177] but has not previously been fully characterised.

NaH (60% in mineral oil) (76 mg, 1.9 mmol) was washed in anhydrous hexane (3 cm^3) to remove the oil. The hexane was removed *via* a needle and syringe with cotton wool and filter paper secured to the end of the needle. Any residual hexane was then removed under vacuum and the flask cooled to 0°C with an ice bath. Anhydrous THF (6 cm^3) was added and the resulting solution stirred. To it was then added (S)-2-((diphenylphosphino)methyl)pyrrolidine **163** (135 mg, 0.501 mmol) and the reaction stirred for 40 min at 0°C. After this benzyl bromide (64 mg, 0.37 mmol) was added and the reaction solution heated and stirred at reflux for 2.5 hours. After this the reaction was cooled to room temperature and water and EtOAc were added. The product was extracted with EtOAc (3 x 10 cm^3). The EtOAc phases were combined, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to leave the crude as an orange oil. The crude was purified by column chromatography (silica gel, 0-75% EtOAc in petroleum ether, TLC: silica plate, 1:1

EtOAc:petroleum ether, visualisation by $KMnO_4$, Rf product = 0.60) to give the product as a colourless oil (68 mg, 0.19 mmol, 51%). $[\alpha]_D^{30}$ -94.9 (*c* 1 in $CHCl_3$) (*S*); (found (EI): M^+ + H, 360.1873 $C_{24}H_{27}NP$ requires M, 360.1876); υ_{max} 3054, 2936, 2787, 1433, 1117, 738, 694 cm^{-1} ; δ_H (300MHz, $CDCl_3$) 7.50-7.42 (4H, m, CHAr), 7.35-7.29 (6H, m, CHAr), 7.27-7.22 (5H, m, CHAr), 4.04 (1H, d, *J* 12.8 Hz, C*H*^{a}H^b), 3.17 (1H, d, *J* 12.8 Hz, CH^a*H*^{b}), 2.90 (1H, t, *J* 7.7 Hz, C*H*$_2$N), 2.62 (1H, dt, *J* 13.1 and 3.4 Hz, C*H*$_2$N), 2.46 (1H, m, C*H*N), 2.07 (3H, m, C*H*$_2$), 1.67 (3H, m, C*H*$_2$); δ_C (100MHz, $CDCl_3$) 139.41 (2 *C*Ar, d, J_{CP} 12.8 Hz), 138.18 (*C*Ar), 138.64 (*C*Ar, d, J_{CP} 12.8 Hz), 133.12 (2 *C*HAr, d, J_{CP} 19.1 Hz), 132. 59 (2 *C*HAr, d, J_{CP} 19.1 Hz), 129.04 (2 *C*HAr), 128.76 (*C*HAr), 128.54 (*C*HAr), 128.36 (2 *C*HAr, d, J_{CP} 3.0 Hz), 128.41 (2 *C*HAr, d, J_{CP} 3.0 Hz), 128.18 (*C*HAr), 126.84 (*C*HAr), 61.64 (*C*H, d, J_{CP} 18.7 Hz), 58.22 (*C*H$_2$), 53.84 (*C*H$_2$), 34.10 (*C*H$_2$, d, J_{CP} 13.3 Hz), 31.90 (*C*H$_2$, d, J_{CP} 7.8 Hz), 22.15 (*C*H$_2$); δ_p (300MHz, $CDCl_3$) -21.8; *m/z* (ESI) 360.1 (M^+ + 1) and 376.1 (M^+ + 17).

1,3-Bis-((*S*)-2-((Diphenylphosphino)methylpyrrolidin-1-yl)methyl)benzene (165).



This compound is novel.

This compound was prepared as for **164** using NaH (60% in mineral oil) (120 mg, 3.00 mmol), anhydrous THF (9 cm^3), (S)-2-((diphenylphosphino)methyl)pyrrolidine **163** (200 mg, 0.742 mmol) and α,α-dibromo-*m*-xylene (79 mg, 0.30 mmol). The crude was purified by column chromatography (silica gel, 0-100% EtOAc in

petroleum ether, TLC: silica plate, 1:1 EtOAc:petroleum ether, visualisation by $KMnO_4$, Rf product = 0.1) to give the product as a yellow oil (24 mg, 0.038 mmol, 13%). $[\alpha]_D^{30}$ – 24.6 (*c* 0.5 in $CHCl_3$) (*S*); (found (EI): $M^+ + H$, 641.3211 $C_{42}H_{47}N_2P_2$ requires 641.3209; υ_{max} 2922, 2791, 1655, 1434, 1159, 1118, 906, 798, 738, 694 cm^{-1}; δ_H (300MHz, $CDCl_3$) 7.47-7.39 (9H, m, C*H*Ar), 7.33-7.28 (11H, m, C*H*Ar), 7.16-7.14 (2H, m, C*H*Ar), 7.10-7.04 (2H, m, C*H*Ar), 4.00 (2H, d, *J* 12.8Hz, CH^aH^bPh), 3.09 (2H, d, *J* 12.8Hz, CH^aH^bPh), 2.88-2.83 (2H, m, $CH^aH^bPPh_2$), 2.64-2.58 (2H, m, $CH^aH^bPPh_2$), 2.47-2.39 (2H, m, C*H*N), 2.10-1.93 (6H, m, CH_2), 1.63 (6H, m, CH_2); δ_C (75 MHz, $CDCl_3$) 138.52 (2 *C*Ar), 137.88 (2 *C*Ar), 132.59 (*C*HAr), 132.33 (*C*HAr), 132.06 (*C*HAr), 131.82 (*C*HAr), 129.10 (2 *C*Ar), 128.99 (*C*HAr), 128.14 (2 *C*HAr), 127.91 (2 *C*HAr), 127.81 (4 *C*HAr), 127.76 (4C), 127.71 (*C*HAr), 127.38 (*C*HAr), 126.99 (2 *C*HAr), 61.24 (2 *C*H), 57.69 (2 CH_2), 53.25 (2 CH_2), 33.42 (2 CH_2, d, J_{CP} 13.2 Hz), 31.25 (2 CH_2, d, J_{CP} 7.6 Hz), 21.47 (CH_2); δ_P (300MHz, $CDCl_3$) -21.6; *m/z* (ESI) 641.2 ($M^+ + 1$).

Tetraethylammonium undecacarbonylhydridotriferrate (166).

$[Et_3NH]\ [HFe_3(CO)_{11}]$.

This compound is known in the literature.[128, 136] Full characterisation is difficult due to the air sensitive nature of the compound, but NMR data has been previously reported.[136]

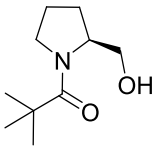
To degassed water (1 cm^3, 18 mmol) and degassed triethylamine (349 μL, 2.5 mmol). To this was then added $Fe(CO)_5$ (460 μL, 3.5 mmol). The reaction was connected to a reflux condenser and stirred vigorously at 80°C for 20 hours. After this the reaction was cooled to room temperature. The reaction was filtered under nitrogen and washed with degassed, distilled water. The residue was then dried under

vacuum. The product, a red dark red solid was stored under nitrogen. δ_H (300MHz, C_6D_6) 1.90 (1H, br s, N*H*), 1.40 (2H, br q, CH_2), 0.00 (3H, br t, CH_3) and -15.25 (0.2H, s, Fe*H*). Data matches that previously reported for this compound although the integral of the Fe*H* signal was expected to be 1.[136]

General procedure 2: asymmetric transfer hydrogenation with [Et_3NH] [$HFe_3(CO)_{11}$].[128, 129]

The reaction was carried out under an argon atmosphere. To [Et_3NH] [$HFe_3(CO)_{11}$] **166** (3 mg, 0.005 mmol), KOH (1.6 mg, 0.03 mmol), acetophenone (60 mg, 0.5 mmol) and anhydrous, degassed *iso*-propanol (1 cm^3) all taken from a freshly prepared stock solution, was added the required ligand (3mol% for a tetradentate ligand, 6mol% for a bidentate ligand). The resulting solution was stirred under argon at 45°C. The reaction solution was filtered through silica with 1:1 EtOAc:petroleum ether 40-60°C. The filtrate was analysed by GC.

(*S*)-(2-(Hydroxymethyl)pyrrolidine)-*N*-2,2-dimethylpropan-1-one (167).

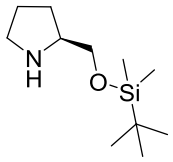


This compound is known in the literature but has not previously been fully characterised.[178]

To a nitrogen purged, dried flask was added (*L*)-prolinol (202 mg, 2.00 mmol) in chloroform (1.5 cm^3) that had been dried over molecular sieves. The resulting solution was cooled to 0°C and to it was added Et_3N (405 mg, 4.00 mmol) followed by the dropwise addition of trimethylacetyl chloride (265 mg, 2.20 mmol). The resulting solution was allowed to warm to room temperature and stirred overnight.

Chloroform (10 cm^3) and saturated $NaHCO_3$ aq. (10 cm^3) was added. The chloroform phase was collected and washed with further $NaHCO_3$ (aq.) followed by saturated NaCl (aq.) before being dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give the crude product as an orange oil. The crude was purified by column chromatography (silica gel, 0-100% EtOAc in petroleum ether, TLC: silica plate, 1:1 EtOAc:petroleum ether, visualisation by $KMnO_4$, product Rf = 0.12) to give the product as a white solid (191 mg, 1.0 mmol, 50%). Mp 78-79°C; $[\alpha]_D^{34}$ -55.5 (*c* 1 in $CHCl_3$) (*S*); (found (ESI): M^+ + H, 208.1304. $C_{10}H_{19}NNaO_2$ requires M, 208.1308); υ_{max} 3388, 2956, 2872, 1589, 1410, 1365, 1225, 1155, 1053, 752 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.02 (1H, br s, O*H*), 4.14-4.06 (1H, m, C*H*N), 3.68-3.60 (1H, m, CH_2N), 3.42-3.38 (2H, m, CH_2OH), 3.33-3.25 (1H, m, CH_2N), 1.98-1.70 (2H, m, CH_2), 1.65-1.53 (1H, m, CH_2), 1.43-1.35 (1H, m, CH_2), 1.26 (9H, s, (CH_3)$_3$); δ_C (75 MHz, $CDCl_3$) 178.08 (1*C*=O), 66.11 (*C*H), 61.40 (*C*H_2), 47.77 (*C*H_2), 38.39 (*C*$(CH_3)_3$), 26.83 (3 *C*H_3), 26.4 (*C*H_2), 24.6 (*C*H_2); *m/z* (ESI) 186.2 (M^+ + 1), 208.1 (M^+ + 23). Data matches that previously reported for this compound.[178]

(*S*)-2-((*tert*-Butyldimethylsilyloxy)methylpyrrolidine (168).

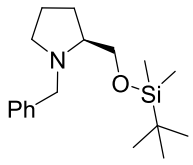


This compound is known in the literature but has not previously been fully characterised.[179]

To (*L*)-prolinol (303 mg, 2.99 mmol) was added triethylamine (405 mg, 4.00 mmol). To this was then added anhydrous Et_2O (5 cm^3), anhydrous THF (5 cm^3) and the

solution cooled to 0°C. TBDMSCl (603 mg, 4.00 mmol) was then added. The resulting solution was allowed to warm to room temperature and stirred overnight. After this 5 cm^3 of 50% K_2CO_3 solution (aq.) was slowly added to the reaction. The organic phase was separated and washed with saturated $NaHCO_3$ solution (aq.) and brine. The organic phase was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to leave the crude product (**179**) as an orange oil. (634 mg, 2.94 mmol, 98%). Further purification was not necessary. $[\alpha]_D^{20}$ – 1.8 (*c* 0.25 in $CHCl_3$) (*S*); (found (EI): M^+ + H, 216.1779 $C_{11}H_{26}NOSi$ requires 216.1778; υ_{max} 2953, 2927, 2855, 1462, 1406, 1252, 1090, 832, 771, 664 cm^{-1}; δ_H (300MHz, $CDCl_3$) 3.59-3.45 (2H, m, C*H*$_2$OSi), 3.14-3.06 (1H, m, C*H*N), 2.98-2.90 (1H, m, C*H*$_2$N), 2.82-2.74 (1H, m, C*H*$_2$N), 2.64 (1H, br s, N*H*), 1.76-1.64 (3H, m, C*H*$_2$), 1.46-1.38 (1H, m, C*H*$_2$), 0.87 (9H, s, (C*H*$_3$)$_3$), 0.3 (6H, s, 2 x C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 65.34 (*C*H$_2$), 59.85 (*C*H), 46.36 (*C*H$_2$), 27.35 (*C*H$_2$), 25.88 (3 *C*H$_3$), 25.40 (2 *C*H$_2$), 18.27 (*C*), -5.42 (*C*H$_3$); *m/z* (ESI) 216.2 (M^+ + H). Data matches that previously reported for this compound.[179]

(*S*)-1-Benzyl-2-((*tert*-butyldimethylsilyloxy)methyl)pyrrolidine (169).

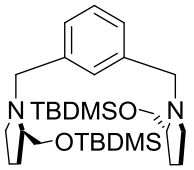


This compound is known in the literature but has not previously been fully characterised.[179]

This compound was prepared as for compound **175** using NaH (60% in mineral oil) (88 mg, 2.20 mmol) anhydrous THF (8 cm^3), *O*-(*tert*-butyldimethylsilyl)prolinol **168** (120 mg, 0.557 mmol) and benzyl bromide (89 mg, 0.56 mmol) The crude product

was purified by column chromatography (silica gel, 0-20% EtOAc in petroleum ether, TLC: silica plate, 1:1 EtOAc:petroleum ether, visualisation by $KMnO_4$, product Rf = 0.81) to give the product as a colourless oil (80 mg, 0.26 mmol, 46%). $[\alpha]_D^{30}$ -26.5° (*c* 0.5 in $CHCl_3$) (*S*); (found (EI): M^+ + H, 306.2249 $C_{18}H_{32}NOSi$ requires M, 306.2248); υ_{max} 2955, 2927, 2856, 2787, 2361, 1461, 1252, 1076, 834, 774, 735, 697 cm^{-1}; δ_H (300MHz, $CDCl_3$)7.24-7.14 (5H, m, C*H*Ar), 4.04 (1H, d, *J* 13.3 Hz, C*H*^{a}H^{b}Ar), 3.57 (1H, dd, *J* 9.9 and 5.4 Hz, C*H*^{a}H^{b}OSi), 3.42-3.32 (2H, m (dd and d overlapping), CH^a*H*^{b}Ar and CH^a*H*^{b}OSi overlapping), 2.87-2.81 (1H, m, C*H*$_2$N), 2.65-2.56 (1H, m, C*H*N), 2.19-2.10 (1H, m, C*H*$_2$N), 1.86-1.77 (1H, m, C*H*$_2$), 1.64-1.51 (3H, m, C*H*$_2$), 0.81 (9H, s, (C*H*$_3$)$_3$), 0.04 (6H, s, C*H*$_3$); δ_C (75MHz, $CDCl_3$) 139.25 (*C*Ar), 128.40 (2 *C*HAr), 127.53 (2 *C*HAr), 126.14 (*C*HAr), 66.56 (*C*H$_2$), 64.46 (*C*H), 59.39 (*C*H$_2$), 54.21 (*C*H$_2$), 27.82 (*C*H$_2$), 25.36 (3 *C*H$_3$), 22.22 (*C*H$_2$), 17.71 (*C*), -5.95 (2 *C*H$_3$); *m/z* (ESI) 306.2 (M^+ + 1). Data matched that previously reported for this compound.[179]

1,3-Bis-((*S*)-2-((*tert*-butyldimethylsilyloxy)methyl)pyrrolidine)methyl)benzene (170).

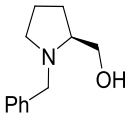


This compound is novel.

Prepared as for **169** using NaH (60% in mineral oil) (112 mg, 2.80 mmol), anhydrous THF (9 cm^3), *O*-(*tert*-butyldimethylsilyl)prolinol **168** (150 mg, 0.696 mmol) and α,α-dibromo-*m*-xylene (46 mg, 0.28 mmol). The crude product was purified by column chromatography (silica gel, 0-20% EtOAc in petroleum ether, TLC: silica plate, 1:1 EtOAc:petroleum ether, visualisation by $KMnO_4$, product Rf =

0.56) to give the product as a colourless oil (54 mg, 0.10 mmol, 36%). $[\alpha]_D^{32}$ -22.3° (*c* 0.3 in $CHCl_3$) (*S*); (found (EI): M^+ + H, 533.3967 $C_{30}H_{57}N_2O_2Si_2$ requires M, 533.3953); υ_{max} 2953, 2927, 2855, 2784, 1461, 1360, 1251, 1083, 834, 774, 704, 665 cm^{-1}; δ_H (300MHz, $CDCl_3$) 7.24 (1H, s, C*H*Ar), 7.20-7.15 (3H, m, CHAr), 4.06 (2H, d, *J* 12.8 Hz, 2 x C*H*^{a}H^{b}Ar), 3.62 (2H, dd, *J* 10.0 and 5.3 Hz, 2 x C*H*^{a}H^{b}OSi), 3.46-3.36 (4H, m (d and dd overlapping), 2 x C*H*^{a}H^{b}Ar and 2 x C*H*^{a}H^{b}OSi overlapping), 2.90-2.85 (2H, m, CH_2N), 2.68-2.60 (2H, m, C*H*N), 2.20 (2H, q, *J* 8 Hz, CH_2N), 1.94-1.82 (2H, m, CH_2), 1.71-1.52 (6H, m, CH_2), 0.87 (18H, s, 2 x (CH_3)$_3$), 0.02 (12H, s, 4 x CH_3); δ_C (75 MHz, $CDCl_3$) 139.06 (2 *C*Ar), 128.96 (1 *C*HAr), 127.31 (*C*HAr), 126.89 (2 *C*HAr), 66.56 (2 *C*H_2), 64.48 (2 *C*H), 59.39 (2 *C*H_2), 54.20 (2 *C*H_2), 27.87 (2 *C*H_2), 25.36 (6 *C*H_3), 22.23 (2 *C*H_2), 17.71 (2 *C*), -5.9 (4 *C*H_3); *m/z* (ESI) 533.3 (M^+ + 1). (For procedure see reference 169-171).

(*S*)-(1-benzylpyrrolidin-2-yl)methanol (171).

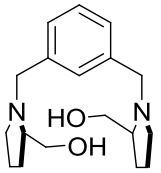


This compound is known and has previously been fully characterised.[180]

To a nitrogen purged flask, dried by heating under vacuum was added(*S*)-1-benzyl-2-(*tert*-butyldimethylsilyloxy)methylpyrroliodine **169** (76 mg, 0.25 mmol) and anhydrous THF (4 cm^3). The solution was cooled to 0°C and TBAF 1M solution in THF (0.4 cm^3, 0.4 mmol) was added. The solution was stirred at O°C and monitored by TLC (1:1 EtOAc:pet ether, visualisation by $KMnO_4$, product Rf = 0.51). Additional TBAF (0.2 cm^3, 0.2 mmol) was added after 2 hours and the solution was allowed to warm to room temperature and stirred for an hour. Once complete by TLC the reaction was quenched by the slow addition of saturated Na_2HCO_3 solution

(aq.). The reaction was washed with water (10 cm^3) and extracted with Et_2O (3 x 10 cm^3). The Et_2O phases were combined, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to leave the crude product as an orange oil. The crude was purified by column chromatography (silica gel, 0-100% EtOAc in petroleum ether, TLC: as above) to give the pure product as a yellow oil, (33 mg, 0.17 mmol, 68%). $[\alpha]_D^{34}$ -43.3 (*c* 0.8 in $CHCl_3$) (*S*) (lit.[180] $[\alpha]_D^{20}$ -24 (*c* 0.4 in $CHCl_3$) (*S*)); (found (ESI): $M^+ + H$, 192.1384. $C_{12}H_{18}NO$ requires M, 192.1383); υ_{max} 3330, 2956, 2872, 2791, 1452, 1074, 1028, 737, 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.33-7.26 (5H, m, C*H*Ar), 4.02 (1H, d, *J* 13.0 Hz, C*H*^{a}H^{b}Ar), 3.68 (1H, dd, *J* 11.0 and 3.4 Hz, C*H*^{a}H^{b}OH), 3.49-3.43 (2H, m, CH^a*H*^{b}Ar and CH^a*H*^{b}OH overlapping), 3.06-3.01 (1H, m, C*H*^{a}H^{b}N), 2.96-2.64 (2H, br s and m overlapping, C*H*N and O*H* overlapping), 2.39-2.33 (1H, m, CH^a*H*^{b}N), 1.98-1.81 (2H, m, C*H*$_2$), 1.77-1.69 (2H, m, C*H*$_2$); δ_C (100 MHz, $CDCl_3$) 139.24 (*C*Ar), 128.98 (2 *C*HAr), 128.46 (2 *C*HAr), 127.38 (*C*HAr), 64.71 (*C*H), 61.67 (*C*H$_2$), 58.64 (*C*H$_2$), 54.39 (*C*H$_2$), 27.65 (*C*H$_2$), 23.48 (*C*H$_2$); *m/z* (ESI) 192.1 (M^+ + 1). Data matches that previously reported for this compound.[180]

1,3-Bis-((*S*)-2-((pyrrolidin-1-yl)methanol)methyl)benzene (172).

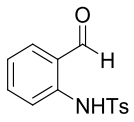


This compound is novel.

The compound was prepared as for (*S*)-(1-benzylpyrrolidin-2-yl)methanol **171** using (*S*)-1-((1,2*R*)-3-(((2*R*)-2-((*tert*-butyldimethylsilyloxy)methyl)cyclopentyl)methyl)-

benzyl)-2-((*tert*-butyldimethylsilyloxy)methyl)pyrrolidine **170** (512 mg, 0.96 mmol), anhydrous THF (3 cm^3) and TBAF 1M solution in THF (2.9 cm^3, 2.9 mmol). The crude product was purified by column chromatography (silica gel, 0-50% MeOH in DCM followed by flushing with 100% MeOH, TLC: silica plate, 20% MeOH in DCM, visualisation by $KMnO_4$, product Rf = 0) to give the pure product as an orange/yellow oil (64 mg, 0.21 mmol, 22%). $[\alpha]_D^{34}$ -47.8 (*c* 0.5 in $CHCl_3$) (*S*); (found (ESI): M^+ + H, 305.2220. $C_{18}H_{29}N_2O_2$ requires M, 305.2224); υ_{max} 3323, 2948, 2871, 2793, 1443, 1351, 1079, 1038, 905, 753, 704 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.27-7.16 (4H, m, C*H*Ar), 3.89 (2H, d, *J* 13.0 Hz, C*H*^{a}H^{b}Ar), 3.57 (2H, dd, *J* 10.7 and 3.6 Hz, C*H*^{a}H^{b}OH), 3.40-3.35 (4H, m, CH^a*H*^{b}Ar and CH^a*H*^{b}OH overlapping), 2.99-2.93 (2H, m, C*H*^{a}H^{b}N), 2.84-2.44 (4H, m and br s overlapping, C*H*N and O*H* overlapping), 2.33-2.25 (2H, m, CH^a*H*^{b}N), 1.95-1.75 (4H, m, CH_2), 1.72-1.64 (4H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 139.35 (2 *C*Ar), 129.15 (1 *C*HAr), 128.40 (1 *C*HAr), 127.63 (2 *C*HAr), 64.49 (2 *C*H), 61.93 (2 *C*H_2), 58.73 (2 *C*H_2), 54.67 (2 *C*H_2), 27.84 (2 *C*H_2), 23.51 (2 *C*H_2); *m/z* (ESI) 305.2 (M^+ + 1), 327.2 (M^+ + 23).

2-*N*-Tosylbenzaldehyde (173).

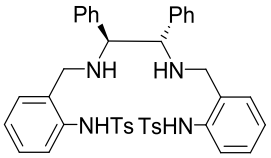


This compound is known in the literature and has previously been fully characterised.[181, 182]

To 2-aminobenzyl alcohol (1 g, 8 mmol) was added anhydrous chloroform (8 cm^3), pyridine (800 μL, 9.89 mmol) and *p*-toluenesulfonyl chloride (1.6 g, 8.4 mmol). The resulting solution was stirred for 3 hours at room temperature. After this the solvent

was removed under reduced pressure to give a brown solid. This was dissolved in EtOAc and washed with saturated NH_4Cl solution (aq.). The EtOAc phases were combined, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to give an off-white solid. This was then purged with nitrogen and to it was added anhydrous DCM (40 cm^3) and MnO_2 (5.6 g, 64 mmol). The resulting black solution was stirred at room temperature for 1.5 hours before being filtered through celite and the solvent removed from the filtrate under reduced pressure to leave the crude product as an off-white solid. This was purified by column chromatography (silica gel, 3:1 petroleum ether:EtOAc, TLC: silica plate, 25% EtOAc in petroleum ether, visualisation by $KMnO_4$, product Rf = 0.50) to give the product as a white solid (430 mg, 1.56 mmol, 20%). Mp 135°C; (found (EI): M^+ + Na, 298.0509 $C_{14}H_{13}N_2NaO_3S$ requires M, 298.0508); υ_{max} 3119, 2849, 2766, 1662, 1581, 1493, 1455, 1404, 1337, 1291, 1150, 1087, 929, 811, 758, 657 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.80 (1H, s, N*H*), 9.82 (1H, s, CO*H*), 7.77 (2H, d, *J* 8.3 Hz, C*H*ArSO_2), 7.70 (1H, d, *J* 8.0 Hz, C*H*Ar), 7.59 (1H, dd, *J* 7.5 Hz and 1.7 Hz, C*H*Ar), 7.51 (1H, t, *J* 8.0 Hz and 1.7 Hz, C*H*Ar), 7.24 (2H, d, *J* 8.3 Hz, C*H*ArSO_2), 7.16 (1H, td, *J* 7.5 and 0.75 Hz, C*H*Ar), 2.36 (3H, s, CH_3). δ_C (75MHz, $CDCl_3$) 195.10 (*C*=O), 146.89 (*C*Ar), 144.25 (*C*Ar), 139.90 (*C*Ar), 136.32 (*C*Ar), 136.18 (*C*HAr), 135.84 (*C*HAr), 129.79 (2 *C*HAr), 127.27 (2 *C*HAr), 123.00 (*C*HAr), 117.70 (*C*HAr), 21.6 (*C*H_3); *m/z* (ESI) 276.0 (M^+ + 1) and 298.0 (M^+ + 23). Data matches that previously reported for this compound. [181, 182]

(1*S*,2*S*)-*N*, *N*-Bis(2-*N*-tosylbenzyl)-1,2-diphenylethane-1,2-diamine (174).



This compound is novel.

To 2-*N*-tosylbenzaldehyde **173** (430 mg, 1.56 mmol) was added Na_2SO_4 (680 mg, 4.79 mmol) and anhydrous DCM (7 cm^3). To this was then added (*S*,*S*)-DPEN (170 mg, 0.801 mmol). The resulting bright yellow solution was stirred at room temperature for 24 hours. After this, the reaction solution was filtered and the solvent removed under reduced pressure to leave a bright yellow solid. The solid was dissolved in anhydrous THF (8 cm^3) and cooled to 0°C. $LiAlH_4$ solution 2M in THF (2.4 cm^3, 4.8 mmol) was then added dropwise. The solution was stirred overnight and allowed to warm to room temperature. After this the reaction was cooled to 0°C and water was slowly added. The THF was removed under reduced pressure. The aqueous residue was then extracted with Et_2O (4 x 20 cm^3). The Et_2O phases were combined, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to leave the product as a pale yellow, viscous oil (198 mg, 0.27 mmol, 59%). Further purification was not necessary. Mp 87°C; $[\alpha]_D^{32}$ + 13.2° (*c* 0.5 in $CHCl_3$) (*S*, *S*); (found (EI): M^+ + H, 731.2740 $C_{42}H_{43}N_4O_4S_2$ requires M, 731.2734); υ_{max} 2970, 2901, 1707, 1586, 1493, 1330, 1155, 1090, 931, 812, 756, 700, 656 cm^{-1}; δ_H (700MHz, $CDCl_3$) 7.49-7.46 (6H, m, C*H*ArSO_2 and C*H*Ar overlapping), 7.25-7.19 (10H, m, C*H*Ar in DPEN, N*H*Ts and C*H*Ar), 7.10 (4H, d, *J* 7.7 Hz, C*H*ArCH_3), 6.99 (4H, d, *J* 6.8 Hz, C*H*Ar in DPEN), 6.94 (2H, t, *J* 7.0 Hz, C*H*Ar), 6.81 (2H, d, *J* 7.0 Hz, C*H*Ar), 3.78 (2H, s, CH), 3.33 (2H, d, *J* 13.0 Hz, C*H*^{a}H^b), 3.23 (2H, d, *J* 13.0 Hz, CH^a*H*^{b}), 2.32 (6H, s, CH_3) ; δ_C (175 MHz, $CDCl_3$) 143.29 (2 *C*Ar), 138.60 (2

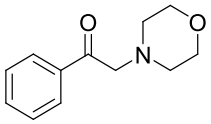
*C*Ar, s), 137.62 (2 *C*Ar), 137.43 (2 *C*Ar), 129.77 (2 *C*HAr), 129.49 (4 *C*HAr), 128.63 (2 *C*HAr), 128.57 (4 *C*HAr), 128.50 (2 *C*Ar), 128.99 (4 *C*HAr), 127.74 (2 *C*HAr), 126.90 (4 *C*HAr, s), 124.40 (2 *C*HAr), 121.76 (2 *C*HAr), 67.61 (2 *C*H), 50.44 (2 *C*H_2), 21.48 (2 *C*H_3); *m/z* (ESI) 731.1 (M^+ + 1) and 753.0 (M^+ + 23).

General procedure 3: rhodium and ruthenium-catalysed transfer hydrogenation of acetophenone.

To a nitrogen purged, dried test tube containing the desired ligand (0.002 mmol, 1 mol% for tetradentate ligands and 0.004 mmol, 2 mol% for bidentate ligands) was added from a stock solution, acetophenone (24 mg, 0.2 mmol), anhydrous IPA (2 cm^3), KOH (0.11 mg, 0.0020 mmol) and either $[Rh(COD)Cl]_2$ (0.99 mg, 0.002 mmol) or $[Ru(benzene)Cl_2]_2$ (1.0 mg, 0.002 mmol). The resulting solution stirred under nitrogen at 82°C. The reaction solution was filtered through silica with 1:1 EtOAc:petroleum ether 40-60°C. The filtrate was analysed by GC.

5.3.3 Synthetic procedures for Section 2.3

2-morpholino-1-phenylethanone.

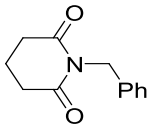


This compound is known in the literature and has previously been fully characterised. [183]

To a dried, nitrogen purged flask was added 2-bromoacetophenone (1.0 g, 5.0 mmol). To this was then added anhydrous DCM (20 cm^3) and the resulting solution was stirred and Et_3N (1.01 g, 10 mmol) was added followed by morpholine (436 mg, 5 mmol). The reaction was stirred at room temperature overnight. The reaction was

washed with saturated $NaHCO_3$ solution and brine. The organic phase was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to give the crude product as a yellow oil. The crude was purified by column chromatography (silica gel, 0-100% EtOAc in petroleum ether, TLC: silica gel, 1:1 EtOAc:petroleum ether, visualisation by $KMnO_4$, product Rf = 0.36) to give the product as a yellow oil (556 mg, 2.7 mmol, 54%). The product was unstable at room temperature and decomposed to its enamine over time. (Found (ESI): M^+ + H, 206.1181 $C_{12}H_{16}NO_2$ requires M, 206.1176); υ_{max} 2968, 2906, 2814, 1691, 1451, 1278, 1215, 1112, 971, 864, 759, 691 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.04-8.01 (2H, m, C*H*Ar), 7.63-7.57 (1H, m, C*H*Ar), 7.51-7.46 (2H, m, C*H*Ar), 3.85 (2H, s, CH_2CO), 3.82-3.79 (4H, m, 2 x CH_2CH_2N), 2.65-2.62 (4H, m, 2 x OCH_2CH_2); δ_C (75 MHz, $CDCl_3$) 196.09 (*C*=O), 135.94 (*C*Ar), 133.35 (*C*HAr), 128.59 (2 *C*HAr), 128.07 (2 *C*HAr), 66.81 (2 *C*H_2), 64.69 (*C*H_2), 53.88 (2 *C*H_2); *m/z* (ESI) (M^+ + 1), (M^+ + 23). Data matches that previously reported for this compound.[183]

1-Benzylpiperidine-2,6-dione.



