Asymmetric Transfer Hydrogenation Reductions Using Tethered Ruthenium (II) Catalysts

By

Vimal Parekh

A thesis submitted in fulfilment for the degree of Doctor of Philosophy in Chemistry

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Declaration.

The research shown in this thesis is an account of my own independent research, unless otherwise stated. These studies were carried out at the Department of Chemistry, University of Warwick between October 2007 and September 2011. The research reported in this thesis has not been submitted, either wholly, or partially for a degree at any other academic institution.

Some of this work has appeared in the scientific literature in the following publications:


Abbreviations.

\( \delta_C \) 13C-NMR chemical shift (ppm)

\( \delta_H \) 1H-NMR chemical shift (ppm)

\([\alpha]_D\) optical rotation

Å Angstroms

Ac acetyl

ACN acetonitrile

AcOH acetic acid

AcOK potassium acetate

Ar aryl group

ATH Asymmetric Transfer Hydrogenation

atm atmospheric

BINAP 2,2’-bis(diphenylphosphino)-1,1’-binaphthyl

BINOL 1,1’-bi-2-naphthol

bipy 2,2’-bipyridine

[BMIM]PF\(_6\) 1-butyl-3-methylimidazolium hexafluorophosphate

Boc di-tert-butyl dicarbonate

bp boiling point

br s broad singlet

Bu butyl

tBu tertiary butyl

c concentration

CDA chiral derivatizing agent

conv. conversion

Cp* pentamethylcyclopentadiene

d doublet

DABCO 1,4-diazabicyclo[2.2.2]octane
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<td>DCC</td>
<td>dicyclohexyl carbodiimide</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>dd</td>
<td>doublet of doublets</td>
</tr>
<tr>
<td>dec.</td>
<td>decomposition temperature</td>
</tr>
<tr>
<td>DFT</td>
<td>density function theory</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-dimethoxy ethane</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>DPEN</td>
<td>1,2-diphenyl ethylenediamine</td>
</tr>
<tr>
<td>EDC</td>
<td>1-ethyl-3-(3-dimethylaminopropyl)carbodiimide</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization</td>
</tr>
<tr>
<td>Et₃N</td>
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<td>sodium formate</td>
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<tr>
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<td>HPLC</td>
<td>high performance liquid chromatography</td>
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<td>high resolution mass spectrometry</td>
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<tr>
<td>IPA</td>
<td>isopropanol</td>
</tr>
<tr>
<td>IR</td>
<td>infra red</td>
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<tr>
<td>J</td>
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<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>LR MS</td>
<td>low resolution mass spectrometry</td>
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</tr>
<tr>
<td>MPV</td>
<td>Meerwein-Ponndorf-Verley</td>
</tr>
<tr>
<td>Ms</td>
<td>mesyl</td>
</tr>
<tr>
<td>MsCl</td>
<td>methanesulfonyl chloride</td>
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<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
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<tr>
<td>o</td>
<td>ortho</td>
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<td>octet</td>
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</tr>
<tr>
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<td>isopropyl</td>
</tr>
<tr>
<td>$^i$PrOK</td>
<td>potassium isopropoxide</td>
</tr>
<tr>
<td>$^i$PrONa</td>
<td>sodium isopropoxide</td>
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<td>pound-force per square inch</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
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quin  quintet
rt    room temperature
s     singlet
S/C   substrate to catalyst ratio
t     triplet
T     temperature
TBAB  tetrabutylammonium bromide
TBDPSCl  tert-butyldiphenylchlorosilane
t or tert  tertiary
TEA    triethylamine
TFA    trifluoroacetic acid
THF    tetrahydrofuran
TLC    thin layer chromatography
TS     transition state
Ts     toluenesulphonyl
TsCl   4-toluene sulfonic acid
TsCYDN N-((p-toluenesulfonyl)-1,2-cyclohexanediamine
TsDPEN 1,2-diphenyl-N-(p-toluenesulfonyl)ethylenediamine
TsOH   tosyllic acid
tt     triplet triplet
UV     ultraviolet
ν<sub>max</sub>  wavenumber (cm<sup>-1</sup>)
v/v    volume to volume ratio
Abstract.

By asymmetric transfer hydrogenation, substituted quinolines, which are generally regarded as challenging substrates for reduction, were successfully converted into tetrahydroquinolines using “tethered” Ru(II) and “tethered” Rh(III) complexes in formic acid/triethylamine.

An ether-linked “tethered” catalyst was successfully synthesized through a sequence that avoids the use of a Birch reduction for the formation of a 1,4-cyclohexadiene moiety. The ether link is incorporated between the basic amine of the ligand and the $\eta^6$-arene ring, giving results comparable to the alkyl-“tethered” complexes.

$N$-alkylated complexes containing a straight-chain substituent attached to a hydroxyl, ether or ester function can act as effective catalysts for the reduction of ketones, and also contains the required functionality for attachment of the catalyst to a heterogeneous support.
1. Introduction.

1.1 Chirality.

Figure 1. Lord Kelvin (William Thomson), Professor of Natural Philosophy in the University of Glasgow from 1846-1899.

The term chirality is derived from the Greek word for hand (cheir), which is a mathematical approach to the concept of “handedness”-the existence of left/right opposition, and was coined by Lord Kelvin in his Baltimore lectures on molecular dynamics and the wave theory of light in which he stated “I call any geometrical figure, or group of points, chiral, and say it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself”. Human hands are perhaps the most universally recognized example of chirality: The left hand is non-superimposable mirror image of the right hand and no matter how the two hands are oriented, it is impossible for all the major feature of both hands to coincide (Figure 2).¹

Figure 2. Human hands, an example of chirality.

In the context of chemistry, two structures that are not identical, but are mirror images of each other are called enantiomers (Scheme 1). Enantiomers are a type of isomer called stereoisomers, as the isomers differ not in the connectivity of the atoms, but only
in the overall shape of the molecule. Structures that are not superimposable on their mirror image, and therefore can exist as two enantiomers, are called chiral.

![Scheme 1. Enantiomers of cyanohydrin from the reaction between an aldehyde and cyanide.](image)

Structures that are superimposable on their mirror images are called achiral (Scheme 2). The essential difference between the two examples shown is symmetry. Acetone cyanohydrin has a plane of symmetry running through the molecule, whereas the aldehyde cyanohydrin has no plane of symmetry, and it cannot have a plane of symmetry, because it contains a tetrahedral carbon atom carrying four different groups: OH, CN, RCH₂ and H. Such a carbon atom is known as a stereogenic centre or chiral centre.

![Scheme 2. Achiral structures of acetone cyanohydrin.](image)

Structures that have more than one stereogenic centre can give rise to stereoisomers that are not mirror images of one another called diastereoisomers. Two diastereoisomers
are different compounds meaning their physical and chemical properties are different, and have different relative stereochemistry. Diastereoisomers maybe achiral (Figure 3) or chiral (Figure 3).

![Achiral and Chiral Diastereoisomers](image)

Enantiomers have identical NMR spectra, IR spectra, physical and chemical properties in the absence of an external chiral influence meaning the same melting point, boiling point, solubility properties and chromatographic retention times. The single exception is the ability of the enantiomers to rotate plane-polarized light. We call the enantiomer that rotates plane-polarized light to the right (gives a positive rotation) the (+)-enantiomer (or the d: dextrorotatory enantiomer) and the enantiomer that rotates plane-polarized light to the left (gives a negative rotation) the (-)-enantiomer (or the l: laevorotatory enantiomer).

The direction in which light is rotated is not dependent on whether a stereogenic centre is R or S. An (R) compound is equally as likely to be (+) as (-), if it is (+) then its (S) enantiomer must be (-). Observation of the rotation of plane-polarized light is known as polarimetry and it is calculated by using the following equation: \([\alpha] = \alpha \times \frac{\text{angle through which the light is rotated by}}{\text{path length in dm}} \times \frac{\text{c (in g/100 cm}^3\text{)}}{\text{and the light usually used is from a sodium lamp (symbol D is used to represent this) with a wavelength of 589 nm. If the angle is very small then mercury lamp with a wavelength of 546 nm can be used for this purpose. The specific rotation \([\alpha] \text{ value obtained can be used as a guide to the enantiomeric purity of a sample, in other words to how much of}}\)
each enantiomer it contains, specific rotation values are usually used for comparison with known literature values in order to confirm the configuration of the enantiomers obtained. Chiral derivatizing agent\(^2\) (CDA) for e.g. Mosher’s acid can be used to determine enantiomeric excess and configuration of simple chiral amines and alcohols as it can convert a mixture of enantiomers into diastereoisomers, which means it can then be possible to distinguish them using NMR. X-Ray crystallography is most commonly used to determine the configuration of novel chiral compounds. The way in which \(R/S\) is assigned to each stereocentre or \(E\) (\(trans\))/\(Z\) (\(cis\)) is assigned to each double bond is by the Cahn-Ingold-Prelog priority rules. For the assignment of \(R/S\), each of the four substituents around the chiral centre is given a priority number. Atoms with higher atomic numbers get higher priority. If two (or more) of the atoms attached to the chiral centre are identical, then the priority number is assigned by assessing the atoms attached to those atoms. The molecules are then arranged so that the lowest priority substituent is pointing away from you. If you move in a clockwise manner from highest to the second lowest assigned substituent, then the chiral centre is given the label \(R\) (for \textit{rectus}, Latin for right), and if you are moving in an anticlockwise manner then the chiral centre is given the label \(S\) (for \textit{sinister}, Latin for left). The procedure is very similar when assigning \(E/Z\), but in this case if two higher groups are \(cis\), the alkene is \(Z\) (from the German \textit{zusammen}, means together), and if they are \textit{trans} the alkene is \(E\) (from the German \textit{entgegen}, means opposite).\(^1\)

### 1.2 Biological significance of chirality.

All proteins, enzymes, amino acids, carbohydrates, nucleosides and a number of alkaloids and hormones are chiral compounds. In contrast to chiral artificial products, almost all (some are racemic or made in both forms) natural compounds are under single enantiomeric form, for example, all natural amino acids are \(L\)-isomer and all
natural sugars (carbohydrates) are $D$-isomers. The D/L notation (a very old convention), not to be confused with d: dextrorotatory and l: laevorotatory, is derived from the signs of optical rotation of $R$ and $S$ glyceraldehyde respectively (Figure 4), with $D$-glucose being the natural enantiomer, and $L$-glucose the unnatural enantiomer.

![D (+)-Glyceraldehyde (also R) vs. L (-)-Glyceraldehyde (also S)](image)

Figure 4. Illustration of glyceraldehyde with D-(natural)/L-(unnatural) and $R/S$ notations.

Amino acids are classified in to $L$-(natural) and $D$-(unnatural), with most $L$-amino acids being of $S$-configuration (Figure 5).

![L-amino acid vs. D-amino acid](image)

Figure 5. Amino acids classified in to $L$-(natural) and $D$-(unnatural).

Although the chemical and physical properties for enantiomers in the absence of an external chiral influence are the same, most enantiomers of drugs exhibit marked differences in biological activities such as pharmacology, toxicology, pharmacokinetics and metabolism when exposed to a chiral surrounding. For example thalidomide 1, which was marketed as the racemate led to a tragedy in the 1960s in Europe. The sedative-hypnotic drug thalidomide exhibited irreversible neurotoxicity and teratological (mutagenic) effects in which babies were born deformed. The drug was prescribed to pregnant women to counter morning sickness. Studies showed that these effects were caused by the ($S$)-enantiomer and that the ($R$)-enantiomer contained the
desired therapeutic activity. More recently studies were concluded that both enantiomers of thalidomide are unstable and spontaneously epimerize to form the racemate in-vivo in humans (Figure 6). 3a

Albuterol (salbutamol) 2 is sold as a racemate, and is the leading bronchodilator, which is a β2-adrenergic receptor agonist that can increase bronchial airway diameter without increasing heart rate. The bronchodilator activity resides in (R)-albuterol also known as levosalbutamol which is sold as the trade name xopenex. The (S)-albuterol enantiomer is not inert as it indirectly antagonizes the benefits of (R)-albuterol and may have proinflammatory effects. These are pharmacokinetic differences between the enantiomers with (S)-albuterol being cleared more slowly. The (S)-enantiomer tends to accumulate in preference to the therapeutically effective (R)-enantiomer. Levosalbutamol sold as the single (R) enantiomer has the same bronchodilator activity as racemic albuterol, but has a superior side-effect profile (Figure 6). 3a,3b

Parkinson’s disease sufferers are treated with the non-proteinogenic amino acid DOPA 3. DOPA is chiral, and only (S)-DOPA (known as L-DOPA) is effective in storing nerve function. The active form of the drug is an achiral compound dopamine which is formed by decarboxylation of 3 and is used to increase dopamine concentrations and dopamine-responsive dystonia, but it cannot cross the blood-brain barrier to reach the site of action. (S)-DOPA can and is then decarboxylated by the enzyme dopamine decarboxylase to dopamine. This enzyme however is not able to metabolize (R)-DOPA (known as D-DOPA), and so to prevent the build-up of (R)-DOPA which could prove to be fatal, it is essential that DOPA is administered pure as the (S)-enantiomer (Figure 6). 3b
Bupivacaine 4, currently the most widely used long acting local anaesthetic agent in both surgery and obstetrics has a good safety record, but its use has resulted in fatal cardiotoxicity, usually after accidental intravascular injection. The single (S)-enantiomer version of bupivacaine called levobupivacaine was introduced, which has clinically equivalent anaesthetic potency to bupivacaine, but with reduced CNS and cardiotoxicity. Due to the differences observed in biological activities for different enantiomers of drugs, all chiral forms of a drug are tested rigorously for possible side effects and for chiral stability in vivo before approval (Figure 6).[^3a][^3c]

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[^3a]:  
[^3c]: Figure 6. Examples of chiral drug molecules, with the tick representing the active enantiomer, and cross representing the toxic enantiomer.
1.3 **Asymmetric catalysis.**

In order to understand the concept of asymmetric reactions you have to focus on the two transition states for the formation of \( R \) and \( S \) enantiomers. In a racemic reaction, where an achiral reagent is reacted with an achiral molecule, the transition states of both \( R \) and \( S \) enantiomers are of equal energy \( (\Delta G^i = \Delta G^{ii}) \), therefore both \( R \) and \( S \) enantiomers are produced in equal amounts to yield a racemic product. In an enantioselective reaction the catalyst used (or reagent) facilitates one of the transition states to be at lower energy than the other as shown in Figure 7 (a reminiscent of an enzyme-catalysed biological reaction). The catalyst interacts with an achiral substrate (the type of substrate used is also important) in the transition state which has lowered in energy by \( \Delta\Delta G^\# \) from \( \Delta G^i \) and in this case it favours the formation of the \((R)\)-enantiomer, whereas transition state for the formation of the \((S)\)-enantiomer may remain unaffected or may increase or decrease (not decrease too much) in energy. The value of \( \Delta\Delta G^\# \) plays a crucial role in determining the selectivity of the reaction.

![Figure 7. Reaction coordinates for the asymmetric synthesis of chiral substrate.](image-url)
The use of catalysts proves to be very economical as very low quantities of catalyst (less than 1 mol%) is usually required in an asymmetric catalysis reaction and the catalyst can also be isolated after a reaction and reused. Some established asymmetric catalytic reactions will now be reviewed.

1.3.1 Sharpless epoxidation.

The Sharpless epoxidation reaction is an enantioselective chemical reaction to prepare 2,3-epoxyalcohols from primary and secondary allylic alcohols. It was discovered in 1980 by Barry K. Sharpless and Tsutomu Katsuki. The simplicity of this metal-catalysed asymmetric epoxidation is what makes this method so attractive, as the necessary components (+) or (-)-diethyl tartrate, titanium tetraisopropoxide and tert-butyl hydroperoxide are all commercially available at low to moderate cost (Scheme 3).

Scheme 3. Asymmetric synthesis of 2,3-epoxyalcohols.

This chiral epoxidation system possesses two key features; first of all it gives uniformly high asymmetric inductions throughout a range of substitution patterns in the allylic
alcohol substrate. Secondly depending on the tartrate enantiomer used, the system is able to deliver the epoxide oxygen from the same enantioface of the olefin regardless of the substitution pattern. As illustrated in Scheme 3 the use of (+)-diethyl tartrate leads to addition of the epoxide oxygen from the bottom face, and using (-)-diethyl tartrate as expected from the top face. Transition-metal-catalysed epoxidations work only on allylic alcohols, so there is one limitation to the method because the coordination of an alcohol to the titanium metal is crucial for the reaction to take place. An example of where Sharpless epoxidation has been employed is for the synthesis of propranolol, which is a sympatholytic non-selective beta blocker and is used to treat hypertension, anxiety and panic. Not many target molecules are themselves epoxides, but one of the great advantages of epoxides is its high versatility, meaning they can react with many types of nucleophiles to give 1, 2-disubstituted products.\textsuperscript{4a}

Scheme 4. Synthesis of (S)-propranolol 8 with the use of Sharpless epoxidation.

The most obvious starting material for this synthesis, allyl alcohol itself gives an epoxide which is hard to handle. So Sharpless instead used the silicon-substituted allylic alcohol 5 for the asymmetric epoxidation step giving 6 in 60% yield and 95% ee. The
hydroxyl group was mesylated and displaced with 1-naphthoxide to give 7 and then after treatment with fluoride to remove the silicon, the epoxide was opened with isopropylamine to give (S)-propranolol 8 (Scheme 4).\textsuperscript{4b}

1.3.2 Hydroboration.

In 1981, Itsuno reported the asymmetric reduction of aromatic ketones utilizing the borane complexes of chiral amino-alcohols (9-12, Figure 8) derived from α-amino-acids to give secondary alcohols with up to 60\% ee.\textsuperscript{5a} Application of such complexes for asymmetric reduction was first reported by Fiaud and Kagan\textsuperscript{5b} who used borane-chiral amine complexes derived from ephedrine in the reduction of ketones but obtained very low ee (3.6 – 5.0\%). Attempts were also made to use the borane complexes with (R)-(+)\textsuperscript{,} (S)-(−)-α-methylbenzylamine, or α-amino-esters in the presence of BF\textsubscript{3}\cdot Et\textsubscript{2}O in asymmetric reductions of ketones but limited success was achieved (ee of up to 20\%).

![Figure 8. Chiral amino-alcohols used for the formation of chiral alkoxy-amine-borane complexes.](image)

In 1983 after 2 years, Itsuno reported very high selectivities for the reduction of aromatic ketones (94 – 100 \%) by using the new chiral borane complex 14 prepared from (S)-(−)-2-amino-3-methyl-1, 1-diphenylbutan-1-ol 13 and borane (Scheme 5).\textsuperscript{5c-5e}
Scheme 5. Itsuno’s chiral amine-borane system for asymmetric reduction of ketones.

Soon after, Corey extended the idea and developed the 1,3,2-oxazaborolidines 16 (Scheme 4) as a new generation of homochiral reduction catalysts, which rapidly reduces ketones with up to 97 % ee in the reduction of acetophenone.

Scheme 6. Proposed mechanism for the catalytic enantioselective reduction of ketones by oxazaborolidines 16.

Corey and co-workers had proposed the reaction mechanism shown in Scheme 6, to explain the selectivity obtained in the catalytic reduction. The first step involves the coordination of the reducing agent BH3 with the Lewis basic nitrogen atom of 16, this causes the activation of the BH3 as a hydride donor and also enhances the Lewis acidity
of the catalyst’s endocyclic boron. Subsequently, the endocyclic boron of the catalyst coordinates to the ketone at the sterically more accessible electron lone pair (i.e. the lone pair closer to the smaller substituent). This preferential binding in 18 acts to minimize the steric interactions between the ketone (the large substituent directed away) and the R group of the catalyst, and aligns the carbonyl and the coordinated borane for a favourable, face-selective hydride transfer through a six-membered transition state 18. Hydride transfer then yields chiral boron enolate 20, which upon acidic work-up yields the chiral alcohol. Dissociation of the reduction product from 19 may occur by two different pathways: 1) reaction of the alkoxide ligand attached to the endocyclic boron atom with the adjacent boron atom of 19 to regenerate 16 and form the borinate 20 by cyclo-elimination; or 2) by the addition of BH₃ to 19 to form a six-membered BH₃-bridged species 21, which decomposes to produce the catalyst-BH₃ complex 17 and borinate 20.₅f

Oxazaborolidines are excellent homogeneous catalysts for the enantioselective reductions of prochiral carbonyl compounds and have gained significant synthetic utility in the synthesis of a significant number of natural products, including lactones, terpenoids, alkaloids, steroids and biotins.₅f, ₅g, ₅h

1.3.3 Asymmetric Hydrogenations.

1.3.3.1 Wilkinson’s Catalyst.

Asymmetric hydrogenation plays an important role in today’s synthesis world. In 1966 Sir Geoffrey Wilkinson who received the Nobel Prize in 1973 for his work on organometallic compounds introduced the first example of homogeneous catalysis. Chlorotris(triphenylphosphine)rhodium(I) known as the Wilkinson’s catalyst [RhCl(PPh₃)₃] 22 (Scheme 7) is able to catalyse the hydrogenation of simple unhindered
alkenes in organic solvents rapidly under mild conditions. The mechanism of Wilkinson’s catalytic system is reasonably well-established, and it involves the initial dissociation of one or two triphenylphosphine ligands to give 14 e⁻ or 12 e⁻ complexes, respectively, followed by oxidative addition of H₂ to the metal. Subsequent π-complexation of alkene, intramolecular hydride transfer (olefin insertion), and reductive elimination results in extrusion of the alkane product as shown in Scheme 7. The reaction rates are dependent on the steric hindrance of the substrates.

Scheme 7. Catalytic hydrogenation of propylene.
1.3.3.2 Schrock-Osborn catalyst.

The Schrock-Osborn catalyst 23 (Figure 9), discovered in 1976 by 2005 Nobel Prize winner Richard R. Schrock and John Osborn, who carried out his doctoral study with Sir Geoffrey Wilkinson, is another example of a homogeneous catalyst for hydrogenation reactions and is more active than Wilkinson’s catalyst due to the cationic metal centre being more electrophilic, favouring alkene coordination, which is often the rate determining step.\textsuperscript{6d}

\[
\begin{array}{c}
\text{Schrock-Osborn catalyst} \\
23
\end{array}
\]

Figure 9. Schrock-Osborn catalyst.

1.3.3.3 Crabtree’s catalyst.

In 1979 Professor Robert H. Crabtree developed an iridium based complex with 1,5-cyclooctadiene, tris-cyclohexylphosphine and pyridine also known as Crabtree’s catalyst 24 (Figure 10) while working on iridium analogues of the Wilkinson’s rhodium-based catalyst.

\[
\begin{array}{c}
\text{Crabtree’s catalyst} \\
24
\end{array}
\]

Figure 10. Crabtree’s catalyst.
Crabtree’s catalyst is another homogeneous catalyst for hydrogenation reactions and is more active than the Schrock-Osborn catalyst and at least 100 times more active than Wilkinson’s catalyst. Crabtree’s catalyst is also able to reduce tri- and tetra substituted alkenes, which the Wilkinson’s catalyst and the Schrock-Osborn catalyst are unsuccessful in reducing (Table 1). It also gives superior directing effect for cyclic substrates.  

<table>
<thead>
<tr>
<th>Substrate =</th>
<th>Turnover Frequency (TOF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[\text{Wilkinson's catalyst}] Benzene/EtOH, 25 °C</td>
<td>650 \hspace{1cm} 700 \hspace{1cm} 13 \hspace{1cm} -</td>
</tr>
<tr>
<td>[\text{Schrock-Osborn Catalyst}] CH\textsubscript{2}Cl\textsubscript{2}, 25 °C</td>
<td>4000 \hspace{1cm} 10 \hspace{1cm} - \hspace{1cm} -</td>
</tr>
<tr>
<td>[\text{Crabtree's catalyst}] CH\textsubscript{2}Cl\textsubscript{2}, 0 °C</td>
<td>6400 \hspace{1cm} 4500 \hspace{1cm} 3800 \hspace{1cm} 4000</td>
</tr>
</tbody>
</table>

Table 1. Rates (in mol of substrate reduced (mol of catalyst)\(^{-1}\) h\(^{-1}\)) of hydrogenation of variously substituted olefins with active catalysts of different types.

1.3.3.4 Asymmetric Hydrogenation using DIPAMP complexes.

Since the discovery of Wilkinson’s catalyst, it has inspired many research scientists to synthesise tertiary stereogenic carbon atoms by asymmetric hydrogenation of alkenes using optically active transition metal complexes. In 1977, William S. Knowles (Nobel Prize winner in 2001) and his collaborators Billy D. Vineyard and M. Jerry Sabacky discovered a bidentate C\(_2\) symmetric version 25 of the cationic Schrock-Osborn catalyst, giving very high enantioselectivities in the hydrogenation of achiral enamides. This was the first demonstration that a chiral transition metal complex could effectively transfer chirality to a non-chiral substrate with selectivities that rival those observed in enzymes, and lead to the 1\(^{st}\) commercialized asymmetric process for the synthesis of L-
DOPA 3 (Scheme 8), a drug used for the treatment of Parkinson’s disease as previously described.

Scheme 8. Monsanto research group led by Knowles established a method for the industrial synthesis of $L$-DOPA 3.

1.3.3.5 Asymmetric Hydrogenation using Ru(II)/Rh(III)-BINAP complexes.

The discovery of BINAP-Ru complexes in the mid 1980’s extensively broadened the scope of olefinic and ketonic substrates for asymmetric hydrogenation. In 1984 the axially disymmetric bis(triaryl)phosphine ligand discovered by Noyori and co-workers was first used for Rh(I)-catalysed asymmetric hydrogenations of $\alpha$-(acylamino) acrylic acids and esters. The use of BINAP when combined with Ru, proved to be a successful combination for the asymmetric hydrogenation of various unsaturated substrates (C=O and C=C bonds). The synthesis of the anti-inflammatory drug naproxen 27' was successfully carried with the use of this catalytic system, reducing the acrylic acid 27 using $[(S)$-BINAP-Ru(OAc)$_2$] 26b, giving the product 27' in 100% yield and 97% ee (Scheme 9).
Introduction

Scheme 9. The use of asymmetric hydrogenation for the synthesis of naproxen 27'.

Asymmetric hydrogenation using various Ru-BINAP\textsuperscript{8c,8d}, and Rh-BINAP\textsuperscript{8e-8g} derived complexes have been successfully applied to the reduction of β-keto esters\textsuperscript{8h-8o} and ketones\textsuperscript{8p,8q}.

1.3.3.6 Asymmetric Hydrogenation using Ir(I) and Ru(II) complexes for the reduction of quinolines.

Optically active tetrahydroquinoline derivatives are an important class of building blocks for asymmetric synthesis in pharmaceutical and agrochemical industries and for the total synthesis of natural products (Figure 11). The (S)-enantiomer of flumequine 28 is an antibacterial agent of the quinolone family. Several other derivatives such as torcetrapib 29 and compound A 30, have attracted much attention as potent inhibitors of the cholesterol ester transfer protein, which is a target for the treatment of low high-density lipoprotein cholesterol and atherosclerosis.\textsuperscript{9a} The conversion of quinolines to tetrahydroquinolines is a useful direct method for the synthesis of chiral, non-racemic N-containing heterocycles from readily available starting materials. A number of reports on the pressure hydrogenation of quinolines have been published.\textsuperscript{9-11}
Figure 11. Examples of important 1,2,3,4-tetrahydroquinoline derivatives.

The first example reported by Zhou and co-workers in 2003 of asymmetric quinoline hydrogenation employed chiral biaryldiphosphine ligands 31 with an Ir(I) salt, and gave products with ee’s of up to 96% and conversion of up to 95% (Scheme 10). Iodine was found to be an essential additive.

Scheme 10. Highly enantioselective iridium-catalyzed hydrogenation of heteroaromatic compounds, quinolines. Reaction conditions: substrate (1 mmol), [Ir(COD)Cl]2 (0.5%), (R)-MeO-Biphep 31 (1.1%), I2 (10%), toluene (5 cm³), H2 (600-700 psi), 25 °C.

This method was applied for the asymmetric synthesis of three naturally occurring alkaloids angustureine 32, galipinine 33 and cuspareine 34 (Figure 12).
Figure 12. Bioactive compounds derived from chiral 1, 2, 3, 4-tetrahydroquinoline.

A variety of iridium complexes have been reported using chiral phosphorous ligands, including diphosphines, diphosphites, monodentate phosphorous ligands, P, N ligands and other examples to catalyze the enantioselective hydrogenation of a wide range of 2-alkyl-substituted quinoline derivatives, giving good to excellent enantioselectivities. Examples of some of these ligands have been shown (Scheme 11-16).

The activation of quinolines with chloroformates has been reported to improve the rates of reactions, giving up to 90% ee and 95% conversion for quinolines and up to 83% ee and 87% conversion for isoquinolines\(^9c\) (Scheme 11).

Scheme 11. AH of quinolines and isoquinolines activated by chloroformates.\(^9c\) Reaction conditions: substrate (1.0 mmol), [Ir(COD)Cl]\(_2\) (0.5%), (S)-SegPhos \(35\) (1.1%), THF (5 cm\(^3\)), Li\(_2\)CO\(_3\) (1.2 mmol), ClCO\(_2\)Bn (1.1 mmol).

Asymmetric Ir-catalyzed hydrogenation of quinolines using BINOL-derived diphosphonites \(36\) gave enantioselectivity of up to 96% and conversion of up to 96%, with a chiral diphenyl backbone\(^9d\) (Scheme 12).

Ir complexes with chiral ferrocenyloxazoline P, N ligands 37 are effective catalysts for the AH of heteroaromatic compounds such as quinolines, and up to 92% ee was obtained with conversions up to 95% (Scheme 13).  

Scheme 13. AH of quinolines catalyzed by iridium with chiral ferrocenyloxazoline derived P, N ligands 37. Reaction conditions: substrate (1 mmol) / $[\text{Ir(COD)Cl}]_2$ / chiral ligand 37/$I_2= 100/0.5/1.1/5$, toluene (5 cm$^3$), $H_2$ (600 psi), rt.

The use of nitrogen-donor ligands, such as diamines, in this application is less developed. In 2006, Noyori and co-workers reported that chiral $\eta^6$-arene-TsDPEN-Ru(II) complex is not only excellent for ATH, but also for the AH reduction of aromatic
Fan and co-workers later demonstrated that the AH of quinolines using chiral $\eta^6$-arene-TsDPEN-Ru(II) complex 38 (Scheme 14) in an ionic liquid gave excellent results. In this process, the ionic liquid was essential – reactions in methanol proceeded with much lower activity.

![Scheme 14](image)

Quinoline substrates were efficiently hydrogenated to give tetrahydroquinolines with up to 99% ee and up to 97% conversion, without the need for additives via this first phosphine free cationic Ru/TsDPEN catalyst. The use of ionic liquid not only facilitates the recyclability, but also enhances the stability and selectivity of the catalyst.

A new kind of highly effective phosphine-free Ir-catalysts for the asymmetric hydrogenation of quinolines was developed, giving products in up to 99% ee. The reaction did not require inert gas protection throughout the entire operation, Scheme 15. The use of an acidic additive was demonstrated to be important for optimal activity. These results suggested that the reduction of quinolines was proceeding by an ionic catalytic pathway in which N-protonation was required to activate the hydride addition process, which was different from the mechanism of the AH of ketones.
Scheme 15. Air-stable and phosphine-free iridium catalysts for highly enantioselective hydrogenation of quinoline derivatives.\(^{9h}\) Reaction conditions: substrate (0.75 mmol) in undegassed MeOH (1 cm\(^3\)), (S, S)-40 (0.2 mol%), TFA (10 mol%), H\(_2\) (50 atm), 15 °C, 24-28 hrs.

Despite the significant progress made, the mechanism of quinoline reductions with these types of catalysts remained to be elucidated, in contrast to the better known asymmetric reduction of ketones. Fan and co-workers very recently reported the systematic study on the AH of a broad range of quinoline derivatives using Ru-diamine catalysts together with a detailed mechanistic study through experiments and DFT calculations.

A wide range of quinoline derivatives, including 2-alkylquinolines, 2-arylquinolines, 2-functionalized and 2,3-disubstituted quinolines were efficiently hydrogenated under mild conditions with up to >99% ee and up to 5000 TON, using \(\eta^6\)-arene-N-tosylethlenediamine-Ru(II) complexes 41 and 42 (Scheme 16).\(^{9a}\)
Scheme 16. Asymmetric hydrogenation of 2-alkylquinolines, 2-arylquinolines, 2-functionalized and 2, 3-disubstituted quinolines. Reaction conditions: 0.15-0.20 mmol substrate, 1 cm³ of MeOH/2 cm³ EtOH (2-arylquinolines), 0.2-1.0 mol% cat, 0-25 °C, H₂ (50 atm), 12-48 hrs.

The cascade hydrogenation of quinoline occurs through an ionic instead of a concerted catalytic pathway, involving 1,4-hydride transfer, isomerization, and 1,2-hydride transfer. As illustrated in Scheme 17, the ionized ruthenium complex Ru⁺ 43 reversibly accommodates a dihydrogen to form dihydrogen complex H₂-Ru⁺ 44. Deprotonation of the dihydrogen ligand 44 by quinoline A generates both the active Ru-H 45 species and the activated substrate B. A subsequent 1,4-hydride transfer affords the enamine intermediate C and the regenerated Ru⁺ 43. Similarly, the enamine C serves as a base to deprotonate the dihydrogen ligand 44, resulting in the Ru-H 45 and the iminium cation D. Then 1,2-hydride transfer gives the final product, 1,2,3,4-tetrahydroquinoline E, enantioselectively and regenerates Ru⁺ 43. The dihydroquinoline intermediate C can be reversibly dehydrogenated by Ru-catalyst 43 to give the quinoline A, while the 1,2-hydride transfer step is irreversible under the asymmetric hydrogenation conditions. The reaction between the activated iminium cation D and the Ru-H 45 takes place via a cyclic 10-membered transition structure TS-45, with the participation of TfO⁻ anion. Similarly to what has been shown by Noyori for ketone reductions, the enantioselectivity in this system originates from the CH/π interaction between the η⁶-arene ligand in the Ru-complex and the fused phenyl ring of the dihydroquinoline.⁹ᵃ
Scheme 17. Proposed mechanism for the asymmetric hydrogenation of quinoline (ethylenediamine ligands and OTf- are omitted for clarity).
1.4 Asymmetric transfer hydrogenation

1.4.1 Traditional mechanisms

\[
\text{DH}_2 + \text{A} \xrightarrow{\text{cat}} \text{D} + \text{AH}_2
\]

\[\text{DH}_2 = \text{hydrogen donor; A = hydrogen acceptor}\]

Scheme 18. Reduction of multiple bonds via transfer hydrogenation.

Transfer hydrogenation or hydrogen-transfer is the reduction of multiple bonds with the use of a hydrogen donor in the presence of a catalyst (Scheme 18). The process involves abstraction of hydrogen from the reagent (hydrogen donor) with the involvement of catalyst, followed by (or in concert with) hydride addition to the unsaturated functional group of the substrate (hydrogen acceptor). The benefits of transfer hydrogenation as opposed to pressure hydrogenation include procedural simplicity, avoidance of hazardous reagents such as molecular hydrogen and borane, as well as the need of pressure vessels (saving costs, as purchasing expensive equipment for handling these reagents is not required). In addition to this, the use of a specific hydrogen donor can favourably affect the rate and selectivity of a given reaction. However, the drawback with transfer hydrogenation is its unfavourable thermodynamics for the reduction of ketones, using alcohols, especially propan-2-ol, as hydrogen source. This means careful selection of hydrogen donor and reaction conditions are required if good conversion and ee are to be obtained.\textsuperscript{13a-13c}

From a mechanistic point of view, transfer hydrogenation of ketones can occur via two general reaction paths: (a) concerted process called, \textit{direct hydrogen transfer} and (b) step-wise process called, the \textit{hydridic route}.\textsuperscript{13a}
(a) Direct hydrogen transfer:

This is a concerted process, and it involves the formation of a six-membered cyclic transition state in which both the hydrogen donor (PrOH) and hydrogen acceptor (ketone) are held together in close proximity to the metal centre (TS-46, Scheme 19). This mechanism is similar to that proposed for the Meerwein-Ponndorf-Verley (MPV) reduction.\(^{13d-13g}\)

\[
\begin{align*}
\text{TS-46} & \\
\end{align*}
\]

Scheme 19. Mechanism for the Meerwein-Ponndorf-Verley (MPV) reduction.

(b) Hydridic route:

Transfer hydrogenation via the hydridic route takes place in a step-wise manner, and it involves the intermediate formation of metal hydride 47 by interaction of catalyst with hydrogen donors such as IPA and formic acid 48, eliminating either acetone or carbon dioxide. The metal hydride 47 then undergoes hydride transfer with a coordinated ketone TS-47 (Scheme 20).

\[
\begin{align*}
\text{TS-47} & \\
\end{align*}
\]

Scheme 20. Hydridic mechanism for transfer hydrogenation of ketones.
The route taken in a particular system is dependent on the metal catalyst and hydrogen donor. Main group elements such as aluminium in the MPV reduction\textsuperscript{13e,13f} have been reported to take the hydrogen transfer route. As oppose to this, transition metal complexes, as stated by Noyori, “prefer the hydride mechanism”.\textsuperscript{13h} An example of this is shown with [RhH(bipy)$_2$], in the mechanism of [Rh(bipy)$_2$Cl]-catalysed dehydrogenation of ethanol in the presence of a base.\textsuperscript{13h} Also, the involvement of a ruthenium dihydride species in a [RuCl$_2$(PPh$_3$)$_3$] and NaOH catalyst system for the transfer hydrogenation of ketones was suggested by Bäckvall.\textsuperscript{13i}

In 1991, Bäckvall reported the enhanced activity of [RuCl$_2$(PPh$_3$)$_3$] for the transfer hydrogenation of ketones by isopropanol with the use of catalytic amount of NaOH. No transfer hydrogenation took place without base.\textsuperscript{13i} This finding was important, as in previous ruthenium-catalysed transfer hydrogenation of ketones, the reaction took place at high temperatures.\textsuperscript{13j,13k}

\section*{1.4.2 Hydrogen sources.}

In transfer hydrogenation, one of the most common sources of hydrogen donors are secondary alcohols, in particular isopropanol. The use of isopropanol and other secondary alcohols however has the inherent problem of ketone/alcohol equilibrium, preventing high conversion being obtained. This is due to the similarity of the hydrogen source and the product; both being secondary alcohols. In effect, the reverse process may take place, where the chiral secondary alcohol (product) acts as the hydrogen donor, transferring its hydrogen and oxidising back to the starting ketone (starting material), and reducing the acetone back to isopropanol.\textsuperscript{14a} The reverse process which can be enhanced by elongated reaction times or high substrate concentration, has frequently caused deterioration in optical purity of the chiral
product. The oxidation potential of the substrate controls the position in which the equilibrium lies,\textsuperscript{14b} therefore 100\% conversion is theoretically impossible and it is often required to use low substrate concentration to maximise the yield in the reaction. A base is normally used in transfer hydrogenation reactions, when isopropanol is utilized as the source of hydrogen (a), Scheme 21).

In recent years, formic acid/triethylamine (5:2) mixture (triethylammonium formate), which is a highly activated form of formic acid,\textsuperscript{14c} has been used as the source of hydrogen in transfer hydrogenation reactions. The use of formic acid eradicates the problem of reversibility encountered with isopropanol, as the dehydrogenation of formic acid generates gaseous carbon dioxide which is usually released in to the atmosphere in an open system. This process is therefore irreversible, meaning complete reduction can now be theoretically achieved, and with enantioselectivity being under kinetic control. (b), Scheme 21)

\begin{align*}
\begin{array}{c}
\text{Scheme 21. Transfer hydrogenation reaction using a) isopropanol and b) formic acid as source of hydrogen.}
\end{array}
\end{align*}
**1.4.3 Ligands for Asymmetric Transfer Hydrogenation.**

A general review on the more recently developed ligands used in asymmetric transfer hydrogenation will be presented. Acetophenone 49a is usually used, unless stated, as a model substrate for comparing the reactivity of the ligands.

Throughout the years various phosphine 50-52, pyridine-based 53-55, tetrahydrobi(oxazole) 56-58, diamine 59-62, diimine 63, BINOL-derived diphosphonite 64, tridentate 65-69 and tetradeinate 70-71 ligands have been used in conjunction with either Ru, Rh and Ir as ATH catalysts, giving poor to excellent enantioselectivity for the reduction of acetophenone 49a (Figure 13).

**Phosphine-based:**

\[
\text{(R, R)-DIOp} \quad 50 \\
\text{(R)-PROPHOS} \quad 51 \\
\text{(S)-(R)-PIGIPOS} \quad 52
\]

**Pyridine-based:**

\[
\begin{align*}
\text{53} \\
\text{54} \\
\text{55}
\end{align*}
\]

**Tetrahydrobi(oxazole)-based:**

\[
\begin{align*}
\text{56} \\
\text{57} \\
\text{58}
\end{align*}
\]

**Diamine-based:**

\[
\begin{align*}
\text{59} \\
\text{60} \\
\text{61} \\
\text{62}
\end{align*}
\]
Figure 13. Types of ligands used over the years for the ATH of 49a.
These processes could still be further improved for practical use in organic synthesis, being limited by low catalytic activity, insufficient enantioselectivity, low substrate/catalyst molar ratio (S/C), or narrow scope.

1.4.3.1 β-Amino alcohol ligands.

In 1996, Noyori and co-workers discovered that the ATH reduction of aromatic ketones, using chiral β-amino alcohols 72-74 in propan-2-ol catalysed by arene-ruthenium(II) complex showed high-ligand acceleration effects, and high enantioselectivity (Scheme 22). \(^{17d}\)

![Scheme 22. ATH of 49a using Ru(II) complexes of 72, 73 and 74.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Time (hrs)</th>
<th>% Yield</th>
<th>% ee</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(1S,2S)-72</td>
<td>1</td>
<td>96</td>
<td>78</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>(1S,2S)-73</td>
<td>1</td>
<td>94</td>
<td>92</td>
<td>S</td>
</tr>
<tr>
<td>3</td>
<td>(1S,2R)-74</td>
<td>1</td>
<td>95</td>
<td>91</td>
<td>S</td>
</tr>
</tbody>
</table>

Table 2. ATH of 49a using Ru(II) complexes of 72, 73 and 74. Reaction was carried out at 28 °C using a 0.1 moldm\(^{-3}\) solution (5 mmol) in IPA. Ketone:Ru:ligand:KOH = 200:1:2:5.

The highest chiral efficiency (Table 2) was shown by hexamethylbenzene-(1S, 2S)-2-methylamino-1,2-diphenylethanol [(1S, 2S)-73], giving 49a’ in 92% ee and 94% yield after 1 hr at 28 °C. The reduction proceeded 5x faster than the reaction using
Introduction

\[
[\{\text{RuCl}_2(\eta^6-C_6H_{13}Me_3-1,3,5)\}_2\}-\text{(1S,2S)-N-(toluene-\text{p}-sulfonyl)-1,2-diphenylethylene diamine system which was reported by Noyori in 1995.}^{17e}
\]

Intrigued by this, Wills (Scheme 23, 75-77)\textsuperscript{17f} and Anderson (Scheme 24, 78-80)\textsuperscript{17g} investigated the use of stereochemically rigid \(\beta\)-amino alcohol ligands with Ru(II) complexes, in the attempt to increase the activity of the catalyst, decrease the catalyst loading and to maximise enantioinduction for industrial applications.

![Chemical structures](image)

Scheme 23. ATH of 49a using Ru(II) complexes of 75, 76 and 77.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Time (hrs)</th>
<th>% Yield</th>
<th>% ee</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(1R,2S)-75</td>
<td>1.5</td>
<td>70</td>
<td>91</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>(R)-76</td>
<td>2</td>
<td>95</td>
<td>23</td>
<td>S</td>
</tr>
<tr>
<td>3</td>
<td>(1S,2R)-77</td>
<td>15</td>
<td>33</td>
<td>27</td>
<td>S</td>
</tr>
</tbody>
</table>

Table 3. ATH of 49a using Ru(II) complexes of 75, 76 and 77. Reaction was carried out at 28 °C using 1 mol% of 75, 76 or 77, 0.25 mol% of \([\text{RuCl}_2(p\text{-cymene})]_2\), 2.5 mol% of KOH, IPA.

The stereochemically rigid amino alcohol 75 in conjunction with \([\text{RuCl}_2(p\text{-cymene})]_2\) proved to be an excellent catalyst for the reduction of 49a, giving 49a’ in 70% yield and 91% ee (Table 3, Entry 1). The results obtained for the reduction of a series of aromatic ketones under identical conditions using 75 gave the corresponding alcohols in good to excellent yield’s and ee’s. In contrast to this, using a non-rigid amino alcohol 76 for the reduction of 49a did give a relatively high conversion of 95 % but quite a low ee of 23%
The importance of a primary amine group was clearly identified due to the low conv/ee (Table 3, Entry 3) obtained when 77 was employed for the ATH reduction.\textsuperscript{17f}

A new generation of 2-azonorbornyl stereochemically rigid amino alcohol ligands were highly active for the reduction of aromatic ketones and extremely active when a ketal function was introduced into the ligands 78-80.\textsuperscript{17g}

\[
\text{Scheme 24. ATH of } 49a \text{ using Ru(II) complexes of 78, 79a-79d and 80.}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Time (hrs)</th>
<th>% conv</th>
<th>% ee</th>
<th>Product TOF (h\textsuperscript{-1})</th>
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<td>94</td>
<td>1050</td>
</tr>
<tr>
<td>2</td>
<td>79a</td>
<td>1</td>
<td>92</td>
<td>96</td>
<td>3000</td>
</tr>
<tr>
<td>3</td>
<td>79b</td>
<td>1</td>
<td>72</td>
<td>95</td>
<td>1900</td>
</tr>
<tr>
<td>4</td>
<td>79c</td>
<td>1</td>
<td>90</td>
<td>96</td>
<td>2800</td>
</tr>
<tr>
<td>5</td>
<td>79d</td>
<td>1</td>
<td>73</td>
<td>96</td>
<td>1500</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
<td>0.25</td>
<td>97</td>
<td>96</td>
<td>8500</td>
</tr>
</tbody>
</table>

Table 4. ATH of 49a using Ru(II) complexes of 78, 79a-79d and 80. S/C = 1000

The ATH reduction of 49a using [Ru(p-cymene)(79a)], showed an increase in conversion, ee and a threefold increase in rate when compared to [Ru(p-cymene)(78)].

The DFT studies showed that the possible explanation for this enhancement in rate is due to the presence of a dioxolane ring in 79a which lowers the energy in the transition
state caused by van der Waals attractions between the dipole in the dioxolane ring and the dipole in the substrate. Modifications made to the substituents on the ketal group (79b-79d) did not further enhance the activity of the catalyst. However when [Ru(p-cymene)(80)] was used for the reduction of 49a, the activity of the catalyst was far greater than [Ru(p-cymene)(79a)], giving 97% conversion, 96% ee within 25 minutes with product TOF (h⁻¹) of 8500 in comparison to 3000 for [Ru(p-cymene)(79a)]. Encouraged by this a study of different S/C ratios using [Ru(p-cymene)(80)] was carried out, and showed that even at an S/C ratio of 5000 the reaction proceeded to full conversion after 90 mins, but at an S/C ratio of 7000 the reaction stopped at 85% conversion (Table 5). The enantioselectivity was unaffected by lowering the quantity of catalyst and prolonged reaction times. The studies also showed that a wide range of aromatic ketones were reduced successfully, giving high rates/enantioselectivities with catalyst loading being as low as S/C = 1000.¹⁷g

<table>
<thead>
<tr>
<th>Entry</th>
<th>S/C</th>
<th>Time (mins)</th>
<th>% conv</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>200</td>
<td>6</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
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<td>15</td>
<td>97</td>
<td>96</td>
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<tr>
<td>3</td>
<td>3000</td>
<td>45</td>
<td>96</td>
<td>96</td>
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<tr>
<td>4</td>
<td>4000</td>
<td>70</td>
<td>95</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>5000</td>
<td>90</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>7000</td>
<td>110</td>
<td>85</td>
<td>96</td>
</tr>
</tbody>
</table>

Table 5. Catalyst-loading study for the ATH of 49a using [Ru(p-cymene)(80)] was carried out.

The highest levels of acceleration to ATH reduction reactions was obtained by beta-amino alcohols (some 70-fold over the background rate),¹⁷h with mono-tosylated ligands coming second (ca. 30-fold over background rate), and the others giving slightly more than 7- to 8-fold acceleration. The major drawback with the use of beta-amino alcohol ligands is its incompatibility like most other ligands with the formic acid/triethylamine
system, solving the reversibility issue which occurs in the IPA/KOH system (Section 1.4.2). Monotosylated ligands however work well with both systems.

1.4.3.2 1,2-Monotosylated ligands.

The development in the area of monotoyslated ligands out of all has been the most significant and important for ATH reactions. This area has been led by Noyori, who was the first to report the use of monoarylsulfonylated diamines, in particular 81, as ligands in Ru(II)-catalysed transfer hydrogenation, giving excellent conversions and enantioselectivities for aromatic ketones.\(^{17e}\)

Scheme 25. The first reported use of 1,2-monotosylated diamine ligand 81 in Ru(II)-catalysed transfer hydrogenation using IPA/KOH and FA/TEA system.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (hrs)</th>
<th>% conv</th>
<th>% ee</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^a)</td>
<td>(S,S)-82</td>
<td>15</td>
<td>95</td>
<td>97</td>
<td>S</td>
</tr>
<tr>
<td>2(^b)</td>
<td>(S,S)-82</td>
<td>20</td>
<td>&gt;99</td>
<td>98</td>
<td>S</td>
</tr>
</tbody>
</table>

Table 6. ATH reduction of 49a using (S, S)-82 in IPA/KOH and FA/TEA. \(^a\) The reaction was carried out at room temperature using a 0.1 M solution of ketone (5.0 mmol) in IPA, KOH (0.13 mmol) with S/C = 200. \(^b\) The reaction was carried out at 28 °C using a ketone (5.0 mmol) in FA/TEA (5:2, 2.5 cm\(^3\)) with S/C = 200.
The results show that both IPA and formic acid/triethylamine azeotrope can be utilized as hydrogen donors (Entry 1 and 2, Table 6), but the FA/TEA system using 82,\textsuperscript{17i} usually obtained \textit{in situ} by heating a mixture of [RuCl\textsubscript{2}(η\textsuperscript{6}-mesitylene)]\textsubscript{2} with 81 in IPA at 80 °C for 20 mins under argon, afforded excellent enantioselectivities (83-99% ee) for a wide range of substrates, as the method overwhelms the energetic requirement of the reduction process (irreversible), in comparison to using IPA as the hydrogen donor where an unfavourable thermodynamic balance is expected (reversible). The activity and the ability to carry out reductions enantioselectively with such catalysts are dependent on the steric and electronic properties of the arene ligand and the chiral diamine auxiliary. The reactivity decreases in the order benzene > p-cymene and mesitylene > hexamethylbenzene as ligand, while mesitylene or p-cymene displays a better enantioselection than unsubstituted benzene.\textsuperscript{17i} In the TsDPEN auxiliary, the presence of the NH\textsubscript{2} terminus was crucial as the NHCH\textsubscript{3} analogue gave much lower activity but comparable enantioselectivity; the N(CH\textsubscript{3})\textsubscript{2} derivative not only gave poor reactivity but also poor stereoselectivity.\textsuperscript{17i} Wills demonstrated that instead of forming the catalyst \textit{in situ}, reductions with isolated N-alkylated TsDPEN Ru(II) complexes bearing a small alkyl group proved to be highly active and enantioselective for the ATH reduction of ketones (Scheme 26).\textsuperscript{17j}

\textbf{Scheme 26.} ATH reduction of 49a using Ru(II) complexes of N-alkylated TsDPEN ligands.
Introduction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (hrs/days)</th>
<th>% yield</th>
<th>% ee</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R,R)-83</td>
<td>26 hrs</td>
<td>99</td>
<td>95</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
<td>(R,R)-84</td>
<td>11 hrs</td>
<td>99</td>
<td>96</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>(R,R)-85</td>
<td>3 days</td>
<td>99</td>
<td>96</td>
<td>R</td>
</tr>
<tr>
<td>4</td>
<td>(R,R)-86</td>
<td>3 days</td>
<td>99</td>
<td>96</td>
<td>R</td>
</tr>
<tr>
<td>5</td>
<td>(R,R)-87</td>
<td>7 days</td>
<td>88</td>
<td>98</td>
<td>R</td>
</tr>
<tr>
<td>6</td>
<td>(R,R)-88</td>
<td>7 days</td>
<td>97</td>
<td>95</td>
<td>R</td>
</tr>
<tr>
<td>7</td>
<td>(R,R)-89</td>
<td>7 days</td>
<td>97</td>
<td>96</td>
<td>R</td>
</tr>
</tbody>
</table>

Table 7. ATH reduction of 49a using Ru (II) complexes of N-alkylated TsDPEN ligands. Reaction was carried out at room temperature using a ketone (1.0 mmol) in FA/TEA (5:2, 1.0 cm$^3$) with S/C = 100 and C$_6$D$_6$ (0.05 cm$^3$, for NMR studies).

