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**Asymmetric Transfer Hydrogenation using Ru(II)
Complexes of Heterocyclic TsDPEN Ligands**

by

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for the degree of
Doctor of Philosophy in Chemistry

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Declaration

This thesis is submitted to the University of Warwick in support of my application for the degree of Doctor of Philosophy. It has been composed by myself and has not been submitted in any previous application for any degree. The work presented, including data generated and data analysis, was carried out by the author.

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4. J. Barrios-Rivera, Y. Xu, M. Wills, V. K. Vyas., *Org. Chem. Front.*, 2020, **7**, 3312-3342
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Abstract

TsDPEN ligands containing a pyridine or a triazole group on the amine nitrogen atom work effectively in a tridentate catalyst system with $\text{Ru}_3(\text{CO})_{12}$ in the asymmetric transfer hydrogenation of ketones. Derivatives of the pyridine ligand have been synthesised for further investigation of the catalyst system.

A range of TsDPEN ligands containing heteroaromatic groups on the amine nitrogen atom were also synthesised and evaluated as either bidentate or tridentate ligands in the asymmetric transfer hydrogenation of ketones. These bidentate and tridentate ligands demonstrate a mutual exclusivity directly related to their function as catalysts.

Substituted-acetophenones are reduced with the bidentate ligands using either a preformed catalyst or through an *in situ* catalyst. A series of ketones were reduced with the corresponding catalysts, formed from the bidentate and tridentate ligands, permitting the ready identification of an optimal catalyst for the ATH of each ketone.

TsDPEN ligands containing non-aromatic heterocyclic groups on the amine nitrogen atom were also synthesised and evaluated as either bidentate or tridentate ligands. Such ligands contain a third chiral centre leading to either active or inactive ligands in ATH.

The asymmetric transfer hydrogenation of 1-phenyl-3,4-dihydroisoquinolines with a furan-containing catalyst results in the formation of the corresponding product in high enantiomeric excess. A further application of the catalyst on to the reduction of 1-aryl-3,4-dihydroisoquinolines containing *meta* or *para*-substituted aromatic groups gave products in high enantiomeric excess. The approach solves a long-standing challenge in the asymmetric transfer hydrogenation of dihydroisoquinolines.

Derivatives of a furan-containing catalyst have been synthesised and compared in the ATH of acetophenone. A scale up of the preparation of a furan catalyst has been attempted. A variety of synthetic methods to support a furan catalyst on to a solid support have been designed and executed.

A range of α -heteroaromatic ketones were synthesised and asymmetrically reduced with the furan-containing catalyst. Alcohol products were obtained in high enantiomeric excess.

Abbreviations

δ_C	^{13}C NMR chemical shift (ppm)
δ_F	^{19}F NMR chemical shift (ppm)
δ_H	^1H NMR chemical shift (ppm)
$[\alpha]_D$	Optical rotation
Å	Angstroms
AH	Asymmetric hydrogenation
aq	Aqueous
ATH	Asymmetric transfer hydrogenation
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
Boc	<i>tert</i> -Butoxycarbonyl
b.s	Broad signal
Cat.	Catalyst
CDI	1,1'-Carbonyldiimidazole
CIP	Cahn, Ingold and Prelog
COD	Cyclooctadiene
Conv	Conversion
Cp*	Pentamethylcyclopentadienyl
CuAAC	Copper-catalysed azide–alkyne cycloadditions
d	Doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
dd	Doublet of doublets

DHIQ	3,4-Dihydroisoquinoline
DKR	Dynamic kinetic resolution
DMAP	4-Dimethylaminopyridine
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethylsulfoxide
DPEN	1,2-Diphenylethylenediamine
dt	Doublet of triplets
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
ee	Enantiomeric excess
ESI	Electrospray ionisation
FA	Formic acid
FA/TEA	Formic acid-triethylamine azeotrope
FsDPEN	<i>N</i> -(2-Amino-1,2-diphenylethyl)-pentafluorobenzenesulfonamide
GC	Gas chromatography
h	Hour(s)
HFIP	Hexafluoroisopropanol
HPLC	High performance liquid chromatography
HRMS	High-resolution mass spectrometry
ICP	Inductively coupled plasma mass spectrometry
IR	Infrared
<i>J</i>	Coupling constant (Hz)
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
min	Minute(s)
Mol-S	Molecular sieves
Mp	Melting point (° C)
MsDPEN	<i>N</i> -Methanesulfonyl-1,2-diphenylethylenediamine

MS	Mass spectrometry
<i>m/z</i>	Mass to charge ratio
NBS	<i>N</i> -Bromosuccinimide
NMR	Nuclear magnetic resonance
nr	No reduction
Pet. ether	Petroleum ether
PPA	Polyphosphoric acid
ppm	Parts per million
PTA	<i>para</i> -Tartaric acid
q	Quartet
rt	Room temperature
s	Singlet
S/C	Substrate to catalyst ratio
t	Triplet
td	Triplet of doublets
Tf	Triflate
TFA	Trifluoroacetic acid
TfDPEN	<i>N</i> -Triflyl-1,2-diphenylethylenediamine
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TrisDPEN	<i>N</i> -(2,4,6-Triisopropylbenzenesulfonyl)-1,2-diphenylethylene diamine
TS	Transition state
TsDACH	<i>N</i> -(2-Aminocyclohexyl)-4-methylbenzenesulfonamide
TsDPEN	<i>N</i> -(<i>p</i> -Toluenesulfonyl)-1,2-diphenylethanediamine

Chapter 1: Introduction

1.1. Chirality

Chirality refers to the property of handedness, an object is defined as chiral if it is non-superimposable on its own mirror image. The notion of chirality first began in 1815, when Jean Baptise Biot found that polarized light travelling through an organic substance could be rotated clockwise or anticlockwise, a concept known as optical rotation, which was dependent on molecular structure.¹ Later, in 1848 the concept of molecular chirality was fully conceptualised by Louis Pasteur. Pasteur examined the crystal habit of the sodium salt of naturally occurring tartaric acid and compared it to *para*-tartaric acid (PTA), which was isolated on a single occasion at the time. PTA was known to have the same properties as natural tartaric acid but differed in other respects, like crystal habit, solubility and optical activity.² Pasteur found that the sodium ammonium salt of PTA crystallised as a conglomerate of two distinct crystal types; Pasteur dissolved the two crystal types from the PTA salt separately and revealed that they displayed optical activity equal in magnitude but opposite in direction, with one variant being identical to the naturally occurring tartaric acid originally examined.² It was concluded that these molecules of tartaric acid are chiral, derived from the Greek word for hand, “ $\chi\epsilon\iota\rho$ ” (kheir).

Therefore chiral molecules are compounds with the same molecular formula and chemical substituents, but with a different configuration in space. Handedness is often used to describe chiral molecules, as with human left- and right-hands, which are non-superimposable, non-identical, mirror images of each other.³ As a result, organic compounds with four different substituents bonded to a tetrahedral carbon are chiral compounds, with the tetrahedral carbon centre regarded as the chiral (asymmetric) centre, and an enantiomer is the term used for one variant of a chiral molecule.

Herein tartaric acid has been used to describe a chiral molecule further with the prefixes (+) and (-) used to characterise the rotation of polarised light to the right or left respectively (Figure 1). Alternatively, the terms *d*-dextrorotary (+) and *l*-levorotary (-) can be used to describe the rotation of light, with *dextro*- meaning to the right or a clockwise rotation, and *levo*- meaning to the left or anti-clockwise rotation of polarised light.

Enantiomeric excess (ee) is the method used to measure the purity of a mixture of chiral substances and reflects the degree of enantiomeric purity. The ee can be calculated from the mole fraction of the major and minor enantiomers (Equation 1). Therefore, a racemic mixture has an ee of 0%, and an enantiopure sample has an ee of 100%. Asymmetric synthesis refers to any synthetic process that introduces one or more new elements of chirality during functional group transformation. Consequently, in successful asymmetric synthesis the reactions can be highly enantioselective (high % ee), or enantiospecific (100% ee).

$$ee = 100 \times \frac{x_{major} - x_{minor}}{x_{major} + x_{minor}} \quad \text{Equation 1}$$

1.1.2. Importance of Chiral Molecules

In nature, proteins, enzymes, amino acids, carbohydrates, nucleosides and several alkaloids and hormones exist in a single enantiomerically pure form.⁷ All naturally derived amino acids, except glycine, are L-isomers and all naturally derived carbohydrates (sugars) are D-isomers. Chiral molecules have been used in therapeutic applications for years, for example the poppy plant *Papaver somniferum* synthesises the pain relief drug, morphine. Morphine contains five asymmetric centres; hence it is costly to produce synthetically due to the technical difficulties in its preparation, therefore it is economically attractive and favoured to extract the morphine directly from poppies for mass production.⁸

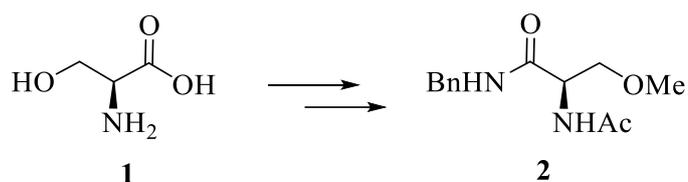
However, in pharmacology more than half of the synthetic drugs manufactured are chiral molecules, with 88% of these chiral synthetic drugs used as racemates for therapeutic treatments.⁹ The human body contains numerous homochiral compounds which are selective for chiral species, therefore the majority of enantiomers in racemic drugs exhibit differences in biological activity, which includes toxicology, metabolism and pharmacokinetics.⁷ Most racemic pharmaceuticals have one bio-active enantiomer, named eutomer, and one inactive or less active enantiomer, named distomer, the latter can even in some cases be toxic or exert other pharmacological properties which can be either desirable or undesirable. In 1994, the European Union also adopted guidelines from the European Medicines Agency to ensure the safety and

efficacy of drugs, requiring full characterisation of the final product, as well as intermediates and starting materials which applies to their purity, and stereoisomers and thus includes full determination of chirality.¹⁰ Single-enantiomers or achiral drugs now dominate newly approved drugs in the world, and drugs previously granted patent protection and commercialised as racemates are now candidates for a ‘chiral switch’.¹¹ In the late 1990s, the field of chiral drugs became increasingly of interest, and the definition of the term ‘chiral switching’ has evolved since 1999.^{12–14} Chiral switching refers to the development of a single enantiomer from a chiral drug that has been previously used and marketed as a racemate. The non-steroidal anti-inflammatory drug ibuprofen was the first drug to be switched to a single-enantiomer, with the (*S*)-enantiomer being over 100-fold more potent, even though it was found that when administered the (*R*)-enantiomer would convert into the (*S*)-form, therefore acting as a pro-drug. Nevertheless, the administration of the (*S*)-ibuprofen favours faster onset of relief at a lower dosage.¹³

1.2. Methods to Prepare Chiral Molecules

1.2.1. Chiral Pool Synthesis

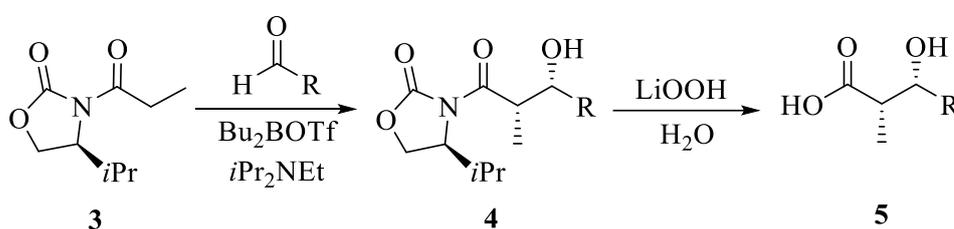
One approach to prepare an enantiomerically pure compound is to utilise a chiral pool, these are a collection of abundant enantiopure substances available in nature. Common chiral pool reagents include amino acids, chiral carboxylic acids and monosaccharides, and these reagents allow for the transfer of chirality to a pro-chiral substrate which usually involves the conversion of an sp^2 carbon to an sp^3 carbon centre through substitution or addition reactions. The chiral centre in the chiral pool starting reagent may not always be preserved in the target synthetic molecule being synthesised. An example of the chiral pool strategy is the synthesis of the epilepsy drug (*R*)-lacosamide **2** from the natural and inexpensive amino acid (*S*)-serine (Scheme 1).¹⁵



Scheme 1. Multi-step synthesis of (*R*)-lacosamide **2** from (*S*)-serine **1** using the chiral pool strategy.

1.2.2. Chiral Auxiliaries

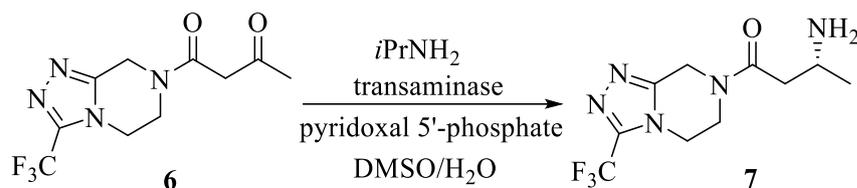
A chiral auxiliary is a chiral molecule that can be temporarily incorporated into an achiral substrate in order to guide the stereochemical outcome of the synthesis to selectively give a single-enantiomer. Evans introduced a range of successful chiral auxiliaries, an example of which is illustrated in Scheme 2.¹⁶ The chiral auxiliary **3** can block one of two reaction pathways of attack on the intermediate substrate that would otherwise form both enantiomers, in turn leaving only the desired pathway for attack available to afford an enantiopure product **4**. As a result, one enantiomer is formed predominantly over the other.



Scheme 2. Stereoselective aldol reaction using a chiral auxiliary and subsequent cleavage of the auxiliary.

1.2.3. Biocatalysis

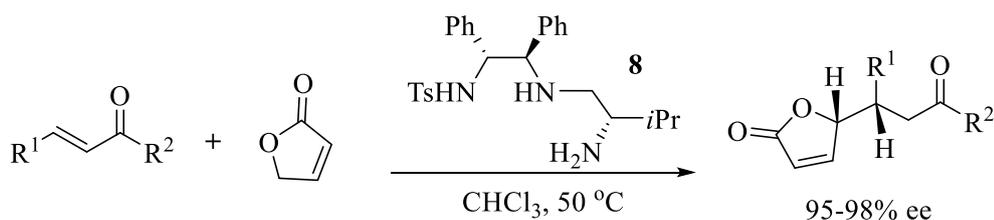
Enzymes are nature's catalysts; the most important difference between enzymes and synthetic catalysts is that the former are more restrictive and selective in the area of substrate scope. This is largely due to the three-dimensional structure of enzymes which only allows certain substrates to be transformed.¹⁷ Enzymes employed for *in vitro* studies are called biocatalysts which can be used to produce optically active substrates and can offer high regio-, chemo-, and stereoselectivity. Biocatalysis became increasingly popular in the 1980s, especially in industry with early successful applications in asymmetric ester hydrolysis being reported with a range of pig-liver esterases.^{18,19} An example of biocatalysis is in the transaminase-catalysed reaction of Sitagliptin, an anti-diabetic medicine used to treat type-2 diabetes, favoured by excess isopropylamine (Scheme 3).²⁰



Scheme 3. Synthesis of Sitagliptin using an engineered transaminase.

1.2.4. Asymmetric Organocatalysis

An organocatalyst is a small organic molecule, usually employed in substoichiometric quantities, to catalyse transformations. Organocatalysis was introduced in the late 1990s to mimic biocatalysts for their success in asymmetric reactions, and research still continues in this field.^{21,22} Chiral organocatalysts are able to catalyse asymmetric transformations, such as the TsDPEN-derived ligand **8** used in the asymmetric Michael additions of unsaturated lactones to enones (Scheme 4).²³



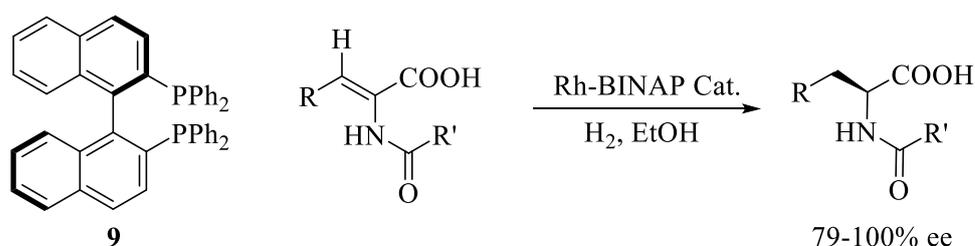
Scheme 4. Asymmetric Michael additions of unsaturated lactones to enones.

1.2.5. Asymmetric Catalysis

Asymmetric catalysis uses a homochiral catalyst in substoichiometric quantities to carry out transformations where one enantiomer of a chiral compound is formed preferentially. Some common chiral catalysts are composed of transition metal centres complexed to enantiomerically-pure ligands. A desirable trait of this method is the high substrate to catalyst ratio [S/C] of the chiral catalysts utilised. Transformations which can be achieved with chiral catalysts include asymmetric reductions through the formation of C-H bonds, asymmetric oxidations through C-O bond formations and the generation of chiral carbon centres through C-C bond formation.²⁴

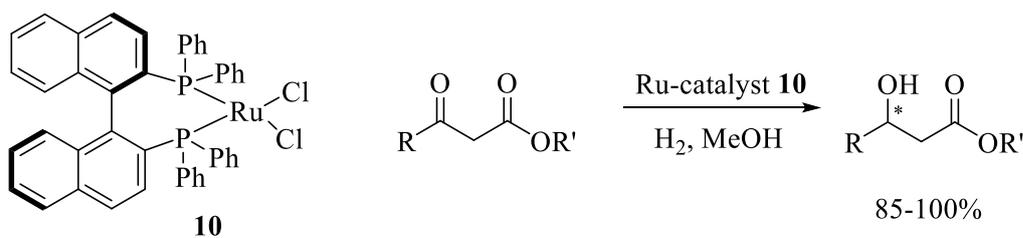
1.3. Asymmetric Pressure Hydrogenation

Ryoji Noyori was awarded the Nobel Prize in Chemistry in 2001 (jointly with W. Knowles and K.B. Sharpless) for his work on asymmetric catalysis, and notably in chiral hydrogenations. The development of the ligand BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) **9**, a C₂ symmetric molecule exhibiting axial chirality, has been a crucial step in achieving practical asymmetric pressure hydrogenation of organic molecules.^{25,26} Noyori and co-workers were able to achieve high ee in the asymmetric hydrogenation (AH) of olefins by making use of the BINAP ligand **9** in a cationic rhodium complex with hydrogen gas as the reducing agent. Their early work focussed mainly on the AH of α -(acylamino)acrylic acids; these reactions achieved high conversions and high ee (79 – 100%) after being run for 48 h at room temperature (Scheme 5).²⁷



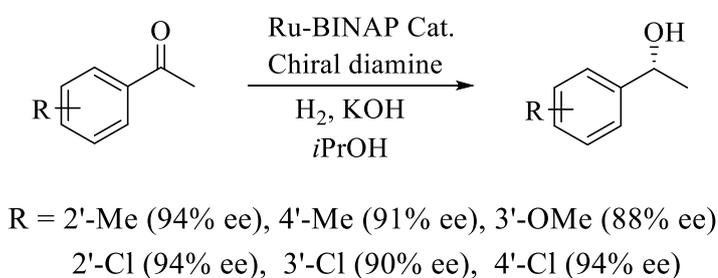
Scheme 5. Asymmetric hydrogenation of α -(acylamino)acrylic acids with BINAP ligand **9**.

However, the substrate scope of the Rh-BINAP catalyst was limited and later work focussed on the use of ruthenium rather than rhodium for catalysis. Complexes of RuX₂(BINAP), where X is a halide, were later developed and these catalysts could efficiently reduce substrates such as β -keto esters with high enantioselectivities (85 – 100%) and in many cases quantitative yields (Scheme 6).²⁸



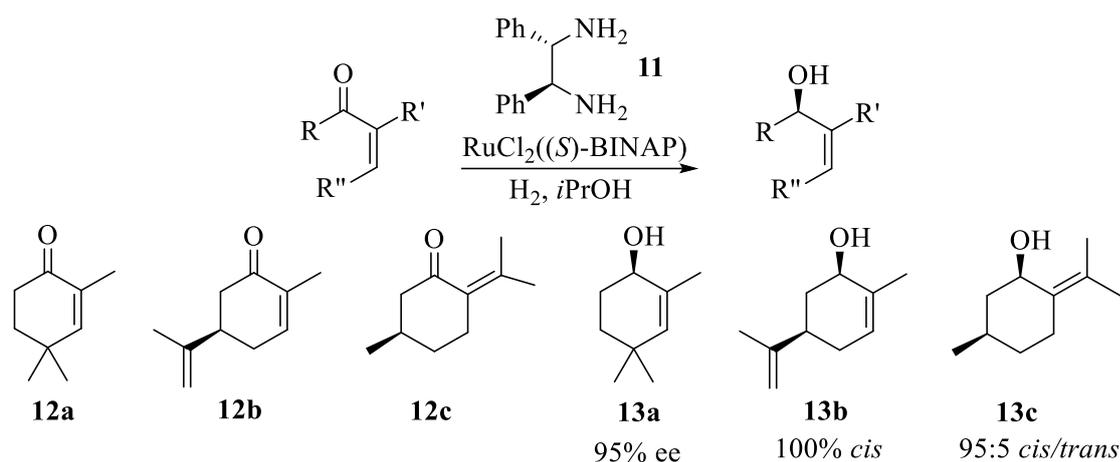
Scheme 6. Asymmetric hydrogenation of β -keto esters using a Ru-BINAP complex **10**.

The use of BINAP **9** in hydrogenation could also be extended to the asymmetric hydrogenation of aromatic ketones. Phosphine-Ru(II) catalysts have proven less effective in the hydrogenation of acetophenone and similar compounds. However, the addition of a chiral diamine ligand to the phosphine-Ru provides catalysts which show enhanced activity in the hydrogenation of aromatic ketones. More specifically the use of a chiral diamine to the BINAP-Ru catalyst results in reduction of acetophenone to 1-phenylethanol in 90% ee.²⁹ The enantioselectivity was found to not be affected by the pressure of hydrogen but was affected by the base employed. A range of *meta*- and *para*-substituted acetophenones, formed products in higher enantioselectivity compared to acetophenone, irrespective of the electronic properties of the group (Scheme 7).



Scheme 7. Application of a Ru-BINAP catalyst with diamine ligands in the ATH of substituted acetophenones.

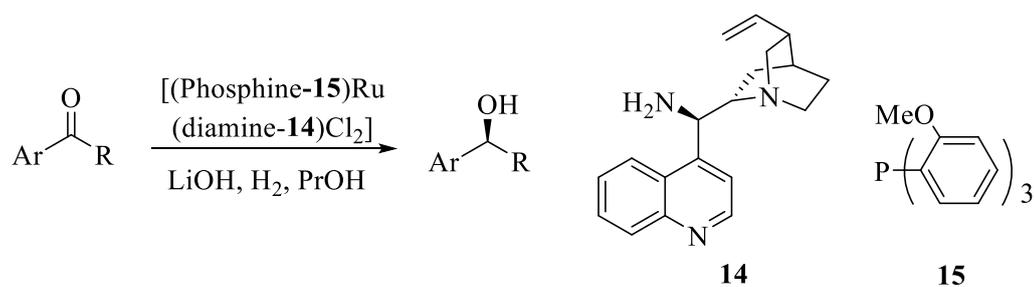
The chiral diamine **11**, (*R,R*)-DPEN, was used in the [RuCl₂((*S*)-BINAP)] catalysis of cyclic α,β unsaturated ketones.³⁰ The ketone **12a** was reduced both enantioselectively and chemoselectively, with selective reduction of the carbonyl functionality, to afford the allylic alcohol **13a** in 100% yield and 95 % ee (Scheme 8). The inclusion of an isopropenyl group at the C-5 position of the cyclic ketone **12b** did not cause issues in the catalysis and the reaction produced solely the *cis*-isomer of the allylic alcohol **13b**. It is worth noting that the reduction of **12b** with NaBH₄ /CeCl₃ forms the allylic alcohol but also reduces the isopropenyl functionality. Ketone **12c** also undergoes chemoselective reduction of the carbonyl to alcohol **13c**, forming the mixture of *cis/trans* in the ratio of 95:5.



Scheme 8. Application of $\text{RuCl}_2((S)\text{-BINAP})$ with $(S,S)\text{-DPEN 11}$ in the ATH of α,β unsaturated ketones and examples.

The area of asymmetric pressure hydrogenation has been studied considerably since, with some notable studies such as those by Feringa *et al.* through iridium and rhodium-catalysed hydrogenations with phosphorus-based ligands.^{31,32} Brown *et al.*³³ reported rhodium-catalysed hydrogenation of dehydroaminoesters using diphosphines whilst the groups of Feringa *et al.*³², Pringle *et al.*^{34,35} and Wills *et al.*^{36–40} published on ruthenium-catalysed hydrogenation of ketones using phosphorus-donor ligands based on BINOL.

A more recent application to the phosphine/ruthenium/diamine catalysis has been carried out by Li and co-workers.⁴¹ A series of complexes with achiral phosphines were tested on acetophenone. The phosphines with hindered aryl groups, such as **15** gave the best enantioselectivity in the presence of the diamine **14**. A range of monosubstituted acetophenones were reduced with the catalytic system to give the corresponding alcohol products in high enantioselectivity, 93–98% ee (Table 1). When the aryl group was changed to a thiophene the reduction gave a low conversion of 29% and 89% ee. Further monosubstituted-thiophenes produced alcohols in 83–97% ee.



Ar	R	Conv (%)	ee (%)
Ph	Me	99	95
2-FC ₆ H ₄	Me	99	95
2-ClC ₆ H ₄	Me	94	98
2-BrC ₆ H ₄	Me	50	94
2-CF ₃ C ₆ H ₄	Me	35	98
2-MeC ₆ H ₄	Me	69	97
2-OMeC ₆ H ₄	Me	72	91
4-OMeC ₆ H ₄	Me	73	93
Ph	Pr	93	88
Thiophene	Me	29	89

Table 1. Hydrogenation of acetophenone derivatives using Ru(II) complexes containing diamine **14** and phosphine **15**.

1.4. Asymmetric transfer hydrogenation

Another method to add hydrogen atoms to a substrate is through transfer hydrogenation. In this method, hydrogen gas is substituted by a hydrogen donor source such as isopropanol or formic acid, and a catalyst aids in the transfer of the hydrogen atoms from the donor to the substrate. The resultant products are the oxidised donor, as a byproduct, and the reduced substrate. The first examples of transfer hydrogenation reactions were reported by Meerwein⁴², Ponndorf⁴³ and Verley⁴⁴ who used the catalyst Al(O*i*Pr)₃ to reduce aldehydes and ketones using *i*PrOH. Density functional theory studies to determine the mechanism showed that the formation of a metal-hydride would be more energetically demanding than a concerted mechanism. Therefore a direct concerted mechanism was found to be favourable and this is illustrated in Figure 3.⁴⁵

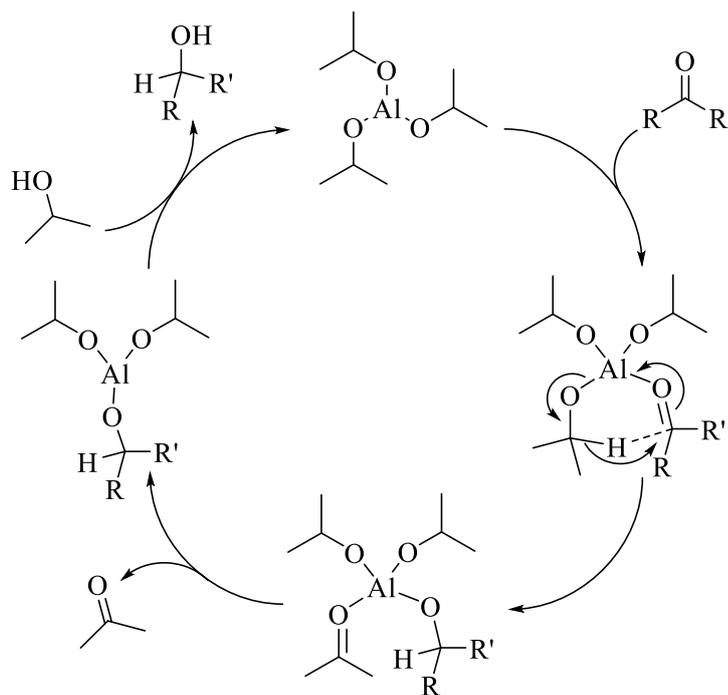
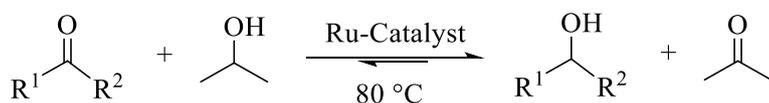


Figure 3. Mechanism of the Meerwein, Ponnorf and Verley transfer hydrogenation reaction.

Through the employment of a $\text{RuCl}_2(\text{PPh}_3)_2$ catalyst, Chowdhury and Bäckvall were able to efficiently reduce ketones using a ruthenium complex and *i*PrOH as the hydrogen source (Scheme 9). Chowdhury and Bäckvall reasoned that the ruthenium complex had the ability to dehydrogenate the *i*PrOH and efficiently transfer hydrogen atoms to the substrate.⁴⁶ This method has proven to be desirable as *i*PrOH (hydrogen source) is easier to handle than hydrogen gas, and can also be used as the solvent in the reactions. However, these reactions are reversible which therefore requires an excess of the *i*PrOH and elevated temperatures to drive the reaction to near completion.



Scheme 9. Asymmetric transfer hydrogenation of ketones with 2-propanol.

1.4.1. Ru(arene)/TsDPEN Catalysts

Noyori and co-workers later engineered ruthenium(II) arene complexes with chiral diamine ligands for use in the asymmetric transfer hydrogenation (ATH) of ketones to

form products in high ee (Figure 4).⁴⁷ Unlike previous Ru(II) catalysts based on the BINAP ligand, these catalysts were designed with a chiral TsDPEN ligand. Prepared *in situ* from $[\text{RuCl}_2(\eta^6\text{-arene})]$ and (1*S*,2*S*)-*N*-(tosyl)-1,2-diphenylethylenediamine (TsDPEN) alongside KOH, the catalysts are able to asymmetrically reduce acetophenone to (*S*)-1-phenylethanol in 95% conversion and 97% ee. Studies on the ruthenium complexes presented in Figure 4, have served to show that the ATH reactions proceed faster when the arene ligand is benzene (**16**) followed by decreased reactivity in the order *p*-cymene (**18**) \approx mesitylene (**17**) > hexamethylbenzene (**19**). However it has been found that greater enantioselectivities are obtained when the *p*-cymene or mesitylene-containing catalysts are employed.⁴⁸

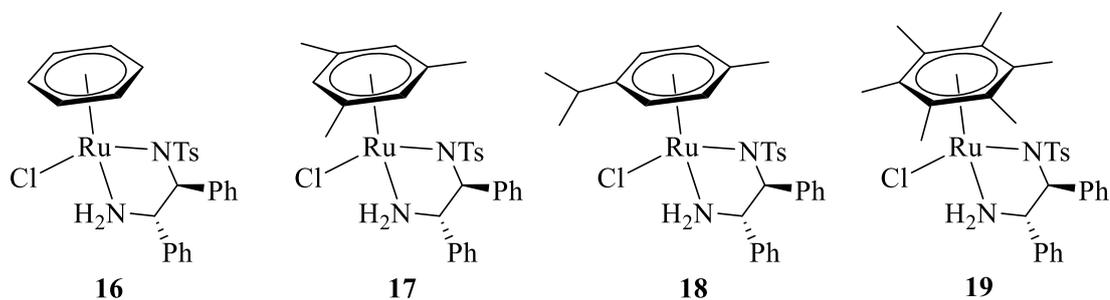
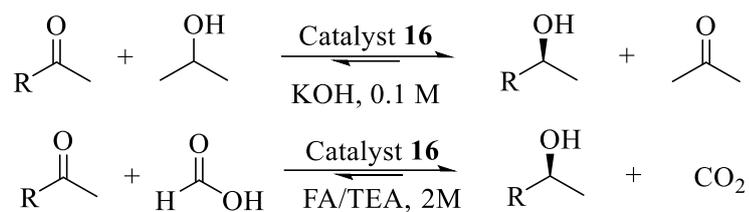


Figure 4. Structure of Noyori-Ikariya ATH catalysts based on (*S,S*)-TsDPEN.

Changing the group on the sulfonamide of the TsDPEN results in a decrease in reactivity of catalyst **16** when greater electron-withdrawing substituents are present. A DPEN containing a triflyl group in the diamine proved to be less reactive than the tosyl derivative, however substituting with a benzamide group showed enhanced reactivity but lower enantioselectivity. Although it has been proven to be less reactive, the *p*-toluenesulfonyl group is still employed due to its high enantioselectivity in these reactions.⁴⁷ More importantly the arene/Ru/TsDPEN catalysts have proven effective with other hydrogen sources in ATH reactions such as the azeotropic mixture of formic acid-triethylamine (FA/TEA, 5:2 molar ratio). The use of FA/TEA 5:2 results in enhanced reactivity when compared to *i*PrOH and also leads to an essentially irreversible reaction (Scheme 10).⁴⁸



Scheme 10. ATH of ketones using catalyst **16** showing the reversible reaction in *i*PrOH and the irreversible reaction with FA/TEA.

Further studies into the active catalyst uncovered the importance of a hydrido ligand bonded to the ruthenium centre and the presence of an acidic amine for ATH reactions in *i*PrOH.⁴⁹ The asymmetric transfer hydrogenation to the ketone is proposed to occur via an outer-sphere concerted mechanism illustrated in Figure 5. The transition state has a favourable C-H/ π interaction between the η^6 -arene of the catalyst and an electron rich group of the substrate. This gives rise to the enantioselectivity observed in the reduced alcohol products.⁵⁰

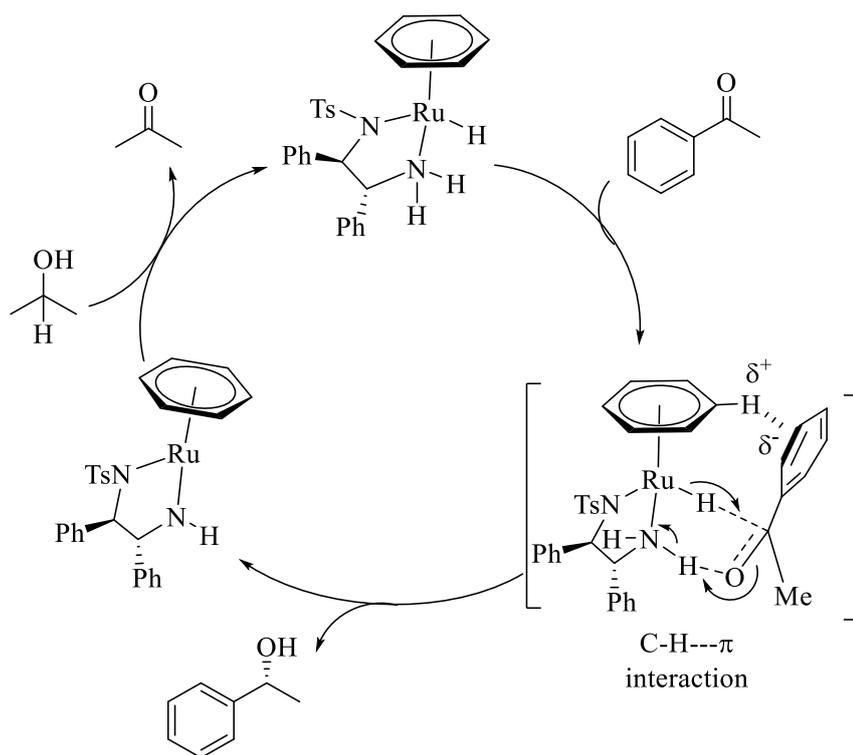


Figure 5. The mechanism for the ATH of ketones using Noyori-Ikariya catalyst (*R,R*)-**16**.

1.4.2. Tethered Catalysts

Research by Wills *et al.* introduced the chiral TsDPEN unit bonded directly to an arene allowing a “three point” coordination of the ligand to the ruthenium centre as illustrated in Figure 6.⁵¹ ATH with the amino alcohol catalyst **20** using *i*PrOH and KOH achieved a 96% conversion of acetophenone to 1-phenylethanol in 66% ee. More importantly, the sulfonated tethered catalyst **21** achieved a 99% conversion of acetophenone in 96% ee under FA/TEA 5:2. High yields and enantioselectivities were also observed with ketone substrates containing heteroatoms using catalyst **21**; for example the reduction of α -phenoxyacetophenone was achieved in 100% conversion and 80% ee.⁵² More successful was the attachment of the arene to the basic amine of the TsDPEN ligand for the formation of catalyst **22**.⁵³ This catalyst, initially coined the “reverse tethered”, has shown to be more reactive than the previously reported catalysts and the Noyori-Ikariya catalysts in Figure 4. Acetophenone reduction with catalyst **21** was achieved in full conversion with 96% ee within 3 h whilst catalyst **20** required 21 h to achieve the same results. A comparative study between catalyst **18** and catalyst **22** proved the tethered catalyst to be more reactive and enantioselective in asymmetric pressure hydrogenation reactions even when catalyst loadings of the tethered catalyst was reduced.⁵⁴

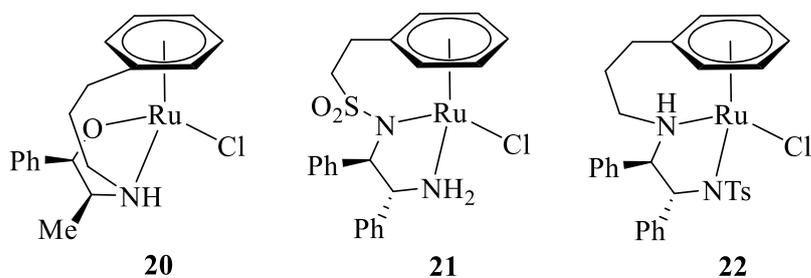
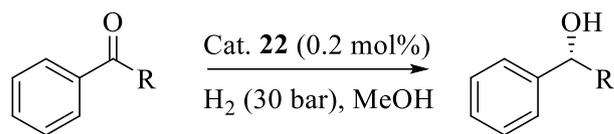


Figure 6. Structure of tethered catalysts by Wills and co-workers.

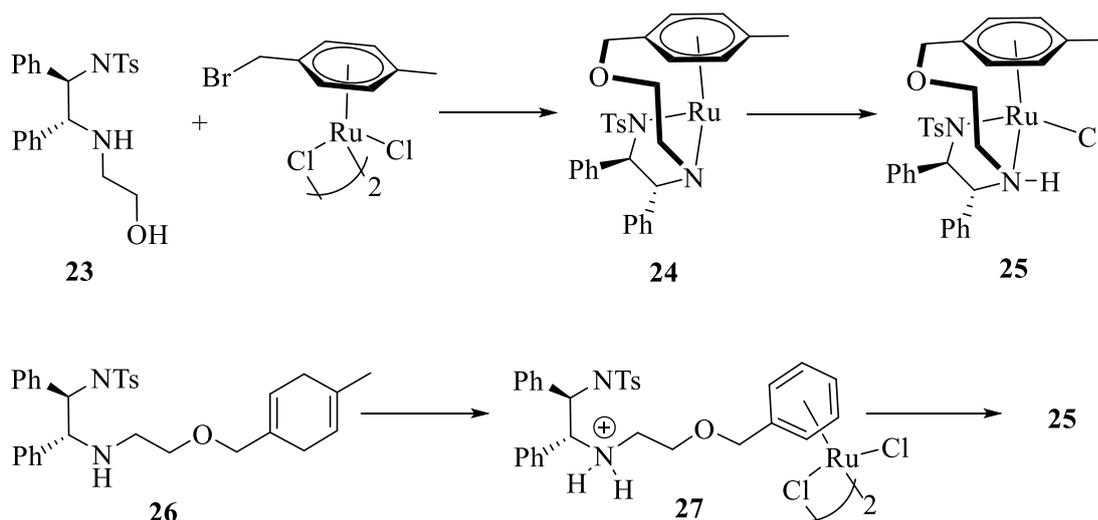
Wills *et al.* have also investigated the asymmetric pressure hydrogenation using tethered catalyst **22** on a series of ketone substrates.⁵⁵ The hydrogenation at 0.2 mol% of catalyst and 30 bar of H₂ reduced substituted-acetophenones in 70-99% ee. More significantly, functionalised substrates were obtained in high enantioselectivity, as presented in Table 2.



R group	Time (h)	Conv (%)	ee (%)
Et	48	99.9	90
CH ₂ OPh	24	99.9	84
CH ₂ OH	24	99	99
tBu	48	74	69
CH ₂ -morpholine	48	88	95
CH ₂ Cl	16	95	94

Table 2. Pressure hydrogenation of aryl ketones with tethered catalyst **22**.

An ether connected tethered catalyst was synthesised independently by both Ikariya *et al.* and Wills *et al.* around similar times.^{56,57} Ikariya and co-workers complexed the diamine **23**, containing a hydroxyl chain, with [Ru(bromoxylene)Cl₂]₂ to form the active catalyst **24** in a one-pot reaction (Scheme 11). On the other hand, Wills and co-workers synthesised the diamine ligand **26**, containing the cyclohexadiene functionality, prior to complexation with RuCl₃ and the subsequent complex **27** was then ligated to form ether catalyst **25**.

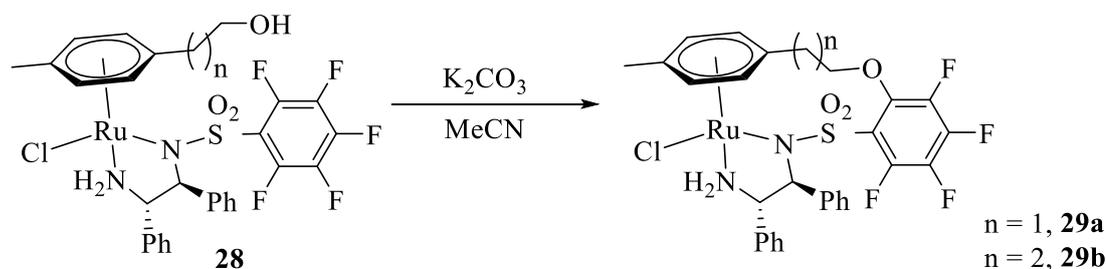


Scheme 11. Top: Ikariya's synthetic route to ether-tethered catalyst **25**. Bottom: Wills' synthetic route to ether-tethered catalyst **25**.

Ikariya compared the activity of the oxo-tethered catalyst to a 4C, length of carbon chain between amine and arene, tethered catalyst. Employing a [S/C] of 40000 found

catalyst **25** to reduce acetophenone with 75% yield and 97% ee after 72 h.⁵⁶ The 4C tethered catalyst reduced acetophenone in 15% yield and 96% ee. Wills also applied catalyst **25** to substituted-acetophenones, which gave alcohol products in high ee and yields.⁵⁷ On functionalised substrates, catalyst **25** also produced interesting results with α -chloroacetophenone reducing quantitatively giving the alcohol in 98% ee. Also the α -phenoxyacetophenone reducing quantitatively to form the alcohol in 95% ee.

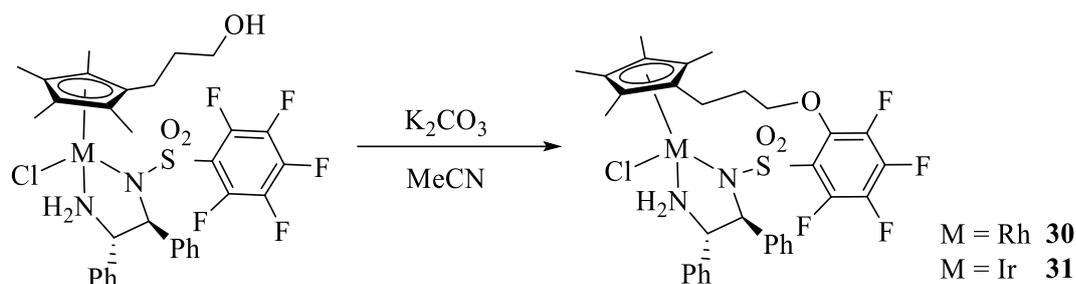
Kayaki developed another route to making O-linked tethered catalysts, **29**, through an oxydefluorination reaction.⁵⁸ The oxy-tether is constructed through the intramolecular nucleophilic aromatic substitution between the hydroxyl group, 2-3 carbon atoms linked through to an arene, and a pentafluorobenzenesulfonyl on **28** (Scheme 12). In all cases the reaction occurs at the *ortho*-fluorine of the sulfonyl group.



Scheme 12. Oxydefluorination reaction to form catalysts **29a** and **29b**.

Applying the catalyst **29a** in the ATH of acetophenone gave the alcohol product in quantitative yield and 96% ee whilst catalyst **29b** gave the alcohol product in 97% yield and 94% ee. The non-tethered derivative containing an FsDPEN and a *p*-cymene reduced acetophenone in only 52% yield but the enantioselectivity was unchanged. The ATH with O-linked catalysts **29a-b** on *ortho*-substituted acetophenones also reduced in high yields and enantioselectivity; catalyst **29a** formed products in 86-88% ee and **29b** formed products in 90-92% ee. On functionalised substrates, α -chloroacetophenone was reduced in 96% ee and the α -hydroxy in 90% ee using **29a**.

More recent work by Kayaki describes the syntheses of rhodium and iridium analogues using the same technique (Scheme 13).⁵⁹ These catalyst work in the dehydrogenation of formic acid for hydrogen gas evolution. The rhodium catalyst **30** however has low activity with a low turnover number. The iridium catalyst **31** on the other hand had good activity with a maximum turnover number of 8300.



Scheme 13. Oxydefluorination reaction to form rhodium and iridium derivatives **30** and **31**.

1.4.3. Other Ru(arene)/diamine catalysts

The basic amine functionality was generated by Wills and co-workers with a range of alkyl groups (Figure 7).⁶⁰ The ligand with a methyl group on the TsDPEN ligand generated a more active catalyst, **32a**, compared to its non-alkylated derivative in the reduction of acetophenone. The longer-chained alkyl substituents produced less active catalysts but without detrimental effects on the enantioselectivity, typically >95% ee. These catalysts were also applied in the reduction of an imine as shown in Figure 7. In this case, many of the alkylations had detrimental effects on the enantioselectivity apart from the benzyl derivative which gave the product in 85% ee, the non-alkylated catalysts gives the corresponding amine product in 80% ee. In a further application of the methyl catalyst **32a**, a range of substituted-acetophenones were studied that were reduced in high enantioselectivity; 88 to 96% ee, apart from *ortho*-substituted acetophenones where the enantioselectivity dropped to between 64 and 81% ee.⁶¹

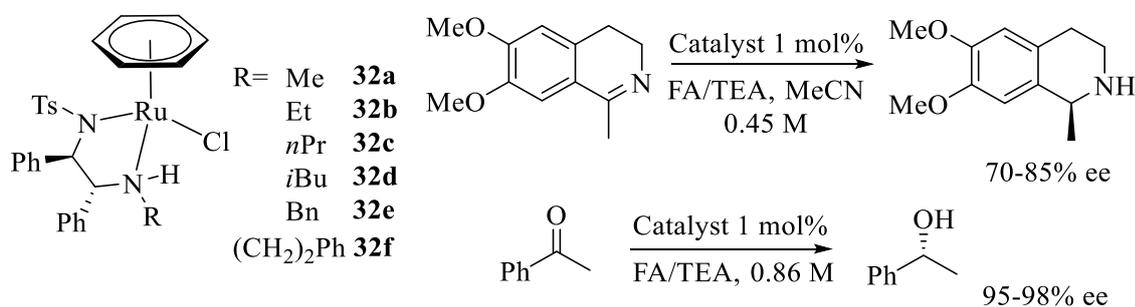


Figure 7. Structure of alkylated Ru-catalysts **32a-f** and applications in imine and ketone ATH.

Somanathan and co-workers have also alkylated TsDACH ligands, forming a mixture of bidentate and tridentate ligands.⁶² Catalytic reduction of acetophenone with ligands **33a-f** and $[\text{Ru}(\text{benzene})\text{Cl}_2]_2$, gave the 1-phenylethanol products in up to 30% yield and ee of 47-87% (Table 3). The low yields are proposed to result from either steric crowding at the metal centre or from binding of the heteroatom to the ruthenium, forming inactive species. Ligand **33a** gave no reduction when used with the ruthenium (II) species but was found to work with rhodium (III), reducing acetophenone racemically in 90% yield.

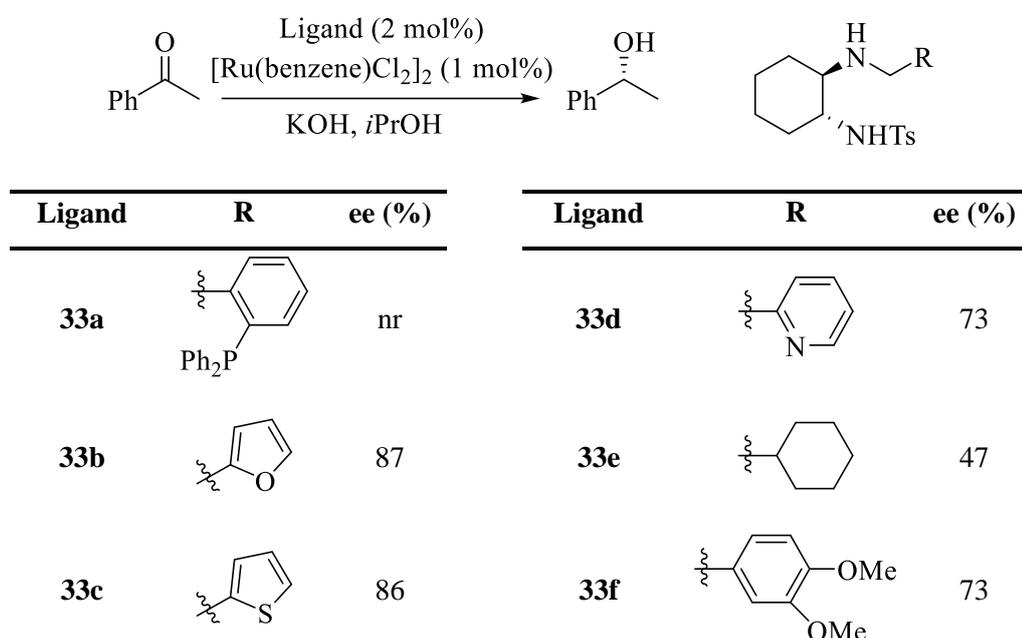
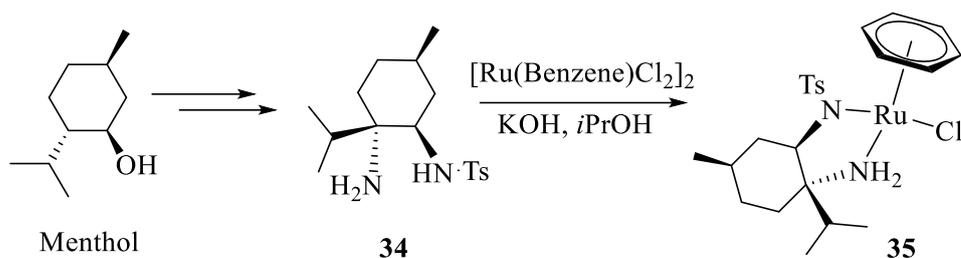


Table 3. ATH of acetophenone with TsDACH containing ligands **33a-f** and $[\text{Ru}(\text{benzene})\text{Cl}_2]_2$ in KOH and *i*PrOH. Yields reported between 20-30%.

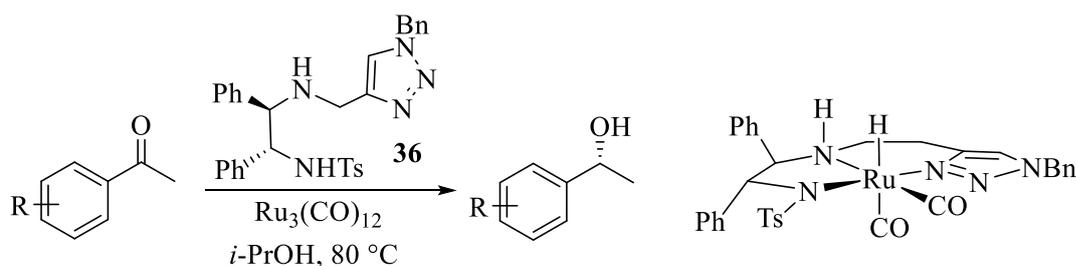
Other chiral ethylenediamine ligands for ATH have also been investigated, with one notable study forming a chiral diamine from the natural product menthol. Ligand **34** was synthesised from naturally occurring menthol in five steps; Czarnocki and co-workers included a tosylated amine in the ligand structure similar to those seen in the Noyori-Ikariya catalysts. Reacting ligand **34** with $[\text{Ru}(\text{benzene})\text{Cl}_2]_2$ resulted in the formation of complex **35** (Scheme 14) that could be utilised in ATH reductions with FA/TEA azeotrope or KOH/*i*-PrOH as hydrogen sources. Low yields between 2 – 15% were obtained for ketone reductions with low ee (7 – 32%) using the FA/TEA hydrogen source at 40 °C for 92 h. Changing the hydrogen source to *i*-PrOH gave better results with good yields of alcohol products between 23 – 84% ee.⁶³



Scheme 14. Formation of ligand **34** from menthol and its reducing complex **35**.

1.4.4. Tridentate Ligands in ATH

More recent developments have demonstrated the use of tridentate ligands in Ru(II) catalysed ATH reactions. In 2012, Wills *et al.* reported the synthesis of ligand **36** that was effective in the ATH of a range of ketones, using $\text{Ru}_3(\text{CO})_{12}$ in *i*PrOH where a catalytic complex forms *in situ* (Scheme 15).⁶⁴ Various acetophenone derivative reductions were achieved in good enantioselectivity with this ligand and unlike other *i*PrOH reductions, these can be carried out without the need for a base. *ortho*-Substituted acetophenones have proven challenging in previous ATH reductions when carried out with the Noyori-Ikariya catalysts **16-19**. However employment of the tridentate ligand **36** accomplished conversions in up to 99% and enantioselectivities of up to 87% ee for challenging *ortho*-substituted acetophenones.



Scheme 15. Catalytic reduction of acetophenones and the proposed catalyst formed from ligand **36** with $\text{Ru}_3(\text{CO})_{12}$.

Similarly, ligands **37** containing a triazole ring attached distal to TsDPEN have also shown high enantioselectivities and conversions in the ATH of acetophenone; these ligands however are not tridentate. The ligands in Figure 8, synthesised with the triazole ring distant to the TsDPEN unit, rather than proximal as ligand **36**, were developed to determine suitability for ligand attachment to a soluble polymer support.

The complex formation with $[\text{Ru}(\text{benzene})\text{Cl}_2]_2$, followed by reduction in FA:TEA successfully reduced acetophenone in up to 99% conversion and 95% ee. Unfortunately, these ligands show decreased reactivity in comparison to Noyori-Ikariya catalyst **16**; ligand derivatives of **37** required reaction times of up to 136 h, whilst catalyst **16** achieved the same results within 6 h.

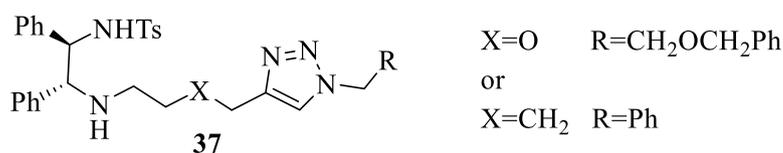


Figure 8. Structure of triazole ligands for attachment to polymer support.

Another tridentate ligand able to catalyse ketone reductions is ligand **38** (Figure 9). Similar to ligand **36**, the ligand **38** also has a third *N*-donor attached to the TsDPEN unit and is believed to form an active catalyst with $\text{Ru}_3(\text{CO})_{12}$, in the same manner as illustrated in Scheme 15. Reduction of acetophenone with ligand **38** at 1 mol% loading, under the same conditions as in Scheme 15, gave (*R*)-1-phenylethanol with a 90% conversion and 93% ee after 48 h. The challenging *ortho*-methoxy substituted acetophenone reduction was achieved in 99% conversion and 89% ee (*R*) using 2 mol% of catalyst. Also *ortho*-fluoro-, bromo- and chloro-acetophenones were reduced in excellent conversions (99 – 99.9%) and good ee (84 – 88%). The cyclohexane ligand derivative **39** under the same conditions reduced acetophenone in 62% conversion and 91% ee. Increasing the loading to a 2 mol% of catalyst gave 97% conversion to 1-phenylethanol in 90% ee.⁶⁵ The proposed mechanism for this tridentate catalyst reduction is illustrated in Figure 10.

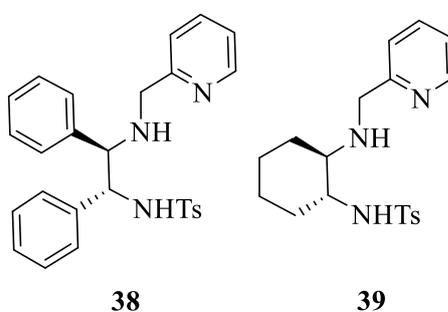


Figure 9. Pyridine-containing tridentate ligands.

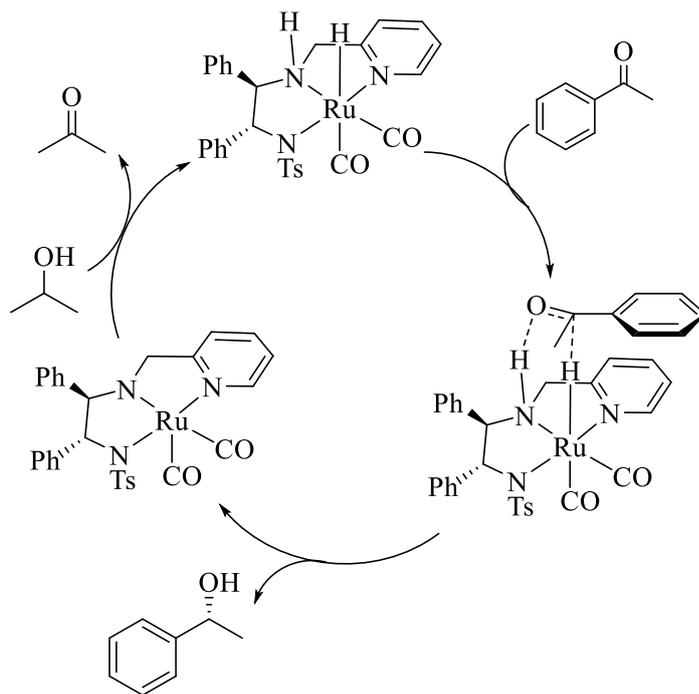


Figure 10. Proposed mechanism for the ATH of ketones using tridentate ligand **38**.

Other pyridine-containing ligands have demonstrated to be effective in ruthenium catalysed reduction of ketones. Yu's research into the pyridine containing ligand **40** has shown it to be highly efficient in transfer hydrogenation (Figure 11). Such ligands when coordinated to $\text{Ru}(\text{PPh}_3)_2\text{Cl}_2$ can reduce acetophenone to racemic 1-phenylethanol in 98% within 10 min at a low catalyst loading of 0.2 mol%. Reactions have been reported to proceed in *i*PrOH with *i*PrOK as an additive at 82 °C and a ketone concentration of 0.1 M. *ortho*-Halide-containing acetophenones can also be reduced in short reaction times (reduction within 1-5 min using 0.1 mol% of catalyst) with yields of up to 98%.⁶⁶ Similar results were also obtained when $\text{RuCl}_3 \cdot \text{XH}_2\text{O}$ was used as the ruthenium source to make the preformed catalyst.

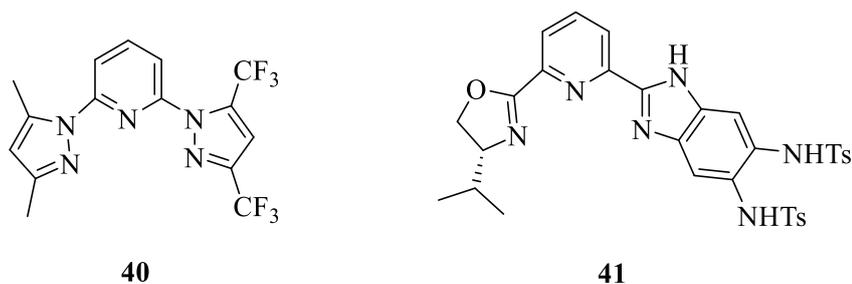
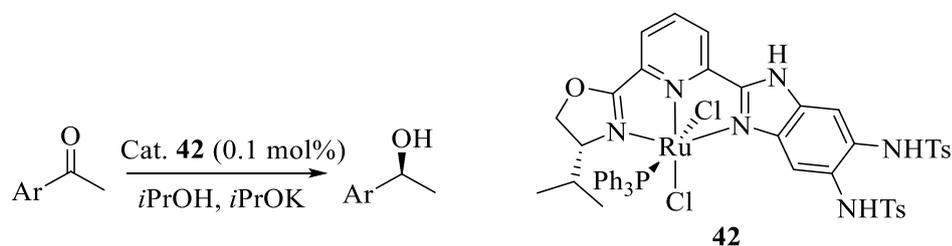


Figure 11. Tridentate ligands in transfer hydrogenation by Yu.

Later Yu *et al.* introduced chiral groups and NHTs groups to the pincer-type ligands with the most effective ligand from a series being **41**. Ligand **41** was ligated to Ru(PPh₃)Cl₂, forming the catalyst **42**, which was effective in the ATH of acetophenone. Similar to reductions with ligand **40**, catalyst **42** could reduce ketones within 3 min at 0.1 mol% loading and gives product in both high yields and high ee. Reduction of acetophenone with 0.1 mol% of the catalyst yielded the (*S*)-1-phenylethanol in 97% yield and 98% ee. The reductions were reported to proceed within 3 min in *i*PrOK at 28°C and a ketone concentration of 0.1 M. *ortho*-Substituted acetophenones were reduced within 7 – 30 min with yields of 73 – 99% (Table 4). But more importantly, high ee were obtained for the reduced products ranging from 85 – 99.9%.⁶⁷

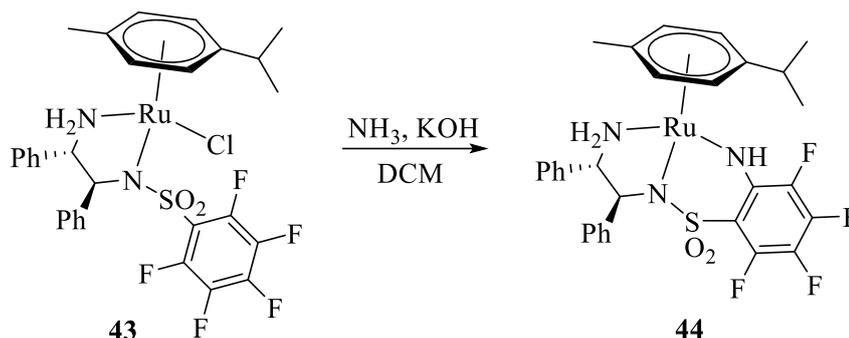


Ketone (Ar)	Time (min)	Yield (%)	ee (%)
Ph	3	97	98
2-ClC ₆ H ₄	7	99	99.9
3-ClC ₆ H ₄	2	98	99.9
4-ClC ₆ H ₄	4	97	97
2-BrC ₆ H ₄	30	100	99.9
3-BrC ₆ H ₄	4	100	97
4-BrC ₆ H ₄	5	98	95
2-MeC ₆ H ₄	20	99	98
2-OMeC ₆ H ₄	20	73	99.9
2-CF ₃ C ₆ H ₄	30	83	85

Table 4. ATH of substituted-acetophenones using catalyst **42**.

A tridentate ruthenium catalyst was investigated by Dub *et al.*; the pentafluoro catalyst **43** was demonstrated to be effective in the ATH of ketones and is analogous to Noyori catalyst **18**.⁶⁸ The reaction of **43** with ammonia results in the cleavage of the C-F bond through an S_NAr reaction to form the amine-containing intermediate. The amine group

coordinates to form the tridentate complex **44** (Scheme 16). The reduction of acetophenone and α -hydroxyacetophenone with complex **44** gives the alcohol products in high enantioselectivity, and similar to those obtained from reduction with parent catalyst **43** (Table 5). The method demonstrates the newly formed amino-type ligand to be weakly coordinating which in turn allows the dissociation of this amino ligand forming a vacant site in the catalyst for ATH reactions to proceed.

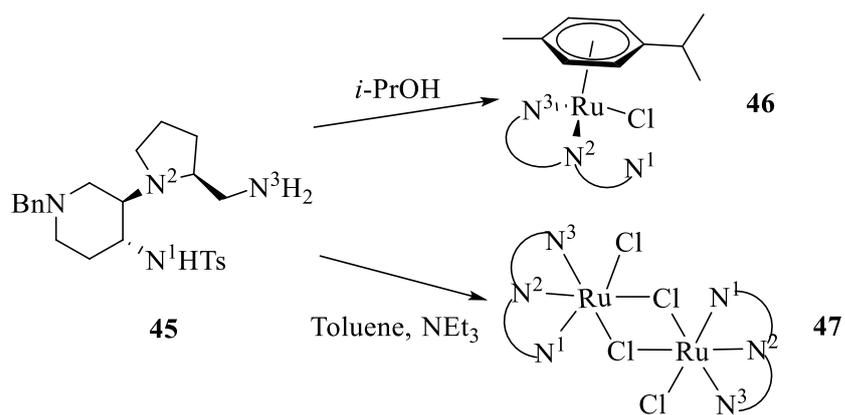


Scheme 16. Transformation of pentafluoro **43** catalyst to tridentate catalyst **44**.

Ketone	Catalyst	Yield (%)	ee (%)
Acetophenone	43	91	97
Acetophenone	44	83	98
α -Hydroxyacetophenone	43	99	94
α -Hydroxyacetophenone	44	100	93

Table 5. Comparison of bidentate **43** and tridentate **44** catalysts in ATH.

More recent applications of tridentate ligands have seen the use of ligand **45** in the formation of a bidentate or tridentate ruthenium complex (Scheme 17). The reaction between ligand **45** with $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ in *i*PrOH gives the bidentate catalyst **46** however using toluene and NEt_3 forms the tridentate catalyst **47**. A range of hydrogen sources were tested and sodium formate/ H_2O gave the best results in the ATH of acetophenone. Catalyst **46** at 0.5 mol% reduced acetophenone with 85% conversion and 81% ee whilst catalyst **47** at 0.5 mol% achieved 63% conversion and 44% ee. For other acetophenone derivatives, catalyst **46** gave products in higher conversions and ee than catalyst **47**, although the ee of the alcohol products varied largely from 9 – 96%.⁶⁹



Scheme 17. Formation of complexes from ligand **45** and $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$.

1.4.5. Tetradentate Ligands in ATH

Tetradentate ligands bearing metal centres can also be used for asymmetric transfer hydrogenation. Noyori introduced a P,N,N,P ligand, containing C₂ symmetry, that works as a tetradentate ligand when ligated to ruthenium centres (Figure 12).⁷⁰ Catalytic ATH of acetophenone was carried out with a [S/C] of 200 and a 0.1 M substrate solution in *i*PrOH using *i*PrOK as a base. The diimine catalyst **48** reduced acetophenone in low yield of 3% and just 18% ee. The amine catalyst **49** on the other hand, reduced acetophenone to the alcohol product in 93% yield and 97% ee. Further acetophenone derivatives were reduced with catalyst **49** in 58-96% ee.

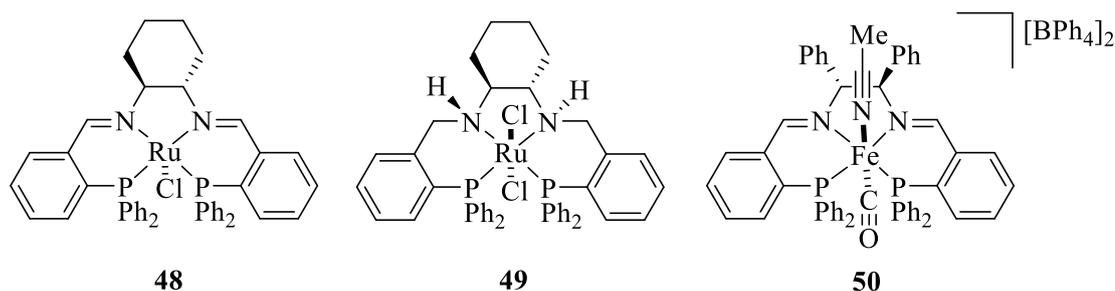


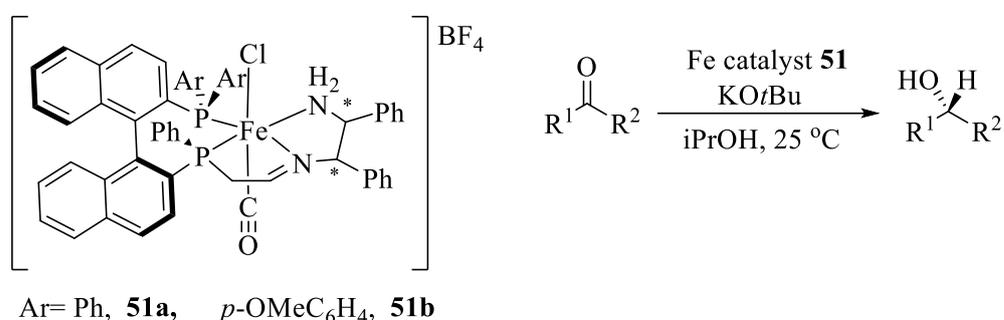
Figure 12. Structure of tetradentate complexes containing P,N,N,P ligands.

A DPEN derivative of the imine P,N,N,P ligand **48** was found to be effective in an iron catalysed ATH. Catalyst **50** was employed in the ATH of acetophenone, forming the alcohol product in 80% yield and 83% ee.⁷¹ Higher enantioselectivities were obtained with bulkier groups adjacent to the acetophenone such as the use of a ketone

containing a *t*Bu in place of the methyl, which was reduced in 99% ee. Morris reported this method as the first iron-catalysed ATH of ketones with useful activity and enantioselectivity. The mechanism is proposed to proceed through an outer-sphere mechanism analogous to the Noyori-Ikariya half-sandwich catalysts, with a metal hydride formed in the active catalyst.⁷²

1.4.6. Other Metals used in Hydrogenations

ATH using catalysts containing iron metal centres can be more challenging. However, Zuo and co-workers have developed a catalyst exhibiting three different chiral properties. Catalysts **51** contain a chiral TsDPEN group providing C-centred chirality, phosphines exhibiting P-centred chirality and the binaphthyl group giving rise to axial chirality. Catalyst **51a** was then employed at 0.023 mol% loading in the reduction of acetophenone, producing the product in 90% ee (Scheme 18). α,β -Unsaturated aldehydes were also reduced to unsaturated alcohols with these catalysts in 3 min, showing chemoselectivity for the C=O over the C=C bond. Additionally the reduction of substituted-acetophenone derivatives produced products in high enantioselectivity of up to 99% ee with the catalysts after 3 h.⁷³



Scheme 18. Reduction of ketones using catalysts **51a** and **b**.

A P,N,N pincer ligand has been developed for the asymmetric pressure hydrogenation of ketones using catalysts containing manganese metal centres.⁷⁴ The Mn catalyst **52** was found to hydrogenate a diverse range of ketones in high activity and good enantioselectivities (Figure 13). Various substituted acetophenones were reduced in quantitative yields and in 85-97% ee. More interestingly, functionalised substrates could be reduced in high enantioselectivity, with α -substituted ketones of **53a** and **53b** undergoing hydrogenation in quantitative yields and in 95% and 93% ee respectively.

The hydrogenation with catalyst **52** is highly chemoselective towards carbonyls, with the γ -olefin being tolerated in **53c** and giving a product of 91% ee.

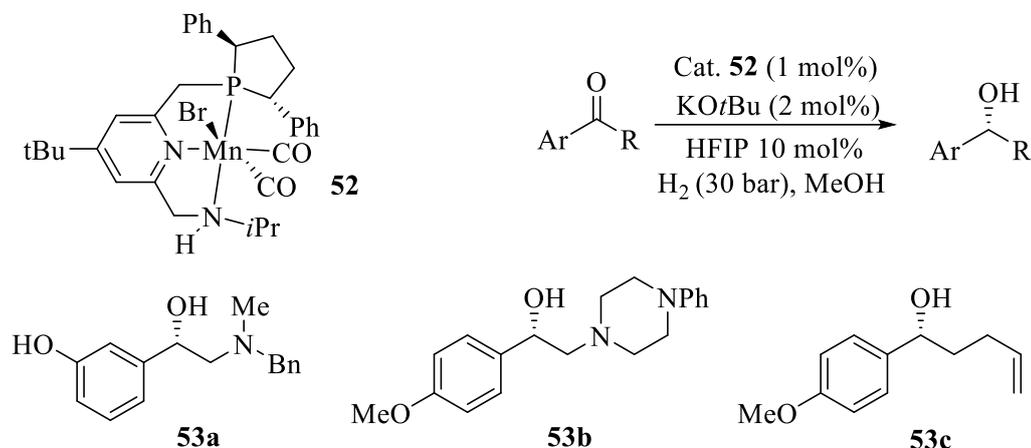
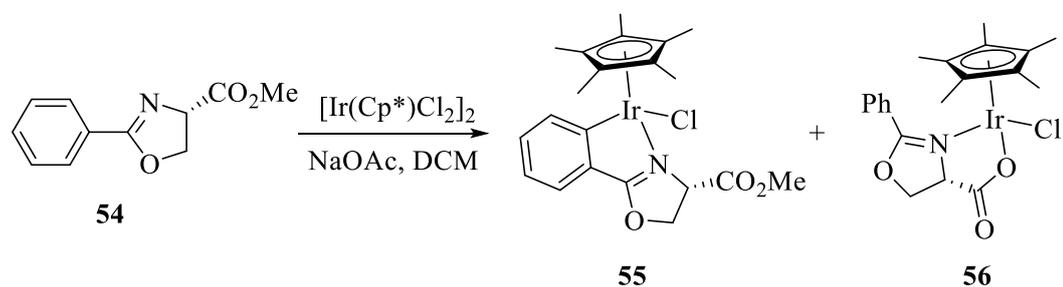


Figure 13. Asymmetric hydrogenation using catalyst **52** and selected alcohol examples.

Xiao utilised the chiral oxazoline **54** in iridium half-sandwich complexes; remarkably the catalyst generation reaction leads to the formation of two complexes.⁷⁵ Complex **55** is formed from the N,C chelation of the ligand whilst complex **56** arises from N,O chelation (Scheme 19). The formation of the complexes is determined by the presence of water, where the addition of molecular sieves to ensure anhydrous conditions can form **55** in a 99:1 ratio. On the contrary the addition of water to the reaction forms **56** in 99:1 ratio. Catalyst **55** showed very low enantioselectivity in the reduction of acetophenones. However **56** reduced a range of substituted acetophenones using FA/TEA (and the additive *i*PrNH₂) to form alcohol products in 90-99% ee.



Scheme 19. Formation of N,O and N,C chelated iridium catalysts.

1.5. Application of catalysts to the ATH of Functionalised ketones

The tethered catalyst **22** has proven to be versatile in a range of applications and to date is still employed in the ATH of functionalised ketone substrates. A recent application, by Lu and co-workers, uses this catalyst in the ATH of an intermediate to form alcohol **58** in 98% ee.⁷⁶ The alcohol product is then transformed to product **59**, an antidepressant drug. Another application is in the synthesis of Lorlatinib, an inhibitor of tumour mutations, where a key intermediate is lactone **62** that can be prepared from ketone **60** (Figure 14). From a range of enzymatic, asymmetric pressure hydrogenation and transfer hydrogenation methods to form alcohol **61** in high ee, the tethered catalyst **22** gave the best result; employed through ATH was found to form the alcohol in full conversion and 99.9% ee.⁷⁷ The method was then applied on the kg scale, forming alcohol **61** in 94% yield and 99.9% ee.

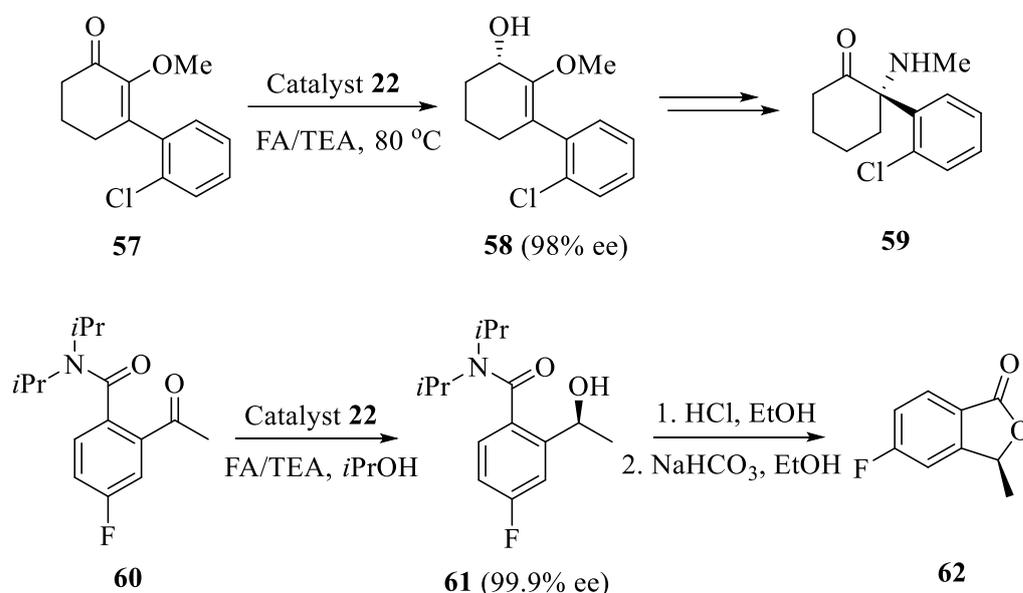
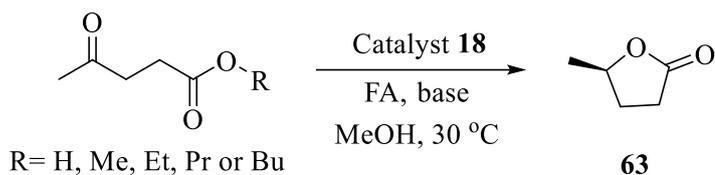


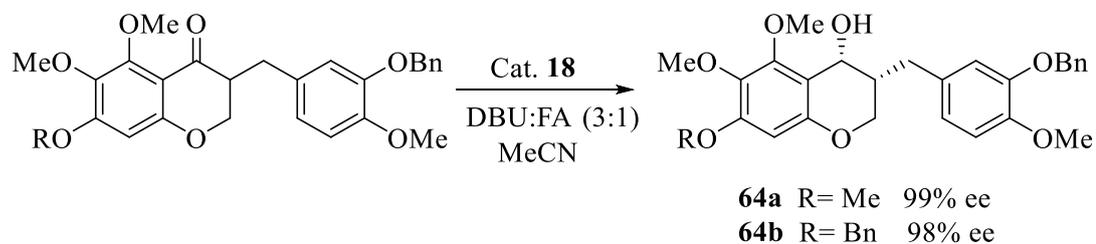
Figure 14. Applications of tethered catalyst **22** on functionalised substrates.

Bhanage and co-workers investigated the conversion of levulinic acid derivatives to enantiomerically pure γ -valerolactone **63** through ATH (Scheme 20). The *p*-cymene catalyst **18** produced the best enantioselectivity from a diverse range of catalysts containing different arenes, sulfonyls and alternative metal centres such as rhodium. The study of changing the solvent mixture from FA/TEA 5:2 to formic acid/*N*-methylpiperidine 1:1 increased the ee from 68 to 93%. The method was also found to work using ester derivatives to give products in 81-85% ee.⁷⁸



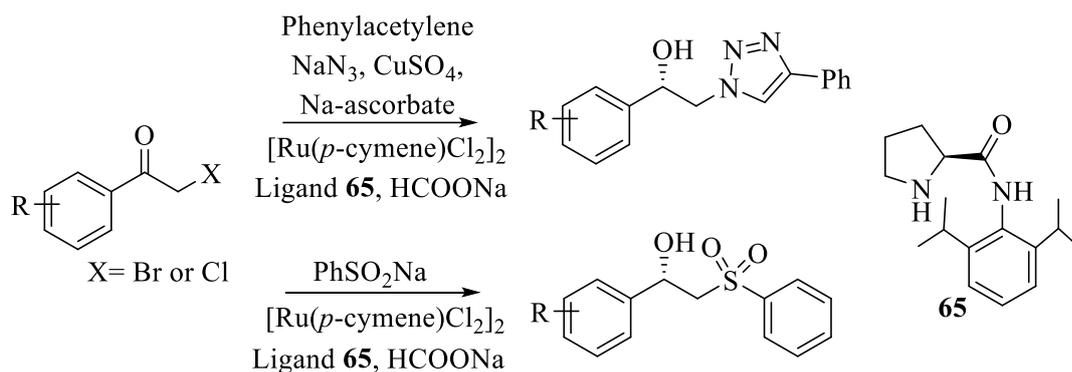
Scheme 20. Conversion of levulinic acid derivatives to (*R*)- γ -valerolactone **63**.

Seo and co-workers modified the natural products, homoisoflavanones, that portray a wide range of biological activities including anti-inflammatory and anticancer. Products containing the modifications were accessible through a dynamic kinetic resolution (DKR) of various substituted chromanone-type molecules using the Noyori-Ikariya catalyst **18** (Scheme 21). However, 30 mol% of catalyst was required for high yields, and products were obtained in 98-99% ee.⁷⁹



Scheme 21. ATH on chromanone-type molecules using the Noyori-Ikariya catalyst **18**.

A one pot synthesis of β -substituted triazole and sulfone alcohols in high enantioselectivity was demonstrated by Bhanage and co-workers.⁸⁰ The method makes use of an *in situ* formed catalyst consisting of the prolinamide **65** and [Ru(*p*-cymene)Cl₂]₂ (Scheme 22). α -Haloketones were converted to the functionalised ketone substrate prior to the ATH reaction. Kinetic studies gained insight to the one-pot transformation and indicated that there was no formation of the β -haloalcohol product during the reaction. A range of aryl groups were found to be tolerated affording the triazole alcohol products in 92-96% ee and the sulfone alcohol products in 97-99.9% ee (Table 6).

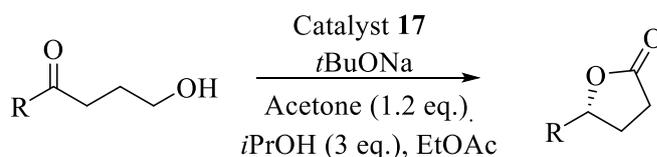


Scheme 22. ATH using the prolinamide ligand **65** on functionalised substrates.

R group	α -Triazole		α -Sulfone	
	Yield (%)	ee (%)	Yield (%)	ee (%)
Ph	90	94	83	97
4-MeC ₆ H ₄	92	93	88	99
3-OMeC ₆ H ₄	88	96	87	99.9
4-FC ₆ H ₄	84	92	90	97
1-naphthalene	95	93	93	98
2-naphthalene	93	95	92	97

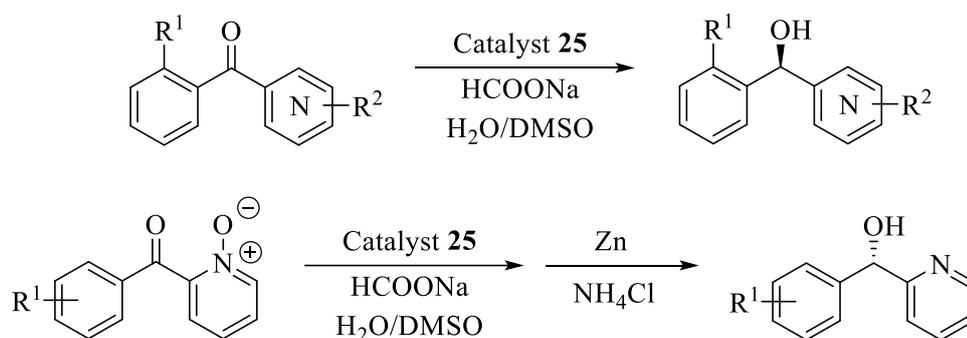
Table 6. Reduction results from the one-pot reaction using prolinamide ligand **65**.

Dong and Murphy found that the mesitylene catalyst **17** was able to form lactone products in high ee from 1,4-keto alcohols.⁸¹ Using the reducing and oxidation capabilities of the Noyori-Ikariya catalyst, the ketone could be reduced in high enantioselectivity. Then proposed that the resultant diol could also be oxidised at the primary alcohol, forming the aldehyde intermediate. This proved to be the case, and the aldehyde then formed a hemiacetal that was dehydrogenated to the lactone product. A range of lactones were obtained in high enantioselectivity ranging from 87 to 93% ee (Scheme 23). The scope was then expanded to substituted 1,5-keto alcohols, forming a range of δ -valerolactones in high ee.



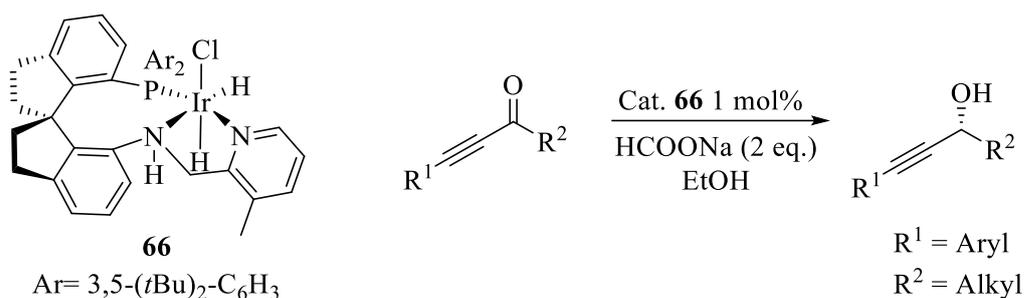
Scheme 23. Formation of lactone products from 1,4-keto alcohols.

An efficient method to asymmetrically reduce aryl *N*-heteroaryl ketones in high ee has been developed by Jiang *et al.* using oxo-tethered catalyst (*S,S*)-**25**.⁸² Initially, the ATH of *ortho*-substituted aryl *N*-heteroaryl ketones was investigated. For substrates containing the *N*-heteroaryl 2-pyridyl, a series of R¹ groups are tolerated in the *ortho* position, forming products in 93.3-97.7% ee (Scheme 24a). However lower enantioselectivity was observed when a 3- or 4-pyridyl group is in place as the *N*-heteroaryl. Other *N*-heteroaryls such as quinoxaline and isoquinolines formed products in 70-97% ee. To expand the substrate scope to non-*ortho* substrates, Jiang adapted the methodology to reduce *N*-oxide-pyridyl ketones (Scheme 24b). Substrates containing phenyl and *meta* and *para*-substituted aryl groups were reduced in 97.8-99.9% ee in the presence of the *N*-oxide in the substrate. Subsequently, the *N*-oxide was deoxygenated to form the desired alcohol products.



Scheme 24. ATH of aryl *N*-heteroaryl ketones using DENE (*S,S*)-**25**. Top scheme (a): ATH of *ortho*-substituted aryl *N*-heteroaryl ketones. Bottom scheme (b): ATH of non-*ortho*-substituted aryl *N*-oxide-heteroaryl ketones and subsequent deoxygenation.

Zhou has previously reported a tridentate Ir-complex for the asymmetric transfer hydrogenation of acetophenones.⁸³ A slight modification to this catalyst on the pyridine to form the catalyst **66**, was effective for reducing alkynyl ketones in high enantioselectivity.⁸⁴ The catalyst, in sodium formate and ethanol, hydrogenates 4-phenylbut-3-yn-2-one at the carbonyl to give the alcohol product in 97% ee (Scheme 25). Interestingly EtOCO₂Na is formed as a by-product from the reaction and has been reported as promising for applications in other fields. The catalyst can also be recovered and the recycling shows that this complex retains its catalytic activity.



Scheme 25. Tridentate Ir-complex **66** in the ATH of alkynyl ketones.

Rhodium(III)/(Cp*) complexes with TsDPEN ligands, that are isoelectronic to the Ru(arene)/TsDPEN, were first reported by Blacker and Mellor in the ATH of ketones.⁸⁵ Later Wills *et al.* formed a benzyl tethered rhodium catalyst that in some cases gives better enantioselectivity than ruthenium-based catalysts. Catalyst **67** was applied to a range of imines and worked specifically well with a dihydroisoquinoline being reduced in 87% ee.⁸⁶ Applying this to α -substituted ketones containing ether and amine groups gave products in 92 and 98% ee respectively. Ratovelomanana-Vidal *et al.* later modified the catalyst with the introduction of the methoxy group on the benzyl functionality to give catalyst **68** (Figure 15).⁸⁷ This catalyst was reported to have higher activity than the parent catalyst **67** reducing acetophenone in full conversion in 5 h as opposed to 10 h, at 0.5 mol% of catalyst. Application of the catalyst to a range of aryl ketones gave products in 70-99% ee. A more recent application of catalyst **68** has been in the reduction of β -keto- γ -acetal enamides.⁸⁸ Ratovelomanana-Vidal found the catalyst to be chemoselective for the C=O over the C=C bond. A range of β -keto enamides were also reduced using the catalyst **68** in FA/TEA to form alcohol products in 94-99% ee.

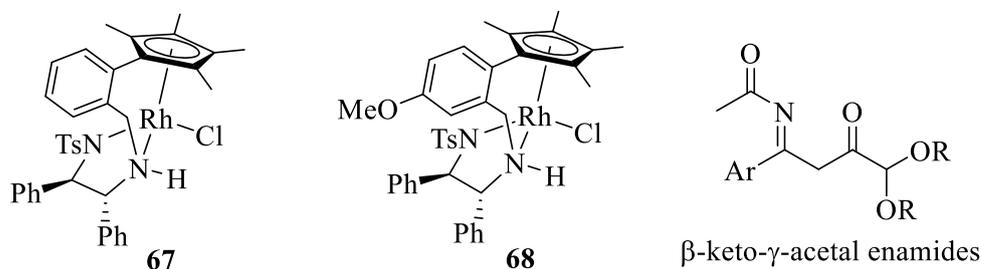


Figure 15. Structure of Rhodium catalysts by Wills and Vidal and basic structure of β -keto- γ -acetal enamides.

Wills *et al.* also investigated the ATH on 1,3-dialkoxy/aryloxy propan-2-ones with tethered catalyst **22** (Figure 16), as well as both substituted aryloxy vs aryloxy groups. Generally, substrates containing *ortho*-groups on the aryloxy give alcohol products in higher ee than those without *ortho*-groups; with an *ortho*-NHtBoc group providing products in 46-68% ee.⁸⁹ The transition state was proposed to form a stabilising interaction between the η^6 -arene in the catalyst and an electron-rich oxygen of the substrate. This also accounts for the observation that *ortho*-groups provided products of higher enantioselectivity by being sterically hindering and forcing these to position in a distal position from the η^6 -arene of the catalyst. Additionally, substrates containing other phenolic groups gave products in 0 to 46% ee.

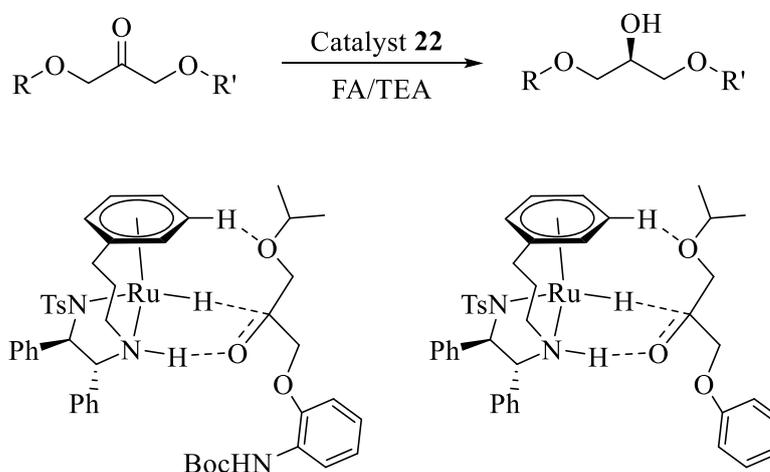
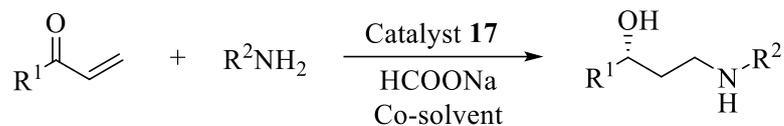


Figure 16. ATH of 1,3-alkoxy/aryloxy propan-2-ones and proposed transition states.

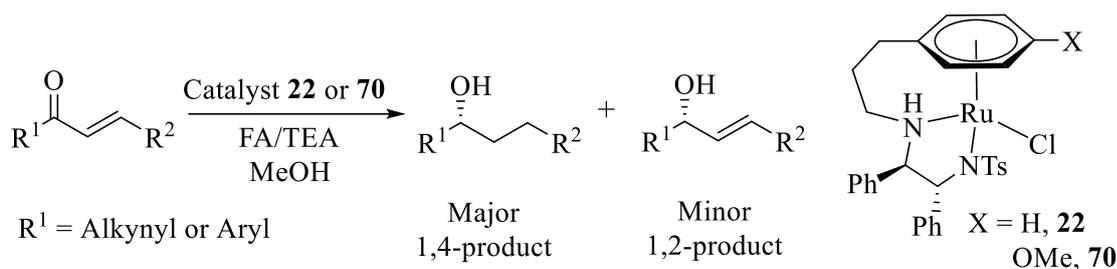
Later Wills presented a solution to obtaining the aryloxy/alkoxy alcohol products in higher ee. The incorporation of a phenyl sulfone in the α -position to the ketones was found to form products in high enantioselectivity, the cyclohexyl alcohol as in **69a** was obtained in 87% ee (Figure 17).⁹⁰ The sulfone was proposed to adopt the position distal to the η^6 -arene and thus allow other groups, such as alkoxy groups, to position themselves adjacent to the η^6 -arene of the catalyst in the reduction step, as confirmed by X-ray crystallography of the products. With these results, the sulfone directing effect was integrated into ATH/DKR studies which gave the alcohol products in both high dr and ee, an example being alcohol **69b**. The cleavage of the sulfone with Mg(0) yielded the alcohol products in high ee, such as **69c** formed in 99% ee, which is a significant improvement over the direct reduction method (Figure 16) which formed the alcohol product in only 30% ee.