This compound is known in the literature and has previously been fully characterised.[184]

To a dried, nitrogen purged flask was added glutaric anhydride (571 mg, 5.00 mmol) and anhydrous THF (10 cm^3). The resulting solution was stirred and to it was added benzylamine (643 mg, 6.00 mmol). The reaction was stirred for 30 min at room temperature. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc (10 cm^3) and the solution was washed with 1 M HCl (aq.) (10

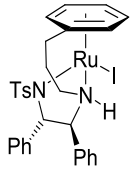
cm^3). The EtOAc phase was collected and the aqueous phase washed with a further 2 portions of EtOAc. The EtOAc phases were combined and washed with brine before being dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to leave the crude intermediate. To the intermediate, at room temperature and under nitrogen was then added Et_3N (759 mg, 7.50 mmol) and acetic anhydride (5 cm^3). The reaction was then connected to a reflux condenser and stirred at 80°C for 1 hour. The reaction was then cooled to room temperature and dried under reduced pressure. The residue was dissolved in EtOAc (10 cm^3) and the resulting solution was washed with 1 M HCl (aq.) and brine. The EtOAc phase was dried over $MgSO_4$, filtered and the solvent removed by evaporation to leave the crude product as an orange oil. The crude was purified by column chromatography (silica gel, 0-100% EtOAc in petroleum ether 40-60, TLC: 1:1 EtOAc:petroleum ether, visualisation by $KMnO_4$, product Rf = 0.53) to give the product as a white solid (596 mg, 2.9 mmol, 58%). Mp 54°C; (found (ESI): $M^+ + H$, 204.1015 $C_{12}H_{14}NO_2$ requires M, 204.1019); υ_{max} 2964, 1668, 1422, 1354, 1228, 1168, 1133, 1013, 717, 703 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.35-7.33 (2H, m, C*H*Ar), 7.29-7.22 (3H, m, C*H*Ar), 4.93 (2H, s, NCH_2), 2.64 (4H, t, *J* 6.5 Hz, 2 x CH_2CH_2), 1.94-1.87 (2H, quin, *J* 6.5 Hz,$CH_2CH_2CH_2$); δ_C (100 MHz, $CDCl_3$) 172.54 (2 *C*=O), 137.44 (*C*Ar), 128.54 (2 *C*HAr), 128.35 (2 *C*HAr), 127.31 (*C*HAr), 42.56 (CH_2), 32.72 (2 CH_2), 16.98 (CH_2); *m/z* (ESI) 204.1 ($M^+ + 1$), 226.1 ($M^+ + 23$). Data matches that previously reported for this compound.[184]

General procedure 4: pressure hydrogenation of ketones catalysed by tethered ruthenium catalysts (S/C 500/1).

To an oven dried test tube was added the catalyst (1.2 mg, 0.002 mmol) and ketone (1 mmol). To the test tube was then added anhydrous MeOH (2 cm^3) and the tube was transferred to the Parr reactor which was then sealed and purged with H_2 before being charged with H_2 to 30 bar. The reactor was then heated to 60°C and the reactions stirred at this temperature and pressure for the required time. The reactions were cooled, the pressure released and the reaction mixture filtered through silica with 1:1 EtOAc:petroleum ether 40-60. The filtrate was then analysed by GC. The remainder of the filtrate was concentrated under vacuum to leave the alcohol product which was then analysed by ^1H and ^{13}C NMR and its optical rotation obtained. Where necessary the product was purified by column chromatography (silica gel, 0-50% EtOAc in petroleum ether 40-60) to remove residual starting material.

5.3.4 Synthetic procedures for Sections 2.4 and 2.5.

_N_-[(1_S_, 2_S_)-1, 2-Diphenyl-2-(3-phenypropylamino)ethyl)-4-methylbenzenesulfonamide)ruthenium(II)iodide monomer (181).

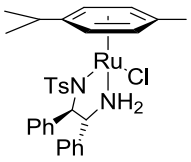


This compound is novel.

To an argon purged flask was added (*S*,*S*)TsDPEN 3C tethered RuCl **97** catalyst (40 mg, 0.060 mmol) and KI (25 mg, 0.15 mmol). To this was then added 50% v/v EtOH/H_2O (4 cm^3). The resulting orange solution was stirred under reflux at 80°C for 2 hours. After this the reaction solution which had become a red/purple colour was cooled to room temperature and filtered. The collected precipitate was dried to

give a red/purple solid (42 mg, 0.059 mmol, 98%). Purification was not necessary. Mp 170°C (decomposed); $[\alpha]_D^{28}$ +565 (*c* 0.1 in $CHCl_3$) (*S*, *S*); (found (ESI): M^+ - I +H, 585.1161 $C_{30}H_{32}N_2O_2RuS$ requires M, 585.1151); υ_{max} 3495, 3212, 2940, 1455, 1263, 1128, 1084, 936, 905, 806, 701, 659 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.17 (2H, d, *J* 7.6 Hz, C*H*Ar in tosyl), 7.12-7.07 (3H, m, C*H*Ar), 6.82-6.76 (5H, m, C*H*Ar), 6.66 (H, t, *J* 7.5 Hz, C*H*Ar), 6.59 (2H, d, *J* 7.6 Hz, C*H*Ar in tosyl), 6.48 (1H, t, *J* 5.6 Hz, C*H*Ar-Ru), 6.25 (1H, t *J*, 5.6 Hz, C*H*Ar-Ru), 6.10 (1H, t *J* 5.6 Hz, C*H*Ar-Ru), 5.60 (1H, d, *J* 5.6 Hz, C*H*Ar-Ru), 5.05 (1H, d, *J* 5.6 Hz, C*H*Ar-Ru), 4.81-4.78 (1H, m, N*H*), 4.09 (1H, d, *J* 11.0 Hz, C*H*NTs), 3.69 (1H, t, *J* 11.0 Hz, C*H*NH), 2.80-2.74 (1H, m, CH_2NH), 2.64-2.52 (2H, m, CH_2CH_2NH), 2.29-2.24 (4H, m and s overlapping, C*H* in CH_2NH and CH_3 overlapping), 2.19-2.10 (1H, m, CH_2ArRu), 1.99-1.93 (1H, m, CH_2ArRu); δ_C (100 MHz, $CDCl_3$) 142.40 (*C*Ar), 139.16 (*C*Ar), 138.50 (*C*Ar), 136.51 (*C*Ar), 129.20 (2 *C*HAr), 128.68 (*C*HAr), 128.26 (2 *C*HAr), 128.03 (4 *C*HAr), 127.19 (2 *C*HAr), 126.81 (2 *C*HAr), 126.27 (*C*HAr), 98.87 (*C*Ar-Ru), 93.44 (*C*HAr-Ru), 89.61 (*C*HAr-Ru), 81.98 (*C*HAr-Ru), 79.36 (*C*HAr-Ru), 77.44 (*C*HAr-Ru), 77.20 (*C*H), 70.00 (*C*H), 48.57 (*C*H_2), 29.59 (*C*H_2), 26.08 (*C*H_2), 21.25 (*C*H_3); *m/z* (ESI) 585.0 (M^+ + 1); X-ray crystallography data is given in Appendix 2. For procedure see reference 185.

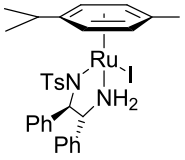
_N_-[(1_R_,2_R_)-2-(Amino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide(_p_-cymene)ruthenium(II)chloride monomer (57a).



This compound is known and has previously been fully characterised.[74]

To a nitrogen purged, dried round bottom flask, was added [(*p*-cymene)$RuCl_2$]$_2$ (50 mg, 0.080 mmol) was added (*R*,*R*)TsDPEN (59 mg, 0.16 mmol). To this was then added Et_3N (32 mg, 0.32 mmol) and degassed anhydrous IPA (5 cm^3). The resulting orange solution was stirred at reflux (80°C) for 1 hour. After this the reaction was cooled to room temperature, and the solvent removed under reduced pressure to leave an orange solid. The solid was washed with water and filtered. The solid was dried and then recrystallised from hot MeOH to give the product as an orange solid (75 mg, 0.12 mmol, 75%). Mp 182-184°C; $[\alpha]_D^{27}$ -45 (*c* 0.01 in $CHCl_3$) (*R*,*R*) (lit.[186] $[\alpha]_D^{29}$ -80.5 (*c* 1.05 in $CHCl_3$) (*R*,*R*)); (found (ESI): M^+ + H, 601.1468. $C_{31}H_{35}N_2O_2RuS$ requires M, 601.1465); υ_{max} 3216, 1452, 1265, 1126, 1083, 913, 806, 696, 572 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.98-6.96 (5H, m, C*H*Ar), 6.72-6.68 (5H, m, C*H*Ar), 6.56 (2H, t *J* 7.7 Hz, C*H*Ar), 6.38-6.37 (2H, m, C*H*Ar), 5.90 (1H, br s, C*H*Ar-Ru), 5.80 (1H, br s, C*H*Ar-Ru), 5.73-5.70 (2H, m, C*H*Ar-Ru), 3.73 (1H, d *J* 10.5 Hz, C*H*NTs), 3.61-3.56 (1H, m, C*H*NH_2), 3.24-3.11 (1H, m, N*H*$_2$), 3.11-3.09 (1H, m, C*H*$(CH_3)_2$), 2.31 (3H, s, *p*-C*H*$_3(C_6H_4)SO_2$), 2.21 (3H, s, ^{i}Pr(C_6H_4)C*H*$_3$), 1.63 (1H, br s, N*H*$_2$), 1.20 (6H, d *J* 6.0 Hz, (C*H*$_3)_2$CH); δ_C (100 MHz, $CDCl_3$) 143.34 (*C*Ar), 139.74 (*C*Ar), 138.89 (*C*Ar), 138.67 (*C*Ar), 129.03 (*C*HAr), 127.83 (2 *C*HAr), 127.78 (2 *C*HAr), 127.30 (4 *C*HAr), 126.70 (2 *C*HAr), 126.56 (2 *C*HAr), 125.87 (*C*HAr), 93.89 (*C*Ar-Ru), 85.63 (*C*HAr-Ru), 82.00 (*C*HAr-Ru), 80.11 (*C*HAr-Ru), 71.60 (*C*HAr-Ru), 69.39 (*C*HAr-Ru), 46.18 (*C*H), 30.54 (2 *C*H_3), 22.15 (*C*H_3), 18.84 (*C*H_3); *m/z* (ESI) 601 (M^+ -35 + 1,). Data matches that previously reported for this compound.[74]

_N_-[(1_R_,2_R_)-2-(Amino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide(_p_-cymene)ruthenium(II)iodide monomer (183).



This compound is novel.

Method A:

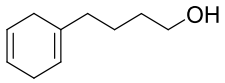
To an argon purged flask was added [Ru(*p*-cymene)Cl_2]$_2$ **182** (50 mg, 0.080 mmol) was added KI (133 mg, 0.80 mmol) followed by 50% v/v EtOH/H_2O. The resulting red solution was then stirred under reflux at 80°C for 2 hours. The reaction solution which had become purple, was cooled to room temperature and filtered. The collected precipitate was dried to give a purple solid [Ru(*p*-cymene)I_2]$_2$ (**184**) (68 mg, 0.070 mmol). To the purple solid (60 mg, 0.060 mmol) in an argon purged, dried flask was then added (*R,R*)TsDPEN (44 mg, 0.12 mmol), followed by Et_3N (24 mg, 0.24 mmol) and anhydrous IPA (5 cm^3). The resulting purple solution was stirred under reflux at 80°C for 1 hour. After this the reaction was cooled to room temperature and the solvent removed under reduced pressure. The residue was then washed with 1 cm^3 of water before again being dried to leave the crude as a purple solid. The solid was recrystallised from hot MeOH to leave the purified product as a purple/red solid (26 mg, 0.035 mmol, 29% based on mmol Ru). For procedure see reference 185.

Method B:

To Noyori RuCl complex **57a** (130 mg, 0.216 mmol) was added KI (83 mg, 0.50 mmol) and anhydrous IPA (10 cm^3). The reaction was stirred at reflux (80°C) for 2 hours and then cooled to room temperature. The solid was collected by filtration to

give the product as a red solid (67 mg, 0.10 mmol, 46%). For procedure see reference TT. Mp 198°C (decomposed); $[\alpha]_D^{28}$ +13 (*c* 0.05 in $CHCl_3$) (*R*,*R*); (found (ESI): M^+ - I + H, 601.1466. $C_{31}H_{36}N_2O_2RuS$ requires M, 601.1465); υ_{max} 3494, 3213,2935, 1455, 1263, 1128, 1084, 1059, 937, 906, 806, 701, 659 cm^{-1}; δ_H (400 MHz, MeOD) 7.14-7.11 (5H, m, C*H*Ar), 6.93-6.90 (2H, m, C*H*Ar), 6.86-6.79 (3H, m, C*H*Ar), 6.69-6.61 (4H, m, C*H*Ar), 5.74-5.72 (1H, m, C*H*Ar-Ru), 5.68-5.65 (2H, m, C*H*Ar-Ru), 5.57 (1H, br s, C*H*Ar-Ru), 4.61 (1H, br s, NH_2), 4.01-3.98 (1H, m, C*H*NTs), 3.78-3.75 (1H, m, C*H*NH_2), 3.34 (2H, br s, MeOH, C*H*$(CH_3)_2$ and NH_2 overlapping), 2.56 (3H, s, *p*-C$H_3(C_6H_4)SO_2$), 2.27 (3H, s, ^{i}Pr-(C_6H_4)-CH_3), 1.42 (6H, d *J*, 6.8 Hz, CH(C$H_3)_2$); δ_C (150 MHz, d_6-DMSO) δ_C (150 MHz, DMSO) 140.35 (*C*Ar), 139.79 (*C*Ar), 138.99 (*C*Ar), 135.03 (*C*Ar), 129.45 (2 *C*HAr), 129.28 (*C*HAr), 128.63 (4 *C*HAr), 128.12 (2 *C*HAr), 127.32 (2 *C*HAr), 126.83 (2 *C*HAr), 126.56 (*C*HAr), 88.25 (*C*HAr-Ru), 86.45 (*C*HAr-Ru), 73.77 (*C*HAr-Ru), 72.04 (*C*HAr-Ru), 55.39 (*C*Ar-Ru), 40.53 (*C*Ar-Ru), 40.42 (*C*H), 40.39 (*C*H), 33.46 (2 *C*H_3), 24.46 (*C*H), 23.63 (*C*H_3), 21.21 (*C*H_3); *m/z* (ESI) 601.0 (M^+ + 1); X-ray crystallographic data given in Appendix 2. For procedure see reference 185.

4-(Cyclohexa-1,4-diphenyl)butan-1-ol (185).



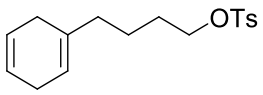
This compound is known in the literature and has previously been fully characterised.[101]

A 1L, 3-necked round bottom flask was connected to a condenser and pressure equalising dropping funnel. The flask and condenser were then cooled to -78°C with a dry ice/acetone mixture and maintained at this temperature throughout the reaction.

The system was purged with nitrogen and then to the addition funnel was added 4-phenyl-1-butanol (10g, 66.7 mmol) and anhydrous EtOH (30 cm^3). To the round bottom flask was then added ammonia gas which condensed to a volume of 250cm^3. The ethanolic solution of 4-phenyl-1-butanol was added to the flask dropwise with stirring. During the addition a white precipitate began to form in the reaction solution, additional EtOH was added in 2-3 cm^3 portions to help maintain stirring and dissipate the precipitate. A total of 20 cm^3 of additional EtOH was added in this way during the course of the 4-phenyl-1-butanol addition. Once all of the alcohol had been added, sodium was added to the reaction slowly. Upon addition of sodium, blue flecks appeared in the reaction solution and copper coloured droplets formed on the reaction surface. Sodium was added until the reaction solution was a homogenous intense, dark blue colour. Stirring was continued and when the blue colour faded (initially quickly over 2-5 mins) additional sodium was added, now in larger pieces (500 mg) until the blue colour persisted. A total of 10g of sodium was added. The reaction was then slowly warmed to room and stirred overnight. Saturated $NaHCO_3$ solution (200 cm^3) was slowly added to the reaction, initially dropwise in case of any unreacted sodium. The resulting solution was then extracted with DCM (4 x 50 cm^3). The DCM layers were collected, combined and dried over $MgSO_4$ before being filtered and the DCM then removed under reduced pressure to leave the product as a colourless oil (9.92g, 65 mmol, 98%). υ_{max} 3318, 2932, 2859, 2820, 1632, 1428, 1053, 957, 959 cm^{-1} δ_H (400 MHz, $CDCl_3$) 5.75-5.68 (2H, m, *H*C=C*H*), 5.44-5.43 (1H, m, *H*C=CCH_2), 3.66-3.63 (2H, m, C*H*$_2$), 2.72-2.67 (2H, m, C*H*$_2$), 2.62-2.57 (2H, m, C*H*$_2$), 2.02-1.95 (3H, m, C*H*$_2$ and O*H*), 1.61-1.46 (4H, m, 2 x C*H*$_2$); δ_C (75 MHz, $CDCl_3$) 134.10 (C*C*=C), 123.70 (H*C*=C) 123.68 (H*C*=C), 117.88 (H*C*=C), 62.22 (*C*H_2), 36.54 (*C*H_2), 31.79 (*C*H_2), 28.23 (*C*H_2), 26.12 (*C*H_2),

22.80 (*C*H_2); *m/z* (CI) 153.2 (M^+ + 1). Data matches that previously reported for this compound.[101] The compound was stored under nitrogen at < 0°C.

4-(Cyclohexa-1,4-dien-1-yl)buty-4-methylbenzenesulfonate (186).

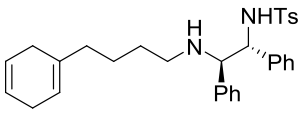


This compound is novel.

To a nitrogen purged, oven dried 2-necked round bottom flask was added 4-(cyclohexa-1,4-diphenyl)butan-1-ol **185** (456 mg, 3 mmol) and anhydrous toluene (5 cm^3). To this was then added triethylamine (455 mg, 4.5 mmol), 1-methylimidazole (369 mg, 4.5 mmol). The reaction solution was then degassed and stirred. To the reaction solution, under a flow of nitrogen was added 4-methylbenzenesulfonyl chloride (858 mg, 4.5 mmol). The reaction was then stirred overnight. Once deemed complete by TLC (silica plate, 25% EtOAc in petroleum ether, visualisation by $KMnO_4$, product Rf = 0.6) 2M HCl aq. solution (4 cm^3) was added to the reaction solution which was then stirred. The product was extracted with DCM (3 x 10 cm^3) and the DCM phase washed with brine (10 cm^3) and water (10 cm^3), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to leave the crude as a yellow oil. The crude product was purified by column chromatography (silica gel, 0-25% EtOAc in petroleum ether, TLC: as above) to give the product as a colourless oil (768 mg, 2.5 mmol, 83%). (found (ESI): M^+ + Na, 329.1175 $C_{17}H_{22}NaO_3S$ requires M, 329.1182); υ_{max} 2972, 1356, 1173, 1097, 955, 918, 813, 774, 660, 579, 555, 520 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.72-7.70 (2H, d, *J* 8.0 Hz, C*H*Ar), 7.28-7.26 (2H, d, *J* 8.0 Hz, C*H*Ar), 5.61 (2H, s, *H*C=C*H*), 5.27 (1H, s, CH_2C=C*H*), 3.97-3.94 (2H, t, *J* 6.4 Hz, CH_2OTs), 2.61-2.55 (2H, m, CH=CHC*H*-

$_2$CH), 2.46-2.41 (2H, m, C*H*$_2$C=CH), 2.37 (3H, s, C*H*$_3$), 1.85-1.81 (2H, m, CH=CC*H*$_2$(CH$_2$)$_3$), 1.59-1.52 (2H, m, C*H*$_2$CH$_2$OTs), 1.39-1.31 (2H, m, CH=CCH$_2$C*H*$_2$); δ_C (100 MHz, $CDCl_3$) 144.68 (*C*Ar), 134.08 (C*C*=C), 133.23 (*C*Ar), 129.83 (2 *C*HAr), 127.89 (2 *C*HAr), 124.26 (H*C*=C), 124.20 (H*C*=C), 118.93 (H*C*=C), 70.55 (*C*H$_2$), 36.60 (*C*H$_2$), 28.75 (*C*H$_2$), 28.38 (*C*H$_2$), 26.73 (*C*H$_2$), 22.97 (*C*H$_2$), 21.65 (*C*H$_3$); *m/z* (ESI) 328.9 (M^+ + 23), 306.9 (M^+ + 1).

_N_-(1_R_,2_R_)-(2-(4-(Cyclohexa-1,4-dienyl)butyl)-1,2-diphenylethyl)-4-methylbenzenesulfonamide (187).

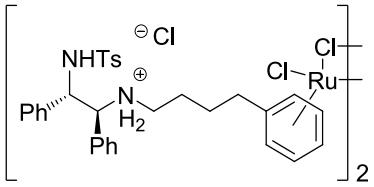


This compound is known in the literature and has previously been fully characterised.[101]

To a nitrogen purged, oven dried flask connected to a reflux condenser was added the 4-(cyclohexa-1,4-dien-1-yl)buty-4-methylbenzenesulfonate **186** (306 mg, 1.00 mmol) and anhydrous toluene (5 cm^3). To this was then added *N*,*N*-diisopropylethylamine (194 mg, 1.50 mmol) and (*R*,*R*)-TsDPEN (403 mg, 1.10 mmol). The resulting solution was degassed and then stirred at 135°C overnight. After this the reaction solution was concentrated under reduced pressure to leave the crude product as a yellow/orange oil. The crude product was purified by column chromatography (silica gel, 0-50% EtOAc in petroleum ether 40-60, TLC: silica plate, 25% EtOAc in petroleum ether, visualisation by $KMnO_4$, product Rf = 0.55) to give the product as a viscous colourless oil (441 mg, 0.88 mmol, 88%). $[\alpha]_D^{26}$ -12.1 (*c* 1.0 in $CHCl_3$) (*R*, *R*) (lit.[101] $[\alpha]_D^{25}$ -15.6 (*c* 0.5 in $CHCl_3$) (*R*,*R*)); (δ_H (400 MHz, $CDCl_3$) 7.38-7.36 (2H, d, *J* 8.0 Hz, C*H*Ar), 7.15-7.12 (3H, m, C*H*Ar), 7.07-7.01 (5H,

m, C*H*Ar), 6.95-6.90 (4H, m, C*H*Ar), 6.32 (1H, br s, N*H*), 5.71-5.69 (2H, m, *H*C=C*H*), 5.36 (1H, br s, C=C*H*), 4.24-4.22 (1H, d, *J* 8.0, C*H*NHTs), 3.61-3.59 (1H, d, *J* 8.0, C*H*NH) 2.70-2.66 (2H, m, CHCH_2CH=CH), 2.56-2.51 (2H, m, CH_2C=CH), 2.42-2.36 (1H, m, CH_2), 2.34 (3H, s, CH_3), 2.29-2.26 (1H, m, CH_2) 1.90-1.87 (2H, m, CH_2), 1.40-1.32 (4H, m, 2 x CH_2); δ_C (100 MHz, $CDCl_3$) 142.68 (*C*Ar), 139.40 (*C*Ar), 138.40 (*C*Ar), 137.09 (*C*Ar), 134.70 (C*C*=C), 129.09 (2 *C*HAr), 128.30 (2 *C*HAr), 127.90 (2 *C*HAr), 127.59 (2 *C*HAr), 127.44 (*C*HAr), 127.39 (2 *C*HAr), 127.25 (*C*HAr), 127.15 (2 *C*HAr), 124.35 (H*C*=C), 124.32 (H*C*=C), 118.50 (H*C*=C), 67.86 (*C*H), 63.08 (*C*H), 47.04 (*C*H_2), 37.20 (*C*H_2), 29.64 (*C*H_2), 28.87 (*C*H_2), 26.77 (*C*H_2), 24.76 (*C*H_2), 21.45 (*C*H_3);*m/z* (ESI) 501.2 (M^+ + 1). Data matches that previously reported for this compound.[101]

_N_-[(_R,R_)-1,2-Diphenyl-2-(4-phenylbutylamino)-ethyl]-4-methylbenzenephonamide ammonium chloride ruthenium dimer (188).

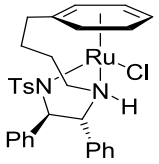


This compound is known in the literature and has previously been fully characterised.[101]

To a nitrogen purged, oven dried flask connected to a reflux condenser was added (*R*,*R*)-*N*-(4-(cyclohexa-1,4-dienyl)butyl)-1,2-diphenyl-*N'*-tosylethane-diamine **187** (1.00 g, 2.00 mmol) and anhydrous DCM (30 cm^3). The resulting solution was then stirred and cooled to 0°C with an ice/water bath. To the cooled solution was then added dropwise 2M HCl in Et_2O solution (3 cm^3, 6 mmol). The reaction solution was then stirred at room temperature for 30 min and became a yellow colour.

Volatile material was removed under reduced pressure to leave the HCl salt as an off white solid. To the salt was then added $RuCl_3.xH_2O$ (418 mg, 1.60 mmol assuming $RuCl_3.3H_2O$) and EtOH (40 cm^3). The resulting brown/black solution was stirred at reflux overnight. After this the reaction was cooled to room temperature and filtered to collect a brown/black precipitate. The precipitate was washed with Et_2O and dried to give the clean product as a brown/black solid (1.05 g, 0.74 mmol, 93%). Mp 247°C (decomposed); δ_H (400 MHz, d_6-DMSO) 9.59 (2H, br s, N*H*H), 9.10 (2H, br s, NH*H*), 8.77 (2H, d, *J* 9 Hz, N*H*H), 7.20 (8H, d, *J* 8 Hz, C*H*Ar), 7.13-7.11 (6H, m, C*H*Ar), 6.90 (4H, d, *J* 8 Hz, C*H*Ar), 6.80-6.78 (2H, m, C*H*Ar), 6.72-6.70 (8H, m, C*H*Ar), 5.91 (4H, t, *J* 5.0 Hz, C*H*Ar-Ru), 5.67-5.64 (6H, m, C*H*Ar-Ru), 4.69 (2H, t, *J*, 9.0 Hz, C*H*), 4.45 (2H, t, *J* 9.0 Hz, C*H*), 2.64-2.61 (4H, m, CH_2), 2.34-2.31 (4H, m, CH_2), 2.12 (6H, s, CH_3), 1.70-1.56 (4H, m, CH_2), 1.47-1.41 (4H, m, CH_2); δ_H (100 MHz, d_6-DMSO) 142.00 (2 *C*Ar), 137.88 (2 *C*Ar), 135.66 (2 *C*Ar), 131.58 (2 *C*Ar), 129.15 (4 *C*HAr), 128.81 (4 *C*HAr), 128.63 (4 *C*HAr), 128.28 (2 *C*HAr), 127.78 (4 *C*HAr), 127.54 (4 *C*HAr), 127.12 (2 *C*HAr), 126.26 (4 *C*HAr), 107. 15 (*C*Ar-Ru), 88.91 (4 *C*HAr-Ru), 84.91 (4 *C*HAr-Ru), 83.15 (2 *C*HAr-Ru), 64.27 (2 *C*H), 60.64 (2 CH), 45.21 (2 *C*H_2), 31.75 (2 *C*H_2), 25.66 (2 *C*H_2), 24.41 (2 *C*H_2), 20.85 (2 *C*H_3). Data matches that previously reported for this compound.[101]

_N_-[(_R,R_)-1,2-Diphenyl-2-(4-phenylbutylamino)-ethyl]-4-methylbenzenesulfonamide)ruthenium(II)chloride (101).



This compound is known in the literature and has previously been fully characterised.[101]

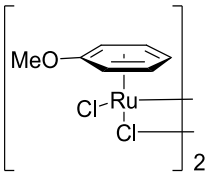
To a nitrogen purged, oven dried flask connected to a reflux condenser was added *N*-[(*R*,*R*)-1,2-diphenyl-2-(4-phenylbutylamino)-ethyl]-4-methylbenzenesulfonamide ammonium chloride ruthenium dimer **188** (1.00 g, 0.90 mmol). To this was then added anhydrous IPA (40 cm^3) and triethylamine (425 mg, 4.20 mmol). The solution was stirred at reflux for 90 min. The reaction was cooled to room temperature and volatile material was removed under reduced pressure to leave a brown/beige solid. The solid was dissolved in DCM and washed with brine. The DCM phase was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to leave the crude product as a brown solid (849 mg, 1.3 mmol, 72%). $[\alpha]_D^{26}$ -250 (*c* 0.01 in $CHCl_3$) (*R*,*R*) (lit.[101] $[\alpha]_D^{27}$ -333 (*c* 0.0096 in $CHCl_3$) (*R*,*R*)); found (ESI): [M^+ - Cl + H], 599.1308 $C_{31}H_{33}N_2O_2RuS$ requires M, 599.1308); υ_{max} 3204, 3025, 2922, 1453, 1270, 1125, 1082, 970, 904, 807, 697, 655 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.17 (2H, d, *J* 8 Hz, C*H*Ar) 7.03-6.99 (3H, m, C*H*Ar), 6.75 (3H, d, *J* 8.0 Hz, C*H*Ar), 6.63 (4H, d, *J* 8.0 Hz, C*H*Ar), 6.49 (2H, d, *J* 7.0 Hz, C*H*Ar), 6.21 (1H, t, *J* 5.0 Hz, C*H*Ar-Ru), 6.02-5.94 (2H, m, C*H*Ar-Ru), 5.41 (1H, d, *J* 5.0 Hz, C*H*Ar-Ru), 5.33 (1H, d, *J*, 5.0 Hz, C*H*Ar-Ru), 4.21-4.16 (1H, m, N*H*), 3.93 (1H, d, *J* 11.0 Hz, C*H*NHTs), 3.68-3.63 (1H, m, C*H*NH), 3.27-3.22 (1H, m, CH_2), 3.3.13-3.10 (1H, m, CH_2), 2.60-2.58 (2H, m, CH_2), 2.23-2.17 (4H, m, CH_3 and CH_2), 2.01-1.99 (1H, m, CH_2), 1.81-1.78 (1H, m, CH_2), 1.71-1.67 (1H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 141.35 (*C*Ar), 138.31 (*C*Ar), 138.18 (*C*Ar), 135.68 (*C*Ar), 127.92 (2 *C*HAr), 127.48 (2 *C*HAr), 127.06 (2 *C*HAr), 126.93 (2 *C*HAr), 126.46 (1 *C*HAr), 126.24 (2 *C*HAr), 125.81 (2 *C*HAr), 125.19 (*C*HAr), 97.56 (*C*Ar-Ru), 86.31 (*C*HAr-Ru), 84.71 (*C*HAr-Ru), 83.87 (1C *C*HAr-Ru), 83.37 (*C*HAr-Ru), 78.89 (*C*HAr-Ru), 78.00 (*C*H), 68.62 (*C*H), 50.85 (CH_2), 29.06 (CH_2), 24.63 (CH_2), 23.24 (CH_2), 20.21 (CH_3); *m/z* (ESI) 599.1 (M^+ + 1 - 35). Data matches that previously reported for this compound.[101]

Pressure hydrogenation of ketones and aldehydes catalysed by tethered ruthenium catalysts (S/C 500/1).

This was carried out according to General procedure 4.

5.3.5 Synthetic procedures for Section 2.6.

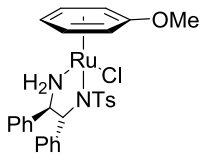
Methoxybenzene ruthenium(II)chloride dimer (192).



This compound is known in the literature but has not previously been fully characterised.[152, 153]

To a nitrogen purged flask was added RuCl.3H_2O (261 mg, 1 mmol) and MeOH (13.5 cm^3). To this was then added 1-methyl-1,4-cyclohexadiene (1.22 g, 11 mmol) and the reaction was stirred at reflux for 6 hours. The reaction solution was cooled to room temperature and filtered to give a black solid (138 mg, 0.25 mmol, 50%). δ_H (400 MHz, d_6-DMSO) 6.21 (2H, t, *J* 6 Hz, C*H*Ar-Ru), 5.59 (2H, d, *J* 6.0 Hz, C*H*Ar-Ru), 5.42 (1H, t, *J* 6.0 Hz, C*H*Ar-Ru), 3.97 (3H, s, CH_3); δ_C (100 MHz, DCMSO) 140.43 (2 *C*Ar-Ru), 94.10 (4 *C*HAr-Ru), 74.39 (2 *C*HAr-Ru), 65.19 (4 *C*HAr-Ru), 57.20 (2 *C*H_3).

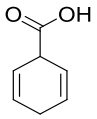
***N*-[(1*R*,2*R*)-2-(Amino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide methoxybenzene ruthenium(II)iodide monomer (193).**



This compound is novel.