N-Methylated complex 84 (Entry 2, Table 7) showed superior catalytic activity than Noyori’s 83 (Entry 1, Table 7) and equally enantioselective. These results suggest the despite having an alkyl group on the nitrogen, the complexes are still capable of reducing ketones through the six-membered transition state established for the parent non-alkylated catalyst (Section 1.4.4). The activity however was reduced when ligands contained bulkier substituents (Entry 5-7, Table 7).$^{17j}$

The use of a ‘roofed’ cis-1,2-diamine-Ru(II) complex 90 which is both conformationally and sterically rigid developed by Matsunaga, proved to be an excellent catalyst for the ATH of ketones, and showed higher catalytic activity than 83 and 38 (Scheme 27, Table 8), also giving higher enantioselectivity for certain bulky aromatic ketones. $^{17k}$
**Scheme 27. ATH reduction of 49a using catalyst 83, 90 and 38.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (hrs)</th>
<th>% yield</th>
<th>% ee</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S,R)-90</td>
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<td>98</td>
<td>93</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>(R,R)-83</td>
<td>16</td>
<td>98</td>
<td>96</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>(R,R)-38</td>
<td>20</td>
<td>&gt;99</td>
<td>98</td>
<td>R</td>
</tr>
</tbody>
</table>

Table 8. ATH reduction of 49a using catalysts 83, 90 and 38. Reaction was carried out at 25 °C using a ketone (2.0 mmol) in FA/TEA (5:2, 1.0 cm³) with S/C = 200.

The ATH of 49a using catalyst 90 completed the reduction process within 15 hrs, giving 98% yield and 93% ee (Entry 1, Table 8). Although 83 and 38 were slightly more enantioselective in comparison to 90, catalyst 83 and 38 were less active, completing the reaction within 16 hrs and 20 hrs respectively.\(^{17k}\)

Another example of a highly active transfer hydrogenation ligand is 91, commonly known as TsCYDN, which was first employed in conjunction with [RuCl(p-cymene)]₂ forming 92, for the reduction of 49a, giving 49a’ in >99% conversion and 94 ee (Scheme 28).
Scheme 28. Knochel demonstrated the use of 91 with [RuCl\((p\text{-cymene})\)_2] for the ATH reduction of 49a. Reaction was carried out at 30 °C in FA/TEA (5:2) with the presence of [RuCl\((p\text{-cymene})\)_2] (0.5 mol%), and TsCYDN (2 mol%).

Further investigations using 91 and 81 were carried out by Ikariya, forming new chiral rhodium and iridium complexes [Cp*MCl(Tsdiamine) (M = Rh, Ir) 93-95 for the ATH reduction of aromatic ketones. The structures of the rhodium and iridium complexes formed has a structure isoelectronic with the chiral Ru complex 83 (Scheme 29).

Scheme 29. ATH reduction of 49a using new chiral rhodium and iridium complexes with chiral diamine ligands.
Table 9. ATH reduction of 49a using catalyst 83, 93-95. Reaction was carried out at 30 °C using a 0.1 M solution of the ketone in IPA. Ketone/cat./BuOK = 200:1:1.2.

The rate and enantioselectivity of the reaction are strongly affected by the metal used and the structure of the chiral diamine ligands (Table 9). The use of TsCYDN 91 was better utilized by Rh, with complex 94 giving 49a’ in 85% conv. and 97% ee (Entry 3, Table 9) within 12 hrs in comparison to 36% conv. and 96% ee (Entry 4, Table 9) obtained within 12 hrs for Ir complex 95. The enantioselectivity obtained with both complexes 94 and 95 were comparable, but the conversion obtained for 95 was fairly low. The use of 93, when TsDPEN (R,R-81) is combined with [Cp*RhCl2]2 for the reduction of 49a, gave 49a’ in 14% conv. and 90% ee (Entry 2, Table 9), showing it’s reactivity isn’t as high as the analogous Ru complex 83 (Entry 1, Table 9), and the enantioselectivity is lower. Complexes containing diamine TsCYDN 91 might not be as reactive as its competitor diamine 81, but the enantioselectivity obtained is higher (Entry 1, 3 and 4, Table 9).  

1.4.4 Mechanistic studies.

The structural and mechanistic theory behind the successful new classes of β-aminoalcohol and monotosylated complexes synthesized by Noyori et al became targets of intense research. Noyori had proposed the metal ligand bifunctional catalytic mechanism shown in Scheme 30, which functions through a concerted transfer of a hydride and proton. It is sometimes referred to as the “outer sphere” mechanism because of the substrate having no direct contact with the metal centre. The process is initiated by the elimination of HCl via an E1cb mechanism from the 18-electron “precatalyst”
complex 38, upon treatment with an appropriate base (KOH in IPA, or triethylamine when formic acid is used as hydrogen donor). This results in the formation of the active 16 electron species 96, which abstracts two hydrogen atoms 97 from the donor (isopropanol or formic acid) via a six-membered pericyclic transition state forming the hydride 98.\textsuperscript{18a} The kinetic isotope effect for the dehydrogenation of isopropanol was investigated by Casey et al,\textsuperscript{18b} showing that hydride and proton transfer takes place simultaneously, which is in correspondence to what Noyori has shown. In a concerted process the hydride and proton is then transferred to the ketone asymmetrically via a six-membered transition state, giving the product and also regenerating the active 16-electron species. Primary and secondary amines are usually very weak acids, but after complexation with a lewis acidic metal, the NH acidity is increased allowing the NH--O=C hydrogen bond formation in the transition state TS-98. The rapid H/D exchange with CH\textsubscript{3}OD also confirms the acidity of the protons prior to complexation.
Noyori et al. isolated and characterized the three key intermediates (38, 96 and 98) using X-ray crystallography. They also proved that the role of base is to only generate the active 16 electron species from 38\textsuperscript{18a} as after isolation, 96 and 98 were both tested for the reduction of ketones, giving results comparable to in situ formed complex. This also eliminated the possibility of a direct hydrogen transfer mechanism, as this would require the participation of a ruthenium isopropoxide intermediate. Further investigations carried out by Noyori\textsuperscript{18c} and Andersson\textsuperscript{18d} confirmed this.
1.4.5 **Origin of Enantioselection.**

Noyori has demonstrated that both Ru(II) chloride 38 and Ru(II) hydride 98 exist predominantly in the diastereoisomeric form (via X-ray crystallography and molecular modelling). This preference also extends to the amino alcohol systems, which means the chiral ligand renders the metal center a single configuration. Andersson had mentioned that the generation of an enantiopure metal centre with the use of a suitable rigid ligand that disapproves other configurations of the coordinated NH group can help achieve good product enantioselectivity.\(^{18c,18d,19a-19c}\)

The absolute stereochemistry for each “2H” transfer process is controlled via a six-membered transition state. The favoured approach of the substrate to the metal hydride is the conformation in which its aromatic ring is adjacent to the arene group on the metal. The aromatic group of acetophenone interacts with the \(\eta^6\)-arene element on the catalyst through a favourable CH/\(\pi\) interaction (Si-TS-99) indicated in Figure 14, and is supported by DFT calculations carried out by Noyori, which also showed that the addition of six-electron-donating alkyl groups on the \(\eta^6\)-arene further stabilises the TS, increasing the rate of the reaction with a drop in selectivity however (Si-TS-100).\(^{19d-19g}\)

This supports the observation that asymmetric reduction only takes place in high ee when aryl/alkyl ketones are used as substrates, but not with dialkyl ketones, as no CH/\(\pi\) interaction is present.

![Diagram showing favoured and disfavoured approaches due to CH/\(\pi\) interaction](image-url)
Noyori also investigated the effects of having electron-donating/withdrawing groups on the aryl substituent of the substrate, and its effects on the enantioselectivity. It was discovered that electron-donating substituents on the aryl group increase the enantioselectivity due to an enhanced CH accepting ability by the electron rich aromatic ring, while electron withdrawing substituents reduce the enantioselectivity.\textsuperscript{19d, 19f, 19g}

Wills’ and co-workers had investigated the \textit{anti}-orientation, and the importance of 1,2-disubstitution pattern of phenyl groups in TsDPEN on the rate and the stereo-outcome of Ru(II) catalysed ATH reactions. It was discovered that 81 was the best ligand for Ru(II) catalysed transfer hydrogenation reduction in terms of rate and enantioselectivity in comparison to ligands 101-103, giving 49a’ in 100% conv., 98% ee (R) at 28 °C in 22 hrs. Identifying the importance of having matching stereogenic centres and \textit{trans} orientation of the phenyl groups, providing extra element of stereo control and rate enhancement (Scheme 31).\textsuperscript{19c}

![Scheme 31](image)

Scheme 31. ATH reduction of 49a, using ligands 81, 101-103 in conjunction with $[\text{Ru(p-cymene)Cl}_2]_2$ (S/C = 200).
1.4.6 Range of Substrates for Asymmetric Transfer Hydrogenation.

1.4.6.1 Aryl Alkyl Ketones.

The most commonly used substrate in asymmetric transfer hydrogenation reduction are aromatic ketones, especially using monotosylated diamine or $\beta$-amino alcohol ligands.

A variety of aromatic ketones were reduced using catalyst (S,S)-82 (S/C = 200), in FA/TEA at 28 °C, giving the resulting secondary alcohols with excellent yields and enantioselectivities. The reason for why the reductions proceed with excellent kinetic enantioface discrimination, is due to the CH/π interaction between the Ru-arene ring and the aryl group on the ketone, along with the favourable diastereomeric transition state exerted by the monotosylated diamine ligand (Scheme 32, Table 10).\textsuperscript{17i}

![Scheme 32. A range of aryl alkyl ketones were reduced using (S,S)-82.](image)

<table>
<thead>
<tr>
<th>Ketone</th>
<th>$R^2$</th>
<th>$R^1$</th>
<th>Time (hrs)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>49a</td>
<td>H</td>
<td>CH$_3$</td>
<td>20</td>
<td>&gt;99</td>
<td>98</td>
<td>$S$</td>
</tr>
<tr>
<td>49b</td>
<td>$m$-Cl</td>
<td>CH$_3$</td>
<td>21</td>
<td>&gt;99</td>
<td>97</td>
<td>$S$</td>
</tr>
<tr>
<td>49c</td>
<td>$p$-Cl</td>
<td>CH$_3$</td>
<td>24</td>
<td>&gt;99</td>
<td>95</td>
<td>$S$</td>
</tr>
<tr>
<td>49d</td>
<td>$p$-CN</td>
<td>CH$_3$</td>
<td>14</td>
<td>&gt;99</td>
<td>90</td>
<td>$S$</td>
</tr>
<tr>
<td>49e</td>
<td>$m$-OCH$_3$</td>
<td>CH$_3$</td>
<td>50</td>
<td>&gt;99</td>
<td>98</td>
<td>$S$</td>
</tr>
<tr>
<td>49f</td>
<td>$p$-OCH$_3$</td>
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<td>60</td>
<td>&gt;99</td>
<td>97</td>
<td>$S$</td>
</tr>
<tr>
<td>49g</td>
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<td>C$_2$H$_5$</td>
<td>60</td>
<td>96</td>
<td>97</td>
<td>$S$</td>
</tr>
<tr>
<td>49h</td>
<td>H</td>
<td>(CH$_2$)$_2$CO$_2$C$_2$H$_5$</td>
<td>90</td>
<td>99</td>
<td>95</td>
<td>$S$</td>
</tr>
</tbody>
</table>

Table 10. A range of aryl alkyl ketones were reduced using (S,S)-82. (S/C = 200)

1.4.6.2 Dialkyl ketones.

ATH reduction of dialkyl ketones have proved to be problematic with the use of $\beta$-amino alcohol and monotosylated diamine ligands in conjunction with a metal precursor. This is due to the absence of the CH/π interaction, as the aromatic moiety isn’t present, which earlier existed for aryl alkyl ketones. In effect, the difference in
energy between the two possible diastereomeric transition states are now narrow, resulting in poor enantioselectivity.

Wills had recently reported the reduction of cyclohexymethyl ketone using 3C “tethered” dimethyl functionalized catalyst 168 (Section 1.4.7) in FA/TEA, giving the alcohol in 100% conversion and 90% ee,\textsuperscript{20a} which was the highest reported ee for a Ru/TsDPEN based catalyst. Other successful examples for the reduction of dialkyl ketones by ATH have been reported by Zhang\textsuperscript{16i,16j} and Hidai.\textsuperscript{20b} In Hidai’s report, successful reduction of dialkyl ketones 104 and 105 was carried out, using ferrocene based complex \([\text{Ru(PPh}_3\text{)(osazolinyl ferrocenylphosphine)}\text{Cl}_2] 106\) and sodium isopropoxide in isopropanol at 50 °C. This gave 104’ in 99% ee and 81% conv., in 16 hrs, and 105’ in 98% ee and 78% conv., in 3 hrs (Scheme 33).\textsuperscript{20b}

![Scheme 33. ATH reduction of dialkyl ketone 104 and 105 using complex 106.](image)

1.4.6.3 Heterocyclic ketones.

Optically active pyridyl alcohols are useful key compounds, not only as pharmaceutical intermediates, but also as useful chiral ligands and auxiliaries in asymmetric synthesis.
Ikariya reported the reduction of nitrogen-containing pyridyl ketones, using Ru(II) complex (S,S)-38 in FA/TEA, giving the corresponding optically active pyridylethanols with excellent conversions and enantioselectivities. ATH reduction of 2-acetylpyridine 107a, using Ru(II) complex (S,S)-38 (S/C = 200) in a mixture of FA/TEA (acetylpyridine: FA: TEA molar ratio = 1:4.3:2.5) at 27 °C, gave (S)-1-(2-pyridyl)ethanol 107a' with 97% yield and 95% ee in 12 hrs. The reduction of various derivatives 107b-107e, gave good to excellent conversions (up to 100%) and ee’s (up to 99.6%), except for benzoylpyridine 107e, which gave a poor ee (9%) (Scheme 34, Table 11).21a

![Scheme 34. ATH reduction of 107a-107e using catalyst (S,S)-38. Ketone/FA/TEA molar ratio = 1:4.3:2.5.]

<table>
<thead>
<tr>
<th>Ketone</th>
<th>S/C</th>
<th>Temp (°C)</th>
<th>Time (hrs)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>107a</td>
<td>200</td>
<td>27</td>
<td>12</td>
<td>97</td>
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<td>107a</td>
<td>200</td>
<td>50</td>
<td>12</td>
<td>99</td>
<td>91</td>
<td>S</td>
</tr>
<tr>
<td>107a'</td>
<td>200</td>
<td>27</td>
<td>24</td>
<td>24</td>
<td>89</td>
<td>S</td>
</tr>
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<td>78</td>
<td>S</td>
</tr>
<tr>
<td>107b</td>
<td>200</td>
<td>27</td>
<td>24</td>
<td>99</td>
<td>89</td>
<td>S</td>
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<td>200</td>
<td>10</td>
<td>24</td>
<td>95</td>
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</tr>
<tr>
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<td>200</td>
<td>10</td>
<td>24</td>
<td>36</td>
<td>85</td>
<td>S</td>
</tr>
</tbody>
</table>
Table 11. ATH reduction of \textbf{107a-107e} using catalyst (S,S)-38. Ketone/FA/TEA molar ratio = 1:4.3:2.5. \textsuperscript{a} Reaction in 2-propanol: (S,S)-Ru cat (38), 1.0 equiv 'BuOK, ketone:Ru = 200:1, 0.1 M in 2-propanol. \textsuperscript{b} 1.0 M in CH\textsubscript{2}Cl\textsubscript{2}. \textsuperscript{c} Ketone/FA/TEA molar ratio = 1:8.6:5.0.

Asymmetric transfer hydrogenation reduction of α, β-acetylenic ketones,\textsuperscript{21b} cyclic α, β-unsaturated ketones,\textsuperscript{21c} and for the synthesis of styrene oxides\textsuperscript{21d} and aziridines\textsuperscript{21e} has also been successfully carried out.

\textbf{1.4.6.4 Imines.}

The synthesis of chiral amines in pharmaceuticals and agrochemical substances is highly demanding, and requires efficient catalytic asymmetric reduction of imines. Noyori reported the first highly efficient asymmetric reduction of a range of imines, using suitably designed chiral Ru(II) complexes 38, 108a-108c in formic-acid-triethylamine mixtures under mild conditions. The reactions worked best in aprotic solvents including MeCN, DMF, DMSO and CH\textsubscript{2}Cl\textsubscript{2}, but not in ethereal or alcoholic media, and neat FA/TEA (slow reaction rate). The structure of the Ar group and the substitution pattern of η\textsuperscript{6}-arene ligand on the Ru complex, were fine-tuned depending on the substrates used. The ATH reduction of imine 109a was most successful, using (S, S)-38 (S/C = 200) in FA/TEA (5:2) and acetonitrile at 28 °C, giving salsolidine 109a’ (R) in 95% ee and >99% yield in 3 hrs. Various other cyclic imine derivatives 109b-109e were reduced, giving excellent conversions (up to >99%) and enantioselectivities (up to 95%). This method was further applied to the synthesis of indoles 110a-110b, giving good yields (up to 89%) and excellent enantioselectivities (up to 97%), and the reduction of acyclic imines 111-113, which gave good conversions (up to 90%) but were less stereoselective (ee’s of up to 89%) (Scheme 35, Table 12).\textsuperscript{22}
Scheme 35. ATH reduction of 109a-109e and 110-113, using catalyst 38, 108a-108c.

<table>
<thead>
<tr>
<th>Imine</th>
<th>Catalyst</th>
<th>S/C</th>
<th>Solvent</th>
<th>Time (hrs)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>109a</td>
<td>(S,S)-38</td>
<td>200</td>
<td>CH₃CN</td>
<td>3</td>
<td>&gt;99</td>
<td>95</td>
<td>R</td>
</tr>
<tr>
<td>109a</td>
<td>(S,S)-38</td>
<td>1000</td>
<td>CH₃CN</td>
<td>12</td>
<td>97</td>
<td>94</td>
<td>R</td>
</tr>
<tr>
<td>109b</td>
<td>(R,R)-108a</td>
<td>200</td>
<td>(CH₃)₂NCHO</td>
<td>7</td>
<td>90</td>
<td>95</td>
<td>S</td>
</tr>
<tr>
<td>109c</td>
<td>(R,R)-108a</td>
<td>200</td>
<td>CH₂Cl₂</td>
<td>12</td>
<td>99</td>
<td>92</td>
<td>S</td>
</tr>
<tr>
<td>109d</td>
<td>(S,S)-108c</td>
<td>200</td>
<td>CH₂Cl₂</td>
<td>8</td>
<td>99</td>
<td>84</td>
<td>R</td>
</tr>
<tr>
<td>109e</td>
<td>(R,R)-108c</td>
<td>100</td>
<td>CH₂Cl₂</td>
<td>12</td>
<td>&gt;99</td>
<td>84</td>
<td>S</td>
</tr>
<tr>
<td>110a</td>
<td>(S,S)-38</td>
<td>200</td>
<td>(CH₃)₂NCHO</td>
<td>5</td>
<td>86</td>
<td>97</td>
<td>R</td>
</tr>
<tr>
<td>110a</td>
<td>(S,S)-38</td>
<td>1000</td>
<td>(CH₃)₂NCHO</td>
<td>12</td>
<td>89</td>
<td>93</td>
<td>R</td>
</tr>
<tr>
<td>110b</td>
<td>(S,S)-38</td>
<td>200</td>
<td>(CH₃)₂NCHO</td>
<td>5</td>
<td>83</td>
<td>96</td>
<td>R</td>
</tr>
<tr>
<td>111</td>
<td>(S,S)-108b</td>
<td>200</td>
<td>CH₂Cl₂</td>
<td>36</td>
<td>72</td>
<td>77</td>
<td>S</td>
</tr>
<tr>
<td>112</td>
<td>(S,S)-108c</td>
<td>100</td>
<td>CH₂Cl₂</td>
<td>6</td>
<td>90</td>
<td>89</td>
<td>S</td>
</tr>
<tr>
<td>113a</td>
<td>(S,S)-108c</td>
<td>100</td>
<td>CH₃CN</td>
<td>12</td>
<td>82</td>
<td>85</td>
<td>S</td>
</tr>
<tr>
<td>113b</td>
<td>(S,S)-108c</td>
<td>100</td>
<td>CH₃CN</td>
<td>5</td>
<td>84</td>
<td>88</td>
<td>S</td>
</tr>
</tbody>
</table>
Table 12. ATH reduction of 109a-109e and 110-113, using catalyst 38, 108a-108c.

### 1.4.6.5 Quinolines.

Asymmetric hydrogenation of quinolines, giving 1, 2, 3, 4-tetrahydroquinolines has been described earlier in Section 1.3.3.6, along with its synthetic importance. The first example of a metal-free transfer hydrogenation reduction of quinolines was reported in 2006. Rueping used his expertise and extended his research from the already developed enantioselective Brønsted acid catalysed hydrogenation of imines, in to the enantioselective reduction of quinolines.

Using Brønsted acid 114, 2-phenylquinoline 115a as a test substrate for reduction and dihyropyridine 116 as the source of hydride, the structure of catalyst 114 was studied (Scheme 36, Table 13).

![Scheme 36. Reduction of 2-phenylquinoline, using 114 and 116.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Ar</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>114a</td>
<td>Phenyl</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>114b</td>
<td>4-biphenyl</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>114c</td>
<td>1-naphthyl</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>114d</td>
<td>2-naphthyl</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>114e</td>
<td>3,5-(CF₃)-C₆H₃</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td>114f</td>
<td>9-phenanthryl</td>
<td>97</td>
</tr>
</tbody>
</table>
Table 13. Studying acid 114 for the cascade transfer hydrogenation of 2-phenylquinoline. Reaction was carried out in benzene at 60 °C, with 115a, 116 (2.4 equiv) and 114 (5 mol %).

The results showed that sterically congested Brønsted acids were best catalysts for hydride transfer and gave good to excellent enantioselectivities, with the highest selectivity being obtained using 114f, providing 2-phenyltetrahydroquinoline 115a’ in 97% ee. Investigation on various solvents was also carried out with nonpolar solvents (chlorinated: CH₂Cl₂, CHCl₃, CCl₄ and aromatic: benzene, toluene) proving to be crucial for high asymmetric induction. Benzene emerged to be the best solvent in this system giving the highest enantioselectivity.²³a

Scheme 37. Brønsted acid catalysed cascade transfer hydrogenation of 2-substituted quinolines under optimized conditions.

<table>
<thead>
<tr>
<th>Quinoline</th>
<th>R</th>
<th>Time (hrs)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>115a</td>
<td>phenyl</td>
<td>12</td>
<td>92</td>
<td>97</td>
</tr>
<tr>
<td>115b</td>
<td>2-fluorophenyl</td>
<td>30</td>
<td>93</td>
<td>98</td>
</tr>
<tr>
<td>115c</td>
<td>2-methylphenyl</td>
<td>48</td>
<td>54</td>
<td>91</td>
</tr>
<tr>
<td>115d</td>
<td>2,4-dimethylphenyl</td>
<td>60</td>
<td>65</td>
<td>97</td>
</tr>
<tr>
<td>115e</td>
<td>2-naphthyl</td>
<td>12</td>
<td>93</td>
<td>&gt;99</td>
</tr>
<tr>
<td>115f</td>
<td>3-bromophenyl</td>
<td>18</td>
<td>92</td>
<td>98</td>
</tr>
<tr>
<td>115g</td>
<td>4-(CF₃)-C₆H₃</td>
<td>30</td>
<td>91</td>
<td>&gt;99</td>
</tr>
<tr>
<td>115h</td>
<td>1,1’-biphenyl-4-yl</td>
<td>12</td>
<td>91</td>
<td>&gt;99</td>
</tr>
<tr>
<td>115i</td>
<td>4-methoxyphenyl</td>
<td>12</td>
<td>90</td>
<td>98</td>
</tr>
<tr>
<td>115j</td>
<td>2-furyl</td>
<td>12</td>
<td>93</td>
<td>91</td>
</tr>
<tr>
<td>115k</td>
<td>chloromethyl</td>
<td>12</td>
<td>91</td>
<td>88</td>
</tr>
<tr>
<td>115l</td>
<td>n-butyl</td>
<td>12</td>
<td>91</td>
<td>87</td>
</tr>
</tbody>
</table>
Table 14. Transfer hydrogenation reduction of 2-substituted quinolines. Reaction was carried out in benzene at 60 °C with 115a-m and 117a-c, 116 (2.4 equiv) and catalyst 114f (2 mol%).

<table>
<thead>
<tr>
<th></th>
<th>Substituent</th>
<th>115m</th>
<th>117a</th>
<th>117b</th>
<th>117c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n-pentyl</td>
<td>12</td>
<td>88</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2-phenylethyl</td>
<td>12</td>
<td>90</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OMe</td>
<td></td>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>OMe</td>
<td></td>
<td></td>
<td></td>
<td>95</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90</td>
</tr>
</tbody>
</table>

Bronsted acid catalysed cascade transfer hydrogenation reduction using the optimized conditions were carried out on a series of 2-substituted quinolines (Scheme 37, Table 14). The results showed that high enantioselectivites (up to >99%) and good yields (up to 95%) of several tetrahydroquinolines, with aromatic, heteroaromatic residues as well as aliphatic substituents were obtained. The system was also compatible with halogenated aromatic and aliphatic residues.23a

The proposed mechanism for this process: initiation with Brønsted acid catalyst 114 protonating quinoline 115, forming the active iminium ion A. Subsequent transfer of hydride from 116, gives the enamine 118 and pyridinium salt B. Brønsted acid 114 is regenerated after proton transfer from B, forming Hantzsch pyridine 119. The desired tetrahydroquinoline is formed 115', after the reaction of enamine 118 in a second cycle with Brønsted acid 114, forming iminium C which is subjected to hydride transfer from dihydropyridine 116 (Scheme 38).23a
Scheme 38. Proposed mechanism for the Brønsted acid catalysed cascade transfer hydrogenation.
The use of Hantzsch esters was further applied by Zhou in his system. In 2007, Zhou reported the first metal catalysed asymmetric transfer hydrogenation of quinolines 120a-f, 115a, 115l-m, 117a-c, using [Ir(COD)Cl]$_2$/((S)-SegPhos 35/I$_2$ and a Hantzsch ester 121 (Scheme 39).

![Scheme 39. Ir-catalysed asymmetric transfer hydrogenation of quinolines.](image)

The optimized conditions for this system were obtained from studying the effects of solvents, different ligands, and different sizes of Hantzsch esters. In the study of solvent effects, solvents including THF, DME, toluene, DCM and dioxane were used. The two solvents that gave great results were toluene and dioxane, with the highest reactivity given by dioxane and highest enantioselectivity by toluene. Some commercially available ligands (Figure 15) were screened including (S)-MeO-BiPhep 31, (S)-SegPhos 35, (S)-SynPhos 122, (R, R)-Me-DuPhos 123, (R)-Cl-MeOBiPhep 124 and (S)-BINAP 125, with the best result given by (S)-SegPhos 35.
Introduction

Figure 15. Commercially available chiral ligands screened.

In the investigation of different Hantzsch ester sizes, dimethyl Hantzsch 121 ester out of diethyl-, di-‘propyl- and di-‘butyl gave the highest rate and enantioselectivity. The ATH reduction of 2-methylquinoline 120a was then carried out using [Ir(CODCl)]2 / (S)-SegPhos 35, dimethyl Hantzsch ester 121, 2/1 toluene/dioxane in presence of iodine at rt (Scheme 40), and the best overall result was obtained, giving 2-methyl-1,2,3,4-tetrahydroquinoline 120a’ in 86% yield and 87% ee (Entry 1, Table 15). Once the optimal conditions were established, various quinolines were reduced (Entry 2-12, Table 15). 23d

Scheme 40. Ir-catalysed asymmetric transfer hydrogenation of quinolines, using optimal conditions.
**Table 15.** Ir-catalysed asymmetric transfer hydrogenation of quinolines, using optimal conditions. Reaction was carried out at rt using quinoline (0.25 mmol), [Ir(COD)Cl]_2 (1 mol%), ligand (2.2 mol%), I\(_2\) (5 mol%), solvent (2.5 cm\(^3\)) and Hantzsch ester (2.0 equiv)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R’/R</th>
<th>Yield (%)</th>
<th>Time (hrs)</th>
<th>ee (%)</th>
<th>Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H/Me</td>
<td>86 (120a)</td>
<td>42</td>
<td>87</td>
<td>(S)</td>
</tr>
<tr>
<td>2</td>
<td>H/Et</td>
<td>92 (120b)</td>
<td>42</td>
<td>87</td>
<td>(S)</td>
</tr>
<tr>
<td>3</td>
<td>H/(n)-Bu</td>
<td>98 (115i)</td>
<td>42</td>
<td>81</td>
<td>(S)</td>
</tr>
<tr>
<td>4</td>
<td>H/(n)-Pentyl</td>
<td>94 (115m)</td>
<td>45</td>
<td>68</td>
<td>(S)</td>
</tr>
<tr>
<td>5</td>
<td>F/Me</td>
<td>90 (120c)</td>
<td>45</td>
<td>86</td>
<td>(S)</td>
</tr>
<tr>
<td>6</td>
<td>Me/Me</td>
<td>82 (120d)</td>
<td>56</td>
<td>86</td>
<td>(S)</td>
</tr>
<tr>
<td>7</td>
<td>MeO/Me</td>
<td>43 (120e)</td>
<td>74</td>
<td>81</td>
<td>(S)</td>
</tr>
<tr>
<td>8</td>
<td>H/Phenethyl</td>
<td>88 (117a)</td>
<td>45</td>
<td>87</td>
<td>(S)</td>
</tr>
<tr>
<td>9</td>
<td>H/3,4-Methylenedioxyphenethyl</td>
<td>87 (117b)</td>
<td>46</td>
<td>87</td>
<td>(S)</td>
</tr>
<tr>
<td>10</td>
<td>H/3,4-(MeO)(_2)C(_6)H(_5)(CH(_2))(_2)-</td>
<td>92 (117c)</td>
<td>46</td>
<td>88</td>
<td>(S)</td>
</tr>
<tr>
<td>11</td>
<td>H/Ph(_2)C(OH)CH(_2)-</td>
<td>76 (120f)</td>
<td>79</td>
<td>78</td>
<td>(R)</td>
</tr>
<tr>
<td>12</td>
<td>H/Ph</td>
<td>90 (115a)</td>
<td>69</td>
<td>10</td>
<td>(R)</td>
</tr>
</tbody>
</table>

The results showed that for 2-alkyl substituted quinolines, good yields (up to 98% yield), and enantioselectivities (up to 87%) were obtained, with the enantioselectivity decreasing when the length of the side chain is increased (Entry 1-4, Table 15). The reaction time had increased when having substituents at the 6-position (Entry 5-7, Table 15), with low conversion also being obtained if the group at the 6-position is electron donating. 2-(2-Arylethyl)-substituted quinolines (Entry 8-11, Table 15) were reduced in good yields (up to 92% yield) and enantioselectivities (up to 88% ee), and the system can also withstand substrates that have a hydroxyl group present (Entry 11, Table 15). Good yield was obtained with 2-aryl substituted quinoline, but the enantioselectivity was poor (10% ee) (Entry 12, Table 15).

ATH reduction using Hantzsch esters as the source of hydrogen have given excellent results with both metal-free and Ir/diphosphine-catalysed methods. Xiao et al. in 2010...
reported the first ATH of quinolines in aqueous solution using a metal catalyst (Scheme 41),\textsuperscript{23e} with the reaction being carried out in air, giving excellent enantioselectivities for a wide range of substrates. The use of water does not only offer new reactivity and selectivity patterns but also advantageous economic and ecological gains.\textsuperscript{23e}

![Scheme 41. ATH of quinolines in water, and showing the possible reaction intermediate.](image)

Previously, ATH reduction of ketones and imines was studied in neat water,\textsuperscript{23e} using TsDPEN 81 with Ir \([(\text{Cp}\text{*}\text{IrCl}_2)_2]\), Rh \([(\text{Cp}\text{*}\text{RhCl}_2)_2]\) and Ru \[{\text{RuCl}_2(p-cymene)}_2]\) metals, from which Rh-TsDPEN catalyst showed highest reactivity and selectivity.\textsuperscript{23f}

Due to this, initial studies for the reduction of 2-methylquinoline 120a were carried out using presynthesized Rh-TsDPEN catalyst\textsuperscript{23g} with HCOONa in water. This particular method gave a very poor conversion but excellent enantioselectivity. Xiao and co-workers had previously studied the ATH of ketones in water, and had established that the rate of reaction was dependant on the pH of the solution.\textsuperscript{23f,23h} Taking this into account, the pH effect of solution for the reduction of quinolines was examined, by monitoring the conversion at initial pH values of solution, from 3 up to 8 (via altering HCOOH/HCOONa ratio). The results showed that the highest conversion was obtained at initial pH of 5, which gets very close to the pK\textsubscript{a} of protonated quinoline 120a\textsuperscript{**} (5.4), supporting the ionic mechanism pathway that has been previously suggested for the
reduction of quinolines in its protonated form. \(^{9g, 17j, 23a, 23i}\) This also explains why such a low conversion was obtained in the earlier studies as the pH of the solution at the start of the reaction was 8 (Scheme 41).

\[
\begin{align*}
\text{HCOOH} & \rightleftharpoons \text{HCOO}^- + \text{H}^+ \quad (1) \\
120a'' & \rightleftharpoons 120a + \text{H}^+ \quad (2)
\end{align*}
\]

Scheme 42. The pH effect can be expressed with the two opposing equilibria shown: (1) and (2).

The concentration of 120a” decreases at high pH values (pH > 5.4), and at low pH values (pH < 3.6) the concentration of formate becomes low. So having a pH between 3.6 and 5.4 would be ideal for obtaining high reaction rates as it would provide a high concentration of both reactants (Scheme 42).\(^{23e}\)

The use of a buffered solution had resolved this issue, as it was able to maintain the pH of solution and avoid pH fluctuation. The buffer capacity of HCOOH/HCOONa pair with a \(pK_a\) value of 3.6 was not sufficient, but the use of HOAc/NaOAc, having maximum buffer capacity of pH 5 proved to be ideal in this ATH system. ATH of 120a in 2 M HOAc/NaOAc buffer solution gave the resulting 1,2,3,4-tetrahydroquinoline 120a’ with 95% conversion and 96% ee in 3 hrs.\(^{23e}\)

In the attempt to further improve the ATH efficiency, various metal precursors (Entry 1-3, Table 16) and ligands (Entry 4-12, Table 16) were tested for the reduction of 120a using the optimized conditions (Scheme 43). The metal precursor [(Cp*RhCl\(_2\))]\(_2\), in comparison to the isoelectronic [(RuCl\(_2\)(p-cymene))]\(_2\) and [(Cp*IrCl\(_2\))] (Entry 1-3,
Table 16, gave the best result with TsDPEN 81 as the ligand. Using [(Cp*RhCl₂)₂], various ligands were tested (Entry 4-12, Table 16) from which 122d gave the best reactivity and selectivity.²³e

Scheme 43. Reduction of 120a using different metal precursors and various ligands.

<table>
<thead>
<tr>
<th>Entry</th>
<th>M</th>
<th>Ligand</th>
<th>R</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[{RuCl₂(p-cymene)}₂]</td>
<td>81</td>
<td><img src="120a" alt="Image" /></td>
<td>32</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>[(Cp*IrCl₂)₂]</td>
<td>81</td>
<td><img src="120a" alt="Image" /></td>
<td>88</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>[(Cp*RhCl₂)₂]</td>
<td>81</td>
<td><img src="120a" alt="Image" /></td>
<td>95</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>[(Cp*RhCl₂)₂]</td>
<td>81</td>
<td><img src="120a" alt="Image" /></td>
<td>49</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>[(Cp*RhCl₂)₂]</td>
<td>122a</td>
<td><img src="120a" alt="Image" /></td>
<td>13</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>[(Cp*RhCl₂)₂]</td>
<td>122b</td>
<td><img src="120a" alt="Image" /></td>
<td>12</td>
<td>74</td>
</tr>
<tr>
<td>7</td>
<td>[(Cp*RhCl₂)₂]</td>
<td>122c</td>
<td><img src="120a" alt="Image" /></td>
<td>34</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>[(Cp*RhCl₂)₂]</td>
<td>122d</td>
<td><img src="120a" alt="Image" /></td>
<td>55</td>
<td>97</td>
</tr>
<tr>
<td>9</td>
<td>[(Cp*RhCl₂)₂]</td>
<td>122e</td>
<td><img src="120a" alt="Image" /></td>
<td>48</td>
<td>96</td>
</tr>
<tr>
<td>10</td>
<td>[(Cp*RhCl₂)₂]</td>
<td>122f</td>
<td><img src="120a" alt="Image" /></td>
<td>31</td>
<td>94</td>
</tr>
</tbody>
</table>
Table 16. Reduction of 120a using different metal precursors and various ligands.

<table>
<thead>
<tr>
<th>Entry</th>
<th>[(Cp*RhCl₂)₂]</th>
<th>122g</th>
<th>122h</th>
<th>CH₃</th>
<th>27</th>
<th>94</th>
</tr>
</thead>
</table>

Reaction was carried out at 40 °C, using quinoline (0.5 mmol), metal precursor (2.5 µmol), ligand (6 µmol), HCOONa (5 mmol) and 2 M HOAc/NaOAc buffer solution (5 cm³). Reaction time was 12 hrs for entries 1-3 and 0.5 hrs for entries 4-12.

As a result (Entry 8, Table 16), complex 123 (Scheme 44) was prepared using ligand 122d and [(Cp*RhCl₂)₂], which was selected as the catalyst for the ATH reduction of a series of quinolines (Entry 1-25, Table 17) in an aqueous formate solution buffered to pH 5 with HOAc/NaOAc.²³e

Excellent enantioselectivities and yields were observed for a range of substrates, with the alkyl chain length in the 2-position, and substituents in 6- or 7- position having little effect on the enantioselectivity. The yield was however lowered with having electron-rich substituents at the 6-position. 2-Phenyl-substituted quinolines were better reduced at a lowered pH value of 4, with the catalyst formed when ligand 122f was combined with [(Cp*RhCl₂)₂].²³e

Scheme 44. ATH reduction of a range of quinolines using catalyst 123.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>120a'</td>
<td><img src="image1" alt="Image" /></td>
<td>96</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>120b'</td>
<td><img src="image2" alt="Image" /></td>
<td>95</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>124a'</td>
<td><img src="image3" alt="Image" /></td>
<td>93</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>115l'</td>
<td><img src="image4" alt="Image" /></td>
<td>94</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>115m'</td>
<td><img src="image5" alt="Image" /></td>
<td>95</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td>124b'</td>
<td><img src="image6" alt="Image" /></td>
<td>92</td>
<td>97</td>
</tr>
<tr>
<td>7</td>
<td>120e'</td>
<td><img src="image7" alt="Image" /></td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>8</td>
<td>124c'</td>
<td><img src="image8" alt="Image" /></td>
<td>95</td>
<td>96</td>
</tr>
<tr>
<td>9</td>
<td>124d'</td>
<td><img src="image9" alt="Image" /></td>
<td>96</td>
<td>95</td>
</tr>
<tr>
<td>10</td>
<td>124e'</td>
<td><img src="image10" alt="Image" /></td>
<td>97</td>
<td>96</td>
</tr>
<tr>
<td>11</td>
<td>120f'</td>
<td><img src="image11" alt="Image" /></td>
<td>91</td>
<td>96</td>
</tr>
<tr>
<td>12</td>
<td>120g'</td>
<td><img src="image12" alt="Image" /></td>
<td>90</td>
<td>98</td>
</tr>
<tr>
<td>13</td>
<td>124f'</td>
<td><img src="image13" alt="Image" /></td>
<td>86</td>
<td>91</td>
</tr>
<tr>
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<td>124g'</td>
<td><img src="image14" alt="Image" /></td>
<td>88</td>
<td>98</td>
</tr>
<tr>
<td>15</td>
<td>124h'</td>
<td><img src="image15" alt="Image" /></td>
<td>87</td>
<td>96</td>
</tr>
</tbody>
</table>
Table 17. ATH reduction of a range of quinolines using catalyst 123. Reaction was carried out at 40 °C, using quinoline (0.5 mmol), 123 (5 µmol), HCOONa (5 mmol) and buffer solution (5 cm$^3$). Reaction time was between 6-24 hrs. [a] 2 mol% of 123 used. [b] ligand 122f used at pH 4 in 2 M HOAc/NaOAc buffer solution (5 cm$^3$) with EtOAc (0.3 cm$^3$). [c] diastereoselectivity in brackets.
1.4.6.6 Synthesis of Biologically Active Compounds.

1.4.6.6.1 (S)-Fluoxetine.

(S)-Fluoxetine 126 is an anti-depressant used for the treatment of clinical depression. A practical method was reported by Ikariya using ATH for the synthesis of (S)-fluoxetine 126. ATH reduction of 2-cyanoacetophenone 125 using catalyst (S,S)-38 in formic acid/triethylamine at 30 °C, gave the key intermediate 125' for the formation of (S)-fluoxetine 126 in 100% yield and 98% ee in 24 hrs (Scheme 45).\textsuperscript{24a}

![Scheme 45. ATH reduction of 125 in FA/TEA (3.1:2.6), using catalyst (S,S)-38 (S/C = 1000) gave the key product 125', for the synthesis of (S)-fluoxetine 126.]

1.4.6.6.2 (S)-MA-20565.

(S)-MA-20565 128 is a wide-spectrum agricultural fungicide, and the formation of the key intermediate step can be carried out using ATH as reported by Tanaka et al. The reduction of 1-(3-(trifluoromethyl)phenyl)ethanone 127, using (S,S)-38 (S/C = 5000) in FA/TEA (5:2) azeotrope at 50 °C, gave the key intermediate 127' in 96% conv., and 91% ee after 30 hrs (Scheme 46).\textsuperscript{24b}
Aprepitant 130 is an antimetic compound that belongs to a class of drugs called substance P antagonists. It mediates its effect by blocking the neurokinin 1 (NK$_1$) receptor, and is used for the prevention of acute and delayed chemotherapy-induced nausea and vomiting. The key intermediate for this drug 129’ can be obtained by ATH. The reduction of 1-(3,5-bis(trifluoromethyl)phenyl)ethanone 129, using Ru(II) complex of (1$S$,2$R$)-cis-aminoindanol 75 combined with [Ru($p$-cymene)Cl$_2$]$_2$ (S/C = 200) and KOH in IPA at rt, gave the key intermediate 129’ of Aprepitant 130 in 98% conv., and 91% ee (R) after 4 hrs. The enantioselectivity of the product can be further enhanced by isolation of the alcohol 129’ as its DABCO complex 129’’, giving >99% ee (Scheme 47).
Scheme 47. ATH of \textit{129} using Ru(II) complex of \textit{75}, giving the key intermediate \textit{129'} followed by \textit{129''} prior to isolation as a DABCO complex.

ATH has also been applied for the synthesis of an intermediate of L-699,392 (LTD$_4$ antagonist)$^{17i}$ and can also be used to reduce sulphur containing ketones in order to prepare the intermediate for MK-0417.$^{17i}$

1.4.7 Asymmetric transfer hydrogenation using ruthenium(II) “tethered” catalysts.

In recent years, successful structural modifications have been carried out on Noyori’s catalysts, based on Ru(II) complexes of amino alcohols and monotosylated diamines such as complex \textit{99} and \textit{38} respectively. A new class of “tethered” Ru(II) catalysts was developed by Wills and co-workers in 2004, where the chiral amino alcohol or monosulfonylated diamine is covalently bound to the $\eta^6$-arene group through a hydrocarbon bridge. The tether link allows “locking” of the otherwise freely rotating aryl group, and permits control over the spatial positions of the substituents on this ring. Furthermore, the stability of the catalyst is increased due to attachment of the ligand to the metal at three points, reducing ligand dissociation from the metal centre.
The synthesis of “tethered” amino alcohol catalyst 135 has been outlined in Scheme 48. The formation of chloro-bridged $\eta^6$-arene ruthenium(II) complex 134, from the reaction of 133.HCl with RuCl$_3$ under reflux in ethanol was the major step towards the formation of 135. The protonation of amine group in 133 is essential to form dimer 134, as the attempted reaction with free amine resulted in formation of complex product mixtures, possibly due to the chelation of Ru(III) by the free amine outpacing arene oxidation.$^{25a}$

Scheme 48. Synthetic route for the formation of dimer 134, forming 135 in situ under the ATH reduction conditions.

Although Wills and co-workers were not able to isolate 135 from the treatment of 134 with base, 135 however did form in situ during reduction of acetophenone 49a by dimer 134 in IPA with KOH, giving the resulting alcohol in 96% yield and 66% ee after 1 hr (Scheme 49). The yield and ee obtained in this reaction is an improvement to what has
been obtained using analogous non-tethered catalyst derived from the combination of 
(1R,2S)-ephedrine and [Ru(benzene)Cl₂]₂ (86% yield, 58% ee). Dimer 134 failed to 
react in formic acid/triethylamine (5:2) azeotrope mixture, like other amino alcohol 
based catalysts previously mentioned (Section 1.4.3.1).²⁵ᵃ

![Scheme 49. ATH reduction of 49a using dimer 134, and its non-tethered analogue.](image)

As well as amino alcohol, monosulfonylated diamine “tethered” catalysts such as 140 
can also be synthesized. But unlike 135, monosulfonylated diamine catalyst 140 can be 
isolated from the reaction of dimer 139, with Et₃N, in refluxing IPA for 1 hr. The X-ray 
crystal structure of 140 confirmed the presence of the “tether” link, and showed that the 
ligand coordinates to the metal centre in a similar manner to the non-tethered analogue 
(Complex formed from the combination of [Ru(benzene)Cl₂]₂ with TsDPEN) (Scheme 
50).²⁵ᵃ
a) CH₃CO₂H (36-40% in acetic acid) (3 eq), DCM, rt, 2 hrs; b) Na, NH₃, EtOH, -78 °C, 3 hrs; c) SOCl₂ (20 eq), DMF (2 eq), DCM, 35 °C, 16 hrs; d) Et₃N (2 eq), DCM, rt, o/n; e) HCl, Et₂O, rt; f) RuCl₃ hydrate, EtOH, reflux, 21 hrs, 66% (two steps); g) in situ during reaction or Et₃N, iPrOH, reflux, 1 hr (preparation of 140).

Scheme 50. Synthetic route for the formation of 140, which can also be formed in situ using dimer 139 under ATH reaction conditions

The reduction of 49a was successfully carried out using 140 in formic acid/triethylamine (5:2) azeotrope, giving 49a' in >99% yield and 96% ee after 18 hrs. The result obtained was comparable to that obtained using the non-tethered analogue, with the same configuration of product formed when the same enantiomer of ligand is used. This shows that the mode of action of the catalyst is unaffected with the presence of the “tether”.²⁵a

Ruthenium dimer 139 can also be used directly for ATH reductions, as it forms 140 in situ. The formation of monomer from dimer involves neutralisation of the salt, splitting of the dimer and wrapping of the ligand around the metal. Reduction of 49a with dimer
139 in formic acid/triethylamine (5:2) azeotrope, gave 49a’ in >99% yield and 96% ee after 21 hrs (Scheme 51), showing same level of reactivity and enantioselectivity in comparison to 140, but with a slight increase in reaction time. This induction period is the time required for the conversion of dimer to the monomer. The increased stability given by the “three-point” ligand attachment to the metal was proved by the studies carried out to test the longetivity of 140. Acetophenone 49a in addition to formic acid/triethylamine (5:2) azeotrope mixture were added consecutively after completion of each reduction, and after 176 hrs, 3 batches of acetophenone were successfully reduced, without loss of enantioselectivity.\textsuperscript{25a}

![Scheme 51. ATH reduction of 49a, using dimer 139 and monomer 140.](image)

The asymmetric reduction of alkyl/alkyl substituted ketones is known to be a challenging transformation, as the important interaction between the aryl ring of the catalyst and that of the substrate is absent (Section 1.4.5). Reduction of cyclohexylmethyl ketone 141 was carried out to determine whether the “tethering” might have an effect on the enantioselectivity of this process. Using catalyst 140, the reduction of 141 was successfully achieved in 84% yield after 63 hrs, but the ee obtained was very low (19%). An improved result was obtained using catalyst 135, giving the reduced product in 78% yield after 2 hrs, but with an improved ee of 69%. The reduction of 141 using the equivalent non-tethered complex \[\text{[((1R,2S)-ephedrine)Ru(p-cymene)Cl]}\] under the same conditions gave product in 27% yield and 6% ee. The tethering group clearly has a dramatic influence on the selectivity of the
Introduction

reduction process. To probe this effect catalysts 142-143 were synthesized. The ephedrine unit in 143 was replaced with a pseudoephedrine unit, giving 144. Catalyst 144 was worthy of investigation as the non-tethered analogue of 144 reported by Noyori ([(1S,2S)-pseudoephedrine]Ru(C₆Me₆)Cl), reduced 141, giving 141’ in 93% yield and 75% ee (S) (Scheme 52).²⁵b

Scheme 52. ATH reduction of 141, using 140, 135 and non-tethered analogue of 135.

The reduction of 141 was effective using catalyst 142 and 143, but 135 was better overall. Catalyst 144 however did give the highest ee of 70%, but the conversion was poor (5%) (Scheme 53). The reduction of 49a was also carried out using catalyst 142-144, with 144 giving the best result (49a’ in 99% yield and 89% ee).²⁵b
The Wills group have previously reported the importance of trans-1,2-diphenyl substitution pattern of TsDPEN 81 on the rate and enantioselectivity of the Ru(II) catalysed ATH reactions (Section 1.4.5). Such modifications of complex 140 were examined by synthesizing complex 145-147 (Scheme 54).\textsuperscript{25b}

Scheme 54. ATH reduction of 49a, using complex “tethered” complex 145-147 (S/C = 200).
Complexes 145-147 shown in Scheme 54 were all effective for the reduction of 49a, giving 49a’ in good conversions, but poor ee’s, and long reaction times.\textsuperscript{25b}

Restriction of conformations available to the arene ring serves to be one of the major advantages of the “tethering” complex, as this allows selective functionalization to be inserted, with predictable spatial arrangement. Sterically hindered groups can be placed at the para position of the metal arene ring (Figure 16), changing the basis of enantiocontrol from electronic to steric in order to target challenging substrates such as 141. Derivatives of the two “tethering” complex 135 and 140, containing an aminoalcohol and a sulfonylated diamine respectively were prepared 148-155. The conventional method approach to synthesize “tethered” catalyst has been to use Birch reduction to prepare the 1,4-cyclohexadiene ring, but for the synthesis of 148-155, an alternative approach based on \([4 + 2]\) cycloaddition strategy between a diene and a functionalised alkyne was employed. (Scheme 55).\textsuperscript{25c}

![Figure 16. Proposed transition state for the ATH of 141, using catalyst 148-155, with a sterically hindered group in the para position.](image)

Catalysts 148-151 and 152-155 were tested for the ATH reduction of 49a and 141. The reactivity and enantioselectivity obtained for 148-155 were much lower than its parent complexes, possibly due to the increased steric hinderance.\textsuperscript{25c}
Scheme 55. ATH reduction of \(49a\) and \(141\), using catalyst 148-155 (S/C = 200).

Recently Wills and co-workers had discovered that the “tethered” catalyst based on monosulfonylated diamine, can be significantly improved by attaching the linking group from the “basic” amine rather than the sulfonyl group (as in 140). The preparation of complex 160, referred to as “reverse-tethered” has been shown in scheme 56.\(^{25d}\)
-a) 4 Å mol. sieves, DCM, o/n then LiAlH₄, THF, 2 hrs. 47% (over 2 steps); b) HCl, Et₂O then RuCl₃·H₂O, EtOH, reflux, o/n, 89% (over 2 steps); c) Et₃N, IPA or formed in situ under reduction conditions.

Scheme 56. Synthesis of the “reverse-tethered” catalyst 160.

Catalyst 160 proved to be highly active as the reduction of acetophenone 49a was achieved in just 3 hrs, at 40 °C (S/C= 200), giving 49a’ in 96% ee (Scheme 57). The catalyst was also active and equally enantioselective at a loading as low as 0.01 mol%, which is unheard of for this class of ATH catalyst.²⁵d

![Scheme 57. ATH reduction of 49a, using dimer 159 forming 160 in situ (S/C = 200).](image)

¹H NMR studies for the reduction of acetophenone 49a was carried out at 40 °C using monomer 160, dimer 159 and untethered catalyst 38 (S/C = 200) in 5:2 formic acid/triethylamine. A mixture of the catalyst in FA/TEA was stirred for 20 mins, followed by the addition of the mixture to an NMR tube along with a small quantity of d₆-benzene and the required quantity acetophenone 49a. The results showed that the reactivity of 160 and 159 is far greater than untethered catalyst 38, with the complete reduction of acetophenone 49a using untethered catalyst 38 being achieved after 18 hrs, 159 after 3 hrs and 160 in 110 minutes. A close examination of the reaction using dimer 159 indicates an initial lag at the start of the reaction, due to the incomplete in situ conversion of the dimeric species to the monomer. Repeating the reaction with the dimer 159 being stirred in FA/TEA for 3.5 hrs prior to the addition of ketone, gave complete conversion of acetophenone in 110 minutes, identical to monomer 160. The
longevity of 160 was also investigated, by consecutive addition of acetophenone 49a and FA/TEA after completion of each reaction. After seven cycles of acetophenone 49a addition, the catalyst remained consistently active throughout with no loss of ee.\textsuperscript{25e}

Investigation on the reduction of dialkyl ketone was next carried out using catalyst 160. Cyclohexylmethyl ketone 141 was fully reduced using dimer 159, giving 141' in 69% ee at 28 °C (S/C = 200) in 10 hrs (Scheme 58).\textsuperscript{25e} In comparison to 140, which gave 141' in 84% conversion and 19% ee after 63 hrs at 28 °C.\textsuperscript{25b}

Scheme 58. ATH reduction of 141, using dimer 159 forming 160 in situ (S/C = 200).