R¹	R²	Time (h)	Yield (%)	ee (%)
Ph	Ph	2	95	95
Ph	4-ClPh	2	83	94
Ph	3-ClPh	2	85	94
Ph	2-ClPh	2	88	94
Ph	4-NO ₂ Ph	5	73	96
Ph	3-OMePh	2	94	95
4-FPh	Ph	5	92	90
4-NO ₂ Ph	Ph	5	86	81
Thienyl	Ph	4	90	98
Ph	Me	10	79	96
Ph	Et	12	81	97
Ph	<i>n</i> Bu	12	80	99

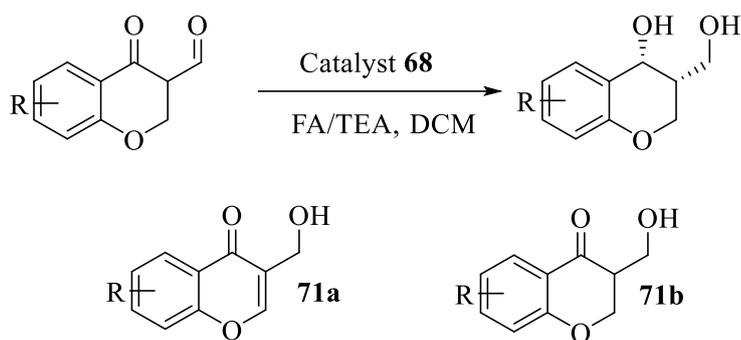
Table 7. One pot transformation of optically active γ -amino alcohols.

The ATH of α,β -unsaturated ketones can be a challenging area for ruthenium-based catalysts due to the formation of a mixture of products including 1,2 and 1,4 reduction products. Some notable reductions of α,β -unsaturated ketones have previously been reported by Deng⁹² and Wills.⁹³ More recently the tethered catalysts **22** and **70** have been found to be highly selective for the 1,4-product in the reduction of α,β -unsaturated ketones (Scheme 26).⁹⁴ For aryl ketones (R^1 is aryl), the 1,4-products were formed in ratios 94:6 to 100:0 and high enantioselectivity of up to 98% ee. For the series of ketones where R^1 is an alkyne the selectivity decreases, however the 1,4-product remains as the major product and was formed in up to 99% ee.



Scheme 26. ATH of α,β -unsaturated ketones with tethered catalysts predominantly forming 1,4-products.

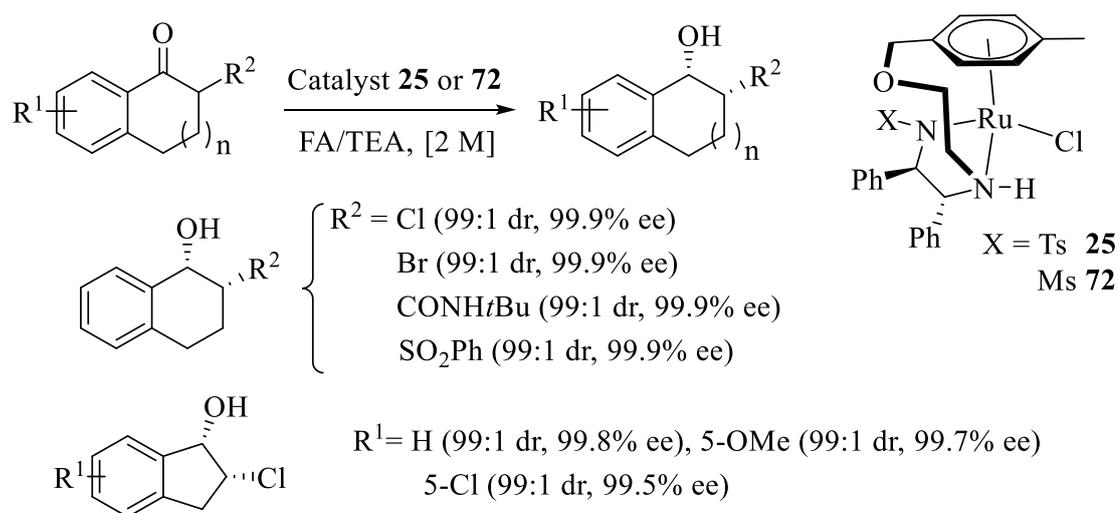
ATH catalysts have also been used in the DKR of ketones. Ratovelomanana-Vidal *et al.* employed the rhodium catalyst **68** in a rhodium-catalysed asymmetric transfer hydrogenation of 3-formylchromones.⁹⁵ Catalyst **68** provided the best dr and ee, 97:3 and 99%, in the ATH of 3-formylchromone from a series of catalysts. The substrate scope of the chromanones was expanded with various electron-donating and electron-withdrawing groups on the phenyl ring forming *cis*-diol products in high dr and ee; up to 98:2 and 99% respectively (Figure 18). Reactions monitored through ¹H NMR show the reduction of the aldehyde and C=C bond to be faster than the ketone reduction, where intermediates **71a** and **71b** are observed during the reaction. The product **71b** was found to be racemic and therefore supports the idea that the desired product is formed through a DKR reaction.



$R = \text{H (98:2 dr, 99\% ee), 6'-Me (97:3 dr, 99\% ee), 7'-F (97:3 dr, 99\% ee)}$
 $6'\text{-iPr (97:3 dr, 99\% ee), 6',8'\text{-diCl (94:6 dr, 97\% ee)}$

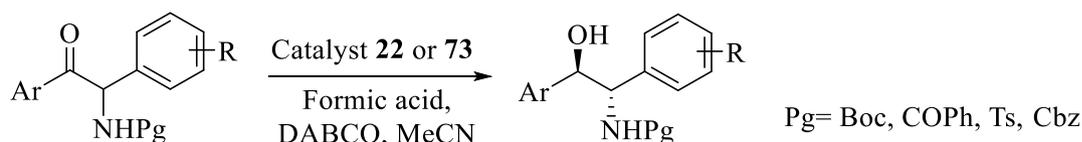
Figure 18. DKR of 3-formylchromones with examples and intermediates **71a** and **b** detected by ¹H NMR.

Kayaki *et al.* recently reported the ATH of α -substituted benzocyclic ketones through DKR using DENEBC catalysts **25** and **72** (Scheme 27).⁹⁶ The ATH of 2-chlorotetralone resulted in formation of the corresponding *cis*-alcohol product in 99:1 dr and 99.9% ee using either catalyst **25** or **72**. The substrate scope for α -haloketones was expanded through the ATH of various substituted aromatic groups which formed the corresponding halo alcohol products in 78 to 99.9% ee. In a further investigation, the ATH was applied to α -ester, amide and sulfone groups delivering *cis*-products in 96-99.9% ee.



Scheme 27. ATH of α -substituted benzocyclic ketones through DKR and examples.

Wills *et al.* have reported the ATH of α -amino ketones through DKR with varying *N*-protected groups using a series of catalysts (Scheme 28).⁹⁷ It was found that the fluorinated catalyst **73** gave higher enantioselectivity with substrates containing an *N*-Boc protecting group; up to 99% ee. On the other hand, the tethered catalyst **22** performed best with substrates containing an *N*-Ts protecting group, forming amino alcohol products in up to 99% ee. The ATH reactions proceed with the preferential formation of the anti-diastereoisomers. With the proposed transition state (Figure 19) stabilised by hydrogen bonding between the amine and sulfonyl and the CH- π interaction between the η^6 -arene and the aromatic group adjacent to the amine functionality.



Scheme 28. Reaction scheme for ATH of α -amino ketones through DKR. Catalyst 1.5 mol%, formic acid 3 eq., DABCO 5 eq., MeCN and [S] = 0.1 M.

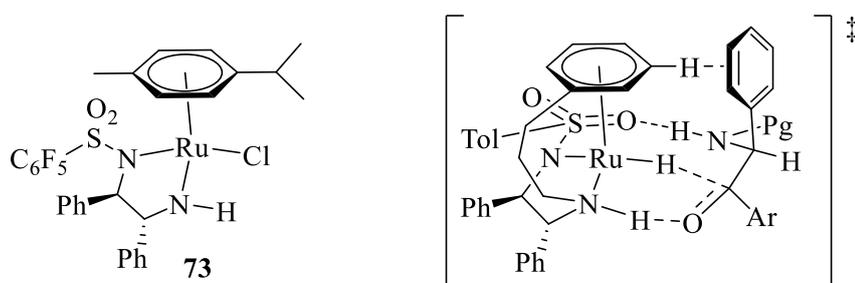
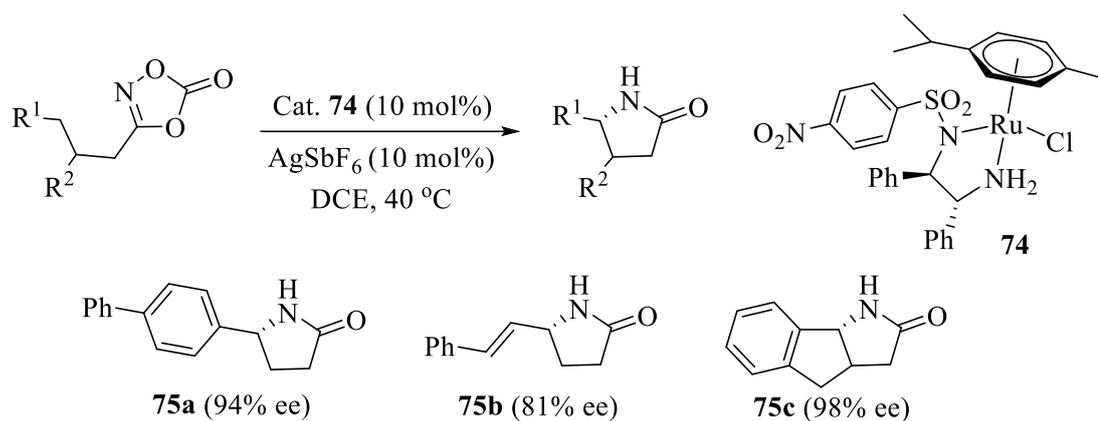


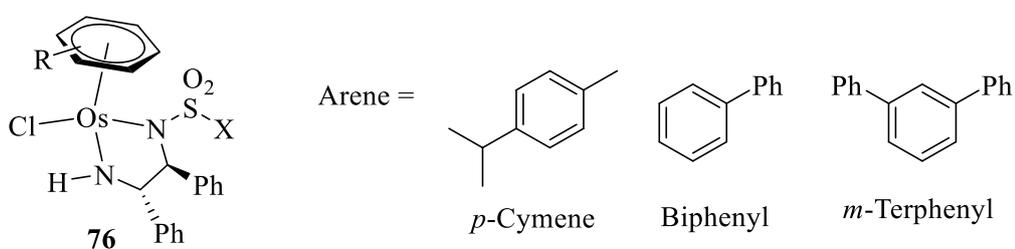
Figure 19. Structure of catalyst **73** and proposed transition state between tethered catalyst **22** and substrate.

Noyori-Ikariya catalysts have also proven resourceful in other enantioselective applications; one example is the enantioselective formation of γ -lactams. Yu applied catalyst **74** to the chemoselective γ -C-H bond amidation of dioxazolones for the formation of γ -lactams in high ee (Scheme 29). Where the nitro group of the sulfonyl on **74** showed the best enantioselectivity from a range of sulfonyl groups tested.⁹⁸ Different aromatic groups on R¹ were tested giving the lactam products in high yield and high ee of 78-98%, with the more electron-withdrawing groups leading to products in higher ee. The substrate scope was extended to alkynes and alkene groups at R¹ which in turn had detrimental effects on the enantioselectivities. Despite this, some substrates were reduced in high ee such as **75b** which was formed in 81% ee. Furthermore, a fused ring linking R¹ and R² as in **75c**, was tolerated and this gave the corresponding product in 98% ee and 20:1 dr.



Scheme 29. Enantioselective formation of γ -lactams and selected examples.

Osmium-based catalysts for ATH containing a mixture of different arenes and sulfonyl groups were introduced by Sadler *et al.*⁹⁹ Catalysts **76a-g** were applied to the ATH of acetophenone, forming the corresponding alcohol products in 95-99% ee (Table 8). All of the osmium complexes revealed higher reaction rates in the ATH of acetophenone than that of the ruthenium catalyst **18**. A further application of the osmium catalysts showed them to be highly enantioselective in the reduction of pyruvate, a key intermediate in metabolic pathways. Such catalysts also demonstrated anticancer selectivity towards cancer cells which in turn undergoes the ATH of pyruvate leading to cell death.



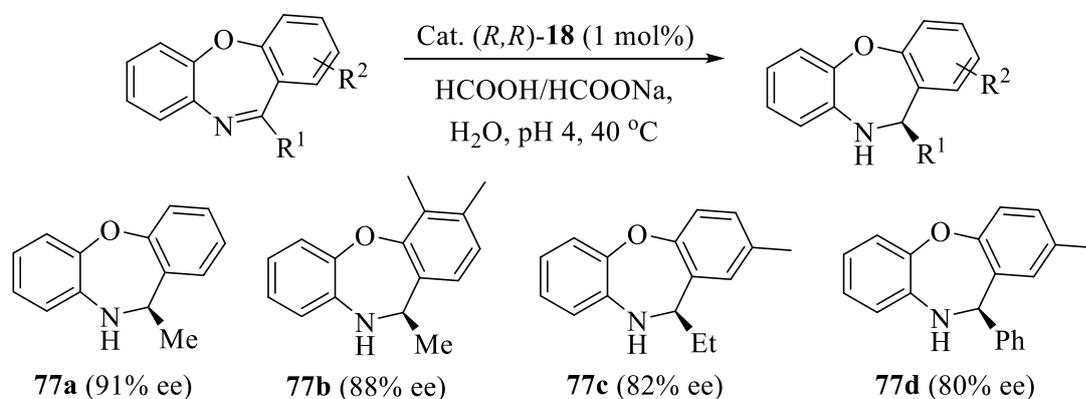
Catalyst	Arene	X	Conv (%)	ee (%)
76a	p -Cymene	4-MePh	99	99
76b	p -Cymene	Methyl	99	96
76c	p -Cymene	4-NO ₂ Ph	99	95
76d	p -Cymene	4-FPh	99	96
76e	p -Cymene	Ph	92	97
76f	Biphenyl	4-MePh	99	95
76g	m -Terphenyl	4-MePh	95	94

Table 8. ATH of acetophenone using osmium catalysts **76a-g**. Reduction in FA/TEA, Catalyst = 0.5 mol%, [S] = 1.4 M.

1.6. ATH of Imines

The reduction of imine substrates through ATH has proven to be more challenging in comparison to the ATH of ketones using ruthenium bifunctional catalysts. This section features a range of imine ATH reactions.

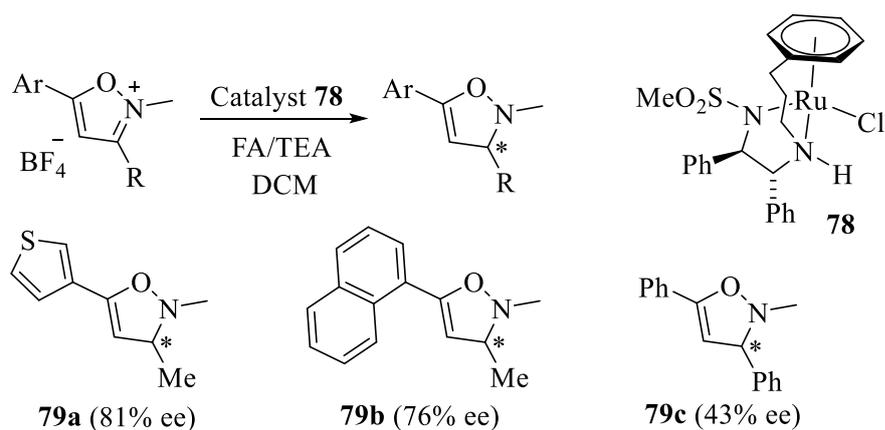
Bhanage and More studied the catalysis of **18** in the ATH of dibenzo[b,f][1,4]oxazepines substrates.¹⁰⁰ The reactions of these substrates were found to be dependent on the pH of the reaction, where a pH greater than 5 causes the conversion to decrease drastically. In contrast, at a pH of 4 using a formic acid/sodium formate mixture, conversions reached up to 99% and afforded the amine product in up to 93% ee (Scheme 30). A range of substrates, where R¹ = Me, was studied with substituted, R², aryl rings, forming the amine products in 85-91% yield and 71-93% ee. Substrates where R¹ = Et in turn produced products of 80-82% ee, whilst R¹=Ph gave 80% ee (Scheme 30).



Scheme 30. ATH of dibenzo[b,f][1,4]oxazepines.

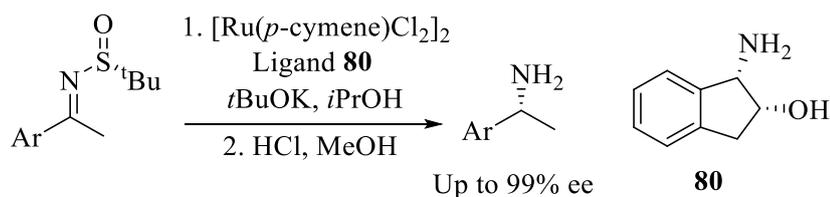
Transfer hydrogenation of aromatic nitrogen heterocycles is more challenging because the aromaticity is broken in the process. Some examples of transfer hydrogenation has been achieved by the formation of activated aromatic compounds, such as pyridinium and quinolinium salts.^{101,102} These types of salts have been useful in the asymmetric pressure hydrogenation of quinolinium and isoquinolinium substrates.¹⁰³ Wills and Chew have demonstrated an asymmetric transfer hydrogenation of isoxazolium salts.¹⁰⁴ *N*-Methylated isoxazolium salts (Scheme 31) where R = Me and

Ar represents aromatic groups, were reduced asymmetrically. The MsDPEN tethered catalyst **78** was found to be the best from a series of catalysts and formed the dihydroisoxazole products in 62-81% ee, e.g. **79a** and **79b**. The mechanism for the transformation is not fully understood however the transition state is most likely to form a favourable interaction between the η^6 -arene of the catalyst and the aromatic group of the substrate. This is supported by the observation that when the R group is a phenyl (**79c**) this causes the enantioselectivity to decrease from 78% to 43% ee in comparison to the methyl analogue.



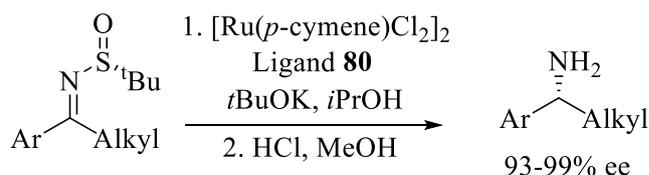
Scheme 31. ATH of *N*-Methylated isoxazolium salts and examples.

The ATH of *N*-(*tert*-butanesulfinyl)imines has proven an effective method to obtain primary amines in high ee. Yus *et al.* employed the amino alcohol **80** with $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ for the diastereoselective ATH of *N*-(*tert*-butanesulfinyl)imines, forming the intermediates in high diastereoselectivities.¹⁰⁵ The intermediates are subjected to an acidic cleavage of the sulfinyl group, forming the primary amine products in high ee (Scheme 32). Preliminary studies have found the aminoalcohol **80** to provide the best diastereoselectivity from a range of amino alcohol ligands tested, when using $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ in KOH. However, the amines were produced in low yields; the reason is due to the formation of water from using KOH, which is able to hydrolyse the imines to the ketone analogues. The optimal conditions were later found to be using *t*BuOK as the base, 20 mol% of ligand and 5 mol% of the ruthenium complex.



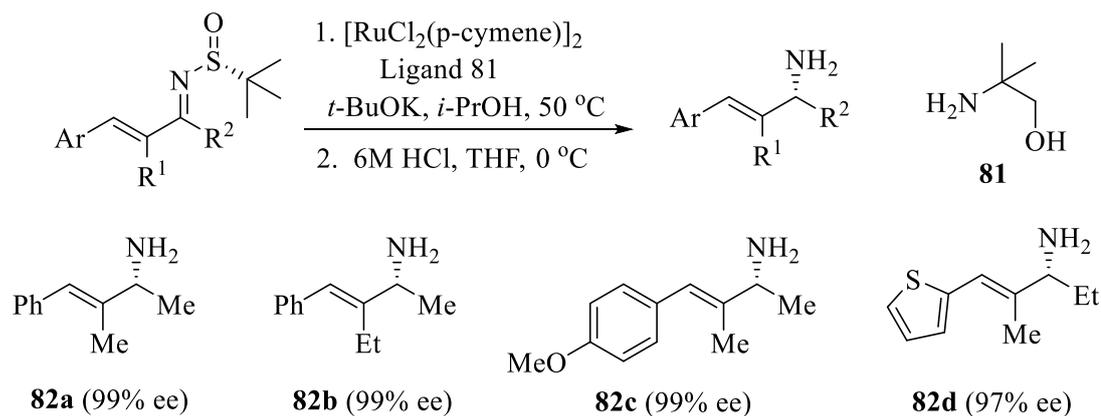
Scheme 32. Diastereoselective ATH of *N*-(*tert*-butanesulfinyl)imines to primary amines.

A follow up study has explored the ATH system on a range of *N*-(*tert*-butanesulfinyl)imines.¹⁰⁶ The methyl group of the substrate was changed for longer alkyl chains to give substrates that were reduced in 98-99% ee and an α -chloro acetophenone was also reduced in 99% ee (Scheme 33). A series of substituted phenyls, including electron donating and withdrawing groups also gave products in high enantioselectivity. Other aromatic derivatives could be tolerated, forming the amine products in 93-99% ee.



Scheme 33. Diastereoselective ATH of *N*-(*tert*-butanesulfinyl)imines to amines.

Guijarro *et al.* applied the amino alcohol ligand **81** to the diastereoselective transfer hydrogenation of α,β -unsaturated *N*-(*tert*-butylsulfinyl) ketimines which were then converted to allyl amines by removal of the sulfinyl group (Scheme 34).¹⁰⁷ Different aromatic groups were tolerated in the case where R¹ and R² are alkyl, the unsaturated amine products formed in 97-99% ee. Some combinations of groups at R¹ and R² were not compatible with the catalytic system and formed mixtures of saturated and unsaturated products. Additionally when Ar and R¹ are phenyl groups and R² is methyl then the α,β -unsaturated amine formed in greater than 99% ee.



Scheme 34. Diastereoselective ATH of α,β -unsaturated N -(*tert*-butanesulfinyl)imines to allylic amines, some examples are displayed.

Noyori *et al.* first reported the use of ruthenium-based catalysts in FA/TEA for the ATH of imines.¹⁰⁸ Catalyst **18** was found, from a series of catalysts, to asymmetrically reduce the salsolidine precursor to salsolidine **84a** in 99% yield and 95% ee (Figure 20). The use of triethylamine is crucial in the reaction as no reduction product is obtained when only formic acid is used. The tolyl group of the catalyst was changed to a 2,4,6-triisopropylbenzene, catalyst **83**, for the reduction of **84b** in high enantioselectivity; a product of 90% yield and 95% ee was formed. Expansion of the study to the indole **85a** with catalyst **18** resulted in formation of the amine product in 86% yield and 97% ee. The presence of an aromatic group as in **85b** did not affect the enantioselectivity, forming the corresponding amine in 83% yield and 96% ee.

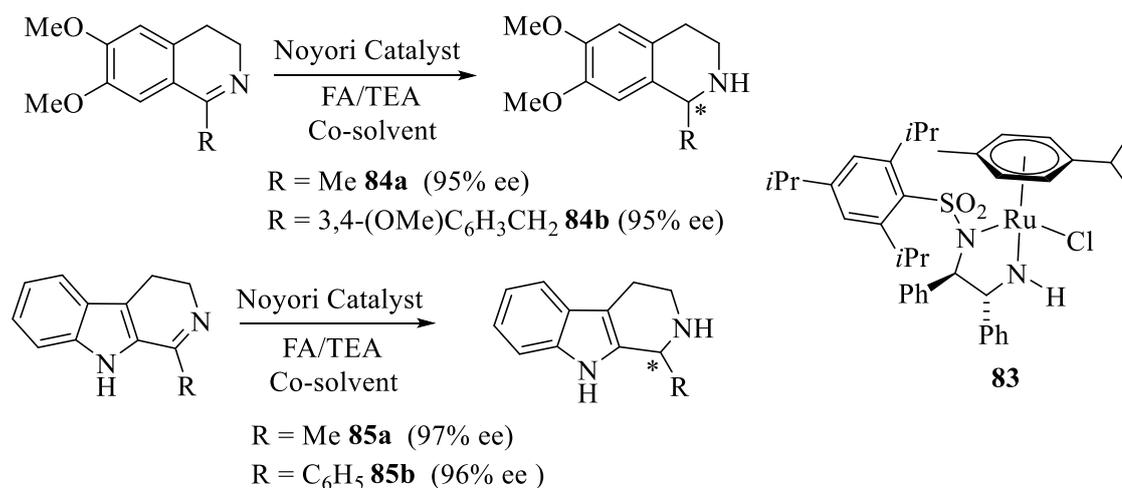
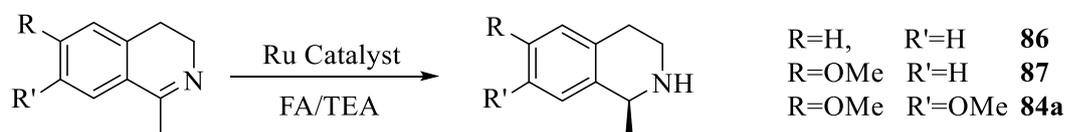


Figure 20. ATH of imines; amines **84**, **85a** and **85b** were obtained from ATH with catalyst **18**. Amine **84b** from ATH with catalyst **83**.

Červený *et al.* investigated the differences in reactivity between Noyori-Ikariya catalysts on three different substituted 3,4-dihydroisoquinolines (DHIQ) (Table 9). The results demonstrate that substrates containing the more electron-rich fused rings of the DHIQ are reduced in much higher ee and have shown faster initial rates of reaction. The benzene catalyst **16** was used to reduce **86**, a non-electron rich DHIQ, and gave a product in moderate ee of 62%. In contrast, the addition of the dimethoxy groups in **84a**, to create an electron-rich fused ring, increases the enantioselectivity of the ATH to 80% ee. A similar trend is observed with the other catalysts **17** and **18**. Červený *et al.* proposed there to be a correlation between the initial reaction rate and the enantioselectivity, where the increased initial rate of reaction produces amines in higher ee.¹⁰⁹



Catalyst	86 (ee)	87 (ee)	84a (ee)
16	62%	74%	80%
17	82%	86%	92%
18	82%	86%	94%

Table 9. ATH of substituted DHIQs with Noyori-Ikariya catalysts **16-18**.

Other work by Kačer *et al.* on the mono-methoxy and dimethoxy-DHIQs, **86** and **84a**, was reported with various catalysts in high ee through pressure hydrogenation methods. However, low enantioselectivity was observed in all cases on the ATH of 1-phenyl-3,4-dihydroisoquinoline using either catalysts **17**, **18**, **22**, **25** or other novel catalysts.¹¹⁰

1.6.1. Mechanism of Imine ATH

Wills *et al.* also reduced the salsolidine precursor **84a** with the *N*-alkylated catalysts **32** (Section 1.4.3.) and the configuration of the major product formed in each case was the *S*-enantiomer.⁶⁰ The same configuration has also been reported in other ATH reactions with (*R,R*)-configuration catalysts. Wills *et al.* reasoned that the mode of reduction of imines is different to that of ketones, as following the ketone mode of

reduction (Figure 5) then the major enantiomer formed should have the *R*-configuration.

Kačer *et al.* investigated the mechanism of DHIQs using the *p*-cymene catalyst **18**. It was reasoned that as there is initial protonation of the imine then the possibility of a six-membered pericyclic transition state is eliminated and therefore the reaction requires a transition state where only a hydride is transferred to the substrate.¹¹¹ An interaction between the protonated imine and the sulfonyl (N-H/O=S) is deemed highly important in the transition state. Also, a further stabilising CH/ π interaction from the η^6 -arene and the electron rich ring of the DHIQ is proposed to exist (Figure 21). In the case of the catalyst **18**, four different CH/ π interactions are possible due to rotation of the arene ligand. A computational study showed the two modes of stabilisation C(sp³)H/ π or C(sp²)H/ π , to have the lowest single-point energy but that the C(sp²)H/ π interaction is favoured due to its lower Gibbs free energy.

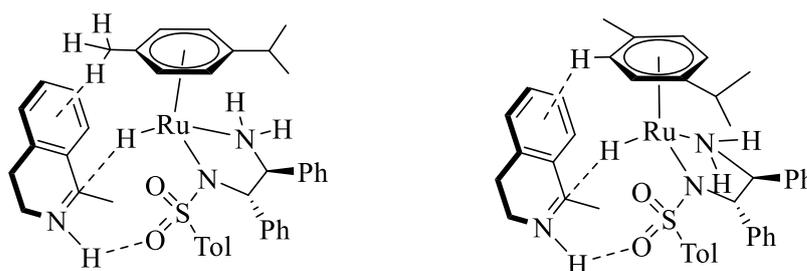


Figure 21. Proposed transition states in the ATH of **86** using the catalyst **18**.

In another computational study by Kačer *et al.*, the mechanism for the ATH of acetophenone-*N*-benzylimine was investigated.¹¹² These types of imines exist as both *E* and *Z* isomers with the equilibrium shifted towards the *E* isomer, in a 94:6 ratio. The computed ATH of these substrates also shows the existence of an interaction between the protonated imine and the sulfonyl of the catalyst, N-H/O=S interaction. The findings present the single-point energy of the favoured TS for the *E* isomer (Figure 22) to be similar to that of the favoured TS for the *Z* isomer. The *E* isomer then delivers the *S*-amine product and the *Z* isomer forms the *R*-amine product predominantly explaining the difficulties of achieving high ee in these types of imine reductions. In comparison, the nature of the endocyclic CN bond found in dihydroisoquinolines suggests that there is no isomerisation thus DHIQs are more compatible substrates for obtaining amine products in high ee using ruthenium-based ATH.

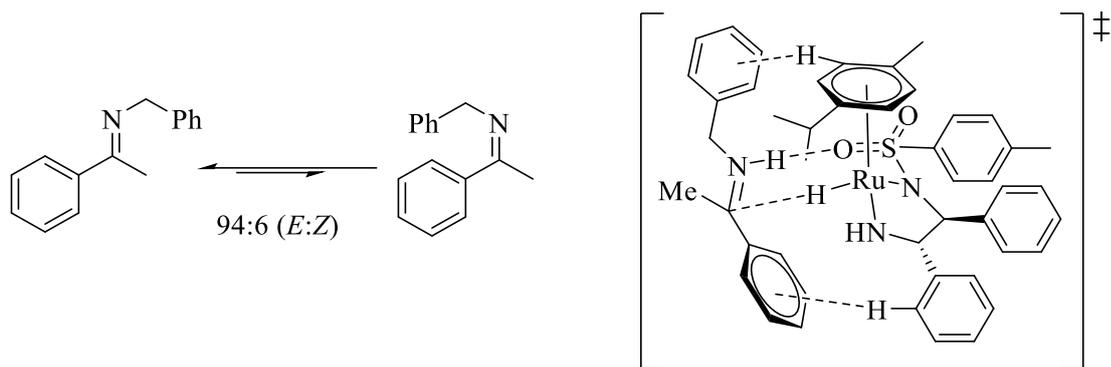


Figure 22. Acetophenone-*N*-benzylimine *E/Z* isomers and favoured transition state for the ATH of *E* isomer.

Kouznetsov and Puerto applied the catalyst **18** to the ATH of the imine intermediates, 1-arylethyl-6,7-dimethoxydihydroisoquinolines, in the total synthesis of *Dysoxylum* alkaloids.¹¹³ The ruthenium-catalysed induction is affected by using sodium formate as a hydrogen source and the amine products were obtained in ee of 88-97%. The amines products formed are prone to racemisation but this can be overcome by subsequent methylation which in turn forms the desired *Dysoxylum* alkaloids. A similar transition state to those reported by Kačer was proposed for the asymmetric transformation where a crucial N-H/O=S interaction is present between the protonated amine and oxygen of the sulfone (Figure 23). The CH/π interaction in this example however is proposed to arise from the proton at the isopropyl.

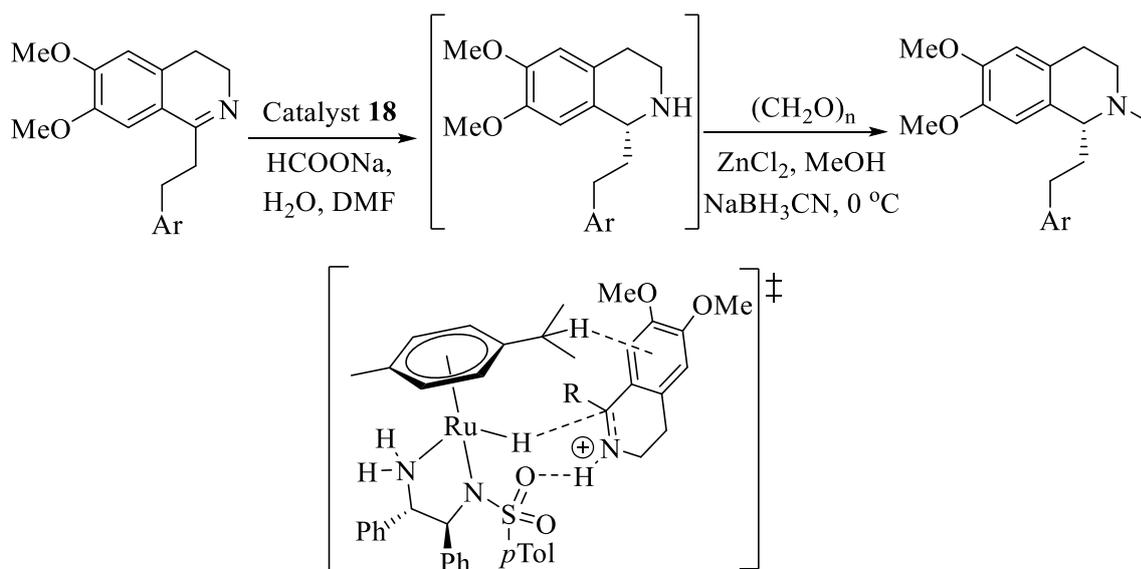
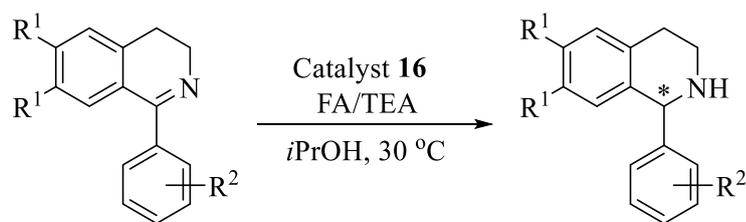


Figure 23. ATH of 1-arylethyl-6,7-dimethoxydihydroisoquinolines and subsequent *N*-methylation. Proposed transition state for the transfer hydrogenation of the imines.

1.6.2. ATH of 1-aryl-3,4-dihydroisoquinolines

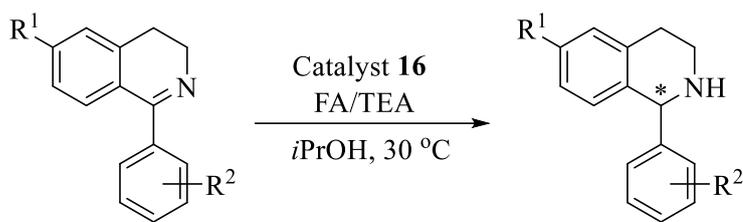
Noyori *et al.* were first to investigate the ATH of a 1-phenyl-dihydroisoquinoline derivative with ruthenium catalysts, forming the corresponding amine product in 84% ee. Ratovelomanana-Vidal *et al.* later investigated the ATH of 1-aryl-3,4-dihydroisoquinoline derivatives with ruthenium-based catalysts. Catalyst **16** gave the best enantioselectivity in the ATH of the 1-phenyl-3,4-dihydro-6,7-dimethoxy isoquinoline, 82% ee, from a range of ruthenium catalysts bearing different arenes and including rhodium and iridium analogues.¹¹⁴ Optimal conditions for the ATH were obtained by employment of FA/TEA as the hydrogen source and iPrOH as a co-solvent. Under these conditions, a series of aryl-DHIQs were reduced (Table 10). Substrates where R¹ is one or more OMe's reduced imines in high yields and enantioselectivity of 82-99% ee. The best enantioselectivity was observed with *ortho*-substituted aryl groups at the DHIQ 1-position, forming products in 96-99% ee. Substrates with no substituent on the fused-ring, i.e. R¹ = H, also work well with the inclusion of an *ortho*-substituent on the 1-aryl ring as these gave the amine products in 90-92% ee. The effect is attributed to the steric hinderance which distorts the coplanarity of the 1-aryl ring with the C=N double bond and was first reported by Vedejs *et al.* where a range of *ortho*-substituents were also found to provide high enantioselectivity in the ATH of 1-aryl-3,4-dihydroisoquinolines.¹¹⁵



R ¹	R ²	Yield (%)	ee (%)	R ¹	R ²	Yield (%)	ee (%)
OMe	Ph	82	82	OMe	2,4-di-OMePh	85	96
OMe	3-MePh	90	84	OMe	1-Naph	86	98
OMe	3-BrPh	90	82	OMe	2-FPh	97	96
OMe	3-ClPh	93	83	OMe	2-ClPh	93	98
OMe	4-OMePh	92	91	OMe	2-BrPh	91	98
OMe	4-FPh	91	87	OMe	2-IPh	92	99
OMe	4-ClPh	94	87	H	2,4-di-MePh	75	90
OMe	2-MePh	86	98	H	1-Naph	74	90
OMe	2-OMePh	84	96	H	2-ClPh	73	92
OMe	2,4-di-MePh	83	98	H	2-IPh	72	92

Table 10. ATH of derivatives of 1-aryl-3,4-dihydroisoquinoline with catalyst **16**.

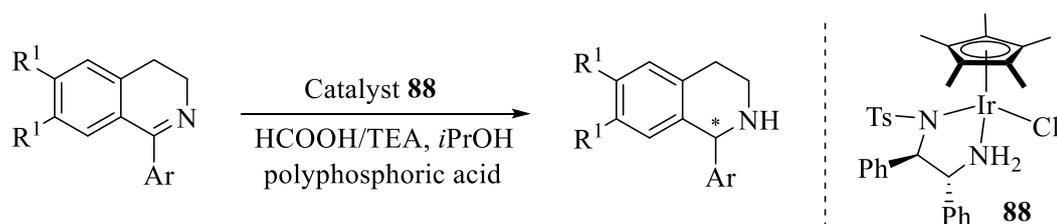
Later another study by Ratovelomanana-Vidal *et al.* applied the same catalyst and conditions to the ATH of a series of non-electron rich dihydroisoquinolines.¹¹⁶ The substrates containing non-substituted fused rings ($R^1 = H$) and 1-*ortho*-substituted aryls were reduced in 79-94% ee (Table 11). Substrates without *ortho* groups had detrimental effects on the enantioselectivity; a substrate containing a 1-phenyl ring was reduced in just 29% ee and the *meta/para* substituted derivatives were reduced in little higher selectivities of 33-39% ee. The introduction of a methyl group to the fused ring ($R^1 = Me$) gave a substrate that also worked well with *ortho*-substituted aryl containing substrates, giving products in 79-93% ee. However poor enantioselectivity was again seen with the DHIQ substrates containing *ortho/meta*-substitutions on the 1-aryl ring; products were obtained in 27-53% ee. This again underlines the importance of having a sterically hindered group at the *ortho* position of the 1-aryl ring of DHIQ substrates in order to yield products in high ee.



R ¹	R ²	Yield (%)	ee (%)	R ¹	R ²	Yield (%)	ee (%)
H	Ph	90	29	H	4-MePh	87	36
H	2-ClPh	73	92	H	4-OMePh	89	39
H	2-BrPh	71	94	Me	2-MePh	90	93
H	2-IPh	72	92	Me	2-OMePh	82	79
H	2-Me	77	84	Me	1-Naph	92	93
H	2-OMePh	78	79	Me	3-ClPh	90	27
H	2,4-di-MePh	75	90	Me	3-MePh	85	39
H	1-Naph	74	90	Me	4-ClPh	86	53
H	3-MePh	88	36	Me	4-MePh	93	50
H	3-OMePh	93	33				

Table 11. ATH of non-electron rich 1-aryl-3,4-dihydroisoquinoline with catalyst **16**. Reductions of substrates without *ortho*-substituents are highlighted in grey.

Červený *et al.* used an [Ir(Cp*)(TsDPEN)Cl], catalyst **88**, for the reduction of 1-aryl DHIQs, using a mixture of FA/TEA with *i*PrOH. In the reduction of 1-phenyl-3,4-dihydroisoquinoline the amine product was formed in 83% conversion and 60% ee.¹¹⁷ A range of additives were tested in an attempt to increase the enantioselectivity and it was found that anhydrous polyphosphoric acid gave the best result, increasing the yield and ee to 90% and 86% respectively. The catalytic system with the additive was expanded to substrates containing various aryl groups, giving rise to products of 64–86% ee (Table 12).



R ¹	Ar	Time (h)	Yield (%)	ee (%)
H	Ph	3	90	86
H	4-NO ₂ Ph	3	90	64
H	4-CF ₃ Ph	6	79	73
H	4-OMePh	3	92	79
H	4-MePh	3	87	83
H	4-BrPh	3	86	76
H	4-CO ₂ MePh	3	90	77
H	3-CF ₃ Ph	18	77	80
H	3,4,5-tri-OMePh	6	90	85

Table 12. ATH of 1-aryl-DHIQs with catalyst **88** and anhydrous polyphosphoric acid.

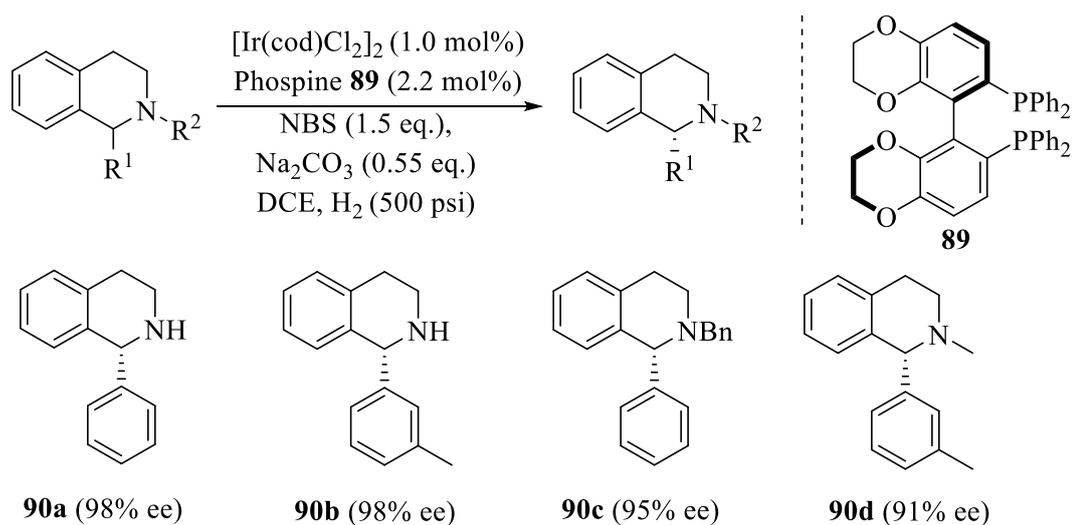
The iridium catalyst **88** however has a limited substrate scope and is less compatible with the 3,4-dimethoxy-DHIQ derivatives such as the salsolidine precursor. Page *et al.* reported the unusual enantiomeric excess behaviour of salsolidine **84a**.¹¹⁸ In this reduction, the *R*-enantiomer is initially formed in greater than 80% ee however as the reaction progresses the ee decreases. This was found to be due to the formation of the *R*-enantiomer following first-order kinetics and the *S*-enantiomer following zero-order kinetics. This was also observed by Červený *et al.* in a reaction where the *R*-enantiomer initially forms in 77% ee and then decreases during the reaction to 58% ee.¹¹⁷ More surprisingly, the addition of anhydrous polyphosphoric acid to the reaction changed the overall enantioselectivity from the *R*-enantiomer in 43% ee to the *S*-enantiomer in 56% ee during the course of the reaction.

1.6.3. Other Methods to Reduce 1-Aryl-3,4-dihydroisoquinolines

Deracemisation

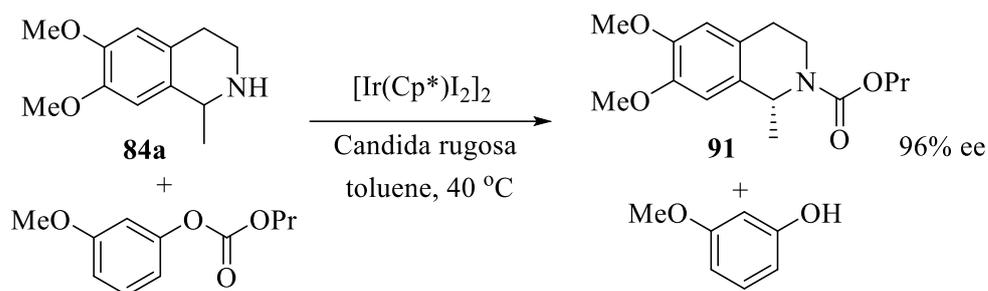
Another method for the formation of enantiopure 1-aryl-tetrahydroisoquinolines is through deracemisation methods. Zhou *et al.* reported the deracemisation of 1-phenyl-1,2,3,4-tetrahydroisoquinoline with [Ir(COD)Cl₂]₂, chiral phosphine **89**, hydrogen gas (500 psi) and the oxidant trichloroisocyanuric acid - forming the enantiomerically pure amine product **90a** in 7% ee.¹¹⁹ The change of oxidant to NBS resulted in an increase

to the enantioselectivity, with the desired product formed in in 93% ee. Zhou *et al.* reasoned the NBS to have a dual role in the transformation as an activator to the metal centre and as an oxidiser to the substrate. A series of 1-aryl-tetrahydroisoquinolines were then deracemised in 88-98% ee (Scheme 35). *N*-Alkylated, such as *N*-methyl and *N*-benzyl tetrahydroisoquinolines, were also tolerated with the catalytic system forming products in 86-95% ee.



Scheme 35. Deracemisation of dihydroisoquinolines by $[\text{Ir}(\text{cod})\text{Cl}_2]_2$ and phosphine **89** with examples.

Blacker *et al.* investigated dehydrogenative racemisation of optically active amines through the use of iridium-based catalysts.^{120,121} A wide range of secondary amines were found to racemise however the use of the TsDPEN ligand on the catalyst, was found to inhibit the racemisations. From a series of amines, (*S*)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline exhibited the fastest rate of racemisation. The DKR of this substrate was then studied through an enzymatic resolution. *Candida rugosa* lipase, an enzyme capable of asymmetrically adding a propyl carbamate group, was added to the racemic isoquinoline **84a**, forming the optically active isoquinoline **110** in 86% yield and 96% ee (Scheme 36).



Scheme 36. Enzymatic deracemisation of a DHIQ.

Pressure hydrogenation

The enantioselective reduction of 1-aryl-3,4-dihydroisoquinolines have also been reported in high ee through pressure hydrogenation methods. The diphosphine **92** (Figure 24) complexed with $[\text{Ir}(\text{cod})\text{Cl}_2]_2$ was employed in the AH of *N*-alkylated iminium salts to form optically active *N*-alkyl-tetrahydroisoquinolines.¹²² An *N*-methyl derivative of the 1-phenyl-DHIQ was reduced in 99% yield and 91% ee, **95a**, through pressure hydrogenation under H_2 (1000 psi) in DCE (Scheme 37). A range of *N*-methyl substrates containing substituted phenyls were also reduced in 87-90% ee. Higher enantioselectivities were obtained through the reduction of *N*-benzyl derivatives of 1-aryl-DHIQs; the corresponding products were formed in in 93-96% ee.

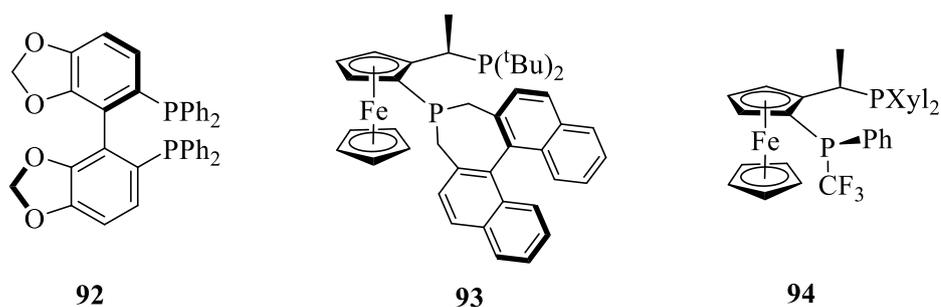
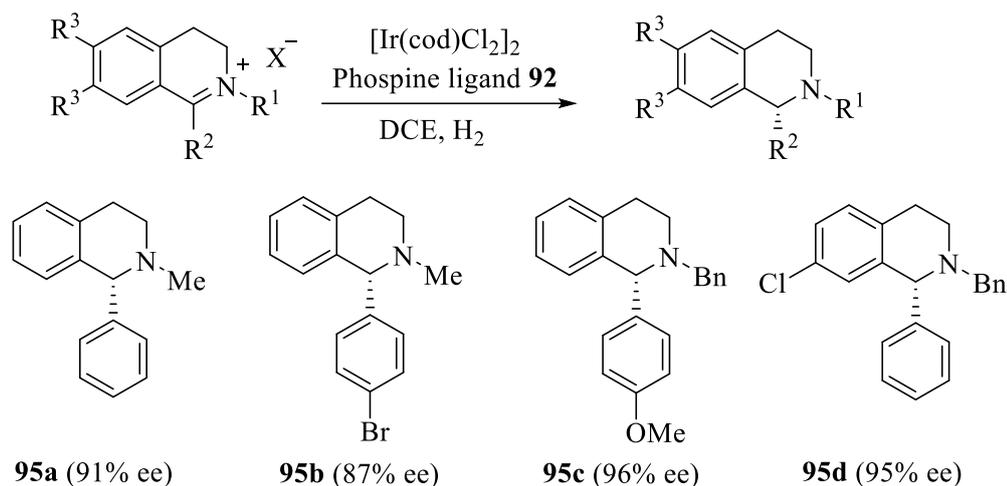


Figure 24. Structure of diphosphine ligands used in pressure hydrogenation methods.



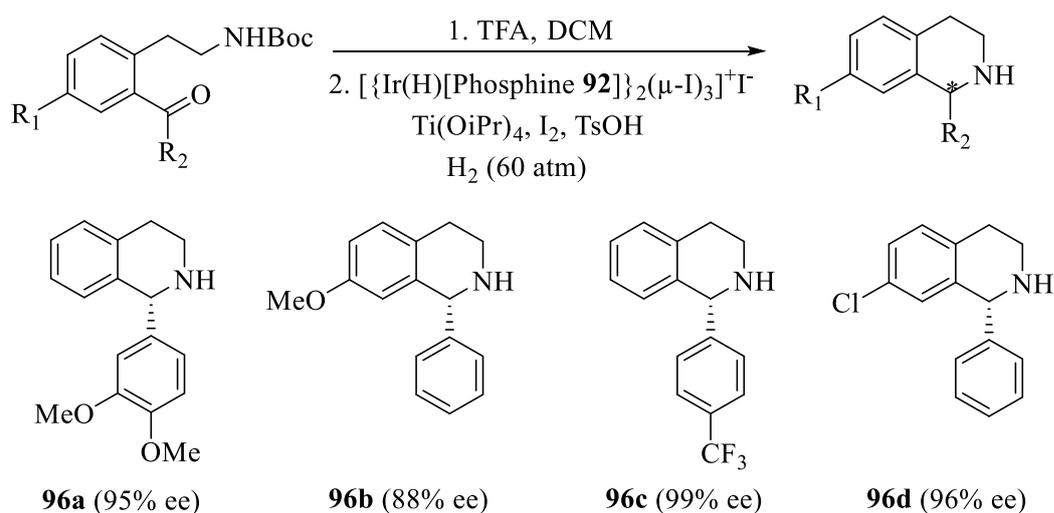
Scheme 37. General reaction scheme for AH of iminium salts with Ir-phosphines and examples.

Josiphos-type ligand **93**, in combination with $[\text{Ir}(\text{cod})\text{Cl}_2]_2$, was applied to the asymmetric hydrogenation of 1-phenyl-3,4-dihydroisoquinoline salts.¹²³ Initial reduction of the free DHIQ using H_2 (100 bar) in *i*PrOH formed the amine in 25% yield and 30% ee. However, the hydrochloride salt of the DHIQ was reduced in 99% yield and 96% ee. The method was also applied to a series of substrates containing substituted phenyl groups on the 3,4-dihydroisoquinoline salts, forming products in 89-94% ee. A series of 6,7-dimethoxy-DHIQs were less compatible, forming products in 34-57% ee. A further study has shown the importance of the counter ion of the iminium salt in the asymmetric reduction where the use of the chloride anion, from the hydrochloride-DHIQ, provides high ee, conversely a PF_6 counter ion in place of chloride creates a substrate which is reduced to the amine in just 28% yield and 12% ee.

A recent study by Zhang *et al.* on the asymmetric pressure hydrogenation of 1-aryl-3,4-dihydroisoquinolines also utilised a Josiphos-type ligand, **94**.¹²⁴ In combination with $[\text{Ir}(\text{cod})\text{Cl}_2]_2$, the catalytic system displayed turnover numbers of up to 4000 and an excellent enantioselectivity of 99% ee in the AH of 1-phenyl-3,4-dihydroisoquinoline. The use of HBr is essential in obtaining high reactivity and enantioselectivity in this catalytic reduction under 50 atm H_2 . The AH of a library of

1-aryl-3,4-DHIQ substrates gave the corresponding tetrahydroisoquinoline products in 85–99% ee.

Chang and co-workers reported the synthesis of optically active 1-substituted tetrahydroisoquinolines via an iridium-catalysed one pot *N*-deprotection and intramolecular asymmetric reductive amination (Scheme 38).¹²⁵ The iodine bridged dimeric $[\{\text{Ir}(\text{H})[(R)\text{-SegPhos}]\}_2(\mu\text{-I})_3]^+\text{I}^-$ complex was used for hydrogenations, assisted by titanium(IV) isopropoxide, iodine and *p*-toluenesulfonic acid as additives for catalyst activation. The reduction of 1-phenyl-3,4-DHIQ with the same catalyst system afforded the amine product **90a** in 97% yield and 97% ee. A range of substrates containing substituted phenyl groups were also reduced affording products in 85-99% ee.



Scheme 38. One pot *N*-deprotection and intramolecular asymmetric reductive amination with examples

1.7. Supported ATH Catalysts

The high cost of ATH complexes due to the rare-metal and chiral ligand can be a disadvantage for their use in reactions. However, immobilization of catalysts onto solid supports permits easier separation of catalysts from reaction media and also for the catalysts to be recycled. The use of solid supports is therefore considered a desirable approach, this coupled with reactions in aqueous media classifies the ATH

method as part of green chemistry. Herein a variety of applications for supported ATH catalysts are reported.

1.7.1. Polymer Supported Catalysts

Polymers have been found to be compatible as supports for Ru(arene)/TsDPEN type catalysts. The various groups found within the catalyst allows different routes to link catalysts to supports. Xiao supported a TsDPEN ligand onto polyethylene glycol through the phenyl groups of the ligand.¹²⁶ Subsequent metalation with $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ produced the supported catalyst **97** (Figure 25). Applying the catalyst to the reduction of acetophenone in FA/TEA at [S/C] of 100 gave the alcohol product in 95% yield and 94% ee. After reduction, the catalyst could be precipitated out with Et_2O and ICP analysis of the solution phase showed less than 0.7% ruthenium leaching. The catalyst could be re-used 3 times with the alcohol products formed in 99%, 95% and 56% yield and 91%, 92% and 82% ee respectively. Catalyst **97** was also applied to the ATH of a range of acetophenone derivatives, giving products in 87-94% ee.

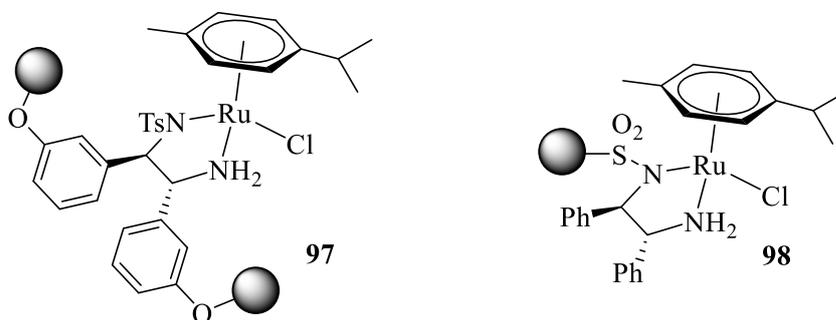


Figure 25. Structure of polymer supported catalysts **97** and **98**.

Xiao later investigated a more effective method to recycle catalyst **97**. The FA/TEA azeotrope was changed to a sodium formate and water system which gave a much faster rate of reaction in the transfer hydrogenation of acetophenone.¹²⁷ Adding Et_2O to separate out the catalyst and following ICP analysis displayed a 0.4% catalyst leaching to organic phase. An investigation into recyclability revealed that the catalyst could be reused more than 10 times without loss of enantioselectivity using the sodium formate and water system. It is thought that catalyst **97** is more stable in the aqueous phase than in FA/TEA where the catalyst is presumed to decompose more rapidly.

An alternative method to add supports can be through the sulfonyl functionality. Pericas *et al.* reacted a chlorosulfonylated polystyrene with a DPEN ligand to form the mono-sulfonylated ligand.¹²⁸ Elemental analysis of the polystyrene-DPEN product showed there was 88% of the mono-sulfonated product at a 1.01 mmol/g loading. Complexation with $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ produced the supported catalyst **98** that was assessed by gel-phase NMR. Catalytic reduction of acetophenone at an [S/C] of 150 in FA/TEA formed the alcohol product in 99% conversion and 97% ee. A range of substituted-acetophenones were also tested with the supported catalyst and these formed alcohol products in 86-99% ee. The catalyst **98** was also tested for recyclability with the first cycle forming the product in 99%, then in the second cycle 93% and in the third cycle in 80% conversion. No loss of enantioselectivity was observed but it was apparent that conversion deteriorated rapidly in later stages.

With ATH reductions in aqueous media showing promising results, Itsuno *et al.* designed an amphiphilic polymer support. Aromatic quarternary ammonium sulfates, acting as hydrophilic groups, were polymerised with a sulfonylated DPEN and divinylbenzene producing the chiral amphiphilic support **99**.¹²⁹ Acetophenone reductions at an [S/C] of 100 in sodium formate and water were carried out with different cross-linking degrees and $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$. The best result was obtained when $l = 0.1$, $m = 0.1$ and $n = 0.8$ (Figure 26) which gave the alcohol product after 3 hours in 100% conversion and 98% ee. The metal centre was also changed and the polymer **99** was reacted with both $[\text{Rh}(\text{Cp}^*)\text{Cl}_2]_2$ and $[\text{Ir}(\text{Cp}^*)\text{Cl}_2]_2$. The rhodium derivative was found to give similar results to ruthenium however the iridium catalyst caused both a reduction in activity and enantioselectivity.

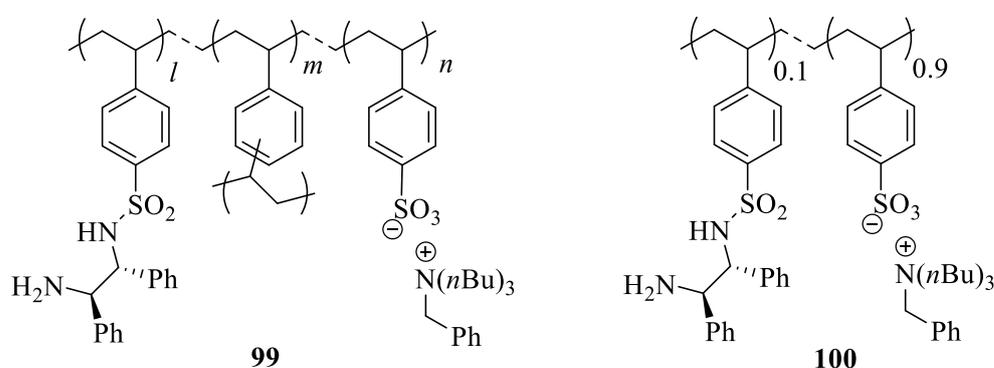
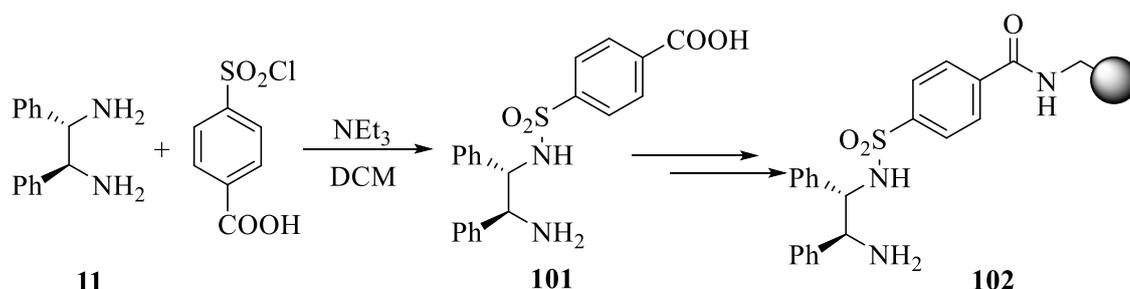


Figure 26. Structure of supported ligands **99** and **100**.

Itsuno tweaked the hydrophilicity-hydrophobicity of the polymer by the removal of the divinyl benzene making the DPEN-Polymer **100** able to ‘nicely swell’ in water.¹³⁰ The reaction between **100** and $[\text{Ru}(\text{benzene})\text{Cl}_2]_2$ formed a catalyst that reduced acetophenone, at an [S/C] of 100 with sodium formate in water, in 100% conversion and 98% ee. The metal centre was also altered and ligand **100** was reacted with both $[\text{Rh}(\text{Cp}^*)\text{Cl}_2]_2$ and $[\text{Ir}(\text{Cp}^*)\text{Cl}_2]_2$. These had no advantage over the ruthenium based-catalyst, instead the iridium catalyst gave much lower conversion and enantioselectivity. A small study on other acetophenone derivatives revealed that they were successfully reduced, forming products in 86-94% ee.

Another form of linking a support on to DPEN ligands is by introducing functional groups through the sulfonyl side of the ligand. Polywka *et al.* functionalised DPEN with 4-(chlorosulfonyl)benzoic acid, forming **101** which contains a carboxylic acid functionality (Scheme 39).¹³¹ The ligand was then coupled to aminomethylated polystyrene reagents to form polymer supported ligands **102**. The ATH of acetophenone, via the formation of a catalyst *in situ* with $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ in FA/TEA, formed the alcohol product in 95% conversion and 97% ee. The catalytic activity is dependent on the polymer and the solvents employed, as one type of polymer was found to have enhanced activity in the presence of DCM as opposed to the reaction being run in neat FA/TEA.



Scheme 39. Formation of polymer supported ligand **102**. Polymers used are polystyrene and polyethylene glycol linked polystyrene.

Similarly, an amine functionality on the sulfonyl group was added onto a DPEN ligand that was later coupled to supports via an amide coupling. Schomäcker *et al.*¹³² formed the tethered rhodium complex **103**, which was supported on a range of polymers (Figure 27). A six-carbon chain between the polymer and catalyst was introduced to avoid unwanted interactions between the catalyst and the polymer functionality. A

polyethylene sinter chip support was found to perform best from different polymers. The supported catalysts then reduced acetophenone, in an [S/C] of 430 in sodium formate and water, forming the alcohol product in 97% conversion and 98% ee. A mixture of sodium formate and FA/TEA, with ratios 1:1, enhanced the activity and the catalyst could be reused 5 times before a sharp decline in activity was observed.

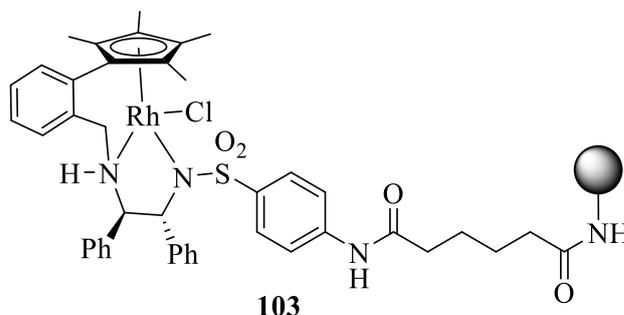


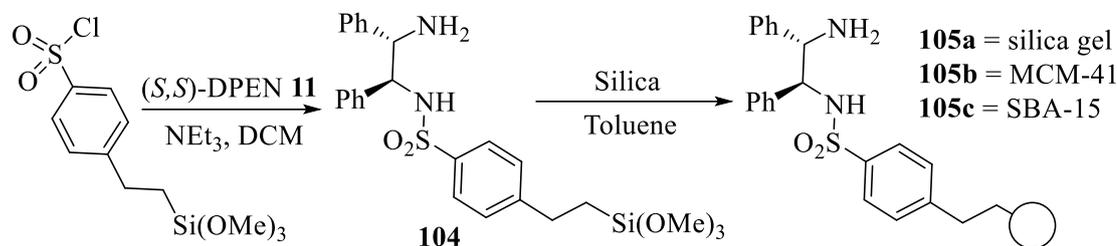
Figure 27. Structure of supported rhodium catalyst **103**.

A follow up study has examined the kinetics and mechanistic investigations of catalyst **103**.¹³³ Differing temperatures, pH, concentrations and atmospheres were investigated to deduce the optimal conditions. An interesting find was that the optimal pH is between 3-4, explaining the enhanced reactivity reported previously, when using a mixture of sodium formate and FA/TEA 1:1. On the other hand, the more basic conditions created through the addition of NaOH led to increased metal leaching. Under the optimal conditions, acetophenone was reduced in 98% ee and after 8 consecutive runs there was a total of 5% ruthenium leaching.

1.7.2. Silica Supported Catalysts

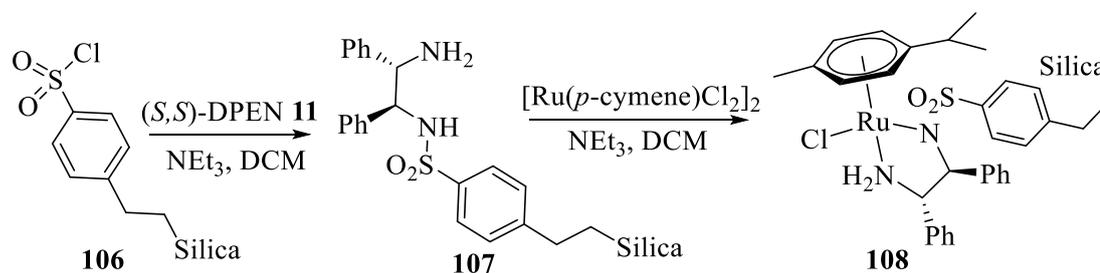
Ma *et al.* have added silicas to a silylether-containing DPEN ligand, **104**, that include amorphous silica gel, mesopores MCM-41 and SBA-15 (Scheme 40).¹³⁴ The product from the cheapest of the silicas, amorphous silica gel, produced the best results in the ATH of acetophenone using $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ with **105a**. An [S/C] ratio of 100 in FA/TEA formed the alcohol with 99% conversion and 97% ee. The catalyst was then recycled and produced similar results after five runs. Other silica containing derivatives **105b** and **105c** gave comparable results in the first catalytic reduction of acetophenone, compared to **105a** but had lower catalytic activity in subsequent runs. As **105a** was the most effective, the methodology was extended to acetophenone

derivatives; for example 4-methoxyacetophenone was reduced in three catalytic cycles all giving the alcohol product in 96% ee. A sodium formate and water system also worked with catalyst **105a** and is recyclable however lower enantioselectivity of 92% ee was observed in the reduction of acetophenone.



Scheme 40. Formation of silica supported catalysts **105a-c**.

Siliceous mesocellular foam, which has an ultralarge and uniform pore size, permits large metal complexes to be immobilised within pores, without negative steric effects, and allows the mass transport of substrates. Ying and Huang developed a 4-ethylbenzenesulfonyl chloride-functionalized silica **106**, containing the siliceous mesocellular foam, which was reacted with (*S,S*)-DPEN to form the immobilised silica ligand **107** (Scheme 41).¹³⁵ Catalyst **108**, formed from $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$, was employed in the ATH of an imine in FA/TEA which gave the salsolidine product in 100% yield and 91% ee. The catalyst was recycled and preserved its catalytic activity and enantioselectivity throughout six runs. The activity of catalyst **108** was less than that of its homogenous derivative catalyst **18**. Catalyst **108** was also applied to the reduction of a series of acetophenone derivatives giving the alcohol products in high enantioselectivity.



Scheme 41. Formation of silica supported catalyst **108**.

In a recent study, a silica support was connected through the arene moiety of an ATH catalyst. Two different silicas were studied; amorphous silica and DAVISIL were both

added via reaction with a triethoxysilyl group to give catalysts **109a** and **109b** respectively (Figure 28). Both catalysts reduced acetophenone in high yields and 97% ee. Catalyst **109b** was taken further to reduce a range of substituted-acetophenones that gave products in high enantioselectivities. The catalyst could also be recycled, where the first run in the reduction of acetophenone gave the alcohol product in 99% conversion followed by 77% and 63% in runs 2 and 3 without the loss of enantioselectivity.¹³⁶

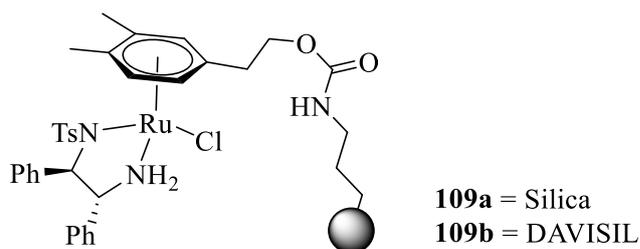


Figure 28. Structure of silica supported catalyst **109**.

1.7.3. Ionically supported catalysts

Dyson *et al.* functionalised a catalyst for the use and recyclability in ionic liquids.¹³⁷ A cyclohexadiene with an imidazolium could be transformed over several steps to form catalyst **110**, which is connected to the imidazolium tag through the η^6 -arene (Figure 29). The ionic liquid 1-butyl-2,3-dimethylimidazolium hexafluorophosphate, performed best of a series of ionic liquids. Subsequent reduction of acetophenone with catalyst **110** in *i*PrOH and KOH formed the reduction product in 80% conversion and 98% ee. The use of *i*PrOH however leads to a biphasic mixture, however a homogenous mixture was obtained using the FA/TEA 5:2 azeotrope. Under the FA/TEA conditions, the reduction of acetophenone with **110** gave the alcohol product in 99% conversion and 99% ee. This system is more efficient than *i*PrOH and the catalyst was recycled alongside the ionic liquid for further use in three runs.

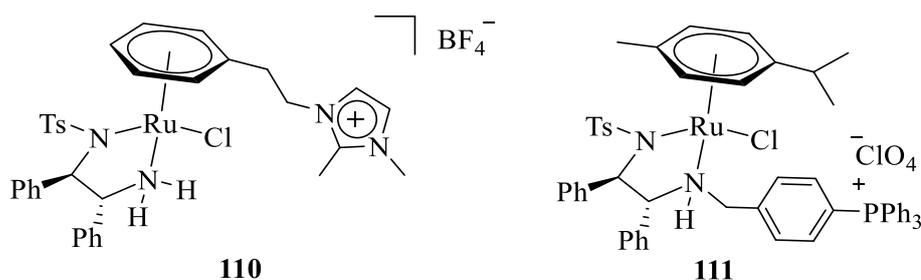
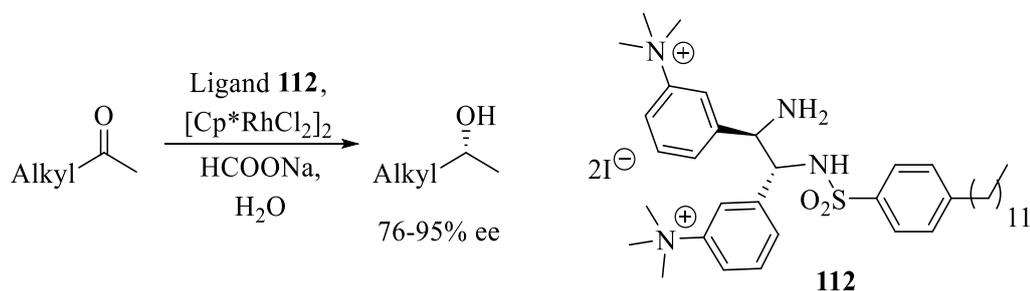


Figure 29. Structure of ionically supported catalysts **110** and **111**.

A tetraarylphosphonium salt in a catalyst has also been investigated for recyclability. Charette *et al.* alkylated a TsDPEN ligand at the basic amine functionality using a tetraarylphosphonium salt that was subsequently complexed to make catalyst **111**.¹³⁸ Catalytic hydrogenation of acetophenone formed the alcohol product in 99% conversion and 95% ee. In this example, basic conditions retard the catalytic activity, and the optimal conditions were found to be with an aqueous mixture using FA/TEA 1.2:1.0 ratio. The catalyst was recycled by precipitation with Et₂O and reused five times.

Deng devised a rhodium-based surfactant-type catalyst for ATH, where the ligand is both amphiphilic and cationic. The complexation of ligand **112** and [Rh(Cp*)Cl₂]₂, resulted in the formation of a metallomicelle in water, which was found to hydrogenate linear alkyl ketones in high enantioselectivity, 76-95% ee (Scheme 42),¹³⁹ where the longer chains in the substrate provide higher enantioselectivity. The reductions work well in aqueous sodium formate, achieving high conversions and ee, conversely the reactions were found to proceed slower and form products in lower ee using organic media. Interestingly, the cyclohexyl methyl ketone reduced in 95% ee and acetophenone in 97% ee. Deng suggested that an attraction between the hydrophobic chains of the catalysts and the substrates forms a stabilising interaction in the transition state, (Figure 30). Whereas in the reduction of acetophenone, it was found that the major product was formed with opposite configuration to the alkyl products. Thus suggesting that a C-H/ π interaction exists in the reduction of aryl ketones and favourable hydrophobic interactions exist when the substrates are alkyl ketones.



Scheme 42. ATH of alkyl ketones using ligand **112** and [Cp**Rh*Cl₂]₂, [S/C] of 100.

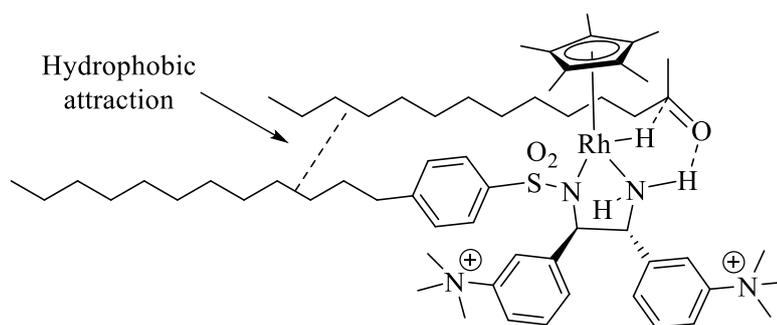
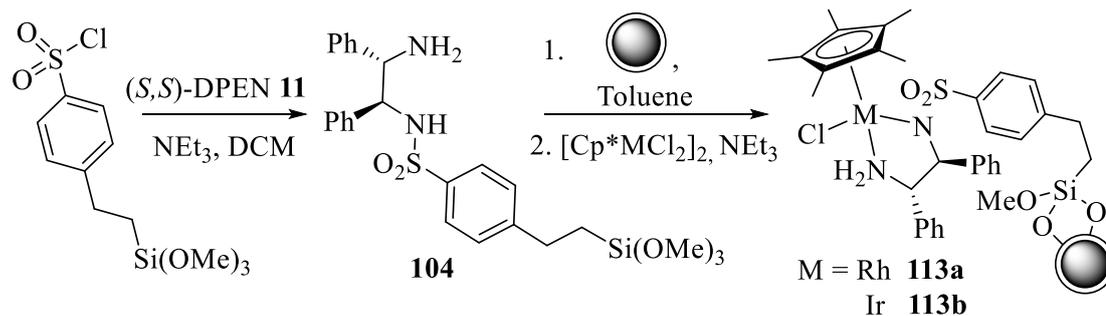


Figure 30. Structure of ionically supported rhodium catalyst from **112** with proposed hydrophobic interaction with alkyl ketones.

In another study by Deng *et al.*, the number of CH₂ groups on the alkyl chain were altered on ligand **112**. Catalysts containing 7, 11 or 15 CH₂ groups were found to form spherical metallomicelles, which were characterised through TEM analyses, whilst those with less CH₂ groups did not form the metallomicelles.¹⁴⁰ The same catalytic system from Scheme 42 was then applied to the ATH of a range of keto esters. Aliphatic α and β -ketoesters were reduced in 82-99% and 85-96% ee respectively, with the catalysts containing longer linear alkyl chains forming products in higher ee. Aromatic and aliphatic γ -ketoesters also formed ATH products in good enantioselectivities in the range of 84-89% ee.

1.7.4. Magnetically Supported Catalysts

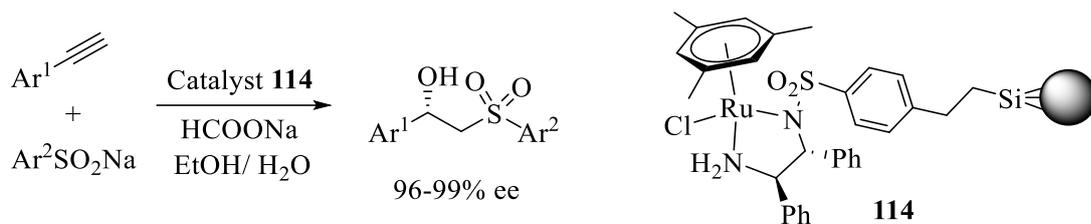
Magnetically recoverable nanoparticles have also been explored as a possible method to recover catalysts. Li *et al.* modified a TsDPEN ligand with SiO₂-coated Fe₃O₄ magnetic nanoparticles and complexed these with rhodium and iridium metals to form the catalysts **113a** and **113b** (Scheme 43).¹⁴¹ Both catalysts were found to be effective in the ATH of ketones using sodium formate in water. The ATH of acetophenone with **113a** gave the alcohol product in 99% yield and 90% ee, then recycling of the catalyst a further 9 times achieved conversions of 96-99% to products in 86-90% ee. In addition, the ATH of acetophenone with **113b** gave the alcohol product in 99% yield and 88% ee and the catalyst could also be recycled a further 9 times, achieving conversions to alcohols in of 98-99.9% and ee of 84-88%.



Scheme 43. Formation of magnetically supported catalysts **113a** and **b**.

Similarly, carbon-coated cobalt nanoparticles have also been incorporated onto the sulfonyl group of TsDPEN ligands, in this case via radical copolymerisation.¹⁴² These types of ligands, prepared by Reiser *et al.*, are then attached onto $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ metal centres and the catalysts have also shown recyclability. The catalytic hydrogenation of acetophenone in FA/TEA formed the alcohol product in 100% conversion and 94% ee.

Liu *et al.*, using a magnetically mesoporous silica as a support, have immobilised a ruthenium catalyst into the nanochannels of the outer mesoporous silica shell and FeCl_3 on the inner magnetic core.¹⁴³ The supported catalyst **114** under aerobic conditions transforms acetylenes with sulfinates to ketosulfones that are subsequently transfer-hydrogenated to the enantiopure hydroxysulfone products (Scheme 44). The supported catalytic system provides better yields than the one pot transformation using FeCl_3 and $\text{Ru}(\text{Mesitylene})/\text{TsDPEN}$ individually. This is believed to be due to the free catalyst interacting with FeCl_3 , however this is restricted in the supported reagents. A range of arylacetylenes were transformed to the alcohol products in 96-99% ee with the majority being formed in 99% ee. Catalyst **114** was easily recycled by placing an outer magnet near the vessel in order to separate it from the liquid phase and then reused for a total of six cycles.



Scheme 44. Structure of magnetically supported ruthenium catalyst **114** and reaction scheme for one pot transformation of hydroxysulfones.

1.7.5. Dendrimer supported catalysts

Dendrimers have been demonstrated to be viable supports for DPEN type ligands. Jiang *et al.* synthesised Frechet-type core dendritic DPEN ligands and hybrid dendritic ligands.¹⁴⁴ The dendritic ligand **115a**, where $n=3$ (Figure 31), was ligated to $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ and formed an active catalyst in FA/TEA. The catalyst formed *in situ* and reduced acetophenone in 98% conversion and 97% ee. The catalyst from **115a** was then reused for six cycles, and 1-phenylethanol was formed in 96-97% conversion during the first five cycles but enantioselectivity and activity dropped in the sixth cycle.

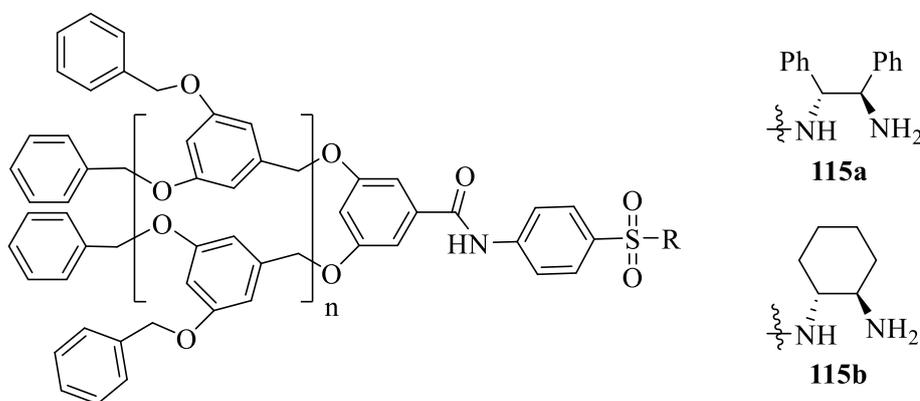


Figure 31. Structure of dendrimer supported ligands **115a** and **b**.

A dendrimer attached to a DACH ligand was synthesised by Deng *et al.*¹⁴⁵ The dendrimer is comparable to that of **115a**, however in this example a DACH replaces a DPEN unit and $n=1$. The catalytic reduction of acetophenone was carried out with **115b** and $[\text{Rh}(\text{Cp}^*)\text{Cl}_2]_2$ in sodium formate and water, forming the alcohol product in 99% conversion and 96% ee. Following precipitation with hexane, the catalyst from

115b was reused in a total of six cycles, displaying little change in activity and enantioselectivity.

Chapter summary

This literature review reveals key advances in the area of asymmetric transfer hydrogenation. Ruthenium-based catalysts such as those developed by Noyori and Ikariya are commonly employed in the ATH of ketones. More recent studies show the use of multidentate ligands, such as tridentate and tetradentate ligands, resulting in metal complexes that offer greater activity and/or enantioselectivity when compared to the Noyori-Ikariya catalysts. Various derivatives of the Ru/arene/diamine type complexes have shown promising applications on the ATH of functionalised ketones to form alcohol products in high ee. These catalysts are also employed in the dynamic kinetic resolution of ketones and even in chemoselective γ -C-H bond amidation where lactams are formed in high ee. On the other hand, ruthenium-based ATH catalysts perform less well in the ATH of imines, although there are few examples where Ru/arene/TsDPEN type catalysts can be effective. Additionally, various methods and solid supports have been evaluated as a means to attach ruthenium-based catalysts onto solid supports. These supported catalysts permit the recovery of catalysts for reusability and ease of extraction from the target product.

Aims of thesis

The aims of this thesis will be to evaluate the extent of which the addition of a heterocyclic group to a TsDPEN ligand influences the ligand's ability to act as a bidentate or tridentate ligand. The tridentate catalyst systems containing a TsDPEN unit will be further investigated to determine substrate scope and limitations to these types of catalysts. Alternatively novel catalysts with heterocyclic groups will also be studied to evaluate their effectiveness in the ATH of ketones.

The ATH of imines with ruthenium catalysts has proven to be more challenging than in the ATH of ketones, therefore there is a need to develop more suitable catalyst. Consequently, a further aim will be to synthesise a catalyst that can asymmetrically reduce imines to amines in high enantioselectivity and that can also be utilised in the ATH of ketones. The main objective here will be to solve the problem of reducing 1-aryl-3,4-dihydroisoquinolines in high ee.

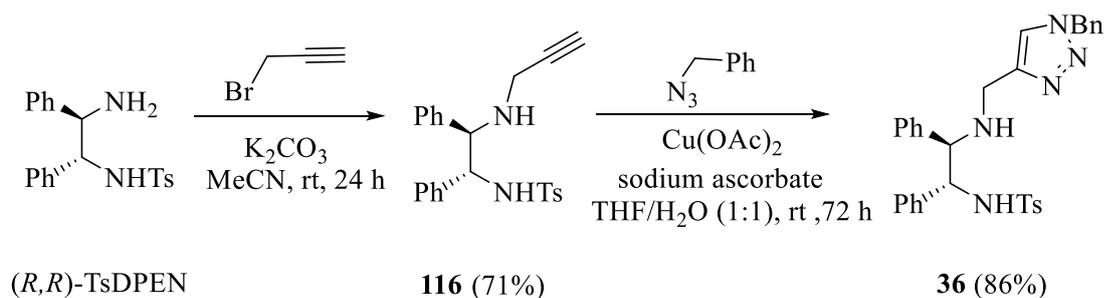
Furthermore, additional methods for linking catalysts on to solid supports will be established that can then be applied to novel catalysts developed. Such catalysts will be coupled to new solid supports to determine the effectiveness as reusable supported catalysts.

***Chapter 2: ATH of Ketones using
Heterocyclic Catalysts***

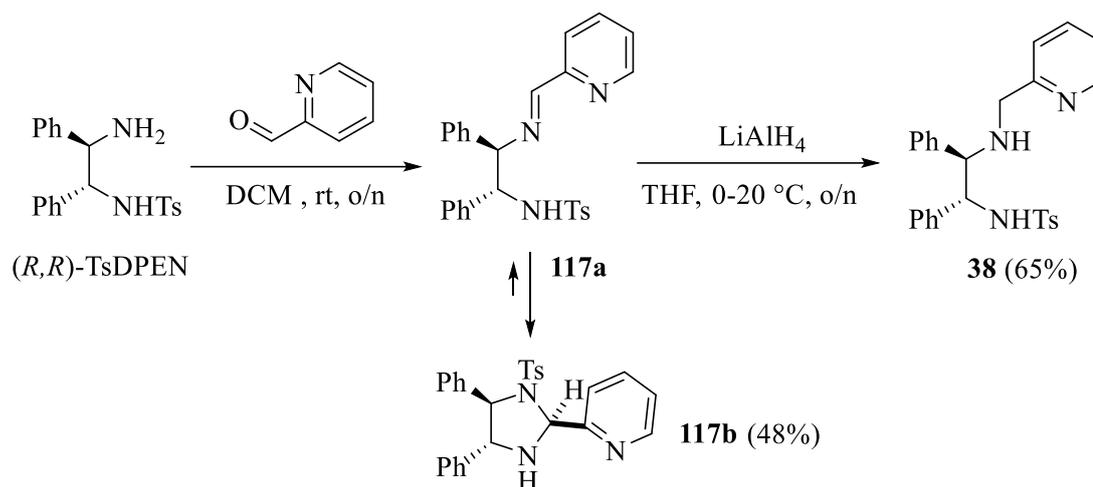
2.1. Investigating Tridentate Ligands in Ruthenium-Catalysed ATH

A main topic of this project is to investigate the effect of heterocyclic groups in TsDPEN ligands. The tridentate catalysts reported by Wills *et al.* were first explored with ligands (*R,R*)-**36** and (*R,R*)-**38** prepared following the reported methods.^{64,65} It was found that the intermediate (*R,R*)-**116** formed in low yields at 80 °C as reported, with the main product being the di-alkylated product. The change of temperature from 80 °C to rt was found to be favourable and the mono-alkylated (*R,R*)-**116** was formed in 71% yield; X-ray crystal structure confirms the product configuration (Figure 32). Subsequently the intermediate was reacted with benzyl azide in a CuAAC reaction forming (*R,R*)-**36** in 86% yield (Scheme 45).

Within the synthesis of the ligand (*R,R*)-**38**, it was found that the desired imine intermediate (*R,R*)-**117a** did not form as reported; instead a stable aminal product **117b** was formed and was isolated in 48% yield. The X-ray crystal structure confirmed the formation of **117b** (Figure 32). Stable aminals of this type have previously been reported and some derivatives have been employed in organocatalysis.¹⁴⁶ In this case the aminal (*R,R*)-**117b** was found to be resistant to NaBH₄ reduction. However the reduction with LiAlH₄ permitted the ring-opening of the aminal to give the desired product (*R,R*)-**38** in 65% yield (Scheme 46); the methodology reported here was also found to be useful for later steps (Section 4.3.).



Scheme 45. Formation of triazole-containing ligand (*R,R*)-**36**.



Scheme 46. Formation of pyridine-containing ligand (R,R) -**38** via the iminal intermediate.

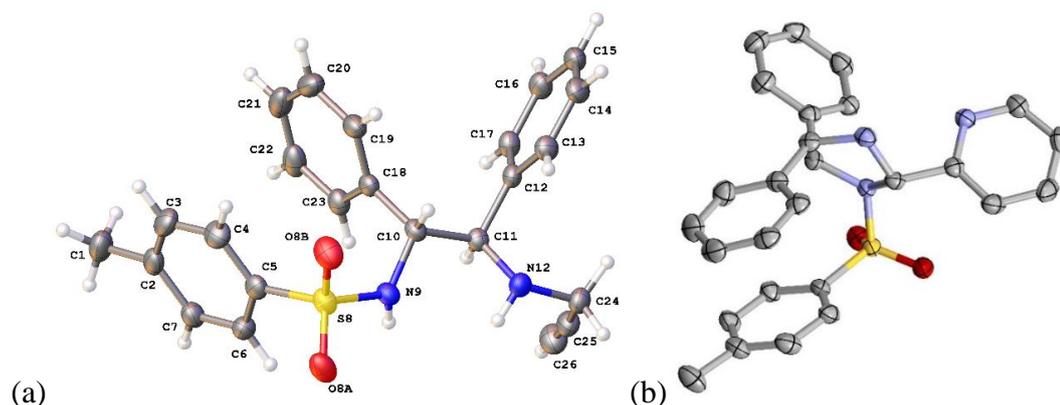
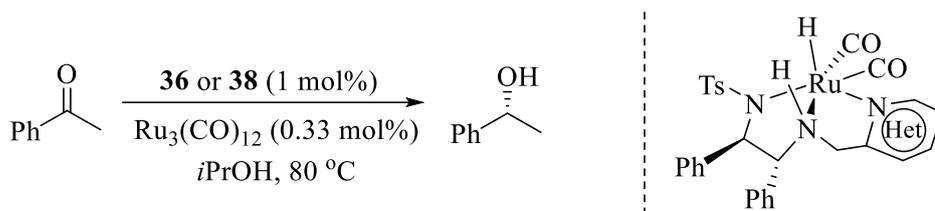


Figure 32. X-ray crystal structures of the intermediates (a): (R,R) -**116**. (b): (R,R) -**117b**.

Acetophenone was used as a model test substrate for ATH with the tridentate ligands and $\text{Ru}_3(\text{CO})_{12}$. In this catalyst system, the catalyst is formed *in situ* by complexation of ligand with $\text{Ru}_3(\text{CO})_{12}$ and *i*PrOH is used as the hydrogen source. The reduction of acetophenone with the triazole ligand (R,R) -**36** gave 98% conversion and 92% ee for the (R) -1-phenylethanol product and the pyridine ligand (R,R) -**38** gave 87% conversion and 93% ee. Both results are comparable to those reported. The structure of the proposed *in situ* catalyst formed is illustrated in Scheme 47.



Scheme 47. Reduction of acetophenone with tridentate ligands (*R,R*)-**36** and (*R,R*)-**38** forming (*R*)-1-phenylethanol in 92% ee and 93% ee respectively. Proposed structure of *in situ* catalyst on the right.

2.1.1. Derivatives of Pyridine-containing Ligands

The next part of the research was to investigate the effect of changing the sulfonyl groups on the tridentate ligands. A reductive amination of 2-pyridinecarboxaldehyde with MsDPEN, TrisDPEN and TfDPEN gave (*R,R*)-**118**, (*R,R*)-**119** and (*R,R*)-**120** respectively (Figure 33). Ligands (*R,R*)-**121** and (*R,R*)-**122** were also made by reductive amination of TsDPEN with the corresponding aldehydes.

The novel ligands were then employed in the reduction of acetophenone under the same conditions as shown in Scheme 47. Ligands containing the smaller mesyl group as in (*R,R*)-**118**, and a bulkier group as in the 2,4,6-triisopropylbenzenesulfonyl derivative, (*R,R*)-**119**, both gave lower yields and ee compared to the tosyl derivative (*R,R*)-**38** (Table 13). The use of trifluoromethylsulfonyl, an electron-withdrawing group, resulted in a small increase in the enantioselectivity.

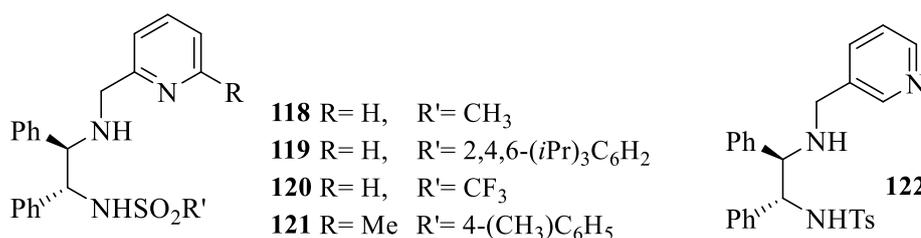
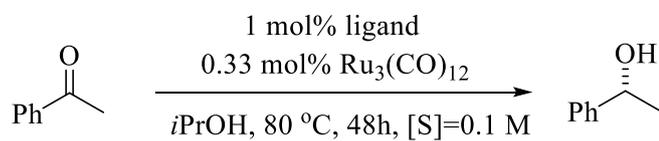


Figure 33. Structure of derivatives of ligand (*R,R*)-**38**.