To a nitrogen purged, dried flask was added methoxybenzene ruthenium(II)chloride dimer **192** (100 mg, 0.180 mmol) was added (*R*,*R*)TsDPEN (147 mg, 0.400 mmol) and triethylamine (152 mg, 1.50 mmol). To this was then added anhydrous IPA (5 cm^3) and the reaction was stirred at 80°C for 1 hour. The reaction was cooled to room temperature. The solvent was removed under reduced pressure and the residue washed with water before being dried to leave the crude product. The crude was recrystallised from MeOH to give the pure product as an orange solid (72 mg, 0.12 mmol, 33%). Mp decomposed 240°C; $[\alpha]_D^{25}$ +1220 (*c* 0.0025 in $CHCl_3$) (*R*,*R*); (found (ESI): M^+ + H, 575.0962 $C_{28}H_{29}N_2O_3RuS$ requires M, 575.0943); υ_{max} 3289, 3229, 3058, 3029, 1524, 1454, 1273, 1262, 1039, 924, 809, 759, 698, 674, 657 cm^{-1}; δ_H (400 MHz, d_6-DMSO) weak spectrum, some impurities present. 7.13-7.11 (2H, m, C*H*Ar), 6.86-6.81 (3H, m, C*H*Ar), 6.69-6.57 (5H, m, C*H*Ar), 6.10-6.06 (1H, m, C*H*Ar-Ru), 5.86-5.77 (1H, m, C*H*Ar-Ru), 5.50-5.48 (1H, m, C*H*Ar-Ru), 5.33-5.31 (1H, m, C*H*Ar-Ru), 5.15-5.14 (1H, m, C*H*Ar-Ru), 4.06 (2H, br s, NH_2), 3.97 (3H, s, CH_3), 3.93-3.91 (1H, m, C*H*), 3.76-3.73 (1H, m, C*H*), 2.23 (3H, s, CH_3); δ_C (150 MHz, DMSO) weak spectrum, quaternary carbons not observed, some impurities present. 128.09 (2 *C*HAr), 127.65 (*C*HAr), 127.51 (2 *C*HAr), 127.05 (2 *C*HAr), 126.64 (*C*HAr), 126.36 (2 *C*HAr), 114.22 (*C*Ar-Ru), 108.54 (*C*HAr-Ru), 104.75 (*C*HAr-Ru), 101.73 (*C*HAr-Ru), 97.28 (*C*Ar-Ru), 68.12 (*C*H), 64.87 (*C*H), 62.11 (*C*H_3), 20.75 (*C*H_3); *m/z* (ESI) 575.0 (M^+ + 1 – 35).

Cyclohexa-2,5-dienecarboxylic acid (200a).



This compound is known in the literature but has not previously been fully characterised.[158]

A dried, nitrogen purged flask was connected to a condenser which was cooled to -78°C with dry ice and acetone. The flask was then also cooled to -78°C. To the cooled flask was added ammonia gas which condensed to give liquid ammonia (120 cm^3). To the ammonia was then added dropwise *via* needle and syringe benzoic acid (8.0 g, 0.065 mol) in dry EtOH (40 cm^3). After addition was complete sodium was added to the reaction slowly in small portions. Initially the reaction solution became a dark blue colour upon addition of sodium but the colour then faded. Addition of sodium was continued until the dark colour persisted. In total 15 g, 0.65 mol sodium was added to the reaction. Additional EtOH was also added to the reaction periodically to help maintain stirring. Once the dark colour persisted the reaction was stirred at -78°C for a further 3 hours and was then allowed to warm to room temperature overnight. Chilled, distilled water was slowly added to the reaction until all of the white solid had dissolved. The solution was acidified to pH 1 with HCl (aq.). The product was then extracted with Et_2O (4 x 20 cm^3). The Et_2O phases were combined, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to leave the product as an orange oil (6.02 g, 0.049 mol, 75%). δ_H (400 MHz, $CDCl_3$) 5.95-5.91 (2H, m, *H*C=CHCH$_2$), 5.86-5.82 (2H, m, CH=C*H*CH$_2$), 3.83-3.76 (1H, m, C*H*COOH), 2.74-2.68 (2H, m, CH_2). The product was seen to rapidly decompose by ^{1}H NMR and also unexpected isomers of product were obtained from subsequent preparation of the product (Figure 76). Further

characterisation was not carried out and a more robust synthesis of the product was sought.

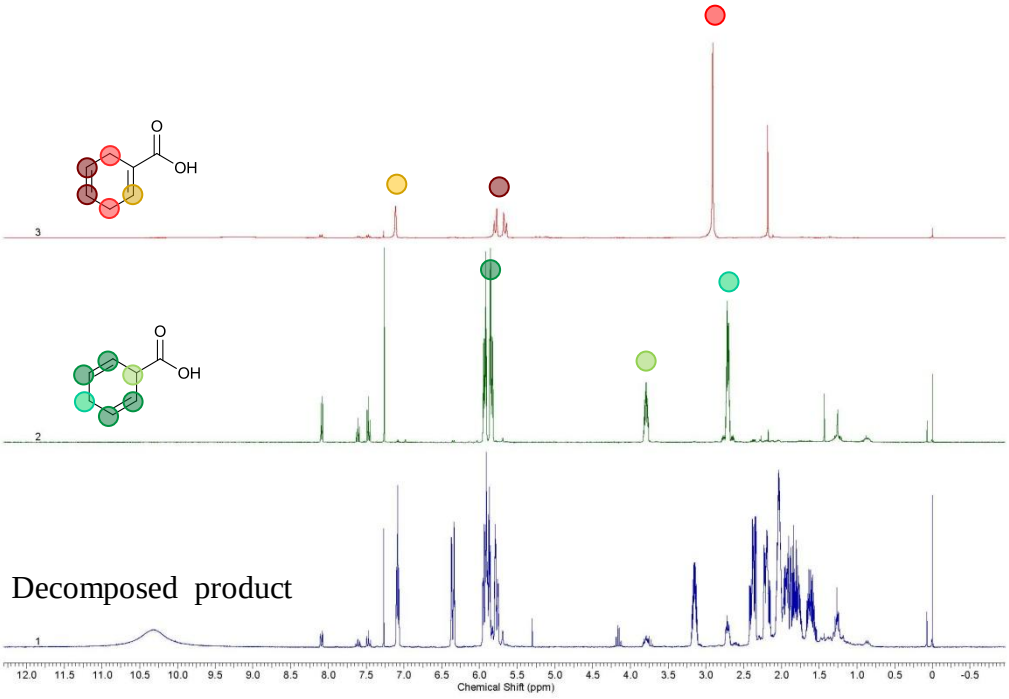
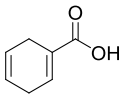


Figure 76. 1. ^{1}H NMR for obtained product after 24 hours at room temperature in air. 2. ^{1}H NMR of expected product. 3. ^{1}H NMR of unexpected product.

Cyclohexa-1,4-dienecarboxylic acid (200b).



Method A: A pre-weighed round bottom flask was purged with N_2 and cooled to -78°C with a dry ice/acetone bath. To a 300 cm^3 glass Parr reactor insert was added propiolic acid (8.6 g, 123 mmol) and the insert was then also cooled to -78°C. To a 100 g cylinder of 1,3-butadiene was fitted a brass hose adapter and to the adapter was fitted a suba seal through which a cannula was inserted. All joints were wrapped with parafilm to avoid leaks. 1,3-Butadiene gas was then added to the cooled round bottom flask in which it condensed. The flask was weighed periodically until the

required amount of liquid 1,3-butadiene had been collected (10 g, 185 mmol). The 1,3-butadiene was then quickly poured into the glass insert containing the propiolic acid. The insert was then sealed in the Parr reactor. The reaction was stirred and allowed to warm to room temperature over 30 min. After this the reaction temperature was increased by 10°C every 30 min until a temperature of 110°C was reached. The pressure change was carefully monitored during this time. The reaction was stirred at 110°C overnight. After this the reaction was allowed to cool to room temperature and the pressure released. The reaction was then removed from the reactor and the product was present as a yellow crystalline solid (12.5 g, 101 mmol, 82%). Purification was not necessary. The reaction gave only the expected isomer A of the product. For procedure see reference 159.

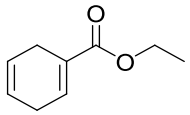
Method B: To a dried, nitrogen purged flask was added butadiene sulfone (1.77g, 15.0 mmol), propiolic acid (701 mg, 10.0 mmol) and anhydrous xylene (3 cm^3). The mixture was stirred at reflux for 3 hours. After this the reaction was cooled and distilled by kugelrohr distillation (0.2 torr, 35°C) to give a colourless oil (400 mg) and a yellow solid (300 mg). The solid was found to be the desired product (2.4 mmol, 24%).

Method A is considered the most appropriate synthesis as it gives a high yield without the need for purification and gave only the expected isomer of product.

Mp 108-109°C; υ_{max} 2972, 2631, 2531, 1686, 1655, 1424, 1286, 1081, 931, 911, 641 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.15 (1H, br s, O*H*), 7.08 (1H, s, C*H*=CCOOH), 5.78-5.74 (1H, m, =C*H*CH_2CCOOH), 5.65-5.61 (1H, m, C*H*=CHCCOOH), 2.88 (4H, s, 2C*H*$_2$); δ_C (75 MHz, $CDCl_3$) 171.86 (*C*=O), 138.58 (C*C*=C), 126.55 (H*C*=C), 123.67 (H*C*=C), 121.47 (H*C*=C), 26.58 (*C*H_2), 24.12 (*C*H_2). Data matches that previously

reported for this compound.[159] The product was directly converted to the more stable ethyl ester (**201**) for storage.

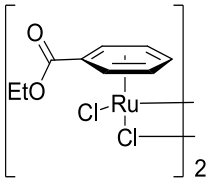
Ethyl cyclohexa-1, 4-dienecarboxylate (201).



This compound is known in the literature but has not previously been fully characterised.[187]

To cyclohexa-1, 4-dienecarboxylic acid **200b** (6 g, 48 mmol) in a dried, nitrogen purged flask connected to a condenser, was added dry EtOH (42 cm^3) and 95% sulfuric acid (2.8 cm^3). The solution was stirred at reflux for 18 hours before being cooled to room temperature. The pH of the solution was adjusted to pH 8 with NaOH (aq.). DCM (20 cm^3) was then added to the solution along with saturated NaCl solution (aq.) (20 cm^3). The DCM phase was removed and the aqueous phase washed with a further DCM (3 x 20 cm^3). The DCM phases were combined, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to give the product as an orange oil (4.6 g, 30 mmol, 62%). Purification was not necessary. (Found (ESI): M^+ + H, 153.0905 $C_9H_{12}O_2$ requires M, 153.0910); υ_{max} 3034, 2982, 1709, 1679, 1641, 1430, 1394, 1243, 1080, 1049, 967, 742, 651 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.96-6.95 (1H, m, C*H*=CCOOH), 5.79-5.62 (2H, m, C*H*=C*H*), 4.20 (2H, q, *J* 7.1 Hz, C$H_2$$CH_3$), 2.91-2.85 (4H, m, C$H_2$), 1.29 (3H, t, *J* 7.1 Hz, CH_2CH_3); δ_C (75 MHz, $CDCl_3$) 166.30 (*C*=O), 135.47 (*C*H), 127.18 (*C*), 123.73 (*C*H), 121.60 (*C*H), 59.61 (*C*H_2), 26.33 (*C*H_2), 24.45 (*C*H_2), 13.59 (*C*H_2). The compound was stored under nitrogen at <0°C.

Ethylbenzoate ruthenium(II)chloride dimer (197).

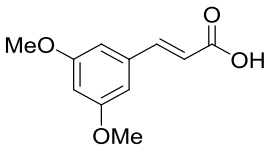


This compound is known in the literature but has not previously been fully characterised.[156, 157]

To ethyl cyclohexa-1, 4-dienecarboxylate **212** (1.60 g, 10.5 mmol) in a dried, nitrogen purged flask connected to a condenser, was added $RuCl_3.xH_2O$ (679 mg, 2.60 mmol assuming 3 H_2O). Dry EtOH (40 cm^3) was then added and the reaction was stirred at reflux for 18 hours. After this the reaction was cooled and filtered. The solid was washed with hexane and Et_2O to leave the product as an orange solid (735 mg, 1.1 mmol, 42%). υ_{max} 3079, 1721, 1513, 1469, 1397, 1286, 1268, 1105, 1021, 977, 864, 770, 677 cm^{-1}; δ_H (300 MHz, d_6-DMSO) 7.69 (2H, d, *J* 6.0Hz, C*H*Ar-Ru), 6.29 (1H, t, *J* 6.0Hz, C*H*Ar-Ru) 6.04 (2H, t, *J* 6.0 Hz, C*H*Ar-Ru), 4.34 (2H, q, *J* 7.0 Hz, CH_2), 1.31 (3H, t, *J* 7.0 Hz, CH_3); δ_C (100 MHz, d_6-DMSO) 163.85 (*C*=O), 92.45 (*C*HAr-Ru), 91.81 (*C*HAr-Ru), 85.20 (*C*HAr-Ru), 82.47 (*C*), 62.09 (*C*H_2), 14.24 (*C*H_3). Data matches that previously reported for this compound.[156, 157]

5.3.5.1 Synthesis of primary alcohol precursors for tethered ligands.

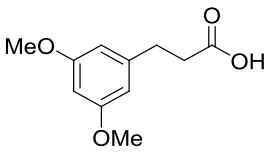
3-(3,5-dimethoxyphenyl)-prop-2-enoic acid (205).



This compound is known in the literature but has not previously been fully characterised.[188]

To a dried, nitrogen purged flask was added 3,5-dimethoxybenzaldehyde (1.00 g, 6.00 mmol) was added malonic acid (3.06 g, 29.4 mmol), piperidine (2.5 cm^3) and anhydrous pyridine (11 cm^3). The solution was stirred at reflux (90°C) for 18 hours. After this the reaction was allowed to cool to room temperature before being poured into chilled distilled water (10 cm^3) and acidified with addition of 6M HCl (aq.) whilst stirring until a white precipitate formed. The white solid was collected by filtration to give the product (860 mg, 4.10 mmol, 68%). Mp 178°C; (found (ESI): M^+ + Na, 231.0630 $C_{11}H_{12}NaO_4$ requires M, 231.0628); υ_{max} 3670, 2971, 2901, 2360, 1683, 1631, 1592, 1431, 1283, 1206, 1161, 1056, 926, 837, 807 and 669 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 12.41 (1 H, br s, O*H*), 7.52 (1 H, d *J*, 16 Hz, CH=C*H*), 6.87 (2H, d *J*, 2.3 Hz, C*H*Ar), 6.59-6.55 (2H, m, C*H*=CH and C*H*Ar overlapping), 3.78 (6H, s, 2 x CH_3); δ_C (100 MHz, DMSO-d_6) 167.55 (*C*=O), 160.66 (2 *C*Ar), 143.94 (H*C*=), 136.19 (*C*Ar), 119.81 (H*C*=), 106.01 (2 *C*HAr), 102.38 (*C*Ar), 55.33 (2 CH_3); *m/z* (ESI) 208.8 (M^+ + 1), 230.7 (M^+ + 23).

3-(3,5-Dimethoxyphenyl)propanoic acid (206).

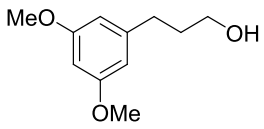


This compound is known in the literature and has previously been fully characterised.[189, 190]

To a dried, nitrogen flask was added 3-(3,5-dimethoxyphenyl)-prop-2-enoic acid **205** (840 mg, 4.00 mmol) and 10% palladium on carbon (218 mg, 0.200 mmol). To this was then added methanol (40 cm^3). A balloon of hydrogen was connected to the reaction flask and the flask purged with hydrogen. The reaction was then stirred at

room temperature under 1 atm. hydrogen overnight. After this the reaction was filtered over celite and the solvent removed under reduced pressure to leave the product as an orange oil (657 mg, 3.10 mmol, 78%). (found (ESI): M^+ + Na, 233.0783. $C_{11}H_{14}NaO_4$ requires M, 233.0781); υ_{max} 2936, 2838, 1705, 1594, 1458, 1429, 1351, 1291, 1204, 1147, 1066, 922, 831 and 691 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.99 (1H, br s, O*H*), 6.43-6.30 (3H, m, C*H*Ar), 3.75 (6H, s, OCH_3), 2.88 (2H, t, *J* 7.7 Hz, CH_2COOH), 2.64 (2H, t, *J* 7.7 Hz, ArCH_2); δ_C (75 MHz, $CDCl_3$) 178.43 (*C*=O), 160.24 (2 *C*Ar), 142.04 (*C*Ar), 105.71 (*C*HAr), 97.63 (*C*HAr), 54.65 (2 *C*H_3), 35.07 (*C*H_2), 30.34 (*C*H_2); *m/z* (ESI) 210.8 (M^+ + 1), 232.7 (M^+ + 23). Data matches that previously reported for this compound.[189, 190]

3-(3,5-Dimethoxylphenyl)propan-1-ol (207).

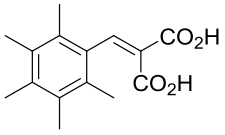


This compound is known in the literature but has not previously been characterised.[191]

To a dried, nitrogen purged flask was added 3-(3,5-dimethoxyphenyl)propanoic acid **206** (627 mg, 3.00 mmol) and anhydrous THF (7.5 cm^3). The solution was stirred and cooled to 0°C. To the cooled solution was added dropwise $LiAlH_4$ (1M in THF) (7.5 cm^3, 7.5 mmol). The reaction was allowed to warm to room temperature and monitored by TLC (silica plate, 20% EtOAc in petroleum ether 40-60°, product Rf = 0.2, starting material Rf = 0.1, visualisation by UV). Once complete (after 3.5 hours), the reaction was cooled to 0°C and water was slowly and carefully added to quench the reaction. THF was then removed under reduced pressure to leave a

cloudy white solution. The product was then extracted with Et_2O (3 x 15 cm^3) and the Et_2O phases were combined, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to leave the crude product as a pale yellow oil (501 mg). The crude was purified by column chromatography (silica gel, 0-50% EtOAc in petroleum ether, TLC: as above) to give the product as a colourless oil (456 mg, 77%). (found (ESI): M^+ + Na, 219.0097. $C_{11}H_{16}NaO_3$ requires M, 219.0989); υ_{max} 3320, 2936, 2837, 1593, 1458, 1427, 1345, 1291, 1203, 1146, 1041, 926, 829 and 694 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.37 (2H, s, C*H*Ar), 6.31 (1H, s, C*H*Ar), 3.78 (6H, s, CH_3), 3.68 (2H, t, *J* 6.3 Hz, CH_2OH), 2.67-2.63 (2H, m, ArCH_2), 1.92-1.85 (2H, m, CH_2CH_2), 1.41 (1H, br s, O*H*); δ_C (100 MHz, $CDCl_3$) 160.82 (*C*Ar), 144.29 (*C*Ar), 106.52 (2 *C*HAr), 97.83 (*C*HAr), 62.29 (*C*H_2), 55.27 (*C*H_2), 34.01 (*C*H_2), 32.44 (*C*H_2); *m/z* (ESI) 196.8 (M^+ + 1), 218.8 (M^+ + 23).

(Pentamethylbenzylidene)propanedioic acid (215).

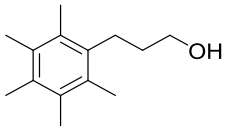


This compound is known but has not previously been published in the literature.

Prepared as for 3-(3,5-dimethoxyphenyl)-prop-2-enoic acid **205** using pentamethylbenzaldehyde (530 mg, 3.00 mmol), malonic acid (1.54 g, 14.8 mmol), pyridine (5.5 cm^3) and piperidine (1.2 cm^3). The desired product was obtained in quantitative yield (785 mg, 3.00 mmol, 100%). Mp 158°C; (found (ESI): M^+ + Na, 285.1093. $C_{15}H_{18}NaO_4$ requires M, 285.1097); υ_{max} 3330, 2973, 2883, 2643, 2362, 1671, 1561, 1425, 1243, 1047, 880 and 704 cm^{-1}; δ_H (400 MHz, DMSO) 7.69 (1H, s, C*H*), 2.17 (3H, s, ArCH_3), 2.14 (6H, s, 2 x ArCH_3), 2.07 (6H, s, 2 x ArCH_3); δ_C (100

MHz, DMSO) 166.49 (*C*=O), 166.83 (*C*=O), 143.44 (*C*Ar) 134.05 (*C*Ar), 132.03 (*C*Ar), 131.52 (*C*Ar), 131.06 (*C*Ar), 129.70 (*C*Ar), 17.58 (2 *C*H_3), 16.42 (*C*H_3), 15.98 (2 *C*H_3); *m/z* (ESI) 262.8 (M^+ + 1), 284.9 (M^+ + 23).

3-(Pentamethylphenyl)propan-1-ol (216).

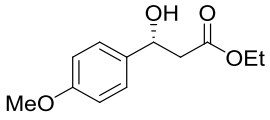


This compound is known in the literature but has not previously been fully characterised.[192, 193]

To a dried, nitrogen purged flask was added **(**pentamethylbenzylidene)propanedioic acid **215** (1.0 g, 3.8 mmol), 10% palladium on carbon (202 mg, 0.190 mmol) and methanol (38 cm^3). A balloon of hydrogen was connected to the reaction flask and the flask purged with hydrogen. The reaction was then stirred at room temperature under 1 atm. hydrogen overnight. After this the reaction was filtered over celite and the solvent removed under reduced pressure to leave the saturated product as a white solid (956 mg, 3.60 mmol). δ_H (400 MHz, $CDCl_3$) 3.25-3.19 (3H, m, C*H* and CH_2 overlapping), 2.17 (6H, s, 2 x CH_3), 2.15 (3H, s, CH_3), 2.13 (6H, s, 2 x CH_3); δ_C (100 MHz, $CDCl_3$) 170.99 (2C, s), 132.37 (1C, s), 132.28 (1C, s), 131.87 (1C, s), 131.71 (2C, s), 131.69 (2C, s), 52.24 (1C, s), 29.21 (1C, s), 16.66 (2C, s), 16.61 (1C, s), 16.50 (2C, s); *m/z* (ESI) 286.9 (M^+ + 23). This solid was then transferred to a flask connected to a bubbler. The flask was heated at 180°C to remove CO_2 until bubbling ceased. The flask was then cooled to leave the mono-acid product as a beige solid (740 mg, 3.40 mmol). δ_H (300 MHz, $CDCl_3$) 10.67 (1H, br s, O*H*), 3.14-3.11 (2H, m, CH_2COOH), 2.60-2.49 (2H, m, CH_2CH_2), 2.34 (6H, s, 2 x CH_3), 2.29 (9H, s, 3 x CH_3); δ_C (75 MHz, $CDCl_3$) 178.94 (*C*=O), 133.43 (*C*Ar), 132.68 (*C*Ar), 132.24 (2

*C*Ar), 131.21 (2 *C*Ar), 33.79 (*C*H_2), 25.55 (*C*H_2), 16.36 (*C*H_3), 16.29 (2 *C*H_3), 15.77 (2 *C*H_3); *m/z* (ESI) 242.9 (M^+ + 23). To the solid was then added anhydrous THF (6.6 cm^3). The solution was stirred and cooled to 0°C and to it was added dropwise $LiAlH_4$ solution (1M in THF) (6.6 cm^3, 6.6 mmol). The reaction was allowed to warm to room temperature and was monitored by TLC (silica plate, 25% EtOAc in petroleum ether, visualisation by $KMnO_4$, product Rf = 0.48). Once complete, the reaction was cooled to 0°C and water was slowly added to quench the reaction. The THF was then removed under reduced pressure to leave a cloudy white solution. The product was then extracted with Et_2O (3 x 15 cm^3). The Et_2O phases were combined and dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to leave the crude product as a pale yellow solid. The crude product was purified by column chromatography (silica gel, 0-50% EtOAc in petroleum ether, TLC: as above) to give the product as a white solid (246 mg, 31% over 3 steps). Mp 111-112°C; (found (ESI): M^+ + Na, 229.1564 $C_{14}H_{22}NaO$ requires M, 229.1563); υ_{max} 3252, 2921, 2859, 1442, 1363, 1158, 1048, 994, 729 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.77 (2H, t, *J* 6.3 Hz, C*H*$_2$), 2.82-2.76 (2H, m, C*H*$_2$OH), 2.28 (6H, s, 2 x C*H*$_3$), 2.26 (3H, s, ArC*H*$_3$), 2.25 (6H, s, 2 x C*H*$_3$), 1.81-1.72 (2H, m, C*H*$_2$CH$_2$), 1.68 (1H, br s, O*H*); δ_C (75 MHz, $CDCl_3$) 135.12 (*C*Ar), 132.06 (*C*Ar), 132.03 (2 *C*Ar), 131.12 (2 *C*Ar), 62.53 (*C*H_2), 32.36 (*C*H_2), 26.34 (*C*H_2), 16.29 (*C*H_2), 16.26 (2 *C*H_2), 15.82 (2 *C*H_2); *m/z* (ESI) 229.1 (M^+ + 23). Data matches that previously reported for this compound.[192, 193]

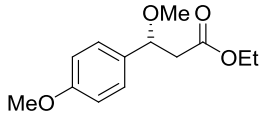
(*R*)-Ethyl-3-hydroxy-3-(4-methoxyphenyl)propanoate (230).



This compound is known in the literature but has not previously been fully characterised.[194, 195]

Ethyl-4-methoxybenzoylacetate (666 mg, 3.00 mmol) was added to a nitrogen purged, dry schlenk tube. To it was added (*R*,*R*) TsDPEN 3C tethered RuCl monomer (9 mg, 0.015 mmol) and degassed formic acid:triethylamine 5:2 complex (1.5 cm^3). The reaction was stirred at 28°C for 5 hours. After this the reaction solution was filtered through silica with 1:1 EtOAc:petroleum ether 40-60 solution to remove the catalyst. The filtrate was dried under reduced pressure to leave the product as a colourless oil (647 mg, 2.9 mmol, 97%). Purification was not necessary. $[\alpha]_D^{30}$ + 41.1 (*c* 1.0 in $CHCl_3$) >99.0% (*R*,*R*,*R*) (lit.[194] $[\alpha]_D^{25}$ + 25.7 (*c* 1.4 in $CHCl_3$) >99% (*R*,*R*,*R*)); (found (ESI): M^+ + H, 247.0947 $C_{12}H_{16}NaO_4$ requires M, 247.0941); υ_{max} 3439, 2982, 2838, 1727, 1613, 1514, 1465, 1372, 1302, 1244, 1172, 1111, 1030, 831 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.29 (2H, d, *J* 8.7 Hz, C*H*Ar), 6.88 (2H, d, *J* 8.7 Hz, C*H*Ar), 5.09-5.05 (1H, m, C*H*), 4.17 (2H, q, *J* 7.2 Hz, C$H_2$$CH_3$), 3.79 (3H, s, C$H_3$), 3.25 (1H, d, *J* 3.3 Hz, O*H*), 2.78-2.64 (2H, m, CH_2CH), 1.26 (3H, t, *J* 7.2 Hz, C$H_3$$CH_2$); δ_C (100 MHz, $CDCl_3$) 172.43 (*C*=O), 159.20 (*C*Ar), 134.78 (*C*Ar), 126.99 (2 *C*HAr), 113.92 (2 *C*HAr), 69.98 (*C*H), 60.84 (*C*H), 55.29 (*C*H_3), 43.38 (*C*H_2), 14.17 (*C*H_3); *m/z* (ESI) 247.1 (M^+ + 23). Data matches that previously reported for this compound.[194, 195]

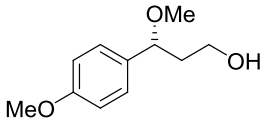
(*R*)-Ethyl-3-methoxy-3-(4-methoxyphenyl)propanoate (231).



This compound is novel.

To (*R*)-ethyl-3-hydroxy-3-(4-methoxyphenyl)propanoate **230** (530 mg, 2.40 mmol) in a dried, nitrogen purged flask was added anhydrous DCM (5 cm^3). To this was then added MeI (1.69 g, 12.0 mmol). The solution was stirred for 15 min at room temperature before Ag_2O (2.78 g, 12.0 mmol) was added. The reaction was then stirred at room temperature overnight. After this further MeI (1.69 g, 12.0 mmol) was added to the reaction which was then stirred at room temperature for a further hour. Et_2O (10 cm^3) was then added to the reaction. The organic phase was washed with saturated NH_4Cl aq. solution, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give the crude as a colourless oil. The crude product was purified by column chromatography (silica gel, 0-30% EtOAc in petroleum ether, TLC: silica plate, 30% EtOAc in petroleum ether, visualisation by $KMnO_4$, product Rf = 0.66) to give the product as a colourless oil (279 mg, 1.2 mmol. 50%). $[\alpha]_D^{23}$ +57.2 (*c* 1.0 in $CHCl_3$) (*R*); (found (ESI): M^+ + H, 261.1102 $C_{13}H_{18}NaO_4$ requires M, 261.1097); υ_{max} 2937, 2825, 1732, 1612, 1512, 1465, 1373, 1304, 1244, 1155, 1096, 1030, 831 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.65 (2H, d, *J* 8.6 Hz, C*H*Ar), 6.89 (2H, d, *J* 8.6 Hz, C*H*Ar), 4.60-4.56 (1H, m, C*H*OCH_3), 4.14 (2H, q, *J* 7.0 Hz, C*H*$_2CH_3$), 3.81 (3H, s, *p*-C*H*$_3(C_6H_4)SO_2$), 3.19 (3H, s, OC*H*$_3$), 2.80 (1H, dd *J*, 15.2 and 9.0 Hz, CHC*H*^{a}H^b), 2.55 (1H, dd, *J* 15.2 and 5.0 Hz, CHCH^a*H*^{b}), 1.23 (3H, t, *J* 7.2 Hz, C*H*$_3CH_2$); δ_C (100 MHz, $CDCl_3$) 171.04 (*C*=O), 159.41 (*C*Ar), 132.57 (*C*Ar), 127.91 (2 *C*HAr), 113.92 (2 *C*HAr), 79.62 (*C*H), 60.50 (*C*H_2), 56.56 (*C*H_3), 55.26 (*C*H_3), 43.51 (*C*H_2), 14.18 (*C*H_3); *m/z* (ESI) 261.1 (M^+ + 23).

(*R*)-3-methoxy-3-(4-methoxyphenyl)propan-1-ol (232).



This compound is novel.

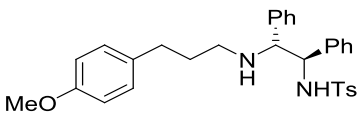
To (*R*)-ethyl-3-methoxy-3-(4-methoxyphenyl)propanoate **231 (**259 mg, 1.1 mmol**)** in a dried, nitrogen purged flask was added anhydrous THF (2.2 cm^3). The solution was then cooled to 0°C with an ice bath and to it was added dropwise $LiAlH_4$ solution (1M in THF) (2.2 cm^3, 2.2 mmol). The reaction was then stirred at room temperature overnight. After this the reaction was cooled to 0°C and water was added dropwise to quench the reaction. The THF was then removed under reduced pressure and to the residue was added water. The product was extracted in EtOAc (3 x 10 cm^3). The EtOAc phases were combined, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to leave the product as a colourless oil (212 mg, 1.08 mmol, 98%). Purification was not necessary. $[\alpha]_D^{26}$ +112.1 (*c* 0.5 in $CHCl_3$) (*R*); (found (ESI): $M^+ + H$, 219.0993 $C_{11}H_{16}NaO_3$ requires M, 219.0992); υ_{max} 3295, 2935, 1611, 1511, 1455, 1424, 1246, 1173, 1098, 1031, 893, 829, 808, 699, 668, 637 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.23 (2H, d, *J* 8.7 Hz, C*H*Ar), 6.90 (2H, d, *J* 8.7 Hz, C*H*Ar), 4.35-4.32 (1H, m, C*H*OCH_3), 3.81 (*p*-C*H*$_3(C_6H_4)SO_2$), 3.76-3.74 (2H, m, CH_2OH), 3.20 (3H, s, OCH_3), 2.70 (1H, br s, O*H*), 2.09-2.00 (2H, ArCH_2), 1.87-1.78 (2H, m, CH_2CH_2OH); δ_C (100 MHz, $CDCl_3$) 159.23 (*C*Ar), 133.46 (*C*Ar), 127.76 (2 *C*HAr), 113.92 (2 *C*HAr), 83.32 (*C*H), 61.14 (*C*H_2), 56.37 (*C*H_3) 55.28 (*C*H_3), 40.34 (*C*H_2); *m/z* (ESI) 219.1 (M^+ + 23).

5.3.5.2 Synthesis of tethered aryl-diamine ligands.

General procedure 5: preparation of tethered aryl-diamine ligands.

To a dried, nitrogen purged flask was added the required aryl-3C-primary alcohol (1.6 eq.), anhydrous DCM (5cm^3 per mmol sulfonated diamine) and 2,6-lutidine (2.1 eq.). The solution was cooled to 0°C and to it was added dropwise a solution of trifluoromethanesulfonic anhydride (1.7 equiv.) in anhydrous DCM (1 cm^3 per mmol of sulfonated diamine). The reaction became pink in colour and was stirred for 30 min at 0°C and then at room temperature for 60 min. After this the reaction was cooled to 0°C and to it was added dropwise a solution of sulfonated diamine (1 eq.), triethylamine (2.4 eq.) and anhydrous DCM (1 cm^3 per mmol of sulfonated diamine). The reaction became yellow/orange and was stirred at 0°C for 30 min and then at room temperature overnight. The reaction was diluted with DCM and saturated $NaHCO_3$ (aq.) solution was added. The product was then extracted with DCM (3 x 20 cm^3). The DCM phases were washed with saturated $NaHCO_3$ (aq.) solution, brine and water sequentially. The DCM phase was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give the crude as a yellow oil. The crude was purified by column chromatography (silica gel, 0-100% EtOAc in petroleum ether) to give the clean ligand products for complex formation. For procedure see reference 145.

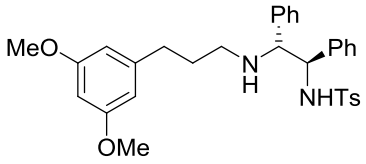
***N*-((1*R*,2*R*)-2-(3-(4-Methoxyphenyl)propylamino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide (198).**



This compound is novel.