The “tethering” at the basic amine has tremendously enhanced the enantioselectivity of dialkyl ketones. The configuration obtained for the reduction of cyclohexylmethyl ketone was opposite to that of acetophenone reduction, which indicates that the large cyclohexyl substituent is directed away from the arene ring of the catalyst. It was possible that the “tether” lies in the region occupied by the group on the ketone, repelling the larger alkyl group away from the “tether” (Figure 17, 160-TS). In order to further investigate this possibility, complex 161 with a dimethyl-substituted “tether” was prepared (Figure 17, 161), in a similar way to 160. As the introduction of the dimethyl-substituent would further increase the steric repulsion (Figure 17, 161-TS), and therefore increase the enantioselectivity.\textsuperscript{25e}
Figure 17. Possible reduction transition state of alkyl/alkyl ketones using 160, and the predicted transition state of complex 161.

Introducing dimethyl substitution on the “tethered” monotosylated diamine gave a positive result for the reduction of 141, as a 5% improvement in ee over 160 to 74% ee was obtained under identical conditions. The rate of reduction was however diminished giving only 48% conversion after 2 days (Scheme 59).25e

Scheme 59. ATH reduction of 141, using monomer 161 (S/C = 200).

In order to increase the activity and versatility of catalyst 160, the effects of “tether” length and η₆-arene ring substitution pattern was examined. Complexes 164-168 were identified as a series of systematically modified catalysts worthy of investigation. These complexes were synthesized in good yields via the route shown in Scheme 60.20a
Precursors **162a-e** were obtained after the Birch reduction of its corresponding arenes. The dimers **163a-e** prepared from **162a-e**, can be used directly in ATH reductions, as it forms monomer **164-168 in situ**, but for accurate comparison and analysis monomer **164-168** were isolated. With the exception of **166**, which has the longest “tether”. Monomer formation took place within a few hours from the reaction of dimer with Et₂N in refluxing IPA, but for **163c** only a small quantity of **166** was produced even after extended reaction times. ATH reduction of **49a**, using **160** and **164-168** were carried out at 40 °C (S/C = 200) in FA/TEA (5:2) azeotrope (Scheme 61, Table 18).

**Scheme 61.** ATH reduction of **49a**, using catalyst **160, 164-168** (S/C = 200).
Table 18. ATH reduction of 49a, using 160 and 164-168 (S/C = 200).

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Loading (mol%)</th>
<th>Temp (°C)</th>
<th>Ketone</th>
<th>Time (hrs)</th>
<th>Conv (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S,S)-160</td>
<td>0.5</td>
<td>40</td>
<td>49a</td>
<td>2</td>
<td>100</td>
<td>96 S</td>
</tr>
<tr>
<td>(R,R)-164</td>
<td>0.5</td>
<td>40</td>
<td>49a</td>
<td>15</td>
<td>19</td>
<td>92 R</td>
</tr>
<tr>
<td>(R,R)-165</td>
<td>0.5</td>
<td>40</td>
<td>49a</td>
<td>1.25</td>
<td>100</td>
<td>96 R</td>
</tr>
<tr>
<td>(R,R)-166</td>
<td>0.5</td>
<td>40</td>
<td>49a</td>
<td>6</td>
<td>38</td>
<td>94 R</td>
</tr>
<tr>
<td>(R,R)-167</td>
<td>0.5</td>
<td>40</td>
<td>49a</td>
<td>4</td>
<td>100</td>
<td>96 R</td>
</tr>
<tr>
<td>(R,R)-168</td>
<td>0.5</td>
<td>40</td>
<td>49a</td>
<td>5</td>
<td>100</td>
<td>93 R</td>
</tr>
</tbody>
</table>

The results obtained from the ATH studies showed that the most active catalyst for the reduction of 49a was 4C-“tethered” complex 165, giving full reduction within 75 min with an ee of 96% (R). Complex 165 proved to be faster than the previously reported 3C-“tethered” complex 160, and significantly faster than the 5C 166 and the 2C 164 “tethered” complexes. The ee’s obtained using 166 and 164 were high, showing that they are still operating through the transition state expected for these compounds. As a result of this increased activity of 165, the catalyst loading can be reduced to as low as 0.01 mol%, matching the level at which 160\textsuperscript{25d} has been used.\textsuperscript{20a}

Kinetic studies on 160, 83 and 164-168 were carried out at 40 °C using 1.62 M ketone in FA/TEA (S/C = 200), with the conversion being monitored by \textsuperscript{1}H NMR and chiral GC. The studies showed that catalysts 160, 164, 166, 167 and 168 for majority of the reaction displayed zero-order kinetics, whereas catalyst 165 showed mixed-order kinetics. Analysis of this data was carried out, assuming that ketone reduction by Ru-H species is second-order kinetics and the regeneration of Ru-H by formic acid is first order kinetics. The results revealed that the high rate obtained with catalyst 165 is due to increased rate of hydride regeneration combined with rapid ketone reduction. Noyori’s untethered catalyst 83 also showed mixed-order kinetics similar to 165, but it took 20 hrs to complete the reduction. For other “tethered” catalysts, the overall reduction is
restricted by the rate of hydride regeneration, until the ketone concentration has dropped to low levels. (Scheme 62).\textsuperscript{20a}

\begin{center}
\begin{tabular}{c|cc}
 & $k_1$ & $k_2$ \\
\hline
(S,S)-160 & 10 & 3.7 \\
(R,R)-164 & >0.5 & 0.034 \\
(R,R)-165 & 11 & 9.3 \\
(R,R)-166 & >3 & 0.25 \\
(R,R)-167 & 11 & 1.2 \\
(R,R)-168 & 2.5 & 1.6 \\
(R,R)-83 & 0.75 & 1.0 \\
\end{tabular}
\end{center}

\textsuperscript{a} M\textsuperscript{-1} min\textsuperscript{-1}, \textsuperscript{b} min\textsuperscript{-1}.

Figure 62. Kinetic data for the reduction of 49a. Reactions were carried out at 40 °C, [ketone] = 1.62 M, FA/TEA (5:2), S/C = 200.

The reduction of a dialkyl ketone using catalyst 165 and 168 was carried out, with both catalysts fully reducing cyclohexylmethyl ketone 141 overnight. Catalyst 165 gave the product in 66% ee; however catalyst 168 gave a product in 90% ee with the configuration of product obtained in both cases being opposite to that of acetophenone, relative to the diamine configuration (Scheme 63).\textsuperscript{20a}

\begin{center}
\begin{tabular}{c}
\textbf{Scheme 63. ATH reduction of 141, using catalyst 165 and 168 (S/C = 200).}
\end{tabular}
\end{center}

This increased ee using 168 suggests that the extra methyl groups on the $\eta^6$-arene ring forces the larger ketone substituent in to the less hindered region (Figure 18). This catalyst was the first example of a Ru/TsDPEN catalyst designed and demonstrated to have useful levels of enantioselectivity for non-aromatic substrates, with the replacement of electronic elements to steric ones.\textsuperscript{20a}
Figure 18. Dimethyl substitution on the $\eta^6$-arene ring 168 increases steric hindrance, which in effect increases the ee (left; 90% ee) for the reduction of cyclohexylmethyl ketone over 160 (right; 69% ee).

Further investigation on “tethered” catalysts was conducted, where a benzylic “tether” 169, in place of the aliphatic one was synthesized and tested along with complex 170, in which the diphenyl substituted diamine ligand 81 is replaced with a homochiral $R,R$-1,2-diaminocyclohexane ($R,R$-TsCYDN) 91 (Figure 19). Derivatives of 1,2-diaminocyclohexane have been reported to be effective for the reduction of ketones in the untethered form as mentioned earlier in Section 1.4.3.2.25f

Figure 19. “Tethered” Ru(II) catalyst 169 and 170.

Both catalysts demonstrated good activity for the ATH of ketones in FA/TEA, but neither gave an improved performance relative to catalyst 165. Reduction of 49a using 169, gave the alcohol in 100% conv., 95% ee after 24 hrs at 40 °C, and using 170, in 100% conv., 92% ee after 12 hrs at 28 °C (Scheme 64).25f
The use of ether-linked “tethered” catalysts 171-173 (Figure 20), which have a stereochemically well-defined structure, and in effect controls the configuration at the metal centre were also examined by the Wills group for ATH.\textsuperscript{25g}

The results obtained showed that out of all, 173b (S/C = 200) proved to be the most active for the ATH reduction of 49a in FA/TEA (5:2) azeotrope at 40 °C, giving 49a' in 100% conversion and 29% ee (R) after an overnight reaction. This shows that the “tether” length is not interfering with the catalytic mechanism, as the activity of the catalyst is unaffected. The catalyst was however lacking the elements which affect the enantioselectivity of ketone reductions.\textsuperscript{25g}

Wills’ group have also synthesized “tethered” rhodium catalysts where the β-amino alcohol and monotosylated diamine is “tethered” to the cyclopentadienyl group. Although tetramethylcyclopentadienyl group is different in structure to the arene ligand, the same CH/π stabilising effect is known to operate through the methyl groups as shown previously in Section 1.4.5. The first rhodium “tethered” catalyst synthesized
was 174,\textsuperscript{25h} which proved to be a highly active catalyst for ketone reduction, but failed to remain stable under reaction conditions (Figure 21). The reduction of acetophenone 49a using 1-5 mol\% of catalyst 174 and KO\textsubscript{t}-Bu in IPA at rt gave ee of up to 75\% and conversion of up to 98\% (\textit{R}), but with decreasing ee as the conversion was increasing. Rhodium “tethered” monotosylated diamine catalysts were later prepared 175-176, which were stable under reactions conditions (using FA/TEA) and showed excellent enantioselectivity and reactivity for a range of ketone reductions. The reduction of 49a using 175,\textsuperscript{25i} gave the alcohol 49a\textsuperscript{*} in 100\% conv., 98\% ee (\textit{R}) within 10 hrs at 25 °C in FA/TEA (S/C = 200), and using 176 in 100\% conv., 96\% ee (\textit{R}) in just 2 hrs at 28 °C in FA/TEA (S/C = 200).\textsuperscript{25j}

![Figure 21. Structures of rhodium(III) “tethered” catalysts.](image-url)
2. Results and Discussion.

2.1 Asymmetric transfer hydrogenation reduction of quinolines using Ru(II) “tethered” catalysts.

Tetrahydroquinoline derivatives have attracted considerable attention owing to their importance as synthetic intermediates for drugs, agrochemicals, and dyes as described earlier in Section 1.3.3.6. Reduction of quinolines to tetrahydroquinolines represents a simple and promising methodology as quinoline derivatives are very easily available. A number of reports on the pressure hydrogenation of quinolines have been published, but very little research has been carried out on the transfer hydrogenation of quinolines (Section 1.4.6.5). It would be of great interest to know whether asymmetric transfer hydrogenation of quinolines can be successfully carried out using “tethered” and untethered Ru(II) catalysts in FA/TEA, as this method if successful, would ensure formation of the desired product under mild conditions.

In the preliminary studies carried out for the ATH reduction of quinolines, Blackmond’s reported method was used, whereby formic acid was added in dropwise by syringe over a duration of 30 mins to a mixture of 4C ‘tethered’ dimer 163b, triethylamine and the substrate 120a, 115a, 177-181 (Figure 22) dissolved in methanol.

![Figure 22. Substrates that were used for preliminary studies.](image-url)
In the previous studies, Wills group had demonstrated that monomer catalysts are formed \textit{in situ} from their dimer precursors (Section 1.4.7). For this reason, a mixture of monomer and dimer catalysts was used (Figure 23), the selection of which depended on their availability and diversity of structure. However, most of the reductions that were conducted on quinolines employed the 4C ‘tethered’ dimer \textbf{163b}, which is converted \textit{in situ} into the monomer \textbf{165}.

![Chemical structures of catalysts](image)

Figure 23. Ru(II) catalysts that were used for the ATH of quinolines.

The first step in this project was to investigate the ATH reduction of isoquinoline, quinoline and quinoxaline rings using the 4C ‘tethered’ dimer \textbf{163b}.

### 2.1.1 Preliminary studies.

**ATH reduction of isoquinolines.**

ATH reduction was carried out on 1-methylisoquinoline \textbf{177} using catalyst \textbf{163b}, giving <5\% conversion of a non-identified product after 24 hrs (Table 19, Scheme 65). This
result shows that the current method used is not suitable for the reduction of isoquinoline substrates.

Scheme 65. ATH of 1-methylisoquinoline 177 using dimer 163b.

<table>
<thead>
<tr>
<th>Imine</th>
<th>Catalyst</th>
<th>Temp (°C)</th>
<th>Time (hrs)</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
<th>Config. (R/S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>177</td>
<td>(R,R)-163b</td>
<td>rt</td>
<td>24</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 19. ATH reduction of 1-methylisoquinoline 177 to give 177’ or 177’’

(Concentration of 0.22 M with respect to imine, dropwise-method of FA employed, FA/TEA (5:2)); Using dimer 163b forming monomer in situ (S/C = 400).

ATH reduction of quinolines.

The next step was to carry out the ATH reduction on 2-methylquinoline 120a, which gave a positive result as 120a was reduced to give 2-methyl-1,2,3,4-tetrahydroquinoline 120a’ in 47% conversion and 50% ee after 96 hrs (Scheme 66, Table 20).

Scheme 66. ATH reduction of 2-methylquinoline 120a using dimer 163b.

<table>
<thead>
<tr>
<th>Imine</th>
<th>Catalyst</th>
<th>Temp (°C)</th>
<th>Time (hrs)</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
<th>Config. (R/S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>120a</td>
<td>(R,R)-163b</td>
<td>rt</td>
<td>96</td>
<td>47</td>
<td>50 R</td>
<td></td>
</tr>
</tbody>
</table>
Table 20. ATH reduction of 2-methylquinoline 120a to tetrahydroquinoline 120a’

(Concentration of 0.22 M with respect to imine, dropwise-method of FA employed, FA/TEA (5:2)); Using dimer 163b forming monomer in situ (S/C = 400).

The result obtained was quite encouraging and represented a good starting point in this project. The racemic standard was obtained by injecting 120a in THF to a solution of [Ru((p-cymene)Cl$_2$)$_2$] and I$_2$ dissolved in THF, after which pressure hydrogenation on the mixture was carried out at 700 psi for 24 hrs giving the racemic 2-methyl-1,2,3,4-tetrahydroquinoline 120a’ in 50% yield (Scheme 67). The ee of the ATH product was obtained by GC, comparing the starting material 120a/racemic standard$^{10b}$ with the asymmetric product 120a’.

![Scheme 67. Pressure hydrogenation of 120a giving a racemic product 120a’, using [Ru((p-cymene)Cl$_2$)$_2$.](image)

ATH reduction of 2-methylquinoline; increasing the quantity of formic acid.

The next objective was to start optimizing the conditions using 2-methylquinoline as a model substrate to achieve a conversion that is acceptable before focusing on increasing the enantioselectivity.

The first optimization was carried out by increasing the quantity of formic acid injected into the solution, as FA decomposes over time and may also act as a protonating source for the C=C bond, more acid may be required for the reaction to go to completion.
Results and Discussion

<table>
<thead>
<tr>
<th>Imine</th>
<th>Catalyst</th>
<th>FA/TEA ratio</th>
<th>Temp (°C)</th>
<th>Time (hrs)</th>
<th>Conversion (%)</th>
<th>ee (%)/ Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>120a</td>
<td>(R,R)-163b</td>
<td>5:2</td>
<td>rt</td>
<td>72</td>
<td>36</td>
<td>48 R</td>
</tr>
<tr>
<td>120a</td>
<td>(R,R)-163b</td>
<td>10:2</td>
<td>rt</td>
<td>72</td>
<td>&gt;99</td>
<td>50 R</td>
</tr>
<tr>
<td>120a</td>
<td>(R,R)-163b</td>
<td>15:2</td>
<td>rt</td>
<td>66.5</td>
<td>94</td>
<td>48 R</td>
</tr>
</tbody>
</table>

Table 21. ATH reduction of 120a to tetrahydroquinoline 120a’ (Concentration of 0.22 M and 0.22 M with respect to imine, dropwise-method of FA employed, FA/TEA (5:2, 10:2 and 15:2)); Using dimer 163b forming monomer *in situ* (S/C = 400).

The results (Table 21) clearly show that changing the formic acid: triethylamine ratio from 5:2 to 10:2 leads to the complete conversion of 120a to give (R)-2-methyl-1,2,3,4-tetrahydroquinoline 120a’ (Scheme 66) with 50% ee. Changing the ratio further to 15:2 gives a respectable conversion of 94% and 48% ee after 67 hrs which would possibly reach >99% conversion by 72 hrs.

**ATH reduction of 2-methylquinoline; comparison of the 4C “tethered” catalyst 163b with the untethered catalyst 38.**

The next task was to see how active the 4C “tethered” catalyst 163b is in comparison to the untethered catalyst 38, and whether or not the ee obtained using catalyst 38 is any different to that obtained using catalyst 163b (Scheme 68).
Results and Discussion

Scheme 68. ATH reduction of 2-methylquinoline 120a using catalyst 163b and 38.

<table>
<thead>
<tr>
<th>Imine</th>
<th>Catalyst</th>
<th>FA/TEA ratio</th>
<th>Temp (°C)</th>
<th>Time (hrs)</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
<th>Config. (R/S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>120a</td>
<td>(R,R)-163b</td>
<td>15:2</td>
<td>rt</td>
<td>186</td>
<td>&gt;99</td>
<td>50 R</td>
<td></td>
</tr>
<tr>
<td>120a</td>
<td>(R,R)-38</td>
<td>15:2</td>
<td>rt</td>
<td>186</td>
<td>20</td>
<td>77 R</td>
<td></td>
</tr>
</tbody>
</table>

Table 22. ATH reduction of 120a to tetrahydroquinoline 120a’ (Concentration of 0.21M with respect to imine, dropwise-method of FA employed, FA/TEA (15:2)); Using dimer 163b forming monomer in situ (S/C = 400) and catalyst 38 (S/C = 200).

The two reactions (Scheme 68, Table 22) were carried out parallel to each other, and the result of the reduction of 120a with catalyst 163b using 15:2 FA:TEA shown previously (Table 21) is from this experiment (Table 22).

The results (Table 23, Figure 24) show that catalyst 163b is much more active than catalyst 38 when it comes to conversion as >99% conversion was obtained after 186 hours with catalyst 163b, and only 20% conversion was obtained after 186 hours with catalyst 38, but the ee obtained with catalyst 38 was much higher than that obtained with catalyst 163b, as 50% ee was obtained with catalyst 163b, but in a high 77% ee, was obtained with catalyst 38 (Table 22), meaning the 4C link is vital for rapid conversion but having a p-cymene arene group on the Ru is essential for achieving high enantioselectivity (Scheme 68).

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>6</td>
</tr>
<tr>
<td>17</td>
<td>33</td>
</tr>
<tr>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>23.25</td>
<td>45</td>
</tr>
<tr>
<td>41</td>
<td>71</td>
</tr>
<tr>
<td>46.5</td>
<td>79</td>
</tr>
<tr>
<td>66.5</td>
<td>94</td>
</tr>
<tr>
<td>186</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

Table 23. Conversion of catalyst 163b vs. 38 over time.
Results and Discussion

Figure 24. Comparing the conversion of 4C “tethered” catalyst 163b vs. untethered catalyst 38 over time.

ATH reduction of 2-methylquinoline; 4C “tethered” catalyst 163b vs untethered catalyst 38 vs untethered catalyst 182.

In the previous comparison it was obvious how active catalyst 163b was when compared to catalyst 38, so at this point it was decided to see whether or not the untethered catalyst 182, which is known for reducing cyclic imines with great conversion and enantioselectivity and with a higher enantioselectivitiy than 38, shows any form of increased activity and enantioselectivity for quinoline reduction (Scheme 69, Table 24).
Scheme 69. ATH reduction of 2-methylquinoline 120a using catalyst 182.

<table>
<thead>
<tr>
<th>Imine</th>
<th>Catalyst</th>
<th>FA/TEA ratio</th>
<th>Temp (°C)</th>
<th>Time (hrs)</th>
<th>Conversion (%)</th>
<th>ee (%) / Config. (R/S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>120a</td>
<td>(R,R)-163b</td>
<td>15:2</td>
<td>rt</td>
<td>23.25</td>
<td>45</td>
<td>50 R</td>
</tr>
<tr>
<td>120a</td>
<td>(R,R)-38</td>
<td>15:2</td>
<td>rt</td>
<td>23.25</td>
<td>2</td>
<td>- -</td>
</tr>
<tr>
<td>120a</td>
<td>(R,R)-182</td>
<td>10:2</td>
<td>rt</td>
<td>22.25</td>
<td>4</td>
<td>- -</td>
</tr>
</tbody>
</table>

Table 24. ATH reduction of 120a to tetrahydroquinoline 120a’ (Concentration of 0.21 M with respect to imine, dropwise-method of FA employed, FA/TEA (15:2 and 10:2)); Using dimer 163b forming monomer in situ (S/C = 400) or catalyst 38/182 (S/C = 200).

The results showed that catalyst 182, with a conversion of 4% after 22 hrs, is more active than catalyst 38 with a conversion of 2% after 23 hrs, but clearly catalyst 163b is even more active, giving a conversion of 45% after 23 hrs and 50% ee (Table 24, Scheme 69).

**ATH reduction of 2-methylquinoline; increasing the overall volume of formic acid:triethylamine.**

Since the formic acid: triethylamine ratio had been studied, seeing whether increasing the overall volume of triethylamine has any effect on the ATH reduction was examined (Scheme 66, Table 25).

<table>
<thead>
<tr>
<th>Imine</th>
<th>Catalyst</th>
<th>FA/TEA ratio</th>
<th>Temp (°C)</th>
<th>Time (hrs)</th>
<th>Conversion (%)</th>
<th>ee (%) / Config. (R/S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>120a</td>
<td>(R,R)-163b</td>
<td>15:6</td>
<td>rt</td>
<td>176.5</td>
<td>96</td>
<td>42 R</td>
</tr>
</tbody>
</table>

Table 25. ATH reduction of 120a to tetrahydroquinoline 120a’ (Concentration of 0.19 M with respect to imine, dropwise-method of FA employed, FA/TEA (15:6)); Using dimer 163b forming monomer in situ (S/C = 400).
The results (Table 25) show that increasing the amount of triethylamine gives a good conversion of 96% after 177 hrs, but an ee of 42% (drop of 8%) was obtained in comparison to the previously obtained ee of 50% (Table 21, 22).

**ATH reduction of 2-methylquinoline; using a different solvent.**

The final optimization involved the ATH reduction of 2-methylquinoline \(120a\) using toluene instead of methanol and to use no solvent (Scheme 66, Table 26).

<table>
<thead>
<tr>
<th>Imine</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>FA/TEA ratio</th>
<th>Temp (°C)</th>
<th>Time (hrs)</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
<th>Config. (R/S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(120a) ((R,R))-163b</td>
<td>Toluene</td>
<td>10:2</td>
<td>rt</td>
<td>103.5</td>
<td>68</td>
<td>51</td>
<td>51 R</td>
<td></td>
</tr>
<tr>
<td>(120a) ((R,R))-163b</td>
<td>-</td>
<td>10:2</td>
<td>rt</td>
<td>103.5</td>
<td>61</td>
<td>46</td>
<td>46 R</td>
<td></td>
</tr>
</tbody>
</table>

Table 26. ATH reduction of \(120a\) to tetrahydroquinoline \(120a'\) (Concentration of 0.21M and 1.48 M with respect to imine, dropwise-method of FA employed, FA/TEA (10:2)); Using dimer \(163b\) forming monomer *in situ* (S/C = 400).

In this final optimization it was quite clear that methanol is a better solvent for ATH reduction of quinolines, as the ee obtained with toluene (51%) and no solvent (46%) is comparable with methanol (50%), the conversion using methanol however is much faster (>99% conversion, 72 hrs, Table 21) than using toluene (68% conversion, 104 hrs, Table 26) or no solvent (61% conversion, 104 hrs, Table 26).

**ATH reduction of 2-phenylquinoline.**

ATH reduction was next carried out on a bulkier substituted quinoline \(115a\), as some work has now been carried out on optimizing the reactions (Scheme 70, Table 27).
Scheme 70. ATH reduction of 2-phenylquinoline 115a using dimer 163b.

<table>
<thead>
<tr>
<th>Imine</th>
<th>Catalyst FA/TEA ratio</th>
<th>Temp (°C)</th>
<th>Time (hrs)</th>
<th>Conversion (%)</th>
<th>ee (%) / Config. (R/S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>115a</td>
<td>(R,R)-163b</td>
<td>10:2</td>
<td>rt</td>
<td>107.3</td>
<td>84</td>
</tr>
</tbody>
</table>

Table 27. ATH reduction of 115a to tetrahydroquinoline 115a’ (Concentration of 0.21 M with respect to imine, dropwise-method of FA employed, FA/TEA (10:2)); Using dimer 163b forming monomer in situ (S/C = 400).

Reduction of 2-phenylquinoline 115a was carried out successfully to give (S)-2-phenyl-1,2,3,4-tetrahydroquinoline 115a’ with 84% conversion and 64% ee after 107 hrs (Table 27). This is a positive result in addition to what has been obtained with the ATH reduction of 2-methylquinoline 120a. The configuration was determined by HPLC data comparison with literature.\textsuperscript{10d}

**ATH reduction of 2-tert-butylquinoline.**

ATH was carried out on 2-tert-butylquinoline 178, synthesized successfully by cleanly converting o-nitrobenzaldehyde to o-aminobenzaldehyde using iron metal (10 eq.) in the presence of aq. HCl (20 mol%) in refluxing EtOH for 30 mins. The solids were removed by filtration and the filtrate was treated with 3,3-dimethylbutan-2-one and powdered KOH (3 eq.). After stirring at reflux for 40 mins, 2-tert-butylquinoline was obtained with >99% yield.\textsuperscript{26b} As 178 is another bulky substrate like 115a, it was considered interesting to establish whether ATH gives a similar result to what was obtained for the reduction of 115a (Scheme 71, Table 28).
Scheme 71. ATH reduction of 2-tert-butylquinoline 178 using dimer 163b.

<table>
<thead>
<tr>
<th>Imine</th>
<th>Catalyst</th>
<th>FA/TEA ratio</th>
<th>Temp (°C)</th>
<th>Time (hrs)</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
<th>Config. (R/S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>178</td>
<td>(R,R)-163b</td>
<td>10:2</td>
<td>rt</td>
<td>120.75</td>
<td>77</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 28. ATH reduction of 178 to tetrahydroquinoline 178' (Concentration of 0.21 M with respect to imine, dropwise-method of FA employed, FA/TEA (10:2)); Using dimer 163b forming monomer in situ (S/C = 400).

2-tert-Butylquinoline 178 was successfully reduced to give 2-tert-butyl-1,2,3,4-tetrahydroquinoline 178' with 77% conversion after 121 hrs, but unfortunately a racemic product was obtained (Table 28).

**ATH reduction of methylquinoline-2-carboxylate.**

The next task was to examine methylquinoline-2-carboxylate 179 reduction by ATH (Scheme 72, Table 29).

Scheme 72. ATH reduction of methylquinoline-2-carboxylate 179 using dimer 163b.

<table>
<thead>
<tr>
<th>Imine</th>
<th>Catalyst</th>
<th>FA/TEA ratio</th>
<th>Temp (°C)</th>
<th>Time (hrs)</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
<th>Config. (R/S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>179</td>
<td>(R,R)-163b</td>
<td>10:2</td>
<td>rt</td>
<td>96</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 29. ATH reduction of 179 to tetrahydroquinoline 179' (Concentration of 0.21 M with respect to imine, dropwise-method of FA employed, FA/TEA (10:2)); Using dimer 163b forming monomer in situ (S/C = 400).
Reduction of 179 was unsuccessful (Table 29), possibly due to the interaction of the carboxylate group with the catalyst 163b, preventing the catalyst 163b from carrying out the reduction.

**ATH reduction of 2-phenylpyridine.**

As it was established that quinoline type substrates can be reduced via ATH, attention turned to a test of ATH on the pyridine substrate 2-phenylpyridine 180 (Scheme 73, Table 30).

![Scheme 73. ATH reduction of 2-phenylpyridine 180 using dimer 163b.](image)

<table>
<thead>
<tr>
<th>Imine</th>
<th>Catalyst</th>
<th>FA/TEA ratio</th>
<th>Temp (°C)</th>
<th>Time (hrs)</th>
<th>Conversion (%)</th>
<th>ee (%)/ Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>180</td>
<td>(R,R)-163b</td>
<td>10:2</td>
<td>rt</td>
<td>96</td>
<td>0</td>
<td>- -</td>
</tr>
</tbody>
</table>

Table 30. ATH reduction of 180 to piperidine 180’ (Concentration of 0.21 M with respect to imine, dropwise method of FA employed, FA/TEA (10:2)); Using dimer 163b forming monomer in situ (S/C = 400).

The reduction on 180 was unsuccessful (Table 30), possibly due to the substrate being far too stable and is able to restore its aromaticity.

**ATH reduction of quinoxaline.**

Another substrate on which ATH was evaluated was quinoxaline 181. Although the reaction does not give an asymmetric product, a successful application could be extended to a prochiral substrate. (Scheme 74, Table 31).
Scheme 74. ATH reduction of quinoxaline 181 using dimer 163b.

<table>
<thead>
<tr>
<th>Imine</th>
<th>Catalyst</th>
<th>FA/TEA ratio</th>
<th>Temp (°C)</th>
<th>Time (hrs)</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
<th>Config. (R/S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>181</td>
<td>(R,R)-163b</td>
<td>10:2</td>
<td>rt</td>
<td>96</td>
<td>17</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 31. ATH reduction of 181 to tetrahydroquinoxaline 181’ (Concentration of 0.21 M with respect to imine, dropwise-method of FA employed, FA/TEA (10:2)); Using dimer 163b forming monomer in situ (S/C = 400).

Reduction on 181 was partially successful giving 1,2,3,4-tetrahydroquinoxaline 181’ in 17% conversion (Table 31).

The preliminary studies carried out above was using the dropwise addition of formic acid, and as complete conversion was taking up to 72 hrs, the Noyori method was tested for comparison (Scheme 66, Table 32). In this method, the azeotrope is used from the outset of the reaction.22

<table>
<thead>
<tr>
<th>Imine</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>FA/TEA ratio</th>
<th>Temp (°C)</th>
<th>Time (hrs)</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
<th>Config. (R/S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>120a</td>
<td>(R,R)-163b</td>
<td>MeOH</td>
<td>5:2</td>
<td>28</td>
<td>24</td>
<td>96</td>
<td>46 R</td>
<td></td>
</tr>
</tbody>
</table>

Table 32. ATH reduction of 120a to tetrahydroquinoline 120a’ (Concentration of 0.45 M with respect to imine, non-dropwise i.e. 5:2 azeotropic mixture used); Using dimer 163b forming monomer in situ (S/C = 400).
Table 33. ATH reduction of **120a** to tetrahydroquinoline **120a’** (Concentration of 0.21 M with respect to imine, dropwise-method of FA employed, FA/TEA (10:2)); Using dimer **163b** forming monomer *in situ* (*S/C* = 400).

The results show (Table 32, 33) that changing the concentration of solution from 0.21 M to 0.45 M with respect to the imine speeds up the reaction rate and the tetrahydroquinoline is formed with complete conversion within 24 hrs.

It is after this point where all the ATH reductions that were carried out were using the non-dropwise method, since it is practically easier and more efficient.

### 2.1.2 ATH reduction of 2-methylquinoline; optimization of solvent.

In order to optimize the outcome of the reaction, systematic variation of the conditions was carried out using **120a** as a model substrate and **163b** as catalyst (Scheme 66). The results of solvent variation are shown (Table 34).

<table>
<thead>
<tr>
<th>Imines</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Catalyst</th>
<th>FA/TEA ratio</th>
<th>Time (hrs)</th>
<th>Conv. (%)</th>
<th>ee (%)/Config. (R/S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>120a</td>
<td>MeOH</td>
<td>28</td>
<td>(R,R)-163b</td>
<td>5:2</td>
<td>24</td>
<td>96</td>
<td>46 R</td>
</tr>
<tr>
<td>120a</td>
<td>ACN</td>
<td>28</td>
<td>(R,R)-163b</td>
<td>5:2</td>
<td>24</td>
<td>79</td>
<td>36 R</td>
</tr>
<tr>
<td>120a</td>
<td>Water</td>
<td>28</td>
<td>(R,R)-163b</td>
<td>5:2</td>
<td>24</td>
<td>23</td>
<td>32 R</td>
</tr>
<tr>
<td>120a</td>
<td>EtOH</td>
<td>28</td>
<td>(R,R)-163b</td>
<td>5:2</td>
<td>24</td>
<td>96</td>
<td>37 R</td>
</tr>
<tr>
<td>120a</td>
<td>DCM</td>
<td>28</td>
<td>(R,R)-163b</td>
<td>5:2</td>
<td>24</td>
<td>92</td>
<td>25 R</td>
</tr>
<tr>
<td>120a</td>
<td>Et₂O</td>
<td>28</td>
<td>(R,R)-163b</td>
<td>5:2</td>
<td>24</td>
<td>98</td>
<td>17 R</td>
</tr>
<tr>
<td>120a</td>
<td>Acetone</td>
<td>28</td>
<td>(R,R)-163b</td>
<td>5:2</td>
<td>24</td>
<td>8</td>
<td>8 R</td>
</tr>
<tr>
<td>120a</td>
<td>Toluene</td>
<td>28</td>
<td>(R,R)-163b</td>
<td>5:2</td>
<td>24</td>
<td>73</td>
<td>22 R</td>
</tr>
<tr>
<td>120a</td>
<td>IPA</td>
<td>28</td>
<td>(R,R)-163b</td>
<td>5:2</td>
<td>24</td>
<td>98</td>
<td>31 R</td>
</tr>
<tr>
<td>120a</td>
<td>EtOAc</td>
<td>28</td>
<td>(R,R)-163b</td>
<td>5:2</td>
<td>24</td>
<td>74</td>
<td>18 R</td>
</tr>
</tbody>
</table>

Table 34. ATH reduction of **120a** to tetrahydroquinoline **120a’** (Concentration of 0.45 M with respect to imine, non-dropwise i.e. 5:2 azeotropic mixture used); Using dimer **163b** forming monomer *in situ* (*S/C* = 400).
The results clearly show that methanol overall proved to be the best solvent giving a respectable conversion of 96% and 46% ee after 24 hrs (Table 34). The reaction conversions were monitored after 2, 4, 6 and 24 hrs (Table 36, Figure 25).

ATH of quinolines was also carried out using ionic liquid as solvent instead of methanol to see if that has any effect on the conversion or enantioselectivity (Scheme 66, Table 35). Chan in 2008 reported the reduction of quinolines using Ru(II) catalysts where ionic liquid (Section 1.3.3.6) was used as solvent and up to 99% conversion and ee was obtained with pressure hydrogenation.

<table>
<thead>
<tr>
<th>Imines</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Catalyst</th>
<th>FA/TEA ratio</th>
<th>Time (days)</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
<th>Config. (R/S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>120a</td>
<td>[BMIM]PF₆</td>
<td>28</td>
<td>(R,R)-163b</td>
<td>5:2</td>
<td>3</td>
<td>88</td>
<td>41</td>
<td>R</td>
</tr>
<tr>
<td>120a</td>
<td>MeOH/[BMIM]PF₆</td>
<td>28</td>
<td>(R,R)-163b</td>
<td>5:2</td>
<td>5</td>
<td>91</td>
<td>52</td>
<td>R</td>
</tr>
</tbody>
</table>

Table 35. ATH reduction of 120a to tetrahydroquinoline 120a' (Concentration of 0.45 M with respect to imine, non-dropwise i.e. 5:2 azeotropic mixture used); Using dimer 163b forming monomer in situ (S/C = 400).

Ionic liquid as solvent and using a 50:50 mixture of ionic liquid and methanol gave good results, but methanol alone proved to be the better solvent (Table 35).
Table 36. ATH reduction of 120a to tetrahydroquinoline 120a’ (Concentration of 0.45 M with respect to imine, non-dropwise i.e. 5:2 azeotropic mixture used); Using dimer 163b forming monomer in situ (S/C = 400). Conversion monitored after 2,4,6 and 24 hrs.

Figure 25. A graph to show conversion vs. time when using different solvents for the ATH reduction of 2-methylquinoline 120a to tetrahydroquinoline 120a’.

2.1.3 ATH reduction of 2-methylquinoline; optimization of temperature.

Since methanol was confirmed to be the best solvent, the reactions were next carried out at different temperatures (Scheme 66, Table 37).

<table>
<thead>
<tr>
<th>Imines</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Catalyst</th>
<th>FA/TEA ratio</th>
<th>Time (hrs)</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
<th>Config. (R/S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>120a</td>
<td>MeOH</td>
<td>28</td>
<td>(R,R)-163b</td>
<td>5:2</td>
<td>24</td>
<td>96</td>
<td>46</td>
<td>R</td>
</tr>
<tr>
<td>120a</td>
<td>MeOH</td>
<td>40</td>
<td>(R,R)-163b</td>
<td>5:2</td>
<td>24</td>
<td>94</td>
<td>44</td>
<td>R</td>
</tr>
<tr>
<td>120a</td>
<td>MeOH</td>
<td>50</td>
<td>(R,R)-163b</td>
<td>5:2</td>
<td>24</td>
<td>94</td>
<td>43</td>
<td>R</td>
</tr>
<tr>
<td>120a</td>
<td>MeOH</td>
<td>60</td>
<td>(R,R)-163b</td>
<td>5:2</td>
<td>24</td>
<td>96</td>
<td>43</td>
<td>R</td>
</tr>
</tbody>
</table>
Table 37. ATH reduction of **120a** to tetrahydroquinoline **120a**' (Concentration of 0.45 M with respect to imine, non-dropwise i.e. 5:2 azeotropic mixture used); Using dimer **163b** forming monomer *in situ* (S/C = 400).

The results show that the reduction of **120a** to the tetrahydroquinoline **120a**' is most rapid when the reaction is carried out at 60 °C with a drop of 3% ee (Table 37). The reaction conversions were monitored after 2, 4, 6 and 24 hrs (Table 38, Figure 26).

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>28 °C</th>
<th>40 °C</th>
<th>50 °C</th>
<th>60 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>74</td>
<td>87</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>52</td>
<td>89</td>
<td>89</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>76</td>
<td>91</td>
<td>90</td>
<td>91</td>
</tr>
<tr>
<td>24</td>
<td>96</td>
<td>94</td>
<td>94</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>46% ee</td>
<td>44% ee</td>
<td>43% ee</td>
<td>43% ee</td>
</tr>
</tbody>
</table>

Table 38. ATH reduction of **120a** to tetrahydroquinoline **120a**' (Concentration of 0.45 M with respect to imine, non-dropwise i.e. 5:2 azeotropic mixture used); Using dimer **163b** forming monomer *in situ* (S/C = 400). Conversion monitored after 2, 4, 6 and 24 hrs.
Figure 26. A graph to show conversion vs. time when carrying out ATH reduction of 2-methylquinoline 120a to tetrahydroquinoline 120a' at different temperatures.

2.1.4 ATH reduction of 2-methylquinoline; using different catalysts.

As now the optimization with temperature was carried out, it was worth testing out ATH using various catalysts (Scheme 75, Table 39) at 60 °C, as this will increase the rate of conversion even for the less active catalysts quite rapidly with only a loss of 3% ee. This would give a good picture for the final conversion/ee that could be obtained with the catalysts 38, 159, 160, 163b-c, 164, 182 and 183.

Scheme 75. ATH reduction of 2-methylquinoline 120a, using catalysts 38, 159, 160, 163b-c, 164, 182 and 183.
Table 39. ATH reduction of 120a to tetrahydroquinoline 120a’ (Concentration of 0.45 M with respect to imine, non-dropwise i.e. 5:2 azeotropic mixture used); Using dimer 159, 163b-c and 183 forming monomer *in situ* (S/C = 400) and catalyst 38, 160, 164 and 182 (S/C = 200).

The results obtained are very encouraging and similar to what was observed in the preliminary studies. Catalyst 163b is the most active catalyst when compared to the other catalysts used, giving the fastest and the most conversion. The reaction conversions were monitored after 2, 4, 6 and 24 hrs (Table 40, Figure 27). Catalyst 38 however gave the best ee of 80% (Table 39), and yet again it is worth pointing out the fact that it is the only catalyst in the list to have a functionalized aromatic ring on the Ru. In view of the high conversion in the reduction of 120a achieved using the 4C ‘tethered’ complex 163b, but the high ee of 80% achieved using the *p*-cymene containing untethered complex 38, catalyst 183 was synthesized, which contains elements of each in order to achieve both high activity and enantioselectivity. This catalyst contains a methyl group in the arene ring, intended to mimic the *p*-cymene ring in 38, which was considered to be important for high enantioselectivity. Catalyst 183 however proved to be unsuccessful as it did not prove to be as active as catalyst 163b.
and it was not able to achieve enantioselectivity near enough catalyst 38 as a conversion of 30% and an ee of 46% was obtained after 24 hrs at 60 °C (Table 39).

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>4C dimer</th>
<th>5C dimer</th>
<th>3C dimer</th>
<th>2C monomer</th>
<th>3C monomer</th>
<th>4C DiMe dimer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>163b</td>
<td>38</td>
<td>182</td>
<td>163c</td>
<td>159</td>
<td>164</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>88</td>
<td>13</td>
<td>46</td>
<td>45</td>
<td>47</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
<td>15</td>
<td>58</td>
<td>77</td>
<td>51</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>91</td>
<td>16</td>
<td>61</td>
<td>83</td>
<td>53</td>
<td>8</td>
</tr>
<tr>
<td>24</td>
<td>96</td>
<td>17</td>
<td>66</td>
<td>87</td>
<td>62</td>
<td>27</td>
</tr>
</tbody>
</table>

Table 40. ATH reduction of 120a to tetrahydroquinoline 120a* (Concentration of 0.45 M with respect to imine, non-dropwise i.e. 5:2 azeotropic mixture used); Using dimer 159, 163b-c and 183 forming monomer in situ (S/C = 400) and catalyst 38, 160, 164 and 182 (S/C = 200). Conversion monitored after 2, 4, 6 and 24 hrs.
Figure 27. A graph to show conversion vs. time when carrying out ATH reduction of 2-methylquinoline 120a to tetrahydroquinoline 120a\textsuperscript{'} using different catalysts at 60 °C.

2.1.5 **Synthesis of catalyst 183 for the ATH reduction of quinolines.**

Dimer 183 was prepared successfully by firstly protecting 4-bromo-1-butanol 184 using tert-butylidiphenylsilyl chloride and imidazole in THF giving (4-bromobutoxy)(tert-butyl)diphenylsilane\textsuperscript{26c} 185 with 31% conversion. The next step was a Br/Li exchange on 5-bromo-m-xylene 186 and reaction with 185 in THF giving tert-butyl(4-(3,5-dimethylphenyl)butoxy)diphenylsilane\textsuperscript{26d} 187 with 70% yield, followed by deprotection of the silyl group using tetrabutylammonium fluoride in THF giving 4-(3,5-dimethylphenyl)butan-1-ol\textsuperscript{26e} 188 in 91% conversion. Birch reduction was then carried out to reduce the aromatic ring on 188 with sodium and ethanol in liquid ammonia to form 4-(3,5-dimethylcyclohexa-1,4-dienyl)butan-1-ol 189 as a red oil in 74% yield. The second step was a Swern oxidation to oxidize 189 to 4-(3,5-dimethylcyclohexa-1,4-dienyl)butanal 190 using oxalyl chloride, dimethyl sulfoxide and triethylamine in DCM. Aldehyde 190 was afforded as a clear yellow oil in 96% yield. Thirdly, reductive amination was carried out in dry methanol using 190, R,R-TsDPEN 81 and glacial acetic acid to form an imine as an intermediate, which then was reduced using sodium cyanoborohydride to give N-\((1R,2R)-2-(4-(3,5\text{-dimethylcyclohexa-1,4-dienyl})\text{-butylamino})\text{-1,2-diphenylethyl})\text{-4-methylbenzenesulfonamide} 191 as a white solid in 37% yield. The final step was the complexation of 191 with via 191.HCl salt formed from the reaction of 191 with 2M HCl in Et\textsubscript{2}O in DCM, followed by the reaction of the salt with ruthenium(III) trichloride hydrate in refluxing ethanol overnight, forming 183 as a black solid in 21% yield. Dimer 183 then forms the monomer 192 \textit{in situ} under ATH reaction conditions (Scheme 76).
Scheme 76. Synthesis of the DiMe 4C “tethered” dimer 183.
2.1.6 ATH reduction of ketones using catalyst 183.

The reduction of substrate 120a was not successful using catalyst 183, so it was considered valuable to establish how well catalyst 183 reduces ketones in comparison to other catalysts, as ‘tethered’ complexes that have been made in the Wills group have given good results for the reduction of certain ketones as shown in Section 1.4.7 (Scheme 77, Table 41).

\[
\text{Scheme 77. ATH reduction of ketones 49a and 141 giving alcohols 49a'}\text{ and 141'}\text{ respectively, using dimer 183. }
\]

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Catalyst</th>
<th>FA/TEA ratio</th>
<th>Time (hrs)</th>
<th>Conv. (%)</th>
<th>ee (%)/ Config. (R/S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>49a</td>
<td>-</td>
<td>28</td>
<td>(R,R)-183</td>
<td>5:2</td>
<td>24</td>
<td>89</td>
<td>97 R</td>
</tr>
<tr>
<td>141</td>
<td>-</td>
<td>28</td>
<td>(R,R)-183</td>
<td>5:2</td>
<td>168</td>
<td>&gt;99</td>
<td>74 S</td>
</tr>
</tbody>
</table>

Table 41. ATH reduction of 49a and 141 giving alcohols 49a’ and 141’ respectively, (Concentration of 1.62 M with respect to ketone, non-dropwise i.e. 5:2 azeotropic mixture used); Using dimer 183 forming monomer 192 in situ (S/C = 400).

The reductions were successful and some good results were obtained. Acetophenone 49a was reduced to the alcohol 49a’ giving 89% conversion and an impressive ee of 97% after 24 hrs, this reaction would possibly have reached >99% conversion if it was left to continue. Cyclohexylmethyl ketone 141 was reduced to the alcohol 141’ giving >99% conversion after 7 days with an ee of 74% (Table 41). Both the reductions are
comparable to the results obtained previously in the Wills’ group for the reduction of ketones using untethered and ‘tethered’ complexes.

**ATH reduction of 6, 7-dimethoxy-2-methylquinoline 193.**

Synthesis of 6,7-dimethoxy-2-quinoline 193 follows the same procedure as 178, via the Friedlander reaction, giving 193 in 76% yield.\(^{26b}\) This reaction was a test to see whether having electron donating groups on the aromatic ring of the substrate has any effect on the conversion or enantioselectivity (Scheme 78, Table 42).

![Scheme 78. ATH reduction of 6, 7-dimethoxy-2-methylquinoline 193 to 193’ using catalyst 38, 159 and 163b.](image)

<table>
<thead>
<tr>
<th>Imine</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Catalyst</th>
<th>FA/TEA ratio</th>
<th>Time (days)</th>
<th>Conv. (%)</th>
<th>ee (%)/$\text{Config. (R/S)}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>193</td>
<td>MeOH</td>
<td>28</td>
<td>(R,R)-163b</td>
<td>5:2</td>
<td>6</td>
<td>53</td>
<td>48 $R$</td>
</tr>
<tr>
<td>193</td>
<td>MeOH</td>
<td>28</td>
<td>(S,S)-159</td>
<td>5:2</td>
<td>4</td>
<td>23</td>
<td>48 $S$</td>
</tr>
<tr>
<td>193</td>
<td>MeOH</td>
<td>28</td>
<td>(R,R)-38</td>
<td>5:2</td>
<td>&gt;5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 42. ATH reduction of 193 to tetrahydroquinoline 193’ (Concentration of 0.45 M with respect to imine, non-dropwise i.e. 5:2 azeotropic mixture used); Using dimer 159 and 163b forming monomer *in situ* ($S/C = 400$) and catalyst 38 ($S/C = 200$).

The results obtained showed that having electron-donating groups on the aromatic ring of the quinoline slows the reaction down as quinoline 193 was reduced to the tetrahydroquinoline 193’ using catalyst 163b with only 53% conversion after 6 days with an ee of 48%, and catalysts 159/38 were much slower as only 23% conversion was
obtained with an ee of 48% after 4 days for catalyst 159, and only >5% conversion obtained using catalyst 38, not enough conversion for determining the ee (Table 42).

2.1.7 ATH reduction of 2-methylquinoline; Using Rh “tethered” catalysts 175 and 176.

Reductions were carried out using ‘tethered’ Rh(III) 175 and analogue 176 catalyst for comparison with Ru(II) catalysts (Scheme 79, Table 43), as recently Xiao et al disclosed the use of Rh-based catalyst in aqueous solution (Section 1.4.6.5), and gave impressive results that required careful control of pH for full reduction to occur.

![Scheme 79. ATH reduction of 2-methylquinoline 120a, using catalyst 175 and 176.](image)

<table>
<thead>
<tr>
<th>Imine</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Catalyst</th>
<th>FA/TEA ratio</th>
<th>Time (hrs)</th>
<th>Conv. (%)</th>
<th>ee (%)/Config. (R/S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>120a</td>
<td>MeOH</td>
<td>28</td>
<td>(R,R)-175</td>
<td>5:2</td>
<td>24</td>
<td>68</td>
<td>93 R</td>
</tr>
<tr>
<td>120a</td>
<td>MeOH</td>
<td>28</td>
<td>(R,R)-176</td>
<td>5:2</td>
<td>24</td>
<td>93</td>
<td>82 R</td>
</tr>
</tbody>
</table>

Table 43. ATH reduction of 120a to tetrahydroquinoline 120a’ (Concentration of 0.45 M with respect to imine, non-dropwise i.e. 5:2 azeotropic mixture used); Using catalyst 175 and 176 (S/C = 200).
ATH reduction using “tethered” Rh(III) catalysts proved successful with catalyst 175 giving the best ee of 93%, and catalyst 176 giving the best conversion of 93% out of the two Rh(III) “tethered” catalyst’s after 24 hours (Table 43).

### 2.1.8 ATH reduction of quinolines; using catalyst 163b and 175.

A series of quinoline substrates 115l, 117a, 120b, 124a, 194-195 (Figure 28) were synthesized from the initial reaction of 2-methylquinoline with nBuLi in dry THF at -78 °C followed by the addition of iodo/bromo containing starting materials. ATH reduction of quinolines 115l, 117a, 120b, 124a, 194-195 along with 115a and 178 was carried out using the most active Ru(II) “tethered” catalyst 163b and the most stereoselective Rh(II) “tethered” catalyst 175 tested (Scheme 80, Figure 28).

**Scheme 80.** ATH reduction of quinolines shown in Figure 28, using catalyst 163b and 175.

**Figure 28.** Substrates used for ATH reduction using catalyst 163b and 175.
The results show that the reductions to tetrahydroquinoline for all the substrates were carried out successfully and with high conversions, with substrate 120a giving the highest conversion of 96% and substrate 178 giving the lowest conversion of 57%. The ee’s obtained for the tetrahydroquinolines were not so high, with substrate 115a giving the highest ee of 73% (Table 44).

As “tethered” Rh(III) catalysts showed good activity and great stereoselectivity for the reduction of quinolines, it was further employed for the reduction of a series of quinolines (Scheme 80, Figure 28).

Table 44. ATH reduction of quinolines to tetrahydroquinolines (Concentration of 0.45 M with respect to imine, non-dropwise i.e. 5:2 azeotropic mixture used); Using dimer 163b forming monomer in situ (S/C = 400). *Substrate 194 did not dissolve in MeOH, EtOH, ACN and IPA.
Results and Discussion

| 194* | DCM | 28 | (R,R)-175 | 5:2 | 48 | 30 (29) | 81 R |
| 195  | MeOH| 28 | (R,R)-175 | 5:2 | 48 | 58 (69) | 94 R |

Table 45. ATH reduction of quinolines to tetrahydroquinolines (Concentration of 0.45 M with respect to imine, non-dropwise i.e. 5:2 azeotropic mixture used); Using catalyst 175 (S/C = 200). *Substrate 194 did not dissolve in MeOH, EtOH, ACN and IPA.

**Figures in parenthesis indicate conversion after 2 days using 2 mol% catalyst. ***ee of product of 0.5 mol% catalyst loading reaction.

The results show that the reductions of quinolines to tetrahydroquinolines for all the substrates were carried out successfully and with high ee’s, with substrate 195 giving the highest ee of 94% (Table 45). As the reactions were not going to completion the catalyst loading was changed to 2 mol%** from 0.5 mol%, and this gave an increase in % conversion for all the substrates, with the highest conversion given by substrate 120a of 85%, but the reductions still did not go to completion.

In summary, it has now been demonstrated that Ru(II) and Rh(II) complexes are effective catalysts for the ATH reduction of substituted quinolines, which are generally regarded as challenging substrates for this application. Also as seen for ketone reductions (Section 1.4.7), the increased reactivity of “tethered” complexes over the untethered catalysts appears to be key to their capacity to work as effective catalysts in this application.
2.2 Synthesis of ether-linked “tethered” catalyst for the ATH reduction of ketones.

The objective of this project was the synthesis of an ether-linked “tethered” catalyst. Wills and co-workers had previously reported the synthesis of a stereochemically well defined catalyst 173b that controlled the configuration of the metal with the use of a ether-linked “tether”, showing good activity but lacked elements which affect the enantioselectivity of ketone reductions (Section 1.4.7). The ether-linked “tethered” catalyst 207 represented an interesting target to synthesize and includes all the necessary features for making it a desirable catalyst in terms of its promise for rate and enantioselectivity for ketone reductions. The “tether” is linked to the “basic” amine which has proved to be vital for achieving high activity, and the “tether” chain has 4 substituents (-CH₂CH₂OCH₂-), as the 4C alkyl chain “tethered” catalyst 165 having 4 substituents had proved to be the most active catalyst among the rest of its class (160 and 165, Figure 29) (Section 1.4.7). TsDPEN 81, with matching stereocentres and a trans orientation of the phenyl groups was also employed for the synthesis of this catalyst (Section 1.4.5), which in effect will help enhance the rate and enantioselectivity of an ATH reaction.