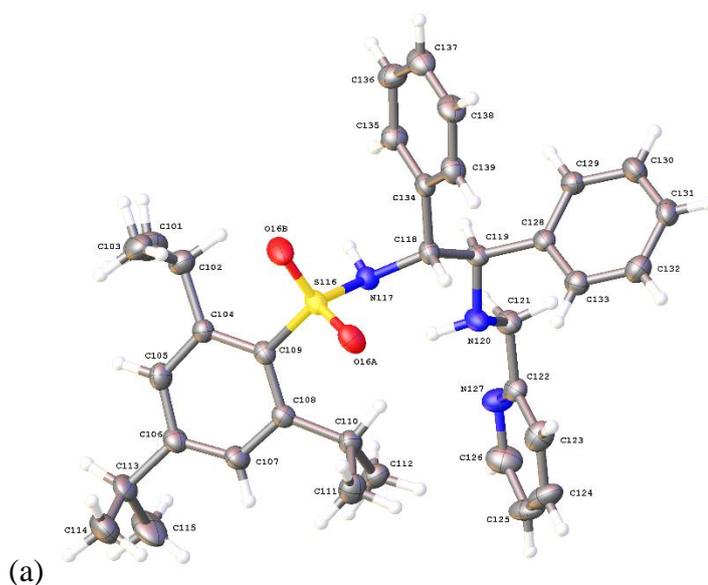
Slight changes to the pyridine heterocycle were studied next; the introduction of a methyl group to the 6' position of the pyridine on the tosyl derivative (*R,R*)-**121** negatively affected conversions and ee in these catalysts systems. Lastly, the effect of having the nitrogen atom of the pyridine in a distal position (*R,R*)-**122** was investigated as opposed to the nitrogen being proximal as in (*R,R*)-**38**. It was found that in this case,

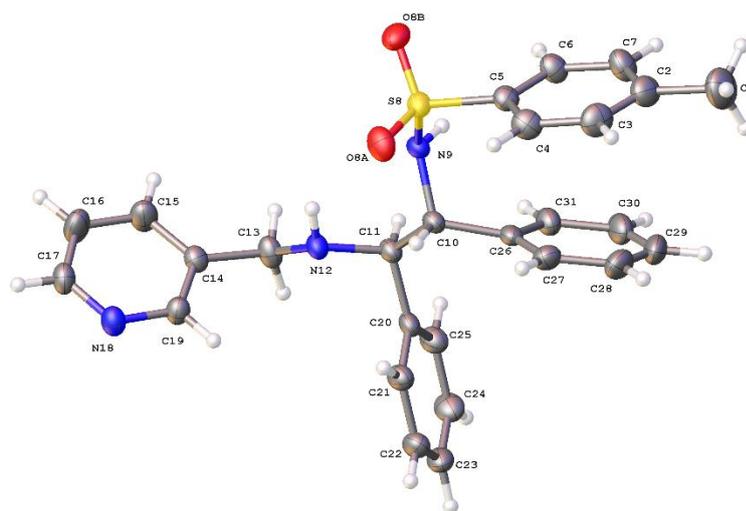
the catalyst system did not reduce acetophenone, indicating that the proximal (2-) position is a requirement for these types of tridentate ligands. X-ray crystal structures of ligands (*R,R*)-**119** and (*R,R*)-**122** are shown in Figure 34.



Ligand	Conv /%	ee /%	<i>R/S</i>
(<i>R,R</i>)- 36	98	92	<i>R</i>
(<i>R,R</i>)- 38	87	93	<i>R</i>
(<i>R,R</i>)- 118	55	82	<i>R</i>
(<i>R,R</i>)- 119	79	73	<i>R</i>
(<i>R,R</i>)- 120	95	93	<i>R</i>
(<i>R,R</i>)- 121	49	76	<i>R</i>
(<i>R,R</i>)- 122	-	-	-
(<i>R,R</i>)- 123	90	83	<i>R</i>

Table 13. Reduction of acetophenone with ligands **36**, **38** and **118-123**.





(b)

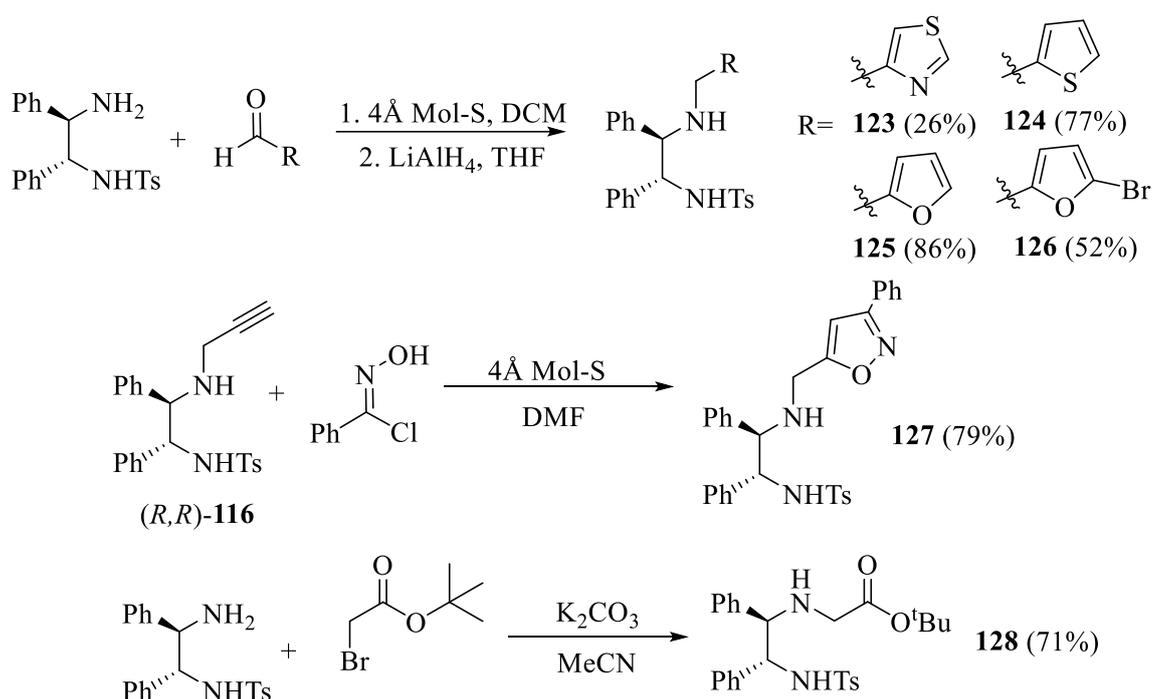
Figure 34. Crystal structures of ligands (a): (*R,R*)-**119**. (b): (*R,R*)-**122**.

2.1.2. Other Heterocyclic groups

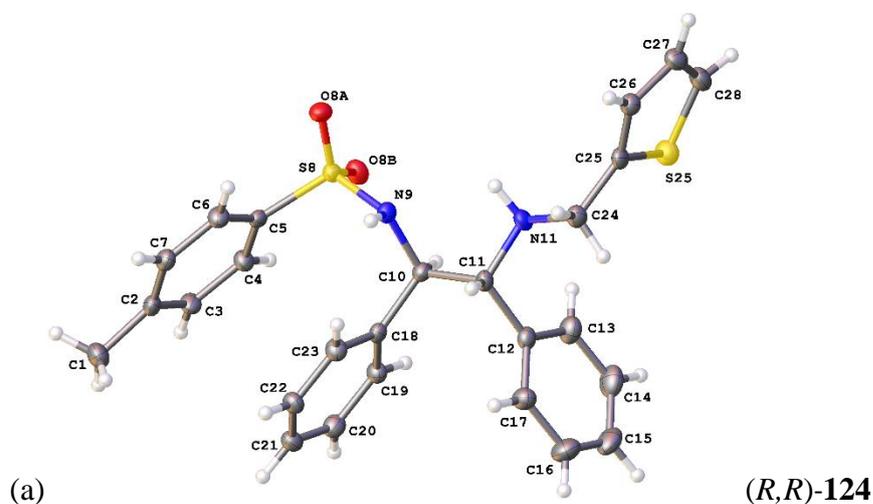
An extended range of heterocyclic groups were also incorporated onto the TsDPEN to study their effectiveness as tridentate ligands. A thiazole, thiophene, furan and bromofuran group were added, using the corresponding aldehydes, using the two-step reductive amination procedure previously described to (*R,R*)-TsDPEN ligands to form respectively (*R,R*)-**123** in 26%, (*R,R*)-**124** in 77%, (*R,R*)-**125** in 86% and (*R,R*)-**126** in 52% yield (Scheme 48). Additionally, an isoxazole group was studied; this was prepared from intermediate (*R,R*)-**116** using a nitrile oxide in a cycloaddition reaction to form (*R,R*)-**127** in 79% yield. Finally, the effect of a bulky ester group was also investigated by the formation of (*R,R*)-**128** in 71% yield from the reaction of *tert*-butylbromoacetate with TsDPEN in the presence of K_2CO_3 . Single crystals of compounds (*R,R*)-**124**, (*R,R*)-**125** and (*R,R*)-**128** were grown and analysed through X-ray crystallography with structures shown in Figure 35.

Ligands **123-128** were then tested in the reduction of acetophenone with the tridentate catalysts conditions as reported in Scheme 47. Thiazole-containing ligand (*R,R*)-**123** was found to reduce acetophenone in 83% ee (Table 13) which is less effective than ligands containing triazole or pyridine groups. A sulfur atom was assessed as a possible coordinator; reduction with thiophene-containing (*R,R*)-**124** in the tridentate catalyst system gave no reduction of acetophenone. For the oxygen-containing

heterocycles, furan and bromo-furan-containing ligands (*R,R*)-**125** and (*R,R*)-**126** respectively also gave no reduction with the tridentate catalyst system. Ligand (*R,R*)-**127**, containing an oxygen atom in the proximal position and a nitrogen atom in a distal position, did not work with the tridentate catalyst systems. The ester-containing (*R,R*)-**128** gave no reduction in this catalytic system too. Therefore it is apparent that the tridentate catalyst systems only work when the heterocycle on the ligand contains a nitrogen donor atom and is in a proximal position where it can readily participate in co-ordination to the metal in the proposed complex.



Scheme 48. Synthetic schemes for the formation of ligands (*R,R*)-**123** - **128**.



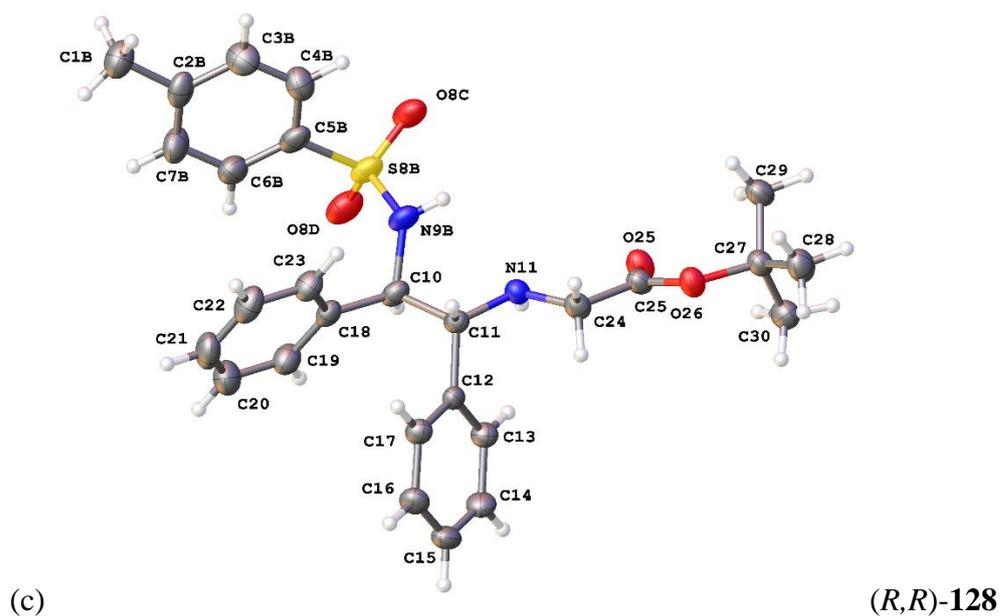
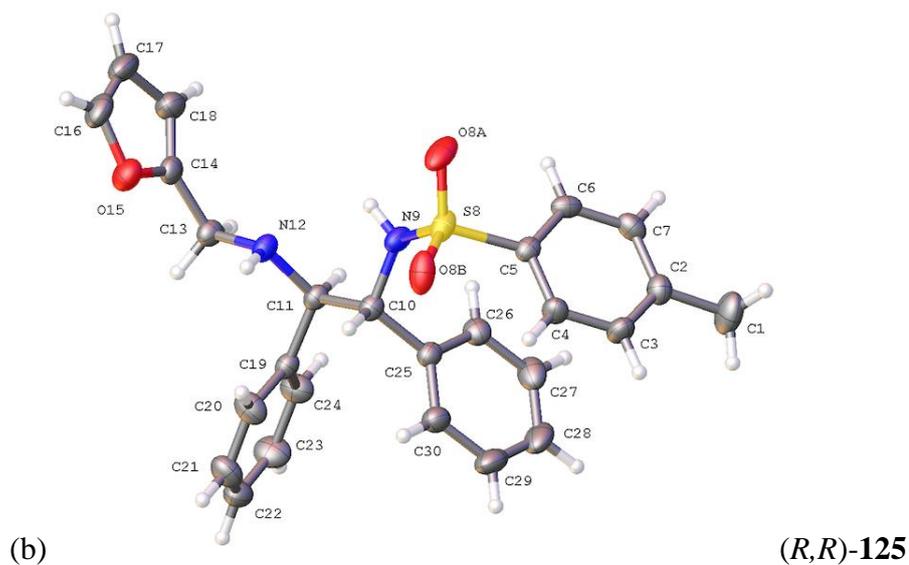


Figure 35. X-ray crystal structures of ligands (a): (*R,R*)-124. (b) (*R,R*)-125. (c) (*R,R*)-128.

2.2. Complexes from Ru(benzene)Cl₂

2.2.1. Tridentate Ligands and Ru(benzene)Cl₂

The tridentate ligands were complexed with [Ru(benzene)Cl₂]₂ to make metal complexes (Figure 36) analogous to Noyori-Ikariya catalyst (*R,R*)-16. It is worth noting that benzene has demonstrated the best activity from the different ruthenium-arene sources. Complexation of the triazole ligand (*R,R*)-36 with [Ru(Benzene)Cl₂]₂

gave a product that was analysed by mass spectrometry giving an m/z measurement of 716.3 for the $[M-Cl]^+$ ion, which is expected for the desired product as these types of complexes are known to lose a chloride ion under mass spectrometry conditions.

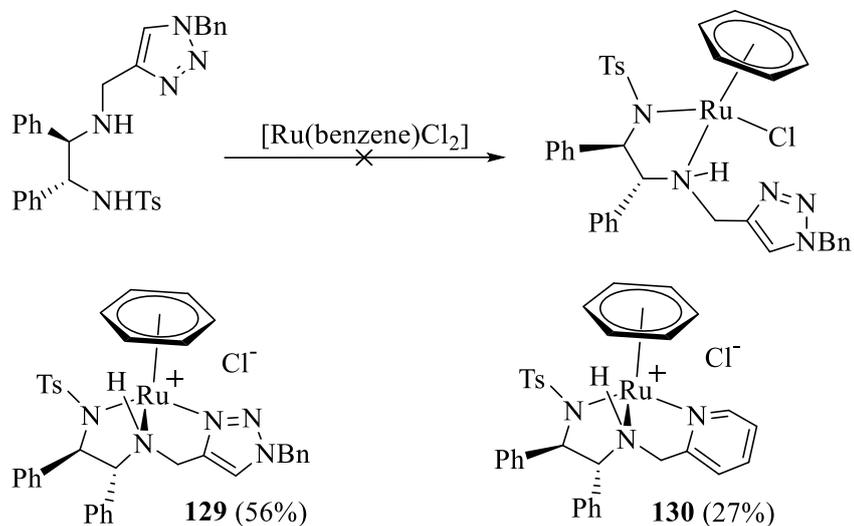


Figure 36. Scheme for desired catalyst formation and the proposed structure of catalysts obtained.

The 1H NMR spectrum for the complexation product however gave a resonance at 10.74 ppm that was assigned to the N-H; this was further confirmed by a COSY spectrum showing a correlation of the N-H with the adjacent PhCH and CH_2 (Figure 37). The highly deshielded proton arises from the complex being cationic as illustrated in **129** (Figure 36). Here the labile chloride ligand is lost and the empty coordination site is replaced by the coordination of the nitrogen atom in the heterocycle of the ligand. Similar results were obtained with the pyridine ligand that also formed a cationic complex, **130**.

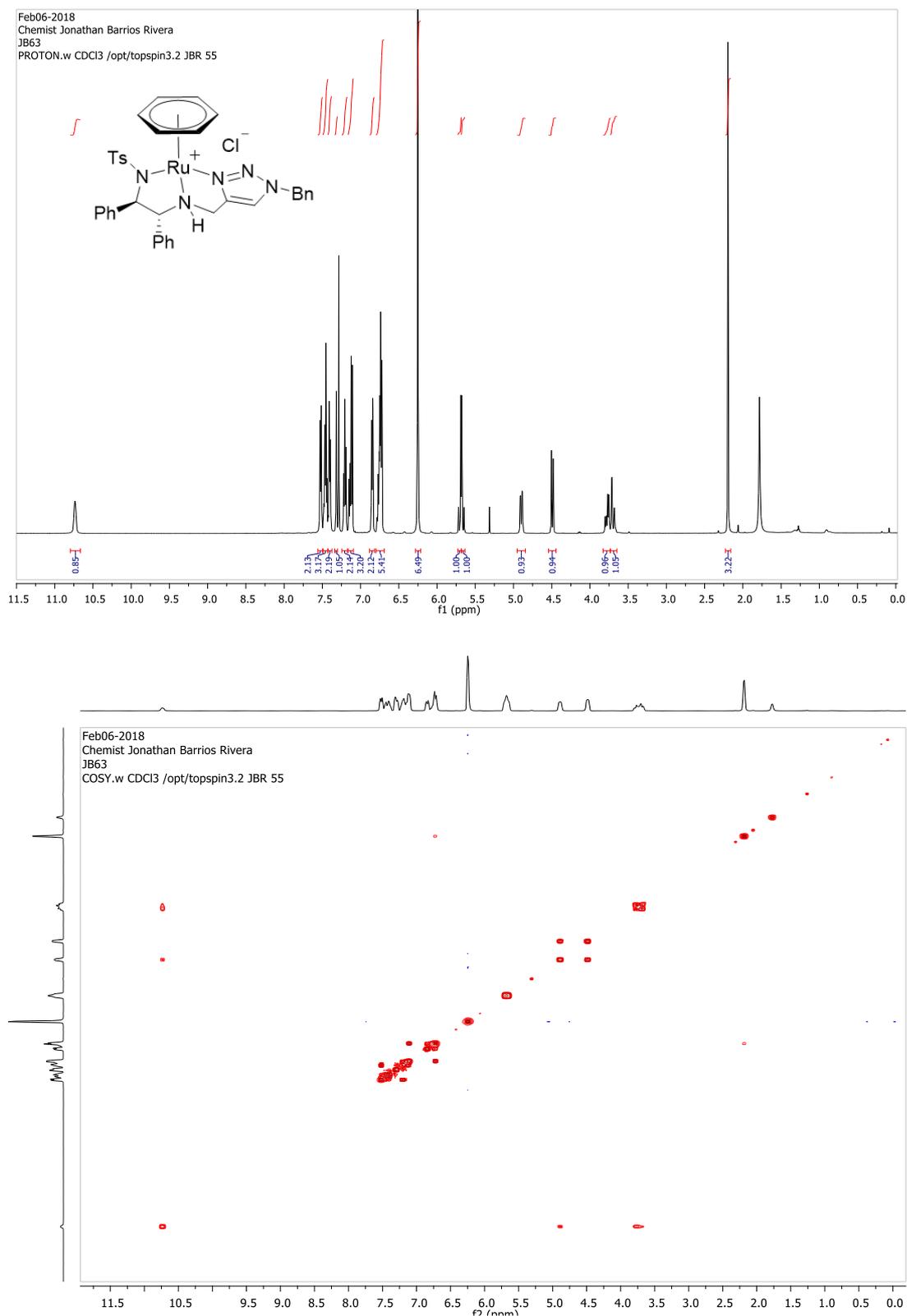


Figure 37. Top: ^1H NMR spectrum of **129**. Bottom: COSY spectrum of **129**.

The two complexes, **129** and **130**, were tested in the reduction of acetophenone where FA/TEA 5:2 was used as the hydrogen source, but these reductions did not work in

this case. Changing the hydrogen source to *i*PrOH with KOH failed to reduce acetophenone also. The third donor atoms in the complexes coordinate strongly to the ruthenium centre that in turn prevents the formation of the hydride containing catalyst. A possible way to overcome this was rationalised by adding a secondary metal to compete with the Ru(II) for the heterocyclic group. A source of Cu²⁺ was added to the reduction but this was unable to free the coordination site on the ruthenium. Hence these cationic complexes have been shown to be stable and inactive in the ATH of acetophenone. Taking into account these observations, the formation of complexes from the tridentate ligands (*R,R*)-**118** -**123** was not investigated.

2.2.2. Bidentate Ligands and Ru(benzene)₂

Given that the ligands containing heterocycles with oxygen and sulfur atoms in the proximal position had not worked in forming active catalysts with Ru₃(CO)₁₂, their ability to work as bidentate ligands was studied. The furan ligand (*R,R*)-**125** was refluxed with [Ru(benzene)Cl₂]₂ in *i*PrOH to give complex (*R,R*)-**131** in 51% yield. Under the same conditions (*R,R*)-**132** and (*R,R*)-**133** complexes, were also formed from their corresponding ligands, in 26% and 46% yields respectively. All complexes were formed as diastereoisomers and this is possibly due to chirality at either the ruthenium metal centre or from the formation of a quaternary amine. The d.r of complexes was determined by ¹H NMR spectrometry and are displayed in Figure 38.

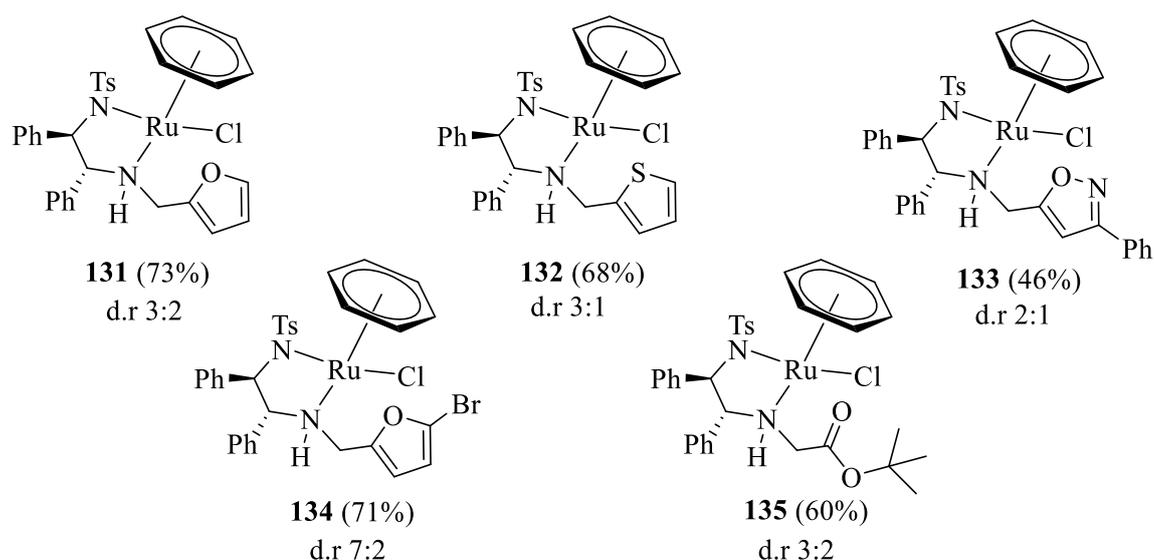


Figure 38. The structure of catalysts formed from bidentate ligands.

The reaction between the bromo-furan ligand and $[\text{Ru}(\text{benzene})\text{Cl}_2]_2$ in *i*PrOH gave a mixture of two additional products alongside the diastereomers of the expected complex. This was determined in the ^1H NMR spectrum where multiple arene and furan signals appear (Figure 39). The ^1H NMR spectrum was compared to that from the furan complex (*R,R*)-**131** that showed one of the products to be this complex. An explanation for this is due to the complexation solvent *i*PrOH, also a hydrogen donor source for ATH, can assist in the formation of a ruthenium hydride during complexation. The resulting hydride then promotes a substitution of the bromide of the heterocycle with hydride, giving the furan product.

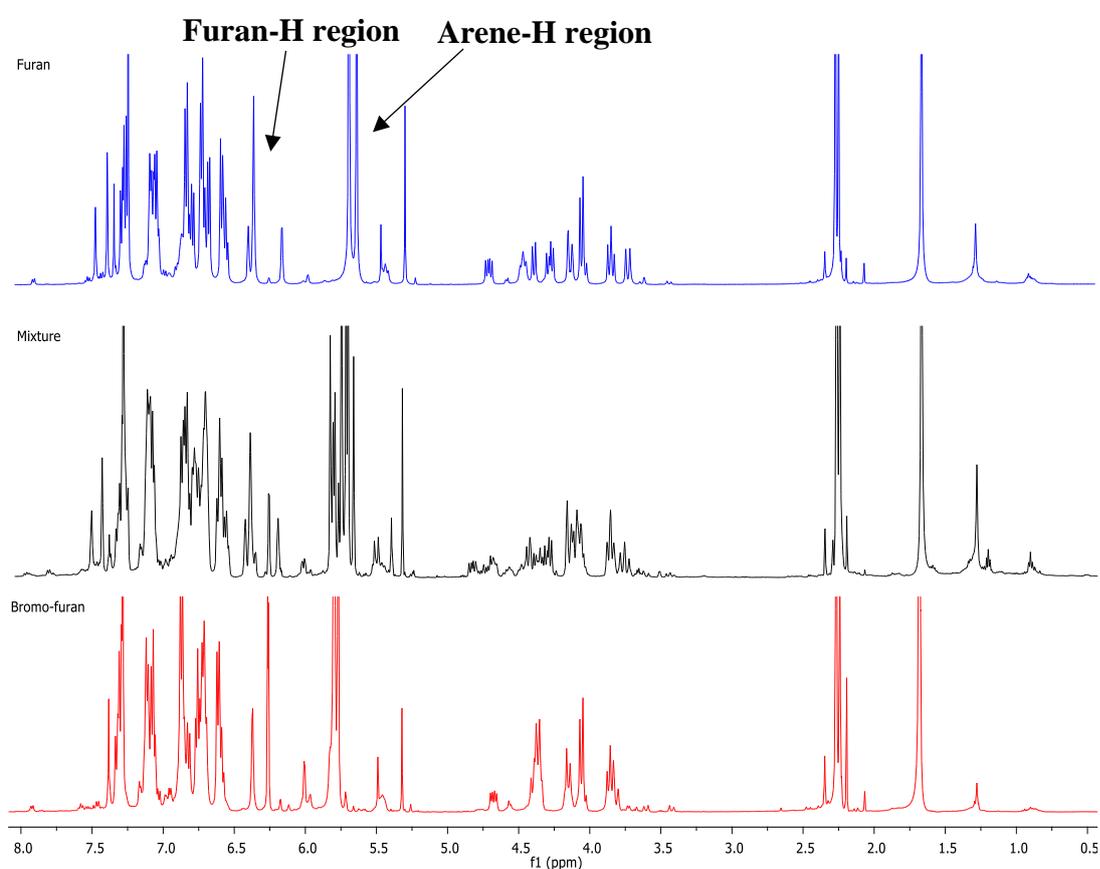


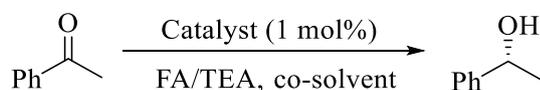
Figure 39. The effect of solvent in the formation of catalyst **134**. Top: ^1H NMR spectrum of furan Cat. **131**. Middle: Formation of catalyst **134** in *i*PrOH showing some formation of **131**. Bottom: Formation of catalyst **134** in PhCl.

To prevent the formation of the ruthenium-hydride in the catalyst formation, the reaction solvent was changed to chlorobenzene. This gave the desired catalyst **134** in

71% yield. The solvent was also compatible in forming some of the other catalysts in higher yields compared to *i*PrOH. The yield of the furan catalyst **131** was increased to 88% and **132** to 68% yield. Ester catalyst **135** was formed under the same conditions in 60% yield.

2.2.3. ATH of Acetophenone with Bidentate Catalysts

The novel catalysts **131-135** were tested in the reduction of acetophenone, using 1% catalyst in an FA/TEA (5:2) complex to form (*R*)-1-phenylethanol. Employment of catalyst **131** at a 1 mol% loading and substrate concentration of 2 M gave 99% conversion and 92% ee of the (*R*)-1-phenylethanol after 24 h (Table 14). Catalyst **132** under the same conditions gave the same result whilst both **133** and **135** were sluggish, giving lower conversions. The mechanism for the ATH with these catalysts is expected to involve a bifunctional catalysis mechanism analogous to the Noyori-Ikariya type catalyst **16**. The catalysts **131-135** display much lower activity and slightly less enantioselectivity in the ATH of acetophenone at [S]=2M in comparison to the tethered catalyst (*S,S*)-**22**.



Catalyst (1 mol%)	Co-solvent	[S] (M)	Time (h)	Conversion (%)	ee (%)
(<i>R,R</i>)- 131	-	2	24	99	92
(<i>R,R</i>)- 132	-	2	48	98	92
(<i>R,R</i>)- 133	-	2	72	96	90
(<i>R,R</i>)- 135	-	2	156	90	93
(<i>S,S</i>)- 22 ^a	-	2	3	100	96
(<i>R,R</i>)- 131	DCM	1	72	95	92
(<i>R,R</i>)- 132	DCM	1	72	62	93
(<i>R,R</i>)- 133	DCM	1	72	99	95
(<i>R,R</i>)- 134	DCM	1	86	73	95
(<i>R,R</i>)- 135	DCM	1	159	63	96

Table 14. ATH of acetophenone with bidentate catalysts **131-135** at 1 mol% loading in FA/TEA at rt. ATH of acetophenone with (*S,S*)-**22** using 0.25 mol% at 28°C (lit.¹⁴⁷).

Changing the substrate concentration from 2 M to 1 M by addition of the co-solvent DCM led to slightly different results. Most of the catalysts were much slower in the reduction of acetophenone apart from the isoxazole **133** which gave slightly better conversion and an increase in the enantioselectivity (Figure 40). The bromo-furan **134** was also tested under these conditions, giving the reduced product in 73% conversion and 95 % ee.

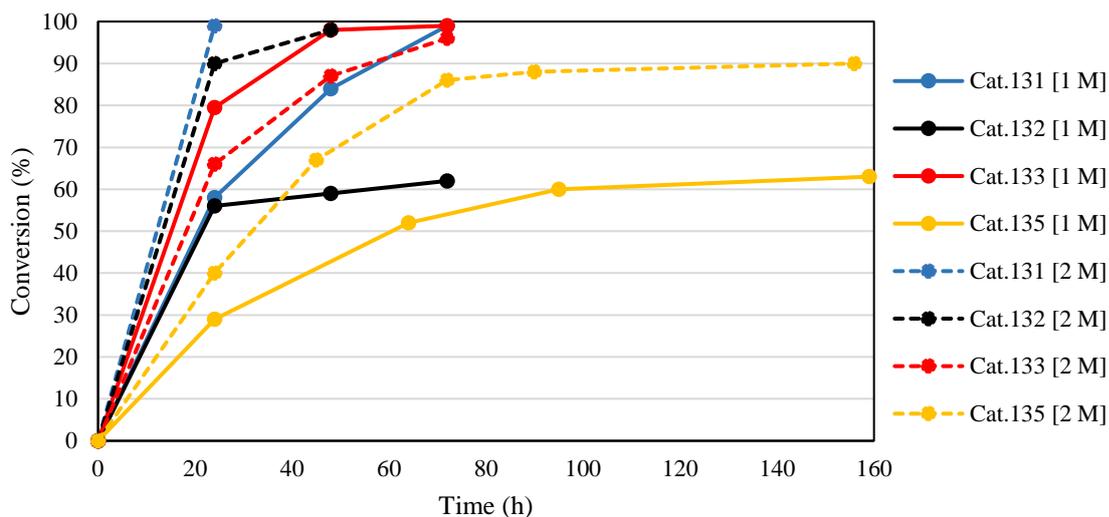
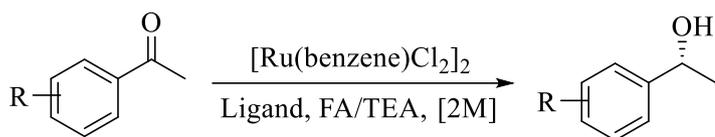


Figure 40. Conversion vs time graph for the reduction of acetophenone with catalysts **131-135** at $[S] = 1$ M and 2 M.

2.2.4. *In Situ* reactions

To avoid having to synthesise the pre-catalysts **131-133** and **135**, an *in situ* catalyst formation was attempted in the reduction of acetophenones. Furan ligand **125** was combined with $[\text{Ru}(\text{benzene})\text{Cl}_2]_2$ in FA/TEA before the addition of the acetophenone substrate. The 2 M *in situ* reaction proceeded at a lower rate compared to the precatalyst reaction; 98% conversion after 48 h as opposed to 99% in 24 h. However there was no change to the enantioselectivity observed with a product of 92% ee formed in both cases. The *in situ* reduction methodology was applied to a small scope of substituted acetophenone derivatives, this is summarised in Table 15 which includes literature results from the ATH with catalysts **17** and **22** for comparison.



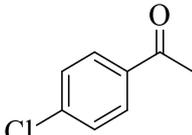
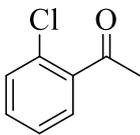
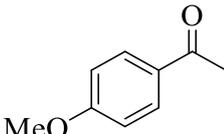
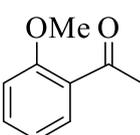
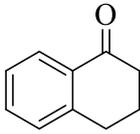
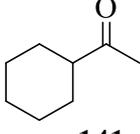
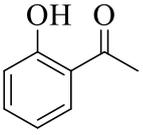
Ketone	Ligand (loading %)	Time (h)	Conv %	ee %	R/S
 136	(<i>R,R</i>)- 125 (1%) ^a	47	99.8	87	<i>R</i>
	(<i>R,R</i>)- 124 (1%) ^a	94	99	87	<i>R</i>
	(<i>R,R</i>)- 127 (1%) ^a	156	99	89	<i>R</i>
	(<i>R,R</i>)- 128 (1%) ^a	96	99	90	<i>R</i>
	(<i>S,S</i>)- 17 (0.5%) ^b	24	99	95	<i>S</i>
 137	(<i>R,R</i>)- 125 (1%) ^a	72	99	57	<i>R</i>
	(<i>R,R</i>)- 124 (1%) ^a	165	99	57	<i>R</i>
	(<i>R,R</i>)- 127 (1%) ^a	185	80	66	<i>R</i>
	(<i>R,R</i>)- 128 (1%) ^a	96	98	61	<i>R</i>
 138	(<i>R,R</i>)- 125 (1%) ^a	184	91	87	<i>R</i>
	(<i>R,R</i>)- 124 (1%) ^a	200	70	87	<i>R</i>
	(<i>R,R</i>)- 127 (1%) ^a	190	63	87	<i>R</i>
	(<i>R,R</i>)- 128 (1%) ^a	96	51	87	<i>R</i>
	(<i>S,S</i>)- 17 (0.5%) ^b	60	99	97	<i>S</i>
 139	(<i>R,R</i>)- 125 (1%) ^a	164	90	65	<i>R</i>
	(<i>R,R</i>)- 124 (1%) ^a	166	87	66	<i>R</i>
	(<i>R,R</i>)- 127 (1%) ^a	166	63	63	<i>R</i>
	(<i>R,R</i>)- 128 (1%) ^a	164	97	68	<i>R</i>
	(<i>S,S</i>)- 22 (0.5%) ^c	1	100	70	<i>S</i>
 140	(<i>R,R</i>)- 125 (1%) ^a	72	99.6	99	<i>R</i>
	(<i>R,R</i>)- 124 (1%) ^a	96	95	99	<i>R</i>
	(<i>R,R</i>)- 127 (1%) ^a	96	96	99	<i>R</i>
	(<i>R,R</i>)- 128 (1%) ^a	70	99	99	<i>R</i>
	(<i>S,S</i>)- 17 (0.5%) ^b	48	99	99	<i>S</i>
 141	(<i>R,R</i>)- 125 (1%) ^a	144	92	53	<i>S</i>
	(<i>R,R</i>)- 124 (1%) ^a	144	75	35	<i>S</i>
	(<i>R,R</i>)- 127 (1%) ^a	144	70	36	<i>S</i>
	(<i>R,R</i>)- 128 (1%) ^a	120	98	48	<i>S</i>
	(<i>S,S</i>)- 22 (0.5%) ^c	10	100	69	<i>R</i>

Table 15.	 142	(<i>R,R</i>)- 125 (1%) ^a	96	97	94	<i>R</i>
		(<i>R,R</i>)- 124 (1%) ^a	168	99	93	<i>R</i>
		(<i>R,R</i>)- 127 (1%) ^a	168	99	95	<i>R</i>
		(<i>R,R</i>)- 128 (1%) ^a	72	99	96	<i>R</i>

Reduction of substituted-acetophenones. (a) **136-142** with 1 mol% of *in situ* formed catalysts in FA/TEA (5:2), [S] = 2 M, rt. (b) ATH with (*S,S*)-**17** at 0.5 mol% of preformed catalyst using FA/TEA (5:2), [S] = 2 M, 28 °C (lit.⁴⁸). (c) ATH with (*S,S*)-**22** at 0.5 mol% of preformed catalyst using FA/TEA (5:2), [S] = 2 M, 28 °C (lit.¹⁴⁷)

Reduction of ketone **136** with the *in situ* formed catalysts formed the target alcohol in 87-90% ee. This ketone has also been reported to reduce in 95% ee with the Noyori-Ikariya catalyst **17** at a lower loading of 0.5 mol%.⁴⁸ The reduction of ketone **138** with *in situ* formed catalysts resulted in alcohol products of 87% ee but in poor conversions even after prolonged reaction times. These are inferior results when compared to the reduction with catalyst **17** that achieves 99% conversion and 97% ee for this substrate.⁴⁸ On the other hand, tetralone **140** was reduced to the corresponding alcohol in 99% ee with all of the *in situ* catalysts and is a similar result as to that obtained from catalyst **17**. Reduction of ketone **139** with the *in situ* catalysts formed alcohol products in 63-68% ee with reaction times of up to 166 h. Tethered catalyst **22** has reported to reduce **139** in similar enantioselectivity forming the alcohol in 70% ee however a much lower catalyst loading and reaction time is required.¹⁴⁷ Overall the novel bidenatate catalysts display lower activity and enantioselectivity in the ATH of substituted acetophenones derivatives compared to the Noyori-Ikariya catalyst **17** and tethered catalyst **22**.

The *in situ* reactions in Table 15 were carried at a 1:1 ratio of ligand to ruthenium metal and to optimise the reaction, the molar ratios were altered. Taking a ruthenium metal to ligand ratio of 1:2 i.e 0.5 mol% [Ru(benzene)Cl₂]₂ and 2 mol% ligand **125** to form the *in situ* catalyst resulted in reduction of 4-chloroacetophenone after 24 h in 99% conversion and 87% ee. The change of ruthenium metal to ligand ratio of 2:1 gave the same result in the reduction of 4-chloroacetophenone of 99% conversion and 87% ee within 24 h. The results indicate that the increased molar ratios, of either ligand or metal, increase the rate of reaction however there is no change to the enantioselectivity observed.

To eliminate inconsistencies in the results, substrates were randomly selected and reduced with a preformed catalyst. Reduction of ketone **139** under the same conditions using the preformed catalyst **131** gave the alcohol in 65% ee and catalyst **133** gave this in 63%. Substrate **138** with catalyst **135** gave the same enantioselectivity as its *in situ* reaction. The results demonstrate that there is no change in enantioselectivity from using either a preformed or an *in situ* catalyst, the differences are in the reaction rate where the preformed catalysts perform faster.

Summary

A tridentate catalyst system previously reported, was further investigated by changing sulfonyl groups and a triflate group which gave slightly better conversion and ee than the reported tosyl derivative in the ATH of acetophenone. Changing the heterocycle of the TsDPEN ligand revealed that a nitrogen donor atom, in a proximal position of a heterocycle, strongly coordinates to $\text{Ru}_3(\text{CO})_{12}$ allowing for the catalysis using the tridentate catalyst system. In contrast the use of non-nitrogen donor atoms on a heterocycle work as weak coordinators to ruthenium centres and the ligands are therefore bidentate. Such ligands make effective catalysts with $[\text{Ru}(\text{benzene})\text{Cl}_2]_2$ sources forming half-sandwich complexes and reduce acetophenone in the ‘bidentate catalyst system’ (Figure 41). The complexes from the bidentate ligands can reduce ketones asymmetrically using FA/TEA as a hydrogen source. However, these catalysts have shown lower activity and enantioselectivity in the ATH of acetophenone derivatives in comparison to Noyori-Ikariya catalysts and tethered catalyst **22**.

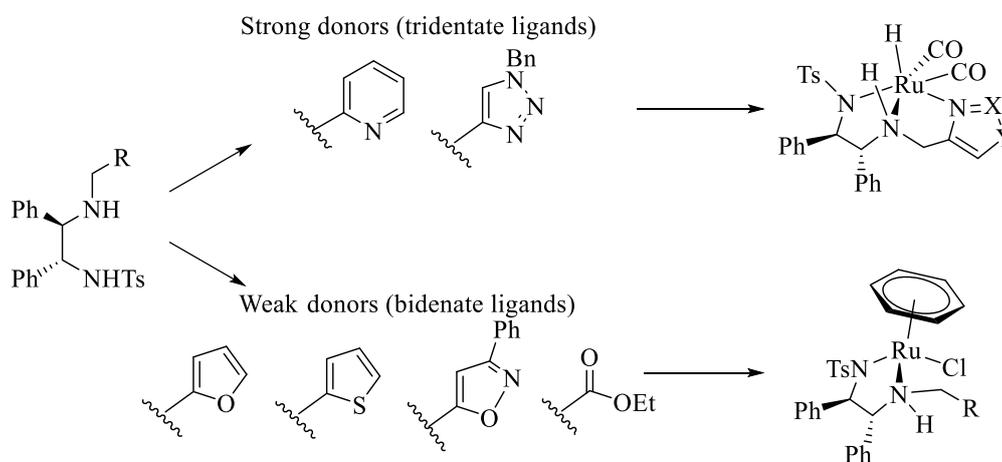


Figure 41. Tridentate and bidentate ligands with corresponding ATH catalysts.

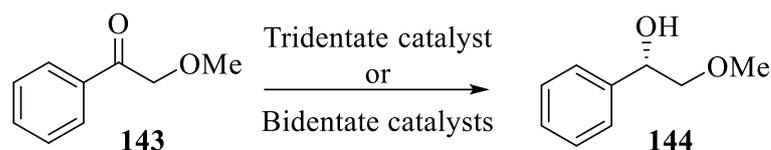
2.3. Application of Catalysts to Functionalised Ketones

At this point in the project, two different systems had been developed; both were able to undergo ATH, one of which uses the tridentate ligands with $\text{Ru}_3(\text{CO})_{12}$ in *i*PrOH and the other system that makes use of complexes from bidentate ligands in the FA/TEA medium. The catalysts in both systems had been shown to reduce acetophenone with excellent conversions and ee. Ligands (*R,R*)-**36** and (*R,R*)-**38** were then chosen for the tridentate ligands in exploring the ATH of ketones containing a variety of functional groups. These tridentate ligands were complexed with $\text{Ru}_3(\text{CO})_{12}$ *in situ* at 80 °C and a substrate concentration of 0.1 M in *i*PrOH. Initially reductions of substituted ketones were carried out using 1% catalyst but this resulted in low conversion of the substrates in many cases, therefore to overcome this the catalyst loading was increased to 5%.

The novel catalysts **131-133** and **135** were also further explored as high conversions and enantioselectivities were obtained in the ATH of acetophenone. Although some of the highest reaction rates for these catalysts were observed at a 2 M concentration, the reductions of substrates were carried out at a 1 M concentration by addition of DCM due to the poor solubility of some of the substrates in the FA/TEA 5:2 azeotrope.

2.3.1. α -Substituted Ketones

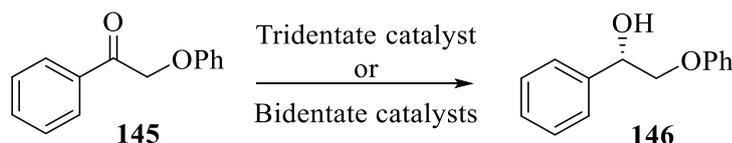
The asymmetric reduction of α -methoxyacetophenone **143** was attempted with tridentate ligands (*R,R*)-**36** and (*R,R*)-**38** under the conditions above. No reduction was observed with either ligand and it was assumed that the catalyst was being poisoned by the substrate. To test this, 0.5 mmol of the α -methoxyacetophenone and 0.5 mmol of acetophenone were added to the catalysts in *i*PrOH and no reduction of either substrate was observed, thus proving the substrate to be poisoning the catalyst. On the other hand, the bidentate complexes were not poisoned by the substrate and the *S*-alcohol products were obtained in 91-94% ee (Table 16). The most effective catalyst was found to be the furan catalyst **131** which gave an 84% isolated yield and 94% ee.



Catalyst (loading %)	Time (h)	Conversion %	Yield %	ee %	R/S
Ligand 36^a (5%)	48	0	0	-	-
Ligand 38^a (5%)	48	0	0	-	-
Cat. 131^b (1%)	120	nd	84	94	<i>S</i>
Cat. 132^b (1%)	120	nd	41	91	<i>S</i>
Cat. 133^b (1%)	144	nd	74	92	<i>S</i>
Cat. 135^b (1%)	168	82	79	91	<i>S</i>

Table 16. Reduction of α -methoxyacetophenone **143** with the two different catalyst systems. (a) (*R,R*)-Ligand (5 mol%), Ru₃(CO)₁₂ (⁵/₃ mol%) in *i*PrOH, [S] = 0.1 M, 80°C. (b) (*R,R*)-Catalyst (1 mol%), FA/TEA (5:2), DCM, [S] = 1 M, rt.

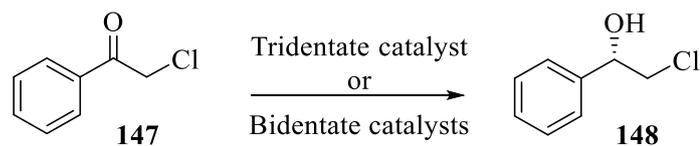
The ATH of α -phenoxyacetophenone **145** was also studied with both catalyst systems. This substrate contains an aromatic group on either side of the ketone, both able to form the favourable C-H/ π interaction with the catalysts. Reduction with the tridentate ligands gave full conversions; with ligand **36** achieving 81% ee of the (*S*)-alcohol product and ligand **38** affording 53% ee of the *S*-alcohol product (Table 17). Higher enantioselectivities were observed with the bidentate complexes with ee ranging from 90-94%, in this case the best catalyst was the thiophene complex **132** with 94% ee. In comparison, tethered catalyst **22** at 0.5 mol% and 2 M concentration was reported to form the alcohol product in 95% ee in 3 h.¹⁴⁷



Catalyst (loading %)	Time (h)	Conversion %	Yield %	ee %	<i>R/S</i>
Ligand 36^a (5%)	72	100	94	81	<i>S</i>
Ligand 38^a (5%)	72	100	96	53	<i>S</i>
Cat. 131^b (1%)	72	100	71	92	<i>S</i>
Cat. 132^b (1%)	120	98	89	94	<i>S</i>
Cat. 133^b (1%)	120	100	91	90	<i>S</i>
Cat. 135^b (1%)	144	100	97	92	<i>S</i>
Cat. 22^c (0.5%)	3	100	-	95	<i>R</i>

Table 17. Reduction of α -phenoxyacetophenone **145** with the two different catalyst systems. (a) (*R,R*)-Ligand (5 mol%), $\text{Ru}_3(\text{CO})_{12}$ ($5/3$ mol%) in *i*PrOH, $[\text{S}] = 0.1$ M, 80°C . (b) (*R,R*)-Catalyst (1 mol%), FA/TEA (5:2), DCM, $[\text{S}] = 1$ M, rt. (c) (*S,S*)-**22** (1 mol%), FA/TEA (5:2), $[\text{S}] = 2$ M, 28°C (lit.¹⁴⁷).

The reduction of α -chloroacetophenone **147** with the tridentate catalysts was unsuccessful. Once again it was suspected that there was catalyst poisoning, as in the methoxy ketone **143**. To test this hypothesis, acetophenone was added to the reductions, which resulted in no reduction of either ketone, with either of the tridentate ligands. Hence the results show ketone **147** to also inhibit the catalyst. In contrast, the bidentate catalysts gave almost full conversion of the substrate to (*S*)-**148**. Catalysts **133** and **135** were the top catalysts in this case with the *S*-alcohol product being formed in up to 91% ee (Table 18). In comparison, tethered catalyst **22** at 0.5 mol% and 2 M concentration was reported to form the alcohol product in 95% ee in 1.5 h.¹⁴⁷



Catalyst (loading %)	Time (h)	Conversion %	Yield %	ee %	R/S
Ligand 36 ^a (5%)	-	-	-	-	-
Ligand 38 ^a (5%)	-	-	-	-	-
Cat. 131 ^b (1%)	96	99	91	90	S
Cat. 132 ^b (1%)	96	100	79	89	S
Cat. 133 ^b (1%)	96	99	87	91	S
Cat. 135 ^b (1%)	168	94	86	91	S
Cat. 22 ^c (0.5%)	1.5	100	-	95	R

Table 18. Reduction of α -chloroacetophenone **147** with the two different catalyst systems. (a) (*R,R*)-Ligand (5 mol%), Ru₃(CO)₁₂ (⁵/₃ mol%) in *i*PrOH, [S] = 0.1 M, 80°C. (b) (*R,R*)-Catalyst (1 mol%), FA/TEA, DCM, [S] = 1 M, rt. (c) (*S,S*)-**22** (1 mol%), FA/TEA (5:2), [S] = 2 M, 28 °C (lit.¹⁴⁷).

Alpha amino ketone substrates were investigated next through the reduction of α -dimethylamino ketone **149** with the tridentate ligands. Both tridentate ligands failed to reduce **149**, leading to an investigation into the extent to which the dimethylamino group could be tolerated (Figure 42). An attempt to also reduce ketone **150** with the tridentate ligands was made and once again both failed to reduce this ketone, therefore the dimethylamino group appears to not be compatible with the tridentate ligands. It was suspected that the lone pair of the amine may be affecting the catalyst system, to overcome this, α -aminoacetophenone **151** was protected with Boc₂O to give ketone **152**, where the lone pair of the nitrogen is delocalised within the carbamate structure.

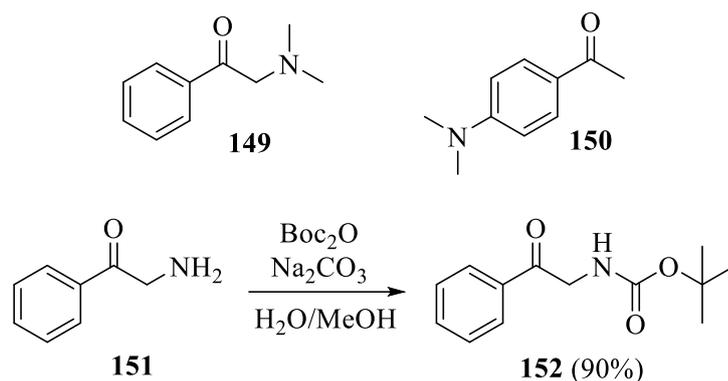
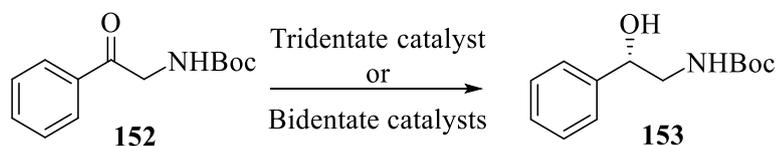


Figure 42. Structure of α -amino ketones and synthesis of Boc-protected α -amino ketone.

ATH with the tridentate ligands in this case was found to be successful allowing for full conversion to the (*S*)-alcohol product with the best catalyst being **36**, of the tridentate ligands, giving the product in 97% ee. The bidentate catalysts gave conversions of 98-100% and good enantioselectivities of 93-97% ee on this substrate, with the furan catalyst **131** being the best of this series (Table 19).

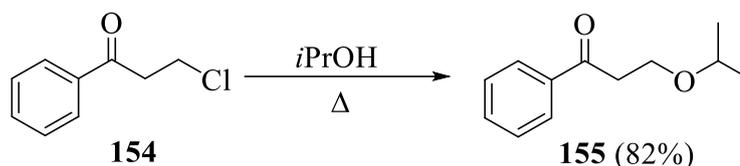


Catalyst (loading %)	Time (h)	Conversion %	Yield %	ee %	<i>R/S</i>
Ligand 36 ^a (5%)	72	100	99	97	<i>S</i>
Ligand 38 ^a (5%)	72	100	92	94	<i>S</i>
Cat. 131 ^b (1%)	109	100	94	97	<i>S</i>
Cat. 132 ^b (1%)	120	100	95	96	<i>S</i>
Cat. 133 ^b (1%)	120	100	95	93	<i>S</i>
Cat. 135 ^b (1%)	168	98	91	95	<i>S</i>

Table 19. Reduction of α -aminoacetophenone **152** with the two different catalyst systems. (a) (*R,R*)-Ligand (5 mol%), $\text{Ru}_3(\text{CO})_{12}$ ($5/3$ mol%) in *i*PrOH, [S] = 0.1 M, 80°C. (b) (*R,R*)-Catalyst (1 mol%), FA/TEA (5:2), DCM, [S]= 1 M, rt.

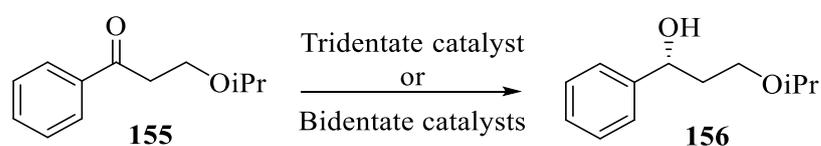
2.3.2. β -Substituted Ketones

An attempt at the reduction of ketone **154** with the tridentate ligands afforded ketone **155** and the same reaction without catalyst (Scheme 48) also gave the ketone **155** in 87% yield. This substrate was used for reductions with the catalysts as it contains a β -alkoxy group to the ketone.



Scheme 48. Formation of ketone **155** from ketone **154**. The product was also formed in attempts at ATH using tridentate ligands.

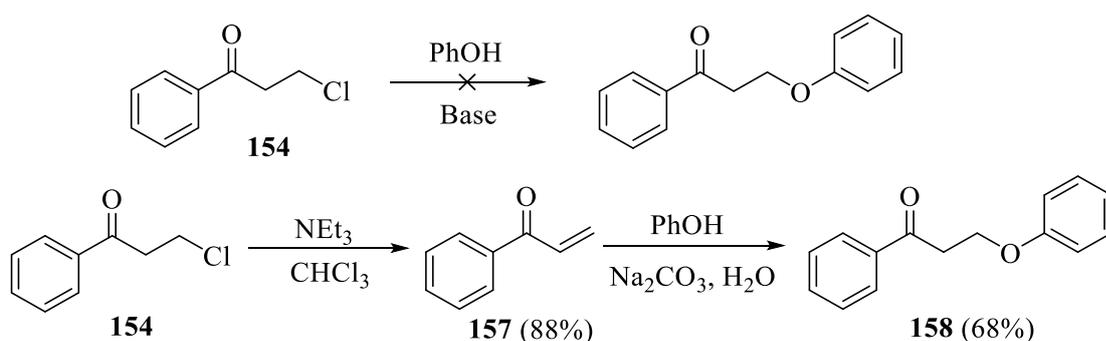
The ketone with the β -isopropoxy group led to interesting results with the tridentate ligands giving full conversion and obtaining 99% ee for the *R*-alcohol product (Table 20). This is interesting given that the reduction of ketone **154** with tridentate ligands affords ketone **155** but does not reduce it. Yet the reduction of the isolated ketone **155** can achieve full conversion, which shows the possibility of catalyst poisoning from **154** or even Cl^- ions. The substrate **155** was less compatible with the bidentate catalysts, affording much lower conversions of 52-87% and hence lower yields. The catalysts were also less enantioselective with ee ranging from 89 – 96% however these are still good results (Table 20).



Catalyst (loading %)	Time (h)	Conversion %	Yield %	ee %	R/S
Ligand 5^a (5%)	72	100	95	99	<i>R</i>
Ligand 6^a (5%)	72	100	96	99	<i>R</i>
Cat. 131^b (1%)	120	80	70	89	<i>R</i>
Cat. 132^b (1%)	132	52	45	92	<i>R</i>
Cat. 133^b (1%)	120	87	73	94	<i>R</i>
Cat. 135^b (1%)	168	55	41	96	<i>R</i>

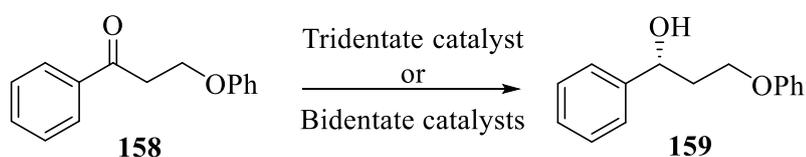
Table 20. Reduction of β -isopropoxy ketone **155** with the two different catalyst systems. (a) (*R,R*)-Ligand (5 mol%), $\text{Ru}_3(\text{CO})_{12}$ ($5/3$ mol%) in *i*PrOH, $[\text{S}] = 0.1$ M, 80°C . (b) (*R,R*)-Catalyst (1 mol%), FA/TEA (5:2), DCM, $[\text{S}]=1$ M, rt.

Attempts to make the β -phenoxy ketone **158** directly from β -chloro **154** was not possible. All reactions via the deprotonation of phenol using a variety of conditions, including different bases such as NaH and Na_2CO_3 , and then reacting with **154** always formed the vinyl ketone **157** as the major product. This is due to the facile β -elimination of the substrate, which was found to occur even by using the weak base NEt_3 . Iwasa *et al.*¹⁴⁸ have reported the reaction of phenol with the vinyl ketone **157** to give ketone **158**. This method was used and ketone **158** was obtained in 68% yield (Scheme 49).



Scheme 49. Routes to forming the β -phenoxy acetophenone

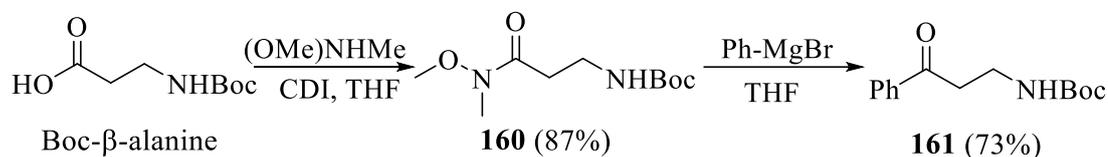
Reduction of the β -phenoxy ketone **158** gave products with similar enantioselectivities with the different catalysts, with ee ranging from 86-91% (Table 21). Both the tridentate ligands allowed for full conversion with the pyridine ligand **38** being the best of the two with 90% ee. The catalysts of bidentate ligands gave a diverse range of conversions with the reaction using catalyst **132** only having 50% conversion and the lowest ee of 87%. The furan **131** and isoxazole **133** catalyst gave almost full conversion and a high ee of 91%.



Catalyst (loading %)	Time (h)	Conversion %	Yield %	ee %	R/S
Ligand 36^a (5%)	72	100	98	86	<i>R</i>
Ligand 38^a (5%)	72	100	96	90	<i>R</i>
Cat. 131^b (1%)	120	98	94	91	<i>R</i>
Cat. 132^b (1%)	120	50	41	87	<i>R</i>
Cat. 133^b (1%)	144	100	93	91	<i>R</i>
Cat. 135^b (1%)	168	72	70	90	<i>R</i>

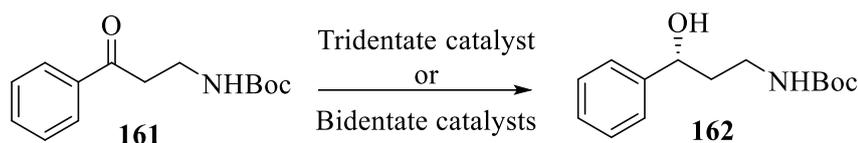
Table 21. Reduction of β -phenoxy ketone **158** with the two different catalyst systems. (a) (*R,R*)-Ligand (5 mol%), Ru₃(CO)₁₂ (⁵/₃ mol%) in *i*PrOH, [S] = 0.1 M, 80 °C. (b) (*R,R*)-Catalyst (1 mol%), FA/TEA (5:2), DCM, [S] = 1 M, rt.

Similar to the Boc-protected α -amino substrate, the β -derivative **161** was also studied in ATH with the different catalysts. Commercially available Boc- β -alanine was converted into the Weinreb amide **160** via CDI activation of the carboxylic acid. The amide **160** was subjected to the Grignard reagent to yield ketone **161** in 64% yield over two-steps (Scheme 50).



Scheme 50. Synthesis of ketone **161** from Boc- β -alanine

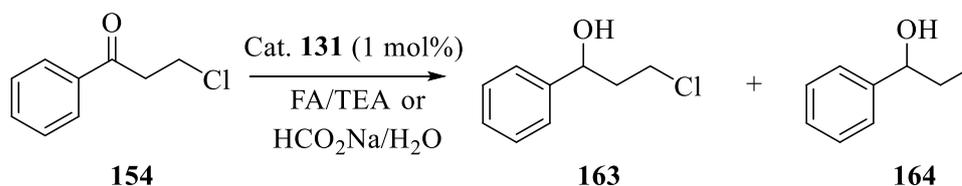
Comparable results were observed for the ee of the *R*-alcohol product with all the catalysts. The ester catalyst **135** proved to be the best catalyst for this substrate with a 96% conversion and 96% ee whilst the thiophene catalyst **132** was the least effective with a low 52% conversion (Table 22).



Catalyst (loading %)	Time (h)	Conversion %	Yield %	ee %	R/S
Ligand 36^a (5%)	72	nd	95	92	<i>R</i>
Ligand 38^a (5%)	72	nd	88	91	<i>R</i>
Cat. 131^b (1%)	120	95	88	91	<i>R</i>
Cat. 132^b (1%)	120	52	41	91	<i>R</i>
Cat. 133^b (1%)	144	85	84	92	<i>R</i>
Cat. 135^b (1%)	144	96	92	96	<i>R</i>

Table 22. Reduction of the β -amino ketone **161** with the two different catalyst systems. (a) (*R,R*)-Ligand (5 mol%), $\text{Ru}_3(\text{CO})_{12}$ ($5/3$ mol%) in *i*PrOH, [S] = 0.1 M, 80 °C. (b) (*R,R*)-Catalyst (1 mol%), FA/TEA (5:2), DCM, [S] = 1 M, rt.

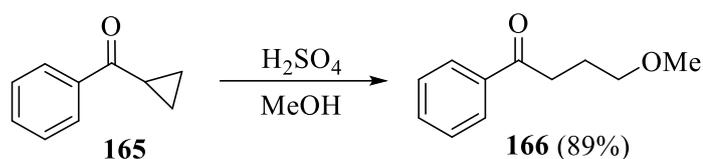
The reduction of β -chloro ketone **154** did not form the desired alcohol product using the tridentate ligand systems but instead gave the β -isopropoxy ketone **155** as previously mentioned. No reduction of the resultant ketone led to the conclusion that the β -chloro substrate was initially inhibiting the catalyst, as it was found that these tridentate catalysts are able to reduce ketone **155** when isolated. Reduction of **154** with catalyst **131** in FA/TEA led to the formation of a mixture of products with **163** and **164** as the major products and a small amount of the vinyl ketone **157** present (Scheme 51). Similar results were also obtained when the hydrogen source was changed to sodium formate in water. These products were not isolated nor were their ee recorded. Also due to the results obtained, the reductions with the other bidentate catalysts were not attempted.



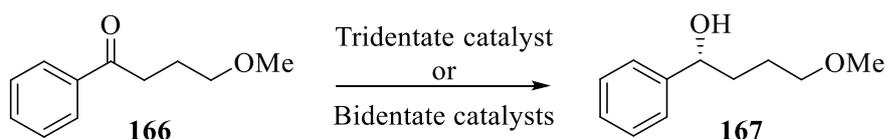
Scheme 51. Reduction of ketone **154**. (*R,R*)-**131** (1 mol%) in FA/TEA (5:2), [S] = 1 M, rt or 1% catalyst in H_2O , HCO_2Na (5 eq.), [S] = 1 M, 40 °C. Ratio of **163** to **164** is 1:2.

2.3.3. γ -Substituted Ketones

The γ -methoxy ketone **166** was prepared by ring-opening of cyclopropyl phenyl ketone **165** with methanol under strong acidic conditions (Scheme 52). Asymmetric reduction of **166** gave a diverse range of results with the catalysts. High conversions of 99% and 95% were obtained with the tridentate catalysts **36** and **38** giving the *R*-alcohol product in 83% and 89% ee (Table 23). The furan catalyst **131** gave an 89% conversion and 88% ee whilst catalyst **132** performed poorly with 55% conversion and 84% ee.



Scheme 52. Synthesis of ketone **166** from cyclopropyl ketone **165**.

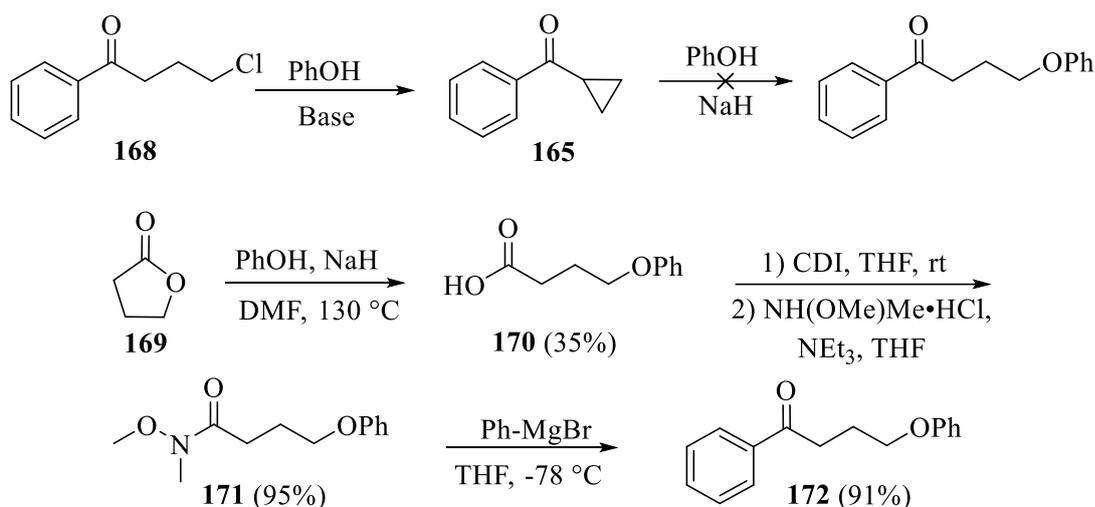


Catalyst (loading %)	Time (h)	Conversion %	Yield %	ee %	<i>R/S</i>
Ligand 36^a (5%)	72	99	91	83	<i>R</i>
Ligand 38^a (5%)	72	95	89	89	<i>R</i>
Cat. 131^b (1%)	144	89	70	88	<i>R</i>
Cat. 132^b (1%)	144	55	49	84	<i>R</i>
Cat. 133^b (1%)	168	66	57	90	<i>R</i>
Cat. 135^b (1%)	168	71	66	92	<i>R</i>

Table 23. Reduction of the γ -methoxy ketone **166** with the two different catalyst systems. (a) (*R,R*)-Ligand (5 mol%), $\text{Ru}_3(\text{CO})_{12}$ ($\frac{5}{3}$ mol%) in *i*PrOH, [S] = 0.1 M, 80 °C. (b) (*R,R*)-Catalyst (1 mol%), FA/TEA (5:2), DCM, [S] = 1 M, rt.

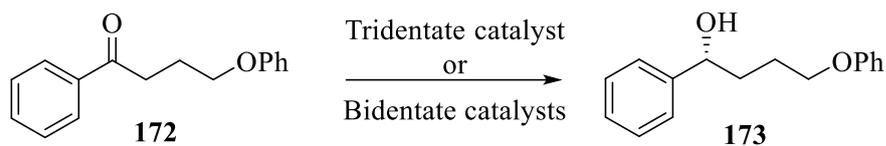
For the preparation of γ -phenoxy ketone **172**, the γ -chloro ketone **168** was treated with sodium phenoxide, prepared from the reaction of phenol and NaH, in an attempt to substitute the chloro group with the phenoxide. However the desired $\text{S}_{\text{N}}2$ reaction did not proceed and alternatively the substrate cyclised to form the cyclopropyl ketone

165. Changing the base from NaH to Na₂CO₃ had no effect and also yielded **165**. With the cyclopropyl ketone in hand, a ring opening under basic conditions was attempted with NaH and phenol but this did not work. An alternative route was taken, where phenoxide was reacted with γ -butyrolactone **169** that surprisingly ring opened to form the carboxylic acid **170**.¹⁴⁹ The carboxylic acid was converted to Weinreb amide **171**, by CDI activation, and this was further reacted with phenylmagnesium bromide to give ketone **172** (Scheme 53).



Scheme 53. Synthetic routes taken to form the γ -phenoxy ketone **172**.

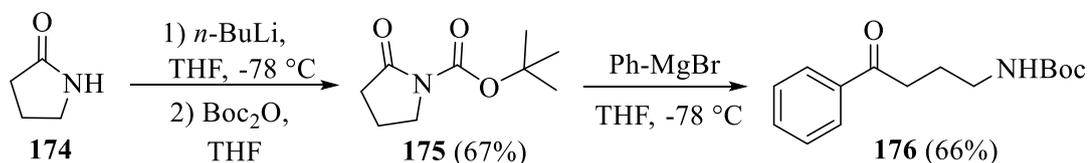
γ -Phenoxy ketone **172** was then reduced with the catalysts and the resultant (*R*)-alcohol **173** was formed in similar enantioselectivities to its α and β -analogues with the ee ranging from 87 to 93% (Table 24). Tridentate catalysts **36** and **38** saw full conversions with excellent yields of 98% and a good ee of 90%. A similar result was also observed with catalyst **133** of the bidentate catalysts with 96% yield and an 89% ee. The furan catalyst **131** did not achieve full conversion but gave a good result of 93% yield and 90% ee.



Catalyst (loading %)	Time (h)	Conversion %	Yield %	ee %	R/S
Ligand 36^a (5%)	72	100	98	90	<i>R</i>
Ligand 38^a (5%)	72	100	98	90	<i>R</i>
Cat. 131^b (1%)	72	93	93	90	<i>R</i>
Cat. 132^b (1%)	168	nd	61	87	<i>R</i>
Cat. 133^b (1%)	144	100	96	89	<i>R</i>
Cat. 135^b (1%)	168	50	48	93	<i>R</i>

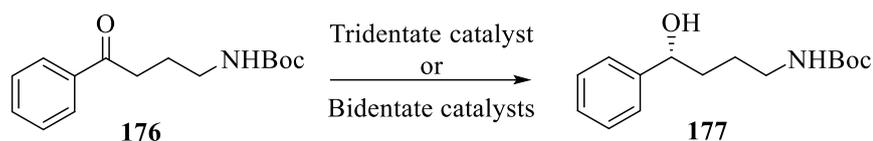
Table 24. Reduction of the γ -phenoxo ketone **172** with the two different catalyst systems. (a) (*R,R*)-Ligand (5 mol%), $\text{Ru}_3(\text{CO})_{12}$ ($5/3$ mol%) in *i*PrOH, [S] = 0.1 M, 80 °C. (b) (*R,R*)-Catalyst (1 mol%), FA/TEA (5:2), DCM, [S] = 1 M, rt.

γ -Butyrolactam **174** was deprotonated with *n*-BuLi and reacted with Boc_2O to give the Boc-protected lactam **175** in 67% yield. The amide was then reacted with phenylmagnesium bromide to afford ketone **176** in 66% yield (Scheme 54).



Scheme 54. Synthesis of γ -amino ketone **176**.

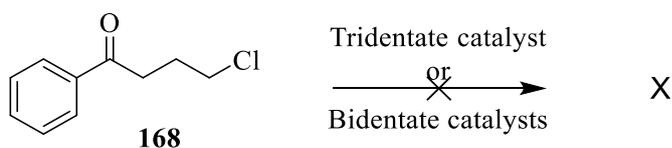
The asymmetric reduction of γ -amino ketone **176** proved to be more challenging with catalysts **132** and **135**, which gave low conversions of 55 and 50% respectively (Table 25). The isoxazole catalyst **133** gave the *R*-alcohol product **177** in the lowest ee of 76% whilst the other catalysts gave products which ranged from 88 to 92% ee. The furan catalyst **131** and both tridentate catalysts were the most successful in achieving full conversion and high ee.



Catalyst (loading %)	Time (h)	Conversion %	Yield %	ee %	R/S
Ligand 36 ^a (5%)	72	100	99	92	R
Ligand 38 ^a (5%)	72	100	92	91	R
Cat. 131 ^b (1%)	80	100	92	93	R
Cat. 132 ^b (1%)	144	55	45	88	R
Cat. 133 ^b (1%)	144	77	73	76	R
Cat. 135 ^b (1%)	168	50	45	90	R

Table 25. Reduction of the γ -amino ketone **176** with the two different catalyst systems. (a) (*R,R*)-Ligand (5 mol%), Ru₃(CO)₁₂ (⁵/₃ mol%) in *i*PrOH, [S] = 0.1 M, 80 °C. (b) (*R,R*)-Catalyst (1 mol%), FA/TEA (5:2), DCM, [S] = 1 M, rt.

Reduction of the γ -chloro substrate **176** with the complexes of the tridentate ligands **36** and **38** was also unsuccessful as only starting material was recovered (Scheme 55); from the results it can be concluded that the presence of an alkyl-chloride in the substrate leads to deactivation/poisoning of the tridentate catalysts. This appears only limited to the alkyl-chlorides as previous results have shown that aryl-chlorides can be reduced in excellent conversions and good ee (84-91%). Employment of catalyst **131** in FA/TEA for the reduction of **176** gave a mixture of products and was not investigated further with the other catalysts.

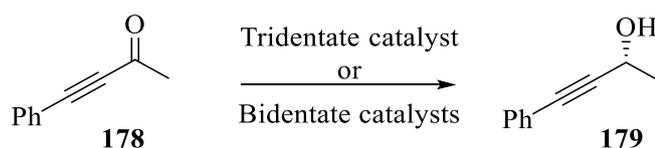


Scheme 55. Attempted ATH of γ -chloro ketone **168**.

2.3.4. Alkynones

Phenyl groups adjacent to the ketone had been investigated but alkynes adjacent to the ketones are unknown in the ATH with the novel catalysts bearing heterocyclic groups. Reduction of alkyne **178** failed using the tridentate ligands, both at 1% and at 5% catalyst loadings. However, reduction with the bidentate catalysts was successful

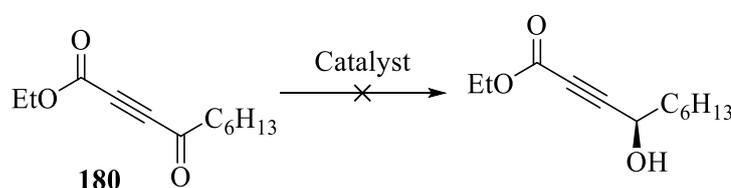
(Table 26), with furan catalyst **131** generating the best yield and thiophene catalyst **132** producing the highest enantioselectivity of 89% ee. The reduction of ketone **178** with tethered catalyst **22** has been reported to form the corresponding alcohol product in 89% ee and 59% conversion.¹⁴⁷ This is a similar result to the reduction with catalyst **132**, however catalyst **131** under the same conditions gives the product in a higher yield.



Catalyst (loading %)	Time (h)	Yield %	ee %	<i>R/S</i>
Ligand 36 ^a (5%)	72	nr	-	-
Ligand 38 ^a (5%)	72	nr	-	-
Cat. 131 ^b (1%)	96	80	86	<i>R</i>
Cat. 132 ^b (1%)	120	57	89	<i>R</i>
Cat. 133 ^b (1%)	120	65	86	<i>R</i>
Cat. 135 ^b (1%)	120	45	84	<i>R</i>
Cat. 22 ^c (0.5%)	22	59 ^d	89	<i>S</i>

Table 26. Reduction of the ketone **178** with the two different catalyst systems. (a) (*R,R*)-Ligand (5 mol%), Ru₃(CO)₁₂ (5/3 mol%) in *i*PrOH, [S] = 0.1 M, 80 °C. (b) (*R,R*)-Catalyst (1 mol%), FA/TEA (5:2), DCM, [S] = 1 M, rt. (c) (*S,S*)-**22** (1 mol%), FA/TEA (5:2), [S] = 2 M, 28 °C (lit.⁵³). (d) % Conversion.

The reduction of an activated alkyne was also attempted with alkynone **180**, prepared following a literature method.¹⁵⁰ The reduction with the bidentate catalysts was unsuccessful due to the substrate decomposing in the formic acid-triethylamine mixture. Reduction with the tridentate ligands appeared feasible due to the milder conditions however complexes of both ligands **36** and **38** gave no reduction (Scheme 56). This suggests that the tridentate catalyst systems are also not compatible with alkynes.



Scheme 56. Failed reduction of alkynone **180** with catalyst systems. (a) (*R,R*)-Ligand (5 mol%), Ru₃(CO)₁₂ (⁵/₃ mol%) in *i*-PrOH, [S] = 0.1 M, 80 °C. (b) (*R,R*)-Catalyst (1 mol%), FA/TEA (5:2), DCM, [S] = 1 M, rt.

Summary

The substrate scope of two different but closely related catalyst systems, one which uses tridentate and the other bidentate ligands, has been investigated. The catalyst system for the tridentate ligands is poisoned by alkyl-chloro containing ketones, α -methoxy ketones, and amino groups. Additionally, the reductions require a 5 mol% catalyst loading to achieve good conversions and are not compatible with alkynones. However these catalysts perform well in the reduction of β - and γ -substituted acetophenones.

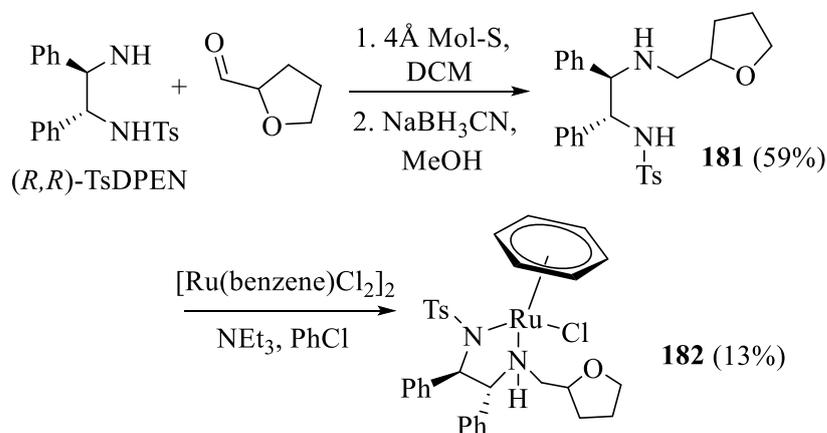
On the other hand, the catalyst system that makes use of the bidentate ligands has shown its versatility with various α , β and γ -substituted ketones being reduced in high enantioselectivity. These catalysts reduce α -methoxy ketones and are not poisoned by alkyl chloro substrates for example α -chloro **147** is reduced in good ee. An alkynone substrate was also reduced in good ee with the bidentate catalyst system. However, these novel catalysts have shown lower activity and enantioselectivity in the ATH of some functionalised ketones such as **145** and **147** when compared to tethered catalyst **22**.

2.4. Ligands containing non-Aromatic Heterocyclic groups

Having explored a range of aromatic heterocycles in TsDPEN ligands that work in the reduction of ketones substrates using [Ru(benzene)Cl₂]₂, ligands containing non-aromatic heterocycles on the TsDPEN ligand were explored to determine their effectiveness as ATH catalysts. The ligands synthesised were tested as tridentate and bidentate ligands in the two different catalysts systems described in Section 2.2.

Ligand **181** was prepared by the reductive amination of racemic tetrahydro-2-furfural and TsDPEN. This ligand is the non-aromatic derivative of **125** and was investigated firstly as a tridentate ligand by reacting with Ru₃(CO)₁₂. As expected, ligand **181** did not reduce acetophenone in the tridentate catalyst system; this too has an oxygen donor

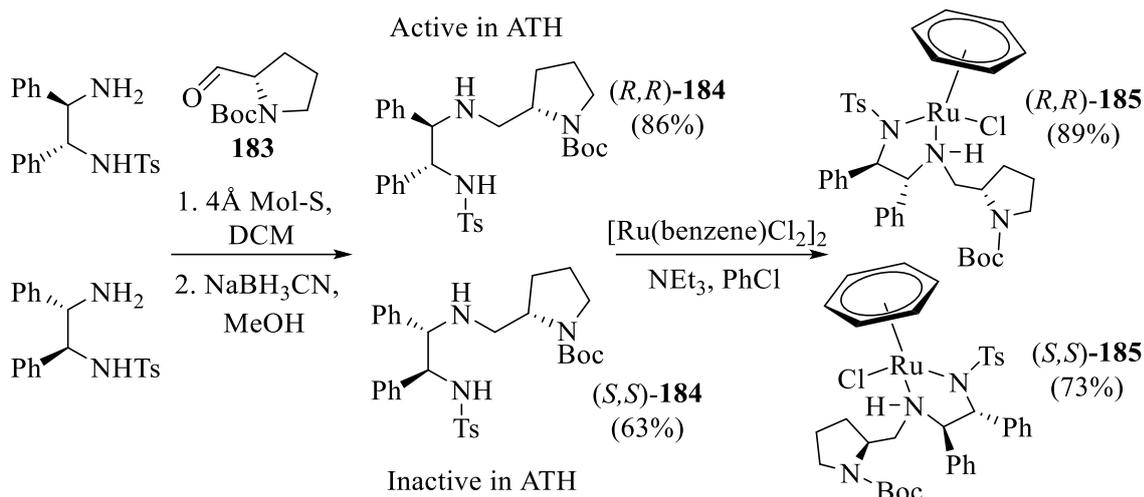
atom that weakly coordinates to ruthenium centres. Efforts turned to forming catalyst **182** by the complexation of ligand **181** and $[\text{Ru}(\text{benzene})\text{Cl}_2]_2$ (Scheme 57). This catalyst was employed in the bidentate catalyst system which reduced acetophenone in 34% conversion and 89% ee.



Scheme 57. Synthesis of ligand **181** and complexation to catalyst **182**.

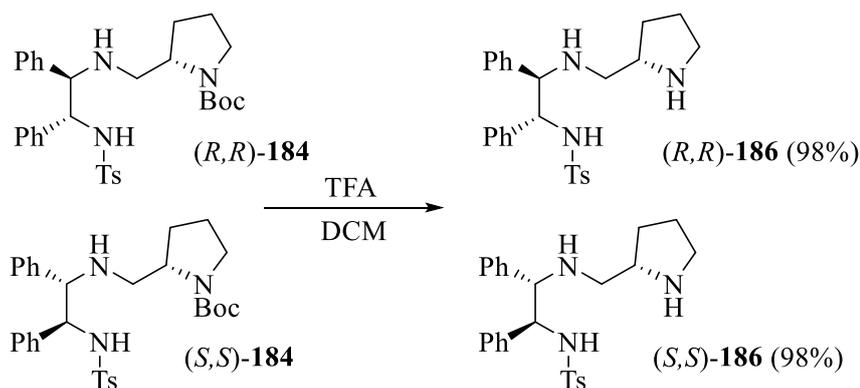
Ligand **181** contains a racemic chiral centre at the C-2 position of the tetrahydrofuran, leading to the formation of diastereomers that may possibly lead to the formation of active and inactive complexes. To avoid complications from the diastereomeric ligand, a ligand with an enantiomerically pure containing-heterocycle was synthesised. Aldehyde **183** was prepared via Swern oxidation from (S) -*N*-Boc-prolinol and was reacted with TsDPEN in a reductive amination (Scheme 58). A Boc derivative was chosen in this case as the lone pair of electrons on the nitrogen is delocalised into the carbamate and less likely to coordinate to ruthenium metal centres. The (R,R) -TsDPEN derivative (R,R) -**184** was converted into complex (R,R) -**185** that subsequently reduced acetophenone in 92% ee. However an interesting result was that ligand (R,R) -**184** was also found to reduce acetophenone in 27% ee under the tridentate catalyst conditions.

On the other hand, the diastereomeric ligand (S,S) -**184**, prepared from (S,S) -TsDPEN, was found to not reduce acetophenone under the tridentate catalyst conditions. Complexation with $[\text{Ru}(\text{benzene})\text{Cl}_2]_2$ formed catalyst (S,S) -**185** which did not reduce acetophenone under the bidentate catalyst conditions. The results demonstrate that the chiral centre of the heterocycle plays an important part in determining if a catalyst is active or inactive.



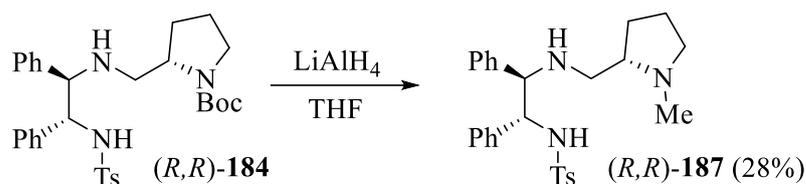
Scheme 58. The formation of ligands **184** and catalysts **185**. The (R,R) -derivative is active in ATH and the (S,S) -derivative is inactive.

Ligands **184** could be deprotected by reacting with TFA to give the free NH-pyrrolidine **186** (Scheme 59). The derivative (R,R) -**186** reduced acetophenone under the tridentate catalyst conditions, but in 0% ee. The (S,S) -**186** derivative also reduced acetophenone under the same conditions however this also gave a product of 0% ee in a lower conversion (Table 27). Neither ligands were able to reduce acetophenone using the bidentate catalyst conditions, indicating that these ligands likely serve as a tridentate species only.

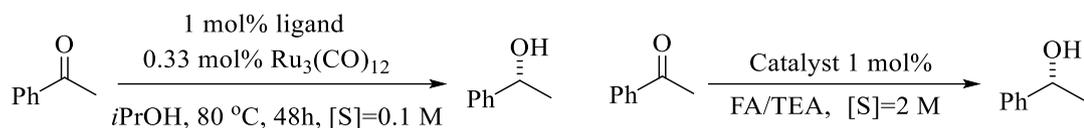


Scheme 59. Deprotection of **184** using TFA to yield **186**.

The reaction between (R,R) -**184** and LiAlH_4 gave the *N*-methylated derivative ligand (R,R) -**187** (Scheme 60). This was also found to work as a tridentate ligand reducing acetophenone in 5% ee. This ligand did not work under the bidentate catalyst conditions. Results for all reductions are summarised in Table 27.



Scheme 60. LiAlH₄ reduction of the carbamate centre of **184** to form **187**.



Ligand/Cat.	Conv /%	ee /%	R/S	Ligand/Cat.	Conv /%	ee /%	R/S
(<i>R,R</i>)- 181	0	-	-	(<i>R,R</i>)- 182	34	89	<i>R</i>
(<i>R,R</i>)- 184	67	27	<i>R</i>	(<i>R,R</i>)- 185	83	92	<i>R</i>
(<i>S,S</i>)- 184	0	-	-	(<i>S,S</i>)- 185	0	-	-
(<i>R,R</i>)- 186	85	0	-	(<i>R,R</i>)- 186	0	-	-
(<i>S,S</i>)- 186	45	0	-	(<i>S,S</i>)- 186	0	-	-
(<i>R,R</i>)- 187	35	5	<i>R</i>				

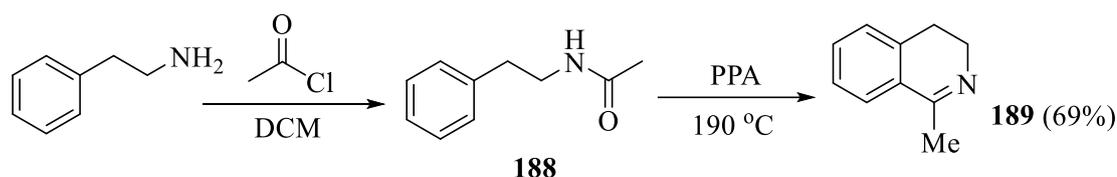
Table 27. Reduction of acetophenone using ligands and catalysts containing non-aromatic heterocycles.

Summary

A range of non-aromatic heterocycles on the TsDPEN unit have been investigated to determine their ability to act as either bidentate or tridentate ligands. A racemic tetrahydrofuran heterocycle has demonstrated to work as a bidentate ligand that can reduce acetophenone to the alcohol in 34% conversion and 89% ee. The use of an enantiomerically pure pyrrolidine heterocycle reveals that the third chiral centre on the ligand is crucial as this leads to either active or inactive ligands in the ATH of acetophenone. The results obtained show the non-aromatic heterocycles to form inferior ligands for ATH compared to the aromatic heterocycles.

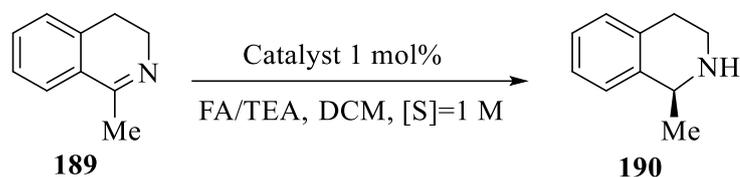
Chapter 3: ATH of Imines

The novel bidentate catalysts (Section 2.2.2.) have shown to be effective in the ATH of ketones however their suitability as catalysts in the ATH of imines had not been explored. Some dihydroisoquinolines have been reported to be compatible substrates in ATH using ruthenium complexes (Section 1.6.). These types of imines were therefore chosen to be tested using the bidentate catalysts alongside some commercially available catalysts as a comparison. Imine **189** was prepared by a Bischler-Napieralski cyclisation of amide **188** using polyphosphoric acid (Scheme 61).



Scheme 61. Formation of the DHIQ **189** from phenethylamine via a Bischler-Napieralski cyclisation.

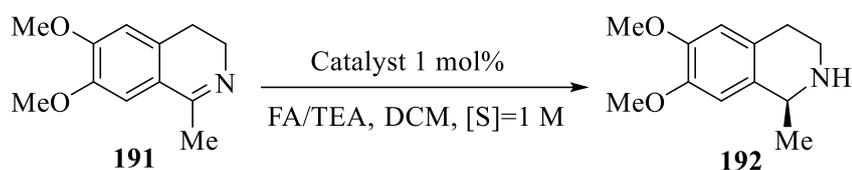
For the reduction of imine **189** the same conditions were employed as for the ATH of ketones, using a mixture of FA/TEA and DCM at 1 M, with furan catalyst (*R,R*)-**131**. The conversion and enantioselectivity were determined by chiral-GC for the *N*-acetylated derivative upon completion of the reaction. Catalyst (*R,R*)-**131** gave the corresponding amine product in 95% conversion and 80% ee; this is analogous to the results of catalyst (*R,R*)-**16** (Table 28). The *p*-cymene derivative (*R,R*)-**18** gave a product of higher ee but the best result was from the tethered catalyst (*R,R*)-**22** with 97% ee. The tridentate catalysts were also tested under the suitable conditions but were found to not reduce imines.



Catalyst	Time (h)	Conv /%	ee /%	<i>R/S</i>
(<i>R,R</i>)- 22	24	100	97	<i>S</i>
(<i>R,R</i>)- 131	72	95	80	<i>S</i>
(<i>R,R</i>)- 16	72	93	80	<i>S</i>
(<i>R,R</i>)- 18	24	85	89	<i>S</i>

Table 28. ATH of DHIQ **189** using catalyst **131** and commercially available catalysts.

An electron-rich ring in the substrate was then investigated with the introduction of two dimethoxy groups, i.e. DHIQ **191**. The dimethoxy groups in this substrate were not compatible with the tethered catalyst (*R,R*)-**22** as the amine product was obtained in just 33% ee, although a reasonable 95% conversion, determined by chiral-GC analysis (Table 29). Catalyst (*R,R*)-**16** also gave poorer enantioselectivity compared to the reduction of **189**. The furan catalyst (*R,R*)-**131** gave a result that was little changed compared to the parent compound **190** and this same trend was exhibited with catalyst (*R,R*)-**18** which is also the best catalyst for the imine (the product was of 90% ee).

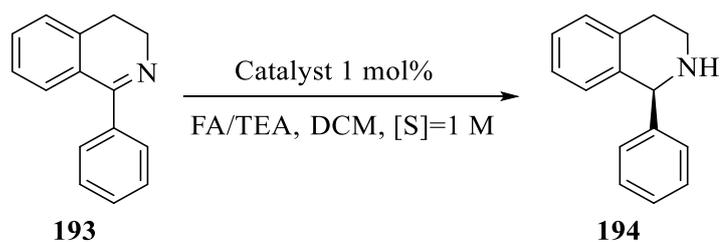


Catalyst	Time (h)	Conv /%	ee /%	<i>R/S</i>
(<i>R,R</i>)- 22	16	95	33	<i>S</i>
(<i>R,R</i>)- 131	72	96	81	<i>S</i>
(<i>R,R</i>)- 16	72	90	51	<i>S</i>
(<i>R,R</i>)- 18	26	96	90	<i>S</i>

Table 29. ATH of DHIQ **191** using furan catalyst (*R,R*)-**131** and related commercially available catalysts.