This compound was prepared according to general procedure 5 using 3-(4-methoxyphenyl)propan-1-ol (500 mg, 3.00 mmol), 2,6-lutidine (418 mg, 3.90 mmol), trifluoromethanesulfonic anhydride (900 mg, 3.20 mmol), (*R*,*R*)-TsDPEN (606 mg, 1.90 mmol), Et_3N (455 mg, 4.50 mmol) and DCM (2 cm^3 followed by 2 cm^3). The product was purified by column chromatography as in the general procedure. TLC: silica plate, 30% EtOAc in petroleum ether, product Rf = 0.57 with visualisation by UV and $KMnO_4$, 2,6-lutidine Rf = 0.40 with visualisation by UV only, 2,6-lutidine elutes with the product. The fractions containing the product were collected and dried under reduced pressure to give a white solid. The solid was washed with pentane and filtered to remove 2,6-lutidine and leave the product as a white solid (962 mg, 1.87 mmol, 98% based on 696 mg, 1.9 mmol (1*R*,2*R*)-*N*-*p*-tosyl-1,2-diphenylethylenediamine). Mp 101°C; $[\alpha]_D^{30}$ -21.0 (*c* 1.0 in $CHCl_3$) (*R*,*R*); (found (ESI): M^+ + H, 515.2369 $C_{31}H_{35}N_2O_3S$ requires M, 515.2363); υ_{max} 3303, 2928, 1511, 1454, 1327, 1243, 1158, 1035, 916, 808, 698, 669 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.37 (2H, d, *J* 8.4 Hz, C*H*Ar), 7.12-7.11 (3H, m, C*H*Ar), 7.04-6.98 (7H, m, C*H*Ar), 6.94-6.88 (4H, m, C*H*Ar), 6.89 (2H, d, *J* 8.4 Hz, C*H*Ar), 6.29 (1H, br s, N*H*), 4.25 (1H, d, *J* 7.8 Hz, C*H*), 3.77 (3H, s, CH_3), 3.59 (1H, d, *J* 7.8 Hz, C*H*), 2.50-2.38 (3H, m, CH_2), 2.31-2.25 (4H, m, CH_3 and CH_2 overlapping), 1.68-1.63 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 157.79 (*C*Ar), 142.72 (*C*Ar), 139.34 (*C*Ar), 138.40 (*C*Ar), 137.11 (*C*Ar), 133.86 (*C*Ar), 129.24 (2 *C*HAr), 129.12 (2 *C*HAr), 128.32 (2 *C*HAr), 127.94 (2 *C*HAr), 127.58 (2 *C*HAr), 127.47 (*C*HAr) 127.44 (2 *C*HAr), 127.28 (*C*HAr), 127.14 (2 *C*HAr), 113.80 (2 *C*HAr), 67.79 (*C*H), 63.12 (*C*H), 55.29 (*C*H_3), 46.47 (*C*H_2), 32.38 (*C*H_2), 31.72 (*C*H_2), 21.46 (*C*H_3); *m/z* (ESI) 515.1 (M^+ + 1).

_N_-((1_R_,2_R_)-2-(3-(3.5-Dimethoxyphenyl)propylamino)-1,2-diphenylethyl)-4-methylbenzeneulphonamide (208).

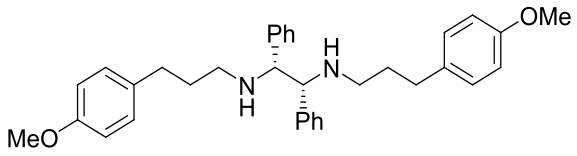


This compound is novel.

This compound was prepared according to general procedure 5 using 3-(3,5-dimethoxyphenyl)propan-1-ol **207** (400 mg, 2.00 mmol), 2,6-lutidine (279 mg, 2.60 mmol), trifluoromethanesulfonic anhydride (590 mg, 2.10 mmol), (*R*,*R*)-TsDPEN (458 mg, 1.25 mmol), Et_3N (304 mg, 3.00 mmol) and DCM (1.3 cm^3 followed by 1.3 cm^3). The product was purified by column chromatography as in the general procedure. TLC: silica gel, 1:1 EtOAc:petroleum ether, product Rf = 0.68 with visualisation by UV and $KMnO_4$, 2,6-lutidine Rf = 0.36 with visualisation by UV only. 2,6-lutidine elutes with the product. The fractions containing the product were collected and dried under reduced pressure to give a colourless oil. Pentane was added and the mixture stirred. The pentane was then decanted and residual pentane removed under reduced pressure to leave the clean product as a colourless oil (377 mg, 0.69 mmol, 55% based on 458 mg, 1.25 mmol (1*R*,2*R*)-*N*-*p*-tosyl-1,2-diphenylethylenediamine). $[\alpha]_D^{30}$ -14.8 (*c* 1.0 in $CHCl_3$) (*R*, *R*); (found (ESI): M^+ + H, 545.2471 $C_{32}H_{37}N_2O_4S$ requires M, 545.2469); υ_{max} 3259, 2937, 1595, 1455, 1324, 1204, 1147, 1055. 924, 813, 760, 697cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.37 (2H, d, *J* 8.3 Hz, C*H*Ar), 7.13-7.12 (3H, m, C*H*Ar), 7.04-7.01 (5H, m, C*H*Ar), 6.94-6.88 (4H, m, C*H*Ar), 6.30-6.29 (1H, m, C*H*Ar), 4.25 (1H, d, *J* 8.1 Hz, C*H*), 3.77 (6H, s, CH_3), 3.60 (1H, d, *J* 8.1 Hz, C*H*), 2.52-2.41 (3H, m, CH_2), 2.32-2.30 (4H, m, CH_3 and CH_2 overlapping), 1.73-1.65 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 160.8 (2 *C*Ar), 144.3 (*C*Ar), 142.7 (*C*Ar), 139.3 (*C*Ar), 138.3 (*C*Ar), 137.1 (*C*Ar), 129.1 (2

*C*HAr), 128.3 (2 *C*HAr), 127.9 (2 *C*HAr), 127.6 (2 *C*HAr), 127.5 (2 *C*HAr), 127.4 (*C*HAr), 127.3 (*C*HAr), 127.1 (2 *C*HAr), 106.4 (2 *C*HAr), 97.9 (*C*HAr), 67.7 (*C*H), 63.1 (*C*H), 55.3 (CH_3), 46.60 (CH_2), 33.70 (CH_2), 31.3 (CH_2), 21.4 (CH_3); *m/z* (ESI) 545.2 ($M^+ + 1$).

(1*R*,2*R*)-*N*,*N*-Bis(3-(4-methoxyphenyl)propyl)-1,2-diphenylethane-1,2-diamine (210).

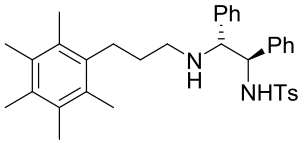


This compound is novel.

To a nitrogen purged, dried flask was added 3-(4-methoxyphenyl)propan-1-ol (416 mg, 2.50 mmol) was added 2,6-lutinine (321 mg, 3.00 mmol) and anhydrous DCM (5 cm^3). The solution was cooled to 0°C and to it as added a solution of Tf_2O (759 mg, 2.70 mmol) in anhydrous DCM (1 cm^3). The reaction was stirred at 0°C for 30 min and then at room temperature for 60 min. After this the reaction was again cooled to 0°C and to it was added a solution of (*R*,*R*)-DPEN (212 mg, 1.00 mmol) and Et_3N (354 mg, 3.5 mmol) in anhydrous DCM (1 cm^3). The reaction was stirred at 0°C for 30 min and then at room temperature overnight. After this DCM was added and the reaction washed with saturated $NaHCO_3$ solution (aq.). (3 x 10 cm^3). The organic phase was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to leave the crude as a yellow oil. The crude product was purified by column chromatography (silica gel, 0-50% EtOAc in petroleum ether, TLC: silica gel, 30% EtOAc in petroleum ether, product Rf = 0.18 visualisation by UV and $KMnO_4$, 2,6-lutidine Rf = 0.38 visualisation by UV, 2,6-lutidine elutes before product) to give the product as a white solid (326 mg, 0.64 mmol, 64% based on (*R*,*R*)-DPEN). $[\alpha]_D^{26}$+4.4 (*c* 0.5 in $CHCl_3$) (*R*,*R*); (found (ESI): M^+ + H, 509.3164

$C_{34}H_{41}N_2O_2$ requires M, 509.3163); υ_{max} 2931, 2834, 1510, 1452, 1243, 1035, 830, 810, 731, 698, cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.17-7.12 (6H, m, C*H*Ar), 7.07-7.02 (8H, m, C*H*Ar), 3.77 (6H, s, CH_3), 3.63 (2H, s, C*H*N), 2.57-2.36 (8H, m, ArCH_2 and CH_2NH overlapping), 1.79-1.69 (4H, m, $CH_2CH_2CH_2N$); δ_C (75 MHz, $CDCl_3$) 157.06 (2 *C*Ar), 141.00 (2 *C*Ar), 133.76 (2 *C*Ar), 128.67 (4 *C*HAr), 127.32 (4 *C*HAr), 127.28 (4 *C*HAr), 126.22 (2 *C*HAr), 113.09 (4 *C*HAr), 68.66 (2 *C*H), 54.65 (2 *C*H_3), 46.45 (2 *C*H_2), 31.97 (2 *C*H_2), 31.44 (2 *C*H_2); *m/z* (ESI) 509.3 (M^+ + 1).

4-Methyl-*N*-((1*R*,2*R*)-2-(3-(2,3,4,5,6-pentamethylphenyl)propylamino)-1,2-diphenylethyl)benzenesulfonamide (217).

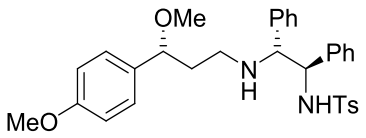


This compound is novel.

This compound was prepared according to general procedure 5 using 3-(pentamethylphenyl)propan-1-ol **216** (106 mg, 0.50 mmol), 2,6-lutidine (75 mg, 0.70 mmol), trifluoromethanesulfonic anhydride (141 mg, 0.50 mmol), (*R*,*R*)-TsDPEN (110 mg, 0.30 mmol), Et_3N (81 mg, 0.80 mmol) and DCM (0.3 cm^3 followed by 1 cm^3). The product was purified by column chromatography as in the general procedure. TLC: silica gel, 30% EtOAc in petroleum ether, product Rf = 0.58 with visualisation by UV and $KMnO_4$, 2,6-lutidine Rf = 0.30 with visualisation by UV only, 2,6-lutidine elutes with the product. The fractions containing the product were collected and dried under reduced pressure to give a colourless oil. Pentane was added and the mixture stirred. A white solid precipitated out and was collected by filtration to give the product as a white solid (77 mg, 47% based on 110 mg, 0.3 mmol (1*R*,2*R*)-*N*-*p*-tosyl-1,2-diphenylethylenediamine).). Mp 152-153°C; $[\alpha]_D^{26}$ -19

(*c* 0.5 in $CHCl_3$) (*R*,*R*); (found (ESI): M^+ + H, 555.3049. $C_{35}H_{43}N_2O_2S$ requires M, 555.3040); υ_{max} 2988, 2901, 1452, 1331, 1154, 1066, 1055, 906, 804, 767, 696 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38 (2H, d, *J* 8.3 Hz, C*H*Ar), 7.14-7.13 (3H, m, C*H*Ar), 7.03-7.01 (5H, m, C*H*Ar), 6.94-6.92 (4H, m, C*H*Ar), 4.27 (1H, d, *J* 8.1 Hz, C*H*), 3.68 (1H, d, *J* 8.1 Hz, C*H*), 2.62-2.51 (4H, m, CH_2), 2.31 (3H, s, CH_3), 2.22 (3H, s, CH_3), 2.21 (6H, s, 2 x CH_3), 2.19 (6H, s, 2 x CH_3), 1.57-1.51 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 142.74 (*C*Ar), 142.34 (*C*Ar), 137.08 (*C*Ar), 135.68 (*C*Ar), 132.66 (*C*Ar), 132.58 (2 *C*Ar), 131.58 (2 *C*Ar), 129.12 (2 *C*HAr), 128.43 (*C*HAr), 127.95 (*C*HAr), 127.71 (*C*HAr), 127.62 (4 *C*HAr), 127.31 (*C*HAr), 127.13 (2 *C*HAr), 67.66 (*C*H), 62.98 (*C*H), 47.36 (CH_2), 29.87 (CH_2), 28.25 (CH_2), 21.45 (CH_3), 16.90 (CH_3), 16.86 (2 CH_3), 16.45 (2 CH_3); *m/z* (ESI) 555.3 (M^+ + 1).

_N_-((1_R_,2_R_)-2-((_R_)-3-methoxy-3-(4-methoxyphenyl)propylamino)-1,2-diphenylethyl)-4-methylbenzeneaulfonamide (233).

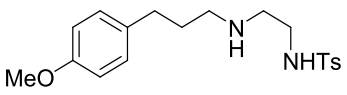


This compound is novel.

This compound was prepared according to general procedure 5 using (*R*)-3-methoxy-3-(4-methoxyphenyl)propan-1-ol **232** (196 mg, 1.00 mmol), 2,6-lutidine (139 mg, 2.10 mmol), trifluoromethanesulfonic anhydride (309 mg, 1.10 mmol), (*R*,*R*)-TsDPEN (231 mg, 0.63 mmol), Et_3N (152 mg, 2.40 mmol) and DCM (0.67 cm^3 followed by 0.67 cm^3). The product was purified by column chromatography as in the general procedure. TLC: silica gel, 30% EtOAc in petroleum ether , product Rf = 0.62 with visualisation by UV and $KMnO_4$, 2,6-lutidine Rf = 0.36 with visualisation by UV only, 2,6-lutidine elutes with the product. The fractions containing the

product were collected and dried under reduced pressure to give a colourless oil. Pentane was added and the mixture stirred. The pentane was decanted and residual pentane was removed under reduced pressure to leave the clean product as an orange oil (270 mg, 0.5 mmol, 79% based on 231 mg, 0.63 mmol *N*-(2-aminoethyl)-4-methylbenzenesulfonamide). Mp 125-126°C; $[\alpha]_D^{28}$ +7.6 (*c* 1.0 in $CHCl_3$) (*R*, *R*, *R*); (found (ESI): M^+ + H, 545.2480. $C_{32}H_{37}N_2O_4S$ requires M, 545.2469); υ_{max} 3279, 2923, 1452, 1330, 1246, 1153, 1074, 1027, 826, 698, 666 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38 (2 H, d, *J* 7.5 Hz, C*H*Ar), 7.13-7.01 (10 H, m, C*H*Ar) 6.96-6.94 (2 H, m, C*H*Ar), 6.89-6.83 (4H, m, C*H*Ar), 4.22 (1 H, d, *J* 8 Hz, C*H*NTs), 4.02 (1H, dd, *J* 8 and 5 Hz, C*H*OCH_3), 3.80 (3 H, s, ArOC*H*$_3$), 3.55 (1H, d, *J* 8 Hz, C*H*NH), 3.09 (3 H, s, CHOC*H*$_3$), 2.49-2.41 (1 H, m, C*H*$_2$), 2.37-2.31 (4 H, m, SO_2ArCH_3 and C*H*$_2$NH overlapping), 1.91-1.82 (1 H, m, C*H*$_2$C*H*OCH_3), 1.73-1.67 (1 H, m, C*H*$_2$CHOMe); δ_C (100 MHz, $CDCl_3$) 142.63 (*C*Ar), 139.36 (*C*Ar), 138.42 (*C*Ar), 137.10 (*C*Ar), 133.71 (2 *C*Ar), 129.10 (2 *C*HAr), 128.26 (2 *C*HAr), 127.87 (2 *C*HAr), 127.75 (2 *C*HAr), 127.66 (2 *C*HAr), 127.42 (2 *C*HAr), 127.40 (*C*HAr), 127.25 (*C*HAr), 127.16 (2 *C*HAr), 113.83 (2 *C*HAr), 82.56 (*C*H_3), 67.94 (*C*H), 63.18 (*C*H), 56.31 (*C*H), 55.27 (*C*H_3), 44.59 (*C*H_2), 37.96 (*C*H_2), 21.45 (*C*H_3); *m/z* (ESI) 545.3 (M^+ + 1).

Attempted synthesis of *N*-(2-(3-(4-methoxyphenyl)propylamino))ethyl)-4-methylbenzenesulfonamide (235).



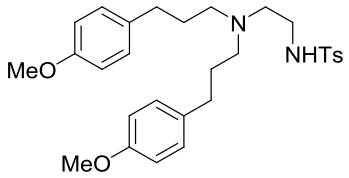
This compound would be novel.

Attempts to prepare this compound were carried out according to general procedure 5 using 3-(4-methoxyphenyl)propan-1-ol (500 mg, 3.00 mmol), 2,6-lutidine (418

mg, 3.90 mmol), trifluoromethanesulfonic anhydride (900 mg, 3.20 mmol), *N*-(2-aminoethyl)-4-methylbenzenesulfonamide (407 mg, 1.90 mmol), Et_3N (455 mg, 4.50 mmol) and DCM (13.6 cm^3). The product was purified by column chromatography as in the general procedure. TLC: silica gel, 30% EtOAc in petroleum ether, product Rf = 0.36 with visualisation by UV and $KMnO_4$, 2,6-lutidine Rf = 0.42 with visualisation by UV only. The product elutes after 2,6-lutidine, no pentane wash is necessary. The product was obtained as a yellow oil but was found to be the di-alkylated product shown below rather than the expected mono-alkylated product. (123 mg, 0.24 mmol, 24% base on 279 mg, 1.30 mmol *N*-(2-aminoethyl)-4-methylbenzenesulfonamide).

Reducing the number of equivalents of 3-(4-methoxyphenyl)propan-1-ol to 1 equivalent relative to *N*-(2-aminoethyl)-4-methylbenzenesulfonamide gave no improvement with the di-alkylated *N*-(2-(bis(3-(4-methoxyphenyl)propylamino)) ethyl)-4-methylbenzenesulfonamide still being the major product formed in the reaction.

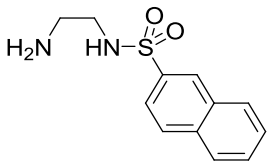
_N_-(2-(bis(3-(4-methoxyphenyl)propylamino))ethyl)-4-methylbenzenesulfonamide (236).



(Found (ESI): M^+ + H, 511.2627 $C_{29}H_{38}N_2O_4S$ requires M, 511.2625); υ_{max} 2936, 1510, 1463, 1324, 1242, 1158, 1091, 1033, 812, 660 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.72 (2H, d, *J* 8.1 Hz, C*H*ArSO_2), 7.23 (2H, d, *J* 8.1 Hz, C*H*ArCH_3), 7.03 (4H, d, *J* 8.7 Hz, C*H*ArOCH_3), 6.82 (4H, d, *J* 8.7 Hz, C*H*ArCH_2), 3.78 (6H, s, OC*H*$_3$), 2.91

(2H, t, *J* 5.8 Hz, SO_2NCH_2), 2.45-2.38 (9H, m, CH_3ArSO_2, $CH_2CH_2CH_2NH$ and $SO_2NCH_2CH_2N$ overlapping), 2.31-2.26 (CH_2Ar), 1.62-1.51 ($CH_2CH_2CH_2$); δ_C (75 MHz, $CDCl_3$) 177.17 (2 *C*Ar), 142.71 (*C*Ar), 136.08 (*C*Ar), 133.31 (2 *C*Ar), 129.08 (*C*HAr), 128.55 (4 *C*HAr), 126.53 (2 *C*HAr), 113.18 (4 *C*HAr), 54.65 (2 CH_3), 52.41 (2 CH_2), 51.78 (CH_2), 39.79 (2 CH_2), 32.06 (CH_2), 28.15 (2 CH_2), 20.91 (2 CH_3); *m/z* (ESI) 511.3 ($M^+ + 1$).

_N_-((Naphthalene-2-ylsulfonyl)methyl)ethane-1, 2-diamine.

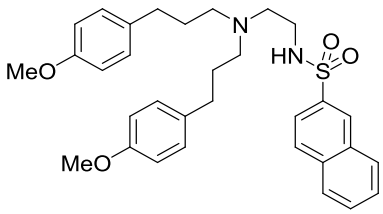


This compound is known in the literature but has not previously been fully characterised.[196]

To ethylene diamine (1.2 g, 20 mmol) in anhydrous DCM (5 cm^3) was added a solution of 2-napthalenesulfonyl chloride (453 mg, 2.00 mmol) in anhydrous DCM (5 cm^3). The resulting solution was stirred at room temperature for 30 min. Water was added to the reaction and the organic phase was separated and washed with further water. The aqueous washings were then combined and washed with DCM. The organic phases were combined, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to give the product as a white solid (270 mg, 1.1 mmol, 55%). Purification was not necessary. Mp 129-131°C; (found (ESI): $M^+ + H$, 251.0851 $C_{12}H_{15}N_2O_2S$ requires M, 251.0849); υ_{max} 3363, 2849, 1594, 1314, 1151, 1125, 960, 746, 654 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.44 (1H, s, C*H*Ar), 7.96-7.93 (2H, m, C*H*Ar), 7.90-7.83 (2H, m, C*H*Ar), 7.65-7.57 (2H, m, C*H*Ar), 3.02-2.99 (2H, m, CH_2), 2.80-2.77 (5H, m, CH_2 and NH_2 and N*H* overlapping); δ_C (100 MHz, $CDCl_3$)

136.78 (*C*Ar), 134.78 (*C*Ar), 132.17 (*C*Ar), 129.55 (*C*HAr), 129.24 (*C*HAr), 128.76 (*C*HAr), 128.37 (*C*HAr), 127.91 (*C*HAr), 127.56 (*C*HAr), 122.31 (*C*HAr), 45.43 (CH_2), 40.98 (CH_2); *m/z* (ESI) 251.0 (M^+ + 1). This compound is known in the literature but has not previously been fully characterised.[196]

_N_-(2-(Bis(3-(4-methoxyphenyl)propyl)amino)ethyl)naphthalene-2-sulfonamide (236b).

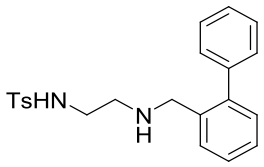


This compound is novel.

This compound was prepared according to general procedure 5 using 3-(4-methoxyphenyl)propan-1-ol (266 mg, 1.60 mmol), 2,6-lutidine (225 mg, 2.10 mmol), trifluoromethanesulfonic anhydride (478 mg, 1.70 mmol), *N*-((naphthalene-2-ylsulfonyl)methyl)ethane-1, 2-diamine (250 mg, 1.00 mmol), Et_3N (243 mg, 2.40 mmol) and DCM (7.3 cm^3). The product was purified by column chromatography as in the general procedure. TLC: 30% EtOAc in petroleum ether, product Rf = 0.21 with visualisation by UV and $KMnO_4$, 2,6-lutidine Rf = 0.31 with visualisation by UV. Product elutes after 2,6-lutidine, no pentane wash required. Product obtained as a yellow oil (110 mg, 0.2 mmol, 25% based on 250 mg, 1 mmol sulfonated diamine). Mp 53°C; (found (ESI): M^+ + H, 547.2624 $C_{32}H_{39}N_2O_4S$ requires M, 547.2625); υ_{max} 2949, 2909, 2850, 2833, 1510, 1326, 1241, 1157, 1031, 810, 746, 657 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.43 (1H, br s, C*H*Ar), 7.93-7.87 (3H, m, C*H*Ar), 7.82-7.80 (1H, m, C*H*Ar), 7.65-7.57 (2H, m, C*H*Ar), 6.96 (4H, d, *J* 8.4 Hz, C*H*ArOCH$_3$), 6.78 (4H, d, *J* 8.4 Hz, C*H*ArCH$_2$), 5.30 (1H, br s, N*H*), 3.77 (6H, s, C*H*$_3$), 2.96 (2H, t, *J* 5.6 Hz,

C*H*$_2$NHSO$_2$), 2.44 (2H, t, *J* 5.6 Hz, SO$_2$HNCH2C*H*$_2$N), 2.36 (4H, t, *J* 7.6 Hz, CH$_2$CH$_2$C*H*$_2$N), 2.28-2.25 (4H, m, ArC*H*$_2$), 1.55 (4H, quin, *J* 7.6 Hz, CH-$_2$C*H*$_2$CH$_2$N); δ_C (100 MHz, CDCl$_3$) 157.80 (2 *C*Ar), 136.54 (*C*Ar), 134.79 (*C*Ar), 133.82 (2 *C*Ar), 132.18 (*C*Ar), 129.49 (*C*HAr), 129.26 (*C*HAr), 129.15 (4 *C*HAr), 128.78 (*C*HAr), 128.45 (*C*HAr), 127.95 (*C*HAr), 127.59 (*C*HAr), 122.44 (*C*HAr), 113.80 (4 *C*HAr), 55.28 (2 *C*H$_3$), 53.00 (*C*H$_2$), 52.46 (*C*H$_2$), 40.42 (2 *C*H$_2$), 32.63 (2 *C*H$_2$), 28.67 (2 *C*H$_2$); *m/z* (ESI) 547.3 (M^+ + 1).

_N_-(2-(Biphenyl-2-yl)methylamino)ethyl)-4-methylbenzenesulfonamide (238).

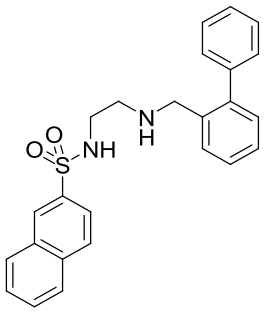


This compound is novel.

To biphenylcarboxaldehyde (182 mg, 1.00 mmol) was added activated molecular sieves (1 g) and anhydrous MeOH (6 cm^3). To this was added TsEN (246 mg, 1.10 mmol) and acetic acid (50 μL). The reaction was stirred at room temperature for 5 hours and then NaBH$_3$CN (251 mg, 4.00 mmol) was added and the reaction stirred at room temperature overnight. After this the reaction was filtered and the solid washed with DCM. The filtrate and DCM washings were combined and dried under reduced pressure. The residue was then dissolved in anhydrous DCM and washed with 1M NaOH (aq.) solution. The DCM phase was separated, dried over Na$_2$SO$_4$, filtered and the solvent removed under reduced pressure to give the product as a pale yellow viscous oil (134 mg, 0.35 mmol, 70%). Purification was not necessary. (found (ESI): M^+ + H, 381.1632 $C_{22}H_{25}N_2O_2S$ requires M, 381.1631); υ_{max} 3272, 2858, 1477, 1450, 1322, 1155, 1091, 814, 775, 750, 703 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 7.67 (2H, d,

J 8.1 Hz, SO_2CHAr), 7.43-7.11 (13H, m, C*H*Ar and N*H* overlapping), 3.58 (2H, s, $ArCH_2N$), 2.84 (2H, dd, *J* 6.5 and 4.8 Hz, CH_2NHSO_2), 2.50 (2H, dd, *J* 6.5 and 4.8 Hz, CH_2NH), 2.40 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 142.64 (*C*Ar), 141.24 (*C*Ar), 140.53 (*C*Ar), 136.39 (*C*Ar), 136.22 (*C*Ar), 129.57 (*C*HAr), 129.04 (2 *C*HAr), 128.50 (*C*HAr), 128.27 (2 *C*HAr), 127.68 (2 *C*HAr), 126.95 (*C*HAr), 126.62 (*C*HAr), 126.55 (*C*HAr), 126.49 (2 *C*HAr), 50.06 (CH_2), 46.65 (CH_2), 41.60 (CH_2), 20.92 (CH_3); *m/z* (ESI) 381.0 ($M^+ + 1$).

_N_-(2-(Biphenyl-2-yl)methylamino)ethyl)naphthalene-2-sulfonamide (241).



This compound is novel.

To biphenylcarboxaldehyde (91 mg, 0.5 mmol) was added activated molecular sieves (500 mg) and anhydrous MeOH (3 cm^3). To this was added *N*-((naphthalene-2-ylsulfonyl)methyl)ethane-1,2-diamine (138 mg, 0.55 mmol) and acetic acid (50 μL). The reaction was stirred at room temperature for 5 hours and then $NaBH_3CN$ (126 mg, 2 mmol) was added and the reaction stirred at room temperature overnight. The reaction was filtered and the solid washed with DCM. The filtrate and DCM washings were combined and dried under reduced pressure. The residue was then dissolved in anhydrous DCM and washed with 1M NaOH (aq.) solution. The DCM phase was separated, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to give the product as a pale yellow oil (134 mg, 0.350 mmol,

70%). Purification was not necessary. (found (ESI): M^+ + H, 417.1635 $C_{25}H_{25}N_2O_2S$ requires M, 417.1631); υ_{max} 3286, 2912, 1451, 1435, 1320, 1154, 1074, 747, 702, 656 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.38-8.37 (1H, , m, C*H*Ar), 7.92-7.86 (3H, m, C*H*Ar), 7.75-7.71 (1H, m, C*H*Ar), 7.65-7.55 (2H, m, C*H*Ar), 7.37-7.17 (11H, m, C*H*Ar and N*H* overlapping), 3.55 (2H, s, CH_2), 2.87 (2H, dd, *J* 6.4 and 4.7 Hz, CH_2NSO$_2$), 2.48 (2H, dd, *J* 6.4 and 4.7 Hz, CH_2NH); δ_C (75 MHz, $CDCl_3$) 141.84 (*C*Ar), 141.12 (*C*Ar), 136.97 (*C*Ar), 136.59 (*C*Ar), 134.76 (*C*Ar), 132.15 (*C*Ar), 130.18 (*C*HAr), 129.47 (*C*HAr), 129.24 (*C*HAr), 129.09 (*C*HAr), 128.86 (2 *C*HAr), 128.77 (*C*HAr), 128.43 (*C*HAr), 128.28 (2 *C*HAr), 127.93 (*C*HAr), 127.57 (2 *C*HAr), 127.21 (*C*HAr), 127.17 (*C*HAr), 122.37 (*C*HAr), 50.63 (*C*H_2), 47.23 (*C*H_2), 42.27 (*C*H_2); *m/z* (ESI) 417.1 (M^+ + 1).

5.3.5.3 Synthesis of tethered ruthenium complexes by aryl substitution methodology.

General procedure 6 and 7: preparation of tethered ruthenium complexes by aryl substitution methodology.

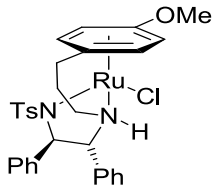
General procedure 6:

To a pressure tube was added the required aryl-3C-TsDPEN ligand (2eq.), ethylbenzoate ruthenium(II)chloride dimer (1 eq.) and anhydrous DCM (4.5 cm^3 per mmol of ligand). The tube was then flushed with N_2 and then sealed. The reaction was stirred for 30 min. at room temperature and then at 90°C for 48 hours. The reaction was allowed to cool to room temperature and the solvent was removed under reduced pressure to give the crude as a dark brown solid. The crude was purified by column chromatography and then recrystallised from minimal hot methanol with DCM.

General procedure 7:

To a nitrogen purged round bottom flask was added the required aryl-3C-TsDPEN ligand (2 eq.), ruthenium dimer (1 eq.) and dry DCM (1.3 cm^3 per 0.05 mmol ligand). The solution was stirred at room temperature for 1 hour. The DCM was removed under reduced pressure to give an orange/red solid. Chlorobenzene (3.3 cm^3 per 0.05 mmol ligand) was then added. The reaction was connected to a reflux condenser, purged with nitrogen and stirred at 90°C until deemed complete by TLC. Once complete the reaction was cooled and the chlrorbenzene removed under reduced pressure to give the crude as an orange/brown solid. The crude product was purified by column chromatography and recrystallisation from minimal hot methanol and DCM.

_N_-((1_R_,2_R_)-2-(3-(4-methoxyphenyl)propylamino)-1,2-diphenyl)-4-methyl benzenesulfonamide) ruthenium chloride (199).



This compound is novel.

The compound was prepared according to general procedures 6 and 7 using _N_-((1_R_,2_R_)-2-(3-(4-methoxyphenyl)propylamino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide **198** (300 mg, 0.58 mmol), ethylbenzoate ruthenium(II)chloride dimer **197** (187 mg, 0.29 mmol) and anhydrous DCM (9 cm^3) for general procedure 6, and _N_-((1_R_,2_R_)-2-(3-(4-methoxyphenyl)propylamino)-1,2-diphenylethyl)-4-methylbenzene sulfonamide **198** (100 mg, 0.20 mmol), ethylbenzoate ruthenium(II)chloride dimer **197** (64 mg, 0.10 mmol) and anhydrous DCM (5.2 cm^3), chlorobenzene (13.2 cm^3) for general procedure 7. In each case the

crude product was purified by column chromatography (florisil 200 mesh, 0-10% MeOH in DCM, TLC: silica plate, 5% MeOH in DCM, visualisation in natural light, product Rf = 0.40 orange) to give the product was an orange solid. This was then further purified by recrystallisation from the minimal hot MeOH and DCM to give the product as orange crystals.

General procedure 6: 150 mg, 40% after column chromatography, 16 mg, 0.025 mmol, 6% from 2 recrystallisations.