![Image](image-url)

Figure 29. Ru(II) “tethered” catalyst.
2.2.1 Synthesis of the ether-linked “tethered” catalyst 207.

The initial step in the route for synthesizing 207, using Birch reduction on 2-(benzyloxy)ethanol 196 was unsuccessful as it resulted in the cleavage of the ether (Scheme 81).

\[
\begin{align*}
\text{Scheme 81. Attempted Birch reduction on 2-(benzyloxy)ethanol 196.}
\end{align*}
\]

With the Birch reduction step being problematic, an alternative approach was devised to gain access to the 1, 4-cyclohexadienyl moiety. In the synthesis of catalyst 207 (Scheme 81), the Diels-Alder cycloaddition was employed to attain the 1,4-cyclohexadienyl containing compound. Cycloaddition of isoprene 197 with propiolic acid 198 in THF at reflux temperature furnished 4-methylcyclohexa-1,4-diene carboxylic acid 199\(^{27a}\) in 54% yield as a white solid, which then was reduced using LiAlH\(_4\) in THF giving (4-methylcyclohexa-1,4-dienyl)methanol 200\(^{17j}\) in 81% yield as a colourless oil. The coupling of 200 with tert-butylbromoacetate 201 in NaOH solution and using TBAB led to the formation of 2-((4-methylcyclohexa-1,4-dienyl)methoxy)acetic acid 202\(^{27b}\) in 75% yield as a light yellow solid. Compound 202 was reduced with LiAlH\(_4\) in THF giving 2-((4-methylcyclohexa-1,4-dien-1-yl)methoxy)ethanol 203\(^{17j}\) in >99% yield (quant.) as a yellow oil, and oxidised via Swern oxidation to form 2-((4-methylcyclohexa-1,4-dienyl)methoxy)acetaldehyde 204\(^{20a}\) in >99% yield (quant.) as an orange oil. Reductive amination was carried out in methanol using 204, \(R,R\)-TsDPEN 81\(^{27c}\) and glacial acetic acid to form an imine as an intermediate, which then was reduced to give 4-methyl-N-((1R,2R)-2-((4-methylcyclohexa-1,4-dienyl)methoxy)ethylamino)-1,2-diphenylethyl)benzenesulfonamide 205\(^{20a}\) as a white
solid in 29% yield using sodium cyanoborohydride. The final step was the complexation of $\text{205}$ with ruthenium(III) trichloride hydrate in refluxing IPA, after formation of $\text{205.HCl}$ using HCl (1.25 M in EtOH) in anhydrous DCM, giving $\text{206}^{20a}$ as a black solid in 88% yield (if carried out in ethanol gives a low yield of 14%). The dimer $\text{206}$ could be directly used in ATH reactions, as it forms $\text{207}$ under reaction conditions, in common with related complexes that are converted from their dimer forms to monomer in situ. The formation of monomer $\text{207}^{20a}$ using Et$_3$N in IPA at 80 °C, was successful as confirmed by mass spectroscopy, and $^1\text{H}$ NMR spectroscopic analysis of the crude product. The isolation of the pure complex $\text{207}$, was however challenging in contrast to the alkyl chain complexes which were universally stable to purification by chromatography. Decomposed material was obtained in the attempt to purify $\text{207}$. For this reason monomer $\text{207}$ was either used in crude form, or more conveniently, the dimeric precursor $\text{206}$ was employed directly in ATH reactions.
Problems encountered during the synthesis of 207.

The formation of 202 was successful after 200 was coupled with tert-butylbromoacetate 201 in NaOH solution and using TBAB. This method was employed as the coupling of 200 using NaH proved to be unsuccessful. A test reaction was first carried out (A, Scheme 83) in which benzyl alcohol 208 was coupled to bromoacetic acid 209 using NaH, with the addition of 208, 209 followed by sodium methoxide and methylchloroformate in to a solution of NaH in DMF were carried out at 0 °C, then allowed to stir at rt overnight resulting in a successful formation of 210. The reaction was repeated using 200, and proved to be unsuccessful (B, Scheme 83), also failing when using 201 (C, Scheme 83), tert-butyl(2-idoethoxy)diphenylsilane 211.
(prepared by the drop wise addition of tert-butyl-chlorodiphenylsilane to a solution of 2-iodoethanol and imidazole dissolved in THF) (D, Scheme 83), and when experimenting with temperature.

Further work on the synthesis of the ether-linked “tethered” catalyst.

In an attempt to form aldehyde 204 in a one-pot reaction, alcohol 200 was reacted with 2-bromomethyl-1,3-dioxolone 212 and TBAB in NaOH solution at 0 °C. Stirring the reaction at 70 °C for 1 day had given 213 with 30% yield, and leaving the reaction for 3 days had further increased the yield to 80%. The addition of 1 M HCl and 5 M HCl to 213 had showed changes in the 1H NMR, but the product had decomposed after the addition of conc. HCl. Further investigations need to be carried out for this step as removing the reduction step for the synthesis of the ester-linked “tethered” catalyst, could be highly beneficial when synthesized on a large scale in industry (Scheme 84)
Results and Discussion

2.2.2 Reduction of imine with ether-linked “tethered” dimer 206.

After the successful formation of catalyst 206, it was worth carrying out an ATH reduction on 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline 109a to see how active and stereoselective the catalyst is for this substrate (Scheme 85, Table 46).

Scheme 85. ATH reduction of 109a using catalyst 206.

<table>
<thead>
<tr>
<th>Imine</th>
<th>Catalyst</th>
<th>Temp (°C)</th>
<th>Time (days)</th>
<th>Conversion (%)</th>
<th>ee (%) / Config. (R/S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>109a</td>
<td>(R,R)-206</td>
<td>28</td>
<td>4</td>
<td>100</td>
<td>87 S</td>
</tr>
</tbody>
</table>

Table 46. ATH reduction of 109a to tetrahydroisoquinoline 109a’ (Concentration of 0.45 M with respect to imine, non-dropwise i.e. azeotropic mixture used); Using dimer 206 forming monomer 207 in situ (S/C = 400).
The results showed that catalyst 206 was successful for the reduction of 109a, giving 6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline 109a’ in 90% conv., and a respectable 87% ee (S) after 4 days (Table 46).

2.2.3 Redundation of quinoline with ether-linked “tethered” dimer 206.

The next task was to carry out the ATH reduction with catalyst 206 on 2-methylquinoline 120a (Scheme 86, Table 47).

![Scheme 86. ATH reduction of 2-methylquinoline 120a using catalyst 206.](image)

<table>
<thead>
<tr>
<th>Imine</th>
<th>Catalyst</th>
<th>Temp (°C)</th>
<th>Time (days)</th>
<th>Conversion (%)</th>
<th>ee (%)/ Config. (R/S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>120a</td>
<td>(R,R)-206</td>
<td>28</td>
<td>6</td>
<td>65</td>
<td>61 R</td>
</tr>
</tbody>
</table>

Table 47. ATH reduction of 2-methylquinoline 120a to tetrahydroquinoline 120a’

(Concentration of 0.45 M with respect to quinoline, non-dropwise i.e. azeotropic mixture used); Using dimer 206 forming monomer 207 in situ (S/C = 400).

The reduction of 120a was successful giving the 2-methyl-1,2,3,4-tetrahydroquinoline 120a’ in 65% conv., 61% ee (R) (Table 47). After 24 hrs, the conversion was 57%, and after 6 days it was 65%. The ee obtained for the reduction of 120a is the highest to have been achieved with any Ru(II) “tethered” catalyst.

2.2.4 Reduction of ketones with ether-linked “tethered” dimer 206.

ATH reductions have now been tested out on an imine and a quinoline with catalyst 206. The next step was to focus on the ATH reduction of ketones to alcohols with catalyst 206 (Scheme 87). The majority of substrates tested were reduced successfully,
giving the alcohols with excellent conversions (in the best cases >99%) and enantioselectivities in some cases of >99%). ATH reduction of acetophenone derivatives containing para- \(49c\) and meta-chloro substituents \(49b\), and bicyclic derivatives such as \(\alpha\)-tetralone \(214\) and 4-chromanone \(215\) were reduced in similar conversions and enantioselectivities to acetophenone itself. The ortho-chloro substituted acetophenone derivative \(216\) however gave a reduced ee of 87%, which has been observed previously for reduction of this substrate with a similar catalyst (Scheme 87, Figure 30, Table 48).  

Scheme 87. ATH reduction of ketones, using catalyst \(206\).
Figure 30. ATH reduction of a series of ketones.

<table>
<thead>
<tr>
<th>Ketones</th>
<th>Catalyst</th>
<th>Temp (°C)</th>
<th>Time (days)</th>
<th>Conversion (%)</th>
<th>ee (%)/ Config. (R/S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>49a</td>
<td>(R,R)-206</td>
<td>28</td>
<td>o/n</td>
<td>&gt;99</td>
<td>99 R</td>
</tr>
<tr>
<td>49c</td>
<td>(R,R)-206</td>
<td>28</td>
<td>o/n</td>
<td>&gt;99</td>
<td>96 R</td>
</tr>
<tr>
<td>49b</td>
<td>(R,R)-206</td>
<td>28</td>
<td>2</td>
<td>&gt;99</td>
<td>94 R</td>
</tr>
<tr>
<td>214</td>
<td>(R,R)-206</td>
<td>28</td>
<td>2</td>
<td>&gt;99</td>
<td>&gt;99 R</td>
</tr>
<tr>
<td>215</td>
<td>(R,R)-206</td>
<td>28</td>
<td>o/n</td>
<td>&gt;99</td>
<td>&gt;99 R</td>
</tr>
<tr>
<td>216</td>
<td>(R,R)-206</td>
<td>28</td>
<td>2</td>
<td>100</td>
<td>87 R</td>
</tr>
<tr>
<td>49g</td>
<td>(R,R)-206</td>
<td>28</td>
<td>2</td>
<td>&gt;99</td>
<td>&gt;99 R</td>
</tr>
<tr>
<td>217</td>
<td>(R,R)-206</td>
<td>28</td>
<td>2</td>
<td>11</td>
<td>27 R</td>
</tr>
<tr>
<td>218</td>
<td>(R,R)-206</td>
<td>28</td>
<td>2</td>
<td>6</td>
<td>14 R</td>
</tr>
<tr>
<td>219</td>
<td>(R,R)-206</td>
<td>28</td>
<td>o/n</td>
<td>&gt;99</td>
<td>98 S</td>
</tr>
<tr>
<td>220</td>
<td>(R,R)-206</td>
<td>28</td>
<td>o/n</td>
<td>&gt;99</td>
<td>96 S</td>
</tr>
<tr>
<td>221</td>
<td>(R,R)-206</td>
<td>28</td>
<td>o/n</td>
<td>&gt;99</td>
<td>97 S</td>
</tr>
<tr>
<td>222</td>
<td>(R,R)-206</td>
<td>28</td>
<td>o/n</td>
<td>&gt;99</td>
<td>95 S</td>
</tr>
<tr>
<td>129</td>
<td>(R,R)-206</td>
<td>28</td>
<td>o/n</td>
<td>&gt;99</td>
<td>60 R</td>
</tr>
<tr>
<td>224</td>
<td>(R,R)-206</td>
<td>28</td>
<td>4</td>
<td>22</td>
<td>17 R</td>
</tr>
<tr>
<td>225</td>
<td>(R,R)-206</td>
<td>28</td>
<td>10</td>
<td>99</td>
<td>&gt;99 S</td>
</tr>
<tr>
<td>107a</td>
<td>(R,R)-206</td>
<td>28</td>
<td>4</td>
<td>0</td>
<td>0 -</td>
</tr>
<tr>
<td>141</td>
<td>(R,R)-206</td>
<td>28</td>
<td>4</td>
<td>&gt;99</td>
<td>0 -</td>
</tr>
<tr>
<td>226</td>
<td>(R,R)-206</td>
<td>28</td>
<td>13</td>
<td>&gt;99</td>
<td>71 R</td>
</tr>
</tbody>
</table>

Table 48. ATH reduction of ketones to alcohols (Concentration of 1.62 M with respect to ketone, non-dropwise i.e. azeotropic mixture used); Using dimer 206 forming monomer 207 in situ (S/C = 400).

Propiophenone 49g was reduced successfully, giving 49g’ in excellent conversion, and ee. Increasing the size of the alkyl group to isopropyl and tert-butyl however resulted in an extreme drop in activity and enantioselectivity, giving 217’ and 218’ in poor conv., and ee. This is dissimilar to the alkyl “tethered” complex 160, which is more versatile in this respect. Excellent results were obtained for α-chloroacetophenones 219-221, which lead to alcohols 219’-221’, and are useful intermediates for the formation of epoxides and other chiral building blocks. Related substrates 222 and 225 that contain an O and N heteroatom on the alkyl substituent side can also be reduced successfully in excellent conversions and ee’s. Introducing electron-withdrawing trifluoromethyl groups in to the
substrate appeared to be detrimental to the enantioselectivity, as $129'$ was formed in just 60% ee whilst the ortho-substituted $224$ was reduced in just 22% conversion and 17% ee. An unexpected result was obtained for 2-acetylpyridine $107a$, which was not reduced at all by catalyst $206$ under the reaction conditions used. The reduction of $223$ was unsuccessful as the starting material was decomposing over time.

The reduction of 2-acetylpyridine $107a$ was carried out using catalyst $165$, with identical conditions to when catalyst $206$ was employed previously in the reaction. Reduction of $107a$ was successful giving $107a'$ in >99% conv., and 88% ee, which is in agreement with another alkyl-“tethered” catalyst $160$ previously used for this reduction (Scheme 88, Table 49).$^{20a}$

![Scheme 88. ATH reduction of $107a$, using catalyst $206$ and $163b$.](image)

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Catalyst</th>
<th>Temp (°C)</th>
<th>Time (days)</th>
<th>Conversion (%)</th>
<th>ee (%)$^R$/ Config. $(R/S)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$107a$</td>
<td>$(R,R)$-206</td>
<td>28</td>
<td>4</td>
<td>0</td>
<td>0 -</td>
</tr>
<tr>
<td>$107a$</td>
<td>$(R,R)$-163b</td>
<td>28</td>
<td>o/n</td>
<td>&gt;99</td>
<td>88 $R$</td>
</tr>
</tbody>
</table>

Table 49. ATH reduction of $107a$ to $107a'$ (Concentration of 1.62 M with respect to ketone, non-dropwise i.e. azeotropic mixture used); Using dimer $206$ forming monomer $207$ in situ also dimer $163b$ (forming $165$) (S/C = 400).

At this stage it was worth investigating to see whether or not the substrate was inhibiting the reaction. To test this, the reduction of a 1 : 1 mixture of 2-acetylpyridine $107a$ and acetophenone $49a$ was attempted with catalyst $206$ (Scheme 89).
Scheme 89. ATH reduction of a 1 : 1 mixture of 107a and 49a, using catalyst 206 (S/C = 400).

The results showed that neither of the ketones were reduced (Scheme 89), suggesting that 2-acetylpyridine 107a is inhibiting the catalysis of the reaction, by a mechanism which is presently unclear but may involve an interaction of the protonated N atom of the pyridine with the oxygen atom on the “tether”. This would stabilise the complex between the catalyst and both the substrate and product to the point where product is not released (Figure 31), hence preventing catalyst turnover as reflected in the competition experiment. This additional interaction is not available to 165 and 160, and so is not inhibited by this substrate.

![Substrate inhibits catalysis](image)

Figure 31. 107a inhibits catalysis due to an additional interaction of the protonated pyridine with the O atom on the “tether” in catalyst 207 (formed from dimer 206).

The reduction of cyclohexymethyl ketone 141, which is a useful test ketone for dialkyl substrates, was catalysed by 206 with full conversion however racemic alcohol 141’ was obtained. This is in contrast to the 69% ee achieved for this substrate using alkyl-“tethered” catalyst 160 (Section 1.4.7). The reduction of a structurally similar but unsaturated ketone 226, in contrast, was achieved in full conversion in 71% ee but after
13 days of reaction. The reduction to form **226** could be directed by a similar CH/π interaction as for acetophenone derivatives (Figure 32).

![CH/π interaction](image)

Figure 32. CH/π interaction between η⁶-arene ring of the catalyst and the aromatic ring of the substrate.

### 2.2.5 Comparative studies.

A comparison in activity and selectivity using catalyst **206** (forming **207**), **163b** (forming **165**) and **159** (forming **160**) was carried out for the reduction of **225**, which showed that catalyst **206**, **163b** and **159** all demonstrated similar activity and reactivity for the reduction of **225** (Scheme 90, Table 50).

![Scheme 90](image)

Scheme 90. ATH reduction of **225**, using catalyst **206**, **163b** and **159**.

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Catalyst</th>
<th>Temp (°C)</th>
<th>Time (days)</th>
<th>Conversion (%)</th>
<th>ee (%) / Config. (R/S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>(R,R)-206</td>
<td>28</td>
<td>10</td>
<td>&gt;99</td>
<td>&gt;99 S</td>
</tr>
<tr>
<td>35</td>
<td>(R,R)-163b</td>
<td>28</td>
<td>8</td>
<td>&gt;99</td>
<td>&gt;99 S</td>
</tr>
<tr>
<td>35</td>
<td>(S,S)-159</td>
<td>28</td>
<td>10</td>
<td>&gt;99</td>
<td>&gt;99 R</td>
</tr>
</tbody>
</table>

Table 50. ATH reduction of **225** to **225**' (Concentration of 1.62 M with respect to ketone, non-dropwise i.e. azeotropic mixture used); Using dimer **206** forming monomer **207** *in situ* and dimers also for **163b** (forming **165**) and **159** (forming **160**) (S/C = 400).
In conclusion, the results suggest that the interaction of certain ketones with the ether-linked “tethered” catalyst 206 (forming monomer 207 in situ) is somewhat different to their interaction with the alkyl-chain version such as catalysts 165 and 160. The sense of reduction in each case however shows that the catalyst 206 operates through a mechanism which is analogous to that of complex 165 and 160. This involves a key stabilising CH/π interaction between \( \eta^6 \)-arene ring of the catalyst and the aromatic ring of the substrate.

During the preparation of this thesis, Ikariya et al, published a synthesis of catalyst 207 via a route different to that in this thesis and tested it in the ATH of a range of ketones distinct from the selection in this thesis. The \(^1\)H NMR spectroscopic data of the monomeric complex obtained by Ikariya matched that of the crude material obtained from dimer 206 in this project.

### 2.3 N-Alkylated TsDPEN ligands for ATH reductions.

As now it was established that ether-linked “tethered” catalysts were capable of reducing ketones, it was worth investigating the effects of having an ether- or alcohol-containing chain on the “basic” nitrogen atom without it being “tethered” to the \( \eta^6 \)-arene ring. This transformation can provide means for attaching the catalyst to a heterogeneous support. As mentioned in Section 1.4.3.2, catalyst 84 can be monosubstituted without the loss of catalytic activity or selectivity, provided that the subsituent is a linear alkyl group, as branched or sterically-hindered substituents cause a sharp reduction of activity. In contrast to extensive studies on the primary amine-containing TsDPEN, a relatively small number of successful applications of N-alkylated TsDPEN-derived catalysts have been reported. These include applications to C=C reduction and use in reversible formate decarboxylation studies. In addition, the
application of $N'$-alkylated derivatives of $N$-tosyl-1,2-diaminocyclohexane (TsDAC) to ketone and imine ATH has been reported.\textsuperscript{28d, 28e} Although oxygen-containing chains has not been previously studied, one report on the successful use in ATH of a TsDPEN ligand containing a PEG chain has been published.\textsuperscript{28f} There appear to be no published studies on the use of $N$-hydroxy-functionalised substituents, which have the potential to interact with the ruthenium atom in an analogous manner to a previously-reported catalyst 227 (Figure 33) containing a 2-hydroxyethyl group on the $\eta^6$-arene ring.\textsuperscript{28g} In other related examples published by Ikariya, and NHTf group at the end of a 3-carbon chain from the $\eta^6$-arene ring, i.e. in 228 (Figure 33), was reported to give improved results in the asymmetric hydrogenation during the catalytic cycle.\textsuperscript{28h, 28i}

![Figure 33. Previously reported functionalized Ru(II) catalysts.](image)

### 2.3.1 Preparing $N$-alkylated ligands.

$N$-Alkylated ligands were prepared by via the route shown in Scheme 91. Diols 229a-c were first of all mono protected with the use of tert-butyldiphenylchlorosilane (TBDPSCl) and imidazole in THF at rt.\textsuperscript{26c} In order to prevent diprotection, solvent for n = 2 and n = 3 in 229b-c was replaced with DCM,\textsuperscript{28j} having a saturated solution (protecting group in excess). The monosilylated diols 230a-c were then oxidized to give the aldehydes 231a-c via Swern oxidation,\textsuperscript{29a} followed by aminal formation 232a-c with $(R,R)$-TsDPEN 81 using glacial acetic acid in dry methanol (Scheme 91).\textsuperscript{29a}
Results and Discussion

Scheme 91. Synthesis of hydroxy N-alkylated ligands.

Reduction of the aminals 232a-c using LiAlH₄, resulted in the formation of 233²₉ᵃ and 234 through aminal reduction coupled with desilylation under the same conditions. Ligands 235 and 236 both containing a linear 4C groups, were prepared by an analogous sequence to 233-234, with the difference that the LiAlH₄ treatment at the end of the sequence did not simultaneously remove the silyl group, i.e. the product was silyl ether 235. The silyl group was however removed in a subsequent step using TBAF to furnish 236.²₉ᵃ

2.3.2 Ester-containing ligands.

The ester-containing ligands 240-241 were prepared by reaction of N-hydroxyethylTsDPEN 233 and 236 with acids 238 and 199, using a combination of DCC and DMAP as the coupling reagent in DCM. DCC was however replaced with ethyl-(N',N'-dimethylamino)propylcarbodiimide hydrochloride (EDC), as this carbodiimide reagent and its urea by-product 237 are water soluble, so the by-product and any excess reagent are removed by aqueous extraction. Dicyclohexylurea, the by-product formed from DCC is nearly insoluble in most organic solvents and precipitates
from the reaction mixture as the reaction progresses (Scheme 92).\textsuperscript{20b} The coupling of 233, with propiolic acid 198 was unsuccessful, with both starting materials obtained unreacted.

![Scheme 92. Synthesis of ester-linked N-alkylated ligands.](image)

Dimeric ligands 242 and 243 were prepared by an analogous process, starting from the 1,4-dicarboxylic acid 239. The initial attempts to form ester-linked N-alkylated ligands had failed considerably with the reaction of alcohol 233 to the carboxylic acid 199 transformed in to acid chloride in DCM.\textsuperscript{29c} Also with another alcohol and acid coupling method using methanesulfonic acid, aluminium oxide, sodium bicarbonate in ethyl acetate.\textsuperscript{29d}

### 2.3.3 N-Alkylated Ru(II) complex formation.

A number of isolated complexes 244-247 were also prepared by the reaction of 233-236 with [RuCl\(_2\)(benzene)]\(_2\) in IPA at 80 °C for 1 hr (noting that the use of \(\eta^6\)-benzene gives
significantly improved results over other $\eta^6$-arenes when N-alkylated TsDPENs are employed in ATH reactions) (Scheme 93).\(^{17j}\)

\[
\begin{align*}
233 : R = H, n = 1 \\
234 : R = H, n = 2 \\
235 : R = \text{TBDPS}, n = 3 \\
236 : R = H, n = 3
\end{align*}
\]

Scheme 93. Synthesis of N-alkylated complexes 244-247.

Complexation of ester-linked ligands 240, 242 and 243 proved problematic as long reaction times were required, or else starting ligand was still present. However, after long reaction times the products were formed in small quantities and were quite unstable, along with large quantities of decomposed material. The complexation of dimeric ligand 243, gave a mixture of two products 248 + 249 as suggested by $^1$H NMR and LR MS, along with the starting unreacted ligand 243 (Figure 34).
Figure 34. Products formed after complexation of ligand 243 with \([\text{RuCl}_2(\text{benzene})]_2\).

An attempt to form a “trimeric” ligand 251 was also carried out using acid 250, proving to be unsuccessful, as an unknown product that couldn’t be identified with very broad \(^1\text{H}\) NMR peaks was formed (Scheme 94). Further work was not conducted using the ester-linked ligands.
Results and Discussion

Scheme 94. Attempted synthesis of “trimeric” ligand 251 using 236 and 250 had failed.

**Attempted formation of Ester-linked “tethered” catalyst 252 (dimer).**

As attempts to form the ester with a 1,4-cyclohexadienyl moiety were successful, it was considered worth testing whether an ester-linked “tethered” catalyst could be formed. Complexation using 240, first forming the ligand salt 240.HCl using HCl in DCM, followed by refluxing of the salt in IPA gave a black solid product 252. Product analysis using $^1$H NMR, LR MS and HR MS showed no signs of product formation. It was still however tested for the ATH reduction of acetophenone 49a and cyclohexylmethyl ketone 141, but no conversion was observed and no presence of the monomeric catalyst was seen by LR MS. Monomer formation was also attempted separately by heating 252 with Et$_3$N in IPA at 80 °C, but no product was formed as confirmed by $^1$H NMR and LR MS (Scheme 95).

Scheme 95. Attempted formation of ester-linked “tether” dimer 252 had failed.
2.3.4 Ether-linked \( N \)-alkylated ligands.

The synthesis of ether-linked \( N \)-alkylated ligand was unsuccessful using NaH in THF with 236 and 1,3,5-tris(bromomethyl)benzene 253 at rt (Scheme 96). In the attempt to not waste ligand 236, 4-phenyl-1-butanol 255 was first used in order to optimize conditions for coupling with 253.

![Scheme 96. Attempted synthesis of a “trimeric” ether-linked ligand 254 using 236 and 253 failed.](image)

Using NaH in THF, the coupling was repeated as previously shown, but using 4-phenyl-1-butanol 255 with 1,3,5-tris(bromomethyl)benzene 253. The reaction was carried out at rt and at 60 °C, but the coupling was unsuccessful on both occasions (Scheme 97).

![Scheme 97](image)
Results and Discussion

Scheme 97. Attempted synthesis of a “trimeric” ether-linked test ligand 256 using 255 and 253 failed.

However when the coupling of 255 with 253 was carried out using K$_2$CO$_3$ in acetone at 0 °C, the coupling was successful (Scheme 98, Figure 35). However due to lack of time further studies were not conducted in this area.

Scheme 98. Synthesis of a “trimeric” ether-linked test ligand 256 using 255 and 253.
2.3.5 **Symmetric transfer hydrogenation reduction using Ru(II) N-alkylated complexes and ligands.**

In the ATH of acetophenone, each of the catalysts, both pre-prepared, and formed *in situ*, proved to be effective and gave a product of high enantiomeric excess (Table 51). The N-alkylated complexes were somewhat less active than the unsubstituted and “tethered” complexes, however, with a typical reaction time of 4 days being required for full reduction at rt at 0.5 mol% catalyst loading. Catalyst 244, with the shortest chain, was the least active, requiring 10 days to achieve >99% conversion to product. This may indicate that there is some reversible interaction of the OH group with the Ru(II) atom, thereby reducing its effective concentration in the reaction. This would have a close analogy to the effect observed by White for hydroxyethyl-substituted complex 227. As the chain becomes longer, this reduction in activity is attenuated and, for the 4C complex, there is essentially no difference in activity between the silylated 247 and the free OH complex 246, as would be expected on entropic grounds. In general, the isolated complexes were more active than the complexes formed *in situ* (Scheme 99, Table 51).
Scheme 99. ATH reduction of acetophenone 49a, using complex 244-247 and ligands 233-236 and 240-243 in conjunction with [RuCl₂(benzene)]₂ (S/C = 200).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (days)</th>
<th>Conv. (%)</th>
<th>ee (%) / Config. (R/S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>233/Ru</td>
<td>13</td>
<td>&gt;99</td>
<td>92 R</td>
</tr>
<tr>
<td>2</td>
<td>234/Ru</td>
<td>8</td>
<td>31</td>
<td>92 R</td>
</tr>
<tr>
<td>3</td>
<td>235/Ru</td>
<td>6</td>
<td>&gt;99</td>
<td>95 R</td>
</tr>
<tr>
<td>4</td>
<td>236/Ru</td>
<td>6</td>
<td>93</td>
<td>94 R</td>
</tr>
<tr>
<td>5</td>
<td>244</td>
<td>3</td>
<td>88</td>
<td>93 R</td>
</tr>
<tr>
<td>6</td>
<td>245</td>
<td>2</td>
<td>&gt;99</td>
<td>94 R</td>
</tr>
<tr>
<td>7</td>
<td>246</td>
<td>2</td>
<td>&gt;99</td>
<td>95 R</td>
</tr>
<tr>
<td>8</td>
<td>247</td>
<td>2</td>
<td>&gt;99</td>
<td>95 R</td>
</tr>
<tr>
<td>9</td>
<td>240/Ru</td>
<td>5</td>
<td>98</td>
<td>95 R</td>
</tr>
<tr>
<td>10</td>
<td>241/Ru</td>
<td>5</td>
<td>97</td>
<td>96 R</td>
</tr>
<tr>
<td>11</td>
<td>242/Ru</td>
<td>5</td>
<td>92</td>
<td>96 R</td>
</tr>
<tr>
<td>12</td>
<td>243/Ru</td>
<td>8</td>
<td>&gt;99</td>
<td>95 R</td>
</tr>
</tbody>
</table>

Table 51. ATH reduction of acetophenone 49a, using complex 244-247 and ligands 233-236 and 240-243 in conjunction with [RuCl₂(benzene)]₂ (S/C = 200).

The ester-terminated complexes formed 240-243 were also efficient catalyst for the ATH of acetophenone, giving products of 95-96% ee in high conversion. The presence
of a nearby ester appears entirely compatible with catalyst activity. It should be noted that all of the reactions in Table 51 were followed over time order to confirm that no racemisation was taking place during their course (Table 52-63).

In conclusion, complexes containing a straight-chain substituent attached to a hydroxyl, ether or ester function also act as effective catalysts. This may represent a useful means for the attachment of the catalyst to a heterogeneous support.

**Conversions and enantioselectivities of complexes 244-247 and ligands 233-236 and 240-243 over time.**

**Catalyst 244**

<table>
<thead>
<tr>
<th>Time</th>
<th>Conversion</th>
<th>Enantiomeric excess (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 hr</td>
<td>1.3</td>
<td>-</td>
</tr>
<tr>
<td>5 hrs 40 mins</td>
<td>6.4</td>
<td>92</td>
</tr>
<tr>
<td>24 hrs 10 mins</td>
<td>28</td>
<td>92</td>
</tr>
<tr>
<td>48 hrs 40 mins</td>
<td>63</td>
<td>93</td>
</tr>
<tr>
<td>72 hrs 40 mins</td>
<td>88</td>
<td>93</td>
</tr>
</tbody>
</table>

Table 52.

**Catalyst 245**

<table>
<thead>
<tr>
<th>Time</th>
<th>Conversion</th>
<th>Enantiomeric excess (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 hrs 40 mins</td>
<td>87</td>
<td>94</td>
</tr>
<tr>
<td>25 hrs 10 mins</td>
<td>96</td>
<td>95</td>
</tr>
<tr>
<td>42 hrs 10 mins</td>
<td>&gt;99</td>
<td>94</td>
</tr>
</tbody>
</table>

Table 53.

**Catalyst 246**

<table>
<thead>
<tr>
<th>Time</th>
<th>Conversion</th>
<th>Enantiomeric excess (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 hrs 40 mins</td>
<td>93</td>
<td>95</td>
</tr>
<tr>
<td>25 hrs 10 mins</td>
<td>98</td>
<td>95</td>
</tr>
<tr>
<td>42 hrs 10 mins</td>
<td>&gt;99</td>
<td>95</td>
</tr>
</tbody>
</table>

Table 54.
## Results and Discussion

### Catalyst 247

<table>
<thead>
<tr>
<th>Time</th>
<th>Conversion</th>
<th>Enantiomeric excess (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 hrs 40 mins</td>
<td>94</td>
<td>95</td>
</tr>
<tr>
<td>25 hrs 10 mins</td>
<td>98</td>
<td>96</td>
</tr>
<tr>
<td>42 hrs 10 mins</td>
<td>&gt;99</td>
<td>95</td>
</tr>
</tbody>
</table>

Table 55.

### Ligand 233

<table>
<thead>
<tr>
<th>Time</th>
<th>Conversion</th>
<th>Enantiomeric excess (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 hrs 50 mins</td>
<td>-</td>
<td>-</td>
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<tr>
<td>23 hrs 5 mins</td>
<td>7.8</td>
<td>91</td>
</tr>
<tr>
<td>94 hrs 20 mins</td>
<td>60</td>
<td>90.4</td>
</tr>
<tr>
<td>141 hrs 50 mins</td>
<td>89</td>
<td>91</td>
</tr>
<tr>
<td>311 hrs 50 mins</td>
<td>&gt;99</td>
<td>92</td>
</tr>
</tbody>
</table>

Table 56.

### Ligand 234

<table>
<thead>
<tr>
<th>Time</th>
<th>Conversion</th>
<th>Enantiomeric excess (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 hrs 45 mins</td>
<td>10</td>
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<tr>
<td>41 hrs 45 mins</td>
<td>20.5</td>
<td>93</td>
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<tr>
<td>116 hrs 45 mins</td>
<td>30</td>
<td>92</td>
</tr>
<tr>
<td>138 hrs 45 mins</td>
<td>30</td>
<td>92</td>
</tr>
<tr>
<td>185 hrs 45 mins</td>
<td>31</td>
<td>92</td>
</tr>
</tbody>
</table>

Table 57.

### Ligand 235

<table>
<thead>
<tr>
<th>Time</th>
<th>Conversion</th>
<th>Enantiomeric excess (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 hrs 45 mins</td>
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<tr>
<td>41 hrs 45 mins</td>
<td>73.4</td>
<td>95</td>
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<tr>
<td>116 hrs 45 mins</td>
<td>&gt;99</td>
<td>95</td>
</tr>
<tr>
<td>138 hrs 45 mins</td>
<td>&gt;99</td>
<td>95</td>
</tr>
</tbody>
</table>

Table 58.
Results and Discussion

Ligand 236

<table>
<thead>
<tr>
<th>Time</th>
<th>Conversion</th>
<th>Enantiomeric excess (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 hrs 45 mins</td>
<td>25</td>
<td>93</td>
</tr>
<tr>
<td>41 hrs 45 mins</td>
<td>67.3</td>
<td>94</td>
</tr>
<tr>
<td>116 hrs 45 mins</td>
<td>93</td>
<td>94</td>
</tr>
<tr>
<td>138 hrs 45 mins</td>
<td>93</td>
<td>94</td>
</tr>
<tr>
<td>185 hrs 45 mins</td>
<td>93</td>
<td>93.4</td>
</tr>
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Table 59.

Ligand 240

<table>
<thead>
<tr>
<th>Time</th>
<th>Conversion</th>
<th>Enantiomeric excess (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 hrs</td>
<td>51</td>
<td>96</td>
</tr>
<tr>
<td>41 hrs</td>
<td>88</td>
<td>97</td>
</tr>
<tr>
<td>113 hrs</td>
<td>98</td>
<td>95</td>
</tr>
</tbody>
</table>

Table 60.

Ligand 241

<table>
<thead>
<tr>
<th>Time</th>
<th>Conversion</th>
<th>Enantiomeric excess (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 hrs</td>
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<td>96</td>
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<tr>
<td>41 hrs</td>
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<td>95</td>
</tr>
<tr>
<td>113 hrs</td>
<td>97</td>
<td>96</td>
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</tbody>
</table>

Table 61.

Ligand 242

<table>
<thead>
<tr>
<th>Time</th>
<th>Conversion</th>
<th>Enantiomeric excess (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 hrs</td>
<td>4</td>
<td>89</td>
</tr>
<tr>
<td>23 hrs</td>
<td>48</td>
<td>95</td>
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<tr>
<td>46 hrs 30 mins</td>
<td>78</td>
<td>97</td>
</tr>
<tr>
<td>119 hrs 30 mins</td>
<td>92</td>
<td>96</td>
</tr>
</tbody>
</table>

Table 62.

Ligand 243

<table>
<thead>
<tr>
<th>Time</th>
<th>Conversion</th>
<th>Enantiomeric excess (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 hrs 45 mins</td>
<td>11</td>
<td>94</td>
</tr>
<tr>
<td>Time</td>
<td>TDI (%)</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>---------------</td>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>41 hrs 45 mins</td>
<td>40.1</td>
<td>95</td>
</tr>
<tr>
<td>116 hrs 45 mins</td>
<td>93</td>
<td>95</td>
</tr>
<tr>
<td>138 hrs 45 mins</td>
<td>96</td>
<td>95</td>
</tr>
<tr>
<td>185 hrs 45 mins</td>
<td>&gt;99</td>
<td>95</td>
</tr>
</tbody>
</table>

Table 63.

2.4 Further work on the synthesis of “tethered” Ru(II) catalysts.

Further work that was carried out during the course of this PhD project, included the attempted synthesis of catalysts 257-261 (Figure 36).

![Figure 36. Attempted synthesis of the Ru(II) “tethered” catalysts 257-261.](image)

2.4.1 Synthesis of the N-linked “tethered” catalyst 257.

The synthesis of the N-linked “tethered” catalyst was the next task in this project after the successful synthesis of the ether-linked catalyst 207, as bulkier groups can be functionalized on the “tether”, and its effects on ATH reductions is worth investigating (Section 1.4.7). In order to proceed with the synthesis, it was vital that 200 was converted into a good leaving group for the successful insertion of benzylamine. The attempts to tosylate and mesylate proved to be unsuccessful as the products formed 262/263 were very sensitive and possibly reacted with other sources/impurities...
present in solution. To overcome this problem, 200 was successfully converted to an aldehyde so that reductive amination with benzylamine could be carried out. 4-methylcyclohexa-1,4-dienecarbaldehyde 264 via Swern oxidation\textsuperscript{20a} with the use of oxalylchloride, dimethylsulfoxide and triethylamine in dichloromethane at -78 °C was successfully formed in >99% yield (quant.) (Scheme 100).

![Scheme 100. Attempted conversion of the alcohol 200 to a good leaving group.](image)

Reductive amination was carried out in methanol using 264, benzylamine and glacial acetic acid to form an imine, which then was reduced to give \(N\)-Benzyl (4-methylcyclohexa-1,4-dienyl) methanamine\textsuperscript{20a} 265 as a yellow oil in 75% yield using sodium cyanoborohydride. The steps that need to be carried out for the completion of this catalyst will now be outlined. The amine 265 needs to be coupled with tert-butylbromoacetate 201 in NaOH solution and using TBAB to give 266,\textsuperscript{27b} which would then be reduced with LiAlH\textsubscript{4} in THF to give 267\textsuperscript{17j}, and oxidised via Swern oxidation to form 268\textsuperscript{20a}. Reductive amination in methanol would then be carried out using 268, \(R,R\)-TsDPEN 81 and glacial acetic acid to form an imine, then reduced to give 269\textsuperscript{20a} using sodium cyanoborohydride. The final step would then be the complexation of 269.HCl salt which is formed by the addition of hydrochloric acid in DCM, and then
complexation with ruthenium(III) trichloride hydrate in IPA at reflux temperature, to form $^{270}^{20a}$, which in situ would form $^{257}$ or can isolate the monomer $^{257}$ by the reaction of dimer $^{270}$ with Et$_3$N in IPA for 1 hr$^{20a}$ (Scheme 101). Due to insufficient time, the synthesis could not be completed.

Scheme 101. Proposed synthesis of the $N$-linked “tethered” catalyst $^{257}$. This synthesis was not completed.

### 2.4.2 Synthesis of the ether-linked “tethered” Ru(II) catalyst with functionalized arene ring.

Investigations into the modification of the $\eta^6$-arene ring have been carried out previously in the Wills group, preparing derivatives of “tethered” catalysts $^{148}$-$^{151}$ and $^{152}$-$^{155}$ with a variety of functional groups on the arene ring using a [4 + 2] cycloaddition step. This area was further investigated, with the replacement of the alkyl “tether” with the ether-linked “tether” and having monotosyl diamine ligand replacing...
the previously used amino alcohol and sulfonylated diamine. It was previously demonstrated by Noyori that mesitylene or \( p \)-cymene arene ligands were less reactive than unsubstituted benzene, but gave better enantioselectivities. For this reason, the mesitylene functionality was incorporated into the original ether-linked “tethered” catalyst 206 (forming 207 \textit{in situ}) to give 258. The synthesis of catalysts 259-261 were carried out as they seemed interesting, and because useful information could be generated with the use of these catalysts for the ATH reduction of aromatic and dialkyl ketones.

The attempted synthesis of the isoprenes required for the cycloaddition step has been shown in Scheme 102. Substrate 272 and 274-275 were readily available; however 273 had to be prepared by the reaction of 271 with AcOK in refluxing ethanol, giving 273 in 31\% yield.\textsuperscript{30a} The conversion of the C=O group to C=C was unsuccessful with 272 using methyltriphenylphosphonium bromide, sodium hexamethyldisilazide in 1,4 dioxane at 60 °C,\textsuperscript{30b} as it was very volatile and difficult to isolate. The same reaction using 273 had formed a mixture of 280 and 281 instead of 277. It was however successful for the formation 278 and 279 (Scheme 102).
Scheme 102. Synthesis of the required isoprene 276-279, with successful product formation of 278-279, but unsuccessful for 276-277.

Cycloaddition reaction of 278 and 279 using 282 and hydroquinone in refluxing toluene had failed to deliver the expected products, instead giving decomposed material (Scheme 103).
Scheme 103. Attempted cycloaddition reaction of 278 and 279 with 282. These reactions were unsuccessful.

3. **Appendix; Additional studies completed within the project.**

3.1 **Asymmetric transfer hydrogenation reductions of imines derived from β-tetralone 223.**

An early objective in this project was to synthesize a series of useful acyclic imine substrates derived from β-tetralone 223 (Figure 37), and then examine their asymmetric reduction using Ru(II) untethered and “tethered” complexes. Synthesizing acyclic imines derived from 223 is unusual, rare and it produces some interesting amine targets as shown in Scheme 104 and Scheme 105.

![Figure 37. Structure of β-tetralone 223.](image)

In mammals, melatonin (N-acetyl-5-methoxytryptamine, MLT) 286, a neurohormone modulates a variety of cellular, neuroendocrine and physiological processes through the activation of at least two high-affinity G-protein coupled receptors, named MT₁ and MT₂. Piersanti developed a novel, efficient and diastereoselective procedure for the gram-scale synthesis of cis-4-phenyl-2-propionamidotetralin (4-P-PDOT) 289, a selective MT₂ melatonin receptor antagonist. The synthetic strategy involved the conversion of 4-phenyl-2-tetralone 287 derived from 223 to enamide 288 by refluxing under nitrogen, 287 with propionamide and p-toluenesulfonic acid in toluene using Dean-Stark apparatus affording 288 as a light yellow oil in 95% yield after column
chromatography and recrystallisation. A diastereoselective reduction of 288 was carried out by cooling down a solution of 288 in trifluoroacetic acid to -10 °C followed by the dropwise addition of triethylsilane affording 289 in 71% yield after column chromatography and recrystallisation\textsuperscript{31c} (Scheme 104).

![Scheme 104. Synthesis of 4-P-PDOT 289, a selective MT\textsubscript{2} melatonin receptor antagonist.](image)

The pharmacological importance of the 2-aminotetralin (2-amino-1,2,3,4-tetrahydronaphthalene) 294 structure has been known for a long time. Initially, aminotetralins were characterized by their sympathomimetic action (causing mydriasis, contraction of the uterus, changes in blood pressure and respiration, and increased intestinal motility in test animals). During the late sixties the dopaminergic activity of 2-aminotetralins was identified which led to an active synthesis program. For the synthesis of a complex 294 carried out by Hans-Jurgen Federsel (Astrazeneca), the nitrogen at the stereogenic centre was introduced by a reductive amination of 8-bromo-5-methyl-3,4-dihydronaphthalen-2(1\textit{H})-one 290 derived from 223 with phenylethylamine, firstly forming the intermediate imine 291 with the addition of p-toluenesulfonic acid, and then forming the resulting amine 292 with a sodium
borohydride reduction. The Buchwald-Hartwig approach with palladium acetate in the presence of BINAP afforded the piperazine coupled product 293. Finally carrying out a hydrogenation followed by the addition of benzoic acid resulted in the formation of the complex 294 in 88% yield\textsuperscript{31d} (Scheme 105).

Scheme 105. Synthesis of a complex 2-Aminotetralin 294, with ‘pharmaceutical significance’

A series of β-tetralone derived imines that were considered worthy of investigation are shown in Figure 38.

Figure 38. C=N reduction substrates
Attempted synthesis of \((E)-1-(3,4\text{-dihydronaphthalen}-2(1\text{H})\text{-ylidene})\text{-2-phenylhydrazine}\) $295$.  

The first objective was to synthesize $295$, however the reaction of a phenylhydrazine with $223$ initially forms $295$, but this can then isomerize to the respective enamine $295'$ (or 'ene-hydrazine'). After protonation, a cyclic [3,3]-sigmatropic rearrangement can occur producing an imine. The resulting imine can form a cyclic aminoacetal (or aminal), which under acid catalysis eliminates NH$_3$, resulting in the energetically favorable aromatic indole $295''$ (Scheme 106). This is the Fischer indole synthesis. Care must be taken to stop at the imine stage.

Scheme 106. Reaction of $223$ with phenylhydrazine to give $295''$ instead of $295$.

In the event, the condensation reaction under acidic conditions resulted in the formation of the aromatic indole $295''$ (in 91% Yield as an orange-red oil) and not the desired $295$. This particular reaction proved to be unsuccessful without acidic conditions and using heat in an attempt to avoid the Fischer indole reaction (Scheme 107).
Scheme 107. Reaction of 223 with phenylhydrazine, with heat and without acidic conditions.

Synthesis of Methyl [3,4-dihydro-2(1H)-naphthalen-ylidene]-hydrazinecarboxylate 296.

The next objective was to successfully synthesize 296 using a method in the literature published by Beam. The reaction was carried out by the addition of methylhydrazinocarboxylate and 223 in methanol, stirring at 50 °C overnight affording 296 as orange-white crystals in 66% yield (Scheme 108). As there were distinctive impurities present in the crude product as shown by NMR analysis, purifying the crude product was necessary before any reductions were carried out.

Scheme 108. Reaction of 223 with methylhydrazinocarboxylate to give 296.

Purification methods such as Column chromatography, Kugelrohr distillation and recrystallization all proved unsuccessful.
The structural properties of 296 were worthy of further investigation, therefore a variable temperature NMR of 296 was recorded at 25 °C, 40 °C and 50 °C (Figure 39).

Figure 39. NMR analysis of 296 at various temperatures.

The results were informative, as the peaks marked with an arrow are increasing in height as the temperature is increased. This indicates that the speed of rotation about the C-N bond is increasing with increasing temperature, as the NMR machine is unable to differentiate between the two different isomers causing a compressed tall peak to appear. The large energy barrier between E/Z isomers clearly eliminates the possibility of ‘flipping’ of the E form to the Z form (rotation about the N-N bond) and vice versa. Rotation about the C-N bond is of low energy barrier, and can be held responsible for the change in NMR with increasing temperature (Figure 39-40).
This substrate was proving to be quite problematic and so it was not further used as part of this project.

**Synthesis of (R,E)-N-(3,4-dihyronaphthalen-2(1H)ylidene)-1-phenylethanamine 297.**

The synthesis of 297 was carried out using (R)-α-methylbenzylamine and 223, which was difficult at first as various procedures from previous literature were tested out, all proving to be unsuccessful. But the procedure published by Carlson, Larsson and Hansson in 1992 proved to be successful giving 297 which is in equilibrium with enamine 297', using titanium tetrachloride as the water trapping agent, deoxygenating every reagent/solvent used, and keeping the reaction under argon at all times, even while filtering out the precipitate formed. The dark green crude product formed was purified using Khugelrohr distillation, giving a clear yellow oil in 36% yield (Scheme 109). This particular product is highly air sensitive, light sensitive and has to be stored at low temperatures in order to avoid colour change and decomposition.
Scheme 109. Reaction of 223 with (R)-alpha-methylbenzylamine giving 297.

Reductions using sodium cyanoborohydride and the untethered catalyst 38 were carried out on 297 to try and obtain N-((R)-1-phenylethyl)-1,2,3,4-tetrahydronaphthalen-2-amine 301.

Sodium cyanoborohydride reduction was successfully carried out to give a standard sample of both diastereoisomers of 301 in 83% yield, as confirmed by $^1$H NMR and MS analysis (Scheme 110, Figure 41).

Scheme 110. Reduction of 297 using NaBH$_3$CN, giving the amine 301.
Reduction using the untethered catalyst 38 was unsuccessful as shown by LR MS (Figure 42) and $^1$H NMR analysis (Scheme 111), giving a ~50:50 mixture of $\beta$-tetralone 223 and an unknown product, which couldn’t be identified. The result was also quite similar when a few attempted reductions were carried out using “tethered” catalyst 163b instead of the untethered catalyst 38.

Scheme 111. Reduction of 297 using the untethered catalyst 38 (S/C = 200).
Figure 42. LR MS of the unknown product formed from the reduction of 297 with the untethered catalyst 38.

**Synthesis of (E)-1-(3,4-dihydronaphthalen-2(1H)-ylidene)semicarbazide 298.**

The preparation of 298 was quite straightforward and followed a literature precedent published by Dimmock and Pandeya.\(^{31h}\) Reacting a mixture of semicarbazide hydrochloride, sodium acetate and water with a solution of 223 in ethanol gave 298 as white crystals in 70% yield (Scheme 112). The reductions carried out with 298 were unsuccessful as a lot of solvent was required to dissolve 298. The two recommended solvents for ATH reductions giving best yields and conversion rates are acetonitrile and methanol, however neither was able to dissolve the product using recommended quantities.

![Scheme 112. Reaction of 223 with semicarbazide, giving 298.](image)

The racemic standard of 298 was however successfully prepared using NaBH\(_3\)CN, acetic acid in methanol, giving 302 after column chromatography (Scheme 113).
Scheme 113. Reduction of 298 using NaBH₃CN giving 302.

Synthesis of (1E,5E)-1,5-bis(3,4-dihyronaphthalen-2(1H)-ylidene)carbonohydrazide 299.

Synthesis of 299 was successfully carried out using the same literature published by Dimmock and Pandeya³¹h for synthesis of 298. The addition of carbohydrazide in methanol to 223 in methanol, and after the solution was stirred for 20 mins, 299 had formed as grey crystals in 46% yield (Scheme 114). The crude product contained some impurities, which even after recrystallisation had remained.

Scheme 114. Reaction of 223 with carbohydrazide, giving 299.

Product 299 encountered similar solubility issues that were previously observed for 298.

Synthesis of (Z)-N-(3,4-dihyronaphthalen-2(1H)-ylidene)benzenamine 300.

The final objective was to successfully synthesize 300. The synthesis of 300 was carried out by following the same procedure as for making 297 as this substrate has not been synthesised before.³¹g An orange-red oil was formed in 75% yield (Scheme 115). ¹H NMR and LR MS analysis of the crude product showed the presence of 300. Distillation and various purification methods such as column chromatograph had proved to be unsuccessful, giving decomposed material.
Scheme 115. Reaction of 223 with aniline, giving 300.

Due to a series of implications in this project, work in this area was not further carried out.

All the air sensitive reactions were carried out under an argon or nitrogen atmosphere. Room temperature (rt) refers to ambient temperature (20-22 °C), 0 °C refers to an ice slush bath and -78 °C refers to a dry ice acetone bath. Heated experiments were conducted using thermostatically controlled oil baths or Asynt aluminium heating blocks. Reactions were monitored by Thin Layer Chromatography (TLC) using aluminium backed silica gel 60 (F₂₅₄) plates, visualised using UV₂₅₄ nm, PMA, iodine, potassium permanganate and ninhydrin dips as appropriate. ¹³C-NMR spectra were recorded on a Bruker DPX-300 (300 MHz) or a Bruker DPX-400 (400 MHz). All chemical shifts are reported in ppm downfield from TMS (Me₄Si). Coupling constants (J) are reported in Hz. Multiplicity in ¹H-NMR is reported as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), octet (oct), double doublet (dd), triple triplet (tt), broad singlet (br s), broad multiplet (br m) and multiplet (m). Mass spectra were recorded on an Esquire 2000. High resolution mass spectra were recorded on Bruker Micro ToF. Infrared spectra were recorded on PerkinElmer spectrum100. The optical rotations were measured on Optical Activity Ltd. AA-1000 Polarimeter. The Chiral HPLC measurements were carried out on HPLC consisting of a Gilson 811B Dynamic Mixer, a Gilson 805 Monometer Module, a Gilson 305 Piston Pump, Merck-Hitachi L-4000 UV detector linked to HEWLETT PACKARD 3396 Series II integrator with CHIRAL PAK IA/IB column (0.46 cm x 25 cm) or CHIRAL CEL OD-H/OD column (0.46 cm x 25 cm). The chiral GC measurements were done on HEWLETT PACKARD 5890 linked to HEWLETT PACKARD HP3396A integrator or PERKIN-ELMER 8500 chromatography linked to PC running DataApex Clarity software with Chrompak CP-Chirasil Dex Cβ column. Melting points were determined on a Stuart scientific melting point apparatus and are uncorrected. Purification of compounds was carried out by
using flash column chromatography using silica gel of mesh size 230-400/ Florisil of mesh 100-200 or Kugelrohr distillation using BÜCHI GKR-51.

4.1 Procedures from Section 2.1

Synthesis of 4-(cyclohexa-1,4-dienyl)butan-1-ol (303).