3.1. ATH of 1-Phenyl-3,4-dihydroisoquinolines

A further study was carried out on the reduction of the more difficult 1-phenyl-3,4-dihydroisoquinoline **193**, given that furan catalyst (*R,R*)-**131** had reduced the other dihydroisoquinolines in good ee. As expected the tethered catalyst (*R,R*)-**22** gave a low ee of 10% due to both the phenyl and fused aromatic ring competing for a CH/ π interaction with the η^6 -arene from the catalyst. The Noyori-Ikariya catalysts (*R,R*)-**16** and (*R,R*)-**18** also gave poor enantioselectivities for amine product **194** which could also be attributed to the competing CH/ π interactions. However a remarkable result was obtained with furan catalyst (*R,R*)-**131** that formed the amine product **194** in 90% ee and 93% conversion (Table 30).



Catalyst	Time (h)	Conv /%	ee /%	R/S
(<i>R,R</i>)- 22	16	97	10	<i>S</i>
(<i>R,R</i>)- 131	24	93	90	<i>S</i>
(<i>R,R</i>)- 16	48	45	24	<i>S</i>
(<i>R,R</i>)- 18	48	11	42	<i>S</i>

Table 30. ATH of DHIQ **193** using furan catalyst (*R,R*)-**131** and related commercially available catalysts.

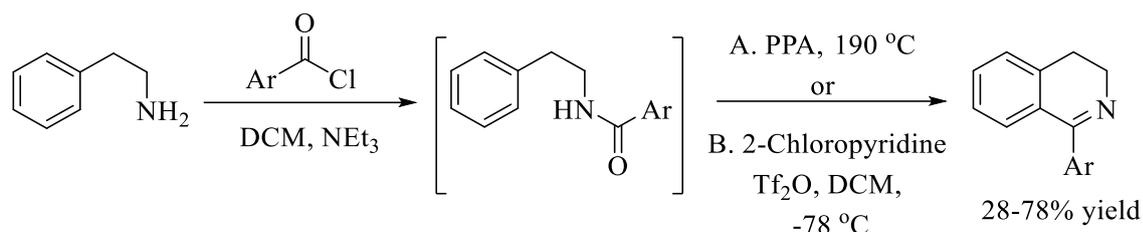
The furan catalyst (*R,R*)-**131** was once again employed to reduce imine **193** with the solvent MeCN that yielded the product in slightly lower conversion but the enantioselectivity remained unchanged. Catalyst (*R,R*)-**132** gave a similar enantioselectivity but was slower reacting and reached a maximum of 86% conversion (Table 31). To test whether the high enantioselectivities were due to the donor atom present, catalyst (*R,R*)-**135** was used in the reduction and this gave a product with a much lower ee of 49%. An *N*-benzyl-containing catalyst, (*R,R*)-**32e**, failed to reduce the imine asymmetrically, and also gave a product of low conversion. These results show that neither an aromatic group alone nor the presence of a heteroatom give high ee. However the results support the theory that a heteroaromatic is crucial for the high enantioselectivity.

Catalyst	Solvent	Time (h)	Conv /%	ee /%	R/S
(<i>R,R</i>)- 131	DCM	24	93	90	<i>S</i>
(<i>R,R</i>)- 131	MeCN	24	90	90	<i>S</i>
(<i>R,R</i>)- 132	DCM	48	86	91	<i>S</i>
(<i>R,R</i>)- 135	DCM	96	77	49	<i>S</i>
(<i>R,R</i>)- 32e	DCM	72	12	0	<i>S</i>

Table 31. ATH of DHIQ **193** using heterocyclic catalysts. Conditions: Catalyst (1 mol%), FA/TEA, Solvent, [S] = 1 M.

3.2. ATH of Substituted 1-Aryl-3,4-dihydroisoquinolines

The next stage in the study was to investigate the effect of different substituents on the non-fused aromatic ring. A diverse range of substituted dihydroisoquinolines were prepared by the Bischler-Napieralski reaction using polyphosphoric acid (PPA). Some amides were not compatible with PPA, such as those containing methoxy groups and therefore required milder conditions of Tf₂O and 2-chloropyridine (Scheme 62).



Scheme 62. Synthetic method for the preparation of 1-aryl-3,4-DHIQ.

1-Tolyl-3,4-dihydroisoquinolines

The furan catalyst (*R,R*)-**131** was used in the investigation of ATH of 1-aryl-3,4-DHIQs starting with tolyl derivatives (Figure 43). Product analysis could not be completed by chiral GC for these amines, however an isolated yield was obtained for each substrate and the ee was determined by chiral-HPLC. From the series, the *para*-substituted derivative **195** was reduced in a good yield and high enantioselectivity of 90% ee. The *meta*-derivative **196** was reduced in a higher ee of 92% ee and also gave a good yield. Both *para* and *meta* substituted dihydroisoquinolines have previously given poor ee in ATH reactions with Noyori-Ikariya type complexes, however catalyst (*R,R*)-**131** is clearly an exception to this. The *ortho*-substituted **197** gave a much lower ee of 76% and was low yielding which is contrary to literature reports showing that substrates containing *ortho*-substituents tended to be reduced in high ee (Section 1.6.2.).

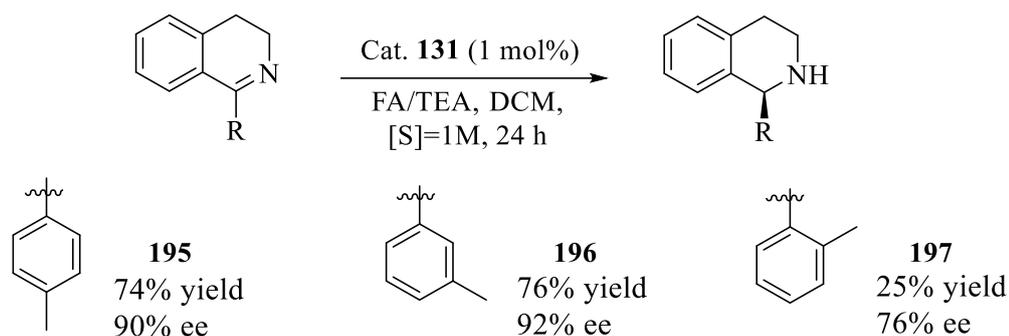


Figure 43. Method for reduction of 1-aryl-3,4-DHIQs and the reduction of tolyl derivatives.

Halo-substituted 1-Aryl-3,4-dihydroisoquinolines

The *ortho*-substituted chloro derivative of **198** was not reduced with furan catalyst (*R,R*)-**131** contrary to these reducing in high ee with the parent catalyst **16**. The *para* and *meta*-chloro-substituted substrates on the other hand were reduced in high ee of 88% and 91% respectively (Figure 44). A *para*-bromo **201** derivative reduced in good yield and high ee of 93% and a larger *para*-iodo-containing substrate **202** was reduced with the same enantioselectivity.

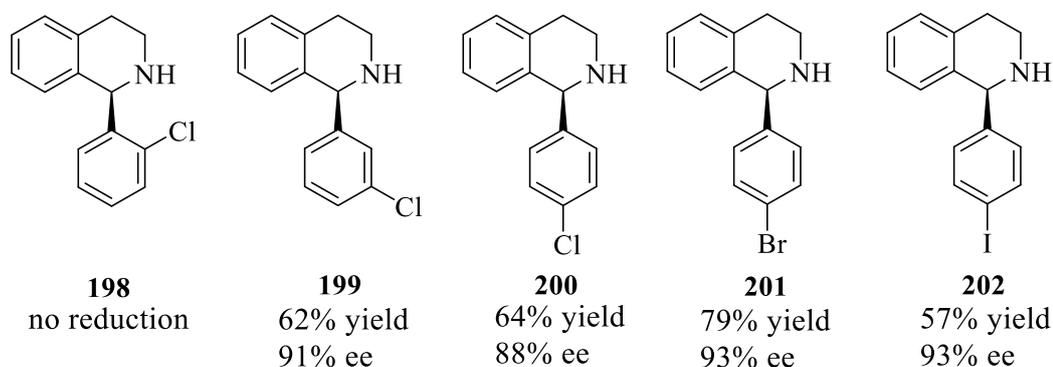


Figure 44. ATH products of halo derivatives **198-202** using furan catalyst **131**. Conditions: Catalyst 1 mol%, FA/TEA, DCM, [S] = 1 M.

Methoxy-substituted 1-Aryl-3,4-dihydroisoquinolines

Substrates containing the electron-donating methoxy groups were tested next, with the *ortho*-methoxyphenyl DHIQ reduced to **203** in 90% ee but here the reaction was slow

and gave a poor yield of 28% (Figure 45). This shows that *ortho* groups are not compatible with catalyst (*R,R*)-**131**, possibly due to steric hindrance. The *para*-methoxyphenyl substrate **204** on the other hand gave a great result of 92% ee and the *meta*-methoxyphenyl DHIQ was better with product **205** formed in 94% ee.

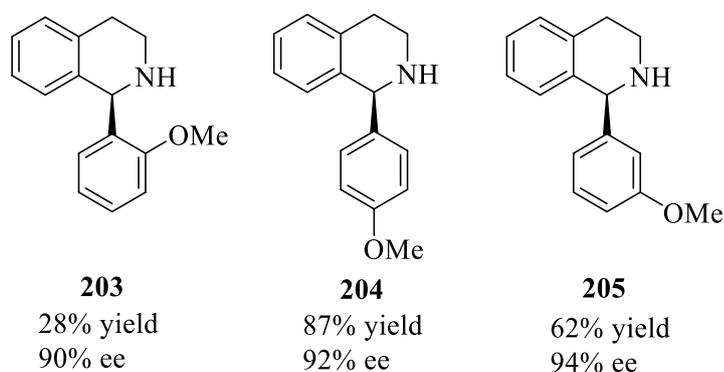


Figure 45. ATH products of methoxy derivatives **203-205** using furan catalyst (*R,R*)-**131**. Conditions: Catalyst 1 mol%, FA/TEA, DCM, [S] = 1 M.

Electron-withdrawing 1-Aryl-3,4-dihydroisoquinolines

The electron-withdrawing group NO₂ in the *para*-position of the 1-aryl group of a DHIQ gave product **206** in a mediocre yield of 50% but the ee was still high at 89%. The reduction of the trifluoromethyl derivative worked well, giving product **207** in high yield and high ee (Figure 46).

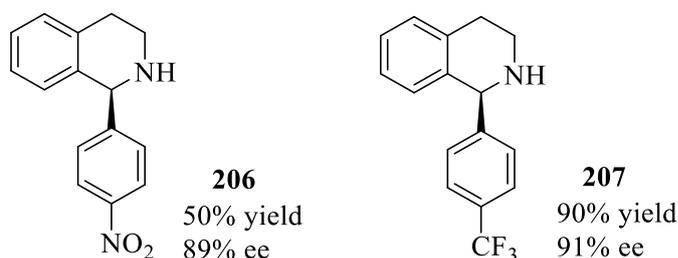


Figure 46. ATH products of electron withdrawing derivatives **206** and **207** using furan catalyst **131**. Conditions: Catalyst 1 mol%, FA/TEA, DCM, [S] = 1 M.

Di-substituted-1-Aryl-3,4-dihydroisoquinoline

Having determined that *para* and *meta* monosubstituted 1-aryl-3,4-DHIQs gave reduction products with good enantioselectivity, the study was expanded onto di-substituted substrates. Substrates with dimethoxy groups on the *para* and *meta* positions gave the amine product **208** in 91% ee (Figure 47). A substrate containing a cyclised ether group on the DHIQ was also tested and reduced to give **209** in a high ee of 90%.

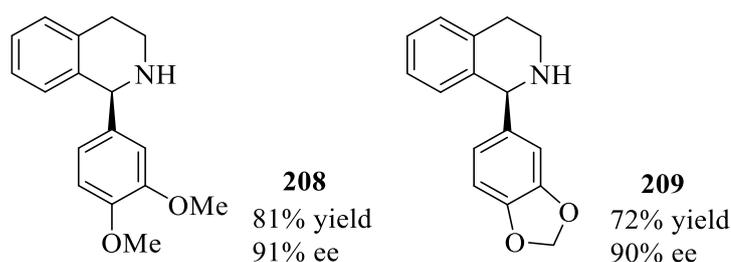
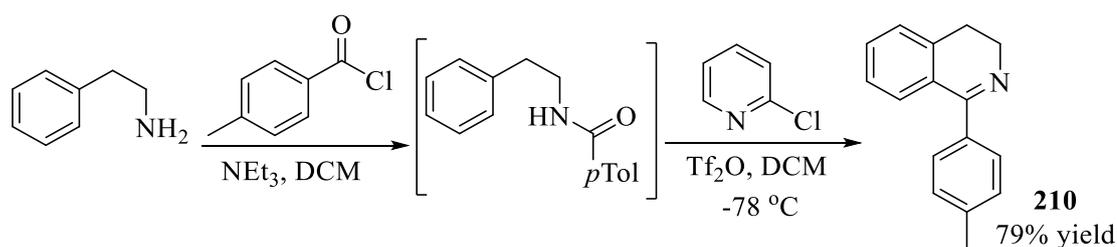


Figure 47. ATH products of di-substituted derivatives **208** and **209** using furan catalyst **131**. Conditions: Catalyst 1 mol%, FA/TEA, DCM, [S] = 1 M.

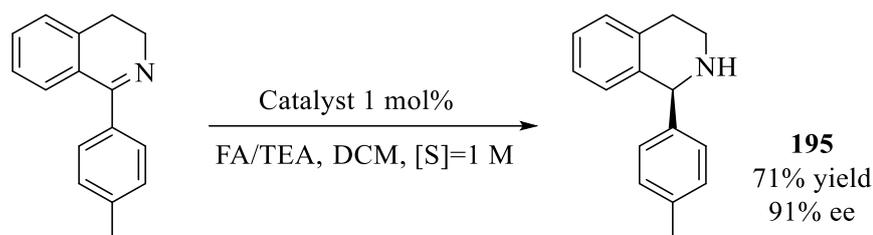
Gram-scale ATH of 1-Aryl-3,4-dihydroisoquinoline

To determine the suitability of the method at a larger scale, imine **210** was chosen for reduction at a gram-scale. The formation of the imine from phenethylamine over 2 steps yielded the product in 79% yield (Scheme 63).



Scheme 63. Gram-scale formation of DHIQ **210**.

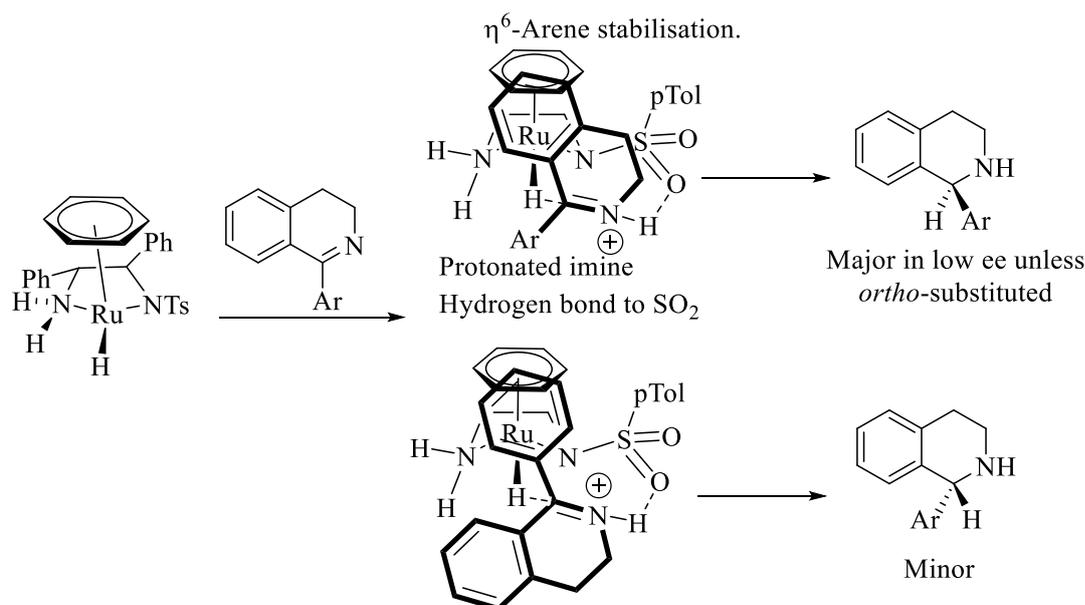
Keeping the conditions for the reduction the same, 1.1 grams of imine **210**, equivalent to 5 mmol, was reduced with the furan catalyst (*R,R*)-**131** (Scheme 64). The amine **195** was obtained in 71% yield and with 91% ee an almost equal result to the smaller-scale reduction. This shows there is no change when the scale of reduction is altered.



Scheme 64. ATH of 1.1 grams of DHIQ 210

3.3. Mechanism for the ATH of 1-Aryl-3,4-dihydroisoquinolines

With the results obtained, the mechanism for the ATH is proposed to be similar to the Noyori-Ikariya catalysts in reducing imines (Section 1.6.1.). The TS has a protonated imine substrate hydrogen bonded to an oxygen atom of the sulfonyl. Additionally an aromatic moiety in the imine can form a CH/ π interaction with the η^6 -arene of the catalyst. In the case of the Noyori-Ikariya catalysts the CH/ π interaction can exist between either the aryl group or the fused aromatic ring of the imine which results in the reduction to either enantiomer and therefore low ee. For the heterocycle-containing catalysts, the heterocycle may add a further stabilising interaction that allows discrimination of the aromatic groups. Here the heterocycle interacts primarily with the aryl group and the arene with the fused-aromatic ring. This in turn predominantly forms one enantiomer, as illustrated in Figure 48.



Proposed ATH Mechanism

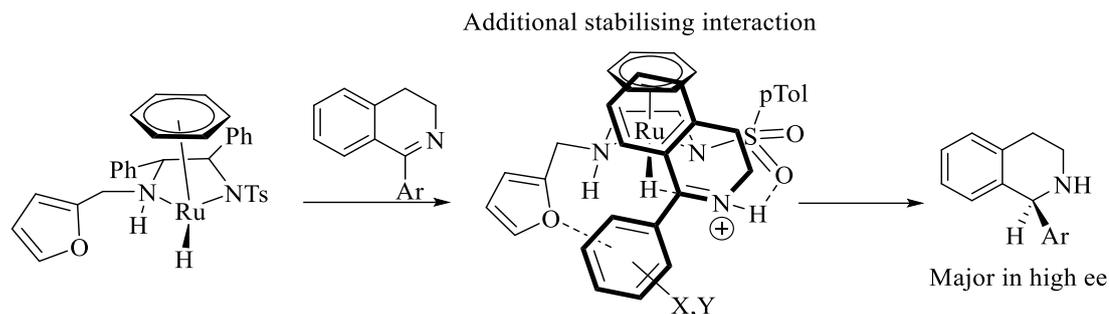
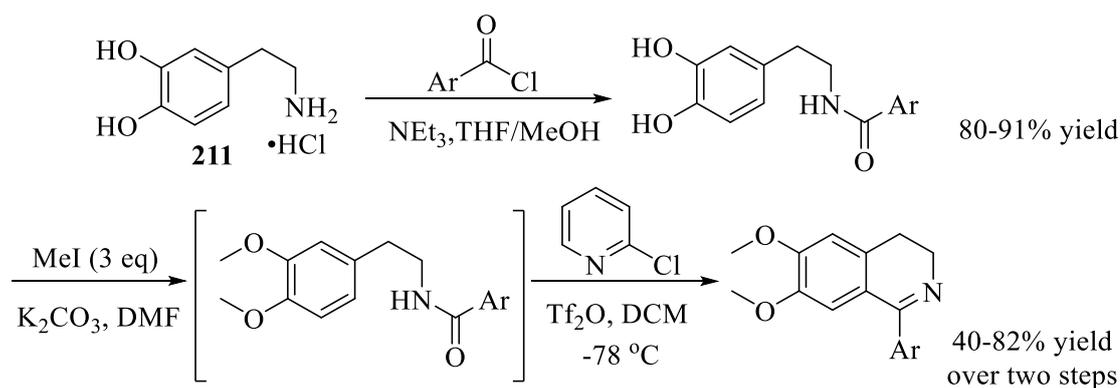


Figure 48. Top: Mechanism for ATH of 1-aryl-DHIQ using Noyori-Ikariya catalysts. Bottom: Proposed mechanism for ATH of 1-aryl-DHIQ using catalyst (*R,R*)-**131**.

3.4. ATH of 1-Aryl-6,7-dimethoxy-3,4-dihydroisoquinolines

Additionally the presence of dimethoxy groups on the fused-aromatic ring of the dihydroisoquinolines was examined. The precursor to making the imines in the same method as Scheme 61 was found to be a controlled substance and to avoid having to use this, an alternative method was chosen. Starting from the dihydroxy derivative, dihydroxyphenethyl amine **211** was converted to the corresponding amide derivatives. The hydroxy groups from the amide products were then methylated and finally a Bischler-Napieralski cyclisation gave the imine substrates (Scheme 65).



Scheme 65. Method for the synthesis of 1-aryl-6,7-dimethoxy-3,4-DHIQ

Amine **212** was obtained in 92% ee by reduction using the furan catalyst, showing that the dimethoxy groups on the fused-aromatic ring could be tolerated (Figure 49). A great result was obtained using the chloro-substituted imine of **213** which was reduced in 97% ee, a result that is higher than other reported ATH methods. Reduction of the methoxyphenyl-substituted derivative resulted in formation of a mixture of the

formylated **214** and the free amine product; the ee of both of these were 95%. These formylated derivatives occur with some substrates due to the formic acid present in the reduction but can be readily converted back to the amine products, by stirring in NaOH, without the loss of enantioselectivity. The ATH of a substrate with two dimethoxy groups on both aromatic groups was also attempted and the amine product **215** was obtained in 93% ee.

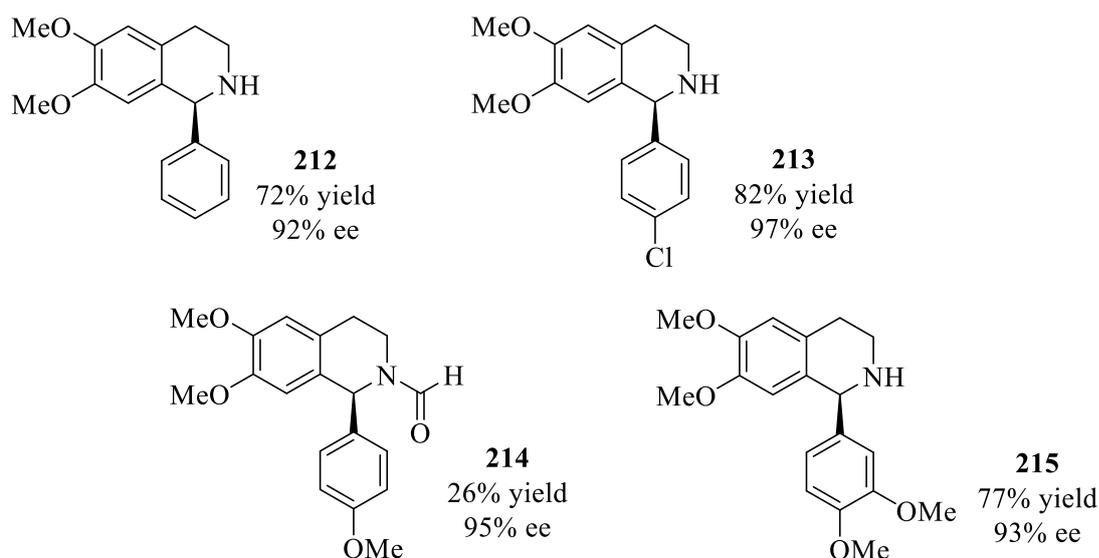


Figure 49. ATH products **212-215** of 1-aryl-6,7-dimethoxy-3,4-DHIQ derivatives using furan catalyst (*R,R*)-**131**. Conditions: Catalyst 1 mol%, FA/TEA, DCM, [S] = 1 M.

3.5. Other Dihydroisoquinolines

The idea of having electron-withdrawing groups in the fused-ring of the dihydroisoquinolines was attempted. A trifluoromethyl-containing phenethyl amine could be converted into the corresponding amide **216** however using the Bischler-Napiralski conditions with Tf₂O failed to give the desired dihydroisoquinoline. A nitro-containing amide **217** also failed to cyclise under these conditions and subjecting the reaction to microwave irradiation did not work either (Figure 50). It is likely that the electron-withdrawing groups in these cases decrease the nucleophilicity of the aromatic ring, preventing the electrophilic aromatic substitution reaction.

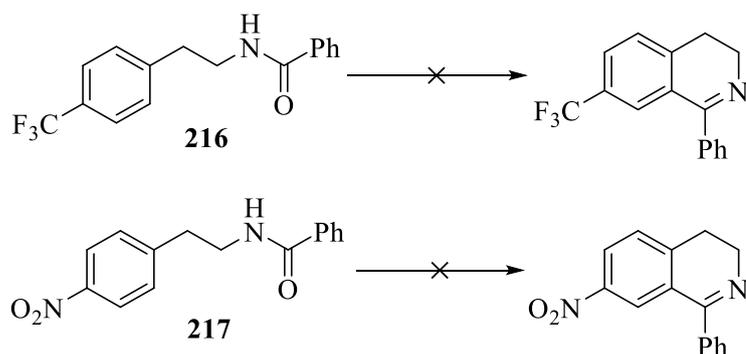


Figure 50. Failed cyclisation of electron-withdrawing phenethylamine. Conditions: (A) PPA, 190 °C or (B) Tf₂O, DCM, -78 °C

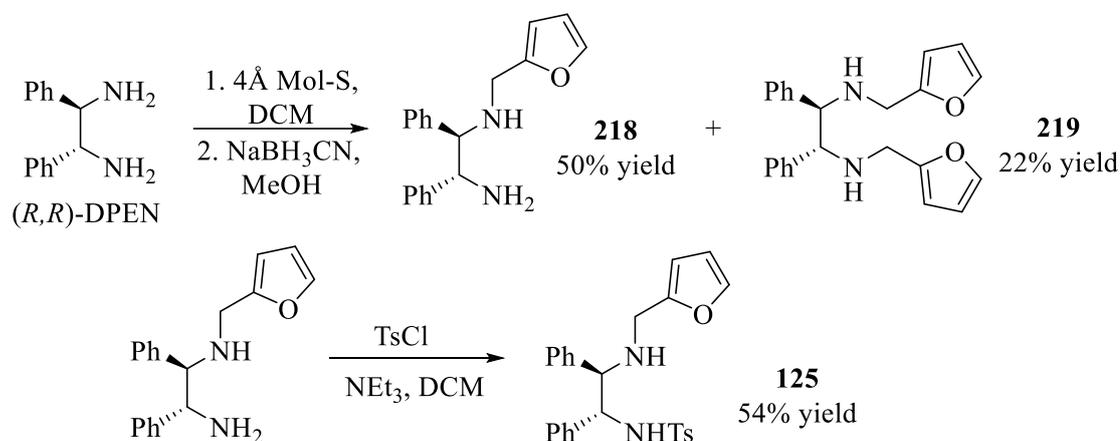
Summary

The heterocyclic containing catalyst (*R,R*)-**131** has proven to reduce substituted 1-aryl-3,4-dihydroisoquinolines in high ee which is unusual behaviour for Ru/arene/TsDPEN type catalysts. Section 1.6.2 shows the Noyori-Ikariya catalysts to reduce 1-aryl-3,4-dihydroisoquinolines in high ee only when there are *ortho*-substituents present in the aryl ring, non-*ortho* containing derivatives reduce in 29-39% ee. Catalyst **131** permits the ATH of 1-aryl-3,4-dihydroisoquinolines containing *meta* and *para* substituents to proceed in high ee, 88-94%, which solves a long-standing problem in the reduction of this class of substrates for ruthenium catalysed ATH. A mechanism has been proposed to show how a heterocyclic group can be responsible for an additional stabilising interaction in the transition state giving the product in high ee. However, DHIQ's containing *ortho*-substituents do not reduce well with catalyst **131** demonstrating a complementary relationship with the Noyori-Ikariya catalysts in the reduction of 1-aryl-3,4-dihydroisoquinolines. Dimethoxy groups on the fused-aromatic ring of the dihydroisoquinolines also make ideal substrates in ATH using furan catalyst (*R,R*)-**131**. The ATH using catalyst **131** has also worked well in a gram-scale ATH which demonstrates the effectiveness of the method.

Chapter 4: Modifications to Furan
Catalyst

4.1. Scale-up of Furan Catalyst **131**

Due to the versatility of catalyst **131** to applications in both ketone and imine ATH, an improved synthesis of the catalyst was attempted. The method was altered for the preparation of ligand (*R,R*)-**125** starting from DPEN and carrying out the reductive amination first. This step yielded the desired heterocycle containing product in 50% yield however a byproduct also formed, that was found to be the difuran containing ligand (*R,R*)-**219**, in 22% yield (Scheme 66). The free amine terminus of ligand (*R,R*)-**218** was tosylated in a further reaction to yield ligand (*R,R*)-**125** in 54% yield. The method was not effective in this case and efforts were returned to utilising the initial method for scale-up.



Scheme 66. Alternative route to forming furan ligand (*R,R*)-**125** and the byproduct (*R,R*)-**219**.

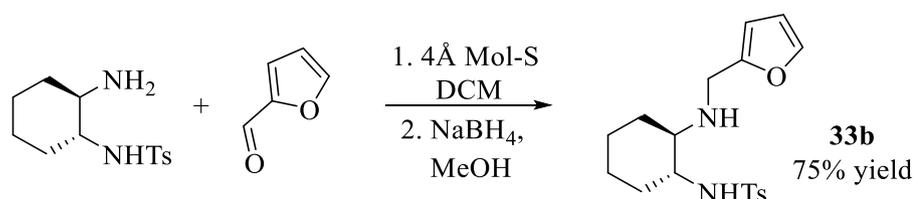
Ligand **125** was then prepared, as previously shown in Scheme 48, firstly on a 1.00 gram scale of the (*S,S*)-TsDPEN derivative and using LiAlH₄ in the reductive amination. A recrystallisation was attempted and the product was isolated in 2 crops in a total of 67% yield. As the recrystallisation gave a good yield, the reductive amination was scaled up further using 5 grams of (*S,S*)-TsDPEN to give the ligand (*S,S*)-**125** in 81% yield (4.91 grams) from 3 crops; 1st crop 50%, 2nd crop 19% and 3rd crop 12%. A 5.00 gram reaction was also carried out with (*R,R*)-TsDPEN which gave the desired ligand (*R,R*)-**125** in 76% yield (4.63 grams) after recrystallisation.

The catalyst synthesis was scaled-up next; 0.500 grams of the (*S,S*)-ligand **125** was reacted with [Ru(benzene)Cl₂]₂ to make catalyst (*R,R*)-**131** using the same method as

reported in Section 2.2.2.. For this experiment the catalyst was purified by reducing the amount of exposure to air and column chromatography was run under a nitrogen atmosphere and with degassed solvents yielding the catalyst in 76% yield (0.565 grams). The same experiment was also attempted however solvents for the purification were not degassed and air was used to elute the product from the column. The yield in this case increased slightly to 82% yield (0.612 grams) and the most likely explanation for this result is the shorter purification time in the column where the catalyst may start to decompose. The synthesis of catalyst (*R,R*)-**131** was also scaled up using 1.00 gram of ligand (*R,R*)-**125** to give the catalyst in 65% yield (0.958 grams).

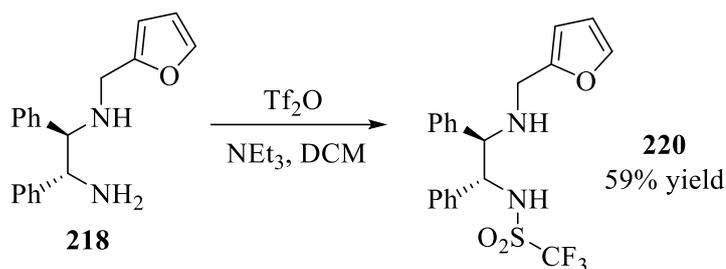
4.2. Derivatives of Furan Catalyst

The novel furan ligand **131** was also compared against a similar reported ligand **33b**.⁶² Ligand **33b** was made by a reductive amination, of *R,R*-cyclohexdiamine using NaBH₄, in 75% yield. An *in situ* complexation resulted in the reduction of acetophenone in 44% conversion and 84% ee after 168 hours. The furan catalyst **131**, under the same conditions generated the reduced product in 98% conversion and 92% ee. The cyclohexyl has an altered effect in the catalysis relative to the diphenyl and shows that the TsDPEN-derivative is a superior catalyst.



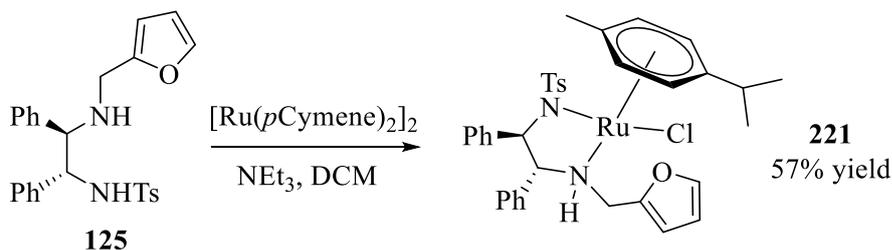
Scheme 67. Preparation of cyclohexyl derivative (*R,R*)-**33b**.

Varying the sulfonyl group of ligand **125** was investigated next. Previously, a triflate group had shown the best enantioselectivity in a pyridine ligand **38** so this sulfonyl was chosen for investigation. The furan ligand (*R,R*)-**218** was reacted with triflic anhydride to give ligand (*R,R*)-**220** in 59% yield (Scheme 68). The reduction of acetophenone with ligand (*R,R*)-**220**, where a catalyst is formed *in situ*, gave the (*R*)-1-phenylethanol product in 42% conversion and 77% ee. The results show that the tosyl group is the better sulfonyl group from the two due to the higher enantioselectivity of the products.



Scheme 68. Preparation of triflate derivative (*R,R*)-**220**.

Ligand (*R,R*)-**125** was also complexed with $[\text{Ru}(p\text{-cymene})_2\text{Cl}_2]_2$ affording catalyst (*R,R*)-**221** in 57% yield (Scheme 69). The effect of having the *p*-cymene arene was investigated in the reduction of acetophenone. The reaction was analysed at different times for the first 66 hours, which gave 36% conversion and then plateaued, reaching a maximum of 41% conversion after 204 hours. The results displayed the ee to remain unchanged however the reaction was much slower than when the benzene derivative was used (Table 32). This may be due to steric crowding at the ruthenium centre leading to the slower reaction.



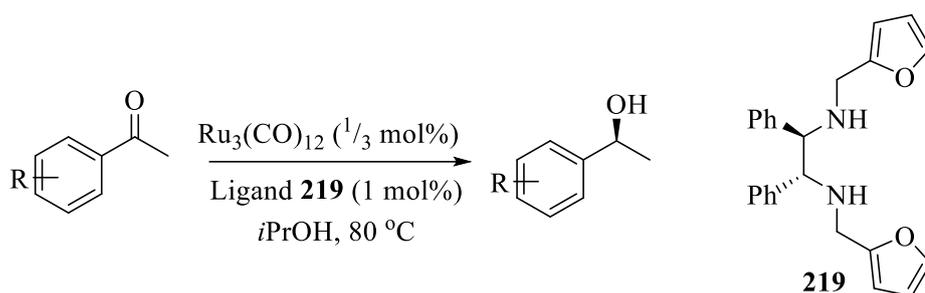
Scheme 69. Complexation of (*R,R*)-**125** with $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$.

Catalyst	Time (h)	Conv /%	ee /%	<i>R/S</i>
(<i>R,R</i>)- 131	72	95	92	<i>R</i>
(<i>R,R</i>)- 221	204	41	92	<i>R</i>

Table 32. Reduction results from the ATH of acetophenone with **131** and *p*-cymene derivative **221**.

The difuran ligand (*R,R*)-**219** was investigated in catalysis, the presence of two furan groups on the ligand first pointed to this ligand acting as a bidentate therefore (*R,R*)-**219** was ligated to $[\text{Ru}(\text{benzene})\text{Cl}_2]_2$ in an *in situ* reduction of acetophenone. Which in this case gave no reduction as a bidentate ligand. Ligand (*R,R*)-**219** was then ligated with $\text{Ru}_3(\text{CO})_{12}$ which formed an effective catalyst, reducing acetophenone in 83%

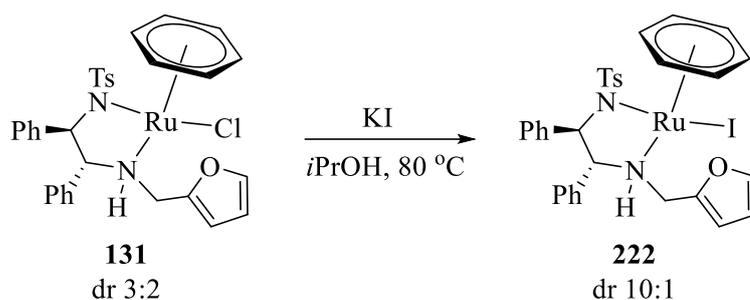
conversion and 50% ee however the *S* enantiomer was the major product. As with previous examples, (*R,R*)-DPEN-containing derivatives furnish the 1-phenylethanol product with the *R* configuration as the major enantiomer but in this example ligand (*R,R*)-**219** produced the *S* configuration product. A 2-methoxyacetophenone substrate **139** was reduced in 30% conversion and low ee of 12% (Table 33), the tridentate ligands previously reduced *ortho*-substituted acetophenones in good ee but this was not the case with this ligand. Lastly, an attempt was made to reduce tetralone **140** using a complex of ligand (*R,R*)-**219** but this substrate was not reduced.



Substrate	Time (h)	Conv (%)	ee (%)	<i>R/S</i>
Acetophenone	72	83	50	<i>S</i>
139	72	30	12	<i>S</i>
140	48	nr	-	-

Table 33. ATH of acetophenone derivatives with difuran ligand (*R,R*)-**219**.

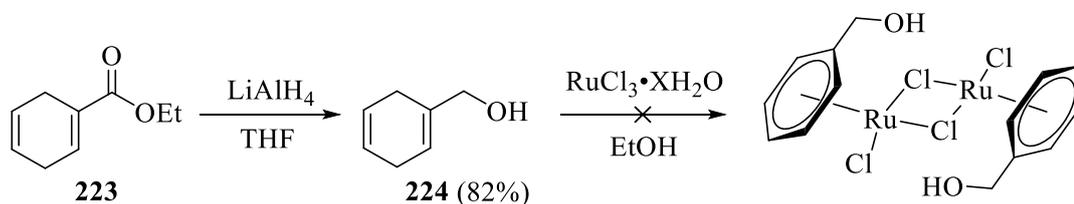
Attempts to grow crystals of catalyst **131** for X-ray crystallography were unsuccessful and is possibly due to the complex forming in a diastereomeric ratio of 3:2. A halide exchange converting **131** to **222** was attempted to increase the diastereomeric ratio. This was successful as the complex formed in a diastereomeric ratio of 10:1 (Scheme 70). Hence a possible explanation for the formation of diastereomers is because of the chirality at the ruthenium centre. However complex **222** also failed to grow single crystals for X-ray crystallography. Complex **222** achieved the same results as **131** in the ATH of acetophenone.



Scheme 70. Conversion of catalyst **131** to **222**.

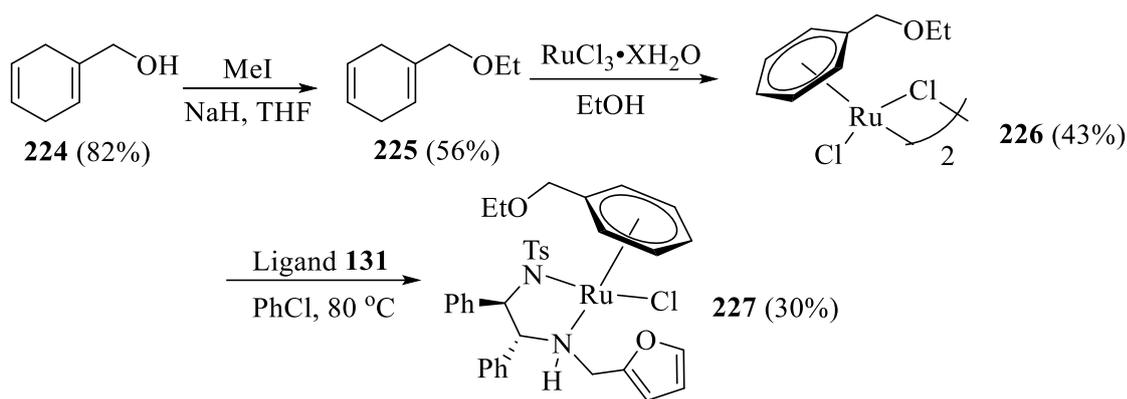
4.3. Coupling Methods to Support Furan Catalyst

The η^6 -arene in the catalyst was determined as a potential site for attaching on to solid supports via a functional group. A hydroxy group was first investigated as a functional group to be added on to the arene of the furan catalyst. Subjecting the cyclohexadiene **223** to a LiAlH_4 reduction gave the hydroxy-containing product **224**. This was then reacted with ruthenium trichloride but failed to form the desired Ru-arene complex (Scheme 71). The idea behind the synthesis would have been to then react the hydroxy group present in the catalyst with an electrophilic group on a solid support.



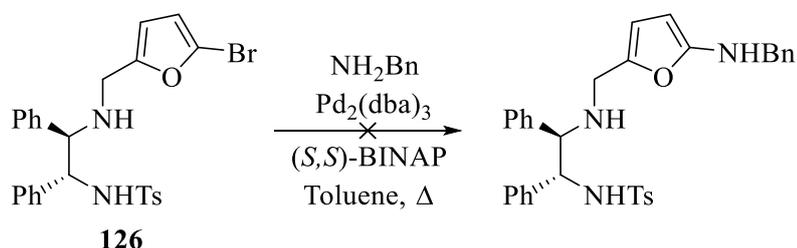
Scheme 71. Attempted synthesis to make hydroxyl-containing arene ruthenium

Alternatively, the hydroxy group could be reacted with an electrophilic group on a solid support followed by catalyst formation. To represent this, the hydroxy group was reacted with iodoethane, forming ether **225** in 56% yield. Refluxing **225** with ruthenium trichloride formed the ruthenium arene species **226** in 43% yield, that was subsequently complexed with the furan ligand (*R,R*)-**131** to give catalyst (*R,R*)-**227** in 30% yield (Scheme 72). The catalyst was employed in the reduction of acetophenone which gave the alcohol product in 94% conversion and 91% ee. The method demonstrates the ability to link a catalyst through the arene that can then be applied to a solid support bearing an alkyl halide.



Scheme 72. Method to add catalyst on to solid support through functional group on the arene. Catalyst **227** reduced acetophenone in 94% conversion and 91% ee.

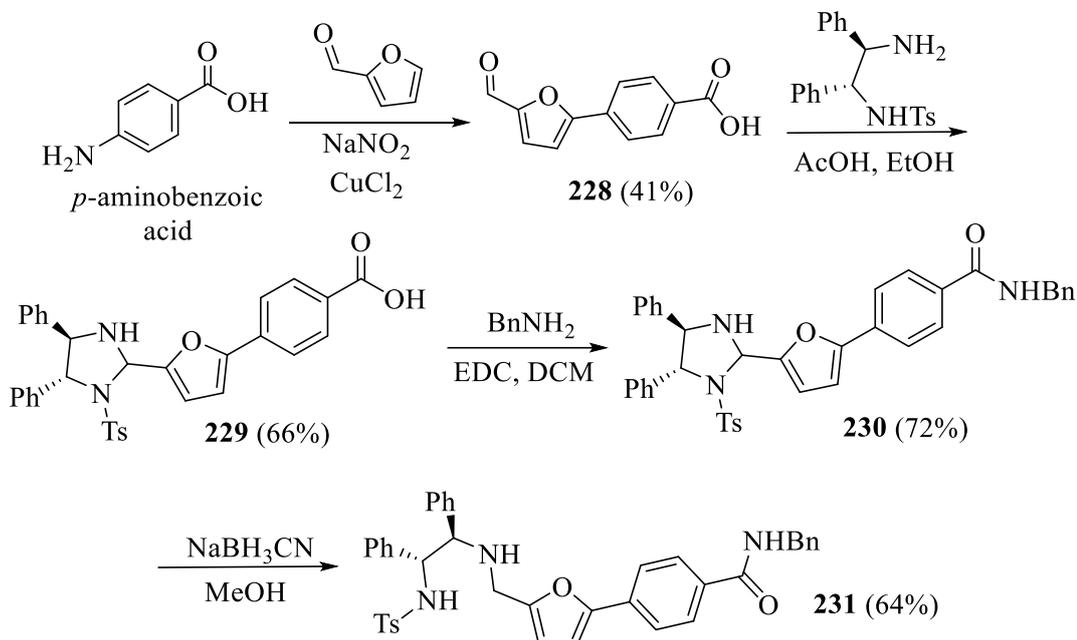
A further study was to link a support through an added functional group on the heterocycle of the ligand. The bromo-furan ligand **126** was refluxed with benzylamine, following the literature precedent of another bromo-furan analogue with benzylamine, however this failed to give the desired amine product (Scheme 73). Other reported palladium based methods¹⁵¹ also failed to couple the bromo-furan **126** with benzylamine; these included methods using Pd(OAc)₂ and Pd₂(dba)₃ with phosphines.



Scheme 73. Failed coupling methods with the bromo-furan ligand **126**.

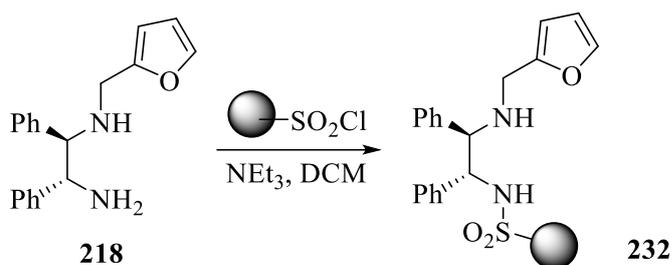
An alternate route (Scheme 74) was also explored; *p*-aminobenzoic acid was reacted with 2-furaldehyde through a Sandmeyer arylation reaction to furnish the carboxylic acid **228**. For the next step, the predominant formation of the aminal was chosen over the imine as the aminal offers greater stability. Aminal formation has been reported to be favourable under reflux, therefore (*R,R*)-TsDPEN was refluxed with the carboxylic acid **228** in order to form the required intermediate (*R,R*)-**229**. Benzylamine was used to imitate the presence of supported reagents with an amine functionality. The EDC coupling at this step allowed the formation of the amide (*R,R*)-**230** in 72% yield and this was reduced to give the furan ligand derivative (*R,R*)-**231** in 64% yield. The catalyst was formed *in situ*, by reacting ligand (*R,R*)-**231** with [Ru(benzene)Cl₂]₂, and

this complex reduced acetophenone at a maximum of 27% conversion and 90% ee. The result implies that the additional group to the furan has a negative effect on the catalyst, which could possibly be due to steric hindrance.



Scheme 74. Method for adding the furan/TsDPEN ligand to a support through an amide functionality. Ligand (*R,R*)-**231** reduced acetophenone in 27% conversion and 90% ee.

Another feasible route to attachments of solid supports was through the sulfonyl moiety of the ligand. A commercially available polymer with a sulfonyl chloride was reacted with the furan ligand (*R,R*)-**218** encountered previously. The product (*R,R*)-**232** obtained could not be characterised with our characterisation techniques and the structure assumed is presented in Scheme 75. An *in situ* catalyst was formed in FA/TEA that reduced acetophenone in good conversion and 85% ee (Table 34). The ligand was also tested by changing the hydrogen donor source to sodium formate in water but this gave a decrease in both conversion and ee. As a comparison, a simple DPEN and polymer derivative (without the furan) was synthesised which reduced acetophenone in 83% ee using FA/TEA.

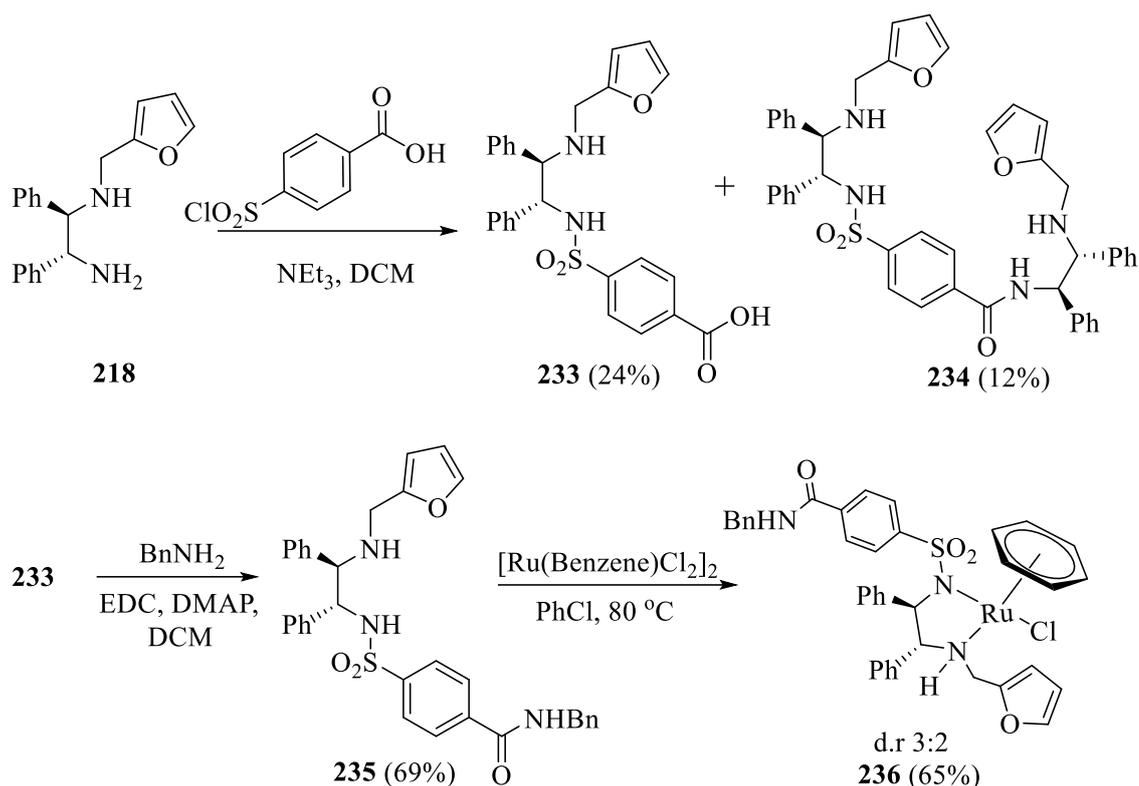


Scheme 75. Formation of polymer ligand (*R,R*)-**232**

Ligand	H ₂ source	Time (h)	Conv /%	ee /%	<i>R/S</i>
(<i>R,R</i>)- 232	FA/TEA	264	82	85	<i>R</i>
(<i>R,R</i>)- 232	HCO ₂ Na	120	30	78	<i>R</i>
DPEN/polymer	FA/TEA	208	72	83	<i>R</i>

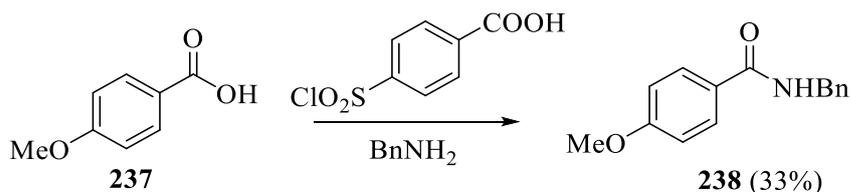
Table 34. Comparison of results from the ATH of acetophenone using polymer ligand (*R,R*)-**232** in different hydrogen donor source and the DPEN derivative.

With the structure of the sulfonyl-polymer in **232** unknown a different method was identified that would retain a sulfonyl group similar to the tosyl group. The furan ligand (*R,R*)-**218** was reacted with a benzoic acid-sulfonyl chloride to give ligand (*R,R*)-**233** (Scheme 76). This reaction also formed ligand **234** as a byproduct with the yields for the formation of each product being dependent on the amount of triethylamine used in the reaction. Using 2 equivalents of NEt₃ afforded (*R,R*)-**233** in 6% yield and the byproduct **234** in 13% yield. Reducing the amount of triethylamine to 1 equivalent gave 24% of ligand (*R,R*)-**233** and 12% of the byproduct. Ligand (*R,R*)-**233** was coupled with benzylamine using EDC to yield (*R,R*)-**235** in 69% yield; once again benzylamine was used to represent a solid support with amine functionality. A catalyst was formed and isolated upon complexation with [Ru(benzene)Cl₂]₂. Reduction of acetophenone, [S] = 1 M, with catalyst (*R,R*)-**236** gave the alcohol product in quantitative conversion and 94% ee.



Scheme 76. Formation of complex (*R,R*)-**236** through intermediate (*R,R*)-**233**. Complex reduced acetophenone to alcohol in quantitative conversion and 94% ee.

Ligand **234** was an interesting find and it was proposed that an additional sulfonyl molecule may react with the carboxylic acid terminus of ligand **233** to form an activated carbonyl. To prove this theory, the carboxylic acid **237** was first reacted with the benzoic acid-sulfonyl chloride (Scheme 77). Benzylamine was then added to the mixture, which gave the amide product in 33% yield. Tosyl chloride was also tested as another sulfonyl chloride under the same conditions and this gave the amide **238** in 63% yield. These results suggest that the sulfonyl chlorides acts as coupling agents in the formation of amide **234** (Figure 51). Mesyl chlorides have also been reported to act as coupling agents previously and are commonly employed for non-nucleophilic amines.^{152,153}



Scheme 77. Test reaction to show the sulfonyl-chloride acts as a coupling agent.

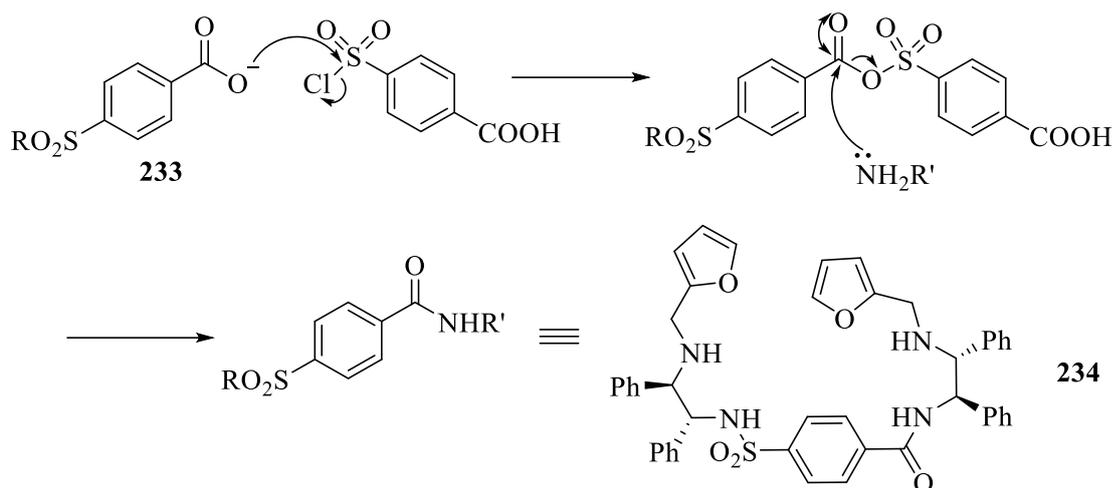
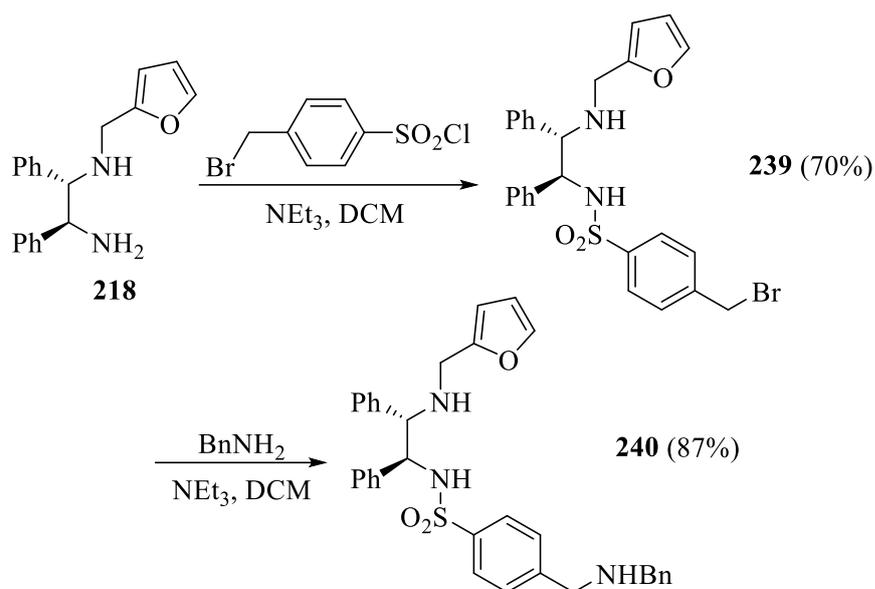


Figure 51. Proposed mechanism for the formation of byproduct **234**.

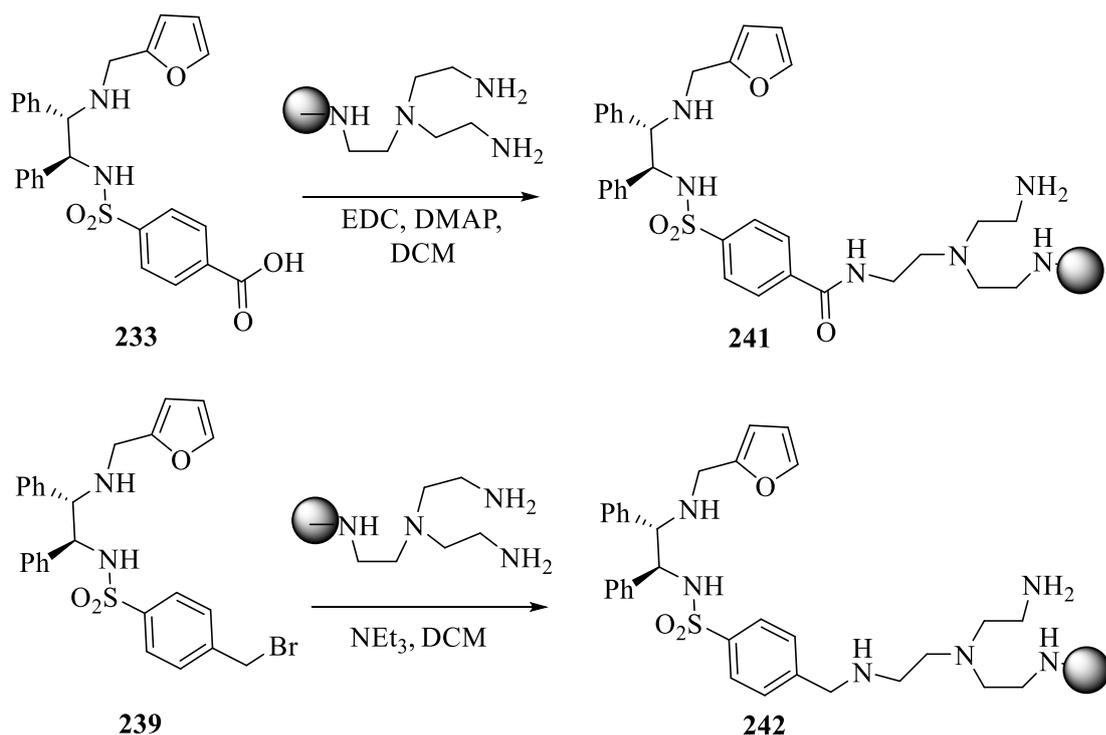
Ligand **234** was tested in an *in situ* reaction with $[\text{Ru}(\text{benzene})\text{Cl}_2]_2$ in which acetophenone was reduced in 100% conversion and 90% ee. The result implies that the catalyst forms between the amine adjacent to the furan and on the sulfonamide, leaving the amide and the amine adjacent to the amide free for a possibly secondary function.

Additionally, a bromomethyl-containing sulfonyl was added onto the furan ligand (*S,S*)-**218**. The reaction between (*S,S*)-**218** and a sulfonyl chloride was found to form (*S,S*)-**239** in 70% yield. Ligand (*S,S*)-**239** was then reacted with benzylamine (representing an amine group on a solid support) to form the amine-linked ligand (*S,S*)-**240** (Scheme 78). Ligand (*S,S*)-**240** was used in an *in situ* reaction with $[\text{Ru}(\text{benzene})\text{Cl}_2]_2$ and this reduced acetophenone in quantitative yield and 94% ee.



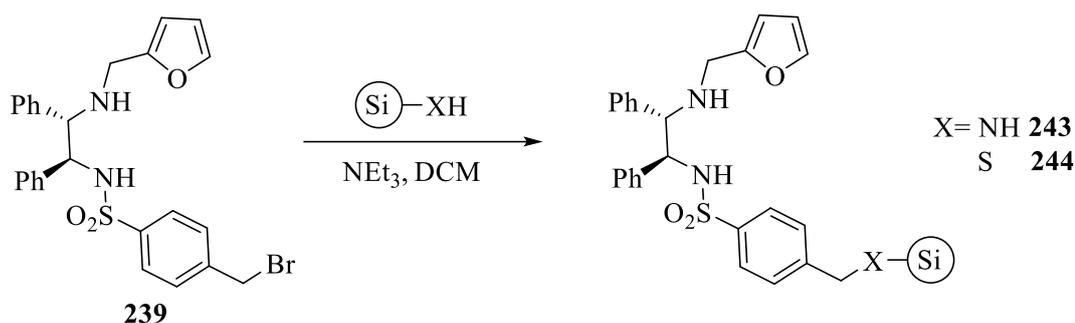
Scheme 78. Formation of ligand (*S,S*)-**240** and the bromomethyl intermediate (*S,S*)-**239**. Ligand (*S,S*)-**240** with $[\text{Ru}(\text{benzene})\text{Cl}_2]_2$ reduced acetophenone in quantitative yield and in 94% ee.

With the coupling methods at hand, a polymer-bound amine was reacted via an EDC coupling with ligand (*S,S*)-**233** and through an $\text{S}_{\text{N}}2$ substitution with ligand (*S,S*)-**239** (Scheme 79). The polymer-bound ligands (*S,S*)-**241** and (*S,S*)-**242** were not characterised and both the purity and loadings are not known. The catalysts were formed *in situ* with each of the polymer-bound ligands; the complex derived from ligand (*S,S*)-**241** reduced acetophenone in 12% conversion and 76% ee. The supported complex from ligand (*S,S*)-**242** on the other hand gave 1% conversion and 47% ee in the ATH of acetophenone.



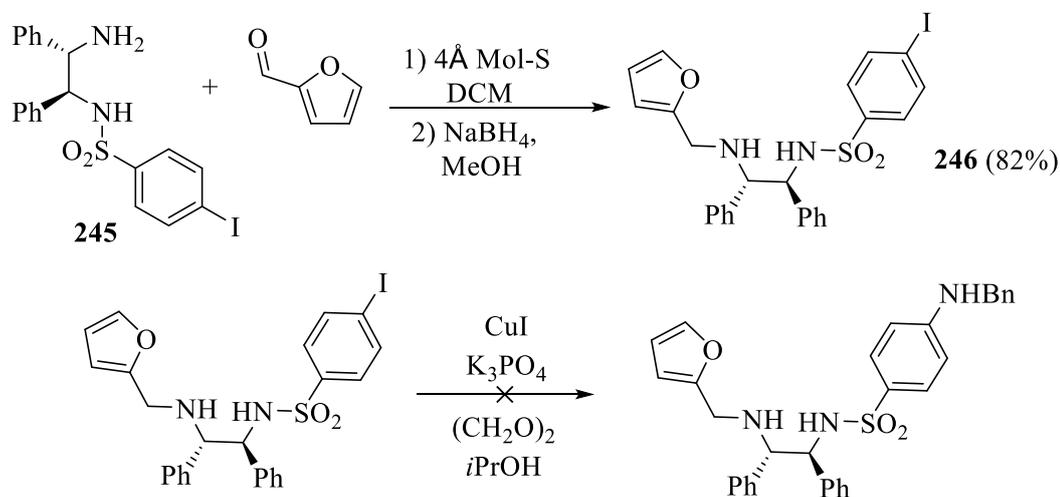
Scheme 79. Addition of polymer amine to ligands (*S,S*)-**233** and (*S,S*)-**239**. Polymer ligand (*S,S*)-**241** reduced acetophenone in 12% conversion and 76% ee. Polymer ligand (*S,S*)-**242** reduced acetophenone in 1% conversion and 47% ee; *in situ* catalyst (1 mol%), FA/TEA, [S] = 2M.

Silica supports were also investigated; an amine linked silica was reacted with ligand (*S,S*)-**239** to make the silica-bound ligand (*S,S*)-**243** (Scheme 80). A thiol-containing silica was also reacted to form ligand (*S,S*)-**244**, characterisation of the supported ligands is difficult so the formation of subsequent species is assumed. Catalysts were then formed *in situ* with each of the silica-bound ligands; the catalyst derived from ligand (*S,S*)-**243** reduced acetophenone in 40% conversion and 84% ee. The complex formed from thiol linked ligand (*S,S*)-**244** however reduced acetophenone in 70% conv and 90% ee. The silica supports produced more effective and better enantioselectivity in catalysis compared to their polymer-bound counterpart.



Scheme 80. Formation of silica-supported ligands (*S,S*)-**243** and -**244** from (*S,S*)-**239**. Catalyst from (*S,S*)-**243** reduced acetophenone in 40% conversion and 84% ee. Catalyst from (*S,S*)-**244** reduced acetophenone in 70% conv and 90% ee; *in situ* catalyst (1 mol%), FA/TEA, [S] = 2M.

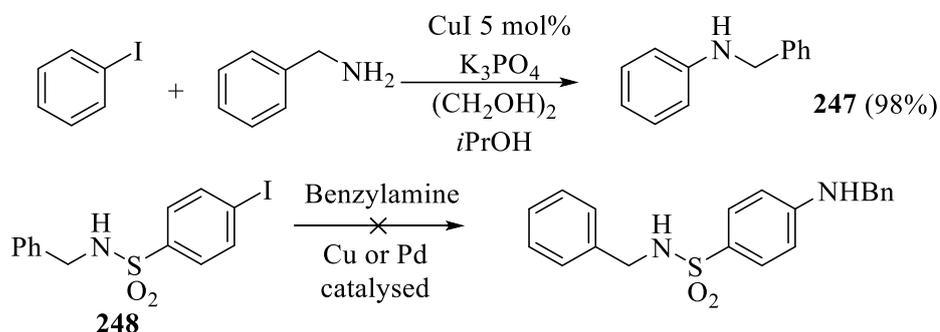
The possibility of having an amino group bonded directly to the aromatic ring of the sulfonyl group was also studied. Ligand (*S,S*)-**245** was reacted with 2-furaldehyde in a reductive amination reaction to give (*S,S*)-**246** in 82% yield (Scheme 81). Ligand (*S,S*)-**246** was reacted with benzylamine in a copper-catalysed coupling reaction adapted from a literature procedure,¹⁵⁴ however the coupling here did not work.



Scheme 81. Formation of ligand (*S,S*)-**246** and unsuccessful coupling to benzylamine.

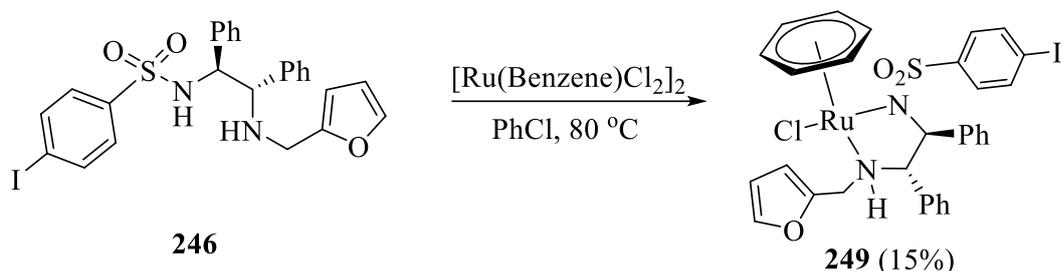
To investigate the reason for the failure of the coupling reaction of (*S,S*)-**246**, the literature reaction was attempted with iodobenzene and benzylamine which gave the corresponding product **247** in 98% yield. Then sulfonamide **248** was reacted with benzylamine under the same conditions but this failed to form the desired product (Scheme 82). The conditions were exchanged for a palladium coupling, using Pd₂(dba)₃ and BINAP, that is also known to work in coupling reactions but this also

also failed to work with the sulfonamide **248**. This leads to the conclusion that the sulfonamide group inhibits the coupling reaction and therefore also occurs in the coupling with (*S,S*)-**246**.



Scheme 82. Coupling reactions between aryl iodides and amines

As amine coupling attempts had been unsuccessful, ligand (*S,S*)-**246** was complexed with $[\text{Ru}(\text{benzene})\text{Cl}_2]_2$ to give catalyst (*S,S*)-**249** in 15% yield (Scheme 83). The reduction of acetophenone with catalyst (*S,S*)-**249** gave quantitative conversion and 95% ee for the (*S*)-alcohol product.



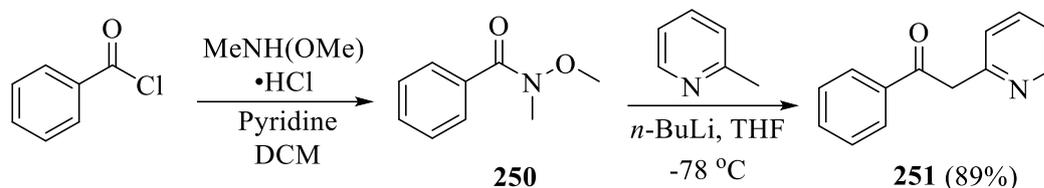
Scheme 83. Formation of catalyst (*S,S*)-**249**. Catalyst (*S,S*)-**249** reduced acetophenone in quantitative conversion and 95% ee.

Summary

The complex of the furan ligand **125** has shown promising results in the ATH of ketones and imines. A further study into different sulfonyl and η^6 -arene groups on the catalyst shows that the tosyl as the sulfonamide and benzene as the arene, catalyst **131**, gives the best enantioselectivity and reactivity. A scale up using 5 grams of TsDPEN formed the furan ligand **125** in up to 81% yield and the use of 1 gram of ligand **125** formed catalyst **131** in up to 82% yield. A range of synthetic methods have been designed and executed to add the desired furan catalyst onto solid supports.

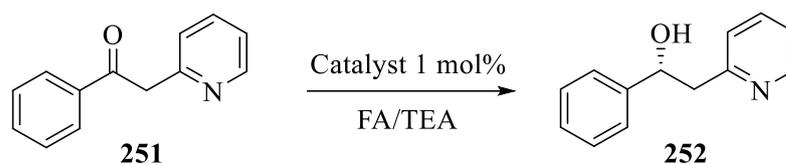
***Chapter 5: ATH of α -Heteroaromatic
Ketones***

In the final study, the reduction of acetophenones with heterocyclic groups in the alpha position to the ketone were investigated. The pyridyl substrate **251** was prepared through the lithiation of 2-picoline followed by addition to Weinreb amide **250** (Scheme 84). This gave product **251** in 89% yield that was subsequently reduced through ATH.



Scheme 84. Preparation of pyridyl ketone **251**.

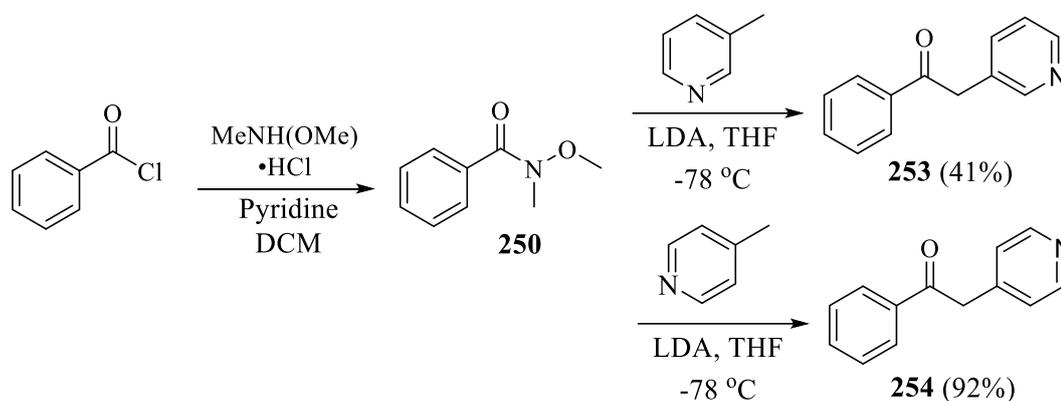
The ATH of **251** using furan catalyst (*R,R*)-**131** and DCM as a co-solvent, under the same conditions as in previous sections, gave the alcohol product in 96% ee and 90% yield (Table 35). The effect of changing solvents was tested, first the solvent was changed to MeCN and MeOH; both reductions gave products in lower yields and slightly less enantioselectivity. The removal of the co-solvent, thus a 2 M concentration, also had a significant effect on the enantioselectivity. Given that DCM was the best co-solvent in this application, different catalysts were investigated, with the thiophene catalyst (*R,R*)-**132** giving 94% ee and a lower yield than the furan counterpart. The ester catalyst (*R,R*)-**135** had the poorest enantioselectivity of 84% whilst the 3C-tethered (*R,R*)-**22** gave the product in 94% ee. The alcohol product **252** has shown potential applications for transformations into drug molecule precursors.¹⁵⁵ Having found the optimal catalyst and conditions, a range of α -heteroaromatic ketones were investigated.



Catalyst	Solvent	[S]	Time (h)	Yield /%	ee /%	<i>R/S</i>
(<i>R,R</i>)- 131	DCM	1 M	72	90	96	<i>R</i>
(<i>R,R</i>)- 131	-	2 M	72	nd	94	<i>R</i>
(<i>R,R</i>)- 131	MeCN	1 M	72	46	95	<i>R</i>
(<i>R,R</i>)- 131	MeOH	1 M	72	34	92	<i>R</i>
(<i>R,R</i>)- 132	DCM	1 M	72	71	94	<i>R</i>
(<i>R,R</i>)- 135	DCM	1 M	72	20	84	<i>R</i>
(<i>R,R</i>)- 22	DCM	1 M	24	86	94	<i>R</i>

Table 35. ATH of ketone **251** with different catalysts and conditions.

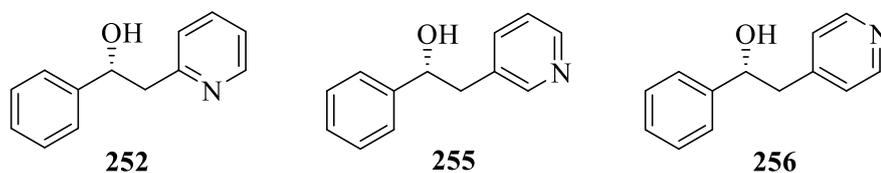
The 3-pyridyl ketone **253** was prepared in a similar method to ketone **251** via the Weinreb amide intermediate **250**. The picoline in this case was not deprotonated with *n*BuLi due to possible deprotonation or alkylation at the 2 position of the pyridine. Instead LDA was used as this favours the deprotonation of the methyl group, the same method was used for the preparation of **254** (Scheme 85).



Scheme 85. Syntheses of ketone **253** and **254**.

Substrates **253** and **254** were reduced with the furan catalyst (*R,R*)-**131**, both of which gave products in high enantioselectivity (Table 36). The enantioselectivities for these were lower than for the 2-pyridyl analogue **252**. A crystal of alcohol product **252** was grown for X-ray crystallography and this determined the configuration to be *R*, with low Flack parameter of 0.03 (Figure 52). The configuration here is as expected on the

basis that the CH/ π interaction of the transition state occurs between the η^6 -arene of the catalyst and the phenyl group of the substrate.



Ketone	Alcohol	Time (h)	Yield /%	ee /%	R/S
251	252	72	90	98	<i>R</i>
253	255	72	56	94	<i>R</i>
254	256	72	90	95	<i>R</i>

Table 36. ATH of pyridyl ketones with furan catalyst (*R,R*)-**131**. Conditions: Catalyst 1 mol%, FA/TEA, DCM, [S] = 1 M.

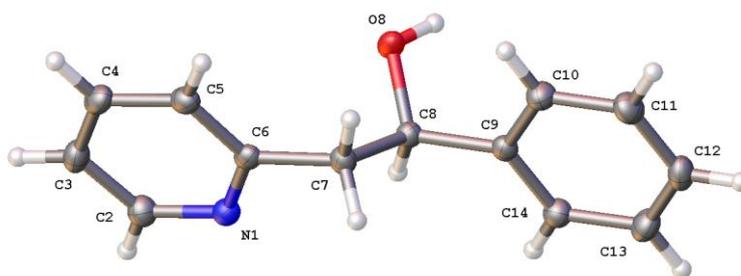
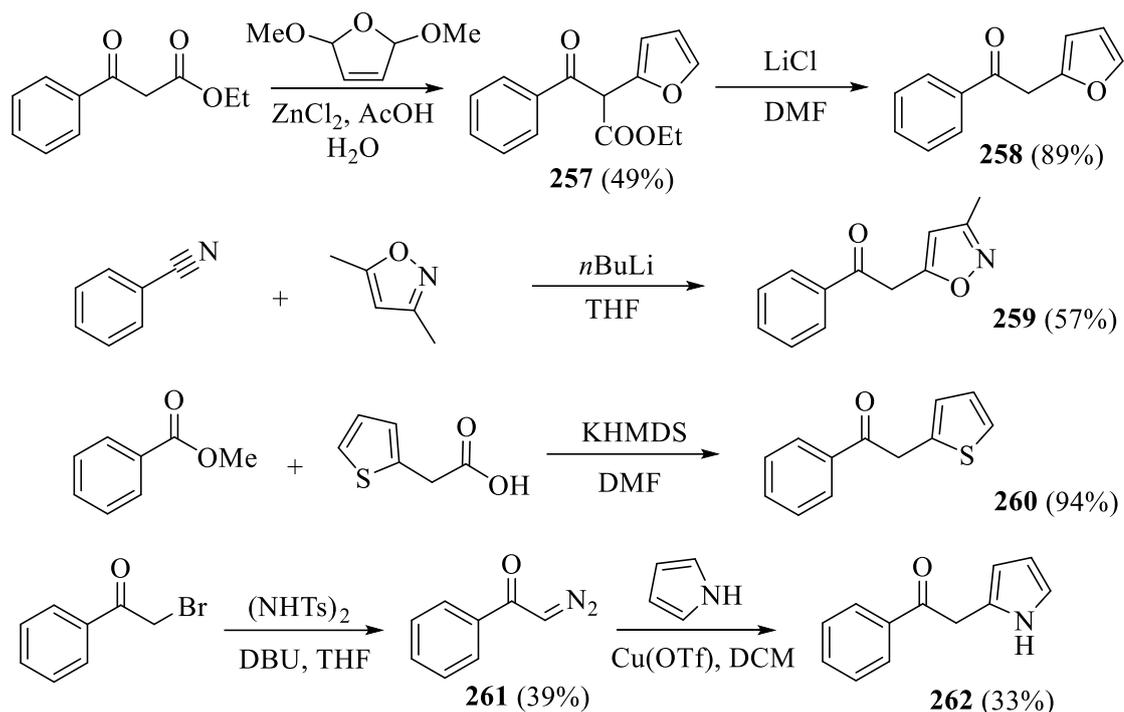


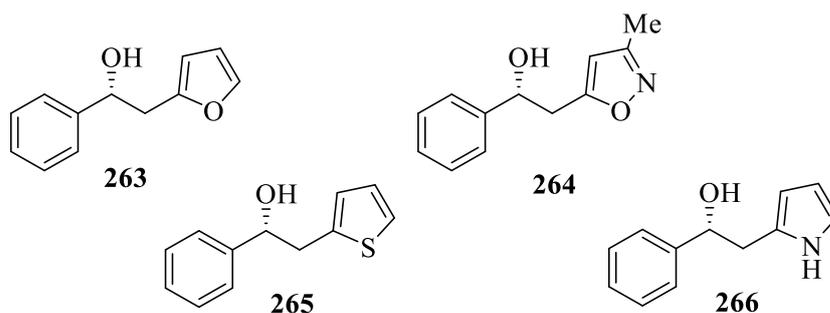
Figure 52. X-ray structure of reduction product **252** showing *R*-configuration

The next stage was to look at the ATH of 5 membered heterocycles including a furan, thiophene and pyrrole at the C2-position of the heterocycles. Furan substrate **258** was prepared in 89% yield via the intermediate **257** starting from a β -keto ester (Scheme 86). The isoxazole **259** was prepared through the deprotonation of the methyl isoxazole and reacted with benzonitrile to give the product in 57% yield. Thiophene **260** was prepared, by slight modification of the literature route,¹⁵⁶ via the double deprotonation of thiophene acetic acid and the dianion was subsequently reacted with methyl benzoate to give **260** in 94% yield. Reacting the diazo ketone **261** with pyrrole gave the pyrrole substrate **262** in 33% yield.



Scheme 86. Routes taken to prepare 5-membered heterocyclic ketones

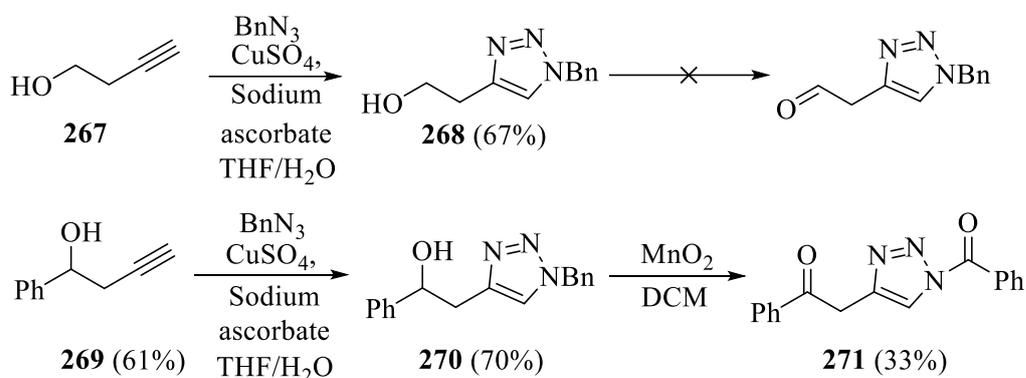
The 5-membered heterocyclic compounds were then reduced with the furan catalyst (*R,R*)-**131** (Table 37). The ATH of furan **258** gave the best result from the series with a 96% yield and 96% ee. Both the isoxazole **259** and thiophene **260** gave a product with an ee of 94%. The pyrrole substrate **262** was reduced in the lowest enantioselectivity of 92% ee.



Ketone	Alcohol	Time (h)	Yield /%	ee /%	<i>R/S</i>
258	263	72	96	96	<i>R</i>
259	264	72	71	94	<i>R</i>
260	265	72	96	94	<i>R</i>
262	266	72	68	92	<i>R</i>

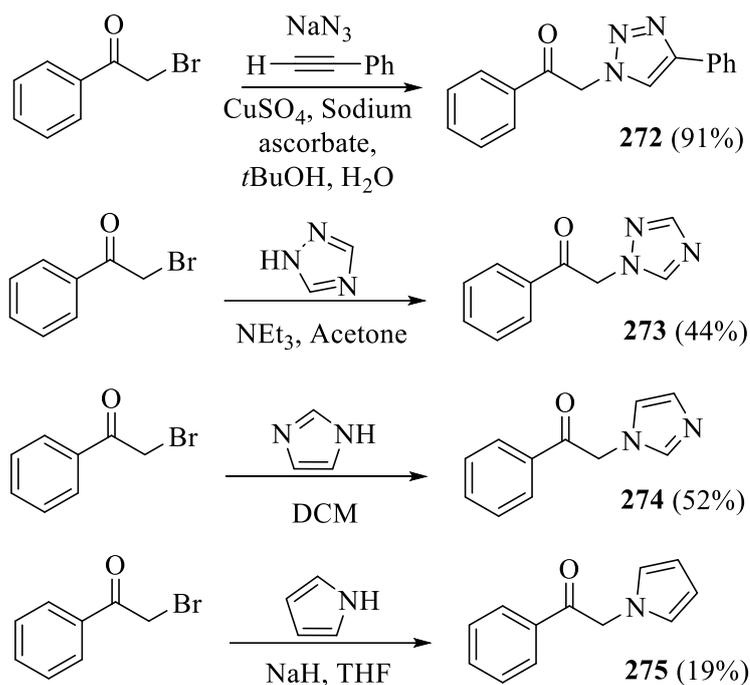
Table 37. ATH results using furan catalyst (*R,R*)-**131**. Conditions: Catalyst 1 mol%, FA/TEA, DCM, [S] = 1 M.

A triazole-containing ketone was found to be problematic to synthesise. Different synthetic routes were attempted but all had issues in the oxidation. Alcohol **267** was coupled in a click reaction to give the triazole **268**, however a Swern oxidation was unsuccessful in the later stage (Scheme 87). Alternatively, alkyne **269**, prepared from benzaldehyde, was also coupled in a click reaction to give **270** but was found not to oxidise in a Swern oxidation. The adjacent phenyl to the alcohol **270** permitted the use of MnO₂ however this resulted in an over oxidation of the compound to give **271**, with the benzyl group from the azide oxidising to an amide. Reduction of ketone **271** produced a compound that was difficult to characterise; mass spectrometry shows a product of [M+4]⁺ *m/z* compared to the ketone, representing a reduction of two carbonyl groups.



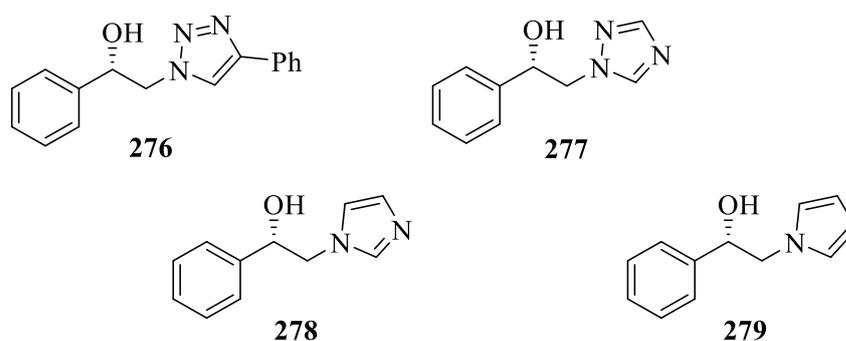
Scheme 87. Methods attempted to make a triazole ketone substrate.

As a triazole substrate connected through a C-C bond to the ketone was proving difficult to prepare, the possibility was explored of forming the triazole through a C-N bond formation. Substrate **272** was prepared in a one-pot reaction of phenylacetylene, sodium azide and 2-bromo acetophenone in 91% yield (Scheme 88). A further triazole example was prepared with 1,2,4-triazole to give compound **273** in 44% yield. Other compounds featuring the C-N bond were synthesised including an imidazole **274** and a pyrrole **275** in 52% and 19% yield respectively.



Scheme 88. Routes taken to prepare 5-membered heterocyclic ketones connected through a C-N bond.

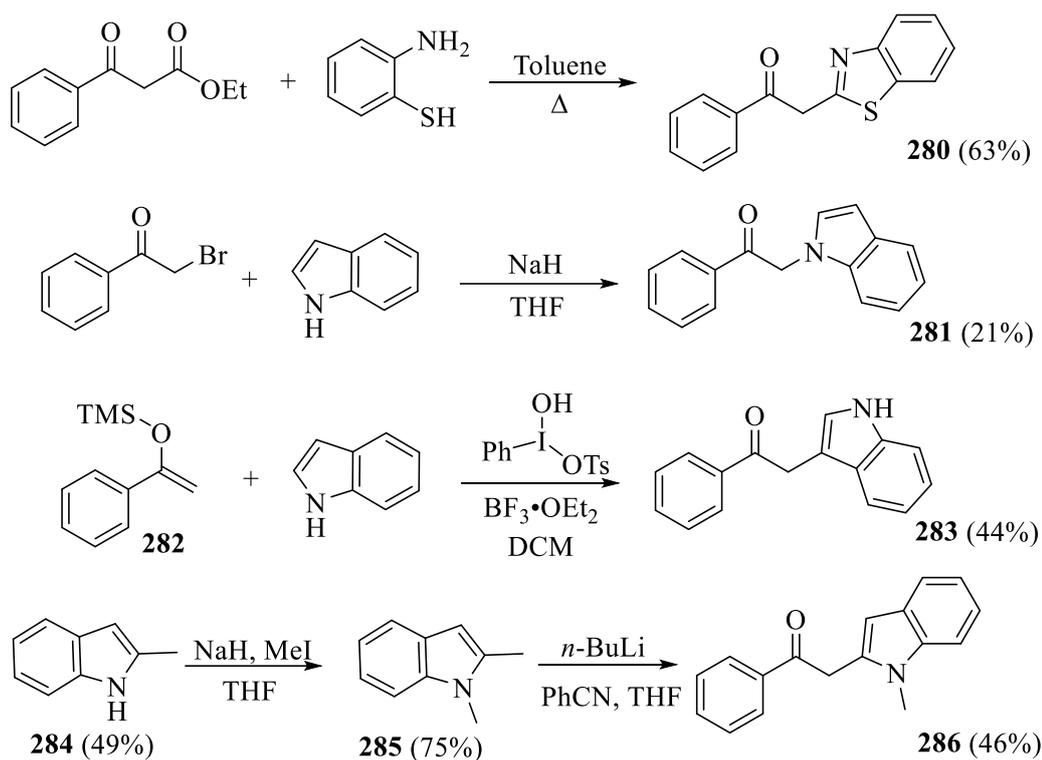
Reduction of the substrates **272-275** with a C-N bond linking to the heterocycle are summarised in Table 38. Ketone **272** was reduced asymmetrically to give alcohol **276** in high yield of 93% and 95% ee. Triazole containing analogue **273** also gave a similar result, showing that triazoles are compatible substrates in this case. The imidazole **274** gave lower enantioselectivity however this was still a good result of 90% ee. To compare the C-N against the C-C bonded heterocycles, pyrrole **275** was reduced to alcohol **279** in 86% yield and 95% ee. This is a slightly better result than for **266**, which is C-C bonded, giving a product in 92% ee.



Ketone	Alcohol	Time (h)	Yield /%	ee /%	R/S
272	276	72	93	95	<i>S</i>
273	277	72	87	96	<i>S</i>
274	278	72	74	90	<i>S</i>
275	279	72	86	95	<i>S</i>

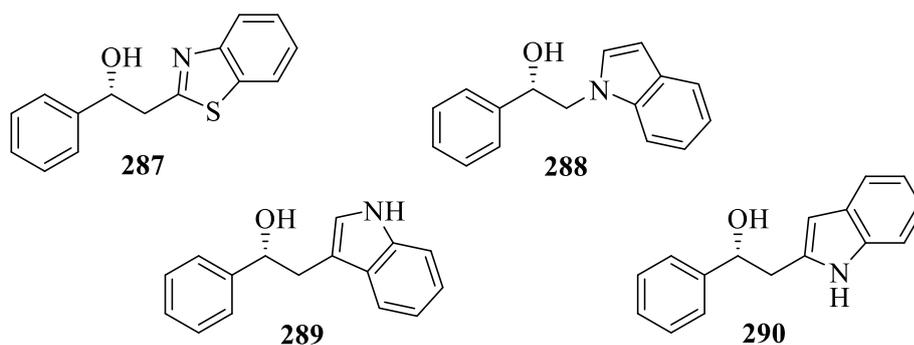
Table 38. ATH results using furan catalyst (*R,R*)-**131**. Catalyst 1 mol%, FA/TEA, DCM, [S] = 1 M.

Benzo-fused five-membered heterocycles were also investigated, a benzothiazole group was introduced by the reaction of a β -ketoester with 2-aminothiophenol to give substrate **280** in 63% yield (Scheme 89). The same conditions failed in cyclisations to form benzoxazole and benzimidazole from 2-aminophenol and phenylenediamine respectively. The reaction between 2-bromoacetophenone and deprotonated indole gave substrate **281** in 21% yield. To form the C3 indole derivative a literature procedure¹⁵⁷ was used in which silyl enol ether **282** reacts with a hypervalent iodine reagent, subsequent addition of indole to the mixture gave the C3-indole **283** in 44% yield. Lastly an indole attached at the C2 position was also investigated, the Fischer indole synthesis between phenylhydrazine and acetone gave indole **284**. The deprotonation of the methyl group of **284** was considered to be potentially problematic at this point due to the N-H and to avoid this, indole **284** was methylated at the nitrogen to give **285**. This was then selectively deprotonated at the C2 methyl of the indole and reacted with benzonitrile to give ketone **285** in 46% yield.



Scheme 89. Synthetic routes to prepare benzofused-heterocyclic ketones.

The reduction of the benzothiazole **280** was found to give low conversions and a poor enantioselectivity of 60% ee (Table 39). Under the conditions employed it was found that substrate **280** only partially dissolves and a precipitate forms during the reaction, as opposed to the other reductions where the reaction mixtures remains homogenous. The other benzo-fused five-membered heterocycles tested did not have this issue, and ketone **281** was reduced to the alcohol in 97% ee. The change of position to a C3 bonded indole **283** gave the alcohol product **289** in similar yield and enantioselectivity. The C2 connected indole **286** was reduced with an excellent enantioselectivity of 99% ee and gave a yield of 98%.



Ketone	Alcohol	Time (h)	Yield /%	ee /%	<i>R/S</i>
280	287	72	16	60	<i>R</i>
281	288	72	90	97	<i>S</i>
283	289	72	89	96	<i>R</i>
286	290	72	98	99	<i>R</i>

Table 39. ATH results of benzofused-heterocyclic ketones using furan catalyst (*R,R*)-**131**. Catalyst 1 mol%, FA/TEA, DCM, [S] = 1 M.

Summary

The catalyst (*R,R*)-**131** was employed in the ATH of α -heterocyclic acetophenones forming alcohol products in up to 99% ee. A range of synthetic methods were devised to produce the α -heterocyclic acetophenones. A series of α -pyridyl substrates were reduced in 95-98% ee and a series of 5-membered α -heterocyclic ketones were reduced in 90-96% ee. The reduction of α -benzofused-heterocyclic ketones reduced in 60-99% ee with catalyst (*R,R*)-**131**. X-ray crystallography of one of the alcohol products suggests the reduction involves a favourable C-H/ π interaction between the η^6 -arene of the catalyst and the phenyl group of the substrate during the hydrogen transfer step.