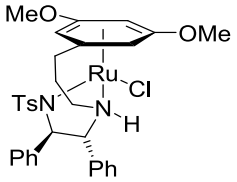
General procedure 7: 103 mg, 80% after column chromatography, 31 mg, 0.05 mmol, 25% from 2 recrystallisations.

Mp 261°C (decomposed); $[\alpha]_D^{30}$ -670 (*c* 0.01 in $CHCl_3$) (*R*,*R*); (found (ESI): $[M^+ + H - Cl]$, 615.1255 $C_{31}H_{33}N_2O_3RuS$ requires M, 615.1257); υ_{max} 3194, 3027, 3938, 1534, 1495, 1466, 1454, 1270, 1256, 1128, 1082, 1039, 1012, 938, 905, 812, 69, 656 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.29-7.27 (2H, m, C*H*Ar), 7.16-7.11 (3H, m, C*H*Ar), 6.85-6.77 (2H, m, C*H*Ar), 6.75-6.73 (3H, d, *J* 8.3 Hz, C*H*Ar), 6.64-6.60 (2H, t, *J* 7.5 Hz, C*H*Ar), 6.55-6.53 (2H, m, C*H*Ar), 5.57 (1H, d, *J* 6.0 Hz, C*H*Ar-Ru), 5.47 (1H, 6.0 Hz, C*H*A-Ru), 5.35 (1H, d, *J* 6.0 Hz, C*H*Ar-Ru), 5.22 (1H, d, *J* 6.0 Hz, C*H*Ar-Ru), 4.33 (1H, d, *J* 11.2 Hz, C*H*NTs), 4.08-4.03 (1H, br m, N*H*$(CH_2)_3$), 3.99 (3H, s, OCH_3), 3.56 (1H, t, *J* 11.2 Hz, C*H*NH), 2.81-2.75 (1H, m, NC$H_2CH_2CH_2$), 2.49-2.39 (2H, m, $NCH_2CH_2CH_2Ar$), 2.32-2.25 (1H, m, NC$H_2CH_2CH_2$), 2.21 (3H, s, SO_2ArCH_3), 2.12-2.00 (2H, m, $NCH_2CH_2CH_2$); δ_C (100 MHz, $CDCl_3$) 143.83 (*C*Ar), 138.67 (*C*Ar), 138.42 (*C*Ar), 136.40 (*C*Ar), 134.69 (*C*Ar), 128.72 (2 *C*HAr), 128.68 (2 *C*HAr), 128.34 (*C*HAr), 127.73 (4 *C*HAr), 127.06 (2 *C*HAr), 126.88 (2 *C*HAr), 126.01 (*C*HAr), 91.20 (*C*Ar-Ru), 84.72 (*C*HAr-Ru), 81.46 (*C*HAr-Ru), 78.77 (*C*HAr-Ru), 72.17 (*C*HAr-Ru), 68.94 (CH_3), 65.49 (*C*H), 56.84 (*C*H), 49.41 (CH_2), 30.32 (CH_2), 27.32 (CH_2), 21.16 (CH_3); *m/z* (ESI) 615.1 ($M^+ + 1 - 35$).

Addition of inorganic base to aryl substitution complexation:

To a nitrogen purged, dried flask was added *N*-((1*R*,2*R*)-2-(3-(4-methoxyphenyl)propylamino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide **198** (100 mg, 0.2 mmol) and ethylbenzoate ruthenium(III)chloride dimer **197** (64 mg, 0.1 mmol). To this was then added $Ca(OH)_2$ (15 mg, 0.2 mmol) and anhydrous DCM (5.2 cm^3). The resulting solution was then stirred at room temperature for 30 min before the DCM was removed under reduced pressure and replaced with chlorobenzene (13.2 cm^3). The reaction was stirred at 90°C for 5 hours. The reaction was cooled and the solvent removed under vacuum. The residue was washed with water and dried to leave the crude product as a black solid. The crude product was purified by column chromatography and recrystallisation as above, however only 1 recrystallisation was required, to give the product (**199**) as an orange solid (118 mg, 91% after column chromatography, 43 mg, 0.066 mmol, 33% from 1 recrystallisation). Data matched that reported above.

***N*-((1*R*,2*R*)-2-(3-(3,5-Dimethoxyphenyl)propylamino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide) ruthenium chloride (209).**



This compound is novel.

The compound was prepared according to the general procedures using *N*-((1*R*,2*R*)-2-(3-(3.5-dimethoxyphenyl)propylamino)-1,2-diphenylethyl)-4-methylbenzeneulphonamide **208** (220 mg, 0.40 mmol), ethylbenzoate ruthenium(II)chloride dimer **197** (130 mg, 0.20 mmol) and anhydrous DCM (6 cm^3)

for general procedure 6, and *N*-((1*R*,2*R*)-2-(3-(3.5-dimethoxyphenyl)propylamino)-1,2-diphenylethyl)-4-methylbenzeneulphonamide **208** (200 mg, 0.36 mmol), ethylbenzoate ruthenium(II)chloride dimer **197** (116 mg, 0.18 mmol) and anhydrous DCM (9 cm^3) and chlorobenzene (23 cm^3) for general procedure 7. In each case the crude product was purified by column chromatography (florisil 200 mesh, 0-10% MeOH in DCM, TLC: silica plate, 5% MeOH in DCM, visualisation in natural light, product Rf = 0.43 orange) to give the product as an orange solid. This was then further purified by recrystallisation from minimal hot MeOH and DCM to give the product as orange crystals.

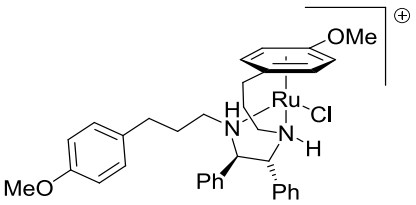
General procedure 6: 220 mg ligand, 238 mg after column chromatography, 16 mg, 0.06 mmol, 15% from 2 recrystallisations.

General procedure 7: 200 mg ligand, 130 mg after column chromatography, 96 mg, 0.14 mmol, 39% from 1 recrystallisation.

Mp 672°C (decomposed); $[\alpha]_D^{30}$ -10.3 (*c* 0.02 in $CHCl_3$) (*R*,*R*); (found (ESI): M^+ + H - Cl, 645.1357 $C_{32}H_{35}N_2O_4RuS$ requires M, 645.1363); υ_{max} 3676, 2988, 2901, 1542, 1407, 1394, 1265, 1125, 1078, 1066, 1056, 895, 833, 691 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.46 (2H, d, *J* 8.3 Hz, C*H*Ar), 7.14-7.06 (3H, m, C*H*Ar), 6.85 (3H, d, *J* 8.0 Hz, C*H*Ar), 6.78-6.72 (4H, m, C*H*Ar), 6.65 (2H, d, *J* 7.3 Hz, C*H*Ar), 5.89 (1H, s, C*H*Ar-Ru), 4.77 (2H, d, *J* 15.2 Hz, C*H*Ar), 4.41-4.38 (1H, m, N*H* $(CH_2)_3$), 4.17 (3H, s, OCH_3), 4.16 (3H, s, OCH_3), 4.07 (1H, d, *J* 10.8 Hz, C*H*NTs), 3.76 (1H, t, *J* 11.7 Hz, C*H*NH$(CH_2)_3$), 2.71-2.58 (3H, m, CH_2), 2.25 (3H, s, SO_2ArCH_3), 2.21-2.04 (2H, m, CH_2), 1.90-1.86 (1H, m, CH_2); δ_C (100 MHz, CD_2Cl_2) 143.57 (*C*Ar), 140.15 (*C*Ar), 139.32 (*C*Ar), 137.23 (*C*Ar), 136.16 (*C*Ar), 135.61 (*C*Ar), 129.46 (2 *C*HAr), 128.94 (2 *C*HAr), 128.51 (*C*HAr), 127.97 (4 *C*HAr), 127.82 (2 *C*HAr), 127.26 (2 *C*HAr), 126.57 (*C*HAr), 96.96 (*C*Ar-Ru), 78.74 (*C*HAr-Ru), 69.55 (*C*HAr-Ru),

65.39 (*C*HAr-Ru), 57.50 (*C*H_3), 57.47 (*C*H_3), 56.46 (*C*H) 53.94 (*C*H), 48.35 (*C*H_2), 29.92 (*C*H_2), 25.86 (*C*H_2), 21.27 (*C*H_3); *m/z* (ESI) 645.1 (M^+ + 1 - 35). X-ray crystallography data is given in Appendix 2.

Cationic tethered ruthenium complex (211).

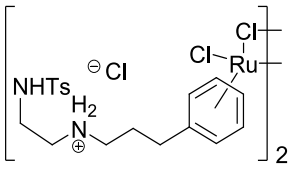


This compound is novel.

This compound was prepared according to general procedure 7 using (1*R*,2*R*)-*N*,*N*-Bis(3-(4-methoxyphenyl)propyl)-1,2-diphenylethane-1,2-diamine **210** (200 mg, 0.40 mmol), ethylbenzoate ruthenium(II)chloride dimer **197** (129 mg, 0.20 mmol), DCM (10.3 cm^3) and chlorobenzene (26.7 cm^3). It was only necessary to stir the reaction in chlorobenzene at 90°C for 1 hour before complete consumption of the ligand was observed by TLC. The crude product was purified by column chromatography (silica gel, 0-30% MeOH in DCM, TLC: silica plate, 5% MeOH in DCM, visualisation in natural light, product Rf = 0.48 yellow) to give the product as a yellow/orange solid (158 mg, 0.24 mmol, 60%). Mp 85°C; $[\alpha]_D^{28}$ +210 (*c* 0.01 in $CHCl_3$) (*R*, *R*); (found (ESI): M^+, 645.1820. $C_{34}H_{40}ClN_2O_2Ru$ requires M, 645.1822); υ_{max} 3059, 2928, 1511, 1454, 1244, 1177, 1029, 1005, 805, 763, 701 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.72 (1H, br s, N*H*), 7.96 (1H, br s, N*H*), 7.12-7.06 (6H, m, C*H*Ar), 6.86-6.81 (4H, m, C*H*Ar), 6.75-6.68 (4H, m, C*H*Ar), 5.69-5.67 (1H, m, C*H*Ar-Ru), 5.45-5.43 (1H, m, C*H*Ar-Ru), 5.18-5.16 (1H, m, C*H*Ar-Ru), 5.10-5.09 (1H, m, C*H*Ar-Ru), 4.39 (1H, br s, C*H*NH), 3.95-3.86 (1H, m, C*H*NH), 3.60 (3H, s, CH_3OAr-Ru), 3.05-3.02 (2H, m,

C*H*$_2$), 2.87 (2H, br s, C*H*$_2$), 2.33-2.30 (4H, m, C*H*$_2$), 2.17 (3H, s, C*H*$_3$OAr(CH$_2$)$_3$N), 1.91 (1H, br s, C*H*$_2$), 1.72-1.59 (3H, m, C*H*$_2$); δ_C (100 MHz, $CDCl_3$) 157.67 (*C*Ar), 137.78 (*C*Ar), 136.34 (*C*Ar), 135.04 (*C*Ar), 134.73 (*C*Ar), 132.78 (*C*Ar), 129.07 (2 *C*HAr), 129.00 (2 *C*HAr), 128.93 (2 *C*HAr), 128.76 (*C*HAr), 128.56 (2 *C*HAr), 128.26 (2 *C*HAr), 127.52 (*C*HAr), 113.65 (2 *C*HAr), 100.47 (*C*Ar-Ru), 86.98 (*C*Ar-Ru), 86.75 (*C*HAr-Ru), 75.53 (*C*HAr-Ru), 71.31 (*C*HAr-Ru), 70.10 (*C*HAr-Ru), 66.97 (*C*H), 56.69 (*C*H), 55.24 (*C*H$_3$), 53.38 (*C*H$_2$), 32.31 (*C*H$_2$), 31.82 (*C*H$_2$), 30.12 (*C*H$_2$), 30.09 (*C*H$_3$), 29.14 (*C*H$_2$), 27.74 (1C, s); *m/z* (ESI) 645.2 (M^+).

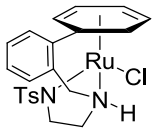
Achiral 3C-tethered dimer 243.



This compound is known in the literature and has been fully characterised.[145]

The batch of dimer **252** used in this thesis had been prepared previously in our group according to literature procedures and was fully characterised in agreement with the literature.[145]

Achiral tethered ruthenium complex (239).

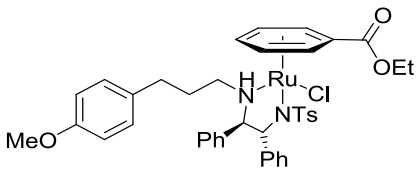


This compound is novel.

This compound was prepared according to general procedure 7 using *N*-(2-(Biphenyl-2-yl)methylamino)ethyl)-4-methylbenzenesulfonamide **238** (100 mg, 0.28 mmol), ethylbenzoate ruthenium(II)chloride dimer **197** (84 mg, 0.14 mmol), DCM

(6.5 cm^3) and chlorobenzene (17 cm^3). It was necessary to stir the reaction at 140°C in chlorobenzene for 7 hours after the initial 30 min in anhydrous DCM. The crude product was purified by column chromatography (floristic 200 mesh, 0-10% MeOH in DCM, TLC: silica plate, 5% MeOH in DCM, visualisation in natural light, product Rf = 0.65) to give the product as a brown/orange solid (50 mg). Mass spectrometry showed 2:1 complex:ligand. Attempts were made to recrystallise the product from hot MeOH and DCM however the product was found to remain in solution. The solid was removed by filtration and the filtrate dried under reduced pressure to give the product as a brown solid (27 mg, 0.055 mmol, 20%). The product contained impurities and minimal data was obtained. ^{1}H NMR analysis showed the presence of resonances expected in the product although the peaks were broad and impurities were present: δ_H (400 MHz, $CDCl_3$) 7.64-7.22 (C*H*Ar and impurities), 6.33 (1H, s, C*H*Ar-Ru), 6.13 (1H, s, C*H*Ar-Ru), 5.39 (1H, s, C*H*Ar-Ru), 2.41 (2H, br s, NCH_2), 2.41 (2H, br s, NCH_2), 1.26 (3H, s, CH_3); *m/z* (ESI) 481.1 (M^++H-Cl).

_N_-((1_R_,2_R_)-2-(3-(4-methoxyphenyl)propylamino)-1,2-diphenylehtyl)-4-methylbenzenesulfonamide)-η^6-(ethyl benzoate) ruthenium chloride (_p_-OMe-202).



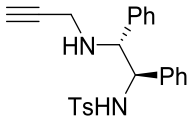
This compound is novel.

To a nitrogen purged, dried flask was added ligand *N*-((1*R*,2*R*)-2-(3-(4-methoyphenyl)propylamino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide **198** (50 mg, 0.1 mmol) and ethylbenzoate ruthenium(II)chloride dimer **197** (32 mg, 0.05

mmol). To this was then added triethylamine (20 mg, 0.2 mmol) and anhydrous *iso*-propanol (4 cm^3). The resulting solution was stirred at reflux under nitrogen for 2 hours. The reaction was cooled to room temperature and the solvent and triethylamine were removed under reduced pressure to leave an orange/brown solid. The solid was purified by column chromatography (florisil 200 mesh, 0-5% MeOH in DCM, TLC: 5% MeOH in DCM, visualisation in natural light, product Rf = 0.35) to give a red solid (33 mg, 0.04 mmol, 40%). Mp 210°C (decomposed 170°C); $[\alpha]_D^{28}$ -30 (*c* 0.005 in $CHCl_3$) (*R*,*R*); (found (ESI): M^+ + H, 765.1944 $C_{40}H_{43}N_2O_5RuS$ requires M, 765.1942); υ_{max} 3028, 2923, 1729, 1512, 1454, 1268, 1125,1103, 1082, 903, 817, 806, 697, 576 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.18 (2H, d, *J* 8.0 Hz, C*H*Ar), 7.04-6.92 (6H, m, 5 x C*H*Ar and C*H*Ar-Ru); 6.75-6.65 (6H, m, C*H*Ar), 6.60 (1H, br s, C*H*Ar), 6.54 (2H, t, *J* 7.5 Hz, C*H*Ar), 6.39 (2H, d, *J* 7.5 Hz, C*H*Ar), 6.29 (1H, t, *J* 5.8 Hz, C*H*Ar-Ru), 6.11-6.09 (1H, m, C*H*Ar-Ru), 5.86 (1H, d, *J* 5.8 Hz, C*H*Ar-Ru), 5.10 (1H, t, *J* 5.8 Hz, C*H*Ar-Ru), 4.59-4.51 (1H, m, C$H_2$$CH_3$), 4.41-4.34 (1H, m, C$H_2$$CH_3$), 4.01 (1H, d, *J* 11.0 Hz, C*H*), 3.82 (1H, t, *J* 11.0 Hz, N*H*), 3.70 (3H, s, OCH_3), 3.55-3.49 (1H, m, C*H*), 3.31-3.22 (1H, m, CH_2), 2.75-2.67 (1H, m, CH_2), 2.64-2.57 (1H, m, CH_2), 2.24-2.16 (1H, m, CH_2), 2.13 (3H, s, S(O_2)CH_3), 2.02-1.97 (1H, m, CH_2), 1.86-1.79 (1H, m, CH_2), 1.45 (3H, t, *J* 7.2 Hz, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 166.50 (*C*=O), 158.22 (*C*Ar), 142.04 (*C*Ar), 139.35 (*C*Ar), 138.30 (*C*Ar), 136.60 (*C*Ar), 132.79 (*C*Ar), 129.53 (2 *C*HAr), 128.87 (2 *C*HAr), 128.63 (*C*HAr), 128.33 (*C*HAr), 127.84 (2 *C*HAr), 127.50 (4 *C*HAr), 126.86 (2 *C*HAr), 126.28 (2 *C*HAr), 114.08 (2 *C*HAr), 94.96 (*C*HAr-Ru), 93.73 (*C*HAr-Ru), 89.25 (*C*HAr-Ru), 81.08 (*C*HAr-Ru), 79.21 (*C*HAr-Ru), 79.13 (*C*HAr-Ru), 75.38 (*C*Ar-Ru), 69.69 (*C*H), 62.76 (*C*H_2), 55.35 (*C*H_3), 53.48 (*C*H_2), 32.08 (*C*H_2), 30.56 (*C*H_2), 21.20 (*C*H_3), 14.44 (*C*H_3); *m/z* (ESI) 765.2 (M^+ + 1).

5.3.5.4 Attempted syntheses of triazole tethered ruthenium complexes.

[(*1R,2R*)-1,2-Diphenyl-*N*-(prop-2-ynylamino)ethyl]-4-methylbenzenesulfonamide (223)

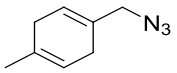


This compound is known in the literature and has previously been fully characterised.[54]

To a dried, argon purged flask was added (*R,R*)TsDPEN (733 mg, 2.00 mmol) and anhydrous K_2CO_3 (719 mg, 5.20 mmol). To this was then added anhydrous MeCN (15 cm^3) and finally propargyl bromide solution (80% in toluene) (327 mg, 2.20 mmol). The reactions was stirred at room temperature overnight. The reaction solution was filtered and the acetonitrile was removed under reduced pressure. The residue was dissolved in chloroform and washed with water. The organic phase was then dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to leave the crude product as an off-white solid. The crude was purified by column chromatography (silica gel, 0-50% EtOAc in petroleum ether, TLC: silica plate, 1:1 EtOAc:petroleum ether, visualisation by $KMnO_4$, product Rf = 0.7) to give the pure product as a white solid (457 mg, 1.13 mmol, 57%). Mp 128-129°C; $[\alpha]_D^{28}$ -70.7 (*c* 0.5 in $CHCl_3$) (*R,R*) (lit.[54] $[\alpha]_D^{27}$ -66.7 (*c* 0.5 in $CHCl_3$) (*R,R*)); (found (ESI): M^+ + H, 405.1633 $C_{24}H_{25}N_2O_2S$ requires M, 405.1631); υ_{max} 3676, 3193, 2987, 2901, 1439, 1331, 1153, 1076, 916, 810, 697, 670 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.39 (2H, d, *J* 8.3 Hz, C*H*$ArSO_2$), 7.11-7.09 (3H, m, C*H*Ar) 7.04-6.94 (7H, m, C*H*Ar) 6.90-6.87 (2H, m, C*H*Ar), 6.17-6.15 (1H, m, N*H*Ts), 4.37 (1H, t, *J* 7.0 Hz, C*H*NHTs), 4.04 (1H, d, *J* 7.5 Hz, C*H*$NHCH_2$), 3.38 (1H, dd, *J* 17.0 and 2.5 Hz, CH^aH^bCCH), 3.02 (1H, dd, *J* 17.0 and 2.5 Hz, CH^aH^bCCH), 2.27 (3H, s, CH_3), 2.22 (1H, t, *J* 2.4 Hz, CH_2CCH),

2.07 (1H, br s, N*H*CH_2); δ_C (100 MHz, $CDCl_3$) 142.17 (*C*Ar), 137.56 (2 *C*Ar 136.37 (*C*Ar), 128.53 (2 *C*HAr), 127.67 (2 *C*HAr), 127.38 (4 *C*HAr), 127.02 (*C*HAr), 126.65 (2 *C*HAr), 126.61 (1 *C*HAr), 126.44 (2 *C*HAr), 80.86 (*C*), 71.40 (*C*H), 65.23 (*C*H), 62.67 (*C*H), 34.98 (CH_2), 20.80 (CH_3); *m/z* (ESI) 405.1 (M^+ + 1), 427.0 (M^+ + 23). Data matches that previously reported for this compound.[54]

3-(Azidomethyl)-6-methylcyclohexa-1,4-diene (225).

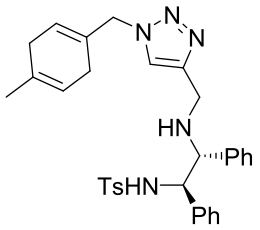


This compound is novel.

To an argon purged, dried flask was added (4-methylcyclohexa-1,4-dien-1-yl)methanol previously prepared in our group (248 mg, 2.00 mmol) and anhydrous THF (8 cm^3). The solution was cooled to 0°C and to it was added diphenylphosphoryl azide (660 mg, 2.40 mmol) and, dropwise, DBU (364 mg, 2.40 mmol). The reaction was stirred at 0°C for 1 hour and then at room temperature overnight. The reaction was heated to 40°C for 3 hours before being allowed to cool to room temperature. Et_2O (10 cm^3) and H_2O (5 cm^3) were then added to the reaction. The aqueous phase was extracted with Et_2O (2 x 10 cm^3). The Et_2O extracts were collected and combined before being dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to leave the crude as a pale yellow oil. The crude was purified by column chromatography using a short silica gel column to minimise decomposition of the azide on the silica (silica gel, 0-10% EtOAc in petroleum ether, TLC: silica plate, 1:1 EtOAc:petroleum ether, visualisation by $KMnO_4$, product Rf = 0.89) to give the purified product as a pale yellow oil (151 mg, 1 mmol, 51%). υ_{max} 3675, 2969, 2901, 2358, 2342, 2090, 1441, 1242, 1065, 950,

783, 668 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.74-5.73 (1H, s, C*H*), 5.44-5.43 (1H, s, C*H*), 3.69 (2H, s, CH_2), 2.66 (4H, s, 2 x CH_2), 1.69 (3H, s, CH_3) ; δ_C (100 MHz, $CDCl_3$) 130.86 (*C*), 192.87 (*C*), 123.96 (*C*H), 117.94 (*C*H), 57.15 (*C*H_2), 31.37 (*C*H_2), 28.32 (*C*H_2), 22.94 (*C*H_3); *m/z* (CI) 107.2 (M^+ - 42) weak spectrum, compound does not ionise readily, HRMS data could not be obtained.

_N_-((1-((4-Methylcyclohexa-1,4-dienyl)methyl)-1_H_-1,2,3-triazol-4-yl)methylamino)-1,2-diphenyl)-4-methylbenzenesulfonamide (224).

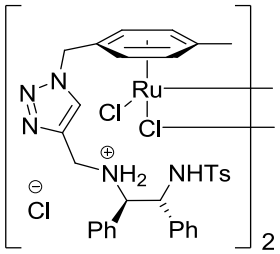


This compound is novel.

To an argon purged dried flask was added the ([(*1R,2R*)-1,2-diphenyl-*N*-(prop-2-ynylamino)ethyl]-4-methylbenzenesulfonamide **223** (113 mg, 0.280 mmol) and degassed anhydrous THF (4 cm^3) and degassed distilled water (4 cm^3). Under a flow of argon the 3-(azidomethyl)-6-methylcyclohexa-1,4-diene **225** (50 mg, 0.34 mmol), $Cu(OAc)_2$ (11 mg, 0.060 mmol) and sodium-(*L*)-ascorbate (22 mg, 0.11 mmol). The reaction turned from blue to cloudy white and was stirred at room temperature for 48 hours. EtOAc was then added to the reaction followed by ammonium hydroxide (36%) solution (aq.). The EtOAc phase was collected and washed with further ammonium hydroxide solution (3 x 10 cm^3). The ammonium hydroxide solution was then extracted with EtOAc (3 x 10 cm^3). The EtOAc phases were combined, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to leave the crude product as a pale blue oil. The crude product was purified by column chromatography (silica gel, 0-5% MeOH in DCM, TLC: silica plate, 5% MeOH in

DCM, visualisation by $KMnO_4$, product Rf = 0.49) to give the product as a white solid (100 mg, 0.18 mmol, 64%). Mp 160-161°C; $[\alpha]_D^{29}$ -25.8 (*c* 0.25 in $CHCl_3$) (*R*,*R*); (found (ESI): M^+ + H, 554.2592. $C_{32}H_{36}N_5O_2S$ requires M, 554.2584 error -1.4 ppm); υ_{max} 3331, 3028, 2817, 2360, 2342, 1453, 1325, 1152, 1052, 911, 813, 697, 666 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.35 (2H, d, *J* 7.5 Hz, C*H*ArSO$_2$), 7.13-7.11 (3H, m, C*H*Ar), 7.04-6.98 (7H, m, C*H*Ar), 6.90 (2H, d, *J* 7.5 Hz, C*H*ArSO$_2$), 6.29 (1H, br s, N*H*Ts), 5.73 (1H, s, NCH$_2$C=C*H*), 5.38 (1H, s, H$_3$CC=C*H*), 4.82 (2H, s, NNC*H*$_2$CH=CH), 4.32 (1H, d, *J* 7.8, C*H*^{a}H^{b}NHCH), 3.76 (2H, d, *J* 7.8 Hz, CH^a*H*^{b}NHCH), 3.72 (1H, d *J*, 13.8 Hz, C*H*NHTs), 3.59 (1H, d *J*, 13.8, C*H*NHCH$_2$), 2.68-2.64 (2H, m, C*H*$_2$CH=CCH$_3$), 2.49-2.43 (2H, m, H$_3$CCC*H*$_2$), 2.31 (3H, s, ArC*H*$_3$), 1.68 (3H, s, C*H*$_3$C=CH); δ_C (100 MHz, $CDCl_3$) 146.51 (*C*Ar), 142.74 (*C*Ar), 138.71 (*C*Ar), 138.23 (*C*Ar), 137.02 (*C*Ar), 130.78 (*C*Ar), 129.68 (*C*Ar), 129.12 (2 *C*HAr), 128.37 (2 *C*HAr), 127.94 (2 *C*HAr), 127.67 (2 *C*HAr), 127.61 (*C*HAr), 127.49 (2 *C*HAr), 127.28 (*C*HAr), 127.06 (2 *C*HAr), 124.95 (H*C*=), 121.42 (H*C*=), 117.64 (H*C*=), 67.15 (*C*H), 63.09 (*C*H), 56.10 (*C*H$_2$), 42.31 (*C*H$_2$), 31.46 (*C*H$_2$), 27.74 (*C*H$_2$), 22.91 (*C*H$_3$), 21.43 (*C*H$_3$); *m/z* (ESI) 554.1 (M^+ + 1), 576.2 (M^+ + 23).

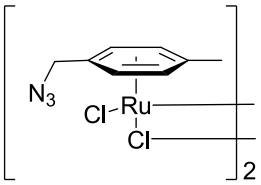
Attempted synthesis of *N*-((1*R*, 2*R*)-2-((1-(4-methylbenzyl)-1*H*-1, 2, 3-triazol-4-yl)methylamino)-1,2-diphenyl)-4-methylbenzenesulfonamide ruthenium(II)chloride dimer, hydrochloride salt (227).



This compound would be is novel.

To an argon purged, dried flask at 0°C was added *N*-((1-((4-methylcyclohexa-1, 4-dienyl)methyl)-1*H*-1, 2, 3-triazol-4-yl)methyl)-1, 2-diphenylethane-1, 2-diamine **224** (50 mg, 0.090 mmol) and EtOH (1.7 cm^3) and concentrated HCl (aq.) (36%) (12 μL). The resulting solution was stirred at 60°C for 30 min. A solution of $RuCl_3.xH_2O$ (18 mg, 0.070 mmol) in EtOH (1.7 cm^3) and water (56 μL) was added to the reaction. The reaction was then stirred at 75°C overnight. After this the reaction was cooled to room temperature and hexane was added and the solution stirred for 5 min before being filtered. The solid was washed with additional hexane before being dried to give the product as a brown solid (27 mg), however no evidence of the desired complex was seen by mass spectrometry or NMR.

4-Methylbenzylazide ruthenium(II)chloride dimer (220).

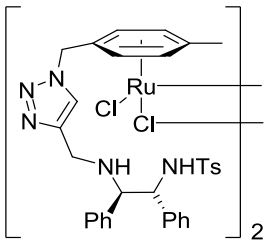


This compound is novel.

To an argon purged, dried flask was added 4-methylbenzylbromide ruthenium(II)chloride dimer previously prepared in our group (100 mg, 0.140 mmol) and NaN_3 (27 mg, 0.42 mmol). To this was then added anhydrous, degassed DCM (6 mL). The reaction was cooled at room temperature for 48 hours. After this the reaction was filtered and the solid washed with water and then further DCM before being dried under vacuum to leave the solid as a red/brown solid (67 mg, 0.11 mmol, 79%). The product was found to be unstable in air and sensitive to shocks with agitation using a spatula causing the compound to violently decompose. It was

stored therefore used directly in subsequent reactions without purification. Minimal characterisation data was obtained. υ_{max} 3676, 2987, 2901, 2362, 2050, 1406, 1380, 1250, 1229, 1066, 1057, 889 cm^{-1}; δ_H (400 MHz, DMSO) 6.23-6.20 (3H, m, C*H*Ar-Ru), 5.90-5.88 (2H, m, C*H*Ar-Ru), 4.43 (2H, s, CH_2), 2.20 (3H, s, CH_3).

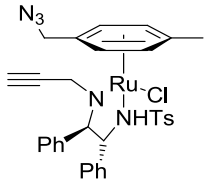
Attempted synthesis of *N*-((1*R*, 2*R*)-2-((1-(4-methylbenzyl)-1*H*-1, 2, 3-triazol-4-yl)methylamino)-1,2-diphenyl)-4-methylbenzenesulfonamide ruthenium(II)chloride dimer (222).



This compound would be novel.

To a nitrogen purged, dried flask containing 4-methylbenzylazide ruthenium(II)chloride dimer (55 mg, 0.085 mmol) was added *N*-((1-((4-methylcyclohexa-1,4-dienyl)methyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1,2-diphenylethane-1,2-diamine **224** (69 mg, 0.17 mmol), $Cu(OAc)_2$ (6 mg, 0.035 mmol) and sodium (*L*) ascorbate (14 mg, 0.070 mmol). To this was then added degassed THF/water 1/1 (4 mL) and the reaction stirred at room temperature for 48 hours. After this EtOAc (10 mL) was added followed by ammonium hydroxide (aq.) (35%) (10 mL). The EtOAc phase was separated and washed with further ammonium hydroxide (aq.) (35%) (10 mL). The ammonium hydroxide phases were combined and washed with EtOAc. The EtOAc phases were combined, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to give a black solid (101 mg) however the desired product was not observed by mass spectrometry or NMR.

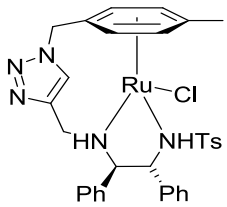
Attempted synthesis of *N*-[(1*R*, 2*R*)-1, 2-diphenyl-2-(prop-2-ynylamino)ethyl)]-4-methylbenzenesulfonamide-(4-methylbenzylazide)ruthenium(II)chloride (221).



This compound would be novel.

To 4-methylbenzylazide ruthenium(II)chloride dimer **220 (**6 mg, 0.09 mmol) was added [(*1R,2R*)-1,2-diphenyl-*N*-(prop-2-ynylamino)ethyl]-4-methylbenzene sulfonamide **223** (73 mg, 0.18 mmol) and anhydrous, degassed IPA (10 mL). To this was then added triethylamine (36 mg, 0.36 mmol) and the reaction was stirred at reflux for 1 hour. After this the reaction was cooled to room temperature and the solvent removed under reduced pressure. The residue was washed with water and dried under vacuum to leave the crude product as a black solid (123 mg, 0.18 mmol). No evidence of the desired complex was seen by mass spectrometry or NMR analysis.