This is a known compound and has been fully characterised.\textsuperscript{20a}

A solution of 4-phenylbutan-1-ol (3.30 g, 3.39 cm\textsuperscript{3}, 22 mmol) in ethanol (10 cm\textsuperscript{3}) was slowly added to a refluxing solution of ammonia (250 cm\textsuperscript{3}) containing ethanol (70 cm\textsuperscript{3}) at -78 °C while stirring. Small cleaned (with hexane) sodium pieces were added to the reaction mixture until the blue colour persisted. After the addition of sodium over the course of 7 hours with regular additions of ethanol (5-10 cm\textsuperscript{3}) to facilitate stirring, the reaction mixture was then left overnight to allow the remaining ammonia to evaporate. Saturated NH\textsubscript{4}Cl\textsubscript{(aq)} (100 cm\textsuperscript{3}) was added to the reaction, which was then extracted using DCM (3 x 30 cm\textsuperscript{3}). The combined organic layers were dried (MgSO\textsubscript{4}), filtered and concentrated under reduced pressure to afford \textbf{303} as a light orange oil (3.30 g, 21.68 mmol, \textgreater99\%); \textdelta\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 5.75-5.67 (2 H, m, HC=CH), 5.48-5.40 (1 H, m, C=CH), 3.65 (2 H, t, J 6.3, CH\textsubscript{2}OH), 2.70-2.67 (2 H, m, C=CCH\textsubscript{2}C=C), 2.60-2.55 (2 H, m, C=CCH\textsubscript{2}C=C), 2.00 (2 H, t, J 7.0, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}OH), 1.65-1.45 (4 H, m, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}OH) and 1.31 (1 H, br s, OH); \textdelta\textsubscript{C} (101 MHz, CDCl\textsubscript{3}) 134.74 (C), 124.31 (CH), 124.27 (CH), 118.45 (CH), 62.63 (CH\textsubscript{2}), 37.16 (CH\textsubscript{2}), 32.33 (CH\textsubscript{2}), 28.86 (CH\textsubscript{2}), 26.73 (CH\textsubscript{2}) and 23.43 (CH\textsubscript{2}). The data matched that previously reported.

Synthesis of 4-(cyclohexa-1,4-dienyl)butanal (304).
This is a known compound and has been fully characterised.\textsuperscript{20a}

The solution of oxalylchloride (2 M in DCM, 7.78 cm\textsuperscript{3}, 15.55 mmol) in anhydrous DCM (20 cm\textsuperscript{3}) was cooled to -78 °C, and to this was slowly added DMSO (2.21 cm\textsuperscript{3}, 31.10 mmol) in DCM (10 cm\textsuperscript{3}) by syringe. The solution was stirred for 30 minutes at -78 °C before 4-(cyclohexa-1,4-dienyl)butan-1-ol \textbf{303} (1.82 g, 11.96 mmol) in DCM (30 cm\textsuperscript{3}) was slowly added at the same temperature. After stirring for 45 minutes at -78 °C, Et\textsubscript{3}N (10 cm\textsuperscript{3}, 71.69 mmol) was added, and the reaction mixture was allowed to warm up to rt. After 60 minutes, water (75 cm\textsuperscript{3}) was added, and the mixture was extracted with DCM (3 x 40 cm\textsuperscript{3}). The combined organic layers were dried (MgSO\textsubscript{4}), filtered and concentrated under reduced pressure to give \textbf{304} as a light orange oil (1.82 g, 12.12 mmol, >99% quantitative conversion, includes traces of solvent); δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 9.77 (1 H, s, CH=O), 5.74-5.66 (2 H, m, HC=CH), 5.42 (1 H, br s, C=CH), 2.72-2.63 (2 H, m, C=CCH\textsubscript{2}C=C), 2.62-2.55 (2 H, m, C=CCH\textsubscript{2}C=C), 2.42 (2 H, t, J 7.3, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CHO), 1.99 (2 H, t, J 7.3, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CHO) and 1.75 (2 H, quin, J 7.3, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CHO); δ\textsubscript{C} (101 MHz, CDCl\textsubscript{3}) 202.63 (CH=O), 133.78 (C), 124.32 (CH), 124.23 (CH), 119.46 (CH), 43.26 (CH\textsubscript{2}), 37.16 (CH\textsubscript{2}), 28.86 (CH\textsubscript{2}), 26.71 (CH\textsubscript{2}) and 20.00 (CH\textsubscript{2}). The data matched that previously reported for this compound.

\textbf{Synthesis of (R, R)-N-(4-cyclohexa-1,4-dienyl)butyl-1,2-diphenyl-N’-tosylethanediamine (162b).}
This is a known compound and has been fully characterised.\textsuperscript{20a}

To a suspension of powdered molecular sieves (4 Å, 0.50 g) in dry methanol (30 cm\(^3\)) was added 4-(cyclohexa-1,4-dienyl)butanal \textbf{304} (265 mg, 1.76 mmol), \((R, R)\)-TsDPEN \textbf{81} (712 mg, 1.94 mmol) and glacial acetic acid (4 drops). The reaction mixture was stirred at rt and monitored by TLC. After 2 hrs, the imine had formed (observed by TLC), and sodium cyanoborohydride (528 mg, 8.44 mmol) was added. The reaction was left to stir overnight at rt. Molecular sieves were removed by filtration, and the solution was concentrated under reduced pressure. The residue was re-dissolved in DCM (40 cm\(^3\)). The organic phase was washed with saturated NaHCO\(_3\) (40 cm\(^3\)) and brine (40 cm\(^3\)), dried (MgSO\(_4\)), filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (10→30 \% v/v ethyl acetate/hexane) to afford \textbf{162b} as a white solid (265 mg, 0.53 mmol, 30 \%); \(\delta_H\) (400 MHz, CDCl\(_3\)) 7.37 (2 H, d, \(J\) 8.5, 2 x NHSO\(_2\)Ar-o-CH\(_3\)), 7.16-7.11 (3 H, m, 3 x Ar-H), 7.08-7.01 (5 H, m, 5 x Ar-H), 6.97-6.89 (4 H, m, 4 x Ar-H), 6.29 (1 H, br s, NHTs), 5.74-5.67 (2 H, m, HC=CH), 5.35 (1 H, br s, C=CH\(_2\)), 4.24 (1 H, d, \(J\) 8.0, TsNHC\(_3\)), 3.60 (1 H, d, \(J\) 8.0, NHCH\(_2\)), 2.72-2.65 (2 H, m, C=CH\(_2\)C=CH\(_2\)), 2.32 (3 H, s, TsCH\(_3\)), 1.90 (2 H, t, \(J\) 6.5, NHCH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)), 1.41-1.30 (5 H, m, NHCH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\)CH\(_2\) + NH); \(\delta_C\) (101 MHz, CDCl\(_3\)) 142.69 (C), 139.40 (C), 138.41 (C), 137.09 (C), 134.70 (C), 129.09 (2 x CH), 128.30 (2 x CH), 127.90 (2 x CH), 127.59 (2 x CH), 127.44 (CH), 127.40 (2 x CH), 127.25 (CH), 127.15 (2 x CH), 124.35 (CH), 124.32 (CH), 118.49 (CH), 67.86 (CH), 63.08 (CH), 47.03 (CH\(_2\)), 37.20 (CH\(_2\)), 29.64 (CH\(_2\)), 28.87 (CH\(_2\)), 24.76 (CH\(_2\)), 23.44 (CH\(_2\)) and 21.44 (CH\(_3\)). The data matched that previously reported for this compound.

\textbf{Synthesis of} \(N-[(1R, 2R)-1,2\text{-Diphenyl-2-(4-phenylbutylamino)-ethyl}]\text{-4-methylbenzenesulfonamide ammonium chloride ruthenium dimer (163b).}
This is a known compound and has been fully characterised.\textsuperscript{20a}

To a stirred solution of \((R,R)-N-(4\text{-cyclohexa-1,4-dienyl})\text{butyl})-1,2\text{-diphenyl-}N'\text{-tosylethane-diamine 162b}\) (265 mg, 0.53 mmol) in anhydrous DCM (8 cm\(^3\)) was added hydrochloric acid (2 M in diethyl ether, 0.80 cm\(^3\), 1.59 mmol) at 0 °C. The reaction mixture was stirred at rt for 20 minutes, and subsequently concentrated under reduced pressure to give a white residue. To a suspension of the residue in ethanol (10 cm\(^3\)) was added ruthenium (III) trichloride hydrate (112 mg, 0.42 mmol). The reaction mixture was refluxed overnight. The precipitate was collected by filtration and washed with cold ethanol to give \(N\text{-[}(1R,2R)-1,2\text{-diphenyl-2-(4-phenylbutylamino)-ethyl]}\text{-4-methylbenzenesulfonamide ammonium chloride ruthenium dimer 163b}\) (200 mg, 0.14 mmol, 54 %) as green-brown crystals; \(\delta\text{H} (400 MHz, DMSO-d\(_6\)) 9.47 (2 H, br s, 2 x NH\(_{1(1)}\text{H}_{(2)}\text{Cl})\), 9.02 (2 H, br s, 2 x NH\(_{1(2)}\text{H}_{(3)}\text{Cl})\), 8.60 (2 H, d, \(J\ 9.5\), 2 x NHTs), 7.30-6.81 (28 H, m, 2 x (14 x Ar-H)), 6.02-5.72 (10 H, m, 2 x (5 x Ru-Ar-H)), 4.82 (2 H, m, 2 x PhCHNHTs), 4.58-4.51 (2 H, m, 2 x PhCHNH\(_2\text{Cl})\), 2.74-2.66 (4 H, m, 2 x NH\(_2\text{Cl}CH\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{H})\), 1.78-1.67 (4 H, m, 2 x NH\(_2\text{Cl}CH\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{H})\); \(\delta\text{C} (101 MHz, DMSO-d\(_6\)) 142.14 (2 x C), 137.67 (2 x C), 135.48 (2 x C), 131.49 (2 x C), 129.15 (2 x CH), 129.07 (2 x CH), 128.84 (2 x (2 x CH)), 128.65 (2 x (2 x CH)), 127.71 (2 x (2 x CH)), 127.54 (2 x (2 x CH)), 127.14 (2 x CH), 126.33 (2 x (3 x CH)), 107.22 (2 x C), 88.87 (2 x (2 x CH)), 84.84 (2 x CH), 84.82 (2 x CH), 83.09 (2 x CH), 64.29 (2 x CH), 60.58 (2 x CH), 45.25 (2 x CH), 31.72 (2 x CH), 31.72 (2 x CH).
Experimental

25.58 (2 x CH₂), 24.38 (2 x CH₂) and 20.82 (2 x CH₃). The data matched that previously reported for this compound.

**Synthesis of N-((1R, 2R)-2-(benzylamino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide (305).**

This is a known compound and has been fully characterised.³²a,³²b

To a stirred solution of (R, R)-TsDPEN 81 (0.60 g, 1.64 mmol) and molecular sieves (4 Å, 2.0 g) in dried methanol (16 cm³), was added benzaldehyde (0.20 cm³, 1.96 mmol) followed by glacial acetic acid (6 drops). The reaction was followed by TLC until the imine was formed (3 hrs), and then sodium cyanoborohydride (0.30 g, 4.8 mmol) was added and the reaction was left overnight at rt. The molecular sieves were filtered through filter paper and the solution was then concentrated under reduced pressure to remove the methanol. The residue was dissolved in chloroform (100 cm³), and was washed with saturated NaHCO₃ solution (60 cm³). The organic layer was then dried (MgSO₄), filtered and concentrated under reduce pressure to give a crude solid which was purified by flash chromatography (10–30 % v/v ethyl acetate/hexane) to afford the product 305 as a while solid (430 mg, 0.94 mmol, 57 %); δH (400 MHz, CDCl₃) 7.36 (2 H, d, J 8.2, 2 x Ar-H o to SO₂NH), 7.32-7.22 (3 H, m, 3 x Ar-H), 7.19-7.12 (5 H, m, 5 x Ar-H), 7.09-6.88 (9 H, m, 9 x Ar-H), 6.13 (1 H, br s , NHTs), 4.31 (1 H, dd, J 7.7, 2.9, CH₁H₂Ph), 3.68 (1 H, d, J 7.7, CH₁H₂Ph), 3.62 (1 H, d, J 13.2, TsNHCH₃H), 3.41 (1 H, d, J 13.2, CHNH), 2.31 (3 H, s, CH₃Ts) and 1.68 (1 H, br s, NHCH₃Ph); δC (101 MHz, CDCl₃) 142.72 (C), 139.37 (C), 138.90 (C), 138.25 (C), 136.99 (C), 129.10 (2 x
Experimental

CH), 128.48 (2 x CH), 128.43 (2 x CH), 128.04 (2 x CH), 127.95 (2 x CH), 127.62 (CH), 127.55 (2 x CH), 127.51 (2 x CH), 127.32 (CH), 127.18 (CH), 127.11 (2 x CH), 66.80 (CH), 63.09 (CH), 50.88 (CH₂) and 21.44 (CH₃). The data matched that previously reported for this compound.

**Synthesis of NBn untethered catalyst (182).**

![Structure of NBn untethered catalyst](image)

This is a known compound and has been fully characterised.¹⁷j

A mixture of benzeneruthenium(II) chloride dimer (0.16 g, 0.33 mmol), \(N\-((1R, 2R)-2-\) (benzylamino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide 305 (0.20 g, 0.44 mmol) and triethylamine (0.24 cm³, 1.7 mmol) in IPA (10 cm³) was heated at 80 °C for 1 hr. The solution was then cooled to rt, and concentrated under reduced pressure. The residue was dissolved in CHCl₃ (20 cm³) and then washed with water (10 cm³) with vigorous stirring for 3 minutes. The organic phase was separated, dried (Na₂SO₄), filtered and then concentrated under reduced pressure giving the crude product, which was then purified by column chromatography (3: 3: 1 v/v/v ethyl acetate/ hexane/ methanol) providing 182 as a brown solid (189 mg, 0.28 mmol, 64 %); \(\delta\)H (400 MHz, CDCl₃) 7.40-6.50 (19 H, m, 19 x Ar-H), 5.60 (6 H, s, 6 x Ru-Ar-H), 4.50-4.40 (1 H, m, CHNTs), 4.29-4.20 (1 H, m, CHNH), 4.16 (1 H, d, \(J\) 10.7, CH(1)H(2)Ph), 3.93 (1 H, t, \(J\) 10.7, CH(1)H(2)Ph) and 2.24 (3 H, s, CH₃); \(\delta\)C (101 MHz, CDCl₃) 141.55 (C), 138.72 (C), 138.55 (C), 136.26 (C), 135.04 (C), 130.29 (2 x CH), 128.50 (2 x CH), 128.21 (3 x CH), 127.89 (2 x CH), 127.57 (CH), 127.40 (2 x CH), 127.11 (CH), 126.90 (CH),
126.71 (2 x CH), 126.22 (2 x CH), 125.66 (CH), 83.47 (6 x CH), 80.51 (CH), 68.96 (CH), 59.52 (CH₂) and 20.61 (CH₃). The data matched that previously reported for this compound.

**Synthesis of (4-bromobutoxy)(tert-butyl)diphenylsilane (185).**

This is a known compound and has been fully characterised.³²c

*tert*-Butyl-chlorodiphenylsilane (7.96 g, 7.53 cm³, 28.97 mmol) was added to a stirred solution of 4-bromo-1-butanol (4.03 g, 26.34 mmol) and imidazole (3.95 g, 57.95 mmol) in THF (150 cm³) under an argon atmosphere. The resulting mixture was stirred over the weekend at rt and quenched with water (150 cm³) followed by the addition of Et₂O (150 cm³). After phase separation and extraction of the aqueous phase with Et₂O (3 x 150 cm³), the combined organic phases were dried (MgSO₄), filtered, concentrated, and purified by flash chromatography (0→10 % v/v ethyl acetate/hexane) to afford the silyl alcohol 185 as a colourless oil (3.23g, 8.25 mmol, 31%); δ_H (300 MHz, CDCl₃) 7.52-7.51 (4 H, m, 4 x Ar-H), 7.45-7.30 (6 H, m, 6 x Ar-H), 3.75 (2 H, t, J 6.1, CH₂OSi), 3.50 (2 H, t, J 6.8, BrCH₂), 2.06-1.93 (2 H, m, BrCH₂CH₂H₂), 1.73-1.65 (2 H, m, CH₂CH₂OSi) and 1.09 (9 H, s, 3 x CH₃); δ_C (75 MHz, CDCl₃) 135.58 (CH), 133.84 (2 x C), 129.65 (3 x CH), 127.69 (6 x CH), 62.93 (CH₂), 33.91 (CH₂), 31.07 (CH₂), 29.48 (CH₂), 26.90 (3 x CH₃) and 19.24 (C). The data matched that previously reported for this compound.

**Synthesis of tert-butyl(4-(3,5-dimethylphenyl)butoxy)diphenylsilane (187).**
This compound is novel.

A Schlenk tube was dried with a heat gun under vacuum, and flushed with argon. 5-Bromo-m-xylene (1.53 g, 1.12 cm$^3$, 8.25 mmol) was injected into the tube followed by freshly distilled THF (16.5 cm$^3$). The tube was then degassed 3 times followed by the reinsertion of argon. tBuLi (1.7 M in pentane, 12.14 cm$^3$, 20.63 mmol) was added dropwise at -78 °C and the tube was again degassed and flushed with argon. The mixture was then stirred at room temperature for 1 hr, and then re-cooled to -78 °C. (4-Bromobutoxy)(tert-butyl)diphenylsilane (3.23 g, 8.25 mmol) was added dropwise to the reaction mixture and then degassed and flushed with argon. The solution was then heated up to 40 °C and allowed to stir at this temperature for 4 days. The mixture was then allowed to cool to room temperature and then was partitioned between diethyl ether (33 cm$^3$) and water (25 cm$^3$). The aqueous phase was extracted with Et$_2$O (2 x 16.5 cm$^3$), and then the combined organic phases were dried (MgSO$_4$), filtered and then evaporated in vacuo to give 187 as a light yellow oil (2.4 g, 5.76 mmol, 70 %); $\nu_{\text{max}}$ 3071, 2931, 2858, 1606, 1472, 1462, 1428, 1390, 1361, 1261, 1189, 1105, 1008, 998, 975, 939, 846, 822, 739 and 699 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 7.70-7.62 (3 H, m, 3 x Ar-H), 7.45-7.30 (7 H, m, 7 x Ar-H), 6.85 (1 H, s, Ar-H), 6.80 (2 H, s, 2 x Ar-H), 3.65 (2 H, t, $J$ 6.2, CH$_2$OSi), 2.53 (2 H, t, $J$ 7.8, ArCH$_2$), 2.25 (6 H, s, 2 x CH$_3$), 1.70 (2 H, m, ArCH$_2$CH$_2$), 1.60 (2 H, m, CH$_2$CH$_2$OSi) and 1.05 (9 H, s, 3 x SiCCH$_3$); $\delta_C$ (101 MHz, CDCl$_3$) 142.60 (C), 137.69 (2 x C), 135.60 (3 x CH), 134.12 (2 x C), 129.52 (2 x CH), 127.60 (5 x CH), 127.28 (CH), 126.28 (2 x CH), 63.76 (CH$_2$), 35.46 (CH$_2$), 32.25 (CH$_3$), 28.92 (C), 27.62 (CH$_2$), 26.89 (3 x CH$_3$) and 21.34 (2 x CH$_3$); $m/z$ (ESI-MS)
Experimental

439.0 [M+Na]$^+$. Found (ESI-HR-MS): 439.2419 [M+Na]$^+$, C$_{28}$H$_{36}$NaOSi requires 439.2428 (1.86 ppm error).

**Synthesis of 4-(3,5-dimethylphenyl)butan-1-ol (188).**

\[
\text{\includegraphics[width=1cm]{synthesis188.png}}
\]

This compound is novel.

Tetrabutylammonium fluoride was added as a 1 M solution in THF (24 cm$^3$) to a solution of tert-butyl(4-(3,5-dimethylphenyl)butoxy)diphenylsilane (2.0 g, 4.8 mmol) in THF (65 cm$^3$). The mixture was allowed to stir for 3 days at 23 °C and the conversion was checked by TLC. After completion the solution was concentrated under reduced pressure and the crude product was purified by flash chromatography (10→50 % v/v ethyl acetate/hexane) to afford 188 as a colourless oil (776 mg, 4.35 mmol, 91 %); $\nu_{\text{max}}$ 3326, 3014, 2928, 2860, 1606, 1459, 1377, 1060, 1036, 985, 933, 894, 843 and 700 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 6.82 (1 H, s, Ar-H), 6.80 (2 H, s, 2 x Ar-H), 3.65 (2 H, t, $J$ 6.2, CH$_2$OH), 2.59 (2 H, t, $J$ 7.6, ArCH$_2$), 2.30 (6 H, s, 2 x CH$_3$) and 1.72-1.56 (4 H, m, CH$_2$CH$_2$CH$_2$OH); $\delta_C$ (101 MHz, CDCl$_3$) 142.28 (C), 137.77 (2 x C), 127.41 (CH), 126.27 (2 x CH), 62.91 (CH$_2$), 35.51 (CH$_2$), 32.46 (CH$_2$), 27.62 (CH$_2$) and 21.29 (2 x CH$_3$); $m/z$ (ESI-MS) 201.1 [M+Na]$^+$. Found (ESI-HR-MS): 201.1247 [M+Na]$^+$, C$_{12}$H$_{18}$NaO requires 201.1250 (1.5 ppm error)

**Synthesis of 4-(3,5-dimethylcyclohexa-1,4-dienyl)butan-1-ol (189).**

\[
\text{\includegraphics[width=1cm]{synthesis189.png}}
\]
This compound is novel.

A solution of 4-(3,5-dimethylphenyl)butan-1-ol (513 mg, 2.8 mmol) in ethanol (2.5 cm$^3$) was slowly added to a refluxing solution of ammonia (50 cm$^3$) containing ethanol (10 cm$^3$) at -78 °C while stirring. Small cleaned (with hexane) sodium pieces were added to the reaction mixture until the blue colour persisted. After the addition of sodium over the course of 7 hours with regular additions of ethanol (2.5 cm$^3$), the reaction mixture was left overnight to evaporate ammonia. The reaction mixture was quenched carefully with saturated ammonium chloride (20 cm$^3$), and extracted using DCM (3 x 6 cm$^3$). The combined organic layers were dried (MgSO$_4$) filtered and concentrated under reduced pressure to afford crude 189 as an orange red oil (374 mg, 3.07 mmol, 74%) which appeared to be a ca 1:1 mixture of isomers D1 and D2. The product was analyzed as a 1:1 mixture of D1 and D2; $\delta_H$ (300 MHz, CDCl$_3$) 5.32 (2 H, br s, 2 x $HC=C$), 3.60-3.55 (2 H, m, $CCH_2OH$), 2.71 (1 H, br s, $OH$), 2.45-2.40 (2 H, m, $=C-CH_2-C=$), 2.10-2.05 (1 H, m, $=C-CH-C=$), 1.65 (4.5 H, br s, $CH_3$), 1.50-1.20 (6 H, m, $(CH_2)_3$) and 0.95 (1.5 H, d, $J$ 7.6, CHCH$_3$). This material was directly used in the next step, and 90 % conversion was obtained after multiple reduction attempts on the same product.

Synthesis of 4-(3,5-dimethylcyclohexa-1,4-dienyl)butanal (190).

This compound is novel.

A solution of oxalylchloride (2 M in DCM, 1.35 cm$^3$, 2.69 mmol) in anhydrous DCM (3 cm$^3$) was cooled to -78 °C, and to this was slowly added a solution of dimethylsulfoxide
Experimental

(0.38 cm$^3$, 5.38 mmol) in DCM (1.5 cm$^3$) by syringe. The solution was stirred for 30 minutes at -78 °C before a solution of 4-(3,5-dimethylcyclohexa-1,4-dienyl)butan-1-ol (375 mg, 2.07 mmol) in DCM (5 cm$^3$) was slowly added at the same temperature. After stirring for 45 minutes at -78 °C, Et$_3$N (1.73 cm$^3$, 12.40 mmol) was added and the reaction mixture was allowed to warm up to rt. After 60 minutes, water (10 cm$^3$) was added, and the mixture was extracted with DCM (3 x 5 cm$^3$). The combined organic layers were dried (MgSO$_4$), filtered and concentrated under reduced pressure to give crude 190 as a light orange oil (355 mg, 1.99 mmol, 96 %) which appeared to be a ca. 1:1 mixture of isomers D1 and D2. The product was analyzed as a 1:1 mixture of D1 and D2; $\delta_H$ (400 MHz, CDCl$_3$) 9.88 (0.5 H, s, CH=O), 9.85 (0.5 H, s, CH=O), 5.30-5.20 (2 H, m, -CH=), 2.35-2.30 (4 H, m, =C-CH$_2$-C=), 2.05-2.00 (0.5 H, m, =C-CH-C=), 1.80-1.70 (0.5 H, m, =C-CH-H=), 1.68 (4.5 H, br s, CH$_3$), 1.65-1.55 (2 H, m, CH$_2$), 1.40-1.30 (2 H, m, CH$_2$), 1.00 (1.5 H, d, J 7.7, CH$_3$); This material was directly used in the next step.

Synthesis of N-((1R,2R)-2-(4-(3,5-dimethylcyclohexa-1,4-dienyl)butylamino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide (191).

To a suspension of powdered molecular sieves (4 Å, 0.50 g) in dry methanol (30 cm$^3$) was added 4-(3,5-dimethylcyclohexa-1,4-dienyl)butanal 190 (355 mg, 2.00 mmol), (R, R)-TsDPEN (806 mg, 2.20 mmol) and glacial acetic acid (4 drops). The reaction
mixture was stirred at rt and monitored by TLC. After 2 hrs, the imine had formed (observed by TLC), and sodium cyanoborohydride (590 mg, 9.38 mmol) was added. The reaction was left overnight at rt. The molecular sieves were then removed by filtration, and the solution was concentrated under reduced pressure. The residue was redissolved in DCM (40 cm$^3$). The organic phase was washed with saturated NaHCO$_3$ (40 cm$^3$) and brine (40 cm$^3$), dried (MgSO$_4$), filtered and concentrated. The resulting residue was purified by flash chromatography (10→30 % v/v ethyl acetate/hexane) to afford 191 as a colourless oil (390 mg, 0.74 mmol, 37 %) which appeared to be a ca. 1:1 mixture of isomers D1 and D2. The product was analyzed as a 1:1 mixture of D1 and D2; $[\alpha]_d^{35}$ -5.3 (c 0.5, CHCl$_3$); $\nu_{max}$ 3299, 3026, 2856, 2257, 1600, 1495, 1455, 1433, 1380, 1352, 1327, 1305, 1184, 1160, 1119, 1093, 1054, 1020, 909, 846, 807, 755, 731, 698 and 667 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 7.37 (2 H, d, J 8.2, 2 x Ar-$H$), 7.05-7.10 (3 H, m, 3 x Ar-$H$), 7.05-7.00 (5 H, m, 5 x Ar-$H$), 6.95-6.85 (4 H, m, 4 x Ar-$H$), 5.35-5.25 (2 H, br s, HC=C), 4.26-4.21 (1 H, m, C$_H$Ts), 3.62-3.57 (1 H, m, C$_H$NH), 2.80-2.59 (1 H, m, CH$_3$CH), 2.43-2.36 (2 H, m, CH$_2$C(CH$_3$)=C), 2.35 (3 H, s, TsC$_H$3), 2.34-2.25 (2 H, m, NHCH$_2$), 1.70 (4.5 H, s, CH$_3$), 1.56-1.14 (6 H, m, NHCH$_2$CH$_2$CH$_2$CH$_2$) and 1.05 (1.5 H, d, J 7.2, CH$_3$); $\delta_C$ (101 MHz, CDCl$_3$) 142.67 (C), 139.43 (C), 138.42 (C), 137.09 (C), 131.05 (2 x C), 129.08 (2 x CH), 128.30 (2 x CH), 127.90 (2 x CH), 127.58 (2 x CH), 127.43 (CH), 127.39 (2 x CH), 127.25 (CH), 127.15 (2 x CH), 125.18 (CH), 124.98 (CH), 123.40 (CH), 67.86 (CH), 63.06 (CH), 47.20 (CH$_2$), 36.12 (CH$_2$), 34.02 (CH$_2$), 30.35 (CH$_2$), 29.63 (CH$_2$), 23.09 (CH$_3$) and 21.44 (2 x CH$_3$); m/z (ESI-MS) 529.3 [M+H]$^+$. Found (ESI-HR-MS): 529.2899 [M+H]$^+$, C$_{33}$H$_{41}$N$_2$O$_2$S requires 529.2883 (-2.9 ppm error).

**Synthesis of** $N$-((1R,2R)-2-(4-(3,5-dimethylphenyl)butylamino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide ammonium chloride dimer (183).
This compound is novel.

To a stirred solution of \(N-((1R,2R)-2-(4-(3,5\text{-dimethylcyclohexa-1,4-dienyl})\text{butylamino})-1,2\text{-diphenylethyl})-4\text{-methylbenzenesulfonamide} \ 191 \) (200 mg, 0.38 mmol) in anhydrous DCM (5.5 cm\(^3\)) was added hydrochloric acid (2 M in diethyl ether, 0.57 cm\(^3\), 1.14 mmol) at 0 °C. The reaction mixture was stirred at rt for 20 minutes, and subsequently concentrated under reduced pressure to give a white residue. To a suspension of the residue in ethanol (7.2 cm\(^3\)) was added hydrate ruthenium (III) trichloride hydrate (62 mg, 0.30 mmol). The reaction mixture was refluxed overnight. The precipitate was collected by filtration and washed with ethanol to give \(183 \) (54 mg, 0.04 mmol, 21 %) as black crystals; Mp 240-250°C (dec.); \(\nu_{\text{max}} \) 3054, 1597, 1456, 1323, 1156, 1091, 1030, 925, 813, 763, 700 and 669 cm\(^{-1}\); \(\delta_{\text{H}} \) (400 MHz, DMSO-\(d_6\)) 9.36 (2 H, br s, 2 x NH(1)H(2)+Cl), 8.95 (2 H, br s, 2 x NH(1)H(2)+Cl), 8.50 (2 H, br s, 2 x NHTs), 7.33-6.70 (28 H, m, 2 x (14 x Ar-H)), 5.55.5.50 (6 H, m, 2 x (3 x Ru-Ar-H)), 4.74-4.66 (2 H, m, 2 x CHNHTs)), 4.50-4.40 (2 H, m, 2 x CHNHS+), 2.80-2.70 (4 H, m, 2 x NH2+CH2), 2.55 (12 H, br s, 2 x (2 x CH2)), 2.40-2.35 (4 H, m, 2 x CH2Ar), 2.20 (6 H, s, SO2ArCH3), 1.83-1.50 (8 H, m, 2 x (2 x CH2)); \(\delta_{\text{C}} \) (101 MHz, DMSO-\(d_6\)) 142.24 (2 x C), 137.50 (2 x C), 135.35 (2 x C), 131.41 (2 x C), 129.22 (2 x CH), 129.07 (2 x (2 x CH)), 128.92 (2 x (2 x CH)), 128.70 (2 x (2 x CH)), 127.70 (2 x (2 x CH)), 127.57 (2 x (2 x CH)), 127.19 (2 x CH), 126.38 (2 x (2 x CH)), 107.10 (2 x C), 104.11 (2 x (2 x C)), 82.80 (2 x CH), 82.16 (2 x CH), 82.11 (2 x CH), 64.37 (2 x CH), 60.49 (2 x CH), 45.40 (2 x CH2), 31.55 (2 x CH2), 26.12 (2 x CH2), 24.51 (2 x CH2), 20.90 (2 x CH3)
and 18.30 (2 x (2 x CH₃); m/z 1321, 1307, 627 (0.5M-2HCl-Cl), 353 (Molecular ion not observed; fragmentation ions with Ru isotope patterns observed). Found (ESI-HR-MS): 627.1631 C₃₃H₃₇N₂O₂¹⁰²RuS (monomer formed in situ from dimer) requires 627.1622 (1.4 ppm error), 314.0841, C₃₃H₃₈N₂O₂¹⁰²RuS(2+) requires 314.0847 (1.9 ppm error).

**Optical rotation could not be obtained due to the product being highly coloured.**

**General procedure for making quinolines.**

2-Methylquinoline and 2-phenylquinoline were purchased from Sigma-Aldrich and Alfa Aesar.

**Synthesis of 2-tert-butylquinoline (178).**

This is a known compound and has been fully characterised.²⁶b

To a solution of 6-nitrobenzaldehyde (3.02 g, 20 mmol) in ethanol (60 cm³) was added iron power (<10 μm, aldrich, 4.47 g, 80 mmol) followed by 0.1 N aq HCl (10 cm³, 1 mmol) and the resulting mixture was vigorously stirred at 95 °C (oil bath) for 2 hrs. TLC analysis revealed that the reduction reaction was complete so 3,3-dimethyl-2-butanone (2.0 g, 2.5 cm³, 20 mmol) and powdered KOH (1.35 g, 24 mmol) were added successively in portions (Caution! Potential exotherm; add KOH slowly). The reaction mixture was stirred at 95 °C, then cooled to rt, diluted with DCM (600 cm³), and filtered through a celite pad. The filtrate was washed with water (100 cm³) and the aqueous
phase was back-extracted with DCM (2 x 40 cm$^3$). The combined organic phases were dried (MgSO$_4$), filtered, and concentrated in vacuo to give 178 as an orange red oil (3.7 g, 20 mmol, >99%); $\delta$$_H$ (400 MHz, CDCl$_3$) 8.08-8.01 (2 H, m, (4)-CH + (8)-CH), 7.73 (1 H, d, J 7.0, (5)-CH), 7.65 (1 H, t, J 7.0, (7)-CH), 7.50 (1 H, d, J 8.6, (3)-CH), 7.45 (1 H, t, J 7.0, (6)-CH) and 1.49 (9 H, s, (2)-3 x CH$_3$); $\delta$$_C$ (101 MHz, CDCl$_3$) 169.28 (C), 147.47 (C), 135.86 (CH), 129.45 (CH), 128.99 (CH), 127.24 (CH), 126.47 (C), 125.63 (CH), 118.24 (CH), 38.16 (C) and 30.18 (3 x CH$_3$). The data matched that previously reported for this compound.

**Synthesis of 6,7-dimethoxy-2-methylquinoline (193).**

This is a known compound and has been fully characterised.$^{32d}$

To a solution of 6-nitroveratraldehyde (2.11 g, 10 mmol) in ethanol (30 cm$^3$) was added iron power (<10μm, aldrich, 2.23 g, 40 mmol) followed by 0.1 N aq HCl (5 cm$^3$, 0.5 mmol) and the resulting mixture was vigorously stirred at 95 °C (oil bath) for 2 hrs. TLC analysis revealed that the reduction reaction was complete so acetone (0.58 g, 0.73 cm$^3$, 10 mmol) and powdered KOH (0.67 g, 12 mmol) were added successively in portions (Caution! Potential exotherm; add KOH slowly). The reaction mixture was stirred at 95 °C, then cooled to rt, diluted with DCM (300 cm$^3$), and filtered through a celite pad. The filtrate was washed with water (50 cm$^3$) and the aqueous phase was back-extracted with DCM (2 x 20 cm$^3$). The combined organic phases were dried (MgSO$_4$), filtered, and concentrated in vacuo to give 193 as brown crystals (1.55 g, 7.63 mmol, 76%); $\delta$$_H$ (400 MHz, CDCl$_3$) 7.88 (1 H, d, J 8.3, (4)-CH), 7.38 (1 H, s, (8)-CH), 7.10 (1 H, d, J 8.3, (3)-CH), 6.95 (1 H, s, (5)-CH), 4.01 (3 H, s, (7)-OCH$_3$), 3.99 (3 H, s,
Experimental

(6)-OCH$_3$) and 2.70 (3 H, s, (2)-CH$_3$); $\delta$C (101 MHz, CDCl$_3$) 156.53 (C), 152.30 (C), 149.06 (C), 144.75 (C), 134.46 (CH), 121.70 (C), 120.08 (CH), 107.54 (CH), 105.09 (CH), 56.05 (CH$_3$), 55.95 (CH$_3$) and 24.97 (CH$_3$). The data matched that previously reported for this compound.

**Synthesis of 2-ethylquinoline (120b).**

![2-ethylquinoline](image)

This is a known compound and has been fully characterised.$^{32e}$

Quinaldine (1.40 g, 1.4 cm$^3$,10 mmol) was dissolved in dry THF (20 cm$^3$). The reaction vessel was cooled to -78 °C and nBuLi in hexane (1.6 M, 6.3 cm$^3$, 10 mmol) was added. After 30 mins, methyl iodide (1.90 g, 0.8 cm$^3$, 13 mmol) was added via syringe. The mixture was allowed to gradually warm to room temperature while being stirred overnight. The resulting light yellow solution was concentrated, diluted with water (40 cm$^3$) and brine (10 cm$^3$), and extracted with DCM (3 x 40 cm$^3$). The combined organic layers were dried (MgSO$_4$), filtered and concentrated to give 120b as an yellow oil (1.46 g, 9.29 mmol, 93 %); $\delta$H (400 MHz, CDCl$_3$) 8.05 (1 H, d, J 8.5, (8)-CH), 7.99 (1 H, d, J 8.5, (4)-CH), 7.70 (1 H, d, J 8.5, (5)-CH), 7.61 (1 H, t, J 7.0, (7)-CH), 7.39 (1 H, t, J 7.0, (6)-CH), 7.25 (1 H, d, J 8.5, (3)-CH), 2.88 (2 H, q, J 7.7, (2)-CH$_2$CH$_3$) and 1.30 (3 H, t, J 7.7 Hz, (2)-CH$_2$CH$_3$); $\delta$C (101 MHz, CDCl$_3$) 163.95 (C), 147.88 (C), 136.30 (CH), 129.31 (CH), 128.81 (CH), 127.47 (CH), 126.72 (C), 125.63 (CH), 120.82 (CH), 32.32 (CH$_2$) and 14.50 (CH$_3$). The data matched that previously reported for this compound.

**Synthesis of 2-propylquinoline (124a).**
Experimental

This is a known compound and has been fully characterised.\textsuperscript{32f}

This compound was prepared as for 2-ethylquinoline using quinaldine (1.40 g, 1.4 cm\textsuperscript{3}, 10 mmol), \textsuperscript{6}BuLi in hexane (1.6 M, 6.3 cm\textsuperscript{3}, 10 mmol) and ethyl iodide (2.0 g, 1.0 cm\textsuperscript{3}, 13 mmol) and was isolated as a yellow oil (1.53 g, 8.93 mmol, 89%); \( \delta \textsuperscript{H} (400 \text{ MHz}, \text{CDCl}_3) \) 8.05 (1 H, d, \( J \) 8.5, (8)-CH), 7.96 (1 H, d, \( J \) 8.4, (4)-CH), 7.78 (1 H, d, \( J \) 8.4, (5)-CH), 7.68 (1 H, t, \( J \) 7.0, (7)-CH), 7.49 (1 H, t, \( J \) 7.0, (6)-CH), 7.25 (1 H, d, \( J \) 8.4, (3)-CH), 2.99 (2 H, t, \( J \) 7.4, (2)-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 1.90 (2 H, sext, \( J \) 7.4, (2)-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}) and 1.05 (3 H, t, \( J \) 7.4, (2)-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}); \( \delta \textsuperscript{C} (101 \text{ MHz}, \text{CDCl}_3) \) 162.80 (C), 147.92 (C), 136.08 (CH), 129.25 (CH), 128.82 (CH), 127.45 (CH), 126.70 (C), 125.59 (CH), 121.33 (CH), 41.26 (CH\textsubscript{2}), 23.24 (CH\textsubscript{2}) and 14.00 (CH\textsubscript{3}). The data matched that previously reported for this compound.

**Synthesis of 2-butylquinoline (115l).**

This is a known compound and has been fully characterised.\textsuperscript{32g}

This compound was prepared as for 2-ethylquinoline using quinaldine (1.40 g, 1.4 cm\textsuperscript{3}, 10 mmol), \textsuperscript{6}BuLi in hexane (1.6 M, 6.3 cm\textsuperscript{3}, 10 mmol) and iodopropane (2.21 g, 1.27 cm\textsuperscript{3}, 13 mmol) and was isolated as a yellow oil (1.70 g, 9.18 mmol, 92%); \( \delta \textsuperscript{H} (400 \text{ MHz}, \text{CDCl}_3) \) 8.06 (1 H, d, \( J \) 8.5, (8)-CH), 7.99 (1 H, d, \( J \) 8.4, (4)-CH), 7.71 (1 H, d, \( J \) 8.4, (5)-CH), 7.64 (1 H, t, \( J \) 7.0, (7)-CH), 7.43 (1 H, t, \( J \) 7.0, (6)-CH), 7.23 (1 H, d, \( J \) 8.4, (3)-CH), 2.98 (2 H, dd, \( J \) 7.6, 8.0, (2)-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 1.83 (2 H, quin, \( J \) 7.6, (2)-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 1.43 (2 H, sext, \( J \) 7.6, (2)-CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}) and 0.95 (3 H, t, \( J \) 7.6,
Experimental

(2)-CH₂CH₂CH₂CH₃); δC (101 MHz, CDCl₃) 163.05 (C), 147.94 (C), 136.11 (CH), 129.27 (CH), 128.84 (2 x CH), 126.70 (C), 125.59 (CH), 121.34 (CH), 39.10 (CH₂), 32.17 (CH₂) and 14.00 (CH₃). The data matched that previously reported for this compound.

Synthesis of 2-phenylethylquinoline (117a).

![Synthesis of 2-phenylethylquinoline (117a).](image)

This is a known compound and has been fully characterised.³²h

This compound was prepared as for 2-ethylquinoline using quinaldine (1.40 g, 1.4 cm³, 10 mmol), "BuLi in hexane (2.5 M, 4.0 cm³, 10 mmol) and benzyl bromide (2.22 g, 1.55 cm³, 13 mmol) and was isolated as a yellow oil (1.90 g, 8.14 mmol, 81 %); δH (400 MHz, CDCl₃) 8.23 (1 H, d, J 8.4, (8)-CH), 7.97 (1 H, d, J 8.4, (4)-CH), 7.77-7.69 (2 H, m, (5)-CH + (7)-CH), 7.49 (1 H, t, J 7.8, (6)-CH), 7.38-7.23 (5 H, m, (2)-CH₂CH₂C₆H₅), 7.18 (1 H, d, J 8.4, (3)-CH), 3.36 (2 H, dd, J 10.1, 9.2, (2)-CH₂CH₂C₆H₅) and 3.24 (2 H, dd, J 10.1, 9.2, (2)-CH₂CH₂C₆H₅); δC (101 MHz, CDCl₃) 161.81 (C), 148.12 (C), 141.63 (C), 136.24 (CH), 129.01 (CH), 128.64 (3 x CH), 128.55 (3 x CH), 126.89 (C), 126.15 (CH), 125.88 (CH) 121.63 (CH), 41.05 (CH₂) and 35.98 (CH₂). The data matched that previously reported for this compound.

Synthesis of 2-(3,5-dimethoxyphenethyl)quinoline (195).
This compound is novel.

This compound was prepared as for 2-ethylquinoline using quinaldine (1.40 g, 1.4 cm$^3$, 10 mmol), $^n$BuLi in hexane (1.6 M, 6.3 cm$^3$, 10 mmol) and 3,5-dimethoxybenzyl bromide (3.0 g, 13 mmol) and was isolated as an orange oil (2.29 g, 7.8 mmol, 78 %); $\nu_{\text{max}}$ 3057, 2998, 2937, 2837, 1735, 1594, 1563, 1504, 1459, 1427, 1349, 1310, 1295, 1204, 1147, 1115, 1065, 826, 750 and 690 cm$^{-1}$; $\delta_H$ (300 MHz, CDCl$_3$) 8.10 - 8.02 (2 H, (8)-CH + (4)-CH), 7.77 (1 H, dd, J 8.1, 1.5, (5)-CH), 7.69 (1 H, dd, J 15.3, 1.5, (7)-CH), 7.49 (1 H, dd, J 15.3, 1.5, (6)-CH), 7.24 (1 H, d, J 8.5, (3)-CH), 6.43 (2 H, d, J 2.3, (2)-CH$_2$CH$_2$Ar(o-CH$_3$)), 6.32 (1 H, t, J 2.3, (2)-CH$_2$CH$_2$Ar(p-CH)) and 3.74 (6 H, s, (2)-CH$_2$CH$_2$Ar(m-OC$_3$H$_7$)); $\delta_C$ (75 MHz, CDCl$_3$) 161.12 (C), 160.16 (2 x C), 147.36 (C), 143.32 (C), 135.64 (CH), 128.81 (CH), 128.23 (CH), 126.93 (CH), 126.20 (C), 125.21 (CH), 120.98 (CH), 105.90 (2 x CH), 97.56 (CH), 54.63 (2 x CH$_3$), 40.21 (CH$_2$) and 35.64 (CH$_2$); $m/z$ (ESI-MS) 294.0 [M+H]$^+$, Found (ESI-HR-MS): 294.1486 [M+H]$^+$, C$_{19}$H$_{20}$NO$_2$ requires 294.1489 (1.0 ppm error).

**Synthesis of 2-(2-(6-bromobenzo[d][1,3]dioxol-5-yl)ethyl)quinoline (194).**

This is a known compound and has been fully characterised.$^{26g}$

This compound was prepared as for 2-ethylquinoline using quinaldine (1.40 g, 1.4 cm$^3$, 10 mmol), $^n$BuLi in hexane (1.6 M, 6.3 cm$^3$, 10 mmol) and 5-bromo-6-bromomethyl-1,3-benzodioxole (3.8 g, 13 mmol) and was isolated as white crystals (1.65 g, 4.63 mmol, 46 %); $\delta_H$ (300 MHz, CDCl$_3$) 8.08-8.00 (2 H, m, (8)-CH + (4)-CH), 7.77 (1 H,
dd, $J$ 1.5, 8.3, (5)-$CH$), 7.68 (1 H, dd, $J$ 15.3, 1.5, (7)-$CH$), 7.48 (1 H, dd, $J$ 15.3, 1.5, (6)-$CH$), 7.27 (1 H, d, $J$ 8.3, (3)-$CH$), 7.00 (1 H, s, (2)-$CH_2CH_2Ar(m-CH)$), 6.72 (1 H, s, (2)-$CH_2CH_2Ar(o-CH)$), 5.91 (2 H, s, (2)-$CH_2CH_2Ar(O_2CH_2)$) and 3.24-3.15 (4 H, m, (2)-$CH_2CH_2Ar$); $\delta_C$ (75 MHz, CDCl$_3$) 160.75 ($C$), 147.34 ($C$), 146.69 ($C$), 146.15 ($C$), 135.70 ($CH$), 133.15 ($C$), 128.81 ($CH$), 128.27 ($CH$), 126.93 ($CH$), 126.23 ($C$), 125.23 ($CH$), 120.95 ($CH$), 113.79 ($C$), 112.10 ($CH$), 109.57 ($CH$), 100.93 ($CH_2$), 38.72 ($CH_2$) and 35.53 ($CH_2$). The data matched that previously reported for this compound.

**Synthesis of methyl quinoline-2-carboxylate (179).**

![Methyl Quinoline-2-carboxylate](image)

This is a known compound and has been fully characterised.$^{32i}$

To a suspension of quinaldic acid (1.73 g, 10.00 mmol) in MeOH (20 cm$^3$) was added a solution of HCl in MeOH (1.25 M, 20 cm$^3$). The resulting solution was refluxed for 15 hrs. The mixture was then cooled to rt and concentrated in vacuo. The residue was partitioned between saturated aqueous NaHCO$_3$ solution (25 cm$^3$) and EtOAc (3 x 20 cm$^3$). The combined organic extracts were further washed with saturated aqueous NaHCO$_3$ solution (7 cm$^3$) and water (7 cm$^3$), dried (Na$_2$SO$_4$), filtered and concentrated in vacuo to give 179 as a white solid (1.43 g, 7.64 mmol, 76 %); $\delta_H$ (400 MHz, CDCl$_3$) 8.35-8.26 (2 H, m, (4)-$CH$ + (8)-$CH$), 8.21 (1 H, d, $J$ 8.4, (5)-$CH$), 7.89 (1 H, d, $J$ 8.4, (3)-$CH$), 7.80 (1 H, t, $J$ 7.4, (7)-$CH$), 7.66 (1 H, t, $J$ 7.4, (6)-$CH$) and 4.09 (3 H, s, OCH$_3$); $\delta_C$ (101 MHz, CDCl$_3$) 166.00 (C=O), 147.92 ($C$), 147.56 ($C$), 137.35 ($CH$), 130.74 ($CH$), 130.33 ($CH$), 129.38 ($C$), 128.66 ($CH$), 127.58 ($CH$), 121.06 ($CH$) and 53.24 ($CH_3$). The data matched that previously reported for this compound.
General procedure for the ATH of Quinolines.\textsuperscript{22}

A solution of ruthenium dimer (0.0025 mmol) and imine (1 mmol) in methanol (1.6 cm\textsuperscript{3}) was stirred in a flame dried Schlenk tube at 28 °C for 10 minutes. Formic acid / triethylamine (5:2) azeotrope (0.5 cm\textsuperscript{3}) was then added (The Schlenk tube was degassed and purged with argon 3x before and after the addition of reagents). The reaction mixture was stirred at 28°C and monitored by TLC or GC, for which a drop of sample was filtered through a small plug of silica in a glass pipette using ethyl acetate and maybe a few drops of methanol depending on the polarity of the compound. After completion, NaHCO\textsubscript{3} solution (5 cm\textsuperscript{3}) was added, and the mixture was extracted with dichloromethane (3 x 10 cm\textsuperscript{3}). The organic phase was dried (MgSO\textsubscript{4}), filtered and concentrated under reduced pressure to give the desired amine.

General procedure for formation of the racemic mixture.\textsuperscript{10b}

To reaction vessel (A) was added [Ru(p-cymene)Cl\textsubscript{2}]\textsubscript{2} (0.0028 g, 0.0045 mmol) and undistilled THF (2 cm\textsuperscript{3}). The mixture was stirred until the solution was homogeneous. At the same time, to reaction vessel (B) was added quinoline (0.13 g, 0.12 cm\textsuperscript{3}, 0.89 mmol) and I\textsubscript{2} (0.012 g, 0.045 mmol), followed by THF (1 cm\textsuperscript{3}). The mixture was stirred until the iodine was dissolved. Then to the reaction bottle (B) was added the solution of [Ru(p-cymene)Cl\textsubscript{2}]\textsubscript{2} in THF from vessel (A). The final mixture in a glass vessel was pressurised to 600 psi hydrogen in a pressure hydrogenator and stirred at 20 °C for 20 hrs. The reaction mixture was concentrated to afford the crude product, which was then filtered through silica before being used for enantiomeric excess analysis on the GC/HPLC.

(R)-2-Methyl-1,2,3,4-tetrahydroquinoline (120a’).
This is a known compound and has been fully characterised.\textsuperscript{10h}

Reduction of 120a using catalyst 163b; 46% ee and 96% conversion, reduction of 120a using catalyst 175; 93% ee and 68% conversion: Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-\(\beta\)-236M-19 50m, T = 125°C, P = 15 psi, He, imine 43.9 min., S isomer 67.5 min (minor), R isomer 68.6 min (major)); \(\\left[\alpha\right]_D^{27} + 46.7\) (c 0.5, CHCl\(_3\)) 43% ee (R) (lit.\textsuperscript{10h} \(\left[\alpha\right]_D^{25} - 78.3\) (c 0.76, CHCl\(_3\)) 91% ee (S)); \(\delta_H\) (300 MHz, CDCl\(_3\)) 6.98-6.95 (2 H, m, (7)-CH + (5)-CH), 6.61 (1 H, td, J 7.2, 1.2, (6)-CH), 6.48 (1 H, dd, J 8.1, 1.3, (8)-CH), 3.70 (1 H, br s, (1)-NH), 3.44-3.38 (1 H, m, (2)-CH), 2.85-2.74 (2 H, m, (4)-CH\(_2\)), 1.94-1.91 (1 H, m, (3)-CH), 1.64-1.55 (1 H, m, (3)-CH) and 1.22 (3 H, d, J 6.3, (2)-CHH\(_2\)); \(\delta_C\) (75 MHz, CDCl\(_3\)) 144.20 (C), 128.67 (CH), 126.09 (CH), 120.50 (C), 116.37 (CH), 113.40 (CH), 46.56 (CH), 29.50 (CH\(_2\)), 26.00 (CH\(_2\)) and 22.02 (CH\(_3\)). The data matched that previously reported for this compound.

\(\left[\alpha\right]_D\) determined on sample with 43% ee.

(R)-2-Ethyl-1,2,3,4-tetrahydroquinoline (120b').

This is a known compound and has been fully characterised.\textsuperscript{10h}

Reduction of 120b using catalyst 163b; 41% ee and 95% conversion: Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-\(\beta\)-236M-19 50m, T = 115°C, P = 15 psi, He, imine 94.6 min., S isomer 174.0 min (minor), R isomer 176.4 min (major)); \(\left[\alpha\right]_D^{28} + 35.6\) (c 0.5, CHCl\(_3\)) 41% ee (R) (lit.\textsuperscript{10h} \(\left[\alpha\right]_D^{25} - 73.2\) (c 0.24, CHCl\(_3\))
Experimental

91% ee (5); δ_H (300 MHz, CDCl_3) 6.98-6.94 (2 H, m, (7)-CH + (5)-CH), 6.60 (1 H, td, J 7.2, 1.2, (6)-CH), 6.47 (1 H, dd, J 8.4, 1.3, (8)-CH), 3.77 (1 H, br s, (2)-NH), 3.19-3.13 (1 H, m, (2)-CH), 2.85-2.69 (2 H, m, (4)-CH_2), 2.00-1.94 (1 H, m, (3)-CH), 1.63-1.48 (3 H, m, (3)-CH + (2)-CHCH_2CH_3) and 0.98 (3 H, t, J 7.5, (2)-CHCH_2CH_3); δ_C (75 MHz, CDCl_3) 144.77 (C), 129.27 (CH), 126.73 (CH), 121.43 (C), 116.89 (CH), 114.02 (CH), 52.06 (CH), 29.44 (CH_2), 27.61 (CH_2), 26.45 (CH_2) and 10.12 (CH_3). The data matched that previously reported for this compound.