***Chapter 6: Conclusions and
Future work***

6.1. Conclusions

In conclusion, TsDPEN ligands containing aromatic heterocyclic groups on the amine nitrogen atom have been synthesised and evaluated as either bidentate or tridentate ligands in the asymmetric transfer hydrogenation of ketones. The donor atoms on the heterocycle determines whether a ligand is bidentate or tridentate; where strong donor atoms lead to tridentate ligands and weak donor atoms to bidentate ligands. Tridentate ligands form active ATH complexes with $\text{Ru}_3(\text{CO})_{12}$ and reduces ketones in *i*PrOH. On the other hand, bidentate ligands form active ATH complexes with $[\text{Ru}(\text{benzene})\text{Cl}_2]_2$ and reduces ketones in a FA/TEA azeotrope. The complexes of bidentate ligands can be isolated or generated *in situ* that reduce ketones in good ee. The novel bidentate catalysts exhibit reduced activity and enantioselectivity compared to a Noyori-Ikariya catalyst in the reduction of acetophenone and substituted-acetophenones. These catalysts also have much slower activity than the tethered catalyst.

A range of α , β and γ -substituted acetophenones were reduced with the catalysts formed from the bidentate and tridentate ligands. This in turn permits the identification of an optimal catalyst for the ATH of each substrate. Such as the ATH of ketone **155** performing well with tridentate ligands this in turn produces the alcohol product in 96% yield and 99% ee. The bidentate catalysts have a greater substrate scope compared to the tridentate catalysts; the tridentate catalysts are poisoned by some ketones such as an α -methoxyacetophenone. The ATH of some ketones reveals the tethered catalyst **22** to have faster activity but similar enantioselectivity than the novel bidentate catalysts.

The presence of a heterocyclic group on the basic nitrogen atom of TsDPEN, such as a furan group, plays a crucial role in reducing 1-phenyl-3,4-dihydroisoquinoline in high enantioselectivity, up to 90% ee. The ATH of 1-aryl-3,4-dihydroisoquinolines containing *meta* and *para* substituents with catalyst **131** forms amine products in 88-94% ee. Catalyst **131** solves a long-standing problem in the reduction of this class of substrates as the Noyori-Ikariya catalyst has previously delivered these products in low enantioselectivity, up to 39% ee. On the other hand, *ortho*-containing 1-aryl-3,4-dihydroisoquinolines are poor substrates for ATH using catalyst **131** but reduce in

high enantioselectivity with Noyori-Ikariya catalysts this demonstrates a complementary relationship in the reduction of 1-aryl-3,4-dihydroisoquinolines.

Derivatives of the versatile furan catalyst were investigated; with different sulfonyl and η^6 -arene groups on the catalyst demonstrate that the tosyl as the sulfonamide and benzene as the arene, catalyst **131**, gives the best enantioselectivity and reactivity in the ATH of acetophenone. A range of synthetic methods have been designed and executed to add the furan-containing catalyst onto solid supports.

A range of synthetic methods were used to produce a series of α -heterocyclic acetophenones. The furan-containing catalyst was selected in the ATH of α -heterocyclic acetophenones forming products in up to 99% ee. The X-ray crystallography of an alcohol product suggests the reduction involves a favourable C-H/ π interaction between the η^6 -arene of the catalyst and the phenyl group of the substrate during the hydrogen transfer step.

6.2. Future work

It would be valuable to further investigate the ATH mechanisms of both ketones and imines with the novel bidentate catalysts, using both computational methods and experimental methods to gain a better understanding. A more detailed study could be conducted to determine the TS in the ATH of ketones using the catalytic system from the tridentate ligands, since the mechanism is less well understood.

Additionally, a study into the effect of different ratios of the FA/TEA azeotrope on the ATH of acetophenone using the heterocycle-containing catalysts and also different hydrogen donor sources, could be carried out. Also, an exciting area to investigate would be the effect of asymmetric pressure hydrogenation in the reduction of ketones using the heterocycle-containing catalysts.

The furan of catalyst **131** may also play a crucial role in the ATH of some ketone substrates; this effect could also be investigated in DKR studies with more complex substrates such as substrate **291** (Figure 53). The ATH of more derivatives of α -heterocyclic acetophenones could also be studied such as those containing *para* and *meta*-substituted phenyl groups, for example ketones **292** and **293**, could be investigated.

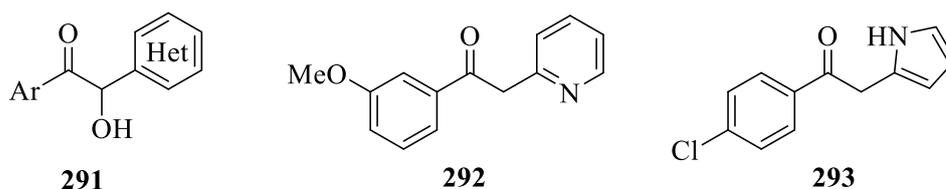
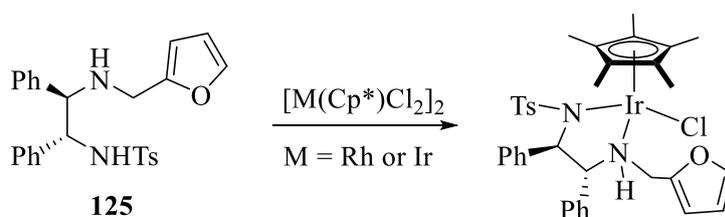


Figure 53. Structures of ketones that could be reduced through ATH using furan catalyst **131**.

Catalyst **131** has shown to solve a long-standing problem in the ATH of 1-aryl-3,4-dihydroisoquinolines and has been effectively scaled-up to a gram this can be taken further for ATH on a kilogram-scale. These heterocycle-containing catalysts may possibly be used in industry for the manufacture of drug precursors in high enantioselectivity. The novel bidentate catalysts perform better in the ATH of imines than that of ketones and have shown to be superior compared to other ruthenium catalysts. Therefore, the ATH of other types of imines should be investigated, more specifically imines that have previously not worked well with the Noyori-Ikariya catalysts.

Iridium catalysts have been reported to give moderate to good enantioselectivity in the ATH of 1-aryl-3,4-dihydroisoquinolines and the furan-containing catalyst **131** has demonstrated high enantioselectivity with these types of substrates. Through a combination of both methodologies, an iridium catalyst containing the furan ligand (Scheme 90) may be capable of reducing the DHIQ substrates in higher enantioselectivity. Rhodium analogues may also possess some desirable traits. Moreover, the ATH of imine **189** with tethered catalyst (*R,R*)-**22** formed the amine product in 97% ee which is an interesting result. This could be further explored with the ATH of a range of derivatives of imine **189** for example in the presence of a range of substituents on the fused-aromatic ring of imine **189**.



Scheme 90. Formation of isoelectronic complexes to (*R,R*)-**131** with rhodium and iridium metal centres.

Finally, all of the coupling methods to attach furan catalyst **131** (reported in section 4.3.) could be attempted with silica-based supports and then an evaluation of the coupling method to determine which one leads to the smallest amount of ruthenium leaching could be completed. Also, magnetically-supported furan catalysts could be synthesised due to the encouraging results reported from such supports.

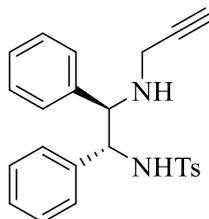
Chapter 7: Experimental

General Experimental

Reagents were used as received from commercial sources. Solvents and reagents for the synthesis of complexes and catalytic reactions were degassed prior to use and all reactions were carried out under a nitrogen atmosphere. Heated experiments were conducted using thermostatically controlled oil baths or aluminium blocks. Reactions at 0 °C refers to an ice slush bath and -78 °C refers to a dry ice-acetone bath. Reactions were monitored by TLC using aluminum backed silica gel 60 (F254) plates, visualized using UV 254 nm and phosphomolybdic acid or potassium permanganate dips. Flash column chromatography was carried out routinely using 60 μm silica gel. ^1H NMR were recorded on a Bruker Avance III (300, 400 or 500 MHz) spectrometer. Chemical shifts are reported in δ units, parts per million relative to the singlet at 7.26 ppm for chloroform and 0.00 ppm for TMS. Coupling constants (J) are measured in Hertz (Hz). Infrared spectra were recorded on a Bruker ALPHA FTIR spectrometer. Mass spectra were recorded on a Bruker Esquire200 or a Bruker MicroTOF mass spectrometer. Melting points were recorded on a Stuart Scientific SMP 1 instrument and are uncorrected. GC analysis was performed using a Hewlett Packard 5890. HPLC analysis was performed using either a Hewlett Packard 1050 instrument or Agilent 1260 Infinity. Optical rotations were measured on an AA-1000 polarimeter.

7.1. Ligands and Complexes

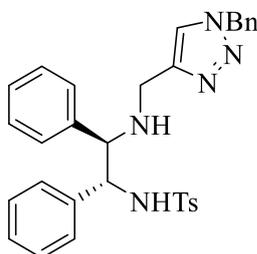
(*R,R*)-*N*-Propargyl-*N'*-4-toluenesulfonyl-1,2-diphenylethylenediamine. (*R,R*)-116



This compound is known.⁶⁴

Propargyl bromide (80% solution in toluene, 0.25 mL, 2.26 mmol) was added dropwise to a solution of (*R,R*)-TsDPEN (0.75 g, 2.05 mmol) and K₂CO₃ (0.43 g, 3.08 mmol) in acetonitrile (7.0 mL). After stirring for 24 h at rt the solvent was removed under reduced pressure. Water (20 mL) was added to the residue and the product extracted with ethyl acetate (3 x 15 mL). The organic layers were combined, dried over MgSO₄, filtered and solvent removed under reduced pressure. The product was purified by column chromatography with a gradient elution of 10-40% EtOAc in pet. ether to afford the product as a white solid (0.590 g, 1.46 mmol, 71%); δ_{H} (300 MHz, CDCl₃) 7.38 (2H, d, *J* 7.7, ArH), 7.17-7.15 (3H, m, ArH), 7.10-6.99 (9H, m, ArH), 5.78 (1H, s, TsNH), 4.39 (1H, t, *J* 5.8, CHNHTs), 4.02 (1H, d, *J* 7.1, CHNHCH₂), 3.33 (1H, d, *J*_{AB} 17.0, CH_AH_BNH), 3.09 (1H, d, *J*_{AB} 17.0, CH_AH_BNH), 2.34 (3H, s, CH₃), 2.17 (1H, s, CCH), 1.65 (1H, br, NHCH₂).

(*R,R*)-*N*-(1-Benzyl-4-methylene-1,2,3-triazole)-*N'*-4-toluenesulfonyl-1,2-diphenylethylenediamine. (*R,R*)-36

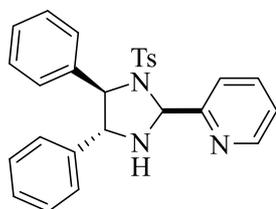


This compound is known.⁶⁴

Benzyl azide (93 mg, 0.69 mmol) in THF/water (1:1, 5 mL) was added dropwise to a solution of (*R,R*)-116 (235 mg, 0.58 mmol), copper(II) acetate (11 mg, 61 μ mol) and sodium ascorbate (23 mg, 0.12 mmol). After stirring the reaction at rt for 72 h the solvent was removed under reduced pressure. The residue was dissolved in ethyl

acetate (20 mL) and washed with 35% ammonia solution (20 mL) and brine (20 mL). The organic fraction was dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The product was purified by column chromatography with gradient elution 0-10% MeOH in DCM to afford the product as an off white solid (269 mg, 0.50 mmol, 86%); δ_{H} (400 MHz, CDCl₃) 7.43-7.41 (3H, m, ArH) 7.34 (2H, d, *J* 7.9, ArH), 7.31-7.23 (2H, m, ArH), 7.15-7.14 (3H, m, ArH), 7.09-6.96 (7H, m, ArH), 6.91 (2H, d, *J* 7.6, ArH), 6.13 (1H, br, TsNH), 5.52 (2H, s, CH₂Ph), 4.31 (1H, d, *J* 6.9, CHNHTs), 3.77-3.75 (1H, m, CHNHCH₂), 3.74-3.71 (1H, m, CH₂NHCH), 3.61 (1H, d, *J* 14.4, CH₂NHCH), 2.34 (3H, s, CH₃); MS (ESI⁺): *m/z*, 538.4 [M + H]⁺.

2-((2*R*,4*R*,5*R*)-4,5-Diphenyl-1-tosylimidazolidin-2-yl)pyridine. (*R,R*)-117b

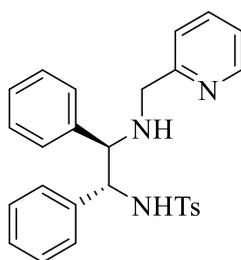


This compound is novel.

2-Pyridinecarboxaldehyde (146 mg, 1.36 mmol) in DCM (10 cm³) added to a solution of (*R,R*)-TsDPEN (500 mg, 1.36 mmol) in DCM (20 mL) and was left to stir overnight at r.t. The organic extracts were dried with anhydrous MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was dissolved in MeOH (20 mL) and NaBH₄ (0.13 g, 3.4 mmol) was added portionwise. After stirring overnight at r.t. the solvent was removed under reduced pressure and diethyl ether (15 mL) and sat. NaHCO₃ (15 mL) was added. The diethyl ether layer was separated and the aqueous layer was extracted with diethyl ether (2x 15 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by column chromatography gradient elution 0-40% EtOAc in hexane gave the product as a white solid (298 mg, 0.654 mmol, 48%); Mp 129.4 – 133.1, $[\alpha]_{\text{D}}^{22}$ -51.7 (*c* 0.3 in CHCl₃); ν_{max} 3286, 1596, 1495, 1474, 1448, 1433, 1366, 1349, 1335, 1305, 1181, 1163, 1132, 1097, 1082 cm⁻¹; δ_{H} (300 MHz, CDCl₃) 8.60 (1H, d, *J* 4.7, 6'-pyH), 7.99 (1H, d, *J* 7.7, 4'-pyH), 7.84 (1H, td, *J* 7.7, 1.6, ArH) 7.60 (2H, d, *J* 8.2, ArH), 7.33-7.29 (1H, dd, *J* 7.1, 4.9 ArH), 7.23-7.17 (10H, m ArH), 7.04 – 6.95 (2H, m, ArH), 5.94 (1H, s, NHCHN), 4.65 (1H, d, *J* 6.6, CHNTs), 4.32 (1H, d, *J* 6.6, CHNH), 3.77 (1H,

br, NH), 2.43 (3H, s, CH₃); δ_C (125 MHz, CDCl₃) 158.65, 149.06, 143.78, 139.65, 139.06, 136.91, 134.30, 129.55, 128.43, 128.27, 127.99, 127.61, 127.52, 127.26, 126.94, 123.75, 123.35, 78.26, 71.98, 69.75, 21.60; MS (ESI⁺): m/z , 456.3 [M + H]⁺; HRMS calcd for C₂₇H₂₆N₃O₂S [M + H]⁺ 456.1740, found 456.1738 (0.5 ppm error).

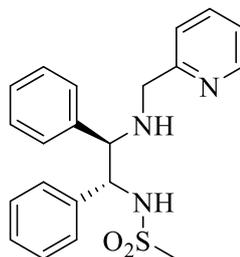
(*R,R*)-*N*-{1,2-Diphenyl-2-[(pyridin-2-ylmethyl)-amino]-ethyl}-4-methylbenzenesulfonamide. (*R,R*)-38



This compound is known.⁶⁵

2-Pyridinecarboxaldehyde (146 mg, 1.36 mmol) in DCM (10 mL) was added to a solution of (*R,R*)-TsDPEN (500 mg, 1.36 mmol) in DCM (20 mL) and was left to stir overnight at r.t. Anhydrous MgSO₄ was added, the solution was filtered and the solvent removed under reduced pressure. The residue was then dissolved in dry THF (8 mL) and the resulting solution cooled to 0 °C. LiAlH₄ (2M in THF, 0.68 mL, 1.36 mmol) was added slowly to the solution and stirred overnight at r.t. The solution was cooled to 0 °C and the reaction was quenched by addition of ethyl acetate (5 mL) and sat. Rochelle salt (15 mL). The product was extracted with EtOAc (3 x 15 mL) and the organic layers combined, dried over MgSO₄, filtered and the solvent removed under reduced pressure. Purification by column chromatography with gradient elution 20-50% EtOAc in pet.ether gave the product as an orange solid (403 mg, 0.882 mmol, 65%); δ_H (400 MHz, CDCl₃) 8.58 (1H, d, J 4.6, ArH), 7.65 (1H, t, J 7.7, ArH), 7.45 (2H, d, J 7.7, ArH), 7.20 (1H, t, J 6.1, ArH), 7.16-7.13 (4H, m, ArH), 7.10-6.97 (8H, m, ArH + NHTs), 6.95 (2H, d, J 7.5, ArH), 4.38 (1H, d, J 8.2, CHNHTs), 3.78 (1H, d, J 15.0, CH_aH_b), 3.73 (1H, d, J 7.9, CHNHCH₂), 3.66 (1H, d, J 15.0, CH_aH_b), 2.36 (3H, s, CH₃); MS (ESI⁺): m/z , 458.3 [M + H]⁺.

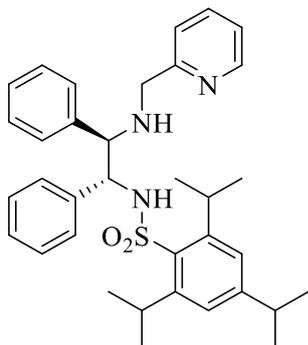
(1*R*,2*R*)-*N*-1,2-Diphenyl-2-((pyridin-2-ylmethyl)amino)ethyl-methanesulfonamide. (*R,R*)-118



This compound is novel.

To a solution of (*R,R*)-MsDPEN (300 mg, 1.03 mmol) in dry DCM (15 mL) with 4 Å molecular sieves was added dropwise a solution of 2-pyridinecarboxaldehyde (111 mg, 1.03 mmol) in dry DCM (6 mL). The molecular sieves were filtered off after stirring overnight and the solvent removed under reduced pressure. The residue was dissolved in dry THF (10 mL) and cooled to 0 °C followed by dropwise addition of LiAlH₄ (2 M in THF, 0.52 mL, 1.04 mmol). After stirring at rt for 5 hours the reaction mixture was cooled to 0°C and quenched by slow addition of EtOAc. Sat. Rochelle salt solution (15 mL) was added and left to stir at rt for 45 min. Following extraction with EtOAc (3 × 15 mL), the organic extracts were combined, dried over MgSO₄, filtered and concentrated under reduced pressure to afford the crude product. Purification by column chromatography (0 – 2% MeOH in DCM) afforded the pure product as a yellow solid (233 mg, 0.611 mmol, 59%); Mp 52.6 – 54.0 °C; [α]_D²² -3.7 (*c* 0.05 in CHCl₃); ν_{max} 3287, 3063, 3026, 2933, 1590, 1570, 1493, 1454, 1433, 1316, 1200, 1143 cm⁻¹; δ_H (500 MHz, CDCl₃) 8.53 (1 H, d, *J* 4.4, 6'-pyH), 7.62 (1 H, t, *J* 7.7, 4'-pyH), 7.25 – 7.09 (12 H, m, ArH) 6.84 – 6.67 (2 H, m, ArH), 4.57 (1 H, d, *J* 7.9 CHNHSO₂), 3.88 – 3.84 (2 H, m, CHNHCH₂ + CH_AH_BNH), 3.67 (1 H, d *J*_{AB} 14.8, CH_AH_BNH), 2.38 (3 H, s, Ms-CH₃); δ_C (125 MHz, CDCl₃) 158.99, 149.14, 139.33, 138.87, 136.55, 128.47, 128.45, 127.86, 127.81, 127.76, 127.63, 122.18, 122.08, 67.05, 63.33, 51.99, 41.32; MS (ESI⁺): *m/z*, 382.2 [M + H]⁺; HRMS calcd for C₂₁H₂₄N₃O₂S [M + H]⁺ 382.1584, found 382.1586 (0.7 ppm error).

(1*R*,2*R*)-*N*-{1,2-Diphenyl-2-[(pyridin-2-ylmethyl)amino]ethyl}-2,4,6-triisopropylbenzenesulfonamide. (*R,R*)-119

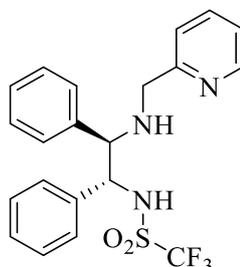


This compound is novel.

To a solution of (*R,R*)-TrisDPEN (479 mg, 1.00 mmol) in dry DCM (14 mL) with 4 Å molecular sieves was added dropwise a solution of 2-pyridinecarboxaldehyde (107 mg, 1.00 mmol) in dry DCM (5 mL). The molecular sieves were filtered off after stirring overnight and the solvent removed under reduced pressure. The residue was dissolved in dry THF (10 mL) and cooled to 0 °C followed by dropwise addition of LiAlH₄ (2 M in THF, 0.5 mL, 1.00 mmol). After stirring at rt for 5 hours the reaction mixture was cooled to 0°C and quenched by slow addition of EtOAc. Sat. Rochelle salt solution (12 mL) was added and left to stir at rt for 30 min. Following extraction with EtOAc (3 × 10 mL), the organic extracts were combined, dried over MgSO₄, filtered and concentrated under reduced pressure to afford the crude product. Purification by column chromatography (40% EtOAc in Pet. Ether) afforded the pure product as a white solid (387 mg, 0.680 mmol, 68%); Mp 152.6 – 153.2 °C; $[\alpha]_D^{22} +10.0$ (*c* 0.05 in CHCl₃); ν_{\max} 3340, 3289, 3061, 3030, 2957, 2928, 2867, 1600, 1569, 1492, 1454, 1432 cm⁻¹; δ_H (500 MHz, CDCl₃) 8.51 (1 H, d, *J* 4.6, 6' py-H), 7.63 (1 H, td, *J* 7.7, 1.4, 4' py-H), 7.22 (1 H, d, *J* 7.7, 3' py-H), 7.17 (1 H, t, *J* 6.1, ArH), 7.14 – 7.09 (3 H, m, ArH), 7.07 (1 H, br. s, NHSO₂), 6.98 (2 H, s, tris-3',5'-H), 6.96 – 6.91 (3 H, m, ArH), 6.87 (2 H, t, *J* 7.4, ArH), 6.75 (2 H, d, 7.4, ArH), 4.51 (1 H, d, *J* 9.3, CHNHSO₂), 3.99 (2 H, sep, Tris-*o*-CH(CH₃)₂), 3.83 (1 H, d, *J*_{AB} 14.8, CH_AH_BNH), 3.69 (1 H, d, *J*_{AB} 14.8, CH_AH_BNH), 3.64 (1 H, d, *J* 9.3, CHNHCH₂), 2.83 (1 H, sep, *J* 6.9, Tris-*p*-CH(CH₃)₂), 1.21 (6 H, d, *J* 6.9, Tris-*p*-CH(CH₃)₂), 1.17 (6 H, d, *J* 6.7, Tris-CH₃), 1.04 (6 H, d, *J* 6.7, Tris-CH₃); δ_C (125 MHz, CDCl₃) 159.25, 152.27, 149.94, 149.05, 139.30, 138.33, 136.52, 133.74, 128.18, 127.87, 127.68, 127.48, 127.05, 123.21, 122.22, 122.02, 67.93, 63.03, 52.07, 34.12, 29.66, 24.96, 24.70, 23.67,

23.61; MS (ESI⁺): m/z , 570.4 [M + H]⁺; HRMS calcd for C₃₅H₄₄N₃O₂S [M + H]⁺ 570.3149, found 570.3148 (0.0 ppm error).

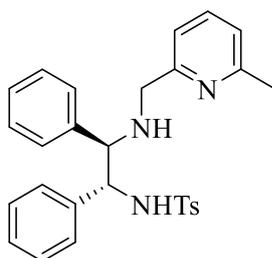
(1*R*,2*R*)-*N*-{1,2-Diphenyl-2-[(6-methyl-pyridin-2-ylmethyl)amino]ethyl}-1,1,1-trifluoromethanesulfonamide. (*R,R*)-120



This compound is novel.

To a solution of (*R,R*)-TfDPEN (50 mg, 0.15 mmol) in dry DCM (3 mL) with 4 Å molecular sieves was added dropwise 2-pyridinecarboxaldehyde (16 mg, 0.15 mmol) in dry DCM (1 mL). The molecular sieves were filtered off after stirring overnight and the solvent removed under reduced pressure. The residue was dissolved in dry THF (10 mL) and cooled to 0 °C followed by dropwise addition of LiAlH₄ (2 M in THF, 75 μL, 0.15 mmol). After stirring at rt for 5 h the reaction mixture was cooled to 0 °C and quenched by slow addition of EtOAc. Sat. Rochelle salt solution (2 mL) was added and left to stir at rt for 30 min. Following extraction with EtOAc (3 × 3 mL), the organic extracts were combined, dried over MgSO₄, filtered and concentrated under reduced pressure to afford the crude product. Purification by column chromatography (10 – 20% EtOAc in DCM) afforded the pure product as a white solid (30 mg, 0.069 mmol, 46%); Mp 59.2 – 62.0 °C; [α]_D²² -62.5 (*c* 0.02 in CHCl₃); ν_{max} 3310, 3064, 3031, 2926, 1720, 1656, 1597, 1571, 1454, 1437, 1368, 1272 cm⁻¹; δ_H (500 MHz, CDCl₃) 8.62 (1 H, d, *J* 4.4 6' py-H), 7.68 (1 H, t, *J* 7.40, ArH), 7.30 – 7.24 (2 H, m, ArH), 7.23 – 7.19 (3 H, m, ArH), 7.18 – 7.14 (3 H, m, ArH), 7.13 - 7.02 (5 H, m, ArH), 4.71 (1 H, d, *J* 8.6, CHNHTf), 4.04 (1 H, d, *J* 16.6, NHCH_AH_B), 3.82 (1 H, d, *J* 16.6, NHCH_AH_B), 3.78 (1 H, d, *J* 8.6, CHNHCH₂); δ_C (125 MHz, CDCl₃) 159.05, 148.47, 139.58, 139.07, 137.15, 128.50, 128.20, 127.86, 127.72, 127.66, 127.09, 122.41, 122.37, 119.71 (q, *J* 322 Hz, CF₃), 67.53, 64.71, 50.86; δ_F (376 MHz, CDCl₃) -77.14 (3 F, s, CF₃); MS (ESI⁺): m/z , 434.0 [M – H]; HRMS calcd for C₂₁H₂₁F₃N₃O₂S [M + H]⁺ 436.1301, found 436.1305 (1.0 ppm error).

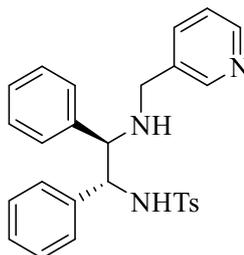
(1*R*,2*R*)-*N*-{1,2-Diphenyl-2-[(6-methyl-pyridin-2-ylmethyl)amino]ethyl}-4-methyl benzenesulfonamide. (*R,R*)-121



This compound is novel.

To a solution of (*R,R*)-TsDPEN (366 mg, 1.00 mmol) in dry DCM (15 mL) with 4 Å molecular sieves was added dropwise a solution of 6-methylpyridine-2-carboxaldehyde (121 mg, 1.00 mmol) in dry DCM (5 mL). The molecular sieves were filtered off after stirring overnight and the solvent removed under reduced pressure. The residue was dissolved in dry THF (8 mL) and cooled to 0 °C followed by dropwise addition of LiAlH₄ (2 M in THF, 0.50 mL, 1.00 mmol). After stirring at rt for 5 h the reaction mixture was cooled to 0 °C and quenched by slow addition of EtOAc. Sat. Rochelle salt solution (12 mL) was added and left to stir at rt for 30 min. Following extraction with EtOAc (3 × 10 mL), the organic extracts were combined, dried over MgSO₄, filtered and concentrated under reduced pressure to afford the crude product. Purification by column chromatography (2% MeOH in DCM) afforded the pure product as an off-white solid (386 mg, 0.819 mmol, 82%); Mp 107.2 – 110.7 °C; [α]_D²² -7.3 (*c* 0.05 in CHCl₃); ν_{\max} 3358, 3338, 3064, 3030, 2924, 2850, 1594, 1578, 1494, 1455, 1435, 1377, 1322, 1290, 1259 cm⁻¹; δ_{H} (500 MHz, CDCl₃) 7.52 (1 H, t, *J* 7.7, 4'pyH), 7.44 (2 H, d, *J* 8.1, Ts-ArH), 7.17 – 7.10 (3 H, m, ArH), 7.10 – 7.01 (7 H, m, ArH), 7.01 – 6.97 (2 H, m, ArH), 6.96 – 6.90 (4 H, m, ArH), 4.39 (1 H, d, *J* 8.1, PhCHNH), 3.78 (1 H, d, *J*_{AB} 15.2, CH_AH_BNH), 3.73 (1 H, d, *J* 8.1, PhCHNHSO₂), 3.60 (1 H, d, *J*_{AB} 15.2, CH_AH_BNH), 2.60 (3 H, s, py-CH₃), 2.35 (3 H, s, Ts-CH₃); δ_{C} (125 MHz, CDCl₃) 158.39, 158.09, 142.56, 139.34, 138.74, 137.37, 136.77, 129.09, 128.21, 127.85, 127.81, 127.55, 127.44, 127.15, 127.08, 121.54, 119.06, 67.21, 63.31, 51.74, 24.36, 21.45; MS (ESI⁺): *m/z*, 472.3 [M + H]⁺; HRMS calcd for C₂₈H₃₀N₃O₂S [M + H]⁺ 472.2053, found 472.2053 (0.0 ppm error).

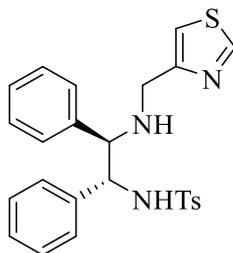
(1*R*,2*R*)-*N*-{1,2-diphenyl-2-[(pyridin-3-ylmethyl)amino]ethyl}-4-methylbenzene sulfonamide. (*R,R*)-122



This compound is novel.

To a solution of (*R,R*)-TsDPEN (366 mg, 1.00 mmol) in dry DCM (15 mL) with 4 Å molecular sieves was added dropwise a solution pyridine-3-carboxaldehyde (107 mg, 1.00 mmol) in dry DCM (5 mL). The molecular sieves were filtered off after stirring overnight and the solvent removed under reduced pressure. The residue was dissolved in dry THF (7 mL) and cooled to 0 °C followed by dropwise addition of LiAlH₄ (2 M in THF, 0.5 mL, 1.00 mmol). After stirring at rt for 5 h the reaction mixture was cooled to 0 °C and quenched by slow addition of EtOAc. Sat. Rochelle salt solution (12 mL) was added and left to stir at rt for 30 min. Following extraction with EtOAc (3 × 10 mL), the organic extracts were combined, dried over MgSO₄, filtered and concentrated under reduced pressure to afford the crude product. Purification by column chromatography (0 – 30 % EtOAc in DCM) afforded the pure product as an off-white solid (185 mg, 0.405 mmol, 40%); Mp 160.5 – 161.0 °C; [α]_D²² -20.7 (*c* 0.05 in CHCl₃); ν_{max} 3312, 3031, 2923, 2854, 2793, 1597, 1584, 1494, 1475, 1450, 1425, 1349, 1327 cm⁻¹; δ_{H} (500 MHz, CDCl₃) 8.52 (1 H, d, *J* 3.8, 6'py-H), 8.36 (1 H, s, 2'py-H), 7.56 (1 H, d, *J* 7.7, 5'py-H), 7.37 (2 H, d, *J* 8.2, ArH), 7.26 (1 H, dd, *J* 7.7, 5.0, 4'py-H), 7.22 – 7.16 (4 H, m, ArH), 7.08 (1 H, d, *J* 7.2, ArH), 7.06 – 6.96 (6H, m, ArH), 6.90 (2 H, d, *J* 7.2, ArH), 6.02 (1 H, br. s, CH₂NH), 4.42 – 4.32 (1 H, m, PhCHNH), 3.71 (1 H, d, *J* 7.8, PhCHNHSO₂), 3.66 (1 H, d, *J*_{AB} 13.6, CH_AH_BNH), 3.46 (1 H, d, *J*_{AB} 13.6, CH_AH_BNH), 2.33 (3 H, s, Ts-CH₃); δ_{C} (125 MHz, CDCl₃) 149.59, 148.73, 142.84, 138.47, 137.96, 136.93, 135.75, 134.75, 129.12, 128.53, 128.01, 127.80, 127.60, 127.41, 127.06, 123.51, 66.85, 48.26, 21.43; MS (ESI⁺): *m/z*, 458.3 [M + H]⁺; HRMS calcd for C₂₇H₂₈N₃O₂S [M + H]⁺ 458.1897, found 458.1891 (1.3 ppm error).

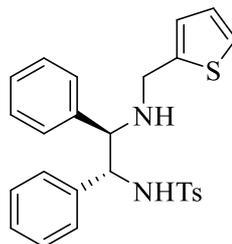
(1*R*,2*R*)-*N*-{1,2-Diphenyl-2-[(thiazol-4-ylmethyl)amino]ethyl}-4-methylbenzene sulfonamide. (*R,R*)-123



This compound is known.¹⁵⁸

To a solution of (*R,R*)-TsDPEN (366 mg, 1.00 mmol) in dry DCM (15 mL) with 4 Å molecular sieves was added dropwise a solution thiazole-4-carboxaldehyde (113 mg, 1.00 mmol) in dry DCM (5 mL). The molecular sieves were filtered off after stirring overnight and the solvent removed under reduced pressure. The residue was dissolved in dry THF (8 mL) and cooled to 0 °C followed by dropwise addition of LiAlH₄ (2 M in THF, 0.5 mL, 1.00 mmol). After stirring at rt for 5 h the reaction mixture was cooled to 0°C and quenched by slow addition of EtOAc. Sat. Rochelle salt solution (12 mL) was added and left to stir at rt for 30 min. Following extraction with EtOAc (3 × 10 mL), the organic extracts were combined, dried over MgSO₄, filtered and concentrated under reduced pressure to afford the crude product. Purification by column chromatography (3% MeOH in DCM) afforded the pure product as a yellow solid (120 mg, 0.259 mmol, 26%); Mp 67.8 – 72.4 °C; [α]_D²² -29.3 (*c* 0.05 in CHCl₃); ν_{max} 3243, 3062, 3029, 2919, 1598, 1493, 1453, 1409, 1322, 1184, 1153, 1090, 1027 cm⁻¹; δ_H (500 MHz, CDCl₃) 8.75 (1 H, s, 2'-thiazole-H), 7.40 (2 H, d, *J* 8.2, ArH), 7.18 – 7.13 (3 H, m, ArH), 7.11- 6.98 (9 H, m, ArH), 6.95 (2 H, d, *J* 7.0, ArH), 6.28 (1 H, br. s, CH₂NH), 4.38 (1 H, d, *J* 7.5 PhCHNH), 3.82 (1 H, d, *J*_{AB} 14.2, CH_AH_BNH), 3.78 (1 H, d, *J* 7.5, PhCHNHSO₂), 3.68 (1 H, d, *J*_{AB} 14.2, CH_AH_BNH), 2.35 (3 H, s, Ts-CH₃); δ_C (125 MHz, CDCl₃) 155.80, 153.01, 142.71, 138.73, 138.31, 137.06, 129.12, 128.39, 127.97, 127.63, 127.45, 127.32, 127.08, 114.46, 67.12, 63.08, 46.80, 21.44; MS (ESI⁺): *m/z*, 464.2 [M + H]⁺; HRMS calcd for C₂₅H₂₆N₃O₂S₂ [M + H]⁺ 464.1461, found 464.1463 (0.4 ppm error).

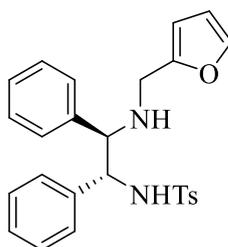
(1*R*,2*R*)-*N*-{1,2-Diphenyl-2-[(thiophen-2-ylmethyl)amino]ethyl}-4-methylbenzene sulfonamide. (*R,R*)-124



This compound is novel.

To a solution of (*R,R*)TsDPEN (400 mg, 1.09 mmol) in dry DCM (15 mL) with 4 Å molecular sieves was added dropwise a solution of 2-thiophenecarboxaldehyde (123 mg, 1.09 mmol) in dry DCM (6 mL). The molecular sieves were filtered off after stirring overnight and the solvent removed under reduced pressure. The residue was dissolved in dry THF (10 mL) and cooled to 0 °C followed by dropwise addition of LiAlH₄ (2 M in THF, 0.55 mL, 1.10 mmol). After stirring at rt overnight the reaction mixture was cooled to 0 °C and quenched by slow addition of EtOAc. Sat. Rochelle salt solution (15 mL) was added and left to stir at rt for 30 min. Following extraction with EtOAc (3 × 15 mL), the organic extracts were combined, dried over MgSO₄, filtered and concentrated under reduced pressure to afford the crude product. Purification by column chromatography (0 – 5% MeOH in DCM) afforded the pure product as an off-white solid (388 mg, 0.840 mmol, 77%); Mp 151.4 – 152.1 °C; $[\alpha]_D^{22}$ -31.0 (*c* 0.05 in CHCl₃); ν_{\max} 3336, 3299, 3031, 2930, 2841, 1598, 1492, 1440, 1424, 1347, 1328, 1304 cm⁻¹; δ_H (500 MHz, CDCl₃) 7.42 (2 H, d, *J* 8.1, Ts-ArH), 7.25 (1 H, d, *J* 5.0, ArH), 7.21 – 7.16 (3 H, m, ArH) 7.10 – 7.01 (5 H, m, ArH), 6.99 – 6.95 (2 H, m, ArH), 6.95 – 6.90 (3 H, m, ArH), 6.75 (1 H, d, *J* 2.5, ArH), 6.11 (1 H, d *J* 2.5, NHSO₂), 4.33 (1 H, dd, *J* 7.9, 2.6, CHNHSO₂), 3.85 (1 H, d, *J*_{AB} 14.0, CH_AH_BNH), 3.75 (1 H, d, *J* 7.9, CHNHCH₂), 3.64 (1 H, d, *J* 14.0, CH_AH_BNH), 2.35 (3 H, s, Ts-CH₃); δ_C (125 MHz, CDCl₃) 143.18, 142.76, 138.54, 138.14, 136.99, 129.13, 128.46, 127.95, 127.71, 127.59, 127.53, 127.33, 127.14, 126.63, 124.97, 124.71, 66.37, 62.97, 45.57, 21.45; MS (ESI⁺): *m/z*, 463.3 [M + H]⁺; HRMS calcd for C₂₆H₂₇N₂O₂S₂ [M + H]⁺ 463.1508, found 463.1511 (0.5 ppm error).

(1*R*,2*R*)-*N*-{1,2-Diphenyl-2-[(furan-2-ylmethyl)amino]ethyl}-4-methylbenzene sulfonamide. (*R,R*)-125

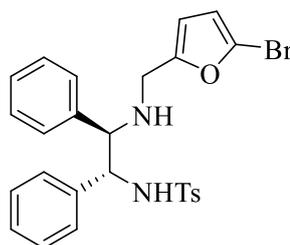


This compound is novel.

To a solution of (*R,R*)TsDPEN (500 mg, 1.36 mmol) in dry DCM (20 mL) with 4 Å molecular sieves was added dropwise a solution of 2-furaldehyde (130 mg, 1.36 mmol) in dry DCM (10 mL). The molecular sieves were filtered off after stirring overnight and the solvent removed under reduced pressure. The residue was dissolved in dry THF (8 mL) and cooled to 0 °C followed by dropwise addition of LiAlH₄ (2 M in THF, 0.68 mL, 1.36 mmol). After stirring at rt for 72 h the reaction mixture was cooled to 0 °C and quenched by slow addition of EtOAc. Sat. Rochelle salt solution (15 mL) was added and left to stir at rt for 30 min. Following extraction with EtOAc (3 × 15 mL), the organic extracts were combined, dried over MgSO₄, filtered and concentrated under reduced pressure to afford the crude product. Purification by column chromatography (10 – 20% EtOAc in Pet. Ether) afforded the pure product as an off-white solid (523 mg, 1.17 mmol, 86%); Mp 128.4 – 129.9 °C; [α]_D²² -41.7 (*c* 0.05 in CHCl₃); ν_{max} 3298, 3061, 3029, 2916, 2847, 1599, 1505, 1493, 1454, 1373, 1354 cm⁻¹; δ_{H} (500 MHz, CDCl₃) 7.35 (2 H, d, *J* 8.1, Ts-ArH), 7.30 (1 H, m, 5'-furan), 7.17 – 7.11 (3 H, m, ArH) 7.10 – 7.02 (4 H, m, ArH), 7.00 (2 H, d, *J* 8.1, Ts-ArH), 6.97 (2 H, m, ArH), 6.92 (2 H, t, *J* 7.0, ArH), 6.26 (1 H, m, 4'-furan), 6.00 (1 H, br. s, NH), 5.98 (1 H, d, *J* 3.1, 3'-furan), 4.31 (1 H, dd, *J* 7.3, 2.9 CHNHSO₂), 3.69 (1 H, d, *J* 7.3, CHNHCH₂), 3.62 (1 H, d, *J*_{AB} 14.4, CH_AH_BNH), 3.42 (1 H, d, *J*_{AB} 14.4, CH_AH_BNH), 2.32 (3 H, s, Ts-CH₃); δ_{C} (125 MHz, CDCl₃) 152.95, 142.70, 141.93, 138.65, 138.29, 137.00, 129.11, 128.41, 127.99, 127.61, 127.58, 127.38, 127.32, 127.08, 110.06, 107.10, 66.51, 62.99, 43.54, 21.43; MS (ESI⁺): *m/z*, 447.3 [M + H]⁺; HRMS calcd for C₂₆H₂₇N₂O₃S [M + H]⁺ 447.1737, found 447.1736 (0.2 ppm error).

This compound was also scaled-up; using (*S,S*)-TsDPEN (5.00 g, 13.6 mmol) and purified by recrystallisation in Et₂O/Pet ether 80:20 (4 crops) to yield the product (*S,S*)-125 (4.91 g, 11.0 mmol, 81%).

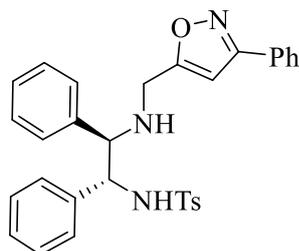
(*R,R*)-2-((5-Bromofuran-2-yl)methyl)amino-1,2-diphenylethyl-4-methylbenzenesulfonamide. (*R,R*)-126



This compound is novel.

To a solution of (*R,R*)-TsDPEN (500 mg, 1.36 mmol) in dry DCM (20 mL) with 4 Å molecular sieves was added dropwise a solution 5-bromo-2-furaldehyde (238 mg, 1.36 mmol) in dry DCM (10 mL). The molecular sieves were filtered off after stirring overnight and the solvent removed under reduced pressure. The residue was dissolved in MeOH (15 mL) and NaBH₄ (103 mg, 2.72 mmol) was added portionwise. The reaction was stirred at room temperature until the imine had reacted completely. Upon completion, the solvent was removed under reduced pressure and the residue partitioned between EtOAc (10 mL) and water (10 mL). The organic fraction collected and extracted again with EtOAc (2 x 10 mL). Organic extracts were combined, dried over MgSO₄, filtered and concentrated under reduced pressure to afford the crude product. Purification by column chromatography in DCM gave the pure product as a orange solid (368 mg, 0.701 mmol, 52%); Mp 94.7 – 100.2 °C; [α]_D²² -41.7 (*c* 0.1 in CHCl₃); ν_{\max} 3062, 3031, 1597, 1494, 1454, 1326, 1205, 1185, 1155, 1122 cm⁻¹; δ_{H} (500 MHz, CDCl₃) 7.37 (2 H, d, *J* 8.1, Ts-ArH), 7.18 - 7.13 (3 H, m, ArH), 7.11 - 7.04 (3 H, m, ArH), 7.02 (2 H, d, *J* 8.1, Ts-ArH), 6.99 - 6.92 (4 H, m, ArH), 6.16 (1 H, d, *J* 3.1, Furan-2'-H), 5.95 (1 H, d, *J* 3.1, Furan-3'-H), 5.93 (1 H, d, *J* 4.4, NHSO₂), 4.33 (1 H, dd, *J* 7.2, 4.4, CHNHSO₂), 3.71 (1 H, d, *J* 7.2, CHNHCH₂), 3.59 (1 H, d, *J* 14.8, CH_AH_BNH) 3.41 (1 H, d, *J* 14.8, CH_AH_BNH) 2.34 (3 H, s, Ts-CH₃), 1.78 (1 H, br. s, NHCH₂); δ_{C} (126 MHz, CDCl₃) δ_{C} 155.07, 142.76, 138.41, 138.17, 136.95, 129.14, 128.44, 128.06, 127.68, 127.54, 127.42, 127.30, 127.06, 120.77, 111.68, 109.94, 66.48, 62.95, 43.57, 21.44; MS (ESI⁺): *m/z* 525.2 [M + H]⁺; HRMS calcd for C₂₆H₂₆BrN₂O₃S [M + H]⁺ 525.0842, found 525.0847 (1.0 ppm error).

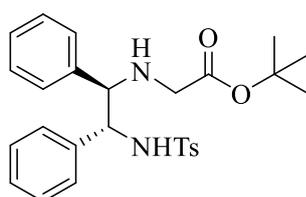
N-((*R,R*)-1,2-Diphenyl-2-(((3-phenylisoxazol-5-yl)methyl)amino)ethyl)-4-methylbenzenesulfonamide. (*R,R*)-127



This compound is novel.

Propargyl/TsDPEN (405 mg, 1.00 mmol) was added to a solution of N-hydroxybenzimidoyl chloride (156 mg, 1.00 mmol) in DMF (2 mL) with 4 Å molecular sieves. After stirring for 96 h, the molecular sieves were filtered off and water (15 mL) was added. The mixture was extracted with EtOAc (3 x 15 mL) and the combined organic extracts were washed with water (3 x 15 mL). The organic layer was then dried over MgSO₄, filtered and the solvent removed under reduced pressure to yield the crude product. Purification by column chromatography in (0 – 30% EtOAc in Pet. Ether) gave the pure product as an off-white solid (416 mg, 0.794 mmol, 79%); Mp 63.6 – 70.4 °C; $[\alpha]_D^{20}$ -43.3 (*c* 0.05 in CHCl₃); ν_{\max} 3244, 3030, 2920, 1727, 1599, 1579, 1494, 1453, 1442, 1407, 1323 cm⁻¹; δ_H (500 MHz, CDCl₃) 7.76 (2H, m, ArH), 7.49 – 7.44 (3H, m, ArH), 7.37 (2H, d, *J* 8.2, Ts-ArH), 7.19 – 7.15 (3H, m, ArH), 7.11 – 7.02 (5H, m, ArH), 7.00 (2 H, d, *J* 8.2, Ts-ArH) 6.94 (2H, d, *J* 7.2, ArH), 6.24 (1H, s, Isoxazole-H), 5.82 (1H, d, *J* 5.3, NHSO₂), 4.40 (1H, t, *J* 6.3, CHNHSO₂), 3.87 – 3.77 (2H, m, CH_AH_BNH + CHNHCH₂), 3.65 (1H, d, *J*_{AB} = 15.5 Hz, CH_AH_BNH), 2.31 (3H, s, Ts-CH₃); δ_C (126 MHz, CDCl₃) 171.38, 162.31, 142.91, 138.01, 136.84, 130.02, 129.19, 128.98, 128.92, 128.56, 128.17, 127.92, 127.64, 127.53, 127.27, 127.03, 126.82, 99.93, 66.83, 63.11, 42.38, 21.42; MS (ESI⁺): *m/z* 524.3 [M + H]⁺; HRMS calcd for C₃₁H₃₀N₃O₃S [M + H]⁺ 524.2002, found 524.2003 (0.1 ppm error).

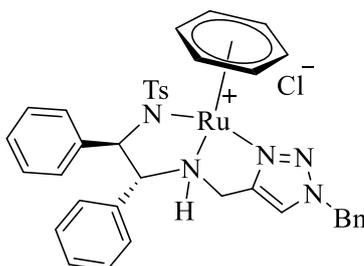
***tert*-Butyl ((*R,R*)-2-((4-methylphenyl)sulfonamido)-1,2-diphenylethyl)glycinate. (*R,R*)-128**



This compound is novel.

tert-Butyl bromoacetate (205 mg, 1.05 mmol, 155 μ L) was added dropwise to a stirring mixture of TsDPEN (366 mg, 1.00 mmol) and K_2CO_3 (207 mg, 1.5 mmol) in MeCN (4 mL). After stirring overnight, the solvent was removed under reduced pressure and the residue dissolved in EtOAc (15 mL) and water (15 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (2 x 15 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to yield the crude product. Purification by column chromatography (0 – 30% EtOAc in Pet. Ether) gave the pure product as a white solid (340 mg, 0.708 mmol, 71%); Mp 79.4 – 83.2 $^{\circ}C$; $[\alpha]_D^{22}$ -18.8 (*c* 0.1 in $CHCl_3$); ν_{max} 3250, 3030, 2979, 2929, 1721, 1599, 1494, 1454, 1368, 1346, 1324 cm^{-1} ; δ_H (500 MHz, $CDCl_3$) 7.40 (2 H, d, *J* 8.1, Ts-ArH), 7.16 – 7.09 (3 H, m, ArH), 7.08 – 7.01 (5 H, m, ArH), 6.98 - 6.94 (2 H, m, ArH), 6.92 (2 H, d, *J* 6.9, ArH), 6.21 (1 H, m, $NHSO_2$), 4.32 (1 H, dd, *J* 7.5, 3.5, $CHNHSO_2$), 3.72 (1 H, d, *J* 7.5, $CHNHCH_2$), 3.14 (1 H, d, *J* 17.2, CH_AH_BNH), 3.03 (1 H, d, *J* 17.2, CH_AH_BNH), 2.34 (3 H, s, Ts- CH_3), 2.06 (1 H, br. s, NH), 1.41 (9 H, s, 3 x CH_3); δ_C (126 MHz, $CDCl_3$) 171.14, 142.67, 138.47, 138.28, 137.17, 129.12, 128.31, 127.97, 127.78, 127.68, 127.44, 127.29, 127.08, 81.46, 67.26, 63.13, 49.04, 28.05, 21.44; MS (ESI⁺): *m/z* 481.3 $[M + H]^+$; HRMS calcd for $C_{27}H_{33}N_2O_4S$ $[M + H]^+$ 481.2156, found 481.2155 (0.1 ppm error).

Complex formed from ligand 36. (*R,R*)-129

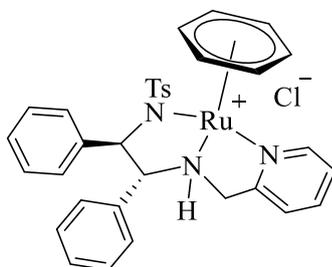


This compound is novel.

To a mixture of benzene ruthenium (II) chloride dimer (47 mg, 0.094 mmol) and (*R,R*)-**36** (100 mg, 0.186 mmol) in dry 2-propanol (5 mL) was added triethylamine (75 mg, 0.744 mmol, 103 μ L) and stirred at 80 $^{\circ}C$ for 1 h. The mixture was allowed to cool to room temperature before removal of the solvent under reduced pressure. The residue was dissolved in chloroform (10 mL) and washed with water (10 mL). The

organic layer separated, dried over MgSO₄, filtered and the solvent removed to afford the crude product. Purification by column chromatography (5% MeOH in DCM) afforded the pure product as a brown solid (78 mg, 0.104 mmol, 56%); Mp > 200 °C (Decomp); $[\alpha]_D^{22} +71.7$ (*c* 0.01 in CHCl₃); ν_{\max} 3369, 3030, 2865, 1599, 1494, 1452, 1434, 1266, 1130, 1084 cm⁻¹; δ_H (500 MHz, CDCl₃) 10.74 (1 H, br, NH), 7.52 (2 H, d, *J* 7.6, ArH), 7.45 (3 H, t, *J* 7.5, ArH), 7.40 (2 H, d, *J* 7.5, ArH), 7.32 (1 H, s, triazole-H), 7.21 (2 H, t, *J* 7.5, ArH), 7.13 (3 H, m, ArH), 6.85 (2 H, d, *J* 7.0, ArH), 6.78 – 6.70 (5 H, m, ArH), 6.25 (6 H, s, benzene), 5.71 (1H, d, *J*_{AB} 14.8, Benzyl-CH_AH_B), 5.66 (1H, d, *J*_{AB} 14.8, Benzyl-CH_AH_B), 4.90 (1 H, dd, *J* 11.8, 3.0, PhCHNH), 4.49 (1H, d, *J* 11.8, PhCHNTs), 3.78 (1H, m, CH_AH_BNH), 3.70 (1H, m, CH_AH_BNH), 2.20 (3 H, s, tosyl-CH₃); δ_C (125 MHz, CDCl₃) 149.30, 141.38, 139.86, 138.90, 133.39, 132.73, 130.50, 129.50, 128.88, 128.62, 128.60, 128.47, 128.15, 127.55, 126.88, 126.59, 119.54, 86.50, 78.82, 62.17, 55.98, 41.73, 21.15; MS (ESI⁺): *m/z*, 716.3 [M – Cl]⁺; HRMS calcd for C₃₇H₃₆N₅O₂SRu [M – Cl]⁺ 716.1628, found 716.1641 (0.5 ppm error).

Complex formed from ligand 38. (*R,R*)-130

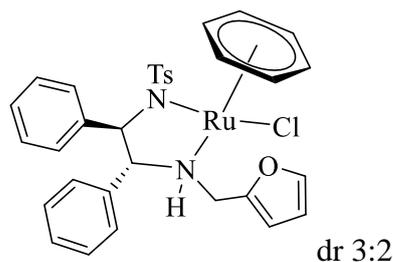


This compound is novel.

To a mixture of benzene ruthenium (II) chloride dimer (54.7 mg, 0.109 mmol) and **5** (100 mg, 0.218 mmol) in dry 2-propanol (5 mL) was added triethylamine (89 mg, 0.875 mmol, 123 μ L) and stirred at 80 °C for 1 h. The mixture was allowed to cool to room temperature before removal of the solvent under reduced pressure. The residue was dissolved in chloroform (10 mL) and washed with water (10 mL). The organic layer separated, dried over MgSO₄, filtered and the solvent removed to afford the crude product. Purification by column chromatography (0 – 10% MeOH in DCM) afforded the pure product as a brown solid (40 mg, 0.059 mmol, 27%); Mp > 200 °C (Decomp); $[\alpha]_D^{22} +71.7$ (*c* 0.01 in CHCl₃); ν_{\max} 3360, 3030, 2873, 1607, 1492, 1451, 1434, 1265,

1128, 1084, 1044 cm^{-1} ; δ_{H} (500 MHz, CDCl_3) 10.45 (1 H, s, NH), 9.54 (1 H, d, J 5.5, 6'-pyH), 7.91 (1 H, t, J 7.5, 4'-pyH) 7.49 (1H, t, J 6.5, 5'-pyH), 7.37 (2H, d, J 7.5, ArH), 7.32 (1 H, d, J 7.8, ArH), 7.21 (2 H, t, J 7.3, ArH), 7.16 (1 H, t, J 7.3, ArH), 7.04 (2 H, d, J 8.1, ArH), 6.76 (2H, d, J 8.0, ArH), 6.72 (2 H, d, J 7.4, ArH), 6.66 (1H, t, J 7.1, ArH), 6.59 (2 H, t, J 7.4, ArH), 6.26 (6 H, s, benzene), 4.67 (1 H, d, J 12.3, PhCHNTs), 4.40 (1 H, d, J_{AB} 18.0, $\text{CH}_\text{A}\text{H}_\text{B}\text{NH}$), 4.08 (1 H, d, J_{AB} 18.0, $\text{CH}_\text{A}\text{H}_\text{B}\text{NH}$), 4.03 (1 H, d, J 12.3, NHCHPh), 2.21 (3 H, s, Ts- CH_3); δ_{C} (125 MHz, CDCl_3) 161.92, 155.91, 142.22, 139.73, 139.45, 136.97, 132.73, 130.50, 129.28, 128.84, 128.55, 128.17, 127.23, 126.71, 126.29, 124.57, 120.24, 86.67, 77.56, 62.94, 54.54, 21.15; MS (ESI⁺): m/z , 636.3 $[\text{M} - \text{Cl}]^+$; HRMS calcd for $\text{C}_{33}\text{H}_{32}\text{N}_3\text{O}_2\text{SRu} [\text{M} - \text{Cl}]^+$ 636.1253, found 636.1260 (0.2 ppm error).

Complex formed from ligand 125. (*R,R*)-131



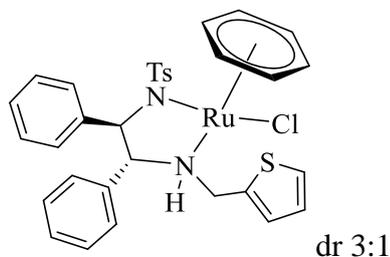
This compound is novel.

To a Schlenk tube charged with benzene ruthenium (II) chloride dimer (56 mg, 0.112 mmol) and (*R,R*)-**125** (100 mg, 0.224 mmol) in dry chlorobenzene (1 mL) was added triethylamine (89 mg, 0.880 mmol, 123 μL). After stirring at 80 $^{\circ}\text{C}$ for 1 h, the solution was allowed to cool to rt and the solvent removed under reduced pressure. The residue was dissolved in CHCl_3 (10 mL) and washed with water (10 mL). The organic layer was dried over MgSO_4 , filtered and solvent removed under reduced pressure to afford the crude mixture. Purification by column chromatography (15% EtOAc in DCM followed by 1-3% MeOH in DCM) afforded the product as a brown solid (130 mg, 0.197 mmol, 88%); Mp 191.2 – 194.5 $^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{22} +100.0$ (c 0.05 in CHCl_3); ν_{max} 3295, 3197, 3061, 3028, 2922, 2871, 1599, 1493, 1453, 1435, 1367, 1329, 1268, 1193, 1148 cm^{-1} ; Major diastereomer: δ_{H} (500 MHz, CDCl_3) 7.41 (1 H, s, ArH), 7.33 – 7.27 (2 H, m, ArH), 7.12 – 7.02 (3 H, m, ArH) 6.92 – 6.82 (3 H, m, ArH), 6.77 – 6.72 (4 H, m, ArH), 6.6 (2 H, d, J 7.3 ArH), 6.37 (2 H, s, ArH), 5.70 (6 H, s, benzene), 4.45 (1 H,

br, NH), 4.32 – 4.24 (1 H, m, CH_AH_BNH), 4.13 (1 H, d J 13.7, CH_AH_BNH), 4.05 (1 H, m, $PhCHNSO_2$), 3.84 (1 H, t, J 11.6, $PhCHNH$), 2.25 (3 H, s, Ts- CH_3); δ_C (125 MHz, $CDCl_3$) 149.38, 141.92, 141.68, 139.49, 139.41, 136.55, 129.86, 128.93, 128.65, 128.02, 127.56, 126.93, 126.71, 126.48, 111.32, 109.39, 84.01, 80.49, 69.66, 51.52, 21.26; Minor diastereomer: δ_H (500 MHz, $CDCl_3$) 7.49 (1 H, s, ArH), 7.36 (1 H, m, ArH), 7.33 – 7.27 (2 H, m, ArH) 7.12 – 7.02 (3 H, m, ArH) 6.82 – 6.80 (3 H, m, ArH), 6.72 – 6.69 (4 H, m, ArH), 6.58 – 6.53 (1 H, m, ArH), 6.41 (1 H, s, ArH), 6.17 (1H, s, ArH), 5.64 (6 H, s, benzene), 5.44 (1H, m, NH), 4.71 (1 H, m, CH_AH_BNH), 4.39 (1 H, m, $PhCHNSO_2$), 4.05 (1 H, m, $PhCHNH$), 3.72 (1 H, d J 14.6, CH_AH_BNH), 2.23 (3 H, s, Ts- CH_3); δ_C (125 MHz, $CDCl_3$) 150.46, 143.08, 142.21, 139.39, 138.44, 136.85, 128.60, 128.35, 128.10, 127.53, 126.71, 126.48, 126.41, 125.96, 111.74, 109.16, 83.72, 74.44, 71.86, 50.02, 21.24; MS (ESI⁺): m/z , 625.2 $[M - Cl]^+$; HRMS calcd for $C_{32}H_{31}N_2O_3SRu [M - Cl]^+$ 625.1093, found 625.1095 (1.0 ppm error).

This compound was also scaled-up; using (*S,S*)-**125** (1.00 g, 2.24 mmol) and benzene ruthenium (II) chloride dimer (560 mg, 1.12 mmol) to yield the product (*S,S*)-**125** (958 mg, 1.45 mmol, 65%).

Complex formed from ligand **124**. (*R,R*)-**132**

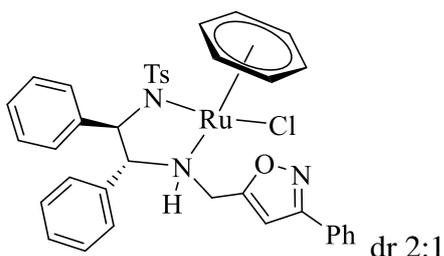


This compound is novel.

To a Schlenk tube charged with benzene ruthenium (II) chloride dimer (65 mg, 0.130 mmol) and (*R,R*)-**124** (120 mg, 0.260 mmol) in dry chlorobenzene (2 mL) was added triethylamine (105 mg, 1.04 mmol, 145 μ L). After stirring at 80 °C for 1 h, the solution was allowed to cool to rt and the solvent removed under reduced pressure. The residue was dissolved in $CHCl_3$ (10 mL) and washed with water (10 mL). The organic layer was dried over $MgSO_4$, filtered and solvent removed under reduced pressure to afford the crude mixture. Purification by column chromatography (20% EtOAc in DCM followed by 1-4% MeOH in DCM) afforded the pure product as a brown solid (119

mg, 0.176 mmol, 68%); Mp 151.4 – 152.1 °C; $[\alpha]_D^{22} +72.2$ (*c* 0.003 in CHCl₃); ν_{\max} 3293, 3062, 3027, 2923, 2868, 1599, 1493, 1453, 1433, 1379, 1328, 1270, 1197; δ_H (500 MHz, CDCl₃) Major diastereomer: 7.27 (1 H, s, ArH), 7.22 (1 H, m, ArH), 7.14 (1 H, ArH), 7.10 – 7.04 (2 H, m, ArH), 7.03 – 6.99 (2 H, m, ArH), 6.95 – 6.89 (1 H, m, ArH), 6.87 - 6.79 (3 H, m, ArH), 6.76 (2 H, d, *J* 7.32, ArH), 6.73 - 6.69 (2 H, m, ArH), 6.60 (2 H, d, *J* 7.5, ArH), 5.66 (6 H, s, benzene), 4.54 – 4.40 (2 H, m, CH_AH_BNH + CH_AH_BNH), 4.31 (1 H, d, *J* 13.7, CH_AH_BNH), 4.10 (1 H, d, *J* 10.8, PhCHNSO₂), 3.91 - 3.80 (1 H, m, PhCHNH), 2.25 (3 H, s, Ts-CH₃); δ_C (125 MHz, CDCl₃) 141.94, 139.43, 139.17, 137.93, 136.70, 129.89, 129.05, 128.67, 128.40, 128.01, 127.57, 127.46, 127.05, 126.89, 126.39, 125.09, 84.08, 81.00, 69.59, 54.47, 21.25; MS (ESI⁺): *m/z*, 641.2 [M – Cl]⁺; HRMS calcd for C₃₂H₃₁N₂O₂S₂Ru [M – Cl]⁺ 641.0865, found 641.0868 (0.7 ppm error).

Complex formed from ligand **127**. (*R,R*)-**133**

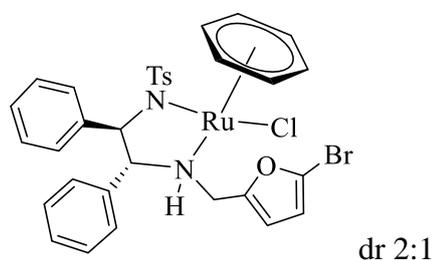


This compound is novel.

To a Schlenk tube charged with benzene ruthenium (II) chloride dimer (58 mg, 0.116 mmol) and (*R,R*)-**127** (120 mg, 0.229 mmol) in PhCl (1.8 mL) was added triethylamine (93 mg, 0.92 mmol, 128 μ L). After stirring at 80 °C for 1 h, the solution was allowed to cool to rt and the solvent removed under reduced pressure. The residue was dissolved in CHCl₃ (15 mL) and washed with water (15 mL). The organic layer was dried over MgSO₄, filtered and solvent removed under reduced pressure to afford the crude mixture. Purification by column chromatography (15% EtOAc in DCM followed by 0-3% MeOH in DCM) afforded the product as a dark brown solid (77 mg, 0.104 mmol, 46%); Mp > 250 °C (Decomp); $[\alpha]_D^{22} +50.0$ (*c* 0.002 in CHCl₃); ν_{\max} 3056, 3029, 1598, 1558, 1493, 1437, 1405, 1374, 1269, 1156, 1127 cm⁻¹; Major: δ_H (500 MHz, CDCl₃) 7.84 – 7.77 (2 H, m ArH), 7.51 - 7.43 (4 H, m, ArH), 7.33 – 7.27 (2 H, m, ArH), 7.11 – 7.06 (3 H, m, ArH), 6.95 – 6.91 (1 H, m, isoxazole-H), 6.86 (2

H, d, J 7.8, ArH), 6.83 – 6.78 (2 H, m, ArH), 6.74 (2 H, t, J 7.3, ArH), 6.72 – 6.67 (1 H, m, ArH), 6.64 (1 H, d, J 7.3, ArH), 5.74 (6 H, s, benzene), 4.58 – 4.41 (2 H, m, $CH_AH_BNH + CHNSO_2$), 4.12 (1 H, d, J 10.68, CH_AH_BNH), 4.05 – 3.90 (1 H, m, $CHNHCH_2$), 2.26 (3 H, s, Ts- CH_3); δ_C (126 MHz, $CDCl_3$) 167.24, 163.04, 141.65, 139.65, 139.19, 135.97, 130.53, 129.79, 129.12, 128.94, 128.82, 128.14, 128.09, 127.48, 127.08, 126.99, 126.82, 126.57, 102.60, 84.19, 80.83, 69.36, 50.80, 21.27; MS (ESI⁺): m/z 702.3 $[M - Cl]^+$; HRMS calcd for $C_{37}H_{33}N_3NaO_3RuS$ $[M - HCl + Na]^+$ 724.1178, found 724.1188 (0.0 ppm error).

Complex formed from ligand 126. (*R,R*)-134

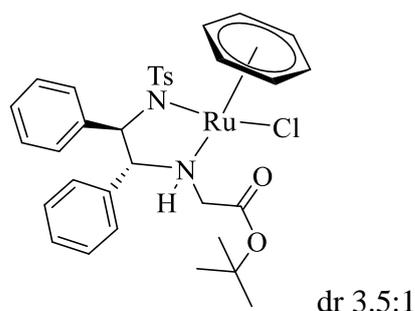


This compound is novel.

To a Schlenk tube charged with benzene ruthenium (II) chloride dimer (40 mg, 0.081 mmol) and (*R,R*)-**126** (85 mg, 0.162 mmol) in PhCl (1.2 mL) was added triethylamine (66 mg, 0.65 mmol, 90 μ L). After stirring at 85 °C for 1 h, the solution was allowed to cool to rt and the solvent removed under reduced pressure. The residue was dissolved in $CHCl_3$ (10 mL) and washed with water (12 mL). The organic layer was dried over $MgSO_4$, filtered and solvent removed under reduced pressure to afford the crude mixture. Purification by column chromatography (15% EtOAc in DCM followed by 0-3% MeOH in DCM) afforded the product as a brown solid (85 mg, 0.115 mmol, 71%); Mp 185.4 – 189.4 °C; $[\alpha]_D^{22} +100.0$ (c 0.05 in $CHCl_3$); ν_{max} 3062, 3027, 2919, 2871, 1599, 1494, 1454, 1436, 1398, 1374 cm^{-1} ; δ_H (500 MHz, $CDCl_3$) 7.34 – 7.28 (2 H, m, ArH), 7.13 – 7.03 (4 H, m, ArH), 6.90 – 6.79 (3 H, m, ArH), 6.78 – 6.66 (3 H, m, ArH), 6.60 (2 H, d, J 7.9 Ts-ArH), 6.36 (1 H, m, 3'furan-H), 6.25 (1 H, d, J 3.20, 2'furan-H), 5.78 (6 H, s, benzene-H), 4.38 – 4.33 (1 H, m, CH_AH_BNH), 4.16 – 4.11 (1 H, m, CH_AH_BNH), 4.04 (1 H, d, J 10.8, $CHNHCH_2$), 3.86 – 3.81 (1 H, m, $CHNSO_2$), 2.25 (3 H, s, Ts-ArH); δ_C NMR (126 MHz, $CDCl_3$) 151.24, 141.57, 139.57, 139.36, 136.30, 129.79, 128.83, 128.63, 128.43, 128.04, 127.55, 126.98,

126.49, 121.33, 112.82, 112.44, 84.17, 80.56, 69.67, 51.60, 21.25; MS (ESI⁺): *m/z* 703.1 [M + H]⁺; HRMS calcd for C₃₂H₃₀BrN₂O₃RuS [M – Cl]⁺ 703.0199, found 703.0202 (0.1 ppm error).

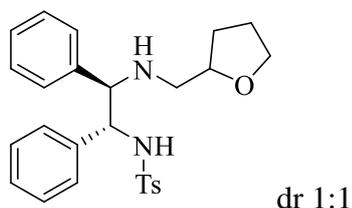
Complex formed from ligand 128. (*R,R*)-135



This compound is novel.

To a Schlenk tube charged with benzene ruthenium (II) chloride dimer (52 mg, 0.104 mmol) and (*R,R*)-**128** (100 mg, 0.208 mmol) in PhCl (1.5 mL) was added triethylamine (84 mg, 0.832 mmol, 116 μ L). After stirring at 80 °C for 1 h, the solution was allowed to cool to rt and the solvent removed under reduced pressure. The residue was dissolved in CHCl₃ (10 mL) and washed with water (15 mL). The organic layer was dried over MgSO₄, filtered and solvent removed under reduced pressure to afford the crude mixture. Purification by column chromatography (10% EtOAc in DCM followed by 0-3% MeOH in DCM) afforded the product as a dark brown solid (87 mg, 0.125 mmol, 60%); Mp > 250 °C (Decomposed); [α]_D²² +631.3 (*c* 0.002 in CHCl₃); ν_{\max} 3060, 3029, 2978, 2931, 1731, 1636, 1600, 1494, 1454, 1436, 1393 cm⁻¹; δ_{H} (500 MHz, CDCl₃) 7.32 (2 H, d, *J* 8.1, Ts-ArH), 7.16 – 7.05 (4 H, m, ArH), 6.82 (2 H, d, *J* 7.9, ArH), 6.79 - 6.75 (1 H, m, ArH), 6.74 - 6.68 (3 H, m, ArH), 6.64 - 6.54 (2 H, m, ArH), 6.06 – 5.94 (1 H, dd, *J* 11.4, 6.6, NH), 5.83 (6 H, s, benzene), 4.41 (1 H, dd, *J* 18.4, 6.6, CH_AH_BNH), 4.32 (1 H, d, *J* 10.8, CHNSO₂), 4.13 (1 H, t, *J* 11.6, CHNHCH₂), 3.27 (1 H, d, *J* 18.4, CH_AH_BNH), 2.23 (3 H, s, Ts-CH₃), 1.44 (9 H, s, 3 x CH₃); δ_{C} (126 MHz, CDCl₃) 170.65, 143.13, 139.40, 138.66, 135.46, 129.82, 128.55, 128.47, 128.44, 128.08, 126.51, 126.49, 125.92, 84.08, 84.03, 73.79, 71.53, 56.57, 27.85, 21.23; MS (ESI⁺): *m/z* 659.3 [M – Cl]⁺; HRMS calcd for C₃₃H₃₇N₂O₄RuS [M – Cl]⁺ 659.1512, found 659.1526 (0.8 ppm error).

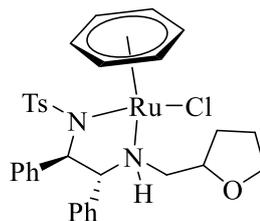
***N*-((1*R*,2*R*)-1,2-diphenyl-2-(((tetrahydrofuran-2-yl)methyl)amino)ethyl)-4-methylbenzenesulfonamide. (*R,R*)-181**



This compound is novel.

To a mixture of *R,R*-TsDPEN (366 mg, 1.0 mmol) and 4Å molecular sieves in DCM (8 mL) was added dropwise a solution of tetrahydrofuran-2-carbaldehyde (100 mg, 1.0 mmol) in DCM (5 mL). The molecular sieves were filtered off after stirring overnight and the solvent was removed under reduced pressure. The residue was dissolved in MeOH (10 mL) and acetic acid was added (6 drops) followed by slow addition of NaBH₃CN (76 mg, 1.2 mmol). After stirring overnight, the solvent was removed under reduced pressure and the residue was partitioned in EtOAc (15 mL) and H₂O (15 mL). The organic layer was collected and further extracted with EtOAc (2 x 15 mL). The organic extracts were combined, dried over MgSO₄, filtered and the solvent removed under reduced pressure. Purification by column chromatography (0-20% EtOAc in Pet. Ether) gave the product as a white solid (265 mg, 0.59 mmol, 59%); Mp 106.4 – 109.3 °C; [α]_D²² -12.0 (*c* 0.2 in CHCl₃); ν_{\max} 3278, 3030, 2922, 2866, 1599, 1494, 1455, 1367 cm⁻¹; δ_{H} (500 MHz, CDCl₃) 7.41 – 7.35 (4H, m, ArH), 7.14 – 7.10 (6H, m, ArH), 7.07 – 6.99 (12H, m, ArH), 6.97 – 6.92 (5H, m, ArH), 6.91 – 6.87 (4H, m, ArH), 4.29 (1H, d, *J* 7.6), 4.20 (1H, d, *J* 8.3), 4.01 – 3.93 (1H, m), 3.90 – 3.84 (1H, m), 3.80 – 3.74 (1H, m), 3.73 – 3.67 (4H, m), 3.62 (1H, d, *J* 8.3), 2.53 (1H, d, *J* 12.1), 2.39 (2H, d, *J* 5.8), 2.34 (3H, s, Ts-CH₃), 2.33 (3H, s, Ts-CH₃), 1.95 – 1.88 (2H, m), 1.87 – 1.76 (6H, m), 1.59 – 1.50 (1H, m), 1.48 – 1.39 (1H, m); δ_{C} (126 MHz, CDCl₃) 142.66, 142.65, 139.21, 139.11, 138.43, 138.18, 137.17, 137.07, 129.09, 129.08, 128.31, 128.27, 127.92, 127.81, 127.72, 127.55, 127.50, 127.45, 127.25, 127.24, 127.19, 127.09, 78.46, 78.12, 68.11, 68.06, 68.01, 67.79, 63.25, 63.07, 51.54, 51.02, 29.04, 29.02, 25.88, 25.72, 21.44; MS (ESI⁺) *m/z* 451.3 [M+H]⁺; HRMS calcd for C₂₆H₃₁N₂O₃S [M+H]⁺ 451.2050, found 451.2053 (0.7 ppm error).

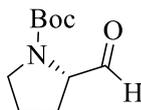
Complex formed from ligand **181**. (*R,R*)-**182**



This compound is novel.

To a Schlenk tube charged with benzene ruthenium (II) chloride dimer (56 mg, 0.11 mmol) and ligand (*R,R*)-**181** (100 mg, 0.22 mmol) in PhCl (1 mL) was added triethylamine (90 mg, 0.89 mmol, 120 μ L). After stirring at 85 $^{\circ}$ C for 1 h, the solution was allowed to cool to rt and the solvent removed under reduced pressure. The residue was dissolved in CHCl₃ (10 mL) and washed with water (10 mL). The organic layer was dried over MgSO₄, filtered and solvent removed under reduced pressure to afford the crude mixture. Purification by column chromatography (15% EtOAc in dichloromethane followed by 0-3% MeOH in DCM) afforded the complex as a brown solid (19 mg, 0.029 mmol, 13%); Mp 200.1 – 203.4 $^{\circ}$ C; $[\alpha]_D^{22}$ +115.0 (*c* 0.01 in CHCl₃); ν_{\max} 3201, 3060, 3029, 2931, 2867, 1598, 1494, 1453 cm^{-1} ; Note: Complicated NMR spectra due to 4 diastereomeric complexes formed, only major peaks highlighted: δ_{H} (500 MHz, CDCl₃) 5.84 (6H, s, Arene-H), 4.59 (1H, bs, CHNTs), 4.22 (1H, bs, CHNHCH₂), 3.85 (2H, bs, NCH₂), 3.28 – 3.20 (2H, m, CH₂O), 2.24 (3H, s, CH₃), 1.87 – 1.73 (4H, m, CH₂ x 2 - tetrahydrofuran); δ_{C} (126 MHz, CDCl₃) 140.77, 140.02, 139.77, 136.62, 129.11, 128.87, 128.44, 128.38, 128.18, 128.11, 127.11, 126.97, 84.68, 75.32, 70.01, 68.13, 67.53, 59.02, 29.07, 25.69, 21.37. MS (ESI⁺): *m/z* 629.3 [M – Cl]⁺; HRMS calcd for C₃₂H₃₅N₂O₃RuS [M – Cl]⁺ 629.1406, found 629.1417 (0.4 ppm error).

tert-Butyl (*S*)-2-formylpyrrolidine-1-carboxylate. (*S*)-**183**

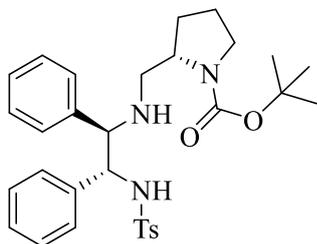


This compound is known.¹⁵⁹

Oxalyl chloride (2 M in DCM, 3 mL, 6.00 mmol) was diluted in DCM (15 mL) and the solution was cooled to -78 $^{\circ}$ C. A solution of DMSO (0.85 mL, 12.0 mmol) in DCM

(10 mL) was added dropwise and the mixture was stirred for 15 min. A solution of *N*-Boc-L-prolinol (600 mg, 2.99 mmol) in DCM (1 mL) was added dropwise to the mixture. After stirring for 15 min, NEt₃ (2.90 mL, 21.0 mmol) was added dropwise and the reaction mixture was left to stir overnight. The reaction was quenched with H₂O (50 mL) and the product extracted with DCM (3 x 50 mL). The organic extracts were combined, dried over MgSO₄, filtered and the solvent removed *in vacuo* by rotary evaporation to give the crude product. Purification by column chromatography (gradient elution 0-40% EtOAc in hexane) gave the product as a clear oil (510 mg, 2.56 mmol, 86%); Rotamer ratio 5:3, data for major rotamer; δ_{H} (400 MHz, CDCl₃) 9.43 (1H, s, CHO), 4.03 (1H, s, CHCHO), 3.48 – 3.39 (2H, m, NCH₂), 1.99 – 1.90 (2H, m, CH₂), 1.89 – 1.81 (2H, m, CH₂), 1.40 (9H, s, CH₃ x 3); δ_{C} (101 MHz, CDCl₃) 200.53, 154.09, 80.77, 65.12, 46.82, 28.36, 28.07, 24.04.

***tert*-Butyl-(*S*)-2-((((1*R*,2*R*)-2-((4-methylphenyl)sulfonamido)-1,2-diphenylethyl)amino)methyl)pyrrolidine-1-carboxylate. (*R,R*)-184**



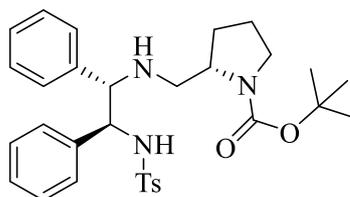
This compound is novel.

Product is a mixture of rotamers.

To a mixture of (*R,R*)-TsDPEN (366 mg, 1.00 mmol) and 4Å molecular sieves in DCM (10 mL) was added dropwise a solution of (*S*)-**183** (199 mg, 1.00 mmol) in DCM (5 mL). The molecular sieves were filtered off after stirring overnight and the solvent was removed under reduced pressure. The residue was dissolved in MeOH (10 mL) and acetic acid was added (6 drops) followed by slow addition of NaBH₃CN (76 mg, 1.2 mmol). After stirring overnight, the solvent was removed under reduced pressure and the residue was partitioned between EtOAc (15 mL) and H₂O (15 mL). The organic layer was collected and further extracted with EtOAc (2 x 15 mL). The organic extracts were combined, dried over MgSO₄, filtered and the solvent removed under reduced pressure. Purification by column chromatography (0-30% EtOAc in Pet. Ether) gave the product as a white solid (471 mg, 0.86 mmol, 86%); Mp 132.8 – 136.4

°C; $[\alpha]_{\text{D}}^{22}$ -41.2 (*c* 0.3 in CHCl_3); ν_{max} 3262, 3064, 3030, 2973, 2929, 2874, 1687, 1600, 1494, 1477 cm^{-1} ; δ_{H} (500 MHz, CDCl_3) 7.36 (2H, d, *J* 7.6, ArH), 7.12 (3H, b. s., ArH), 7.02 (5H, b.s., ArH), 6.91 (4H, bs, ArH), 4.35 – 4.16 (1H, m, PhCHNTs), 3.93 – 3.63 (1H, m, PhCHNH), 3.64 – 3.33 (1H, m, Pyrrolidine-CH), 3.32 – 3.12 (1H, m, Pyrrolidine-NCH₂), 2.61 – 2.36 (2H, m, CH₂N), 2.33 (3H, s, Ts-CH₃), 2.00 – 1.86 (1H, m, Pyrrolidine-NCH₂), 1.85 – 1.63 (3H, m, Pyrrolidine-CH₂), 1.63 – 1.49 (1H, m, Pyrrolidine-CH₂), 1.43 (5H, b.s, Boc-CH₃), 1.26 (4H, s, Boc-CH₃); δ_{C} (126 MHz, CDCl_3) δ 155.02, 142.99, 139.43, 138.30, 137.47, 129.26, 129.18, 128.51, 128.41, 128.02, 127.71, 127.56, 127.23, 79.38, 68.00, 63.24, 57.36, 50.06, 46.95, 29.30, 28.62, 23.96, 21.56; MS (ESI⁺) *m/z* 550.4 $[\text{M}+\text{H}]^+$; HRMS calcd for $\text{C}_{31}\text{H}_{40}\text{N}_3\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 550.2734, found 550.2732 (0.3 ppm error).

***tert*-Butyl-(*S*)-2-(((1*S*,2*S*)-2-((4-methylphenyl)sulfonamido)-1,2-diphenylethyl)amino)methyl)pyrrolidine-1-carboxylate. (*S,S*)-184**



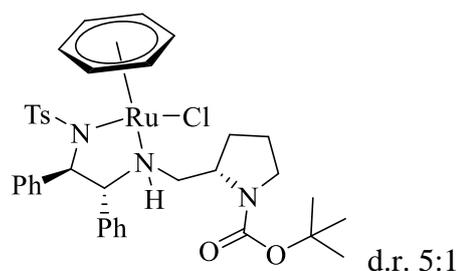
This compound is novel.

Product is a mixture of rotamers.

To a mixture of (*S,S*)-TsDPEN (183 mg, 0.50 mmol) and 4Å molecular sieves in DCM (5 mL) was added dropwise a solution of (*S*)-**183** (100 mg, 0.50 mmol) in DCM (2.5 mL). The molecular sieves were filtered off after stirring overnight and the solvent was removed under reduced pressure. The residue was dissolved in MeOH (5 mL) and acetic acid was added (6 drops) followed by slow addition of NaBH_3CN (38 mg, 0.60 mmol). After stirring overnight, the solvent was removed under reduced pressure and the residue was partitioned in EtOAc (10 mL) and H₂O (10 mL). The organic layer was collected and further extracted with EtOAc (2 x 10 mL). The organic extracts were combined, dried over MgSO_4 , filtered and the solvent removed under reduced pressure. Purification by column chromatography (0-30% EtOAc in Pet. Ether) gave the product as a white solid (173 mg, 0.32 mmol, 63%); Mp 119.4 – 123.1 °C; $[\alpha]_{\text{D}}^{23}$ +14.4 (*c* 0.2 in CHCl_3); ν_{max} 3255, 3064, 3031, 2970, 2930, 2874, 1669, 1598 cm^{-1} ; δ_{H}

(500 MHz, CDCl₃) 7.42 – 7.29 (2H, m, ArH), 7.16 – 7.06 (3H, m, ArH), 7.05 – 6.98 (4H, m, ArH), 6.98 – 6.93 (2H, m, ArH), 6.93 – 6.86 (3H, m, ArH), 6.86 – 6.79 (1H, m, ArH), 4.36 – 4.15 (1H, m, CHPh), 4.05 – 3.73 (1H, m, CHPh), 3.72 – 3.51 (1H, m, Pyrrolidine-CH), 3.41 – 3.33 (1H, m, Pyrrolidine-NCH_AH_B), 3.26 – 3.18 (1H, m, Pyrrolidine-NCH_AH_B), 2.64 – 2.46 (1H, m, NHCH_AH_B), 2.42 – 2.34 (1H, m, NHCH_AH_B), 2.31 (3H, s, Ts-CH₃), 1.97 – 1.85 (1H, m, Pyrrolidine-CH₂), 1.84 – 1.70 (3H, m, Pyrrolidine-CH₂CH₂), 1.50 (6H, s, Boc-CH₃), 1.27 (3H, s, Boc-CH₃); δ_C (126 MHz, CDCl₃) 156.08, 142.50, 139.45, 138.59, 137.57, 129.18, 128.51, 128.21, 128.04, 127.83, 127.64, 127.46, 127.21, 79.70, 67.03, 63.71, 56.34, 51.63, 47.20, 29.89, 28.74, 24.11, 21.54; MS (ESI⁺) *m/z* 550.4 [M+H]⁺.

Complex formed from (*R,R*)-**184**; (*R,R*)-**185**

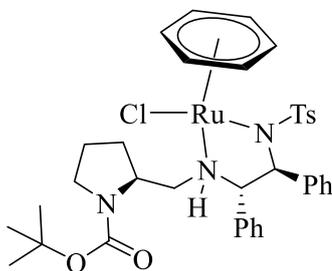


This compound is novel.

To a Schlenk tube charged with benzene ruthenium (II) chloride dimer (50 mg, 0.10 mmol) and (*R,R*)-**184** (110 mg, 0.20 mmol) in PhCl (1.5 mL) was added triethylamine (81 mg, 0.80 mmol, 0.1 mL). After stirring at 80 °C for 1 h, the solution was allowed to cool to rt and the solvent removed under reduced pressure. The residue was dissolved in CHCl₃ (10 mL) and washed with water (10 mL). The organic layer was dried over MgSO₄, filtered and the solvent removed under reduced pressure to afford the crude mixture. Purification by column chromatography (10% EtOAc in DCM followed by 0-3% MeOH in DCM) afforded the product as a brown solid (136 mg, 0.178 mmol, 89%); Decomposes at 226 °C; [α]_D²³ -279.2 (*c* 0.08 in CHCl₃); ν_{max} 3482, 3192, 3060, 3027, 2971, 2924, 2875, 1681, 1600, 1494, 1478, 1454 cm⁻¹; δ_H (500 MHz, CDCl₃) 7.33 (2H, d, *J* 8.1, ArH), 7.16 – 7.07 (3H, m, ArH), 7.06 – 6.98 (1H, m, ArH), 6.87 – 6.82 (3H, m, ArH), 6.80 – 6.73 (3H, m, ArH), 6.59 (2H, d, *J* 7.4, ArH), 6.10 (6H, s, Benzene), 4.50 – 4.43 (1H, m, CHPh), 4.01 (1H, d, *J* 10.5, CHPh), 3.84 (1H, t, *J* 11.4, CH₂CHN), 3.70 – 3.63 (1H, m, CH_AH_BNBoc), 3.53 (1H, t, *J* 12.1, NH),

3.24 – 3.16 (1H, m, $\text{NCH}_A\text{H}_B\text{Pyr}$), 3.06 – 2.99 (1H, m, $\text{NCH}_A\text{H}_B\text{Pyr}$), 2.32 (1H, t, J 11.4, $\text{CH}_A\text{H}_B\text{NBoc}$), 2.23 (3H, s, Ts- CH_3), 2.17 – 2.08 (1H, m, Pyrrolidine- CH_2), 1.67 – 1.62 (1H, m, Pyrrolidine- CH_2), 1.46 – 1.43 (1H, m, Pyrrolidine- CH_2), 1.42 (9H, s, $(\text{CH}_3)_3$), 1.25 – 1.11 (1H, m, Pyrrolidine- CH_2); δ_{C} (126 MHz, CDCl_3) 154.92, 141.31, 140.20, 139.62, 137.27, 128.82, 128.61, 128.50, 128.13, 128.01, 127.96, 127.24, 126.52, 84.68, 81.66, 79.74, 69.37, 55.79, 55.17, 46.95, 29.92, 28.56, 23.43, 21.37; MS (ESI⁺): m/z 728.3 $[\text{M}-\text{Cl}]^+$; HRMS calcd for $\text{C}_{37}\text{H}_{44}\text{N}_3\text{O}_4\text{RuS}$ $[\text{M}-\text{Cl}]^+$ 728.2091, found 728.2104 (0.6 ppm error).

Complex formed from (*S,S*)-**184**; (*S,S*)-**185**

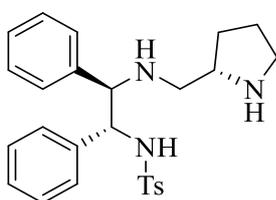


This compound is novel.

To a Schlenk tube charged with benzene ruthenium (II) chloride dimer (32 mg, 64 μmol) and (*S,S*)-**184** (70 mg, 0.13 mmol) in PhCl (1.2 mL) was added triethylamine (52 mg, 0.5 mmol, 70 μL). After stirring at 80 °C for 1 h, the solution was allowed to cool to rt and the solvent removed under reduced pressure. The residue was dissolved in CHCl_3 (10 mL) and washed with water (10 mL). The organic layer was dried over MgSO_4 , filtered and the solvent removed under reduced pressure to afford the crude mixture. Purification by column chromatography (10% EtOAc in DCM followed by 0-3% MeOH in DCM) afforded the product as a brown solid (71 mg, 93 μmol , 73%); Decomposes at 152 °C; $[\alpha]_{\text{D}}^{23}$ -525.0 (c 0.01 in CHCl_3); ν_{max} 3431, 3192, 3061, 3029, 2971, 2875, 1683, 1660, 1600, 1494, 1453 cm^{-1} ; δ_{H} (500 MHz, CDCl_3) 7.32 (2H, d, J 8.1, ArH), 7.09 – 7.01 (3H, m, ArH), 6.91 (1H, dd, J 10.4, 6.8, ArH), 6.84 (2H, d, J 6.8 Hz, ArH), 6.80 (2H, d, J 8.1, ArH), 6.67 (2H, d, J 7.6, ArH), 6.66 – 6.61 (1H, m, ArH), 6.52 (2H, t, J 7.6, ArH), 6.03 (6H, s, Benzene), 4.42 (1H, d, J 10.8, NTsCHPh), 4.39 – 4.31 (1H, m, Pyrrolidine- CHNBoc), 3.87 (1H, ddd, J = 13.1, 6.5, 2.5, NHCH_AH_B), 3.76 (1H, t, J 10.8, NHCHPh), 3.05 – 2.96 (1H, m, Pyrrolidine- $\text{NBocCH}_A\text{H}_B$), 2.61 (1H, t, J 13.1, NHCH_AH_B), 2.22 (3H, s, Ts- CH_3), 2.21 – 2.15 (1H, m, Pyrrolidine- $\text{NBocCH}_A\text{H}_B$), 1.95 – 1.85 (1H, m, Pyrrolidine- CH_2), 1.62 (9H, s,

(CH₃)₃), 1.60 – 1.53 (1H, m, Pyrrolidine-CH₂), 1.45 – 1.36 (1H, m, Pyrrolidine-CH₂), 1.26 – 1.15 (m, 1H, Pyrrolidine-CH₂); δ_C (126 MHz, CDCl₃) 157.84, 143.86, 139.13, 138.98, 137.48, 129.96, 128.90, 128.19, 128.11, 127.88, 126.68, 126.41, 125.79, 83.84, 81.06, 76.13, 71.42, 61.15, 56.55, 46.29, 29.75, 28.78, 23.83, 21.35; MS (ESI⁺) m/z 728.3 [M-Cl]⁺; HRMS calcd for C₃₇H₄₄N₃O₄RuS [M-Cl]⁺ 728.2091, found 728.2094 (0.8 ppm error).

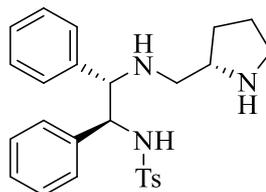
***N*-((1*R*,2*R*)-1,2-Diphenyl-2-(((*S*)-pyrrolidin-2-yl)methyl)amino)ethyl)-4-methylbenzenesulfonamide. (*R,R*)-186**



This compound is novel.

To a solution of ligand (*R,R*)-**184** (100 mg, 0.180 mmol) in DCM (2 mL) was added dropwise trifluoroacetic acid (0.14 mL). After stirring overnight, the mixture was concentrated under reduced pressure and the residue partitioned in DCM (10 mL) and sat. NaHCO₃ (10 mL). Following extraction with DCM (3 x 10 mL) the organic extracts were combined, dried over MgSO₄, filtered and the solvent was removed under reduced pressure. Purification by column chromatography (50% EtOAc in Pet. Ether) gave the product as a white solid (80 mg, 0.178 mmol, 98%); Mp 87.0 – 94.2 °C; $[\alpha]_D^{22} +27.5$ (*c* 0.1 in CHCl₃); ν_{\max} 3259, 3031, 2925, 2868, 1673, 1599, 1494, 1453 cm⁻¹; δ_H (500 MHz, CDCl₃) 7.40 (2H, d, *J* 8.2, ArH), 7.13 – 7.07 (3H, m, ArH), 7.04 – 7.00 (3H, m, ArH), 6.97 (2H, t, *J* 7.2, ArH), 6.94 – 6.90 (2H, m, ArH), 6.88 (2H, d, *J* 7.2, ArH), 4.32 (1H, d, *J* 8.5, NH*CH*Ph), 3.65 (1H, d, *J* 8.5, NTs*CH*Ph), 3.28 – 3.19 (1H, m, Pyrrolidine-CH), 3.03 – 2.91 (2H, m, Pyrrolidine-NHCH₂), 2.47 (1H, dd, *J* 11.8, 4.5, NHCH_AH_B), 2.32 (3H, s, Ts-CH₃), 2.28 (1H, dd, *J* 11.8, 8.4, NHCH_AH_B), 1.86 – 1.67 (3H, m, Pyrrolidine-CH₂CH₂), 1.34 – 1.23 (1H, m, Pyrrolidine-CH₂). δ_C (126 MHz, CDCl₃) 142.69, 139.68, 138.49, 137.53, 129.18, 128.37, 127.90, 127.84, 127.68, 127.49, 127.23, 68.45, 63.48, 58.65, 52.12, 46.39, 29.43, 25.41, 21.55; MS (ESI⁺) m/z 450.3 [M+H]⁺; HRMS calcd for C₂₆H₃₂N₃O₂S [M+H]⁺ 450.2210, found 450.2213 (0.8 ppm error).