Attempted synthesis of *N*-((1*R*,2*R*)-2-((1-(4-methylbenzyl)-1*H*-1, 2, 3-triazol-4-yl)methylamino)-1,2-diphenyl)-4-methylbenzenesulfonamide ruthenium(II)chloride monomer (226).

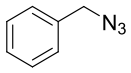


This compound would be novel.

To a nitrogen purged, dried schlenk tube was added *N*-((1-((4-methylcyclohexa-1,4-dienyl)methyl)-1*H*-1,2,3-triazol-4-yl)methylamino)-1,2-diphenyl)-4-methylbenzenesulfonamide **224** (110 mg, 0.200 mmol) and anhydrous toluene (0.6

cm^3). To the stirred solution at 50°C was added HCl (aq.) (37%) (25 μL). The solution was heated to 75°C and $RuCl_3.3H_2O$ (44 mg, 0.16 mmol) in water (50 μL) was added followed by IPA (0.3 cm^3). The reaction was stirred at 75°C overnight. After this the reaction was cooled to 0°C and toluene (0.9 cm^3) and *N,N*-diisopropylethylamine (145 μL, 0.83 mmol) was added with stirring. The reaction was allowed to warm to room temperature and was then heated at 80°C for 30 min before being again cooled to room temperature. DCM (1.5 mL) was added and the reaction solution was filtered over neutral alumina which was then washed with DCM. The filtrate was dried under reduced pressure. IPA (1.5 mL) was then added and the solution stirred at room temperature for 1 hour after which it was filtered and the solid dried to give a black solid (85 mg). No evidence of the desired product was seen by mass spectrometry or NMR analysis.

Benzyl azide.

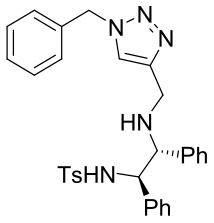


This compound is known in the literature and has been fully characterised.[197]

To a nitrogen purged flask was added sodium azide (215 mg, 3.30 mmol) in DMSO (5 cm^3). To this was then added a solution of benzyl bromide (513 mg, 3.00 mmol) in DMSO (2.5 cm^3). The reaction was stirred at room temperature overnight. After this water was added to the reaction and the product extracted into Et_2O (3 x 15 cm^3). The Et_2O phases were combined, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to leave the product as a colourless oil (303 mg, 2.30 mmol, 77%). Purification was not necessary. υ_{max} 2090, 1496, 1454, 1253, 1201, 876, 735, 694 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.41-7.31 (5H, m, C*H*Ar), 4.33 (2H,

s, C*H*$_2$); δ_C (100 MHz, $CDCl_3$) 135.39 (*C*Ar), 128.87 (2 *C*HAr), 128.34 (*C*HAr), 128.25 (2 *C*HAr), 54.84 (*C*H_2); *m/z* (CI) 91.0 (M^+ - 42). Data matches that reported for this compound.[197]

_N_-((1_R_,2_R_)-2-((1-benzyl-1_H_-1,2,3-triazol-4-yl)methylamino)-1,2-diphenyl)-4-methylbenzenesulfonamide (228).

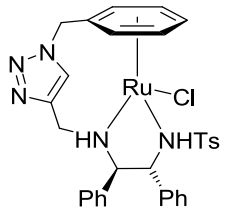


This compound is known in the literature and has previously been fully characterised.[54]

To a nitrogen purged, dried flask was added [(*1R,2R*)-1,2-diphenyl-*N*-(prop-2-ynylamino)ethyl]-4-methylbenzene sulfonamide **223** (202 mg, 0.5 mmol), degassed dry THF (6.5 cm^3) and degassed water (6.5 cm^3). To the stirred solution was then added $Cu(OAc)_2$ (18 mg, 0.10 mmol), sodium ascorbate (40 mg, 0.20 mmol) and benzyl azide (80 mg, 0.60 mmol). The reaction was stirred at room temperature for 48 hours. During this time, the reaction solution turned from blue to cloudy white in colour. After 48 hours, EtOAc was added to the reaction followed by ammonium hydroxide (35% aq.). The EtOAc phase was collected and washed with further ammonium hydroxide. The EtOAc phase was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to give the crude product as an off white solid. The crude product was purified by column chromatography (silica gel, 0-10% MeOH in DCM, TLC: silica plate, 5% MeOH in DCM, visualisation by $KMNO_4$, product Rf = 0.52) to give the product as a white solid (60 mg, 0.11 mmol, 22%). Mp 190°C; $[\alpha]_D^{30}$ -26.4 (*c* 0.5 in $CHCl_3$) (*R,R*) (lit.[54] $[\alpha]_D^{29}$ -21.3 (*c* 0.5 in $CHCl_3$)

(*R*,*R*)); (found (ESI): M^+ + H, 538.2272 $C_{31}H_{32}N_5O_2S$ requires M, 538.2271); υ_{max} 3345, 2976, 1454, 1433, 1323, 1151, 1077, 1051, 933, 812, 714, 694, 662 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38-7.33 (5 H, m, C*H*Ar), 7.27-7.25 (2 H, m, C*H*Ar), 7.23 (1H, s, N*H*), 7.11-7.09 (3H, m, C*H*Ar), 7.04-6.94 (7H, m, C*H*Ar), 6.89-6.87 (2H, m, C*H*Ar), 6.25 (1H, br s, N*H*), 5.50-5.42 (2H, m, CH_2), 4.31 (1H, d, *J* 7.7 Hz, CH^aH^b), 3.74 (1H, d, *J* 7.7 Hz, CH^aH^b), 3.70 (1H, d, *J* 14.2 Hz, CH^aH^b), 3.56 (1H, d, *J* 14.2 Hz, CH^aH^b), 2.30 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 146.75 (*C*Ar), 142.74 (*C*Ar), 138.68 (*C*Ar), 138.25 (*C*Ar), 137.01 (*C*Ar), 129.13 (4 *C*HAr), 128.74 (*C*HAr), 128.37 (2 *C*HAr), 128.10 (2 *C*HAr), 127.94 (2 *C*HAr), 127.66 (2 *C*HAr), 127.61 (*C*HAr), 127.47 (2 *C*HAr), 127.29 (*C*HAr), 127.05 (2 *C*HAr), 121.59 (*C*HAr), 71.83 (*C*), 67.12 (*C*H), 65.93 (*C*H), 63.08 (*C*H), 54.10 (*C*H_2), 42.26 (*C*H_2), 21.44 (*C*H_3); *m/z* (ESI) 538.2 (M^+ + 1). Data matches that previously reported.[54]

Attempted synthesis of triazole tethered monomer 229 using aryl substitution.

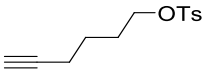


This compound would be novel.

The attempted preparation of this compound was carried out according to the general procedure 7 using *N*-((1*R*,2*R*)-2-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methylamino)-1,2-diphenyl)-4-methylbenzenesulfonamide **228** (28 mg, 0.05 mmol), ethylbenzoate ruthenium(II)chloride dimer **197** (16 mg, 0.025 mmol), DCM (1.3 cm^3) and chlorobenzene (3.3 cm^3). After 5 hours at 90°C no evidence of the formation of the desired monomer **229** was seen by mass spectrometry.

5.3.5.5 Synthesis of polymer supported ligands and ruthenium complexes.

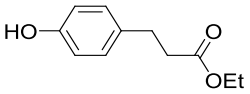
Hex-5-ynyl-4-methylbenzenesulfonate (244).



This compound is known in the literature but has not previously been fully characterised.[198]

To a dried, nitrogen purged flask was added 5-hexyn-1-ol (392 mg, 4.00 mmol) was added anhydrous DCM (24 cm^3). The solution was then cooled to 0°C and to it was added DMAP (49 mg, 0.4 mmol), tosyl chloride (915 mg, 4.8 mmol) and triethylamine (486 mg, 4.8 mmol). The resulting colourless solution was then allowed to warm to room temperature and stirred overnight. Saturated NH_4Cl (aq.) solution was added to quench the reaction and the mixture extracted with EtOAc (3 x 15 cm^3), dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to leave the product as a faint yellow oil (790 mg, 3.10 mmol, 78%). Purification was not necessary. (found (ESI): M^+ + Na, 275.0713 $C_{13}H_{16}NaO_3S$ requires M, 275.0712); υ_{max} 3289, 2958, 1354, 1172, 1097, 1009, 930, 814, 661 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.80 (2H, d, *J* 8.0, C*H*Ar), 7.35 (2H, d, *J* 8.0 Hz, C*H*Ar), 4.06 (2H, t, *J* 6.2 Hz, C$H_2$$OSO_2$Ar), 2.45 (3H, s, C$H_3$), 2.17 (2H, td, *J* 6.9 and 2.7 Hz, HCCCH_2), 1.93 (1H, t, *J* 2.6 Hz, *H*CCCH_2), 1.83-1.73 (2H, m, CH_2C$H_2$$OSO_2$), 1.61-1.51 (2H, m, HCC$H_2CH_2CH_2$); δ_C (100 MHz, $CDCl_3$) 144.79 (*C*Ar), 133.08 (*C*Ar), 129.87 (2 *C*HAr), 127.88 (2 *C*HAr), 83 40 (*C*H), 69.94 (*C*H_2), 68.99 (*C*), 27.76 (*C*H_2), 24.22 (*C*H_2), 21.64 (*C*H_3), 17.73 (*C*H_2); *m/z* (ESI) 275.0 (M^+ + 23). Data matches that previously reported for this compound.[198]

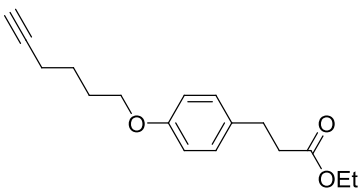
Ethyl-3-(4'-hydroxyphenyl)propanoate (245).



This compound is known in the literature and has previously been fully characterised.[199]

To 3-(4-hydroxyphenyl)propionic acid (664 mg, 4.00 mmol) was added ethanol (4 cm^3) and catalytic H_2SO_4 (98%) (22μL). The solution was stirred at room temperature overnight. The ethanol was removed under reduced pressure and water was added to the residue which was then extracted with EtOAc (3 x 10 cm^3), dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to leave the product as a colourless oil (625 mg, 3.2mmol, 80%). Purification was not necessary. (found (ESI): M^+ + Na, 217.0843. $C_{11}H_{14}NaO_3$ requires M, 217.0835); υ_{max} 3368, 2981, 1703, 1514, 1445, 1372, 1205, 1101, 1035, 828 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.02 (2H, d, *J* 8.3 Hz, C*H*Ar), 6.74 (2H, d, *J* 8.3 Hz, C*H*Ar), 6.45 (1H, br s, O*H*), 4.12 (2H, q, *J* 7.0 Hz, OCH_2), 2.86 (2H, t, *J* 7.7 Hz, C$H_2$$CH_2$CO), 2.58 (2H, t, *J* 7.7 Hz, CH_2CH_2CO), 1.22 (3H, t, *J* 7.0 Hz, CH_3); δ_C (100 MHz,$CDCl_3$) 173.88 (*C*=O), 154.38 (*C*Ar), 132.18 (*C*Ar), 129.39 (2 *C*HAr), 115.41 (2 *C*HAr), 60.78 (*C*H_2), 36.37 (*C*H_2), 30.15 (*C*H_2), 14.16 (*C*H_3); *m/z* (ESI) 217.1 (M^+ + 23). Data matches that previously reported for this compound.[199]

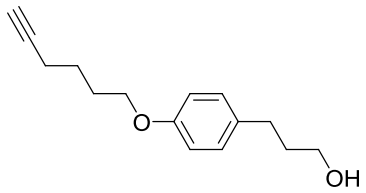
Ethyl-3-(4-(hex-5-ynyloxy)phenyl)propanoate (246).



This compound is novel.

To a nitrogen purged, dried flask was added ethyl-3-(4-hydroxyphenyl)propanoate **245** (543 mg, 2.80 mmol), K_2CO_3 (1.16 g, 8.40 mmol), NaI (42 mg, 0.28 mmol) and anhydrous acetonitrile (17 cm^3). To this was then added hex-5-ynyl-4-methylbenzenesulfonate **244** (857 mg, 3.40 mmol). The reaction was stirred at reflux (80°C) overnight. After this the reaction was cooled to room temperature and the acetonitrile was removed under reduced pressure. Water was added to the residue and the mixture was extracted with EtOAc (3 x 15 cm^3). The EtOAc was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to leave the crude product as an orange oil. The crude product was purified by column chromatography (silica gel, 0-50% EtOAc in petroleum ether, TLC: 30% EtOAc in petroleum ether, visualisation by $KMnO_4$, product Rf 0.70) to give the product as a white solid (788 mg, 2.90 mmol, 85%). (Found (ESI): M^+ + H, 275.1644 $C_{17}H_{23}O_3$ requires M, 275.1642); υ_{max} 3291, 2938, 1729, 1511, 1240, 1176, 1038, 826, 636 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.09 (2H, d, *J* 8.6 Hz, C*H*Ar), 6.79 (2H, d, *J* 8.6 Hz, C*H*Ar), 4.10 (2H, q, *J* 7.1 Hz, CH_2CH$_3$), 3.93 (2H, t, *J* 6.2 Hz, CH_2OAr), 2.89-2.84 (2H, m, CH_2COEt), 2.58-2.53 (2H, m, CH_2CH$_2$CO$_2$Et), 2.25 (2H, td, *J* 7.0 and 2.6 Hz, HCCCH_2), 1.95 (1H, t, *J* 2.6 Hz, *H*CCCH$_2$), 1.90-1.83 (2H, m, CH$_2$CH_2CH$_2$OAr), 1.74-1.64 (2H, m, HCCCH$_2$CH_2), 1.21 (3H, t, *J* 7.1 Hz, OCH$_2$CH_3); δ_C (75 MHz, $CDCl_3$) 172.38 (*C*=O), 156.84 (*C*Ar), 131.98 (*C*Ar), 128.62 (2 *C*HAr), 113.83 (2 *C*HAr), 83.50 (*C*H), 68.03 (*C*), 66.62 (*C*H$_2$), 59.75 (*C*H$_2$), 29.52 (*C*H$_2$), 27.70 (*C*H$_2$), 24.44 (*C*H$_2$), 17.54 (*C*H$_2$), 13.62 (*C*H$_3$); *m/z* (ESI) 275.1 (M^+ + 1), 297.1 (M^+ + 23). For procedure see reference 200.

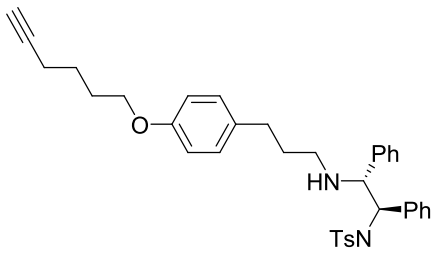
Ethyl-3-(4-(hex-5-ynyloxy)phenyl)propan-1-ol (247).



This compound is novel.

To ethyl-3-(4-(hex-5-ynyloxy)phenyl)propanoate **246** (590 mg, 2.15 mmol) was added anhydrous THF (4.3 cm^3) and the solution cooled to 0°C. $LiAlH_4$ (1M in THF) (4.3 cm^3, 4.3 mmol) was then added dropwise. The reaction was stirred at room temperature and monitored by TLC (1:1 EtOAc:petroleum ether 40-60, Rf product = 0.42) until complete (2 hr). At this point the reaction was again cooled to 0°C and water was added dropwise to quench the reaction. The THF was removed under reduced pressure and the product extracted from the residue with EtOAc (3 x 15 cm^3). The EtOAc phases were combined, dried over Na_2SO_4, filtered and the solvent removed under rotary evaporation to leave the crude as a colourless oil (408 mg, 1.76 mmol, 70%). Purification was not necessary. Mp 28-29°C; (found (ESI): M^+ + Na, 255.1359 $C_{15}H_{20}NaO_2$ requires M, 255.1356); υ_{max} 3284, 2942, 2870, 1510, 1242, 1175, 1053, 1032, 1006, 817, 634 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.09 (2H, d, *J* 8.5 Hz, C*H*Ar), 6.81 (2H, d, *J* 8.5 Hz, C*H*Ar), 3.95 (2H, t, *J* 6.3 Hz, CH_2OAr), 3.65 (2H, t, *J* 6.4 Hz, CH_2OH), 2.64 (2H, t, *J* 7.5 Hz, ArCH_2), 2.27 (2H, td, *J* 7.0 and 2.5 Hz, HCCCH_2), 1.97 (1H, t, *J* 2.6 Hz, *H*CCCH$_2$), 1.93-1.81 (4H, m, $CH_2CH_2CH_2OAr$ and CH_2CH_2OH overlapping), 1.75-1.67 (2H, m, $HCCCH_2CH_2$), 1.59 (1H, br s, O*H*); δ_C (100 MHz, $CDCl_3$) 157.24 (*C*Ar), 133.83 (*C*Ar), 129.31 (2 *C*HAr), 114.46 (2 *C*HAr), 84.18 (*C*H), 68.66 (*C*), 67.32 (*C*H$_2$), 62.26 (*C*H$_2$), 34.45 (*C*H$_2$), 31.16 (*C*H$_2$), 28.36 (*C*H$_2$), 25.09 (*C*H$_2$), 18.18 (*C*H$_2$); *m/z* (ESI) 255.1 (M^+ + 23).

_N_-((1_R_, 2_R_)-2-(3-(4-(Hex-5-ynyloxy)phenyl)propylamino)-1, 2-diphenylethyl)-4-methylbenzenesulfonamide (248).

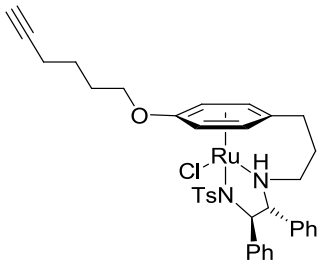


This compound is novel.

This compound was prepared according to general procedure 5 using 3 ethyl-3-(4-(hex-5-ynyloxy)phenyl)propan-1-ol **247** (400 mg, 1.72 mmol), 2,6-lutidine (353 mg, 3.30 mmol), trifluoromethanesulfonic anhydride (787 mg, 2.80 mmol), (*R*,*R*)-TsDPEN (403 mg, 1.10 mmol), Et_3N (263 mg, 2.60 mmol) and DCM (8 cm^3). The product was purified by column chromatography as in the general procedure. TLC: silica gel, 30% EtOAc in petroleum ether, product Rf = 0.36 with visualisation by UV and $KMnO_4$, 2,6-lutidine Rf = 0.29 with visualisation by UV, 2,6-lutidine elutes with the product). The fractions containing the product were collected, combined and dried under reduced pressure to give a white solid. The solid was then washed with pentane to remove residual 2,6-lutidine. The mixture was filtered and the solid dried to give the product as a white solid (524 mg, 0.900 mmol, 82% based on 403 mg, 1.1 mmol *N*-(2-aminoethyl)-4-methylbenzenesulfonamide)). Mp 123-124°C; $[\alpha]_D^{27}$ -25.2 (*c* 0.25 in $CHCl_3$) (*R*,*R*); (found (ESI): M^+ + H, 581.2833 $C_{36}H_{41}N_2O_3S$ requires M, 581.2832); υ_{max} 3286, 3248, 2915, 1510, 1454, 1434, 1316, 1242, 1160, 1031, 808, 700 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.37 (2H, d, *J* 8.5 Hz, C*H*ArSO_2), 7.13-7.11 (3H, m, C*H*Ar), 7.05-6.88 (12H, m, C*H*Ar and N*H*SO_2 overlapping), 6.78 (2H, d, *J* 8.5 Hz, C*H*ArSO_2), 6.28 (1H, br s, N*H*), 4.25 (1H, d, *J* 7.8 Hz, C*H*NSO_2), 3.95 (2H, t, *J* 5.0 Hz, CH_2OAr), 3.59 (1H, d, *J* 7.8 Hz, C*H*N), 2.51-2.38 (3H, m, ArCH_2 and CH_2N

overlapping), 2.31 (3H, s, C*H*$_3$), 2.29-2.24 (3H, m, HCCC*H*$_2$ and C*H*$_2$N overlapping), 1.96 (1H, t, *J* 2.6 Hz, *H*CCCH$_2$), 1.92-1,85 (2H, m, CH$_2$C*H*$_2$CH$_2$OAr), 1.75-1.61 (4H, m, C*H*$_2$CH$_2$N and HCCCH$_2$C*H*$_2$); δ_C (100 MHz, $CDCl_3$) 157.20 (*C*Ar), 142.70 (*C*Ar), 139.33 (*C*Ar), 138.39 (*C*Ar), 137.09 (*C*Ar), 133.79 (*C*Ar), 129.21 (2 *C*HAr), 129.10 (2 *C*HAr), 128.31 (2 *C*HAr), 127.93 (2 *C*HAr), 127.58 (2 *C*HAr), 127.46 (*C*HAr), 127.41 (2 *C*HAr), 127.29 (*C*HAr), 127.13 (2 *C*HAr), 114.39 (2 *C*HAr) 84.18 (*C*), 68.64 (*C*H), 67.77 (*C*H), 67.29 (*C*H$_2$), 63.09 (*C*H), 46.45 (*C*H$_2$), 32.37 (*C*H$_2$), 31.71 (*C*H$_2$), 28.37 (*C*H$_2$), 25.11 (*C*H$_2$), 21.46 (*C*H$_3$), 18.19 (*C*H$_2$); *m/z* (ESI) 581.3 (M^+ + 1).

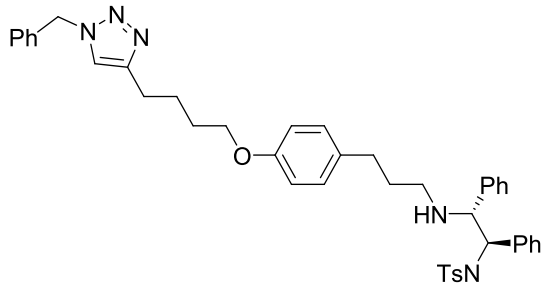
(*R,R*)-3C-tethered monomer with *o*-hexyne substituent (249)



This compound is novel.

This compound was prepared as for general procedure 7 using *N*-((1*R*, 2*R*)-2-(3-(4-(hex-5-ynyloxy)phenyl)propylamino)-1,2-diphenylethyl)-4-methylbenzene sulfonamide **248** (116 mg, 0.2 mmol), ethylbenzoate ruthenium(II)chloride dimer **197** (64 mg, 0.1 mmol), DCM (5 cm^3) and chlorobenzene (13.4 cm^3). After 5 hours at 90°C mass spectrometry analysis showed the desired monomer **248**:**249** 2:1 (*m/z* 681.2 [M^+ + H - Cl]). Due to the small scale of the reaction, the product was not purified. The reaction was carried out as proof of concept for aryl substitution with this ligand structure prior to preparing the polymer supported derivative **253**.

_N_-((1_R_,2_R_)-2-(3-(4-(4-(3-Benzyl-3_H_-1,2,3-triazol-4-yl)butoxy)phenyl) propylamino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide (250).

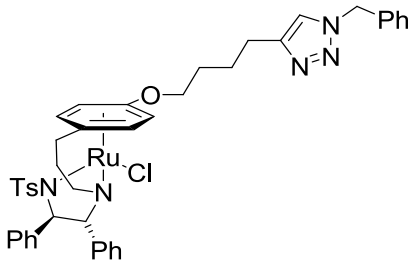


This compound is novel.

To a nitrogen purged flask was added the _N_-((1_R_,2_R_)-2-(3-(4-(hex-5-ynyloxy)phenyl)propylamino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide **248** (116 mg, 0.200 mmol), $Cu(OAc)_2$ (7 mg, 0.04 mmol) and sodium-(_L_)-ascorbate (16 mg, 0.08 mmol) and degassed solution of 1/1 THF/water (5 cm^3). To the stirred solution was then added benzyl azide (32 mg, 0.24 mmol). The reaction became a blue colour when stirred and then became cloudy white. The reaction was stirred at room temperature for 48 hours. After this EtOAc (10 cm^3) was added followed by ammonium hydroxide (35%) solution. The EtOAc was separated and aqueous phase extracted with further EtOAc (2 x 10 cm^3). The EtOAc phases were combined and washed with further ammonium hydroxide (35%) solution. The EtOAc phases were dried over Na_2SO_4, filtered and the solvent removed under reduced pressure to leave the product as a white solid (140 mg, 0.19 mmol, 95%). Purification was not necessary. Mp 123-124°C; $[\alpha]_D^{27}$ -25.2 (_c_ 0.25 in $CHCl_3$) (_R_,_R_); (found (ESI): M^+ + H, 714.3481 $C_{43}H_{48}N_5O_3S$ requires M, 714.3472); υ_{max} 2925, 1510, 1454, 1324, 1241, 1155, 1047, 811, 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.38-7.34 (4H, m, C_H_Ar), 7.25-7.21 (3H, m, C_H_Ar), 7.13-7.10 (3H, m, C_H_Ar), 7.04-7.00 (5H, m, C_H_Ar), 6.97-6.88 (6H, m, C_H_Ar), 6.75 (2H, d, _J_ 8.5 Hz, C_H_Ar), 6.30 (1H, br s, N_H_), 5.46 (2H, s, ArCH_2NNN), 4.25 (1H, d, _J_ 7.9 Hz, C_H_NHSO_2), 3.93 (2H, t, _J_ 5.7 Hz,

C*H*$_2$OAr), 3.59 (1H, d, *J* 7.9 Hz, C*H*NH), 2.76 (2H, t, *J* 7.0 Hz, C*H*$_2$CNNN), 2.49-2.38 (3H, m, C*H*$_2$Ar and C*H*HNH), 2.31-2.24 (4H, m, C*H*$_3$ and CH*H*NH overlapping), 1.84-1.81 (4H, m, CH$_2$C*H*$_2$C*H*$_2$CH$_2$OAr), 1.69-1.61 (2H, m, C*H*$_2$CH$_2$NH); δ_C (100 MHz, $CDCl_3$) 157.18 (*C*Ar), 148.42 (*C*Ar), 142.72 (*C*Ar), 139.31 (*C*Ar), 138.40 (*C*Ar), 137.09 (*C*Ar), 133.76 (*C*Ar), 129.21 (2 *C*HAr), 129.12 (2 *C*HAr), 129.09 (2 *C*HAr), 128.64 (*C*HAr), 128.31 (2 *C*HAr), 128.01 (2 *C*HAr), 127.93 (2 *C*HAr), 127.58 (2 *C*HAr), 127.45 (2 *C*HAr), 127.28 (*C*HAr), 127.11 (2 *C*HAr), 120.72 (*C*HAr), 114.37 (2 *C*HAr), 82.82 (*C*H), 67.76 (*C*H), 67.52 (*C*H$_2$), 65.19 (*C*), 63.14 (*C*H), 62.18 (*C*), 54.01 (*C*H$_2$), 46.44 (*C*H$_2$), 32.37 (*C*H$_2$), 31.70 (*C*H$_2$), 28.88 (*C*H$_2$), 25.98 (*C*H$_2$), 25.46 (*C*H$_2$), 21.46 (*C*H$_3$); *m/z* (ESI) 714.3 (M^+ + 1).

(*R,R*)-3C-tethered ruthenium monomer with triazole linker (251).

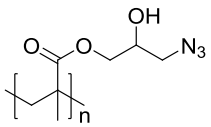


This compound is novel.

This compound was prepared as for general procedure 7 using *N*-((1*R*,2*R*)-2-(3-(4-(4-(3-benzyl-3*H*-1,2,3-triazol-4-yl)butoxy)phenyl)propylamino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide **250** (36 mg, 0.05 mmol), ethylbenzoate ruthenium(II)chloride dimer **197** (16 mg, 0.025 mmol), DCM (1.3 cm^3) and chlorobenzene (3.3 cm^3). After 5 hours mass spectrometry analysis showed the desired monomer **251**:**250** 3:1 (*m/z* 814.2 [M^+ + H - Cl]). Due to the small scale of

the reaction, the product was not isolated. The reaction was carried out as proof of concept for aryl substitution with this ligand structure prior to preparing the polymer supported derivative **253**.

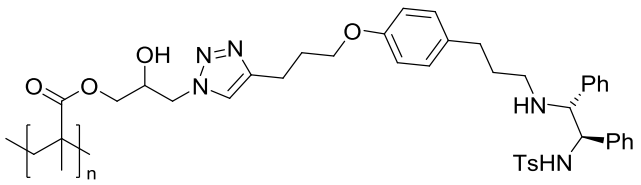
Azido opened polymer (252).



This compound is known in the literature and has previously been fully characterised.[201]

To poly(glycidyl methacrylate) Mn~20,000 (568 mg, 4 mmol epoxide) was added NaN_3 (780 mg, 12 mmol) and NH_4Cl (636 mg, 12 mmol). To this was then added anhydrous DMF (40 cm^3). The reaction was stirred at 50°C for 24 hours. The reaction was cooled to room temperature and water was added until a white precipitate formed. The precipitate was collected by filtration and dried to give the product as a white solid (565 mg, 3.3 mmol repeat units, 83%). Mp 250°C (decomposed); υ_{max} 3427, 2987, 2096, 1720, 1251, 1149, 1089, 747 cm^{-1}; δ_H (300 MHz, THF) 4.71 (1H, br s, O*H*), 3.87-3.84 (3H, m, COOCH_2 and C*H* overlapping), 3.25 (2H, br s, CH_2N_3), 1.86-1.78 (2H, m, CH_2CCH_3), 0.99-0.83 (3H, m, CH_2CCH_3); δ_C (75 MHz, THF) 176.71 (*C*=O), 68.29 (*C*H), 66.11 (*C*H_2), 53.79 (*C*H_2), 44.71 (*C*H_2), 16.78 (*C*H_3).

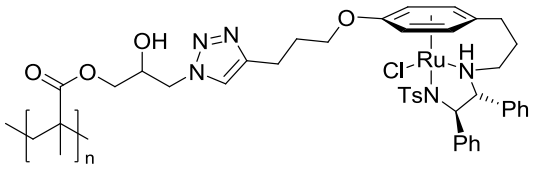
Ligand functionalised polymer (253).



This compound is novel.

To a nitrogen purged flask was added the azido opened polymer **252** (45 mg, 0.20 mmol N_3) and *N*-((1*R*,2*R*)-2-(3-(4-(hex-5-ynyloxy)phenyl)propylamino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide **248** (113 mg, 0.20 mmol). To this was then added $Cu(OAc)_2$ (7 mg, 0.04 mmol) and sodium-(*L*)-ascorbate 16 mg, 0.08 mmol followed by degassed THF/water 1/1 (5 cm^3). The reaction was stirred at room temperature for 48 hours. A blue precipitate formed and was collected by filtration. This was washed with ammonium hydroxide (aq.) and dried to give the product as a blue/green insoluble gel (147 mg, 0.19 mmol clicked ligand). υ_{max} 3375, 2987, 2901, 2103 (weak N_3 signal), 1726, 1241, 1152, 1077, 1056, 810, 698, 665, 548 cm^{-1}.

Polymer supported (*R*,*R*)-3C-tethered Ru complex (254).

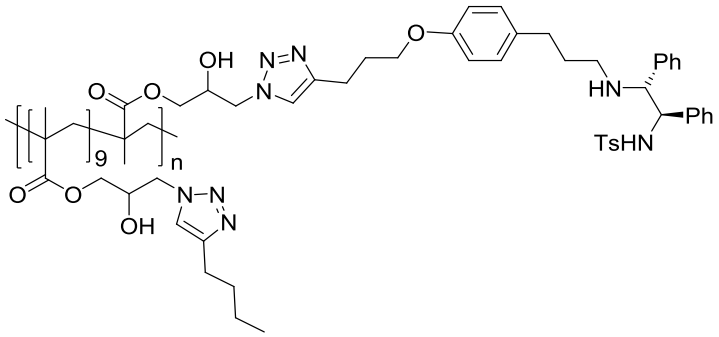


This compound is novel.

To a nitrogen purged flask was added the ligand functionalised polymer **253** (100 mg, 0.13 mmol ligand) was added the ethylbenzoate ruthenium(II)chloride dimer **197** (42 mg, 0.065 mmol). To this was then added anhydrous DCM (3.4 cm^3) and the solution was stirred at room temperature for 30 min. The DCM was removed under

reduced pressure and was replaced with chlorobenzene (8.6 cm^3) and the reaction was stirred at 90°C for 5 hours. The chlorobenzene was removed under vacuum to leave the product as a red/brown insoluble solid. This was washed with further DCM to remove unreacted ethylbenzoate ruthenium(II)chloride dimer to give the product (97 mg, 0.11 mmol Ru catalyst, 85%). MP 234°C (decomposed); υ_{max} 3406, 2931, 1720, 1510, 1445, 1269, 1156, 1106, 1049, 810, 744, 699 cm^{-1};

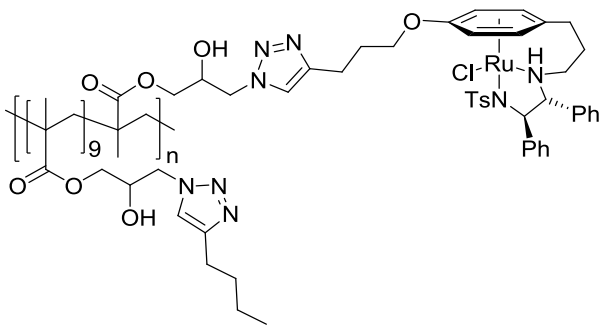
1:9 ligand:hexyne functionalised polymer (255).