Reduction of 120b using catalyst 175; 91% ee and 67% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD-H, hexane:isopropanol = 90:10, flow rate 0.2 ml/min, 254 nm, 17.0°C): t_R = 26.8 min (major), t_S = 30.5 (minor).

(R)-2-Propyl-1,2,3,4-tetrahydroquinoline (124a’).

This is a known compound and has been fully characterised.12b

Reduction of 124a using catalyst 163b; 42% ee and 94% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD, hexane:isopropanol = 90:10, flow rate 0.2 ml/min, 254 nm, 18.0°C): t_R = 23.6 min (major), t_S = 26.8 (minor); [α]_D^{24} +54.1 (c 0.5, CHCl_3) 42% ee (R) (lit.12b [α]_D^{21} -70.8 (c 1.1, CHCl_3) 80% ee (S)); δ_H (400 MHz, CDCl_3) 6.97-6.94 (2 H, m, (7)-CH + (5)-CH), 6.59 (1 H, t, J 7.3, (6)-CH), 6.47 (1 H, d, J 8.0, (8)-CH), 3.76 (1 H, br s, (1)-NH), 3.28-3.21 (1 H, m, (2)-CH), 2.85-2.69 (2 H, m, (4)-CH_2), 1.98-1.92 (1 H, m, (3)-CH), 1.64-1.54 (1 H, m, (3)-CH), 1.51-1.39 (4 H, m, (2)-CHCH_2CH_2CH_3) and 0.96 (3 H, t, J 6.6,
(2)-CHCH$_2$CH$_2$CH$_3$; $\delta_C$ (101 MHz, CDCl$_3$) 144.77 (C), 129.29 (CH), 126.73 (CH), 121.42 (C), 116.91 (CH), 114.06 (CH), 51.33 (CH), 38.93 (CH$_2$), 28.15 (CH$_2$), 26.47 (CH$_2$), 19.00 (CH$_2$) and 14.30 (CH$_3$). The data matched that previously reported for this compound.

Reduction of 124a using catalyst 175; 90% ee and 65% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD-H, hexane:isopropanol = 90:10, flow rate 0.2 ml/min, 254 nm, 14.5°C): $t_R = 24.5$ min (major), $t_S = 28.1$ (minor).

(R)-2-Butyl-1,2,3,4-tetrahydroquinoline (115l’).

![Chemical Structure](image)

This is a known compound and has been fully characterised.$^\text{10h}$

Reduction of 115l using catalyst 163b; 41% ee and 93% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD, hexane:isopropanol = 90:10, flow rate 0.2 ml/min, 254 nm, 18.5°C): $t_R = 21.8$ min (major), $t_S = 24.4$ (minor); $\alpha_D^{26} +46.6$ (c 0.5, CHCl$_3$) 41% ee (R) (lit.$^\text{10h}$ $\alpha_D^{25} -78.2$ (c 0.53, CHCl$_3$) 89% ee (S)); $\delta_H$ (400 MHz, CDCl$_3$) 6.96-6.93 (2 H, m, (7)-CH + (5)-CH), 6.59 (1 H, t, $J=7.4$, (6)-CH), 6.46 (1 H, d, $J=8.3$, (8)-CH), 3.72 (1 H, br s, (1)-NH), 3.24-3.18 (1 H, m, (2)-CH), 2.84-2.68 (2 H, m, (4)-CH$_2$), 1.98-1.91 (1 H, m, (3)-CH), 1.63-1.53 (1 H, m, (3)-CH), 1.51-1.45 (2 H, m, (2)-CHCH$_2$CH$_2$CH$_2$CH$_3$), 1.41-1.32 (4 H, m, (2)-CHCH$_2$CH$_2$CH$_2$CH$_3$), 0.94-0.91 (3 H, t, $J=7.0$, (2)-CHCH$_2$CH$_2$CH$_2$CH$_3$); $\delta_C$ (101 MHz, CDCl$_3$) 144.77 (C), 129.28 (CH), 126.72 (CH), 121.43 (C), 116.90 (CH), 114.05
Experimental

(CH), 51.61 (CH), 36.46 (CH₂), 28.15 (CH₂), 27.96 (CH₂), 26.47 (CH₂), 22.88 (CH₂) and 14.10 (CH₃). The data matched that previously reported for this compound.

Reduction of 115I using catalyst 175; 92% ee and 64% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD-H, hexane:isopropanol = 90:10, flow rate 0.2 ml/min, 254 nm, 14.0°C): tᵣ = 22.8 min (major), tₛ = 25.6 (minor).

(S)-2-Phenyl-1,2,3,4-tetrahydroquinoline (115a').

This is a known compound and has been fully characterised.¹⁰h

Reduction of 115 using catalyst 163b; 73% ee and 68% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD, hexane:isopropanol = 90:10, flow rate 0.5 ml/min, 254 nm, 21.0°C): tᵣ = 17.0 min (major), tₛ = 21.1 (minor); [α]D²⁷ -31.3 (c 0.5, CHCl₃) 73% ee (S) (lit.¹⁰h [α]D²⁵ +71.2 (c 1.0, CHCl₃) 72% ee (R)); δH (400 MHz, CDCl₃) 7.40-7.26 (5 H, m, (2)-CHC₆H₅), 7.00 (2 H, m, (7)-CH + (5)-CH), 6.65 (1 H, t, J 6.7, (6)-CH), 6.55 (1 H, d, J 7.7, (8)-CH), 4.43 (1 H, dd, J 9.6, 3.3, (2)-CH), 4.04 (1 H, br s, (2)-NH), 2.97-2.88 (1 H, m, (4)-CH), 2.73 (1 H, dt, J 4.7, 16.4, (4)-CH), 2.15-2.09 (1 H, m, (3)-CH) and 2.04-1.94 (1 H, m, (3)-CH); δC (101 MHz, CDCl₃) 144.83 (C), 144.75 (C), 129.33 (CH), 128.60 (2 x CH), 127.47 (CH), 126.93 (CH), 126.58 (2 x CH), 120.90 (C), 117.18 (CH), 114.00 (CH), 56.28 (CH), 31.01 (CH₂) and 26.42 (CH₂). The data matched that previously reported for this compound.
Reduction of 115a using catalyst 175; 86% ee and 30% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD-H, hexane:isopropanol = 90:10, flow rate 0.5 ml/min, 254 nm, 19.0°C): $t_s = 17.1$ min (major), $t_R = 21.5$ (minor).

(R)-2-Phenethyl-1,2,3,4-tetrahydroquinoline (117a’).

This is a known compound and has been fully characterised.\textsuperscript{10h}

Reduction of 117a using catalyst 163b; 50% ee and 90% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD, hexane:isopropanol = 90:10, flow rate 0.5 ml/min, 254 nm, 20.0°C): $t_R = 17.8$ min (major), $t_s = 19.5$ (minor); $[\alpha]_D^{25} +45.5$ (c 0.5, CHCl$_3$) 50% ee (R) (lit.\textsuperscript{10i}$[\alpha]_D^{25} -73.1$ (c 0.55, CHCl$_3$) 92% ee (S)); $\delta$H (300 MHz, CDCl$_3$) 7.30-7.16 (5 H, m, (2)-CHCH$_2$CH$_2$C$_6$H$_5$), 6.97-6.92 (2 H, m, (7)-CH + (5)-CH), 6.59 (1 H, td, J 7.5, 1.1, (6)-CH), 6.42 (1 H, dd, J 8.4, 1.3, (8)-CH), 3.80 (1 H, br s, (1)-NH), 3.31-3.22 (1 H, m, (2)-CH), 2.85-2.66 (4 H, m, (4)-CH$_2$ + (2)-CHCH$_2$CH$_2$C$_6$H$_5$), 2.01-1.92 (1 H, m, (3)-CH), 1.84-1.77 (2 H, m, (2)-CHCH$_2$CH$_2$C$_6$H$_5$) and 1.71-1.59 (1 H, m, (3)-CH); $\delta$C (75 MHz, CDCl$_3$) 143.90 (C), 141.30 (C), 128.66 (CH), 127.89 (2 x CH), 127.76 (2 x CH), 126.14 (CH), 125.37 (CH), 120.70 (C), 116.43 (CH), 113.53 (CH), 50.51 (CH), 37.70 (CH$_2$), 31.60 (CH$_2$), 27.40 (CH$_2$) and 25.60 (CH$_2$). The data matched that previously reported for this compound.

Reduction of 117a using catalyst 175; 93% ee and 57% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD-H,
hexane:isopropanol = 90:10, flow rate 0.5 ml/min, 254 nm, 15.0°C): t_R = 19.7 min (major), t_S = 21.7 (minor).

2-tert-Butyl-1,2,3,4-tetrahydroquinoline (178’).

This is a known compound and has been fully characterised.\textsuperscript{32j}

Reduction of 178 using catalyst 163b; 0% ee and 57% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD-H, hexane:isopropanol = 90:10, flow rate 0.5 ml/min, 254 nm, 15.0°C): t_R = 20.5 min, t_S = 27.5; δ_H (300 MHz, CDCl\textsubscript{3}) 6.98-6.94 (2 H, m, (7)-CH + (5)-CH), 6.52 (1 H, td, J 7.5, 1.2, (6)-CH), 6.45 (1 H, d, J 7.7, (8)-CH), 3.78 (1 H, br s, (1)-NH), 3.00-2.96 (1 H, m, (2)-CH), 2.83-2.70 (2 H, m, (4)-CH\textsubscript{2}), 2.00-1.95 (1 H, m, (3)-CH), 1.60-1.55 (1 H, m, (3)-CH), 0.98 (9 H, s, (2)-CHC(CH\textsubscript{3})\textsubscript{3}); δ_C (75 MHz, CDCl\textsubscript{3}) 144.84 (C), 128.40 (CH), 126.10 (CH), 120.86 (C), 116.10 (CH), 113.40 (CH), 60.30 (CH), 32.79 (C), 26.84 (CH\textsubscript{2}), 25.40 (3 x CH\textsubscript{3}), 22.49 (CH\textsubscript{2}). The data matched that previously reported for this compound.

Reduction of 178 using catalyst 175; 0% ee and 16% conversion; HPLC (Chiralcel OD-H, hexane:isopropanol = 90:10, flow rate 0.2 ml/min, 254 nm, 14.0°C): t_R = 20.6 min, t_S = 27.9.

(+)-2-(3,5-Dimethoxyphenethyl)-1,2,3,4-tetrahydroquinoline (195’).
This compound is novel.

Reduction of 195 using catalyst 163b; 67% ee and 93% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD-H, hexane:isopropanol = 80:20, flow rate 0.6 ml/min, 254 nm, 18.0°C): $t_R = 28.1$ min (major), $t_S = 36.8$ (minor); $[^*]D_{24}^{24} +39.5$ (c 0.5, CHCl$_3$) 67% ee (R); $\nu_{\max}$ 3675, 3396, 2935, 2838, 1594, 1460, 1351, 1276, 1254, 1203, 1148, 1114, 1056, 924, 830, 746, 718, 667 cm$^{-1}$; $\delta_H$ (300 MHz, CDCl$_3$) 6.98-6.90 (2 H, m, (7)-CH + (5)-CH), 6.60 (1 H, td, $J$ 7.5, 1.2, (6)-CH), 6.45 (1 H, dd, $J$ 8.4, 1.4, (8)-CH), 6.38-6.35 (2 H, d, $J$ 2.3, (2)-CH$_2$CH$_2$Ar(o-C$_H$)$_3$), 6.32-6.28 (1 H, t, $J$ 2.3, (2)-CH$_2$CH$_2$Ar(p-C$_H$)), 3.77 (6 H, s, (2)-CH$_2$CH$_2$Ar((m-OCH$_3$)$_3$)), 2.81-2.72 (2 H, m, (4)-CH$_2$), 2.69-2.63 (2 H, m, (2)-CH$_3$CH$_2$Ar), 2.2-1.94 (1 H, m, (3)-CH), 1.85-1.75 (2 H, m, (2)-CH$_2$CH$_2$Ar) and 1.72-1.60 (1 H, m, (3)-CH); $\delta_C$ (75 MHz, CDCl$_3$) 160.88 (2 x C), 144.51 (C) 144.28 (C), 129.26 (CH), 126.75 (CH), 121.29 (C), 117.04 (CH), 114.15 (CH), 106.44 (2 x CH), 97.84 (CH), 55.29 (CH), 51.11 (2 x CH$_3$), 37.99 (CH$_2$), 32.49 (CH$_2$), 27.94 (CH$_2$) and 26.17 (CH$_2$); $m/z$ (ESI-MS) 298.1 [M+H]$^+$. Found (ESI-HR-MS): 298.1798 [M+H]$^+$, C$_{19}$H$_{24}$NO$_2$ requires 298.1802 (1.3 ppm error).

Reduction of 195 using catalyst 175; 94% ee and 58% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD-H, hexane:isopropanol = 80:20, flow rate 0.6 ml/min, 254 nm, 19.0°C): $t_R = 27.4$ min (major), $t_S = 35.9$ (minor).

*The absolute configuration has not been determined, but is assigned by analogy with the reduction product of substrate 117a.
Experimental

(+)-2-(2-(6-Bromobenzo[d][1,3]dioxol-5-yl)ethyl)-1,2,3,4-tetrahydroquinoline (194’).

This compound is novel.

Reduction of 194 using catalyst 163b; 47% ee and 86% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD-H, hexane:isopropanol = 80:20, flow rate 0.6 ml/min, 254 nm, 19.0°C): t_S = 21.2 min (major), t_R = 29.2 (minor); [α]_D^25 +25.6 (c 0.5, CHCl_3) 47% ee (R); ν_max 3664, 3410, 2912, 1606, 1585, 1500, 1473, 1434, 1408, 1353, 1309, 1275, 1227, 1111, 1066, 1035, 964, 931, 858, 832, 746, 718 and 657 cm\(^{-1}\); δ_H (300 MHz, CDCl_3) 6.98 (1 H, s, (2)-CH_2CH_2Ar(m-CH)), 6.96-6.92 (2 H, m, (5)-CH + (7)-CH), 6.70 (1 H, s, (2)-CH_2CH_2Ar(o-CH)), 6.59 (1 H, td, J 7.3, 1.2, (6)-CH), 6.45 (1 H, dd, J 8.7, 1.3, (8)-CH), 5.90 (2 H, s, (2)-CH_2CH_2Ar(O_2CH_2)), 3.84 (1 H, br s, (1)-NH), 3.38-3.30 (1 H, m, (2)-CH), 2.88-2.72 (4 H, m, (2)-CH_2CH_2Ar + (4)-CH_2), 2.10-2.00 (1 H, m, (3)-CH) and 1.88-1.60 (3 H, m, (2)-CH_2CH_2Ar + (3)-CH); δ_C (75 MHz, CDCl_3) 146.83 (C), 146.09 (C), 143.89 (C), 133.53 (2 x C), 128.64 (CH), 126.14 (CH), 120.66 (C), 116.46 (CH), 113.55 (CH), 112.12 (CH), 109.11 (CH), 100.99 (CH_2), 50.29 (CH), 36.37 (CH_2), 31.54 (CH_2), 27.22 (CH_2) and 25.60 (CH_2); m/z (ESI-MS) 360.1 [M+H]^+. Found (ESI-HR-MS): 360.0596 [M+H]^+. C_{18}H_{19}BrNO_2 requires 360.0594 (-0.7 ppm error).
Reduction of 194 using catalyst 175; 81% ee and 30% conversion: Enantiomeric excess by HPLC analysis and conversion by NMR analysis (Chiralcel OD-H, hexane:isopropanol = 80:20, flow rate 0.6 ml/min, 254 nm, 19.0°C): $t_S = 21.1$ min (major), $t_R = 29.1$ (minor).

*The absolute configuration has not been determined, but is assigned by analogy with the reduction product of substrate 117a.

(+) 6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydroquinoline (193').

This compound is novel.

Reduction of 193 using catalyst 163b; 48% ee and 53% conversion. Enantiomeric excess and conversion by GC analysis (Chrompach cyclodextrin-β-236M-19 50m, $T = 150$ °C, $P = 15$ psi, H$_2$, imine 111.1 min., $S$ isomer 113.6 min (minor), $R$ isomer 116.0 min (major)); [α]$_D^{30}$ +64.0 ($c$ 0.5, CHCl$_3$) 48% ee (R); $ν_{max}$ 3369, 2930, 2843, 1618, 1516, 1449, 1398, 1375, 1335, 1317, 1255, 1229, 1200, 1133, 1069, 1021, 1001, 962, 937, 909, 844 and 762 cm$^{-1}$; $δ_H$ (400 MHz, CDCl$_3$) 6.53 (1 H, s, (5)-CH), 6.11 (1 H, s, (8)-CH), 3.79 (3 H, s, OCH$_3$), 3.78 (3 H, s, OCH$_3$), 3.55-3.05 (1 H, br s, NH), 3.37-3.27 (1 H, m, (2)-CH), 2.84-2.73 (1 H, m, (4)-CH), 2.69-2.59 (1 H, m, (4)-CH), 1.96-1.86 (1 H, m, (3)-CH), 1.63-1.49 (1 H, m, (3)-CH) and 1.20 (3 H, d, $J = 6.3$, CH$_3$); $δ_C$ (101 MHz, CDCl$_3$) 148.17 (C), 141.37 (C), 138.68 (C), 113.68 (CH), 112.54 (C), 99.57 (CH), 56.71 (CH), 55.84 (CH$_3$), 47.40 (CH$_3$), 30.53 (CH$_2$), 26.16 (CH$_2$) and 22.52 (CH$_3$); $m/z$ (ESI-MS) 208.1 [M+H]$^+$. Found (ESI-HR-MS): 208.1330 [M+H]$^+$, C$_{12}$H$_{18}$NO$_2$ requires 208.1332 (1.1 ppm error).

*The absolute configuration has not been determined, but is assigned by analogy with the reduction product of substrate 120a.
4.2 Procedures from Section 2.2.

Synthesis of 4-methylcyclohexa-1,4-dienecarboxylic acid (199).

\[
\text{\includegraphics[width=0.2\textwidth]{image.png}}
\]

This compound has been reported but not fully characterised.\(^{27a}\)

To a solution of propiolic acid (25.0 g, 22.0 cm\(^3\), 357 mmol) in toluene was added, isoprene (25.28 g, 37.13 cm\(^3\), 371.2 mmol) and hydroquinone (0.55 g, 5.01 mmol). The reaction was fitted with a condenser and heated to 130 °C overnight. The reaction mixture was cooled to room temperature, and a solid precipitate was filtered off and washed with cold toluene to give carboxylic acid 199 (26.5 g, 191.81 mmol, 54 %) as a white crystalline solid; Mp 181-184 °C; \(\nu_{\text{max}}\) 3675, 2963, 2882, 2631, 2532, 1701, 1666, 1645, 1425, 1282, 1161, 1097, 1035, 1027, 957, 922, 800, 780, 736 and 716 cm\(^{-1}\); \(\delta_H\) (400 MHz, CDCl\(_3\)) 7.10 (1 H, br s, CH=CCO\(_2\)H), 5.48 (1 H, br s, CH=CCH\(_3\)), 2.98-2.88 (2 H, m, CH\(_2\)C=CH), 2.82-2.72 (2 H, m, C=CCH\(_2\)) and 1.70 (3 H, s, CH\(_3\)); \(\delta_C\) (101 MHz, CDCl\(_3\)) 172.44 (COOH), 139.17 (CH), 129.23 (C), 127.07 (C), 118.55 (CH), 31.99 (CH\(_2\)), 25.48 (CH\(_3\)), 22.76 (CH\(_3\)); \(m/z\) (ESI-MS) 137.0 [M-H]\(^+\). Found (ESI-HR-MS): 137.0620 [M-H]\(^+\), \(C_8H_9O_2\) requires 137.0608 (-8.6 ppm error). The data matched that previously reported for this compound.

Synthesis of (4-methylcyclohexa-1,4-dien-1-yl)methanol (200).

\[
\text{\includegraphics[width=0.2\textwidth]{image.png}}
\]

This compound is novel.
4-Methylcyclohexa-1,4-dienecarboxylic acid (5.64 g, 40.8 mmol) in THF (50 cm$^3$) was added drop wise to a solution of LiAlH$_4$ (4.64 g, 123 mmol) in THF (250 cm$^3$) stirring at 0 °C. After addition, the solution was allowed to stir at rt over the weekend. The solution was then cooled to 0 °C and quenched with a 50 : 50 mixture of water and THF (50 cm$^3$: 50 cm$^3$), followed by water (50 cm$^3$). Rochelle salt (40 g, 142.12 mmol) was then added followed by DCM (75 cm$^3$) and was further allowed to stir for 3 hrs. As the Rochelle salt absorbs all the water, the remaining solution was then filtered off through celite, dried (MgSO$_4$), filtered and concentrated to give the alcohol as a white solid 200 (4.1 g, 33 mmol, 81 %); Mp 39-43 °C; $\nu_{max}$ 3361, 2963, 2908, 2818, 1429, 1338, 1185, 1140, 1065, 1001, 949, 904, 835 and 783 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 5.70 (1 H, s, $\text{CH}=\text{CCH}_2\text{OH}$), 5.45 (1 H, s, $\text{CH}=\text{CCH}_3$), 4.03 (2 H, s, $\text{CH}_2\text{OH}$), 2.72-2.65 (2 H, m, $\text{CH}_2\text{C}=\text{CH}$), 2.64-2.58 (2 H, m, C=CCH$_2$) and 1.68 (3 H, s, CH$_3$); $\delta_C$ (101 MHz, CDCl$_3$) 134.85 (C), 131.11 (C), 120.30 (CH), 118.25 (CH), 67.08 (CH$_2$), 31.26 (CH$_2$), 27.43 (CH$_2$) and 23.02 (CH$_3$); $m/z$ (ESI-MS) 271.2 [2M+Na]$^+$. Found (ESI-HR-MS): 271.1673 [2M+Na]$^+$, C$_{16}$H$_{24}$NaO$_2$ requires 271.1669 (-1.6 ppm error).

**Synthesis of 2-((4-methylcyclohexa-1,4-dien-1-yl)methoxy)acetic acid (202).**

This compound is novel.

To a flame-dried flask containing (4-methylcyclohexa-1,4-dienyl)methanol 200 (3.73 g, 30.0 mmol), tert-butyl bromoacetate (6.92 g, 5.20 cm$^3$, 35.5 mmol) and TBAB (1.94 g, 6.01 mmol) was added NaOH solution (9.27 g in 9.27 cm$^3$ H$_2$O, 232 mmol) at 0 °C. The reaction mixture was then stirred at 70 °C for 3 days. Saturated NaCl solution (60 cm$^3$) was then added to the reaction mixture and then it was extracted using Et$_2$O (3 x 90
cm$^3$) to remove starting materials and other impurities. Conc. HCl was then added to the aqueous layer to obtain pH 1, and it was then extracted again using Et$_2$O (3 x 90 cm$^3$), dried (MgSO$_4$), filtered and concentrated to give the product **202** as an orange oil (4.1 g, 22.50 mmol, 75 %); $\nu_{\text{max}}$ 2963, 2855, 2819, 1724, 1426, 1244, 1196, 1106, 1055, 952, 903, 834, 786, 764, 734 and 668 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 10.99 (1 H, br s, COOH), 5.74 (1 H, s, CH=CH$_2$O), 5.44 (1 H, s, CH=CH$_3$), 4.08 (2 H, s, OCH$_2$COOH), 4.02 (2 H, s, CH=CH$_2$O), 2.71-2.59 (4 H, m, CH$_2$C(CH$_3$)=CH$_2$) and 1.67 (3 H, s, CH$_3$); $\delta_C$ (101 MHz, CDCl$_3$) 175.51 (COOH), 130.95 (C), 130.74 (C), 124.22 (CH), 118.25 (CH), 75.53 (CH$_2$), 65.93 (CH$_2$), 31.33 (CH$_2$), 27.64 (CH$_2$) and 22.97 (CH$_3$); $m/z$ (ESI-MS) 181.0 [M-H]$^+$. Found (ESI-HR-MS): 205.0840 [M+Na]$^+$, C$_{10}$H$_{14}$NaO$_3$ requires 205.0835 (-2.5 ppm error).

**Synthesis of 2-((4-methylcyclohexa-1,4-dien-1-yl)methoxy)ethanol (203).**

![Chemical structure](image)

This compound is novel.

2-((4-Methylcyclohexa-1,4-dienyl)methoxy)acetic acid **202** (4.10 g, 22.5 mmol) in THF (28 cm$^3$) was added dropwise to a solution of LiAlH$_4$ (2.56 g, 67.5 mmol) in THF (138 cm$^3$) with stirring at 0 °C. After addition, the solution was allowed to stir at rt for 72h. The solution was then cooled to 0 °C and quenched with a 50 : 50 mixture of water and THF (28 cm$^3$: 28 cm$^3$), followed by water (28 cm$^3$). Rochelle salt (40 g, 142.12 mmol) was then added followed by DCM (41 cm$^3$) and was further allowed to stir for 3 hrs. The remaining solution was then filtered off through celite, dried (MgSO$_4$), filtered and concentrated to give a light orange oil **203** (3.92 g, quantitative conversion, includes traces of solvent) which was characterised in crude form due to reoxidation during
Experimental chromatography; \( \nu_{\text{max}} \) 3393, 2855, 2819, 1446, 1428, 1351, 1259, 1142, 1105, 1051, 951, 908, 889, 842, 783, 764 and 712 cm\(^{-1} \); \( \delta_H \) (400 MHz, CDCl\(_3\)) 5.71 (1 H, s, \( \text{CH}=\text{CCH}_2\text{O} \)), 5.44 (1 H, s, \( \text{CH}=\text{CCH}_3 \)), 3.93 (2 H, s, \( \text{CH}=\text{CH}_2\text{O} \)), 3.73 (2 H, t, \( J \) 4.8, \( \text{OCH}_2\text{CH}_2\text{OH} \)), 3.50 (2 H, \( J \) 4.8, \( \text{OCH}_2\text{CH}_2\text{OH} \)), 2.70-2.58 (4 H, m, \( \text{CH}_2\text{C}(\text{CH}_3)=\text{CCH}_2 \)), 2.17 (1 H, br s, \( \text{OH} \)) and 1.68 (3 H, s, \( \text{CH}_3 \)); \( \delta_C \) (101 MHz, CDCl\(_3\)) 132.04 (C), 130.90 (C), 122.55 (CH), 118.34 (CH), 75.26 (CH\(_2\)), 70.75 (CH\(_2\)), 61.92 (CH\(_2\)), 31.31 (CH\(_2\)), 27.74 (CH\(_2\)) and 23.01 (CH\(_3\)); \( m/z \) (ESI-MS) 191.0 [M+Na]\(^+\). Found (ESI-HR-MS): 191.1045 [M+Na]\(^+\), \( \text{C}_{10}\text{H}_{16}\text{NaO}_2 \) requires 191.1043 (-1.1 ppm error).

**Synthesis of 2-((4-methylcyclohexa-1,4-dien-1-yl)methoxy)acetaldehyde (204).**

![Chemical structure of 204](image)

This compound is novel.

The solution of oxalylchloride (2M in DCM, 15.14 cm\(^3\), 30.28 mmol) in anhydrous DCM (30 cm\(^3\)) was cooled to -78 °C, and was slowly added a solution of dimethylsulfoxide (4.73 g, 4.30 cm\(^3\), 60.56 mmol) in DCM (15 cm\(^3\)) by syringe. The solution was stirred for 30 minutes at -78 °C before a solution of 2-((4-methylcyclohexa-1,4-dien-1-yl) methoxy) ethanol 203 (3.92 g, 23.3 mmol) in DCM (50 cm\(^3\)) was slowly added at the same temperature. After stirring for 40 min at -78 °C, Et\(_3\)N (14.22 g, 19.59 cm\(^3\), 139.58 mmol) was added and the reaction mixture was allowed to warm up to rt. After 30 mins, water (100 cm\(^3\)) was added, and extracted with DCM, dried (MgSO\(_4\)), filtered and then concentrated under vacuum to give the product as a orangey brown oil 204 (4.78 g, quantitative conversion, includes traces of solvent) which was characterised in crude form due to reoxidation and decomposition during
attempts to purify; $\nu_{\text{max}}$ 2855, 2820, 1736, 1428, 1380, 1217, 1142, 1099, 952, 908, 752, 733 and 667 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 9.72 (1 H, s, CHO), 5.73 (1 H, s, CH=CCH$_2$O), 5.44 (1 H, s, CH=CCH$_3$), 4.03 (2 H, s, OCH$_2$CHO), 3.99 (2 H, s, CH=CCH$_2$O), 2.72-2.57 (4 H, m, CH$_2$C(=CH)$_3$) and 1.68 (3 H, s, CH$_3$); $\delta_C$ (101 MHz, CDCl$_3$) 200.98 (CHO), 131.16 (C), 130.84 (C), 124.03 (CH), 118.21 (CH), 75.82 (CH$_2$), 74.82 (CH$_2$), 31.33 (CH$_2$), 27.69 (CH$_2$) and 22.99 (CH$_3$); $m/z$ (ESI-MS) 189.2 [$\text{M+Na}^+]$. Found (ESI-HR-MS): 189.0901 [$\text{M+Na}^+]$, C$_{10}$H$_{14}$NaO$_2$ requires 189.0886 (-7.6 ppm error).

**Synthesis of $N$-((1$R$, 2$R$)-2-Amino-1, 2-diphenylethyl)-4-methylbenzenesulfonamide (81).**

![Structure of 81](image)

This is a known compound and has been fully characterised.$^{27c}$

A solution of $p$-TsCl (4.5 g, 24.0 mmol) in THF (50 cm$^3$) was added to a mixture of (1$R$,2$R$)-(-)-1, 2-diphenylethlenediamine (5.0 g, 24.0 mmol) in THF (200 cm$^3$) and triethylamine (10 cm$^3$) over a period of 30 mins at 0 °C. After stirring for 12 hrs the solvent was removed under reduced pressure. The remaining solid was treated with aqueous sat. NaHCO$_3$ solution (400 cm$^3$) and DCM (400 cm$^3$). The organic phase was washed with brine, dried (Na$_2$SO$_4$), and then concentrated in vacuo. The crude product was purified by flash chromatography (100 % ethyl acetate) giving yellow white crystals **81** (7.1 g, 19.37 mmol, 81 %); $\delta_H$ (400 MHz, CDCl$_3$) 7.31 (2 H, d, $J$ 8.3, NHSO$_2$Ar(o-2CH)), 7.20-7.08 (10 H, m, 2C$_6$H$_5$), 6.98 (2 H, d, $J$ 8.3, NHSO$_2$Ar(m-2CH)), 6.00 (1 H, br s, NH$_2$Ts), 4.37 (1 H, d, $J$ 5.1, TsNHCH), 4.13 (1 H, d, $J$ 5.1, NH$_2$CH),...
2.32 (3 H, s, NHSO₂Ar(CH₃); δ_C (101 MHz, CDCl₃) 142.39 (C), 141.27 (C), 139.40 (C), 136.69 (C), 129.12 (CH), 128.43 (CH), 128.26 (CH), 127.39 (CH), 127.06 (CH), 126.99 (CH), 126.85 (CH), 126.50 (CH), 63.11 (CH), 60.52 (CH) and 21.42 (CH₃).

**Synthesis of 4-methyl-N-((1R, 2R)-2-((2-((4-methylcyclohexa-1, 4-dien-1-yl)methoxy)ethyl)amino)-1, 2-diphenylethyl)benzenesulfonamide (205).**

![Chemical structure](image)

This compound is novel.

To a suspension of powdered molecular sieves (4 Å, 4.2 g) in dry methanol (250 cm³) was added 2-((4-methylcyclohexa-1,4-dienyl)methoxy)acetaldehyde 204 (2.90 g, 17.43 mmol), (R,R)-TsDPEN 81 (7.10 g, 19.37 mmol) and glacial acetic acid (51 drops). The reaction mixture was stirred at rt and monitored by TLC. After 2 hrs, the imine had formed, and sodium cyanoborohydride (1.30 g, 21.05 mmol) was added. The reaction was left overnight at rt. The molecular sieves were removed by filtration, and the solution was concentrated under reduced pressure. The residue was re-dissolved in DCM (300 cm³). The organic phase was washed with saturated NaHCO₃ (300 cm³) and brine (300 cm³), dried (MgSO₄), filtered and concentrated. The resulting residue was purified by flash chromatography (10→50 % v/v ethyl acetate/pet ether) to give 205 as a colourless oil (2.58 g, 5.00 mmol, 29 %); [α]_D^{26} -5.6 (c 0.5, CHCl₃); ν max 3270, 3029, 2855, 1599, 1495, 1454, 1397, 1327, 1218, 1184, 1156, 1092, 1027, 931, 812, 752, 699 and 667 cm⁻¹; δ_H (400 MHz, CDCl₃) 7.36 (2 H, d, J 8.2, NHSO₂Ar(o-2CH)), 7.15-6.90 (12 H, m, 2C₆H₅ + NHSO₂Ar(m-2CH)), 6.30 (1 H, br s, NHTs), 5.62 (1 H, s CH=CCH₂O), 5.45 (1 H, s, CH=CCH₃), 4.24 (1 H, d, J 7.6, TsNHCH), 3.77 (2 H, s,
Experimental

CH=CC(2O), 3.66 (1 H, d, J 7.6, NHCH), 3.45-3.32 (2 H, m, NHCH₂CH₂OCH₂), 2.65-
2.54 (5 H, m, NHCH(CH)₂CH₂OCH₂ + CH₂C(CH₃)=CCH₂), 2.48-2.41 (1 H, m,
NHCH(CH)₂CH₂OCH₂), 2.33 (3 H, s, NHSO₂ArCH₂), 1.73 (1 H, br s, NHCH) and 1.69
(3 H, s, CH₂C(CH₃)=CCH₂); δC (101 MHz, CDCl₃) 142.62 (C), 139.21 (C), 138.42 (C),
137.12 (C), 132.17 (C), 130.92 (C), 129.08 (CH), 128.30 (CH), 127.92 (CH), 127.77
(CH), 127.55 (CH), 127.46 (CH), 127.26 (CH), 127.12 (CH), 122.00 (CH), 118.42
(CH), 75.00 (CH₂), 69.00 (CH₂), 67.83 (CH₃), 63.10 (CH₃), 46.74 (CH₂), 31.33 (CH₂)
and 27.74 (CH₂); m/z (ESI-MS) 539.2 [M+Na]+. Found (ESI-HR-MS): 517.2519
[M+H]+, C₃₁H₃₇N₂O₃S requires 517.2519 (0.1 ppm error).

Synthesis of ether linked “tethered” dimer (206).

This compound is novel.

To a stirred solution of 4-methyl-N-((1R,2R)-2-(2-((4-methylocyclohexa-1,4-diaryl)ethoxy)ethylamino)-1,2-diphenylethyl)benzenesulfonamide 205 (1.38 g, 2.67
mmol) in DCM (39 cm³) was added 1.25 M HCl in EtOH (6.4 cm³, 8.01 mmol). The
reaction mixture was stirred for 2 hrs and concentrated under vacuum. To a suspension
of the residue in IPA (28 cm³) was added trihydrated ruthenium trichloride (880 mg,
4.22 mmol). The reaction mixture was stirred at reflux temperature for 2 days. It was
then filtered off and washed with cold IPA to give a dark blue solid 206 (1.70 g, 1.18
mmol, 88 %); v_max 3676, 2988, 2902, 1454, 1406, 1394, 1382, 1324, 1250, 1230, 1155,
1066, 1057, 892, 812, 763, 699 and 669 cm⁻¹; δH (400 MHz, DMSO-d₆) 9.47 (2 H, br s,
2 x NH₃H₂CH₂⁺Cl⁻), 8.90 (2 H, br s, 2 x NH₃H₂CH₂⁺Cl⁻), 8.55 (2 H, d, J 9.8, 2 x NHTs),

192
Experimental

7.35-6.70 (28 H, m, 2 x (14 x Ar-H)), 6.05-5.75 (8 H, m, 2 x (4 x Ru-Ar-H)), 4.80 (2 H, t, J 9.8, 2 x CHNH₂⁺Cl), 4.63-4.50 (2 H, m, 2 x CHNHTs), 4.38 (3.2 H, s, 2 x ArCH₂O), 4.31 (0.8 H, s, 2 x ArCH₂O), 3.90-3.75 (4 H, m, 2 x NH₂⁺ClCH₂CH₂O), 3.10-2.97 (4 H, m, 2 x NH₂⁺Cl’CH₂CH₂O), 2.21 (6 H, s, 2 x CH₃Ts), 2.15 (4.8 H, s, 2 x CH₃Ar) and 2.12 (1.2 H, s, 2 x CH₃Ar); δC (101 MHz, DMSO-d₆) 142.66 (2 x C), 138.06 (2 x C), 135.90 (2 x C), 131.93 (2 x C), 129.52 (2 x (2 x CH)), 129.50 (2 x CH and 2 x (2 x CH)), 129.21 (2 x (2 x CH)), 128.55 (2 x CH), 128.28 (2 x (2 x CH)), 128.15 (2 x (2 x CH)), 126.88 (2 x (2 x CH)), 122.62 (2 x CH), 118.73 (2 x CH), 102.76 (2 x C), 94.90 (2 x C), 65.59 (2 x CH), 62.48 (2 x (2 x CH)), 60.85 (2 x CH), 56.78 (2 x (2 x CH₂)), 48.61 (2 x CH₂), 26.00 (2 x CH₃) and 21.53 (2 x CH₃); m/z (ESI-MS) 615.0 [Monomer+H]⁺. Found (ESI-HR-MS): 615.1266 [Monomer+H]⁺, C₃₁H₃₃N₂O₃RuS (monomer formed in situ from dimer and loss of 3 x HCl) requires 615.1257 (-2.0 ppm error). Optical rotation could not be obtained due to the product being highly coloured.

Synthesis of ether linked “tethered” monomer (207).

This compound is novel.

To a suspension of dimer 206 (98 mg, 0.07 mmol) in IPA (9 cm³) was added Et₃N (0.06 cm³, 0.42 mmol). After stirring at 80 °C for 1.5 hrs, the hot IPA solution was filtered through a layer of cotton wool and filter paper to remove impurities. The solution was then concentrated, re-dissolved in DCM and washed with water. The organic layer was
then dried (Na$_2$SO$_4$), filtered and concentrated to give the monomer 207 as an orange solid (29 mg, 0.0446 mmol, 33 %). The crude product was isolated, and $^1$H NMR, LRMS and HRMS were carried out to confirm the presence of product. Several purification attempts on the crude product led to decomposition of the material; $\delta_H$ (300 MHz, CDCl$_3$) 7.30 (2 H, d, $J$ 8.0, 2 x Ar-H), 7.15-7.10 (4 H, m, 4 x Ar-H), 6.85 (2 H, d, $J$ 8.0, 2 x Ar-H), 6.80-6.70 (2 H, m, 2 x Ar-H), 6.70-6.55 (4 H, m, 4 x Ar-H), 6.15-6.05 (1 H, m, Ru-Ar-H), 5.75 (1H, d, $J$ 6.4, Ru-Ar-H), 5.65 (1H, d, $J$ 6.4, RuArH), 5.50-5.40 (1 H, m RuArH), 4.92 (1 H, brd, $J$ 14.2, CHPh), 4.55-4.45 (2 H, m, CHPh + NH), 4.05-3.88 (4 H, m, 2 x CH$_2$), 3.65-3.55 (1 H, m, CHH), 3.20-3.05 (1 H, m, CHH), 2.60 (3 H, s, CH$_3$), 2.24 (3 H, s, CH$_3$); $m/z$ (ESI-MS) 615.0 [Monomer+H]$^+$. Found (ESI-HR-MS): 615.1264 [Monomer+H]$^+$, C$_{31}$H$_{33}$N$_2$O$_3^{102}$RuS requires 615.1257 (-1.8 ppm error).

The $^1$H NMR spectroscopic data of the monomeric complex obtained by Ikariya matched that of the crude material obtained from dimer 206 in this project.\textsuperscript{27i}

**Synthesis of 2-phenoxy-1-phenylethanone (222).**

\[\text{\includegraphics[width=1cm]{2-phenoxy-1-phenylethanone.png}}\]

This is a known compound and has been fully characterised.\textsuperscript{32k}

Phenol (2.05 g, 1.91 cm$^3$, 21.80 mmol) and potassium carbonate (2.70 g, 19.50 mmol) were dissolved in acetone (40 cm$^3$) and the mixture was stirred for about 10 minutes. Phenacyl bromide (3.53 g, 17.70 mmol) was added to the mixture and the mixture was refluxed for 2 hrs. The reaction mixture was then quenched with water (100 cm$^3$) and the phenacyl ether was extracted with diethyl ether (3 x 50 cm$^3$). The organic extracts were washed with 2M NaOH (3 x 50 cm$^3$), and water (3 x 50 cm$^3$), dried (MgSO$_4$) and
filtered. The solvent was concentrated under reduced pressure and a white solid was obtained. The crude was recrystallized with ethanol to give 222 as a white crystalline solid (1.73 g, 8.15 mmol, 46 %); δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 8.01 (2 H, d, J 7.1, 2 x Ar-H o to C(C=O)CH\textsubscript{2}OPh), 7.62 (1 H, t, J 7.1, Ar-H p to C(C=O)CH\textsubscript{2}OPh), 7.50 (2 H, t, J 7.1, 2 x Ar-H m to C(C=O)CH\textsubscript{2}OPh) 7.33-7.25 (2 H, m, 2 x Ar-H m to OCH\textsubscript{2}OPh), 7.02-6.92 (3 H, m, 2 x Ar-H o and 1 x Ar-H p to OCH\textsubscript{2}OPh) and 5.27 (2 H, s, CH\textsubscript{2}); δ\textsubscript{C} (101 MHz, CDCl\textsubscript{3}) 194.58 (C=O), 158.04 (C), 134.64 (C), 133.88 (CH), 129.60 (2 x CH), 128.85 (2 x CH), 128.18 (2 x CH), 121.68 (CH), 114.84 (2 x CH) and 70.84 (CH\textsubscript{2}); m/z (ESI-MS) 235.1 [M+Na]\textsuperscript{+}. The data matched that previously reported for this compound.

**Synthesis of tert-butyl benzyl(2-oxo-2-phenylethyl)carbamate (225).**

\[ \text{Benzylamine (1.02 g, 9.5 mmol) and triethylamine (5.06 g, 50.0 mmol) were stirred in dichloromethane (20 cm}^3\text{) for 30 minutes. 2-Bromoacetophenone (1.99 g, 10.00 mmol) in dichloromethane (10 cm}^3\text{) was added dropwise and the reaction was stirred for 3 hrs. Di-tert-butyl dicarbonate (2.18 g, 10.0 mmol) in dichloromethane (10 cm}^3\text{) was added and the reaction mixture was stirred overnight. Saturated ammonium chloride solution (30 cm}^3\text{) was added, the phases were separated and the aqueous layer extracted with dichloromethane (3 x 20 cm}^3\text{). The combined organic layers were dried (MgSO}_4\text{), filtered and the solvent removed in vacuo, to give the crude as a yellow oil. Purification by flash chromatography (5→10% v/v ethyl acetate/pet ether) gave 225 as a light yellow solid (1.80 g, 5.53 mmol, 58 %); δ\textsubscript{H} (300 MHz, CDCl\textsubscript{3}) (1 : 1 mixture of NCO...} \]
Experimental

rotamers) 7.93-7.21 (10 H, m, 10 x Aryl-H), 4.63 (1 H, s, C(=O)-CH(1)H(2)), 4.61 (1 H, s, C(=O)-CH(1)H(2)), 4.56 (1 H, s, CH(1)H(2)-Ph), 4.46 (1 H, s, CH(1)H(2)-Ph), 1.50 (4.5 H, s, CH3) and 1.41 (4.5 H, s, CH3); δ(C) (75 MHz, CDCl3) 195.87 (C=O), 155.27 (C=O), 137.24 (C), 134.65 (C), 132.85 (CH), 128.13 (CH), 127.98 (3 x CH), 127.53 (CH), 127.29 (CH), 127.07 (CH), 126.92 (CH), 126.86 (CH), 80.01 ((CH3)3C), 51.51 (N(Boc)CH2), 50.76 (C(=O)CH2) and 27.79 ((CH3)3C). The data matched that previously reported for this compound.

Synthesis of N-(3,4-Dimethoxyphenethyl)acetamide (306).

\[ \text{\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure}
\caption{Structure of N-(3,4-Dimethoxyphenethyl)acetamide (306).}
\end{figure}} \]

This is a known compound and has been fully characterised.\textsuperscript{27h}

2-(3,4-Dimethoxyphenyl)ethylamine (5.00 g, 4.70 cm\textsuperscript{3}, 27.60 mmol) was dissolved in dichloromethane (50 cm\textsuperscript{3}) and stirred. Acetic anhydride (2.80 g, 2.60 cm\textsuperscript{3}, 27.60 mmol) was then added dropwise, and the solution was left to stir for 1 hr. After the stirring was completed, the solution was washed with saturated citric acid (10 cm\textsuperscript{3}), saturated NaHCO\textsubscript{3} (10 cm\textsuperscript{3}), brine (10 cm\textsuperscript{3}) and then dried (MgSO\textsubscript{4}). After filtration the solvent was removed under reduced pressure giving 306 as a white solid (5.50 g, 24.63 mmol, 90 %); δ\textsubscript{H} (300 MHz, CDCl\textsubscript{3}) 6.84-6.79 (1 H, m, Ar-H), 6.77-6.70 (2 H, m, 2 x Ar-H), 5.60 (1 H, br s, NH), 3.88 (3 H, s, OCH\textsubscript{3}), 3.87 (3 H, s, OCH\textsubscript{3}), 3.49 (2 H, d, J 7.0, NHCH\textsubscript{2}), 2.77 (2 H, J 7.0, Ar-CH\textsubscript{2}) and 1.95 (3 H, s, CH\textsubscript{3}); δ\textsubscript{C} (75 MHz, CDCl\textsubscript{3}) 170.40 (C), 149.27 (C), 147.92 (C), 131.58 (C), 120.86 (CH), 112.08 (CH), 111.56 (CH), 56.17 (CH\textsubscript{3}), 56.13 (CH\textsubscript{3}), 41.04 (CH\textsubscript{2}), 35.44 (CH\textsubscript{2}) and 23.61 (CH\textsubscript{3}). The data matched that previously reported for this compound.
Synthesis of 6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline (109a).

\[ \text{O} \quad \text{N} \]

This is a known compound and has been fully characterised.\textsuperscript{27th}

\(N\)-(3,4-Dimethoxyphenethyl)acetamide \textbf{306} (5.50 g, 24.67 mmol) and \(\text{POCl}_3\) (3.78 g, 2.26 cm\(^3\), 24.7 mmol) were refluxed in toluene (50 cm\(^3\)) for 2 hrs. Once the reflux was completed, the solvent was removed \textit{in vacuo} and the residue was re-dissolved in dichloromethane (50 cm\(^3\)). The organic layer was washed with saturated \(\text{K}_2\text{CO}_3\) (2 x 20 cm\(^3\)), brine (20 cm\(^3\)) and was then dried (\(\text{Na}_2\text{SO}_4\)). After filtration the solvent was removed \textit{in vacuo} giving \textbf{109a} (4.44 g, 21.63 mmol, 88 \%) as a yellow solid; \(\delta_H\) (300 MHz, \(\text{CDCl}_3\)) 7.00 (1 H, s, Ar-\(H\)), 6.70 (1 H, s, Ar-\(H\)), 3.91 (6 H, s, 2 x OCH\(_3\)), 3.62 (2 H, t, \(J\) 7.4, NCH\(_2\)), 2.63 (2 H, t, \(J\) 7.4, Ar-CH\(_2\)) and 2.37 (3 H, s, CH\(_3\)); \(\delta_C\) (75 MHz, \(\text{CDCl}_3\)) 164.20 (C), 150.70 (C), 147.30 (C), 130.96 (C), 122.30 (C), 110.11 (CH), 108.86 (CH), 56.07 (CH\(_3\)), 55.82 (CH\(_3\)), 46.83 (CH\(_2\)), 25.61 (CH\(_2\)) and 23.28 (CH\(_3\)).

The data matched that previously reported for this compound.

**Ketone and Imine Reduction.**

**General procedure for the preparation of secondary alcohols and amines.**
Method A (Racemic) To a stirred solution of ketone/imine (1 mmol) in methanol (12 cm³) was added NaBH₄ (3.0 eq.) portion-wise and the reaction mixture was allowed to stir until completion while monitoring the conversion by TLC, after completion the solution was diluted with saturated NH₄Cl (aq) (12 cm³) and extracted with dichloromethane (3 x 12 cm³). The combined extracts were dried (MgSO₄), filtered and concentrated under reduced pressure to give the racemic secondary alcohol or amine.

Method B (Asymmetric) using “tethered” Ru (II) dimer for ketones A solution of ruthenium dimer (0.0025 mmol) in formic acid/triethylamine (5:2) azeotrope (0.5 cm³) was stirred in a flame dried Schlenk tube (The Schlenk tube was degassed and purged with argon 3x before and after the addition of reagents) at 28 °C for 30 minutes. Ketone (1 mmol) was added and dichloromethane (0.5 cm³) was added if required to dissolve the substrate. The reaction mixture was stirred at 28 °C and monitored by TLC or GC, for which a drop of sample was filtered through a small plug of silica in a glass pipette using ethyl acetate and maybe a few drops of methanol depending on the polarity of the compound. After completion, the reaction mixture was diluted with dichloromethane (6.7 cm³) and washed with NaCO₃ solution (3 x 5 cm³). The organic phase was dried (MgSO₄), filtered and concentrated under reduced pressure to give the desired alcohol.

Method C (Asymmetric) using “tethered” Ru (II) dimer for imines A solution of ruthenium dimer (0.0025 mmol) and imine (1 mmol) in methanol (1.6 cm³) was stirred in a flame dried Schlenk tube at 28 °C for 10 minutes. Formic acid/triethylamine (5:2) azeotrope (0.5 cm³) was then added (The Schlenk tube was degassed and purged with argon 3x before and after the addition of reagents). The reaction mixture was stirred at 28 °C and monitored by TLC or GC, for which a drop of sample was filtered through a small plug of silica in a glass pipette using ethyl acetate and maybe a few drops of methanol depending on the polarity of the compound. After completion, NaHCO₃
solution (5 cm³) was added, and was extracted with dichloromethane (3 x 6.7 cm³). The organic phase was dried (MgSO₄), filtered and concentrated under reduced pressure to give the desired amine.

**Reduction product analysis.**

**(R)-1-Phenylethanol (49a').**

\[
\text{OH} \\
\text{C}_6\text{H}_5\text{CH}_2
\]

This is a known compound and has been fully characterised.²⁰a

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β-236M-19 50m, T = 115 °C, P = 15 psi, H₂, R isomer 15.0 min., S isomer 16.7 min.); [α]₂₈° +56.0 (c 1.0, CHCl₃) >99% ee (R) (lit.²⁰a [α]₂₂° +49.0 (c 1.0, CHCl₃) 98% ee (R)); δ_H (400 MHz, CDCl₃) 7.39-7.24 (5 H, m, 5 x Ar-H), 4.88 (1 H, q, J 6.4, CHO), 2.03 (1 H, br s, OH) and 1.49 (3 H, d, J 6.4, CH₃); δ_C (101 MHz, CDCl₃) 145.83 (C), 126.52 (2 x CH), 127.49 (CH), 125.41 (2 x CH), 70.43 (CH) and 25.16 (CH₃). The data matched that previously reported for this compound.

**(S)-1-Cyclohexylethanol (141').**

\[
\text{OH} \\
\text{C}_6\text{H}_{11}
\]

This is a known compound and has been fully characterised.³²m

Using catalyst 183; Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β-236M-19 50m, (Product was converted to (S)-1-cyclohexylethyl acetate.
Experimental

for GC separation) T = 115 °C, P = 15 psi, He, S isomer 24.6 min., R isomer 27.6 min.); [α]$_D^{28}$ +5.6 (c 1.0, CHCl$_3$) 74% ee (S) (lit.$^{32n}$ [α]$_D^{22}$ +2.7 (c 0.5, CHCl$_3$) 75% ee (S)); δ$_H$ (400 MHz, CDCl$_3$) 3.58-3.51 (1 H, m, cyclohexyl), 1.90-1.62 (5 H, m, cyclohexyl), 1.50 (1 H, br s, OH), 1.32-0.91 (6 H, m, cyclohexyl) and 1.16 (3 H, d, J 6.3, CH$_3$); δ$_C$ (101 MHz, CDCl$_3$) 72.22 (CH), 45.13 (CH), 28.71 (CH$_2$), 28.37 (CH$_2$), 26.53 (CH$_2$), 26.24 (CH$_2$), 26.15 (CH$_2$) and 20.37 (CH$_3$). The data matched that previously reported for this compound.

(R)-1-(3,5-Bis(trifluoromethyl)phenyl)ethanol (129’).