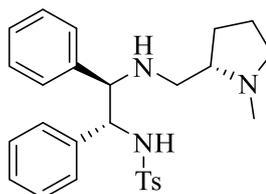
N*-((1*S*,2*S*)-1,2-Diphenyl-2-(((*S*)-pyrrolidin-2-yl)methyl)amino)ethyl)-4-methylbenzenesulfonamide. (*S,S*)-**186*



This compound is novel.

To a solution of ligand (*S,S*)-**184** (45 mg, 82 μmol) in DCM (1.5 mL) was added dropwise trifluoroacetic acid (94 mg, 820 μmol). After stirring overnight, the mixture was concentrated under reduced pressure and the residue partitioned in DCM (10 mL) and sat. NaHCO_3 (10 mL). Following extraction with DCM (3 x 10 mL) the organic extracts were combined, dried over MgSO_4 , filtered and the solvent was removed under reduced pressure. Purification by column chromatography (50% EtOAc in Pet. Ether) gave the product as a white solid (36 mg, 80 μmol , 98%); Mp 93.2 – 98.0 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{23} +28.1$ (*c* 0.1 in CHCl_3); ν_{max} 3257, 3030, 2923, 1672, 1599, 1494, 1454, 1420 cm^{-1} ; δ_{H} (500 MHz, CDCl_3) 7.37 (2H, d, *J* 8.2, ArH), 7.14 – 7.07 (3H, m, ArH), 7.00 (3H, d, *J* 8.2, ArH), 6.96 (2H, t, *J* 7.5, ArH), 6.94 – 6.90 (2H, m, ArH), 6.88 (2H, d, *J* 7.5, ArH), 4.36 (1H, d, *J* 8.5, NTsCHPh), 3.65 (1H, d, *J* 8.5, NHCHPh), 3.25 (1H, b.s, Pyrrolidine-CH), 3.04 – 2.90 (2H, m, Pyrrolidine-NHCH₂), 2.47 (1H, dd, *J* 11.8, 4.5, NHCH_AH_B), 2.32 (3H, s, Ts-CH₃), 2.31 – 2.25 (1H, m, NHCH_AH_B), 1.86 – 1.67 (3H, m, Pyrrolidine-CH₂CH₂), 1.36 – 1.28 (1H, m, Pyrrolidine-CH₂CH₂); δ_{C} (126 MHz, CDCl_3) 142.62, 139.72, 138.39, 137.67, 129.12, 128.37, 127.88, 127.68, 127.48, 127.20, 68.41, 63.41, 58.74, 52.03, 46.44, 29.39, 25.39, 21.54; MS (ESI⁺) *m/z* 450.3 $[\text{M}+\text{H}]^+$; HRMS calcd for $\text{C}_{26}\text{H}_{32}\text{N}_3\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$ 450.2210, found 450.2205 (1.1 ppm error).

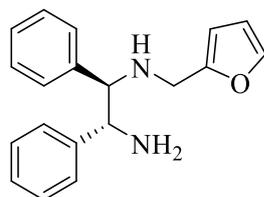
N*-((1*R*,2*R*)-2-(((*S*)-1-Methylpyrrolidin-2-yl)methyl)amino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide. (*R,R*)-**187*



This compound is novel.

A solution of (*R,R*)-**184** (100 mg, 0.18 mmol) in THF (4 mL) was cooled to 0 °C and was added LiAlH₄ (2M in hexanes, 0.18 mL, 0.36 mmol). After refluxing for 3 hours to mixture was allowed to cool and the reaction was quenched with EtOAc. Rochelle salt solution (10 mL) was added and stirred for 30 mins. Following extraction with EtOAc (3 x 10 mL) the organic extracts were combined, dried over MgSO₄, filtered and the solvent removed under reduced pressure. Purification by column chromatography (0-10% MeOH in DCM) gave the product as a white solid (23 mg, 50 μmol, 28%); Decomposes > 252°C; $[[\alpha]_D^{21} + 60.0$ (*c* 0.1 in CHCl₃); ν_{\max} 3256, 3061, 3028, 2970, 2919, 2841, 1599, 1493, 1454 cm⁻¹; δ_H (500 MHz, MeOD) 7.38 (2H, d, *J* 8.2, ArH), 7.14 – 7.07 (5H, m, ArH), 7.03 (2H, d, *J* 8.2, ArH), 6.95 – 6.90 (1H, m, *J* 7.2, ArH), 6.87 (2H, t, *J* 7.4, ArH), 6.74 (2H, d, *J* 7.4, ArH), 4.42 (1H, d, *J* 9.7, NTsCHPh), 3.82 (1H, d, *J* 9.7, NHCHPh), 3.68 – 3.60 (1H, m, NMeCH_AH_B), 3.29 – 3.21 (1H, m, CHNMe), 3.10 – 3.01 (1H, m, NMeCH_AH_B), 2.80 (1H, dd, *J* 13.4, 6.4, NHCH_AH_B), 2.72 (3H, s, NCH₃), 2.66 (1H, dd, *J* 13.4, 5.0, NHCH_AH_B), 2.27 (3H, s, TsCH₃), 2.24 – 2.17 (1H, m, Pyrrolidine-CH₂), 2.14 – 1.96 (2H, m, Pyrrolidine-CH₂), 1.82 – 1.72 (1H, m, Pyrrolidine-CH₂); δ_C (126 MHz, MeOD) 144.22, 140.93, 139.37, 139.33, 130.20, 129.45, 129.37, 128.83, 128.80, 128.72, 128.05, 127.94, 69.67, 69.37, 65.26, 57.60, 47.76, 41.27, 28.60, 23.12, 21.31; MS (ESI⁺) *m/z* 464.3 [M+H]⁺; HRMS calcd for C₂₇H₃₄N₃O₂S [M+H]⁺ 464.2366, found 464.2369 (0.5 ppm error).

(1*R*,2*R*)-*N*¹-(Furan-2-ylmethyl)-1,2-diphenylethane-1,2-diamine. (*R,R*)-218

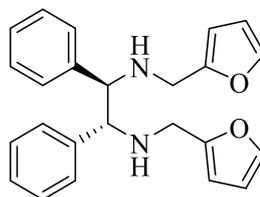


This compound is novel.

To a mixture of *R,R*-TsDPEN (424 mg, 2.0 mmol) and 4Å molecular sieves in DCM (20 mL) was added dropwise a solution of 2-furaldehyde (192 mg, 2.0 mmol) in DCM (10 mL). The molecular sieves were filtered off after stirring overnight and the solvent was removed under reduced pressure. The residue was dissolved in MeOH (15 mL) and acetic acid was added (6 drops) followed by slow addition of NaBH₃CN (190 mg, 3.0 mmol). After stirring overnight, the solvent was removed under reduced pressure and the residue was partitioned in EtOAc (15 mL) and H₂O (15 mL). The organic layer

was collected and further extracted with EtOAc (2 x 15 mL). The organic extracts were combined, dried over MgSO₄, filtered and the solvent removed under reduced pressure. Purification by column chromatography (0-100% EtOAc in Pet. Ether) gave the product as an orange oil (290 mg, 0.99 mmol, 50%); $[\alpha]_D^{23}$ -42.5 (*c* 0.04 in CHCl₃); ν_{\max} 3060, 3027, 2828, 1681, 1600, 1493, 1452, 1346 cm⁻¹; δ_H (500 MHz, CDCl₃) 7.33 – 7.29 (1H, m, ArH), 7.25 – 7.19 (4H, m, ArH), 7.18 – 7.13 (5H, m, ArH), 7.13 – 7.08 (2H, d, *J* 7.1 Hz, ArH), 6.31 – 6.23 (1H, m, ArH), 6.00 (1H, d, *J* 2.8 Hz, ArH), 3.99 (1H, d, *J* 7.2 Hz, CHPh), 3.74 (1H, d, *J* 7.2 Hz, CHPh), 3.67 (1H, d, *J* 14.7 Hz, CH_AH_B), 3.51 – 3.42 (1H, m, CH_AH_B), 1.85 (2H, b.s, NH₂); δ_C (126 MHz, CDCl₃) 154.16, 143.58, 141.81, 140.89, 128.43, 128.25, 128.23, 128.12, 127.26, 127.07, 110.11, 106.85, 68.56, 61.89, 44.06. Note: Unable to obtain mass spectrometry data through different methods, however this is an intermediate and subsequent ligands were formed appropriately.

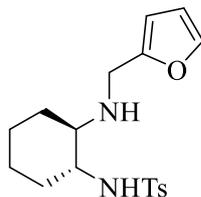
(1*R*,2*R*)-*N*¹,*N*²-bis(furan-2-ylmethyl)-1,2-diphenylethane-1,2-diamine. (*R,R*)-219



This compound is known.¹⁶⁰

This compound was formed as a byproduct (164 mg, 0.44 mmol, 22%) from the reaction forming (*R,R*)-**218**; δ_H (400 MHz, CDCl₃) 7.36 – 7.30 (2H, m, ArH), 7.29 – 7.21 (2H, m, ArH), 7.19 – 7.10 (5H, m, ArH), 7.06 – 6.98 (3H, m, ArH), 6.28 (2H, s, Furan-H), 6.07 – 6.01 (2H, m, Furan-H), 3.74 – 3.62 (4H, m, PhCHN x 2 + CH_AH_B x 2), 3.49 (2H, d, *J* 14.7, CH_AH_B x 2).

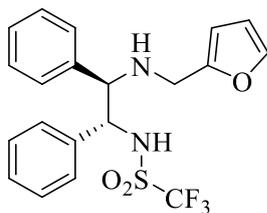
***N*-((1*R*,2*R*)-2-((Furan-2-ylmethyl)amino)cyclohexyl)-4-methylbenzene sulfonamide. (*R,R*)-33b**



This compound is known.⁶²

To a mixture of (1*R*,2*R*)-*N*-*p*-tosyl-1,2-cyclohexanediamine (268 mg, 1.00 mmol) and molecular sieves in DCM (10 mL) was added dropwise a solution of furaldehyde (96 mg, 1.00 mmol) in DCM (10 mL). After stirring overnight, the molecular sieves were filtered off and the solvent removed *in vacuo* by rotary evaporation. The residue was dissolved in MeOH (10 mL) and NaBH₄ (57 mg, 1.5 mmol) was added and stirred for 4 hours. The solvent was removed *in vacuo* by rotary evaporation and H₂O (20 mL) was added. The product was extracted with EtOAc (3 x 20 mL) and the organic extracts were combined, dried over MgSO₄, filtered and the solvent removed *in vacuo* by rotary evaporation to give the crude product. Purification by column chromatography 0-30% EtOAc in Pet. Ether gave the product as an off-white solid (260 mg, 0.75 mmol, 75%); δ_{H} (400 MHz, CDCl₃) 7.74 (2H, d, *J* 7.8, ArH), 7.36 (1H, s, Furan-H), 7.25 (2H, d, *J* 7.8, ArH), 6.34-6.28 (1H, m, Furan-H), 6.11 (1H, d, *J* 3.0, Furan-H), 5.25 (1H, b.s, NHTs), 3.71 (1H, d, *J* 14.4, CH_AH_B), 3.60 (1H, d, *J* 14.4, CH_AH_B), 2.64 (1H, b.s, cyclo-H), 2.40 (3H, s, Ts-CH₃), 2.19 (1H, td, *J* 10.5, 3.8, cyclo-H), 2.11 – 1.95 (2H, m, cyclo-H), 1.71 – 1.53 (2H, m, cyclo-H), 1.33 (1H, s, NH), 1.20 – 1.08 (3H, m, cyclo-H), 1.02 – 0.87 (1H, m, cyclo-H); δ_{C} (101 MHz, CDCl₃) 153.89, 143.33, 141.88, 137.35, 129.70, 127.39, 110.31, 106.82, 59.77, 57.64, 43.14, 32.94, 31.40, 24.71, 24.60, 21.66.

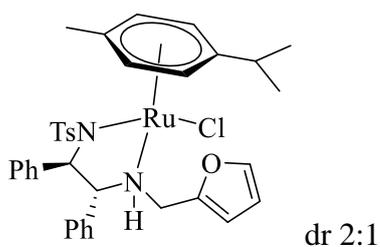
***N*-((1*R*,2*R*)-2-((Furan-2-ylmethyl)amino)-1,2-diphenylethyl)trifluoromethane sulfonamide. (*R,R*)-220**



This compound is novel.

To a solution of (*R,R*)-**218** (50 mg, 0.17 mmol) in DCM (3 mL) was added triethylamine (100 μ L, 0.17 mmol). The mixture was cooled to 0 °C and Tf₂O (1M in DCM, 0.17 mL, 0.17 mmol) was added dropwise. After stirring overnight, the mixture was diluted with DCM (10 mL) and quenched with sat. NaHCO₃ solution (10 mL). Following extraction with DCM (2 x 10 mL) the organic extracts were combined, dried over MgSO₄, filtered and the solvent removed under reduced pressure. Purification by column chromatography (10-30% EtOAc) gave the product as an orange semi-solid (43 mg, 0.10 mmol, 59%); $[\alpha]_D^{23}$ -17.3 (*c* 0.1 in CHCl₃); ν_{\max} 3064, 3034, 2970, 1603, 1496, 1456, 1380 cm⁻¹; δ_H (500 MHz, CDCl₃) 7.39 – 7.30 (5H, m, ArH), 7.30 – 7.26 (2H, m, ArH), 7.26 – 7.17 (4H, m, ArH), 6.29 – 6.23 (1H, m, Furan-H), 5.96 (1H, d, *J* 3.0, Furan-H), 4.70 (1H, d, *J* 5.1, PhCHNTf), 3.94 (1H, d, *J* 5.1, NCHPh), 3.68 (d, *J* 14.8, CH_AH_B), 3.47 (1H, d, *J* 14.8, CH_AH_B); δ_C (126 MHz, CDCl₃) 152.56, 142.26, 138.28, 138.09, 128.95, 128.85, 128.42, 128.32, 127.64, 126.54, 119.31 (q, *J* 321, CF₃), 110.23, 107.53, 66.21, 64.02, 43.55. δ_F (282 MHz, CDCl₃) δ -77.45; MS (ESI⁺) *m/z* 425.2 [M+H]⁺; HRMS calcd for C₂₀H₂₀F₃N₂O₃S [M+H]⁺ 425.1141, found 425.1143 (0.4 ppm error).

Complex formed from (*R,R*)-**125**. (*R,R*)-**221**

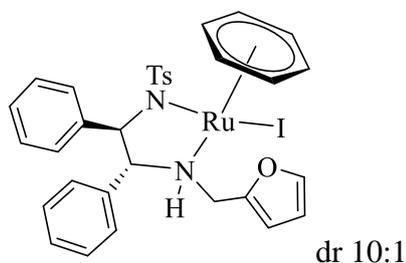


This compound is novel.

To a Schlenk tube charged with *p*-cymene ruthenium (II) chloride dimer (55 mg, 0.09 mmol) and (*R,R*)-**125** (80 mg, 0.18 mmol) in PhCl (1.25 mL) was added triethylamine (73 mg, 0.72 mmol, 0.1 mL). After stirring at 80 °C for 1 h, the solution was allowed to cool to rt and the solvent removed under reduced pressure. The residue was dissolved in CHCl₃ (10 mL) and washed with water (10 mL). The organic layer was dried over MgSO₄, filtered and the solvent removed under reduced pressure to afford the crude mixture. Purification by column chromatography (15% EtOAc in DCM followed by 0-3% MeOH in DCM) afforded the product as a brown solid (74 mg,

0.103 mmol, 57%); Decomposes >135 °C; $[\alpha]_D^{22} +13.3$ (*c* 0.01 in CHCl₃); ν_{\max} 3194, 3062, 3029, 2961, 2922, 2867, 1599, 1494, 1452, 1383 cm⁻¹; δ_H (500 MHz, CDCl₃) 7.41 (1H, s, ArH), 7.21 – 7.17 (2H, m, ArH), 7.10 – 7.05 (3H, m, ArH), 6.78 (2H, d, *J* 8.0, ArH), 6.74 (1H, d, *J* 8.0, ArH), 6.67 (2H, t, *J* 7.6, ArH), 6.61 (1H, d, *J* 7.6, ArH), 6.53 (2H, d, *J* 7.2, ArH), 6.48 (1H, t, *J* 7.6, ArH), 6.42 – 6.38 (2H, m, ArH), 5.54 (1H, b.s, *p*-Cymene ArH), 5.41 (2H, t, *J* 5.7, *p*-Cymene ArH), 5.18 (1H, b.s, *p*-cymene ArH), 4.56 (1H, t, *J* 10.2, NH), 4.20 (1H, dd, *J* 14.8, 10.2, CH_AH_BN), 4.08 (1H, d, *J* 11.5, PhCHNTs), 4.03 (1H, d, *J* 14.8, CH_AH_BN), 3.63 (1H, t, *J* 11.5, PhCHNH), 3.28 – 3.17 (1H, m, *p*-cymene CH(CH₃)₂), 2.32 (3H, s, *p*-cymene ArCH₃), 2.22 (3H, s, Ts-CH₃), 1.40 (3H, d, *J* 7.0, *p*-cymene CH(CH₃)₂), 1.33 (3H, d, *J* 7.0, *p*-cymene CH(CH₃)₂); δ_C (126 MHz, CDCl₃) 149.72, 142.41, 141.77, 139.23, 138.96, 136.89, 129.23, 128.72, 128.34, 127.96, 127.48, 127.03, 126.53, 126.37, 111.46, 109.02, 81.50, 79.73, 78.89, 75.25, 72.21, 70.23, 60.53, 53.57, 51.44, 30.62, 22.59, 22.38, 21.33, 19.19; MS (ESI⁺): *m/z* 681.3 [M-Cl]⁺; HRMS calcd for C₃₆H₃₉N₂O₃RuS [M-Cl]⁺ 681.1719, found 681.1728 (0.1 ppm error).

Complex of [RuI(benzene)((*R,R*)-125)]. (*R,R*)-222

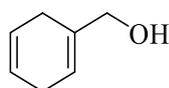


This compound is novel.

Potassium iodide (83 mg, 0.5 mmol) was added to a solution containing catalyst (*R,R*)-**131** (132 mg, 0.2 mmol) in dry *i*PrOH (10 mL) and the mixture was refluxed for 2 h. The reaction mixture was cooled to rt and the solvent removed *in vacuo*. The residue was partitioned between H₂O (10 mL) and DCM (10 mL). The organic extract was collected, dried over MgSO₄, filtered and the solvent removed *in vacuo* by rotary evaporation to give the crude product. Purification by column chromatography 1% MeOH in DCM gave the product as a purple solid (122 mg, 0.16 mmol, 81%); Decomposes at 188 °C; $[\alpha]_D^{23} +41.7$ (*c* 0.01 in CHCl₃); ν_{\max} 3191, 3061, 3027, 2920, 2865, 1599, 1493, 1453 cm⁻¹; δ_H (500 MHz, CDCl₃) 7.43 (1H, bs, ArH), 7.20 (2H, d,

J 7.5, ArH), 7.11 – 7.03 (3H, m, ArH), 6.89 – 6.68 (5H, m, ArH), 6.66 – 6.45 (4H, m, ArH), 6.37 (1H, bs, ArH), 6.32 – 6.19 (1H, m, ArH), 5.76 (6H, s, Arene-H), 4.82 (1H, bs, CHNTs), 4.46 (1H, bs, CHNH), 4.20 – 3.75 (2H, m, CH₂), 2.22 (3H, s, Ts-CH₃); δ_C (126 MHz, CDCl₃) 153.09, 142.84, 142.19, 139.22, 138.78, 138.42, 129.24, 128.76, 128.45, 128.07, 127.71, 127.52, 127.20, 126.35, 110.12, 107.22, 84.04, 66.65, 63.14, 43.68, 21.34. MS (ESI⁺) *m/z* 625.1 [M-I]⁺; HRMS calcd for C₃₂H₃₁N₂O₃RuS [M-I]⁺ 625.1093, found 625.1096 (0.9 ppm error).

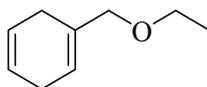
Cyclohexa-1,4-dien-1-ylmethanol. 224



This compound is known.¹⁶¹

A solution of ethyl cyclohexa-1,4-diene-1-carboxylate (456 mg, 3.00 mmol) in anhydrous Et₂O (10 mL) was cooled to -78 °C and LiAlH₄ (2M in hexanes, 3.0 mL, 6.0 mmol) was added dropwise. After stirring for 1.5 h, the reaction was quenched by addition of EtOAc (25 mL) followed by addition of Rochelle salt solution (15 mL) and stirred for 30 min. Following extraction with Et₂O (3 x 15 mL), the organic layers combined, dried over MgSO₄, filtered and the solvent removed under reduced pressure to give the crude product. Purification by column chromatography (40% Et₂O in Pet. Ether) afforded the pure product as a clear oil (270 mg, 2.46 mmol, 82%); δ_H (400 MHz, CDCl₃) δ 5.80 – 5.64 (3H, m, sp²-CH), 4.00 (2H, s, CH₂), 2.77 – 2.61 (4H, m, 2 x CH₂), 1.81 (1H, b.s, OH); δ_C (101 MHz, CDCl₃) δ 134.93, 124.17, 124.12, 120.41, 67.35, 26.54, 26.50.

1-(Ethoxymethyl)cyclohexa-1,4-diene. 225

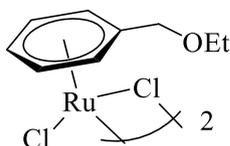


This compound is known.¹⁶¹

To a suspension containing NaH (60% wt, 80 mg, 2.00 mmol) in dry THF (2 mL) was added a solution of cyclohexa-1,4-dien-1-ylmethanol (200 mg, 1.82 mmol) in dry THF (1 mL). After stirring for 1 h, a solution of ethyliodide (284 mg, 1.82 mmol) in dry THF (1 mL) was added and the mixture was stirred overnight. The mixture was

concentrated under reduced pressure and H₂O (10 mL) was added. Following extraction with Et₂O (3 x 10 mL), the organic extracts were combined, dried over MgSO₄, filtered and the solvent removed under reduced pressure to give the crude product. Purification by column chromatography (gradient elution 0-100% DCM in Pet. Ether) afforded the pure product as a clear oil (140 mg, 1.01 mmol, 56%); δ_{H} (500 MHz, CDCl₃) 5.78 – 5.71 (1H, m, Cy-CH), 5.71 – 5.65 (2H, m, Cy-CH), 3.86 (2H, s, CH₂O), 3.45 (2H, q, *J* 7.0, OCH₂), 2.76 – 2.69 (2H, m, Cy-CH₂), 2.69 – 2.63 (2H, m, Cy-CH), 1.20 (3H, t, *J* 7.0, OCH₂CH₃); δ_{C} (126 MHz, CDCl₃) 132.66, 124.36, 124.04, 121.99, 75.15, 65.34, 26.95, 26.61, 15.37.

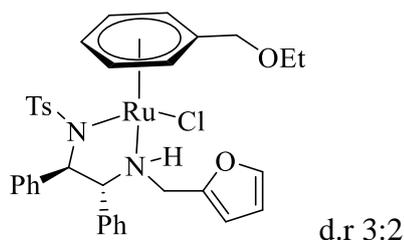
Ruthenium dimer 226.



This compound is known.

To a solution of RuCl₃·xH₂O (91 mg, 0.44 mmol) in EtOH (4 mL) was added a solution of ether compound (132 mg, 0.96 mmol) in EtOH (1 mL). After refluxing for 16 h, the mixture was cooled to rt and the precipitate was filtered. The precipitate was washed with ice-cold EtOH (3 x 2 ml) and then dried to afford the product as a black solid (58 mg, 0.19 mmol, 43%); ν_{max} 3064, 3057, 2967, 2922, 2863, 1443, 1397 cm⁻¹; δ_{H} (400 MHz, CDCl₃) 5.77 – 5.51 (5H, m, ArH), 4.46 (2H, s, ArCH₂), 3.67 (2H, m, CH₂), 1.23 (3H, t, 6.5 Hz, CH₃).

Complex of [RuCl(arene)((*R,R*)-125)]. (*R,R*)-227

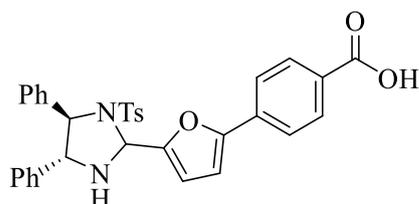


This compound is novel.

To a Schlenk tube charged with ruthenium dimer **226** (25 mg, 41 μmol) and ligand (*R,R*)-**125** (36 mg, 81 μmol) in PhCl (1 mL) was added triethylamine (32 mg, 81 μmol , 45 μL). After stirring at 80 $^{\circ}\text{C}$ for 1 h, the solution was allowed to cool to rt and the solvent removed under reduced pressure. The residue was dissolved in CHCl_3 (10 mL) and washed with water (10 mL). The organic layer was dried over MgSO_4 , filtered and the solvent removed under reduced pressure to afford the crude mixture. Purification by column chromatography (10% EtOAc in DCM followed by 0-3% MeOH in DCM) afforded the product as a brown solid (17 mg, 24 μmol , 30%); Decomposes at 195 $^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{23} +12.5$ (*c* 0.01 in CHCl_3); ν_{max} 3675, 2973, 2901, 1494, 1453, 1394, 1381 cm^{-1} ; δ_{H} (500 MHz, CDCl_3) 7.42 (1H, s, ArH), 7.18 (2H, d, *J* 8.0, ArH), 7.12- 7.00 (3H, m, ArH), 6.83 (2H, d, *J* 7.7, ArH), 6.75 – 6.69 (4H, m, ArH), 6.59 – 6.56 (2H, m, ArH), 6.47 (2H, t, *J* 7.7, ArH), 6.38 – 6.35 (1H, m, ArH), 6.12 (1H, d, *J* 3.0, ArH), 6.06 (1H, t, *J* 5.7, Arene-H), 5.90 – 5.86 (1H, m, Arene-H), 5.77 – 5.71 (1H, m, Arene-H), 5.26 (1H, t, *J* 5.7, Arene-H), 5.15 – 5.10 (1H, m, Arene-H), 4.73 – 4.67 (2H, m, ArCH_2O), 4.54 (1H, d, *J* 11.5, PhCHNTs), 4.30 (1H, d, *J* 11.5, PhCHNH), 3.90 – 3.85 (1H, m, OCH_2), 3.83 – 3.77 (1H, m, OCH_2), 3.74 (1H, t, *J* 11.5, NHCH_2), 3.66 (1H, d, *J* 14.5, NHCH_2), 2.20 (3H, s, Ts- CH_3), 1.47 (3H, t, *J* 7.0, OCH_2CH_3); δ_{C} (126 MHz, CDCl_3) 150.82, 143.47, 142.15, 139.08, 137.56, 137.40, 130.21, 129.13, 128.73, 128.39, 128.18, 128.05, 126.87, 126.45, 111.45, 110.30, 93.23, 89.14, 87.16, 86.42, 82.86, 79.92, 77.96, 75.19, 72.23, 70.60, 68.21, 49.57, 21.32, 15.18; MS (ESI⁺) *m/z* 683.3[M-Cl]⁺; HRMS calcd for $\text{C}_{35}\text{H}_{37}\text{N}_2\text{O}_4\text{RuS}$ [M-Cl]⁺ 683.1512, found 683.1517 (0.7 ppm error).

4-(5-((4*R*,5*R*)-4,5-Diphenyl-1-tosylimidazolidin-2-yl)furan-2-yl)benzoic acid.

(*R,R*)-**229**

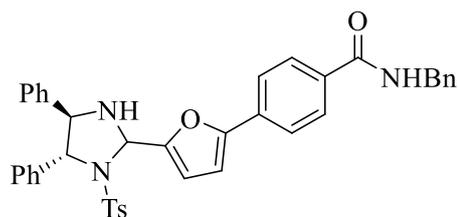


This compound is novel.

To a mixture of (*R,R*)-TsDPEN (50 mg, 0.14 mmol) and 4-(5-formylfuran-2-yl)benzoic acid (30 mg, 0.14 mmol) in EtOH (5 mL) was added 4 drops of acetic acid.

After refluxing for 4h, the solution was cooled to rt and the solvent removed under reduced pressure. DCM (5 mL) was added to the residue and the solution was filtered. The precipitate was washed again with DCM (2 x 5 mL). The filtrates were combined and the solvent was removed under reduced pressure to give the crude product. Purification by column chromatography (50% EtOAc in Pet. Ether) afforded the product as an orange solid (52 mg, 0.092 mmol, 66%); Mp 120.7 – 123.0 °C; $[\alpha]_D^{23} +13.7$ (*c* 0.1 in CHCl₃); ν_{\max} 3030, 2921, 1686, 1609, 1494, 1453, 1418 cm⁻¹; δ_H (400 MHz, CDCl₃) 8.12 (2H, d, *J* 8.4, ArH), 7.67 (2H, d, *J* 8.4, ArH), 7.46 (2H, d, *J* 8.2, ArH), 7.30 – 7.27 (4H, m, ArH), 7.25 – 7.20 (3H, m, ArH), 7.17 – 7.12 (3H, m, ArH), 7.10 (2H, d, *J* 8.2, ArH), 6.84 (1H, d, *J* 3.4, Furan-H), 6.68 (1H, d, *J* 3.4, Furan-H), 6.19 (1H, s, NCHN), 4.88 (1H, d, *J* 6.8, CHPh), 4.55 (1H, d, *J* 6.8, CHPh), 2.33 (3H, s, Ts-CH₃); δ_C (101 MHz, CDCl₃) 171.40, 153.73, 153.16, 143.78, 142.55, 139.08, 137.65, 135.69, 135.17, 130.84, 129.52, 128.91, 128.51, 128.31, 127.87, 127.68, 127.35, 127.08, 123.65, 111.55, 108.59, 78.82, 72.86, 70.82, 21.60; MS (ESI⁺): *m/z* 565.3 [M + H]⁺; HRMS calcd for C₃₃H₂₉N₂O₅S [M + H]⁺ 565.1792, found 565.1794 (0.4 ppm error).

***N*-Benzyl-4-(5-((4*R*,5*R*)-4,5-diphenyl-1-tosylimidazolidin-2-yl)furan-2-yl)benzamide. (*R,R*)-230**

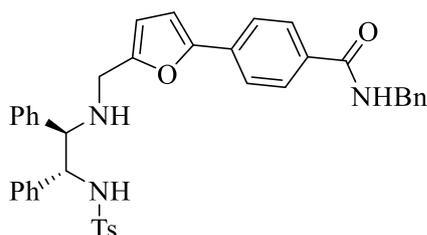


This compound is novel.

To a mixture of carboxylic acid (*R,R*)-**229** (100 mg, 177 μmol), benzylamine (21 mg, 195 μmol) and DMAP (32 mg, 266 μmol) in DCM (5 mL) was added EDC (44 mg, 230 μmol). After stirring at rt for 72 h, the reaction mixture was quenched with water (10 mL). Following extraction with DCM (3 x 10 mL), the organic fractions were combined, dried over MgSO₄, filtered and the solvent removed under reduced pressure. Purification by column chromatography (gradient elution 0-50% EtOAc in Pet. Ether) gave the product as an orange semi-solid (83 mg, 127 μmol, 72%); $[\alpha]_D^{21} +109.0$ (*c* 0.05 in CHCl₃); ν_{\max} 3290, 3034, 2921, 1639, 1535, 1494, 1453 cm⁻¹; δ_H

(300 MHz, CDCl₃) 7.88 (2H, s, ArH), 7.84 – 7.78 (2H, m, ArH), 7.64 (2H, d, *J* 8.3, ArH), 7.45 (1H, d, *J* 8.2, ArH), 7.41 – 7.36 (6H, m, ArH), 7.35 – 7.31 (2H, m, ArH), 7.24 – 7.18 (4H, m, ArH), 7.15 – 7.11 (2H, m, ArH), 7.08 (2H, *J* 8.3, ArH), 6.76 (1H, d, *J* 3.3, Furan-H), 6.65 (1H, d, *J* 3.3, Furan-H), 6.43 (2H, b.s., NH x 2), 6.16 (1H, s, NCHNTs), 4.85 (1H, d, *J* 6.7, CHPh), 4.71 – 4.63 (2H, m, NCH₂Ph), 4.54 (1H, d, *J* 6.7, CHPh), 2.32 (3H, s, Ts-CH₃); δ_C (101 MHz, CDCl₃) 166.91, 153.36, 153.22, 143.74, 139.13, 138.33, 137.76, 135.56, 133.38, 133.02, 129.49, 128.90, 128.85, 128.47, 128.09, 127.86, 127.80, 127.74, 127.64, 127.29, 127.01, 125.40, 123.82, 111.35, 109.13, 107.72, 72.90, 70.80, 44.27, 21.58; MS (ESI) [M-H]⁻ 652.2, [M+H]⁺ 654.3; HRMS calcd for C₄₀H₃₆N₃O₄S [M+H]⁺ 654.2421, found 654.2410 (1.6 ppm error).

N*-Benzyl-4-(5-((((1*R*,2*R*)-2-((4-methylphenyl)sulfonamido)-1,2-diphenylethyl)amino)methyl) furan-2-yl)benzamide. (*R,R*)-**231*

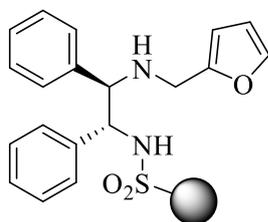


This compound is novel.

The amide (*R,R*)-**230** (50 mg, 76 μ mol) was dissolved in MeOH (1.5 mL) and acetic acid was added (3 drops) followed by slow addition of NaBH₃CN (8 mg, 129 μ mol). After stirring overnight, the solvent was removed under reduced pressure and the residue was partitioned between EtOAc (10 mL) and H₂O (10 mL). The organic layer was collected and further extracted with EtOAc (2 x 15 mL). The organic extracts were combined, dried over MgSO₄, filtered and the solvent removed under reduced pressure. Purification by column chromatography (0-50% EtOAc in Pet. Ether) gave the product as an orange solid (32 mg, 49 μ mol, 64%); Mp 108.1 – 110.4 °C; $[\alpha]_D^{22}$ -63.1 (*c* 0.2 in CHCl₃); ν_{max} 2986, 2926, 2870, 2030, 1680, 1667 cm⁻¹; δ_H (500 MHz, CDCl₃) 7.81 (2H, d, *J* 8.4, ArH), 7.61 (2H, d, *J* 7.7, ArH), 7.40 – 7.34 (5H, m, ArH), 7.32 (3H, d, *J* 8.2, ArH), 7.17 – 7.13 (3H, m, ArH), 7.06 – 6.98 (5H, m, ArH), 6.96 (2H, d, *J* 8.2, ArH), 6.93 (2H, d, *J* 7.2, ArH + NHSO₂), 6.61 (1H, d, *J* 3.2, Furan-H), 6.49 – 6.42 (1H, m, C(O)NH), 6.09 (1H, d, *J* 3.2, Furan-H), 4.67 (2H, d, *J* 5.5,

C(O)NHCH₂), 4.35 (1H, d, *J* 7.3, CHPh), 3.77 – 3.70 (2H, m, CHPh + CH_ACH_B), 3.51 (1H, d, *J* 14.8, CH_ACH_B), 2.30 (3H, s, Ts-CH₃), 1.85 (1H, bs, NH); δ_C (126 MHz, CDCl₃) 166.99, 153.74, 152.42, 142.85, 138.60, 138.32, 137.07, 133.68, 132.64, 129.23, 128.96, 128.59, 128.19, 128.15, 127.82, 127.73, 127.61, 127.52, 127.40, 127.15, 123.65, 109.81, 107.45, 66.54, 63.11, 44.33, 43.74, 21.54.; MS (ESI⁺) *m/z* 656.4 [M+H]⁺; HRMS calcd for C₄₀H₃₈N₃O₄S [M+H]⁺ 656.2578, found 656.2574 (0.5 ppm error).

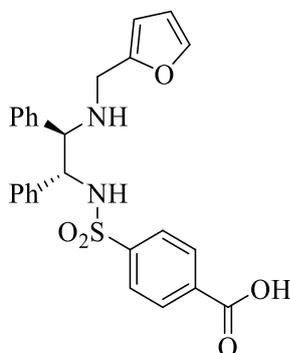
Furan ligand on polymer support. (*R,R*)-232



This compound is novel.

To a suspension of sulfonyl chloride polymer bound (85 mg, 1.5-2.0 mmol/g) and triethylamine (0.1 mL, 0.17 mmol) in DCM (3 mL) was added (*R,R*)-**218** (50 mg, 0.17 mmol). After gentle stirring overnight, the product was filtered off and washed with DCM (3 x 3 mL) and water (3x 3 mL). The precipitate was dried to give the product as an off-white solid (103 mg); ν_{\max} 3060, 3027, 2922, 1653, 1533, 1493 cm⁻¹

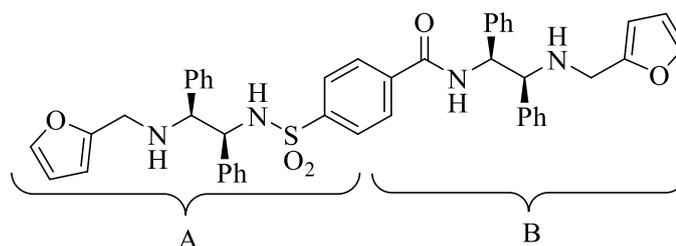
4-(*N*-((1*R*,2*R*)-2-((Furan-2-ylmethyl)amino)-1,2-diphenylethyl)sulfamoyl)benzoic acid. (*R,R*)-233



This compound is novel.

To a solution of (*R,R*)-**218** (275 mg, 0.94 mmol) and triethylamine (95 mg, 131 μ L, 0.94 mmol) in DCM (30 mL) at 0°C was added 4-chlorosulfonylbenzoic acid (207 mg, 0.94 mmol). After stirring overnight at rt, the reaction was quenched by the addition of H₂O (30 mL) and the organic layer was extracted. The mixture was further extracted with DCM (2 x 30 mL), the organic extracts were combined, dried over MgSO₄, filtered and the solvent removed *in vacuo* by rotary evaporation to give the crude product. Purification by column chromatography gradient elution 0-100% EtOAc in Pet. ether gave the product as a yellow solid (110 mg, 0.23 mmol, 22%); Mp 138.7 – 143.8 °C; $[\alpha]_D^{22}$ -2.8 (*c* 0.45 in MeOH); ν_{\max} 3063, 3029, 2924, 2851, 1708, 1653, 1600, 1532, 1495 cm^{-1} ; δ_{H} (400 MHz, CDCl₃) 7.83 (2H, d, *J* 8.4, ArH), 7.47 (2H, d, *J* 8.4, ArH), 7.29 (1H, s, ArH), 7.18 – 7.08 (3H, m, ArH), 7.07 – 6.95 (5H, m, ArH), 6.88 (2H, d, *J* 7.6, ArH), 6.28 – 6.20 (1H, m, ArH), 5.99 (1H, d, *J* 3.1, ArH), 4.41 (1H, d, *J* 7.5, CHNH₂SO₂), 3.76 (1H, d, *J* 7.5, CHNHCH₂), 3.63 (1H, d, *J* 14.5, CH_AH_B), 3.42 (1H, d, *J* 14.5, CH_AH_B), 2.46 (1H, s, COOH), 2.03 (1H, d, *J* 3.0, NH); δ_{C} (101 MHz, MeOD) 152.79, 145.07, 144.86, 143.74, 140.75, 138.63, 138.32, 130.69, 129.82, 129.38, 129.06, 128.88, 128.67, 128.29, 127.84, 111.34, 109.45, 67.66, 64.83, 43.88; MS (ESI⁺) *m/z* 477.1 [M+H]⁺; HRMS calcd for C₂₆H₂₅N₂O₅S [M+H]⁺ 477.1479, found 477.1467 (2.4 ppm error).

N-((1*S*,2*S*)-2-((Furan-2-ylmethyl)amino)-1,2-diphenylethyl)-4-(*N*-((1*S*,2*S*)-2-((furan-2-ylmethyl)amino)-1,2-diphenylethyl)sulfamoyl)benzamide. (*S,S*)-**234**

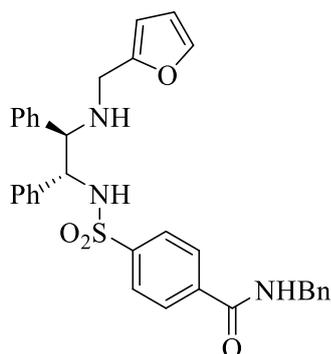


This compound is novel and a byproduct from the formation of ligand **233**.

Same procedure as **233**; using (*S,S*)-**218** (400 mg, 1.37 mmol) gave the product as a white solid (120 mg, 0.16 mmol, 12%); Mp 172.9 – 176.2 °C; $[\alpha]_D$ -27.5 (*c* 0.2 in CHCl₃); ν_{\max} 3367, 3286, 3061, 3032, 2818, 1640, 1600, 1518 cm^{-1} ; δ_{H} (400 MHz, CDCl₃) 7.56 (2H, d, *J* 8.4, ArH), 7.48 (2H, d, *J* 8.4, ArH), 7.43 (1H, d, *J* 7.0 Hz, ArH), 7.36 – 7.33 (2H, m, ArH), 7.31 – 7.20 (8H, m, ArH), 7.17 – 7.09 (4H, m, ArH), 7.08

– 7.02 (3H, m, ArH), 6.99 (2H, dd, J 6.5, 2.8 Hz, ArH), 6.96 – 6.91 (2H, m, ArH), 6.29 – 6.23 (2H, m, ArH-Furan), 5.98 (1H, d, J 3.1, ArH-Furan), 5.96 (1H, d, J 3.1, ArH-Furan), 5.24 (1H, dd, J 6.7, 5.2, PhCHNHCO-B), 4.38 (1H, d, J 7.2, PhCHNH-B), 4.15 – 4.08 (1H, m, PhCHNH-A), 3.75 – 3.67 (2H, m, CH_AH_BNH-B + CHPhNHS-A), 3.63 (1H, d, J 14.5, CH_AH_BNH-B), 3.49 (1H, d, J 14.5, CH_AH_BNH-A), 3.43 (1H, d, J 14.5, CH_AH_BNH-A), 2.09 (3H, bs, NH x3); δ_c (101 MHz, CDCl₃) 165.73, 152.99, 152.85, 142.75, 142.14, 139.53, 139.44, 138.51, 138.07, 137.70, 128.84, 128.79, 128.65, 128.28, 128.04, 127.93, 127.77, 127.69, 127.61, 127.47, 127.33, 127.31, 126.45, 110.27, 110.21, 107.48, 107.37, 66.44, 65.49, 63.22, 59.15, 43.64, 43.61; MS (ESI⁺) m/z 751.4 [M+H]⁺; HRMS calcd for C₄₅H₄₃N₄O₅S [M+H]⁺ 751.2949, found 751.2944 (0.6 ppm error).

***N*-Benzyl-4-(*N*-((1*R*,2*R*)-2-((furan-2-ylmethyl)amino)-1,2-diphenylethyl)sulfamoyl)benzamide. (*R,R*)-235**

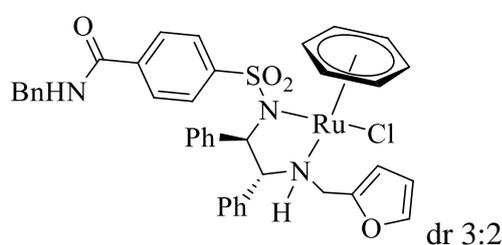


This compound is novel.

To a solution containing carboxylic acid (*R,R*)-**233** (119 mg, 0.25 mmol), DMAP (46 mg, 0.38 mmol) and benzylamine (32 mg, 0.30 mmol) in DCM (10 mL) was added EDCI (62 mg, 0.32 mmol). After stirring for 3 days at rt, the reaction was diluted with DCM (10 mL) and quenched with water (20 mL). The organic layer was separated and the product further extracted with DCM (2 x 20 mL). The organic extracts were combined, dried over MgSO₄, filtered and the solvent removed *in vacuo* by rotary evaporation to give the crude product. Purification by column chromatography 50% EtOAc in Pet. ether gave the product as a white solid (97 mg, 0.17 mmol, 69%); Mp 54.6 – 57.0 °C; $[\alpha]_D^{22}$ -25.6 (*c* 0.16 in CHCl₃); ν_{\max} 3322, 3063, 3030, 1644, 1602, 1537, 1494, 1454 cm⁻¹; δ_H (400 MHz, CDCl₃) 7.57 (2H, d, J 8.3, ArH), 7.45 (2H, d, J 8.3, ArH), 7.39 – 7.28 (6H, m, ArH), 7.18 – 7.10 (4H, m, ArH), 7.07 – 6.99 (3H, m,

ArH), 6.97 (2H, dd, J 6.5, 2.8, ArH), 6.91 (2H, d, J 6.7, ArH), 6.45 (1H, s, CONH), 6.27 – 6.23 (1H, m, ArH), 5.98 (1H, d, J 3.1, ArH), 4.62 (2H, d, J 5.6, CH₂Ph), 4.34 (1H, d, J 7.4, CHNHSO₂), 3.70 (1H, d, J 7.4, PhCHNH), 3.62 (1H, d, J 14.5, CH_AH_B), 3.42 (1H, d, J 14.5, CH_AH_B), 1.75 (1H, s, NH) note: NHSO₂ signal in aromatic region; δ_C (101 MHz, CDCl₃) 166.03, 152.88, 142.13, 138.51, 137.98, 137.91, 137.61, 129.01, 128.63, 128.25, 128.08, 127.96, 127.91, 127.68, 127.60, 127.49, 127.36, 127.30, 110.21, 107.36, 66.49, 63.24, 44.41, 43.63; MS (ESI⁺) m/z 588.2 [M+Na]⁺; HRMS calcd for C₃₃H₃₁N₃NaO₄S [M+Na]⁺ 588.1927, found 588.1915 (2.1 ppm error).

Complex formed from (*R,R*)-235. (*R,R*)-236

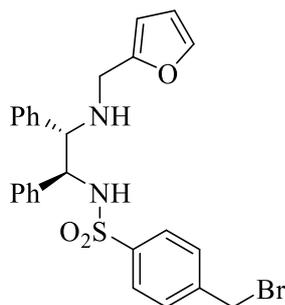


This compound is novel.

A Schlenk tube was charged with ligand (*R,R*)-235 (56 mg, 0.10 mmol) and benzene ruthenium chloride dimer (25 mg, 0.050 mmol) under N₂. Chlorobenzene (1.5 mL) and triethylamine (40 mg, 0.40 mmol) were added. After stirring at 80 °C for 1 h, the reaction was left to cool to rt and the solvent removed under reduced pressure. The residue was partitioned between H₂O (10 mL) and CHCl₃ (10 mL). The organic layer was collected and further extracted with CHCl₃ (2 x 10 mL). The organic extracts were combined, dried over MgSO₄, filtered and the solvent removed *in vacuo* by rotary evaporation to give the crude product. Purification by column chromatography 0-3% MeOH in DCM gave the product as a brown solid (51 mg, 65.4 μmol, 65%); Decomposes 203.2 °C; $[\alpha]_D^{22}$ +15.0 (c 0.1 in CHCl₃); ν_{\max} 3339, 3195, 3062, 3027, 1637, 1600, 1527, 1495 cm⁻¹; δ_H (500 MHz, CDCl₃ + MeOD 1:1) 7.54 – 7.45 (2H, m, ArH), 7.44 – 7.38 (3H, m, ArH), 7.37 – 7.31 (5H, m, ArH), 7.29 – 7.25 (1H, m, ArH), 7.11 – 7.03 (4H, m, ArH), 6.77 (2H, d, J 6.0, ArH), 6.69 – 6.64 (2H, m, ArH), 6.63 – 6.57 (2H, m, ArH), 6.41 – 6.33 (2H, m, ArH), 5.72 (6H, s, arene-H), 4.59 (2H, bs, CH₂-Bn), 4.41 (1H, d, J 14.8, CHNTs), 4.16 (1H, d, J 14.8, CHNH), 4.05 (1H, d, J 10.9, CH_AH_B), 4.01 – 3.91 (1H, m, CH_AH_B), 2.46 (1H, s, NH); δ_C (126 MHz, CDCl₃ + MeOD 1:1) 167.22, 149.39, 148.03, 142.14, 138.29, 137.73, 136.39, 134.96, 130.12,

129.15, 128.76, 128.55, 127.80, 127.53, 127.31, 127.14, 126.64, 126.54, 126.40, 111.26, 109.36, 84.10, 71.27, 69.38, 51.47, 43.95; MS (ESI⁺) *m/z* 744.1 [M-Cl]⁺; HRMS calcd for C₃₉H₃₆N₃O₄RuS [M-Cl]⁺ 744.1465, found 744.1457 (2.4 ppm error).

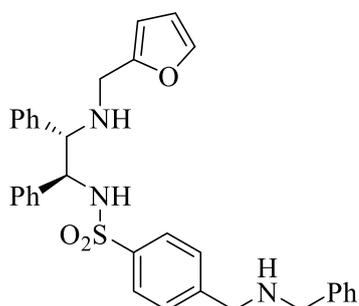
4-(Bromomethyl)-*N*-((1*S*,2*S*)-2-((furan-2-ylmethyl)amino)-1,2-diphenylethyl)benzenesulfonamide. (*S,S*)-239



This compound is novel.

To a stirring solution of (*S,S*)-**218** (126 mg, 0.43 mmol) and triethylamine (43 mg, 0.43 mmol) in DCM (10 mL) was added 4-(bromomethyl)benzenesulfonyl chloride (116 mg, 0.43 mmol). After stirring at rt for 1.5 h, H₂O (10 mL) was added and the product was extracted with DCM (3 x 10 mL). The organic extracts were combined, dried over MgSO₄, filtered and the solvent removed *in vacuo* by rotary evaporation to give the crude product. Purification by column chromatography 0-30% EtOAc in Pet. Ether gave the product as a white solid (157 mg, 0.30 mmol, 70%); Decomposes at 184 °C; [α]_D +2.0 (*c* 0.2 in CHCl₃); ν_{max} 3031, 2764, 1496, 1455, 1406, 1328 cm⁻¹; δ_H (400 MHz, CDCl₃) 7.42 (2H, d, *J* 8.2, ArH), 7.30 (1H, s, ArH), 7.22 – 7.10 (5H, m, ArH), 7.08 – 6.96 (5H, m, ArH), 6.95 – 6.87 (2H, m, ArH), 6.30 – 6.21 (1H, m, ArH), 6.00 (1H, d, *J* 3.0, ArH), 4.49 (2H, s, CH₂), 4.40 (1H, d, *J* 7.4, CHNHSO₂), 3.76 (1H, d, *J* 7.4, CHNHCH₂), 3.65 (1H, d, *J* 14.5, CH_AH_B), 3.45 (1H, d, *J* 14.5, CH_AH_B), 2.20 (1H, b.s, NH); δ_C (101 MHz, CDCl₃) 142.13, 141.43, 140.12, 138.42, 138.40, 137.92, 128.68, 128.60, 128.21, 127.95, 127.68, 127.65, 127.53, 127.47, 110.21, 107.46, 66.43, 63.18, 45.08, 43.58; MS (ESI⁺) *m/z* 525.1 [M+H]⁺; HRMS calcd for C₂₆H₂₆⁷⁹BrN₂O₃S [M+H]⁺ 525.0842, found 525.0840 (0.3 ppm error).

4-((Benzylamino)methyl)-N-((1*S*,2*S*)-2-((furan-2-ylmethyl)amino)-1,2-diphenylethyl)benzenesulfonamide. (*S,S*)-240



This compound is novel.

K_2CO_3 (28 mg, 0.20 mmol) was added to a stirring solution containing amine (*S,S*)-**239** (52 mg, 0.10 mmol) and benzylamine (16 mg, 0.15 mmol) in MeCN (5 mL). After stirring overnight at rt, the solvent was removed under reduced pressure and the residue was partitioned between H_2O (15 mL) and EtOAc (15 mL). The organic layer was collected and further extracted with EtOAc (2 x 15 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and the solvent removed *in vacuo* by rotary evaporation to give the crude product. Purification by column chromatography 0-60% EtOAc in Pet. ether gave the product as a yellow oil (48 mg, 87.0 μ mol, 87%). $[\alpha]_D^{23} +15.0$ (*c* 0.1 in $CHCl_3$); ν_{max} 3248, 3061, 3028, 2835, 1599, 1494, 1453, 1407 cm^{-1} ; δ_H (500 MHz, $CDCl_3$) 7.44 (2H, d, *J* 8.2, ArH), 7.38 – 7.27 (6H, m, ArH), 7.21 (2H, d, *J* 8.2, ArH), 7.15 (3H, t, *J* 7.7, ArH), 7.03 – 6.99 (3H, m, ArH), 6.99 – 6.95 (2H, m, ArH), 6.93 – 6.88 (2H, m, ArH), 6.28 – 6.24 (1H, m, ArH), 6.09 (1H, s, ArH-Furan), 5.99 (1H, d, *J* 3.1, ArH-Furan), 4.34 (1H, d, *J* 7.6, $CHNHCH_2$), 3.77 (2H, s, CH_2NHCH_2), 3.75 (2H, s, CH_2NHCH_2), 3.69 (1H, d, *J* 7.6, $PhCHNHCH_2$), 3.63 (1H, d, *J* 14.5, CH_AH_BNH), 3.43 (d, *J* 14.5, CH_AH_BNH), 1.87 (2H, s, NH x 2); δ_C (126 MHz, $CDCl_3$) 153.04, 144.62, 142.09, 139.63, 138.74, 138.73, 138.25, 128.67, 128.54, 128.33, 128.26, 128.10, 127.79, 127.73, 127.55, 127.48, 127.40, 127.37, 110.20, 107.28, 66.66, 63.13, 52.97, 52.33, 43.66; MS (ESI⁺) *m/z* 552.2 $[M+H]^+$; HRMS calcd for $C_{33}H_{34}N_3O_3S$ $[M+H]^+$ 552.2315, found 552.2309 (1.2 ppm error).

Supported ligand 241

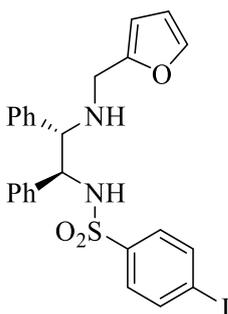
To a solution containing carboxylic acid (*R,R*)-233 (48 mg, 0.10 mmol), DMAP (18 mg, 0.15 mmol) and amine polymer (25 mg, 3.5-5.0 mmol/g, 0.10 mmol) in DCM (10

mL) was added EDCI (25 mg, 0.13 mmol). After stirring for 3 days at rt, the product was filtered out and washed with DCM (10 mL). This product was used without further purification.

Supported ligands 242 -244

NEt₃ (10 mg, 0.10 mmol) was added to a mixture containing amine (*S,S*)-**239** (52 mg, 0.10 mmol) and supported reagent (100 mg, 1.0 mmol/g, 0.10 mmol) in DCM (5 mL). After 3 days, the solid was filtered out and washed with DCM. This product was used without further purification.

N-((1*S*,2*S*)-2-((Furan-2-ylmethyl)amino)-1,2-diphenylethyl)-4-iodobenzene-sulfonamide. (*S,S*)-**246**

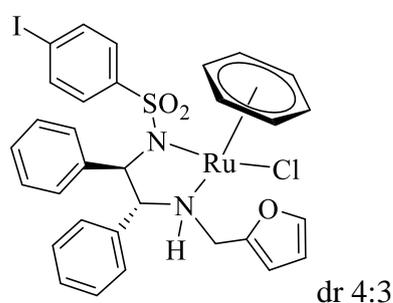


This compound is novel.

To a mixture of (*S,S*)-**245** (478 mg, 1.00 mmol) in DCM (8 mL) and molecular sieves was added a solution of furfuraldehyde (96 mg, 1.00 mmol) in DCM (4 mL). After stirring overnight, the solution was filtered and the solvent removed under reduced pressure. The residue was dissolved in dry MeOH (8 mL) and NaBH₄ (95 mg, 1.50 mmol) was added. The solution was stirred overnight and then concentrated. EtOAc (25 mL) and H₂O (25 mL) were added to the mixture and the EtOAc layer was collected. The aqueous layer was further washed with EtOAc (2 x 25 mL) and the organic extracts were combined, dried over MgSO₄, filtered and the solvent removed under reduced pressure to afford the crude mixture. Purification by column chromatography (gradient elution 0-25% EtOAc in Pet.Ether) afforded the product as a white solid (456 mg, 0.82 mmol, 82%); Mp 143.0 – 146.4 °C; [α]_D²² +23.5 (*c* 0.2 in CHCl₃); ν_{\max} 3288, 3027, 2366, 1569, 1454, 1433, 1384 cm⁻¹; δ_{H} (400 MHz, CDCl₃)

7.52 (2H, d, J 8.4, ArH), 7.30 (1H, s, ArH), 7.20 – 7.04 (8H, m, ArH), 7.03 – 6.98 (2H, m, ArH), 6.95 (2H, d, J 7.1, 2H), 6.30 – 6.22 (1H, m, Furan-H), 6.12 (1H, s, NHSO₂), 5.97 (1H, d, J 3.1 Hz, Furan-H), 4.36 (1H, d, J 7.0, CHNHCH₂), 3.73 (1H, d, J 7.0, CHNHSO₂), 3.63 (1H, d, J 14.5, CH_AH_B), 3.42 (1H, d, J 14.5, CH_AH_B), 1.69 (1H, s, NH); δ_C (101 MHz, CDCl₃) 152.90, 142.12, 139.92, 138.57, 138.07, 137.78, 128.67, 128.49, 128.31, 127.89, 127.68, 127.58, 127.46, 110.21, 107.32, 99.50, 66.40, 63.19, 43.63; MS (ESI⁺) m/z 559.4 [M+H]⁺; HRMS calcd for C₂₅H₂₄IN₂O₃S [M+H]⁺ 559.0547, found 559.0540 (1.2 ppm error).

Complex formed from (*S,S*)-**246**. (*S,S*)-**249**



This compound is novel.

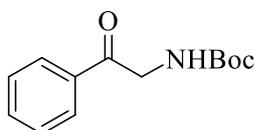
To a Schlenk tube charged with benzene ruthenium (II) chloride dimer (25 mg, 0.05 mmol) and (*S,S*)-**246** (56 mg, 0.10 mmol) in PhCl (1.00 mL) was added triethylamine (73 mg, 0.72 mmol, 0.1 mL). After stirring at 80 °C for 1 h, the solution was allowed to cool to rt and the solvent removed under reduced pressure. The residue was dissolved in CHCl₃ (10 mL) and washed with water (10 mL). The organic layer was dried over MgSO₄, filtered and the solvent removed under reduced pressure to afford the crude mixture. Purification by column chromatography (15% EtOAc in DCM followed by 0-3% MeOH in DCM) afforded the product as a brown solid (12 mg, 0.015 mmol, 15%); Decomposes at 236.4 °C; $[\alpha]_D^{23} +187.5$ (c 0.01 in CHCl₃); ν_{\max} 3202, 3063, 3029, 2861, 1568, 1497, 1471, 1455 cm⁻¹; δ_H (500 MHz, CDCl₃) 7.42 (1H, s, Furan-H), 7.37 (2H, d, J 8.4, ArH), 7.14 – 7.04 (6H, m, ArH), 6.90 – 6.84 (2H, m, ArH), 6.78 – 6.71 (3H, m, 3H), 6.61 – 6.55 (2H, m, ArH), 6.39 – 6.34 (2H, m, Furan-H x2), 5.69 (6H, s, Arene-H), 4.48 – 4.40 (1H, m, CHNSO₂), 4.14 (1H, dd, J 14.8, 2.4, CHNH), 4.05 (1H, d, J 11.2, CH_AH_B), 3.86 (1H, t, J 11.2, CH_AH_B); δ_C (126 MHz, CDCl₃) 149.38, 144.81, 142.12, 139.02, 136.46, 130.32, 129.28, 129.10, 128.87, 128.60, 128.44, 127.29, 126.79, 111.46, 109.53, 96.27, 84.14, 80.41, 69.57, 51.68. MS

(ESI⁺) m/z 737.0 [M-Cl]⁺; HRMS calcd for C₃₁H₂₈IN₂O₃RuS [M-Cl]⁺ 736.9903, found 736.9893 (2.5 ppm error).

7.2. Ketones

Synthetic procedures for ketones that are not commercially available are reported in this section.

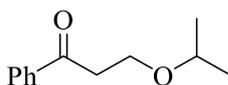
tert-Butyl (2-oxo-2-phenylethyl)carbamate. 143



This compound is known.¹⁶²

NaHCO₃ (840 mg, 10.0 mmol) was added to a solution of 2-aminoacetophenone hydrochloride (687 mg, 4.00 mmol) in water (14 mL). MeOH (14 mL) and Boc₂O (1.31 g, 6 mmol) were then added to the mixture and left to stir at rt for 20 h. The mixture was then transferred to a conical flask with ice-cold water (55 mL) causing a white precipitate to form. The precipitate was filtered off via Büchner filtration, washed with ice-cold water (2 x 10 mL) and dried under vacuum to give the product (846 mg, 3.60 mmol, 90%); δ_{H} (300 MHz, CDCl₃) 7.98 – 7.94 (2 H, m, ArH) 7.65 – 7.59 (1 H, m, ArH) 7.52 - 7.46 (2 H, m, ArH) 5.55 (1 H, br. s, NH) 4.67 (2 H, d, J 4.5, CH₂NH) 1.48 (9 H, s, (CH₃)₃); δ_{C} (101 MHz, CDCl₃) 194.57, 155.88, 134.67, 134.03, 128.98, 127.93, 79.92, 47.62, 28.47.

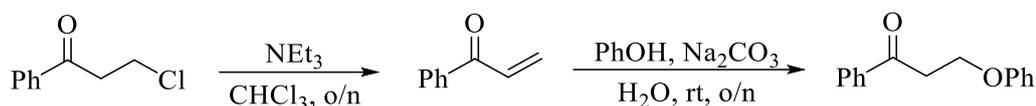
3-Isopropoxy-1-phenylpropan-1-one. 155



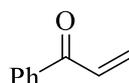
This compound is known.¹⁶³

3-Chloropropiophenone (200 mg, 1.19 mmol) was dissolved in 2-propanol (12 mL) and stirred at 80 °C for 48 h. The solution was then cooled to rt and the solvent removed under reduced pressure. The crude product was then purified by column chromatography with gradient elution 0-50% DCM in Pet. ether to give the product as a colourless oil (188 mg, 0.98 mmol, 82%); δ_{H} (300 MHz, CDCl₃) 7.97 (2 H, d, J 8.0,

ArH), 7.59 - 7.53 (1 H, m, ArH), 7.50 - 7.44 (2 H, m, ArH), 3.86 (2 H, t, J 6.7, CH_2OCH), 3.63 (1 H, spt, J 6.2, $\text{OCH}(\text{CH}_3)_2$), 3.25 (2 H, t, J 6.7, COCH_2), 1.16 (6 H, d, J 6.2, $(\text{CH}_3)_2$); δ_c (101 MHz, CDCl_3) 198.80, 137.20, 133.21, 128.68, 128.24, 72.05, 63.52, 39.42, 22.18.



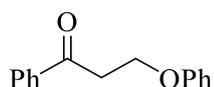
1-Phenylprop-2-en-1-one. 157



This compound is known.¹⁴⁸

Triethylamine (1.69 mL, 12.0 mmol) was added dropwise to a solution of 3-chloropropiophenone (843 mg, 5.00 mmol) in CHCl_3 (12 mL). After stirring o/n at rt, the solution was washed with 0.1 M HCl (10 mL), sat. NaHCO_3 (10 mL) and water (3 x 10 mL). The organic layer was dried over MgSO_4 , filtered and concentrated under reduced pressure to give the product as a clear oil (580 mg, 4.39 mmol, 88%); δ_H (300 MHz, CDCl_3) 7.99 - 7.91 (2 H, m, ArH), 7.62 - 7.55 (1 H, m, ArH), 7.53 - 7.44 (2 H, m, ArH), 7.16 (1 H, dd, J 17.1, 10.6, $\text{C}(\text{O})\text{CH}=\text{CH}_2$), 6.44 (1 H, dd, J 17.1, 1.7, $\text{CH}=\text{CH}_A\text{H}_B$), 5.94 (1 H, dd, J 10.6, 1.7, $\text{CH}=\text{CH}_A\text{H}_B$).

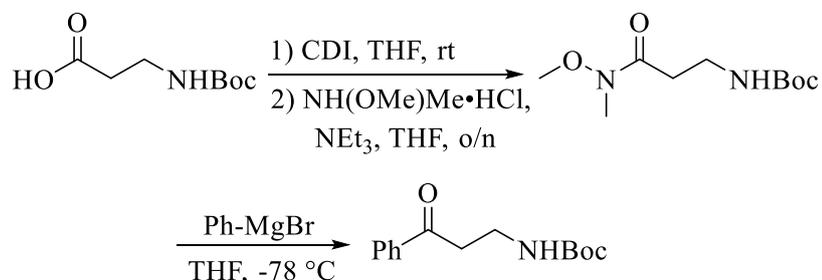
3-Phenoxy-1-phenylpropan-1-one. 158



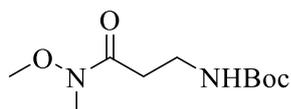
This compound is known.¹⁶³

To a stirring solution of 1-phenylprop-2-en-1-one (580 mg, 4.39 mmol) in phenol (413 mg, 4.4 mmol) was added Na_2CO_3 (1.8 mL, 0.05 M aq.). After stirring o/n, water (25 mL) and EtOAc (25 mL) were added and the organic layer extracted. The compound was extracted again from the aqueous extract with EtOAc (2 x 25 mL). Organic extracts were combined, dried over MgSO_4 , filtered and solvent removed under reduced pressure. The crude product was then purified by column chromatography with gradient elution 0-10% EtOAc in Pet. ether to give the product as a white solid (671 mg, 2.97 mmol, 68%); δ_H (300 MHz, CDCl_3) 8.01 (2 H, d, J 8.2, ArH), 7.63 -

7.56 (1 H, m, ArH), 7.53 - 7.45 (2 H, m, ArH), 7.33 - 7.26 (2 H, m, ArH), 6.99 - 6.89 (3 H, m, ArH), 4.44 (2 H, t, J 6.6, CH₂OPh), 3.48 (2 H, t, J 6.6, COCH₂); δ_c (101 MHz, CDCl₃) 197.78, 158.75, 136.94, 133.48, 129.60, 128.79, 128.27, 121.04, 114.70, 63.30, 38.30.



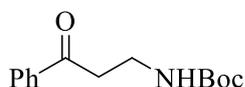
***tert*-Butyl 3-(methoxy(methyl)amino)-3-oxopropylcarbamate. 160**



This compound is known.¹⁶⁴

To a solution of Boc- β -alanine (1.89 g, 10 mmol) in THF (13.5 mL) was added 1,1'-carbonyldiimidazole (1.78 g, 11 mmol) in one portion and stirred at rt for 4 h. Triethylamine (2.23 g, 3.07 mL, 22 mmol) was added to a separate solution containing N,O-dimethylhydroxylamine hydrochloride (1.07 g, 11 mmol) in THF (6 mL) and stirred for 2 h. The Boc- β -alanine containing solution was then added to the second solution. After stirring for 20 h, the mixture was filtered and the solids washed with THF (2 x 7.5 mL). The filtrate was concentrated under reduced pressure and dissolved in DCM (50 mL). The DCM extract washed 0.1 M HCl (20 mL) and water (50 mL). The organic extract was dried over MgSO₄, filtered and solvent removed under reduced pressure to give the product as a white solid (2.02 g, 8.70 mmol, 87%); δ_H (400 MHz, CDCl₃) 5.22 (1 H, br. s, NH), 3.67 (3 H, s, OCH₃), 3.42 (2 H, d, J 5.3, CH₂NH), 3.18 (3 H, s, NCH₃), 2.64 (2 H, br. s, COCH₂), 1.43 (9 H, s, (CH₃)₃).

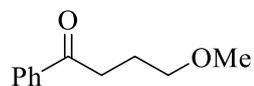
***tert*-Butyl 3-oxo-3-phenylpropylcarbamate. 161**



This compound is known.¹⁶⁵

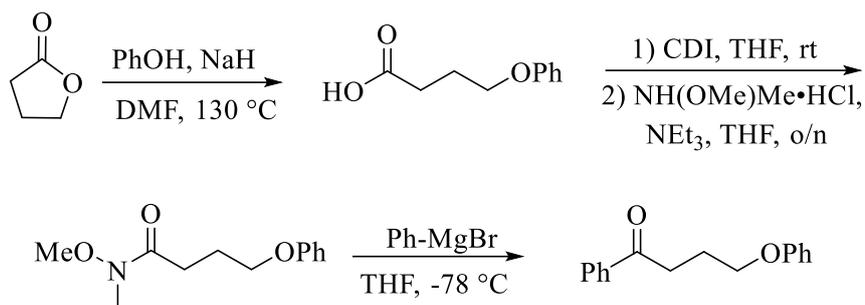
Product from the previous step (2.02 g, 8.70 mmol) was dissolved in dry THF (59 mL) and cooled to -78 °C. Phenylmagnesium bromide (3 M in Et₂O, 6.96 mL, 20.9 mmol) was added dropwise over 30 min to the solution and the mixture was then allowed to warm to rt. After stirring for 2 h, the mixture was cooled to -78 °C and sat. NH₄Cl (100 mL) and EtOAc (100 mL) was added. After warming to rt, the organic extract was collected and the aqueous layer washed with EtOAc (2 x 100 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The crude product was then purified by column chromatography with gradient elution 0-20% EtOAc in Pet. ether to give product as a white solid (1.585 g, 6.36 mmol, 73%); δ_{H} (400 MHz, CDCl₃) 7.96 (2 H, d, *J* 7.7, ArH), 7.61 - 7.54 (1 H, m, ArH), 7.50 - 7.44 (2 H, m, ArH), 5.14 (1 H, br. s, NH), 3.55 (2 H, d, *J* 5.5, CH₂NH), 3.25 - 3.16 (2 H, m, COCH₂), 1.42 (9 H, s, (CH₃)₃); δ_{C} (101 MHz, CDCl₃) 199.44, 156.06, 136.70, 133.48, 128.76, 128.11, 79.29, 38.77, 35.55, 28.49.

4-Methoxy-1-phenylbutan-1-one. 166

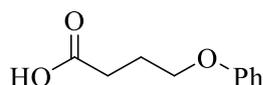


This compound is known.¹⁶⁶

To a solution of cyclopropyl phenyl ketone (1.46 g, 10.0 mmol) in MeOH (8.5 mL) was added dropwise conc. H₂SO₄ (0.436 mL, 802 mg, 8.18 mmol) and the solution was refluxed. After refluxing for 3 days, 0.1 mL of H₂SO₄ and 2 mL of MeOH was added and refluxed for a further 3 days. The solvent was then removed under reduced pressure and Et₂O (40 mL) and water (60 mL) were then added. The ether layer was separated and the aqueous layer extracted again with Et₂O (2 x 40 mL). The ether layers were combined, washed with sat. NaHCO₃ (40 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was then purified by column chromatography with gradient elution 0-5% EtOAc in hexanes to give the product as a clear oil (1.590 g, 8.93 mmol, 89%); δ_{H} (400 MHz, CDCl₃) 7.98 (2 H, d, *J* 7.7, *o*-ArH), 7.60 - 7.52 (1 H, m, *p*-ArH), 7.50 - 7.42 (2 H, m, *m*-ArH) 3.47 (2 H, t, *J* 5.9, CH₂OCH₃), 3.34 (3 H, s, OCH₃), 3.08 (2 H, t, *J* 7.2, CH₂CO) 2.03 (2 H, quin, *J* 6.5, CH₂CH₂OCH₃); δ_{C} (101 MHz, CDCl₃) 200.12, 137.17, 133.10, 128.70, 128.18, 71.92, 58.68, 35.23, 24.29.



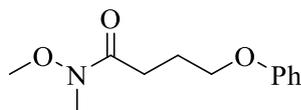
4-Phenoxybutanoic acid. 170



This compound is known.¹⁴⁹

To a suspension of sodium hydride (60% wt, 724 mg, 18.1 mmol) in DMF (18 mL) was added dropwise a solution of phenol (1.69 g, 18.0 mmol) in DMF (9 mL). After stirring for 1h, a solution of γ -butyrolactone (1.50 g, 17.4 mmol) in DMF (9 mL) was added dropwise and the resultant solution was stirred at 130 h for 6.5 h. The solution was cooled to rt and concentrated under reduced pressure. The residue was partitioned between DCM (150 mL) and water (150 mL) and the aqueous layer separated. The organic extract was then washed again with water (2 x 75 mL) and the aqueous extracts were combined and acidified with 1 M HCl (22.5 mL) to a pH of 2. EtOAc (150 mL) was added to the aqueous extract and the organic layer was collected. The aqueous layer was extracted again with EtOAc (2 x 75 mL) and the EtOAc extracts were combined. The EtOAc extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography in (0 – 33% EtOAc in hexane) gave the pure product as clear crystals (1.09 g, 6.05 mmol, 35%); δ_H (300 MHz, $CDCl_3$) 7.33 - 7.24 (2 H, m, ArH), 6.99 - 6.85 (3 H, m, ArH), 4.03 (2 H, t, J 6.0, CH_2OPh), 2.60 (2 H, t, J 7.2, CH_2COOH), 2.13 (2 H, quin, J 6.6, CH_2CH_2OPh).

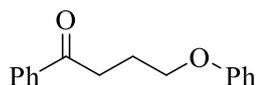
N-Methoxy-*N*-methyl-4-phenoxybutanamide. 171



This compound is known.¹⁶⁷

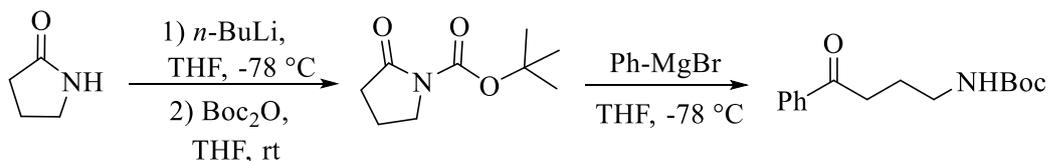
To a solution of 4-phenoxybutanoic acid (1.08 g, 5.99 mmol) in THF (8 mL) was added 1,1'-carbonyldiimidazole (1.07 g, 6.59 mmol) in one portion and stirred at rt for 2 h. Triethylamine (1.46 g, 2.02 mL, 14.5 mmol) was added to a separate solution containing N,O-dimethylhydroxylamine hydrochloride (643 mg, 6.59 mmol) in THF (3.5 mL) and stirred for 2 h. The acid containing solution was then added to the second solution and stirred at rt for 20 h. The solvent was removed under reduce pressure and re-dissolved in DCM (50 mL). The DCM extract was washed with 1 M HCl (15 mL) and water (20 mL). The organic extract was dried over MgSO₄, filtered and solvent removed under reduced pressure to give the product as a white solid (1.28 g, 5.72 mmol, 95%); δ_{H} (300 MHz, CDCl₃) 7.34 - 7.20 (2 H, m, ArH), 6.98 - 6.84 (3 H, m, ArH), 4.03 (2 H, t, *J* 6.0 CH₂OPh), 3.68 (3 H, s, OCH₃), 3.19 (3 H, s, NCH₃), 2.65 (2 H, t, *J* 7.1, CH₂CO), 2.13 (2 H, quin, *J* 6.6, CH₂CH₂OPh)

4-Phenoxy-1-phenylbutan-1-one. 172

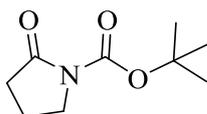


This compound is known.¹⁶⁸

N-Methoxy-*N*-methyl-4-phenoxybutanamide (1.28 g, 5.72 mmol) was dissolved in dry THF (33 mL) and cooled to -78 °C. Phenylmagnesium bromide (3 M in Et₂O, 2.00 mL, 6.00 mmol) was added dropwise over 30 min to the solution and the mixture was then allowed to warm to rt. After stirring for 2 h, the mixture was cooled to -78 °C and sat. NH₄Cl (30 mL) and EtOAc (50 mL) was added. After warming to rt, the organic extract was collected and the aqueous layer washed with EtOAc (2 x 50 mL). The organic extracts were combined, washed with brine, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The crude product was then purified by column chromatography with gradient elution 0-15% EtOAc in Pet. ether to give product xx as a white solid (1.248 g, 5.20 mmol, 91%); δ_{H} (300 MHz, CDCl₃) 7.99 (2 H, d, *J* 8.0, ArH), 7.61 - 7.52 (1 H, m, ArH), 7.51 - 7.41 (2 H, m, ArH), 7.34 - 7.26 (2 H, m, ArH), 7.00 - 6.85 (3 H, m, ArH), 4.08 (2 H, t, *J* 6.0, COCH₂), 3.22 (2 H, t, *J* 7.0, CH₂OPh), 2.25 (2 H, quin, *J* 6.6, CH₂CH₂OPh); δ_{C} (101 MHz, CDCl₃) 199.72, 158.98, 137.05, 133.17, 129.57, 128.71, 128.15, 120.81, 114.60, 66.92, 35.07, 23.94; MS (ESI⁺): *m/z* 263.2 [M+Na⁺]⁺, C₁₆H₁₆NaO₂ requires 263.1043 found 263.1040 (0.9 ppm error).



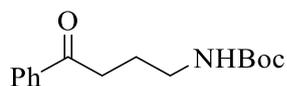
***tert*-Butyl 2-oxopyrrolidine-1-carboxylate. 175**



This compound is known.¹⁶⁹

A solution of 2-pyrrolidinone (851 mg, 10 mmol) in dry THF (20 mL) was cooled to -78 °C. *n*-BuLi (2.5 M in hexanes, 4.8 mL, 12 mmol) was added dropwise to the solution and stirred at -78 °C for 1 h. A solution of di-*tert*-butyl dicarbonate (2.40 g, 11 mmol) in dry THF (2.5 mL) was added dropwise to the pyrrolidinone containing solution and left to stir for 2 h. The solution was warmed to rt and sat. NH₄Cl (10 mL) and water (10 mL) were added. The organic layer was collected and extracted again with Et₂O (3 x 10 mL). Organic extracts were combined, dried over MgSO₄, filtered and concentrated under reduced pressure to afford the crude product. Purification by column chromatography in (20 – 30% EtOAc in Pet. Ether) gave the pure product (1.24 g, 6.70 mmol, 67%); δ_{H} (300 MHz, CDCl₃) 3.74 (2 H, t, *J* 7.2, CH₂NBoc), 2.51 (2 H, t, *J* 8.1, COCH₂), 1.99 (2 H, t, *J* 7.5, CH₂CH₂N), 1.53 (9 H, s, (CH₃)₃); δ_{C} (101 MHz, CDCl₃) 174.39, 150.33, 82.84, 46.56, 33.05, 28.12, 17.50.

***tert*-Butyl (4-oxo-4-phenylbutyl)carbamate. 176**

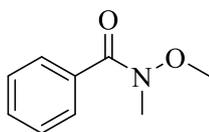


This compound is known.¹⁶⁹

A solution of lactam from the previous step (1.24 g, 6.70 mmol) in dry THF (26 mL) was cooled to -78 °C. Phenylmagnesium bromide (3 M in Et₂O, 2.35 mL, 7.05 mmol) was added dropwise over 1 h to the solution and the mixture was then allowed to warm to rt. 2 M HCl was added until the solution reached pH 2 and the mixture was extracted with DCM (3 x 40 mL). Organic extracts were combined, dried over MgSO₄, filtered

and concentrated under reduced pressure to afford the crude product. Purification by recrystallization in hot Pet. Ether gave the product as yellow crystals (1.16 g, 4.41 mmol, 66%); δ_{H} (300 MHz, CDCl_3) 7.96 (2 H, d, J 7.9, ArH), 7.56 (1 H, m, ArH), 7.51 - 7.41 (2 H, m, ArH), 4.64 (1 H, Br. s, NH), 3.29 - 3.16 (2 H, m, CH_2NH), 3.03 (2 H, t, J 7.1, COCH_2), 1.95 (2 H, quin, J 7.1, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.42 (9 H, s, $(\text{CH}_3)_3$); δ_{C} (101 MHz, CDCl_3) 199.87, 156.18, 136.93, 133.19, 128.70, 128.14, 79.24, 40.24, 35.84, 28.48, 24.62.

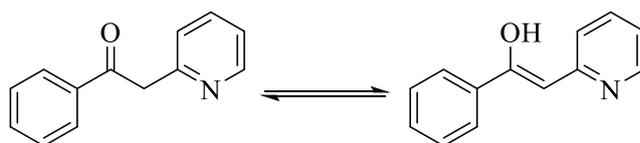
***N*-Methoxy-*N*-methylbenzamide. 250**



This compound is known.¹⁷⁰

Benzoyl chloride (280 mg, 2.00 mmol) was added dropwise to a solution containing *N*,*O* dimethylhydroxylamine hydrochloride (234 mg, 2.40 mmol) and pyridine (348 mg, 4.40 mmol) in DCM (7.5 mL). After stirring for 2 hours at room temperature, DCM (7.5 mL) was added and the reaction was quenched with 1 M HCl (15 mL). The organic layer was collected and the aqueous layer was further extracted with DCM (2 x 15 mL). The organic extracts were combined, dried over MgSO_4 , filtered and the solvent removed in vacuo by rotary evaporation to give the crude product (330 mg, 2.00 mmol) which was used without further purification in subsequent steps. δ_{H} (300 MHz, CDCl_3) 7.70 – 7.62 (2H, m, ArH), 7.48 – 7.35 (3H, m, ArH), 3.55 (3H, s, NCH_3), 3.35 (3H, s, OCH_3).

1-Phenyl-2-(pyridin-2-yl)ethan-1-one. 251



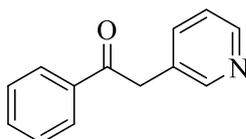
Keto-enol ratio 3:2

This compound is known.¹⁵⁵

A solution of 2-picoline (447 mg, 4.8 mmol, 0.47 mL) and *n*-BuLi (1.6 M in hexanes, 3 mL, 4.8 mmol) in anhydrous THF (5 mL) was stirred for 30 min and added dropwise to a solution of the Weinreb amide **250** in anhydrous THF (10 mL) at -78 °C. After

stirring at rt for 4 h, the reaction was quenched with sat. NH_4Cl (30 mL) and the product extracted with EtOAc (3 x 30 mL). The organic extracts were combined, dried over MgSO_4 , filtered and the solvent removed under reduced pressure to give the product. Purification by column chromatography (0-40% EtOAc in Pet. Ether) yielded the product as a yellow solid (705 mg, 3.58 mmol, 89%); Ketone: δ_{H} (400 MHz, CDCl_3) 8.56 (1H, d, J 4.2, Py-NCH), 8.10 – 8.04 (2H, m, py-CH), 7.49 – 7.36 (4H, m, ArH), 7.31 (1H, d, J 7.8, ArH), 7.17 (1H, dd, J 6.8, 5.2, ArH), 4.50 (2H, s, COCH_2); Enol: δ_{H} (400 MHz, CDCl_3) 15.48 (1H, s, OH), 8.29 (1H, d, J 5.1, ArH), 7.87 – 7.82 (2H, m, ArH), 7.68 – 7.53 (4H, m, ArH), 7.07 (1H, d, J 8.1 Hz, ArH), 7.01 – 6.94 (1H, m, ArH), 6.08 (1H, s, C=CH).

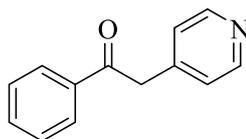
1-Phenyl-2-(pyridin-3-yl)ethan-1-one. **253**



This compound is known.¹⁵⁵

To a solution of 3-picoline (228 mg, 2.40 mmol) in THF (7.5 mL) was added lithium diisopropylamide mono(tetrahydrofuran) solution (1.60 mL, 1.50 M in cyclohexane, 2.40 mmol) at $-78\text{ }^\circ\text{C}$ and the solution was warmed to rt. After stirring for 30 min, the picoline solution was added dropwise to a solution of the Weinreb amide **250** (330 mg, 2.00 mmol) in THF (7.50 mL) and stirred overnight. The reaction was cooled to $0\text{ }^\circ\text{C}$ and quenched by slow addition of water (25 mL) and EtOAc (25 mL). The organic layer was collected and the aqueous layer was further extracted with EtOAc (2 x 25 mL). The organic extracts were combined, dried over MgSO_4 , filtered and the solvent removed *in vacuo* by rotary evaporation to give the crude product. Purification by column chromatography gradient elution 0-50% EtOAc in hexane gave the product as an oil (160 mg, 0.81 mmol, 41%); δ_{H} (300 MHz, CDCl_3) 8.53 (2H, s, ArH), 8.02 (2H, d, J 7.8, ArH), 7.60 (2H, t, J 7.6, 1H), 7.54 – 7.44 (2H, m, ArH), 7.33 – 7.26 (1H, m, ArH), 4.31 (2H, s, CH_2).

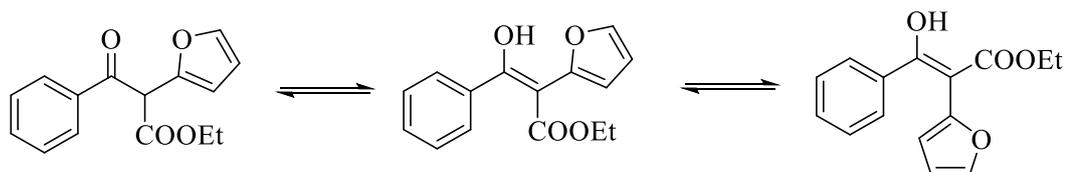
1-Phenyl-2-(pyridin-4-yl)ethan-1-one. 254



This compound is known.¹⁵⁵

To a solution of 4-picoline (228 mg, 3.60 mmol) in THF (10 mL) was added lithium diisopropylamide mono(tetrahydrofuran) solution (2.4 mL, 1.50 M in cyclohexane, 3.60 mmol) at $-78\text{ }^{\circ}\text{C}$ and the solution was warmed to rt. After stirring for 30 min, the picoline solution was added dropwise to a solution of the Weinreb amide **250** (495 mg, 3.00 mmol) in THF (5.0 mL) and stirred overnight. The reaction was cooled to $0\text{ }^{\circ}\text{C}$ and quenched by slow addition of water (25 mL) and EtOAc (25 mL). The organic layer was collected and the aqueous layer was further extracted with EtOAc (2 x 25 mL). The organic extracts were combined, dried over MgSO_4 , filtered and the solvent removed *in vacuo* by rotary evaporation to give the crude product. Purification by column chromatography gradient elution 0-50% EtOAc in hexane gave the product as an oil (546 mg, 2.77 mmol, 92%); δ_{H} (400 MHz, CDCl_3) δ 8.56 (2H, d, J 5.2, ArH), 7.99 (2H, d, J 7.8, ArH), 7.59 (1H, t, J 7.0, ArH), 7.48 (2H, t, J 7.8, ArH), 7.20 (2H, d, J 5.2, ArH), 4.28 (2H, s, CH_2); δ_{C} (101 MHz, CDCl_3) 196.01, 150.09, 143.54, 136.33, 133.77, 128.95, 128.60, 125.02, 44.69.

Ethyl 2-(furan-2-yl)-3-oxo-3-phenylpropanoate. 257

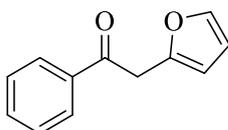


This compound is known.¹⁷¹

Ethyl benzoyl acetate (576 mg, 3.00 mmol) was added to zinc chloride (300 mg, 2.20 mmol) in H_2O (3 mL) and acetic acid (0.75 mL). The mixture was heated to $100\text{ }^{\circ}\text{C}$ and 2,5-dihydro-2,5-dimethoxyfuran (390 mg, 3.00 mmol) was added dropwise. After refluxing for 1 h, the reaction was cooled to rt and water (30 mL) was added. The product was extracted from the mixture with EtOAc (3 x 30 mL) then organic layers were combined, dried over MgSO_4 , filtered and the solvent removed *in vacuo* by rotary evaporation to give the crude product. Purification by column chromatography

gradient elution 0-10% EtOAc in Pet. ether gave the product as an orange solid (382 mg, 1.48 mmol, 49%); this product is a mixture of isomers and the ketone is the major isomer. Ketone data: δ_{H} (400 MHz, CDCl_3) 7.99 (2H, d, J 7.8, ArH), 7.60 (1H, t, J 7.4, ArH), 7.49 (2H, d, J 7.7, ArH), 7.29 (1H, s, Furan-H), 6.44 (1H, d, J 3.2, Furan-H), 6.42 – 6.36 (1H, m, Furan-H), 5.73 (1H, s, CHCO_2Et), 4.27 (2H, q, J 7.1, OCH_2), 1.27 (3H, t, J 7.1, CH_3).

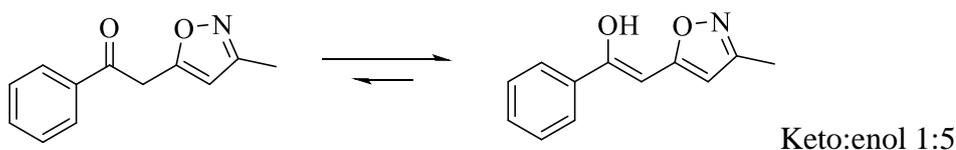
1-Phenyl-2-(furan-2-yl)ethan-1-one. 258



This compound is known.¹⁷¹

LiCl (185 mg, 4.41 mmol) was added to a solution of compound **JB557** (380 mg, 1.47 mmol) in DMF (1.0 mL) and acetic acid (0.2 mL). The mixture was refluxed for 4 hours, TLC indicated full consumption of starting material, and was then cooled to rt. The reaction mixture was quenched with H_2O (20 mL) and Et_2O (20 mL). The organic layer was extracted and the aqueous layer was further extracted with Et_2O (2 x 15 mL). The organic extracts were combined, dried over MgSO_4 , filtered and the solvent removed *in vacuo* by rotary evaporation to give the crude product. Purification by column chromatography gradient elution 0-10% EtOAc in Pet. ether gave the product as a clear oil (244 mg, 1.31 mmol, 89%); δ_{H} (400 MHz, CDCl_3) 8.01 (2H, d, J 7.2, ArH), 7.61 – 7.53 (1H, m, ArH), 7.47 (2H, t, J 7.7, ArH), 7.39 – 7.34 (1H, m, Furan-H), 6.37 – 6.31 (1H, m, Furan-H), 6.24 (1H, d, J 3.2, Furan-H), 4.31 (2H, s, CH_2); δ_{C} (101 MHz, CDCl_3) 195.19, 148.41, 142.22, 136.36, 133.52, 128.81, 128.73, 110.81, 108.44, 38.56.

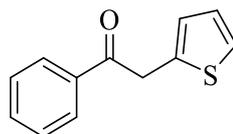
1-Phenyl-2-(3-methylisoxazol-5-yl)ethan-1-one. 259



This compound is known.¹⁷²

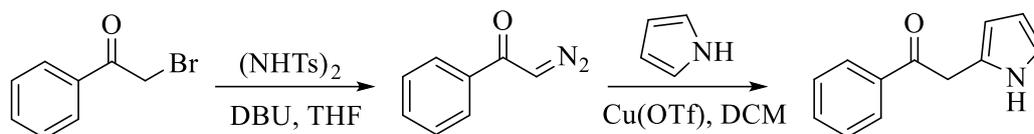
To a solution of 3,5-dimethylisoxazole (243 mg, 2.50 mmol) in dry THF (5 mL) at -78 °C was added dropwise n-BuLi (2.5 M in hexanes, 1.10 mL, 2.75 mmol). The solution was warmed to rt and stirred for 30 minutes. The solution was cooled to -78 °C and benzonitrile (309 mg, 3.00 mmol) was added in one portion. After stirring overnight, sat. NH₄Cl (20 mL) was added and the mixture extracted with EtOAc (3 x 25 mL). The organic extracts were combined, dried over MgSO₄, filtered and the solvent removed *in vacuo* by rotary evaporation to give the crude product. Purification by column chromatography gradient elution 0-15% EtOAc in Pet. ether gave the product as a white solid (287 mg, 1.43 mmol, 57%); Enol data: δ_{H} (400 MHz, CDCl₃) 7.62 – 7.56 (2H, m, ArH), 7.45 – 7.39 (3H, m, ArH), 5.76 (1H, s, CH-enol), 5.40 (1H, s, CH-isoxazole), 5.19 (1H, bs, OH), 2.30 (3H, s, CH₃); δ_{C} (101 MHz, CDCl₃) 170.41, 159.64, 148.56, 138.88, 129.49, 128.87, 126.20, 98.90, 85.14, 11.37.

1-Phenyl-2-(thiophen-2-yl)ethan-1-one. 260

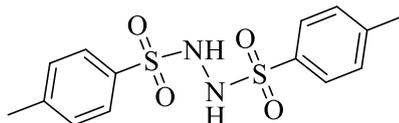


This compound is known.¹⁵⁶

To a solution of methyl benzoate (408 mg, 3.00 mmol) and 2-thiophene carboxylic acid (426 mg, 3.00 mmol) in DMF (20 mL) was added potassium bis(trimethylsilyl)amide solution (20 mL, 0.5 M in toluene, 10.0 mmol) at 0 °C. After stirring overnight at rt, the reaction was cooled to 0 °C and quenched with sat. NH₄Cl (50 mL) followed by extraction with EtOAc (3 x 50 mL). The organic extracts were combined, dried over MgSO₄, filtered and the solvent removed *in vacuo* by rotary evaporation to give the crude product. Purification by column chromatography gradient elution 0-10% EtOAc in Pet. ether gave the product as a yellow solid (570 mg, 2.82 mmol, 94%); δ_{H} (400 MHz, CDCl₃) 8.09 – 7.99 (2H, m, ArH), 7.59 (1H, t, *J* 7.5, ArH), 7.48 (2H, t, *J* 7.6, ArH), 7.23 (1H, dd, *J* 5.1, 1.0, Thiophene-H), 7.01 – 6.96 (1H, m, Thiophene-H), 6.95 – 6.90 (1H, m, Thiophene-H), 4.49 (2H, s, CH₂); δ_{C} (101 MHz, CDCl₃) 196.12, 136.25, 135.66, 133.54, 128.85, 128.72, 127.04, 126.94, 125.23, 39.53.