This compound is novel.

To a nitrogen purged flask was added the azido opened polymer (97 mg, 0.50 mmol N_3) and *N*-((1*R*,2*R*)-2-(3-(4-(hex-5-ynyloxy)phenyl)propylamino)-1,2-diphenylethyl) -4-methylbenzenesulfonamide **253** (29 mg, 0.05 mmol) and hexyne (37 mg, 0.45 mmol). To this was then added $Cu(OAc)_2$ (18 mg, 0.1 mmol) and sodium-(*L*)-ascorbate (40 mg, 0.2 mmol) and THF/water 4/1 (10 cm^3). The reaction was stirred at room temperature for 48 hours. After this the product had separated from solution as a blue/green jelly. This was removed, washed with ammonium hydroxide (aq.) (35%) and dried to give the product as an insoluble blue gel (103 mg, 0.035 mmol ligand/0.32 mmol clicked hexyne, 70%). υ_{max} 3265, 2954, 2931, 2871, 1728, 1453, 1149, 1058, 809, 701, 665, 549 cm^{-1}.

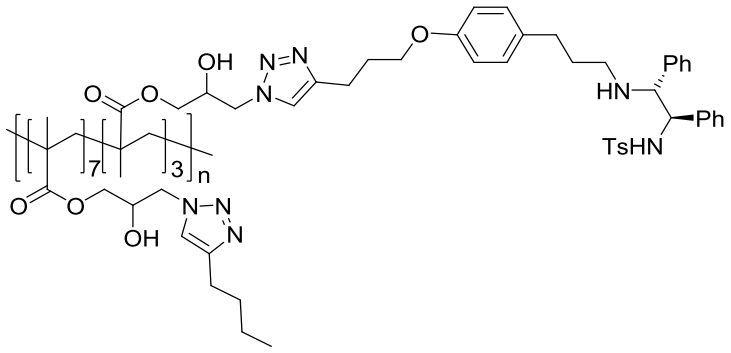
1:9 (*R*,*R*)-3C-tethered Ru complex:hexyne functionalised polymer (256).



This compound is novel.

To a nitrogen purged flask was added 1:9 ligand:hexyne functionalised polymer **255** (100 mg, 0.034 mmol ligand) was added ethylbenzoate ruthenium(II)chloride dimer **197** (11 mg, 0.017 mmol) and anhydrous DCM (0.9 cm^3). The reaction was stirred at room temperature for 30 min before the DCM was removed under reduced pressure. Chlorobenzene (2.2 cm^3) was added and the reaction stirred at 90°C for 5 hours. After this the reaction was cooled to room temperature, filtered and the solid dried to give the product as a red/brown solid. This was washed with further DCM to remove unreacted ethylbenzoate ruthenium(II)chloride dimer to give the product (70 mg, 0.021 mmol Ru catalyst, 62%). υ_{max} 3230, 3079, 2930, 1722, 1443, 1396, 1367, 1288, 1268, 1149, 1105, 1054, 771, 746, 700, 665 cm^{-1}.

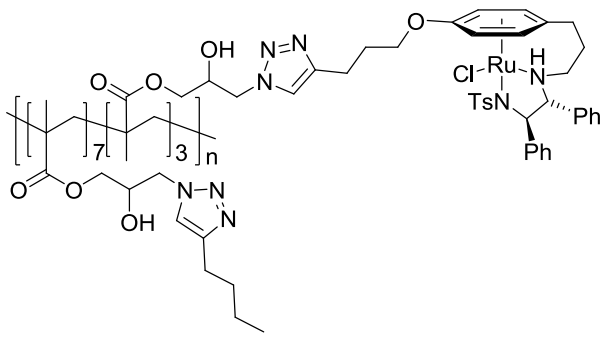
3:7 ligand:hexyne functionalised polymer (257).



This compound is novel.

To a nitrogen purged flask was added the azido opened polymer (93 mg, 0.5 mmol N_3) and *N*-((1*R*,2*R*)-2-(3-(4-(hex-5-ynyloxy)phenyl)propylamino)-1,2-diphenylethyl) -4-methylbenzenesulfonamide **248** (87 mg, 0.15 mmol) and hexyne (29 mg, 0.35 mmol). To this was then added $Cu(OAc)_2$ (18 mg, 0.1 mmol) and sodium-(*L*)-ascorbate (40 mg, 0.2 mmol) and THF/water 4/1 (10 cm^3). The reaction was stirred at room temperature for 48 hours. After this the product had separated from solution as a blue/green jelly. This was removed, washed with ammonium hydroxide (aq.) (35%) and dried to give the product as an insoluble blue gel (180 mg, 0.13 mmol ligand/0.30 mmol clicked hexyne, 87%). υ_{max} 3272, 2930, 2869, 1727, 1454, 1242, 1152, 1055, 810, 699, 665, 548 cm^{-1}.

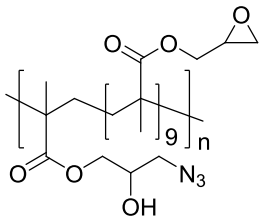
3:7 (*R, R*)-3C-tethered Ru complex:hexyne functionalised polymer (258).



This compound is novel.

This compound was prepared as for **256** using 3:7 ligand:hexyne functionalised polymer **257** (180 mg, 0.13 mmol ligand), ethylbenzoate ruthenium(II)chloride dimer **197** (42 mg, 0.065 mmol), anhydrous DCM (1.2 cm^3) and chlorobenzene (2.8 cm^3) to give the product (189 mg, 0.12 mmol Ru catalyst, 92%). υ_{max} 3687, 3674, 2972, 2901, 1723, 1394, 1251, 1056, 861, 679, 565 cm^{-1}.

10% azido opened poly(glycidyl methacrylate) (259).

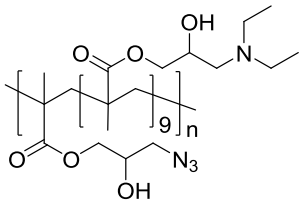


This compound is novel.

To a nitrogen purged flask was added poly (glycidyl methacrylate) Mn 20,000 (568 mg, 4 mmol epoxide) was added NaN_3 (26 mg, 0.4 mmol) and NH_4Cl (21 mg, 0.4 mmol). To this was then added anhydrous DMF (40 cm^3). The reaction was stirred at 50°C overnight. The reaction was cooled to room temperature and DMF removed under vacuum. The residue was then washed with water and dried to leave a viscous, sparingly soluble colourless gel (330 mg, 0.23 mmol N_3/2.0 mmol epoxide, 58%).

υ_{max} 3435 (weak), 2932, 2102 (weak), 1728 (weak), 1665, 1386, 1255, 1148, 1091, 658 cm^{-1}; δ_H (400 MHz, THF) 4.61 (0.1H, br s, O*H*), 4.17 (0.9H, br s, COOCH^aH^b), 3.89-3.84 (0.3H, m, COOCH_2 and C*H*OH overlapping), 3.70 (0.9H, br s, COOCH^aH^b), 3.24 (0.2H, br s, C$H_2$$N_3$), 3.10 (0.9H, br s, $COOCH_2CH$), 2.66 (0.9H, br s, CH^aH^{b}O in epoxide), 2.51 (0.9H, br s, CH^aH^bO in epoxide), 1.91-1.81 (2H, C$H_2$$CCH_3$), 1.00-0.84 (3H, m, C$H_3$); δ_C (100 MHz, DMSO) quaternary carbon *C*C=O not observed 162.28 (1C, s), 143.17 (1C, s), 65.70 (1C, s), 65.45 (1C, s), 48.57 (1C, s), 48.49 (1C, s), 43.79 (1C, s), 39.96 (1C, s), 35.75 (1C, s), 30.67 (1C, s).

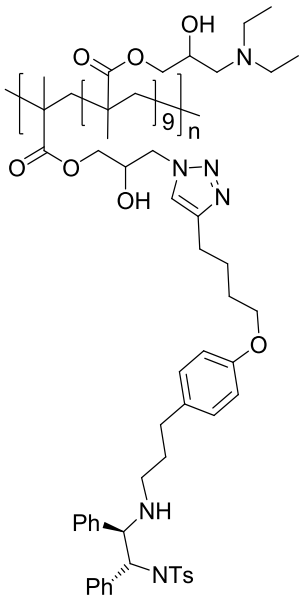
1:9 azido:diethylamine functionalised poly(glycidyl methacrylate) (260).



This compound is novel.

To a nitrogen purged flask connected to a condenser was added 10% azide opened poly (glycidyl methacrylate) **259** (230 mg, 1.44 mmol epoxide/0.16 mmol N_3) was added DMSO (2.5 cm^3) and diethylamine (124 mg, 1.7 mmol). The reaction was stirred at 60°C overnight. After this the reaction was cooled to room temperature and the DMSO removed under vacuum with gentle heating to leave the product as a straw coloured, insoluble, viscous gel (280 mg, 0.15 mmol N_3/1.4 mmol diethylamine, 97%). υ_{max} 3386, 2965, 2931, 2101, 1724, 1438, 1385, 1269, 1152, 1020, 952 cm^{-1}. For procedure see reference 164.

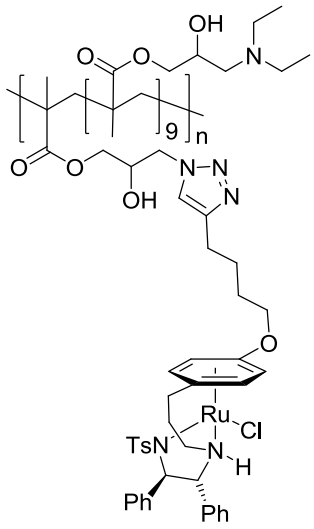
1:9 ligand:diethylamine functionalised polymer (261).



This compound is novel.

To a nitrogen purged flask was added 1:9 azide:diethylamine opened poly (glycidyl methacrylate) **260** (280 mg, 0.15 mmol N_3/1.4 mmol diethylamine) and *N*-((1*R*, 2*R*)-2-(3-(4-(hex-5-ynyloxy)phenyl)propylamino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide **248** (87 mg, 0.15 mmol). To this was then added $Cu(OAc)_2$ (5.5 mg, 0.03 mmol) and sodium-(*L*)-ascorbate (12 mg, 0.06 mmol) followed by THF/water 4/1 (3 cm^3). The reaction was stirred at room temperature for 48 hours. The reaction was filtered and the solid was washed with ammonium hydroxide (aq.) (35 %) and dried to leave a blue/green insoluble solid (250 mg, 0.09 mmol clicked ligand/0.81 mmol diethylamine, 75%). υ_{max} 3344, 2968, 2936, 1726, 1453, 1386, 1374, 1241, 1151, 1060, 811, 700 cm^{-1}.

1:9 (*R*,*R*)-3C-tethered Ru complex:diethylamine functionalised polymer (262).



This compound is novel.

This compound was prepared as for **256** using 1:9 ligand:diethylamine functionalised polymer **261** (250 mg, 0.09 mmol clicked ligand), ethylbenzoate ruthenium(II)chloride dimer **197** (29 mg, 0.045 mmol), anhydrous DCM (0.8 cm^3) and chlorobenzene (2 cm^3) to give the product (141 mg, 0.05 mmol Ru/0.45 mmol diethylamine, 56%). υ_{max} 3374, 2967, 1724, 1665, 1453, 1386, 1266, 1151, 1084, 997, 746, 700 cm^{-1}.

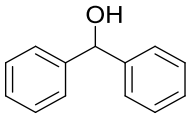
5.3.6 Analysis of reduction products.

All products are known in the literature and have previously been fully characterised. All data matches that reported for each compound.

GC Sample preparation: A small amount of the reaction solution was removed by syringe and filtered through a narrow column of silica with 1:1 EtOAc:petroleum ether 40-60. The filtrate was dried under reduced pressure. 2 mg of the residue was then dissolved in EtOAc (1 cm^3) and 1 μL of this solution was injected on the GC.

HPLC Sample preparation: A small amount of the reaction solution was removed by syringe and filtered through a narrow column of silica with 1:1 EtOAc:petroleum ether 40-60. The filtrate was dried under reduced pressure. 2 mg of the residue was then dissolved in 90:10 Hexane:IPA (1 cm^3) and 20 μL of this was injected on the HPLC system.

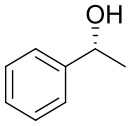
Benzhydrol.



GC analysis : BP20 (WAX) polyethylene glycol 25m x 0.22mm x 0.25μm, helium carrier gas, P=15 psi; T=190°C; ketone 11.4 min., alcohol 23.6 min.

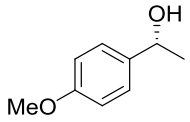
δ_H (300 MHz, $CDCl_3$) 7.41-7.31 (8H, m, C*H*Ar), 7.29-7.26 (2H, m, C*H*Ar), 5.86 (1H, d, *J* 3.6 Hz, O*H*), 2.21 (1H, d, *J* 3.6 Hz, C*H*). Data matches that previously reported for this compound.[202, 203]

(*R*)-1-Phenylethanol.



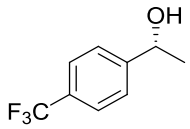
Enantiomeric excess and conversion determined by GC analysis: Chrompac cyclodextrin-β-236M-19 50m x 0.25 mm x 0.25 μm, T = 115°C, P = 15psi H_2, det = FID 220°C, inj = 220°C, ketone 9.2 min., *R* isomer 14.2 min., *S* isomer 15.6 min. $[\alpha]_D^{24}$ +64.5 (*c* 1.0 in $CHCl_3$) 96.7% ee. (*R*) (lit.[96] $[\alpha]_D^{27}$ +54.9 (*c* 1.0 in $CHCl_3$) 96% ee. (*R*)); δ_H (400 MHz, $CDCl_3$) 7.37-7.31 (4H, m, C*H*Ar), 7.28-7.24 (1H, m, C*H*Ar), 4.87 (1H, q, *J* 6.5 Hz, C*H*), 2.00 (1H, br s, O*H*), 1.48 (3H, d, *J* 6.5 Hz, CH_3).

(*R*)-1-(4'-Methoxyphenyl)ethanol.



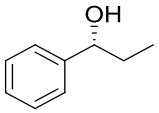
Enantiomeric excess and conversion determined by GC analysis: Chrompac cyclodextrin-β-236M-19 50m x 0.25 mm x 0.25 μm, T = 130°C, P = 15psi H_2, det = FID 220°C, inj = 220°C, ketone 12.6 min., *R* isomer 30.8 min., *S* isomer 33.0 min. $[\alpha]_D^{30}$ +46.6 (*c* 1.0 in $CHCl_3$) 91.7% ee. (*R*) (lit.[96] $[\alpha]_D^{27}$ +32.3 (*c* 1.0 in $CHCl_3$) 90% ee. (*R*)); δ_H (400 MHz, $CDCl_3$) 7.32-7.30 (2H, m, C*H*Ar), 6.91-6.89 (2H, m, C*H*Ar), 4.85 (1H, q, *J* 6.4 Hz, C*H*), 3.82 (3H, s, O*CH*$_3$), 2.28 (1H, br s, O*H*), 1.49 (3H, d, *J* 6.3 Hz, *CH*$_3$).

(*R*)-1-(4'-Trifluoromethylphenyl)ethanol.



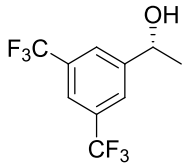
Enantiomeric excess and conversion determined by GC analysis: Chrompac cyclodextrin-β-236M-19 50m x 0.25 mm x 0.25 μm, T = 130°C, P = 15psi H_2, det = FID 220°C, inj = 220°C, ketone 6.9 min., *R* isomer 13.4 min., *S* isomer 14.8 min. $[\alpha]_D^{28}$ +33.5 (*c* 1.0 in $CHCl_3$) 92.4% ee. (*R*) (lit.[204] $[\alpha]_D^{22}$ +29.3 (*c* 1.0 in $CHCl_3$) >99% ee. (*R*));δ_H (400 MHz, $CDCl_3$) 7.62-7.60 (2H, m, C*H*Ar), 7.48-7.46 (2H, m, C*H*Ar), 4.93 (1H, q, *J* 6.5 Hz, C*H*), 2.97 (1H, br s, O*H*), 1.49 (3H, d, *J* 6.5 Hz, C*H*$_3$).

(*R*)-1-Phenylpropan-1-ol.



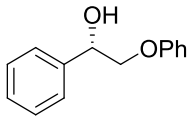
Enantiomeric excess and conversion determined by GC analysis: Chrompac cyclodextrin-β-236M-19 50m x 0.25 mm x 0.25 μm, T = 115°C, P = 15psi H_2, det = FID 220°C, inj = 220°C, ketone 15.7 min., *R* isomer 25.0 min., *S* isomer 26.8 min. $[\alpha]_D^{26}$ +47.6 (*c* 1.0 in $CHCl_3$) 89.7% ee. (*R*) (lit.[99] $[\alpha]_D^{20}$ +47.0 (*c* 1.4 in $CHCl_3$) 95% ee. (*R*)); δ_H (300 MHz, $CDCl_3$) 7.37-7.25 (5H, m, C*H*Ar), 4.57 (1H, t, *J* 6.6 Hz, C*H*), 2.03 (1H, br s, O*H*), 1.86-1.66 (2H, m, CH_2), 0.90 (3H, t, *J* 7.4 Hz, CH_3).

(*R*)-1-(3',5'-Bis(trifluoromethyl)phenyl)ethanol.



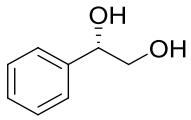
Enantiomeric excess and conversion determined by GC analysis: Chrompac cyclodextrin-β-236M-19 50m x 0.25 mm x 0.25 μm, T = 120°C, P = 15psi H_2, det = FID 220°C, inj = 220°C, ketone 4.8 min., *R* isomer 12.8 min., *S* isomer 12.2 min. $[\alpha]_D^{31}$ +16.5 (*c* 1.0 in $CHCl_3$) 81.8% ee. (*R*) (lit.[105] $[\alpha]_D^{28}$ +11.9 (*c* 1.0 in $CHCl_3$) 96% ee. (*R*)); δ_H (300 MHz, $CDCl_3$) 7.81-7.78 (3H, m, C*H*Ar), 5.00 (1H, q, *J* 6.3 Hz, C*H*), 2.92 (1H, br s, O*H*), 1.51 (3H, d, *J* 6.6 Hz, CH_3).

(*S*)-2-phenoxy-1-phenylethanol.



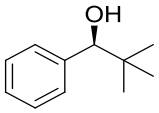
Enantiomeric excess and conversion determined by HPLC analysis: IB column, 0.46 x 25 cm, 0.7 cm^3/min, 95:5 Hexane:2-propanol, RT, ketone 14.2 min, *R* isomer 17.1 min, *S* isomer 22.4 min. Ketone UV response is 12.35 times greater than for the alcohol. $[\alpha]_D^{29}$ +52.2 (*c* 1.0 in $CHCl_3$) 94.5% ee. (*S*) (lit.[105] $[\alpha]_D^{30}$ +58.8 (*c* 1.0 in $CHCl_3$) 95% ee. (*S*)); δ_H (300 MHz, $CDCl_3$) 7.45-7.24 (7H, m, C*H*Ar), 6.98-6.89 (3H, m, C*H*Ar), 5.10 (1H, dd, *J* 8.8 and 3.3 Hz, C*H*), 4.10-4.07 (1H, m, CH_2), 4.02-3.96 (1H, m, CH_2), 2.90 (1H, br s, O*H*).

(*S*)-1-phenylethane-1,2-diol.



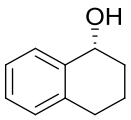
Enantiomeric excess and conversion determined by GC analysis: CP-ChiraSil-DEX CB 25 m x 0.25 mm x 0.25 μm, T = 140°C, P = 18psi He, det = FID 220°C, inj = 220°C, ketone 8.6 min, *S* isomer 31.3 min, *R* isomer 33.3 min. $[\alpha]_D^{27}$ +64.5 (*c* 0.5 in $CHCl_3$) 90.3% ee. (*S*) (lit.[104] $[\alpha]^{20}$ +63 (*c* 1.0 in $CHCl_3$) 96% ee. (*S*)); δ_H (300 MHz, $CDCl_3$) 7.31-7.25 (5H, m, C*H*Ar),4.74-4.70 (1H, m, C*H*), 3.96 (1H, br s, O*H*), 3.68-3.53 (3H, m, CH_2 + O*H*).

1-Phenyl-2,2-dimethyl-1-propanol.



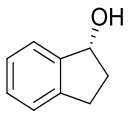
Enantiomeric excess and conversion determined by GC analysis: Chrompac cyclodextrin-β-236M-19 50m x 0.25 mm x 0.25 μm, T = 125°C, P = 15psi H_2, det = FID 220°C, inj = 220°C, ketone 13.9 min., *R* isomer 29.4 min., *S* isomer 30.0 min. $[\alpha]_D^{29}$ +12.7 (*c* 1.0 in $CHCl_3$) 75.9% ee. (*R*) (lit.[204] $[\alpha]_D^{20}$ +12.2 (*c* 1.0 in $CHCl_3$) 45% ee. (*R*)); δ_H (300 MHz, $CDCl_3$) 7.31-7.25 (5H, m, C*H*Ar), 4.39 (1H, s, C*H*), 1.86 (1H, br s, O*H*), 0.92 (9H, s, $(CH_3)_3$).

1-Tetralol.



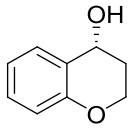
Enantiomeric excess and conversion determined by GC analysis: Chrompac cyclodextrin-β-236M-19 50m x 0.25 mm x 0.25 μm, T = 120°C, P = 15psi H_2, det = FID 220°C, inj = 220°C, ketone 41.3 min., *R* isomer 54.3 min., *S* isomer 54.6 min. $[\alpha]_D^{26}$ -34.2 (*c* 0.5 in $CHCl_3$) 99.0% ee. (*R*) (lit.[96] $[\alpha]_D^{27}$ -32.3 (*c* 1.0 in $CHCl_3$) 98% ee. (*R*)); δ_H (300 MHz, $CDCl_3$) 7.43-7.39 (1H, m, C*H*Ar), 7.23-7.17 (2H, m, C*H*Ar), 7.10-7.07 (1H, m, C*H*Ar), 4.75-7.74 (1H, m, C*H*), 2.86-2.65 (2H, m, CH_2 + O*H*), 2.02-1.70 (5H, m, CH_2).

(*R*)-2,3-dihydroinden-1-ol.



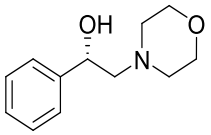
Enantiomeric excess and conversion determined by GC analysis: Chrompac cyclodextrin-β-236M-19 50m x 0.25 mm x 0.25 μm, T = 100°C, P = 15psi H_2, det = FID 220°C, inj = 220°C, ketone 66.9 min., *R* isomer 84.8 min., *S* isomer 84.0 min. $[\alpha]_D^{26}$ -31.6 (*c* 1.0 in $CHCl_3$) 97.5% ee. (*R*) (lit.[96] $[\alpha]_D^{27}$ -30.5 (*c* 1.0 in $CHCl_3$) 84% ee. (*R*)); δ_H (300 MHz, $CDCl_3$) 7.41-7.39 (1H, m, C*H*Ar), 7.25-7.21 (3H, m, C*H*Ar), 5.21 (1H, m, C*H*), 3.08-2.98 (1H, m, CH_2), 2.85-2.74 (1H, m, CH_2), 2.51-2.40 (1H, m, CH_2), 1.97-1.86 (2H, m, O*H* + CH_2).

(*R*)-3,4-Dihydrochromen-4-ol.



Enantiomeric excess and conversion determined by HPLC analysis: IB column, 0.46 x 25 cm, 1 cm^3/min, 95:5 Hexane:2-propanol, RT, ketone 6.6 min, *S* isomer 8.6 min, *R* isomer 9.4 min. Ketone UV response is 20.12 times greater than for the alcohol. $[\alpha]_D^{27}$ +66.5 (*c* 1.0 in $CHCl_3$) 99.0% ee. (*R*) (lit.[205] $[\alpha]_D^{31}$ +60.1 (*c* 0.2 in $CHCl_3$) 96% ee. (*R*)); δ_H (300 MHz, $CDCl_3$) 7.27-7.24 (1H, m, C*H*Ar), 7.19-7.13 (1H, m, C*H*Ar), 6.90-6.85 (1H, m, C*H*Ar), 6.81-6.78 (1H, m, C*H*Ar), 4.67 (1H, t, *J* 4.1 Hz, C*H*), 4.21-4.15 (2H, m, CH_2), 2.76 (1H, br s, O*H*), 2.13 (1H, s, C*H*), 2.09-1.90 (2H, m, CH_2).

(*S*)-2-(morpholin-4-yl)-1-phenylethanol.



Conversion determined by ^{1}H NMR. Enantiomeric excess determined by Mosher's method[146] >95% (*S*). $[\alpha]_D^{24}$ +48.2 (*c* 0.3 in MeOH) >95% ee. (*S*) (lit.[206] $[\alpha]_D^{26}$ +41.8 (*c* 5.07 in MeOH) 89% ee. (*S*)) ; δ_H (400 MHz, $CDCl_3$) 7.38-7.26 (5H, m, C*H*Ar), 4.76 (1H, dd *J*, 10.4 and 3.4 Hz, C*H*), 3.76 (5H, m, CH_2OCH_2 and O*H* overlapping), 2.75 (2H, m, CH_2), 2.54-2.45 (4H, m, -CH_2NCH_2-).

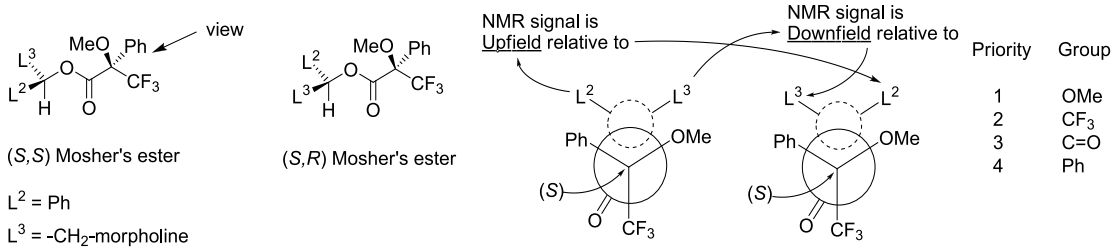
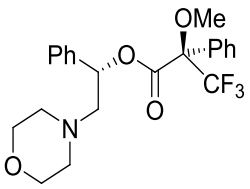


Figure 77. Mosher's ester derivatives and configuration model.

Mosher's ester of (*S*)-2-(morpholin-4-yl)-1-phenylethanol.



To a solution of (*S*)-2-(morpholin-4-yl)-1-phenylethanol) (5 mg, 0.024 mmol) in anhydrous DCM (1 cm^3) was added triethylamine (5 mg, 0.048 mmol) and DMAP (0.3 mg, 0.0024 mmol). To the solution and at 0˚C was then added (*S*)-(+)-MTPA-Cl (8 mg, 0.03 mmol). The reaction was then stirred overnight at room temperature. After this volatile material was removed under reduced pressure to leave the crude which was then analysed by ^{1}H NMR.

^{1}H NMR key peaks for ee. determination: Major isomer δ_H (400 MHz, $CDCl_3$) L^3: 2.83 (1H, dd, *J* 13.7 and 9.9 Hz, C*H*$_2$CHOH), 2.65-2.61 (2H, m, NC*H*$_2$CH$_2$O), 2.55 (1H, dd, *J* 13.6 and 3.0 Hz, C*H*$_2$CHOH), 2.38-2.33 (1H, m, NC*H*$_2$CH$_2$O). Determination of ee.: Only 1 enantiomer visible by NMR so ee. > 95%.

Determination of configuration: Product is the (*S*) enantiomer. Comparison to the Mosher's esters of the racemic alcohol and asymmetric reduction product shows that in the ^{1}H NMR of the asymmetric product the L^3 signals present are upfield.

Mosher's ester of racemic 2-(morpholin-4-yl)-1-phenylethanol.

The racemic alcohol was prepared by $NaBH_4$ reduction of the ketone. The Mosher's ester was then prepared as above. ^{1}H NMR key peaks: δ_H (400 MHz, $CDCl_3$) L^3: 2.93-2.81 (1H, m, C*H*$_2$-CHOH), 2.74-2.71 (1H, m, N-C*H*$_2$CH$_2$O), 2.65-2.61 (1H, m, N-C*H*$_2$CH$_2$O), 2.57-2.54 (1H, m, C*H*$_2$-CHOH), 2.48-2.43 (1H, m, N-C*H*$_2$CH$_2$O), 2.38-2.33 (1H, m, N-C*H*$_2$CH$_2$O).

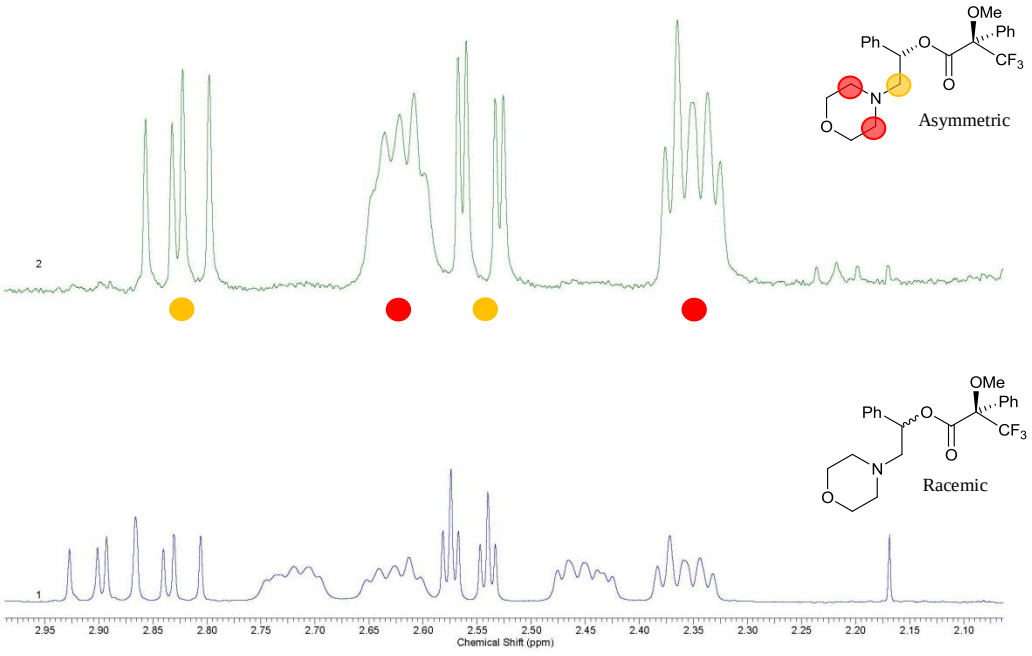
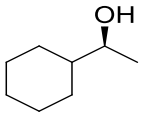


Figure 78. ^{1}H NMR spectra for Mosher's esters of 2-(morpholin-4-yl)-1-phenylethanol.

(*S*)-1-Cyclohexylethanol.

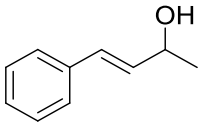


Conversion determined by GC analysis: Chrompac cyclodextrin-β-236M-19 50m x 0.25 mm x 0.25 μm, T = 75°C, P = 15psi H_2, det = FID 220°C, inj = 220°C, ketone 40 min., alcohol 80 min. $[\alpha]_D^{26}$ +3.7 (*c* 1.0 in $CHCl_3$) 81.4% ee. (*S*) (lit.[207] $[\alpha]_D^{22}$ +2.7 (*c* 0.5 in $CHCl_3$) 75% ee. (*R*)); δ_H (300 MHz, $CDCl_3$) 3.54 (1H, q, *J* 6.2 Hz, C*H*), 1.87-1.83 (1H, m, C*H*), 1.79-1.73 (2H, m, CH_2), 1.69-1.65 (3H, m, C*H* + CH_2), 1.32-1.14 (7H, m, CH_2 + O*H*), 1.07-0.93 (2H, m, CH_2).

Enantiomeric excess determined by GC for the acetate derivative of reduction product: Chrompac cyclodextrin-β-236M-19 50m x 0.25 mm x 0.25 μm, T = 115°C, P = 15psi H_2, det = FID 220°C, inj = 220°C, *R* isomer 14.5 min., *S* isomer 13.3 min.

Preparation of acetate derivative: The reduction product (10 mg) was dissolved in 1 cm^3 of DCM. To this was then added acetic anhydride (20 μL) and DMAP (3 crystals). The reaction was stirred over night and then volatiles were removed under reduced pressure. A small amount of the residue was diluted in EtOAc and then injected on the GC.

4-Phenylbut-3-en-2-ol.