This is a known compound and has been fully characterised.$^{32n}$

Enantiomeric excess and conversion by GC analysis (CP-Chirasil-Dex CB, 25 m, 0.25 mm, 0.25 µm, T = 100 °C for 10 minutes then ramp at 10 °C/minute to 200 °C, P = 20 psi, He, S isomer 11.0 min., R isomer 12.0 min.); [α]$_D^{546}$ +11.2 (c 1.0, CHCl$_3$) 60% ee (R) (lit.$^{32n}$ [α]$_D^{546}$ +16.0 (c 1.2, CHCl$_3$) >99% ee (R)); δ$_H$ (400 MHz, CDCl$_3$) 7.85 (2 H, s, 2 x Ar-H o to CHOH), 7.79 (1 H, s, Ar-H p to CHOH), 5.05 (1 H, q, J 6.5, CHOH), 2.02 (1 H, br s, OH) and 1.55 (3 H, d, J 6.5, CH$_3$); δ$_C$ (101 MHz, CDCl$_3$) 148.22 (C), 131.92 (C), 131.59 (C), 125.66 (2 x CH), 124.71 (C), 121.94 (C), 121.31 (CH), 69.28 (CH) and 25.60 (CH$_3$). The data matched that previously reported for this compound.

1-(2-(Trifluoromethyl)phenyl)ethanol (224’).
This is a known compound and has been fully characterised.\textsuperscript{171}

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-\(\beta\)-236M-19 50 m, T = 110 °C, P = 15 psi, H\(_2\), \(R\) isomer 18.3 min., \(S\) isomer 20.0 min.); (lit.\textsuperscript{171} \([\alpha]_D^{29}\) -30.4 (c 1.41, CHCl\(_3\)) 96% ee (\(R\)); \(\delta\)\(_H\) (300 MHz, CDCl\(_3\)) 7.82 (1 H, d, \(J\) 7.8, Ar-\(H\) o to CF\(_3\)), 7.63-7.55 (2 H, m, Ar-\(H\) m to CHOCH\(_3\) and Ar-\(H\) p to CHOCH\(_3\)), 7.40-7.32 (1 H, m, Ar-\(H\) m to CHOCH\(_3\) and p to CF\(_3\)), 5.37-5.27 (1 H, m, CHO), 2.10 (1 H, d, \(J\) 3.0, O\(H\)) and 1.48 (3 H, d, \(J\) 6.3, CH\(_3\)); \(\delta\)\(_C\) (75 MHz, CDCl\(_3\)) 144.41 (C), 131.77 (CH), 126.72 (CH), 126.47 (CH), 125.57 (C), 124.71 (CH), 121.94 (C), 65.06 (CH) and 24.79 (CH\(_3\)). The data matched that previously reported for this compound.

\((S)-2\)-Chloro-1-phenylethanol (219').

\[
\text{\textbf{Experimental}}
\]

\[
\text{\textbf{(S)-2-Chloro-1-phenylethanol (219')}}
\]

This is a known compound and has been fully characterised.\textsuperscript{20a}

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-\(\beta\)-236M-19 50 m, T = 140 °C, P = 10 psi, H\(_2\), \(S\) isomer 29.9 min., \(R\) isomer 31.7 min.); \([\alpha]_D^{28}\) +43.4 (c 1.0, cyclohexane) >98% ee (\(S\)) (lit.\textsuperscript{20a} \([\alpha]_D^{25}\) +51.5 (c 1.1, cyclohexane) 95% ee (\(S\)); \(\delta\)\(_H\) (300 MHz, CDCl\(_3\)) 7.33-7.15 (5 H, m, 5 x Ar-\(H\)), 4.76 (1 H, dd, \(J\) 8.7, 3.4, CHO), 3.61 (1 H, dd, \(J\) 3.4, 11.2 CH\(_{(1)}\)H\(_{(2)}\)(Cl)), 3.51 (1 H, dd, \(J\) 8.7, 11.2, CH\(_{(1)}\)H\(_{(2)}\)(Cl)) and 2.60 (1 H, br s, O\(H\)); \(\delta\)\(_C\) (75 MHz, CDCl\(_3\)) 139.27 (C), 128.07 (2 x CH), 127.87 (CH), 125.44 (2 x CH), 73.46 (CH) and 50.31 (CH\(_2\)). The data matched that previously reported for this compound.

\((R)-1-(4\text{-Chlorophenyl})\text{ethanol (49c')}.\)
Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β- 236M-19 50m, T = 130 °C, P = 15 psi, H₂, R isomer 27.9 min., S isomer 31.4 min.); [α]D° 20 +50.4 (c 1.0, CHCl₃) 96% ee (R) (lit.°°°° [α]D° 22 +45.6 (c 1.0, CHCl₃) 91% ee (R)); δH (400 MHz, CDCl₃) 7.33-7.25 (4 H, m, 4 x Ar-H), 4.87 (1 H, q, J 6.5, CHOH), 2.73 (1 H, br s, OH) and 1.47 (3 H, d, J 6.5, CH₃); δC (101 MHz, CDCl₃) 144.17 (C), 133.12 (C), 128.80 (2 x CH), 126.82 (2 x CH), 69.81 (CH) and 25.24 (CH₃). The data matched that previously reported for this compound.

(R)-1-(3-Chlorophenyl)ethanol (49b').

Enantiomeric excess and conversion by GC analysis (CP-Chirasil-Dex CB, 25 m, 0.25 mm, 0.25 μm, T = 120 °C for 20 minutes then ramp at 15 °C/minute to 200 °C, P = 20 psi, He, R isomer 19.2 min., S isomer 21.1 min.); [α]D° 20 +34.8 (c 1.0, CHCl₃) 94% ee (R) (lit.°°° [α]D° 22 +43.3 (c 1.0, CHCl₃) 90% ee (R)); δH (300 MHz, CDCl₃) 7.37-7.32 (1 H, m, Ar-H o to Cl and CHOHCH₃), 7.30-7.19 (3 H, m, 1 x Ar-H m to Cl/CHOHCH₃ and 1 x Ar-H p to Cl and 1 x Ar-H p to CHOHCH₃), 4.85 (1 H, q, J 6.5, CHOH), 2.50 (1 H, br s, OH) and 1.46 (3 H, d, J 6.5, CH₃); δC (75 MHz, CDCl₃) 147.18 (C), 133.74
(C), 129.18 (CH), 126.92 (CH), 125.02 (CH), 122.93 (CH), 69.29 (CH) and 24.59 (CH₃). The data matched that previously reported for this compound.

**(R)-1-(2-Chlorophenyl)ethanol (216').**

![R-1-(2-Chlorophenyl)ethanol](image)

This is a known compound and has been fully characterised.

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β- 236M-19 50m, T = 130 °C, P = 15 psi, H₂, R isomer 22.9 min., S isomer 28.8 min.); [α]°D +49.2 (c 1.0, CHCl₃) 87% ee (R) (lit. [α]°D +40.8 (c 1.0, CHCl₃) 77% ee (R)); δH (300 MHz, CDCl₃) 7.59 (1 H, dd, J 1.8, 1.8, Ar-H o to Cl), 7.34-7.25 (2 H, m, 1 x Ar-H o to CHOHCH₃ and 1 x Ar-H p to CHOHCH₃), 7.19 (1 H, ddd, J 1.8, 1.8, 1.8, Ar-H p to Cl), 5.29 (1 H, q, J 6.4, CHOH), 2.20 (1 H, br s, OH) and 1.49 (3 H, d, J 6.4, CH₃); δC (75 MHz, CDCl₃) 142.41 (C), 131.02 (C), 128.79 (CH), 127.79 (CH), 126.60 (CH), 125.79 (CH), 66.36 (CH) and 22.88 (CH₃). The data matched that previously reported for this compound.

**(S)-2-Chloro-1-(4-chlorophenyl)ethanol (220').**

![S-2-Chloro-1-(4-chlorophenyl)ethanol](image)

This is a known compound and has been fully characterised.

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β- 236M-19 50m, T = 160 °C, P = 11 psi, H₂, S isomer 38.2 min., R isomer 40.9 min.); [α]°D +49.2 (c 1.0, CHCl₃) 87% ee (R) (lit. [α]°D +40.8 (c 1.0, CHCl₃) 77% ee (R)); δH (300 MHz, CDCl₃) 7.59 (1 H, dd, J 1.8, 1.8, Ar-H o to Cl), 7.34-7.25 (2 H, m, 1 x Ar-H o to CHOHCH₃ and 1 x Ar-H p to CHOHCH₃), 7.19 (1 H, ddd, J 1.8, 1.8, 1.8, Ar-H p to Cl), 5.29 (1 H, q, J 6.4, CHOH), 2.20 (1 H, br s, OH) and 1.49 (3 H, d, J 6.4, CH₃); δC (75 MHz, CDCl₃) 142.41 (C), 131.02 (C), 128.79 (CH), 127.79 (CH), 126.60 (CH), 125.79 (CH), 66.36 (CH) and 22.88 (CH₃). The data matched that previously reported for this compound.
+44.8 (c 1.0, CHCl₃) 96% ee (S) (lit.²⁰ᵃ [α]$_D^{25}$ +47.0 (c 1.1, CHCl₃) 93% ee (S)); δ$_H$ (400 MHz, CDCl₃) 7.37-7.30 (4 H, m, 4 x Ar-$H$), 4.88 (1 H, dd, $J$ 3.5, 8.6, $CHOH$), 3.71 (1 H, dd, $J$ 3.5, 11.3, $CH(1)H(2)$Cl), 3.61 (1 H, dd, $J$ 8.6, 11.3, $CH(1)H(2)$Cl) and 2.95 (1 H, br s, $OH$); δ$_C$ (101 MHz, CDCl₃) 138.37 (C), 134.26 (C), 128.86 (2 x CH), 127.47 (2 x CH), 73.39 (CH) and 50.67 (CH$_2$). The data matched that previously reported for this compound.

(S)-2-Chloro-1-(4-methoxyphenyl)ethanol (221').

![Chemical structure](image)

This is a known compound and has been fully characterised.²⁰ᵃ

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β-236M-19 50m, T = 160 °C, P = 14 psi, H₂, $S$ isomer 33.2 min., $R$ isomer 34.6 min.); [α]$_D^{31}$ +50.0 (c 1.0, CHCl₃) 97% ee (S) (lit.²⁰ᵃ [α]$_D^{24}$ +52.9 (c 1.1, CHCl₃) 95% ee (S)); δ$_H$ (400 MHz, CDCl₃) 7.34-7.27 (2 H, m, 2 x Ar-$H$ o to $CHOHCH₂$Cl), 6.93-6.87 (2 H, m, 2 x Ar-$H$ o to MeO), 4.85 (1 H, dd, $J$ 3.6, 8.7, $CHOH$), 3.81 (3 H, s, $CH₃O$), 3.70 (1 H, dd, $J$ 3.6, 11.2, $CH(1)H(2)$Cl), 3.63 (1 H, dd, $J$ 8.7, 11.2, $CH(1)H(2)$Cl) and 2.65 (1 H, br s, $OH$); δ$_C$ (101 MHz, CDCl₃) 159.72 (C-OMe), 132.06 (C), 127.35 (2 x CH), 114.09 (2 x CH), 73.75 (CH), 55.33 (CH$_₃$) and 50.92 (CH$_₂$). The data matched that previously reported for this compound.

(S)-2-Phenoxy-1-phenylethanol (222').

![Chemical structure](image)
This is a known compound and has been fully characterised.\textsuperscript{33b}

Enantiomeric excess by HPLC analysis and conversion by GC analysis (ChiralPak IA Column: 0.46 cm\(^3\) x 25 cm, hexane:isopropanol = 95:5, flow rate 0.5 ml/min, 254 nm, 24 °C: \(t_R = 28.9\) min (minor), \(t_S = 36.4\) (major)); \([\alpha]_D^{30}\) +58.8 (c 1.0, CHCl\(_3\)) 95% ee (S) (lit.\textsuperscript{33b} \([\alpha]_D^{20}\) +50.0 (c 1.7, CHCl\(_3\)) 98% ee (S)); \(\delta_H\) (400 MHz, CDCl\(_3\)) 7.47-7.23 (7 H, m, 5 x Ar-H and 2 x Ar-H \(m\) to CH\(_2\)O), 6.97 (1 H, t, \(J = 7.4, \) Ar-H \(p\) to CH\(_2\)O), 6.91 (2 H, d, \(J = 7.8, \) 2 x Ar-H \(o\) to CH\(_2\)O), 5.12 (1 H, dd, \(J = 3.2, 8.8, \) CHOH), 4.10 (1 H, dd, \(J = 9.6, 8.8, \) CH(1)H(2)OPh) and 2.90 (1 H, br s, OH); \(\delta_C\) (101 MHz, CDCl\(_3\)) 158.41 (C), 139.66 (C), 129.60 (2 x C\(_6\)H), 128.61 (2 x C\(_6\)H), 128.23 (CH), 126.32 (2 x CH), 121.35 (CH), 114.68 (2 x CH), 73.32 (CH\(_2\)) and 72.63 (CH). The data matched that previously reported for this compound.

\((R)-1\text{-phenylpropan-1-ol (49g')}\).

\[\text{\includegraphics{image.png}}\]

This is a known compound and has been fully characterised.\textsuperscript{32b}

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-\(\beta\)-236M-19 50m, \(T = 110^\circ\)C, \(P = 15\) psi, H\(_2\), \(R\) isomer 31.1 min., \(S\) isomer 33.8 min.); \([\alpha]_D^{26}\) +53.6 (c 1.0, CHCl\(_3\)) >99% ee \((R)\) (lit.\textsuperscript{32b} \([\alpha]_D^{26}\) -40.0 (c 0.85, CHCl\(_3\)) 66% ee (S)); \(\delta_H\) (400 MHz, CDCl\(_3\)) 7.38-7.24 (5 H, m, 5 x Ar-H), 4.59 (1 H, t, \(J = 6.5, \) CHOH), 2.40 (1 H, br s, OH), 1.90-1.68 (2 H, m, CH\(_2\)) and 0.91 (3 H, t, \(J = 7.4, \) CH\(_3\)); \(\delta_C\) (101 MHz, CDCl\(_3\)) 144.55 (C), 128.43 (2 x CH), 127.54 (CH), 125.99 (2 x CH), 76.09 (CH), 31.88 (CH\(_2\)) and 10.15 (CH\(_3\)). The data matched that previously reported for this compound.

\(2\)-Methyl-1-phenylpropan-1-ol (217').
This is a known compound and has been fully characterised.\textsuperscript{33c}

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-\(\beta\)-236M-19 50\(m\), T = 110 °C, P = 15 psi, \(\text{H}_2\), \(R\) isomer 39.4 min., \(S\) isomer 40.8 min.); (lit.\textsuperscript{33c} \([\alpha]_D^{20} +34.6 (c 1.0, \text{CHCl}_3) 68.5\% \text{ ee (}\(R\))\); \(\delta_H\) (400 MHz, CDCl\(_3\)) 7.36-7.22 (5 H, m, 5 x Ar-\(H\)), 4.33 (1 H, d, \(J\) 6.8, \(\text{CHOH}\)), 1.97 (1 H, br s, \(\text{OH}\)), 1.94 (1 H, oct, \(J\) 6.8, \(\text{CH(CH}_3)_2\)), 0.99 (3 H, d, \(J\) 6.8, \(\text{CH}_3\)) and 0.78 (3 H, d, \(J\) 6.8, \(\text{CH}_3\)); \(\delta_C\) (101 MHz, CDCl\(_3\)) 143.68 (\(C\)), 127.94 (2 x CH), 127.01 (CH), 126.60 (2 x CH), 80.05 (CH), 35.09 (CH), 19.02 (CH\(_3\)) and 18.28 (CH\(_3\)). The data matched that previously reported for this compound.

\textit{2,2-Dimethyl-1-phenylpropan-1-ol (218')}.

This is a known compound and has been fully characterised.\textsuperscript{33d}

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-\(\beta\)-236M-19 50\(m\), T = 125 °C, P = 15 psi, \(\text{H}_2\), \(S\) isomer 29.5 min., \(R\) isomer 30.5 min.); (lit.\textsuperscript{33d} \([\alpha]_D^{20} +12.2 (c 1.0, \text{CHCl}_3) 45\% \text{ ee (}\(R\))\); \(\delta_H\) (400 MHz, CDCl\(_3\)) 7.34-7.22 (5 H, m, 5 x Ar-\(H\)), 4.38 (1 H, s, \(\text{CHOH}\)), 1.92 (1 H, br s, \(\text{OH}\)) and 0.92 (9 H, s, 3 x \(\text{CH}_3\)); \(\delta_C\) (101 MHz, CDCl\(_3\)) 142.23 (\(C\)), 127.64 (2 x CH), 127.57 (2 x CH), 127.29 (CH), 82.41 (CH), 35.64 (\(C\)) and 25.96 (3 x \(\text{CH}_3\)). The data matched that previously reported for this compound.
(R)-1,2,3,4-Tetrahydronaphthalen-1-ol (214').

\[
\begin{align*}
&\text{(OH)} \\
&\text{H} \\
&\text{H}
\end{align*}
\]

This is a known compound and has been fully characterised.\textsuperscript{33e}

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β-236M-19 50m, T = 115 °C, P = 15 psi, H\textsubscript{2}, S isomer 74.1 min., R isomer 74.3 min.); [α]\textsubscript{D}\textsuperscript{29} = 19.2 (c 1.0, CHCl\textsubscript{3}) >99% ee (R) (lit.\textsuperscript{33e} [α]\textsubscript{D}\textsuperscript{20} = 38.9 (c 1.45, CHCl\textsubscript{3}) 99% ee (S)); δ\textsubscript{H} (300 MHz, CDCl\textsubscript{3}) 7.45-7.36 (1 H, m, 1 x Ar-H), 7.22-7.04 (3 H, m, 3 x Ar-H), 4.77 (1 H, t, J 4.4, CHO), 2.88-2.62 (2 H, m, CH\textsubscript{2} p to CHOH), 2.50 (1 H, br s, OH) and 2.05-1.69 (4 H, m, 2 x CH\textsubscript{2} o and m to CHOH); δ\textsubscript{C} (75 MHz, CDCl\textsubscript{3}) 138.10 (C), 136.52 (C), 128.42 (CH), 128.06 (CH), 127.00 (CH), 125.58 (CH), 67.57 (CH), 31.62 (C), 28.63 (CH\textsubscript{2}) and 18.16 (CH\textsubscript{2}). The data matched that previously reported for this compound.

(R)-Chroman-4-ol (215').

\[
\begin{align*}
&\text{(OH)} \\
&\text{O} \\
&\text{H}
\end{align*}
\]

This is a known compound and has been fully characterised.\textsuperscript{33e}

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β-236M-19 50m, T = 160 °C, P = 15 psi, H\textsubscript{2}, S isomer 13.4 min., R isomer 13.6 min.); [α]\textsubscript{D}\textsuperscript{30} = 77.6 (c 1.0, CHCl\textsubscript{3}) >99% ee (R) (lit.\textsuperscript{33e} [α]\textsubscript{D}\textsuperscript{20} = 62.0 (c 1.8, CHCl\textsubscript{3}) 98% ee (S)); δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 7.32 (1 H, dd, J 7.6, 1.6, Ar-H), 7.21 (1 H, dt, J 7.4, 1.6, Ar-H), 6.93 (1 H, dt, J 7.4, 1.1, Ar-H), 6.85 (1 H, d, J 8.3, Ar-H), 4.80 (1 H, t, J 4.0, CHO), 4.31-4.24 (2 H, m, CH\textsubscript{2} m to CHOH), 2.18-2.09 (1 H, m, CH\textsubscript{i,j}H\textsubscript{(2)} o to CHOH), 2.08-2.00 (1
H, m, CH$_{(1)}$H$_{(2)}$ o to CH$_{OH}$ and 1.80 (1 H, br s, OH); $\delta$$_C$ (101 MHz, CDCl$_3$) 154.45 (C), 129.76 (CH), 129.64 (CH), 124.42 (C), 120.62 (CH), 117.11 (CH), 63.29 (CH), 61.93 (CH$_2$) and 30.84 (CH$_2$). The data matched that previously reported for this compound.

(R)-1-(Pyridin-2-yl)ethanol (107a').

This is a known compound and has been fully characterised.$^{20a}$

Using catalyst 163b; Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β-236M-19 50m, (Product was converted to (R)-1-(pyridin-2-yl)ethyl acetate for GC separation) $T = 115^\circ$C, $P = 15$ psi, $G = H_2$, $S$ isomer 19.3 min., $S$ isomer 20.0 min.); $[\alpha]_D^{28} +24.8$ (c 1.0, CHCl$_3$) 88% ee (R) (lit.$^{20a}$ $[\alpha]_D^{24} +18.9$ (c 1.5, CHCl$_3$) 91% ee (R)); $\delta$$_H$ (400 MHz, CDCl$_3$) 8.55 (1 H, d, $J$ 4.9, Ar-H o to N), 7.76 (1 H, dt, $J$ 7.8, 1.7, Ar-H p to N), 7.38 (1 H, d, $J$ 7.8, Ar-H o to CHOHCH$_3$), 7.29-7.24 (1 H, m, Ar-H m to N and p to CHOHCH$_3$), 4.95 (1 H, q, $J$ 6.6, CHOH) and 1.53 (3 H, d, $J$ 6.6, CH$_3$); $\delta$$_C$ (101 MHz, CDCl$_3$) 163.01 (C), 147.48 (CH), 137.77 (CH), 122.61 (CH), 120.31 (CH), 68.97 (CH) and 23.95 (CH$_3$). The data matched that previously reported for this compound.

(S)-tert-Butyl benzyl(2-hydroxy-2-phenylethyl)carbamate (225').

This is a known compound and has been fully characterised.$^{321}$
Enantiomeric excess by HPLC analysis and conversion by NMR analysis (ChiralPak IA Column: 0.46 cm x 25 cm, hexane:isopropanol = 98:2, flow rate 0.5 ml/min, 254 nm, 21 °C: t_R = 49.6 min (minor), t_S = 64.9 (major)); [α]_D^{20} +2.4 (c 0.5, ethanol) >99% ee (S) (lit. [32] [α]_D^{20} +3.3 (c 2.0, ethanol) 80% ee (S)); δ_H (400 MHz, CDCl_3) 7.34-7.15 (10 H, m, 10 x Ar-H), 4.92-4.86 (1 H, m, CHOH), 4.51-4.41 (2 H, m, CH(1)-H(2))-Ar and OH), 4.19 (1 H, d, J 14.4, CH(1)H(2)-Ar), 3.64-3.49 (1 H, m, CH(OH)CH(1)H(2)), 3.33 (1 H, d, J 13.0, CH(OH)CH(1)H(2)) and 1.49 (9 H, s, CH_3); δ_C (101 MHz, CDCl_3) 155.91 (C=O) 142.39 (C), 137.96 (C), 128.62 (4 x CH), 128.41 (CH), 127.51 (CH), 127.38 (CH), 127.34 (CH), 125.80 (2 x CH), 81.51 ((CH_3)_3C), 74.23 (CH(OH)), 57.30 (CH_2), 52.53 (CH_2) and 28.42 ((CH_3)_3C); m/z (ESI-MS) 350.2 [M+Na]^+. The data matched that previously reported for this compound.

(R)-1-(Cyclohex-1-en-1-yl)ethanol (226').

This is a known compound and has been fully characterised. [33f]

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β-236M-19 50m, T = 115 °C, P = 15 psi, H_2, S isomer 13.5 min., R isomer 13.9 min.); [α]_D^{30} +26.4 (c 0.5, CHCl_3) 71% ee (R) (lit. [33f] [α]_D^{20} +19.7 (c 1.69, CHCl_3) 83% ee (R)); δ_H (400 MHz, CDCl_3) 5.66 (1 H, s, CH=C), 4.16 (1 H, q, J 6.4, CHOH), 2.10-1.90 (4 H, m, 2 x CH_2), 1.72-1.49 (5 H, m, 2 x CH_2 + OH) and 1.25 (3 H, d, J 6.4, CH_3); δ_C (101 MHz, CDCl_3) 141.27 (C), 121.49 (CH), 72.14 (CH), 24.89 (CH_2), 23.67 (CH_2), 22.66 (CH_2), 22.60 (CH_2) and 21.50 (CH_3). The data matched that previously reported for this compound.
(S)-6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (109a').

This is a known compound and has been fully characterised.\textsuperscript{26a}

Enantiomeric excess and conversion by GC analysis (Chrompac cyclodextrin-β-236M-19 50m, T = 170 °C, P = 15 psi, He, S isomer 35.5 min., R isomer 36.1 min.); \([\alpha]_D\textsuperscript{27} = -40.0\) (c 0.5, CHCl\(_3\)) 87% ee (R) (lit.\textsuperscript{26a} [\(\alpha\]_D\textsuperscript{28} = -32.9 (c 0.3, CHCl\(_3\)) 84% ee (S)); \(\delta_H\) (400 MHz, CDCl\(_3\)) 6.63 (1 H, s, Ar-\(H\)), 6.57 (1 H, s, Ar-\(H\)), 4.05 (1 H, q, \(J\) 6.6, C\(H\)NH), 3.85 (6 H, s, 2 x C\(H\)\(_3\)O), 3.29-3.21 (1 H, m, CH\(_{(1)}\)H\(_{(2)}\) \(p\) to CH(CH\(_3\))), 3.04-2.95 (1 H, m, CH\(_{(1)}\)H\(_{(2)}\) \(p\) to CH(CH\(_3\))), 2.85-2.73 (1 H, m, CH\(_{(1)}\)H\(_{(2)}\) \(m\) to CH(CH\(_3\))), 2.69-2.60 (1 H, m, CH\(_{(1)}\)H\(_{(2)}\) \(m\) to CH(CH\(_3\))), 1.73 (1 H, br s, NH) and 1.44 (3 H, d, \(J\) 6.6, CH\(_3\)); \(\delta_C\) (101 MHz, CDCl\(_3\)) 147.30 (\(C\)), 147.22 (\(C\)), 132.52 (\(C\)), 126.85 (\(C\)), 111.77 (CH), 109.04 (CH), 56.00 (1 x CH\(_3\)O), 55.86 (1 x CH\(_3\)O), 51.25 (CH), 41.89 (CH\(_2\)), 29.61 (CH\(_2\)) and 22.90 (CH\(_3\)). The data matched that previously reported for this compound.

4.3 Procedures from Section 2.3.

Synthesis of 2-((\textit{tert}-butyldiphenylsilyl)oxy)ethanol (230a).

This is a known compound and has been fully characterised.\textsuperscript{26c}

\textit{tert}-Butyl-chlorodiphenylsilane (2.29 g, 2.17 cm\(^3\), 8.33 mmol) was added to a stirred solution of ethane-1,2-diol (3.10 g, 2.79 cm\(^3\), 50.00 mmol) and imidazole (0.63 g, 9.18 mmol) in THF (43 cm\(^3\)) under argon atmosphere. The resulting mixture was stirred for
24 hrs at rt and quenched with water (43 cm$^3$) followed by the addition of Et$_2$O (43 cm$^3$). After phase separation and extraction of the aqueous phase with Et$_2$O (3 x 43 cm$^3$), the combined organic phases were dried (MgSO$_4$), filtered, concentrated and purified by flash chromatography (10→20 % v/v ethyl acetate/pentane) to afford the monosilyl alcohol 230a as a colourless oil (1.1 g, 3.66 mmol, 44 %); $\delta$$_H$ (400 MHz, CDCl$_3$) 7.74-7.64 (4 H, m, 4 x Ar-H), 7.48-7.35 (6 H, m, 6 x Ar-H), 3.80-3.74 (2 H, m, SiOC$_2$H$_2$), 3.72-3.65 (2 H, m, CH$_2$OH), 2.16 (1 H, t, $J$ 6.2, OH) and 1.07 (9 H, s, 3 x CH$_3$); $\delta$$_C$ (101 MHz, CDCl$_3$) 135.57 (4 x CH), 133.32 (2 x C), 129.84 (2 x CH), 127.81 (4 x CH), 65.03 (CH$_2$), 63.75 (CH$_2$), 26.88 (3 x CH$_3$) and 19.26 ((CH$_3$)$_3$C). The data matched that previously reported for this compound.

Synthesis of 2-((tert-butyldiphenylysilyl)oxy)acetaldehyde (231a).

![Chemical Structure](image)

This is a known compound and has been fully characterised.$^{26c}$

A solution of oxalylchloride (2M in DCM, 2.4 cm$^3$, 4.75 mmol) in anhydrous DCM (5 cm$^3$) was cooled to -78 °C, and was slowly added to a solution of dimethylsulfoxide (0.74 g, 0.68 cm$^3$, 9.52 mmol) in DCM (2.5 cm$^3$) by syringe. The solution was stirred for 30 minutes at -78 °C before a solution of 2-((tert-butyldiphenylysilyl)oxy)ethanol 230a (1.10 g, 3.66 mmol) in DCM (8 cm$^3$) was slowly added at the same temperature. After stirring for 40 min at -78 °C, Et$_3$N (2.24 g, 3.1 cm$^3$, 21.94 mmol) was added and the reaction mixture was allowed to warm up to rt. After 30 mins, water (16 cm$^3$) was added, and extracted with DCM, dried (MgSO$_4$), filtered and then concentrated under vacuum to give the product as a orange oil 231a (1.09 g, 3.66 mmol, >99 % quantitative conversion, includes traces of solvent); $\delta$$_H$ (400 MHz, CDCl$_3$) 9.72 (1 H, s, CHO), 7.68-
Experimental

7.64 (4 H, m, 4 x Ar-H), 7.48-7.37 (6 H, m, 6 x Ar-H), 4.22 (2 H, s, CH₂) and 1.10 (9 H, s, 3 x CH₃); δ (101 MHz, CDCl₃) 201.73 (CH=O), 135.52 (4 x C), 132.49 (2 x C), 130.08 (2 x CH), 127.94 (4 x CH), 70.00 (CH₂), 26.71 (3 x CH₃) and 19.27 ((CH₃)₃C).

The data matched that previously reported for this compound.

**Synthesis of (2S,4R,5R)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-4,5-diphenyl-1-tosylimidazolidine (232a).**

![Chemical Structure](image)

This is a known compound and has been fully characterised.²⁹a

To a stirred solution of (R, R)-TsDPEN 81 (1.11 g, 3.04 mmol) and molecular sieves (4 Å, 2.1 g) in dry methanol (24 cm³) was added a solution of 2-((tert-butyldiphenylsilyl)oxy)acetaldehyde 231a (1.09 g, 3.66 mmol) in methanol (10 cm³) followed by the addition of glacial acetic acid (0.21 cm³). The reaction was stirred for 4 hrs during which time a white precipitate formed. The precipitate (molecular sieves and the product) was filtered off and washed with cold methanol. The remaining solid was washed thoroughly with DCM to separate the product from molecular sieves, and was then concentrated *in vacuo*. **232a** was obtained as a white solid (690 mg, 1.07 mmol, 35 %); δH (400 MHz, CDCl₃) 7.72 (4 H, td, J 8.2, 1.3, 4 x Ar-H), 7.51 (2 H, d, J 8.2, 2 x Ar-H), 7.48-7.34 (6 H, m, 6 x Ar-H), 7.29-7.12 (10 H, m, 10 x Ar-H), 6.90 (2 H, d, J 7.0, 2 x Ar-H), 4.91 (1 H, dd, J 6.1, 3.2, TsNCHNH), 4.48 (1 H, d, J 6.1, CHNTs), 4.17 (1 H, d, J 6.1, CH(1)H(2)OSi), 4.15 (1 H, d, J 6.1, CHNH), 4.07 (1 H, dd, J 10.7, 3.2, CH(1)H(2)OSi), 2.81 (1 H, br s, NH), 2.40 (3 H, s, CH₃Ts) and 1.09 (9 H, s, 3 x CH₃); δC (101 MHz, CDCl₃) 143.63 (C), 139.81 (C), 138.76 (C), 135.74 (2 x CH), 135.70 (2 x
CH), 134.00 (C), 133.08 (C), 133.04 (C), 129.87 (2 x CH), 129.52 (2 x CH), 128.46 (2 x CH), 128.33 (2 x CH), 127.86 (4 x CH), 127.82 (2 x CH), 127.57 (CH), 127.48 (CH), 126.89 (2 x CH), 126.75 (2 x CH), 77.30 (CH), 71.06 (CH), 69.07 (CH), 65.03 (CH₂), 26.97 (3 x CH₃), 21.56 (CH₃) and 19.29 (C). The data matched that previously reported for this compound.

**Synthesis of** N-((1R,2R)-2-((2-hydroxyethyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide (233).

![Diagram](image)

This is a known compound and has been fully characterised.²⁹a

(2S,4R,5R)-2-(((tert-Butyldiphenylsilyl)oxy)methyl)-4,5-diphenyl-1-tosylimidazolidine 232a (3.24 g, 5 mmol) in THF (7 cm³) was added dropwise to a solution of LiAlH₄ (0.60 g, 15 mmol) in THF (31 cm³) stirring at 0 °C. After addition, the solution was allowed to stir at rt over the weekend. The solution was then cooled to 0 °C and quenched with a 50 : 50 mixture of water and THF (6 cm³; 6 cm³), followed by water (6 cm³). Rochelle salt (4.91 g, 17.40 mmol) was then added followed by DCM (9 cm³) and was further allowed to stir for 3 hrs. The remaining solution was then filtered off through celite, dried (MgSO₄), filtered and concentrated to give the alcohol as a white solid 233 (1.58 g, 3.85 mmol, 77 %); δ_H (400 MHz, CDCl₃) 7.39 (2 H, d, J 8.2, 2 x Ar-H), 7.16-7.10 (3 H, m, 3 x Ar-H), 7.06-6.92 (7 H, m, 7 x Ar-H), 6.88-6.84 (2 H, m, 2 x Ar-H), 4.36 (1 H, d, J 8.2, CHTs), 3.73 (1 H, d, J 8.2, CHNH), 3.71-3.63 (1 H, m, CHi(H2)OH), 3.63-3.55 (1 H, m, CHi(H2)OH), 2.62-2.47 (2 H, m, CH₂NH) and 2.32 (3 H, s, CH₃); δ_C (101 MHz, CDCl₃) 142.83 (C), 139.00 (C), 137.96 (C), 137.05 (C), 213
129.12 (2 x CH), 128.35 (2 x CH), 127.91 (2 x CH), 127.63 (2 x CH), 127.58 (CH), 127.55 (2 x CH), 127.26 (CH), 127.10 (2 x CH), 67.80 (CH), 63.32 (CH), 61.74 (CH₂), 49.03 (CH₂) and 21.45 (CH₃). The data matched that previously reported for this compound.

Synthesis of 2-(((1R,2R)-2-(4-methylphenylsulphonamido)-1,2-diphenylethyl)amino)ethyl 4-methylcyclohexa-1,4-dienecarboxylate (240).

This compound is novel.

4-Methylcyclohexa-1,4-diene carboxylic acid (18 mg, 0.13 mmol) was added to a solution of N-(((1R,2R)-2-((2-hydroxyethyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulphonamide 233 (53 mg, 0.13 mmol) in DCM (2 cm³) at rt, followed by addition of DCC (165 mg, 0.80 mmol) and DMAP (16 mg, 0.13 mmol). The resulting mixture was stirred overnight and the concentrated under reduced pressure. The crude white residue was then purified by flash chromatography (10→30 % v/v ethyl acetate/hexane) giving 240 as a colourless gum (58 mg, 0.11 mmol, 84 %); [α]D²² -10.4 (c 0.5, CHCl₃); νmax 3663, 3259, 2902, 1712, 1690, 1651, 1600, 1495, 1454, 1395, 1327, 1304, 1252, 1185, 1157, 1092, 1048, 960, 920, 812, 756, 719, 699 and 668 cm⁻¹; δH (400 MHz, CDCl₃) 7.38 (2 H, d, J 8.3, 2 x Ar-H), 7.16-7.10 (3 H, m, 3 x Ar-H), 7.09-7.03 (3 H, m, 3 x Ar-H), 7.02-6.94 (6 H, m, 6 x Ar-H), 6.90-6.85 (1 H, m, CH=C(CO₂)), 6.04 (1 H, d, J 3.3, NHTs), 5.50-5.45 (1 H, m, CH=C(CH₃)), 4.30 (1 H, dd, J 7.3, 3.3, CHNHTs), 4.25-4.17 (1 H, m, CH₁H₂OC=O), 4.09-4.02 (1 H, m, CH₁H₂OC=O),
3.74 (1 H, d, $J$ 7.3, $\text{CHNH}$), 2.87-2.75 (4 H, m, $\text{CH}_2\text{C} = \text{CCH}_2$), 2.75-2.67 (1 H, m, $\text{CH}_1(1)\text{H}(2)\text{NH}$), 2.62-2.53 (1 H, m, $\text{CH}_1(1)\text{H}(2)\text{NH}$), 2.32 (3 H, s, $\text{CH}_3\text{Ts}$) and 1.72 (3 H, s, $\text{CH}_3$); $\delta_{C}$ (101 MHz, CDCl$_3$) 166.85 ($\text{C} = \text{O}$), 142.67 ($\text{C}$), 138.78 (2 x $\text{C}$), 138.36 (2 x $\text{C}$), 137.67 (CH), 129.39 (C), 129.10 (2 x CH), 128.42 (2 x CH), 128.04 (2 x CH), 127.66 (CH), 127.44 (2 x CH), 127.35 (3 x CH), 127.03 (2 x CH), 118.55 (CH), 67.14 (CH), 63.13 (CH$_2$), 63.07 (CH$_2$), 45.66 (CH$_2$), 31.89 (CH$_2$), 26.07 (CH$_2$), 22.83 (CH$_3$) and 21.42 (CH$_3$); $m/z$ (ESI-MS) 531.1 [M+H]$^+$, 553.1 [M+Na]$^+$. Found (ESI-HR-MS): 531.2330 [M+H]$^+$, $C_{31}H_{35}N_2O_4S$ requires 531.2312 (-3.2 ppm error).

**Synthesis of 2-(((1R,2R)-2-(4-methylphenylsulfonamido)-1,2-diphenylethyl)amino)ethyl 4-methylbenzoate (241).**

This compound is novel.

$p$-Toluic acid (18 mg, 0.13 mmol) was added to a solution of $N$-(((1R, 2R)-2-((2-hydroxyethyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide 233 (53 mg, 0.13 mmol) in DCM (2 cm$^3$) at rt, followed by addition of DCC (165 mg, 0.80 mmol) and DMAP (16 mg, 0.13 mmol). The resulting mixture was stirred overnight and then concentrated under reduced pressure. The crude white residue was then purified by flash chromatography (10→30 % v/v ethyl acetate/hexane) giving 241 as white crystals (58 mg, 0.11 mmol, 84 %); Mp 61-64 °C; [$\alpha$]$_D^{23}$ -17.6 (c 0.5, CHCl$_3$); $\nu_{\text{max}}$ 3266, 3031, 1712, 1611, 1495, 1453, 1406, 1327, 1271, 1178, 1156, 1093, 1020, 917, 841, 812, 753, 698 and 666 cm$^{-1}$; $\delta_{\text{H}}$ (400 MHz, CDCl$_3$) 7.83 (2 H, d, $J$ 8.1, 2 x Ar-$H$), 7.33 (2 H, d, $J$ 8.1, 2 x Ar-$H$), 7.17 (2 H, d, $J$ 8.1, 2 x Ar-$H$), 7.08 (2 H, 2 x Ar-$H$), 5.16 (1 H, m, $\text{CH} = \text{CH}$), 3.87 (2 H, m, $\text{CH}_2\text{CH}_2\text{N}$), 3.78 (2 H, m, $\text{CH}_2\text{CH}_2\text{N}$), 3.71 (2 H, m, $\text{CH}_2\text{CH}_2\text{N}$), 3.58 (2 H, m, $\text{CH}_2\text{CH}_2\text{N}$), 3.43 (2 H, 2 x Ar-$H$), 3.39 (2 H, 2 x Ar-$H$), 3.32 (2 H, 2 x Ar-$H$), 3.17 (2 H, 2 x Ar-$H$), 3.09 (2 H, 2 x Ar-$H$), 2.93 (2 H, 2 x Ar-$H$), 2.83 (2 H, 2 x Ar-$H$), 2.75 (2 H, 2 x Ar-$H$), 2.63 (2 H, 2 x Ar-$H$), 2.35 (3 H, s, $\text{CH}_3$), 2.06 (3 H, s, $\text{CH}_3$), 1.87 (3 H, s, $\text{CH}_3$), 1.74 (3 H, s, $\text{CH}_3$), 1.30 (3 H, s, $\text{CH}_3$), 0.97 (3 H, s, $\text{CH}_3$), 0.90 (3 H, s, $\text{CH}_3$), 0.81 (3 H, s, $\text{CH}_3$), 0.78 (3 H, s, $\text{CH}_3$), 0.75 (3 H, s, $\text{CH}_3$), 0.72 (3 H, s, $\text{CH}_3$), 0.69 (3 H, s, $\text{CH}_3$), 0.67 (3 H, s, $\text{CH}_3$), 0.64 (3 H, s, $\text{CH}_3$), 0.62 (3 H, s, $\text{CH}_3$), 0.59 (3 H, s, $\text{CH}_3$), 0.57 (3 H, s, $\text{CH}_3$), 0.55 (3 H, s, $\text{CH}_3$), 0.53 (3 H, s, $\text{CH}_3$), 0.51 (3 H, s, $\text{CH}_3$), 0.49 (3 H, s, $\text{CH}_3$), 0.47 (3 H, s, $\text{CH}_3$), 0.45 (3 H, s, $\text{CH}_3$), 0.43 (3 H, s, $\text{CH}_3$), 0.41 (3 H, s, $\text{CH}_3$), 0.39 (3 H, s, $\text{CH}_3$), 0.37 (3 H, s, $\text{CH}_3$), 0.35 (3 H, s, $\text{CH}_3$), 0.33 (3 H, s, $\text{CH}_3$), 0.31 (3 H, s, $\text{CH}_3$), 0.29 (3 H, s, $\text{CH}_3$), 0.27 (3 H, s, $\text{CH}_3$), 0.25 (3 H, s, $\text{CH}_3$), 0.23 (3 H, s, $\text{CH}_3$), 0.21 (3 H, s, $\text{CH}_3$), 0.19 (3 H, s, $\text{CH}_3$), 0.17 (3 H, s, $\text{CH}_3$), 0.15 (3 H, s, $\text{CH}_3$), 0.13 (3 H, s, $\text{CH}_3$), 0.11 (3 H, s, $\text{CH}_3$), 0.09 (3 H, s, $\text{CH}_3$), 0.07 (3 H, s, $\text{CH}_3$), 0.05 (3 H, s, $\text{CH}_3$), 0.03 (3 H, s, $\text{CH}_3$), 0.01 (3 H, s, $\text{CH}_3$), 0.00 (3 H, s, $\text{CH}_3$).
8.1, 2 x Ar-H), 7.25 (2 H, d, J 7.7, 2 x Ar-H), 7.18-7.09 (3 H, m, 3 x Ar-H), 7.08-7.01 (3 H, m, 3 x Ar-H), 6.98 (6 H, d, J 7.7, 6 x Ar-H), 6.07 (1 H, br s, NHTs), 4.40-4.28 (1 H, m, CH\(_{(1)}\)H\(_{(2)}\)OC=O), 4.31 (1 H, d, J 7.3, CHNHTs), 4.26-4.17 (1 H, m, CH\(_{(1)}\)H\(_{(2)}\)OC=O), 3.77 (1 H, d, J 7.3, CHNH), 2.84-2.75 (1 H, m, CH\(_{(1)}\)H\(_{(2)}\)NH), 2.71-2.62 (1 H, m, CH\(_{(1)}\)H\(_{(2)}\)NH), 2.44 (3 H, s, CH\(_{3}\)Ts), 2.30 (3 H, s, CH\(_{3}\)) and 1.76 (1 H, br s, NH); \(\delta_{\text{C}}\) (101 MHz, CDCl\(_3\)) 166.53 (C\(_{=\text{O}}\)), 143.79 (C), 142.68 (C), 138.80 (C), 138.37 (C), 137.01 (C), 129.69 (2 x CH), 129.15 (2 x CH), 129.11 (2 x CH), 128.43 (2 x CH), 128.06 (2 x CH), 127.66 (CH), 127.46 (2 x CH), 127.35 (3 x CH), 127.20 (C), 127.04 (2 x CH), 67.29 (CH), 63.72 (CH\(_{2}\)), 63.11 (CH), 45.73 (CH\(_{2}\)), 21.72 (CH\(_{3}\)) and 21.41 (CH\(_{3}\)); m/z (ESI-MS) 529.1 [M+H]\(^+\), 551.2 [M+Na]\(^+\). Found (ESI-HR-MS): 529.2159 [M+H]\(^+\), \(C_{31}H_{33}N_{2}O_{4}\)S requires 529.2156 (-0.6 ppm error).

**Synthesis of bis(2-(((1R,2R)-2-(4-methylphenylsulfonyl)-1,2-diphenylethyl)amino)ethyl) terephthalate (242).**

![Synthesis of bis(2-(((1R,2R)-2-(4-methylphenylsulfonyl)-1,2-diphenylethyl)amino)ethyl) terephthalate (242).](image)

This compound is novel.

Terephthalic acid (11 mg, 0.065 mmol) was added to a solution of \(N\)-((1R, 2R)-2-((2-hydroxyethyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide 233 (53 mg, 0.13 mmol) in DCM (2 cm\(^3\)) at rt, followed by addition of EDC (150 mg, 0.80 mmol) and DMAP (16 mg, 0.13 mmol). The resulting mixture was stirred overnight and then water (2 cm\(^3\)) was added. The organic phase was separated from the aqueous, and then
Experimental

DCM (2 x 2 cm³) was further added to extract the remaining product from the aqueous layer. The organic layers were then combined, dried (MgSO₄), filtered and concentrated under reduced pressure giving the crude product, which was then purified by flash chromatography (10→30 % v/v ethyl acetate/hexane) giving 242 as white crystals (14.5 mg, 0.02 mmol, 24 %); Mp 80-83 °C; [α]D⁺₂₂⁻ -54.4 (c 0.25, CHCl₃); νmax 3272, 1716, 1599, 1495, 1454, 1408, 1325, 1267, 1155, 1092, 1018, 918, 876, 812, 767, 731, 698 and 667 cm⁻¹; δH (400 MHz, CDCl₃) 8.10 (4 H, s, 4 x CO₂Ar-H), 7.36 (4 H, d, J 8.2, 4 x Ar-H), 7.21-7.06 (6 H, m, 6 x Ar-H), 7.05-6.91 (14 H, m, 14 x Ar-H), 6.91-6.84 (4 H, m, 4 x Ar-H), 6.20 (2 H, br s, 2 x NHTs), 4.51-4.28 (2 H, m, 2 x CH(1)H(2)OC=O), 4.35-4.21 (4 H, m, 2 x CH(1)H(2)OC=O + CHNHTs), 3.81 (2 H, d, J 7.9, 2 x CHNH), 2.86-2.76 (2 H, m, 2 x CH(1)H(2)NH), 2.76-2.66 (2 H, m, 2 x CH(1)H(2)NH) and 2.29 (6 H, s, 2 x CH₃Ts); δC (101 MHz, CDCl₃) 165.61 (2 x C), 142.83 (2 x C), 138.76 (2 x C), 138.26 (2 x C), 136.96 (2 x C), 133.90 (2 x C), 129.77 (4 x CH), 129.14 (5 x CH), 128.38 (4 x CH), 128.01 (4 x CH), 127.63 (5 x CH), 127.30 (6 x CH), 127.09 (4 x CH), 67.44 (2 x CH), 64.24 (2 x CH₂), 63.52 (2 x CH), 45.74 (2 x CH₂) and 21.42 (2 x CH₃); m/z (ESI-MS) 951.1 [M+H]+, 973.1 [M+Na]+. Found (ESI-HR-MS): 476.1755 [M+2H]₂⁺, C₅₄H₆₀N₄O₈S₂ requires 476.1764 (2.6 ppm error).

Synthesis of 3-((tert-butyldiphenylsilyl)oxy)propan-1-ol (230b).

![Structure](image)

This is a known compound and has been fully characterised. 33g

To a solution of 1,3-propanediol (0.85 g, 0.80 cm³, 11.1 mmol) and imidazole (1.0 g, 14.45 mmol) in dry DCM (35 cm³) was added tert-butyl-chlorodiphenylsilane (6.1 g, 5.8 cm³, 22.2 mmol) dropwise under a nitrogen atmosphere at rt followed by stirring at
the same temperature for 4 hrs. The reaction mixture was then concentrated under reduced pressure and the residue was then purified by flash chromatography (1→9 % v/v ethyl acetate/pet ether) to give 230b as a colourless oil (1.54 g, 4.90 mmol, 44 %); ν\text{max} 3349, 3072, 2938, 2858, 1712, 1590, 1472, 1390, 1361, 1264, 1189, 1106, 1083, 1008, 965, 822, 735, 688 and 700 cm\(^{-1}\); δ\text{H} (400 MHz, CDCl\(_3\)) 7.68 (4 H, dd, J 7.6, 1.3, 4 x Ar-H), 7.47-7.33 (6 H, m, 6 x Ar-H), 3.93-3.77 (4 H, m, CH\(_2\)CH\(_2\)CH\(_2\)OH + CH\(_2\)CH\(_2\)CH\(_2\)OH), 2.70 (1 H, br s, OH), 1.81 (2 H, quin, J 5.3, CH\(_2\)CH\(_2\)CH\(_2\)OH) and 1.06 (9 H, s, 3 x CH\(_3\)); δ\text{C} (101 MHz, CDCl\(_3\)) 135.59 (4 x C\(_\text{H}\)), 133.29 (2 x C), 129.82 (2 x CH), 127.79 (4 x CH), 63.28 (CH\(_2\)), 61.94 (CH\(_2\)), 34.31 (CH\(_2\)), 26.86 (3 x CH\(_3\)) and 19.11 ((CH\(_3\))\(_3\)C); m/z (ESI-MS) 337.1 [M+Na]\(^+\). Found (ESI-HR-MS): 337.1587 [M+Na]\(^+\), C\(_{19}\)H\(_{26}\)NaO\(_2\)Si requires 337.1594 (2.0 ppm error). The data matched that previously reported for this compound.

**Synthesis of 3-((tert-butyldiphenylsilyl)oxy)propanal (231b).**

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

This is a known compound and has been fully characterised.\(^{33g}\)

The solution of oxalylchloride (2M in DCM, 3.2 cm\(^3\), 6.37 mmol) in anhydrous DCM (6.8 cm\(^3\)) was cooled to -78 °C, and was slowly added a solution of dimethylsulfoxide (1.0 g, 0.90 cm\(^3\), 12.74 mmol) in DCM (3.4 cm\(^3\)) by syringe. The solution was stirred for 30 minutes at -78 °C before a solution of 3-((tert-butyldiphenylsilyl)oxy)propan-1-ol 230b (1.54 g, 4.90 mmol) in DCM (10.6 cm\(^3\)) was slowly added at the same temperature. After stirring for 40 min at -78 °C, Et\(_3\)N (3.0 g, 4.13 cm\(^3\), 29.4 mmol) was added and the reaction mixture was allowed to warm up to rt. After 30 mins, water (21.2 cm\(^3\)) was added, and extracted with DCM, dried (MgSO\(_4\)), filtered and then
Experimental

concentrated under vacuum to give the product as an orange oil **231b** (1.53 g, 4.90 mmol, >99 % quantitative conversion, includes traces of solvent); \(\nu_{\text{max}}\) 3072, 2932, 2858, 1726, 1589, 1473, 1428, 1390, 1266, 1212, 1106, 1008, 998, 971, 875, 823, 737 and 701 cm\(^{-1}\); \(\delta_H\) (400 MHz, CDCl\(_3\)) 9.81 (1 H, t, J 2.1, CHO), 7.66 (4 H, dd, J 7.8, 1.5, 4 x Ar-\(H\)), 7.46–7.34 (6 H, m, 6 x Ar-\(H\)), 4.01 (2 H, t, J 6.0, SiOC\(_2\)H\(_2\)), 2.60 (2 H, td, J 6.0, 2.1, CH\(_2\)CHO) and 1.04 (9 H, s, 3 x CH\(_3\)); \(\delta_C\) (101 MHz, CDCl\(_3\)) 201.91 (CH=O), 135.56 (4 x CH), 133.27 (2 x C), 129.84 (2 x CH), 127.80 (4 x CH), 58.31 (CH\(_2\)), 46.40 (CH\(_2\)), 26.77 (3 x CH\(_3\)) and ((CH\(_3\))\(_3\)C); \(m/z\) (ESI-MS) 335.1 [M+Na]\(^+\). Found (ESI-HR-MS): 367.1707 [M+MeOH+Na]\(^+\), \(C_{20}H_{28}NaO_3Si\) requires 367.1700 (-2.0 ppm error). The data matched that previously reported for this compound.

**Synthesis of (2S,4R,5R)-2-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-4,5-diphenyl-1-tosylimidazolidine (232b).**

![Structural diagram](image)

This compound is novel.

To a suspension of powdered molecular sieves (4 Å, 1.2 g) in dry methanol (70 cm\(^3\)) was added 3-((tert-butyldiphenylsilyl)oxy)propanal **231b** (1.53 g, 4.90 mmol), (1R, 2R)-TsDPEN (2.0 g, 5.44 mmol) and glacial acetic acid (14 drops). The reaction mixture was stirred at rt and monitored by TLC. After 2 hrs, the imine had formed, and sodium cyanoborohydride (0.92 g, 14.70 mmol) was added. The reaction was left to stir overnight at rt. Molecular sieves were removed by filtration, and the solution was concentrated under reduced pressure. The residue was re-dissolved in DCM (90 cm\(^3\)). The organic phase was washed with saturated NaHCO\(_3\) (90 cm\(^3\)) and brine (90 cm\(^3\)).
dried (MgSO\textsubscript{4}), filtered and concentrated under reduced pressure to give 232b as a white solid (1.12 g, 1.70 mmol, 35 %); Mp 64-67 °C; [α]\textsubscript{D}\textsuperscript{22}-64 (c 0.5, CHCl\textsubscript{3}); ν\textsubscript{max} 3322, 3030, 2856, 1600, 1495, 1472, 1450, 1428, 1349, 1305, 1258, 1163, 1091, 1028, 949, 821, 736, 698 and 664 cm\textsuperscript{-1}; δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 7.72-7.66 (4 H, m, 4 x Ar-H), 7.60 (2 H, d, J 8.2, 2 x Ar-H), 7.46-7.33 (6 H, m, 6 x Ar-H), 7.31-7.12 (10 H, m, 10 x Ar-H), 6.94 (2 H, d, J 6.6, 2 x Ar-H), 5.18 (1 H, d, J 7.2, NTsCHNH), 4.62 (1 H, d, J 6.3, CHNTs), 4.21 (1 H, br s, CHN), 4.02-3.93 (1 H, m, CH(1)H(2)OSi), 3.92-3.84 (1 H, m, CH(1)H(2)OSi), 2.54 (1 H, br s, NH), 2.49-2.37 (1 H, m, CHCH(1)H(2)), 2.40 (3 H, s, CH\textsubscript{3}Ts), 2.09-1.98 (1 H, m, CHCH(1)H(2)) and 1.06 (9 H, s, 3 x CH\textsubscript{3}); δ\textsubscript{C} (101 MHz, CDCl\textsubscript{3}) 143.57 (C), 140.41 (C), 138.45 (C), 135.65 (2 x CH), 135.61 (2 x CH), 134.52 (C), 133.63 (C), 133.58 (C), 129.71 (CH), 129.69 (CH), 129.59 (2 x CH), 128.59 (2 x CH), 128.45 (2 x CH), 127.79 (2 x CH), 127.72 (4 x CH), 127.64 (CH), 127.43 (CH), 126.84 (2 x CH), 126.49 (2 x CH), 76.22 (CH), 71.05 (CH), 69.90 (CH), 60.98 (CH\textsubscript{2}), 38.63 (CH\textsubscript{2}), 26.88 (3 x CH\textsubscript{3}), 21.55 (CH\textsubscript{3}) and 19.21 ((CH\textsubscript{3})\textsubscript{3}C); m/z (ESI-MS) 661.2 [M+H]\textsuperscript{+}, 683.2 [M+Na]\textsuperscript{+}. Found (ESI-HR-MS): 661.2920 [M+H]\textsuperscript{+}, C\textsubscript{40}H\textsubscript{45}N\textsubscript{2}O\textsubscript{3}SSi requires 661.2915 (0.1 ppm error).

**Synthesis of N-((1R,2R)-2-((3-hydroxypropyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide (234).**

![Chemical structure](image)

This compound is novel.

(2S,4R,5R)-2-((tert-Butyldiphenylsilyl)oxy)ethyl)-4,5-diphenyl-1-tosylimidazolidine 232b (143 mg, 0.22 mmol) in THF (0.32 cm\textsuperscript{3}) was added dropwise to a solution of
LiAlH₄ (25 mg, 122.52 mmol) in THF (1.4 cm³) with stirring at 0 °C. After addition, the solution was allowed to stir at rt over the weekend. The solution was then cooled to 0 °C and quenched with a 50 : 50 mixture of water and THF (0.32 cm³ : 0.32 cm³), followed by water (0.32 cm³). Rochelle salt (216 g, 0.77 mmol) was then added followed by DCM (0.40 cm³) and was further allowed to stir for 3 hrs. The remaining solution was then filtered off through celite, dried (MgSO₄), filtered and concentrated to give the crude product, which was then purified by flash chromatography (10→30 % v/v ethyl acetate/pet ether) to give 234 as a white solid (22 mg, 0.05 mmol, 24 %); Mp 110-113 °C; [α]D²⁷ -12.8 (c 0.25, CHCl₃); νmax 3274, 3029, 2922, 1599, 1495, 1454, 1321, 1184, 1153, 1091, 1052, 922, 845, 812, 758, 698 and 667 cm⁻¹; δH (400 MHz, CDCl₃) 7.40 (2 H, d, J 8.3, 2 x Ar-H), 7.16-7.11 (3 H, m, 3 x Ar-H), 7.05-6.92 (7 H, m, 7 x Ar-H), 6.84 (2 H, dd, J 8.0, 1.2, 2 x Ar-H), 4.35 (1 H, d, J 8.0, CHNHTs), 3.74 (1 H, d, J 8.0, CHNH), 3.73-3.64 (2 H, m, CH₂OH), 2.58-2.52 (2 H, m, CH₂NH), 2.31 (3 H, s, CH₃Ts) and 1.76-1.56 (2 H, m, CH₂CH₂OH); δC (101 MHz, CDCl₃) 142.80 (C), 138.56 (C), 137.91 (C), 137.11 (C), 129.14 (2 x CH), 128.37 (2 x CH), 127.94 (2 x CH), 127.75 (2 x CH), 127.65 (CH), 127.49 (2 x CH), 127.30 (CH), 127.09 (2 x CH), 67.94 (CH), 63.05 (CH), 62.34 (CH₂), 45.70 (CH₂), 31.72 (CH₂) and 21.42 (CH₃); m/z (ESI-MS) 425.1 [M+H]⁺. Found (ESI-HR-MS): 425.1895 [M+H]⁺, C₂₄H₂₉N₂O₃S requires 425.1893 (+0.3 ppm error).

**Synthesis of 4-((tert-butyldiphenylsilyl)oxy)butan-1-ol (230c).**

![Diagram of the compound](image)

This is a known compound and has been fully characterised.²⁸j
To a solution of 1,4-butanediol (1.0 g, 1.0 cm³, 11.1 mmol) and imidazole (1.0 g, 14.45 mmol) in dry DCM (35 cm³) was added tert-butyl-chlorodiphenylsilane (6.1 g, 5.8 cm³, 22.2 mmol) dropwise under a nitrogen atmosphere at rt followed by stirring at the same temperature for 4 hrs. The reaction mixture was then concentrated under reduced pressure and the residue was then purified by flash chromatography (1→9 % v/v ethyl acetate/pet ether) to give 230c as a colourless oil (1.1 g, 3.35 mmol, 30 %); ν_max 3349, 3072, 2932, 2858, 1712, 1590, 1472, 1428, 1389, 1361, 1265, 1188, 1107, 998, 940, 861, 822, 793, 739, 700 and 688 cm^{-1}; δ_H (400 MHz, CDCl_3) 7.67 (4 H, dd, J 7.7, 1.4, 4 x Ar-H), 7.46-7.33 (6 H, m, 6 x Ar-H), 3.70 (2 H, t, J 5.9, SiOC_H_2), 3.66 (2 H, t, J 5.9, CH_2OH), 2.4 (1 H, br s, OH), 1.75-1.60 (4 H, m, CH_2CH_2CH_2OH) and 1.05 (9 H, s, 3 x CH_3); δ_C (101 MHz, CDCl_3) 135.60 (4 x C_H), 133.67 (2 x C), 129.68 (2 x CH), 127.70 (4 x CH), 64.05 (CH_2), 62.85 (CH_2), 29.86 (CH_2), 29.30 (CH_2), 26.86 (3 x CH_3) and 19.20 ((CH_3)_3C); m/z (ESI-MS) 351.2 [M+Na]^+. Found (ESI-HR-MS): 351.1745 [M+Na]^+. C_{20}H_{28}NaO_2Si requires 351.1751 (1.4 ppm error). The data matched that previously reported for this compound.

**Synthesis of 4-((tert-butyldiphenylsilyl)oxy)butanal (231c).**

![Chemical Structure](https://via.placeholder.com/150)

This is a known compound and has been fully characterised.\(^{28j}\)

A solution of oxalyl chloride (2M in DCM, 2.18 cm³, 4.36 mmol) in anhydrous DCM (4.6 cm³) was cooled to -78 °C, and was slowly added a solution of dimethylsulfoxide (0.68 g, 0.62 cm³, 8.71 mmol) in DCM (2.3 cm³) by syringe. The solution was stirred for 30 minutes at -78 °C before a solution of 4-((tert-butyldiphenylsilyl)oxy)butan-1-ol 230c (1.1 g, 3.35 mmol) in DCM (7.3 cm³) was slowly added at the same temperature.
Experimental

After stirring for 40 min at -78 °C, Et₃N (2.1 g, 2.82 cm³, 20.1 mmol) was added and the reaction mixture was allowed to warm up to rt. After 30 mins, water (14.5 cm³) was added, and the mixture was extracted with DCM, dried (MgSO₄), filtered and then concentrated under vacuum to give the product as a orange oil 231c (1.1 g, 3.37 mmol, >99 % quantitative conversion, includes traces of solvent); νmax 3072, 2932, 2858, 1724, 1472, 1428, 1390, 1110, 1008, 822, 737 and 701 cm⁻¹; δH (400 MHz, CDCl₃) 9.79 (1 H, t, J 1.5, CHO), 7.64 (4 H, dd, J 7.8, 1.5, 4 x Ar-H), 7.46-7.35 (6 H, m, 6 x Ar-H), 3.69 (2 H, t, J 6.0, SiOCH₂), 2.55 (2 H, td, J 7.2, 1.6, CH₂CHO), 1.89 (2 H, quin, J 6.0, CH₂CH₂CHO) and 1.04 (9 H, s, 3 x CH₃); δC (101 MHz, CDCl₃) 202.57 (C HO), 135.56 (4 x C), 133.61 (2 x C), 129.70 (2 x CH), 127.71 (4 x CH), 62.93 (CH₂), 40.78 (CH₂), 26.84 (3 x CH₃), 25.27 (CH₂) and 19.20 ((CH₃)₃C); m/z (ESI-MS) 349.1 [M+Na]+. Found (ESI-HR-MS): 327.1781 [M+H]+, C₂₀H₂₇O₂Si requires 327.1775 (-1.7 ppm error). The data matched that previously reported for this compound.

(2S,4R,5R)-2-(3-((tert-butyldiphenylsilyl)oxy)propyl)-4,5-diphenyl-1-tosylimidazolidine (232c).

![Structure of 232c](image)

This compound is novel.

To a stirred solution of (R,R)-TsDPEN 81 (117 mg, 0.32 mmol) and molecular sieves (4 Å, 221 g) in dry methanol (2.5 cm³) was added a solution of 4-((tert-butyldiphenylsilyl)oxy)butanal 231c (125 mg, 0.38 mmol) in methanol (1.0 cm³) followed by the addition of glacial acetic acid (0.022 cm³). The reaction was stirred for 4 hrs during which time a white precipitate formed. The precipitate (molecular sieves
and the product) was filtered off and washed with cold methanol. The remaining solid was washed thoroughly with DCM to separate the product from molecular sieves, and was then concentrated in vacuo. Aminal 232c was obtained as a white solid (78 mg, 0.12 mmol, 36 %); Mp 45-47 °C; [α]D^25 -45.6 (c 0.5, CHCl_3); ν_max 3069, 2930, 2857, 1600, 1495, 1472, 1449, 1428, 1349, 1304, 1163, 1091, 1029, 867, 821, 758, 741, 698 and 664 cm^-1; δ_H (400 MHz, CDCl_3) 7.71-7.65 (4 H, m, 4 x Ar-H), 7.60 (2 H, d, J 8.2, 2 x Ar-H), 7.46-7.32 (6 H, m, 6 x Ar-H), 7.27-7.14 (10 H, m, 10 x Ar-H), 6.88 (2 H, d, J 6.7, 2 x Ar-H), 5.01 (1 H, dd, J 8.5, 5.2, NTsCHNH), 4.59 (1 H, d, J 6.8, CHNTs), 4.22 (1 H, d, J 6.8, CHNH), 3.77 (2 H, t, J 6.1, CH_2OSi), 2.40 (3 H, s, CH_3Ts), 2.31-2.13 (2 H, m, CH(CH_2OSi + NH)), 2.02-1.88 (1 H, m, CH(CH(CH_2OSi), 1.87-1.76 (2 H, m, CHCH_2) and 1.06 (9 H, s, 3 x CH_3); δ_C (101 MHz, CDCl_3) 143.62 (C), 140.10 (C), 138.15 (C), 135.63 (3 x CH), 135.03 (C), 133.99 (C), 133.93 (C), 129.64 (2 x CH), 129.59 (CH), 128.71 (2 x CH), 128.43 (2 x CH), 127.88 (CH), 127.76 (2 x CH), 127.68 (3 x CH), 127.67 (3 x CH), 127.40 (CH), 126.90 (2 x CH), 126.45 (2 x CH), 78.75 (CH), 70.81 (CH), 70.48 (CH), 63.48 (CH_2), 33.20 (CH_2), 29.22 (CH_2), 26.92 (3 x CH_3), 21.55 (CH_3) and 19.27 ((CH_3)_3C); m/z (ESI-MS) 675.2 [M+H]^+, 697.2 [M+Na]^+. Found (ESI-HR-MS): 675.3082 [M+H]^+, C_{41}H_{47}N_2O_3SSi requires 675.3071 (-1.5 ppm error).

Synthesis of N-((1R,2R)-2-((4-((tert-butyldiphenylsilyl)oxy)butyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide (235).
This compound is novel.

To a suspension of powdered molecular sieves (4 Å, 0.8 g) in dry methanol (48 cm$^3$) was added 4-((tert-butyldiphenylsilyl)oxy)butanal 231c (1.1 g, 3.35 mmol), (1R,2R)-TsDPEN 81 (1.36 g, 3.72 mmol) and glacial acetic acid (10 drops). The reaction mixture was stirred at rt and monitored by TLC. After 2 hrs, the imine had formed, and sodium cyanoborohydride (0.63 g, 10.05 mmol) was added. The reaction was left to stir overnight at rt. Molecular sieves were removed by filtration, and the solution was concentrated under reduced pressure. The residue was re-dissolved in DCM (64 cm$^3$). The organic phase was washed with saturated NaHCO$_3$ (64 cm$^3$) and brine (64 cm$^3$), dried (MgSO$_4$), filtered and concentrated under reduced pressure to give the crude product, which after purification by flash chromatography (10→30 % v/v ethyl acetate/pet ether) gave 235 as a colourless gum (0.9 g, 1.33 mmol, 40 %); [α]$^D_{23}$ -8.8 (c 0.5, CHCl$_3$); $\nu_{\text{max}}$ 3262, 3030, 2857, 1737, 1600, 1495, 1472, 1455, 1428, 1390, 1328, 1185, 1154, 1108, 1091, 1027, 998, 927, 812, 771, 740, 698 and 667 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 7.63 (4 H, d, $J$ 7.5, 4 x Ar-H), 7.47-7.33 (8 H, m, 8 x Ar-H), 7.18-6.98 (8 H, m, 8 x Ar-H), 6.94 (2 H, d, $J$ 7.5, 2 x Ar-H), 6.91-6.85 (2 H, m, 2 x Ar-H), 6.30 (1 H, br s, NH$_T$), 4.23 (1 H, d, $J$ 7.9, CHNHTs), 3.64-3.54 (3 H, m, CHNH + CH$_2$OSi), 2.42-2.34 (1 H, m, CH$_{(1,2)}$H(NH)), 2.32 (3 H, s, CH$_3$Ts), 2.30-2.22 (1 H, m, CH$_{(1,2)}$H(NH)), 1.54-1.38 (4 H, m, CH$_2$CH$_2$CH$_2$OSi) and 1.03 (9 H, s, 3 x CH$_3$); $\delta_C$ (101 MHz, CDCl$_3$) 142.67 (C), 139.35 (C), 138.40 (C), 137.10 (C), 135.57 (4 x CH), 133.99 (2 x C), 129.58 (2 x CH), 129.08 (2 x CH), 128.32 (2 x CH), 127.91 (2 x CH), 127.64 (4 x CH), 127.59 (2 x CH), 127.45 (CH), 127.38 (2 x CH), 127.26 (CH), 127.15 (2 x CH), 67.79 (CH), 63.61 (CH$_2$), 63.06 (CH), 47.00 (CH$_2$), 30.11 (CH$_3$), 26.90 (3 x CH$_3$), 26.45 (CH$_2$), 21.45 (CH$_3$) and 19.23 ((CH$_3$)$_3$C); $m/z$ (ESI-MS) 677.2 [M+H]$^+$, 699.2 [M+Na]$^+$. 

225
Experimental

Found (ESI-HR-MS): 677.3231 [M+H]+, C_{41}H_{49}N_{2}O_{3}SSi requires 677.3228 (-0.3 ppm error).

Synthesis of \(N-((1R,2R)-2-((4\text{-hydroxybutyl})amino)-1,2\text{-diphenylethyl})-4\text{-methylbenzenesulfonamide (236)}\).

This compound is novel.

To a solution of \(N-((1R,2R)-2-((4\text{-((tert-butyldiphenylsilyl)oxy})butyl)amino)-1,2\text{-diphenylethyl})-4\text{-methylbenzenesulfonamide 235}\) (730 mg, 1.08 mmol) in dry THF (7 cm\(^3\)) was added TBAF (1 M solution in THF, 1.62 cm\(^3\), 1.62 mmol) at 0 °C. The resulting mixture was stirred at rt for 24 hrs. The reaction mixture was then concentrated under reduced pressure to give a residue. The residue was purified by flash chromatography (10→100 % v/v ethyl acetate/pet ether) to give 236 as a white solid (360 mg, 0.82 mmol, 76 %); Mp 135-138 °C; \([\alpha]_D^{22}\) -12.8 (c 0.25, CHCl\(_3\)); \(\nu_{\text{max}}\) 3278, 3091, 2836, 1598, 1495, 1450, 1429, 1350, 1333, 1259, 1215, 1189, 1181, 1156, 1090, 1060, 1046, 1030, 1011, 996, 962, 922, 903, 843, 832, 820, 773, 757, 727, 698 and 668 cm\(^{-1}\); \(\delta_H\) (400 MHz, CDCl\(_3\)) 7.39 (2 H, d, J 8.2, 2 x Ar-H), 7.15-7.10 (3 H, m, 3 x Ar-H), 7.08-6.97 (5 H, m, 5 x Ar-H), 6.96-6.91 (2 H, m, 2 x Ar-H), 6.88 (2 H, d, J 6.9, 2 x Ar-H), 4.30 (1 H, d, J 8.0, CHNHTs), 3.67 (1 H, d, J 8.0, CHNH), 3.64-3.55 (2 H, m, \(CH_2OSi\)), 2.50-2.34 (2 H, m, \(CH_2NH\)), 2.32 (3 H, s, \(CH_3TS\)) and 1.60-1.40 (4 H, m, \(CH_2CH_2CH_2OSi\)); \(\delta_C\) (101 MHz, CDCl\(_3\)) 142.80 (C), 138.98 (C), 138.13 (C), 137.04 (C), 129.13 (2 x CH), 128.31 (2 x CH), 127.93 (2 x CH), 127.59 (2 x CH), 127.52 (3 x CH), 127.29 (CH), 127.14 (2 x CH), 67.82 (CH), 63.04 (CH), 62.62 (CH\(_2\)), 47.01
Experimental

(CH₂), 30.72 (CH₂), 26.79 (CH₂) and 21.44 (CH₃); m/z (ESI-MS) 439.1 [M+H]+, 461.1 [M+Na]+. Found (ESI-HR-MS): 439.2050 [M+H]+, C₂₅H₃₁N₂O₃S requires 439.2050 (-0.5 ppm error).

Synthesis of bis(4-(((1R,2R)-2-(4-methylphenylsulfonamido)-1,2-diphenylethyl)amino)butyl) terephthalate (243).

This compound is novel.

Terephthalic acid (11 mg, 0.065 mmol) was added to a solution of N-((1R,2R)-2-((4-hydroxybutyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide 236 (57 mg, 0.13 mmol) in DCM (2 cm³) at rt, followed by addition of EDC (153 mg, 0.80 mmol) and DMAP (16 mg, 0.13 mmol). The resulting mixture was stirred overnight and then water (2 cm³) was added. The organic phase was separated from the aqueous, and then DCM (2 x 2 cm³) was further added to extract the remaining product from the aqueous. The organic layers were then combined, dried (MgSO₄), filtered and concentrated under reduced pressure giving the crude product, which was then purified by flash chromatography (10→30 % v/v ethyl acetate/pet ether) giving 243 as white crystals (20 mg, 0.02 mmol, 31 %); Mp 199-202 °C; [α]₀²⁷ -12.8 (c 0.25, CHCl₃); νmax 3267, 2931, 1716, 1600, 1495, 1454, 1408, 1325, 1269, 1184, 1154, 1117, 1093, 1018, 928, 875, 843, 812, 762, 731, 698 and 666 cm⁻¹; δH (400 MHz, CDCl₃) 8.04 (4 H, s, 4 x CO₂Ar-H), 7.37 (4 H, d, J 8.0, 2 x Ar-H), 7.16-7.08 (6 H, m, 6 x Ar-H), 7.07-6.97 (10 H, m, 10
x Ar-H), 6.96-6.88 (8 H, m, 8 x Ar-H), 4.34-4.24 (6 H, m, 2 x CHNHTs + 2 x CH₂OC=O), 3.65 (2 H, d, J 8.0, 2 x CHNH), 2.52-2.42 (2 H, m, 2 x CH₄H₂NH), 2.41-2.33 (2 H, m, 2 x CH₄H₆NH), 2.31 (6 H, s, 2 x CH₄Ts), 1.80-1.65 (4 H, m, 2 x CH₂CH₂OC=O) and 1.63-1.45 (4 H, m, 2 x CH₂CH₂CH₂OC=O); δC (101 MHz, CDCl₃) 165.82 (2 x C=O), 142.74 (2 x C), 139.16 (2 x C), 138.24 (2 x C), 137.06 (2 x C), 134.10 (2 x C), 129.57 (4 x CH), 129.10 (4 x CH), 128.36 (4 x CH). 127.93 (4 x CH), 127.55 (6 x CH), 127.42 (4 x CH), 127.29 (2 x CH), 127.12 (4 x CH), 67.87 (2 x CH), 65.17 (2 x CH₂), 63.11 (2 x CH), 46.76 (2 x CH₂), 26.58 (2 x CH₂), 26.37 (2 x CH₂) and 21.43 (2 x CH₃); m/z (ESI-MS) 1007.2 [M+H]⁺, 1029.1 [M+Na]⁺. Found (ESI-HR-MS): 504.2095 [M+2H]²⁺, C₅₈H₆₆N₄O₈S₂ requires 504.2077 (-2.1 ppm error).

**Synthesis of catalyst (244).**

![Synthesis of catalyst (244)](image)

This compound is novel.

A mixture of benzeneruthenium (II) chloride dimer (40 mg, 0.08 mmol), N-((1R,2R)-2-((2-hydroxyethyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide 233 (46 mg, 0.11 mmol) and triethylamine (0.06 cm³, 0.43 mmol) in IPA (2.4 cm³) was heated at 80 °C for 1 hr. The solution was then cooled to rt, and concentrated under reduced pressure. The residue was dissolved in CHCl₃ (4.8 cm³) and then washed with water (2.4 cm³) over vigorous stirring for 3 minutes. The organic phase was separated, dried (Na₂SO₄), filtered and then concentrated under reduced pressure giving 244 as a brown solid (58 mg, 0.09 mmol, 85 %); Mp 250-253 °C (dec); [α]D²⁷ +120 (c 0.02, CHCl₃);
$\nu_{\text{max}}$ 3435, 3063, 3030, 2917, 1730, 1599, 1453, 1435, 1398, 1266, 1128, 1084, 1059, 1003, 932, 834, 808, 749, 697 and 663 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 7.55-6.65 (14 H, m, 14 x Ar-H), 6.01 (6 H, s, 6 x Ar-H), 4.86 (1 H, d, $J$ 10.3, CHNTs), 4.51 (1 H, d, $J$ 10.3, CHNH), 3.80-3.40 (1 H, br m, $CH_{1(1)}H_{2(2)}OH$), 3.35-3.10 (1 H, br m, $CH_{1(1)}H_{2(2)}OH$), 2.50-2.25 (2 H, br m, $CH_2$NH) and 2.20 (3 H, s, $CH_3$Ts); $\delta_C$ (101 MHz, CDCl$_3$) 140.12 (C), 130.67 (CH), 128.84 (CH), 128.36 (5 x CH), 128.21 (CH), 127.63 (2 x CH), 126.86 (4 x CH), 83.67 (6 x CH), 82.89 (2 x CH), 74.28 (2 x CH$_2$) and 21.22 (CH$_3$); m/z (ESI-MS) 589.0 [M-Cl]$^+$. Found (ESI-HR-MS): 589.1106 [M-Cl]$^+$, $C_{29}H_{31}N_2O_3^{102}$RuS requires 589.1100 (-0.3 ppm error).

**Synthesis of catalyst (245).**

![Synthesis of catalyst (245).](image)

This compound is novel.

A mixture of benzeneruthenium(II) chloride dimer (13 mg, 0.025 mmol), $N$-((1R,2R)-2-((3-hydroxypropyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide 234 (14 mg, 0.033 mmol) and triethylamine (0.018 cm$^3$, 0.13 mmol) in IPA (0.75 cm$^3$) was heated at 80 °C for 1 hr. The solution was then cooled to rt, and concentrated under reduced pressure. The residue was dissolved in CHCl$_3$ (1.5 cm$^3$) and then washed with water (0.75 cm$^3$) over vigorous stirring for 3 minutes. The organic phase was separated, dried (Na$_2$SO$_4$), filtered and then concentrated under reduced pressure giving 245 as a brown solid (13.4 mg, 0.02 mmol, 64 %); Mp 210-213 °C (dec); $[\alpha]_D^{27}$ -360 (c 0.02, CHCl$_3$); $\nu_{\text{max}}$ 3436, 3204, 3064, 3029, 2922, 2853, 1730, 1600, 1494, 1454, 1437, 1381,
1267, 1185, 1083, 1004, 912, 812, 759, 698, 682 and 658 cm\(^{-1}\); \(\delta_H\) (400 MHz, CDCl\(_3\)) 7.30-6.50 (14 H, m, 14 x Ar-\(H\)), 5.90 (6 H, s, 6 x Ru-Ar-\(H\)), 4.18-4.05 (1 H, br m, CHNTs), 3.99-3.86 (1 H, br m, CHNH), 3.68-3.58 (1 H, br m, CH\(_{(1)}\)H\(_{(2)}\)OH), 3.57-3.46 (1 H, br m, CH\(_{(1)}\)H\(_{(2)}\)OH), 3.16-3.04 (1 H, br m, CH\(_{(1)}\)H\(_{(2)}\)NH), 2.96-2.82 (1 H, br m, CH\(_{(1)}\)H\(_{(2)}\)NH), 2.22 (3 H, s, CH\(_3\)Ts), 2.12-2.01 (2 H, br m, CH\(_2\)CH\(_2\)OH) and 1.41-1.33 (1 H, br m, NH); \(\delta_C\) (101 MHz, CDCl\(_3\)) 141.50 (C), 139.64 (C), 139.54 (C), 136.91 (C), 128.60 (2 x CH), 128.50 (2 x CH), 128.17 (CH), 128.07 (4 x CH), 127.54 (2 x CH), 127.06 (2 x CH), 126.37 (CH), 84.72 (6 x CH), 81.43 (CH), 69.84 (CH), 61.27 (CH\(_2\)), 53.62 (CH\(_2\)), 29.70 (CH\(_2\)) and 21.23 (CH\(_3\)); \(m/z\) (ESI-MS) 603.0 [M-Cl]\(^+\). Found (ESI-HR-MS): 603.1259 [M-Cl]\(^+\), C\(_{30}\)H\(_{33}\)N\(_2\)O\(_3\)\(^{102}\)RuS requires 603.1257 (0.1 ppm error).

**Synthesis of catalyst (246).**

\[
\text{Ru-Cl} \quad \text{TsN} \quad \text{N-H} \quad \text{OH}
\]

This compound is novel.

A mixture of benzeneruthenium(II) chloride dimer (28 mg, 0.056 mmol), N-((1\text{R},2\text{R})-2-((4-hydroxybutyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide 236 (32 mg, 0.074 mmol) and triethylamine (0.04 cm\(^3\), 0.29 mmol) in IPA (2.2 cm\(^3\)) was heated at 80 °C for 1 hr. The solution was then cooled to rt, and concentrated under reduced pressure. The residue was dissolved in CHCl\(_3\) (4.4 cm\(^3\)) and then washed with water (2.2 cm\(^3\)) over vigorous stirring for 3 minutes. The organic phase was separated, dried (Na\(_2\)SO\(_4\)), filtered and then concentrated under reduced pressure giving 246 as orange
brown crystals (43 mg, 0.07 mmol, 89 %); Mp 220-223 °C (dec); [α]_D^{26} -480 (c 0.02, CHCl₃); v_max 3428, 3062, 2863, 1599, 1494, 1455, 1347, 1385, 1267, 1127, 1083, 1054, 992, 915, 809, 750, 697, 681 and 656 cm⁻¹; δ_H (400 MHz, CDCl₃) 7.25 (2 H, d, J 7.8, 2 x Ar-H), 7.15-7.00 (3 H, m, 3 x Ar-H), 6.80 (3 H, d, J 7.8, 3 x Ar-H), 6.75-6.64 (4 H, m, 4 x Ar-H), 6.56 (2 H, d, J 6.8, 2 x Ar-H), 5.90 (6 H, s, 6 x Ar-Ru-H), 3.99 (1 H, t, J 10.2, CHNTs), 3.92 (1 H, t, J 10.2, CHNH), 3.76 (1 H, br m, CHN), 3.60 (2 H, br m, CH₂OH), 3.44-3.30 (1 H, br m, CHₓHᵧH₁H₂NH), 2.85-2.65 (1 H, br m, CHₓHᵧH₁H₂NH), 2.22 (3 H, s, CH₃Ts), 2.16-1.98 (1 H, br m, CHₓHᵧH₁H₂NH), 1.80-1.66 (1 H, br m, CHₓHᵧH₁H₂NH), 1.64-1.48 (1 H, br m, CHₓHᵧH₁H₂NH) and 1.43-1.29 (1 H, br m, CHₓHᵧH₁H₂NH); δ_C (101 MHz, CDCl₃) 141.80 (C), 139.57 (C), 139.45 (C), 137.10 (C), 128.66 (2 x CH), 128.56 (2 x CH), 128.24 (CH), 128.06 (4 x CH), 127.43 (2 x CH), 127.04 (2 x CH), 126.32 (CH), 86.64 (6 x CH), 80.89 (CH), 69.61 (CH), 61.62 (CH₂), 54.82 (CH₂), 29.83 (CH₂), 25.43 (CH₂) and 21.23 (CH₃); m/z (ESI-MS) 617.0 [M-Cl]⁺. Found (ESI-HR-MS): 617.1414 [M-Cl]⁺, C₃₁H₃₅N₂O₃¹⁰²RuS requires 617.1406 (-2.03 ppm error).

**Synthesis of catalyst (247).**

![Synthesis of catalyst (247).](image)

This compound is novel.

A mixture of benzeneruthenium(II) chloride dimer (28 mg, 0.056 mmol), N-((1R,2R)-2-((4-((tert-butyldiphenylsilyl)oxy)butyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide 235 (50 mg, 0.074 mmol) and triethylamine (0.04 cm³, 0.29
mmol) in IPA (2.2 cm\(^3\)) was heated at 80 °C for 1 hr. The solution was then cooled to rt, and concentrated under reduced pressure. The residue was dissolved in CHCl\(_3\) (4.4 cm\(^3\)) and then washed with water (2.2 cm\(^3\)) over vigorous stirring for 3 minutes. The organic phase was separated, dried (Na\(_2\)SO\(_4\)), filtered and then concentrated under reduced pressure giving 247 as orange brown crystals (58 mg, 0.07 mmol, 88 %); Mp 205-208 °C (dec); [\(\alpha\)]\(_D\)\(^{26}\) -240 (c 0.02, CHCl\(_3\)); \(\nu\)\(_{\text{max}}\) 3067, 2930, 2856, 1600, 1494, 1455, 1428, 1387, 1361, 1289, 1126, 1108, 1083, 992, 915, 822, 759, 728, 697 and 657 cm\(^{-1}\);
\(\delta\)\(_H\) (400 MHz, CDCl\(_3\)) 7.60 (4 H, d, \(J\) 7.2, 4 x Ar-\(H\)), 7.45-7.25 (6 H, m, 6 x Ar-\(H\)), 7.13-6.99 (4 H, m, 4 x Ar-\(H\)), 6.90-6.79 (4 H, m, 4 x Ar-\(H\)), 6.74 (2 H, t, \(J\) 7.2, 2 x Ar-\(H\)), 6.65 (2 H, d, \(J\) 6.5, 2 x Ar-\(H\)), 6.59 (2 H, d, \(J\) 7.2, 2 x Ar-\(H\)), 5.79 (6 H, s, 6 x Ar-\(H\)), 3.97 (1 H, d, \(J\) 10.3, CHNHTs), 3.84 (1 H, t, \(J\) 11.4, CHNH), 3.70 (1 H, t, \(J\) 11.4, CHNH), 3.61-3.50 (2 H, m, CH\(_2\)OSi), 3.30-3.10 (1 H, br m, CH\(_2\)(1)H\(_2\)(2)NH), 2.85-2.70 (1 H, br m, CH\(_4\)(1),CH\(_2\)(1)NH), 2.22 (3 H, s, CH\(_3\)Ts), 2.15-2.01 (1 H, br m, CH\(_4\)(1),CH\(_2\)(1)CH\(_2\)NH), 1.72-1.60 (1 H, br m, CH\(_4\)(1),CH\(_2\)(1)CH\(_2\)NH), 1.58-1.46 (1 H, br m, CH\(_4\)(1),CH\(_2\)(1)CH\(_2\)OSi), 1.42-1.27 (1 H, br m, CH\(_4\)(1),CH\(_2\)(1)CH\(_2\)OSi) and 1.03 (9 H, s, 3 x CH\(_3\)); \(\delta\)\(_C\) (101 MHz, CDCl\(_3\)) 141.54 (C), 139.83 (C), 139.46 (C), 137.01 (C), 133.55 (4 x CH), 133.76 (C), 133.62 (C), 129.72 (2 x CH), 128.68 (2 x CH), 128.59 (2 x CH), 128.27 (CH), 128.01 (2 x CH), 127.77 (5 x CH), 127.68 (2 x CH), 127.46 (CH), 127.04 (2 x CH), 126.37 (CH), 84.51 (6 x CH), 81.05 (CH), 69.67 (CH), 63.16 (CH\(_2\)), 54.88 (CH\(_2\)), 30.12 (CH\(_2\)), 27.00 (3 x CH\(_3\)), 25.39 (CH\(_2\)), 21.26 (CH\(_3\)) and 19.25 ((CH\(_3\))\(_2\)C); \textit{m/z} (ESI-MS) 855.0 [M-Cl]\(^+\).

Found (ESI-HR-MS): 855.2596 [M-Cl]\(^+\), C\(_{47}\)H\(_{53}\)N\(_2\)O\(_3\)\(^{102}\)RuSSi requires 855.2584 (0.13 ppm error).

4.4 Procedures from Section 2.4.

Synthesis of \((E)-(3\text{-Methylbuta-1,3-dien-1-yl})\text{benzene (278).}
This is a known compound and has been fully characterised.

To a solution of methyltriphenylphosphonium bromide (3.93 g, 11.0 mmol) in 1,4-dioxane (100 cm³), was added sodium hexamethyldisilazide (2.02 g, 11.0 mmol). The resulting yellow mixture was stirred for 1 hour at 60 °C. 4-Phenyl-3-buten-2-one (1.50 g, 10.0 mmol) was then added and the solution was stirred at 60 °C until completion. The reaction was completed after 4 hrs as shown by TLC analysis, after which the solution was concentrated under reduced pressure, and purified by flash chromatography (pentane : diethyl ether/99 : 1) giving 278 as a colourless oil (720 mg, 5.00 mmol, 50 %); δ_H (400 MHz, CDCl₃) 7.43 (2 H, d, J 7.8, 2 x Ar-H o to C=C), 7.31 (2 H, d, J 7.8, 2 x Ar-H m to C=C), 7.25-7.19 (1 H, m, Ar-H p to C=C), 6.88 (1 H, d, J 16.1, CH=CH cis to Ar ring), 6.53 (1 H, d, J 16.1, CH=CH cis to C(CH₃)=CH₂), 5.11 (1 H, s, C(CH₃)=CHH₁H₂), 5.07 (1 H, s, C(CH₃)=CHH₁H₂) and 1.97 (3 H, s, CH₃); δ_C (101 MHz, CDCl₃) 142.07 (C), 137.41 (C), 131.71 (CH), 128.70 (CH), 128.62 (2 x CH), 127.44 (CH), 126.49 (2 x CH), 117.37 (CH₂) and 18.62 (CH₃). The data matched that previously reported for this compound.

**Synthesis of (E)-buta-1,3-diene-1,3-diyl dibenzene (279).**

This is a known compound and has been fully characterised.³³i

To a solution of methyltriphenylphosphonium bromide (3.93 g, 11.0 mmol) in 1,4-dioxane (100 cm³), was added sodium hexamethyldisilazide (2.02 g, 11.0 mmol). The
resulting yellow mixture was stirred for 1 hour at 60 °C. 1,3-Diphenyl-2-propenone (2.10 g, 10.0 mmol) was then added and the solution was stirred at 60 °C until completion. The reaction was completed after 4 hrs as shown by TLC analysis, after which the solution was concentrated under reduced pressure, and purified by flash chromatography (pentane : ethyl acetate/ 99 : 1) giving 279 as a colourless oil (241 mg, 1.17 mmol, 12 %); δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 7.45-7.20 (10 H, m, 10 x Ar-H), 7.05 (1 H, d, J 16.1, CH=CH), 6.49 (1 H, d, J 16.1, CH=CH), 5.42 (1 H, s, CH\textsubscript{(1)}H\textsubscript{(2)}=C) and 5.24 (1 H, d, J 1.6, CH\textsubscript{(1)}H\textsubscript{(2)}=C); δ\textsubscript{C} (101 MHz, CDCl\textsubscript{3}) 148.18 (C), 140.23 (C), 137.21 (C), 131.94 (CH), 130.38 (CH), 128.62 (2 x CH), 128.48 (2 x CH), 128.24 (2 x CH), 127.68 (CH), 127.57 (CH), 126.58 (2 x CH) and 117.39 (CH\textsubscript{2}). The data matched that previously reported for this compound.

**Synthesis of 1-phenylprop-2-en-1-one (273).**

![](attachment:image.png)

This is a known compound and has been fully characterised.\textsuperscript{30a}

A mixture of 3-chloro-1-phenyl-1-propanone (2.0 g, 11.8 mmol) and AcOK (1.28 g, 13 mmol) in EtOH (100 cm\textsuperscript{3}) was stirred under reflux for 4 hrs. After stirring overnight at rt, the solvent was evaporated off under reduced pressure. The residue was dissolved in AcOEt (100 cm\textsuperscript{3}) and washed with H\textsubscript{2}O (3 x 100 cm\textsuperscript{3}). Organic phase was dried (MgSO\textsubscript{4}), filtered, and concentrated under reduced pressure giving the crude product, which was then purified by flash chromatography (pentane: ethyl acetate/ 20 : 1) giving 273 as a colourless oil (480 mg, 3.63 mmol, 31 %); δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 7.98 (2 H, m, 2 x Ar-H o to C=O), 7.58 (1 H, tt, J 7.4, 2.2, 1 x Ar-H p to C=O), 7.52-7.45 (2 H, m, 2 x Ar-H m to C=O), 7.17 (1 H, dd, J 17.1, 10.6, CH=CH\textsubscript{2}), 6.44 (1 H, dd, J 17.1, 1.7,
CH=CH_{1,2} and 5.94 (1 H, dd, J 10.6, 1.7, CH=CH_{1,2}); δ_C (101 MHz, CDCl₃) 191.07 (C=O), 137.28 (C), 133.00 (CH), 132.39 (CH), 130.21 (CH₂), 128.71 (2 x CH) and 128.63 (2 x CH). The data matched that previously reported for this compound.

4.5 Procedures from Section 3.1 (Appendix).

(E)-Methyl 2-(3,4-dihyronaphthalen-2(1H)-ylidene)hydrazinecarboxylate (296).

This is a known compound and has been fully characterised.³¹e

A solution of β-tetralone (1.46 g, 1.32 cm³, 10.00 mmol) and methylhydrazinocarboxylate (0.90 g, 10.00 mmol) in MeOH (20 cm³) was heated at 50 °C for 8 hrs, after which the reaction was stirred at rt for 5 days. The solution was then filtered through a filter paper leaving behind impurities, and the filtrate was then concentrated under reduced pressure giving 296 as a yellow solid (1.44 g, 6.60 mmol, 66 %); δ_H (400 MHz, CDCl₃) (E/Z) 7.18-7.02 (4 H, m, 4 x Ar-H), 3.90-3.75 (3 H, br m, OCH₃), 3.62 (0.8 H, br s C=CCH₂C=N), 3.59 (1.2 H, s, C=CCH₂C=N), 2.68 (2 H, q, J 5.6, C=CCH₂CH₂), 2.63 (1 H, t, J 5.6, C=CCH₂CH_{1,2}) and 2.51-2.40 (1 H, br m, C=CCH₂CH_{1,2}); δ_C (101 MHz, CDCl₃) (E/Z) 154.75 (C), 137.51 (C), 135.08 (C), 128.68 (CH), 128.28 (CH), 127.52 (CH), 127.00 (CH), 126.89 (CH), 50.56 (CH₃), 32.18 (CH₂), 30.41 (CH₂), 29.03 (CH₂), 27.56 (CH₂) and 25.53 (CH₂). The data matched that previously reported for this compound.

(R)-N-(1-Phenylethyl)-3,4-dihyronaphthalen-2-amine (297).
This is a known compound and has been fully characterised.\textsuperscript{31g}

Synthesis of the imine from β-tetralone and \((R)-(+)\-α\-methylbenzylamine; All solvents were dried and deoxygenated before use. Deoxygenation was carried out by passing a rapid stream of dry nitrogen through the dry solvent for ca. 15 min. Without this precaution highly coloured products were obtained. An oven-dried three-necked flask (100 cm\(^3\)) was equipped with a dropping funnel, a Herschberg stirrer, and a reflux condenser. The flask was purged with nitrogen prior to introduction of the reagents, and a positive pressure of nitrogen was maintained in the apparatus throughout the whole operation. The flask was charged with \((R)-(+)\-α\-methylbenzylamine (1.21 g, 1.27 cm\(^3\), 10.00 mmol), triethylamine (6.07 g, 3.36 cm\(^3\), 60.00 mmol) and hexane (20 cm\(^3\)). The mixture was cooled ca. 5 °C by means of an ice bath and a solution of titanium (IV) chloride (1.52 g, 0.88 cm\(^3\), 8.00 mmol) in hexane (10 cm\(^3\)) was added dropwise over a period of ca. 10 min. The precipitated titanium (IV) chloride-amine complexes were homogenized and suspended by vigorous stirring for a few minutes prior to introduction of the ketone. The vigorous stirring of the suspended complexes was maintained and a solution of β-tetralone (1.46 g, 1.32 cm\(^3\), 10.00 mmol) in diethylether-hexane (1 : 1, 5 cm\(^3\) : 5 cm\(^3\)) was added in one batch. The ice bath was removed and the reaction was cooled to rt and diethylether (40 cm\(^3\)) was added to precipitate the titanium complexes. Under a protective nitrogen atmosphere, the reaction mixture was filtered through a sintered glass filter. The solid material in the reaction flask and on the filter was rinsed with diethylether (4 x 10 cm\(^3\)). The solvent was removed under reduced pressure and the residual crude product was obtained as a dark green oil, and after purification by
Kugelrohr distillation (200 °C) 297 was obtained as yellow oil (0.88 g, 3.53 mmol, 36 %), which was stored under inert conditions; \( \delta_H (300 \text{ MHz, CDCl}_3) 7.35-6.68 \) (9 H, m, 9 x Ar-\( H \)), 5.03 (1 H, s, \( \text{HC} = \text{CNH} \)), 4.49 (1 H, q, \( J 6.4, \text{CHCH}_3 \)), 3.58 (1 H, br s, NH), 2.80 (2 H, t, \( J 8.0, \text{CH}_2\text{CH}_2\text{C(NH)=C} \)), 2.30 (2 H, t, \( J 8.0, \text{CH}_2\text{CH}_2\text{C(NH)=C} \)) and 1.48 (3 H, d, \( J 6.4, \text{CH}_3 \)); \( \delta_C (75 \text{ MHz, CDCl}_3) 144.79 \text{ (C)}, 144.61 \text{ (C)}, 137.40 \text{ (C)}, 130.85 \text{ (C)}, 128.60 \text{ (2 x CH)}, 126.92 \text{ (CH)}, 126.74 \text{ (CH)}, 126.48 \text{ (CH)}, 125.80 \text{ (2 x CH)}, 123.49 \text{ (CH)}, 122.40 \text{ (CH)}, 94.52 \text{ (CH)}, 52.79 \text{ (CH)}, 29.30 \text{ (CH)}_2, 28.49 \text{ (CH)}_2 \) and 24.29 \text{ (CH)}_3. The data matched that previously reported for this compound.

\( N-((R)-1-\text{Phenylethyl})-1,2,3,4-\text{tetrahydronaphthalen}-2\text{-amine (301).} \)

\[ \text{\begin{figure}[h]
\centering
\includegraphics[width=0.3\textwidth]{image.png}
\end{figure}} \]

This compound is novel.

A solution of \( (R)-N-(1\text{-Phenylethyl})\text{-3,4-dihydropaphthalen-2-amine 297} \) (0.42 g, 1.69 mmol) with acetic acid (0.1 cm\(^3\)) in MeOH (3 cm\(^3\)) was stirred for an hour. Sodium cyanoborohydride (0.12 g, 1.69 mmol) was then added portionwise to the solution. The reaction mixture was stirred at rt until completion. After completion, the solution was concentrated under reduced pressure and water (5 cm\(^3\)) was added, and the product was then extracted with DCM (3 x 5 cm\(^3\)). The organic layers were combined, dried (MgSO\(_4\)), filtered and concentrated under reduced pressure, giving 301 as a colourless oil after distillation (0.35 g, 1.39 mmol, 83 %); \( \delta_H (400 \text{ MHz, CDCl}_3) 7.40-6.95 \) (9 H, m, 9 x Ar-\( H \)), 4.04 (1 H, q, \( J 6.6, \text{CHCH}_3 \)), 3.12-2.50 (5 H, m, \text{CH}_2\text{CH}_2\text{CH(NH)CH}_2\)), 1.66-1.49 (2 H, m, \text{CH}_2\text{CH}_2\text{CH(NH)CH}_2\)) and 1.37 (3 H, d, \( J 6.6, \text{CH}_3 \)); \( \delta_C (101 \text{ MHz, CDCl}_3) 145.94 \text{ (C)}, 136.36 \text{ (C)}, 136.31 \text{ (C)}, 128.54 \text{ (2 x CH)}, 128.52 \text{ (2 x CH)}, 126.93 \text{ (CH)}_3 \).
Experimental

(\text{CH}), 126.57 (4 \times \text{CH}), 54.84 (\text{CH}), 50.53 (\text{CH}), 30.60 (\text{CH}_2), 28.98 (\text{CH}_2), 28.05 (\text{CH}_2) and 24.95 (\text{CH}_3); m/z (\text{ESI-MS}) 252.1 [\text{M+H}]^+.

\textit{(E)-2-(3,4-Dihydronaphthalen-2(1H)-ylidene)hydrazinecarboxamide (298).}

![Chemical structure of 298](image)

This is a known compound and has been fully characterised.\textsuperscript{31g}

A mixture of semicarbazide hydrochloride (1.12 g, 10.00 mmol), sodium acetate (0.82 g, 10.00 mmol) and water (10 cm\textsuperscript{3}) was added slowly to a stirred solution of \(\beta\)-tetralone (1.46 g, 1.32 cm\textsuperscript{3}, 10.00 mmol) in ethanol (95 %, 30 cm\textsuperscript{3}). The reaction mixture was stirred at \(\text{rt}\) for 24 hrs. The precipitate was collected, washed with ether and water and dried. Recrystallization from ethanol (95 %) gave 298 as white crystals (1.42 g, 7.00 mmol, 70 %); \(\nu\)\textsubscript{max} 3437, 3186, 1682, 1580, 1462, 1423, 1411, 1267, 1204, 1178, 1137, 1108, 1137, 1108, 1074, 995, 948, 760, 751, 740 and 662 cm\textsuperscript{-1}; \(\delta\)\textsubscript{H} (400 MHz, DMSO-d\textsubscript{6}) 8.90 (1 H, s, \text{NH}), 7.25-7.16 (4 H, m, 4 \times \text{Ar-H}), 6.25 (2 H, s, \text{NH}_2), 3.51 (2 H, s, \text{CH}_2\text{CH}_{2}(=\text{N})\text{CH}_2), 2.85 (2 H, t, J 6.6, \text{CH}_2\text{CH}_{2}(=\text{N})\text{CH}_2) and 2.46 (2 H, t, J 6.6, \text{CH}_2\text{CH}_{2}(=\text{N})\text{CH}_2); \(\delta\)\textsubscript{C} (101 MHz, DMSO-d\textsubscript{6}) 157.32 (C=O), 150.15 (C=N), 138.19 (C), 135.70 (C), 127.05 (CH), 126.97 (CH), 126.37 (CH), 126.27 (CH), 37.68 (CH\textsubscript{2}), 27.05 (CH\textsubscript{2}) and 25.68 (CH\textsubscript{2}); m/z (ESI-MS) 204.0 [\text{M+H}]^+, 226.0 [\text{M+Na}]^+. The data matched that previously reported for this compound.

\textbf{Compound (299).}

![Chemical structure of 299](image)
This is a known compound and has been fully characterised. A solution of carbohydrazine (0.90 g, 10.00 mmol) in MeOH (20 cm$^3$) was added to a solution of $\beta$-tetralone (2.92 g, 2.64 cm$^3$, 20.00 mmol) in MeOH (25 cm$^3$) and the resultant mixture was stirred at rt for 20 min. The solid was collected and recrystallization from ethanol (95 %) gave 299 as a white solid (1.59 g, 4.59 mmol, 46 %); $\delta_H$ (400 MHz, CD$_3$CN-d$_3$) 7.30-7.20 (8 H, m, 8 x Ar-H), 3.73-3.58 (4 H, m, 2 x CH$_2$CH$_2$C(=N)C$_2$H$_2$), 3.03-2.90 (4 H, m, 2 x C$_2$H$_2$CH$_2$C(=N)CH$_2$) and 2.70-2.50 m, 2 x CH$_2$CH$_2$C(=N)CH$_2$); m/z (ESI-MS) 347.1 [M+H]$^+$, 369.1 [M+Na]$^+$. The data matched that previously reported for this compound.

**N-(3,4-Dihydronaphthalen-2(1H)-ylidene)aniline (300).**

This compound is novel.

Procedure from 297 was used for the formation of 300 as a brown oil (1.66 g, 7.50 mmol, 75 %); $\delta_H$ (400 MHz, CDCl$_3$) 7.32-6.86 (9 H, m, 9 x Ar-H), 6.03 (1 H, s, CH=CH-NH), 5.19 (1 H, br s, NH), 2.89 (2 H, t, J 8.4, CH$_2$CH$_2$C(NH)=CH) and 2.41 (2 H, t, J 8.4, CH$_2$CH$_2$C(NH)=CH); $\delta_C$ (101 MHz, CDCl$_3$) 141.74 (C), 141.37 (C), 136.41 (C), 131.72 (C), 129.28 (2 x CH), 126.96 (CH), 126.66 (CH), 124.24 (CH), 123.79 (CH), 121.95 (CH), 120.39 (2 x CH), 99.19 (CH), 29.20 (CH$_2$) and 28.52 (CH$_2$); m/z (ESI-MS) 222.0 [M+H]$^+$.

**2-(1,2,3,4-Tetrahydronaphthalen-2-yl)hydrazinecarboxamide (302).**
This compound is novel.

Procedure from 301 was used for the formation of 302 as a light yellow oil after flash chromatography (10→100 % v/v methanol/ethyl acetate) (0.04 g, 0.19 mmol, 19 %); \( \nu_{\text{max}} \) 3444, 3288, 3062, 2982, 2930, 2841, 2580, 2384, 2329, 1616, 1486, 1452, 1436, 1345, 1312, 1254, 1238, 1164, 1135, 1071, 1062, 1038, 949, 925, 839, 814, 768, 741 and 723 cm\(^{-1}\); \( \delta_{\text{H}} \) (400 MHz, MeOD-d\(_4\)) 7.11-7.03 (4 H, m, 4 x Ar-\( \text{H} \)), 3.20-3.10 (1 H, m, \( CH_{(1)}H_{(2)}CH_{2}CH(NH)CH_{2} \)), 3.02-2.87 (2 H, m, \( CH_{2}CH_{2}CH(NH)CH_{2} \)), 2.85-2.74 (1 H, m, \( CH_{(1)}H_{(2)}CH_{2}CH(NH)CH_{2} \)), 2.65 (1 H, dd, \( J \) 16.1, 9.0, \( CH_{2}CH_{2}CH(NH)CH_{2} \)), 2.12-2.01 (1 H, m, \( CH_{2}CH_{(1)}H_{(2)}CH(NH)CH_{2} \)) and 1.70-1.57 (1 H, m, \( CH_{2}CH_{(1)}H_{(2)}CH(NH)CH_{2} \)); \( \delta_{\text{C}} \) (400 MHz, MeOD-d\(_4\)) 137.29 (C), 135.86 (C), 130.33 (CH), 129.59 (CH), 126.89 (CH), 126.81 (CH), 57.27 (CH), 34.87 (CH\(_2\)), 28.49 (CH\(_2\)) and 28.47 (CH\(_2\)); \( m/z \) (ESI-MS) 206.1 [M+H]\(^+\), 228.0 [M+Na]\(^+\).
5. References.


References


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