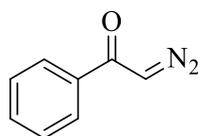
4-Methyl-N'-tosylbenzenesulfonohydrazide.



This compound is known.¹⁷³

A mixture of p-toluenesulfonyl hydrazide (1.86 g, 10 mmol) and p-toluenesulfonyl chloride (2.48 g, 13 mmol) in DCM (10.5 mL) was cooled to 0 °C. Pyridine (1.03 g, 1.05 mL, 13 mmol) was added dropwise and the solution was stirred for 30 min at rt. The solution was then cooled to 0 °C, n-hexane (15 mL) and H₂O (25 mL) was added and stirred for 15 min. The precipitate formed was filtered and washed with ice-cold Et₂O (15 mL). The remaining solid was dissolved in boiling acetone (24 mL) and H₂O (11 mL) was added slowly. Upon cooling in an ice-bath a precipitate formed that was filtered and washed with ice-cold Et₂O. The precipitate was dried under reduced pressure to give a white solid (1.795 g, 5.28 mmol, 53%); δ_{H} (400 MHz, DMSO) 9.57 (2H, s, NH), 7.64 (4H, d, *J* 8.2, ArH), 7.38 (4H, d, *J* 8.1, ArH), 2.40 (6H, s, CH₃).

2-Diazo-1-phenylethan-1-one. 261

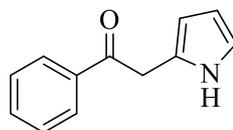


This compound is known.¹⁷⁴

A mixture of 4-methyl-N'-tosylbenzenesulfonohydrazide (1.12 g, 3.30 mmol) and 2-bromoacetophenone (597 mg, 3.00 mmol) in dry THF (15 mL) was cooled to 0 °C. DBU (684 mg, 4.50 mmol) was added dropwise to the solution and left to stir for 20 min. The reaction mixture was concentrated *in vacuo* by rotary evaporation to give the crude product. Purification by column chromatography gradient elution 0-20% EtOAc in Pet. ether gave the product as a yellow solid (170 mg, 1.16 mmol, 39%); δ_{H} (400

MHz, CDCl₃) 7.76 (2H, d, *J* 7.5, ArH), 7.54 (1H, t, *J* 7.5, ArH), 7.45 (2H, t, *J* 7.5, ArH), 5.90 (1H, s, CHN₂).

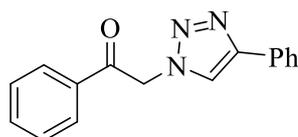
1-Phenyl-2-(1H-pyrrol-2-yl)ethan-1-one. 262



This compound is known.¹⁷⁵

To a solution of pyrrole (78.0 mg, 1.16 mmol) and 2-diazo-1-phenylethan-1-one (170 mg, 1.16 mmol) in dry DCM (5 mL) under N₂ was added Cu(OTf)₂ (21 mg, 58 μmol). After stirring for 4 h, the mixture was diluted with H₂O (10 mL) and extracted with DCM (3 x 10 mL). The organic extracts were combined, dried over MgSO₄, filtered and the solvent removed *in vacuo* by rotary evaporation to give the crude product. Purification by column chromatography gradient elution 0-10% EtOAc in Pet. ether gave the product as a brown solid (71 mg, 0.38 mmol, 33%); δ_H (400 MHz, CDCl₃) 8.88 (1H, s, NH), 8.06 – 8.00 (2H, m, ArH), 7.59 (1H, t, *J* 7.4, ArH), 7.48 (2H, t, *J* 7.6, ArH), 6.77 (1H, dd, *J* 4.1, 2.7, Pyrr-H), 6.16 (1H, dd, *J* 5.8, 2.7, Pyrr-H), 6.07 (1H, s, Pyrr-H), 4.33 (2H, s, CH₂); δ_C (101 MHz, CDCl₃) 197.89, 136.51, 133.62, 128.86, 128.62, 124.10, 118.00, 108.41, 107.61, 37.09.

1-Phenyl-2-(4-phenyl-1,2,3-triazol-1-yl)ethan-1-one. 272

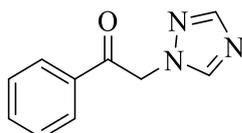


This compound is known.¹⁷⁶

Sodium azide (273 mg, 4.20 mmol) was added to a solution containing 2-bromoacetophenone (798 mg, 4.00 mmol) and phenylacetylene (408 mg, 4.00 mmol) in 1:1 ^tBuOH/H₂O (12 mL). Copper (II) sulfate pentahydrate (50 mg, 0.20 mmol) and sodium ascorbate (79 mg, 0.40 mmol) were added sequentially to the mixture and left to stir at 60 °C for 5 h. The reaction was cooled to rt and poured into ice-cold water (40 mL) and a 10% ammonium hydroxide solution (10 mL) was added. Upon stirring a solid precipitate formed that was collected by filtration to give the crude product. Purification by column chromatography gradient elution 50% EtOAc in hexane gave the product as an off-white solid (960 mg, 3.65 mmol, 91%); δ_H (400 MHz, CDCl₃)

8.05 – 7.91 (3H, m, ArH), 7.82 (2H, d, J 7.7, ArH), 7.65 (1H, t, J 7.4, ArH), 7.51 (2H, t, J 7.7, ArH), 7.40 (2H, t, J 7.4, ArH), 7.32 (1H, t, J 7.3, ArH), 5.88 (2H, s, CH₂); δ_C (101 MHz, CDCl₃ + MeOD) 190.52, 134.73, 133.98, 130.42, 129.26, 128.94, 128.36, 128.25, 125.86, 55.63.

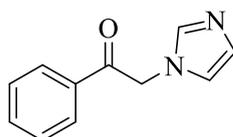
1-phenyl-2-(1H-1,2,4-triazol-1-yl)ethan-1-one. 273



This compound is known.¹⁷⁷

To a solution of 2-bromoacetophenone (1.09 g, 5.50 mmol) and triethylamine (556 mg, 5.50 mmol) in acetone (10 mL) was added 1,2,4-triazole (345 mg, 5.0 mmol). After stirring overnight the solution was filtered and the solvent removed under reduced pressure. Water (50 mL) and DCM (50 mL) were added and the organic layer was separated. The aqueous layer was washed again with DCM (2 x 50 mL) and the organic extracts were combined. They were then dried over MgSO₄, filtered and the solvent removed *in vacuo* by rotary evaporation to give the crude product. Purification by column chromatography gradient elution 0-50% EtOAc in Pet. ether gave the product as an off-white solid (416 mg, 2.22 mmol, 44%); δ_H (400 MHz, CDCl₃) 8.26 (1H, s, ArH), 7.99 (2H, d, J 5.3, ArH), 7.97 (1H, s, ArH), 7.66 (1H, t, J 7.5, ArH), 7.53 (2H, t, J 7.5 Hz, ArH), 5.68 (2H, s, CH₂); δ_C (101 MHz, CDCl₃) 190.66, 151.94, 144.96, 134.68, 134.11, 129.28, 128.22, 55.15.

1-Phenyl-2-(imidazol-1-yl)ethan-1-one. 274

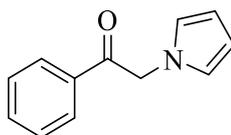


This compound is known.¹⁷⁸

To a solution of imidazole (428 mg, 6.30 mmol) in DCM (5 mL) was added portionwise 2-bromoacetophenone (597 mg, 3.00 mmol). After stirring for 3 h the mixture was diluted with DCM (10 mL) and quenched with H₂O (10 mL). The organic layer was separated and washed with brine causing a white solid to precipitate that

was removed by filtration. The solvent was removed *in vacuo* by rotary evaporation to give the product as a brown solid (290 mg, 1.56 mmol, 52%); δ_{H} (400 MHz, CDCl_3) 7.96 (2H, d, J 7.9 Hz, ArH), 7.65 (1H, t, J 7.4 Hz, ArH), 7.57 – 7.48 (3H, m, ArH), 7.12 (1H, s, ArH), 6.94 (1H, s, ArH), 5.40 (2H, s, CH_2); δ_{C} (101 MHz, CDCl_3) 191.74, 138.24, 134.48, 134.27, 129.59, 129.22, 128.07, 120.42, 52.59.

1-Phenyl-2-(pyrrol-1-yl)ethan-1-one. 275



This compound is known.¹⁷⁹

NaH (60% wt, 120 mg, 3.00 mmol) was added portionwise to a solution of pyrrole (201 mg, 3.00 mmol) in dry DMF (15 mL). After stirring for 1 h, 2-bromoacetophenone (597 mg, 3.00 mmol) was added to the mixture and was left to stir at rt overnight. The reaction was quenched with water (50 mL) followed by extraction with Et_2O (3 x 50 mL). The organic extracts were combined and washed with water (50 mL) and brine (50 mL). The organic extract was dried over MgSO_4 , filtered and the solvent removed under reduced pressure to give the crude product. Purification by column chromatography gradient elution 0-10% EtOAc in Pet. ether gave the product as a light brown solid (104 mg, 0.56 mmol, 19%); δ_{H} (400 MHz, CDCl_3) 7.97 (2H, d, J 7.7, ArH), 7.63 (1H, t, J 7.3, ArH), 7.51 (2H, t, J 7.7, ArH), 6.68 (2H, s, Pyrrole-H), 6.26 (2H, s, Pyrrole-H), 5.32 (2H, s, CH_2); δ_{C} (101 MHz, CDCl_3) 193.48, 134.85, 134.05, 129.07, 128.11, 122.05, 109.20, 55.52.

1-Phenyl-2-(benzo[d]thiazol-2-yl)ethan-1-one. 280



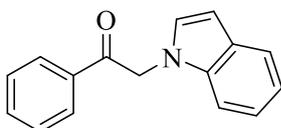
Keto:enol 5:4

This compound is known.¹⁸⁰

A solution containing ethylbenzoyl acetate (384 mg, 2.00 mmol) and 2-aminothiophenol (250 mg, 2.00 mmol) in toluene (6 mL) was refluxed overnight. The

solvent was removed *in vacuo* by rotary evaporation to give the crude product. Purification by column chromatography gradient elution 0-20% EtOAc in Pet. ether gave the product as a yellow solid (321 mg, 1.27 mmol, 63%); Ketone isomer δ_{H} (400 MHz, CDCl_3) 8.09 (2H, d, J 6.6, ArH), 8.03 (1H, d, J 7.6, ArH), 7.89 (3H, d, J 3.0, ArH), 7.64 – 7.57 (1H, m, ArH), 7.52 – 7.40 (2H, m, ArH), 4.84 (2H, s, CH_2). Note: 6.38 (1H, s, enol-CH).

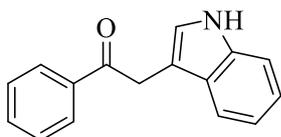
1-Phenyl-2-(indol-1-yl)ethan-1-one. 281



This compound is known.¹⁷⁹

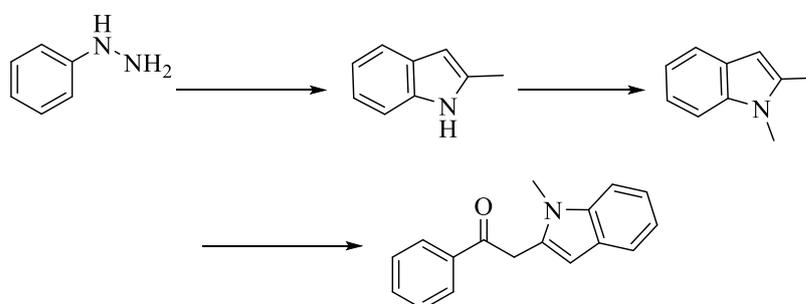
A solution of indole (468 mg, 4.00 mmol) in DMF (24 mL) was cooled to 0°C and NaH (60% wt, 320 mg, 8.00 mmol) was added portionwise. After stirring at rt for 1h, 2-bromoacetophenone (796 mg, 4.00 mmol) was added and left to stir overnight. The reaction was quenched with water (50 mL) followed by extraction with Et_2O (3 x 50 mL). The organic extracts were combined and washed with water (50 mL) and brine (50 mL). The organic extract was dried over MgSO_4 , filtered and the solvent removed under reduced pressure to give the crude product. Purification by column chromatography gradient elution 0-10% EtOAc in Pet. ether gave the product as a yellow solid (194 mg, 0.83 mmol, 21%); δ_{H} (400 MHz, CDCl_3) 8.01 (2H, d, J 7.6, ArH), 7.70 – 7.61 (2H, m, ArH), 7.53 (2H, t, J 7.7, ArH), 7.22 – 7.18 (2H, m, ArH), 7.17 – 7.10 (2H, m, ArH), 6.63 (1H, d, J 3.1, ArH), 5.50 (2H, s, CH_2); δ_{C} (101 MHz, CDCl_3) 193.25, 136.80, 134.89, 134.13, 129.11, 129.04, 128.78, 128.16, 122.10, 121.32, 119.89, 109.06, 102.63, 52.38.

1-Phenyl-2-(1H-indol-3-yl)ethan-1-one. 283

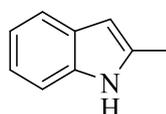


This compound is known.¹⁵⁷

To a cooled solution of [hydroxy(tosyloxy)iodo]benzene (600 mg, 1.53 mmol) in dry DCM (8 mL) at -78 °C was added BF₃•OEt₂ (690 mg, 4.86 mmol). The solution was warmed to rt until the formation of a yellow solution that was then cooled again to -78 °C. A solution of α -(trimethylsiloxy)styrene (240 mg, 1.25 mmol) in dry DCM (4 mL) was added dropwise to the yellow solution. After 5 min a solution of indole (294 mg, 2.00 mmol) in dry DCM (4 mL) was added dropwise. The mixture was warmed to -61 °C and stirred for 30 min before being quenched by the addition of water. The mixture was raised to rt and extracted with DCM (3 x 25 mL). The organic extracts were combined, dried over MgSO₄, filtered and the solvent removed *in vacuo* by rotary evaporation to give the crude product. Purification by column chromatography gradient elution 0-10% EtOAc in Pet. ether gave the product as a white solid. (128 mg, 0.54 mmol, 44%); δ_{H} (400 MHz, CDCl₃) 8.16 (1H, bs, NH), 8.07 (2H, d, *J* 7.6, ArH), 7.63 (1H, d, *J* 7.8, ArH), 7.57 – 7.53 (1H, m, ArH), 7.45 (2H, t, *J* 7.8, ArH), 7.36 – 7.31 (1H, m, ArH), 7.23 – 7.11 (2H, m, ArH), 7.07 (1H, s, ArH), 4.42 (2H, s, CH₂); δ_{C} (101 MHz, CDCl₃) 198.11, 136.79, 136.26, 133.16, 128.76, 128.72, 127.44, 123.38, 122.31, 119.80, 118.86, 111.40, 108.95, 35.68.



2-Methyl-1H-indole. 284

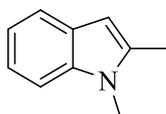


This compound is known.¹⁸¹

To a stirring solution of phenylhydrazine (2.5 mL, 25.4 mmol) was added slowly acetone (3.82 mL, 50.8 mmol). The exothermic reaction was cooled to rt and ZnCl₂ (6.92 g, 50.8 mmol) was added and the temperature was raised slowly to 190 °C (Note: An exothermic reaction initiates above 130 °C). After stirring for 20 min, the mixture was cooled to rt followed by addition of H₂O (100 mL) and extraction with EtOAc (3

x 100 mL). The organic extracts were combined, dried over MgSO₄, filtered and the solvent removed *in vacuo* by rotary evaporation to give the crude product. Purification by column chromatography gradient elution 0-10% EtOAc in Pet. ether gave the product as an off-white solid (1.63 g, 12.4 mmol, 49%); δ_{H} (400 MHz, CDCl₃) 7.95 – 7.67 (1H, bs, NH), 7.57 (1H, d, *J* 7.5, ArH), 7.31 (1H, d, *J* 7.9, ArH), 7.19 – 7.09 (2H, m, ArH), 6.27 (1H, s, ArH), 2.47 (3H, s, CH₃); δ_{C} (101 MHz, CDCl₃) 136.17, 135.17, 129.19, 121.04, 119.74, 110.33, 100.50, 13.82.

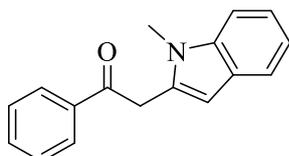
1,2-Dimethylindole. 285



This compound is known.¹⁸²

To a solution of 2-methyl-1*H*-indole (377 mg, 2.88 mmol) in dry THF (10 mL) was added NaH (60% wt, 173 mg, 4.32 mmol). After stirring for 1.5 h, the solution was cooled to 0 °C and methyl iodide (406 mg, 2.88 mmol) was added. The reaction was left to stir overnight and was quenched with sat. NH₄Cl (50 mL). Following extraction with EtOAc (3 x 50 mL), the organic extracts were combined, dried over MgSO₄, filtered and the solvent removed *in vacuo* by rotary evaporation to give the crude product. Purification by column chromatography gradient elution 0-4% EtOAc in Pet. ether gave the product as an off-white solid (312 mg, 2.15 mmol, 75%); δ_{H} (400 MHz, CDCl₃) 7.56 (1H, d, *J* 7.7, ArH), 7.32 – 7.26 (1H, m, ArH), 7.19 (1H, t, *J* 7.5, ArH), 7.14 – 7.06 (1H, m, ArH), 6.21 (1H, bs, ArH), 3.68 (3H, s, NCH₃), 2.46 (3H, s, CH₃); δ_{C} (101 MHz, CDCl₃) 137.43, 136.90, 128.06, 120.53, 119.72, 119.34, 108.82, 29.46, 12.87.

1-Phenyl-2-(1-methyl-indol-2-yl)ethan-1-one. 286



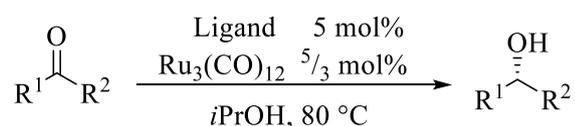
This compound is known.¹⁸³

To a solution of 1,2-dimethylindole (196 mg, 1.35 mmol) in dry THF (8 mL) at -78 °C was added dropwise n-BuLi (2.5 M in hexanes, 568 μ L, 1.42 mmol). After stirring at -78 °C for 1 h, benzonitrile (167 mg, 1.62 mmol) was added in one portion. After stirring overnight, sat. NH₄Cl (15 mL) was added and the mixture extracted with EtOAc (3 x 15 mL). The organic extracts were combined, dried over MgSO₄, filtered and the solvent removed *in vacuo* by rotary evaporation to give the crude product. Purification by column chromatography gradient elution 0-15% EtOAc in Pet. ether gave the product as a white solid (156 mg, 0.63 mmol, 46%); δ_{H} (400 MHz, CDCl₃) 8.07 (2H, d, *J* 7.7, ArH), 7.64 – 7.54 (2H, m, ArH), 7.50 (2H, t, *J* 7.7, ArH), 7.31 (1H, d, *J* 8.2, ArH), 7.21 (1H, t, *J* 7.5, ArH), 7.10 (1H, t, *J* 7.5, ArH), 6.40 (1H, s, CH-Indole), 4.47 (2H, s, CH₂), 3.70 (3H, s, NCH₃); δ_{C} (101 MHz, CDCl₃) 195.95, 137.86, 136.31, 133.64, 133.42, 128.88, 128.71, 127.81, 121.37, 120.31, 119.58, 109.24, 102.23, 37.83, 30.15.

7.3. Alcohol Products

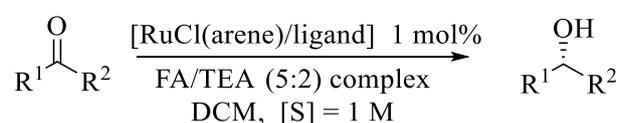
General reduction procedures

Tridentate ligand reductions (Method 1A)



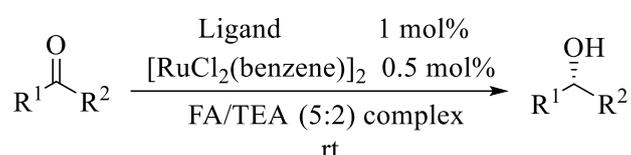
A mixture of ligand (5 mol%) and Ru₃(CO)₁₂ (⁵/₃ mol%) in *i*PrOH (10 mL) was stirred at 80 °C under an inert atmosphere for 30 min in a Schlenk tube. Ketone (1 mmol) was then added to the solution and the resulting mixture was stirred at 80 °C for 72 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (0 – 50% EtOAc in Pet. Ether). Enantiomeric excess was determined by GC or chiral HPLC.

[RuCl(arene)/(ligand)] reductions (Method 1B).



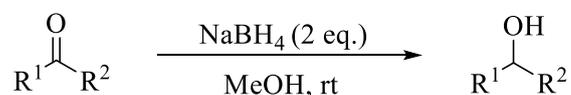
Catalyst (1 mol%) in FA/TEA 5:2 complex (0.5 mL) was stirred under an inert atmosphere at rt for 15 min. The ketone (1 mmol) in DCM (0.5 mL) was then added to the mixture and stirred at rt. Sat. NaHCO₃ (10 mL) was added and the product extracted with EtOAc (10 mL). The aqueous layer was further extracted with EtOAc (2 x 10 mL). Organic fractions were then combined, dried over MgSO₄, filtered and the solvent removed under pressure. The crude products were purified by column chromatography (0 – 50% EtOAc in Pet. Ether). Enantiomeric excess was determined by chiral GC or HPLC.

***In situ* procedure (Method 1C).**



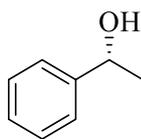
To a Schlenk tube charged with [RuCl₂(Benzene)]₂ (2.50 mg, 0.5 mmol) and ligand (1 mmol) was added formic acid/triethylamine 5:2 complex (0.5 mL). After stirring for 30 min, the ketone (1 mmol) was added and left to stir. Upon completion, NaHCO₃ (10 ml) was added and the product was extracted with EtOAc (3 x 10 mL). The organic extracts were combined, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The crude products were purified by column chromatography (0 – 50% EtOAc in Pet. Ether). Enantiomeric excess was determined by chiral GC or HPLC.

Racemic alcohols procedure.



To a solution of ketone (1 eq.) in MeOH (0.1 M) was added NaBH₄ (2 eq.) portion-wise. The solution was stirred at rt until the ketone had consumed. The solvent was then removed under reduced pressure and the residue partitioned between water and EtOAc. The organic extract was collected and the aqueous layer extracted a further 2 times with EtOAc. Organic layers were combined, dried over MgSO₄, filtered and the solvent removed under reduced pressure. Products were purified by column chromatography gradient elution 0-40% EtOAc in Pet. ether.

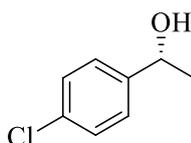
(R)-1-Phenylethan-1-ol



This compound is known.¹⁸⁴

δ_{H} (300 MHz, CDCl_3) 7.42 - 7.32 (4 H, m, ArH), 7.32 - 7.27 (1 H, m, ArH), 4.90 (1 H, q, J 6.4, CHOH), 1.94 (1 H, br. s, OH), 1.50 (3 H, d, J 6.4, CH_3); δ_{C} (101 MHz, CDCl_3) 145.94, 128.63, 127.60, 125.51, 70.54, 25.28; $[\alpha]^{28} +54.3$ (c 0.25 in CHCl_3) 94% ee (R) (lit.¹⁸⁴ $[\alpha]^{28}$: +58.1 (c 0.73 in CH_2Cl_2) 96.3% ee (R)); GC analysis (CHROMPAC CYCLODEXTRIN- β -236M-19, 50 m \times 0.25 mm \times 0.25 μm , gas H_2 , $T = 110$ $^\circ\text{C}$, $P = 15$ psi, FID temp 250 $^\circ\text{C}$, injector temp 220 $^\circ\text{C}$, ketone 9.82 min., R isomer 15.51 min., S isomer 16.50 min.)

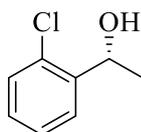
(R)-1-(4-Chlorophenyl)ethan-1-ol.



This compound is known.¹⁸⁵

δ_{H} (300 MHz, CDCl_3) 7.34 - 7.29 (4 H, m, ArH), 4.93 - 4.84 (1 H, m, CHOH), 1.87 - 1.80 (1 H, br. m, OH), 1.48 (3 H, d, J 6.4, CH_3); δ_{C} (101 MHz, CDCl_3) 144.37, 133.19, 128.72, 126.92, 69.86, 25.38; $[\alpha]^{26} +37.8$ (c 0.2 in CHCl_3) 87% ee (R) (lit.¹⁸⁵ $[\alpha] +51.7$ (c 0.23 in CHCl_3) 94% ee (R)); GC analysis (CHROMPAC CYCLODEXTRIN- β -236M-19, 50 m \times 0.25 mm \times 0.25 μm , gas H_2 , $T = 125$ $^\circ\text{C}$, $P = 15$ psi, FID temp 250 $^\circ\text{C}$, injector temp 220 $^\circ\text{C}$, ketone 14.82 min., R isomer 27.56 min., S isomer 29.77 min.)

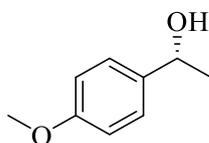
(R)-1-(2-Chlorophenyl)ethan-1-ol.



This compound is known.¹⁸⁵

δ_{H} (300 MHz, CDCl_3) 7.60 (1 H, d, J 7.61, ArH), 7.37 - 7.27 (2 H, m, ArH), 7.24 - 7.16 (1 H, m, ArH), 5.34 - 5.26 (1 H, m, CHOH), 1.97 (1 H, d, J 3.2, OH), 1.50 (3 H, d, J 6.3, CH_3); δ_{C} (101 MHz, CDCl_3) 143.19, 131.78, 129.53, 128.53, 127.34, 126.54, 67.10, 23.63; $[\alpha]^{28} +37.8$ (c 0.4 in CHCl_3) 57% ee (R) (lit.¹⁸⁵ $[\alpha] +64.8$ (c 0.42 in CHCl_3) 88% ee (R)); GC analysis (CHROMPAC CYCLODEXTRIN- β -236M-19, 50 m \times 0.25 mm \times 0.25 μm , gas H_2 , T = 150 $^\circ\text{C}$, P = 15 psi, FID temp 250 $^\circ\text{C}$, injector temp 220 $^\circ\text{C}$, ketone 6.12 min., R isomer 8.84 min., S isomer 9.47 min.)

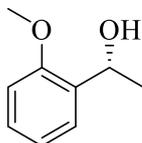
(R)-1-(4-Methoxyphenyl)ethan-1-ol



This compound is known.¹⁸⁵

δ_{H} (300 MHz, CDCl_3) 7.33 - 7.28 (2 H, m, ArH), 6.92 - 6.86 (2 H, m, ArH), 4.86 (1 H, qd, J 6.5, 3.6, CHOH), 3.81 (3 H, s, OCH_3), 1.73 (1 H, br. s, OH), 1.48 (3 H, d, J 6.5, CH_3); δ_{C} (101 MHz, CDCl_3) 159.11, 138.14, 126.79, 113.98, 70.10, 55.42, 25.14; $[\alpha]^{25} +49.1$ (c 0.2 in CHCl_3) 87% ee (R) (lit.¹⁸⁵ $[\alpha] +58.3$ (c 0.53 in CHCl_3) 96% ee (R)); GC analysis (CHROMPAC CYCLODEXTRIN- β -236M-19, 50 m \times 0.25 mm \times 0.25 μm , gas H_2 , T = 120 $^\circ\text{C}$, P = 15 psi, FID temp 250 $^\circ\text{C}$, injector temp 220 $^\circ\text{C}$, ketone 36.18 min., R isomer 39.16 min., S isomer 41.02 min.)

(R)-1-(2-Methoxyphenyl)ethan-1-ol

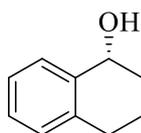


This compound is known.¹⁸⁶

δ_{H} (300 MHz, CDCl_3) 7.38 (1 H, d, J 7.5, ArH), 7.32 - 7.27 (1 H, m, ArH), 7.00 (1 H, t, J 7.5, ArH), 6.92 (1 H, d, J 8.2, ArH), 5.13 (1 H, quin, J 6.2, CHOH), 3.91 (3 H, s, OCH_3), 2.66 (1 H, d, J 5.3, OH), 1.55 (3 H, d, J 6.5, CHOH CH_3); δ_{C} (101 MHz, CDCl_3) 156.69, 133.55, 128.42, 126.22, 120.93, 110.56, 66.67, 55.38, 22.97; $[\alpha]^{25} +17.3$ (c 0.3 in CHCl_3) 65% ee (R) (lit.¹⁸⁶ $[\alpha] +16.0$ (c 1.0 in CHCl_3) 66% ee (R)), GC analysis

(CHROMPAC CYCLODEXTRIN- β -236M-19, 50 m \times 0.25 mm \times 0.25 μ m, gas H₂, T = 130 °C, P = 15 psi, FID temp 250 °C, injector temp 220 °C, ketone 16.47 min., *R* 19.07 isomer min., *S* 19.89 isomer min.)

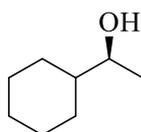
(*R*)-1,2,3,4-Tetrahydronaphthalen-1-ol



This compound is known.¹⁸⁵

δ_{H} (300 MHz, CDCl₃) 7.48 - 7.41 (1 H, m, ArH), 7.24 - 7.17 (2 H, m, ArH), 7.14 - 7.08 (1 H, m, ArH), 4.84 - 4.75 (1 H, m, CHOH), 2.90 - 2.66 (2 H, m), 2.07 - 1.88 (3 H, m), 1.85 - 1.73 (1 H, m), 1.72 - 1.65 (1 H, m); δ_{C} (101 MHz, CDCl₃) 138.93, 137.24, 129.14, 128.78, 127.71, 126.31, 68.28, 32.40, 29.37, 18.92; $[\alpha]_{\text{D}}^{25}$ -33.1 (*c* 0.4 in CHCl₃) 99% ee (*R*) (lit.¹⁸⁵ $[\alpha]_{\text{D}}^{25}$ -34.4 (*c* 0.57 in CHCl₃), 99% ee (*R*)); GC analysis (CP-CHIRALSIL-DEX-CB, 25 m \times 0.25 mm \times 0.25 μ m, gas He, T = 120 °C, P = 12 psi, FID temp 250 °C, injector temp 220 °C, ketone 38.54 min., *R* isomer 65.74 min., *S* isomer 61.42 min.)

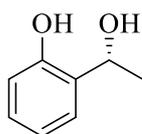
(*S*)-1-Cyclohexylethan-1-ol



This compound is known.¹⁸⁵

δ_{H} (300 MHz, CDCl₃) ppm 3.55 (1 H, t, *J* 6.0, CHOH), 1.90 - 1.61 (5 H, m), 1.34 - 1.12 (8 H, m), 1.08 - 0.92 (2 H, m); δ_{C} (101 MHz, CDCl₃) δ 72.34, 45.25, 28.83, 28.49, 26.64, 26.36, 26.26, 20.50; $[\alpha]_{\text{D}}^{25}$ +1.13 (*c* 0.2 in CHCl₃) 53% ee (*S*) (lit.¹⁸⁵ $[\alpha]_{\text{D}}^{25}$ -1.20 (*c* 0.57 in CHCl₃) 71% ee (*R*)); GC analysis of (*S*)-1-cyclohexylethyl acetate (CHROMPAC CYCLODEXTRIN- β -236M-19, 50 m \times 0.25 mm \times 0.25 μ m, gas hydrogen, T = 92 °C, P = 12 psi, FID temp 250 °C, injector temp 220 °C, ketone 19.28 min., *R* isomer 37.37 min., *S* isomer 32.72 min.)

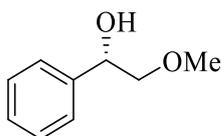
(R)-2-(1-hydroxyethyl)phenol



This compound is known.¹⁸⁴

δ_{H} (300 MHz, CDCl_3) 7.91 (1 H, s, ArOH), 7.23 - 7.15 (1 H, m, ArH), 7.00 (1 H, dd, J 7.5, 1.3, ArH), 6.92 - 6.81 (2 H, m, ArH), 5.10 (1 H, d, J 4.5, CHOH), 2.43 (1 H, br. s, CHOH), 1.61 (3 H, d, J 6.6, CH_3); δ_{C} (101 MHz, CDCl_3) 155.46, 129.05, 128.55, 126.60, 120.04, 117.19, 71.69, 23.54; $[\alpha]_{\text{D}}^{19}$ +13.8 (c 0.2 in CHCl_3) 94% ee (R) (lit.¹⁸⁴ $[\alpha]^{32}$: +22.3 (c 0.65 in CH_2Cl_2) 98.8% ee (R)); GC analysis (CP-CHIRALSIL-DEX-CB, 25 m x 0.25 mm x 0.25 μm , gas He, $T = 150$ °C, $P = 15$ psi, FID temp 250 °C, injector temp 220 °C, ketone 3.26 min., R isomer 15.02 min., S isomer 17.40 min.)

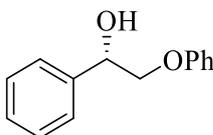
(S)-2-Methoxy-1-phenylethan-1-ol. 144



This compound is known.¹⁸⁷

δ_{H} (300 MHz, CDCl_3) 7.42 - 7.30 (5 H, m, ArH), 4.90 (1 H, dd, J 8.85, 3.20, CHOH), 3.59 - 3.52 (1 H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{OMe}$), 3.48 - 3.42 (4 H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{OMe} + \text{OCH}_3$), 2.73 (1H, br. s, OH); δ_{C} (101 MHz, CDCl_3) 140.36, 128.53, 127.97, 126.26, 78.30, 72.76, 59.14; $[\alpha]_{\text{D}}^{22}$ +45.6 (c 0.2 in CHCl_3) 92% ee (S) (lit.¹⁸⁷ $[\alpha]_{\text{D}}^{20}$ +33.8 (c 1.3 in CH_2Cl_2) 81% ee (S)); HPLC analysis (Chiralcel OD-H, 250 x 4.6 mm column, hexane/2-propanol 95:5, 1 mL/min, 254 nm, ketone 12.28 min., S isomer 11.55 min., R isomer 13.15 min.)

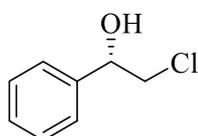
(S)-2-Phenoxy-1-phenylethan-1-ol. 146



This compound is known.¹⁸⁵

δ_{H} (300 MHz, CDCl_3) 7.50 - 7.43 (2 H, m, ArH), 7.40 (2 H, t, J 7.3, ArH), 7.36 - 7.26 (3 H, m, ArH), 7.02 - 6.88 (3 H, m, ArH), 5.13 (1 H, d, J 9.0, CHOH), 4.16 - 4.07 (1 H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{OPh}$), 4.06 - 3.96 (1 H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{OPh}$), 2.76 (1 H, d, J 2.2, OH); δ_{C} (101 MHz, CDCl_3) 158.50, 139.77, 129.69, 128.70, 128.31, 126.41, 121.44, 114.77, 73.42, 72.71; $[\alpha]_{\text{D}}^{29} +50.4$ (c 0.2 in CHCl_3) 81% ee (S) (lit.¹⁸⁵ $[\alpha]_{\text{D}} +56.6$ (c 0.35 in CHCl_3), 93% ee (S)); HPLC analysis (Chiralcel OD-H, 250×4.6 mm column, hexane/2-propanol 93:7, 1 mL/min, 254 nm, ketone 22.26 min., S isomer 35.91 min., R isomer 19.84 min.)

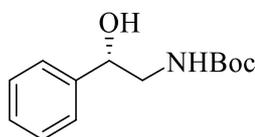
(S)-2-Chloro-1-phenylethan-1-ol. 148



This compound is known.¹⁸⁴

δ_{H} (300 MHz, CDCl_3) 7.37(5H, m, ArH), 4.93 (1H, dt, J 8.7, 3.3, CHOH), 3.77 (1H, dd, J 11.2, 8.7, $\text{CH}_\text{A}\text{H}_\text{B}\text{Cl}$), 3.67 (1H, dd, J 11.2, 8.3, $\text{CH}_\text{A}\text{H}_\text{B}\text{Cl}$), 2.64 (1H, d, J 3.3, CHOH); δ_{C} (101 MHz, CDCl_3) 140.03, 128.81, 128.60, 126.18, 74.20, 51.05; $[\alpha]_{\text{D}}^{29} +56.3$ (c 0.2 in CHCl_3) 91% ee (S) (lit.¹⁸⁴ $[\alpha]_{\text{D}}^{32} +61.8$ (c 0.81 in CHCl_3) 96.8% ee (S)); GC analysis (CP-CHIRALSIL-DEX-CB, 25 m x 0.25 mm x 0.25 μm , gas He, $T = 140$ °C, $P = 18$ psi, FID temp 250 °C, injector temp 220 °C, ketone 3.06 min., R isomer 12.26 min., S isomer 11.57 min.).

***tert*-Butyl (S)-(2-hydroxy-2-phenylethyl)carbamate. 153**

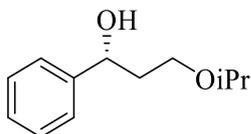


This compound is known.¹⁸⁸

δ_{H} (300 MHz, CDCl_3) ppm 7.43 - 7.30 (5 H, m, ArH), 4.98 (1 H, Br. s, NH), 4.84 (1 H, d, J 3.2, CHOH), 3.54 - 3.46 (1 H, Br. m, $\text{CH}_\text{A}\text{H}_\text{B}\text{NH}$), 3.32 - 3.23 (1 H, m, $\text{CH}_\text{A}\text{H}_\text{B}\text{NH}$), 3.14 (1 H, br. s, OH), 1.47 (9 H, s, $(\text{CH}_3)_3$); δ_{C} (101 MHz, CDCl_3) 157.14, 141.96, 128.61, 127.90, 126.01, 79.96, 74.06, 48.47, 28.48; $[\alpha]_{\text{D}}^{29} +52.5$ (c 0.2 in CHCl_3) 93% ee (S) (lit.¹⁸⁸ $[\alpha]_{\text{D}}^{25} +45.1$ (c 0.6 in CHCl_3) 93 % ee (S)); HPLC analysis

(Chiralcel OD-H, 250 × 4.6 mm column, hexane/2-propanol 95:5, 1 mL/min, 254 nm, ketone 11.70 min., *S* isomer 11.85 min., *R* isomer 13.98 min.)

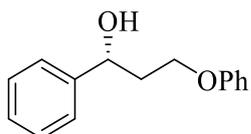
(*R*)-3-Isopropoxy-1-phenylpropan-1-ol. 156



This compound is novel.

This product is a colourless oil; ν_{\max} 3414, 3062, 3030, 2971, 2926, 2868, 1493, 1453, 1421, 1380 cm^{-1} ; δ_{H} (300 MHz, CDCl_3) 7.39 - 7.31 (4 H, m, ArH), 7.28 - 7.22 (1 H, m), 4.97 - 4.90 (1 H, m, *CHOH*), 3.81 (1 H, d, *J* 2.8, OH), 3.67 - 3.53 (3 H, m, CH_2OCH), 2.06 - 1.92 (2 H, m, CHOHCH_2), 1.21 (3 H, d, *J* 4.4), 1.18 (3 H, d, *J* 4.4); δ_{C} (101 MHz, CDCl_3) 144.64, 128.41, 127.27, 125.82, 74.30, 72.38, 67.01, 38.81, 22.22, 22.13; MS (ESI⁺): *m/z* 217.2 [$\text{M}+\text{Na}$]⁺; HRMS calcd. for $\text{C}_{12}\text{H}_{18}\text{NaO}_2$ [$\text{M}+\text{Na}$]⁺ 217.1199, found 217.1197 (0.9 ppm error); $[\alpha]_{\text{D}}^{25}$ +51.66 (*c* 0.05 in CHCl_3) 95% ee (*R*); HPLC analysis (CHIRALPAK IA, 250 × 4.6 mm column, hexane/2-propanol 96:4, 0.7mL/min, 254 nm, ketone 7.79 min., *S* isomer 7.60 min., *R* isomer 10.38 min.)

(*R*)-3-Phenoxy-1-phenylpropan-1-ol. 159

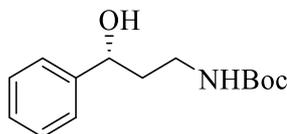


This compound is novel.

This compound is a white solid; ν_{\max} 3441, 3030, 2949, 2927, 2886, 1599, 1588, 1493, 1476, 1466, 1454 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 7.43 - 7.34 (4 H, m, ArH), 7.30 (3 H, t, *J* 7.40, ArH) 6.97 (1 H, t, *J* 7.4, ArH), 6.92 (2 H, d, *J* 7.9, ArH), 5.06 - 4.99 (1 H, m, *CHOH*), 4.22 - 4.15 (1 H, m, $\text{CH}_A\text{H}_B\text{OPh}$), 4.09 - 4.03 (1 H, m, $\text{CH}_A\text{H}_B\text{OPh}$), 2.52 (1 H, br. s, OH), 2.32 - 2.14 (2 H, m, CHOHCH_2); δ_{C} (101 MHz, CDCl_3) 158.78, 144.30, 129.63, 128.67, 127.76, 125.91, 121.09, 114.69, 72.32, 65.49, 38.54; MS (ESI⁺): *m/z* 251.2 [$\text{M}+\text{Na}$]⁺; HRMS calcd. for $\text{C}_{15}\text{H}_{16}\text{NaO}_2$ [$\text{M}+\text{Na}$]⁺ 251.1043, found 251.1041 (0.7 ppm error); $[\alpha]_{\text{D}}^{25}$ +8.5 (*c* 0.2 in CHCl_3) 91% ee (*R*); HPLC analysis

(CHIRALCEL OD-H, 250 × 4.6 mm column, hexane/2-propanol 95:5, 0.8 mL/min, 254 nm, ketone 16.72 min., *S* isomer 24.24 min., *R* isomer 22.48 min.).

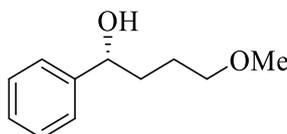
***tert*-Butyl (*R*)-(3-hydroxy-3-phenylpropyl)carbamate. 162**



This compound is known.¹⁸⁹

δ_{H} (400 MHz, CDCl_3) 7.40 - 7.28 (5 H, m, ArH), 4.88 (1 H, br s, NH), 4.75 (1 H, br s, CHOH), 3.60 - 3.42 (1 H, m, CHOH), 3.24 - 3.08 (2 H, m, CH_2NH), 1.86 (2 H, d, *J* 5.6 Hz), 1.46 (9 H, s); δ_{C} (101 MHz, CDCl_3) 157.02, 144.41, 128.57, 127.51, 125.77, 79.69, 71.82, 39.76, 37.70, 28.52; $[\alpha]_{\text{D}}^{27}$ +11.3 (*c* 0.3 in CHCl_3) 92% ee (*R*) (lit.¹⁸⁹ $[\alpha]_{\text{D}}^{20}$ -18.9 (*c* 0.4 in CHCl_3) 98% ee (*S*); HPLC analysis (CHIRALCEL OD-H, 250 × 4.6 mm column, hexane/2-propanol 95:5, 1 mL/min, 254 nm, ketone 9.70 min., *S* isomer 21.82 min., *R* isomer 13.64 min.).

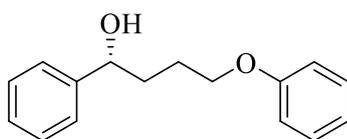
(*R*)-4-Methoxy-1-phenylbutan-1-ol. 167



This compound is known.¹⁹⁰

δ_{H} (400 MHz, CDCl_3) 7.40 - 7.30 (4 H, m, ArH), 7.29 - 7.22 (1 H, m, ArH), 4.70 (1 H, br. s, CHOH), 3.42 (2 H, t, *J* 5.5, CH_2OCH_3), 3.35 (3 H, s, OCH_3), 2.83 (1 H, br. s., OH), 1.91 - 1.80 (2 H, m, CH_2CHOH), 1.79 - 1.61 (2 H, m, $\text{CH}_2\text{CH}_2\text{OCH}_3$); δ_{C} (101 MHz, CDCl_3) 144.97, 128.50, 127.46, 125.95, 74.29, 72.98, 58.75, 36.80, 26.38; $[\alpha]_{\text{D}}^{25}$ +53.3 (*c* 0.1 in CHCl_3) 88% ee (*R*) (lit.¹⁹⁰ $[\alpha]_{\text{D}}$ +44.6 (*c* 0.82 in cyclopentane) 84% ee (*R*)); HPLC analysis (CHIRALPAK IC, 250 × 4.6 mm column, hexane/2-propanol 95:5, 1 mL/min, 210 nm, ketone 12.18 min., *S* isomer 16.18 min., *R* isomer 18.51 min.).

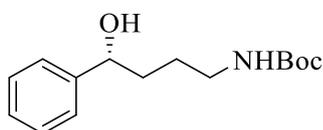
(R)-4-phenoxy-1-phenylbutan-1-ol. 173



This compound is novel.

This compound is a clear oil; ν_{\max} 3322, 3062, 3030, 2948, 2872, 1599, 1586, 1494, 1472, 1453 cm^{-1} , δ_{H} (400 MHz, CDCl_3) 7.39 – 7.33 (4 H, m, ArH), 7.31 - 7.27 (2 H, m, ArH), 6.94 (1 H, t, J 7.5, ArH), 6.89 (2 H, d, J 7.5, ArH), 4.78 (1 H, br. s, CHOH), 3.99 (2 H, d, J 5.4, CH_2OPh), 2.08 (1 H, br. s, OH), 2.00 – 1.80 (4 H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$); δ_{C} (101 MHz, CDCl_3) 159.01, 144.69, 129.57, 128.64, 127.74, 126.01, 120.81, 114.63, 74.37, 67.81, 35.89, 25.86; MS (ESI⁺): m/z 265.2 [M+Na]⁺; HRMS calcd. for $\text{C}_{16}\text{H}_{18}\text{NaO}_2$ [M+Na]⁺ 265.1199, found 265.1195 (1.4 ppm error); $[\alpha]_{\text{D}}^{28}$ +35.5 (c 0.3 in CHCl_3) 95% ee (*R*); HPLC analysis (Chiralcel OD-H, 250 × 4.6 mm column, hexane/2-propanol 90:10, 1 mL/min, 254 nm, ketone 13.83 min., *S* isomer 19.90 min., *R* isomer 28.85 min.).

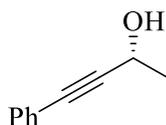
***tert*-Butyl (*R*)-(4-hydroxy-4-phenylbutyl)carbamate. 177**



This compound is known.¹⁹¹

δ_{H} (300 MHz, CDCl_3) 7.37 - 7.32 (4 H, m, ArH), 7.30 - 7.23 (1 H, m), 4.76 - 4.68 (1 H, m, CHOH), 4.54 (1 H, br. s, NH), 3.16 (2 H, d, J 6.9, CH_2NH), 2.06 (1 H, br. s., OH) 1.86 - 1.67 (2 H, m, CH_2CHOH), 1.66 - 1.49 (2 H, m, $\text{CH}_2\text{CH}_2\text{NH}$, overlap H_2O peak), 1.43 (9 H, s, $(\text{CH}_3)_3$); δ_{C} (101 MHz, CDCl_3) 156.23, 144.83, 128.60, 127.68, 125.93, 79.28, 74.28, 40.43, 36.15, 28.54, 26.62; $[\alpha]_{\text{D}}^{29}$ +27.6 (c 0.2 in CHCl_3) 93% ee (*R*); HPLC analysis (CHIRALPAK IA, 250 × 4.6 mm column, hexane/2-propanol 95:5, 1 mL/min, 254 nm, ketone 13.86 min., *S* isomer 20.93 min., *R* isomer 26.52 min.)

(R)-4-phenylbut-3-yn-2-ol. 179

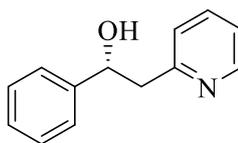


This compound is known.⁸⁴

δ_{H} (400 MHz, CDCl_3) 7.49 - 7.28 (5 H, m, ArH), 4.76 (1 H, d, J 6.0, CHOH), 1.92 (1 H, br. s, OH), 1.56 (3 H, d, J 6.0, CH_3); δ_{C} (101 MHz, CDCl_3) 131.78, 128.50, 128.40, 122.72, 91.10, 84.13, 58.97, 24.51; $[\alpha]_{\text{D}}^{29}$ +25.4 (c 0.2 in CHCl_3) 84% ee (R) (lit.⁸⁴ $[\alpha]_{\text{D}}^{20}$ +43.8 (c 1.0 in Et_2O) 96% ee (R)); HPLC analysis (Chiralcel OD-H, 250×4.6 mm column, hexane/2-propanol 90:10, 1 mL/min, 220 nm, Ketone: 6.59 min, S isomer: 19.32 min, R isomer: 8.12 min)

Products from Chapter 5

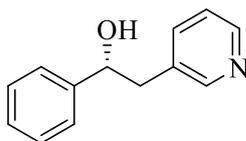
(R)-1-Phenyl-2-(pyridin-2-yl)ethan-1-ol. 252



This compound is known.¹⁵⁵

This product was prepared through method 1B using ketone **251** (98 mg, 0.50 mmol), FA/TEA 5:2 (0.25 mL), DCM (0.25 mL), complex (R,R)-**131** (3.3 mg, 5.0 μmol) to give the product (89 mg, 0.45 mmol, 90%); $[\alpha]_{\text{D}}^{22}$ +41.4 (c 0.3 in CHCl_3) 98% ee (R) (lit.¹⁵⁵ $[\alpha]_{\text{D}}^{20}$ +38.1 (c 0.72 in CHCl_3) 99% ee (R)); δ_{H} (400 MHz, CDCl_3) 8.54 (1H, d, J 4.4, ArH), 7.63 (1H, td, J 7.7, 1.7, ArH), 7.47 - 7.39 (2H, m, ArH), 7.35 (2H, t, J 7.5 Hz, ArH), 7.29 - 7.23 (1H, m, ArH), 7.19 (1H, dd, J 7.1, 5.3, ArH), 7.11 (1H, d, J 7.8 Hz, ArH), 5.17 (1H, dd, J 7.9, 4.2, CHOH), 3.17 - 3.11 (2H, m, CH_2); δ_{C} (101 MHz, CDCl_3) 159.82, 148.56, 144.15, 137.13, 128.45, 127.42, 125.97, 124.02, 121.90, 73.45, 45.75; HPLC analysis (Chiralcel OD-H, 250×4.6 mm column, hexane/2-propanol 90:10, 1 mL/min, 254 nm, S isomer 15.46 min., R isomer 9.59 min.).

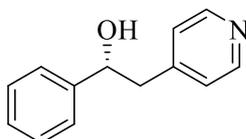
(R)-1-Phenyl-2-(pyridin-3-yl)ethan-1-ol. 255



This compound is known.¹⁵⁵

This product was prepared through method 1B using ketone **253** (98 mg, 0.50 mmol), FA/TEA 5:2 (0.25 mL), DCM (0.25 mL), complex (*R,R*)-**131** (3.3 mg, 5.0 μ mol) to give the product as a white solid (56 mg, 0.28 mmol, 56%); $[\alpha]_{\text{D}}^{22} +11.9$ (*c* 0.1 in CHCl_3) 94% ee (*R*) (lit.¹⁵⁵ $[\alpha]_{\text{D}}^{20} -13.8$ (*c* 0.85 in CHCl_3) 99% ee (*S*)); δ_{H} (400 MHz, CDCl_3) 8.41 (1H, d, *J* 4.3, ArH), 8.36 (1H, s, ArH), 7.46 (1H, d, *J* 7.8, ArH), 7.38 – 7.25 (5H, m, ArH), 7.18 (1H, dd, *J* 7.5, 5.0, ArH), 4.93 – 4.85 (1H, m, *CHOH*), 3.09 – 2.95 (2H, m, CH_2Ar), 2.32 (1H, bs, OH); δ_{C} (101 MHz, CDCl_3) 150.69, 147.75, 143.62, 137.47, 133.89, 128.68, 128.03, 126.02, 123.34, 75.05, 42.98; HPLC analysis (Chiralcel OD-H, 250 \times 4.6 mm column, hexane/2-propanol 90:10, 1 mL/min, 210/230/250 nm, *S* isomer 30.56 min., *R* isomer 21.59 min.).

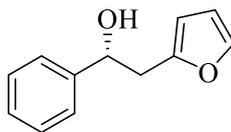
(R)-1-Phenyl-2-(pyridin-4-yl)ethan-1-ol. 256



This compound is known.¹⁵⁵

This product was prepared through method 1B using ketone **254** (197 mg, 1.00 mmol), FA/TEA 5:2 (0.50 mL), DCM (0.50 mL), complex (*R,R*)-**131** (6.6 mg, 10 μ mol) to give the product (179 mg, 0.90 mmol, 90%); $[\alpha]_{\text{D}}^{22} +21.3$ (*c* 0.15 in CHCl_3) 95% ee (*R*) (lit.¹⁵⁵ $[\alpha]_{\text{D}}^{20} -16.1$ (*c* 0.83 in CHCl_3) 99% ee (*S*)); δ_{H} (400 MHz, CDCl_3) 8.43 – 8.31 (2H, m, Py-H), 7.39 – 7.24 (5H, m, ArH), 7.07 (2H, d, *J* 4.9, Py-H), 4.92 (1H, dd, *J* 7.7, 5.4, *CHOH*), 3.09 – 2.91 (3H, m, $\text{CH}_2 + \text{OH}$); δ_{C} (101 MHz, CDCl_3) 149.53, 147.65, 143.67, 128.66, 128.01, 125.98, 125.08, 74.56, 45.26; HPLC analysis (CHIRALPAK IG, 250 \times 4.6 mm column, hexane/2-propanol 85:15, 0.5 mL/min, 210/230/250 nm, *S* isomer 29.51 min., *R* isomer 25.74 min.).

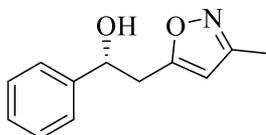
(R)-1-Phenyl-2-(furan-2-yl)ethan-1-ol. 263



This compound is known.¹⁹²

This product was prepared through method 1B using ketone **258** (93 mg, 0.50 mmol), FA/TEA 5: (0.25 mL), DCM (0.25 mL), complex (*R,R*)-**131** (3.3 mg, 5.0 μ mol) to give the product (89 mg, 0.48 mmol, 96%); $[\alpha]_D^{22} +31.5$ (*c* 0.3 in CHCl_3) 96% ee (*R*); δ_{H} (400 MHz, CDCl_3) 7.39 – 7.35 (5H, m, ArH), 7.32 – 7.27 (1H, m, ArH), 6.33 – 6.30 (1H, m, ArH), 6.09 (1H, d, *J* 3.1, ArH), 5.01 (1H, t, *J* 6.5, *CHOH*), 3.06 (2H, d, *J* 6.5, CH_2Ar), 2.24 (1H, bs, OH); δ_{C} (101 MHz, CDCl_3) 152.46, 143.49, 141.83, 128.61, 127.87, 125.86, 110.52, 107.48, 73.08, 38.46; HPLC analysis (Chiralcel OD-H, 250 \times 4.6 mm column, hexane/2-propanol 95:5, 0.5 mL/min, 210/230/250 nm, *S* isomer 24.15 min., *R* isomer 21.81 min.).

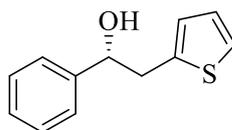
(R)-1-Phenyl-2-(3-methylisoxazol-5-yl)ethan-1-ol. 264



This compound is known.¹⁹³

This product was prepared through method 1B using ketone **259** (101 mg, 0.50 mmol), FA/TEA (0.25 mL), DCM (0.25 mL), complex (*R,R*)-**131** (3.3 mg, 5.0 μ mol) to give the product (72 mg, 0.353 mmol, 71%); $[\alpha]_D^{22} +41.9$ (*c* 0.1 in CHCl_3) 94% ee (*R*); δ_{H} (400 MHz, CDCl_3) 7.40 – 7.33 (4H, m, ArH), 7.32 – 7.27 (1H, m, ArH), 5.87 (1H, s, CH-isoxazole), 5.06 (1H, dd, *J* 8.4, 4.8, *CHOH*), 3.17 (1H, dd, *J* 15.2, 8.4, CH_AH_B), 3.09 (1H, dd, *J* 15.2, 4.8, CH_AH_B), 2.50 (1H, bs, OH), 2.23 (3H, s, CH_3); δ_{C} (101 MHz, CDCl_3) 169.69, 159.99, 143.05, 128.76, 128.19, 125.81, 103.52, 72.30, 36.78, 11.50; HPLC analysis (CHIRALPAK IG, 250 \times 4.6 mm column, hexane/2-propanol 85:15, 0.6 mL/min, 210/230/250 nm, *S* isomer 22.44 min., *R* isomer 20.46 min.).

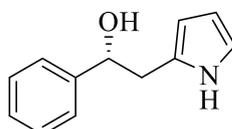
(R)-1-Phenyl-2-(thiophen-2-yl)ethan-1-ol. 265



This compound is known.¹⁹⁴

This product was prepared through method 1B using ketone **260** (101 mg, 0.50 mmol), FA/TEA 5:2 (0.25 mL), DCM (0.25 mL), complex (*R,R*)-**131** (3.3 mg, 5.0 μ mol) to give the product (98 mg, 0.48 mmol, 96%); $[\alpha]_D^{22} +28.5$ (*c* 0.15 in CHCl_3) 94% ee (*R*); δ_H (400 MHz, CDCl_3) 7.41 – 7.34 (4H, m, ArH), 7.33 – 7.28 (1H, m, ArH), 7.19 (1H, dd, *J* 5.1, 0.9, Thio-H), 6.95 (1H, dd, *J* 5.1, 3.3, Thio-H), 6.85 (1H, d, *J* 3.3, Thio-H), 4.94 – 4.87 (1H, m, *CHOH*), 3.25 (1H, s, *CH_AH_B*), 3.23 (1H, d, *J* 3.0, *CH_AH_B*), 2.21 – 2.15 (1H, m, OH); δ_C (101 MHz, CDCl_3) 143.38, 140.20, 128.62, 127.93, 127.06, 126.43, 126.02, 124.55, 75.15, 40.15; HPLC analysis (CHIRALPAK IG, 250 \times 4.6 mm column, hexane/2-propanol 97:3, 0.5 mL/min, 210/230/250 nm, *S* isomer 37.52 min., *R* isomer 34.72 min.).

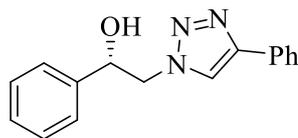
(R)-1-Phenyl-2-(1H-pyrrol-2-yl)ethan-1-ol. 266



This compound is known.¹⁹⁵

This product was prepared through method 1B using ketone **262** (46 mg, 0.25 mmol), FA/TEA 5:2 (0.12 mL), DCM (0.12 mL), complex (*R,R*)-**131** (1.6 mg, 2.5 μ mol) to give the product (32 mg, 0.17 mmol, 68%); $[\alpha]_D^{22} +45.0$ (*c* 0.01 in CHCl_3) 92% ee (*R*); δ_H (400 MHz, CDCl_3) 8.37 (1H, bs, NH), 7.31 – 7.25 (3H, m, ArH), 7.24 – 7.15 (2H, m, ArH), 6.61 (1H, d, *J* 1.4, Pyr-H), 6.09 – 6.01 (1H, m, *J* 5.7, 2.8, Pyr-H), 5.90 (1H, s, Pyr-H), 4.82 (1H, dd, *J* 6.9, 5.5, *CHOH*), 2.96 – 2.90 (2H, m, CH_2), 2.20 (1H, bs, OH); δ_C (101 MHz, CDCl_3) 144.04, 128.87, 128.70, 127.94, 125.81, 117.32, 108.20, 106.93, 74.68, 37.59; HPLC analysis (CHIRALPAK IA, 250 \times 4.6 mm column, hexane/2-propanol 88:12, 0.5 mL/min, 210/230/250 nm, *S* isomer 19.81 min., *R* isomer 22.49 min.).

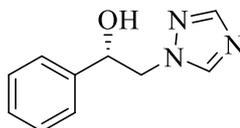
(S)-1-Phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethan-1-ol. 276



This compound is known.¹⁹⁶

This product was prepared through method 1B using ketone **272** (132 mg, 0.50 mmol), FA/TEA 5:2 (0.25 mL), DCM (0.25 mL), complex (*R,R*)-**131** (3.3 mg, 5.0 μ mol) to give the product (123 mg, 0.465 mmol, 93%); $[\alpha]_D^{22} +54.4$ (*c* 0.1 in CHCl_3) 95% ee (*S*) (lit.¹⁹⁶ $[\alpha]_D^{25} +86.3$ (*c* 0.1 in CHCl_3) 99% ee (*S*)); δ_H (400 MHz, CDCl_3) 7.78 (1H, s, ArH), 7.68 (2H, d, *J* 7.4, ArH), 7.45 – 7.26 (8H, m, ArH), 5.19 (1H, dd, *J* 8.8, 3.1, *CHOH*), 4.62 (1H, dd, *J* 13.9, 3.1, *CH_AH_B*), 4.41 (1H, dd, *J* 13.9, 8.8, *CH_AH_B*), 2.02 (1H, bs, OH); δ_C (101 MHz, CDCl_3) 147.37, 140.50, 130.33, 128.91, 128.85, 128.46, 128.22, 126.00, 125.69, 121.50, 72.69, 57.69; HPLC analysis (CHIRALPAK IA, 250 \times 4.6 mm column, hexane/2-propanol 80:20, 0.6 mL/min, 210/230/250 nm, *S* isomer 17.29 min., *R* isomer 22.88 min.).

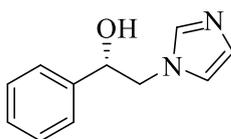
(S)-1-Phenyl-2-(1,2,4-triazol-1-yl)ethan-1-ol. 277



This compound is known.¹⁹⁷

This product was prepared through method 1B using ketone **273** (94 mg, 0.50 mmol), FA/TEA (0.25 mL), DCM (0.25 mL), complex (*R,R*)-**131** (3.3 mg, 5.0 μ mol) to give the product (89 mg, 0.43 mmol, 87%); $[\alpha]_D^{23} +61.7$ (*c* 0.1 in CHCl_3) 96% ee (*S*); δ_H (400 MHz, CDCl_3) 7.98 (1H, s, ArH-triazole), 7.83 (1H, s, ArH-triazole), 7.43 – 7.28 (5H, m, ArH), 5.08 (1H, dd, *J* 8.6, 3.1, *CHOH*), 4.36 (1H, dd, *J* 13.9, 3.1, *CH_AH_B*), 4.25 (1H, dd, *J* 13.9, 8.6, *CH_AH_B*), 4.07 – 3.75 (1H, bs, OH); δ_C (101 MHz, CDCl_3) 151.81, 144.04, 140.39, 128.91, 128.52, 125.92, 72.39, 57.06; HPLC analysis (CHIRALPAK IA, 250 \times 4.6 mm column, hexane/2-propanol 90:10, 0.8 mL/min, 210/230/250 nm, *S* isomer 21.51 min., *R* isomer 23.96 min.).

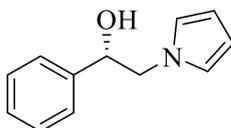
(S)-1-Phenyl-2-(imidazol-1-yl)ethan-1-ol. **278**



This compound is known.¹⁹⁸

This product was prepared through method 1B using ketone **274** (93 mg, 0.50 mmol), FA/TEA 5:2 (0.25 mL), DCM (0.25 mL), complex (*R,R*)-**131** (3.3 mg, 5.0 μ mol) to give the product (70 mg, 0.37 mmol, 74%); $[\alpha]_D^{22} +39.2$ (*c* 0.12 in CHCl_3) 90% ee (*S*) (lit.¹⁹⁸ $[\alpha]_D^{20} -37.5$ (*c* 0.001 in chloroform) 61% ee (*R*)); δ_H (400 MHz, DMSO) 7.49 (1H, s, ArH-Imidazole), 7.38 – 7.30 (4H, m, ArH), 7.29 – 7.22 (1H, m, ArH), 7.11 (1H, s, ArH-Imidazole), 6.82 (1H, s, ArH-Imidazole), 5.74 (1H, bs OH), 4.86 – 4.76 (1H, m, CHOH), 4.13 (1H, dd, *J* 13.9, 4.0, CH_AH_B), 4.03 (1H, dd, *J* 13.9, 7.9, CH_AH_B); δ_C (101 MHz, DMSO) δ 142.66, 137.72, 128.08, 127.71, 127.34, 126.03, 120.05, 72.09, 53.56. HPLC analysis (CHIRALPAK IC, 250 \times 4.6 mm column, hexane/2-propanol 80:20, 0.5 mL/min, 210/230/250 nm, *S* isomer 53.33 min., *R* isomer 46.90 min.).

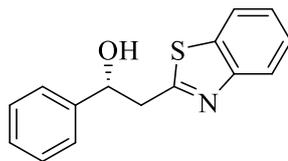
(S)-1-Phenyl-2-(pyrrol-1-yl)ethan-1-ol. **279**



This compound is novel.

This product was prepared through method 1B using ketone **275** (61 mg, 0.33 mmol), FA/TEA 5:2 (0.16 mL), DCM (0.16 mL), complex (*R,R*)-**131** (2.2 mg, 3.3 μ mol) to give the product (53 mg, 0.28 mmol, 86%); $[\alpha]_D^{22} +26.5$ (*c* 0.1 in CHCl_3) 95% ee (*S*); ν_{max} 3337, 3062, 3029, 2927, 1693, 1598, 1494 cm^{-1} ; δ_H (400 MHz, CDCl_3) 7.48 – 7.27 (5H, m, ArH), 6.69 (2H, s, ArH-pyrrole), 6.18 (2H, s, ArH-pyrrole), 4.93 (1H, dd, *J* 8.3, 3.9, CHOH), 4.12 (1H, dd, *J* 14.2, 3.9, CH_AH_B), 4.03 (1H, dd, *J* 14.2, 8.3, CH_AH_B), 2.12 (1H, bs, OH); δ_C (101 MHz, CDCl_3) 140.93, 128.78, 128.34, 126.02, 121.35, 108.73, 74.69, 57.49; HRMS calcd for $\text{C}_{12}\text{H}_{13}\text{NNaO}$ $[\text{M}+\text{Na}]^+$ 210.0889, found 210.0889 (0.1 ppm error); HPLC analysis (Chiralcel OD-H, 250 \times 4.6 mm column, hexane/2-propanol 95:5, 0.6 mL/min, 210/230/250 nm, *S* isomer 26.65 min., *R* isomer 29.27 min.).

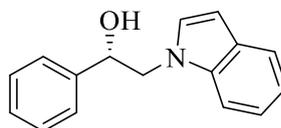
(R)-2-(Benzo[d]thiazol-2-yl)-1-phenylethan-1-ol. 287



This compound is known.¹⁹⁹

This product was prepared through method 1B using ketone **280** (126 mg, 0.50 mmol), FA/TEA (0.25 mL), DCM (0.25 mL), complex (*R,R*)-**131** (3.3 mg, 5.0) to give the product (20 mg, 78 μ mol, 16%); $[\alpha]_D^{22} +13.0$ (*c* 0.1 in CHCl_3) 60% ee (*R*) (lit.¹⁹⁹ $[\alpha]_D^{25} +25.54$ (*c* 1.00 in CHCl_3) 92% ee (*R*)); δ_H (400 MHz, CDCl_3) 8.01 (1H, d, *J* 8.0, ArH), 7.85 (1H, d, *J* 8.0, ArH), 7.52 – 7.44 (3H, m, ArH), 7.42 – 7.34 (3H, m, ArH), 7.33 – 7.28 (1H, m, ArH), 5.34 – 5.27 (1H, m, *CHOH*), 4.01 (1H, bs, OH), 3.47 (1H s, *CH_AH_B*), 3.45 (1H, s, *CH_AH_B*); δ_C (101 MHz, CDCl_3) 169.07, 152.81, 142.86, 134.78, 128.71, 127.98, 126.33, 125.95, 125.25, 122.79, 121.66, 72.82, 43.10. HPLC analysis (Chiralcel OD-H, 250 \times 4.6 mm column, hexane/2-propanol 95:5, 0.6 mL/min, 210/230/250 nm, *S* isomer 46.51 min., *R* isomer 31.17 min.).

(S)-1-Phenyl-2-(indol-1-yl)ethan-1-ol. 288

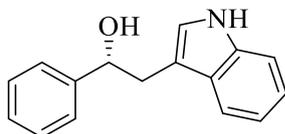


This compound is known.²⁰⁰

This product was prepared through method 1B using ketone **281** (118 mg, 0.50 mmol), FA/TEA 5:2 (0.25 mL), DCM (0.25 mL), complex (*R,R*)-**131** (3.3 mg, 5.0 μ mol) to give the product (107 mg, 0.45 mmol, 90%); $[\alpha]_D^{22} +15.0$ (*c* 0.05 in CHCl_3) 97% ee (*S*); δ_H (400 MHz, CDCl_3) 7.55 (1H, d, *J* 7.9, ArH), 7.33 – 7.21 (6H, m, ArH), 7.17 – 7.10 (1H, m, ArH), 7.03 (1H, t, *J* 7.4, ArH), 6.99 (1H, d, *J* 2.8, ArH-indole), 6.41 (1H, d, *J* 2.8, ArH-indole), 4.95 (1H, dd, *J* 8.2, 4.0, *CHOH*), 4.25 (1H, dd, *J* 14.6, 4.0, *CH_AH_B*), 4.17 (1H, dd, *J* 14.6, 8.2, *CH_AH_B*), 1.90 (1H, bs, OH); δ_C (101 MHz, CDCl_3) 141.18, 136.30, 128.86, 128.77, 128.41, 125.99, 121.82, 121.22, 119.72, 109.51, 101.68, 73.71, 54.35; HPLC analysis (CHIRALPAK IA, 250 \times 4.6 mm column,

hexane/2-propanol 95:5, 0.6 mL/min, 210/230/250 nm, *S* isomer 21.84 min., *R* isomer 25.39 min.).

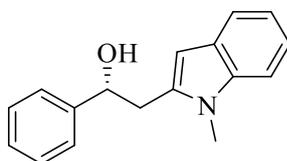
(*R*)-1-Phenyl-2-(1H-indol-3-yl)ethan-1-ol. 289



This compound is known.²⁰¹

This product was prepared through method 1B using ketone **283** (80 mg, 0.34 mmol), FA/TEA (0.16 mL), DCM (0.16 mL), complex (*R,R*)-**131** (2.2 mg, 3.3 μ mol) to give the product (72 mg, 0.30 mmol, 89%); $[\alpha]_D^{22} +19.2$ (*c* 0.1 in CHCl_3) 96% ee (*R*); δ_H (400 MHz, CDCl_3) 8.06 (1H, s, NH), 7.64 (1H, d, *J* 7.9, ArH), 7.44 (2H, d, *J* 7.5 Hz, ArH), 7.38 (3H, t, *J* 7.5, ArH), 7.34 – 7.29 (1H, m, ArH), 7.23 (1H, t, *J* 7.5, ArH), 7.15 (1H, t, *J* 7.5, ArH), 7.01 (1H, s, ArH), 5.01 (1H, dd, *J* 8.9, 4.3, CHOH), 3.26 (1H, dd, *J* 14.5, 4.3, CH_AH_B), 3.13 (1H, dd, *J* 14.5, 8.9, CH_AH_B), 2.18 (1H, bs, OH); δ_C (101 MHz, CDCl_3) 144.26, 136.49, 128.53, 127.61, 126.02, 123.22, 122.38, 119.70, 119.01, 112.09, 111.37, 74.03, 36.06; HPLC analysis (CHIRALPAK IA, 250 \times 4.6 mm column, hexane/2-propanol 85:15, 0.6 mL/min, 210/230/250 nm, *S* isomer 34.95 min., *R* isomer 26.27 min.).

(*R*)-1-Phenyl-2-(1-methylindol-2-yl)ethan-1-ol. 290



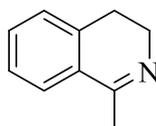
This compound is novel.

This product was prepared through method 1B using ketone **286** (84 mg, 0.334 mmol), FA/TEA 5:2 (0.2 mL), DCM (0.2 mL), complex (*R,R*)-**131** (2.2 mg, 3.33 μ mol) to give the product as a white solid (83 mg, 0.328 mmol, 98%); Mp 82.2 – 84.5 $^\circ\text{C}$; $[\alpha]_D^{22} +61.5$ (*c* 0.1 in CHCl_3) 99% ee (*R*); ν_{max} 3357, 3031, 2939, 2913, 1543, 1466 cm^{-1} ; δ_H (400 MHz, CDCl_3) 7.60 (1H, d, *J* 7.8, ArH), 7.42 – 7.37 (4H, m, ArH), 7.36 – 7.32 (1H, m, ArH), 7.29 (1H, d, *J* 8.2, ArH), 7.22 (1H, t, *J* 7.5, 1H), 7.13 (1H, t, *J* 7.5 Hz,

ArH), 6.43 (1H, s, ArH), 5.03 – 4.95 (1H, m, CHOH), 3.57 (3H, s, NCH₃), 3.22 – 3.18 (2H, m, CH₂), 2.38 (1H, bs, OH); δ_C (101 MHz, CDCl₃) 143.52, 137.68, 136.71, 128.68, 127.95, 127.84, 125.82, 121.23, 120.15, 119.65, 109.23, 101.10, 73.36, 37.27, 29.65; HRMS calcd for C₁₇H₁₇NNaO [M+Na]⁺ 274.1202, Found 274.1213 (3.8 ppm error); HPLC analysis (CHIRALPAK IB, 250 × 4.6 mm column, hexane/2-propanol 93:7, 0.6 mL/min, 210/230/250 nm, *S* isomer 26.65 min., *R* isomer 33.25 min.).

7.4. Imines

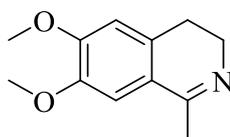
1-Methyl-3,4-dihydroisoquinoline. 189



This compound is known.²⁰²

δ_H (400 MHz, CDCl₃) 7.48 (1H, d, *J* 7.6, ArH), 7.35 (1H, td, *J* 7.4, 1.4, ArH), 7.28 (1H, dd, *J* 12.4, 5.1, ArH), 7.18 (1H, d, *J* 7.3, ArH), 3.66 (2H, td, *J* 7.4, 1.4, CH₂N), 2.73 – 2.67 (2H, m, CH₂Ar), 2.39 (3H, s, CH₃); δ_C (101 MHz, CDCl₃) 164.5, 137.5, 130.7, 129.7, 127.5, 127.0, 125.4, 47.0, 26.1, 23.4.

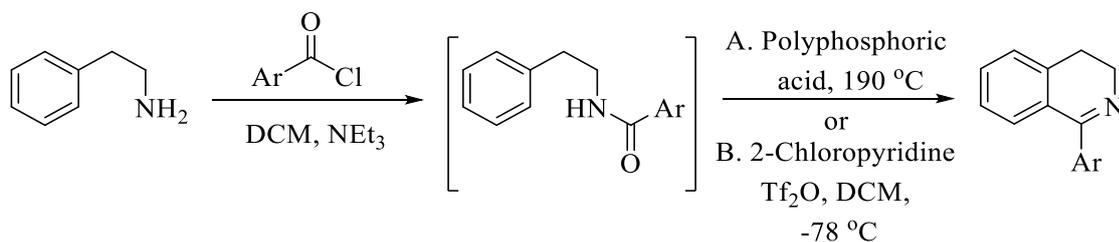
6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline. 191



This compound is known.²⁰³

δ_H (400 MHz, CDCl₃) 6.99 (1H, s, ArH), 6.68 (1H, s, ArH), 3.91 (3H s, OMe), 3.90 (3H, s, OMe), 3.62 (2H, td, *J* 7.5, 1.3, CH₂N), 2.66 – 2.59 (2H, m, CH₂Ar), 2.36 (3H, s, CH₃); δ_C (101 MHz, CDCl₃) 163.8, 151.0, 147.6, 131.3, 122.7, 110.4, 109.2, 56.4, 56.1, 47.1, 25.9, 23.6

General procedure 2A and 2B for synthesis of tetrahydroisoquinoline derivatives from 2-phenethylamine.

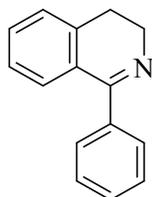


General procedure 2A. To a solution of 2-phenethylamine (302 mg, 2.50 mmol) and triethylamine (0.52 mL, 3.75 mmol) in DCM (8 mL) was added dropwise acid chloride (2.50 mmol). After stirring overnight, the reaction was diluted with DCM (12 mL) and quenched with 1 M HCl (15 mL). The organic layer was separated and further washed with 1 M NaOH (15 mL). The organic extract was then collected and dried over MgSO₄, filtered and concentrated under reduced pressure to yield the intermediate amide. The amide product was stirred at 190 °C in polyphosphoric acid (4.00 g). After stirring for 4 h the reaction mixture was left to cool to rt and was then poured into ice-cold water (20 mL). The mixture was basified to pH 8 with 20% w/w NaOH solution and the product was extracted with EtOAc (3 x 30 mL). The organic layers were combined, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The product was purified by column chromatography (0-50% EtOAc in Pet. Ether).

General procedure 2B. To a solution of 2-phenethylamine (242 mg, 2.00 mmol) and triethylamine (0.42 mL, 3.00 mmol) in DCM (8 mL) was added dropwise/portion wise the acid chloride (2.00 mmol). After stirring overnight, the reaction was diluted with DCM (12 mL) and quenched with 1 M HCl (15 mL). The organic layer was separated and further washed with 1 M NaOH (15 mL). The organic extract was then collected and dried over MgSO₄, filtered and concentrated under reduced pressure to yield the intermediate amide. The amide product was dissolved in anhydrous DCM (12 mL) and 2-chloropyridine (0.26 mL, 2.75 mmol) was added. The solution was cooled to -78 °C and trifluoromethanesulfonic anhydride (0.46 mL, 2.75 mmol) was added dropwise. After stirring overnight at rt, the reaction was diluted with DCM (12 mL) and quenched with sat. NaHCO₃ (25 mL). The organic layer was separated and further extracted with DCM (2 x 15 mL). The organic layers were combined, dried over

MgSO₄, filtered and the solvent removed under reduced pressure. The product was purified by column chromatography (0-50% EtOAc in Pet. Ether).

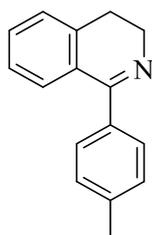
1-Phenyl-3,4-dihydroisoquinoline. 193



This compound is known.²⁰⁴

This was prepared by general procedure 2A using 2-phenethylamine (605 mg, 5.00 mmol), triethylamine (1.05 mL, 7.50 mmol), benzyl chloride (700 mg, 5.00 mmol), DCM (12 mL), polyphosphoric acid (8.00 g, 5.00 mmol) and then purified by column chromatography (0-50% EtOAc in Pet. Ether) to give the product as a yellow oil (706 mg, 3.41 mmol, 68%); δ_{H} (400 MHz, CDCl₃) 7.67 - 7.59 (2 H, m, ArH), 7.50 - 7.38 (4 H, m, ArH), 7.32 - 7.23 (3 H, m, ArH), 3.93 - 3.83 (2 H, m, CH₂N), 2.88 - 2.78 (2 H, m, ArCH₂); δ_{C} (101 MHz, CDCl₃) 167.4, 139.0, 138.9, 130.8, 129.4, 128.9, 128.2, 128.1, 127.5, 126.7, 47.7, 26.4.

1-(*p*-Tolyl)-3,4-dihydroisoquinoline.

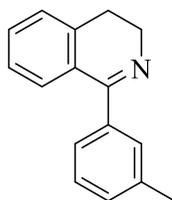


This compound is known.²⁰⁵

This was prepared by general procedure 2B using 2-phenethylamine (302 mg, 2.50 mmol), triethylamine (0.52 mL, 3.75 mmol), *p*-toluoyl chloride (390 mg, 2.50 mmol), DCM (6 mL), 2-chloropyridine (0.26 mL, 2.75 mmol), trifluoromethanesulfonic anhydride (0.46 mL, 2.75 mmol) and anhydrous DCM (12 mL) then purified by column chromatography (0-50% EtOAc in Pet. Ether) to give the product as a white solid (431 mg, 1.95 mmol, 78%); δ_{H} (400 MHz, CDCl₃) 7.51 (2 H, d, *J* 8.1, ArH), 7.41 - 7.35 (1 H, m, ArH), 7.31 - 7.20 (5 H, m, ArH), 3.88 - 3.79 (2 H, m, CH₂N), 2.84 -

2.75 (2 H, m, ArCH₂), 2.41 (3 H, s, CH₃); δ_C (101 MHz, CDCl₃) 167.3, 139.4, 139.0, 136.2, 130.7, 129.0, 128.9, 128.9, 128.1, 127.5, 126.6, 47.6, 26.5, 21.5.

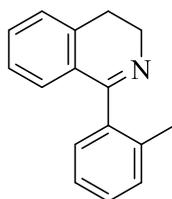
1-(*m*-Tolyl)-3,4-dihydroisoquinoline.



This compound is known.²⁰⁵

This was prepared by general procedure 2B using 2-phenethylamine (302 mg, 2.50 mmol), triethylamine (0.52 mL, 3.75 mmol), *m*-toluoyl chloride (390 mg, 2.50 mmol), DCM (6 mL), 2-chloropyridine (0.26 mL, 2.75 mmol), trifluoromethanesulfonic anhydride (0.46 mL, 2.75 mmol) and anhydrous DCM (12 mL) then purified by column chromatography (0-50% EtOAc in Pet. Ether) to give the product as a clear oil (412 mg, 1.86 mmol, 74%); δ_H (400 MHz, CDCl₃) 7.45 (1H, s, ArH), 7.41 – 7.33 (2H, m, ArH), 7.33 – 7.28 (1H, m, ArH), 7.28 – 7.20 (4H, m, ArH), 3.88 – 3.80 (2H, m, CH₂N), 2.84 – 2.76 (2H, m, ArCH₂), 2.39 (3H, s, ArCH₃); δ_C (101 MHz, CDCl₃) 167.6, 139.0, 138.9, 138.1, 130.8, 130.2, 129.5, 129.0, 128.2, 128.0, 127.5, 126.7, 126.1, 47.6, 26.4, 21.5.

1-(*o*-Tolyl)-3,4-dihydroisoquinoline.

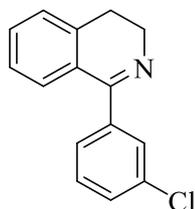


This compound is known.²⁰⁵

This was prepared by general procedure 2B using 2-phenethylamine (302 mg, 2.50 mmol), triethylamine (0.52 mL, 3.75 mmol), *o*-toluoyl chloride (390 mg, 2.50 mmol), DCM (6 mL), 2-chloropyridine (0.26 mL, 2.75 mmol), trifluoromethanesulfonic anhydride (0.46 mL, 2.75 mmol) and anhydrous DCM (12 mL) then purified by column chromatography (0-50% EtOAc in Pet. Ether) to give the product as a white solid (200 mg, 0.90 mmol, 36%); δ_H (400 MHz, CDCl₃) 7.39 (1 H, td, *J* 7.5, 1.1, ArH), 7.36 – 7.32 (1 H, m, ArH), 7.32 – 7.23 (4 H, m, ArH), 7.20 (1 H, t, *J* 7.5, ArH), 6.95

(1 H, d, J 7.5, ArH), 3.91 (2 H, s, CH_2NH), 2.89 (2 H, t, J 7.5, ArCH_2), 2.16 (3 H, s, ArCH_3); δ_{C} (101 MHz, CDCl_3) 168.5, 138.9, 137.6, 135.9, 131.0, 130.4, 129.6, 128.8, 128.7, 127.6, 127.5, 127.1, 125.9, 47.5, 26.2, 19.8.

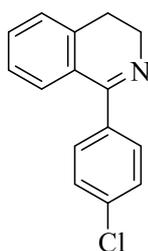
1-(3-Chlorophenyl)-3,4-dihydroisoquinoline.



This compound is known.²⁰⁵

This was prepared by general procedure 2B using 2-phenethylamine (302 mg, 2.50 mmol), triethylamine (0.52 mL, 3.75 mmol), 3-chlorobenzyl chloride (438 mg, 2.50 mmol), DCM (6 mL), 2-chloropyridine (0.26 mL, 2.75 mmol), trifluoromethanesulfonic anhydride (0.46 mL, 2.75 mmol) and anhydrous DCM (12 mL) then purified by column chromatography (0-50% EtOAc in Pet. Ether) to give the product as a yellow oil (452 mg, 1.88 mmol, 75%); δ_{H} (400 MHz, CDCl_3) 7.64 – 7.60 (1H, m, ArH), 7.48 (1H, dt, J 7.5, 1.3, ArH), 7.44 – 7.38 (2H, m, ArH), 7.38 – 7.32 (1H, m, ArH), 7.30 – 7.26 (2H, m, ArH), 7.25 – 7.23 (1H, m, ArH), 3.90 – 3.82 (2H, m, CH_2N), 2.85 – 2.76 (2H, m, CH_2Ar); δ_{C} (101 MHz, CDCl_3) 166.2, 140.9, 138.9, 134.4, 131.1, 129.5, 129.5, 129.0, 128.5, 127.7, 127.7, 127.1, 126.9, 47.8, 26.3.

1-(4-Chlorophenyl)-3,4-dihydroisoquinoline.

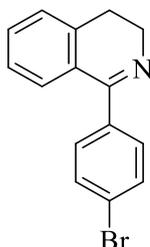


This compound is known.²⁰⁵

This was prepared by general procedure 2A using 2-phenethylamine (605 mg, 5.00 mmol), triethylamine (1.05 mL, 7.50 mmol), 4-chlorobenzyl chloride (875 mg, 5.00 mmol), DCM (12 mL), polyphosphoric acid (8.00 g, 5.00 mmol) and then purified by column chromatography (0-50% EtOAc in Pet. Ether) to give the product as an off-white solid (835 mg, 3.46 mmol, 69%); δ_{H} (400 MHz, CDCl_3) 7.59 - 7.52 (2 H, m,

ArH), 7.44 - 7.37 (3 H, m, ArH), 7.30 - 7.27 (1 H, m, ArH), 7.25 - 7.20 (2 H, m, ArH), 3.85 (2 H, t, J 7.3, CH₂N), 2.81 (2 H, d, J 7.3, CH₂Ar); δ_C (101 MHz, CDCl₃) 166.4, 139.0, 137.4, 137.4, 135.5, 131.1, 130.3, 128.5, 127.8, 127.7, 126.8, 47.7, 26.3.

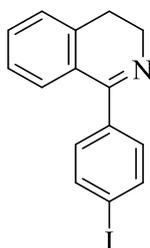
1-(4-Bromophenyl)-3,4-dihydroisoquinoline.



This compound is known.²⁰⁶

This was prepared by general procedure 2B using 2-phenethylamine (302 mg, 2.50 mmol), triethylamine (0.52 mL, 3.75 mmol), 4-bromobenzoyl chloride (549 mg, 2.50 mmol), DCM (6 mL), 2-chloropyridine (0.26 mL, 2.75 mmol), trifluoromethanesulfonic anhydride (0.46 mL, 2.75 mmol) and anhydrous DCM (12 mL) and then purified by column chromatography (0-50% EtOAc in Pet. Ether) to give the product as a yellow solid (410 mg, 1.44 mmol, 58%); δ_H (400 MHz, CDCl₃) 7.59 - 7.53 (2 H, m, ArH), 7.51 - 7.45 (2 H, m, ArH), 7.43 - 7.36 (1 H, m, ArH), 7.29 - 7.19 (3 H, m, ArH), 3.87 - 3.79 (2 H, m, CH₂N), 2.83 - 2.75 (2 H, m, ArCH₂); δ_C (101 MHz, CDCl₃) 166.5, 138.9, 137.9, 131.5, 131.1, 130.6, 128.5, 127.8, 127.7, 126.8, 123.8, 47.7, 26.3.

1-(4-Iodophenyl)-3,4-dihydroisoquinoline.

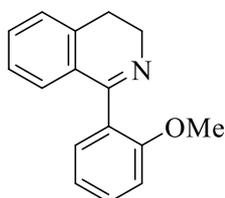


This compound is novel.

This was prepared by general procedure 2B using 2-phenethylamine (302 mg, 2.50 mmol), triethylamine (0.52 mL, 3.75 mmol), 4-iodobenzoyl chloride (549 mg, 2.50 mmol), DCM (6 mL), 2-chloropyridine (0.26 mL, 2.75 mmol), trifluoromethanesulfonic anhydride (0.46 mL, 2.75 mmol) and anhydrous DCM (12

mL) then purified by column chromatography (0-50% EtOAc in Pet. Ether) to give the product as a white solid (515 mg, 1.55 mmol, 62%); Mp: 136.6 – 139.7 °C; ν_{\max} 3047, 2948, 2933, 2889, 2841, 1640, 1596, 1583, 1566 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 7.76 (2 H, d, J 8.3, ArH), 7.41 - 7.36 (1 H, m, ArH), 7.34 (2 H, d, J 8.3, ArH), 7.29 - 7.18 (3 H, m, ArH), 3.87 - 3.77 (2 H, m, CH_2N), 2.79 (2 H, t, J 7.30, ArCH_2); δ_{C} (101 MHz, CDCl_3) 166.6, 138.9, 138.4, 137.4, 131.1, 130.7, 128.4, 127.8, 127.7, 126.8, 95.8, 47.7, 26.3; MS (ESI) m/z : 334.4 $[\text{M} + \text{H}]^+$; HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{13}\text{N}$ 334.0087; Found 334.0090 (0.7 ppm error).

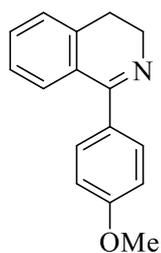
1-(2-Methoxyphenyl)-3,4-dihydroisoquinoline.



This compound is known.²⁰⁵

This was prepared by general procedure 2B using 2-phenethylamine (302 mg, 2.50 mmol), triethylamine (0.52 mL, 3.75 mmol), *o*-anisoyl chloride (427 mg, 2.50 mmol), DCM (6 mL), 2-chloropyridine (0.26 mL, 2.75 mmol), trifluoromethanesulfonic anhydride (0.46 mL, 2.75 mmol) and anhydrous DCM (12 mL) then purified by column chromatography (0-50% EtOAc in Pet. Ether) to give the product as a yellow solid (240 mg, 1.01 mmol, 40%); δ_{H} (400 MHz, CDCl_3) 7.43 - 7.29 (3 H, m, ArH), 7.22 (1 H, d, J 7.4, ArH), 7.16 (1 H, t, J 7.6, ArH), 7.04 (1 H, td, J 7.4, 0.7, ArH), 6.98 (1 H, d, J 7.7, ArH), 6.95 (1 H, d, J 8.3, ArH), 3.91 (2 H, br. s., CH_2N), 3.68 (3 H, s, OMe), 2.86 (2 H, t, J 7.1, ArCH_2); δ_{C} (101 MHz, CDCl_3) 166.5, 157.4, 137.2, 130.6, 130.4, 130.2, 129.8, 128.7, 127.4, 127.3, 126.7, 120.9, 111.2, 55.7, 47.7, 26.1.

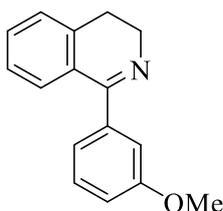
1-(4-Methoxyphenyl)-3,4-dihydroisoquinoline.



This compound is known.²⁰⁶

This was prepared by general procedure 2B using 2-phenethylamine (424 mg, 3.50 mmol), triethylamine (0.73 mL, 5.25 mmol), 4-methoxybenzyl chloride (595 mg, 3.50 mmol), DCM (10 mL), 2-chloropyridine (0.33 mL, 3.50 mmol), trifluoromethanesulfonic anhydride (0.59 mL, 3.50 mmol) and anhydrous DCM (15 mL) then purified by column chromatography (0-50% EtOAc in Pet. Ether) to give the product as a clear oil (516 mg, 2.17 mmol, 62%); δ_{H} (400 MHz, CDCl_3) 7.61 - 7.55 (2 H, m, ArH), 7.42 - 7.36 (1 H, m, ArH), 7.34 - 7.30 (1 H, m, ArH), 7.30 - 7.23 (2 H, m, ArH), 6.98 - 6.93 (2 H, m, ArH), 3.86 (3 H, s, OMe), 3.85 - 3.79 (2 H, m, ArCH₂), 2.83 - 2.75 (2 H, m, CH₂N); δ_{C} (101 MHz, CDCl_3) 166.8, 160.8, 139.2, 131.5, 130.7, 130.4, 129.0, 128.1, 127.5, 126.6, 113.6, 55.5, 47.5, 26.5.

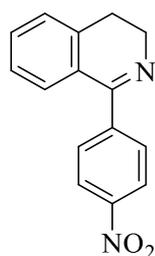
1-(3-Methoxyphenyl)-3,4-dihydroisoquinoline.



This compound is known.¹²⁴

This was prepared by general procedure 2B using 2-phenethylamine (302 mg, 2.50 mmol), triethylamine (0.52 mL, 3.75 mmol), 3-methoxybenzyl chloride (426 mg, 2.50 mmol), DCM (6 mL), 2-chloropyridine (0.26 mL, 2.75 mmol), trifluoromethanesulfonic anhydride (0.46 mL, 2.75 mmol) and anhydrous DCM (12 mL) then purified by column chromatography (0-50% EtOAc in Pet. Ether) to give the product as a clear oil (423 mg, 1.78 mmol, 71%); δ_{H} (400 MHz, CDCl_3) 7.31 (1H, td, J 7.3, 1.6, ArH), 7.25 (1H, t, J 7.9, ArH), 7.23 - 7.14 (3H, m, ArH), 7.11 - 7.05 (2H, m, ArH), 6.92 (1H, ddd, J 8.2, 2.5, 0.6, ArH), 3.81 - 3.77 (2H, m, ArCH₂), 3.76 (3H, s, OMe), 2.77 - 2.70 (2H, m, CH₂N); δ_{C} (101 MHz, CDCl_3) 167.38, 159.63, 140.31, 138.92, 130.90, 129.22, 128.89, 128.17, 127.50, 126.71, 121.53, 115.79, 113.81, 55.49, 47.61, 26.42.