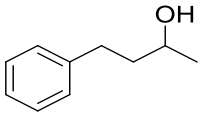


Conversion determined by ^1H NMR. δ_H (300 MHz, $CDCl_3$) 7.38-7.17 (5H, m, C*H*Ar), 6.55 (1H, d *J*, 15.9 Hz, C*H*=CHCHOH), 6.25 (1H, dd, *J* 15.9 and 6.4 Hz,

CH=C*H*CHOH), 4.51-4.42 (1H, m, C*H*OH), 1.94 (1H, br s, O*H*), 1.36 (3H, d, *J* 13.0 Hz, CH_3).

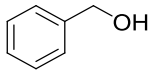
Enantiomeric excess determined by conversion of the unsaturated/saturated alcohol product mixture into 4-phenylbutan-2-ol and analysis by HPLC as detailed below.

4-Phenylbutan-2-ol.



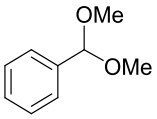
To 4-phenylbut-3-en-2-ol: 4-phenylbutan-2-ol 1:1 mixture (45 mg, 0.30 mmol) was added anhydrous MeOH (1 cm^3) and 10% Pd/C (18 mg, 0.015 mmol Pd). The flask was connected to a balloon of hydrogen (1 atm.), purged with hydrogen and stirred at room temperature overnight. The reaction was filtered through celite with EtOAc and the filtrate dried under reduced pressure to give the product as a colourless oil (29 mg, 0.2 mmol, 67%). Enantiomeric excess determined by HPLC analysis: IB column, 0.46 x 25 cm, 0.8 cm^3/min, 95:5 Hexane:2-propanol, RT, ketone 7.0 min, *R* isomer 8.9 min, *S* isomer 10.9 min. $[\alpha]_D^{28}$ +0.67 (*c* 0.3 in $CHCl_3$) 4.7% ee. (*S*) (lit.[208] $[\alpha]^{25}$ +7.9 (*c* 1.0 in $CHCl_3$) 33% ee. (*S*); δ_H (400 MHz, $CDCl_3$) 7.30 – 7.25 (2H, m, C*H*Ar), 7.21-7.16 (3H, m, C*H*Ar), 3.87-3.79 (1H, m, C*H*OH), 2.80-2.63 (2H, m, CH_2CHOH), 1.80-1.74 (2H, m, CH_2CH_2CHOH), 1.40 (1H, br s, O*H*), 1.23 (3H, d, *J* 6.3 Hz, CH_3).

Benzyl alcohol.



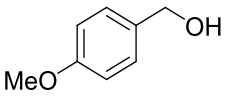
Conversion determined by GC analysis: Chrompac cyclodextrin-β-236M-19 50m x 0.25 mm x 0.25 μm, T = 100°C, P = 15psi H_2, det = FID 220°C, inj = 220°C, benzaldehyde 9.6 min., (dimethoxymethyl)benzene 15.6 min., benzyl alcohol 27.1 min. δ_H (300 MHz, $CDCl_3$) 7.33-7.22 (5H, m, C*H*Ar), 4.55 (2H, s, CH_2), 3.04 (1H, br s, O*H*).

(Dimethoxymethyl)benzene.



Conversion determined by GC analysis: Chrompac cyclodextrin-β-236M-19 50m x 0.25 mm x 0.25 μm, T = 100°C, P = 15psi H_2, det = FID 220°C, inj = 220°C, (dimethoxymethyl)benzene 15.6 min. δ_H (400 MHz, $CDCl_3$) 7.46-7.44 (2H, m, C*H*Ar), 7.38-7.32 (3H, m, C*H*Ar), 5.39 (1H, s, C*H*), 3.33 (6H, s, OCH_3)

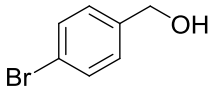
(4-Methoxyphenyl)methanol.



Conversion determined by GC analysis: Chrompac cyclodextrin-β-236M-19 50m x 0.25 mm x 0.25 μm, T = 135°C, P = 15psi H_2, det = FID 220°C, inj = 220°C, 4-methoxybenzaldehyde 10.1 min., (4-methoxyphenyl)methanol 21.9 min. δ_H (400

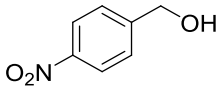
MHz, $CDCl_3$) 7.30-7.28 (2H, m, C*H*Ar), 6.90-6.89 (2H, m, C*H*Ar), 4.62 (2H, s, CH_2), 3.81 (3H, s, CH_3), 1.62 (1H, br s, O*H*).

(4-Bromophenyl)methanol.



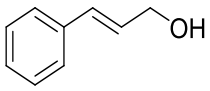
Conversion determined by GC analysis: Chrompac cyclodextrin-β-236M-19 50m x 0.25 mm x 0.25 μm, T = 150°C, P = 15psi H_2, det = FID 220°C, inj = 220°C, 4-bromobenzaldehyde 9.5 min., (4-bromophenyl)methanol 18.5 min. δ_H (400 MHz, $CDCl_3$) 7.50-7.46 (2H, m, C*H*Ar), 7.25-7.22 (2H, m, C*H*Ar), 4.65 (2H, s, CH_2), 1.78 (1H, br s, O*H*).

(4-Nitrophenyl)methanol.



Conversion determined by GC analysis: Chrompac cyclodextrin-β-236M-19 50m x 0.25 mm x 0.25 μm, T = 180°C, P = 15psi H_2, det = FID 220°C, inj = 220°C, 4-nitrobenzaldehyde 7.9 min., (4-aminophenyl)methanol 9.7 min., (4-nitrophenyl)methanol 23.2 min. δ_H (300 MHz, $CDCl_3$) 8.23-8.20 (2H, m, C*H*Ar), 7.55-7.52 (2H, m, C*H*Ar), 4.84 (2H, s, CH_2), 2.00 (1H, br s, O*H*).

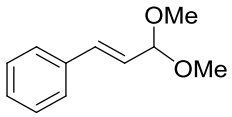
3-Phenylprop-2-en-1-ol.



Conversion determined by GC analysis: Chrompac cyclodextrin-β-236M-19 50m x 0.25 mm x 0.25 μm, T = 130°C, P = 15psi H_2, det = FID 220°C, inj = 220°C, cinnamaldehyde 21.8 min., 3-phenylprop-2-enal 11.2 min, 3-phenylpropan-1-ol 20.4

min., (3,3-dimethoxyprop-1-en-1-yl)benzene 26.2 min., 3-phenylprop-2-en-1-ol 31.6 min. δ_H (400 MHz, $CDCl_3$) 7.38-7.23 (5H, m, C*H*Ar), 6.60 (1H, d, *J* 16.1 Hz, C*H*), 6.38-6.31 (1H, m, C*H*), 4.30 (2H, d, *J* 5.5 Hz, CH_2), 1.85 (1H, br s, O*H*).

(3,3-Dimethoxyprop-1-en-1-yl)benzene.



Conversion determined by GC analysis: Chrompac cyclodextrin-β-236M-19 50m x 0.25 mm x 0.25 μm, T = 130°C, P = 15psi H_2, det = FID 220°C, inj = 220°C, (3,3-dimethoxyprop-1-en-1-yl)benzene 26.2 min. δ_H (400 MHz, $CDCl_3$) 7.46-7.38 (2H, m, C*H*Ar), 7.34-7.25 (3H, m, C*H*Ar), 6.72 (1H, d, *J* 16.0 Hz, C*H*), 6.15 (1H, dd, *J* 16.0 and 4.9 Hz, C*H*), 4.96 (1H, d, *J* 4.9 Hz, C*H*), 3.38 (6H, s, OCH_3).

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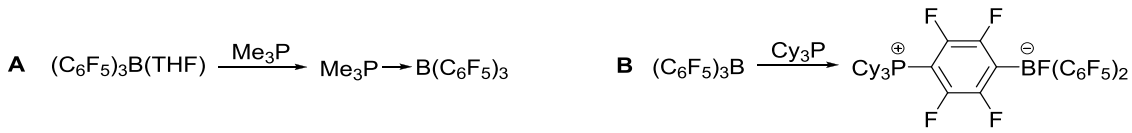
7. Appendix 1-Hydrogenation of imines using Frustrated Lewis Pair catalysts.

7.1 Introduction: Frustrated Lewis Pairs.

Several systems have been reported for non-metal catalysed hydrogenation reactions. MacMillan has developed a series of imidazolidinone catalysts which have been applied to ATH of α,β-unsaturated carbonyl compounds [209, 210] reactions as well as many other transformations.[211-214] Corey, Bakshi and Shibata have reported the ATH of ketones using an oxaborolidine catalyst and stoichiometric borane.[215]

More recently, the non-metal-catalysed pressure hydrogenation of imines has been reported by Stephan [217-218] using Frustrated Lewis Pairs (FLPs) as the catalytic species. FLPs are combinations of Lewis acids and bases that are sterically prevented from forming a Lewis acid-base adduct meaning that the Lewis acid and base components remain available to interact with other molecules.[219] Conventionally the interaction of a Lewis acidic borane and Lewis basic phosphine would result in formation of a dative bond between the lone pair of electrons on the phosphorus and the empty p-orbital of the boron, with FLPs this interaction is prevented due to steric hindrance.

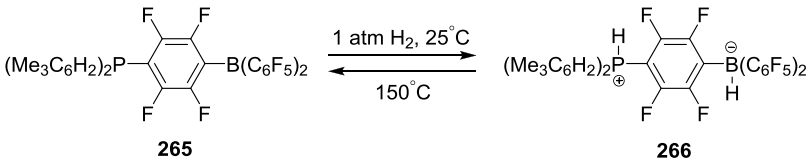


Scheme 102. Reactivity of 'classical' (A) and 'frustrated' (B) Lewis pairs.

Scheme 102 A shows the classical interaction of a borane with a non-sterically hindered tertiary phosphine. The THF group on the boron is replaced with the phosphine which joins to the boron *via* a dative bond. Scheme 102 B shows a

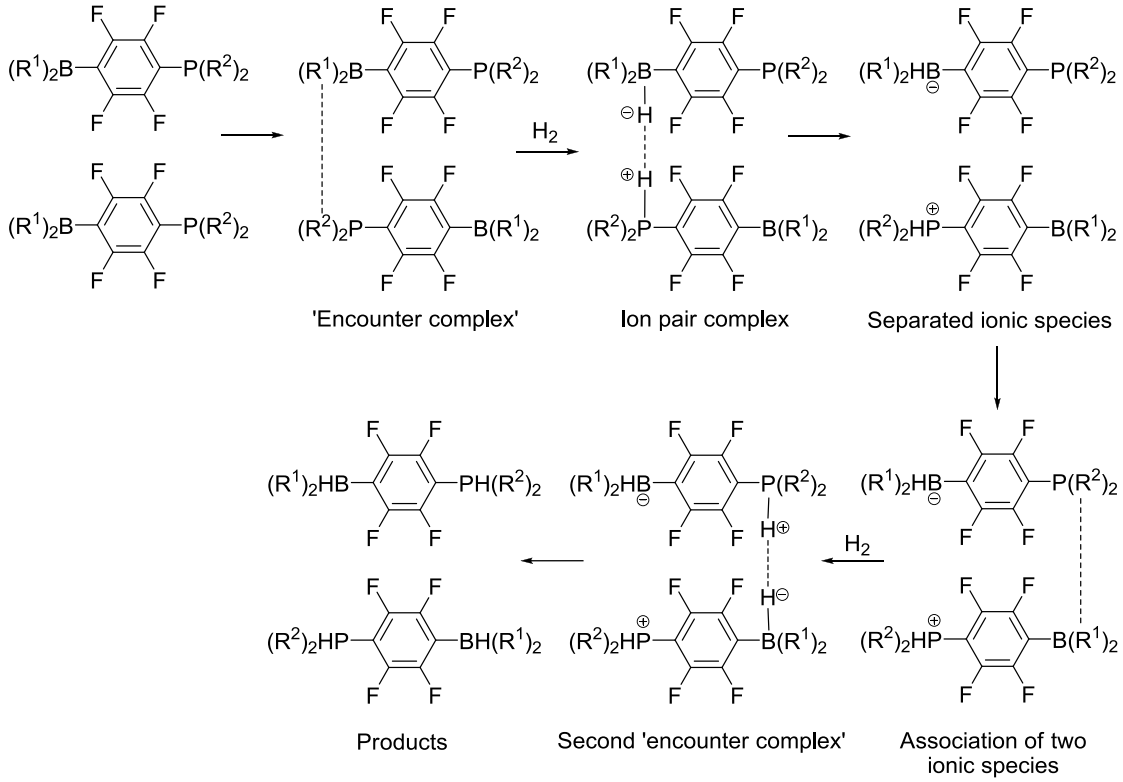
'frustrated' interaction where, due to steric hindrance, direct interaction between the phosphorus and boron atoms is prevented. Instead, nucleophilic substitution occurs on the borane species at the carbon *para* to the boron and the displaced fluorine migrates to the boron to give the zwitterionic phosphonium borate product. Due to the charges on the phosphorus and boron, they each retain their respective Lewis basicity and acidity, allowing interaction with other molecules.

Stephan has reported the application of FLPs to hydrogen activation.[220] Phosphinoborane **265** readily cleaves hydrogen to form phosphonium borate **266**. Upon heating hydrogen is reformed and liberated as illustrated in Scheme 103.



Scheme 103. Activation of hydrogen by phosphine-borane.

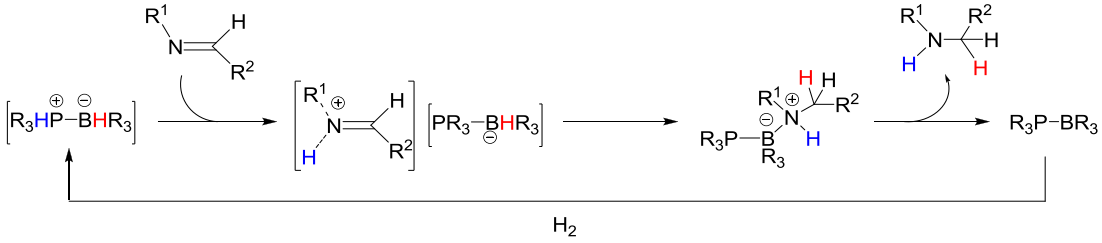
The process was thought to involve activation of molecular hydrogen by the boron Lewis acid and protonation of the phosphorus Lewis base. The mechanism of hydrogen activation was investigated by Guo and Li[221] who report the process to involve the formation of an 'encounter complex' (Scheme 104) between two phosphinoborane molecules held together by hydrogen bonding. The hydrogen molecule inserts between the boron and phosphorus at one end of the encounter complex and cleaves to form an ion pair complex. The process repeats with the other boron-phosphorus pair in the complex interacting with a second molecule of hydrogen. Final dissociation of the complex leads to the formation of two phosphonium borate complexes.



Scheme 104. 'Encounter complex' mechanism of hydrogen activation by FLPs.

Papai and co-workers also investigated the method of hydrogen activation by FLPs.[222] Investigations into the mechanism found no dative P-B bond but a weakly bound, non-covalent $[R_3P]...[B(C_6F_5)_3]$ complex was observed. It was thought that this complex was a reactive intermediate in the activation process and also that it may provide a pre-organised active centre for H-H bond activation. The group suggested that the complex represented an energetically strained species which lowered the barrier to hydrogen activation.

The ability of the FLP system to activate hydrogen lead to its application to metal-free catalysed hydrogenation of imines *via* proton and hydride transfer from the phosphonium borate to the polar C=N bond of the imine.[216-220, 223] A mechanism for the reaction has been proposed and is shown in Scheme 105.[218-221, 223]

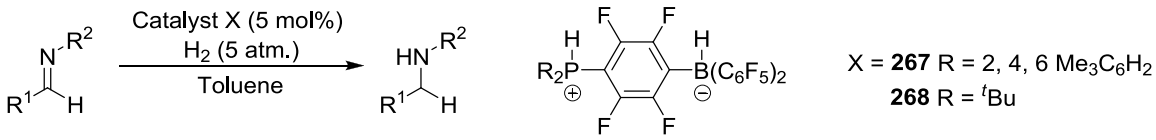


Scheme 105. Mechanism of imine hydrogenation with phosphinoborane FLPs.

Initially the phosphinoborane interacts with hydrogen to form the phosphonium borate species. A proton is then transferred from the phosphorus to the nitrogen of the imine. Hydride transfer from the boron to the imino carbon atom followed by coordination of the nitrogen to the boron then occurs before the amine product is released to reform the phosphinoborane.

Phosphinoborane FLP catalysts have been successfully applied to the Pressure hydrogenation of a series of imines as shown in Table 37.[218]

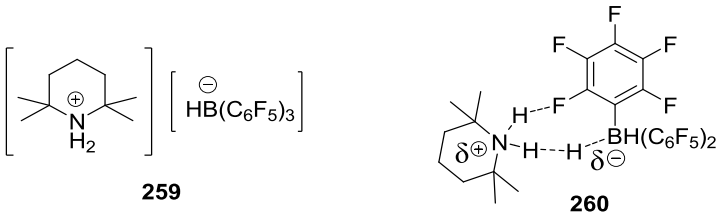
Table 37. Application of FLP phosphinoborane catalysts **267** and **268** to pressure hydrogenaiton of imines.



Entry	R^1	R^2	Catalyst	Temp. (°C)	Time (hours)	Yield (%)
1	Ph	^{t}Bu	**267**	80	1	79
2	Ph	^{t}Bu	**268**	80	1	98
3	Ph	SO_2Ph	**267**	120	10.5	97
4	Ph	SO_2Ph	**268**	120	16	87
5	Ph	$CHPh_2$	**267**	140	1	88
6	Ph	CH_2Ph	**267**	120	48	5
7	Ph	$CH_2Ph(B(C_6F_5)_3)$	**267**	120	46	57
8	PhCHCHPhNPh		**267**	120	1.5	98

A sterically hindered imine could itself act as the Lewis base, removing the need for the phosphine.[220] The imine acts in the same way as the hindered phosphine in Scheme 105. Acting as a Lewis base, the imine is able to accept a proton from the cleaved hydrogen molecule. This is followed, as before, by hydride transfer from the borate to give the hydrogenated product.

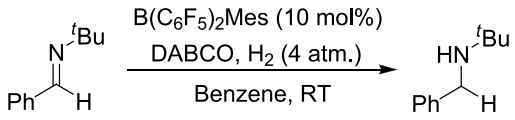
In similar work Repo and co-workers reported the activation of hydrogen by amines and $B(C_6F_5)_3$.[224] Reaction of 2,2,6,6-tetramethylpiperidine with $B(C_6F_5)_3$ under atmospheric hydrogen afforded 95% yield of ammonium borate **259**. The process proceeds *via* a 6-membered transition state **260** shown in Figure 79.



259 **260**

Figure 79. Cleavage of hydrogen by amines and $B(C_6F_5)_3$.

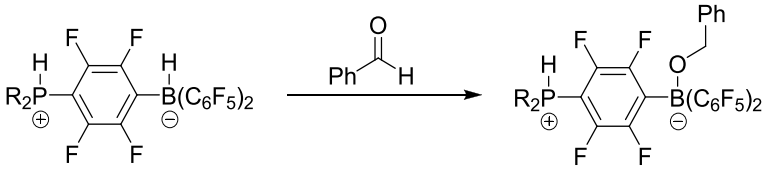
Soos has reported the use of amine Lewis bases in the FLP-catalysed hydrogenation of imines finding DABCO to be particularly successful (Scheme 106).[225]



Scheme 106. Hydrogenation of imines with DABCO and hindered borane.

FLPs were successfully applied to catalytic hydrogenation of imines, nitriles and aziridines, however aldehydes were found to only react stoichiometrically. Both Stephan[218] and Repo[224] have reported hydrogenation of benzaldehyde with phosphinoborane and amine/borane FLP systems respectively. In both cases, benzaldehyde underwent hydride attack to form an alkoxide bound to the boron as

shown in Scheme 107, however due to the reduced basicity of oxygen compared to nitrogen, protonation of oxygen to yield the alcohol product was not achieved.



Scheme 107. Attempted hydrogenation of benzaldehyde with FLPs.

7.1.1.1 Asymmetric hydrogenation of imines with FLP catalysts.

The first example of asymmetric hydrogenation of imines using FLP catalysts was reported by Klankermayer.[226] Chiral borane **156** (Figure 80) derived from (+)-α-pinene was applied to the asymmetric hydrogenation of *N*-(1-phenylethylidene)aniline. The reaction gave complete conversion to product with an ee. of 13%, thus illustrating the scope for APH of imines with this system.

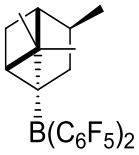


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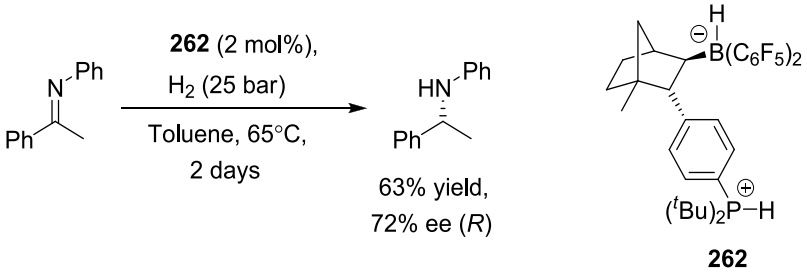
Figure 80. Chiral borane derived from (+)-α-pinene.

More recently, Klankermayer has reported the use of other asymmetric boranes for asymmetric hydrosilylylation[227] and APH of imines as shown in Scheme 108[228]achieving increased enantioselectivity.

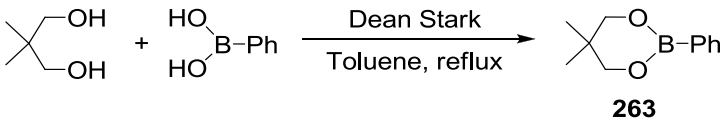


262

Scheme 108. APH of *N*-(1-phenylethylidene)aniline using FLP catalst **262**

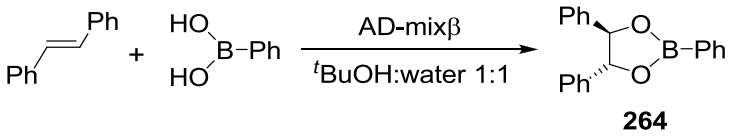
7.2 Results and Discussion.

The development of metal free catalysts for hydrogenation and asymmetric hydrogenation was also investigated during the course of my studies. The initial synthesis of asymmetric boranes focused on the condensation of diols with boronic acids to give dioxaborolanes (Scheme 109).[229, 230] An asymmetric derivative was prepared by asymmetric Sharpless dihydroxylation of stilbene followed by *in situ* coupling with the boronic acid (Schemes 110).[231]



263

Scheme 109. Preparation of achiral dioxaborolane 263

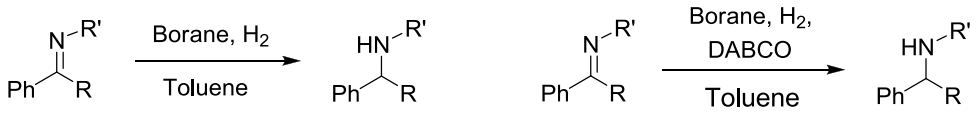


264

Scheme 110. Preparation of asymmetric dioxaborolane 264.

Application of boranes **263** and **264** to the hydrogenation of imines was found to be unsuccessful with no significant formation of amine achieved. Attempts to repeat literature reactions using commercially available tris(pentafluorophenyl)borane were also unsuccessful with NMR analysis of reaction solutions showing hydrolysis of the imine substrates to be occurring preferentially to hydrogenation (Tabel 38).

Table 38. APH of imines using boron catalysts.



Entry	R	R'	Catalyst	H_2 (bar)	Temp. (°C)	Time (hr)	Conv. to amine[a] (%)
1[b]	Me	Ph	$B(C_6F_5)_3$ 10 mol%	10	80	15	99
2	Me	Ph	$B(C_6F_5)_3$ 10 mol%	10	80	26	None
3	Me	Ph	$B(C_6F_5)_3$ 10 mol%	15	100	48	None
4[c]	Me	Ph	$B(C_6F_5)_3$ 10 mol%	10	80	23	None
5	Me	Ph	**263** 10 mol%	5	80	26	Trace
6	Me	Ph	**263** 10 mol%	5	80	64	None
7	Me	Ph	**264**10 mol%	5	80	26	Trace
8	Me	Ph	**264** 10 mol%	5	80	64	None
9	H	Ts	$B(C_6F_5)_3$ 10 mol%	20	80	24	None
10	H	Ph	$B(C_6F_5)_3$ 10 mol%, DABCO 10 mol%	5	RT	24	None
11[d]	H	^{t}Bu	$B(C_6F_5)_2$Mes 10 mol%, DABCO 10 mol%	4	RT	42	100
12[e]	Me	Ph	$B(C_6F_5)_3$ 20 mol%	20	80	24	15.3

[a]Determined by ^{1}H NMR. [b]Reaction reported in literature.[226] [c]4Å molecular sieves used in reaction [d]Reaction reported in literature.[225]. [e]4Å molecular sieves used, reaction set up and sealed under argon.

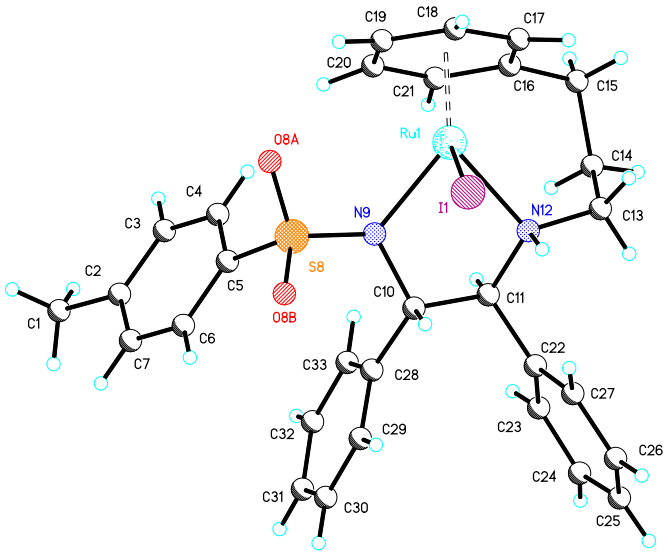
Initial hydrogenations were carried out on Phenyl-(1-phenylethylidene)amine (Table 38 entries 2-8) as a comparison to the literature result for the same imine (entry 1).[226] Repetition of the literature reaction (entry 2) and also the use of increased H_2 pressure, temperature and reaction time (entry 3) showed no conversion of imine to its amine prodict. The addition of 4Å molecular sieves to remove water from the reaction also showed no improvement (entry 4). Application of boranes **263** and **264** to the reaction showed no improvement with only a trace of the desired amine product seen by GC analysis of the reaction solution (entries 5-8). Use of less sterically encumbered imines as substrates and also the addition of DABCO which

has been shown in the literature to promote hydrogenation if imines (entry 11)[225] also showed no improvement to the conversion to amine product (entries 9-10).

Despite attempts to exclude water from the reaction solutions and reagents it was necessary for the reaction solutions to be open to the air briefly whilst the Parr reactor was sealed before being purged with hydrogen. This brief exposure may allow sufficient moisture into the reaction to allow imine hydrolysis rather than hydrogenation. Only in one case (Table 38, entry 12), where the reaction solution was prepared with rigorous exclusion of water and set up under a flow of argon, was hydrogenation of the imine achieved. The conversion to amine was low at only 15.3% and ^{1}H NMR analysis also showed evidence of hydrolysis of the imine. The aim of this work was to develop an active, robust, metal free catalyst that is accessible and convenient to use for asymmetric hydrogenation of imines, the need for stringent moisture and air exclusion does not fit with this criteria and so work on the development of this type of catalyst was halted at this point.

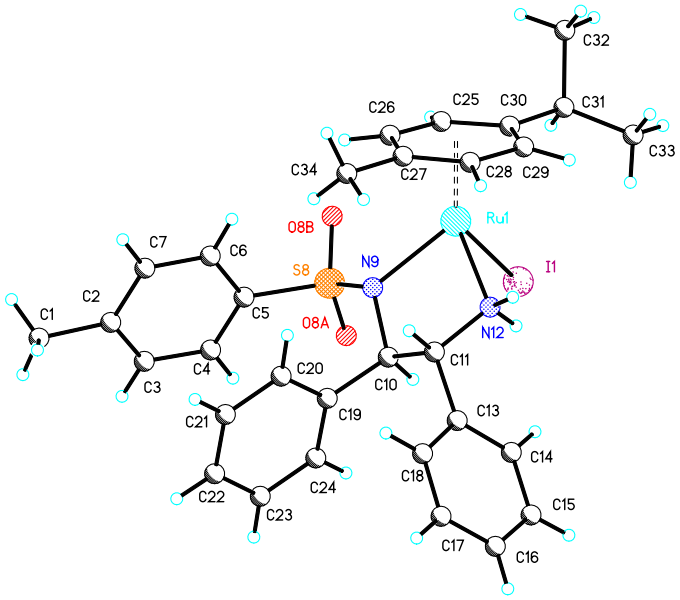
8. Appendix 2-X-ray crystallography data.

X-ray crystallography data of *N*-[(1*S*, 2*S*)-1, 2-Diphenyl-2-(3-phenypropyl amino)ethyl)-4-methylbenzenesulfonamide)ruthenium(II)iodide monomer 181.



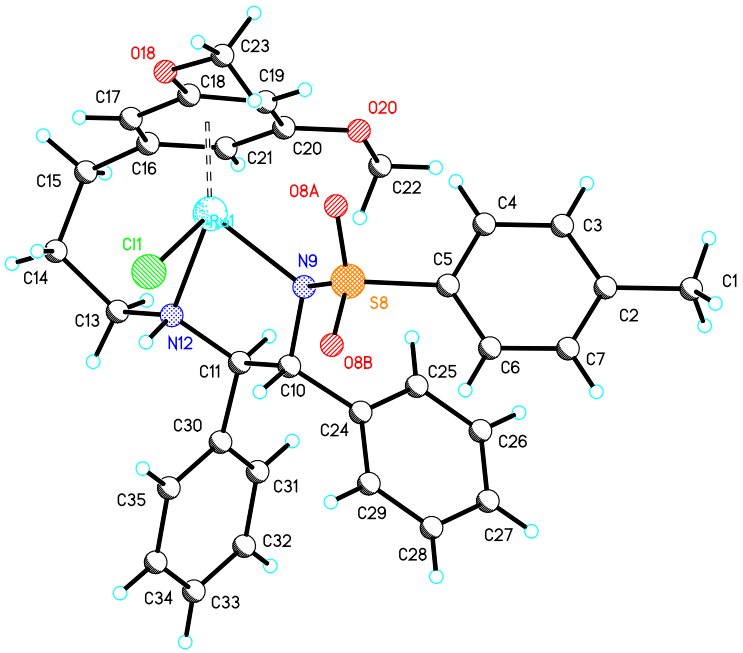
Crystal data: $C_{31}H_{35}IN_2O_3RuS$, M = 743.64, Monoclinic, space group P2(1), a = 11.7063(2), b = 9.65672(16), c = 13.5915(3) A , α = 90°, β = 98.9689(17)°, γ = 90°, U = 1517.66(5) A^3 (by least squares refinement on 8297 reflection positions), T =298(2)K, λ = 0.71073 A, Z = 2, D(cal) = 1.627 Mg/m^3, F(000) = 744. mu(MoK-α) = 1.636 mm^{-1}. Crystal character: brown block. Crystal dimensions 0.24 x 0.12 x 0.12 mm.

X-ray crystallography data of *N*-[(1*R*,2*R*)-2-(Amino)-1,2-diphenylethyl]-4-methylbenzenesulfonamide(*p*-cymene)ruthenium(II)iodide monomer 183.



Crystal data: $C_{31}H_{35}IN_2O_2RuS$, M = 727.64, Orthorhombic, space group P2(1)2(1)2(1), a = 8.8762(6), b = 13.4321(7), c = 26.712(3) A , α = 90°, β = 90°, γ = 90°, U = 3184.7(4) A^3 (by least squares refinement on 9388 reflection positions), T =298(2)K, λ = 0.71073 A, Z = 4, D(cal) = 1.518 Mg/m^3, F(000) = 1456. mu(MoK-α) = 1.555 mm^{-1}. Crystal character: brown block. Crystal dimensions 0.24 x 0.12 x 0.04 mm.

X-ray crystallography data of *N*-((1*R*,2*R*)-2-(3-(4-methoxyphenyl)propylamino)-1,2-diphenyl)-4-methylbenzenesulfonamide) ruthenium chloride 209.



Crystal Data: C32 H35 Cl N2 O4 Ru S, M = 680.20, Orthorhombic, space group P2(1)2(1)2(1), a = 7.58370(10), b = 10.22300(10), c = 38.6764(3) A, α = 90°,β = 90°, γ = 90°, U = 2998.51(5) A^3 (by least squares refinement on 12912 reflection positions), T =150(2)K, λ = 1.54178 A, Z = 4, D(cal) = 1.507 Mg/m^3, F(000) = 1400. mu(MoK-α) = 6.026 mm^{-1}. Crystal character: orange plate. Crystal dimensions 0.40 x 0.10 x 0.01 mm.