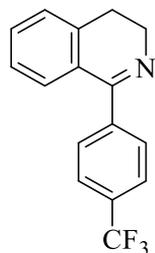
1-(4-Nitrophenyl)-3,4-dihydroisoquinoline.



This compound is known.²⁰⁷

This was prepared by general procedure 2B using 2-phenethylamine (302 mg, 2.50 mmol), triethylamine (0.52 mL, 3.75 mmol), 4-nitrobenzoyl chloride (464 mg, 2.50 mmol), DCM (6 mL), 2-chloropyridine (0.26 mL, 2.75 mmol), trifluoromethanesulfonic anhydride (0.46 mL, 2.75 mmol) and anhydrous DCM (12 mL) then purified by column chromatography (0-50% EtOAc in Pet. Ether) to give the product as a yellow solid (291 mg, 1.15 mmol, 46%); δ_{H} (400 MHz, CDCl_3) 8.33 - 8.25 (2 H, m, ArH), 7.78 (2 H, d, J 8.7, ArH), 7.47 - 7.39 (1 H, m, ArH), 7.35 - 7.23 (2 H, m, ArH), 7.15 (1 H, d, J 7.6, ArH), 3.95 - 3.85 (2 H, m, CH_2N), 2.87 - 2.78 (2 H, m, Ar CH_2); δ_{C} (101 MHz, CDCl_3) 165.9, 148.5, 145.1, 138.8, 131.5, 129.9, 128.1, 127.9, 127.4, 127.0, 123.6, 48.0, 26.2.

1-(4-(Trifluoromethyl)phenyl)-3,4-dihydroisoquinoline.

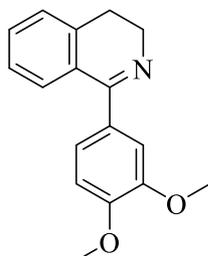


This compound is known.²⁰⁶

This was prepared by general procedure 2B using 2-phenethylamine (302 mg, 2.50 mmol), triethylamine (0.52 mL, 3.75 mmol), 4-(trifluoromethyl)benzoyl chloride (521 mg, 2.50 mmol), DCM (6 mL), 2-chloropyridine (0.26 mL, 2.75 mmol), trifluoromethanesulfonic anhydride (0.46 mL, 2.75 mmol) and anhydrous DCM (12 mL) then purified by column chromatography (0-50% EtOAc in Pet. Ether) to give the product as a yellow solid (405 mg, 1.47 mmol, 59%); δ_{H} (400 MHz, CDCl_3) 7.76 - 7.67 (4 H, m, ArH), 7.45 - 7.39 (1 H, m, ArH), 7.33 - 7.24 (2 H, m, ArH), 7.22 - 7.16 (1 H, m, ArH), 3.92 - 3.85 (2 H, m, CH_2N), 2.87 - 2.80 (2 H, m, Ar CH_2); δ_{C} (101 MHz,

CDCl₃) 166.5, 142.4, 138.9, 131.3, 129.3, 128.4, 127.8, 127.7, 126.9, 125.6, 125.3, 47.8, 26.3; δ_F (376 MHz, CDCl₃) -62.65

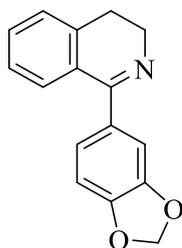
1-(3,4-Dimethoxyphenyl)-3,4-dihydroisoquinoline.



This compound is known.²⁰⁸

This was prepared by general procedure 2B using 2-phenethylamine (302 mg, 2.50 mmol), triethylamine (0.52 mL, 3.75 mmol), 3,4-dimethoxybenzoyl chloride (502 mg, 2.50 mmol), DCM (6 mL), 2-chloropyridine (0.26 mL, 2.75 mmol), trifluoromethanesulfonic anhydride (0.46 mL, 2.75 mmol) and anhydrous DCM (12 mL) then purified by column chromatography (0-50% EtOAc in Pet. Ether) to give the product as a white solid (184 mg, 0.69 mmol, 28%); δ_H (400 MHz, CDCl₃) 7.44 - 7.38 (1 H, m, ArH), 7.36 (1 H, d, *J* 7.5, ArH), 7.31 - 7.23 (3 H, m, ArH), 7.15 (1 H, dd, *J* 8.3, 1.9, ArH), 6.91 (1 H, d, *J* 8.3, ArH), 3.94 (3 H, s, OMe), 3.93 (3 H, s, OMe), 3.86 - 3.79 (2 H, m, CH₂N), 2.85 - 2.76 (2 H, m, ArCH₂); δ_C (101 MHz, CDCl₃) 166.9, 150.4, 149.0, 139.3, 131.6, 130.8, 128.9, 128.2, 127.5, 126.6, 122.2, 111.8, 110.4, 56.1, 47.5, 26.5.

1-(Benzo[d][1,3]dioxol-5-yl)-3,4-dihydroisoquinoline.



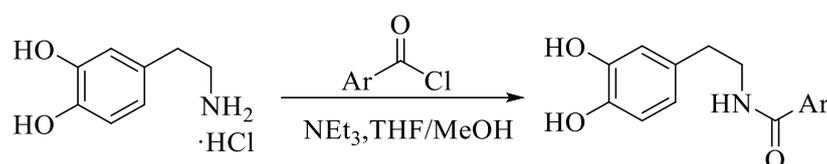
This compound is known.²⁰⁸

This was prepared by general procedure 2B using 2-phenethylamine (302 mg, 2.50 mmol), triethylamine (0.52 mL, 3.75 mmol), piperonyl chloride (461 mg, 2.50 mmol), DCM (6 mL), 2-chloropyridine (0.26 mL, 2.75 mmol), trifluoromethanesulfonic

anhydride (0.46 mL, 2.75 mmol) and anhydrous DCM (12 mL) then purified by column chromatography (0-50% EtOAc in Pet. Ether) to give the product as a white solid (307 mg, 1.22 mmol, 49%); δ_{H} (400 MHz, CDCl_3) 7.42 - 7.36 (1 H, m, ArH), 7.34 - 7.30 (1 H, m, ArH), 7.29 - 7.27 (1 H, m, ArH), 7.25 - 7.23 (1 H, m, ArH), 7.15 - 7.09 (2 H, m, ArH), 6.85 (1 H, d, J 8.1, ArH), 6.01 (2 H, s, OCH_2), 3.84 - 3.77 (2 H, m, CH_2N), 2.81 - 2.75 (2 H, m, ArCH_2); δ_{C} (101 MHz, CDCl_3) 166.7, 148.8, 147.7, 139.2, 133.0, 130.9, 128.8, 128.1, 127.5, 126.7, 123.4, 109.4, 108.0, 101.4, 47.5, 26.5.

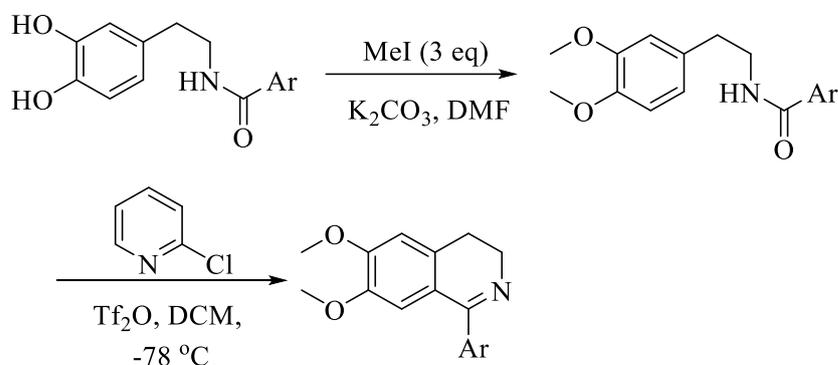
General procedure 2C for the synthesis of 6,7-dimethoxytetrahydroisoquinoline derivatives.

2C-1:



To a solution of dopamine hydrochloride (285 mg, 1.50 mmol) in MeOH (3 mL) was added triethylamine (0.21 mL, 1.50 mmol). A solution of the acid chloride (1.80 mmol) in THF (0.2 mL) and a solution of triethylamine (2.25 mmol) in MeOH (0.3 mL) were both added dropwise and simultaneously to the dopamine solution. After stirring overnight, the reaction was quenched with 1 M HCl (15 mL) and the product extracted with EtOAc (3 x 15 mL). The organic extracts were combined, dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue was purified by column chromatography gradient elution 0-50% EtOAc in Pet. Ether.

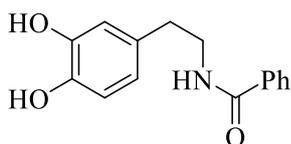
2C-2:



A solution of iodomethane (0.19 mL, 3.00 mmol) in DMF (1 mL) was added dropwise to a suspension containing the amide (1.00 mmol) and K_2CO_3 (415 mg, 3.00 mmol)

in DMF (2 mL). After stirring for 24 h, the reaction was quenched with H₂O (15 mL) and the product extracted with EtOAc (3 x 15 mL). The organic layers were combined, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The residue was dissolved in anhydrous DCM (4 mL) and 2-chloropyridine (0.10 mL, 1.00 mmol) was added. The solution was cooled to -78 °C and trifluoromethanesulfonic anhydride (0.17 mL, 1.00 mmol) was added dropwise. After stirring overnight at rt, the reaction was diluted with DCM (12 mL) and quenched with sat. NaHCO₃ (25 mL). The organic layer was separated and further extracted with DCM (2 x 15 mL). The organic layers were combined, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The product was purified by column chromatography gradient elution 0-100% EtOAc in Pet. Ether.

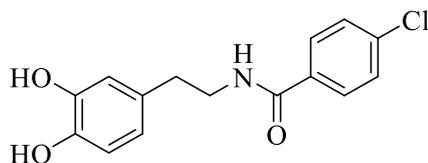
***N*-(3,4-Dihydroxyphenethyl)benzamide.**



This compound is known.²⁰⁹

This was prepared by general procedure 2C-1 using dopamine hydrochloride (285 mg, 1.50 mmol), triethylamine (0.52 mL, 1.50 mmol + 2.25 mmol), benzoyl chloride (252 mg, 1.8 mmol), MeOH (3.00 mL + 0.3 mL), THF (0.2 mL) and then purified by column chromatography (0-50% EtOAc in Pet. Ether) to give the product as a white solid (310 mg, 1.20 mmol, 80%); δ_H (400 MHz, MeOD) 7.80 – 7.73 (2H, m, ArH), 7.54 – 7.48 (1H, m, ArH), 7.47 – 7.40 (2H, m, ArH), 6.73 – 6.68 (2H, m, ArH), 6.57 (1H, dd, J 8.0, 1.8, ArH), 3.53 (2H, t, J 7.4, CH₂N), 2.76 (2H, t, J 7.4, CH₂Ar); δ_C (101 MHz, MeOD) 170.2, 146.3, 144.8, 135.8, 132.5, 132.1, 129.5, 128.2, 121.1, 116.9, 116.4, 43.0, 36.0.

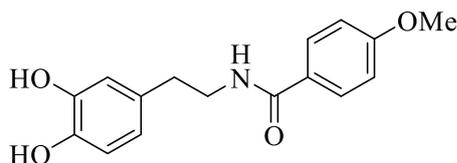
4-Chloro-*N*-(3,4-dihydroxyphenethyl)benzamide



This compound is known but not fully characterised.²¹⁰

This was prepared by general procedure 2C-1 using dopamine hydrochloride (285 mg, 1.50 mmol), triethylamine (0.52 mL, 1.50 mmol + 2.25 mmol), 4-chlorobenzoyl chloride (315 mg, 1.8 mmol), MeOH (3 mL + 0.3 mL), THF (0.2 mL) and then purified by column chromatography (0-50% EtOAc in Pet. Ether) to give the product as a white solid (377 mg, 1.30 mmol, 86%); Mp: 135.2 – 137.0 °C; δ_{H} (400 MHz, MeOD) 7.81 - 7.71 (2 H, m, ArH), 7.46 (2 H, d, J 8.7, ArH), 6.74 - 6.66 (2 H, m, ArH), 6.57 (1 H, dd, J 8.2, 1.9, ArH), 3.54 (2 H, t, J 7.4, CH₂N), 3.37 (1 H, s, NH), 2.77 (2 H, t, J 7.4, ArCH₂); δ_{C} (101 MHz, MeOD) 169.0, 146.3, 144.8, 138.6, 134.5, 132.1, 129.9, 129.7, 121.1, 117.0, 116.4, 43.0, 35.9; MS (ESI) m/z : 314.0 [M + Na]⁺; HRMS (ESI) m/z : [M + Na]⁺ Calcd for C₁₅H₁₄ClNNaO₃ 314.0554; Found 314.0548 (2.2 ppm error).

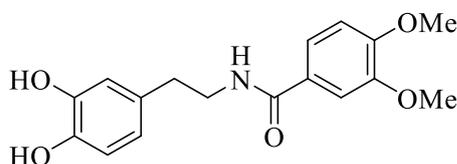
***N*-(3,4-Dihydroxyphenethyl)-4-methoxybenzamide.**



This compound is known but not fully characterised.²¹¹

This was prepared by general procedure 2C-1 using dopamine hydrochloride (285 mg, 1.50 mmol), triethylamine (0.52 mL, 1.50 mmol + 2.25 mmol), 4-methoxybenzoyl chloride (252 mg, 1.8 mmol), MeOH (3 mL + 0.3 mL), THF (0.2 mL) and then purified by column chromatography (0-50% EtOAc in Pet. Ether) to give the product as a yellow oil (391 mg, 1.36 mmol, 91%); δ_{H} (400 MHz, MeOD) 7.74 (2 H, d, J 8.9, ArH), 6.94 (2 H, d, J 8.9, ArH), 6.71 - 6.67 (2 H, m, ArH), 6.56 (1 H, dd, J 8.0, 1.8, ArH), 3.81 (3 H, s, OMe), 3.50 (2 H, t, J 7.5, CH₂N), 2.74 (2 H, t, J 7.5, ArCH₂); δ_{C} (101 MHz, MeOD) 169.8, 163.8, 146.2, 144.7, 132.2, 130.0, 127.8, 121.1, 116.9, 116.4, 114.7, 55.9, 42.9, 36.0; MS (ESI) m/z : 310.3 [M+Na]⁺; HRMS (ESI) m/z : [M+Na]⁺ Calcd for C₁₆H₁₇NNaO₄ 310.1050; Found 310.1037 (4.3 ppm error).

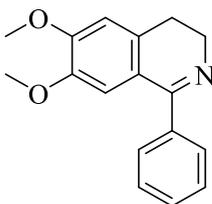
***N*-(3,4-Dihydroxyphenethyl)-3,4-dimethoxybenzamide.**



This compound is novel.

This was prepared by general procedure 2C-1 using dopamine hydrochloride (378 mg, 2.00 mmol), triethylamine (0.70 mL, 2.00 mmol + 3.00 mmol), 3,4-dimethoxybenzoyl chloride (481 mg, 2.4 mmol), MeOH (4 mL + 0.4 mL), THF (0.3 mL) and then purified by column chromatography (0-50% EtOAc in Pet. Ether) to give the product as a white solid (570 mg, 1.80 mmol, 90%); Mp: 151.2 – 153.9 °C; ν_{\max} 3252, 2936, 2838, 2471, 1602, 1577, 1515, 1459, 1431; δ_{H} (400 MHz, MeOD) 7.42 - 7.34 (2 H, m, ArH), 6.95 (1 H, d, J 8.3, ArH), 6.72 - 6.67 (2 H, m, ArH), 6.56 (1 H, dd, J 8.1, 1.8, ArH), 3.84 (6 H, s, OCH₃), 3.51 (2 H, t, J 7.4, CH₂N), 2.74 (2 H, t, J 7.4, CH₂Ar); δ_{C} (101 MHz, MeOD) 169.8, 153.3, 150.1, 146.2, 144.7, 132.2, 128.2, 121.7, 121.1, 117.0, 116.4, 112.0, 111.8, 56.4, 42.9, 36.0; MS (ESI) m/z : 340.1 [M + Na]⁺; HRMS (ESI) m/z : [M + Na]⁺ Calcd for C₁₇H₁₉NNaO₅ 340.1155; Found 340.1147 (2.5 ppm error).

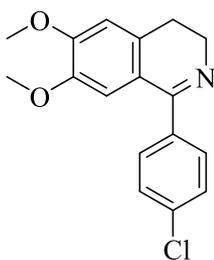
6,7-Dimethoxy-1-phenyl-3,4-dihydroisoquinoline.



This compound is known.²¹²

This was prepared by general procedure 2C-2 using *N*-(3,4-dihydroxyphenethyl)benzamide (257 mg, 1.00 mmol), K₂CO₃ (415 mg, 3.00 mmol), iodomethane (426 mg, 3.00 mmol), DMF (3 mL), 2-chloropyridine (0.10 mL, 1.00 mmol), trifluoromethanesulfonic anhydride (0.17 mL, 1.00 mmol) and anhydrous DCM (4 mL) then purified by column chromatography (0-100% EtOAc in Pet. Ether) to give the product as a white solid (220 mg, 0.82 mmol, 82%); δ_{H} (400 MHz, CDCl₃) 7.64 - 7.56 (2 H, m, ArH), 7.47 - 7.38 (3 H, m, ArH), 6.79 (2 H, d, J 5.6, ArH), 3.94 (3 H, s, OCH₃), 3.85 - 3.77 (2 H, m, CH₂N), 3.72 (3 H, s, OCH₃), 2.78 - 2.68 (2 H, m, ArCH₂); δ_{C} (101 MHz, CDCl₃) 166.9, 151.1, 147.2, 139.2, 132.7, 129.5, 128.9, 128.3, 121.6, 111.7, 110.4, 56.3, 56.1, 47.7, 26.1.

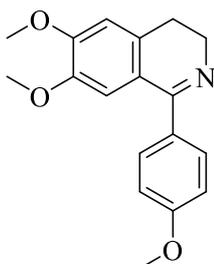
1-(4-Chlorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline.



This compound is known.¹²⁴

This was prepared by general procedure 2C-2 using 4-chloro-*N*-(3,4-dihydroxyphenethyl)benzamide (352 mg, 1.20 mmol), K₂CO₃ (497 mg, 3.60 mmol), iodomethane (512 mg, 3.60 mmol), DMF (3 mL), 2-chloropyridine (0.13 mL, 1.32 mmol), trifluoromethanesulfonic anhydride (0.22 mL, 1.32 mmol) and anhydrous DCM (5 mL) then purified by column chromatography (0-100% EtOAc in Pet. Ether) to give the product as a white solid (190 mg, 0.63 mmol, 53%); δ_{H} (400 MHz, CDCl₃) 7.55 (2 H, d, *J* 8.4, ArH), 7.40 (2 H, d, *J* 8.4, ArH), 6.78 (1 H, s, ArH), 6.73 (1 H, s, ArH), 3.94 (3 H, s, OMe), 3.83 - 3.76 (2 H, m, CH₂N), 3.73 (3 H, s, OMe), 2.75 - 2.69 (2 H, m, ArCH₂); δ_{C} (101 MHz, CDCl₃) 165.9, 151.2, 147.3, 137.6, 135.5, 132.8, 130.3, 128.5, 121.3, 111.3, 110.5, 56.3, 56.2, 47.8, 26.0.

6,7-Dimethoxy-1-(4-methoxyphenyl)-3,4-dihydroisoquinoline.

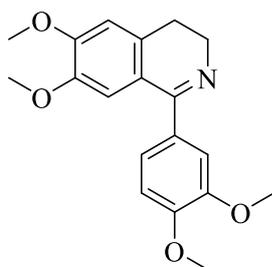


This compound is known.¹²⁴

This was prepared by general procedure 2C-2 using *N*-(3,4-dihydroxyphenethyl)-4-methoxybenzamide (375 mg, 1.30 mmol), K₂CO₃ (539 mg, 3.90 mmol), iodomethane (554 mg, 3.90 mmol), DMF (3 mL), 2-chloropyridine (0.14 mL, 1.43 mmol), trifluoromethanesulfonic anhydride (0.24 mL, 1.43 mmol) and anhydrous DCM (5 mL) then purified by column chromatography (0-100% EtOAc in Pet. Ether) to give the product as a white solid (265 mg, 0.89 mmol, 68%); δ_{H} (400 MHz, CDCl₃) 7.57 (2 H, d, *J* 8.6, ArH), 6.94 (2 H, d, *J* 8.6, ArH), 6.83 (1 H, s, ArH), 6.77 (1 H, s, ArH),

3.94 (3 H, s, OMe), 3.85 (3 H, s, OMe), 3.80 - 3.75 (2 H, m, CH₂N), 3.74 (3 H, s, OMe), 2.74 - 2.68 (2 H, m, ArCH₂); δ_C (101 MHz, CDCl₃) 166.2, 160.7, 150.9, 147.1, 132.9, 131.8, 130.3, 121.8, 113.6, 111.7, 110.4, 56.3, 56.1, 55.4, 47.6, 26.2.

1-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline.

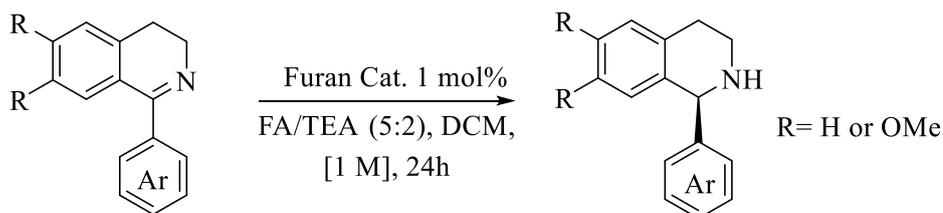


This compound is known.¹²⁴

This was prepared by general procedure 2C-2 using *N*-(3,4-dihydroxyphenethyl)-3,4-dimethoxybenzamide (545 mg, 1.70 mmol), K₂CO₃ (718 mg, 5.10 mmol), iodomethane (739 mg, 5.10 mmol), DMF (5 mL), 2-chloropyridine (0.17 mL, 1.80 mmol), trifluoromethanesulfonic anhydride (0.3 mL, 1.80 mmol) and anhydrous DCM (6 mL) then purified by column chromatography (0-100% EtOAc in Pet. Ether) to give the product as a white solid (220 mg, 0.67 mmol, 40%); δ_H (400 MHz, CDCl₃) 7.25 (1 H, d, *J* 2.0, ArH), 7.18 (1 H, dd, *J* 8.4, 2.0, ArH), 6.93 (1 H, d, *J* 8.4, ArH), 6.90 (1 H, s, ArH), 6.82 (1 H, s, ArH), 3.97 (3 H, s, OMe), 3.94 (3 H, s, OMe), 3.92 (3 H, s, OMe), 3.86 - 3.80 (2 H, m, CH₂N), 3.75 (3 H, s, OMe), 2.84 - 2.77 (2 H, m, CH₂Ar); δ_C (101 MHz, CDCl₃) 167.7, 152.4, 151.4, 149.2, 147.4, 133.6, 129.4, 123.0, 120.6, 112.8, 112.1, 110.6, 110.6, 56.3, 56.2, 56.1, 45.9, 26.2.

7.5. Amine Products

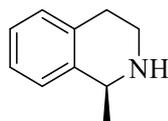
General procedure 3A for ATH of imines.



To a Schlenk tube charged with catalyst (*R,R*)-**131** (5.00 μ mol) was added formic acid/triethylamine 5:2 (0.25 mL) and left to stir for 15 min under a N₂ atmosphere. A

solution of the imine (0.50 mmol) in DCM (0.25 mL) was added to the mixture and left to stir at rt overnight. The reaction was quenched with sat. NaHCO₃ (5 mL) and extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried over MgSO₄, filtered and the solvent removed under reduced pressure. The product was purified by column chromatography gradient elution 0-60% EtOAc in Pet. Ether.

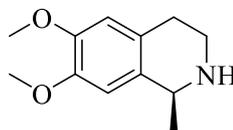
(S)-1-Methyl-1,2,3,4-tetrahydroisoquinoline. 190



This compound is known.²¹³

This was prepared by general procedure 3A using imine **189** (72 mg, 0.50 mmol), FA/TEA (0.25 mL), DCM (0.25 mL), catalyst (*R,R*)-**131** (3.3 mg, 5.00 μmol) and then purified by column chromatography (0-60% EtOAc in Pet. Ether) to give the product as an oil (64 mg, 0.44 mmol, 87%); [α]_D²² +58.2 (c 0.2, CHCl₃) 80% ee (*S*) (lit.²¹³ [α]_D²⁰ -82.5 (c 1.1 in CHCl₃) 99% ee); δ _H (400 MHz, CDCl₃) 7.18 – 7.04 (4H, m, ArH), 4.11 (1H, q, *J* 6.7, CHMe), 3.27 (1H, dt, *J* 12.4, 4.8, CH_AH_BN), 3.07 – 2.98 (1H, m, ArCH₂), 2.93 – 2.82 (1H, m, ArCH₂), 2.74 (1H, dt, *J* 16.4, 4.8, CH_AH_BN), 1.46 (3H, d, *J* 6.7, CH₃); GC analysis (CHROMPAC CYCLODEXTRIN- β -236M-19, 50 m × 0.25 mm × 0.25 μm, gas H₂, T = 100 °C, P = 15 psi, FID temp 250 °C, injector temp 220 °C, imine 49.51 min., *R* isomer 56.04 min., *S* isomer 54.99 min.).

(S)-6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline. 192

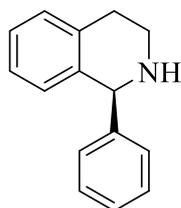


This compound is known.²⁰³

This was prepared by general procedure 3A using imine **191** (102 mg, 0.50 mmol), FA/TEA (0.25 mL), DCM (0.25 mL), catalyst (*R,R*)-**131** (3.3 mg, 5.0 μmol) and then purified by column chromatography (0-60% EtOAc in Pet. Ether) to give the product as a brown solid (74 mg, 0.36 mmol, 71%); [α]_D²³ -36.3 (c 0.1, CHCl₃) 81% ee (*S*) (lit.²⁰³ [α]_D²² -40.1 (c 0.06 in CHCl₃) 94 % ee); δ _H (400 MHz, CDCl₃) 6.59 (1H, s,

ArH), 6.57 (1H, s, ArH), 4.26 (1H, q, J 6.5, CHN), 3.85 (6H, s, 2 x OCH₃), 3.41 – 3.32 (1H, m, CH_AH_BN), 3.25 (1H, b.s, NH), 3.19 – 3.10 (1H, m, CH_AH_BN), 3.00 – 2.90 (1H, m, CH_AH_BAr), 2.87 – 2.77 (1H, m, CH_AH_BAr), 1.59 (3H, d, J 6.5, CHCH₃); GC analysis (CHROMPAC CYCLODEXTRIN- β -236M-19, 50 m \times 0.25 mm \times 0.25 μ m, gas H₂, T = 170 °C, P = 15 psi, FID temp 250 °C, injector temp 220 °C, imine 30.35 min., *R* isomer 28.11 min., *S* isomer 27.58 min.).

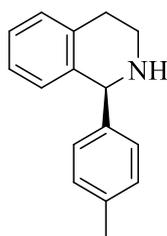
(*S*)-1-Phenyl-1,2,3,4-tetrahydroisoquinoline. 194



This compound is known.¹¹⁷

This was prepared by general procedure 3A using imine **193** (104 mg, 0.50 mmol), FA/TEA (0.25 mL), DCM (0.25 mL), catalyst (*R,R*)-**131** (3.3 mg, 5.0 μ mol) and then purified by column chromatography (0-60% EtOAc in Pet. Ether) to give the product as an off-white solid (74 mg, 0.35 mmol, 70%); $[\alpha]_D^{23} +8.5$ (c 0.1 in CHCl₃) 90% ee (*S*) (lit.¹¹⁷ $[\alpha]_D^{20} -14.6$ (c 0.418 in CHCl₃), 86% ee); δ_H (300 MHz, CDCl₃) 7.40 – 7.23 (5H, m, ArH), 7.15 (2H, d, J 4.0, ArH), 7.10 – 6.98 (1H, m, ArH), 6.76 (1H, d, J 7.6, ArH), 5.11 (1H, s, CHN), 3.35 – 3.21 (1H, m, CH₂N), 3.17 – 2.97 (2H, m, CH₂Ar), 2.92 – 2.77 (1H, m, CH₂N), 1.90 (1H, b.s, NH); GC analysis (CHROMPAC CYCLODEXTRIN- β -236M-19, 50 m \times 0.25 mm \times 0.25 μ m, gas H₂, T = 170 °C, P = 15 psi, FID temp 250 °C, injector temp 220 °C, *R* isomer 35.28 min., *S* isomer 34.76 min.).

(*S*)-1-(*p*-Tolyl)-1,2,3,4-tetrahydroisoquinoline. 195

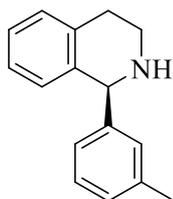


This compound is known.²¹⁴

This was prepared by general procedure 3A using imine (110 mg, 0.50 mmol), FA/TEA (0.25 mL), DCM (0.25 mL), catalyst (*R,R*)-**131** (3.3 mg, 5.0 μ mol) and then purified by column chromatography (0-60% EtOAc in Pet. Ether) to give the product as a clear oil (82 mg, 0.37 mmol, 74%); $[\alpha]_D^{22}$ -2.5 (*c* 0.1 in CHCl₃) 90% ee (*S*) (lit.²¹⁴ $[\alpha]_D^{20}$ +8.3 (*c* 0.41 in CHCl₃), 90% ee); δ_H (400 MHz, CDCl₃) 7.19 – 7.10 (6H, m, ArH), 7.04 (1H, dt, *J* 8.4, 4.2, ArH), 6.77 (1H, d, *J* 7.7, ArH), 5.09 (1H, s, CHNH), 3.33 – 3.23 (1H, m, CH_AH_BN), 3.15 – 2.98 (2H, m, CH_AH_BN + CH_AH_BAr), 2.90 – 2.77 (1H, m, CH_AH_BAr), 2.35 (3H, s, ArCH₃), 2.14 (1H, bs, NH); δ_C (101 MHz, CDCl₃) 141.9, 138.5, 137.1, 135.5, 129.2, 129.1, 129.0, 128.2, 126.3, 125.7, 61.9, 42.3, 29.8, 21.2; HPLC analysis (Chiralcel OD-H, 250 \times 4.6 mm column, hexane/2-propanol 90:10, 1 mL/min, 210 nm, *S* isomer 7.85 min., *R* isomer 9.76 min.).

This product was also prepared on a larger scale using general procedure 3A using imine (1.105 g, 5.00 mmol), FA/TEA (2.5 mL), DCM (2.5 mL), catalyst (*R,R*)-**131** (33 mg, 50 μ mol) and then purified by column chromatography (0-60% EtOAc in Pet. Ether) to give the product as a brown solid (788 mg, 3.53 mmol, 71%). In this reaction the product was formed in 91% ee.

(*S*)-1-(*m*-Tolyl)-1,2,3,4-tetrahydroisoquinoline. **196**

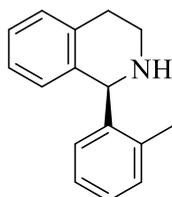


This compound is known.²¹⁴

This was prepared by general procedure 3A using imine (110 mg, 0.50 mmol), FA/TEA (0.25 mL), DCM (0.25 mL), catalyst (*R,R*)-**131** (3.3 mg, 5.0 μ mol) and then purified by column chromatography (0-60% EtOAc in Pet. Ether) to give the product as a yellow oil (84 mg, 0.37 mmol, 76%); $[\alpha]_D^{22}$ +9.0 (*c* 0.1 in CHCl₃) 92% ee, (*S*) (lit.²¹⁴ $[\alpha]_D^{20}$ +7.6 (*c* 0.22 in CHCl₃) 90% ee); δ_H (400 MHz, CDCl₃) 7.24 (1H, t, *J* 7.5, ArH), 7.17 (2H, d, *J* 4.2, ArH), 7.15 – 7.10 (2H, m, ArH), 7.09 – 7.02 (2H, m, ArH), 6.79 (1H, d, *J* 7.7, ArH), 5.10 (1H, s, ArCHNH), 3.36 – 3.27 (1H, m, CH_AH_BN), 3.17 – 3.04 (2H, m, CH_AH_BN + CH_AH_BA), 2.92 – 2.81 (1H, m, CH_AH_BAr), 2.36 (3H, s,

ArCH₃), 2.09 (1H, bs, NH); δ_C (101 MHz, CDCl₃) δ 144.7, 138.4, 138.1, 135.4, 129.6, 129.0, 128.3, 128.2, 128.1, 126.2, 126.1, 125.7, 62.2, 42.4, 29.8, 21.4; HPLC analysis (Chiralcel OD-H, 250 \times 4.6 mm column, hexane/2-propanol 90:10, 1 mL/min, 210 nm, *S* isomer 6.15 min., *R* isomer 8.91 min.).

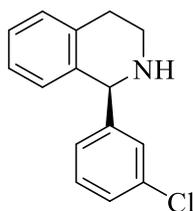
(*S*)-1-(*o*-Tolyl)-1,2,3,4-tetrahydroisoquinoline. 197



This compound is known.¹¹⁷

This was prepared by general procedure 3A using imine (110 mg, 0.50 mmol), FA/TEA (0.25 mL), DCM (0.25 mL), catalyst (*R,R*)-**131** (3.3 mg, 5.0 μ mol) and then purified by column chromatography (0-60% EtOAc in Pet. Ether) to give the product as a clear oil (28 mg, 0.13 mmol, 25%); $[\alpha]_D^{24} +6.9$ (*c* 0.1 in CHCl₃) 76% ee (*S*) (lit.¹¹⁷ $[\alpha]_D^{20} -16.0$ (*c* 0.243 in CHCl₃) 77% ee); δ_H (400 MHz, CDCl₃) 7.22 – 7.17 (2 H, m, ArH), 7.16 – 7.13 (2 H, m, ArH), 7.13 – 7.08 (1 H, m, ArH), 7.07 – 7.00 (2 H, m, ArH), 6.69 (1 H, d, *J* 7.7, ArH), 5.37 (1 H, s, CHNH), 3.34 – 3.24 (1 H, m, CH_AH_BN), 3.16 – 3.02 (2 H, m, CH_AH_BN + CH_AH_BAr), 2.90 – 2.79 (1 H, m, CH_AH_BAr), 2.42 (3 H, s, ArCH₃), 2.20 – 2.06 (1 H, m, NH); δ_C (101 MHz, CDCl₃) 142.6, 138.6, 136.8, 135.6, 130.9, 129.7, 129.1, 127.7, 127.4, 126.2, 126.1, 125.9, 59.1, 42.7, 29.9, 19.6; HPLC analysis (CHIRALPAK IC, 250 \times 4.6 mm column, 250 \times 4.6 mm column, hexane/2-propanol 95:5, 1 mL/min, 210 nm, *S* isomer 5.60 min., *R* isomer 6.30 min.).

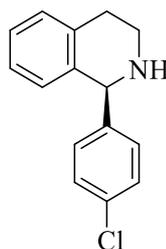
(*S*)-1-(3-Chlorophenyl)-1,2,3,4-tetrahydroisoquinoline. 199



This compound is known.¹²⁵

This was prepared by general procedure 3A using imine (121 mg, 0.50 mmol), FA/TEA (0.25 mL), DCM (0.25 mL), catalyst (*R,R*)-**131** (3.3 mg, 5.0 μ mol) and then purified by column chromatography (0-60% EtOAc in Pet. Ether) to give the product as a white solid (76 mg, 0.31 mmol, 62%); $[\alpha]_D^{22}$ -27.9 (*c* 0.1 in CHCl₃) 91% ee (*S*); δ_H (300 MHz, CDCl₃) 7.31 - 7.22 (3 H, m, ArH), 7.19 - 7.13 (3 H, m, ArH), 7.06 (1 H, dt, *J* 8.1, 4.2, ArH), 6.74 (1 H, d, *J* 7.5, ArH), 5.09 (1 H, s, CHNH), 3.32 - 3.19 (1 H, m, CH_AH_BN), 3.15 - 2.98 (2 H, m, CH_AH_BN + CH_AH_BAr), 2.90 - 2.76 (1 H, m, CH_AH_BAr), 2.25 (1 H, br. s., NH); δ_C (101 MHz, CDCl₃) δ 146.9, 137.4, 135.5, 134.4, 129.8, 129.3, 129.2, 128.1, 127.8, 127.4, 126.7, 125.9, 61.7, 42.2, 29.7; HPLC analysis (Chiralcel OD-H, 250 \times 4.6 mm column, hexane/2-propanol 90:10, 1 mL/min, 210 nm, *S* isomer 6.89 min., *R* isomer 9.46 min.).

(*S*)-1-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinoline. 200

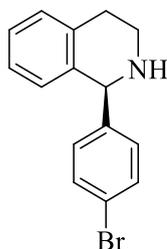


This compound is known.²¹⁴

This was prepared by general procedure 3A using imine (121 mg, 0.50 mmol), FA/TEA (0.25 mL), DCM (0.25 mL), catalyst (*R,R*)-**131** (3.3 mg, 5.0 μ mol) and then purified by column chromatography (0-60% EtOAc in Pet. Ether) to give the product as a white solid (78 mg, 0.32 mmol, 64%); $[\alpha]_D^{23}$ +25.0 (*c* 0.1 in CHCl₃) 88% ee, (*S*) (lit.²¹⁴ $[\alpha]_D^{20}$ +17.8 (*c* 0.21 in CHCl₃) 93% ee (*S*)); δ_H (400 MHz, CDCl₃) 7.32 - 7.27 (2 H, m, ArH), 7.24 - 7.19 (2 H, m, ArH), 7.17 - 7.12 (2 H, m, ArH), 7.05 (1 H, dt, *J* 8.1, 4.1, ArH), 6.72 (1 H, d, *J* 7.7 ArH), 5.09 (1 H, s, CHNH), 3.31 - 3.20 (1 H, m, CH_AH_BN), 3.14 - 2.99 (2 H, m, CH_AH_BN + CH_AH_BAr), 2.88 - 2.78 (1 H, m, CH_AH_BAr), 2.17 (1 H, br. s., NH); δ_C (101 MHz, CDCl₃) 143.4, 137.8, 135.5, 133.3, 130.5, 129.3, 128.7, 128.1, 126.6, 125.9, 61.5, 42.3, 29.8; HPLC analysis (Chiralcel OD-H, 250 \times 4.6 mm column, hexane/2-propanol 80:20, 1 mL/min, 210 nm, *S* isomer 6.28 min., *R* isomer 8.43 min.).

Note: The reduction was stopped at 16 h as a longer reaction time (24 h) resulted in the formation of the formylated derivative. However, the formylated derivative could be converted back to the amine product without loss of enantioselectivity; to a solution of the formylated amine (65 mg, 0.24 mmol) in EtOH (3 mL) was added 10% NaOH solution (0.8 mL). After refluxing overnight, the solution was cooled to rt and concentrated under reduced pressure. The mixture was partitioned between CHCl₃ (10 mL) and 10% NaOH solution (10 mL). The CHCl₃ extract was collected, dried over MgSO₄, filtered and the solvent removed under reduced pressure to give the product (54 mg, 0.22 mmol, 93%).

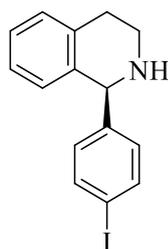
(S)-1-(4-Bromophenyl)-1,2,3,4-tetrahydroisoquinoline. 201



This compound is known.¹¹⁷

This was prepared by general procedure 3A using imine (144 mg, 0.50 mmol), FA/TEA (0.25 mL), DCM (0.25 mL), catalyst (*R,R*)-**131** (3.3 mg, 5.0 μmol) and then purified by column chromatography (0-60% EtOAc in Pet. Ether) to give the product as an orange solid (117 mg, 0.40 mmol, 80%); $[\alpha]_D^{23} +4.9$ (*c* 0.1 in CHCl₃) 93% ee (*S*) (lit.¹¹⁷ $[\alpha]_D^{20} -18.5$ (*c* 0.308 in CHCl₃) 76% ee); δ_H (400 MHz, CDCl₃) 7.45 (2 H, d, *J* 8.4, ArH), 7.20 – 7.13 (4 H, m, ArH), 7.08 – 7.01 (1 H, m, ArH), 6.72 (1 H, d, *J* 7.7, ArH), 5.07 (1 H, s, CHNH), 3.30 – 3.20 (1 H, m, CH_AH_BN), 3.14 – 2.99 (2 H, m, CH_AH_BN + CH_AH_BAr), 2.88 – 2.78 (1 H, m, CH_AH_BAr), 2.09 (1 H, s, NH); δ_C (101 MHz, CDCl₃) 143.9, 137.7, 135.5, 131.6, 130.9, 129.3, 128.1, 126.6, 125.9, 121.4, 61.6, 42.3, 29.7; HPLC analysis (CHIRALPAK IA, 250 × 4.6 mm column, 250 × 4.6 mm column, hexane/2-propanol 90:10, 1 mL/min, 210 nm, *S* isomer 9.40 min., *R* isomer 8.04 min.).

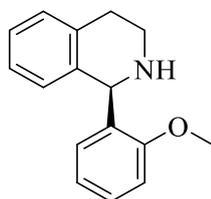
(S)-1-(4-Iodophenyl)-1,2,3,4-tetrahydroisoquinoline. 202



This compound is novel.

This was prepared by general procedure 3A using imine (166 mg, 0.50 mmol), FA/TEA (0.25 mL), DCM (0.25 mL), catalyst (*R,R*)-**131** (3.3 mg, 5.0 μ mol) and then purified by column chromatography (0-60% EtOAc in Pet. Ether) to give the product as a white solid (95 mg, 0.285 mmol, 57%); Mp: 87.2 – 89.0 °C; $[\alpha]_D^{22} +30.0$ (*c* 0.1 in CHCl₃) 93% ee (*S*); ν_{\max} 3245, 3055, 3020, 2965, 2916, 2818, 1666, 1601, 1495 cm⁻¹; δ_H (400 MHz, CDCl₃) 7.66 - 7.61 (2 H, m, ArH), 7.17 - 7.12 (2 H, m, ArH), 7.08 - 6.99 (3 H, m, ArH), 6.72 (1 H, d, *J* 7.70, ArH), 5.08 (1 H, s, CHNH), 3.39 (1 H, br. s., NH), 3.29 - 3.20 (1 H, m, CH_AH_BN), 3.14 - 2.98 (2 H, m, CH_AH_BN + CH_AH_BAr), 2.90 - 2.78 (1 H, m, CH_AH_BAr); δ_C (101 MHz, CDCl₃) 144.2, 137.7, 137.3, 135.3, 131.2, 129.3, 128.1, 126.7, 125.9, 93.2, 61.4, 42.0, 29.5; MS (ESI⁺) *m/z*: 336.1 [M+H]⁺; HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₁₅H₁₅NI 336.0240; Found 336.0241 (0.7 ppm error); HPLC analysis (CHIRALPAK IC, 250 × 4.6 mm column, 250 × 4.6 mm column, hexane/2-propanol 90:10, 1 mL/min, 210 nm, *S* isomer 5.92 min., *R* isomer 7.89 min.).

(R)-1-(2-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline. 203

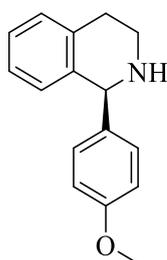


This compound is known.¹¹⁶

This was prepared by general procedure 3A using imine (80 mg, 0.33 mmol), FA/TEA (0.17 mL), DCM (0.17 mL), catalyst (*R,R*)-**131** (2.2 mg, 3.3 μ mol) and then purified by column chromatography (0-60% EtOAc in Pet. Ether) to give the product as an off-white solid (22 mg, 0.09 mmol, 28%); $[\alpha]_D^{23} -16.4$ (*c* 0.08 in CHCl₃) 90% ee (*R*) (lit.¹¹⁶ $[\alpha]_D^{23} +39.3$ (*c* 0.80 in CHCl₃) 79% ee); δ_H (400 MHz, CDCl₃) 7.28 - 7.21 (1 H, m,

ArH), 7.15 (2 H, d, J 4.0, ArH), 7.06 (1 H, dt, J 8.1, 4.0, ArH), 6.93 (1 H, d, J 8.1, ArH), 6.87 - 6.78 (3 H, m, ArH), 5.56 (1 H, s, CHNH), 3.86 (3 H, s, OCH₃), 3.18 - 3.09 (1 H, m, CH_AH_BNH), 3.07 - 2.99 (1 H, m, CH_AH_BNH), 2.95 - 2.88 (2 H, m, ArCH₂), 2.52 (1 H, br. s., NH); δ_C (101 MHz, CDCl₃) 157.4, 137.7, 135.9, 132.6, 130.5, 129.1, 128.5, 128.2, 126.3, 125.7, 120.3, 110.6, 55.6, 55.1, 41.0, 29.7; HPLC analysis (CHIRALPAK IA, 250 \times 4.6 mm column, 250 \times 4.6 mm column, hexane/2-propanol 80:20, 1 mL/min, 210 nm, *S* isomer 8.63 min., *R* isomer 7.08 min.).

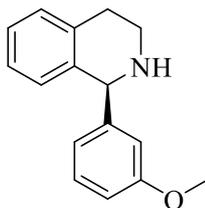
(*S*)-1-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline. 204



This compound is known.¹¹⁶

This was prepared by general procedure 3A using imine (119 mg, 0.50 mmol), FA/TEA (0.25 mL), DCM (0.25 mL), catalyst (*R,R*)-**131** (3.3 mg, 5.0 μ mol) and then purified by column chromatography (0-60% EtOAc in Pet. Ether) to give the product as a clear oil (104 mg, 0.44 mmol, 87% yield); $[\alpha]_D^{23}$ +12.8 (*c* 0.2 in CHCl₃) 92% ee (*S*) (lit.¹¹⁶ $[\alpha]_D^{23}$ +96.3 (*c* 1.01 in CHCl₃) 39% ee); δ_H (400 MHz, CDCl₃) 7.22 - 7.16 (2 H, m, ArH), 7.14 (2 H, d, J 4.0, ArH), 7.04 (1 H, dt, J 8.1, 4.2, ArH), 6.90 - 6.82 (2 H, m, ArH), 6.76 (1 H, d, J 7.7, ArH), 5.07 (1 H, s, CHNH), 3.80 (3 H, s, OCH₃), 3.32 - 3.21 (1 H, m, CH_AH_BN), 3.15 - 2.98 (2 H, m, CH_AH_BN + CH_AH_BAr), 2.89 - 2.76 (1 H, m CH_AH_BAr), 2.13 (1 H, br. s., NH); δ_C (101 MHz, CDCl₃) 158.9, 138.5, 137.0, 135.4, 130.0, 129.0, 128.1, 126.2, 125.6, 113.8, 61.4, 55.3, 42.3, 29.8; HPLC analysis (CHIRALPAK IC, 250 \times 4.6 mm column, 250 \times 4.6 mm column, hexane/2-propanol 80:20, 1 mL/min, 210 nm, *S* isomer 7.54 min., *R* isomer 11.25 min.).

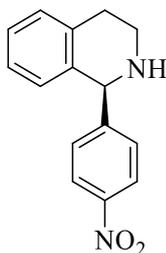
(S)-1-(3-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline. 205



This compound is novel.

This was prepared by general procedure 3A using imine (119 mg, 0.50 mmol), FA/TEA (0.25 mL), DCM (0.25 mL), catalyst (*R,R*)-**131** (3.3 mg, 3.3 μ mol) and then purified by column chromatography (0-60% EtOAc in Pet. Ether) to give the product as a greenish oil (74 mg, 0.31 mmol, 62%); $[\alpha]_D^{25} +28.0$ (*c* 0.05 in CHCl_3) 94% ee (*S*); ν_{max} 3328, 3059, 3019, 2935, 2832, 1598, 1582, 1486 cm^{-1} ; δ_{H} (400 MHz, CDCl_3) δ 7.26 – 7.21 (1H, m, ArH), 7.17 – 7.11 (2H, m, ArH), 7.08 – 7.00 (1H, m, ArH), 6.89 – 6.75 (4H, m, ArH), 5.09 (1H, s, *CHNH*), 3.78 (3H, s, OCH_3), 3.33 – 3.24 (1H, m, CH_2), 3.14 – 2.98 (2H, m, CH_2), 2.89 – 2.78 (1H, m, CH_2), 2.19 (1H, s, NH); δ_{C} (101 MHz, CDCl_3) δ 159.82, 146.44, 138.08, 135.44, 129.49, 129.15, 128.20, 126.45, 125.80, 121.55, 114.75, 112.96, 62.14, 55.34, 42.32, 29.80; HRMS calcd for $\text{C}_{16}\text{H}_{18}\text{NO}$ $[\text{M}+\text{H}]^+$ 240.1383, found 240.1389 (2.7 ppm error); HPLC analysis (Chiralpak IC, 250 \times 4.6 mm column, hexane/2-propanol 85:15, 0.5 mL/min, 210/230/250 nm, *S* isomer 14.27 min., *R* isomer 20.43 min.).

(S)-1-(4-Nitrophenyl)-1,2,3,4-tetrahydroisoquinoline. 206

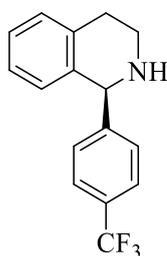


This compound is known.¹¹⁷

This was prepared by general procedure 3A using imine (126 mg, 0.50 mmol), FA/TEA (0.25 mL), DCM (0.25 mL), catalyst (*R,R*)-**131** (3.3 mg, 5.0 μ mol) and then purified by column chromatography (0-60% EtOAc in Pet. Ether) to give the product as yellow solid (64 mg, 0.25 mmol, 50%); $[\alpha]_D^{22} +3.5$ (*c* 0.05 in CHCl_3) 89% ee (*S*) (lit.¹¹⁷ $[\alpha]_D^{20} -25.9$ (*c* 0.189 in CHCl_3) 64% ee); δ_{H} (400 MHz, CDCl_3) 8.23 - 8.12 (2

H, m, ArH), 7.47 (2 H, d, J 8.6, ArH), 7.22 - 7.14 (2 H, m, ArH), 7.12 - 7.02 (1 H, m, ArH), 6.68 (1 H, d, J 7.6, ArH), 5.23 (1 H, s, CHNH), 3.30 - 3.18 (1 H, m, CH_AH_BN), 3.17 - 2.99 (2 H, m, CH_AH_BN + CH_AH_BAr), 2.91 - 2.78 (1 H, m, CH_AH_BAr), 2.39 (1 H, br. s, NH); δ_C (101 MHz, $CDCl_3$) 152.0, 147.5, 136.5, 135.4, 130.1, 129.6, 128.0, 127.1, 126.1, 123.8, 61.3, 42.1, 29.5; HPLC analysis (CHIRALPAK IC, 250×4.6 mm column, 250×4.6 mm column, hexane/2-propanol 95:5, 1 mL/min, 210 nm, *S* isomer 16.20 min., *R* isomer 18.58 min.).

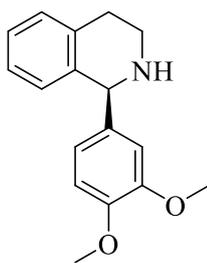
(*S*)-1-(4-(Trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline. 207



This compound is known.¹¹⁷

This was prepared by general procedure 3A using imine (138 mg, 0.50 mmol), FA/TEA (0.25 mL), DCM (0.25 mL), catalyst (*R,R*)-**131** (3.3 mg, 5.0 μ mol) and then purified by column chromatography (0-60% EtOAc in Pet. Ether) to give the product as a white solid (125 mg, 0.45 mmol, 90%); $[\alpha]_D^{21} +26.9$ (c 0.1 in $CHCl_3$) 91% ee (*S*) (lit.¹¹⁷ $[\alpha]_D^{20} -15.4^\circ$ (c 0.279 in $CHCl_3$) 73% ee); δ_H (400 MHz, $CDCl_3$) 7.58 (2 H, d, J 8.1, ArH), 7.41 (2 H, d, J 8.1, ArH), 7.19 - 7.15 (2 H, m, ArH), 7.05 (1 H, s, ArH), 6.70 (1 H, d, J 7.6, ArH), 5.17 (1 H, s, CHNH), 3.30 - 3.20 (1 H, m, CH_AH_BN), 3.15 - 3.00 (2 H, m, CH_AH_BN + CH_AH_BAr), 2.90 - 2.79 (1 H, m, CH_AH_BAr), 2.15 - 2.03 (1 H, br. s, NH); δ_C (101 MHz, $CDCl_3$) 148.8, 137.3, 135.5, 130.0, 129.5, 129.4, 128.1, 126.8, 126.0, 125.5, 61.7, 42.2, 29.7; HPLC analysis (Chiralcel OD-H, 250×4.6 mm column, hexane/2-propanol 90:10, 1 mL/min, 210 nm, *S* isomer 7.00 min., *R* isomer 10.35 min.).

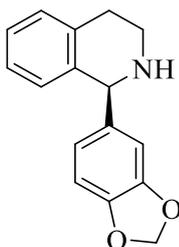
(S)-1-(3,4-Dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline. 208



This compound is known.¹²⁵

This was prepared by general procedure 3A using imine (107 mg, 0.40 mmol), FA/TEA (0.20 mL), DCM (0.20 mL), catalyst (*R,R*)-**131** (2.7 mg, 4.1 μ mol) and then purified by column chromatography (0-60% EtOAc in Pet. Ether) to give the product as a white solid (87 mg, 0.32 mmol, 81%); $[\alpha]_D^{22} +12.8$ (*c* 0.1 in CHCl_3) 91% ee (*S*); δ_{H} (400 MHz, CDCl_3) 7.16 - 7.11 (2 H, m, ArH), 7.08 - 7.00 (1 H, m, ArH), 6.85 - 6.75 (4 H, m, ArH), 5.05 (1 H, s, CHNH), 3.87 (3 H, s, OCH₃), 3.82 (3 H, s, OCH₃), 3.33 - 3.24 (1 H, m, CH_AH_BN), 3.15 - 3.00 (2 H, m, CH_AH_BN + CH_AH_BAr), 2.87 - 2.76 (1 H, m, CH_AH_BAr), 2.22 (1 H, br. s, NH); δ_{C} (101 MHz, CDCl_3) 149.2, 148.5, 138.4, 137.3, 135.4, 129.1, 128.1, 126.4, 125.8, 121.4, 112.0, 110.8, 62.1, 56.0, 56.0, 42.6, 29.7; HPLC analysis (Chiralcel OD-H, 250 \times 4.6 mm column, hexane/2-propanol 80:20, 1 mL/min, 210 nm, *S* isomer 13.6 min., *R* isomer 24.2 min.).

(S)-1-(Benzo[d][1,3]dioxol-5-yl)-1,2,3,4-tetrahydroisoquinoline. 209

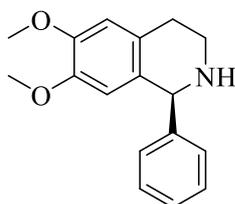


This compound is novel.

This was prepared by general procedure 3A using imine (126 mg, 0.50 mmol), FA/TEA (0.25 mL), DCM (0.25 mL), catalyst (*R,R*)-**131** (3.3 mg, 5.0 μ mol) and then purified by column chromatography (0-60% EtOAc in Pet. Ether) to give the product as a white solid (91 mg, 0.36 mmol, 72%); $[\alpha]_D^{23} +7.8$ (*c* 0.1 in CHCl_3) 90% ee (*S*); Mp: 66.8 – 68.5 $^{\circ}\text{C}$; δ_{H} (400 MHz, CDCl_3) 7.17 - 7.10 (2 H, m, ArH), 7.09 - 7.01 (1 H, m, ArH), 6.79 (1 H, d, *J* 7.7, ArH), 6.77 - 6.71 (3 H, m, ArH), 5.93 (2 H, s, OCH₂O), 5.03 (1 H, s, CHNH), 3.34 - 3.20 (1 H, m, CH_AH_BN), 3.14 - 2.96 (2 H, m CH_AH_BN +

CH_AH_BAr), 2.89 - 2.72 (1 H, m, CH_AH_BAr), 2.03 (1 H, br. s, NH); δ_C (101 MHz, $CDCl_3$) 147.9, 147.0, 139.0, 138.4, 135.5, 129.1, 128.2, 126.4, 125.8, 122.5, 109.3, 108.0, 101.1, 61.9, 42.4, 29.8; MS (ESI) m/z : 254.3 $[M + H]^+$; HRMS (ESI) m/z : $[M + H]^+$ calcd for $C_{16}H_{16}NO_2$ 254.1176; Found 254.1174 (0.8 ppm error); HPLC analysis (CHIRALPAK IC, 250×4.6 mm column, 250×4.6 mm column, hexane/2-propanol 90:10, 1 mL/min, 210 nm, *S* isomer 9.82 min., *R* isomer 13.91 min.).

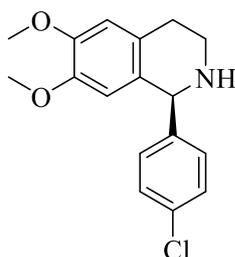
(*S*)-6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline. 212



This compound is known.¹¹⁴

This was prepared by general procedure 3A using imine (133 mg, 0.50 mmol), FA/TEA (0.25 mL), DCM (0.25 mL), catalyst (*R,R*)-**131** (3.3 mg, 5.0 μ mol) and then purified by column chromatography (0-60% EtOAc in Pet. Ether) to give the product as an off-white solid (97 mg, 0.36 mmol, 72%); $[\alpha]_D^{22}$ -14.8 (*c* 0.05 in $CHCl_3$) 92% ee (*S*) (lit.¹¹⁴ $[\alpha]_D^{23}$ +13.7 (*c* 1.02 in $CHCl_3$) 82% ee); δ_H (400 MHz, $CDCl_3$) 7.35 - 7.22 (5 H, m, ArH), 6.63 (1 H, s, ArH), 6.24 (1 H, s, ArH), 5.05 (1 H, s, $CHNH$), 3.87 (3 H, s, OMe), 3.63 (3 H, s, OMe), 3.26 - 3.16 (1 H, m, CH_AH_BN), 3.09 - 2.99 (1 H, m, CH_AH_BN), 2.98 - 2.87 (1 H, m, $ArCH_AH_B$), 2.80 - 2.69 (1 H, m, $ArCH_AH_B$), 2.08 (1 H, br. s, NH); δ_C (101 MHz, $CDCl_3$) δ 147.8, 147.2, 144.8, 129.8, 129.0, 128.5, 127.7, 127.5, 111.5, 111.1, 61.5, 56.0, 56.0, 41.9, 29.4; HPLC analysis (Chiralcel OD-H, 250×4.6 mm column, hexane/2-propanol 90:10, 1 mL/min, 210 nm, *S* isomer 16.31 min., *R* isomer 22.67 min.).

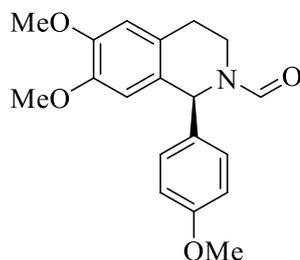
(*S*)-1-(4-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. 213



This compound is known.¹¹⁴

This was prepared by general procedure 3A using imine (120 mg, 0.40 mmol), FA/TEA (0.20 mL), DCM (0.20 mL), catalyst (*R,R*)-**131** (2.7 mg, 4.1 μ mol) and then purified by column chromatography (0-60% EtOAc in Pet. Ether) to give the product as yellow solid (99 mg, 0.33 mmol, 82%); $[\alpha]_{\text{D}}^{22} +177.1$ (*c* 0.1 in CHCl_3) 97% ee (*S*) (lit.¹¹⁴ $[\alpha]_{\text{D}}^{23} -99.6$ (*c* 0.51 in CHCl_3) 87% ee); δ_{H} (400 MHz, CDCl_3) 7.31 - 7.27 (2 H, m, ArH), 7.19 (2 H, d, *J* 8.4, ArH), 6.63 (1 H, s, ArH), 6.20 (1 H, s, ArH), 5.02 (1 H, s, CHNH), 3.87 (3 H, s, OMe), 3.65 (3 H, s, OMe), 3.23 - 3.14 (1 H, m, $\text{CH}_A\text{H}_B\text{N}$), 3.05 (1 H, m, $\text{CH}_A\text{H}_B\text{N}$), 2.97 - 2.86 (1 H, m, $\text{CH}_A\text{H}_B\text{Ar}$), 2.74 (1 H, dt, *J* 15.8, 4.6, $\text{CH}_A\text{H}_B\text{Ar}$), 1.85 (1 H, br. s, NH); δ_{C} (101 MHz, CDCl_3) 147.9, 147.3, 143.6, 133.2, 130.4, 129.5, 128.7, 127.8, 111.6, 110.9, 60.9, 56.0, 56.0, 42.0, 29.4; HPLC analysis (CHIRALPAK IA, 250 \times 4.6 mm column, 250 \times 4.6 mm column, hexane/2-propanol 80:20, 1 mL/min, 210 nm, *S* isomer 16.60 min., *R* isomer 14.40 min.).

(*S*)-6,7-Dimethoxy-1-(4-methoxyphenyl)-3,4-dihydroisoquinoline-2(1H)-carbaldehyde. 214

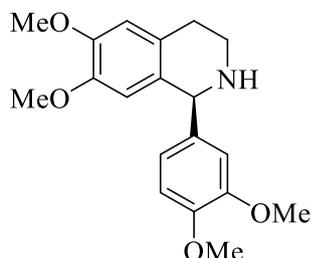


This compound is known.¹¹⁴

This was prepared by general procedure 3A using imine (148 mg, 0.50 mmol), FA/TEA (0.25 mL), DCM (0.25 mL), catalyst (*R,R*)-**131** (3.3 mg, 5.0 μ mol) and then purified by column chromatography (0-60% EtOAc in Pet. Ether) to give the product as an off-white solid (43 mg, 0.13 mmol, 26%); $[\alpha]_{\text{D}}^{23} -35.0$ (*c* 0.05 in CHCl_3) 95% ee (*S*); δ_{H} (400 MHz, CDCl_3) 8.29 (1H, s, CHO), 7.19 (2H, d, *J* 8.5, ArH), 6.85 (2H, d, *J* 8.5, ArH), 6.61 (1H, s, ArH), 6.22 (1H, s, ArH), 5.25 (1H, s, CHN), 3.86 (3H, s, OMe), 3.77 (3H, s, OMe), 3.64 (3H, s, OMe), 3.23 - 3.12 (1H, m, $\text{CH}_A\text{H}_B\text{N}$), 3.10 - 2.99 (2H, m, $\text{CH}_A\text{H}_B\text{N}$ + $\text{CH}_A\text{H}_B\text{Ar}$), 2.92 - 2.80 (1H, m, $\text{CH}_A\text{H}_B\text{Ar}$); δ_{C} (101 MHz, CDCl_3) 168.6, 160.0, 148.7, 147.9, 131.3, 130.9, 125.5, 125.3, 114.1, 111.1, 110.7, 58.7, 56.0, 56.0, 55.4, 39.4, 26.1; HPLC analysis (CHIRALPAK IG, 250 \times 4.6 mm column, 250

× 4.6 mm column, hexane/2-propanol 93:7, 1 mL/min, 210 nm, *S* isomer 21.71 min., *R* isomer 25.08 min).

(*S*)-1-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. 215



This compound is known.¹¹⁴

This was prepared by general procedure 3A using imine (109 mg, 0.33 mmol), FA/TEA (0.17 mL), DCM (0.16 mL), catalyst (*R,R*)-**131** (2.2 mg, 3.3 μ mol) and then purified by column chromatography (0-60% EtOAc in Pet. Ether) to give the product as a clear oil (85 mg, 0.26 mmol, 77%); $[\alpha]_{\text{D}}^{23}$ -125.6 (c 0.02 in CHCl_3) 93% ee (*S*) (lit.¹¹⁴ $[\alpha]_{\text{D}}^{23}$ -28.3 (c 1.05 in CHCl_3) 75% ee); δ_{H} (400 MHz, CDCl_3) 6.81 (1H, s, ArH), 6.79 (1H, s, ArH), 6.78 – 6.74 (1H, m, ArH), 6.61 (1H, s, ArH), 6.26 (1H, s, ArH), 5.01 (1H, s, CHN), 3.87 (6H, s, 2 x OMe), 3.82 (3H, s, OMe), 3.64 (3H, s, OMe), 3.27 – 3.18 (1H, m, $\text{CH}_\text{A}\text{H}_\text{BN}$), 3.10 – 3.00 (1H, m, $\text{CH}_\text{A}\text{H}_\text{BN}$), 3.00 – 2.89 (1H, m, $\text{CH}_\text{A}\text{H}_\text{BAr}$), 2.80 (1H, b.s, NH), 2.73 (1H, dt, J 9.4, 4.5, $\text{CH}_\text{A}\text{H}_\text{BAr}$); δ_{C} (101 MHz, CDCl_3) 149.2, 148.6, 147.9, 147.3, 136.5, 129.4, 127.3, 121.5, 111.9, 111.5, 111.0, 110.8, 61.3, 56.0, 56.0, 56.0, 56.0, 42.0, 28.9; HPLC analysis (CHIRALPAK IC, 250 × 4.6 mm column, 250 × 4.6 mm column, hexane/2-propanol 80:20, 1 mL/min, 210 nm, *S* isomer 28.85 min., *R* isomer 48.18 min.).

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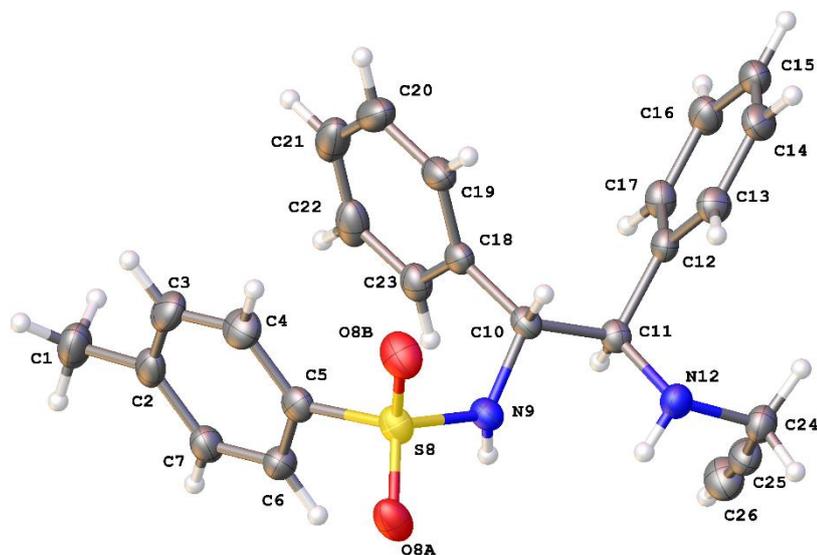
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Appendix

A1. X-Ray crystallography of (*R,R*)-116



Solid state structure of (*R,R*)-116 with atom labelling and thermal ellipsoids drawn at 50% probability level

A suitable crystal was selected and mounted on a glass fibre with Fomblin oil and placed on a Rigaku Oxford Diffraction SuperNova diffractometer with a dual source (Cu at zero) equipped with an AtlasS2 CCD area detector. The crystal was kept at 150(2) K during data collection. Using Olex2,¹ the structure was solved with the ShelXT² structure solution program using Intrinsic Phasing and refined with the ShelXL³ refinement package using Least Squares minimisation.

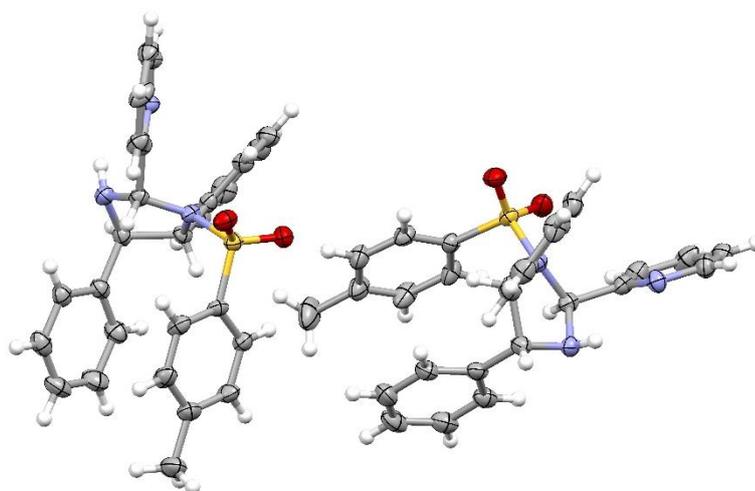
1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), *J. Appl. Cryst.* 42, 339-341.
2. Sheldrick, G.M. (2015). *Acta Cryst.* A71, 3-8.
3. Sheldrick, G.M. (2015). *Acta Cryst.* C71, 3-8.

Crystal data and structure refinement for (*R,R*)-116.

Empirical formula	C ₂₃ H ₂₃ N ₃ O ₂ S
Formula weight	405.50
Temperature/K	150(2)
Crystal system	monoclinic

Space group	P2 ₁
a/Å	11.81334(9)
b/Å	6.41415(6)
c/Å	14.72004(12)
α /°	90
β /°	109.3145(8)
γ /°	90
Volume/Å ³	1052.598(16)
Z	2
ρ_{calc} /cm ³	1.279
μ /mm ⁻¹	1.554
F(000)	428.0
Crystal size/mm ³	0.3 × 0.08 × 0.06 colourless block
Radiation	CuK α (λ = 1.54184)
2 Θ range for data collection/°	6.362 to 147.182
Index ranges	-14 ≤ h ≤ 14, -7 ≤ k ≤ 7, -18 ≤ l ≤ 18
Reflections collected	26467
Independent reflections	3963 [R _{int} = 0.0311, R _{sigma} = 0.0170]
Data/restraints/parameters	3963/3/269
Goodness-of-fit on F ²	1.031
Final R indexes [I ≥ 2 σ (I)]	R ₁ = 0.0312, wR ₂ = 0.0853
Final R indexes [all data]	R ₁ = 0.0316, wR ₂ = 0.0859
Largest diff. peak/hole / e Å ⁻³	0.34/-0.29
Flack parameter	0.002(8)

A2. X-Ray crystallography of (*R,R*)-117b



Single crystal X-ray structure of the asymmetric unit (*R,R*)-117b (ellipsoids are plotted at the 50% probability level)

A suitable crystal was mounted on a Mitegen head with Fomblin oil and collected on an Xcalibur Gemini diffractometer with a Ruby CCD area detector at 150(2) K. The structure was solved using Olex2¹ and the ShelXT² structure solution program using Direct Methods and refined with the ShelXL³ refinement package using Least Squares refinement.

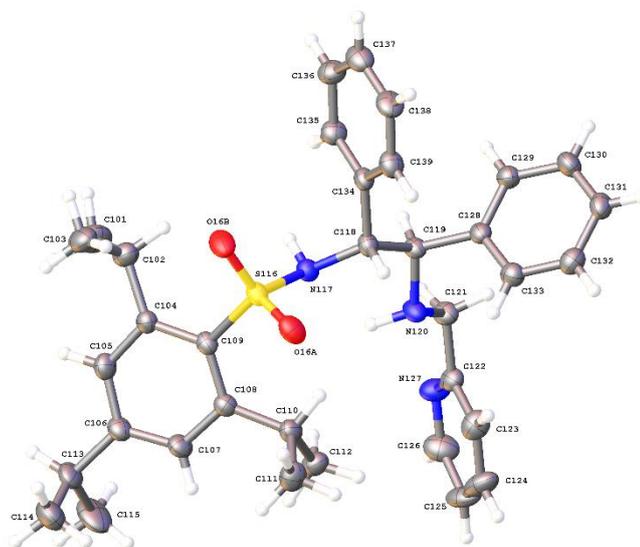
1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), *J. Appl. Cryst.* 42, 339-341.
2. Sheldrick, G.M. (2015). *Acta Cryst.* A71, 3-8.
3. Sheldrick, G.M. (2015). *Acta Cryst.* C71, 3-8

The asymmetric unit contains the disastereomerically pure aminal, with two molecules in the unit cell. The molecules exhibits intramolecular aromatic donor-acceptor (π - π) interactions between one of the TsDPEN phenyl and the tosylate phenyl rings.

The molecules exhibits an absolute configuration of *R,R* at the TsDPEN chiral centres, which were of a known configuration and *S* stereochemistry at the remaining chiral centre, which was inferred through comparison of the known *R,R* stereocentres. Additionally the Flack and Hooft parameters were obtained and found to be 0.008(14) and 0.008(14) respectively, albeit with an anomalous completeness of 76%

(R,R)-117b

Chemical Formula	C ₂₇ H ₂₅ N ₃ O ₂ S
Formula Mass	455.56
Crystal system	monoclinic
<i>a</i> / Å	10.0605(2)
<i>b</i> / Å	9.1219(2)
<i>c</i> / Å	25.0950(5)
α / °	90
β / °	92.345(2)
γ / °	90
Unit cell volume/ Å ³	2301.06(8)
Temperature/ K	150(2) K
Space group	P 2 ₁ b
Crystal size/ mm	0.05 × 0.07 × 0.15
Radiation	Cu K α
Goodness-of-fit on F ²	1.049
No. of formula units per unit cell, Z	4
No. of reflections measured	10648
No. of independent reflections	7679
Final R ₁ vaules (<i>I</i> > 2 σ (<i>I</i>))	0.0459
Final <i>wR</i> (F ²) values (<i>I</i> > 2 σ (<i>I</i>))	0.1254
Final <i>R_I</i> values (all data)	0.0479
Final <i>wR</i> (F ²) (all data)	0.1273

A3. X-ray crystallography of (R,R)-119

Solid state structure of one of the crystallographically independent but chemically identical molecule in the asymmetric unit of (*R,R*)-119

A suitable crystal was selected and mounted on a glass fibre with Fomblin oil and placed on a Rigaku Oxford Diffraction SuperNova diffractometer with a dual source (Cu at zero) equipped with an AtlasS2 CCD area detector. The crystal was kept at 150(2) K during data collection. Using Olex2,¹ the structure was solved with the ShelXT² structure solution program using Intrinsic Phasing and refined with the ShelXL³ refinement package using Least Squares minimisation.

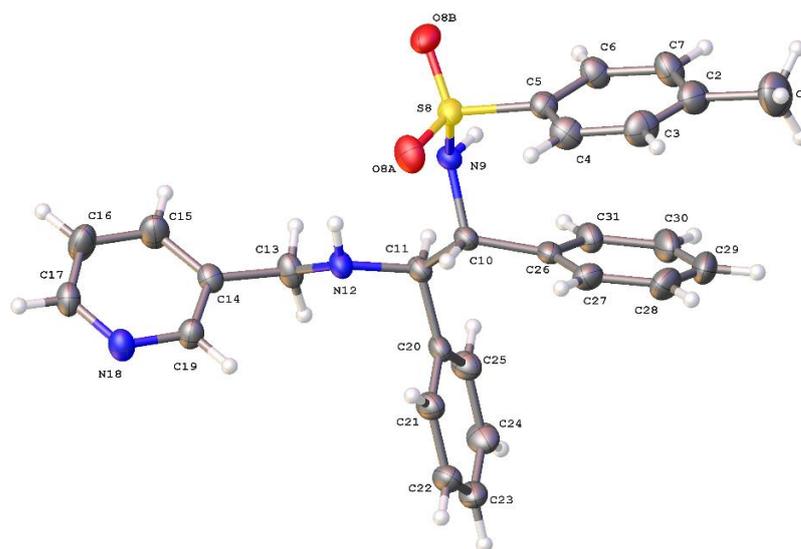
1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), *J. Appl. Cryst.* 42, 339-341.
2. Sheldrick, G.M. (2015). *Acta Cryst.* A71, 3-8.
3. Sheldrick, G.M. (2015). *Acta Cryst.* C71, 3-8.

Crystal data and structure refinement for (*R,R*)-119.

Empirical formula	C ₃₅ H ₄₃ N ₃ O ₂ S
Formula weight	569.78
Temperature/K	150(2)
Crystal system	monoclinic
Space group	P2 ₁
a/Å	5.7017(2)
b/Å	22.1965(7)
c/Å	24.7545(8)
α/°	90
β/°	92.712(3)
γ/°	90
Volume/Å ³	3129.37(18)
Z	4
ρ _{calc} /cm ³	1.209
μ/mm ⁻¹	1.185

F(000)	1224.0
Crystal size/mm ³	0.22 × 0.1 × 0.05 colourless block
Radiation	CuKα (λ = 1.54184)
2θ range for data collection/°	5.35 to 147.54
Index ranges	-6 ≤ h ≤ 6, -27 ≤ k ≤ 27, -30 ≤ l ≤ 29
Reflections collected	14623
Independent reflections	14623 [R _{int} = ?, R _{sigma} = 0.0429]
Data/restraints/parameters	14623/1/758
Goodness-of-fit on F ²	0.994
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0379, wR ₂ = 0.0990
Final R indexes [all data]	R ₁ = 0.0428, wR ₂ = 0.1007
Largest diff. peak/hole / e Å ⁻³	0.26/-0.27
Flack parameter	0.020(13)

A4. X-ray crystallography of (*R,R*)-**122**



Solid state structure of (*R,R*)-**122** with atom labeling and thermal ellipsoids draw at 50% probability level

A suitable crystal was selected and mounted on a glass fibre with Fomblin oil and

placed on a Rigaku Oxford Diffraction SuperNova diffractometer with a dual source (Cu at zero) equipped with an AtlasS2 CCD area detector. The crystal was kept at 150(2) K during data collection. Using Olex2,¹ the structure was solved with the ShelXT² structure solution program using Intrinsic Phasing and refined with the ShelXL³ refinement package using Least Squares minimisation.

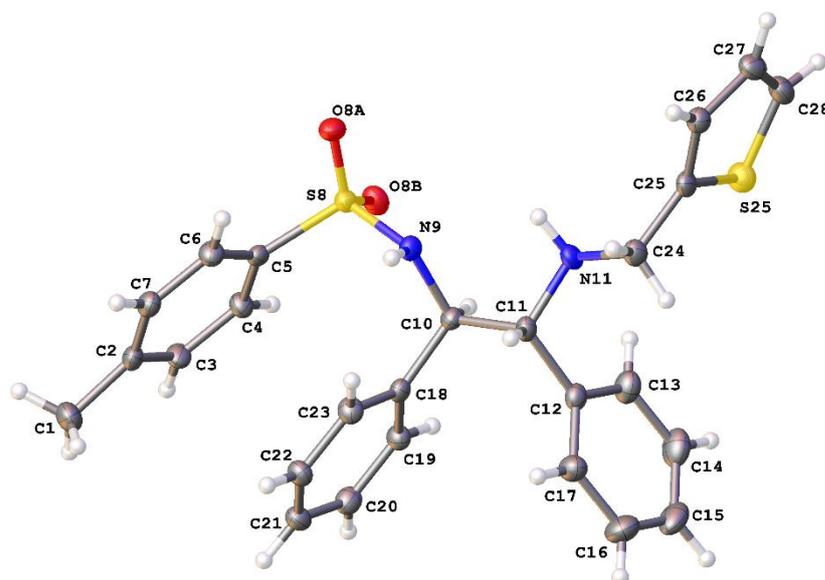
1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2. Sheldrick, G.M. (2015). Acta Cryst. A71, 3-8.
3. Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.

Crystal data and structure refinement for (*R,R*)-122.

Empirical formula	C ₂₇ H ₂₇ N ₃ O ₂ S
Formula weight	457.57
Temperature/K	150(2)
Crystal system	monoclinic
Space group	P2 ₁
<i>a</i> /Å	8.87107(3)
<i>b</i> /Å	12.12252(5)
<i>c</i> /Å	11.62129(4)
α /°	90
β /°	103.0074(4)
γ /°	90
Volume/Å ³	1217.682(8)
<i>Z</i>	2
ρ_{calc} /cm ³	1.248
μ /mm ⁻¹	1.403
F(000)	484.0
Crystal size/mm ³	0.3 × 0.2 × 0.1 colourless block
Radiation	CuK α (λ = 1.54184)
2 θ range for data collection/°	7.808 to 146.716
Index ranges	-10 ≤ <i>h</i> ≤ 11, -15 ≤ <i>k</i> ≤ 14, -14 ≤ <i>l</i> ≤ 14

Reflections collected	36327
Independent reflections	4831 [$R_{\text{int}} = 0.0260$, $R_{\text{sigma}} = 0.0129$]
Data/restraints/parameters	4831/2/302
Goodness-of-fit on F^2	1.035
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0241$, $wR_2 = 0.0641$
Final R indexes [all data]	$R_1 = 0.0242$, $wR_2 = 0.0642$
Largest diff. peak/hole / $e \text{ \AA}^{-3}$	0.14/-0.26
Flack parameter	0.007(3)

A5. X-ray crystallography of (*R,R*)-124



Solid state structure of (*R,R*)-124 with atom labelling and thermal ellipsoids drawn at 50% probability level

A suitable crystal was selected and mounted on a glass fibre with Fomblin oil and placed on a Rigaku Oxford Diffraction SuperNova diffractometer with a dual source (Cu at zero) equipped with an AtlasS2 CCD area detector. The crystal was kept at 150(2) K during data collection. Using Olex2,¹ the structure was solved with the ShelXT² structure solution program using Intrinsic Phasing and refined with the ShelXL³ refinement package using Least Squares minimisation.

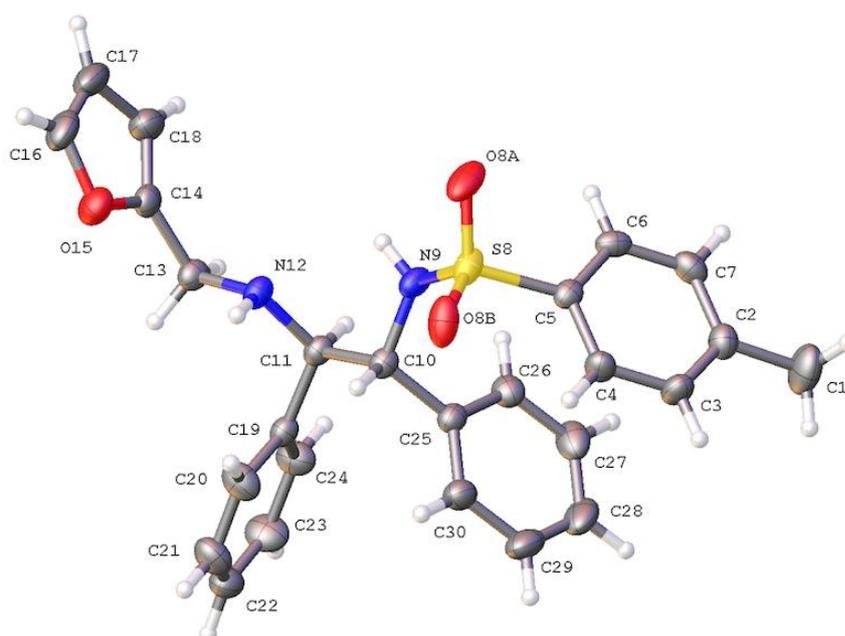
1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), *J. Appl. Cryst.* 42, 339-341.
2. Sheldrick, G.M. (2015). *Acta Cryst. A* 71, 3-8.
3. Sheldrick, G.M. (2015). *Acta Cryst. C* 71, 3-8.

Crystal data and structure refinement for (*R,R*)-124.

Empirical formula	C ₂₆ H ₂₆ N ₂ O ₂ S ₂
Formula weight	462.61
Temperature/K	150(2)
Crystal system	orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
a/Å	5.52132(13)
b/Å	18.8093(5)
c/Å	21.8599(4)
α/°	90
β/°	90
γ/°	90
Volume/Å ³	2270.20(9)
Z	4
ρ _{calc} /cm ³	1.353
μ/mm ⁻¹	2.334
F(000)	976.0
Crystal size/mm ³	0.14 × 0.02 × 0.01 colourless block
Radiation	CuKα (λ = 1.54184)
2θ range for data collection/°	6.198 to 147.366
Index ranges	-6 ≤ h ≤ 6, -23 ≤ k ≤ 23, -26 ≤ l ≤ 26
Reflections collected	22353
Independent reflections	4544 [R _{int} = 0.0480, R _{sigma} = 0.0380]

Data/restraints/parameters	4544/0/293
Goodness-of-fit on F^2	1.042
Final R indexes [$I \geq 2\sigma(I)$]	$R_1 = 0.0292$, $wR_2 = 0.0716$
Final R indexes [all data]	$R_1 = 0.0326$, $wR_2 = 0.0734$
Largest diff. peak/hole / $e \text{ \AA}^{-3}$	0.17/-0.30
Flack parameter	0.000(9)

A6. X-ray crystallography of (*R,R*)-**125**



Solid state structure of (*R,R*)-**125** with atom labelling and thermal ellipsoids drawn at 50% probability level.

A suitable crystal was selected and mounted on a glass fibre with Fomblin oil and placed on a Rigaku Oxford Diffraction SuperNova diffractometer with a dual source (Cu at zero) equipped with an AtlasS2 CCD area detector. The crystal was kept at 150(2) K during data collection. Using Olex2,¹ the structure was solved with the ShelXT² structure solution program using intrinsic phasing and refined with the ShelXL³ refinement package using Least Squares minimisation.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), *J. Appl. Cryst.* 42, 339-341.

2. Sheldrick, G.M. (2015). Acta Cryst. A71, 3-8.
3. Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.

Crystal data and structure refinement for (*R,R*)-125

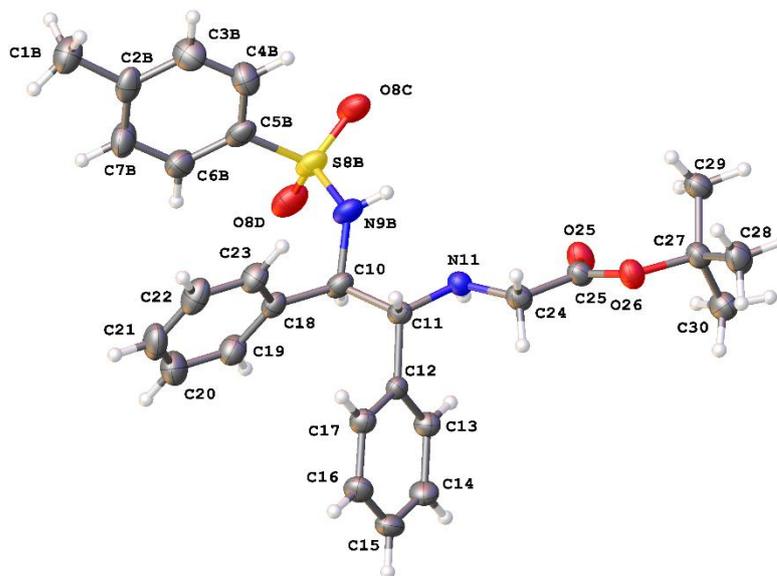
Empirical formula	C ₂₆ H ₂₆ N ₂ O ₃ S
Formula weight	446.55
Temperature/K	150(2)
Crystal system	orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
a/Å	8.12409(5)
b/Å	13.68892(8)
c/Å	20.78605(11)
α/°	90
β/°	90
γ/°	90
Volume/Å ³	2311.62(2)
Z	4
ρ _{calc} /cm ³	1.283
μ/mm ⁻¹	1.485
F(000)	944.0
Crystal size/mm ³	0.2 × 0.1 × 0.08
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.734 to 147.288
Index ranges	-9 ≤ h ≤ 10, -17 ≤ k ≤ 16, -25 ≤ l ≤ 25
Reflections collected	35565
Independent reflections	4654 [R _{int} = 0.0300, R _{sigma} = 0.0164]
Data/restraints/parameters	4654/1/296
Goodness-of-fit on F ²	1.069
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0269, wR ₂ = 0.0695

Final R indexes [all data] $R_1 = 0.0273$, $wR_2 = 0.0699$

Largest diff. peak/hole / $e \text{ \AA}^{-3}$ 0.15/-0.40

Flack parameter 0.000(3)

A7. X-ray crystallography of (*R,R*)-128



Solid state structure of (*R,R*)-128 with atom labeling and thermal ellipsoids drawn at 50% probability level. Solvent and disorder removed for clarity

A suitable crystal was selected and mounted on a glass fibre with Fomblin oil and placed on a Rigaku Oxford Diffraction SuperNova diffractometer with a dual source (Cu at zero) equipped with an AtlasS2 CCD area detector. The crystal was kept at 150(2) K during data collection. Using Olex2¹, the structure was solved with the ShelXT² structure solution program using Intrinsic Phasing and refined with the ShelXL³ refinement package using Least Squares minimisation.

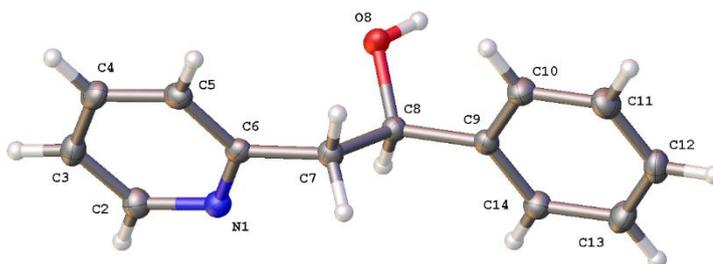
1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), *J. Appl. Cryst.* 42, 339-341.
2. Sheldrick, G.M. (2015). *Acta Cryst.* A71, 3-8.
3. Sheldrick, G.M. (2015). *Acta Cryst.* C71, 3-8.

Crystal data and structure refinement for (*R,R*)-128.

Empirical formula $C_{29}H_{32}N_2O_{4.5}S$

Formula weight	512.62
Temperature/K	150(2)
Crystal system	tetragonal
Space group	P4 ₃ 2 ₁ 2
a/Å	10.85404(3)
b/Å	10.85404(3)
c/Å	47.5784(2)
α/°	90
β/°	90
γ/°	90
Volume/Å ³	5605.22(4)
Z	8
ρ _{calc} /cm ³	1.215
μ/mm ⁻¹	1.329
F(000)	2176.0
Crystal size/mm ³	0.16 × 0.16 × 0.1 colourless block
Radiation	CuKα (λ = 1.54184)
2θ range for data collection/°	7.432 to 147.206
Index ranges	-13 ≤ h ≤ 11, -13 ≤ k ≤ 13, -58 ≤ l ≤ 58
Reflections collected	62063
Independent reflections	5645 [R _{int} = 0.0236, R _{sigma} = 0.0092]
Data/restraints/parameters	5645/5/360
Goodness-of-fit on F ²	1.060
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0453, wR ₂ = 0.1370
Final R indexes [all data]	R ₁ = 0.0457, wR ₂ = 0.1376
Largest diff. peak/hole / e Å ⁻³	0.75/-0.36
Flack parameter	0.007(3)

A8. X-ray crystallography of (*R*)-252

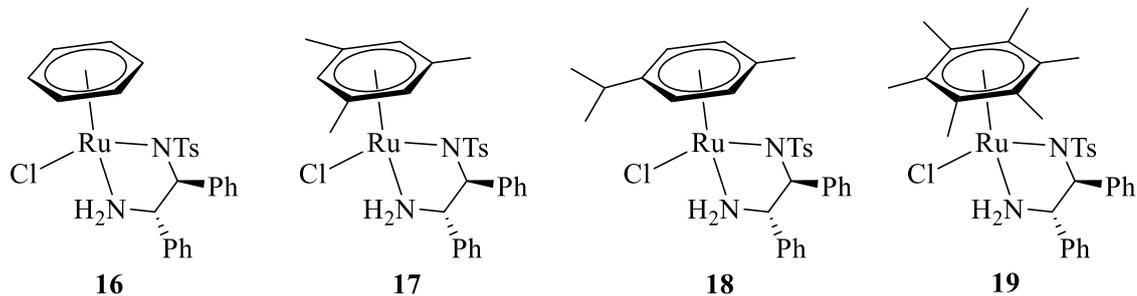


A suitable crystal 0.32x0.22x0.18 mm³ was selected and mounted on a Mitegen support on an XtaLAB Synergy, Dualflex, HyPix diffractometer. The crystal was kept at a steady $T = 100(2)$ K during data collection. The structure was solved with the ShelXT 2018/2 (Sheldrick, 2018) structure solution program using the Intrinsic Phasing solution method and by using **Olex2** (Dolomanov et al., 2009) as the graphical interface. The model was refined with version 2018/3 of ShelXL 2018/3 (Sheldrick, 2015) using Least Squares minimisation.

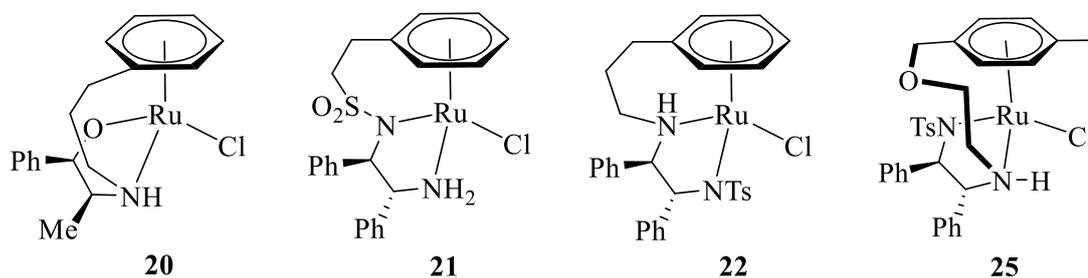
Compound	(R)-252
Formula	C ₁₃ H ₁₃ NO
<i>D</i> _{calc.} / g cm ⁻³	1.274
<i>μ</i> /mm ⁻¹	0.637
Formula Weight	199.24
Colour	colourless
Shape	block
Size/mm ³	0.32◊0.22◊0.18
<i>T</i> /K	100(2)
Crystal System	monoclinic
Flack Parameter	0.03(11)
Hooft Parameter	0.10(5)
Space Group	<i>P</i> 2 ₁
<i>a</i> /≈	5.22850(10)
<i>b</i> /≈	8.31810(10)
<i>c</i> /≈	12.03890(10)
<i>α</i> /°	90
<i>β</i> /°	97.2890(10)
<i>γ</i> /°	90
<i>V</i> /≈ ³	519.355(13)
<i>Z</i>	2
<i>Z</i> '	1
Wavelength/≈	1.54184
Radiation type	Cu K _α
<i>θ</i> _{min} /°	3.701
<i>θ</i> _{max} /°	79.453
Measured Refl.	15915
Independent Refl.	2238
Reflections with <i>I</i> > 2(<i>I</i>)	2228
<i>R</i> _{int}	0.0563
Parameters	137
Restraints	1
Largest Peak	0.216
Deepest Hole	-0.235
GooF	1.065
<i>wR</i> ₂ (all data)	0.0928
<i>wR</i> ₂	0.0928
<i>R</i> ₁ (all data)	0.0357
<i>R</i> ₁	0.0356

Ligands and Catalysts Insert

Noyori-Ikariya Catalysts:



Tethered Catalysts:



Heterocyclic Ligands and Catalysts:

