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Iron and Ruthenium Catalysts for Asymmetric Synthesis

By

Moftah Darwish

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

University of Warwick, Department of Chemistry

December 2012

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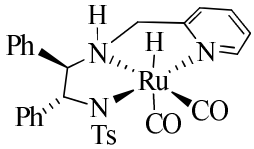
Declaration

The research described in this thesis is solely the work of the author unless otherwise stated. These studies were carried out at the Department of Chemistry, University of Warwick between September 2008 and August 2012. The content of this thesis has not been submitted, either wholly or partially for a degree at any other academic institution.

Abstract

A series of chiral di-, tri- and tetra amine ligands were synthesised from enantiomerically pure 1,2-cyclohexanediamine and 1,2-diphenylethanediamine and, in combination with Ru(II) or Fe(II), employed as asymmetric catalysts in the epoxidation of aromatic alkenes, hydrosilylation of acetophenone, nitro-aldol reaction and asymmetric transfer hydrogenation (ATH) of different ketones.

A novel class of tridentate ruthenium catalysts of general structure **239** below were developed. Specifically, a novel class of tridentate ligand was synthesised and a derivative of (*R*,*R*)-*N*-tosyl-1,2-diphenyl-1,2-ethylenediamine ((*R*,*R*)-TsDPEN) and was found to provide the best activity and selectivity in reduction reactions with $Ru_3(CO)_{12}$.



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Reaction conditions were optimised using **239** for the ruthenium-catalysed ATH of a number of ketones. In particular, it was found that the presence of *meta*-methoxy substituent on the aromatic ring of the substrate yields optimal results under the ATH conditions employed for 48 h (98% conv., 94% ee). Also, aryl ketones substituted at the *ortho* position were reduced in almost quantitative yield, with enantiomeric excesses greater than 90% in some cases.

List of abbreviations

^{o}C	Degrees Celsius
δc	^{13}C-NMR chemical shift (ppm)
δ_H	^{1}H-NMR chemical shift (ppm)
δ_P	^{31}P-NMR chemical shift (ppm)
$[\alpha]_D$	Optical rotation
abs. config	Absolute configuration
Å	Angstroms
Ac	Acetyl
AcOH	Acetic acid
aq	Aqueous
Ar	Aryl
ATH	Asymmetric transfer hydrogenation
atm	Atmospheric pressure
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	*t*-Butoxycarbonyl
Bopa	*N*,*N*,*N*-bis(oxazolinylphenyl)amine
br d	Broad doublet
br m	Broad multiplet
br s	Broad singlet
^{t}Bu	*tert*-Butyl
c	Concentration in grams per 100 cm^3
calcd	Calculated
$CHCl_3$	Chloroform
Cs	Camphorsulfonyl
CI	Chemical ionisation
Compd.	Compound
Conf.	Configuration
Conv.	Conversion

Cp*	Pentamethylcyclopentadienyl
CYDN	1,2-Cyclohexanediamine
d	Doublet
dd	Doublet of doublets
dt	Doublet of triplet
td	Triplet of doublet
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DFT	Density functional theory
DIAD	Diisopropyl azodicarboxylate
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DPEN	1,2-Diphenylethanediamine
dr	Diastereomeric ratio
DTAD	Di-*tert*-butyl azodicarboxylate
ee	Enantiomeric excess
eeaux	enantiomeric excess of the auxiliary
eeprod	enantiomeric excess of the product
EI	Electron impact
equiv.	Equivalents
ESI	Electron spray ionisation
Et	Ethyl
FA	Formic acid
FA:TEA	Formic acid: triethylamine azeotrope (5:2)
FID	Flame ionisation detector
GC	Gas chromatography
h	Hour
HMB	Hexamethylbenzene
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
H_2pydic	Pyridine-2,6-dicarboxylic acid
IPA	Isopropyl alcohol
inj.	Injection

J	Coupling constant (Hz)
m	Multiplet
M	Mol dm^{-3}
Me	Methyl
min.	Minutes
mp	Melting point
Ms	Mesyl
MTPA -Cl	α-Methoxy-α-trifluoromethylphenylacetyl chloride
MPV	Meerwein-Ponndorf-Verley reduction
NMR	Nuclear magnetic resonance
n/o	Not obtained
o-	*Ortho*
o/n	Overnight
p-	*Para*
Ph	Phenyl
PODPEN	1-Diphenylphosphinic-1,2-diphenylethanediamine
ppm	Parts per million
^{i}Pr	Isopropyl
PTC	Phase Transfer Catalyst
PTSA	*para*-Toluenesulfonic acid
PTsDPEN	Polyethylene glycol supported *N*-tosyl-1,2-diphenylethanediamine
q	Quartet
r.t.	Room temperature
s	Singlet
S/C	Substrate/Catalyst ratio
t	Triplet
t or *tert*	Tertiary
$16e^{-}$	16 electron complex
$18e^{-}$	18 electron complex
2-PCA	2-pyridine carboxylic anhydride
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammonium fluoride
TBSCl	*tert*-butyl(chloro)dimethylsilane
TBAS	Tetrabutylammonium hydrogen sulfate

TBDPS	*tert*-Butyldiphenylsilyl
TEA	Triethylamine
Temp.	Temperature
TBHP	*tert*-butyl hydroperoxide
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Ts	*para*-Toluenesulfonyl (Tosyl)
TsDPEN	*N*-Tosyl-1,2-diphenylethanediamine
UV	Ultraviolet
υ_{max}/cm^{-1}	Wave number (cm^{-1})

1. Introduction

1.1. Chirality

Chirality: A molecule that is non-superimposable upon its mirror image is considered to be chiral.

Chirality has extremely important connotations in chemistry; any molecule that possesses an element of chirality can exist in two distinct mirror image forms, known as enantiomers. The physical and chemical properties of two enantiomers of a compound are identical in the absence of an external chiral source.[1] One notable characteristic of an enantiomeric pair is their equal and opposite rotation (clockwise (+) and anticlockwise (-)) of plane-polarised light. This has been extremely useful as a directly observable property in assigning stereochemistry to chiral molecules. A simple compound that exhibits this enantiomeric property is chlorofluorobromomethane, which can be resolved into two enantiomeric forms (Figure 1).

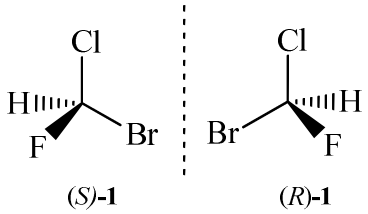


Figure 1: The two optical isomers of chlorofluorobromomethane.

The two enantiomers will rotate plane-polarised light by the same amount but in opposite directions. This leads to one way of labelling enantiomers; enantiomers that rotate plane-polarised light to the right are called *dextro* isomers and are given the label (*d*) or (+), and enantiomers that rotate plane-polarised light to the left are called

levo isomers and are given the label (*l*) or (-). Due to this effect on light, enantiomers are often referred to as optical isomers.[2] The Cahn-Ingold-Prelog[3] system was devised to specify the absolute configuration at any sterogenic centre. Figure 2 shows how the configuration is worked out. First of all the atoms directly attached to the asymmetric centre and their atomic numbers are identified. Next the attached atoms are given a priority based on their atomic numbers. If there are two carbon atoms, and hence the same atomic numbers, attached to the centre then they cannot be given a priority. In this instance move to the next atoms along for each carbon and identify which has the highest atomic number. This substituent takes priority over the other. If the priority order of the groups decreases clockwise, then the stereogenic centre is called *rectus* and given the label (*R*), If the priority decreases anticlockwise, then the stereogenic centre is called *sinister* and given the label (*S*). In the case below the priority rules order the groups in decreasing atomic mass in a clockwise direction and the stereocentre has an (*R*) configuration.

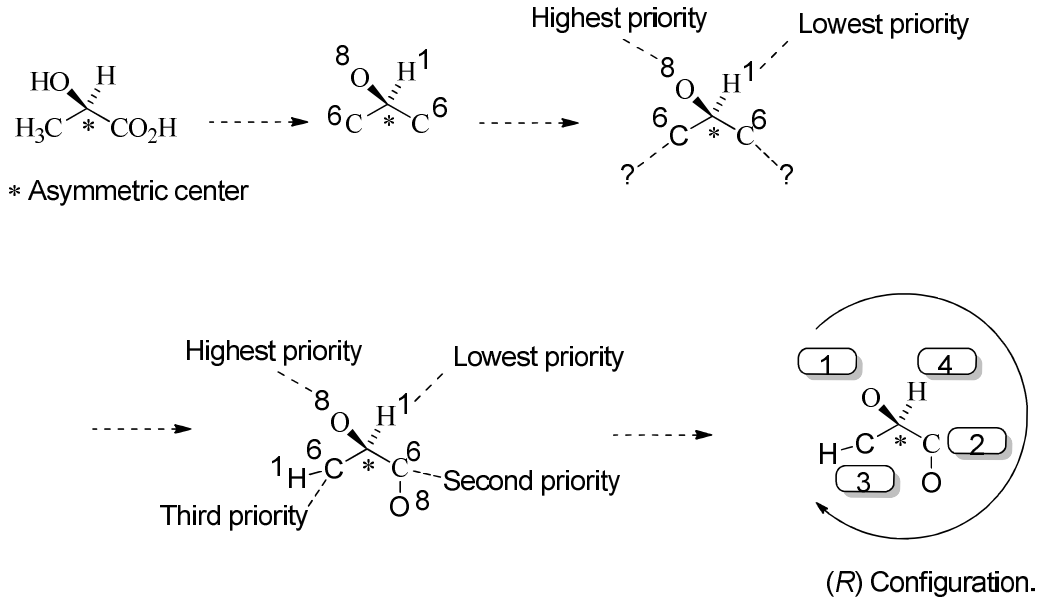
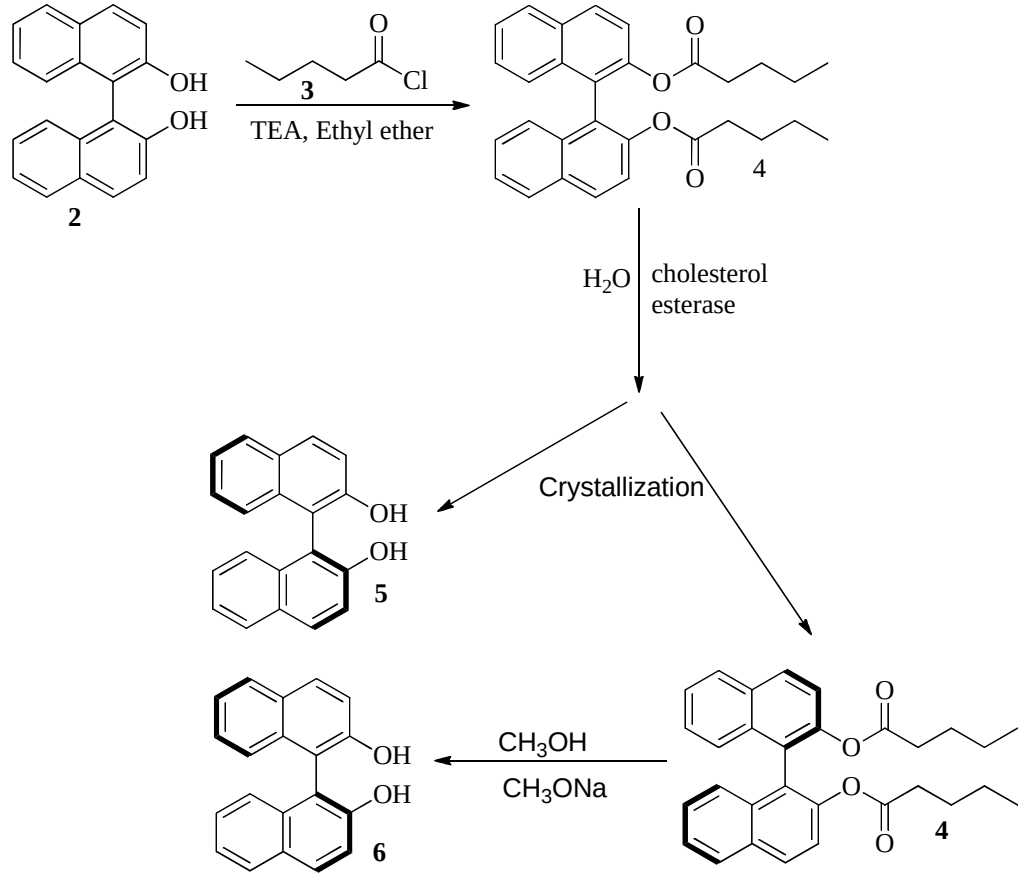


Figure 2: Assigning priorities to substituents of an asymmetric centre.

1.1.1. Chiral resolution

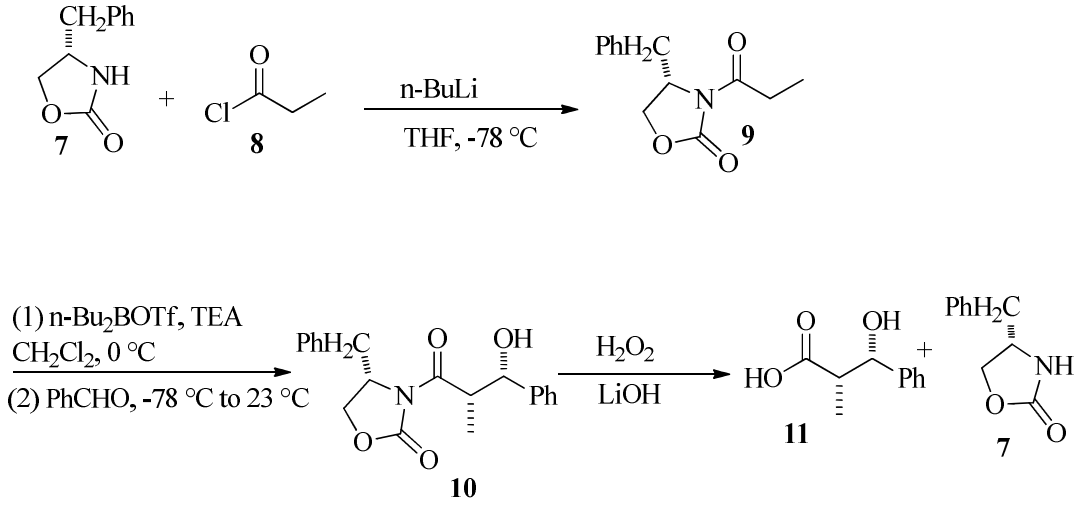
This is a process for the separation of racemic compounds into their enantiomers. A common way of separating enantiomers is the conversion of the enantiomers into diastereomers that are not mirror images of each other. 1,1′-Bi-2-naphthol[4] can be resolved in various ways. Here, the diol is first converted into a diester. Cholesterol esterase is then used to hydrolyse the (*S*)-enantiomer of the ester, which then precipitates from solution. The (*R*)-enantiomer can be obtained after the workup of the mother liquors (Scheme 1).



Scheme1: Separation of enantiomers of 1,1′-bi-2-naphthol by resolution.

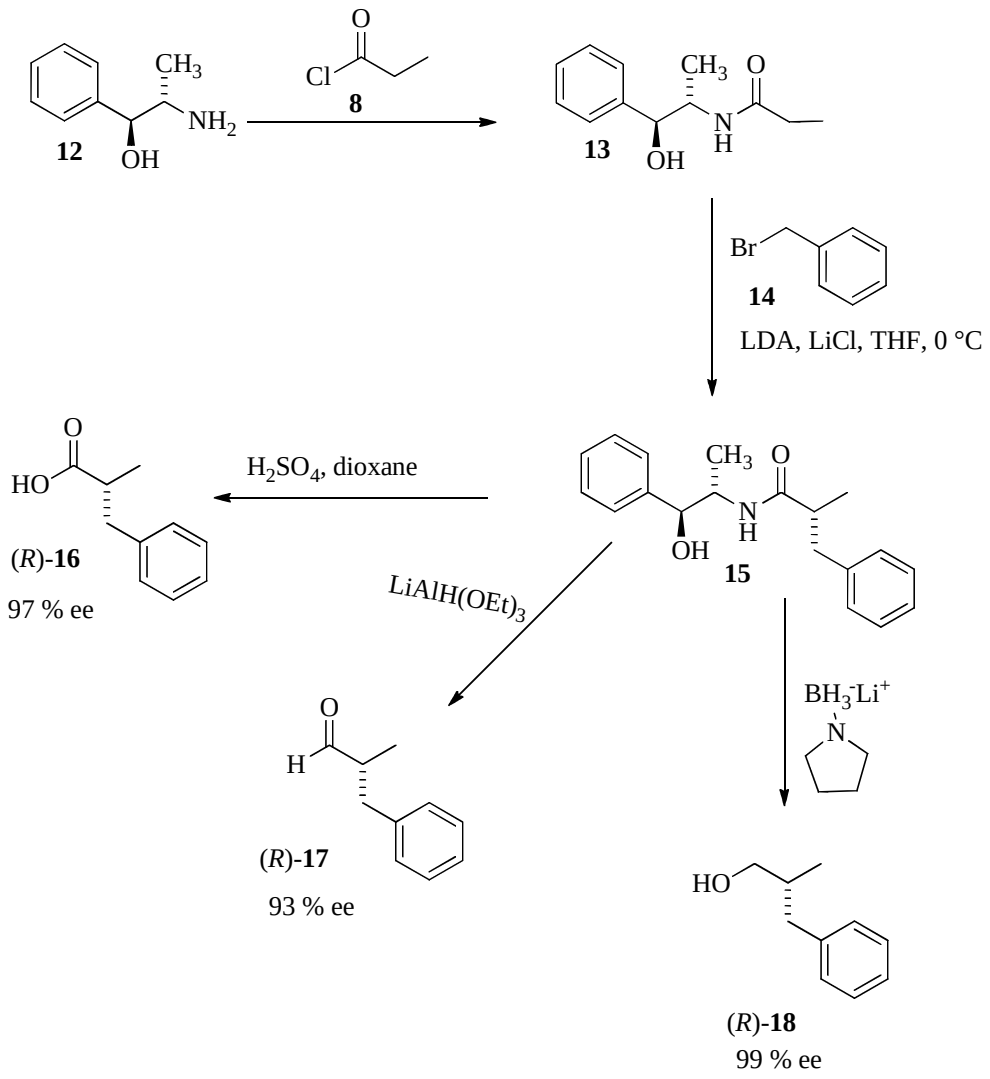
1.1.2. Chiral auxiliary

An auxiliary is a chiral agent that is introduced to a molecule in order to create internal asymmetric induction in a subsequent reaction, and can then be removed and recycled. Chiral auxiliaries were introduced by E. J. Corey in 1978 with chiral 8-phenylmenthol[5] and by B. M. Trost in 1980 with chiral mandelic acid.[6] An example of a chiral auxiliary is the use of Evans auxiliaries, such as oxazolidinone **7**, which when coupled to propanyl chloride **8** to form compound **9**, which can then undergo a stereoselective aldol reaction with aldehyde[7] (Scheme 2).



Scheme 2: Diastereoselective aldol condensation using chiral auxiliary **7**.

Pseudoephedrine **12** can also be used as a chiral auxiliary in stereoselective nucleophilic addition to an amide.[8] The reaction between pseudoephedrine **12** and propanoyl chloride **8** forms compound **13**, which when added to benzyl bromide **14** forms **15** with high enantioselectivity. Removal of the chiral auxiliary by different methods gives the products **16**- **18** (Scheme 3).



Scheme 3: The use of pseudoephedrine **12** in the stereoselective alkylation of an amide.

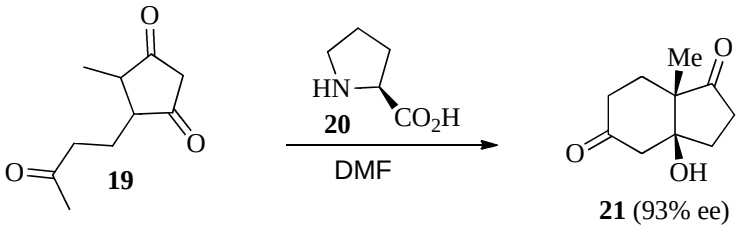
1.2. Catalytic methods

1.2.1. Organocatalysis

Organocatalysis is a form of catalysis whereby the rate of a chemical reaction is increased by an organic compound referred to as an organocatalyst, normally consisting of carbon, hydrogen, sulfur and other non-metal elements.

Regular achiral organocatalysts are based on nitrogen such as piperidine as used in the Knoevenagel condensation,[9] 4-dimethylaminopyridine (DMAP) used in

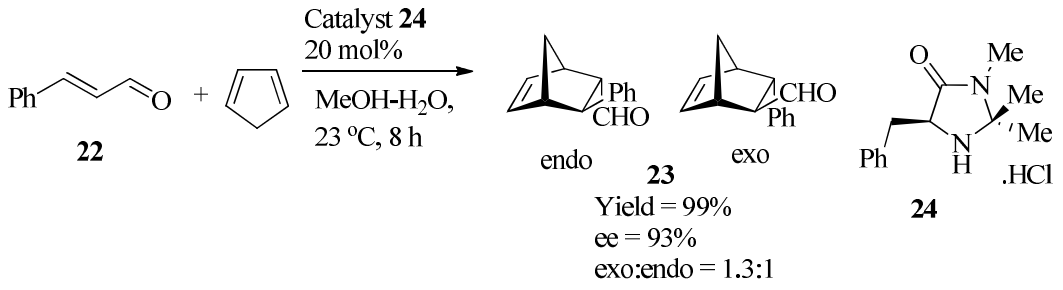
esterfications and 1,4-diazabicyclo[2.2.2]octane (DABCO) used in the Baylis-Hillman reaction. Current interest in organocatalysis is focused on asymmetric catalysis with chiral catalysts and this particular branch is generally referred to as asymmetric organocatalysis or enantioselective organocatalysis. In the 1970s, the Hajos–Parrish–Eder–Sauer–Wiechert reaction was developed (Scheme 4).



Scheme 4: *L*-Proline-catalysed Hajos-Parrish-Eder-Sauer-Wiechert reaction.

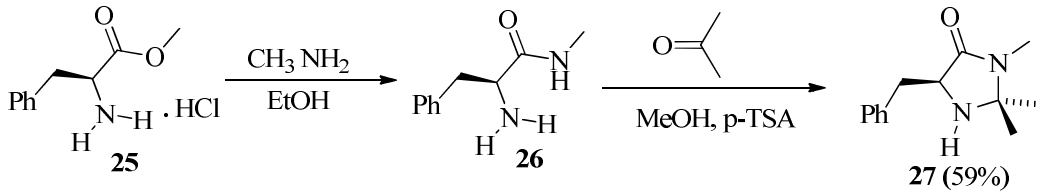
In this reaction proline, a naturally occurring chiral amino acid, is the chiral catalyst in an aldol reaction. The starting material **19** is an achiral triketone and it requires just 3% of proline to obtain the product **21** in 93% enantiomeric excess.

A particular class of imidazolidinone compounds are suitable catalysts for many asymmetric reactions such as asymmetric Diels-Alder reactions. These are very useful reaction for synthesising bicyclic derivatives and can be used to synthesise chiral building blocks. This reaction is a fundamental C-C bond forming reaction and during this process,[10-12] cyclic rings are constructed with a number of stereocenters.[11] (Scheme 5).



Scheme 5: Asymmetric organocatalysis of an asymmetric Diels-Alder reactions.

The original representative of the imidazolidinone class of compounds was derived from phenylalanine in two chemical steps (amidation with methylamine followed by condensation reaction with acetone) which leave the chirality intact (Scheme 6).[13]



Scheme 6: Synthesis of (5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one.

1.2.2. Biocatalysis

Biocatalysis involves the use of enzymes to perform chemical transformations on organic compounds. Most classes of enzymes can be employed as biocatalysts.[14-16]

Enzymes display three major types of selectivity:

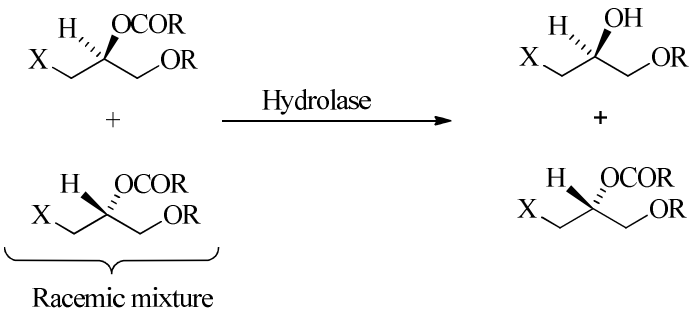
Chemoselectivity; since the purpose of an enzyme is to act on a single type of functional group.

Regioselectivity and diastereoselectivity; due to their complex three-dimensional structure enzymes may distinguish between functional groups which are chemically situated in different regions of the substrate molecule.

Enantioselectivity; since almost all enzymes are made from *L*-amino acids, enzymes are chiral catalysts. As a consequence, any type of chirality present in a substrate molecule is recognized upon the formation of the enzyme substrate complex. Thus a prochiral substrate may be transformed into an optically active product and each enantiomer of a racemic substrate may react at different rates.

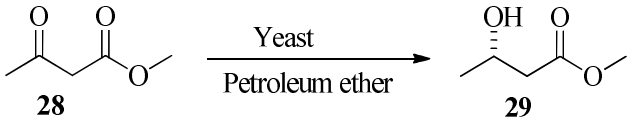
In asymmetric biocatalysis the methods by which enantiopure compounds are obtained can be divided into two different methods:

1. Kinetic resolution of a racemic mixture; the enzyme converts one of the enantiomers into product at a greater reaction rate than the other enantiomer (Scheme 7).



Scheme 7: Kinetic resolution of a racemic mixture by a chiral enzyme.

2. Biocatalysed asymmetric synthesis: a non-chiral unit becomes chiral in such a way that the different possible enantiomers are formed in different quantities. The chirality is introduced into the substrate through the influence of an enzyme which is enantiomerically pure (Scheme 8).



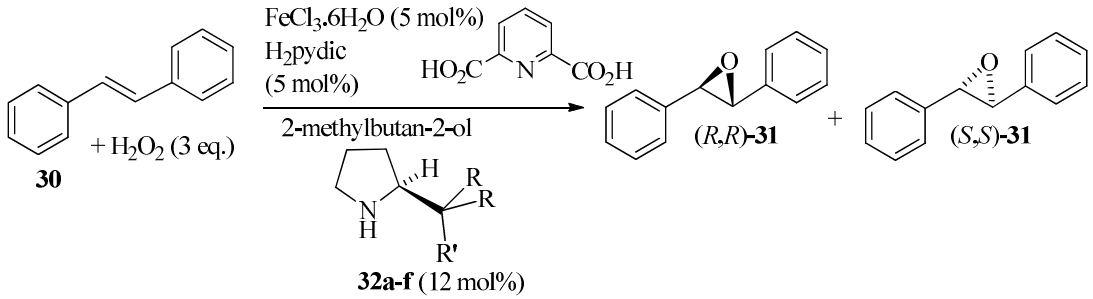
Scheme 8: Asymmetric synthesis using an enzyme contained in yeat.

1.3. Metal catalysed reactions

1.3.1. Iron catalysed epoxidation of alkenes

Beller has reported extensively on the development of iron catalysts for the oxidation of alkenes[17] and has recently published details of an asymmetric system which employs hydrogen peroxide as the oxidant and a simple catalyst consisting of ferric

chloride hexahydrate ($FeCl_3.6H_2O$), pyridine-2,6-dicarboxilic acid (H_2pydic), and a carefully chosen chiral *N*-sulfonated ethylene diamine derivative.[18,19] For the initial investigation, *trans*-stilbene was used as a model substrate because of its nonvolatility and the stability of the epoxide product. A series of chiral pyrrolidine derivatives were used as ligands (Table 1).



Scheme 9: Epoxidation of *trans*-stilbene.

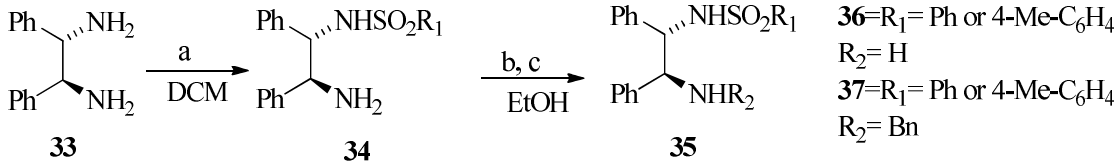
A closer look at the effect of different chiral pyrrolidine derivatives **32a-f** as ligands revealed a relationship between the type and size of substituents adjacent to the chiral centre and the ee values achieved. The diphenyl-substituted **32d** led to product formation in 10% ee (Table 1, entry 4). Replacing the hydroxyl group in **32d** with a fluoride led to a much more active catalyst and increased the ee value from 10 to 17% (Table 1, entries 5 and 6). This suggested the importance of H-bonding in addition to steric factors in the enantioselectivity-determining step. Chiral *N*-sulfonated diamine derivatives ligands **34**-**37** were synthesized by monosulfonation of C_2-symmetrical 1,2-diamines with *p*-toluenesulfonyl chloride in the presence of a base such as diisopropyl ethylamine (DIPEA). Where necessary, reductive *N*-alkylation of the resulting products was carried out in the presence of a suitable aldehyde and sodium borohydride ($NaBH_4$), (Scheme 10).

Table 1: Iron-catalyzed asymmetric epoxidation of *trans*-stilbene **30** using ligands **32a-f**.

Entry	Ligand, abs. config.	R	R′	t[h]	% Conv.[a]	% Yield[a]	% ee [b] abs. config.[c]
1	**32a**, (*S*)	H	OH	1	95	73	0
2	**32b**, (*S*)	H	NH_2	36	60	58	1, (-)-(2*S*,3*S*)
3	**32c**, (*S*)	Ph	H	60	61	45	0
4	**32d**, (*S*)	Ph	OH	36	78	53	10, (+)-(2*R*,3*R*)
5	**32e**, (*R*)	Ph	F	1	100	90	16, (-)-(2*S*,3*S*)
6[d]	**32e**, (*R*)	Ph	F	14	100	98	17, (-)-(2*S*,3*S*)
7	**32f**, (*S*)	F	F	1	100	93	2, (+)-(2*R*,3*R*)

[a] Determined by G.C using dodecane as the internal standard. [b]Determined by chiral HPLC.
[c]Determined by the sign of optical rotation of isolated product . [d]Reaction at 0 °C.

The influence of various ligands on the conversion and enantioselectivity of the reaction is summarized in Table 2.

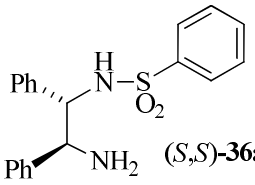
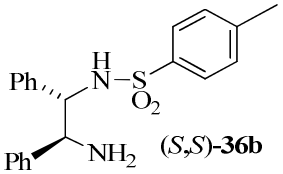
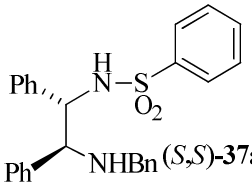
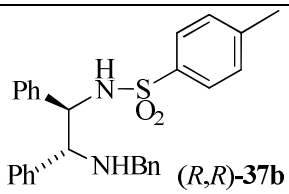
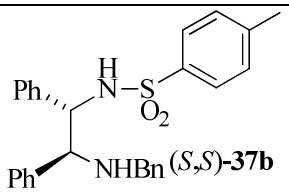


33 **34** **35**

Scheme 10: General synthesis of the chiral ligands. a) R_1SO_2Cl, DIPEA, 0 °C to r.t; b) PhCHO, EtOH, reflux; c) $NaBH_4$, EtOH, r.t.

Ligand **36b** gave *trans*-stilbene oxide (-)-(2*S*,3*S*) **31** in 28% ee under the standard reaction conditions (Table 2, entry 2).

Table 2: Iron-catalyzed asymmetric epoxidation *of trans*-stilbene using ligands **36a-b** and **37a-b**.[a]

Entry	Ligand	% Conv[b]	% Yield[c]	% ee[d]
1	 (*S*,*S*)-**36a**	100	88	26 (-)-(2*S*,3*S*)
2	 (*S*,*S*)-**36b**	100	86	28 (-)-(2*S*,3*S*)
3	 (*S*,*S*)-**37a**	100	98	36 (+)-(2*R*,3*R*)
4	 (*R*,*R*)-**37b**	100	92	41 (-)-(2*S*,3*S*)
5	 (*S*,*S*)-**37b**	100	87	42 (+)-(2*R*,3*R*)
6[e]	(*S*,*S*)-**37b**	100	97	47 (+)-(2*R*,3*R*)

[a]Substrate (0.5 mmol), H_2O_2 (1mmol), $FeCl_3.6H_2O$ (5 mol%), H_2pydic (5 mol%), ligand (12 mol%), 2-methylbutane-2-ol, r.t., 1h. [b]Determined by G.C using dodecane as the internal standard. [c]Determined by chiral HPLC. [d]Determined by the sign of optical rotation of isolated product and chiral HPLC. [e]Reaction at -8 to -10 °C, 24 h.

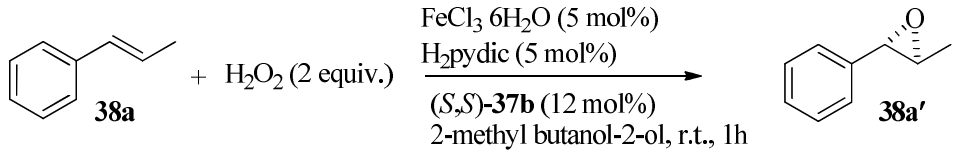
Benzylation of the remaining amino group in the ligand generally resulted in further enhancement of the product ee value. Among these *N*-benzyl-substituted (*S*,*S*)-**37b** led to the most significant increase in ee value, giving (+)-(2*R*,3*R*) **31** in 42% ee (Table 2, entry 5) at room temperature which improved to 47% ee when the

temperature was lowered to -8 °C (Table 2, entry 6). Interestingly, the absolute configuration reversed upon changing from the ligand **36** series to the *N*-benzylated **37** ligand series.

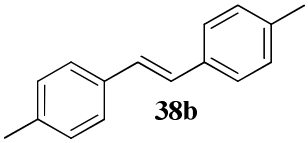
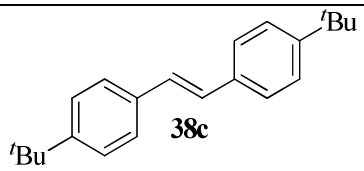
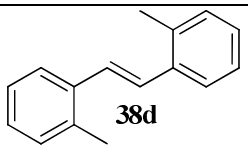
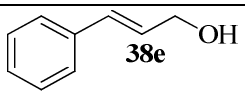
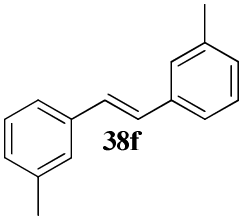
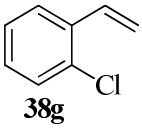
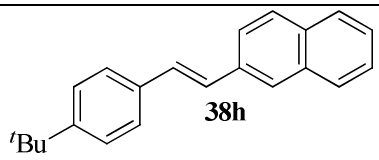
This result suggested the existence of several catalytic species, the importance of the specific spatial orientation of the chiral ligand imposed by a rigid aromatic system, and the possible role of π-π interactions and hydrogen bonding in controlling enantioselectivities.

To explore the scope of the reaction, a series of aromatic olefins were epoxidized in the presence of (*S*,*S*)-**37b**, which was the best ligand in the model reaction in terms of costs, selectivity, and product yields (Table 3). Among *trans*-stilbene derivatives, the substrates with substituents in the *para* position were more reactive than the analogous *ortho* or *meta*-substituted compounds, probably because of steric effects (Table 3 entries 2, 3, 4 and 6). The enantioselectivities of small alkenes, such as the styrenes, are lower than those achieved with large alkenes. The highest enantioselectivities were obtained using sterically bulky 4,4-dialkyl-substituted *trans*-stilbenes such as (*E*)-2-(4-*tert*-butylstyryl)naphthalene (**38h**) which gave a product of 91% ee (Table 3, entry 8), which could be enhanced to 97% ee when the reaction temperature was lowered to 10 °C.

Table 3: Iron-catalyzed asymmetric epoxidation of different aromatic alkenes.[a]



Alkene **38a-j** Epoxide **38a′-j′**

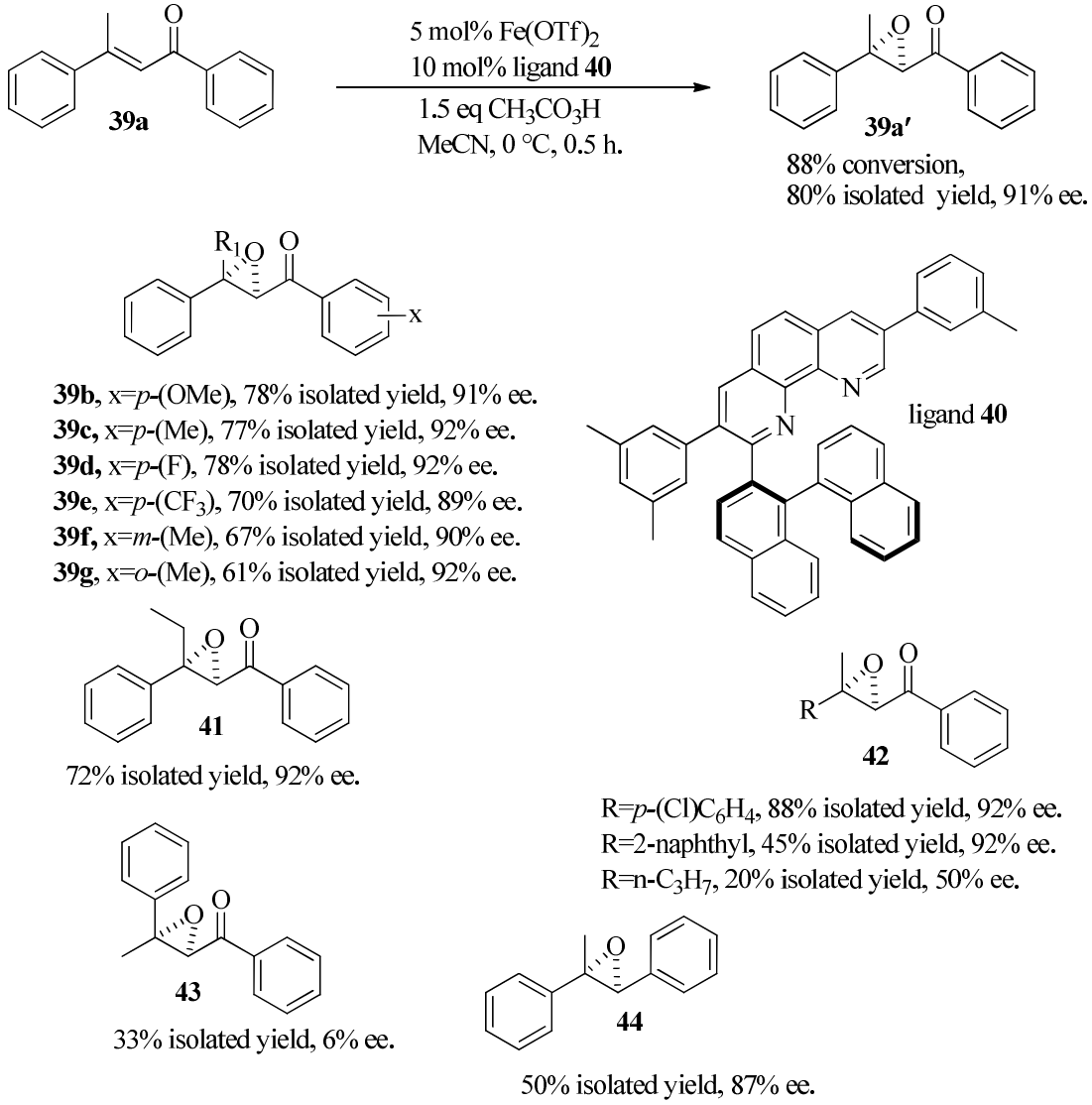
Entry	Alkene	% Conv.[b]	% Yield[c]	% ee[d], abs. config.
1	**38a**	100	94	28, (+)-(2*R*,3*R*)
2	 **38b**	100	92	64, (+)-(2*R*,3*R*)
3	 **38c**	100	82	81, (+)-(2*R*,3*R*)
4	 **38d**	60	57	55 (+)-(2*S*,3*S*)
5	 **38e**	100	49	48 (-)-(2*S*,3*S*)
6	 **38f**	95	88	27 (+)-(2*R*,3*R*)
7	 **38g**	91	62	14 (+)-(2*R*,3*R*)
8[e]	 **38h**	100	46	91 (+)-(2*R*,3*R*)
9[f]	**38h**	100	40	97 (+)-(2*R*,3*R*)

[a]Substrate (0.5 mmol), H_2O_2 (1mmol), $FeCl_3.6H_2O$ (5 mol%), H_2pydic (5 mol%), ligand (12 mol%), 2-methylbutane-2-ol, r.t., 1h. [b]Determined by G.C using dodecane as the internal standard. [c]Determined by chiral HPLC. [d]Determined by the sign of optical rotation of isolated product and chiral HPLC. [e] Determined after 24h. [f] 10 °C, equiv H_2O_2, 10 mol% H_2pydic, 10 mol% $FeCl_3$. $6H_2O$, 24 mol% (*S*,*S*)-**37b**.

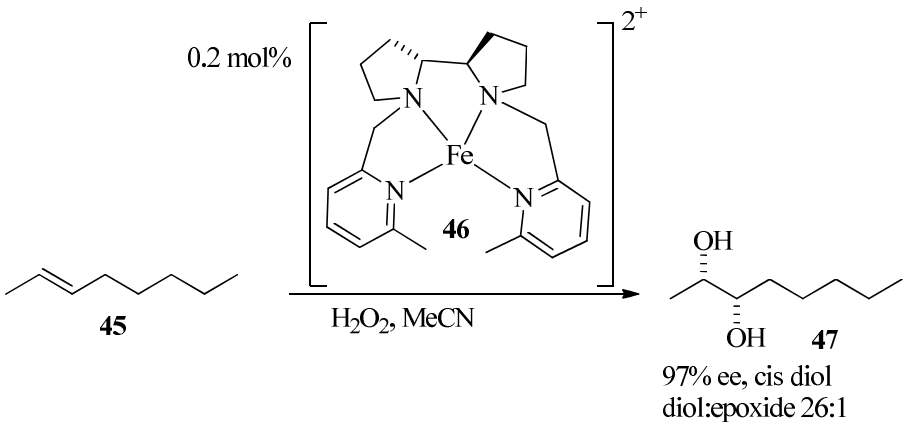
1.3.2. Iron-catalyzed asymmetric epoxidation of enones

An asymmetric epoxidation of β,β-disubstituted enones has been achieved using an iron-catalysed approach. In this process, the combination of a chiral bipyridine derivative complexed to $Fe(OTf)_2$ directs the reaction of a peracid with enones achieving ees of up to 91% ee in preliminary studies (Scheme 11).[20] In this process the formation of a very hindered (2:1) complex between the ligand and the iron(II) was isolated and characterised by X-ray crystallography. This creates a bulky catalyst with a well-defined chiral environment, however the means by which asymmetric induction is achieved still remains unclear and is the subject of ongoing investigations. Intriguingly, even a non-activated alkene could be epoxidised; *trans*-α-methylstilbene was converted to the epoxide in 50% yield and 87% ee.

Following on from a series of papers related to non-chiral alkene oxidation using biomimetic iron/amine complexes,[21] Que *et al*. reported in 2008 the use of a series of C_2-symmetric tetradonor ligands containing a combination of pyridyl and tertiary amine donors.[22] A difference with this system, however, was the preference for diol products over epoxides. Of the series of five ligands tested, in combination with Fe(II), complex **46** gave the best result for *cis*-dihydroxylation of *trans*-2-heptene (Scheme 12). An X-ray crystallographic structure solution on complex **46** confirmed a C_2-symmetric environment around the metal, created by the tetradentate ligand. A good result (96% ee, diol:epoxide 13:1) was achieved with *trans*-4-octene, whilst 1-octene was dihydroxylated in 76% ee with a 64:1 diol:epoxide ratio. Ethyl *trans*-crotonate gave a diol of 78% ee, and dimethyl fumarate a diol of just 23% ee, indicating the loss of enantioselectivity related to electron-withdrawing groups on the substrate.



Scheme 11: Enantioselective epoxidation of enones.

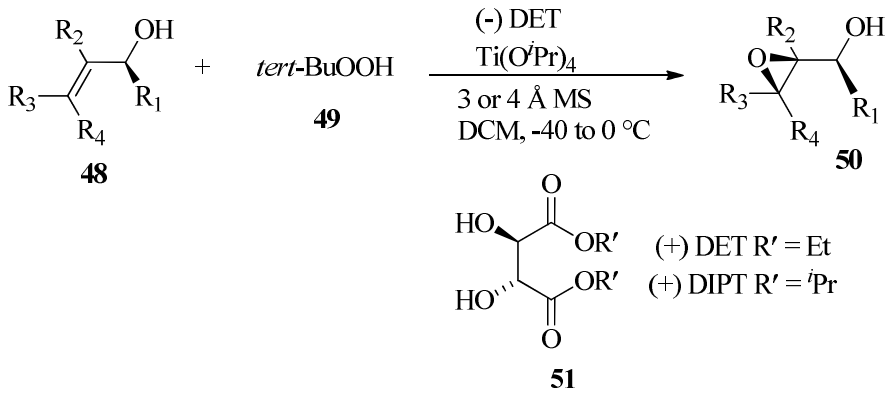


Scheme 12: Enantioselective alkene epoxidation using a mixed pyridyl/tertiary amine ligand.

Other alkenes tested included allyl chloride (70% ee) and *tert*-butyl acrylate (68% ee). Compounds **41-44**, are epoxidised from corresponding alkenes using same procedure.

1.3.3. Sharpless epoxidation reaction

In the last decades a great number of new catalytic asymmetric reactions have been discovered. A good example is the asymmetric epoxidation of allylic alcohols or Sharpless asymmetric epoxidation (SAE) or Sharpless-Katsuki epoxidation. This was a breakthrough in asymmetric synthesis at the beginning of the 1980′s (Scheme 13).[23] The reaction has a wide scope and is characterized by simplicity, high selectivity and versatility. The obtained epoxides are useful intermediates in asymmetric synthesis.

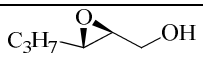
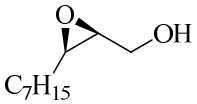
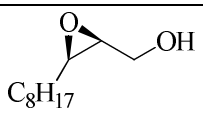
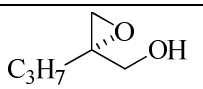
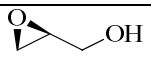
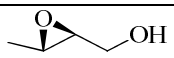


Scheme 13: Sharpless asymmetric epoxidation of allylic alcohols.

The oxidizing agent in the above reaction is *tert*-butyl hydroperoxide **49** (TBHP). Enantioselectivity is achieved by a catalyst formed from titanium tetra(isopropoxide) and diethyl tartrate (DET). Only 5-10 mol% of the catalyst in the presence of 3Å molecular sieves (3Å MS) is required[24] for reaction of the allylic alcohol with TBHP **49** in the presence of $Ti(O^iPr)_4$ and DET to form an epoxy alcohol of high enantiomeric purity. A typical *trans*-disubstituted allylic alcohol (Table 4, entries 1

and 2) can be epoxidized at –20 °C in at least 94% conversion with just 5% $Ti(O^iPr)_4$ and 6-7.5% tartarate. The reactions are quite rapid, generally reaching completion in 2-3 h. However, *cis*-disubstituted allylic alcohols (Table 4, entries 3 and 4) require longer reaction times (1-2 days).

Table 4: Asymmetric epoxidation of allylic alcohols (Scheme 13).[a]

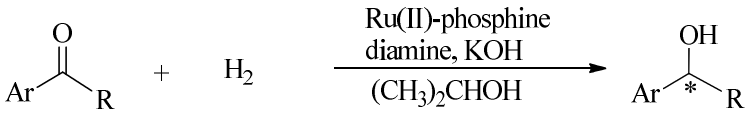
Entry	Product	Ti %	Tartarate %	°C	Time (h)	%Yield[b]	%ee[c]
1		5	(+) DET (6.0)	-20	2.5	85	94
2		5	(+) DIPT (7.5)	-20	3	89	>98
3		10	(+) DET (14)	-10	29	74	86
4		5	(+) DIPT (7.4)	-12	42	63	80
5		4.7	(+) DET (5.9)	-12	11	91	96
6		5	(+) DIPT (7.5)	-35	2	79	98
7		5	(+) DIPT (6.0)	0	5	65	90
8		5	(+) DIPT (6.0)	-20	2	70	91

[a]All reaction were carried out with TBHP. [b]Yields reported are isolated yields. [c] Determined by GC analysis.

It was found that such slow-reacting substrates require more catalyst (10%) and a slightly higher temperature than in case of *trans*-disubstituted allylic alcohol in order to achieve complete reaction with minimal loss of selectivity. The unsymmetrical disubstituted allylic alcohol (Table 4, entry 5) was amongst the best substrates, both in terms of yield and enantioselectivity. Tri-disubstituted allylic alcohol (Table 4, entry 6) tend to react very rapidly under these catalytic conditions. Also low molecular weight allylic alcohols (Table 4, entries 7 and 8) at -20 to 0 °C in 2-5 h give slightly lower conversion (65-70%) but high enantioselectivity (~ 90%).

1.4. BINAP/diamine-Ru enantioselective transfer hydrogenation of aromatic ketones

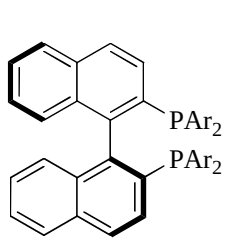
Although BINAP-Ru(II) complexes such as [BINAP=2,2′-bis(diphenylphosphino)1,1′-binaphthyl] have proved extremely efficient as catalyst for asymmetric hydrogenation of functionalized ketones,[25,26] they are unable to hydrogenate simple ketones that lack heteroatoms to anchor the Ru metal. Noyori *et al*[27] developed a catalytic system that can hydrogenate simple aromatic ketones (Scheme 14), this asymmetric synthesis has proven to be efficient compared to other catalytic enantioselective reductions.[28-30]



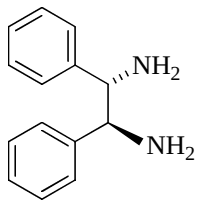
Scheme 14: Hydrogenation of aromatic ketones by BINAP/diamine-Ru catalyst.

Phosphine-Ru(II) complexes are normally not very active as catalysts for hydrogenation of acetophenone.[31] In this case however, the activity of $RuCl_2[P(C_6H_5)_3]_3$ was remarkably enhanced with the addition of 1 equivalent of

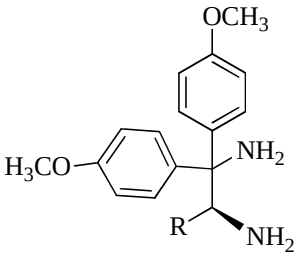
diamine and >2.8 mM of KOH in 2-propanol. The hydrogenation of 1′-acetonaphthone with a catalyst system consisting of RuCl-[(*S*)-binap](dmf)$_n$,[32] (*S*,*S*)-1,2-diphenylethylenediamine [(*S*,*S*)-**33**], and KOH (1:1:2 mole ratio) in 2-propanol (S/C=500, 4 atm of H_2, 28 °C, 6 h) afforded (*R*)-1-(1-naphthyl)ethanol in 97% ee and >99% yield. The high enantioselectivity obtained is a result of synergetistic effects of diphosphine and diamine, which exhibit a matched asymmetric directing effect. Replacenent of *S*,*S* diamine by the *R*,*R* enantiomer under the same conditions gave the *R* alcohol in only 14% ee. A combination of the (*S*)-BINAP-Ru complex and achiral ethylenediamine or achiral $RuCl_2[P(C_6H_5)_3]_3$ and (*S*,*S*)-**33** provided the *R* product in 57% and 75% ee, respectively.



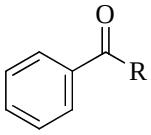
(*S*)-**52**: Ar=C_6H_5 (BINAP)
(*S*)-**53**: Ar=*p*-$CH_3C_6H_4$



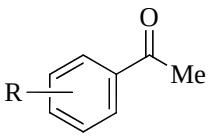
(*S*,*S*)-**33**



(*S*)-**54**: R=CH_3
(*S*)-**55**: R=$(CH_3)_2CHCH_2$
(*S*)-**56**: R=$(CH_3)_2CH$



57a: R=CH_3
57b: R=n-C_4H_9
57c: R=$(CH_3)_2CH$
57d: R=$(CH_3)_3C$



58a: R=CH_3
58b: R=$(CH_3)_3C$
58c: R=CH_3O
58d: R=Cl

Figure 3: Reduction of aromatic ketones by BINAP/diamine-Ru catalyst

Using the BINAP-Ru(II)-diamine-inorganic base combined catalytic system a variety of aromatic ketones were reduced. Diamines **33** and **54**-**56**[33-34] are the most effective chiral controllers (Table 5). The enantioselectivity appears to be influenced

by the structure of the diamine auxiliaries as well as the substituents in the substrates. In the reaction of alkyl/aryl ketones **57a-c**, the enantioselectivity was noticeably increased by increasing the bulkiness of the alkyl group from methyl to primary alkyl to isopropyl. Alkyl, methoxy or chloro substituents at the *meta* or *para* position of acetophenone increase the enantioselectivities.

Table 5: Enantioselective transfer hydrogenation of aromatic ketones catalysed by a BINAP-Ru(II) complex-chiral diamine-KOH system.[a]

Entry	Substrate	Chiral element		Conditions		Alcohol product	
		Phos-phine	diamine	H_2 atm	Time (h)	% yield[c]	% ee[d] abs. config.[e]
1	**57a**	(*S*)-**52**	(*S*)-**55**	4	3	>99	87(*R*)
2	**57b**	(*S*)-**52**	(*S*)-**54**	4	3	>99	90(*R*)
3	**57c**	(*S*)-**52**	(*S*)-**56**	8	6	>99	95(*R*)
4	*o*-**58a**	(*S*)-**52**	(S,S)-**53**	4	5	>99	94(*R*)
5	*o*-**58d**	(*S*)-**53**	(S,S)-**33**	50	3	>99	94(*R*)
6	*m*-**58c**	(*R*)-**52**	(*R*)-**56**	8	3	99	88(S)
7	*m*-**58d**	(*S*)-**53**	(*S*)-**56**	8	1	96	90(*R*)
8	*p*-**58a**	(*R*)-**52**	(*R*)-**56**	4	3	>99	91(S)
9	*p*-**58b**	(*S*)-**53**	(S,S)-**33**	4	1.5	>99	96(*R*)
10	*p*-**58c**	(*R*)-**52**	(*R*)-**56**	4	3	>99	92(*S*)
11	*p*-**58d**	(*S*)-**52**	(*S*)-**56**	8	16	>99	94(*R*)
12	1′-*N*pAc	(*S*)-**53**	(S,S)-**33**	4	16	>99	97(*R*)

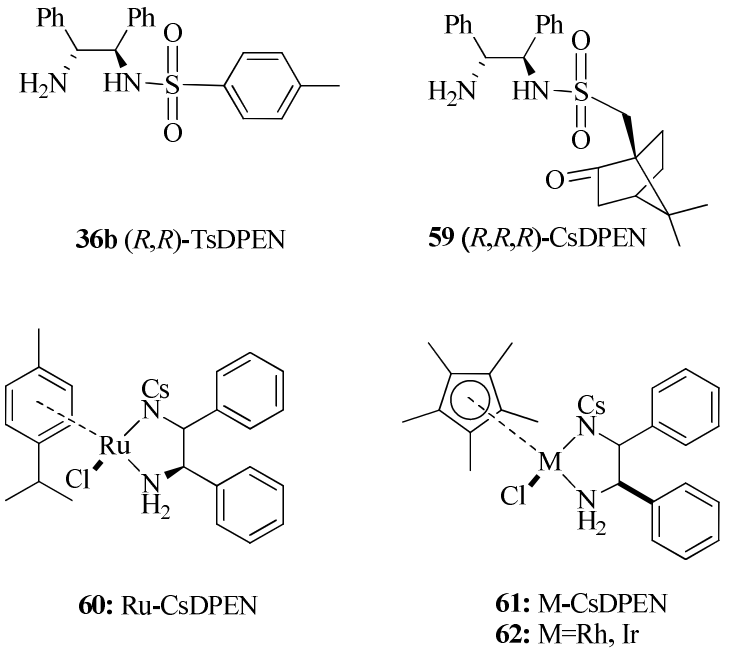
Conditions: 1.4 M of substrate (5mmol) in 2-propanol. Substrate:Ru:diamine:KOH=500:1:1:2, 11-30 °C. [b]Np= naphthyl. [c]Determined by chiral GC and ^{1}H NMR analysis. [d]Determined by HPLC analysis using a DAICEL CHIRAL CEL OB column (eluent, 10:90 2-propanol:hexane; flow rate, 0.5 cm^3/min). [e]Determined by sign of optical rotation.

The hydrogenation of *ortho*-methylated and chlorinated acetophenones, *o*-**58a** and *o*-**58d**, proceeded with high stereoselectivity. The ketones *m*-**58c-d** and *p*-**58a-d** were reduced with higher enantioselectivity than unsubstituted acetophenone **57a** highlighting the effect of the electronic properties of the substituents. In conclusion a BINAP-Ru(II) complex-chiral diamine-KOH system acts as a very practical catalyst for enantioselective hydrogenation of simple aromatic ketones.

1.5. Asymmetric transfer hydrogenation (ATH) of ketones by Ir(III) camphor modified diamine ligand

Catalysis in water is a field of increasing interest in modern chemistry, as its environmental and economic gains are potentially significant.[35] Among many reactions using water as the solvent or cosolvent which have been reported, asymmetric transfer hydrogenation (ATH) has recently attracted a great deal of attention.[36-37] ATH provides a powerful alternative to asymmetric hydrogenation for the catalytic reduction of ketones and imines because of its combined versatility and practical simplicity.[38-41] Among the various chiral catalysts reported for ATH reactions, the most notable is the Ru-TsDPEN [TsDPEN =(1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenyl ethylenediamine] complex developed by Noyori, Ikariya, Hashiguchi and co-workers.[41] Xiao *et al.* recently reported that the ATH of the aromatic ketones with the Ru-(*R,R*)-TsDPEN catalyst[37a] or its polymer analogue Ru-PTsDPEN[37b] can be greatly accelerated using water as the solvent. Also they reported that a camphor modified 1,2-diphenylethylenediamine ligand forms an excellent catalyst with iridium for the ATH of ketones in neat water[42] (Figure 4). Camphorsulfonyl (Cs) has also been used as a chiral auxiliary in amine and amino alcohol ligands to promote reactions such as enantioselective addition to aldehydes and ketones upon coordination with copper or titanium species.[43-44]

Initially the ATH was carried out at a S/C ratio of 100. Table 6 summarises the results obtained with Ru-, Rh- and Ir-CsDPEN complexes. The reactions were nearly complete within 0.7 h with Rh- and Ir-(*R*,*R*,*R*)CsDPEN (Table 6, entry 1). Using the opposite configuration M-(*S*,*S*,*S*)CsDPEN complexes gave the product of opposite configuration (Table 6, entry 2), indicating that the enantioselective reduction is determined by the chelating amino component of the ligand.



36b (*R*,*R*)-TsDPEN

59 (*R*,*R*,*R*)-CsDPEN

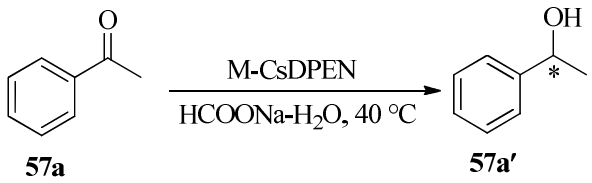
60: Ru-CsDPEN

61: M-CsDPEN
62: M=Rh, Ir

Figure 4: Camphor modified 1,2-diphenylethylenediamine ligand.

By increasing the S/C ratio to 1000, the Ir-CsDPEN is the most effective catalyst for the reduction of acetophenone as the reaction reaches near completion in about 2.5 h, whereas with the other two Rh and Ru catalysts the reaction was not complete even after 20 h. However the enantioselectivities for the three catalysts all remain as high as when a S/C ratio of 100 is used. The Ir-(*R*,*R*,*R*)CsDPEN catalyst was extended to a range of different ketones under the same conditions at a S/C ratio of 1000. Table 7 shows a summary of the results obtained.

Table 6: ATH of acetophenone with M-(*R*,*R*,*R*)CsDPEN in water.[a]



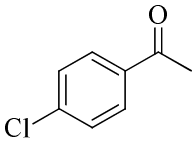
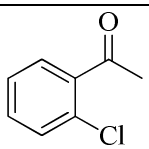
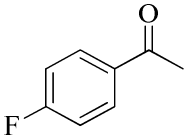
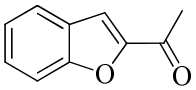
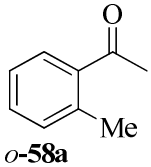
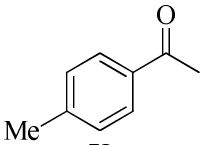
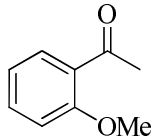
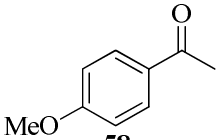
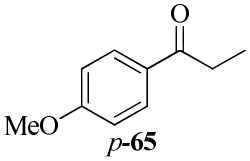
57a **57a′**

Entry	S/C	Rh (III)			Ru (II)			Ir (III)		
		Time (h)	Conv.[b] %	ee[b] %	Time (h)	Conv.[b] %	ee[b] %	Time (h)	Conv.[b] %	ee[b] %
1	100	0.7	99	99	2	99	97	0.7	98	97
2[c]	100	0.7	97	98	2	99	96	0.7	99	96
3	1000	20	89	99	20	95	96	2.5	97	98

[a]Conditions: 40 °C, acetophenone (1 mmol), HCOONa (5 equiv.), S/C=100, in 2 cm^3, HCOONa (5 equiv.), S/C=1000, in 8 cm^3. [b]Determined by GC. [c]Using (*S*,*S*,*S*)CsDPEN as a ligand, the configuration of the product was *S*, whereas using (*R*,*R*,*R*)CsDPEN, the configuration was *R*.

It is noteworthy that the ATH of 1-(benzofuran-2-yl)ethanone was nearly complete in about 45 min. with 94% ee (Table 7, entry 4), also for substrates containing electron withdrawing substituents full conversions were achieved within a few hours. Steric effects may play a role; ATH of 4′-chloroacetophenone gave 96% ee, (Table 7, entry1), however a lower enantioselectivity of 88% ee (Table 7, entry 2) was obtained for the ATH of 2′-chloroacetophenone. Although the reactions were performed under nitrogen no significant decrease in conversion or enantioselectivity was observed in the ATH of 4′-chloroacetophenone without nitrogen. In the case of ATH for the electron-donating substituents, the reaction was slower in most cases, thus for the 2′- and 4′-methyl substituted acetophenone, the reaction requires longer times for completion (Table 7, entries 5 and 6).

Table 7: ATH of aryl ketones substituents by with Ir-(*R*,*R*,*R*)CsDPEN in water.[a]

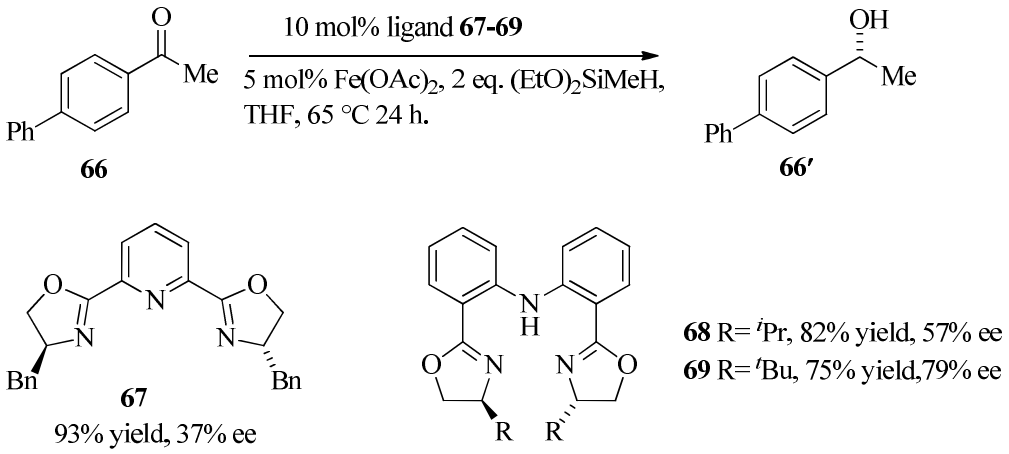
Entry	Ketone	Time (h)	% Conv.[b]	% ee[b]
1	 *p*-**58d**	2	50	96
2	 *o*-**58d**	3	98	88
3	 ***p*-63**	3.1	99	96
4	 **64**	0.75	99	94
5	 *o*-**58a**	29	84	93
6	 *p*-**58a**	8.5	94	92
7	 *o*-**58c**	21	99	85
8	 *p*-**58c**	22	94	97
9	 *p*-**65**	50	78	86

[a]Conditions: 40 °C, acetophenone (1 mmol), HCOONa (5 equiv.), S/C=1000, in 8 cm^3. [b]Determined by GC. [c]Using (*R*,*R*,*R*)CsDPEN as a ligand, the configuration of the product was *R*.

The 2′- and 4′-methoxy substituted acetophenone (Table 7, entries 7 and 8) also required longer reaction times. The ATH of 4-methylpropiophenone was slowest, giving only 78% conversion after a reaction time of 50 h (Table 7, entry 9).

1.6. Hydrosilylation of ketones

Asymmetric hydrosilylation represents an alternative method for the generation of enantiomerically enriched alcohols from ketones. Iron-catalysed hydrosilylation has been achieved using a number of catalysts[45] with examples dating from 1990. Nishiyama has published a number of findings in this area. In early work the catalysis of ketone hydrosilylation with iron complexes of bis(oxazolinyl)pyridine ligands was disclosed, including several asymmetric applications (Scheme 15).[46] In further extended studies on the more promising *N*-bridged bisoxazoline ligands such as **67** to **70** (Scheme 15, Figure 5), the derivative **70** derived from the diphenylmethyl-substituted amino alcohol (Bopa-dpm) proved to be the most enantioselective when used in conjunction with iron diacetate.[47] Products of up to 80% ee were formed with conversions as high as 99% in many cases (Figure 5).



Scheme 15: Asymmetric hydrosilylation of ketones using bis(oxazoline) complexes of iron.

The suggested mechanism involves the formation of a metal hydride and transfer of the hydride to the ketone substrate *via* a complex in which the ketone is co-ordinated to the iron.

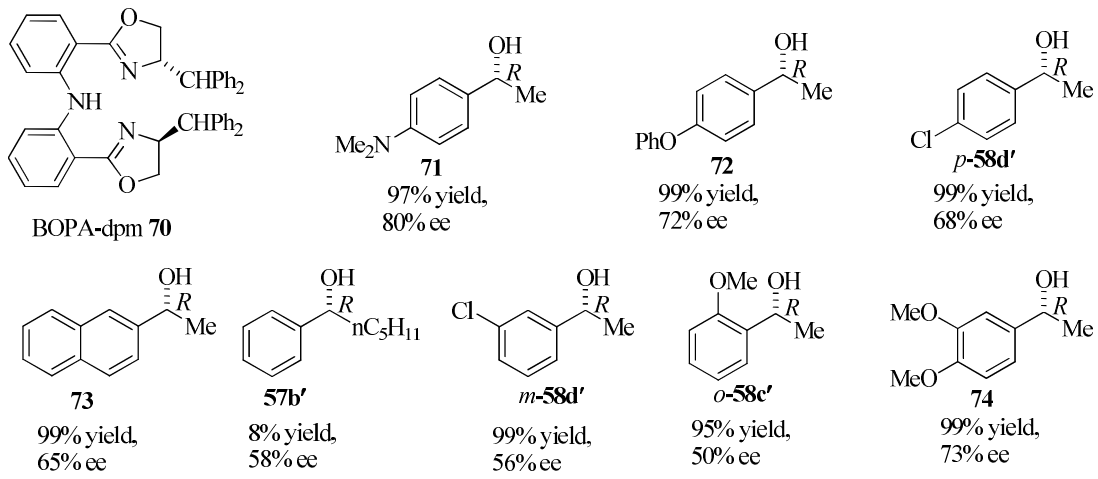
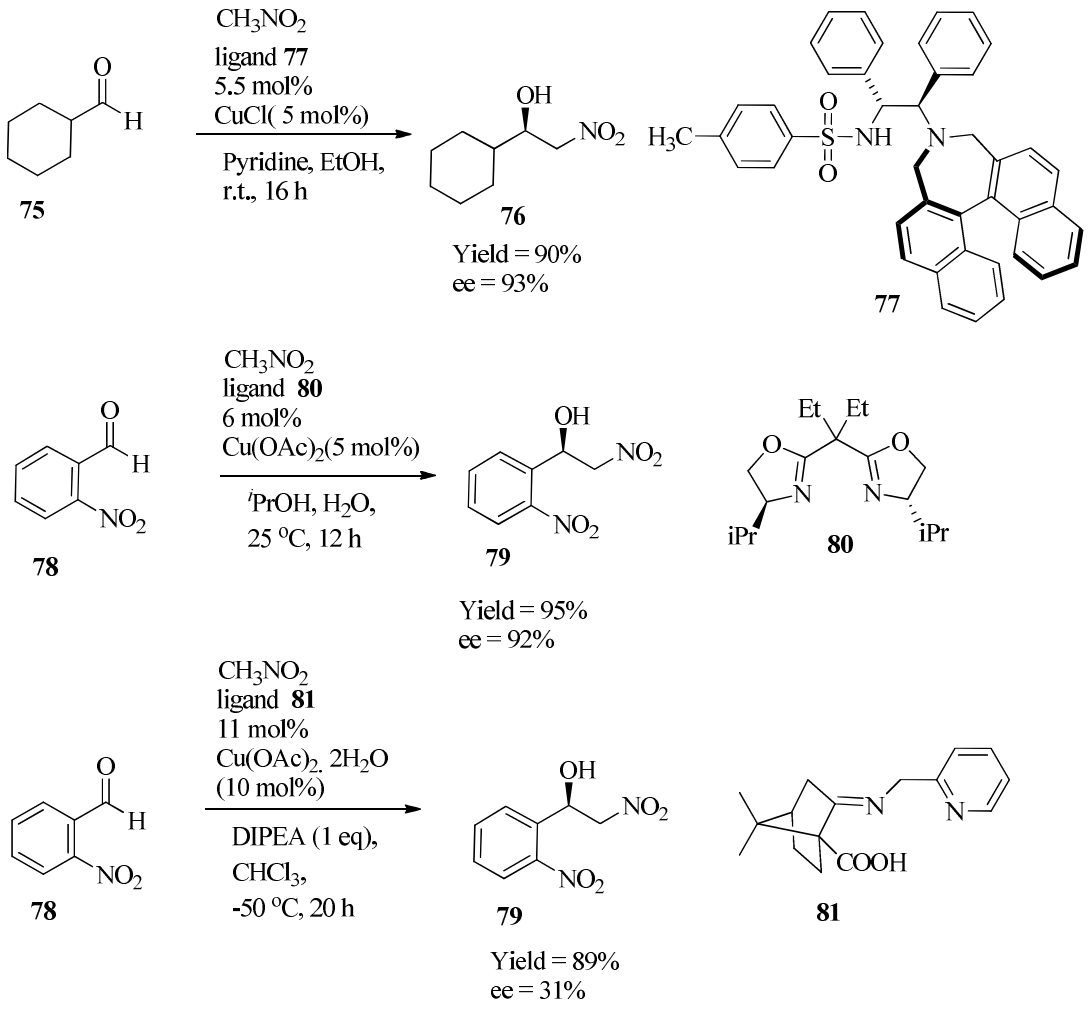


Figure 5: Asymmetric reduction of ketones by $Fe(OAc)_2$/BPA-dpm complexes.

1.7. Henry reaction

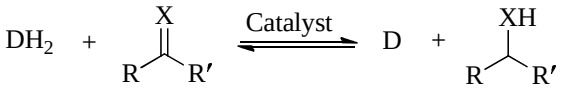
The Henry (nitroaldol) reaction is an efficient C-C bond forming reaction. This reaction allows a stereogenic centre to be generated at the β-position to the nitro functionality. The resulting β-nitro alcohol products can be converted to α-hydroxy ketones. Both products are very useful as chiral building blocks for natural products. Due to the recent development of asymmetric organocatalysis, research groups have focused on asymmetric versions of the Henry reaction. In earlier work, metal complexes have been combined with different chiral ligands.[48] Recently chiral ligands with Cu salts have been found to be very promising in this application (Scheme 16).[49-50]



Scheme 16: Chiral ligands developed for Henry reactions.

1.8. Asymmetric transfer hydrogenation

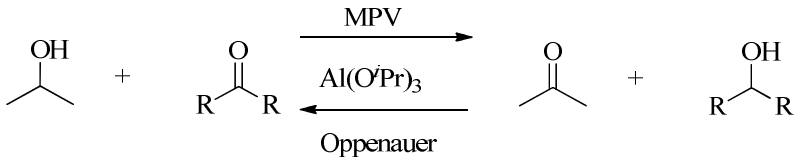
Asymmetric transfer hydrogenation (ATH) can be defined as the reduction of prochiral compounds with a hydrogen donor other than hydrogen gas in the presence of a chiral catalyst (Scheme 17).[51] It is generally regarded as a safer and more practical alternative to hydrogenation since high pressures of hydrogen gas are not required.



Scheme 17: A transfer hydrogenation reaction where X = O, NR or CR_2, DH_2 = hydrogen donor.

1.8.1. The Meerwein-Ponndorf-Verley reduction

The first reported example of a transfer hydrogenation reaction was the Meerwein-Ponndorf-Verley (MPV) reduction which was independently reported by Meerwein and Schmidt,[52] Ponndorf[53] and Verley[54] in the mid 1920s. It was found that a stoichiometric amount of an aluminium alkoxide reagent would facilitate the transfer of hydrogen from 2-propanol to aldehydes and ketones to give the corresponding primary and secondary alcohols selectively. Over a decade later, Oppenauer reported the reverse reaction, where alcohols were oxidised to aldehyde and ketones by aluminium *tert*-butoxide using acetone as the hydrogen acceptor (Scheme 18).[55]



Scheme 18: The MPV reduction and Oppenauer oxidation reaction.

The reaction is thought to proceed through a six-membered cyclic transition state in which the hydrogen donor is coordinated to the aluminium centre as an alkoxide and the hydrogen acceptor is coordinated by a Lewis acidic interaction. Direct hydride transfer from the donor to the acceptor takes place to give an alkoxide product which is released from the metal by an alcoholysis reaction with the bulk solvent (Figure 6).

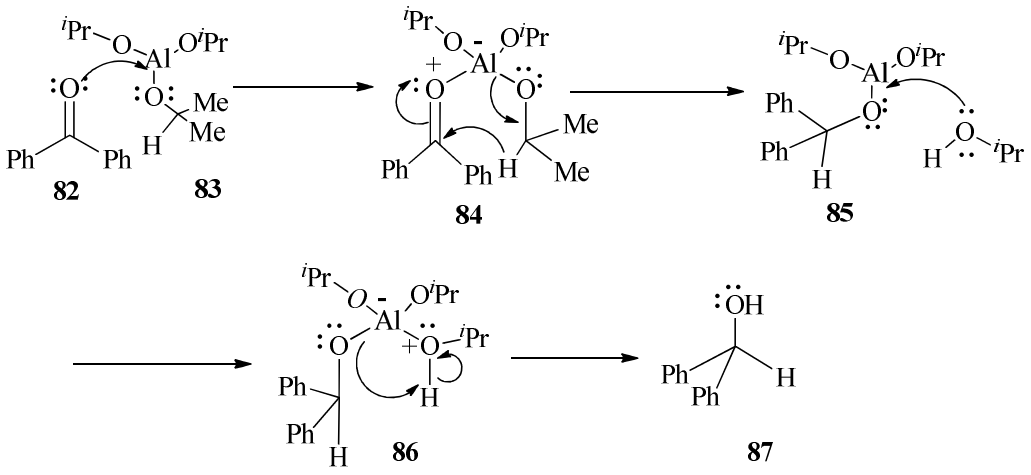


Figure 6: Mechanism of the MPV reduction.

1.8.2. Ligand used in ATH

The chiral catalysts used in this reaction most often consist of a transition metal ion in combination with chiral ligands.[56] However in recent years simple organic chiral catalysts have also been used for this particular transformation.[57]

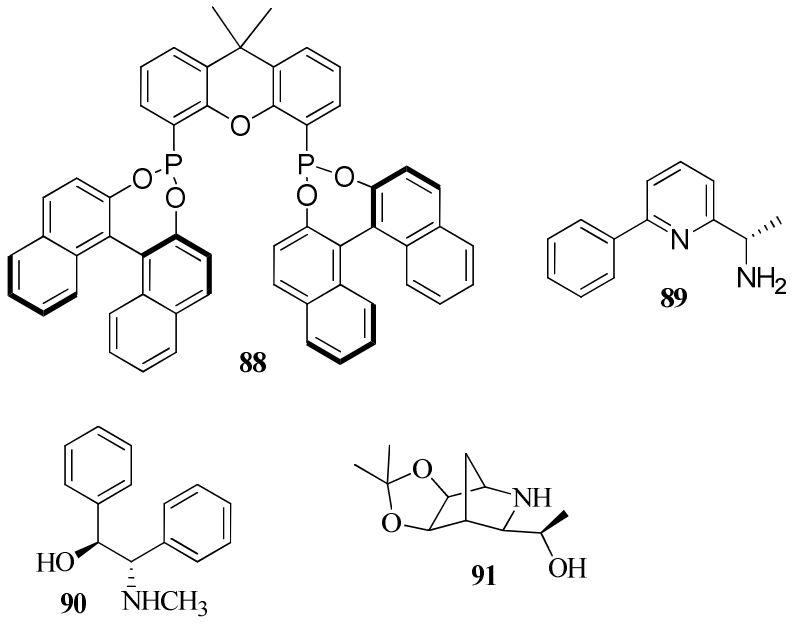


Figure 7: Chiral ligands used in ATH reaction.

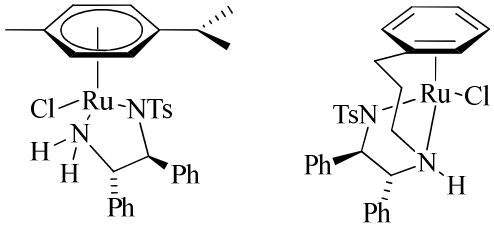
Among the most active and selective catalysts reported so far are those containing the ligands diphosphonite **88**,[58] pyridine derivative **89**,[59] amino alcohol **90**[60] and aza-

norbornyl alcohol **91**,[61] as well as complexes **92**[62] and **93**,[63] which are based on monotosylated diamine ligands.

Bidentate phosphorus donor ligands generally work better in enantioselective hydrogenation reactions than in asymmetric hydrogen transfer reactions. An exception is ligand **88**, which has a large bite angle and generates a highly efficient and selective catalyst for ketone reductions under transfer hydrogenation conditions when used together with $[Ru(p\text{-cymene})Cl_2]_2$.[58,64]

The pyridine-derived ligand **89** binds in a pincer-type fashion when coordinated to $[RuCl_2(PPh_3)_3]$. When this complex is combined with a chiral diphosphine ligand, the catalyst formed shows astonishingly high turnover frequencies at loadings as low as 0.005 mol%.[59]

Amino alcohols and monotosylated diamine ligands are normally used together with Ru, Rh or Ir complexes to form bifunctional catalysts.[56] In a bifunctional catalyst, besides inducing enantioselectivity, the chiral ligand accepts and donates a proton with its basic nitrogen, whereas the hydride is received and delivered by the transition metal, as illustrated in Scheme 19.[65]

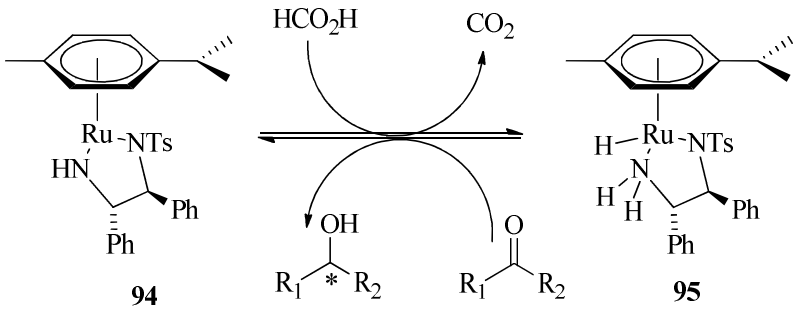


(*S*,*S*)-**92** (*R*,*R*)-**93**

Figure 8: Chiral ligands derived from TsDPEN used in ATH reaction.

Complex **92**, developed and thoroughly studied by Noyori, is perhaps the most well known and successful catalyst for asymmetric transfer hydrogenation.[66] The tethered version of this catalyst **93**, shows enhanced activity and selectivity in several cases

over the untethered diamine due to the locked conformation of the arene providing by the tether.[63]

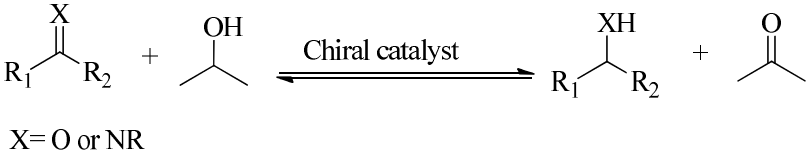


Scheme 19: Formation of the complex hydride.

The class of substrates that can be highly selectively reduced by catalysts containing Ru, Rh or Ir complexes is limited to aryl alkyl ketones. The high selectivity associated with these reactions is attributed to a stabilizing dipolar interaction between the arene-CH of the catalyst (e.g. *p*-cymene) and the π-system of the substrate. [67] When reducing dialkyl ketones in hydrogen transfer reactions, the resulting enantioselectivities have so far been rather moderate. The only exceptions are the ruthenium catalysts based on either a β-cyclodextrin coupled amino alcohol ligand presented by Woggon and co-workers,[68] or ligand **88** developed by Reetz, which have shown promising selectivities for this transformation.[58,64]

1.8.3. Hydrogen donors in ATH

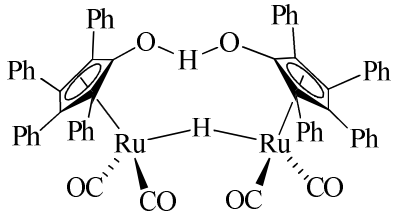
Isopropanol (IPA) and formic acid (FA)/triethylamine (TEA) are by far the most commonly used sources of hydrogen in transfer hydrogenation. During the process, IPA is oxidized to acetone (Scheme 20).



Scheme 20: Transfer hydrogenation using isopropanol as source of hydrogen.

This makes the reduction of ketones by IPA a reversible process. To shift the equilibrium towards the desired product IPA is most frequently used as the solvent of the reaction as the life-time of many metal catalysts in IPA solution is usually reasonably long even at reflux temperature to allow most reactions to be driven to high conversions. When IPA is the hydrogen donor a base is usually required for the activation of the starting complex for catalysis. Sodium or potassium carbonates, hydroxides or alkoxides at various concentrations have been employed for this purpose. Quite few catalytic precursors do not require any base (Shvo catalyst, Figure 9)[69] or need just two equivalents for metal atom (Noyori's and similar catalysts).[70]

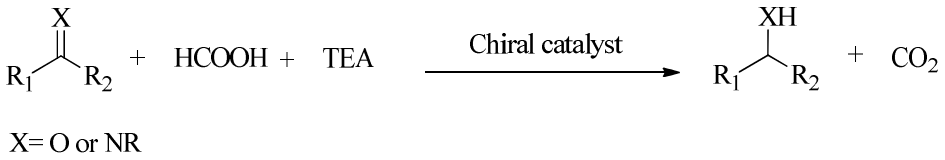
Although IPA is environmentally friendly and easy to handle, the reversibility of the reaction remains a major drawback in asymmetric hydride transfer. At low conversions the reaction is kinetically controlled and the stereoselectivity may be high. As the conversion increases, the rate of the reverse reaction becomes higher and the ratio of enantiomers falls under thermodynamic control with gradual loss of the enantiomeric purity of the product. This limitation can be overcome by continuously distilling off the acetone as soon as it is formed or by operating in dilute solution.



96

Figure 9: Shvo catalyst.

Formic acid and its salts are better suited hydrogen donors than IPA because their dehydrogenation in open systems is substantially irreversible due to the evolution of CO_2 (Scheme 21).[71]



Scheme 21: Transfer hydrogenation using formic acid as source of hydrogen.

An azeotropic 5:2 mixture of FA and TEA is most frequently employed as the reducing agent. This gives a single phase at room temperature; it is miscible with many solvents at 20–60 °C; it allows for high substrate concentrations to give high conversions without back-reaction and racemization. There are however some restrictions to the use of FA/TEA; several complexes undergo fast decomposition on attempted dissolution in formic acid and some other ones lose their catalytic activity completely probably because the acid inhibits one of the steps of the activation process promoted by the base.

1.8.4. Factors affecting Enantioselectivity in ATH

In asymmetric transfer hydrogenation the stable complex **92** has been used, which can be easily prepared *in situ* or isolated by reaction of $[Ru(arene)Cl_2]_2$ with chiral ligands such as TsDPEN.

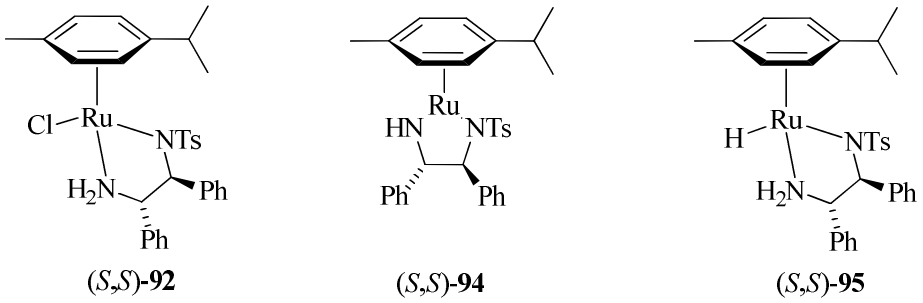
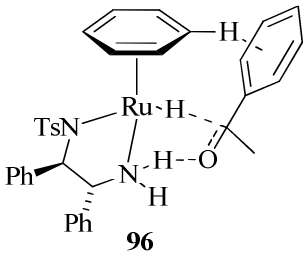


Figure 10: Complex **92** and intermediates formed during catalytic cycle.

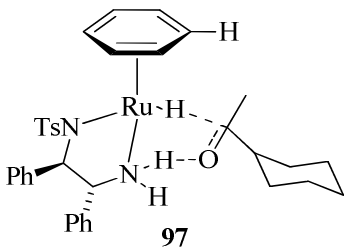
Complex **92** is a precatalyst, as during the reaction it is converted into the 16 electron species **94** by reaction with KOH in toluene. The 16 electron species reacts with IPA to give the hydride form of the catalyst **95**.[69] The enantioselectivity may arise due to a stereodetermining transition state with electronic influences around the metal centre and also *via* space interactions between the catalyst and substrate. The transition state structure was studied by hybrid density functional theory (DFT)-based calculations for compound **95**. This study has revealed that enantioselectivity originates not only from the well-defined cyclic transition state but also through a CH/π interaction of η^6-arene of the complex and the aryl group of the substrate as shown in Figure 11.[73-74]

Andersson *et al*. also reported the DFT calculation for three different mechanistic models for the asymmetric transfer hydrogenation with Ru(arene)-aminoalcohol, (**A**) direct transfer of hydrogen of an alcohol to the carbonyl carbon of a ketone, (**B**) migratory insertion (MI) of a coordinated ketone into a metal hydride bond, or (**C**) a concerted mechanism where a proton and a hydride are transferred simultaneously to the ketone (Figure 12).[75] The computational data has shown that the six membered transition state has a strong preference for planarity.



96

Stabilising CH/π interaction
(*R*) product with high
enantioselectivity

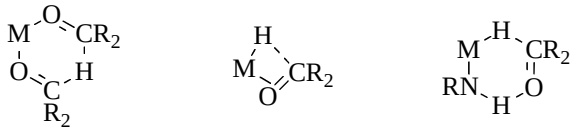


97

Favoured orientation,
CH/π interaction not possible
(*S*) product with high enantioselectivity

Figure 11: CH/π interaction in asymmetric transfer hydrogenation of ketones.

The planarity of the transition state is also dependent on the conformational behavior of the *O*,*N*-linkage of the amino alcohol ligand.[75] In 2004, Brandt, Roth and Andersson reported more experiments which provide an insight into the asymmetric transfer hydrogenation of ketones.[76] They reported asymmetric transfer hydrogenation of different substituted aliphatic and aromatic ketones and used the data for DFT calculations.



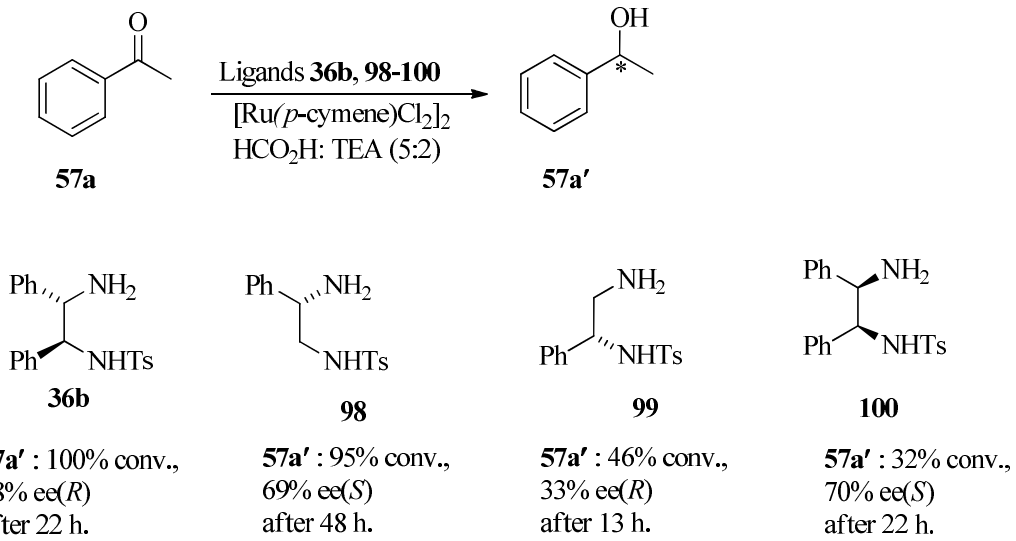
A B C

Figure 12: Possible model for transfer hydrogenation between metal hydride and ketones.

Both experimental and computational data were found which provided additional support for the interaction between the substrate phenyl ring and metal arene ring, which is in contrast to aliphatic ketones. At the same time, enantioselectivity in transfer hydrogenation of ketones is also influenced by steric, electrostatic, dispersion and solvent effects.[76] As a result excellent enantiomeric excesses are observed for substrates containing a combination of aryl and alkyl substituents on the carbonyl group. For substrates not fitting this model, enantioselectivities are frequently lower and unpredictable, although there are examples of alternative asymmetric transfer hydrogenation catalysts which have a broad substrate range.[76]

Noyori also investigated the effects of having electron-donating/withdrawing groups on the aryl substituent of the substrate, and its effects on the enantioselectivity. It was discovered that electron-donating substituents on the aryl group increase the enantioselectivity due to an enhanced CH accepting ability by the electron rich

aromatic ring, while electron withdrawing substituents reduce the enantioselectivity.[77-79] Wills and co-workers[80] had investigated the *anti*-orientation, and the importance of 1,2-disubstitution pattern of phenyl groups in TsDPEN on the rate and the stereo-outcome of Ru(II) catalysed ATH reactions. It was discovered that ligand **36b** was the best ligand for Ru(II) catalysed transfer hydrogenation reduction in-terms of rate and enantioselectivity in comparison to ligands **98-100**, giving **57a′** in 100% conv., 98% ee (*R*) at 28 °C in 22 h. Identifying the importance of having matching stereogenic centres and *trans* orientation of the phenyl groups, provides an extra element of stereo control and rate enhancement (Scheme 22).



Scheme 22: ATH reduction of **57a**, using ligands **36b**, **98-100** in conjunction with Ru(*p*-cymene)$Cl_2]_2$ (S/C = 200).

1.8.5. Mechanistic studies

Noyori proposed the metal ligand bifunctional catalytic mechanism shown in Figure 13, which functions through a concerted transfer of a hydride and proton. It is sometimes referred to as the "outer sphere" mechanism because of the substrate having no direct contact with the metal centre.

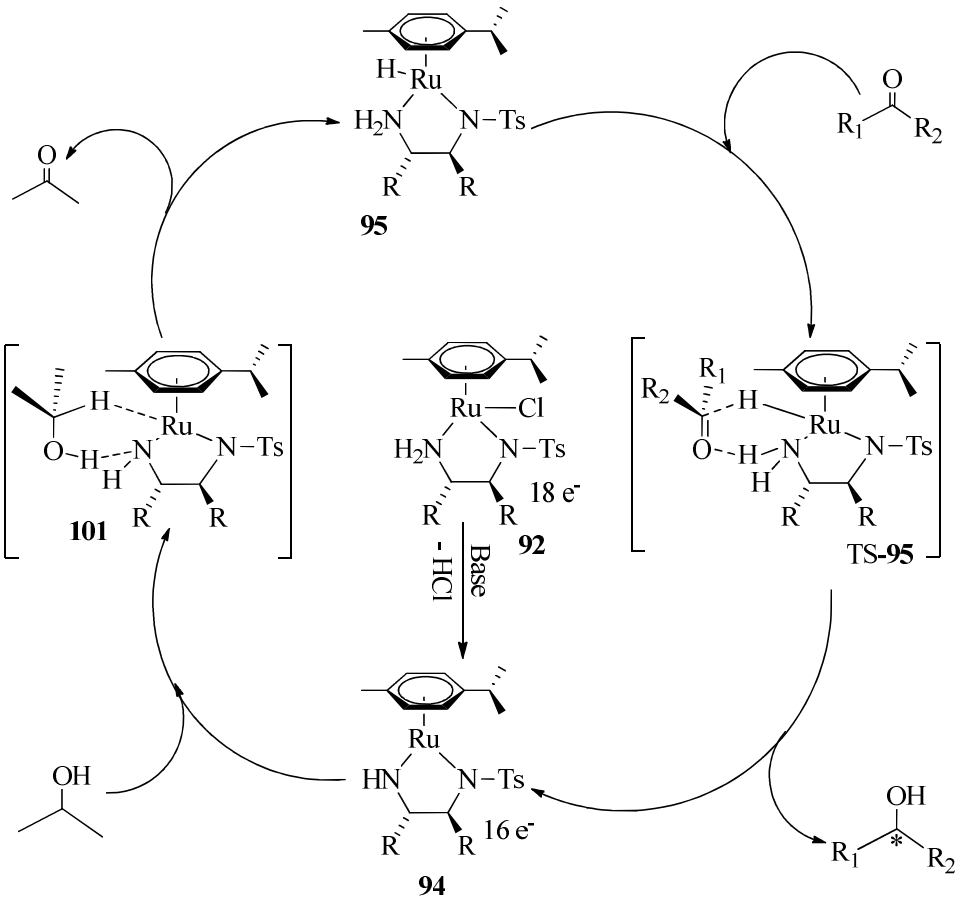


Figure 13: ATH reduction mechanism of ketones using catalyst **92**.

The process is initiated by the elimination of HCl from the 18 electron "precatalyst" complex **92**[81] upon treatment with an appropriate base (KOH in IPA, TEA if formic acid is used as hydrogen donor). This results in the formation of the active 16 electron species **94** , that gains two hydrogens from the hydrogen donor (IPA or formic acid) to give the 18 electron species **95** and acetone or CO_2 as a side product. The kinetic isotope effect for the dehydrogenation of isopropanol was investigated by Casey *et al*,[82] showing that hydride and proton transfer takes place simultaneously, which is in agreement with what Noyori has shown. In a concerted process the hydride and the proton are then transferred to the ketone asymmetrically *via* a six-membered transition state giving the product and also regenerating the active 16 electron species **94** to complete the cycle. In contrast to the bifunctional

TsDPEN-Ru catalysts developed by Noyori, the orientation of approach may be dominated by a favourable π/π interaction between the arene group in the ligand and the aromatic substituent on the respective ketone.

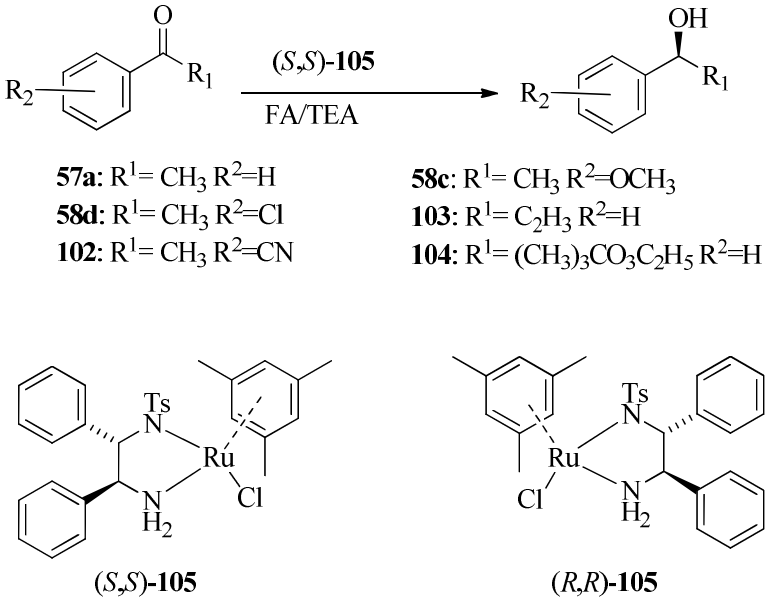
Noyori *et al* isolated and characterised the three key intermediates (**92**, **94** and **95**) using X-ray crystallography. They also proved that the role of the base is only to generate the active 16 electron species from **92**,[81] as after isolation **94** and **95** were both tested for the reduction of ketones, giving results comparable to the *in situ* formed complex. This also eliminated the possibility of the direct hydrogen transfer mechanism, as this would require the participation of the ruthenium isopropoxide intermediate. Further investigation carried out by Noyori[83] and Andersson[84] confirmed this.

1.8.6. Substrates scope for transfer hydrogenation

Substrates for transfer hydrogenations are typically carbon-carbon double bonds,[85] carbon-oxygen double bonds in ketones and aldehydes[85], and carbon-nitrogen double bonds in imines.[85]

1.8.6.1. Aryl alkyl ketones

Aromatic ketones are the most commonly used substrates in asymmetric transfer hydrogenation reduction, especially using monotosylated diamines or β-amino alcohol ligands. A variety of aromatic ketones were reduced using catalyst (*S*,*S*)-**105**.[86] ATH reactions were carried out using 2M solution of substrate in a 5:2 FA/TEA azeotrope. A range of aromatic ketones can be reduced to the secondary alcohols with a high yield and satisfactory enantioselectivity (S/C=200), in FA/TEA at 28 °C, giving the resulting secondary alcohols with the excellent yields and enantioselectivities (Scheme 23, Table 8).



Scheme 23: A range of aryl ketones were reduced using (*S*,*S*)-**105**.

Table 8: A range of aryl ketones were reduced using (*S*,*S*)-**105**[a]

Entry	Substrate	Catalyst **105**	Time/h	% yield[b]	% ee[c]	abs. config.[d]
1	**57a**	*S*,*S*	20	>99	98	*S*
2	*m*-**58d**	*S*,*S*	21	>99	97	*S*
3	*p*-**58d**	*S*,*S*	24	>99	95	*S*
4	*p*-**102**	*S*,*S*	14	>99	90	*S*
5	*m*-**58c**	*S*,*S*	50	>99	98	*S*
6	*p*-**58c**	*S*,*S*	60	>99	97	*S*
7	**103**	*S*,*S*	60	96	97	*S*
8	**104**	*S*,*S*	90	99	95	*S*

[a]The reaction was carried out at 28 °C using a ketone (5.0 mmol) in FA/TEA mixture (5:2, 2.5 cm^3), S/C = 200. [b]Determined by GC or 400 MHz ^1H NMR analysis. [c]Determined by chiral HPLC. [d]Determined by the sign of optical rotation of the isolated product.

The justification for why the reductions proceed with excellent enantioselectivities, is due to the CH/π interaction between the Ru-arene ring and the aryl group on the

ketone, along with the favourable diastereomeric transition state extracted by the monotosylated diamine ligand.

The pyridine bridged compounds **106-111** were employed for enantioselective reduction of ketones using $Sn(OTf)_2$ and polymethylhydrosiloxane (PMHS) as the reducing agent, This process is related to the hydrosilylation of ketones.

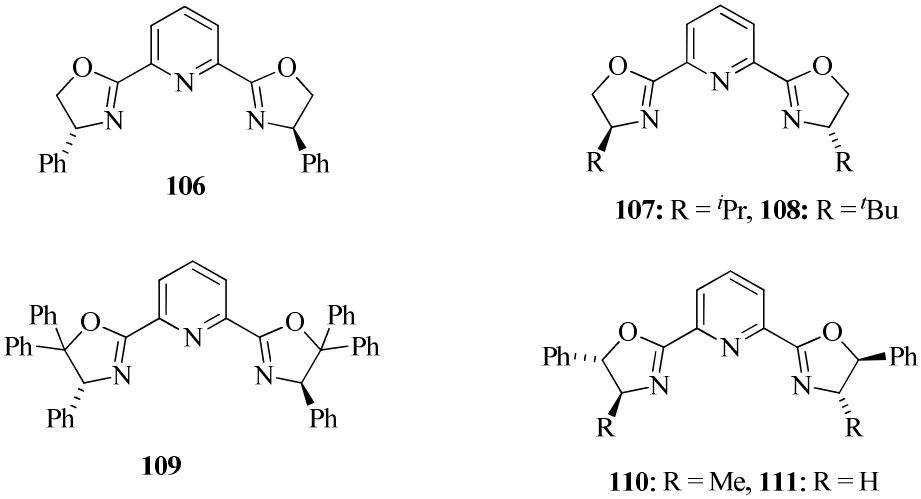


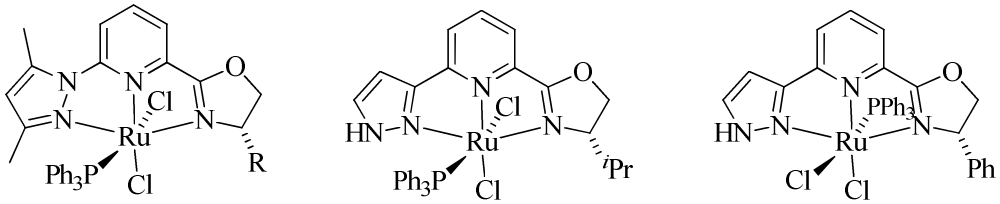
Figure 14: Hydrosilylation of ketones by pyridine ligands.

Table 9: Reduction of acetophenone to 1-phenylethanol with tin(II) triflate (10 mol%)/**106-111** (10 mol%), and PMHS (200 mol%).

Entry	Ligand	% Conversion	% ee	Config.
1	**106**	95	58	*R*
2	**107**	78	54	*S*
3	**108**	50	13	*S*
4	**109**	30	44	*R*
5	**110**	50	58	*R*
6	**111**	82	0	-

Among these ligands compound **106** gave a good conversion (95%) over a period of 12-14 h, but enantioselectivity was quite low (58% ee) for reduction of acetophenone (Table 9).[87]

Recently Zhengkun[88] *et al* reported versatile unsymmetrical pyridyl-based *NNN* ligands and their active Ru(II) complexes **112-115** for the ATH of ketones. Results of ATH for acetophenone, 3′-bromoacetophenone and 3′-chloroacetophenone in presence of the ^{i}PrOK base in 2-propanol using these ligands are summarised in Table 10.



112: R= Ph
113: R = ^{t}Bu

114

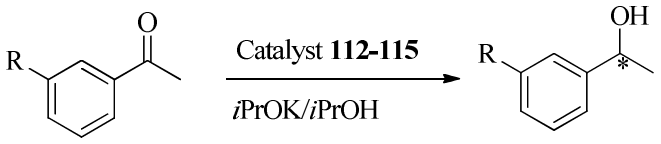
115

Figure 15: ATH of ketones by pyridyl-based *NNN* ligands.

Acetophenone was reduced to the corresponding alcohol at 40 °C in 98% yield and 36% ee within 60 min by using 0.5 mol% **112** as the catalyst, whereas **113** exhibited a much lower catalytic activity (Table 10, entry 1 and 2). Complex **114** showed higher catalytic activity, reaching 93-96% yields and 90-93% ee over a period of 8-10 min at 30-40 °C (Table 10, entry 3 and 4). Although complex **115** also exhibited good catalytic activity, the desired product was only formed with poor enantiopurity (23% ee). These results suggest that the convertible NH group in the ligand has a remarkable enhancing effect on the catalyst activity (Table 10, entry 1-5). Complex **114** gave better catalyst activity, this may be because it could be easily converted into the coordinatively unsaturated 16-electron complex in *situ* under the basic conditions,[89-90] which were then transformed into the catalytically active RuH species

and thus facilitated the catalytic reaction. Next the ATH of various aromatic ketones was explored under optimal reaction conditions, 30-40 °C, with 0.3-0.4 mol% **114** as the catalyst (Table 11). At 40 °C and with 0.3 mol% **114** as the catalyst, propiophenone, 3′-methylacetophenone, and 2′-bromoacetophenone were reduced to the corresponding alcohols in 95-99% yields with 90-97% ee within 5-45 min, reaching final TOFs of up to 3960 h^{-1} (Table 11, entries 1, 3 and 4).

Table 10: ATH of ketones catalysed by complexes **112-115**.[a]



57a: R = H
116: R = Br
m-**58d**: R = Cl

57a′: R = H
116′: R = Br
m-**58d′**: R = Cl

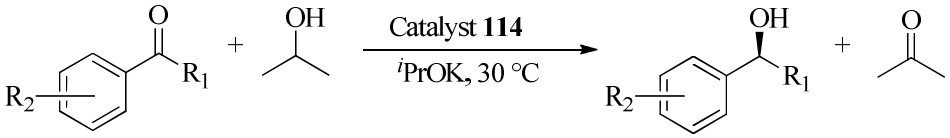
Entry	Ketone	Catalyst (mol%)	T (°C)	t (min)	%Conv.[b]	% ee[b]	abs. Config.[c]
1	**57a**	**112** (0.5)	40	60	98	36	*R*
2	**57a**	**113** (1.0)	40	120	94	27	*R*
3	**57a**	**114** (0.3)	40	8	96	93	*S*
4	**57a**	**114** (0.4)	30	10	93	90	*S*
5	**57a**	**115** (0.4)	30	15	97	23	*R*
6	**116**	**114** (0.3)	40	5	99	84	*S*
7	**116**	**114** (0.4)	30	10	98	85	*S*
8	*m*-**58d**	**114** (0.4)	30	20	97	84	*S*

[a]Conditions: ketone (2.0 mmol); 0.1 M in 20 cm_3 ^{i}PrOH, ^{i}PrOK/cat. = 20:1; N_2 (0.1 MPa). [b]Determined by GC analysis using a chiral column β-DEX 225. [c]Determined by the sign of optical rotation of isolated product.

2′-Methylacetophenone and chloro, bromo-substituted acetophenone reached 97-98% yield with 73-98% ee for their reduction over a period of 5-20 min (Table 11,

entries 2 and 5-7). Surprisingly 2′-trifluoromethylacetophenone gave the desired product in 99% yield and 99% ee (Table 11, entry 8).

Table 11: ATH of ketones catalysed by complex **114**.[a]



57b: R_1=Et., R_2=H
o-**58a**: R_1=Me, R_2=Me
m-**58a**: R_1=Me, R_2=Me
o-**116**: R_1=Me, R_2=Br
m-**116**: R_1=Me, R_2=Br
o-**58d**: R_1=Me, R_2=Cl
m-**58d**: R_1=Me, R_2=Cl
o-**58b**: R_1=Me, R_2=CF_3
m-**58b**: R_1=Me, R_2=CF_3

57b′: R_1=Et., R_2=H
o-**58a′**: R_1=Me, R_2=Me
m-**58a′**: R_1=Me, R_2=Me
o-**116′**: R_1=Me, R_2=Br
m-**116′**: R_1=Me, R_2=Br
o-**58d′**: R_1=Me, R_2=Cl
m-**58d′**: R_1=Me, R_2=Cl
o-**58b′**: R_1=Me, R_2=CF_3
m-**58b′**: R_1=Me, R_2=CF_3

Entry	Ketone	t (min)	%Conv.[b]	% ee[b]	Final TOF
1	**57b**	40	96	93	480
2	*o*-**58a**	5	97	98	2910
3	*m*-**58a**	45	95[c]	90	423
4	*o*-**116**	5	99[d]	97	3960
5	*m*-**116**	10	98	85	1470
6	*o*-**58d**	20	98	96	735
7	*m*-**58d**	20	97	84	728
8	*o*-**58b**	10	99[e]	99	743
9	*m*-**58b**	20	99	77	743

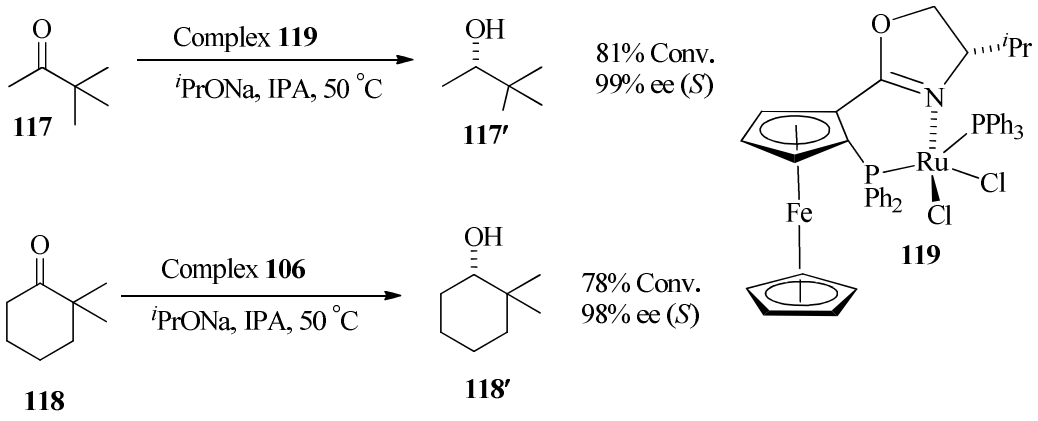
[a]Ketone (2 mol%; 0.1 M in 20 cm^3 ^{i}PrOH), ^{i}PrOK/cat. = 10:1; N_2(0.1 MPa), 30 °C. [b]Determined by chiral GC. [c]**114** (0.3 mol%), 40 C, [d]**114** (0.6 mol%. [e]**114** (0.8 mol%). All the configuration are *S*.

1.8.6.2. Dialkyl ketones

Dialkyl ketones have proven to be more difficult substrates for transfer hydrogenation due to the loss of the directing effect of the π-face interaction between aryl groups on the substrate and the catalyst.[91] Selective hydrogenation can be performed however, if there is a large difference between the steric bulk on one side

of the ketone compared to the other.[91] The steric interaction between the aryl ring on the catalyst and a bulky alkyl group on the substrate can be enough to create selectivity in the reaction. The product of this type of directing interaction is of the opposite configuration compared to the product of a π-face interaction, due to steric interaction pushing the bulky alkyl group away from the aryl ring, whilst the π-face interaction pulls the aryl group towards the phenyl ring.[91]

A successful example of the reduction of dialkyl ketones by ATH has been reported by Zhang[92,93] and Hidi[94], in which reduction of dialkyl ketones **117** and **118** was carried out using ferrocene based complex [Ru(PPh_3)(oxazolinyl ferrocenylphosphine)Cl_2] **119** and sodium isopropoxide in isopropanol at 50 °C. This gave **117′** in 99% ee and 81% conv., in 16 h, and **118′** in 98% ee and 78% conv., in 3 h (Scheme 24).[94]

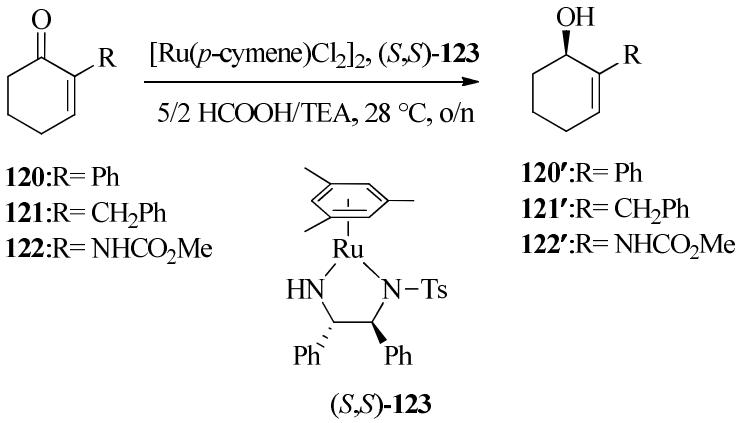


Scheme 24: ATH reduction of dialkyl ketone **117** and **118** using complex **119**.

1.8.6.3. Cyclic α,β-unsaturated ketones

The reduction of α-phenyl substituted cyclohex-2-en-1-one **120**, catalysed by complex (*S*,*S*)-**123** gave the allylic alcohol **120′** in a modest yield and enantioselectivity (Scheme 25, Table 12, entry 1).[95] Excellent enantioselectivities

were obtained for the reduction of cyclic enones **121** and **122**, which were reduced to the allylic alcohols **121′** and **122′** with enantioselectivities of 99%, and reasonable yields (Table 12, entries 2 and 3).[95]



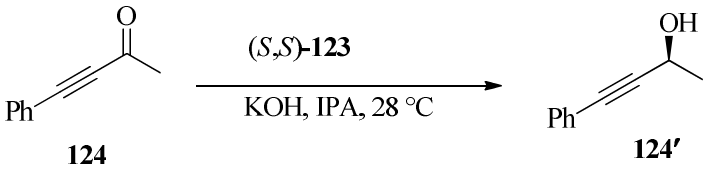
Scheme 25: ATH of cyclic α,β-unsaturated ketones.

Table 12. ATH of cyclic α,β-unsaturated ketones catalysed by complex (*S*,*S*)-**123**.

Entry	Ketone	% Yield	% ee
1	**120**	47	72 (*R*)
2	**121**	78	99 (*R*)
3	**122**	54	>99 (*R*)

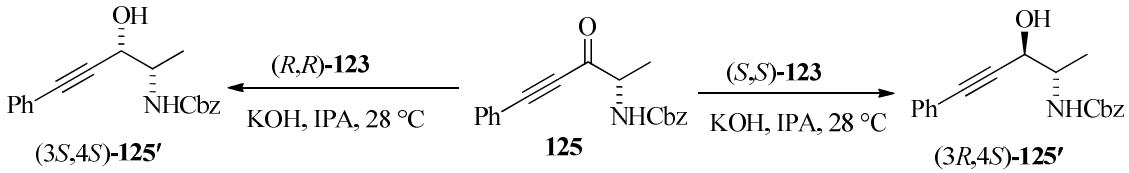
1.8.6.4. α, β-Acetylenic ketones

Asymmetric reduction of α,β-acetylenic ketones has also been shown to demonstrate high reactivity and enantioselectivity in ATH catalysed by complex **123**. The phenyl substituted acetylenic ketone **124** was reduced by (*S*,*S*)-**123** to afford alcohols (*S*)-**124′** in 97% ee and 99% yield using isopropanol as a hydrogen donor (Scheme 26). However, when the FA/TEA system was used as a hydrogen source in the same reduction, the reactivity of the catalyst diminished with (*S*)-**124′** obtained in 91% ee but only 55% yield with a 20 h reaction time.[96]



Scheme 26: ATH of **124** catalysed by (*S*,*S*)-**123**.

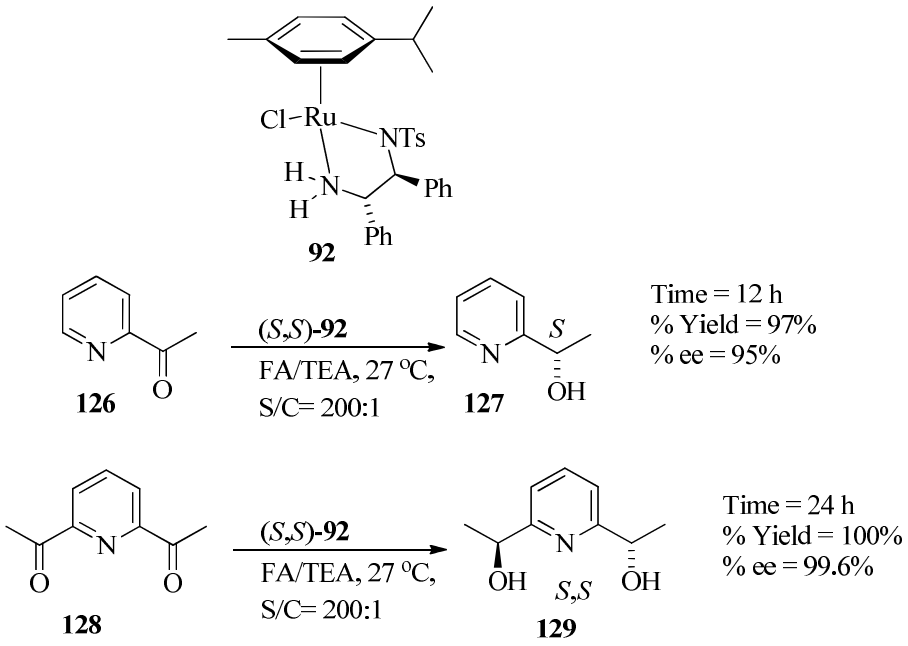
Other acetylenic ketones which contained a pre-existing stereogenic centre such as **125** may also be employed as a substrate in ATH. Both diastereomers of **125′** can be accessed by using (*R*,*R*)- or (*S*,*S*)-**123** giving (3*S*,4*S*)-**125′** in 99% ee and 97% yield when (*R*,*R*)-**123** is employed. Similary when (*S*,*S*)-**123** is used as the catalyst, (3*R*,4*S*)- **125′** is achieved in 99% ee and 97% yield (Scheme 27).[96]



Scheme 27: ATH of α,β-acetylenic ketones containing a stereogenic centre.

1.8.6.5. Heterocyclic ketones

Chiral heterocyclic alcohols are useful intermediates for the synthesis of biologically active molecules, novel chiral ligands and natural products (Scheme 28). In 2000, Ikariya reported the reduction of 2-pyridyl alkyl ketone **126** using compound **92** with a high yield of up to 97% and high enantioselectivity of up to 95% ee using FA:TEA.[97] Interesting results were also obtained for compound **128** which converted to alcohol **129**.

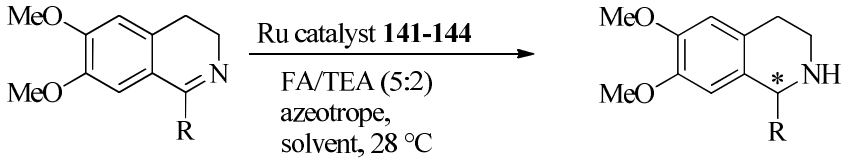


Scheme 28: Asymmetric transfer hydrogenation of heterocyclic ketones.

1.8.6.6. Imines

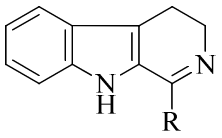
The synthesis of chiral amines in pharmaceuticals and agrochemical substances is highly demanding, and requires efficient catalytic asymmetric reduction of imines. Noyori reported the first highly efficient asymmetric reduction of a range of imines, using suitably designed chiral Ru(II) complexes **141-144** in FA/TEA (5:2) mixture under mild conditions. The reactions worked best in aprotic solvents including MeCN, DMF, DMSO and CH_2Cl_2, but not in ethereal or alcoholic media, and neat FA/TEA due to slow reaction rate. The structure of the aryl group and the substitution pattern of η_6-arene ligand on the Ru complex were fine-tuned depending on the substrates used. The ATH of imine **130** was most successful, using (*S,S*)-**141** (S/C = 200) in FA/TEA (5:2) and acetonitrile at 28 °C, giving salsolidine **130′** (*R*) in 95% ee and >99% yield in 3 h. Various other cyclic imine derivatives **131-134** were reduced giving excellent conversions (up to >99%) and enantioselectivities (up to 95%). This method was further applied to the reduction of indoles **135-136**, giving

good yields (up to 89%) and excellent enantioselectivities (up to 97%), and the reduction of acyclic imines **137-140**, which gave good conversions (up to 90%) but were less stereoselective (ee′s of up to 89%) (Scheme 29, Table 13).[98]

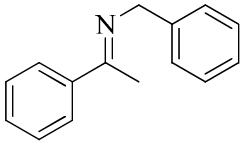


130: R= CH_3
131: R= 3,4-$(CH_3O)_2C_6H_3CH_2$
132: R= 3,4-$(CH_3O)_2C_6H_3(CH_2)_2$

133: R= C_6H_5
134: R= 3,4-$(CH_3O)_2C_6H_3$



135: R= CH_3
136: R= C_6H_5



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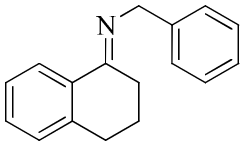

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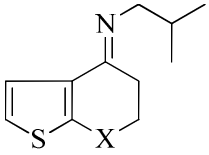
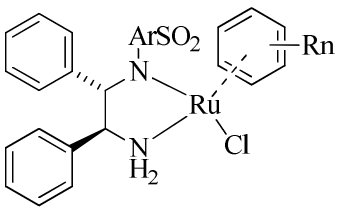
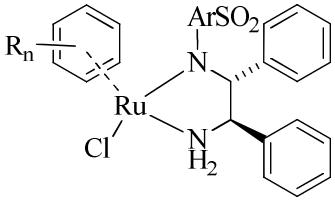


139: X= S
140: X= SO_2



(*S*,*S*)



(*R*,*R*)

141: η^6-arene = *p*-cymene; Ar= 4-$CH_3C_6H_4$
142: η^6-arene = *p*-cymene; Ar= 2,4,6-$(CH_3)_3C_6H_2$
143: η^6-arene = benzene; Ar= 2,4,6-$(CH_3)_3C_6H_2$
144: η^6-arene = benzene; Ar= 1-naphthyl

Scheme 29: ATH reduction of imine derivatives using catalysts **141-144**.

Table 13: ATH reduction of imine derivatives using catalysts **141-144**.[a]

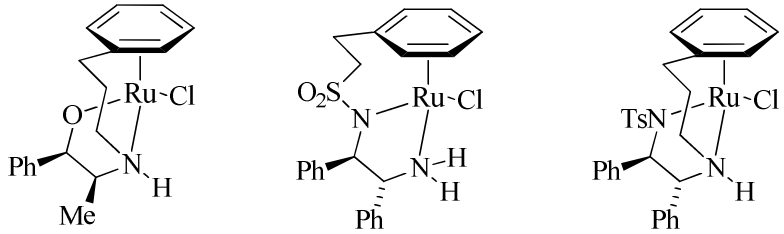
Imine	Catalyst	S/C	Solvent	Time(h)	%Yield[b]	%ee[b]	Config.[c]
130	(*S*,*S*)-**141**	200	CH_3CN	3	>99	95	*R*
130	(*S*,*S*)-**141**	1000	CH_3CN	12	97	94	*R*
131	(*R*,*R*)-**142**	200	DMF	7	90	95	*S*
132	(*R*,*R*)-**142**	200	CH_2Cl_2	12	99	92	*S*
133	(*S*,*S*)-**144**	200	CH_2Cl_2	8	99	84	*R*
134	(*R*,*R*)-**144**	100	CH_2Cl_2	12	>99	84	*S*
135	(*S*,*S*)-**141**	200	DMF	5	86	97	*R*
135	(*S*,*S*)-**141**	1000	DMF	12	89	93	*R*
136	(*S*,*S*)-**141**	200	DMF	5	83	96	*R*
137	(*S*,*S*)-**143**	200	CH_2Cl_2	36	72	77	*S*
138	(*S*,*S*)-**144**	100	CH_2Cl_2	6	90	89	*S*
139	(*S*,*S*)-**144**	100	CH_3CN	12	82	85	*S*
140	(*S*,*S*)-**144**	100	CH_3CN	5	84	88	*S*

[a](S/C = 200) in FA/TEA (5:2) and acetonitrile at 28 °C. [b]Determined by chiral GC. [c]Determined by the sign of optical rotation of isolated product and chiral HPLC.

1.8.7. Tethered complxes for transfer hydrogenation

One of the most successful modifications to the Noyori TsDPEN in recent years has been the synthesis of tethered ligands.[99-101] These complexes contain connecting carbon linker between the chiral ligand and the phenyl ring. This linkage creates a tridentate ligand, where previously a bidentate and a monodentate ligands was used. This tridentate ligand improves the stability and longevity of the catalyst and subsequently the activity and enantioselectivity of the reaction.[99-101] The tethered

complexes (*R*,*S*)-**145**, (*R*,*R*)-**146** and (*R*,*R*)-**93** have all been synthesised and used for the ATH of ketones.



(*R*,*S*)-**145** (*R*,*R*)-**146** (*R*,*R*)-**93**

Figure 16: Tethered complexes for ATH.

Investigations have indicated that the length of the carbon tether between the chiral portion of the ligand and the phenyl ring has a large effect on the selectivity of the catalyst.[99] If the tether is too short then the phenyl group cannot sit on the top of the metal centre and the complex does not form. Conversely, if the tether is too long, the activity of the catalyst is also decreased.[99]

1.9. Summary

Various methods for epoxidation of different substrates, including alkenes, enones and allylic alcohols have been outlined, high conversions and enantioselectivities were obtained.

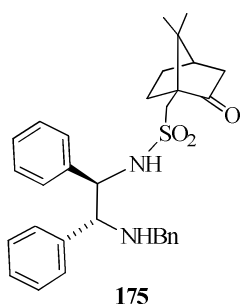
Chiral ligands and metal complexes developed for asymmetric transfer hydrogenation of ketones and imines have been discussed. Of these, 1,2-monotosylated diamine and β-amino alcohol ligands were found to be the most effective for this process when incorporated with a metal (arene) system as developed by Noyori. Mechanistic studies revealed that the ATH by such system operate *via* the metal ligand bifunctional catalysis mechanism through a concerted transfer of a hydride and a proton with no direct coordination of the substrate to the

metal centre of the catalyst. Theoretical and experimental data found that the origin of the enantioselectivity for the reduction of aryl/alkyl ketones by these systems is due to the CH/π attractive interaction that exist between the arene ligand on the metal of the catalyst and the aryl substituent on the substrate which afford highly optical active product. Asymmetric transfer hydrogenation using η^6-arene-Ru-complexes was found to be highly efficient and selective for a range of substrates such as aryl alkyl ketones, heterocyclic ketones, α,β-acetylenic ketones, cyclic α,β-unsaturated ketones and imines.

1.10. Aims and Objectives

The aim of this project is the synthesis of novel chiral di-, tri- and tetra amine ligands, together with their ruthenium and iron metal complexes and the subsequent investigation of their application as asymmetric catalysts.

Specifically, a series of chiral di-, tri- and tetra amines ligands based on a combination of camphor compounds and diamines (such as **175** and **187**), a combination of 2-formylbenzenesulfonic chloride and diamines (such as **196** and **204**) were synthesised and, in conjunction with Ru(II) or Fe(II), employed as asymmetric catalysts. The synthesized ligands were studied for optimization of reaction conditions and stereoselectivity for a range of different asymmetric reactions including as epoxidation, hydrosilylation and asymmetric transfer hydrogenation.



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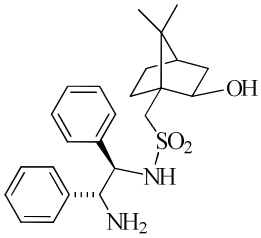

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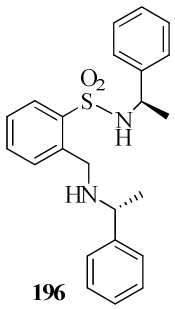

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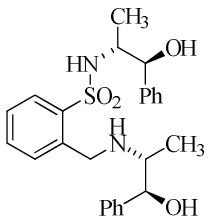

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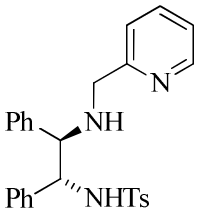
Also a novel class of tridentate ruthenium catalysts of general structure below were developed and employed as asymmetric catalysts in different applications including ATH of a number of ketones.



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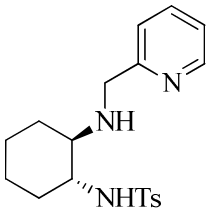

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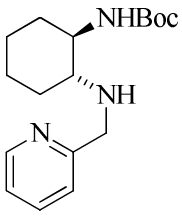

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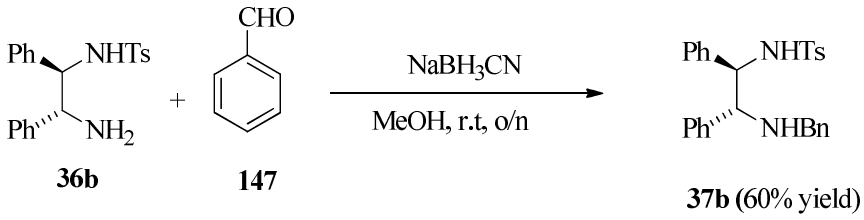
2. Results and discussion

2.1. Iron-catalyzed asymmetric epoxidation of aromatic alkenes using hydrogen peroxide.

Among commonly available oxidants, hydrogen peroxide is one of the most practical reagents in terms of cost and atom efficiency. In this respect the work of Beller *et al.*,[102] who developed a convenient catalyst consisting of ferric chloride hexahydrate ($FeCl_3.6H_2O$), pyridine-2,6-dicarboxylic acid (H_2pydic), and organic base, for epoxidation of aromatic alkenes, is most notable. In order to gain experience in asymmetric processes using iron catalysts, this reaction was selected for further investigation. New ligands and additives were applied to the reaction in order to identify the ideal features required in a good catalytic system.

2.1.1 Synthesis of *(R,R)*-*N*-(2-benzylamino-1,2-diphenyl-ethyl)-4-methylbenzenesulfonamide 37b

For initial tests, the reported asymmetric epoxidation reported by Beller was selected for investigation. The key ligand required was prepared by reacting *(R,R)*-TsDPEN **36b** with benzaldehyde **147** in methanol. The imine formed was then reduced by $NaBH_3CN$ to give *N′*-BnTsDPEN **37b** (Scheme 30).

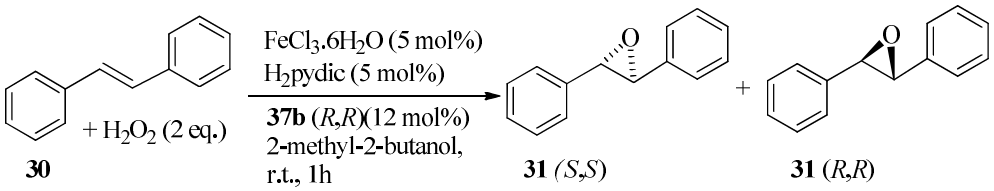


36b **147** **37b** (60% yield)

Scheme 30: Reaction scheme illustrating the synthesis of compound **37b**.

2.1.1.1 Optimisation of the reaction conditions for epoxidation

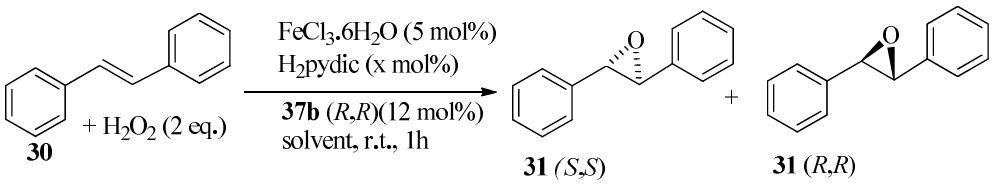
To optimise the reaction conditions, the epoxidation of *trans*-stilbene to *trans*-stilbene oxide under published conditions was repeated and the product isolated in 88% yield (100% conversion) with 40.6% ee (2*S*,3*S*) (Scheme 31, Table 14). This closely matched the reported results.



Scheme 31: The asymmetric epoxidation of *trans*-stilbene.

In the asymmetric epoxidation reaction of *trans*-stilbene to *trans*-stilbene oxide, reducing the amount of ligand to 6 mol% resulted in 62% conversion to product (Table 14, entry 2) and no epoxide was formed without adding H_2pydic (Table 14, entry 3). Usually, 1 mmol of aqueous (30%) H_2O_2 dissolved in 2-methyl butan-2-ol was added to the reaction mixture over one hour using a syringe pump. In some cases (Table 14, entry 4) the reactants were dissolved in the total amount of the solvent (2-methyl-butan-2-ol), stirred for 30 min., then 1 mmol of H_2O_2 was added in one portion. After completing the reaction, essentially the same conversion and ee value (~50% ee) was obtained. Many solvents were examined in the epoxidation reaction and gave products with the following conversions; dichloromethane (0%), 2-propanol (78%), ethanol (20%), 1-butanol (27%) and 2-butanol (77%). Their conversion efficiency followed the order: 2-methyl-2-butanol<*tert*-butanol< acetonitrile<2-propanol. H_2pydic is crucial for the reaction to occur and at least 10% of the ligand **37b** is needed to obtain full conversion (Table 14).

Table 14: Epoxidation of *trans*-stilbene.[a]



Entry	H_2pydic (xmol%)	Solvent	(%) Conv.[b]	(%) ee[c]	Remarks
1	5	2-Methyl-2-butanol	100	41 (*S*,*S*)	
2	5	2-Methyl-2-butanol	62	n/o[d]	6 % ligand
3	0	2-Methyl-2-butanol	0	-	
4	5	2-Methyl-2-butanol	100	50 (*S*,*S*)	H_2O_2 added together
5	5	Dichloromethane	0	n/o[d]	
6	6	2-Propanol	78	34 (*S*,*S*)	
7	5	Ethanol	20	n/o[d]	
8	5	1-Butanol	27	n/o[d]	
9	5	2-Butanol	67	n/o[d]	
10	5	*tert*-butanol	92	44 (*S*,*S*)	
11	6	Acetonitrile	91	39 (*S*,*S*)	

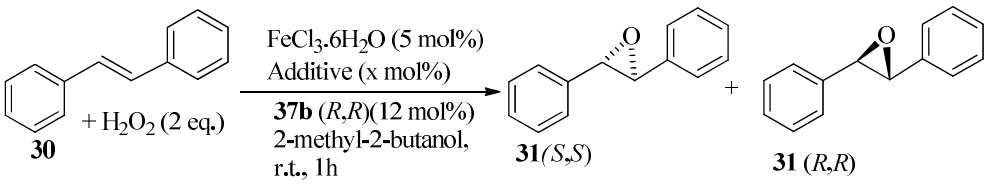
[a]**30** (0.5 mmol), H_2O_2 (1mmol), H_2pydic (x mol%), $FeCl_3$ $6H_2O$ (5 mol%), ligand (12 mol%), solvent (10 cm^3), r.t., 1 h.[b]Determined by H^1 NMR. [c]Determined by HPLC on a chiral column. [d]Not obtained.

To identify alternative additives and substrates for the asymmetric epoxidation reaction, several additives (in place of the H_2pydic) and varying conditions (Table 15) were examined including pyridine, benzoic acid, pyridine-3-carboxaldehyde, 2-picolinic acid, isonicotinic acid, nicotinic acid, *L*-proline and 2,6-pyridine dicarbonyl dichloride.

These additives were selected in order to establish which groups were essential for promotion of the reaction. Most of the compounds gave products in low conversion; only pyridine compounds with a carboxylic acid group substitution in the *ortho* position (2-picolinic acid) gave encouraging results that enhanced with increasing concentration (88%, but low %ee, Table 15, entry 9). This suggests that the carboxylic acid may be coordinating to the metal in some way, possibly chelating

with the pyridine group adjacent to it. Figure 17 shows the structures of the additives used in the epoxidation reaction.

Table 15: Comparison of some additives used in the epoxidation of *trans*-stilbene .[a]



Entry	Additive (x)	x(mol%)	(%)Conv.[b]	(%) ee[c]
1	Pyridine (**149)**	5	12	n/o[d]
2	Benzoic acid (**150)**	5	6	-
3	Pyridine-3-carboxaldehyde (**151)**	5	13	-
4	2-Picolinic acid (**152)**	5	44	-
5	Nicotinic acid (**153)**	5	7	-
6	Isonicotinic acid (**154)**	5	6	-
7	*L*-proline (**155)**	5	0	-
8	2-Picolinic acid (**152)**	8	71	-
9	2-Picolinic acid (**152)**	12	88	2 (*S*,*S*)
10	2,6-Pyridine dicarbonyl dichloride (**156**)	5	15	n/o[d]

[a]**30** (0.5 mmol), H_2O_2 (1mmol), Additive (x mol%), $FeCl_3$ $6H_2O$ (5 mol%), ligand (12 mol%), 2-methyl-2-butanol (10 cm^3), r.t., 1 h.[b] Determined by H^1 NMR, [c]Determined by HPLC on a chiral column. [d]Not obtained.

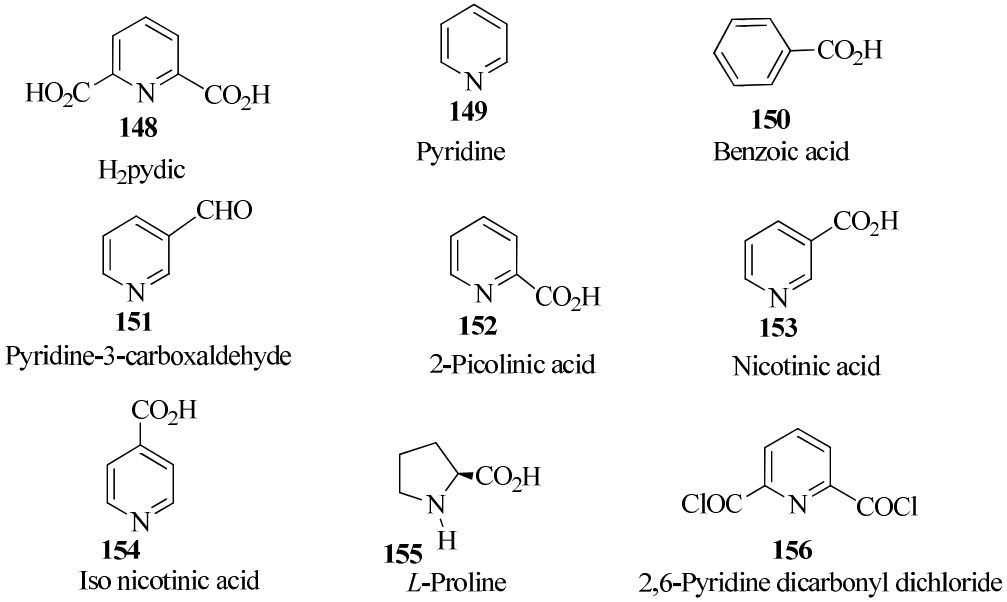


Figure 17: Structure of some additives used for the epoxidation of *trans*-stilbene.

2.1.1.2. Other ligands investigated for epoxidation reaction

Investigations into the epoxidation of *trans*-stilbene to *trans*-stilbene oxide by using 30% H_2O_2 as the oxidant were carried out. The catalyst system consisting of an iron salt ($FeCl_3$ $6H_2O$) and H_2pydic was extended using chiral ligands derived from *N*-sulfonated diamines. The ligands were synthesized by monosulfonation of C_2-symmetrical 1,2-diamines with *p*-toluenesulfonyl chloride in the presence of a base such as triethylamine (TEA).

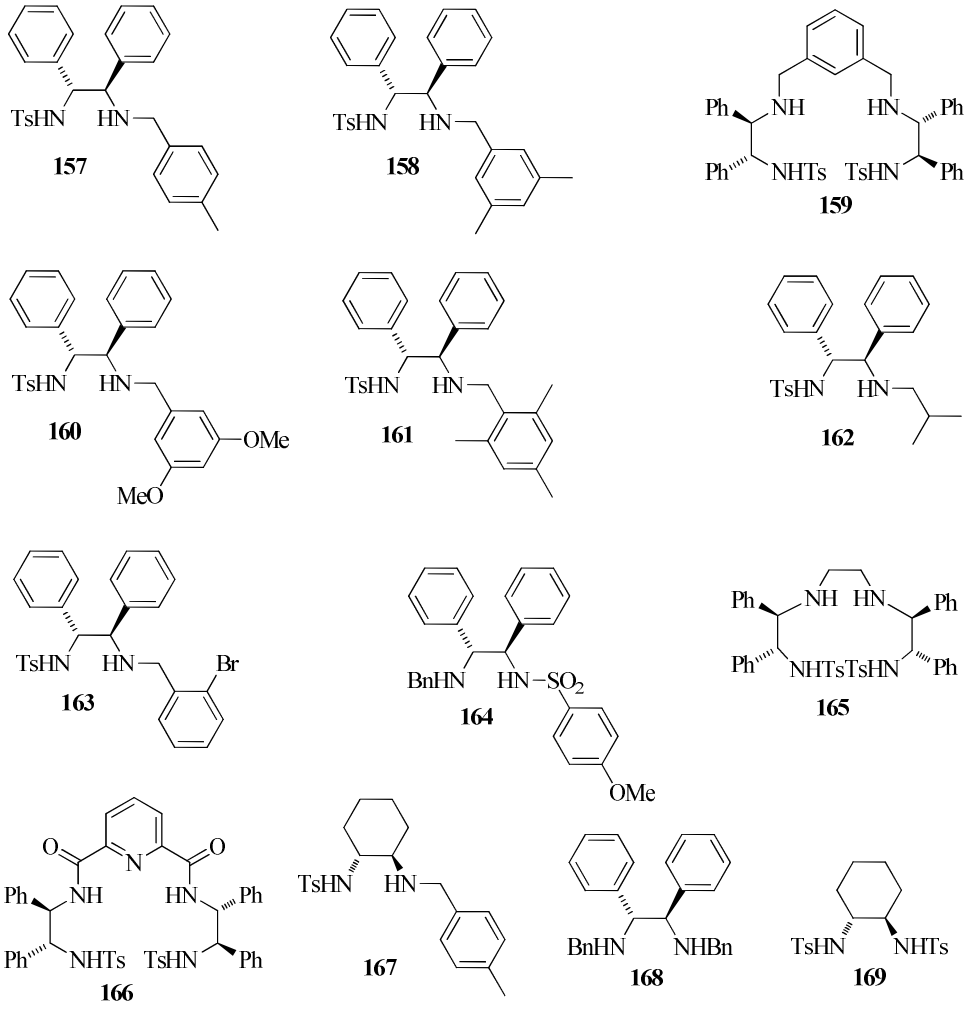
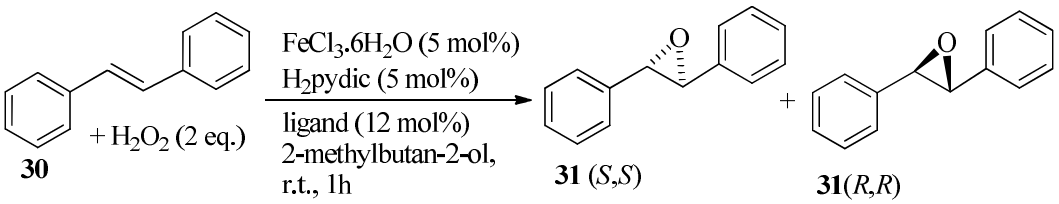


Figure 18: Structure of ligands used for the epoxidation of *trans*-stilbene.

Where necessary, reductive *N*-alkylation of the resulting products was carried out in the presence of a suitable aldehyde and sodium borohydride (**157**, **158**, **159, 160**,

161, **162, 163** and **167**). Monobenzylation of *N*-(2-amino-1,2-diphenyl)-4-methoxy-benzenesulfonamide was also carried out to give **164.** The combination of *(R,R)*-TsDPEN and 1,2-dibromoethane was used to form **165**. Reaction of (*R,R*)-TsDPEN and 2,6-pyridinedicarbonyl dichloride gave **166**, dibenzylation of DPEN gave **168** and tosylation of (*R,R*)-(−)-*N*-*p*-tosyl-1,2-cyclohexanediamine gave **169**.

Table16: Comparison of ligand efficiency used in the epoxidation of *trans*-stilbene .[a]



Entry	Ligand	% Conv.[b]	% ee[c]
1	**157**	100%	31% (*S,S*)
2	**158**	100%	50% (*S,S*)
3	**159**	42%	n/o[d]
4	**160**	18%	-
5	**161**	23%	-
6	**162**	41%	7% (*S,S*)
7	**163**	89%	36% (*R,R*)
8	**164**	95%	44% (*R,R*)
9	**165**	14%	n/o[d]
10	**166**	38%	-
11	**167**	100%	9% (*R,R*)
12	**168**	71%	38% (*S,S*)
13	**169**	94%	16% (*R,R*)

[a]**30** (0.5 mmol), H_2O_2 (1mmol), H_2pydic (5 mol %), $FeCl_3$ $6H_2O$ (5 mol %), ligand (12 mol %), 2-methyl-2-butanol (10 cm^3), r.t., 1 h.[b]Determined by H^1 NMR. [c]Determined by HPLC on a chiral column. [d]Not obtained.

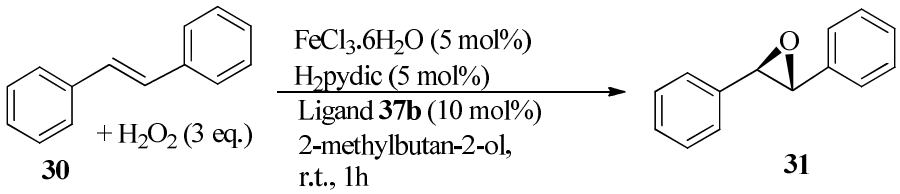
Figure 18 shows the structure of ligands used for the epoxidation of *trans*-stilbene, the influence of various ligands on the epoxidation reaction is summarized in Table 16. It is obvious that among these compounds, ligands **158**, **164, 168, 163** and **157** gave the highest conversion and highest ee (50, 44, 38, 36 and 31% respectively). In most cases these are the ligands which most resemble the 'initial' ligand. Tetradentate ligands **159** and **165** gave poor results indicating that it may either be too hindered or that four groups of attachment may destroy the catalytic potential of the iron centre. Ligands, which were very hindered appeared to give poor results, as did those lacking a basic nitrogen atom (e.g. **166** and **169**). The number and position of the methyl group (donating group) on the benzyl attached to a basic nitrogen is important in controlling the reaction. 3,5-Dimethyl phenyl derivatives (**158**) gave full conversion and led to the most significant increase in ee (50%) , 4-Methyl phenyl derivatives (**157**) gave full conversion and 31% ee while 2,4,6-trimethyl phenyl derivatives (**161**) gave poor conversion. Bromo substituted (**163**) (electron withdrawing group) also gave good conversion and 36% ee. *N*-Benzylsubstituted derivatives led to the highest ee compared to other ligands.

2.2. Nonlinear effects in asymmetrical stereoselective reactions.[103-105]

In many asymmetric syntheses, the enantiomeric excess of the product (eeprod) is not always proportional to enantiomeric excess of the auxiliary (eeaux). A positive non-linear effect (+)-NLE is obtained with amplified enantioselectivity if eeprod is higher than eeaux. Conversely, if eeprod is lower than eeaux, (-)-NLE is obtained with depleted enantioselectivity. There are several advantages of NLE investigations with partially resolved chiral ligands. The first advantage is that NLEs which arise from the association of the chiral auxiliaries in solution can be used to understand subtle diastereomeric interactions between enantiomers. Secondly, NLEs can be

useful in understanding the species involved in the catalytic cycle and their behaviour in solution. Thirdly, NLEs can be used to generate products with high ee′s from enantiomerically impure chiral auxiliaries.

Using the epoxidation reaction described above to study the effect of the combination of *RR* and *SS* configuration ligands on the ee value, a series of solutions of substrates were prepared, then the solutions we mixed together to make the required percentage for both ligands configuration (Table 17).



Scheme 32: Investigation into nonlinear effects using *RR* and *SS* ligand enantiomers.

Procedure**:** *Trans* stilbene (0.449 g, 2.5 mmol), H_2pydic (0.021g, 0.125 mmol) and $FeCl_3.6H_2O$ (0.034g, 0.125 mmol) were mixed in 40 cm^3 of 2-methyl-2-butanol to make solution 1.

(R,R)-Ligand (0.115g, 0.25 mmol) was dissolved in 10 cm^3 of 2-methyl-2-butanol to make solution 2.

(S, S)-Ligand (0.115 g, 0.25 mmol) was dissolved in 10 cm^3 of 2-methyl-2-butanol to make solution 3. The required formulation in each entry was prepared by combining the reagents as mentioned in Table 17.

Table 17: *RR* and *SS* ligands configurations percentage.

Substrates	90% *RR*, 10% *SS*	80% *RR*, 20% *SS*	70% *RR*, 30% *SS*	60% *RR*, 40% *SS*	50% *RR*, 50% *SS*
Solution 1	4 cm^3	4 cm^3	4 cm^3	4 cm^3	4 cm^3
Solution 2	0.9 cm^3	0.8 cm^3	0.7 cm^3	0.6 cm^3	0.5 cm^3
Solution 3	0.1 cm^3	0.2 cm^3	0.3 cm^3	0.4 cm^3	0.5 cm^3

Table 18: Ligand and product ees.

Entry	**Ligands %**	**Ligand ee %**	**product ee %**
1	100% *RR*	100 (*R*)	41 (*R*)
2	90% *RR*, 10% *SS*	80 (*R*)	35 (*R*)
3	80% *RR*, 20% *SS*	60 (*R*)	26 (*R*)
4	70% *RR*, 30% *SS*	40 (*R*)	17 (*R*)
5	60% *RR*, 40% *SS*	20 (*R*)	9 (*R*)
6	50% *RR*, 50% *SS*	0.0	0.1 (*R*)

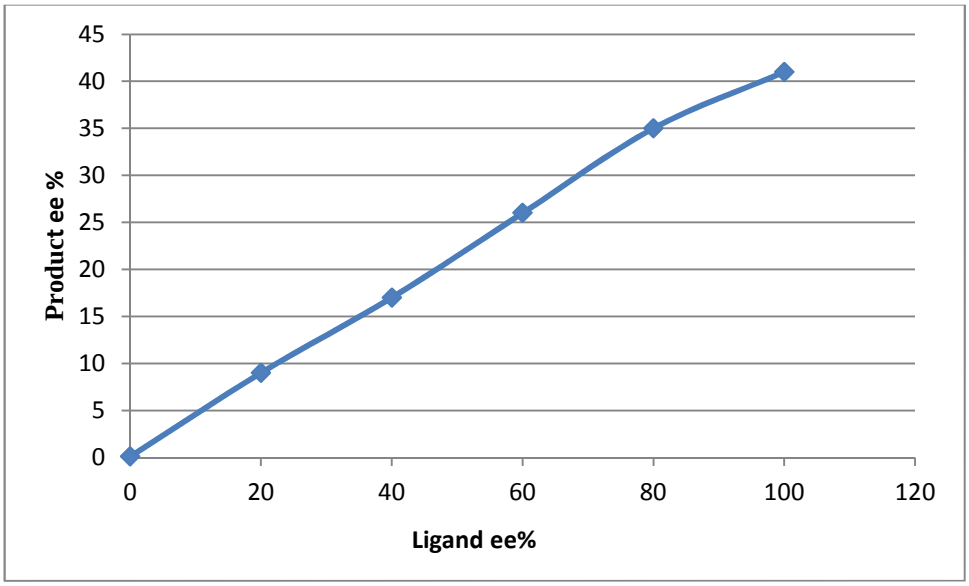
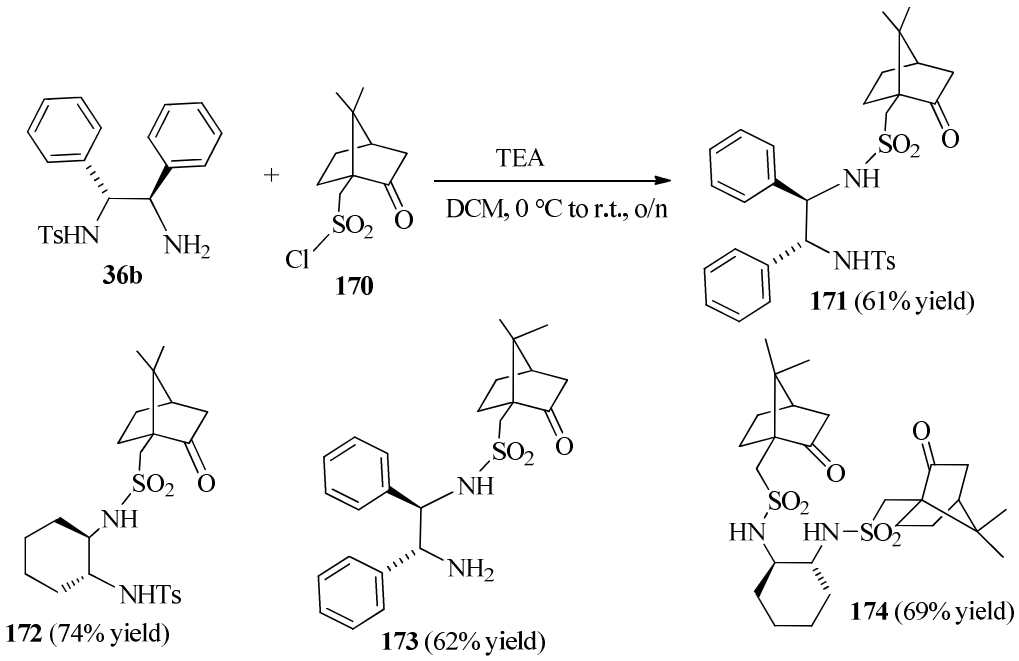


Figure 19. Product ees vs ligand ees.

Plotting the ligand ees against the product ees from the experiments shows no non-linear effect, suggesting that there is no interaction between the ligands of each configuration *(RR* and *SS*). Although it cannot be confirmed definitively using this test, the evidence suggests the formation of a 1:1 ligand:metal complex in the formation of diastereoisomeric compounds with different properties.

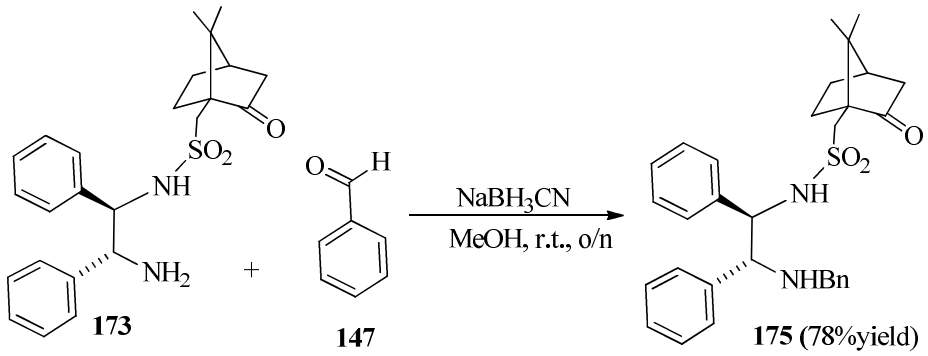
2.3. Synthesis of camphor-derived ligands.

The next series of studies involved the use of chiral compounds based on the combination of diamine and a camphor compound. Such ligands have been synthesised and evaluated as chiral ligands in the epoxidation, hydrosilylation and ATH. The results are summarised (section 2.7, Table 24, entries 1, 4, 5 and 8) for hydrosilylation, nitroaldol reaction (section 2.6, Table 23, entries 1, 5 and 6) and ATH (section 2.5.1.1, Table 19, entries 1, 2, 3, 4 and 8, section 2.5.1.2, Table 20, entries 1, 2, 3, 4 and 8, section 2.5.2, Table 21 and section 2.5.3, Table 22). In the first attempt to synthesise camphor derived bidentate ligands, (1*S*)-(+)-camphor sulfonyl chloride was reacted with (*R,R)*-TsDPEN and TEA in DCM to give compound **171** (61% yield)**.**



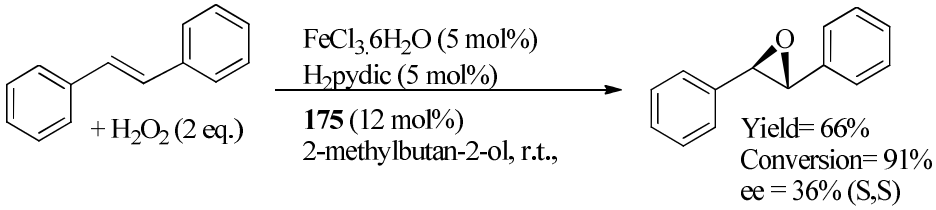
Scheme 33: Synthesis of compounds **171**-**174**.

Compound **172** was prepared using compound (*R*,*R*)-(−)-*N*-*p*-tosyl-1,2-cyclohexanediamine and 1 equiv. of compound **170** (74% yield),[106] Compound **173** was prepared using compound[111] (*R,R)*-DPEN and 1 equiv. of compound **170** (62% yield),[107-111] while compound **174** was prepared using compound (*R*,*R*)-1,2-diaminocyclohexane and 2 equiv. of compound **170** (69% yield), Scheme 33. Reaction of compound **173** with benzaldehyde in methanol, then reduction of the imine formed by $NaBH_3CN$ gave *N*-(2-benzylamino-1,2-diphenyl-ethyl)-*C*-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-methanesulfonamide **175** (78% yield, Scheme 34).



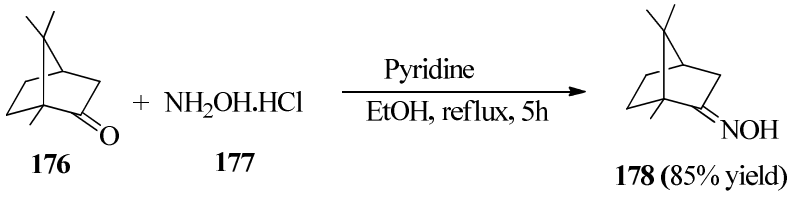
Scheme 34: Synthesis of compound 1**75**.

Epoxidation of *trans*-stilbene by the Beller epoxidation reaction method using compound **175** gave the epoxide in 91% conv., 36% ee (*S,S*), (Scheme 35) .



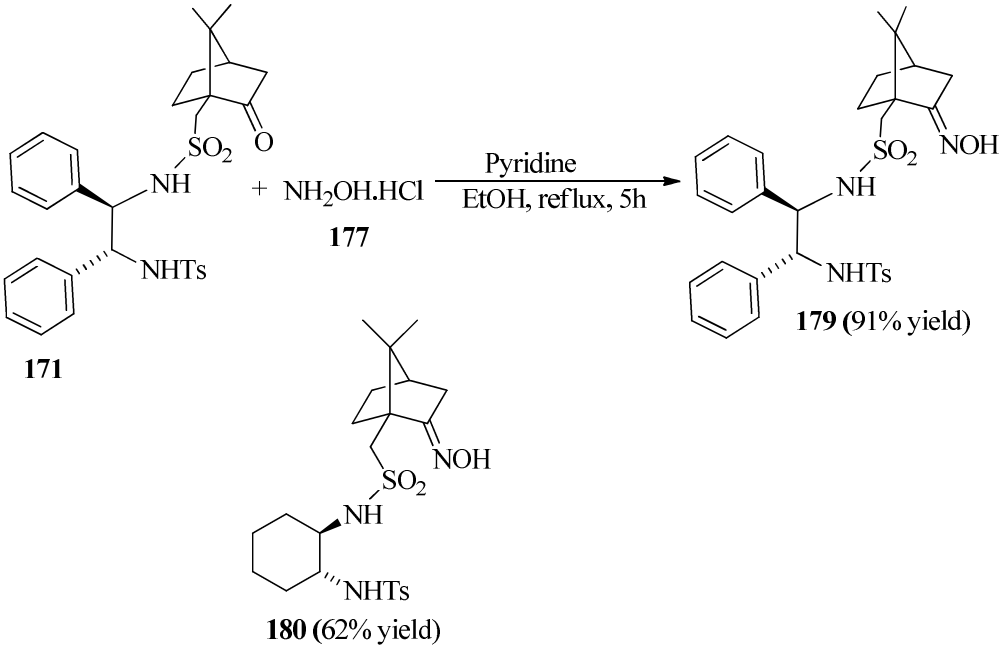
Scheme 35: Epoxidation of *trans*-stilbene by compound **175**.

In order to form tetradentate ligands, the formation of oxime compounds was followed by reducing the oxime to an amine which could then be functionalised further. This was considered to be a practical approach. In order to test this approach, (1*R*,4*S*)-(-)-camphor oxime **178** (85% yield),[112] was made by combination of (1*R*)-(+)-camphor **176** (1mmol), hydroxylamine hydrochloride **177** and pyridine under reflux in EtOH (Scheme 36).



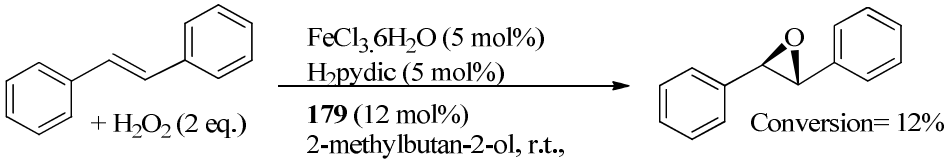
Scheme 36: Synthesis of compound **178**.

By applying the same protocol compound **179** (91% yield) and compound **180** (62% yield) were prepared (Scheme 37).



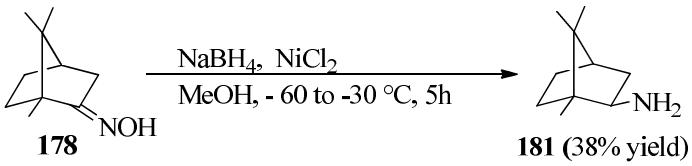
Scheme 37: Synthesis of compounds **179** and **180.**

Epoxidation of *trans*-stilbene by Beller epoxidation reaction method using compound **179** gave a product in only 12% conversion (Scheme 38).



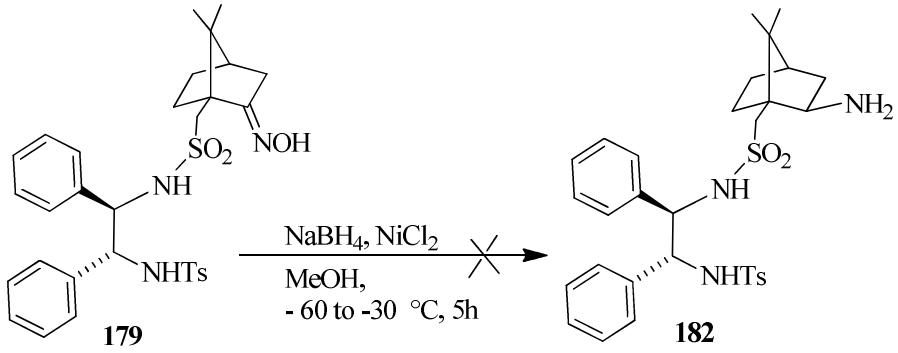
Scheme 38: Epoxidation of *trans*-stilbene by compound **179**.

Compound **178** was reduced by $NaBH_4$ and $NiCl_2$ in anhydrous MeOH at -60 °C to afford *exo*-(-)-bornylamine **181** as a foamy white solid (38% yield, Scheme 39).[113-114]



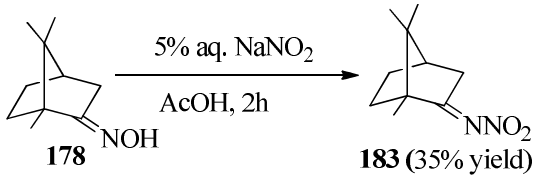
Scheme 39: Synthesis of compound **181**.

Attempts to reduce compound **179** by $NaBH_4$ and $NiCl_2$ in anhydrous MeOH were unsuccessful, as only starting materials were recovered (Scheme 40).



Scheme 40: Attempts to reduce compound **179**.

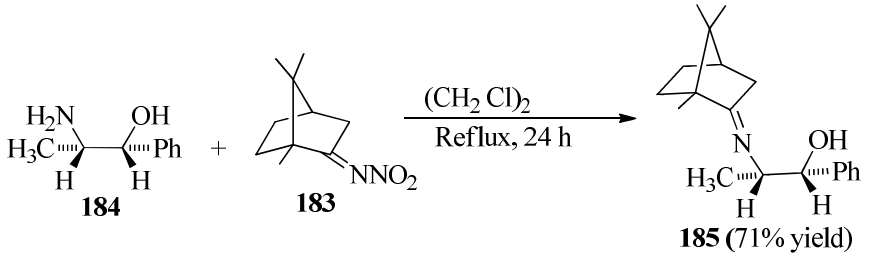
In another approach (1*R*,4*S*)-(-)-camphor nitrimine[112] **183** was made by dissolving compound **178** in glacial AcOH, treated with 5% aqueous $NaNO_2$ to give the product **183** in 35% yield (Scheme 41).



Scheme 41: Synthesis of compound **183**.

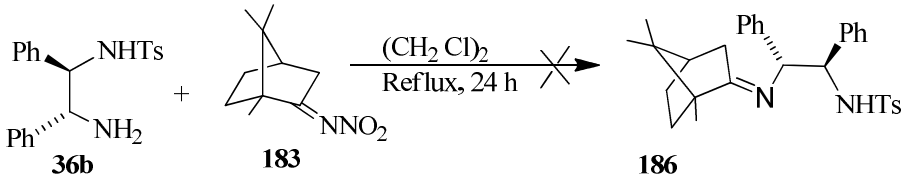
Addition of norephedrine **184** to (1*R*,4*S*)-(-)-camphor nitrimine **183** in 1,2-dichloroethane afforded (1*R*,1′*R*,2*S*,4′*R*)-1-phenyl-2-(1,7,7-

trimethylbicyclo[2.2.1]hept-2-ylideneamino)propan-1-ol **185** as colourless crystals (71% yield, Scheme 42).[115]



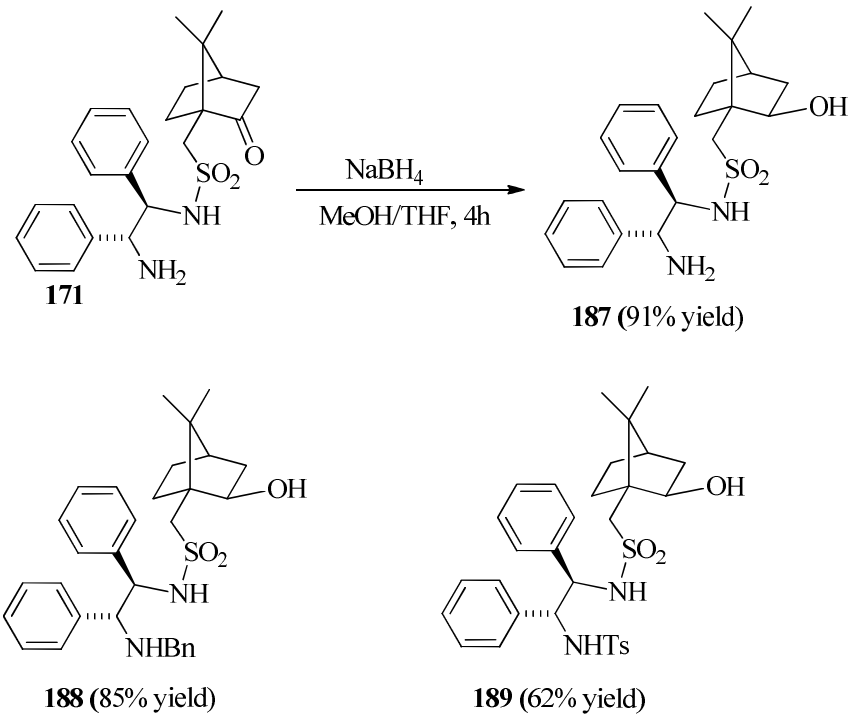
Scheme 42: Synthesis of compound **185**.

In contrast, addition of (*R*,*R*)-TsDPEN **36b** to (1*R*,4*S*)-(-)-camphor nitrimine **183** in the same condition gave no reaction (Scheme 43). As a result, no attempt was made to use a camphor nirimine product to make a tetradentate ligands.



Sheme 43: Addition of (*R*,*R*)-TsDPEN **36b** to compound **183**.

Different classes of compound were made by reduction of compounds[116] **173**, **175** and **171** to afford *N*-(2-amino-1,2-diphenyl-ethyl)-C-(2-hydroxy-7,7-dimethyl-bicyclo[2.2.1]hept-1-yl)-methanesulfonamide **187** (91% yield), *N*-(2-benzylamino-1,2-diphenyl-ethyl)-C-(2-hydroxy-7,7-dimethyl-bicyclo[2.2.1]hept-1-yl)-methanesulfonamide **188** (85% yield) and *N*-[2-(2-hydroxy-7,7-dimethyl-bicyclo[2.2.1]hept-1-ylmethanesulfonylamino)-1,2-diphenyl-ethyl]-4-methyl-benzenesulfonamide **189** (62% yield), Scheme 44.



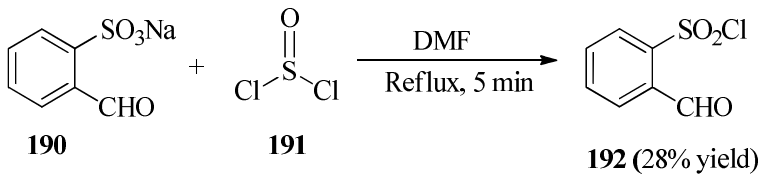
Scheme 44: Synthesis of compounds **187-189**.

2.4. Synthesis of chiral amine ligands derived from 2-formylbenzenesulfonyl chloride

As formation of tetradentate ligands based on the combination of diamine and (1*S*)-(+)-camphorsulfonyl chloride compound were not possible, the next target was formation of tetradentate ligands using 2-formylbenzenesulfonyl chloride and diamine compounds. The new novel compounds were evaluated as chiral ligands in the epoxidation, hydrosilylation and ATH. The results are summarised in section 2.7, Table 24, entries 2, 3 and 7 for hydrosilylation, nitroaldol reaction section 2.6, Table 23, entries 2, 3, 4, 7, 8 and 9 and ATH section 2.5.1.1, Table 19, entries 5, 6 and 7 and section 2.5.1.2, Table 20, entries 5, 6 and 7.

Synthesis of 2-formyl benzene sulfonyl chloride

Chlorination of 2-formylbenzenesulfonic acid sodium salt **190** with $SOCl_2$ **191** in the presence of catalytic amount of *N*,*N*-dimethylformamide (DMF) gave the relatively unstable 2-formylbenzenesulfonyl chloride **192** (28% yield, Scheme 45).[117-118]

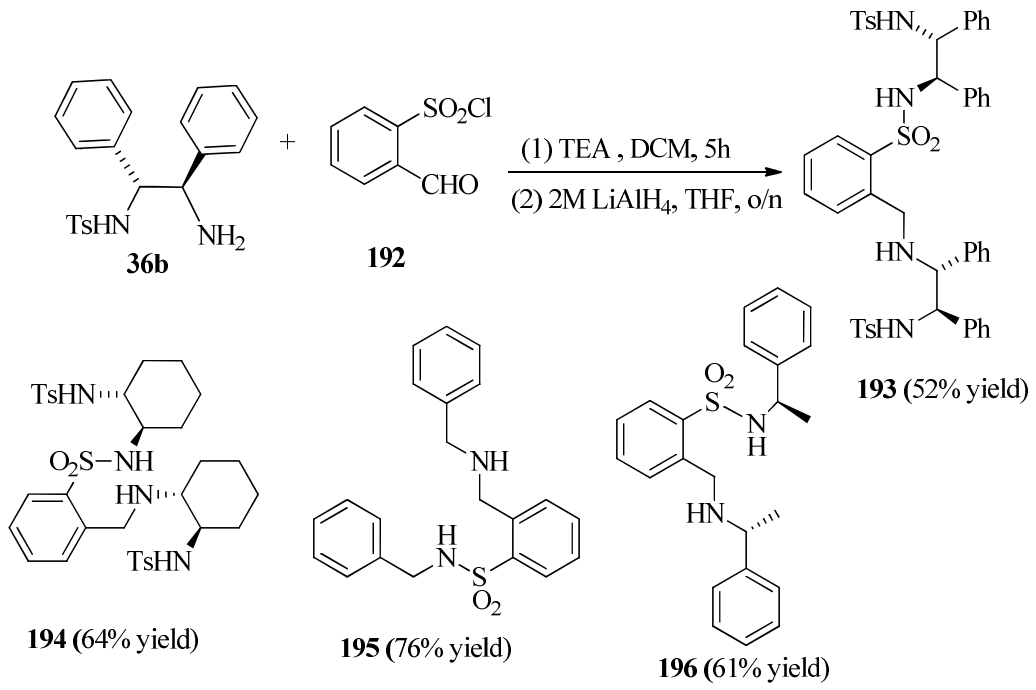


Scheme 45: Synthesis of compound **192**.

Synthesis of *N*-tosyl-*N*′-((2-methyl(*o*-(*p*-tosyl-1,2-diphenylethyl)-aminophenyl)sulfonyl)-1′,2′-diphenyl-1′,2′-diaminoethane

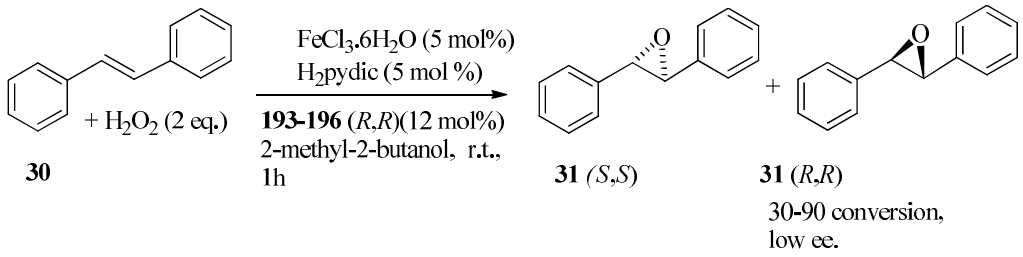
Sulfonyl chloride **192** reacted with *N*-tosyl-1,2-diphenylethanediamine (TsDPEN) in the presence of TEA to give the imine, which was then reduced by $LiAlH_4$ to afford *N*-tosyl-*N*′-((2-methyl(*o*-(*p*-tosyl-1,2-diphenylethyl)-aminophenyl)sulfonyl)-1′,2′-diphenyl-1′,2′-diaminoethane **193** (52% yield, Scheme 46).[119]

Compound **194** was prepared using 2 equiv. of (*R*,*R*)-toluene sulfonyl-1,2-diaminocyclohexane and 1 equiv. of compound **192** (64% yield). Compound **195** was prepared using 2 equiv. of benzyl amine and 1 equiv. of compound **192** (76% yield) while compound **196** was prepared using 2 equiv. of *R*-(+)-α-methylbenzyl amine and 1 equiv. of compound **192** (61% yield).



Scheme 46: Synthesis of compound **193-196**.

Epoxidation of *trans*-stilbene by Beller epoxidation reaction method using different compounds (**193-196**) gave moderate to good conversion (30-90%) but low ee (Scheme 47).

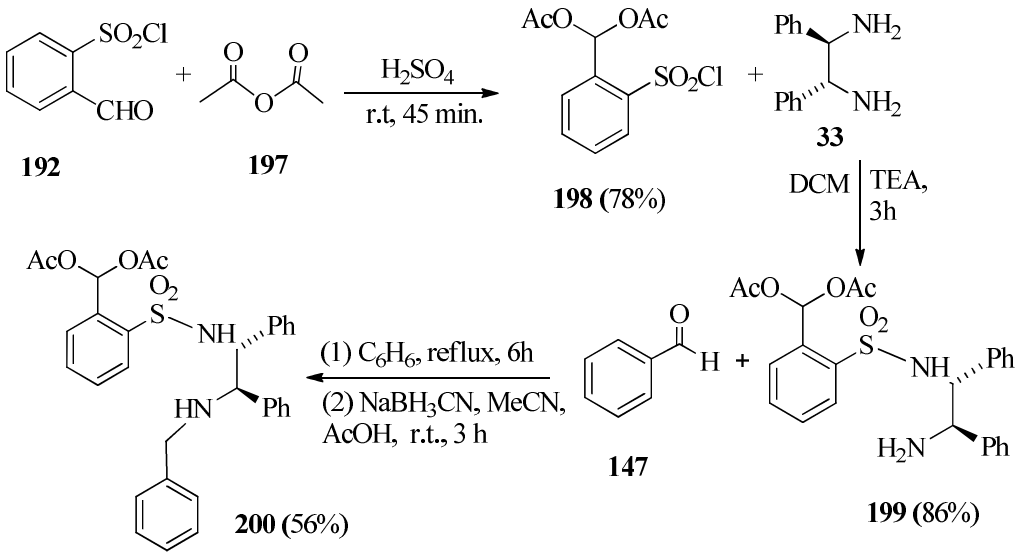


Scheme 47: Epoxidation of *trans*-stilbene using compounds **193-196**.

Synthesis of (*R,R*)-acetic acid acetoxy-[2-(2-benzylamino-1,2-diphenyl-ethylsulfamoyl)-phenyl]-methyl ester

Sulfonyl chloride **192** was treated with acetic anhydride **197** in the presence of a catalytic amount of H_2SO_4 to give acetic acid acetoxy-(2-chlorosulfonyl-phenyl)-methyl ester **198,** which then reacted with 1,2-diphenylethanediamine **33** (DPEN),

TEA in DCM to give (*R,R*)-acetic acid acetoxy-[2-(2-amino-1,2-diphenyl-ethylsulfamoyl)-phenyl]-methyl ester **199** (86% yield). This was added to benzaldehyde **147** and refluxed in benzene, then reduced by $NaBH_3CN$ to afford (*R,R*)-acetic acid acetoxy-[2-(2-benzylamino-1,2-diphenyl-ethylsulfamoyl)-phenyl]-methyl ester **200** (56% yield, Scheme 48).[120] This compound was tested as a chiral ligand in ATH of acetophenone using a FA:TEA mixture. The results are shown in section *2*.5.1.1, Table 19, entry 5).

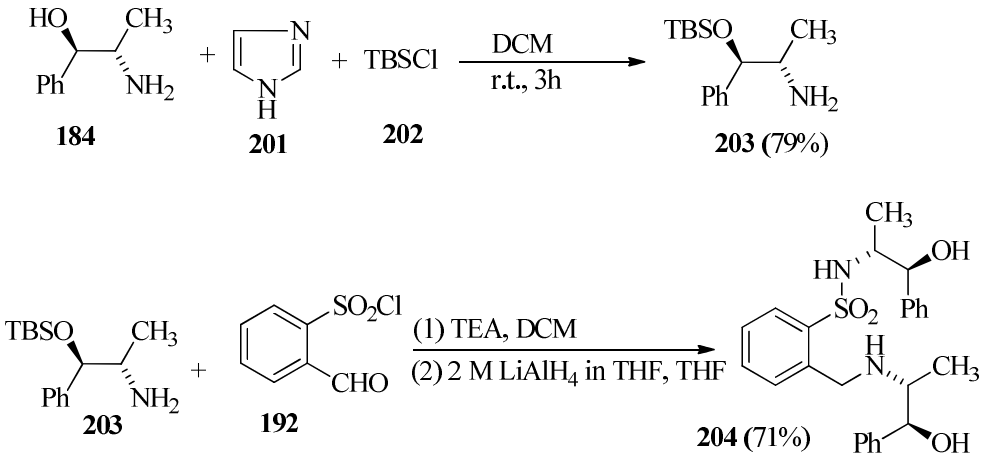


Scheme 48: Synthesis of compound **200**.

Synthesis of *N*-(2-hydroxy-1-methyl-2-phenyl-ethyl)-2-[(2-hydroxy-1-methyl-2-phenyl-ethylamino)-methyl]-benzenesulfonamide

L-(-)-norephedrine **184** and imidazole **201** were mixed together in DCM, then was added under nitrogen *tert*-butyl(chloro)dimethylsilane **202** (TBSCl) to give 2-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-2-phenyl-ethylamine **203** (79% yield).[121] Sulfonyl chloride **192** was dissolved in DCM, then compound **203** was added followed by TEA. The unisolated intermediate was then reduced by $LiAlH_4$ to afford *N*-(2-hydroxy-1-methyl-2-phenyl-ethyl)-2-[(2-hydroxy-1-methyl-2-phenyl-ethylamino)-methyl]-benzenesulfonamide **204** (71% yield, Scheme 49). This

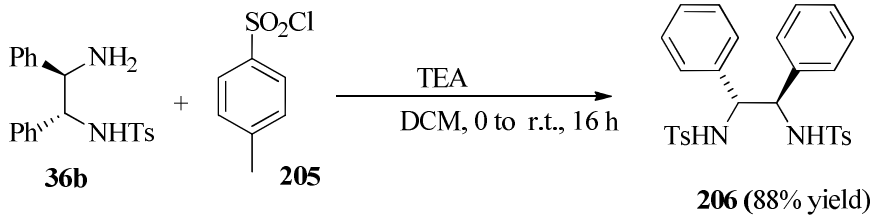
compound was tested as chiral ligand in ATH of acetophenone using a formic acid-triethylamine 5:2 mixture. The results are shown in section 2.5.1.1, Table 19, entry 6) Scheme 49.



Scheme 49: Synthesis of compound **204**.

Synthesis of 4-methyl-*N*-((*R*,*R*)-2{[(4-methylphenyl)sulfonyl]amino}-1,2-diphenylethyl)benzenesulfonamide

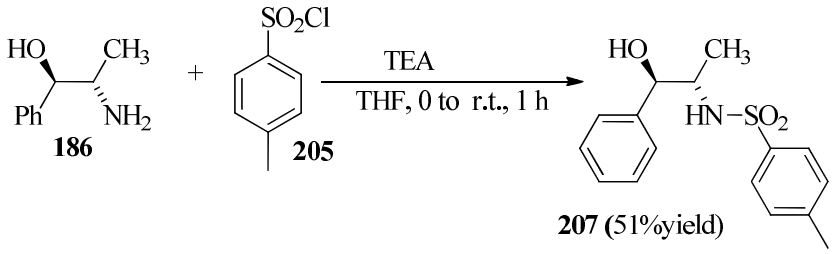
Compounds **206** and **207** were made and tested as chiral ligands in the nitroaldol reaction (Henry Reaction). The results are shown in section 2.6, Table 23, entry 2, 7 and 9). (*R*,*R*)-TsDPEN **36b** and TEA in DCM, was added *p*-toluenesulfonyl chloride **205** to give 4-methyl-*N*-((*R*,*R*)-2{[(4-methylphenyl)sulfonyl]amino}-1,2-diphenylethyl)benzenesulfonamide **206** (88% yield, Scheme 50).[122-123]



Scheme 50: Synthesis of compound **206**.

Synthesis of *N*-((*1R,2S*)-1-hydroxy-1-phenyl-2-propyl)-*p*-toluenesulfonamide:

(1*R*,2*S*)-Norephedrine **186** was dissolved in THF, and to this solution TEA and *p*-toluenesulfonyl chloride **205** was added to afford *N*-((1*R*,2*S*)-1-hydroxy-1-phenyl-2-propyl)-*p*-toluenesulfonamide **207** (51% yield, Scheme 51).[124]



Scheme 51: Synthesis of compound **207**.

2.5. Asymmetric transfer hydrogenation (ATH) of ketone derivatives using a FA:TEA mixture

Catalytic transfer hydrogenation of ketones to alcohols with 2-propanol sometimes offers an attractive alternative to the reaction with molecular hydrogen because of the favourable properties of the organic hydrogen source.[125] However when the method is applied to the asymmetric version,[126-128] there are some downsides. The occurrence of the reverse process originating from the structural similarity of the hydrogen donor and product, both being secondary alcohols, frequently deteriorates the enantiomeric purity of the chemical product.[129] In addition, the unfavourable ketone:alcohol equilibrium ratio often prevents a high conversion. Use of formic acid[130] in place of 2-propanol presents an obvious possibility for solving these problems. Noyori[131] *et al.*, who found that Ru (II) complex modified with an arene and a chiral *N*-tosylated 1,2-diamine serve as efficient catalysts for the asymmetric reduction using a 5:2 FA:TEA azeotropic mixture under mild conditions. The mechanism of hydrogen transfer from catalyst to ketones proceeds as classified by

Morris,[132] whereby two hydrogen atom are transferred to a substrate *via* a six-membered transition state (TS) (Figure 20). A π/CH interaction between a hydrogen atom on the η^6- arene and the aromatic ring of a substrate is pivotal to the control of the absolute product stereochemistry.

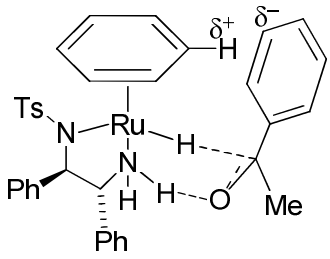


Figure 20: Orientation of substrate acetophenone in ATH by catalyst.

2.5.1. Ruthenium (II)-catalyzed ATH of acetophenone using FA:TEA mixture.

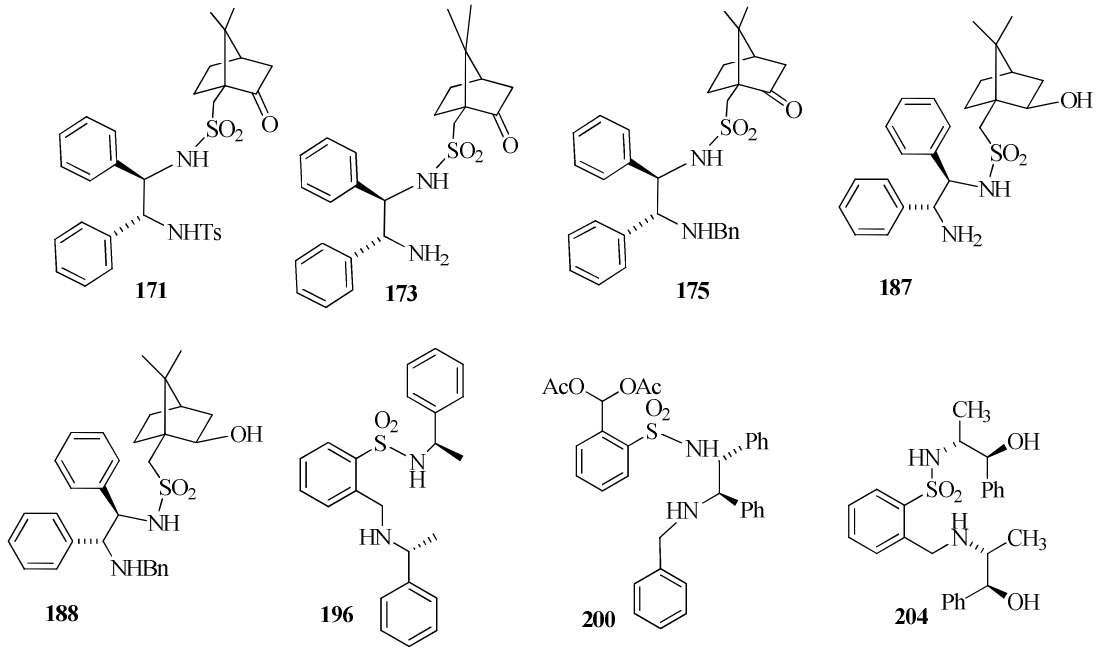


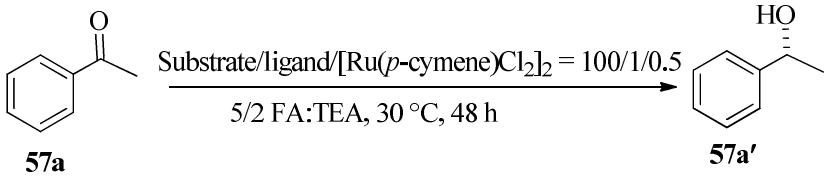
Figure 21: Chiral nitrogen ligands used for ATH of ketones.

The reduction of acetophenone to 1-phenylethanol was carried out, the catalyst of choice was the chiral Ru complex, consisting of $[Ru(p\text{-cymene})Cl_2]_2$ or

$[Ru(C_6H_6)Cl_2]_2$ with chiral amine ligand (Figure 21) and a 5:2 FA:TEA azotropic mixture.

2.5.1.1. ATH of acetophenone using $[Ru(p\text{-cymene})Cl_2]_2$ with chiral amine ligand (Table 19).

Table 19: ATH of acetophenone in FA:TEA mixture catalysed by chiral Ru(II) Complexes.[a]



57a **57a′**

Entry	Ligand	% yield[b]	% ee[c]	abs. config[d]
1	**173**	99	98	*R*
2	**187**	98	97	*R*
3	**175**	22	93	*R*
4	**188**	18	93	*R*
5	**200**	11	13	*R*
6	**204**	7	10	*R*
7	**196**	4	n/o[e]	-
8	**171**	0	n/o[e]	-

[a]The reaction was carried out at 28 °C using acetophenone (1 mmol), in a FA:TEA mixture (5:2, 2.5 cm^3) with S/C=100. [b,c]Enantiomeric excess and conversion are determined by chiral GC. [d]Determined by the sign of optical rotation of isolated product. [e]Not obtained.

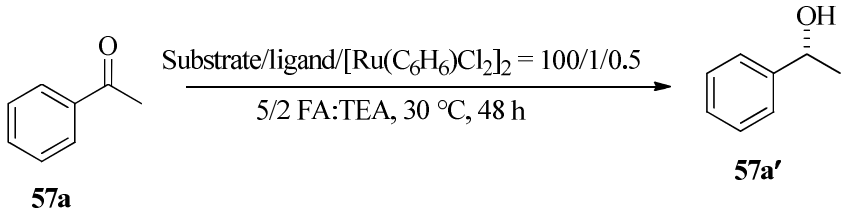
Different chiral amine ligands were evaluated including ligands based on a combination of camphor compounds and diamines (**171**, **173**, **175**, **187** and **188**), ligands based on a combination of 2-formylbenzenesulfonic chloride and diamines (**196**, **200** and **204**). They were chosen with a range of different backbone structures and functionalities in order to identify which ligands in combination with Ru (II)

would form an active catalyst for the selective reduction of various ketones. The results from a series of tests on these ligands are given in Table 19 and Table 20.

2.5.1.2. ATH of acetophenone using $[Ru(C_6H_6)Cl_2]_2$ with chiral amine ligand (Table 20).

For the reduction of acetophenone, the presence of NH_2 in the ligands based on a combination of camphor compounds and diamines (**173** and **187**), is crucially important to get high yields and excellent selectivities. Ligands with benzyl group substitution (**175** and **188**) gave only moderate yields and good selectivities.

Table 20: ATH of acetophenone in a FA:TEA mixture catalysed by chiral Ru(II) complexes.[a]



57a **57a′**

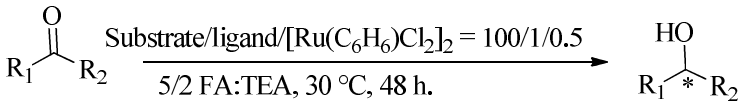
Entry	Ligand	% yield[b]	% ee[c]	abs. config[d]
1	**173**	99	97	*R*
2	**187**	99	96	*R*
3	**175**	45	96	*R*
4	**188**	16	95	*R*
5	**200**	8	20	*R*
6	**204**	2	n/o[e]	-
7	**196**	2	n/o[e]	-
8	**171**	0	n/o[e]	-

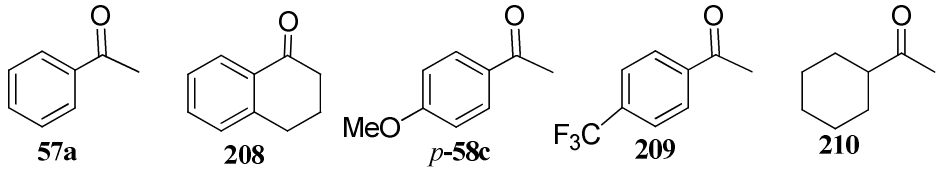
[a]The reaction was carried out at 28 °C using acetophenone (1 mmol), in a FA:TEA mixture (5:2, 2.5 cm^3) with S/C=100. [b,c]Enantiomeric excess and conversion determined by chiral GC. [d]Determined by the sign of optical rotation of isolated product. [e]Not obtained.

As a result of lacking a basic nitrogen atom, compound **171** gave no reduction due to conjugations, Whereas other ligands based on a combination of 2-formyl benzenesulfonyl chloride and diamine (**196**, **200** and **204**) were not compatible with this methodology; they gave poor conversion. Encouraged by these results, the study on the ATH of various ketones using *N*-substituted DPEN derivatives (ligands **173**, **187**, **175** and **188**) was investigated further.

2.5.2. ATH of ketones derivatives using $[Ru(C_6H_6)Cl_2]_2$ with chiral ligands **173**, **187**, **175** and **188** (Table 21).

Table 21: ATH of ketones in a FA:TEA mixture catalysed by chiral Ru(II) complexes.[a]



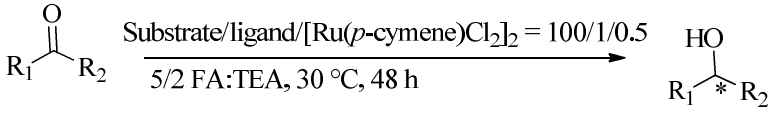


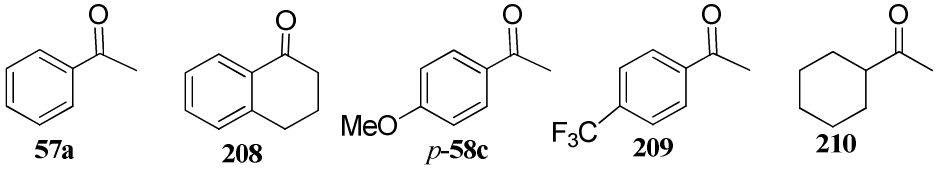
Entry	Ketone	Ligand							
		173		**187**		**175**		**188**	
		% Conv[b]	% ee[b,c]	% Conv[b]	% ee[b,c]	% Conv[b]	% ee[b,c]	% Conv[b]	% ee[b,c]
1	**57a**	99	96(*R*)	99	96(*R*)	45	96(*R*)	16	95(*R*)
2	**208**	98	97(*R*)	20	78(*R*)	0	-	0.00	-
3	*p*-**58c**	95	94(*R*)	87	98(*R*)	52	95(*R*)	15	87(*R*)
4	**209**	99	92(*R*)	98	92(*R*)	99	90(*R*)	99	91(*R*)
5	**210**	99	8(*S*)	95	18(*S*)	98	10(*S*)	77	14(*S*)

[a]The reaction was carried out at 28 °C using ketone (1 mmol), in a FA/TEA mixture (5:2, 2.5 cm^3) with S/C=100. [b]Enantiomeric exess and conversion determined by chiral GC. [c]Determined by the sign of optical rotation of isolated product.

2.5.3. ATH of ketones derivatives using [Ru(*p*-cymene)Cl_2]$_2$ with chiral ligands **173**, **187**, **175** and **188** (Table 22).

Table 22: ATH of ketones in FA:TEA mixture catalysed by chiral Ru(II) complex[a].





57a **208** ***p*-58c** **209** **210**

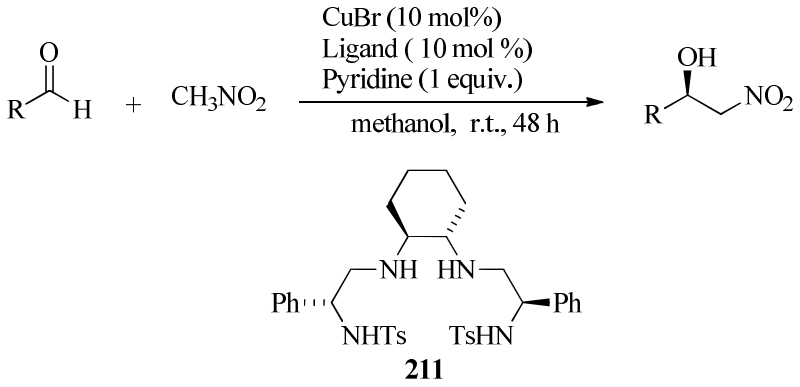
Entry	Ketone	Ligand							
		173		**187**		**175**		**188**	
		% Conv.[b.]	% ee[b,c]	% Conv.[b.]	% ee[b,c]	% Conv.[b.]	% ee[b,c]	% Conv.[b.]	% ee[b,c]
1	**57a**	99	97(*R*)[c]	98	98(*R*)	22	93(*R*)	18	93(*R*)
2	**208**	0.00	-	78	97(*R*)	0.00	-	0.00	-
3	***p*-58c**	67	99(*R*)[c]	20	96(*R*)	0.00	-	0.00	-
4	**209**	97	95(*R*)[c]	99	96(*R*)	99	99(*R*)	79	92(*R*)
5	**210**	98	46(*S*)[c]	90	47(*S*)	0.00	-	0.00	-

[a]The reaction was carried out at 28 °C using ketone (1 mmol), in a FA/TEA mixture (5:2, 2.5 cm^3) with S/C=100. [b,c]Enantiomeric excess and conversion determined by chiral GC. [d]Determined by the sign of optical rotation of isolated product.

Four organometallic catalysts consisting of *N*-substituted DPEN derivatives (ligands **173**, **187**, **175** and **188)** in combination with Ru(II) have been applied and have demonstrated good activity in ATH of different ketones using FA:TEA as the solvent and hydrogen source. The results clearly indicate that ligands in combination with Ru(II) forms a competent catalyst for the selective reduction of various ketones. substituted aryl ketones are highly compatible with this methodology. Near quantitative conversion and high enantioselectivity were achieved for the majority of substrates tested.

Trifluoromethyl substitution reduced completely in most cases with excellent ee in both Table 21 and Table 22. Acetophenone was reduced completely (ligands **173** and **187**), lower conversion (16-45 %) (ligands **175** and **188**) in both Table 21 and Table 22 with excellent ee. The *p*-methoxy substituted acetophenone was reduced completely in most cases in Table 21 (only with ligand **188** ~15% conv.) and with low to moderate conversion (ligand **173** and **187**) in Table 22 with excellent ee. The bicyclic compound (α-tetralone) was reduced only by ligands **173** and **187** in Table 21, and ligand **187** in Table 22 with high ee. The non aromatic compound, acetylcyclohexane, was reduced completely in most cases in Table 21 and with ligands **173** and **187** in Table 22, However the enantiomeric excesses were low. The reversed enantioselectivities for these reductions, relative to acetophenone derivatives, suggest that (weaker) steric factors are directing the reaction, rather than electronic ones.[133]

2.6. Copper(I)-Catalysed Henry reaction using chiral amine ligands



Scheme 52: Nitroaldol reaction.

The nitroaldol reaction is one of the most atom economic C-C bond forming reactions.[134] The resulting products, β-nitroalcohols, are widely used organic intermediates because of the many possible transformations of the nitro group into other functional groups.[135] A bis(sulphonamide)-diamine ligand **211**, coordinated

with Cu(I), catalyses various aldehyde substrate and gives the corresponding product with high yield and selectivity.[136]

A series of chiral diamine ligands were applied to catalysis with various aldehyde substrates to afford the corresponding nitroaldol products. As shown in Table 23, good to moderate conversions were obtained, but the enantiomeric selectivities were low in most cases. As mentioned by W. Jin[137] *et al*., it may be the design of the ligand that plays a pivotal role in the development of efficient metal-catalysed asymmetric reactions such that the reactivity and enantiomer selectivity are closely related to the chiral backbone and the substituents of the ligand moiety.

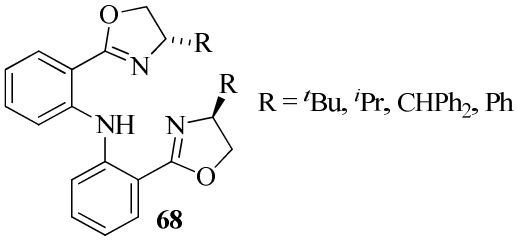
Table 23: Asymmetric Henry reaction of nitromethane and aldehyde catalysed by CuBr-amine ligands[a].

Entry	R	Ligand	Time (h)	% Conv.[b]	% ee[c]
1	2-NO_2-C_6H_4	**171**	48	96	5 (*R*)
2	2-NO_2-C_6H_4	**206**	48	97	3 (*R*)
3	2-NO_2-C_6H_4	**204**	48	49	25 (*R*)[d]
4	2-NO_2-C_6H_4	**194**	48	88	2 (*R*)
5	2-NO_2-C_6H_4	**172**	48	94	3 (*R*)
6	2-NO_2-C_6H_4	**175**	48	47	5 (*R*)
7	4-NO_2-C_6H_4	**207**	48	72	24 (*R*)
8	4-NO_2-C_6H_4	**193**	48	68	6 (*R*)
9	2-MeO-C_6H_4	**207**	48	90	13 (*R*)

[a]Reaction were carried out using aldehyde (0.25 mmol) , CuBr (10 mol%), ligand (10 mol%), pyridine (1 equiv.) and nitromethane (10 equiv.) in methanol (1.0 cm^3) at r.t. [b and c]Determined by chiral HPLC analysis. [d]Determined by the sign of optical rotation of isolated product.

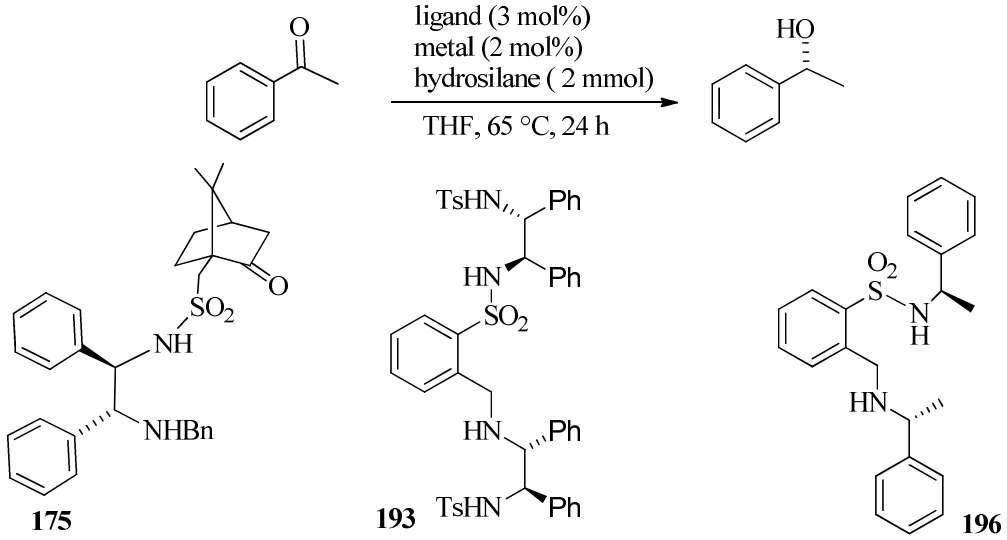
2.7. Iron-catalyzed asymmetric hydrosilylation of acetophenone with chiral amine ligands

Nishiyama *et al*,[138] found that $Fe(OAc)_2$-catalyzed hydrosilylation of ketones with several hydrosilanes can be readily promoted in the presence of *N*,*N*,*N*-bis(oxazolinylphenyl)amine **68** as a chiral ligand.



68

In this project, chiral bidentate and tetradentate amine ligands were evaluated in this reaction but unfortunately using the procedure as reported by Nishiyama *et al*, it seems to be that these types of ligands did not catalyse the reaction effectively and a moderate to good conversion with low enantiomeric selectivity (5.0-0.8% ee) was achieved, even without the ligand (53% conversion, Table 24, entry 6) or without the iron metal (~50% conversion, Table 24, entry 7 and 8).



175 **193** **196**

Scheme 53: Hydrosilylation of acetophenone by chiral amine ligands.

Table 24: Asymmetric hydrosilylation of acetophenone with iron salts and nitrogen based ligands catalyst.[a]

Entry	Cat. precursor	Hydrosilane	Ligand	% Yield[b]
1	$FeCl_2$	Triethoxysilane	**175**	94
2	$FeCl_2$	Triethoxysilane	**196**	82
3	$FeCl_2$	Triethoxysilane	**193**	56
4	$Fe(OAc)_2$	Triethoxysilane	**175**	66
5	$FeCl_2$	Poly(methyl)hydrosiloxane	**175**	93
6	$FeCl_2$	Triethoxysilane	-	53
7	-	Poly(methyl)hydrosiloxane	**193**	51
8	-	Triethoxysilane	**175**	54

[a]Reaction were carried out using acetophenone (1mmol), iron salt (2.0 mol %), ligand (3.0 mol %), hydrosilane (2.0 mmol), THF (3.0 cm^3), 65 °C, 24 h. [b]Determined by chiral GC.

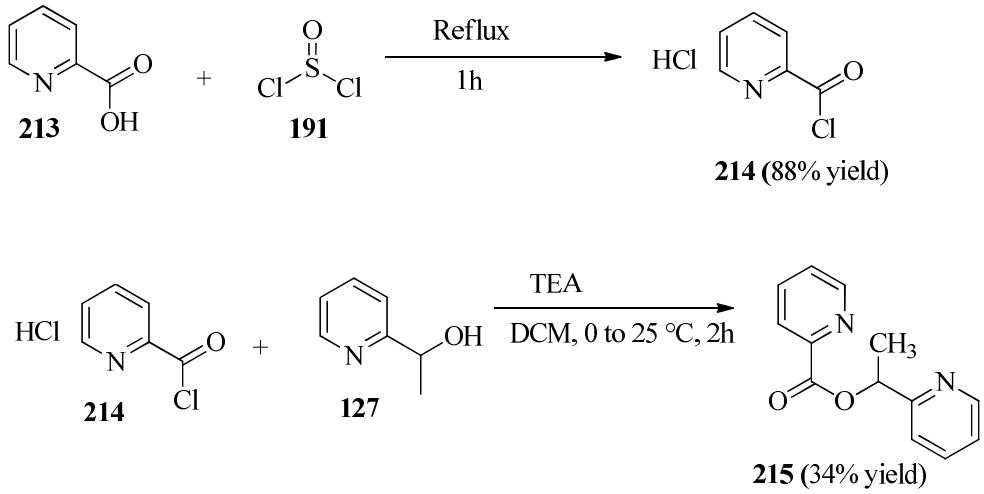
2.8. Synthesis of pyridine compounds.

The pyridine substructure is one of the most prevalent heterocycles found in natural products, pharmaceuticals, and functional materials.[139] Many powerful methodologies for the synthesis of these heterocycles rely on condensation of amines and carbonyl compounds or cycloaddition reactions.[140-141] Cross-coupling chemistry also allows introduction of substituents to activated heterocycles.[142] A series of pyridine compounds were synthesised from pyridine derivatives using acid chloride, coupling method, Mitsunobu reaction and pyridine-2-carboxylic anhydride. These compunds used initially as a rate enhancing additive in the $Pd(OAc)_2$ catalysed acetoxylation of benzene.[143]

2.8.1. Attempts to synthesise pyridine compounds:

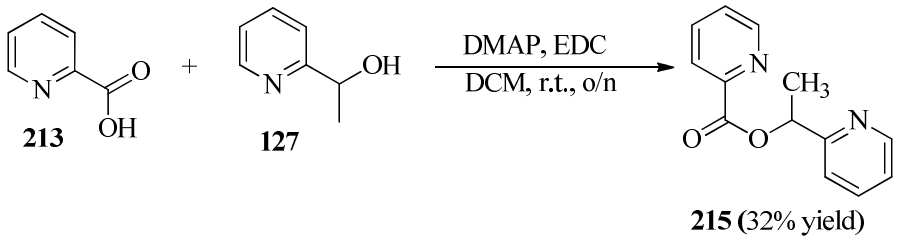
Thionyl chloride[144] **191** was added to pyridine-2-carboxylic acid **213** under reflux to give a white crystalline residue of compound **214** (88% yield) which was dissolved

in DCM, then reacted with 2-(1-hydroxyethyl)pyridine **127**, and TEA to afford pyridine-2-carboxylic acid 1-pyridin-2-yl-ethyl ester **215** (34% yield, Scheme 54).



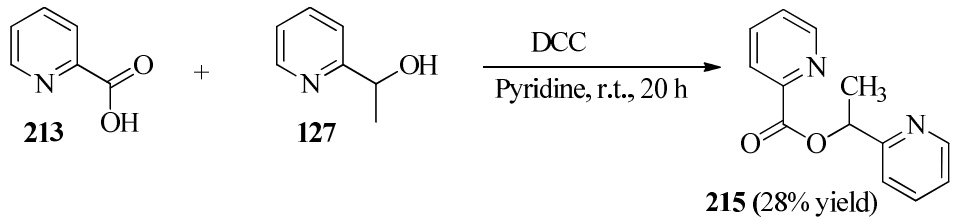
Scheme 54: Synthesis of compound **215** *via* acid chloride.

Pyridine-2-carboxylic acid[145] **213** was dissolved in DCM, added to 2-(1-hydroxyethyl) pyridine **127,** 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), and 4-(dimethylamino)pyridine (DMAP) to afford pyridine-2-carboxylic acid 1-pyridin-2-yl-ethyl ester **215** (32% yield, Scheme 55).



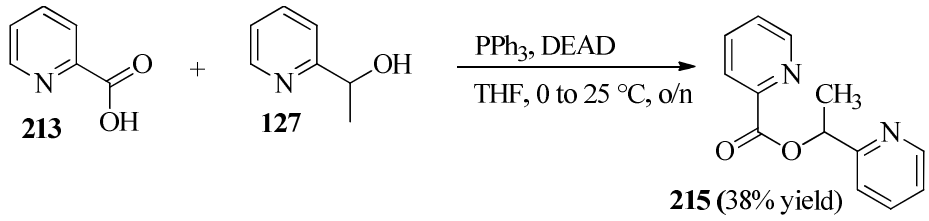
Scheme 55: Synthesis of compound **215** by coupling with EDC.

Pyridine-2-carboxylic acid[146] **213** was mixed with pyridine, added to 2-(1-hydroxyethyl) pyridine **127**, *N*,*N*′-dicyclohexylcarbodiimide (DCC) to afford pyridine-2-carboxylic acid 1-pyridin-2-yl-ethyl ester **215** (28% yield, Scheme 56).



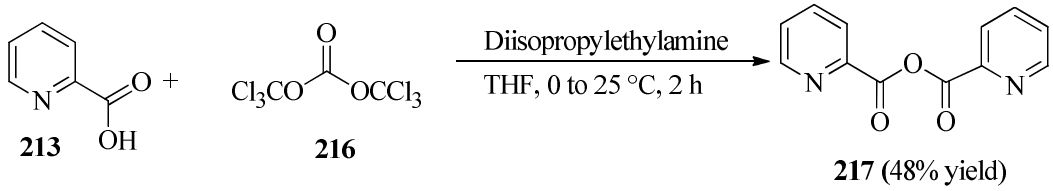
Scheme 56 Synthesis of compound **215** by coupling with DCC.

Pyridine-2-carboxylic acid[147] **213** was dissolved in THF, added to 2-(1-hydroxyethyl) pyridine **127** and triphenylphosphine (PPh_3) at 0 °C. Diethyl azodicarboxylate (DEAD) was then added (below 10 °C) to afford pyridine-2-carboxylic acid 1-pyridin-2-yl-ethyl ester **215** (38% yield, Scheme 57).



Scheme 57: Synthesis of compound **215** by a Mitsunobu reaction.

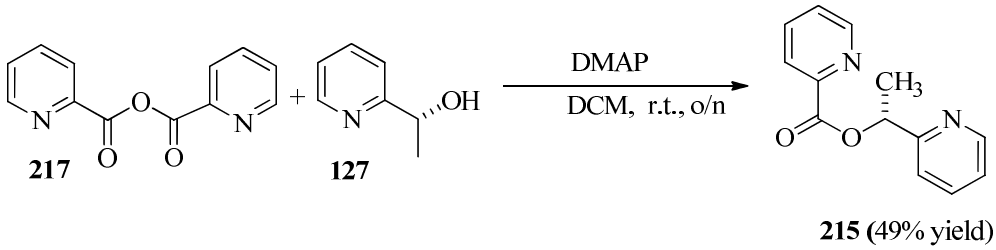
A solution of pyridine-2-carboxylic acid[148] **213** and diisopropylethylamine in THF was stirred for 10 min. at 0 °C. To the reaction mixture a solution of triphosgene **216** in THF was added at 0 °C and stirred for 1 h at r.t. to offered pyridine-2-carboxylic anhydride **217** (48% yield, Scheme 58).



Scheme 58: Synthesis of compound **217**.

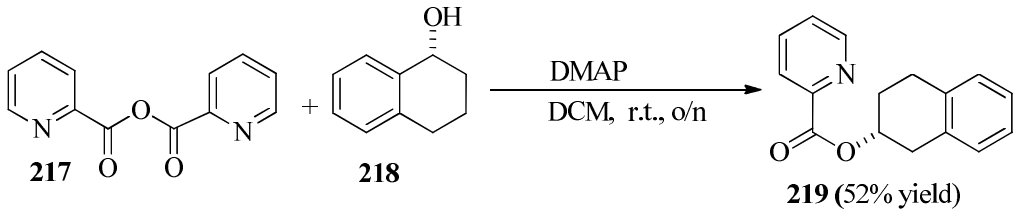
To a stirred solution of pyridine-2-carboxylic anhydride **217** and DMAP in DCM at r.t. for 10 min, a solution of 2-(1-hydroxyethyl) pyridine **127** in DCM was added,

and stirring overnight afforded (*R*)-pyridine-2-carboxylic acid 1-pyridin-2-yl-ethyl ester **215** (49% yield, Scheme 59).

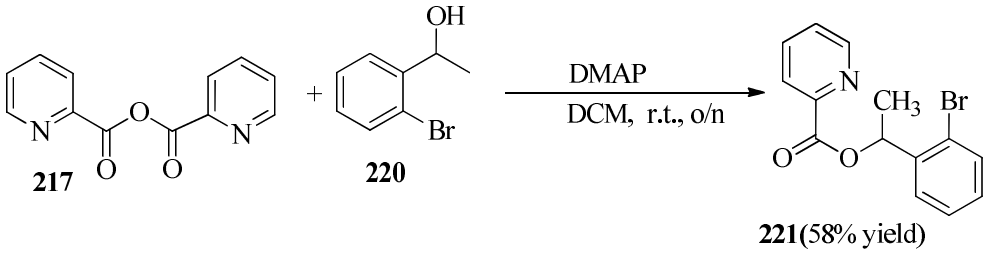


Scheme 59: Synthesis of compound **215** using **217**.

Using this protocol**,** relatively higher yields were obtained (49% yield) compared to other methods, so other pyridine compounds were made in the same way using pyridine-2-carboxylic anhydride **217** and the corresponding alcohol to afford (*R*)-pyridine-2-carboxylic acid 1,2,3,4-tetrahydro-naphthalen-1-yl ester **219** (52% yield, Scheme 60), and pyridine-2-carboxylic acid 1-(2-bromo-phenyl)-ethyl ester **221** (58% yield, Scheme 61).



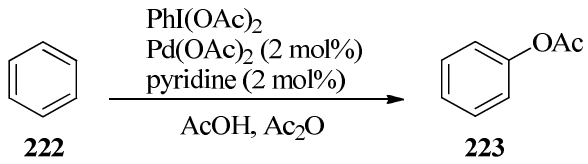
Scheme 60: Synthesis of compound **219**.



Scheme 61: Synthesis of compound **221**.

2.9. C-H Activation.*

The role of pyridine as a rate enhancing additive in the $Pd(OAc)_2$ catalysed acetoxylation of benzene was investigated, as reported by Sanford (Scheme 62).[143] Three novel pyridine compounds **215, 219** and **221** were used as enhancing additive.



Scheme 62: $Pd(OAc)_2$ catalysed acetoxylation of benzene with added pyridine.

As each compound (**215**, **219** and **221**) contains a pyridine group, it was decided to study whether these compounds would also be capable of coordination to $Pd(OAc)_2$ to induce a rate enhancement. Initial investigation looked at reproductions of the acetoxylation of benzene with added pyridine (25% scaling ratio) for 20 h.

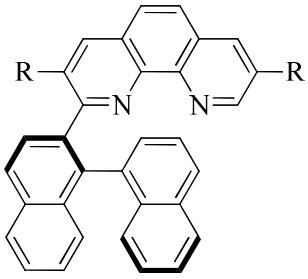
The initial results showed only a minimum amount of the product (<5% by quantitative GC analysis) using 1 equivalent chlorobenzene (PhCl). The reaction was also carried out using compounds **215** and **219** for 20 h to obtain about 11% yield. The ratio of $Pd(OAc)_2$:pyridine is extremely important as an excess of pyridine quickly becomes inhibitory. The reaction was run on the same scale as has been reported, without any ligand, with pyridine and with compounds **215**, **219** and **221** for 3 h to yield 6.7%, 33.10%, 30.7%, 0.0 % and 0.0% respectively, and for 20 h to yield 27.5%, 33.20%, 28.80%, 37.60% and 33.0% respectively. No appreciable difference was seen for **215** as compared to pyridine, implying that only one of the two pyridine groups coordinate to $Pd(OAc)_2$ at any given time and that chelation

*This work was done in collaboration with M. Chem. final year student A. Wallace, under my supervision.

does not occur. Despite the slightly increased conversion achieved, they were still considered too low to be any practical value with respect to their role in the reaction.

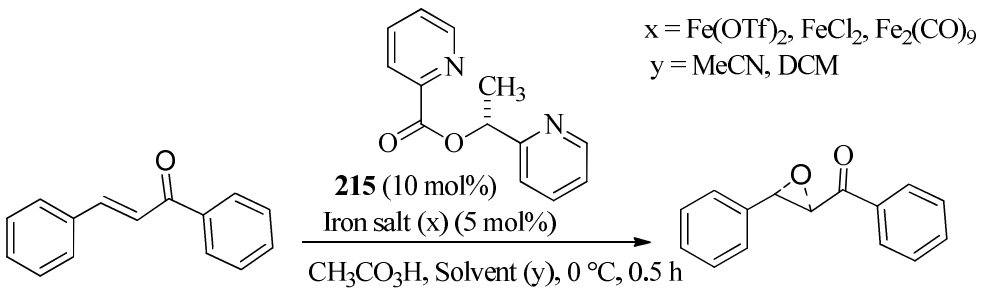
2.10. Iron-catalyzed asymmetric epoxidation of aromatic olefins.

Nishikawa *et al.*,[149] studied iron-catalyzed asymmetric epoxidation of β,β-disubstituted enones using a variety of complexes consisting of iron salts [$FeCl_2$ and $Fe(OTf)_2$] and phenanthroline ligands attached to binaphthyl moieties **224**.



224 R= *m*-xylyl

Epoxidation of aromatic olefins *(trans*-stilbene or *trans*-chalcone, Scheme 63) were investigated using iron compounds ($FeCl_2$, $Fe_2(CO)_9$ and $Fe(OTf)_2$) and chiral ligand **215** in MeCN or DCM in presence of peracetic acid solution as an oxidant. Although moderate to good conversion was obtained, the results shown that the iron complex does not coordinate to the ligand (low selectivity in all cases).



Scheme 63: Epoxidation of aromatic olefins.

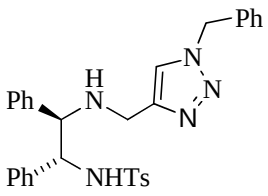
Table 25: Asymmetric epoxidation of olefins.[a]

Entry	Substrate	Metal	Solvent	% Conv.[b]	% ee[c]
1	*trans*-stilbene	$Fe(OTf)_2$	DCM	30%	4% (*R*)
2	*trans*-stilbene	$Fe(OTf)_2$	MeCN	24%	25% (*R*)
3	*trans*-stilbene	$FeCl_2$	DCM	82%	2% (*R*)
4	*trans*-stilbene	$FeCl_2$	MeCN	55%	8% (*R*)
5	*trans*-stilbene	$Fe_2(CO)_9$	DCM	60%	6% (*R*)
6	*trans*-stilbene	$Fe_2(CO)_9$	MeCN	58%	8% (*R*)
7	*trans*-chalcone	$Fe(OTf)_2$	DCM	34%	6% (*R*)
8	*trans*-chalcone	$Fe(OTf)_2$	MeCN	2%	-
9	*trans*-chalcone	$FeCl_2$	DCM	45%	2% (*R*)
10	*trans*-chalcone	$FeCl_2$	MeCN	90%	4% (*R*)
11	*trans*-chalcone	$Fe_2(CO)_9$	DCM	43%	6% (*R*)
12	*trans*-chalcone	$Fe_2(CO)_9$	MeCN	31%	2% (*R*)

[a]The reaction was carried out at 0 °C, ligand **215** (10 mol %), iron salt (5 mol %), peracetic acid solution (1.5 equiv.) DCM or MeCN, 0.5 h. [b]Conversion determined by ^{1}NMR analysis. [c]Enantiomeric excess determined by chiral HPLC analysis.

2.11. Asymmetric transfer hydrogenation (ATH) of ketone derivatives by mono-ruthenium tridentate complexes.

At this point related work in the group had demonstrated that acetophenone could be reduced with high enantioselectivity using compound **225** as a coordinating ligand. It is proposed that this forms an active mono-ruthenium, tridentate complex *in situ* from $Ru_3(CO)_{12}$.[150]

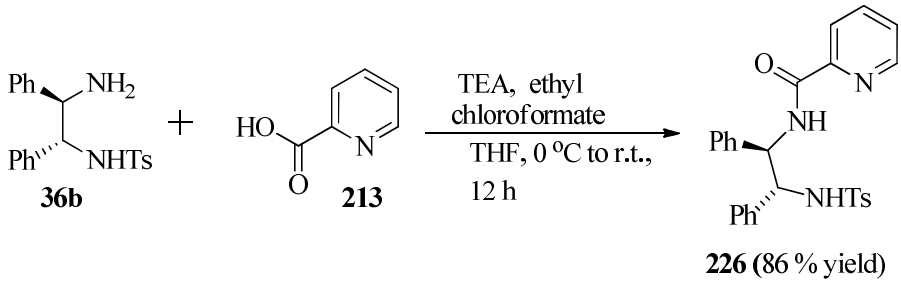


225

Given the limited progress regarding use of the tridentate ligand complexes to study of rate enhancement by pyridine in C-H activation and iron-catalyzed asymmetric epoxidation of aromatic olefins, it was decided to further study the tridentate ligand complexes with regard to their efficiency as ligands in the ATH of aryl ketones derivatives.

2.11.1. Ligands design for ATH of ketones

Synthesis of (*R,R*)-pyridine-2-carboxylic acid [2-(toluene-4-sulfonylamino)-1, 2-diphenyl-1, 2-ethylenediamine]-amide:[151]



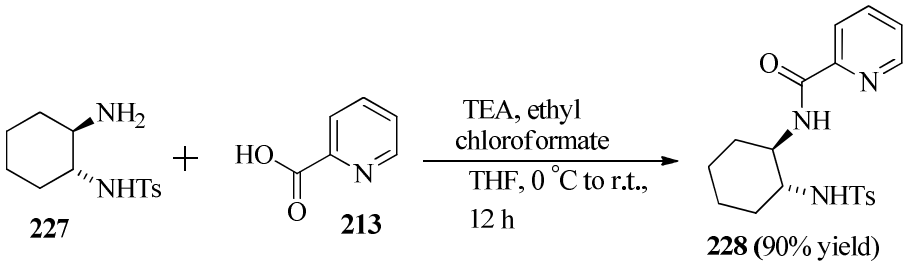
Scheme 64: Synthesis of compound **226.**

Pyridine-2-carboxylic acid **213** and TEA in anhydrous THF, was treated with ethyl chloroformate at 0 °C for 30 min. A solution of (1*R*,2*R*)-TsDPEN **36b** in THF was added dropwise and the reaction mixture was left at r.t. to yield (*R,R*)-pyridine-2-carboxylic acid [2-(toluene-4-sulfonylamino)-1,2-diphenyl-1,2-ethylenediamine]-amide **226** (86% yield, Scheme 64).

Synthesis of (*R,R*)-pyridine-2-carboxylic acid [2-(toluene-4-sulfonylamino)-cyclohexyl]-amide:

Pyridine-2-carboxylic acid **213** and TEA in anhydrous THF was treated with ethyl chloroformate at 0 °C for 30 min. A solution of (*R,R*)-(−)-*N*-(4-toluenesulfonyl)-1,2-diaminocyclohexane **227** in THF was added dropwise and the reaction mixture was

left at r.t. to give (*R,R*)-pyridine-2-carboxylic acid [2-(toluene-4-sulfonylamino)-cyclohexyl]-amide **228** (90% yield, Scheme 65).

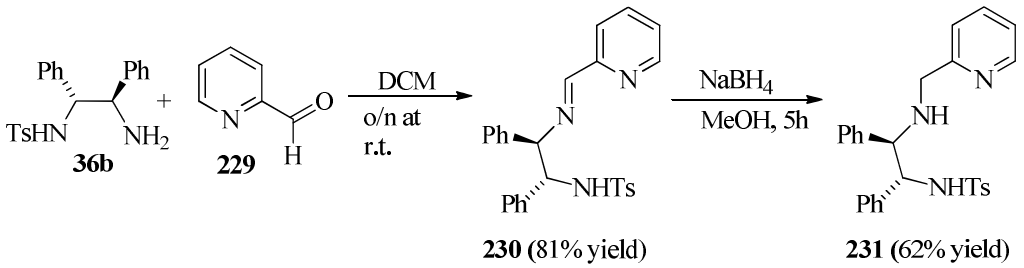


Scheme 65: Synthesis of compound **228**.

The reduction of secondary amides has been reported to be difficult, presumably due to the unfavourable loss of stability due to conjugation of the amide bond.[152-153] Therefore the reduced form of compounds **226** and **228** was thought to be best achieved by reductive amination.

Synthesis of (*R,R*)-*N*-{1,2-diphenyl-2-[(pyridin-2-ylmethyl)-amino]-ethyl}-4-methyl-benzenesulfonamide:[154]

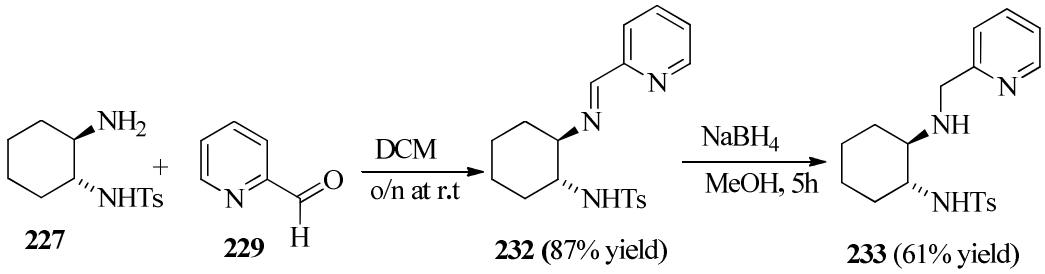
To a stirred solution of (1*R*,2*R*)-TsDPEN **36b** in DCM was added at r.t. 2-pyridincaboxaldehyde **229** in DCM. The mixture was stirred o/n at r.t. to obtain (*R,R*)-*N*-{1,2-diphenyl-2-[(pyridin-2-ylmethylene)-amino]-ethyl}-4-methyl-benzenesulfonamide **230** (81% yield). This was dissolved in MeOH and $NaBH_4$ was added portionwise and the reaction allowed to stir until all the imine had been consumed to afford (*R,R*)-*N*-{1,2-diphenyl-2-[(pyridin-2-ylmethyl)-amino]-ethyl}-4-methyl-benzenesulfonamide **231** (62% yield, Scheme 66).



Scheme 66: Synthesis of compound **231**.

Thus, imine **230** was prepared in reasonably high yield from (*R,R*)-TsDPEN and 2-pyridine carboxaldehyde. Compound **230** was found to be surprisingly stable over a period of weeks and could even be purified by column chromatography.

Synthesis of (*R,R*)-4-Methyl-*N*-{2-[(pyridin-2-ylmethyl)-amino]-cyclohexyl}-benzenesulfonamide:[155-156]

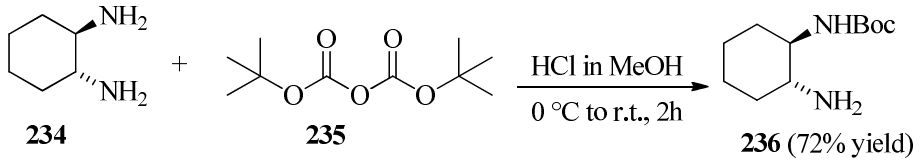


Scheme 67: Synthesis of compound **233**.

To a stirred solution of (1*R*,2*R*)-(−)-*N*-*p*-tosyl-1,2-cyclohexanediamine **227** in DCM was added at r.t. 2-pyridincaboxaldehyde **229** in DCM. The mixture was stirred o/n at r.t. to obtain (*R,R*)-4-methyl-*N*-{2-[(pyridin-2-ylmethylene)-amino]-cyclohexyl}-benzenesulfonamide **232** (87% yield). This was dissolved in MeOH and $NaBH_4$ was added portion wise and the reaction allowed to stir until all the imine has been consumed to afford (*R,R*)-4-methyl-*N*-{2-[(pyridin-2-ylmethyl)-amino]-cyclohexyl}-benzenesulfonamide **233** (61% yield, Scheme 67).

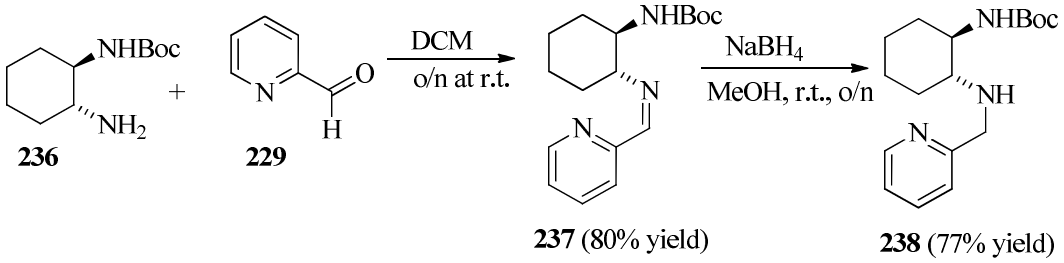
Synthesis of (*R,R*)-{2-[(pyridin-2-ylmethyl)-amino]-cyclohexyl}-carbamic acid tert-butyl ester:

(*R,R*)-1,2-Diaminocyclohexane **234** was first add to di-*tert*-butyl dicarbonate **235** to give *t*-Boc derivative **236** (72% yield, Scheme 68).[157]



Scheme 68: Synthesis of compound **236**.

The mono-Boc product **236** treated with 2-pyridinecaboxaldehyde **229** in DCM to give the imine **237** (80% yield), that was reduced by $NaBH_4$ to afford (*R,R*)-{2-[(pyridin-2-ylmethyl)-amino]-cyclohexyl}-carbamic acid t*ert*-butyl ester **238** (77% yield, Scheme 69).



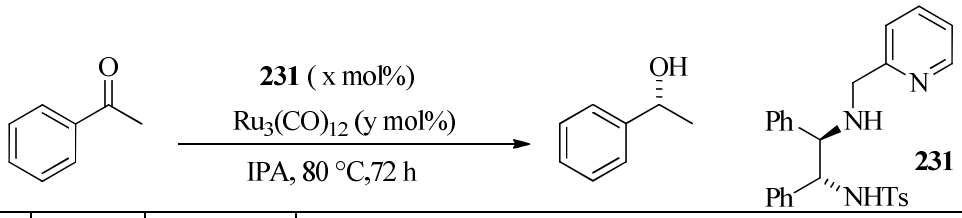
Scheme 69: Synthesis of compound **238**.

2.11.2. Optimisation of reaction conditions for ATH of ketones.

ATH is the reduction of a multiple bond with the aid of a hydrogen donor in the presence of a catalyst.[158] To carry out the ATH of ketone substrates, reaction were first optimised with respect to reaction time, concentration and catalyst loading using compound **231** and acetophenone as an representive ketone (Table 26). An optimum ratio of 1:3 $Ru_3(CO)_{12}$: ligand was determined. This is rationalised by the decomposition of the ruthenium trimer to generate 3 equivalents of ruthenium *in situ*

that is a 1:1 ratio of Ru: ligand. Thus, a catalyst loading of 2 mol% refers to 0.66 mol%: 2 mol% $Ru_3(CO)_{12}$: ligand. Experiments were carried out using different concentrations and catalyst loading for 72 h (Table 26). In all cases, conversion increase with respect to time while enantiomeric excesses decreased with respect to time possibly due to slow racemisation of the products.

Table 26: A summary of initial ATH of acetophenone with ligand **231** in order to optimise reaction conditions.[a]



Entry	Conc.	x mol%: y mol%	Time/h					
			24		48		72	
			% Conv.[b]	% ee[c]	% Conv.[b]	% ee[c]	% Conv.[b]	% ee[c]
1	0.1 m	1 : 0.33	86	95 (*R*)[d]	90	93 (*R*)	90	92 (*R*)
2	0.2 m	1 : 0.33	95	92 (*R*)	97	86 (*R*)	97	85 (*R*)
3	0.5 m	1 : 0.33	95	89 (*R*)	97	84 (*R*)	97	83 (*R*)
4	0.1 m	2 : 0.66	96	95 (*R*)	97	92 (*R*)	98	91 (*R*)

[a]The reaction was carried out at 80 °C using acetophenone (1 mmol), ligand (2 mol %) and $Ru_3(CO)_{12}$ (0.66 mol %) in 10 cm^3 IPA, 72 h. [b,c]Enantiomeric excess and conversion determined by chiral GC. [d]Determined by the sign of optical rotation of isolated product.

Among different concentration and catalyst loading used in the reactions, it was found that a reaction concentration of 0.1 mol dm^{-3} combined with a catalyst loading of 2 mol% returned optimal results.

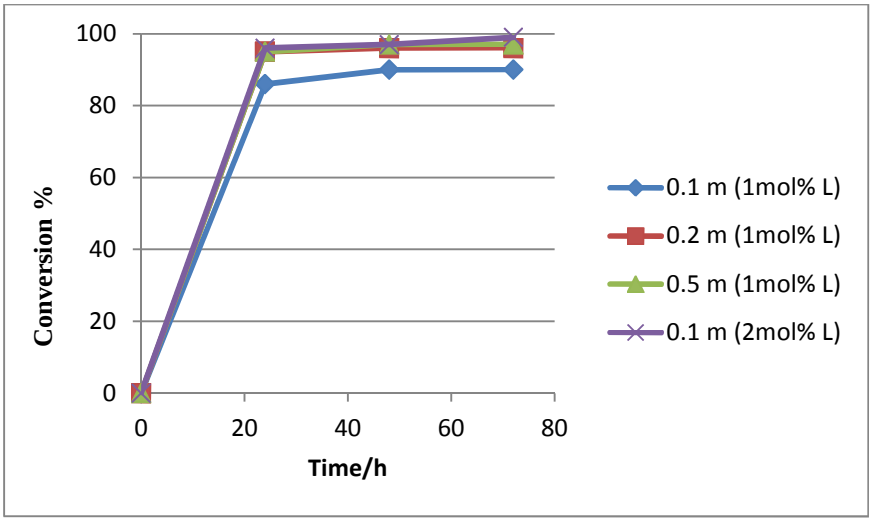


Figure 22: Comparison of ATH of acetophenone conversion at different concentrations using compound **231**.

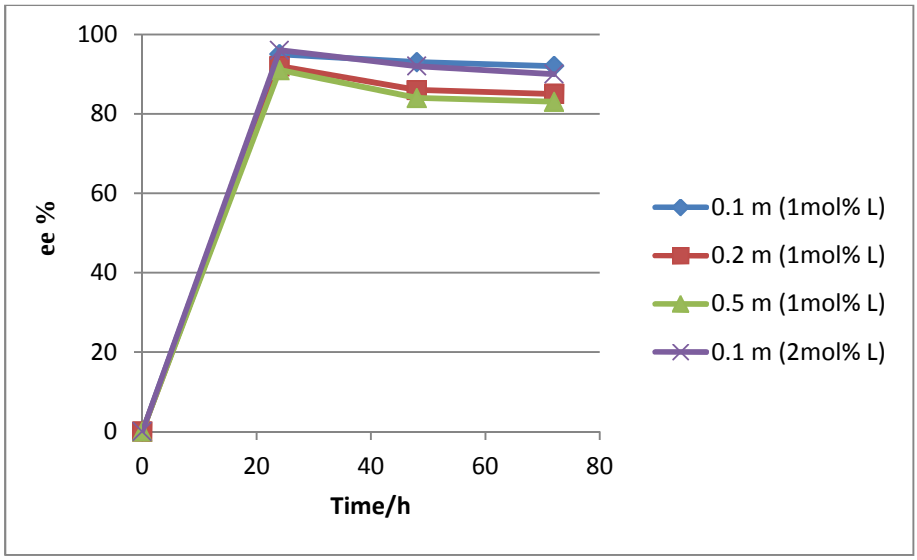
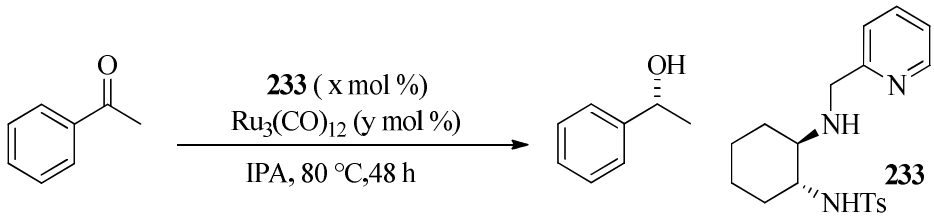


Figure 23: Comparison of ee of ATH of acetophenone at different concentrations using compound **231**.

The reaction reached completion after only 48 h, so the reaction was repeated using compound **233** (Table 27), which gave almost the same trends of results. Figure 22 shows a comparison of ATH of acetophenone at different concentrations using compound **231**, and Figure 23 shows a comparison of ee for ATH of acetophenone at different concentrations using compound **231**. Surprisingly the reduction of

acetophenone using compound **238** for 48 h (0.1 mol dm^{-3} concentration, 2 mol% catalyst loading) gave almost the same conversion and ees compared to compounds **231** and **233** (96%, 88% respectively).

Table 27: A summary of initial ATH of acetophenone with ligand **233** in order to optimise reaction conditions.[a]



Entry	Conc.	x mol%: y mol%	Time/h			
			24		48	
			% Conv.[b]	% ee[c]	% Conv.[b]	% ee[c]
1	0.1 m	1 : 0.33	47	92 (*R*)[d]	62	91 (*R*)
2	0.2 m	1 : 0.33	89	91 (*R*)	96	88 (*R*)
3	0.5 m	1 : 0.33	93	88 (*R*)	94	87 (*R*)
4	0.1 m	2 : 0.66	96	94 (*R*)	97	90 (*R*)

[a]The reaction was carried out at 80 °C using acetophenone (1 mmol), ligand (2 mol %) and $Ru_3(CO)_{12}$ (0.66 mol %) in 10 cm^3 IPA, 48 h. [b,c]Enantiomeric excess and conversion determined by chiral GC. [d]Determined by the sign of optical rotation of isolated product.

2.11.3. Mechanistic considerations.

A suggested mechanism of action for the ATH of an aryl ketone using compound **231** as a ligand is illustrated in Figure 24: Initial decomposition of $Ru_3(CO)_{12}$ with CO release, then ligation by **231** and proton transfer forms the coordinatively saturated active species **239**. Aryl ketones can be reduced by **239** *via* an outer sphere, concerted mechanism as shown in transition state **240**.

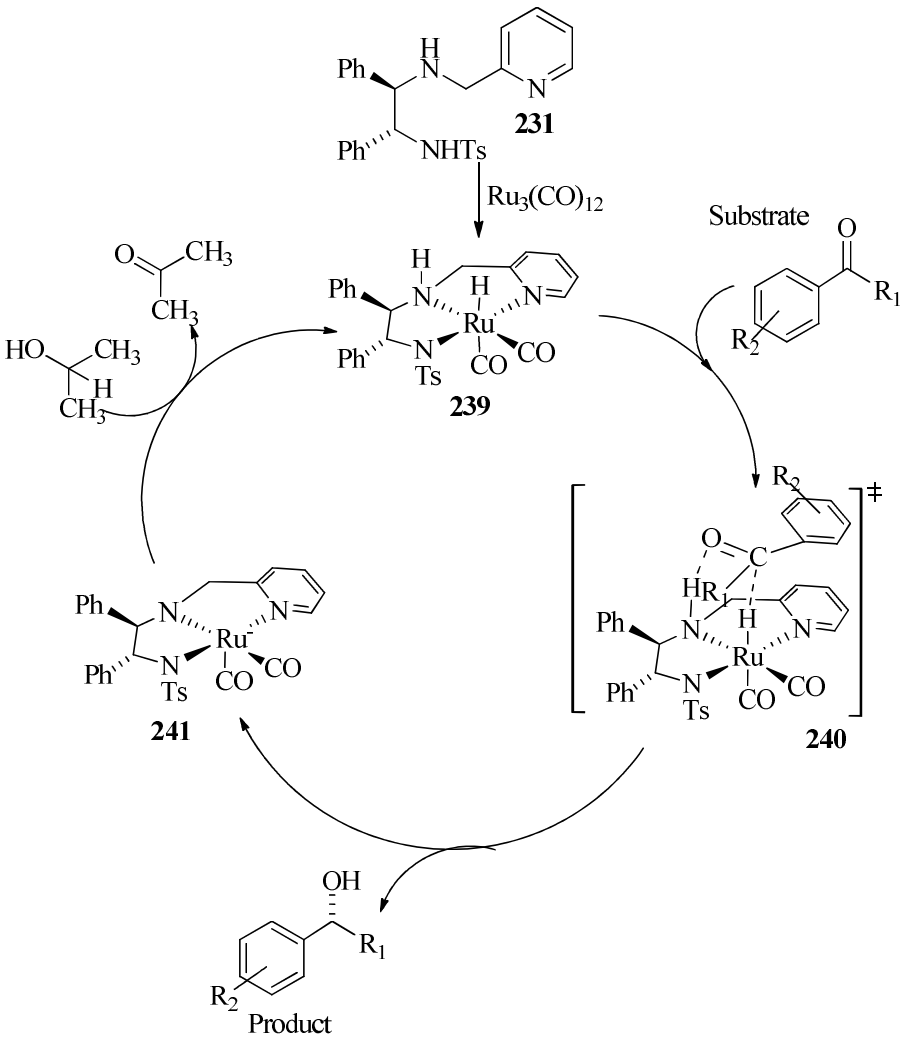


Figure 24: Possible mechanism of action for class of tridentate catalysts, using **231** as an example.

In contrast to the bifunctional TsDPEN-Ru catalysts developed by Noyori, the orientation of approach may be dominated by a favourable π/π interaction between the pyridine group in the ligand and the aromatic substituent on the respective ketone. Hydrogen donation by IPA solvent regenerates **239** to complete the catalytic cycle.

Compound **226** was employed as a ligand in the ATH of acetophenone. As expected, given the proposed need for a basic amine in the catalyst, no reduction product was observed after two days. The amide bond functionality appears to prevent the

coordination of the corresponding nitrogen to ruthenium to form the active catalyst, and the lone pair is not available due to conjugation (Figure 25).

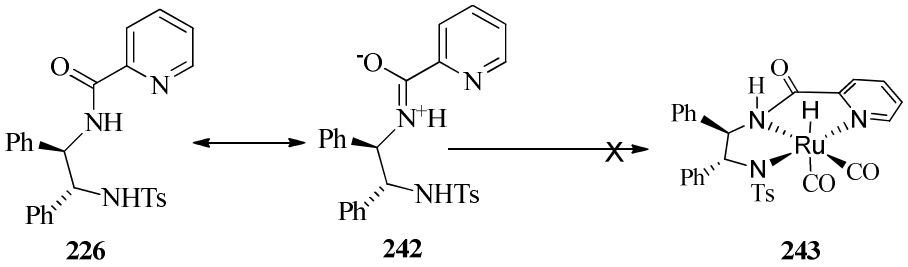


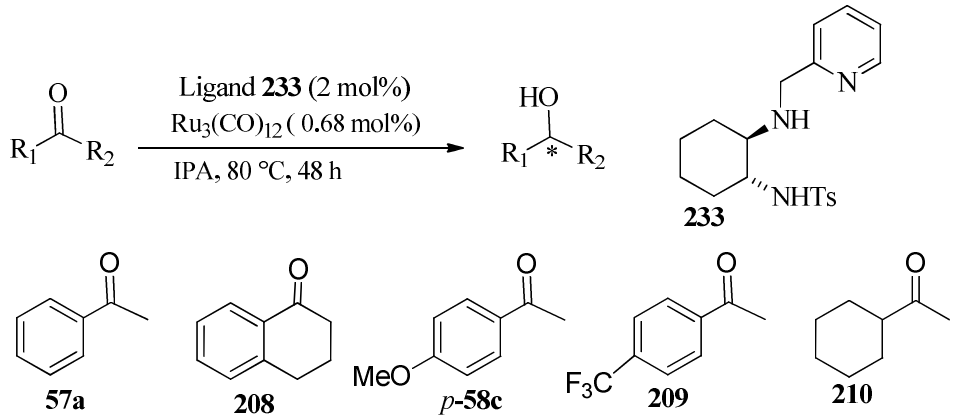
Figure 25: Illustration of how the amide bond functionality in compound **226** prevents coordination to form the active catalyst.

A substrate concentration of 0.1 mol dm^{-3} combined with a catalyst loading of 2 mol% returned optimal results for ATH of acetophenone, a series of ketone derivatives were then reduced by ATH using compound **231** and **233**, the results of the reaction were summarised in Table 28 and Table 29 respectively.

Clearly, substituted aryl ketones are highly compatible with this methodology. Near quantitative conversion and high enantioselectivity were achieved for the majority of substrates tested.

Most of the substituted aryl ketones gave high conversion and good enantioselectivities (Table 29). Among the substituted aryl ketones tested, it was found that the presence of *meta*-methoxy substituent on the aromatic ring yields optimal results under the ATH conditions employed for 48 h (98% conv., 94% ee). Acetophenone was reduced completely with only 88% ee compared to other substituted aryl ketones, which may indicate the effect of substitution on enhancing ee. Trifluoromethyl and chloro substituted acetophenone were reduced completely with 91% ees.

Table 28: A summary of ATH of ketone derivatives with compound **233** in conjunction with $Ru_3(CO)_{12}$.[a]



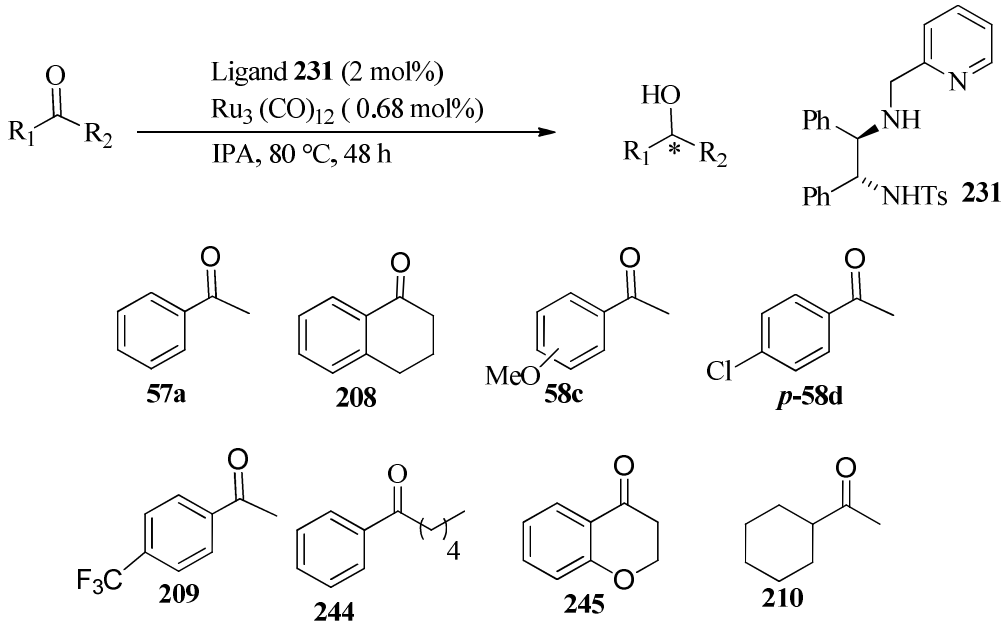
Entry	Ketones	Time			
		24 h		48 h	
		% Conv.[b]	% ee[c]	% Conv.[b]	% ee[c]
1	**57a**	96	94 (*R*)[d]	97	90 (*R*)
2	**208**	18	89 (*R*)	26	86 (*R*)
3	*p*-**58c**	53	93 (*R*)	68	88 (*R*)
4	**209**	92	87 (*R*)	100	86 (*R*)
5	**210**	80	17 (*S*)	86	17 (*S*)

[a]The reaction was carried out at 80 °C using acetophenone (1 mmol), ligand (2 mol %) and $Ru_3(CO)_{12}$ (0.66 mol %) in 10 cm^3 IPA, 48 h. [b,c]Enantiomeric excess and conversion determined by chiral GC. [d]Determined by the sign of optical rotation of isolated product.

The bicyclic compounds **208** and **245** were reduced in 84 and 95% with 91 and 93% ees respectively, also the long chain high molecular weight compound **244** reduced in 85% with 91% ee (Table 29, entries 2 and 10).

Acetylcyclohexane (Table 29, entry 10) was reduced in lower rates compared to aryl ketones, however the enantiomeric excesses was low (Table 29 entry 10), the reversed enantioselectivities for these reductions, relative to acetophenone derivatives, suggest that weaker steric factors are directing the reaction, rather than electronic ones.

Table 29: A summary of ATH of ketone derivatives with compound **231** in conjunction with $Ru_3(CO)_{12}$.[a]



Entry	Ketones	Time					
		24 h		30 h		48 h	
		%Conv.[b]	% ee[c]	%Conv.[b]	% ee[c]	%Conv.[b]	% ee[c]
1	**57a**	96	94(*R*)[d]	97	90(*R*)	97	88(*R*)
2	**208**	72	95(*R*)	81	93(*R*)	84	93(*R*)
3	*o*-**58c**	98	90(*R*)	99	90(*R*)	99	89(*R*)
4	*m*-**58c**	97	96(*R*)	98	94(*R*)	98	94(*R*)
5	*p*-**58c**	89	96(*R*)	90	93(*R*)	90	92(*R*)
6	*p*-**58d**	98	92(*R*)	99	91(*R*)	99	91(*R*)
7	**209**	98	93(*R*)	99	91(*R*)	99	91(*R*)
8	**244**	81	91(*R*)	84	90(*R*)	85	90(*R*)
9	**245**	90	99(*R*)	94	94(*R*)	95	91(*R*)
10	**210**	79	20(*S*)	85	19(*S*)	88	19(*S*)

[a]The reaction was carried out at 80 °C using acetophenone (1 mmol), ligand (2 mol %) and $Ru_3(CO)_{12}$ (0.66 mol %) in 10 cm^3 IPA, 48 h. [b,c]Enantiomeric excess and conversion determined by chiral GC. [d]Determined by the sign of optical rotation of isolated product.

Figure 26 shows the observed conversion as a function of time for different ketones reduction and Figure 27 shows the observed ees as a function of time for different ketones reduction.

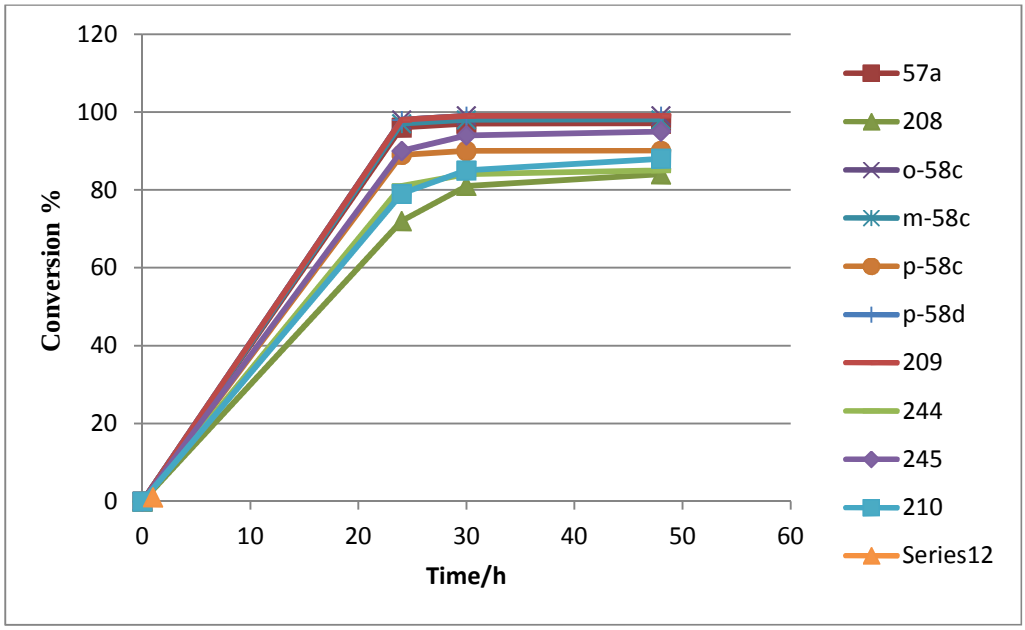


Figure 26: Conversion to products in ATH of ketones derivatives using **231**.

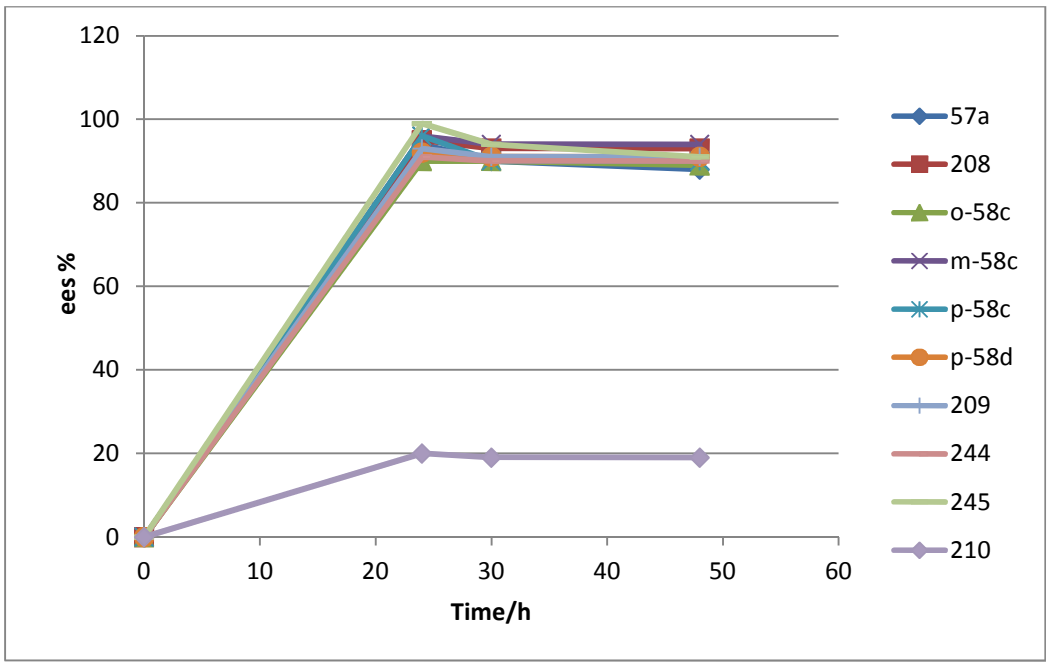


Figure 27: Comparison of ee in ATH reduction of ketones using compound **231.**

2.11.4. Investigation into ATH of *ortho*-substituted aryl ketones.

As the ATH of the different aryl ketone derivatives were successful, almost quantitative conversion and high ees was obtained for most of the reduced substrates. An investigation was carried out into *ortho*-substituted aryl ketones and the results summarised in Table 30. Principally, different groups *ortho*-substituted were investigated as this would allow for a systematic investigation into the importance of the nature of the substituent at the *ortho* position, from which it was thought that a distinct trend would emerge.

Most of the substrates were reduced in near quantitative conversion and high enantioselectivity and are highly compatible with this methodology. Conversion improved with smaller sized electron withdrawing groups (fluorine and chlorine) compared to unsubstituted acetophenone. Among the reduced substituents, lower conversion was obtained for large substituents iodide and trifluoromethyl groups. Justification for the low conversion of the large iodide would be that this substituent becomes too great and causes an unfavourable orthogonal orientation of the arene group to undergo this π/π interaction. Alternatively, these substituents may simply cause the ketone to become too bulky to effectively interact with the active catalyst. Whereas in the aryl ketone being less bulky and so increases conversion, whilst retaining selectivity induced by the favourable π/π interaction.

Data for the ATH of 2′-iodo- and 2′-trifluoromethyl- acetophenone have been excluded due to low conversions. Among the substrates reduced, 2′-methyl acetophenone yielded optimal results after 48 h, achieving almost quantitative conversion and ee of 93.8%. The electron donating effect of the methyl substituent may encourage more favourable π/π interaction to achieve this selectivity, whilst

sterically it appears to be of optimum size to encourage high conversion without being too large to prevent approach to the catalyst. Figure 28 shows the observed conversion as a function of time for reduction of different *ortho*-substituted aryl ketones, and Figure 29 shows the observed ee's as a function of time for reduction of different *ortho*-substituted aryl ketones reduction.

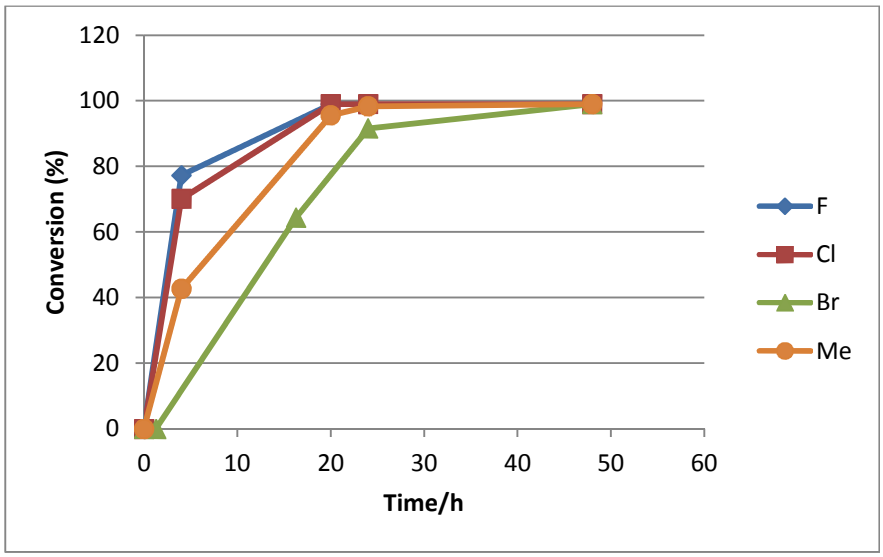


Figure 28: Comparison of conversion of substrates containing different substituents at the *ortho* position of the arene group.

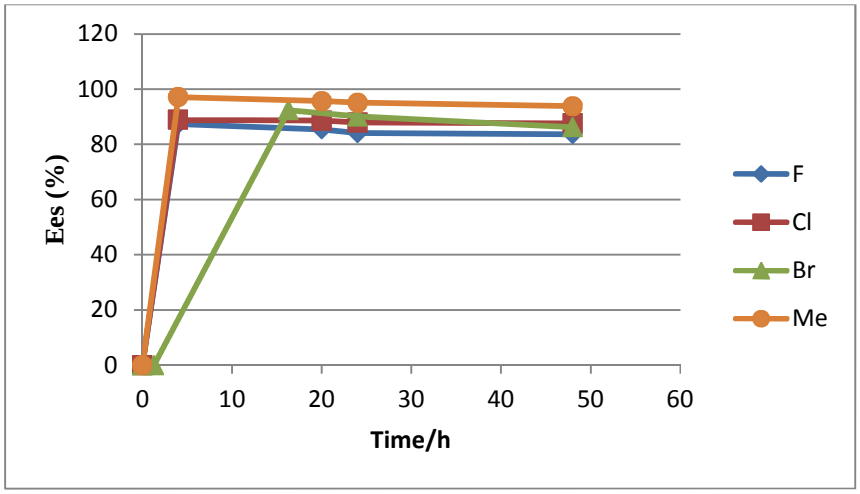
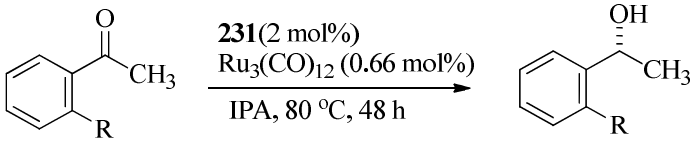


Figure 29: Comparison of ee of products containing different substituents at the *ortho* position of the arene group.

Table 30: A summary of ATH of a number of aryl ketones containing a substituent at the *ortho* position.[a]

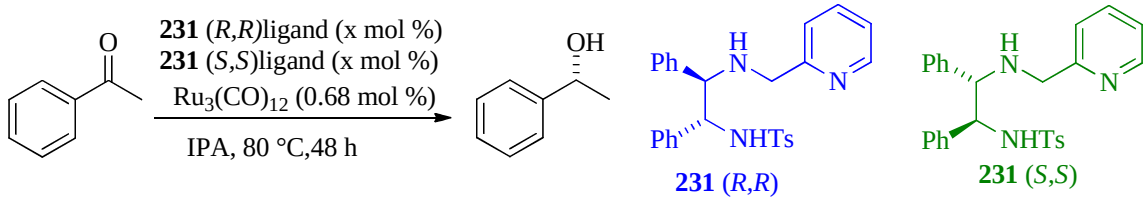


Entry	R	Time/h							
		4.0		20		24		48	
		%Conv[b]	%ee[c]	%Conv[b]	%ee[c]	%Conv[b]	%ee[c]	%Conv[b]	%ee[c]
1	H	41.1	97	92.8	94.1	93.9	92.7	95.2	91.1
2	F	77.3	87.3	>99	85.4	>99	84.1	>99	83.7
3	Cl	70.1	88.9	>99	88.6	>99	87.9	>99	87.6
4	Br	0.0	-	64.4	92.4	91.6	90.1	99.0	86.2
5	I	0.0	-	0.0	-	0.0	-	3.1	9.1
6	CF_3	0.00	-	0.00	-	28.0	19.8	33.3	17.6
7	Me	42.7	97.1	95.6	95.6	98.3	95.1	>99	93.8

[a]The reaction was carried out at 80 °C using substrate (1 mmol), ligand (2 mol %) and $Ru_3(CO)_{12}$ (0.66 mol %) in 10 cm^3 IPA, 48 h. [b,c]Enantiomeric excess and conversion determined by chiral GC. [d]This work was done in collaboration with M. Chem. final year student A. Wallace, under my supervision.

2.12. Non linear experiment of chiral tridentate pyridine ligand 231

To study the effect of the combination of *RR* and *SS* configurated chiral tridentate pyridine ligands **231** on the ee values of the ATH of acetophenone mentioned above series of experiments were carried out. Solutions of both ligand enantiomers in 2-propanol were prepared, then mixed together to make the required percentage for both ligand enantiomers configurations (Table 31).



Scheme 70: ATH of acetophenone by ligand **231** enantiomers.

Table 31: Ligand required ees.

Entry	*RR* enantiomer	*SS* enantiomer	Ligand ees
1	2 mol%	0.00 mol%	100% (*R*)
2	1.8 mol%	0.20 mol%	80% (*R*)
3	1.6 mol%	0.40 mol%	60% (*R*)
4	1.4 mol%	0.60 mol%	40% (*R*)
5	1.2 mol%	0.80 mol%	20% (*R*)
6	1.0 mol%	1.0 mol%	0.00

Then the ATH of acetophenone with chiral mono-ruthenium tridentate ligand **231** (both ligand enantiomers *RR* and *SS*) were carried out to get the product ees. Table 32 shows the ligand and product ees and Figure 30, shows the relation between ligand and product ees.

Table 32: Ligand and product ees.

Entry	ligand ees	product ees
1	100	90
2	80	70.5
3	60	46.2
4	40	28.1
5	20	12.4
6	0	2

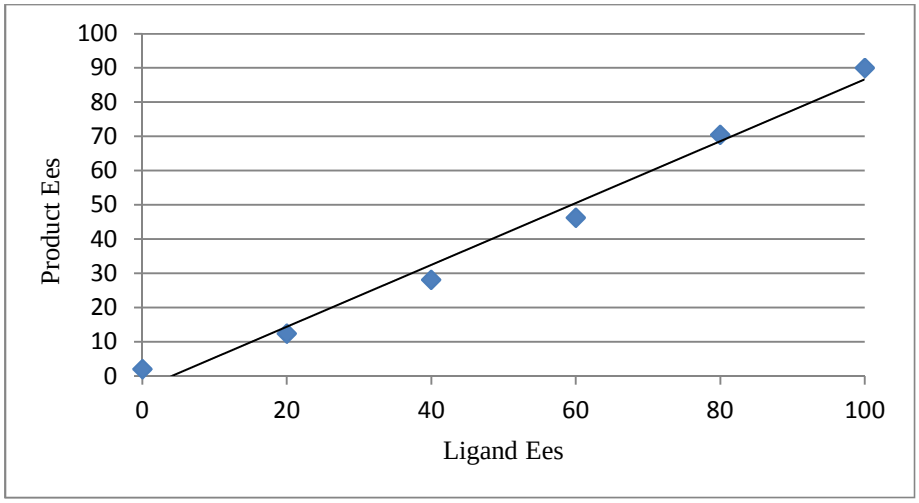


Figure 30: Ligands and product ee's

Plotting the ligand ees% against the product ees% shows no interaction between the ligand of both configuration (*RR* and *SS*) or no non-linear effect between both ligands configuration *(RR* and *SS*).

2.13. Conclusions

Although the synthesis of tetradentate amine ligands based on a combination of diamine and camphor compounds was not possible, bidentate ligands have been synthesised and evaluated as chiral ligands. The epoxidation of *trans*-stilbene, ligand **175** gave the epoxide in 91% conv., 36% ee (*S*,*S*) and compound **179** gave only 12% conversion. In hydrosilylation reactions, ligand **175** gave 94% yield with low enantiomeric induction this may indicate that such ligands do not catalyse the reaction. Ligands **173**, **187**, **175** and **188** in combination with Ru(II) using a 5:2 FA/TEA azeotropic mixture have been applied to and demonstrated good activity in ATH of different ketones. No reduction was seen using ligand **171**, indicating the need for a basic amine in the catalyst as the lone pair is not available in **171** due to conjugation. In nitroaldol reactions, ligands **171**, **172** and **206** gave products with

high yield but low ee in all cases. This is because the selectivity is related to the chiral ligand backbone.

Formation of bidentate and tetradentate ligands using 2-formylbenzenesulfonyl chloride and diamine compounds was successful, and the new novel compounds were evaluated as chiral ligands in the epoxidation of *trans*-stilbene using compounds **193**, **194**, **195** and **196** to give moderate to good conversion (30-90%) but low ees. For hydrosilylation reactions compound **196** gave high conversion but low ee. Compounds **196**, **200** and **204** gave poor conversion for ATH of acetophenone.

The rate enhancement induced by 1 equivalent of pyridine in the $Pd(OAc)_2$ catalysed acetoxylation of benzene was carried out as reported by Sanford. Three novel compounds were prepared **215, 219** and **221**, each containing at least one pyridine group and so enabling coordination to $Pd(OAc)_2$. Additional functionalities were incorporated in compounds **215, 219** and **221** (an extra pyridine group, a large bicyclic group and a halide, respectively) that were envisaged to provide further assessment as to the role of pyridine in causing such a rate enhancement. The reaction was carried out (25% scaling ratio) for 20 h using pyridine, compounds **215** and **219**, low conversion was obtained in all cases (<5%). The reaction was then run on the same scale as had been reported, using pyridine, compounds **215, 219** and **221**. Despite the slightly increased conversion achieved, they were still considered too low to be any practical value with respect to their role in the reaction.

Epoxidation of aromatic olefins (*trans*-stilbene or *trans*-chalcone) have been studied using iron complex ($FeCl_2$, $Fe_2(CO)_9$ and $Fe(OTf)_2$) and chiral ligand **215** in MeCN or DCM using peracetic acid as an oxidant, although moderate conversions were

obtained, the results show that the iron complex does not coordinated to the ligand (low selectivity in all cases).

Inspired by the development of a class of mono-ruthenium tridentate ligands, several novel compounds were prepared (**226**, **231**, **233** and **238**). Compound **226** was not effective as a coordinating ligand using ATH conditions. This helps to support the proposal that 3 available sites are needed to ligate to ruthenium to form the active catalyst.

ATH conditions were optimised using compound **231** or **233** and $Ru_3(CO)_{12}$ as reagents. It is noteworthy to mention that the use of a base to form the active catalyst is not needed. A variety of ketones were observed to undergo reduction with high, and in some cases, almost quantitative conversion. High enantioselectivity was also achieved, which may be induced *via* a favourable π/π interaction between the substrate and active catalyst. It was found that the presence of *meta*-methoxy substituent on the aromatic ring yields optimal results under the ATH conditions employed (98% conv., 94% e.e.). Also for the reduction of *ortho*-substituted aryl ketones, 2′-methyl acetophenone yielded optimal results after 48 h, achieving almost quantitative conversion and e.e. of 93.8%.

In the ATH of acetophenone, combination of both enantiomers of ligand **231** in the reaction shows no non-linear effect between both ligands configuration *(RR* and *SS*).

3 Experimental

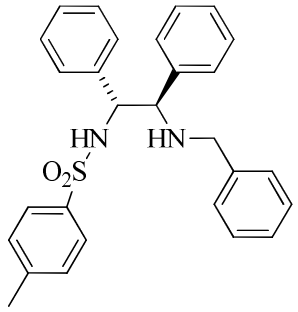
3.1. General experimental:

All the air sensitive reactions were carried out under an argon atmosphere. NMR spectra were recorded on a Bruker DPX-300 (300 MHz) or a Bruker DPX-400 (400 MHz). All chemical shifts are reported in ppm downfield from TMS (Me_4Si). Coupling constants (*J*) are reported in Hz. Multiplicity in ^{1}H-NMR is reported as singlet (s), doublet (d), broad singlet (br s), broad doublet (br d), triplet (t), quartet (q) and multiplet (m). Mass spectra were recorded on an Esquire 2000. High resolution mass spectra were recorded on Bruker Micro ToF. Infrared spectra were recorded on PerkinElmer spectrum100. The optical rotations were measured on Optical Activity Ltd. AA-1000 Polarimeter. The Chiral HPLC measurements were carried out on HPLC consisting of a Gilson 811B Dynamic Mixer, a Gilson 805 Monometer Module, a Gilson 305 Piston Pump, Merck-Hitachi L-4000 UV detector linked to HEWLETT PACKARD 3396 Series II integrator with CHIRAL PAK IA/IB column (0.46 cm x 25 cm). The chiral GC measurements were done on HEWLETT PACKARD 5890 linked to HEWLETT PACKARD HP3396A integrator or PERKIN-ELMER 8500 chromatography linked to PC running DataApex Clarity software with Chrompak CP-Chirasil Dex Cβ column. Melting points were determined on a Stuart scientific melting point apparatus and are uncorrected. Purification of compounds was done by flash column chromatography using silica gel LC60A40-63 micron.

The known compounds **160**,[159] **161**[159], **181**[113, 114] and **192**[117, 118] were not included.

3.2. Procedures for section 2.1

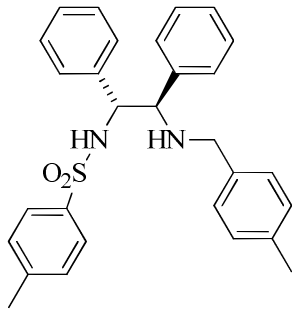
Synthesis of (*R*,*R*)-*N*-(2-benzylamino-1,2-diphenyl-ethyl)-4-methylbenzenesulfonamide (37b):



This compound is known and fully characterised.[102,160] To a stirred solution of *(R,R)*-TsDPEN (300 mg, 0.82 mmol) and molecular sieves (1.0 g) in dry MeOH (8.0 cm^3), was added benzaldehyde (0.10 cm^3, 0.94 mmol) followed by 3 drops of glacial AcOH. The reaction was followed by TLC until the imine was formed (3 h) and then $NaBH_3CN$ (0.15 g, 2.39 mmol) was added and the reaction was stirred o/n at r.t. The molecular sieves were filtered through filter paper and the solution was concentrated under reduced pressure to remove the MeOH. The residue was dissolved in $CHCl_3$ (50 cm^3), washed with saturated $NaHCO_3$ solution (30 cm^3) and then dried over anhydrous $MgSO_4$. The solvent was removed to give a crude product which was purified by silica gel column chromatography (EtOAc:Hexane, 30:70), to give (*R,R*)-*N*-(2-benzylamino-1,2-diphenyl-ethyl)-4-methylbenzenesulfonamide **37b** as a white solid (0.22 g, 0.48 mmol, 60%). Mp 138-141 °C; $[\alpha]_D^{20}$ = +58.0 (*c* 0.72, $CHCl_3$); ν_{max}(neat) 3338, 3308, 3086, 3064, 3028, 2788, 2713, 1599, 1494, 1453, 1348, 1324 and 1152 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37-7.32 (2H, m, ArH), 7.30-7.23 (3H, m, ArH), 7.18-7.10 (5H, m, ArH), 7.07-7.01 (5H, m, ArH), 6.90-6.07 (4H, m, ArH), 6.15 (1H, br s, NH), 4.30 (1H, d, *J* 7.8, *CH*Ph), 3.68 (1H, d, *J* 7.8, *CH*Ph), 3.62 (1H,

d, *J* 13.2, C*H*$_a$H$_b$), 3.41 (1H, d, *J* 13.2, CH$_a$*H*$_b$), 2.32 (3H, s, CH_3), 1.67 (1H, br s, NH), δ_C (75 MHz, $CDCl_3$) 142.66 (C), 139.26 (C), 138.96(C), 138.21 (C), 136.93 (C), 129.04 (2 x CH), 128.40 (2 x CH), 128.35 (2 x CH), 128.20 (CH), 127.97 (2 x CH), 127.88 (2 x CH), 127.52 (3 x CH), 127.45 (2 x CH), 127.23 (CH), 127.09 (CH), 127.04 (2 x CH), 66.74 (CHPh), 63.06 (CHPh), 50.85 (CH_2), 21.37 (CH_3). *m/z* (ESI) 457.1 $[M+H]^+$. HRMS found (ESI) 455.1784 ($C_{28}H_{27}N_2O_2S$ $[M-H]^-$ requires 455.1788 , error = 0.9 ppm).

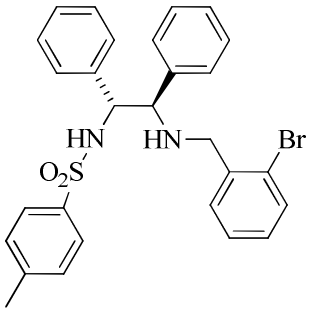
Synthesis of (*R*,*R*)-*N*-4-methylbenzyl-1,2-diphenyl-*N*′-tosylethane-1,2-diamine (157):



This compound has been reported but not fully characterised.[159] To a stirred solution of (*R*,*R*)-TsDPEN (300 mg, 0.82 mmol) and molecular sieves (1.0 g) in dry MeOH (8.0 cm^3), was added *p*-tolualdehyde (0.14 cm^3, 1.2 mmol) followed by 3 drops of glacial AcOH. The reaction was followed by TLC until the imine was formed (3 h) and then $NaBH_3CN$ (0.16 g, 2.39 mmol) was added and the reaction was stirred o/n at r.t. The molecular sieves were filtered through filter paper and the solution was concentrated under reduced pressure to remove the MeOH. The residue was dissolved in $CHCl_3$ (50 cm^3), washed with saturated $NaHCO_3$ solution (30 cm^3) and then dried over anhydrous $MgSO_4$. The solvent was removed to give a crude solid which was purified by silica gel column chromatography (EtOAc:Hexane 35:65) to

give (*R*,*R*)-*N*-4-methylbenzyl-1,2-diphenyl-*N*′-tosylethane-1,2-diamine **157** as a white solid **(**0.27 g, 0.57 mmol, 69%). Mp 150-153 °C; $[\alpha]_D^{20}$ = -38.9 (*c* 0.50, $CHCl_3$); ν_{max}(neat) 3668, 3269, 2974, 2901, 1902, 1600, 1514, 1436, 1325, 1159, 1087, 799, 753, 697 and 669 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36 (2H, d, *J* 8.0, ArH), 7.20-7.08 (6H, m, ArH), 7.10-6.90 (10H, m, ArH), 6.15 (1H, br s , NH), 4.29 (1H, d, *J* 7.8, C*H*Ph), 3.60 (1H, d, *J* 7.8, C*H*Ph), 3.57 (1H, d, *J* 13.2, CH_aH_b), 3.37 (1H, d, *J* 13.2, CH_aH_b), 2.34 (3H, s, CH_3), 2.31 (3H, s, CH_3), 1.68 (1H, br s, NH); δ_C (75.47 MHz,$CDCl_3$) 142.70 (C), 138.98 (C), 138.27 (C), 136.99 (C), 136.82 (C), 136.25 (C), 129.15 (2 x CH), 129.11 (2 x CH), 128.41 (2 x CH), 127.99 (2 x CH), 127.94 (2 x CH), 127.58 (3 x CH), 127.54 (2 x CH), 127.29 (CH), 127.12 (2 x CH), 66.95 (CHPh), 63.11 (CHPh), 50.58 (CH_2), 21.17 (CH_3), 21.13 (CH_3. *m/z* (ESI) 471.2 $[M+H]^+$. HRMS found (ESI) 471.2085 ($C_{29}H_{31}N_2SO_2$ $[M+H]^+$ requires 471.2069, error = 3.4 ppm).

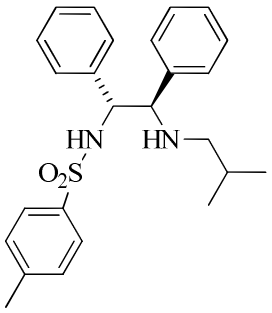
Synthesis of *N*-[2-(2-bromo-benzylamino)-1,2-diphenyl-ethyl]-4-methyl-benzenesulfonamide (163):



This compound is novel. The procedure is as same as for preparation of compound (*R*,*R*)-*N*-(2-benzylamino-1,2-diphenyl-ethyl)-4-methylbenzenesulfonamide **36b**, using (*R*,*R*)-TsDPEN (300 mg, 0.82 mmol), molecular sieves (1.0 g), dry MeOH (10 cm^3), *o*-bromobenzaldehyde (0.11 cm^3, 0.94 mmol) glacial AcOH (3 drops) and $NaBH_3CN$ (0.15 g, 2.39 mmol to give *N*-[2-(2-bromo-benzylamino)-1,2-diphenyl-

ethyl]-4-methyl-benzenesulfonamide **163** as a white solid compound (0.62 g, 1.16 mmol, 85%), Mp 46-49 °C; $[\alpha]_D^{25}$ = -36 (*c 0.1*, $CHCl_3$); ν_{max}(neat) cm^{-1} 3248, 3028, 1602, 1589, 1389, 1452, 1323, 1153, 1090, 1024, 811, 750 and 665 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.48 (1H, d, *J* 7.6, ArH), 7.35 (2H, d, *J* 8.0, ArH), 7.22 (1H, t, *J* 7.4, ArH), 7.16-7.15 (3H, m, ArH), 7.11-7.06 (5H, m, ArH), 7.05-6.95 (6H, m, ArH), 6.05 (1H, br s, N*H*), 4.32-4.29 (1H, q, *J* 4.0, C*H*Ph), 3.69 (1H, d, *J* 7.2, C*H*Ph), 3.64 (1H, d, *J* 13.2, CH_aH_b), 3.48 (1H, d, *J* 13.2, CH_aH_b), 2.32 (3H, s, CH_3); δ_C (100MHz,$CDCl_3$) 142.64 (C), 138.67 (C), 138.36 (C), 136.89 (C), 132.83 (CH), 130.41 (CH), 129.06 (2 x CH), 128.80 (CH), 128.35 (2 x CH), 127.99 (2 x CH), 127.57 (CH), 127.51 (2 x CH), 127.34 (CH), 127.30 (3 x CH), 127.07 (2 x CH), 124.09 (C), 67.01 (CHPh), 63.13 (CHPh), 51.26 (CH_2), 21.39 (CH_3). *m/z* (ESI) 557.0 $[M+Na]^+$. HRMS found (ESI) 535.1048 ($C_{28}H_{28}{}^{79}Br\ N_2O_2S\ [M+H]^+$ requires 535.1049, error = 0.3 ppm), found 537.1030 ($C_{28}H_{28}{}^{81}Br\ N_2O_2S\ [M+H]^+$ requires 537.1030, error = 0.0 ppm).

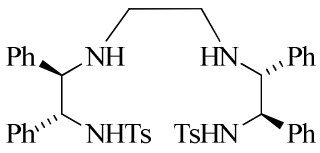
Synthesis of (*R*,*R*)-*N*-isobutyl-1,2-diphenyl-*N*′-tosylethane-1,2-diamine (162) :



This compound is known and fully characterised.[161] To a stirred solution of (*R*,*R*)-TsDPEN (0.30 g, 0.82 mmol) and molecular sieves (1.0 g) in dry MeOH (8 cm^3), was added isobutyraldehyde (0.08 cm^3, 0.96 mmol) followed by 3 drops of glacial AcOH. The reaction was followed by TLC until the imine was formed (3 h) and then

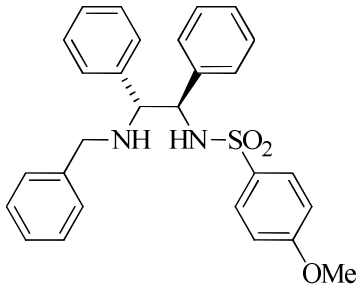
$NaBH_3CN$ (0.15 g, 2.5 mmol) was added and the reaction was stirred o/n at r.t. The molecular sieves were filtered through filter paper and the solution was concentrated under reduced pressure to remove the MeOH. The residue was dissolved in $CHCl_3$ (50 cm^3), washed with saturated $NaHCO_3$ solution (30 cm^3) and then dried over anhydrous $MgSO_4$. The solvent was removed to give a crude solid which was purified by silica gel column chromatography (EtOAc:Hexane 30:70) to afford (*R,R*)-*N*-isobutyl-1,2-diphenyl-*N*′-tosylethane-1,2-diamine **162** as a white solid (0.22 g, 0.52 mmol, 63%). Mp 112–114 °C; $[\alpha]_D^{20}$ = –27 (*c* 0.5, $CHCl_3$); ν_{max}(neat) 3358, 3272, 3031, 2958, 2822, 1599, 1495, 1432, 1326, 1275, 1156, 1147, 1089, 915, 844, 807, 765, 753, 697 and 672 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36 (2H, d, *J* 10.8, ArH), 7.13-7.11 (3H, m, ArH), 7.05-7.01 (5H, m, ArH), 6.95-6.87 (4H, m, ArH), 4.23 (1H, d, *J* 7.9, C*H*Ph), 3.57 (1H, d, *J* 7.9, C*H*Ph), 2.33 (3H, s, $CH_3(C_6H_4)$ SO_2), 2.22-2.06 (2H, m, CH_2), 1.65-1.56 (1H, m, CH), 1.37 (1H, br s, NH), 0.82 (3H, d, *J* 9.2, CH_3), 0.80 (3H, d, *J* 9.2, CH_3); δ_C (75 MHz, $CDCl_3$) 142.69 (C), 139.42 (C), 138.45 (C), 137.05 (C), 129.10 (2 x CH), 128.30 (2 x CH), 127.91 (2 x CH), 127.57 (2 x CH), 127.42 (CH), 127.36 (2 x CH), 127.27 (CH), 127.15 (2 x CH), 68.01 (CH), 63.20 (CH) , 55.25 (CH_2), 28.52 (CH) , 21.45 (CH_3) , 20.66 (CH_3) , 20.41 (CH_3). *m/z* (ESI) 423.2 $[M+H]^+$. HRMS found (ESI) 423.2114 ($C_{25}H_{31}N_2O_2S$ $[M+H]^+$ requires 423.2096, error = 4.2 ppm).

Synthesis of (*R,R*)-*N*-(2-((*R,R*)-1,2-diphenyl-2-(tosylamino)ethylamino)ethyl)-1,2-diphenyl-*N*′-tosylethane-1,2-diamine (165):



This compound is known and fully characterised.[161] (*R*,*R*)-TsDPEN (1.5 g, 4.0 mmol) and 1,2-dibromoethane (0.17 cm^3, 2 mmol) were placed in a glass sealed vessel and heated at 130 °C o/n. The crude product was dissolved in $CHCl_3$ (30 cm^3) and washed with a 20 % NaOH solution (15 cm^3). When the NaOH solution was added, a white solid precipitated. The compound was extracted with $CHCl_3$ (3 x 40 cm^3), dried over $MgSO_4$ and the solvent was evaporated providing the crude product which consisted of the tetradentate ligand and unreacted TsDPEN. The crude product was purified by silica gel column chromatography (EtOAc:Hexane 40:60) to afford (*R*,*R*)-*N*-(2-((*R*,*R*)-1,2-diphenyl-2-(tosylamino)ethylamino)ethyl)-1,2-diphenyl-*N*′-tosylethane-1,2-diamine **165** as a white solid (0.73 g, 0.96 mmol, 46%). Mp 169–172 °C; $[\alpha]_D^{20}$ = +22 (*c* 0.5, $CHCl_3$); ν_{max}(neat) 3269, 3030, 1599, 1495, 1453, 1329, 1149, 1090, 1056, 937, 809, 763, 696 and 672 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.45-7.43 (4H, m, ArH), 7.14-7.11 (6H, m, ArH), 7.01-6.92 (12H, m, ArH), 6.87-6.83 (6H, m, ArH), 4.40 (2H, d, *J* 8.7, 2PhC*H*NHTs), 3.72 (2H, d, *J* 8.7, 2PhC*H*NHR), 2.40–2.25 (4H, m, 2 x CH_2), 2.29 (6H, s, 2 x CH_3); δ_C (75 MHz, $CDCl_3$) 142.69 (2C), 139.47 (2C), 138.17 (2C), 137.53 (2C), 129.04 (4 x CH), 128.27 (4 x CH), 127.93 (4 x CH), 127.84 (4 x CH), 127.49 (4 x CH), 127.45 (2 x CH), 127.16 (2 x CH), 126.99 (4 x CH), 68.02 (2 x CH), 63.75 (2 x CH), 46.59 (2 x CH_2), 21.42 (2 x CH_3). *m/z* (ESI) 759.3 $[M+H]^+$. HRMS found (ESI) 759.3080 ($C_{44}H_{47}N_4S_2O_4$ $[M+H]^+$ requires 759.3022, error = 7.6 ppm).

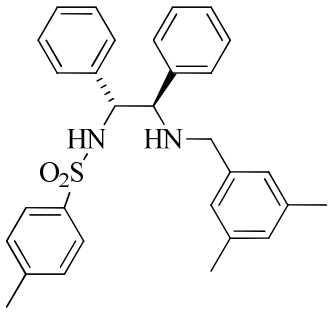
Synthesis of (*S*,*S*)-*N*-benzyl-1,2-diphenyl-*N'*-tosylethan-1,2-diamine (164):



This compound is novel. To a stirred solution of *N*-(2-amino-1,2-diphenyl)-4-methoxy-benzenesulfonamide (0.10 g, 0.26 mmol) and molecular sieves (0.50 g) in dry MeOH (5.0 cm^3), was added benzaldehyde (0.020 cm^3, 0.28 mmol) followed by 2 drops of glacial AcOH. The reaction was followed by TLC until the imine was formed (3 h) and then $NaBH_3CN$ (0.065 g, 1.04 mmol) was added and the reaction was stirred o/n at r.t. The molecular sieves were filtered through filter paper and the solution was concentrated under reduced pressure to remove the MeOH. The residue was dissolved in $CHCl_3$ (20 cm^3), washed with saturated $NaHCO_3$ solution (10 cm^3) and then dried over anhydrous $MgSO_4$. The solvent was removed to give the crude compound which was purified by silica gel column chromatography (EtOAc:Hexane 30:70), to afford (*S*,*S*)-*N*-benzyl-1,2-diphenyl-*N'*-tosylethan-1,2-diamine **164** as a white solid (0.088 g, 0.18 mmol, 69%). Mp 78–81 °C; $[\alpha]_D^{31}$ = + 27.6 (*c* 0.5, $CHCl_3$); ν_{max}(neat) 3325, 3028, 2785, 2362, 1595, 1578, 1496, 1453, 1437, 1323, 1263, 1150, 1048, 1024, 922, 842, 819, 754, 729, 697 and 669 cm^{-1}; δ_H(300 MHz; $CDCl_3$) 7.42–7.40 (2H, d, *J* 8.8, ArH), 7.31-7.24 (3H, m, ArH), 7.17-7.14 (5H, m, ArH), 7.05-6.99 (3H, m, ArH), 6.97-6.89 (4H, m, ArH), 6.65 (2H, d, *J* 8.8, ArH), *6*.16 (1H, br s, N*H*Ts), 4.30 (1H, d, *J* 8.0, PhC*H*NHTs), 3.76 (3H, s, OCH_3), 3.68 (1H, d, *J* 8.0, PhC*H*NBn), 3.62 (1H, d, *J* 13.2, CH_aH$_b$), 3.41 (1H, d, *J* 13.2, CH$_a$$H_b$), 1.71 (1H, br s, N*H*benzyl); δ_C (75 MHz; $CDCl_3$): 162.37 (C), 139.19 (C), 138.74 (C),

137.99 (C), 131.51(C) , 139.14 (2 x CH), 128.42 (2 x CH), 128.38 (2 x CH), 128.01 (2 x CH), 127.91 (2 x CH), 127.69 (CH), 127.54 (2 x CH), 127.48 (2 x CH), 127.28 (CH), 127.21 (CH), 113.60 (2 x CH), 66.76 (CH), 63.09 (CH), 55.46 (CH_3), 50.94 (CH_2). *m/z* (ESI) 473.2 $[M+H]^+$. HRMS found (ESI) 473.1895 ($C_{28}H_{29}N_2SO_3$ $[M+H]^+$ requires 473.1898, error = 0.6 ppm).

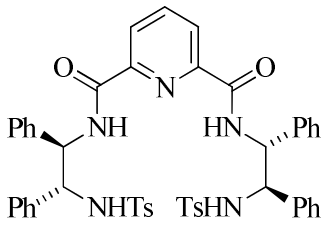
Synthesis of (*1R,2R*)-*N*^{1}-(3,5-Dimethylbenzyl)-1,2-diphenyl-*N*^{2}-tosylethane-1,2-diamine (158):



This compound is known and fully characterised.[159] The procedure is as same as for preparation of compound (*R,R*)-*N*-isobutyl-1,2-diphenyl-*N*′-tosylethane-1,2-diamine **162** to afford (1*R*,2*R*)-*N*^{1}-(3,5-Dimethylbenzyl)-1,2-diphenyl-*N*^{2}-tosylethane-1,2-diamine **158** as a white solid (0.35 g, 0.72 mmol, 88%). Mp 127–129 °C; $[\alpha]_D^{22}$ = –36.4 (*c* 0.48, $CHCl_3$); ν_{max}(neat) 3340, 3291, 3034, 2915, 2767, 1600, 1493, 1454, 1426, 1323, 1152, 1114, 1088, 1029, 915, 854, 802, 714, 697 and 671 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 7.64 – 6.96 (17H, m, ArH), 6.42 (1H, br s, NHTs), 4.56 (1H, d, *J* 7.2, PhC*H*NHTs), 3.95 (1H, d, *J* 7.3, PhC*H*Nbenzyl), 3.80 (1H, d, *J* 13.1, CH_aH_b), 3.59 (1H, d, *J* 13.1, CH_aH_b), 2.58 (3H, s, CH_3), 2.54 (6H, s, $2CH_3$), 1.87 (1H, br s, NHbenzyl); δ_C (75 MHz; $CDCl_3$) 142.62 (C), 139.28 (C), 139.09 (C), 138.43 (C), 137.96 (C), 136.94 (C), 136 23 (C), 129.16 (2 x CH), 129.11 (2 x CH), 128.72 (2 x CH), 128.41 (3 x CH), 127.98 (2 x CH), 127.5 (2 x CH), 127.93, 127.35 (2 x CH),

125.62 (CH), 66.8 (CH), 63.0 (CH), 50.8 (CH_2), 21.42 (CH_3), 21.20 (CH_3), 21.11 (CH_3). *m/z* (ESI) 485.2 $[M+H]^+$. HRMS found 485.2259 ($C_{30}H_{33}N_2SO_2$ $[M+H]^+$ requirs 485.2252, error = 1.4 ppm).

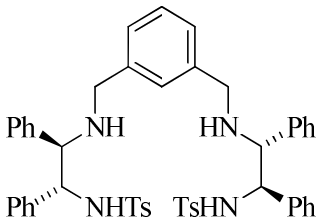
Synthesis of *N,N′*-bis((*R,R*)-1,2-diphenyl-2-(tosylamino)ethyl)pyridine-2,6-dicarboxamide (166):



This compound is novel. (*R,R*)-TsDPEN (0.3 g, 0.8 mmol) was dissolved[161] in DCM (15 cm^3) and then 2,6-pyridinedicarbonyl dichloride (0.08 g, 0.4 mmol) and TEA (0.1 cm^3, 0.8 mmol) were added and the reaction was stirred o/n at r.t. The mixture was washed with saturated $NaHCO_3$ solution (20 cm^3), extracted with $CHCl_3$ (3 x 25 cm^3) and then dried over anhydrous $MgSO_4$. The solvent was removed to afford *N,N′*-bis((*R,R*)-1,2-diphenyl-2-(tosylamino)ethyl)pyridine-2,6-dicarboxamide **166** as a light yellow solid (0.34 g, 0.4 mmol, 98 %). Mp 168–170 °C; $[\alpha]_D^{20}$ = +192 (*c* 0.5, $CHCl_3$); ν_{max}(neat) 3338, 3175, 1664, 1524, 1445, 1319, 1152, 1090, 931, 812, 697 and 667 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.62 (2H, d, *J* 8.4, ArH), 8.18 (2H, d, *J* 8.0, ArH), 7.62 (4H, d, *J* 8.0, ArH), 7.34-7.32 (4H, m, ArH), 7.17-7.08 (6H, m, ArH), 7.02-6.94 (13H, m, ArH), 6.65 (1H, br s, NH), 5.51 (2H, dd, *J* 8.4, 8.6, 2Ph*CH*NHTs), 5.10 (2H, d, *J* 10.4, 2Ph*CH*NHR), 2.27 (6H, s, $2CH_3$); δ_C (75 MHz; $CDCl_3$) 163.76 (2 x C=O), 147.76 (2C), 142.50 (2C), 139.20 (2C), 138.75 (CH), 138.23 (2C), 138.02 (2C), 129.07 (6 x CH), 128.20 (3 x CH), 128.08 (3 x CH), 127.95 (3 x CH), 127.69 (4 x CH), 127.33 (CH), 127.24 (2 x CH), 127.06 (6 x CH),

125.06 (2 x CH), 62.21 (2 x CH), 59.62 (2 x CH), 21.34 (2 x CH_3). *m/z* (ESI) 886.2 $[M+Na]^+$. HRMS found (ESI) 886.2717 ($C_{49}H_{45}N_5NaS_2O_6$ $[M+Na]^+$ requires 886.2703, error = 2.9 ppm).

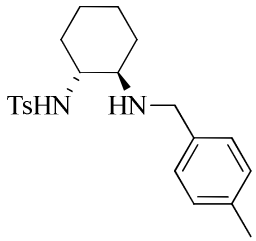
Synthesis of (*R*,*R*)-*N*-3-(((*R*,*R*)-1,2-diphenyl-2-(tosylamino)ethylamino)methyl)benzyl)-1,2-diphenyl-*N*′-tosylethane-1,2-diamine (159):



This compound is novel. The procedure is as same as for preparation of compound *N*,*N*′-bis((*R*,*R*)-1,2-diphenyl-2-(tosylamino)ethyl)pyridine-2,6-dicarboxamide **166**, using (*R*,*R*)-TsDPEN (200 mg, 0.55 mmol), molecular sieves (1.0 g), dry MeOH (10 cm^3), phthaldialdehyde (0.04 cm^3, 0.27 mmol) glacial AcOH (3 drops) and $NaBH_3CN$ (0.16 g, 2.50 mmol) to give (*R*,*R*)-*N*-3-(((*R*,*R*)-1,2-diphenyl-2-(tosylamino)ethylamino)methyl)benzyl)-1,2-diphenyl-*N*′-tosylethane-1,2-diamine **159** as a white solid (0.18 g, 0.21 mmol, 77%). Mp 70–73 °C; $[\alpha]_D^{20}$ = –57 (*c* 0.5, $CHCl_3$); ν_{max}(neat) 3247, 3028, 2324, 1599, 1493, 1453, 1321, 1153, 1091, 919, 811, 774, 697 and 667 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 7.38-7.36 (4H, m, ArH), 7.24-7.12 (8H, m, ArH), 7.04-6.94 (15H, m, ArH), 6.85-6.83 (5H, m, ArH), 6.34 (2H, br s, 2NH), 4.32 (2H, d, *J* 8.3, 2PhC*H*NHTs), 3.77 (2H, d, *J* 8.0, 2 PhC*H*NHR), 3.65 (2H, d, *J* 13.2, 2 x CH_aH$_b$), 3.41 (2H, d, *J* 13.2, 2 x CH$_a$$H_b$), 2.29 (6H, s, 2 x CH_3); δ_C (75 MHz; $CDCl_3$) 142.67 (2C), 139.97 (2C), 139.04 (2C), 138.05 (2C), 136.95 (2C), 129.03 (5 x CH), 128.45 (CH), 128.27 (4 x CH), 127.83 (4 x CH), 127.75 (4 x CH),

127.52 (2 x CH), 127.46 (5 x CH), 127.41 (CH), 127.08 (4 x CH), 126.95 (2 x CH), 67.17 (2 x CH), 63.38 (2 x CH), 50.40 (2 x CH_2), 21.36 (2 x CH_3). *m/z* (ESI) 835.3 $[M+H]^+$. HRMS found (ESI) 835.3360 ($C_{50}H_{51}N_4S_2O_4$ $[M+H]^+$ requires 835.3334, error = 3.1 ppm).

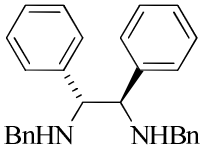
Synthesis of (*R*,*R*)-*N*-4-methylbenzyl-*N*′-tosylcyclohexane-1,2-diamine (167):



This compound is novel. To a stirred solution of (*R*,*R*)-(−)-*N*-*p*-tosyl-1,2-cyclohexanediamine (0.30 g, 1.1 mmol) and molecular sieves (1.0 g) in dry MeOH (8.0 cm^3), was added *p*-tolualdehyde (0.14 cm^3, 0.1.2 mmol) followed by 3 drops of glacial AcOH, the reaction was followed by TLC until the imine was formed (3h) and then $NaBH_3CN$ (0.15 g, 2.39 mmol) was added and the reaction was stirred o/n at r.t. The molecular sieves were filtered through filter paper and the solution was concentrated under reduced pressure to remove the MeOH. The residue was dissolved in $CHCl_3$ (50 cm^3), washed with saturated $NaHCO_3$ solution (30 cm^3) and then dried over anhydrous $MgSO_4$. The solvent was removed to give a crude product which was purified by silica gel column chromatography (EtOAc:Hexane 30:70), to give (*R*,*R*)-*N*-4-methylbenzyl-*N*′-tosylcyclohexane-1,2-diamine **167** as a white solid (0.35 g, 0.94 mmol, 85%). Mp 120-123°C; $[\alpha]_D^{20}$= -4.60 (*c* 5.65, $CHCl_3$); ν_{max}(neat) 3319, 3200, 2942, 2868, 1597, 1448, 1389, 1336, 1272, 1154, 1091, 800, 773, 692 and 660 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.72 (2H, d, *J* 8.2 ArH), 7.21 (2H, , d, *J* 8.0 ArH), 7.13 (4H, s, ArH), 3.73 (1H, d, *J* 13.1 C*H*$_a$H$_b$), 3.53 (1H, d, *J* 13.1 CH$_a$*H*$_b$),

2.71-2.65 (1H, m, C*H*NHTs), 2.38 (3H, s, CH_3), 2.35 (3H, s, CH_3), 2.28-2.23 (1H, m, *CH*NHbenzyl), 2.15-2.07 (2H, m, CH_2), 1.70-1.62 (2H, m, CH_2), 1.22-0.95 (4H, m, 2 x CH_2); δ_C (100 MHz; $CDCl_3$) 142.91 (C), 137.15 (C), 136.62 (C), 136.28 (C), 129.35 (2 x CH), 128.85 (2 x CH), 127.78 (2 x CH), 126.92 (2 x CH), 59.42 (CH), 57.12 (CH), 49.44 (CH_2), 32.66 (CH_2), 30.81 (CH_2), 24.33 (CH_2), 24.30 (CH_2), 21.27 (CH_3), 20.64 (CH_3). *m/z* (ESI) 373.2 $[M+H]^+$. HRMS found (ESI) 373.1939 ($C_{21}H_{29}N_2SO_2$ $[M+H]^+$ requires 373.1944, error = 1.4 ppm).

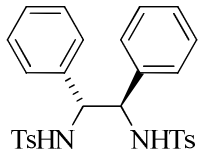
Synthesis of (*R,R*)-*N,N′*-dibenzyl-1,2-diphenylethane-1,2-diamine (168) :



This compound has been reported and fully characterised.[162-166] (*R,R)*-DPEN (0.50 g, 2.36 mmol), benzyl bromide (0.56 cm^3, 4.72 mmol), K_2CO_3 (0.72 g, 5.19 mmol), and THF (20 cm^3) were stirred at r.t for 48 h. The reaction mixture was concentrated under reduced pressure, diluted with EtOAc (40 cm^3), washed with water (3x 20 cm^3), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure, the product was isolated by gradient flash column chromatography (EtOAc:Hexane 10:90), to give (*R,R*)-*N,N′*-dibenzyl-1,2-diphenylethane-1,2-diamine **168** as a clear colourless oil (0.49 g, 1.25 mmol, 53%). $[\alpha]_D^{27}$ = +32.4 (c 1.0 in $CHCl_3$); v_{max} (neat) 3058.9, 2115.6, 2004.8, 1735.3 and 1589.6 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 7.30-7.19 (10H, m, ArH), 7.19-7.12 (6H, m, ArH), 7.05-7.03 (4H, m, ArH), 3.71 (2H, s, 2 x C*H*Ph), 3.66 (2H, d, *J* 13.3, 2 x CH_aH_b), 3.49 (2H, d, *J* 13.3, 2 x CH_aH_b), 2.33 (2H, br s, NH_2); δ_C (75 MHz) 141.18 (2C), 140 61 (2C), 128.28 (3 x CH), 128.07 (3 x CH), 127.95 (5 x CH), 127.44 (5 x CH), 126.88 (2 x CH), 126.74 (2 x CH), 68.36 (2

x C*H*Ph), 51.35 (2 x CH_2). *m/z* (ESI) 393.2 $[M+H]^+$. HRMS found (ESI) 393.2328 ($C_{28}H_{29}N_2$ $[M+H]^+$ requires 393.2325, error = 7.6 ppm).

Synthesis of 4-methyl-*N*-((*R*,*R*)-2{[(4-methylphenyl)sulfonyl]amino}-1,2-diphenylethyl)benzenesulfonamide (206):



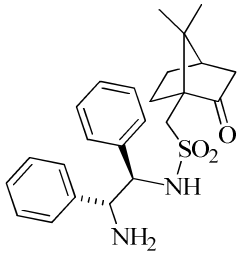
This compound has been reported but not fully characterised.[161, 102, 103]

To a solution of (*R*,*R*)-TsDPEN (0.5 g, 1.37 mmol) and TEA (0.21 cm^3, 1.5 mmol) in DCM (10 cm^3) cooled in an ice-bath was added *p*-toluenesulfonyl chloride (0. 26 g, 1.37 mmol) in DCM (2 cm^3) in a dropwise manner. The mixture was stirred for 30 min and then warmed to r.t. The reaction progress was monitored by TLC and the reaction was found to be complete after 16 h. The resulting mixture was washed with water (20 cm^3), saturated $NaHCO_3$ (20 cm^3), brine (20 cm^3) and then was dried over anhydrous $MgSO_4$. The product was isolated by gradient flash column chromatography (EtOAc:Hexane 30:70), to give 4-methyl-*N*-((*R*,*R*)-2{[(4-methylphenyl)sulfonyl]amino}-1,2-diphenylethyl)benzenesulfonamide **206** as a fine white solid (0.25 g, 0.48 mmol, 88%). Mp 209–210 $^{\circ}$C; $[\alpha]_D^{22}$ = +40.5 (*c* 1.76, $CHCl_3$); ν_{max}(neat) 3311, 1456, 1326, 1152, 1082, 1062, 913, 807, 754, and 666 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.47 (4H, d, *J* 8.0, ArH), 7.71-6.93 (10H, m, ArH), 6.71 (4H, d, *J* 8.0, ArH), 5.45-5.42 (2H, m, 2x N*H*), 4.46-4.43 (2H, m, 2 x C*H*NH), 2.33 (6H, s, *2* x $C_6H_4CH_3$); δ_C (100 MHz; $CDCl_3$) 143.11 (2C), 136.82 (2C), 136.21 (2C), 129.24 (4 x CH), 128.01 (4 x CH), 127.62 (2 x CH), 127.55 (4 x CH), 127.10 (4 x CH), 62.33 (2 x C*H*Ph), 21.41 (2 x CH_3). *m/z* (ESI) 543.1 $[M+Na]^+$.

HRMS found (ESI) 543.1379 ($C_{28}H_{28}N_2NaO_4S_2$ $[M+Na]^+$ requires 543.1383, error = 0.7 ppm); found: C, 64.8; H, 5.3; N, 5.6; S, 13.4 %. Calculated for $C_{28}H_{28}N_2O_4S_2$: C, 64.6; H, 5.4; N, 5.5; S, 12.3 %.

3.3. Procedures for section 2.3

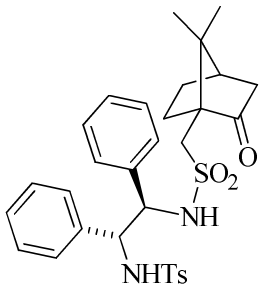
Synthesis of *N*-(2-amino-1,2-diphenyl-ethyl)-*C*-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-methanesulfonamide (173):



This compound is known and fully characterized.[107-111] (*R,R)*-DPEN (0.2 g, 0.94 mmol) was dissolved in DCM (15 cm^3) and the reaction was cooled to 0 °C, then TEA (0.14 cm^3, 1mmol) was added followed by (1*S*)-(+)-camphorsulfonyl chloride (0.25 g, 1mmol). The system was allowed to stay at r.t. and stirred o/n. The mixture was washed with water (10 cm^3) and the organic phase was separated, dried over anhydrous $MgSO_4$ and solvent removed, which was purified by silica gel column chromatography using (EtOAc:Hexane:MeOH 1:1:1), to give *N*-(2-amino-1,2-diphenyl-ethyl)-C-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-methanesulfonamide **173** as a white solid compound (0.25 g, 0.60 mmol, 60%). Mp 58-61 °C; $[\alpha]_D^{25}$ = +40.3 (*c* 0.12, $CHCl_3$); ν_{max}(neat) 3276, 2954, 1735, 1601, 1453, 1321, 1143, 1049, 919, 765, 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.25-7.22 (3H, m, ArH), 7.21-7.18 (4H, m, ArH), 7.17-7.12 (3H, m, ArH), 6.60 (1H, br s, NH), 4.60 (1H, m, C*H*Ph), 4.25 (1H, d, *J* 6.9, C*H*Ph), 2.63 (1H, d, *J* 15.0, CH_aH_b), 2.47 (1H, d, *J* 15.0, CH_aH_b), 2.44 (1H, m, -CH-camphor), 1.99 (4H, m, 2 x CH_2(camphor)), 1.87

(1H, m, -CH_2(camphor)), 1.67 (1H, br s, NH), 1.37 (1H, m, -CH_2(camphor)), 0.78 (3H, s, CH_3), 0.39 (3H, s, CH_3); δC (75 MHz,$CDCl_3$) 216.65 (C=O), 141.43 (C), 139.23 (C), 128.48 (2 x CH), 128.28 (2 x CH), 127.68 (CH), 127.60 (2 x CH), 127.51 (CH), 127.17 (2 x CH), 64.93 (C*H*Ph), 60.66 (C*H*Ph), 59.39, 51.68 (CH_2), 48.17, 43.03 (CH_2), 42.43 (CH_2), 27.24 (CH_2), 26.73 (CH_2), 19.50 (CH_3), 19.24 (CH_3). *m/z* (ESI) 425.0 $[M-H]^-$. HRMS found (ESI) 427.2049 ($C_{24}H_{31}N_2O_3S$ $[M+H]^+$ requires 427.2050, error = 0.2 ppm).

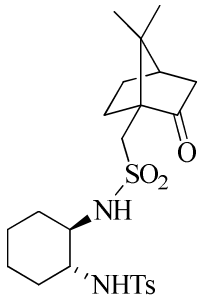
Synthesis of *N*-[2-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-ylmethanesulfonylamino)-1,2-diphenyl-ethyl]-4-methyl-benzenesulfonamide(171):



This compound is novel. The procedure is as same as for preparation of compound *N*-(2-amino-1,2-diphenyl-ethyl)-C-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-methanesulfonamide **173** using (*R*,*R*)-TsDPEN (513 mg, 1.40 mmol), TEA (0.21 cm^3, 1.50 mmol), DCM (15 cm^3) was added to (*1S*)-(+)-camphorsulfonyl chloride (0.38 g, 1.50 mmol) to give *N*-[2-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-ylmethanesulfonylamino)-1,2-diphenyl-ethyl]-4-methyl-benzenesulfonamide **171** as a white solid compound (0.49 g, 0.83 mmol, 61%). Mp 93-96 °C; $[\alpha]_D^{24}$ = +56.1 (*c* 0.10, $CHCl_3$); ν_{max}(neat) 3670, 2979, 1733, 1382, 1242, 1056, 892, and 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.48 (2H, d, *J* 6.3, Ar-H), 7.13-7.08 (4H, m, Ar-H), 7.04-6.93 (5H, m, Ar-H), 6.83-6.81 (2H, m, Ar-H), 6.58 (1H, d, *J* 7.2, Ar-H), 5.6 (1H, d *J* 3.3,

NH), 4.59 (1H, t, *J* 7.2, C*H*Ph), 4.52 (1H, q, *J* 3.3, C*H*Ph), 2.67 (1H, d, *J* 11.4, CH_aH$_b$), 2.59 (1H, d, *J* 11.4, CH$_a$*H$_b$*), 2.34 (3H, s, -CH$_3$-tosyl), 2.23 (1H, m, -CH-camphor), 1.92-1.86 (4H, m, 2 x CH$_2$-camphor), 1.38 (1H, t, *J* 7.2, CH$_2$-camphor), 1.26 (1H, t, *J* 5.4, CH$_2$-camphor), 0.76 (3H, s, CH$_3$), 0.30 (3H, s, CH$_3$); δ_C (75 MHz,CDCl$_3$) 216.69 (C=O), 142.96 (C), 137.05 (C), 136.64 (2 x C), 136.61 (2 x C), 129.18 (2 x CH), 128.57 (2 x CH), 128.24 (CH), 128.09 (2 x CH), 127.96 (2 x CH), 127.89 (2 x CH), 127.57 (CH), 127.24 (2 x CH), 63.29 (C*H*Ph), 62.19 (C*H*Ph), 59.47 (C), 52.19 (CH$_2$), 48.74 (C), 43.01 (CH$_2$), 42.95 (CH), 27.62 (CH$_2$), 26.98 (CH$_2$), 21.46 (CH$_3$), 19.40 (CH$_3$), 19.08 (CH$_3$). *m/z* (ESI) 579.0 $[M-H]^-$. HRMS found(ESI) 579.1975 ($C_{31}H_{37}N_2O_5S_2$ $[M-H]^-$ requires 579.1983, error = 2.1 ppm).

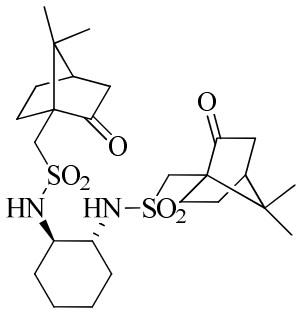
Synthesis of *N*-[2-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-ylmethanesulfonylamino)-cyclohexyl]-4-methyl-benzenesulfonamide (172):



This compound is known and fully characterized[106], The procedure is as same as for preparation of compound *N*-(2-amino-1,2-diphenyl-ethyl)-C-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-methanesulfonamide **173**, using (*R*,*R*)-(−)-*N*-*p*-tosyl-1,2-cyclohexanediamine (380 mg, 1.40 mmol), TEA (0.21 cm^3, 1.50 mmol), DCM (15 cm^3) (1*S*)-(+)-camphorsulfonyl chloride (0.38 g, 1.5 mmol) to give *N*-[2-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-ylmethanesulfonylamino)-cyclohexyl]-4-methyl-benzenesulfonamide **172** as a white solid (0.49 g, 1.02 mmol, 73%). Mp 67-

69 °C; $[\alpha]_D^{24}$ = +27.4 (*c* 1.0, $CHCl_3$), lit[17] $[\alpha]_D^{22}$= 23.3 (*c* 1.2, $CHCl_3$); ν_{max}(neat) 3275, 2938, 1737, 1599, 1444, 1322, 1152, 1090, and 901 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.78 (2H, d, *J* 8.4, Ar*H*), 7.30 (2H, d, *J* 8.4, Ar*H*), 5.41 (1H, br s, N*H*), 5.13 (1H, d, *J* 6.8, N*H*), 3.39 (1H, d, *J* 15.2, CH_aH_b), 3.12 (1H, m, C*H*NHTs), 3.02 (1H, d, *J* 15.2, CH_aH_b), 2.84-2.76 (1H, m, C*H*NHSO$_2$), 2.42 (3H, s, CH_3-Ar), 2.30-1.15 (15H, m, $(CH_2)_4$, $(CH_2)_2$ $CHCH_2$), 1.03 (3H, s, C(*CH*$_3$)), 0.903 (3H, s, C(C*H*$_3$); δC (75 MHz,$CDCl_3$) 216.77 (C=O), 143.21 (C), 137.33 (C), 129.61 (2 x CH), 127.13 (2 x CH), 59.29 (C), 57.31 (CH), 56.88 (CH), 51.23 (CH_2), 48.72 (C), 42.90 (CH_2), 42.66 (CH), 33.59 (CH_2), 33.33 (CH_2), 27.08 (CH_2), 26.52 (CH_2), 24.49 (CH_2), 24.12 (CH_2), 21.51 (CH_3), 19.80 (CH_3), 19.61 (CH_3). *m/z* (ESI) 481.0 $[M-H]^-$. HRMS found (ESI) 483.1830 ($C_{23}H_{35}N_2O_5S_2$ $[M+H]^+$ requires 483.1836, error = 1.4 ppm).

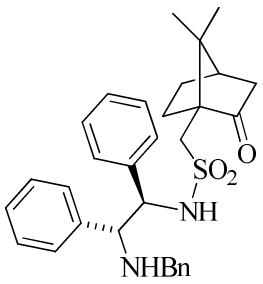
Synthesis of C-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-*N*-[2-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-ylmethanesulfonylamino)-cyclohexyl]-methanesulfonamide (174):



This compound is novel. The procedure is as same as for preparation of compound *N*-(2-amino-1,2-diphenyl-ethyl)-C-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-methanesulfonamide **173**, using (*R*,*R*)-1,2-diaminocyclohexane (432 mg, 3.78 mmol), TEA (0.56 cm^3, 4.03 mmol), DCM (15 cm^3) was added to (1*S*)-(+)-

camphorsulfonyl chloride (1.01 g, 4.03 mmol) to give C-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-*N*-[2-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-ylmethanesulfonylamino)-cyclohexyl]-methanesulfonamide **174** as a white solid (0.86 g, 1.6 mmol, 69%). Mp 188-190 °C; $[\alpha]_D^{25}$ = +52.3 (*c* 0.11, $CHCl_3$); ν_{max}(neat) 3221, 2932, 1735, 1466, 1313, 1200, 1181, 1067, 1046, 898, 757, 709 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.44 (2H, d, *J* 4.8, 2 x N*H*), 3.55 (2H, d, *J* 11.4, CH_2), 3.28 (2H, m, 2 x C*H*), 2.99 (2H, d, *J* 11.1, CH_2), 2.41-1.25 (22H, m, (CH_2)$_4$, 2 x (CH_2)$_2$ C*H*CH_2), 1.07 (6H, s, 2 x CH_3), 0.89 (6H, s, 2 x CH_3); δ_C (75 MHz,$CDCl_3$) 216.99 (2 x CO), 58.99 (2 C), 56.56 (2 x CH), 51.10 (2 x CH_2), 48.36 (2 x C), 43.09 (2 x CH_2), 42.73 (2 x CH), 34.09 (2 x CH_2), 27.01 (2 x CH_2), 25.31 (2 x CH_2), 24.06 (2 x CH_2), 19.79 (2 x CH_3), 19.66 (2 x CH_3). *m/z* (ESI) 541.0 $[M-H]^-$. HRMS found (ESI) 541.2413 ($C_{26}H_{41}N_2O_6S_2$ $[M-H]^-$ requires 541.2412, error = 0.3 ppm).

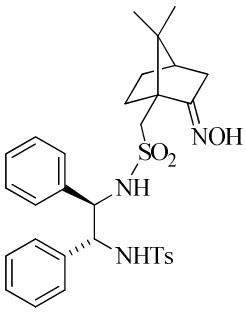
Synthesis of *N*-(2-benzylamino-1,2-diphenyl-ethyl)-*C*-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-methanesulfonamide (175):



This compound is novel**.** To a stirred solution of *N*-(2-amino-1,2-diphenyl-ethyl)-C-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-methanesulfonamide **173** (0.48 g, 1.13 mmol) and molecular sieves (1.0 g) in dry MeOH (8.0 cm^3), was added benzaldehyde (0.18 cm^3, 1.25 mmol) followed by 3 drops of glacial AcOH, the reaction was followed by TLC until the imine was formed (3h) and then $NaBH_3CN$

(0.21 g, 3.30 mmol) was added and the reaction left to stirrer o/n at r.t. The molecular sieves were filtered through filter paper and the solution was concentrated under reduced pressure to remove the MeOH. The residue was dissolved in $CHCl_3$ (50 cm^3), washed with saturated $NaHCO_3$ solution (30 cm^3) and then dried over anhydrous $MgSO_4$. The solvent was removed to give a crude solid compound, which was purified by silica gel column chromatography (EtOAc:Hexane 30:70), to give *N*-(2-benzylamino-1,2-diphenyl-ethyl)-C-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-methanesulfonamide **175** as a white solid (0.48 g, 0.93 mmol, 83%). Mp 52-55 °C; $[\alpha]_D^{24}$ = +22.5 (*c* 0.12, $CHCl_3$); ν_{max}(neat) 3662, 2964, 1736, 1454, 1328, 1145, 1048, 918 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.37-7.28 (2H, m, ArH), 7.26-7.23 (4H, m, ArH), 7.18-7.12 (7H, m, ArH), 7.09-7.06 (2H, m, ArH), 6.54 (1H, d, *J* 7.2, NH), 4.62 (1H, t, *J* 7.8, C*H*Ph), 3.87 (1H, d, *J* 8.4, C*H*Ph), 3.73 (1H, d, *J* 13.5, CH_aH_b), 3.49 (1H, d, *J* 13.5, CH_aH_b), 2.68 (1H, d, *J* 15.0, CH_cH_d), 2.40 (1H, d, *J* 15.0, CH_cH_d), 2.29-1.35 (7H, m, $(CH_2)_2CHCH_2$-camphor), 0.75 (3H, s, CH_3), 0.35 (3H, s, CH_3); δ_C (75 MHz,$CDCl_3$) 139.93 (C), 139.35 (C), 138.49 (C), 128.32 (4 x CH), 128.15 (4 x CH), 128.05 (2 x CH), 127.99 (2 x CH), 127.68 (CH), 127.47 (CH), 126.88 (CH), 66.45 (CHPh), 64.09 (CHPh), 59.11 (C), 51.16 (CH_2), 50.84 (CH_2), 48.34 (C), 42.76 (CH_2), 42.48 (CH), 26.91 (CH_2), 26.86 (CH_2), 19.40 (CH_3), 19.21 (CH_3). *m/z* (ESI) 517.2 $[M+H]^+$. HRMS found (ESI) 517.2517 ($C_{31}H_{37}N_2O_3S$ $[M+H]^+$ requires 517.2519, error = 1.2 ppm).

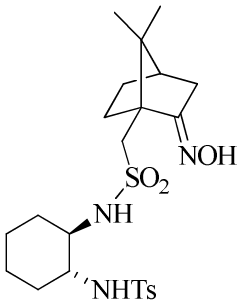
Synthesis of *N*-[2-(2-hydroxyimino-7,7-dimethyl-bicyclo[2.2.1]hept-1-ylmethanesulfonylamino)-1,2-diphenyl-ethyl]-4-methyl-benzenesulfonamide (179):



This compound is novel. Hydroxylamine hydrochloride[167] (0.171 g, 2.46 mmol), *N*-[2-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-ylmethanesulfonylamino)-1,2-diphenyl-ethyl]-4-methyl-benzenesulfonamide **171** (0.66 g, 1.13 mmol) and pyridine (0.16 cm^3, 2.07 mmol), were heated under reflux in EtOH (10 cm^3) for 5 h. After cooling most of the EtOH in the reaction mixture was removed. Water was then added causing the crude oxime to precipate from the solution as a white crystals which was isolated by filtration and washed by distilled water. The crystals materials was collected, dried under vacuum to afford *N*-[2-(2-hydroxyimino-7,7-dimethyl-bicyclo[2.2.1]hept-1-ylmethanesulfonylamino)-1,2-diphenyl-ethyl]-4-methyl-benzenesulfonamide **179** as a white fine solid (0.64 g, 1.07 mmol, 91%). Mp 120-124 °C; $[\alpha]_D^{24}$ = -24.5 (*c* 0.10, $CHCl_3$); ν_{max}(neat) 3261, 2294, 1457, 1319, 1147, 1057, 926, 811, 768, 768 and 698 cm^{-1}; δ_H (100 MHz, $CDCl_3$) 8.16 (1H, s, N*OH*), 7.45 (2H, d, *J* 8.4, ArH), 7.18-7.09 (4H, m, ArH), 7.03-6.94 (6H, m, ArH), 6.85-6.82 (2H, m, ArH), 6.01 (1H, br, s, NH), 4.68 (2H, d, *J* 6.9, 2 x C*H*Ph), 2.76 (1H, d, *J* 15.0, CH_aH$_b$), 2.55 (1H, d, *J* 15.0, CH$_a$$H_b$), 2.30 (3H, s, CH_3), 2.10-1.81 (6H, m, 3 x CH_2-camphor), 1.32-1.25 (1H, m, CH-camphor), 0.73 (3H, s, CH_3), 0.46 (3H, s, CH_3), 0.31 (1H, br s, *NH*); δ_C (75 MHz,$CDCl_3$) 167.31 (C), 143.07 (C), 137.24 (C), 137.01 (C), 136.89 (C), 129.07 (2 x CH), 128.40 (2 x CH), 128.36 (2 x CH), 127.98 (CH), 127.77 (2 x CH), 127.67 (2 x CH), 127.38 (CH), 127.05 (2 x CH), 62.92 (*CH*Ph), 61.93 (*CH*Ph), 54.58 (CH_2), 53.09 (C), 50.71 (C), 42.83 (CH), 33.01 (CH_2),

30.62 (CH_2), 27.39 (CH_2), 21.26 (CH_3), 19.35 (CH_3), 18.46 (CH_3). *m/z* (ESI) 594.0 $[M–H]^-$. HRMS found (ESI) 594.2109 ($C_{31}H_{36}N_3O_5S_2$ $[M–H]^-$ requires 594.2102, error = 1.1 ppm).

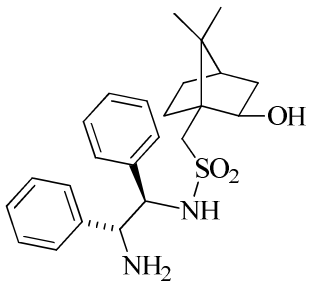
Synthesis of *N*-[2-(2-hydroxyimino-7,7-dimethyl-bicyclo[2.2.1]hept-1-ylmethanesulfonylamino)-cyclohexyl]-4-methyl-benzenesulfonamide (180):



This compound is novel. The procedure is as same as for preparation of compound *N*-[2-(2-hydroxyimino-7,7-dimethyl-bicyclo[2.2.1]hept-1-ylmethanesulfonylamino)-1,2-diphenyl-ethyl]-4-methyl-benzenesulfonamide **179**, using hydroxylamine hydrochloride (97.8 mg, 1.35 mmol), *N*-[2-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-ylmethanesulfonylamino)-cyclohexyl]-4-methyl-benzenesulfonamide (300 mg, 0.622 mmol), dry EtOH (10 cm^3), pyridine (0.08 cm^3, 0.94 mmol), to give *N*-[2-(2-hydroxyimino-7,7-dimethyl-bicyclo[2.2.1]hept-1-ylmethanesulfonylamino)-cyclohexyl]-4-methyl-benzenesulfonamide **180** as a white solid (0.19 g, 0.38 mmol, 62%). Mp 118-122 °C; $[\alpha]_D^{24}$ = -13.5 (*c* 0.10, $CHCl_3$); ν_{max}(neat) 3244, 2938, 1595, 1440, 1317, 1184, 1091, 928, 905, 843 and 665cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.32 (1H, s, N*OH*), 7.76 (2H, d, *J* 8.1, ArH), 7.29 (2H, d, *J* 8.1 ArH), 6.09 (1H, d, *J* 6.3, NH), 5.59 (1H, d, *J* 6.3, NH), 3.48 (1H, d, *J* 15.0, CH), 3.15 (1H, d, *J* 15.0, CH), 2.99-2.89 (1H, m, C$H_a$$H_b$), 2.66-2.62 (1H, m, C$H_a$$H_b$), 2.43 (3H, s, CH_3), 2.28-1.14 (15H, m, $(CH_2)_2CHCH_2$-camphor, $(CH_2)_4$-hexyl), 0.97 (3H, s, CH_3), 0.87 (3H, s,

CH_3); δ_C (100 MHz,$CDCl_3$) 167.83 (C), 143.11 (C), 137.55 (C), 129.69 (2 x CH), 127.07 (2 x CH), 57.07 (CH), 56.71 (CH), 54.90 (2 x CH_2), 53.02 (C), 50.81 (C), 43.03 (CH), 33.95 (CH_2), 33.30 (CH_2), 33.18 (CH_2), 29.52 (CH_2), 27.33 (CH_2), 24.33 (CH_2), 21.53 (CH_3), 19.49 (CH_3), 18.87 (CH_3). *m/z* (ESI) 496.0 $[M–H]^-$. HRMS found (ESI) 496.1942 ($C_{23}H_{34}N_3O_5S_2$ $[M–H]^-$ requires 496.1945, error = 0.7 ppm).

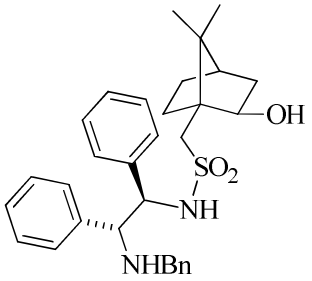
Synthesis of *N*-(2-amino-1,2-diphenyl-ethyl)-C-(2-hydroxy-7,7-dimethyl-bicyclo[2.2.1]hept-1-yl)-methanesulfonamide (187):



This compound is novel. In a three-necked flask[168] equipped with a reflux condenser, *N*-(2-amino-1,2-diphenyl-ethyl)-C-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-methanesulfonamide **173** (2.05 g, 4.80 mmol) was dissolved in a mixed solvent (10 cm^3, MeOH/THF 1:1). To this, $NaBH_4$ (0.70 g, 18.2 mmol) was added slowly. The mixture was stirred for another 4 h. The reaction mixture was quenched with saturated aqueous ammonium chloride, and the solid was filtered. The filtrate was extracted with DCM (3 x 10 cm^3). The organic phase was washed with water (3 x 10 cm^3) and was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The crude product was recrystallized from acetone and n-hexane to give *N*-(2-amino-1,2-diphenyl-ethyl)-C-(2-hydroxy-7,7-dimethyl-bicyclo[2.2.1]hept-1-yl)-methanesulfonamide **187** as a white crystals (1.96 g, 4.6 mmol, 91%). Mp 66-69 °C; $[\alpha]_D^{25}$ = -47.8 (*c* 0.10, $CHCl_3$); ν_{max}(neat) 3510, 2951, 1602, 1453, 1389, 1371,

1138, 1074, 1057, 762 and 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.44-7.42 (4H, m, ArH), 7.40-7.35 (4H, m, ArH), 7.33-7.29 (2H, m, ArH), 6.10 (1H, br s, NH), 4.56 (1H, d, *J* 4.3, *CH*Ph), 4.40 (1H, d, *J* 4.3, *CH*Ph), 3.92-3.88 (1H, m, C*H*), 2.59 (1H, d, *J* 13.6, C$H_a$$H_b$), 1.89 (1H, d, *J* 13.6, $CH_a$$H_b$), 1.71-1.33 (7H, m, $(CH_2)_2CHCH_2$-camphor), 1.03-0.96 (1H, m, N*H*), 0.81 (3H, s, CH_3), 0.49 (3H, s, CH_3); δ_C (100 MHz,$CDCl_3$) 141.84 (C), 139.98 (C), 128.77 (2 x CH), 128.72 (2 x CH), 128.15 (CH), 127.86 (CH), 126.77 (2 x CH), 126.67 (2 x CH), 76.47 (*CH*Ph), 63.33 (*CH*Ph), 59.88 (CH), 52.18 (CH_2), 50.01 (C), 48.31 (C), 44.28 (CH), 38.77 (CH_2), 30.47 (CH_2), 27.11 (CH_2), 20.09 (CH_3), 19.53 (CH_3). *m/z* (ESI) 427.0 $[M–H]^-$. HRMS found (ESI) 429.2206 ($C_{24}H_{33}N_2O_3S$ $[M+H]^+$ requires 429.2206, error = 0 ppm).

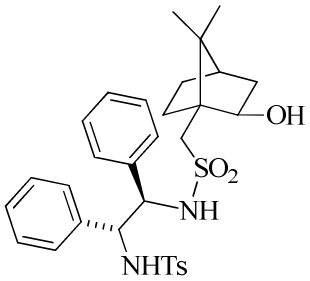
Synthesis of *N*-(2-benzylamino-1,2-diphenyl-ethyl)-C-(2-hydroxy-7,7-dimethyl-bicyclo[2.2.1]hept-1-yl)-methanesulfonamide (188):



This compound is novel. The procedure is as same as for preparation of compound *N*-(2-amino-1,2-diphenyl-ethyl)-C-(2-hydroxy-7,7-dimethyl-bicyclo[2.2.1]hept-1-yl)-methanesulfonamide **187**, using *N*-(2-benzylamino-1,2-diphenyl-ethyl)-C-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-yl)-methanesulfonamide **175** (280 mg, 0.54 mmol), MeOH/THF 1:1, 10 cm^3), was added $NaBH_4$ (0.78 mg, 2.06 mmol) to give *N*-(2-benzylamino-1,2-diphenyl-ethyl)-C-(2-hydroxy-7,7-dimethyl-bicyclo[2.2.1]hept-1-yl)-methanesulfonamide **188** as a white solid compound (0.24 g, 0.46 mmol, 85%). Mp 65-68 °C; $[\alpha]_D^{25}$ = -40.6 (*c* 0.10, $CHCl_3$); ν_{max}(neat) cm^{-1}

3255, 2949, 1453, 1389, 1204, 1059, 1027, 845, and 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.32-7.21 (13H, m, ArH), 7.13 (2H, , d, *J* 7.2, ArH), 6.1 (1H, br s, NH), 4.53 (1H, d, *J* 6.8, *CHPh*), 3.94 (1H, d, *J* 6.2, *OH*), 3.52 (1H, d, *J* 6.8, *CH*Ph), 3.63 (1H, d, *J 13.2*, CH_aH_b), 3.45 (1H, d, *J 13.2*, CH_aH_b), 2.73 (1H, d, *J 13.6*, CH_cH_d), 1.90 (1H, d, *J 13.6*, CH_cH_d), 1.72-1.64 (2H, m, CH_2-camphor), 1.59-1.56 (2H, m, CH_2-camphor), 1.39-1.35 (2H, t, *J* 6.8, CH_2-camphor, 1.02-0.96 (1H, m, CH-camphor), 0.82 (3H, s, CH_3), 0.43 (3H, s, CH_3); δ_C (100 MHz,$CDCl_3$) 139.15 (2C), 138.79 (C), 128.65 (2 x CH), 128.52 (2 x CH), 128.44 (2 x CH), 128.01 (CH), 127.94 (3 x CH), 127.70 (2 x CH), 127.44 (2 x CH), 127.15 (CH), 76.24 (*CH*Ph), 65.76 (*CH*Ph), 63.17 (CH), 52.70 (C), 50.72 (C), 50.0 (CH_2), 48.33 (CH_2), 44.20 (CH), 38.76 (CH_2), 30.32 (CH_2), 26.99 (CH_2), 20.01 (CH_3), 19.55 (CH_3). *m/z* (ESI) 517.0 $[M-H]^-$. HRMS found (ESI) 519.2669 ($C_{31}H_{39}N_2O_3S$ $[M+H]^+$ requires 519.2676, error = 1.4 ppm).

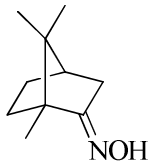
Synthesis of *N*-[2-(2-hydroxy-7,7-dimethyl-bicyclo[2.2.1]hept-1-ylmethanesulfonylamino)-1,2-diphenyl-ethyl]-4-methyl-benzenesulfonamide (189):



This compound is novel. The procedure is as same as for preparation of compound *N*-(2-amino-1,2-diphenyl-ethyl)-C-(2-hydroxy-7,7-dimethyl-bicyclo[2.2.1]hept-1-yl)-methanesulfonamide **187**, using *N*-[2-(7,7-dimethyl-2-oxo-bicyclo[2.2.1]hept-1-ylmethanesulfonylamino)-cyclohexyl]-4-methyl-benzenesulfonamide **171** (504 mg, 0.87 mmol), MeOH/THF 1:1, 10 cm^3), was added $NaBH_4$ (125 mg, 3.3 mmol) to

give *N*-[2-(2-hydroxy-7,7-dimethyl-bicyclo[2.2.1]hept-1-ylmethanesulfonylamino)-1,2-diphenyl-ethyl]-4-methyl-benzenesulfonamide **189** as a white solid compound (0.31 g, 0.53 mmol, 62%). Mp 107-110 °C; $[\alpha]_D^{26}$ = +5.85 (*c* 0.10, $CHCl_3$); ν_{max}(neat) cm^{-1} 3265, 2952, 1455, 1315, 1206, 1155, 1090, 1059, 930, 764, 750 and 669 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.45 (2H, d, *J* 8.1, ArH), 7.20-7.08 (5H, m, ArH), 7.04-6.95 (5H, m, ArH), 6.80 (2H, d, *J* 6.9, ArH), 5.96 (1H, d, *J* 7.5, NH), 4.70 (1H, d, *J* 7.2, *CH*Ph), 4.59 (1H, d, *J* 7.3, *CH*Ph), 4.04-3.99 (1H, m, C*H*), 3.25 (1H, d, *J 3.6*, OH), 3.02 (1H, d, *J* 13.8, CH_aH_b), 2.30 (3H, s, CH_3), 2.17 (1H, d, *J* 13.8, CH_aH_b), 1.72-1.22 (6H, m, 3 x CH_2-camphor), 1.07-0.99 (IH, m, N*H*), 0.86 (3H, s, CH_3), 0.46 (3H, s, CH_3); δ_C (75 MHz,$CDCl_3$) 144.33 (C), 141.05 (C), 140.41 (C), 139.85 (C), 130.90 (2 x CH), 130.06 (2 x CH), 129.85 (2 x CH), 129.69 (4 x CH), 129.49 (CH), 129.09 (CH), 128.57 (2 x CH), 77.88 (CHPh), 64.53 (CHPh), 64.17 (CH), 55.20 (CH_2), 52.01 (C), 50.07 (C), 46.13 (CH), 40.79 (CH_2), 32.08 (CH_2), 28.84 (CH_2), 22.38 (CH_3), 21.52 (CH_3), 21.11 (CH_3). *m/z* (ESI) 605.0 $[M+Na]^+$. HRMS found (ESI) 605.2135 ($C_{31}H_{38}N_2NaO_5S_2$ $[M+Na]^+$ requires 605.2114, error = 3.3 ppm).

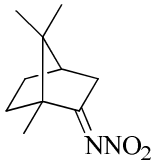
Synthesis of (1*R*,4*S*)-(-)-camphor oxime (178):



This compound is known and fully characterized.[167] Hydroxylamine hydrochloride (0.20 g, 2.83 mmol), (1*R*)-(+)-camphor (0.21 g, 1.37 mmol) and pyridine (0.16 cm^3, 1.95 mmol) were heated under reflux in EtOH (10 cm^3) for 5 h. After cooling, most of the EtOH in the reaction mixture was removed in *vacuo*. Water was then added, causing the crude oxime to precipitate from the solution as colourless crystals, which

were isolated by filtration and washed with distilled water. The crystalline material was collected, dried under vacuum and recrystallized from absolute EtOH to afford (1*R*,4*S*)-(-)-camphor oxime **178** (0.1 g, 0.60 mmol, 44%); Mp 119-121 °C; $[\alpha]_D^{20}$ = -30 (*c* 1.0, $CHCl_3$); ν_{max}(neat) cm^{-1} 3293,1684 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.30 (1H, s, N*OH*), 2.56 (1H, dt, *J* 17.9, 3.9, CH_2-camphor), 2.06 (1H, d, *J* 17.9, CH_2-camphor), 1.94-1.66 (3H, m, CH_2 and CH-camphor), 1.51-1.41 (1H, m, CH_2-camphor), 1.29-1.20 (1H, m, CH_2-camphor), 1.03 (3H, s, CH_3), 0.92 (3H, s, CH_3), 0.81 (3H, s, CH_3); δ_C (75 MHz,$CDCl_3$) 170.13 (C), 51.79 (C), 48.25 (C), 43.71 (CH), 33.04 (CH_2), 32.62 (CH_2), 27.06 (CH_2), 19.43 (CH_3), 18.51 (CH_3), 11.09 (CH_3). *m/z* (ESI) 168.0 $[M+H]^+$. HRMS found (ESI) 168.1309 ($C_{10}H_{17}NO$ $[M+H]^+$ requires 168.1310, error = 1.4 ppm).

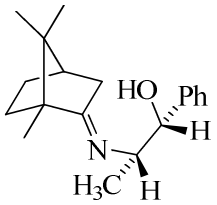
Synthesis of (1*R*,4*S*)-(-)-camphor nitrimine (183):



This compound is known and fully characterized.[167] (1*R*, 4*S*)-(-)-Camphor oxime (0.15 g, 0.91 mmol) in glacial AcOH (5.0 cm^3) was treated with 5% aqueous sodium nitrite (2.5 cm^3). A bright yellow colour developed and dispersed over 30 min. After a further 1.5 h, the crude product was precipitated as a colourless solid by the addition of water and isolated by filtration. After drying under vacuum, the crude product was recrystallized from EtOH to afford (1*R*, 4*S*)-(-)-camphor nitrimine **183** as a colourless crystalline solid (0.013g, 0.067 mmol, 44%). Mp 42-45 °C; $[\alpha]_D^{20}$ = -10 (*c* 1.0, $CHCl_3$); ν_{max}(neat) 1645 and 1569 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.69 (1H, td, *J* 18.6, 4.8, CH), 2.13 (1H, d, *J* 18.6, CH), 2.05-1.79 (3H, m, CH_2 and CH), 1.65-

1.51 (1H, m, CH), 1.37-1.28 (1H, m, CH), 1.04 (3H, s, CH_3), 0.98 (3H, s, CH_3), 0.88 (3H, s, CH_3); δ_C (75 MHz,$CDCl_3$) 189.80 (C), 51.79 (C), 48.25 (C), 43.71 (CH), 33.04 (CH_2), 32.62 (CH_2), 27.06 (CH_2), 19.43 (CH_3), 18.51 (CH_3), 11.09 (CH_3). found: C, 60.47; H, 8.14; N, 14.07. Calculated for $C_{10}H_{16}N_2O_2$: C, 60.58; H, 8.17; N, 14.01.

Synthesis of (1*R*, 1′*R*, 2*S*, 4′*R*)-1-phenyl-2-(1,7,7-trimethylbicyclo[2.2.1]hept-2-ylideneamino)propan-1-ol (185):

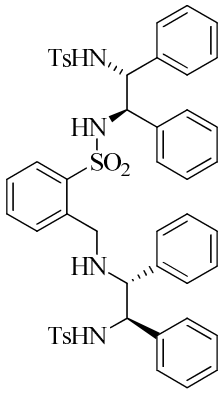


This compound is known and fully characterized.[115] In a round-bottomed flask, containing a minimal amount of pre-dried 4 A molecular sieves, (1*R*, 4*S*)-(-)-camphor nitrimine (0.12 g, 0.59 mmol) was dissolved in 1,2-dichloroethane (20 cm^3). To the resulting solution was added norphedrine (0.08 g, 0.54 mmol) and the reaction was heated under reflux for 24 h under a nitrogen atmosphere. The reaction was then gravity filtered and the filtrate was washed with $CHCl_3$ (20 cm^3). The resulting solution was extracted with a saturated aqueous solution of $NaHCO_3$ (3x 15 cm^3). The organic layer was washed with a saturated aqueous solution of brine (20 cm^3) and dried over anhydrous $MgSO_4$. The solvents was removed by rotary evaporation and crude product was purified by column chromatography (EtOAc:Hexane, 30:70), to give ((1*R*,1′*R*,2*S*,4′*R*)-1-phenyl-2-(1,7,7-trimethylbicyclo[2.2.1]hept-2-ylideneamino)propan-1-ol **185** as a colourless crystals (0.12 g, 0.42 mmol, 71%). Mp 84-85 °C; $[\alpha]_D^{20}$ = -2.9 (*c* 1.0, MeOH); ν_{max}(neat) 3200, 288, 1668, 1043 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.38-7.24 (5H, m, ArH), 4.64

(1H, d, *J* 5.2, OH(*CH*)Ph), 3.55-3.49 (1H, m, CH_3(*CH*)NR), 3.36 (1H, br s, O*H*), 2.27-2.04 (2H, m, CH_2-camphor), 1.89-1.68 (3H, m, CH_2-camphor and C*H*), 11.09-1.04 (2H, m, CH_2-camphor), 0.96 (3H, d, *J* 6.4, *CH*$_3$ (CH)NR), 0.91 (3H, s, CH_3), 0.87 (3H, s, CH_3), 0.70 (3H, s, CH_3); δ_C (75 MHz,$CDCl_3$) 141.93 (C), 127.87 (2 x CH), 127.02 (CH), 126.42 (2 x CH), 76.53 (CH), 62.01 (CH), 46.80 (C), 43.42 (CH), 35.44 (C), 31.88 (C), 31.27 (CH_2), 27.33 (CH_2), 26.64 (CH_2), 19.37 (2 x CH_3), 18.92 (CH_3), 11.47 (CH_3). *m/z* (ESI) 486.1 $[M+H]^+$. HRMS found (ESI) 286.2163 ($C_{19}H_{27}NO$ $[M+H]^+$ requires 286.2152, error = 3.8 ppm). Analysis calculated for $C_{19}H_{27}NO$: C, 79.95; H, 9.54; N, 4.91. Found: C, 79.88; H, 9.69; N, 5.12.

3.4. Procedures for section 2.4

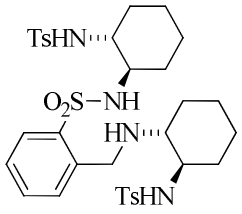
Synthesis of *N*-Tosyl-*N′*-((2-methyl(o-(p-tosyl-1,2-diphenylethyl)-aminophenyl)sulfonyl)-1′,2′-diphenyl-1′,2′-diaminoethane (193):



This compound is novel. 2-Formylbenzenesulfonyl chloride[119] **192** (0.215 g, 1.05 mmol) was dissolved in DCM (5 cm^3) and stirred at r.t. for 10 min, then (*R*,*R*)-TsDPEN (0.771 g, 2.10 mmol) was added followed by TEA (0.3 cm^3, 2.10 mmol) and the reaction kept stirring for o/n. The reaction diluted with $CHCl_3$, washing with water (1 cm^3), brine (1 cm^3), drying over anhydrous $MgSO_4$ and then solvent removed to give the imine (0.96 g, 1.09 mmol, 52 %), as a complex mixture and this

was used directly in the next step. To a stirred solution of the imine (0.803 g, 0.91 mmol) in dry THF (20 cm^3) was slowly added 0.5 cm^3 $LiAlH_4$ (1M in THF), The resulting mixture was stirred at r.t. for o/n, the reaction was carefully quenched with water (0.5 cm^3), 15 % NaOH solution (0.5 cm^3) and water (1.5 cm^3), filtered through silica, washed with DCM, the organic layer was separated, dried over anhydrous $MgSO_4$ and then solvent removed. The crude compound was purified by column chromatography (EtOAc:Hexane 1:1) to give *N*-Tosyl-*N*′-((2-methyl(o-(p-tosyl-1,2-diphenylethyl)-aminophenyl)sulfonyl)-1′,2′-diphenyl-1′,2′-diaminoethane **193** as a white solid compound (0.51 g, 0.58 mmol, 64%). Mp 124-128 °C; $[\alpha]_D^{25}$ = + 38.75 (*c* 0.12, $CHCl_3$); ν_{max}(neat) 3254, 3030, 1599, 1455, 1319, 1154, 1091, 1063, 925, 810, 757, 697 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.51-7.36 (8H, m, ArH), 7.23-7.14 (5H, m, ArH), 6.94-6.87 (12H, m, ArH), 6.85 (3H, q, *J* 5.7, ArH), 6.75 (4H, t, *J* 6.6, ArH), 6.11 (1H, d, *J* 4.5, NH), 6.05 (1H, d, *J* 5.1, NH), 4.81 (1H, q, *J* 4.8, C*H*Ph), 4.71 (1H, t, *J* 5.7, C*H*Ph), 4.42 (1H, d, *J* 7.2, C*H*Ph), 4.09 (1H, d, *J* 9.6, CH_aH_b), 3.92 (1H, d, *J* 7.2, C*H*Ph), 3.83 (1H, d, *J* 9.6, CH_aH_b), 2.68 (1H, br s, NH), 2.27 (3H, s, CH_3); 2.24 (3H, s, CH_3), 1.7 (1H, br s, NH); δ_C (75 MHz,$CDCl_3$) 142.84 (2C), 138.32 (C), 137.93 (C), 137.66 (C), 137.18 (C), 137.04 (C), 136.85(C) , 136.39 (C), 136.19 (C), 132.27 (CH), 131.75 (CH), 129.15 (CH), 129.07 (3 x CH), 129.02 (3 x CH), 128.59 (2 x CH), 128.26 (2 x CH), 128.04 (2 x CH), 127.81 (4 x CH), 127.69 (3 x CH), 127.48 (CH), 127.27 (3 x CH), 127.20 (3 x CH), 127.10 (2 x CH), 126.90 (CH), 69.30 (CH), 63.81 (CH), 63.46 (CH), 62.18 (CH), 50.67 (CH_2), 21.36 (CH_3), 21.32 (CH_3). *m/z* (ESI) 885.4 $[M+H]^+$. HRMS found (ESI) 885.2801 ($C_{49}H_{49}N_4O_6S_3$ $[M+H]^+$ requires 885.2809, error 1.1 ppm).

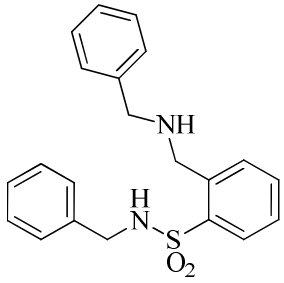
Synthesis of *N*-tosyl-*N′*-(2-methyl(o-(*p*-tosyl-1,2 -diaminocyclohexyl)sulfonyl)-1′,2′-diaminocyclohexane) (178):



This compound is novel, The procedure is as same as for preparation of compound *N*-tosyl-*N′*-((2-methyl(o-(*p*-tosyl-1,2-diphenylethyl)-aminophenyl)sulfonyl)-1′,2′-diphenyl-1′,2′-diaminoethane **193**, using 2-formylbenzenesulfonyl chloride (0.24 g, 1.16 mmol), DCM (5 cm^3), (*R*,*R*)-toluene sulfonyl-1,2-diaminocyclohexane (0.85 g, 2.23 mmol), TEA (0.32 cm^3, 2.32 mmol), 1.3 cm^3 $LiAlH_4$ (1M in THF) to give *N*-tosyl-N′-(2-methyl(o-(*p*-tosyl-1,2-diaminocyclohexyl)sulfonyl)-1′,2′-diaminocyclohexane **194** as a white solid compound (0.65 g, 0.94 mmol, 67%). Mp 118-121 °C; $[\alpha]_D^{25}$ = +11 (*c* 0.10, $CHCl_3$); ν_{max}(neat) 3267, 2933, 1599, 1448, 1319, 1154, 1092, 899, 813, 762, 662 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.96 (1H, dd, *J* 1.6, 7.5, ArH), 7.84 (2H, d, *J* 6.6, ArH), 7.74 (2H, d, *J* 8.1, ArH) 7.75-7.40 (3H, m, ArH), 7.31-7.28 (4H, m, ArH), 5.43 (1H, br s, NH), 4.75 (1H d, *J* 8.7, NH), 4.56 (1H, d, *J* 12.0, C*H*$_a$H$_b$), 3.68 (1H, d, *J* 12.0, CH$_a$*H*$_b$), 3.10 (1H, t, *J* 10.2, CH), 2.98 (1H, d, *J* 8.7, CH), 2.86 (1H, t, *J* 10.8, CH), 2.43 (3H, s, CH_3), 2.41 (3H, s, CH_3), 2.33-2.28 (1H, m, CH), 1.99-96 (16H, m, CH_2-hexyl); δ_C (75 MHz,$CDCl_3$) 143.61 (C), 142.96 (C), 139.97 (C), 138.18 (C), 137.82 (C), 137.13 (C), 132.92 (CH), 132.59 (CH), 129.86 (2 x CH), 129.45 (2 x CH), 128.55 (CH), 127.91 (CH), 127.26 (2 x CH), 126.88 (2 x CH), 62.25 (CH), 57.59 (CH), 57.36 (CH), 56.97 (CH), 50.48 (CH_2), 33.20 (CH_2), 32.99 (CH_2), 31.49 (CH_2), 31.12 (CH_2), 28.88 (CH_2), 24.41 (CH_2), 24.25 (CH_2), 23.76 (CH_2), 21.54 (CH_3), 21.52 (CH_3). *m/z* (ESI) 689.4 $[M+H]^+$.

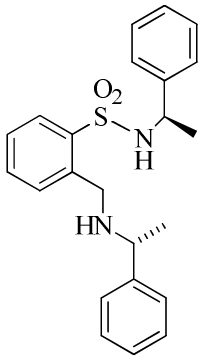
HRMS found (ESI) 689.2500 ($C_{33}H_{45}N_4O_6S_3$ $[M+H]^+$ requires 689.2496, error = 0.6 ppm).

Synthesis of *N*-benzyl-2-(benzylamino-methyl)-benzenesulfonamide (179):



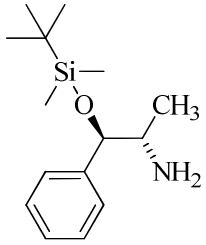
This compound is novel, The procedure is as same as for preparation of compound *N*-tosyl-*N*′-((2-methyl(o-(p-tosyl-1,2-diphenylethyl)-aminophenyl)sulfonyl)-1′,2′-diphenyl-1′,2′-diaminoethane **193**, using 2-formylbenzenesulfonyl chloride (0.52 g, 2.54 mmol), DCM (5 cm^3), benzyl amine (0.55 g, 5.08 mmol), TEA (0.70 cm^3, 5.08 mmol), 0.40 cm^3 $LiAlH_4$ (1M in THF) to give *N*-benzyl-2-(benzylamino-methyl)-benzenesulfonamide **195** as a white solid compound (0.33 g, 0.88 mmol, 74%). Mp 99-103 °C; ν_{max}(neat) 3676, 2988, 1453, 1394, 1230, 1056, 868 and 731 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.05 (1H, d, *J* 5.7, ArH), 7.52-7.43 (2H, m, ArH), 7.30 (1H, m, ArH), 7.21-7.12 (6H, m, ArH), 7.07-7.02 (4H, m, ArH), 6.7 (1H, br s, NH), 4.24 (2H, s, CH_2), 3.94 (2H, s, CH_2), 3.69 (2H, s, CH_2), 1.59 (1H, br s, NH); δ_C (75 MHz,$CDCl_3$) 139.21 (C), 138.43 (C), 136.77 (C), 136.57 (C), 132.67 (CH), 132.41 (CH), 129.74 (CH), 128.62 (2 x CH), 128.37 (2 x CH), 128.09 (3 x CH), 127.92 (2 x CH), 127.39 (CH), 127.36 (CH), 53.65 (CH_2), 52.51 (CH_2), 47.48 (CH_2). *m/z* (ESI) 367.2 $[M+H]^+$. HRMS found 367.1470 ($C_{21}H_{23}N_2O_2S$ $[M+H]^+$ requires 367.1475, error = 1.2 ppm).

Synthesis of 2-(1-benzylamino-ethyl)-*N*-(1-phenyl-ethyl)-benzenesulfonamide (180):



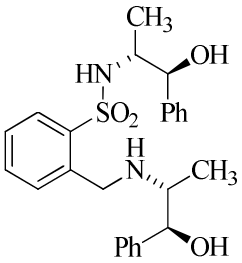
This compound is novel, The procedure is as same as for preparation of compound *N*-tosyl-*N*′-((2-methyl(o-(*p*-tosyl-1,2-diphenylethyl)-aminophenyl)sulfonyl)-1′,2′-diphenyl-1′,2′-diaminoethane **193**, using 2-formylbenzenesulfonyl chloride (0.63 g, 3.06 mmol), DCM (8 cm^3), *R*-(+)-α-methyl benzyl amine (0.80 cm^3, 6.12 mmol), TEA (0.85 cm^3, 6.12 mmol), 1.4 cm^3 $LiAlH_4$ (1M in THF) to give 2-(1-benzylamino-ethyl)-*N*-(1-phenyl-ethyl)-benzenesulfonamide **196** as a white solid compound (0.61 g, 1.55 mmol, 56%). Mp 94-97 °C; $[\alpha]_D^{24}$ = +67.7 (*c* 0.11, $CHCl_3$); ν_{max}(neat) 3676, 2973, 1453, 1394, 1309, 1155, 1065, 756 and 696 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.88 (1H, m, ArH), 7.43-7.23 (7H, m, ArH), 7.16-7.13 (4H, m, ArH), 7.01-6.98 (2H, m, ArH), 4.37 (1H, q, *J* 6.7, CH), 4.03 (1H, d, *J* 12.0, CH_aH_b), 3.93 (1H, d, *J* 12, CH_aH_b), 3.75 (1H, q, *J* 6.6, CH), 1.28 (3H, d, *J* 6.9, CH_3), 1.25 (3H, d, *J* 6.8, CH_3); δ_C (75 MHz,$CDCl_3$) 143.66 (C), 142.36 (C), 140.08 (C), 136.48 (C), 132.27 (CH), 132.03 (CH), 128.88 (CH), 128.57 (2 x CH), 128.19 (2 x CH), 127.68 (CH), 127.29 (CH), 127.12 (CH), 126.50 (2 x CH), , 126.20 (2 x CH), 58.31 (CH), 54.02 (CH), 50.49 (CH_2), 22.79 (CH_3), 22.50 (CH_3). *m/z* (ESI) 395.2 $[M+H]^+$. HRMS found (ESI) 395.1785 ($C_{23}H_{27}N_2O_2S$ $[M+H]^+$ requires 395.1788, error = 0.2 ppm).

Synthesis of 2-(tert-butyl-dimethyl-silanyloxy)-1-methyl-2-phenyl-ethylamine (203):



This compound is known and was fully characterised.[121] To a magnetically stirred solution of *L*-(-)-norphedrine (0.30 g, 1.98 mmol) and imidazole (0.27 g, 3.98 mmol) in DCM (5.0 cm^3) under nitrogen was added TBSCl (0.32 g, 2.08 mmol). The reaction was stirred at r.t. for 3 h, quenched with water (3.0 cm^3) and extracted with DCM (5.0 x 3 cm^3), the combined organic layer were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to yield 2-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-2-phenyl-ethylamine **203** as a viscous yellow compund (0.37 g, 1.39 mmol, 70%); $[\alpha]_D^{28}$ = -35.8, (*c* 0.12, $CHCl_3$); ν_{max}(neat) 2955, 1752, 1471, 1251, 1085, 1061, 915, 773, 743, and 700 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.30-7.7.23 (5H, m, ArH), 4.41 (1H, d, *J* 7.2, CH_3(*CH*)NH_2), 3.05-2.97 (1H, m, Ph(*CH*)O), 1.19 (1H, br s, NH), 1.02 (3H, d, *J* 8.4, C*H*$_3$(CH)NH_2), 0.90 (9H, s, 3 x *CH*$_3$(CH)Si), 0.03 (3H, s, C*H*$_3$-Si), -0.18 (3H, s, C*H*$_3$-Si); δ_C (100 MHz,$CDCl_3$) 141.83 (C), 127.82 (2 x CH), 127.25 (CH), 127.01 (2 x CH), 80.01(CH-OSi), 53.47 (*CH*NH_2), 25.92 (3 x CH_3-C), 18.87 (*CH*$_3$CHNH_2), 18.143 (CH_3), -4.65(CH_3-Si), -5.08 (CH_3-Si). *m/z* (ESI) 266.1 $[M+H]^+$. HRMS found(ESI) 266.1930 ($C_{15}H_{28}NOSi$ $[M+H]^+$ requires 266.1935, error = 1.7 ppm).

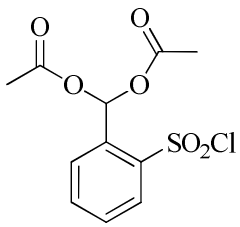
Synthesis of *N*-(2-hydroxy-1-methyl-2-phenyl-ethyl)-2-[(2-hydroxy-1-methyl-2-phenyl-ethylamino)-methyl]-benzenesulfonamide (204):



This compound is novel. 2-Formylbenzenesulfonyl chloride[119] (0.44 g, 2.13 mmol) was dissolved in DCM (20 cm^3), then 2-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-2-phenyl-ethylamine **203** (1.13 g, 4.26 mmol) was added followed by TEA (0.60 cm^3, 4.26 mmol) and the reaction kept stirred at r.t. for o/n, diluted with $CHCl_3$ (10 cm^3), washed with water (10 cm^3) and then with brine (10 cm^3), drying over anhydrous $MgSO_4$. The solvent was removed to give an imine intermediate (1.14 g, 1.67 mmol, 40 %), which used directly in the next step. To the imine (1.10 g, 1.60 mmol) in dry THF (20 cm^3) was slowly added 1.5 cm^3 $LiAlH_4$ (1M in THF), the resulting mixture was stirred at r.t. for o/n, the reaction was carefully quenched with water (0.5 cm^3), 15% NaOH aqeous solution (0.5 cm^3), and water (1.50 cm^3), filtered through silica, washed with DCM (10 cm^3), the organic layer was separated, dried over anhydrous $MgSO_4$ and solvent removed . Purified by column chromatography (EtOAc:hexane 60:40) to give *N*-(2-hydroxy-1-methyl-2-phenyl-ethyl)-2-[(2-hydroxy-1-methyl-2-phenyl-ethylamino)-methyl]-benzenesulfonamide **204** as a white solid compound (0.52 g, 1.2 mmol, 71%). Mp 64-68 °C; $[\alpha]_D^{26}$ = + 16.3 (*c* 0.1, $CHCl_3$); ν_{max}(neat) 3483, 2978, 1449, 1317, 1160, 1065, 968, 830, 747, and 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.11 (1H, dd, *J* 2.4, 7.5, ArH), 7.54-7.45 (2H, m, ArH), 7.38-7.35 (2H, m, ArH), 7.33-7.29 (4H, m, ArH), 7.25-7.22 (2H, m, ArH), 7.18-7.15 (3H, m, ArH), 6.80 (1H, br s, NH), 5.07 (1H, d, *J* 3.3, *CH*), 4.48 (1H, d, *J* 2.7, CH),

4.45 (1H, d, *J* 12.0, C*H*$_a$H$_b$), 4.16 (1H, d, *J* 12.0, CH$_a$*H*$_b$), 3.69-3.66 (1H, m, CH), 3.08-3.05 (1H, m, CH), 0.97 (3H, d, *J* 6.6, CH_3), 0.82 (3H, d, *J* 6.9, CH_3); δ_C (75MHz,$CDCl_3$) 141.36 (C), 140.80 (C), 140.43 (C), 137.13 (C), 132.75 (CH), 132.39 (CH), 129.10 (CH), 128.33 (2 x CH), 128.25 (CH), 128.15 (2 x CH), 127.39 (CH), 127.29 (CH), 125.82 (4 x CH), 74.51 (CH), 73.49 (CH), 59.31 (CH), 55.89 (CH), 50.07 (CH_2), 13.81 (CH_3), 13.29 (CH_3). *m/z* (ESI) 453.0 $[M–H]^–$. HRMS found (ESI) 455.2001 ($C_{25}H_{31}N_2O_4S$ $[M+H]^+$ requires 455.1999, error = 0.4 ppm).

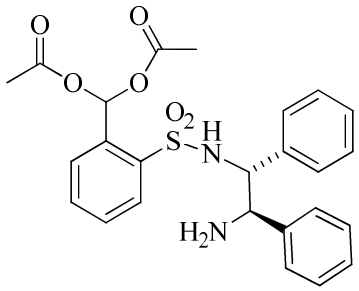
Synthesis of acetic acid acetoxy-(2-chlorosulfonyl-phenyl)-methyl ester (198):



This compound is known but not fully characterized.[117] Conc. H_2SO_4 (2 drops) was added to a solution of 2-formylbenzenesulfonyl chloride (1.05 g, 5.12 mmol) in acetic anhydride (1.26 cm^3, 12.3 mmol), then the mixture was stirred for 45 min. Then solvent removed, purified by flash column chromatography using (EtOAc:hexane 30:70), to give acetic acid acetoxy-(2-chlorosulfonyl-phenyl)-methyl ester **198** as a white solid (1.13 g, 3.96 mmol, 72%). Mp 72-75 °C. ν_{max}(neat) 3107, 1752, 1437, 1365, 1195, 1178, 1163, 1072, 999, 907, 780 and 733 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.40 (1H, s,Ar*CH*$(OAc)_2$), 8.17 (1H, dd, *J* 1.6, 8.0, ArH), 7.91 (1H, dd, *J* 1.6, 7.6, ArH), 7.82 (1H, td, *J* 1.2, 8.8, ArH), 7.67 (1H, td, *J* 1.6, 9.2, ArH), 2.16 (6H, s, 2 x *CH*$_3$(COO)); δ_C (100 MHz,$CDCl_3$) 168.11 (2 x CO), 142.25 (C), 135.61 (CH) , 134.41 (C), 130.56 (CH), 129.44 (CH), 128.39 (CH), 85.46 (CH),

20.60 (2 x CH_3). *m/z* (ESI) 328.9 $[M+Na]^+$. HRMS found (ESI) 328.9852 ($C_{11}H_{11}NaClO_6S$ $[M+Na]^+$ requires 328.9857, error= 1.4 ppm).

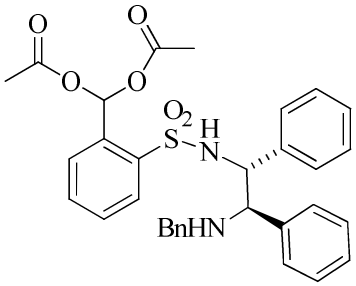
Synthesis of (*R,R*)-acetic acid acetoxy-[2-(2-amino-1,2-diphenyl-ethylsulfamoyl)-phenyl]-methyl ester (199):



This compound is novel. A solution of acetic acid acetoxy-(2-chlorosulfonyl-phenyl)-methyl ester **198** (0.2 g, 0.67 mmol) in DCM (5.0 cm^3) was added to (*R,R*)-DPEN (0.14 g, 0.67 mmol), TEA (0.1 cm^3 , 0.8 mmol) and DCM (5.0 cm^3). The mixture was stirred for 3 h at r.t., then washed with water (10 cm^3), brine (10 cm^3) and dried over anhydrous $MgSO_4$, solvent removed, The product was purified by flash column using (EtOAc:Hexane 40:60), to give (*R,R*)-acetic acid acetoxy-[2-(2-amino-1,2-diphenyl-ethylsulfamoyl)-phenyl]-methyl ester **199** as a white solid compound (0.28 g, 0.58 mmol, 87%). Mp = 122-125 °C; $[\alpha]_D^{22}$ = +18.2 (*c 0.5*, $CHCl_3$); ν_{max}(neat) 3032, 1751, 1455, 1369, 1325, 1158, 1130, 1044, 723 and 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.45 (1H, s, Ar*CH*$(OAc)_2$), 7.63 (1H, dd, *J* 1.6, 10.4, ArH), 7.40 (1H, td, *J* 1.6, 10.0, ArH), 7.33 (1H, dd, *J* 1.6, 10.4, ArH), 7.14-7.04 (6H, m, ArH), 6.96-6.88 (5H, m, ArH), 4.53 (1H, d, *J* 7.2, *CH*Ph), 4.09 (1H, d, *J* 7.2, *CH*Ph), 2.18 (3H, s, CH_3), 2.14 (3H, s, CH_3); δ_C(100 MHz,$CDCl_3$) 171.02 (C=O), 169.94 (C=O), 160.79, 138.61, 137.28, 132.96, 129.68 (CH), 129.34 (CH), 128.47 (CH), 128.18 (2 x CH), 127.91 (2 x CH), 127.84 (CH), 127.06 (2 x CH), 127.36

(CH), 127.29 (CH), 127.22 (CH), 127.10 (CH), 86.11 (CH), 59.84 (CH), 57.34 (CH), 20.65 (CH_3), 20.57 (CH_3). *m/z* (ESI) 483.0 $[M+H]^+$. HRMS found (ESI) 483.1574 ($C_{25}H_{27}N_2O_6S$ $[M+H]^+$ requires 483.1584, error = 0.1 ppm).

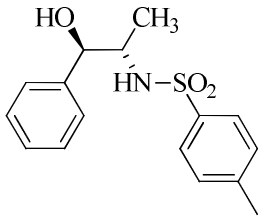
Synthesis of (*R*,*R*)-acetic acid acetoxy-[2-(2-benzylamino-1,2-diphenyl-ethylsulfamoyl)-phenyl]-methyl ester (200):



This compound is novel. A solution[120] of (*R*,*R*)-acetic acid acetoxy-[2-(2-amino-1,2-diphenyl-ethylsulfamoyl)-phenyl]-methyl ester **199** (0.15 g, 0.31 mmol) and benzaldehyde (0.1 cm^3, 0.89 mmol) in benzene was refluxed to achieve azeotropic removal of water for 6 h. After removal of the solvent, a solution of the imine (0.56 g, 0.98 mmol) in acetonitrile (10 cm^3) was stirred in an ice bath for 15 min., then $NaBH_3CN$ was added (0.12 g, 1.96 mmol), followed by a few drops of AcOH. Stirring was continued for additional 3 h at r.t. After solvent removed , the product was dissolved in DCM, washed with saturated $NaHCO_3$, the organic layer was separated, dried over anhydrous $MgSO_4$ and solvent removed. The product was purified by flash column using (EtOAc:Hexane 30:70), to give (*R*,*R*)-acetic acid acetoxy-[2-(2-benzylamino-1,2-diphenyl-ethylsulfamoyl)-phenyl]-methyl ester **200** as a white solid (0.43 g, 0.75 mmol, 76%). Mp 134-137 °C; $[\alpha]_D^{25}$ = +11 (*c* 0.1, $CHCl_3$); ν_{max}(neat) 2987, 2901, 1750, 1494, 1554, 1240, 1199, 1055, 904 and 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.43 (1H, s, Ar*CH*$(OAc)_2$), 7.63 (1H, dd, *J* 1.6, 10.4, ArH), 7.44-7.28 (6H, m, ArH), 7.12-6.77 (12H, m, ArH), 4.86 (1H, d, *J* 11.6,

*CH*Ph), 3.77 (1H, d, *J* 11.6, *CH*Ph), 3.66 (1H, d, *J* 12.0, CH_aH_b), 3.52 (1H, d, *J* 12.0, CH_aH_b), 2.17 (3H, s, CH_3(CO), 2.09 (3H, s, CH_3(CO)); δ_C (100 MHz,$CDCl_3$) 168.89 (C=O), 168.85 (C=O), 139.44 (C), 138.96 (C), 138.55 (C), 137.29 (C), 133.35 (C), 132.23 (CH), 129.34 (CH), 129.27 (CH), 128.33 (3 x CH), 128.15 (3 x CH), 127.83 (4 x CH), 127.55 (3 x CH), 127.42 (CH), 127.13 (CH), 126.90 (CH), 86.44 (Ar(CH)-Ac), 66.80 (CH), 63.93 (CH), 50.74 (CH_2), 20.78 (CH_3), 20.69 (CH_3). *m/z* (ESI) 571.2 $[M–H]^-$. HRMS found (ESI) 573.2049 ($C_{32}H_{33}N_2O_6S$ $[M+H]^+$ requires 573.2054, error = 0.8 ppm).

Synthesis of *N*-((*R,S*)-1-hydroxy-1-phenyl-2-propyl)-*p*-toluenesulfonamide (207):

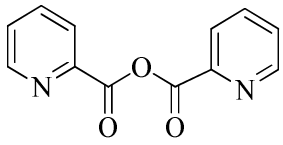


This compound is known but not fully characterised.[124] (1*R*,2*S*)-Norephedrine (0.27 g, 1.85 mmol) was dissolved in THF (20 cm^3). To this solution TEA (0.28 cm^3, 2.05 mmol) was added and the solution was placed in an ice bath. To this solution, *p*-toluenesulfonyl chloride (0.35 g, 1.85 mmol) was added and the water bath was removed after several minutes. After 1 h, the reaction was quenched with saturated $NaHCO_3$ (15 cm^3) and the THF removed under vacuum after which the sulphonamide was extracted with EtOAc and the solvents were removed. The resulting white solid was triturated with diethyl ether to afford *N*-((1*R*,2*S*)-1-hydroxy-1-phenyl-2-propyl)-*p*-toluenesulfonamide **207** as viscous white compound (0.24 g, 0.89 mmol, 51%); $[\alpha]_D^{24}$ = -2.3 (c 1.0, CH_2Cl_2); ν_{max}(neat) 3509, 3208, 1598, 1324, 1160, 1092 and 702; δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J* 8.4, Ar-H),

7.34-7.24 (7H, m, Ar-H), 4.85 (1H, d, *J* 8.4, OH), 4.78 (1H, t, *J* 4.0, *CH*), 3.62-3.54 (1H, m, *CH*), 2.59 (1H, d, *J* 4.8, NH), 2.42 (3H, s, CH_3(Tosyl), 0.84 (3H, d, *J* 6.8, *CH_3*(CH)NH; δ_C (100 MHz,$CDCl_3$) 143.48 (C), 140.26 (C), 137.84 (C), 129.75 (2 x CH), 128.30 (2 x CH), 127.66 (CH), 126.99 (2 x CH), 126.04 (2 x CH), 75.67 (CH), 54.90 (CH), 21.45 (CH_3), 14.43 (CH_3). *m/z* (ESI^+) 328.1 $[M+Na]^+$ HRMS found 306.1168 ($C_{16}H_{19}NO_3S$ $[M+H]^+$ requires 306.1164, error = 1.3 ppm).

3.5. Procedures for section 2.8

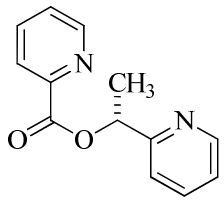
Synthesis of pyridine-2-carboxylic acid 1-pyridin-2-yl-ethyl ester (217):



This compound is known but not fully characterized.[148] A solution of pyridine-2-carboxylic acid (1.0 g, 8.12 mmol) and diisopropylethylamine (1.50 cm^3, 8.12 mmol) in THF (15 cm^3) was stirred for 10 min. at 0 °C. To the reaction mixture a solution of triphosgene (0.40 g, 1.35 mmol) in THF (3.00 cm^3) was added at 0 °C, then stirred for 1 h. The reaction mixture was additionally stirred for 1 h at r.t. After filtration of the reaction mixture to remove diisopropylethylammonium chloride, the filtrate was concentrated under reduced pressure, EtOAc was added to the residue (20 cm^3), the mixture was washed with water (10 cm^3). The organic layer was separated and washed with water (10 cm^3), brine (10 cm^3), dried over anhydrous $MgSO_4$. The solvent was evaporated to offered pyridine-2-carboxylic anhydride **217** as brown viscous compound (0.84 g, 3.68 mmol, 46%); ν_{max}(neat) 3057, 1781, 1735, 1582, 1467, 1436, 1271, 1243, 1219, 1009, 801, 741 and 691 cm^{-1}; δ_H (400 MHz, acetone-d_6) 8.68-8.66 (2H, m, PyH), 8.30-8.28 (2H, m, PyH), 8.08 (2H, td, *J* 1.6, 7.6, PyH),

7.69-7.65 (2H, m, PyH); δ_C (100 MHz, acetone-d_6) 207.34 (2 x C=O), 164.39 (C), 151.52 (2 x CH), 148.17 (C), 139.61 (2 x CH), 129.94 (2 x CH), 127.91 (2 x CH). *m/z* (ESI) 251.0 $[M+Na]^+$. HRMS found (ESI) 229.0609 ($C_{12}H_9N_2O_3$ $[M+H]^+$ requires 229.0608, error = 0.4 ppm).

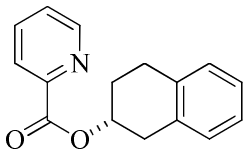
Synthesis of (*R*)-pyridine-2-carboxylic acid 1-pyridin-2-yl-ethyl ester (215):



This compound is novel. To a stirred solution of pyridine-2-carboxylic anhydride **217** (0.80 g, 3.51 mmol) and DMAP (0.043 g, 0.351 mmol) in DCM (10 cm^3) at r.t. for 10 min, a solution of (*R*)-1-(pyridin-2-yl) ethanol (0.43 g, 3.51 mmol) in DCM (3.00 cm^3) was added. After the reaction mixture had been stirred for 1 h, it was quenched with saturated aqueous $NaHCO_3$ (10 cm^3). The organic layer was separated, dried over anhydrous $MgSO_4$, and solvent removed, purified on silica gel column chromatography (EtOAc:hexane 90:10) to give (*R*)-pyridine-2-carboxylic acid 1-pyridin-2-yl-ethyl ester **215** as a viscous yellow compound (0.39 g, 1.70 mmol, 49%); $[\alpha]_D^{28}$ = +11.2, (*c* 0.13, $CHCl_3$); ν_{max}(neat) 2984, 1717, 1588, 1512, 1435, 1242, 1087, 1067, 993 and 744 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.80 (1H, d, *J* 5.6, PyH), 8.60 (1H, d, *J* 4.8, PyH), 8.17 (1H, d, *J* 8.0, PyH), 7.84 (1H, td, *J* 2.0, 8.0, PyH), 7.69 (1H, td, *J* 1.6, 7.6, PyH), 7.51-7.47 (2H, m, PyH), 7.22-7.19 (1H, m, PyH), 6.26 (1H, q, *J* 6.8, CH), 1.8 (3H, d, *J* 6.8, CH_3); δ_C (100MHz,$CDCl_3$) 164.29 (C=O), 159.92 (C), 149.75 (CH), 148.99 (CH), 147.87 (C), 136.72 (CH), 136.58 (CH), 126.68 (CH), 125.04 (CH), 122.48 (CH), 120.07 (CH), 74.21 (CH), 20.45

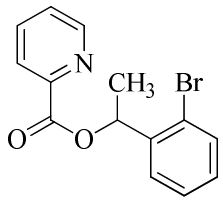
(CH_3). *m/z* (ESI) 251.1 $[M+Na]^+$. HRMS found (ESI) 229.0965 ($C_{13}H_{13}N_2O_2$ $[M+H]^+$ requires 229.0972, error= 2.7 ppm).

Synthesis of (*R*)-pyridine-2-carboxylic acid 1,2,3,4-tetrahydro-naphthalen-1-yl ester (219):



This compound is novel. The procedure is as same as for the preparation of compound (*R*)-pyridine-2-carboxylic acid 1-pyridin-2-yl-ethyl ester **215**, using pyridine-2-carboxylic anhydride **217** (1.4 g, 6.0 mmol), in DCM (10 cm^3), DMAP (0.15 g, 0.6 mmol), (*R*)-1,2,3,4-tetrahydronaphthalen-1-ol (0.90 cm3, 6.0 mmol) in DCM (3.00 cm^3) to give (*R*)-pyridine-2-carboxylic acid 1,2,3,4-tetrahydro-naphthalen-1-yl ester **219** as dark brown solid compound (0.28 g, 1.10 mmol, 48%). Mp 80-83 °C; $[\alpha]_D^{28}$ = +42.8, (*c* 0.1, $CHCl_3$); ν_{max}(neat) 2940, 1703, 1585, 1435, 1288, 1245, 1132, 1058, 995, 741, and 693 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.79-8.76 (1H, m, PyH), 8.10 (1H, d, *J* 10.4, PyH), 7.80 (1H, td, *J* 2.0, 10.0, PyH), 7.47-7.43 (1H, m, PyH), 7.37 (1H, d, *J* 10.0, ArH), 7.24-7.14 (3H, m, ArH), 6.35 (1H, t, *J* 6.8, CH), 2.97-2.75 (2H, m, CH_2-hexyl), 2.20-2.06 (3H, m, CH_2-hexyl), 1.94-1.85 (1H, m, CH_2-hexyl); δ_C (100 MHz,$CDCl_3$) 164.21 (C=O), 149.65 (CH), 147.95 (C), 137.68 (C), 136.54 (CH), 133.82 (C), 129.17 (CH), 128.72 (CH), 127.83 (CH), 126.40 (CH), 125.78 (CH), 124.78 (CH), 71.29 (CH), 28.80 (CH_2), 28.66 (CH_2), 18.60 (CH_2). *m/z* (ESI) 276.0 $[M+Na]^+$. HRMS found (ESI) 276.0992 ($C_{16}H_{15}NNaO_2$ $[M+Na]^+$ requires 276.0995, error = 0.2 ppm).

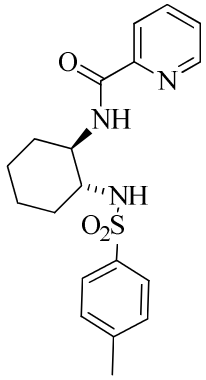
Synthesis of pyridine-2-carboxylic acid 1-(2-bromo-phenyl)-ethyl ester (221):



This compound is novel. The procedure is as same as for the preparation of compound (*R*)-pyridine-2-carboxylic acid 1-pyridin-2-yl-ethyl ester **215,** using pyridine-2-carboxylic anhydride **217** (1.76 g, 7.7 mmol), in DCM (10 cm^3), DMAP (0.19 g, 0.77 mmol), 1-(2-bromophenyl) ethanol (1.55 cm^3, 7.7 mmol) in DCM (3.00 cm^3) to give pyridine-2-carboxylic acid 1-(2-bromo-phenyl)-ethyl ester **221** as a viscous dark brown compounds (1.5 g, 4.92 mmol, 63%); ν_{max}(neat) 2983, 1717, 1570, 1436, 1301, 1242, 1121, 1086, 1040, 993, 744, and 706 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.80-8.78 (1H, m, PyH), 8.13 (1H, d, *J* 8.0, ArH), 7.83 (1H, td, *J* 2.0, 8.0, ArH), 7.61 (1H, dd, *J* 1.6, 7.6, ArH), 7.55 (1H, dd, *J* 1.2, 8.0, PyH), 7.49-7.44 (1H, m, PyH), 7.32 (1H, td, *J* 1.2, 7.6, PyH), 7.14 (1H, td, *J* 1.6, 7.6, ArH), 6.49-6.47 (1H, q, *J* 6.8, CH), 1.72 (1H, d, *J* 6.4, CH_3); δ_C (100 MHz,$CDCl_3$) 164.26 (C=O), 149.83 (CH), 147.99 (C), 140.63(C), 136.84 (CH), 132.75 (CH), 129.10 (CH), 127.75 (CH), 126.78 (CH), 126.74 (CH), 125.13 (CH), 121.68 (C), 72.94 (CH), 21.03 (CH_3). *m/z* (ESI) 327.9 $[M+Na]^+$. HRMS found (ESI) 327.9944 ($C_{14}H_{12}{}^{79}BrNaNO_2$ requires 327.9944 $[M+Na]^+$ error = 0.00 ppm), found 329.9924 ($C_{14}H_{12}{}^{81}BrNaNO_2$ requires 329.9924 $[M+Na]^+$ error = 0.00 ppm).

3.6. Procedures for section 2.10

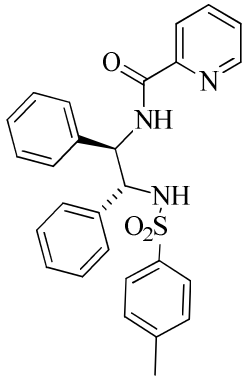
Synthesis of (*R,R*)-pyridine-2-carboxylic acid [2-(toluene-4-sulfonylamino)-cyclohexyl]-amide (228):



This compound is known and fully characterized.[151] A solution of pyridine-2-carboxylic acid (0.23 g, 1.86 mmol) and TEA (0.80 cm^3, 5.58 mmol) in inhydrous THF (10 cm^3) was treated with ethyl chloroformate (0.16 cm^3, 2.05 mmol) at 0 °C for 30 min. A solution of (*R*,*R*)-(−)-*N*-(4-toluenesulfonyl)-1,2-diaminocyclohexane (0.50 g, 1.86 mmol) in THF (5 cm^3) was added dropwise and the reaction mixture was left at r.t. for o/n. After completion of the reaction (checked by TLC), most of the THF was removed in *vacuo* and the crude reaction mixture was partitioned between EtOAc and water. The organic layer was washed with water (5.0 cm^3), brine (5.0 cm^3), and dried over anhydrous $MgSO_4$. It was concentrated in *vacuo* to give a crude product, which was purified by silica gel column chromatography using (EtOAc:Hexane 60:40) to give (*R*,*R*)-pyridine-2-carboxylic acid [2-(toluene-4-sulfonylamino)-cyclohexyl]-amide **228** as a white solid compound (0.63 g, 1.69 mmol, 90%). Analysis was carried out without further purification. Mp 179-182°C; $[\alpha]_D^{25}$ = -1.2, (*c* 0.1, $CHCl_3$); ν_{max}(neat) 3319, 3062, 2937, 2859, 1657 (C=O stretch), 1594, 1516, 1443, 1318, 1154, 1084 and 1000 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.42-8.40 (1H, m, PyH), 8.11 (1H, d, *J* 10.4, PyH), 7.88 (1H, td, *J* 2.4, 10.4, PyH), 7.65 (1H, d, *J* 11.2, PyH), 7.53 (2H, d, *J* 11.2, ArH), 7.48-7.42 (1H, m, ArH), 6.75 (2H, d, *J* 10.8, ArH and NH), 5.98 (1H, d, *J* 7.2, N*H*), 3.84-3.76 (1H, m, TosylNH(C*H*), 3.04-2.96 (1H, m, CONH(*CH*)), 2.26-2.22 (1H, m, CH_2-hexyl), 2.12 (3H, s, CH_3), 1.98-

1.95 (1H, m, CH_2-hexyl), 1.78-1.73 (2H, m, CH_2-hexyl), 1.51-1.25 (4H, m, 2 x CH_2-hexyl); δ_C (100 MHz,$CDCl_3$) 165.35 (C=O), 148.79 (C), 147.72 (CH), 142.11(C), 137.86 (C), 137.25 (CH), 129.06 (2 x CH), 126.48 (2 x CH), 126.21 (CH), 122.28 (CH), 60.14 (CH), 51.89 (CH), 34.91 (CH_2), 32.22 (CH_2), 24.53 (CH_2), 24.35 (CH_2), 21.29 (CH_3). *m/z* (ESI) 374.1 $[M+H]^+$. HRMS found (ESI) 374.1534 ($C_{19}H_{24}N_3O_3S$ $[M+H]^+$ requires 374.1533, error = 0.3 ppm).

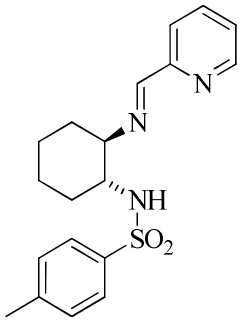
Synthesis of (*R,R*)-pyridine-2-carboxylic acid [2-(toluene-4-sulfonylamino)-1, **2-diphenyl-1, 2-ethylenediamine]-amide (226):**



This compound is novel. The procedure is as same as for preparation of compound (*R,R*)-pyridine-2-carboxylic acid [2-(toluene-4-sulfonylamino)-cyclohexyl]-amide **228** using pyridine-2-carboxylic acid (0.11 g, 0.82 mmol) and TEA (0.34 cm^3, 2.46 mmol) in inhydrous THF (10 cm^3),(1*R*,2*R*-TsDPEN) (0.3 g, 0.82 mmol), ethyl chloroformate (0.09 cm^3, 0.90 mmol) to yield (*R,R*)-pyridine-2-carboxylic acid [2-(toluene-4-sulfonylamino)-1, 2-diphenyl-1, 2-ethylenediamine]-amide **226** as a white crystalline powder (0.33 mg, 0.708 mmol, 86.5%). Analysis was carried out without further purification. Mp 229-230 °C; $[\alpha]_D^{27}$ -52.75 (*c* 0.40 in $CHCl_3$); ν_{max} 3351 (N-H stretch), 3064, 3034, 2934, 1651 (C=O stretch), 1507 , 1331, 1159 (S=O stretch) and 697 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.78 (1 H, d, *J* 7.6, NH), 8.48 (1 H, d, *J* 4.7,

PyH), 8.21 (1 H, d, *J* 7.8, PyH), 7.83-7.79 (1 H, m, PyH), 7.42-7.36 (3 H, m, 2 x ArH + PyH), 7.20-6.9 (10 H, m, ArH), 6.84 (2 H, d, *J* 4.7, ArH), 5.37 (1 H, dd, *J* 8.4, 10.0, C*H*Ph), 4.76 (1 H, dd, *J* 7.6, 10.2, C*H*Ph), 2.19 (3 H, s, CH_3); δ_C (100 MHz, $CDCl_3$); 165.33 (C=O), 148.68 (C), 148.04 (CH), 142.26 (C), 138.04 (C), 137.95 (2 x C), 137.33 (CH), 128.93 (2 x CH), 128.54 (2 x CH), 127.94 (CH), 127.91(2 x CH), 127.63 (2 x CH), 127.57 (2 x CH), 127.25 (CH), 126.69 (2 x CH), 126.36 (CH), 122.51 (CH), 64.01 (CH), 59.15 (CH), 21.29 (CH_3). *m/z* (ESI) 472.2 $[M+H]^+$. HRMS found (ESI) 472.1693 ($C_{27}H_{26}N_3O_3S$ $[M+H]^+$ requires 472.1689, error = 0.8 ppm).

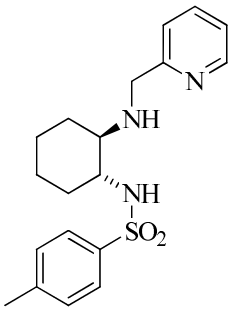
Synthesis of (*R,R*)-4-methyl-*N*-{2-[(pyridin-2-ylmethylene)-amino]-cyclohexyl}-benzenesulfonamide (232):



This compound is known but not fully characterized.[169-170] To a stirred solution of (1*R*,2*R*)-(−)-*N*-*p*-tosyl-1,2-cyclohexanediamine (0.5 g, 1.86 mmol) in DCM (20 cm^3) were added at r.t. to 2-pyridincaboxaldehyde (0.28 g, 1.86 mmol) in DCM (10 cm^3). The mixture was stirred o/n at r.t. Anhydrous $MgSO_4$ was added, the solution filtered and solvent removed at reduced pressure to obtain (*R,R*)-4-methyl-*N*-{2-[(pyridin-2-ylmethylene)-amino]-cyclohexyl}-benzenesulfonamide **232** as a white solid compound (0.57 g, 1.59 mmol, 87%). Mp 134-137 °C; $[\alpha]_D^{27}$ = +22.5, (*c* 0.5, $CHCl_3$); ν_{max}(neat) 2933, 1654, 1473, 1312, 1091, 1061, 944 932, 733 and 657 cm^{-1};

δ_H (400 MHz, $CDCl_3$) 8.62-8.60 (1H, m, PyH), 8.25 (1H, s, PyH), 7.67-7.62 (4H, m, PyH + ArH), 7.33-7.28 (1H, m, ArH), 7.03 (2H, d, *J* 8.4, ArH + NH), 4.89 (1H, s, N=CH), 3.36-3.29 (1H, m, C*H*), 3.08-3.02 (1H, m, C*H*), 2.29 (3H, s, CH_3), 2.26-2.25 (1H, m, CH_2-hexyl), 1.74-1.70 (4H, m, 2 x CH_2-hexyl), 1.61-1.55 (1H, m, CH_2-hexyl), 1.38-1.31 (2H, m, CH_2-hexyl); δ_C (100 MHz,$CDCl_3$) 161.92 (CH), 154.10 (C), 149.16 (CH), 142.49 (C), 138.06 (C), 136.14 (CH), 129.24 (2 x CH), 126.92 (2 x CH), 124.66 (CH), 121.44 (CH), 72.63 (CH), 57.54 (CH), 33.15 (CH_2), 33.02 (CH_2), 24.60 (CH_2), 23.79 (CH_2), 21.45 (CH_3). *m/z* (ESI) 358.1 $[M+H]^+$. HRMS found (ESI) 358.1595 ($C_{19}H_{24}N_3O_2S$ $[M+H]^+$ requires 358.1584, error = 1.4 ppm).

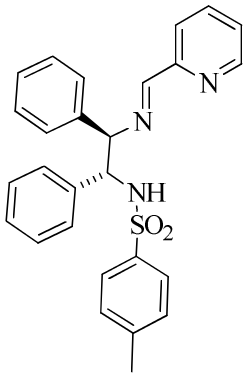
Synthesis of (*R*,*R*)-4-Methyl-*N*-{2-[(pyridin-2-ylmethyl)-amino]-cyclohexyl}-benzenesulfonamide (233):



This compound is known and fully characterized.[155-156] (*R*,*R*)-4-methyl-*N*-{2-[(pyridin-2-ylmethylene)-amino]-cyclohexyl}-benzenesulfonamide **232** (0.50 g, 1.4 mmol) was dissolved in MeOH (20 cm^3) and $NaBH_4$ (0.16 g, 4.2 mmol) was added portionwise and the reaction allowed to stir until all the imine consumed. The solvent was evaporated and the residue taken up in diethyl ether (15 cm^3) and sat. $NaHCO_3$ (15 cm^3). The organic layer was separated and the aqueous layer extracted with diethyl ether (2 x 15 cm^3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in *vacuo* to afford the crude product, which was

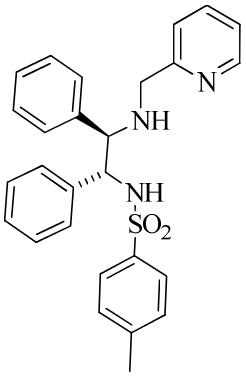
purified by silica gel column chromatography using (EtOAc:Hexane 30:70) to give (*R,R*)-4-methyl-*N*-{2-[(pyridin-2-ylmethyl)-amino]-cyclohexyl}-benzenesulfonamide **233** as a white solid (0.31 g, 0.86 mmol, 61%). Mp 102-105 °C; $[\alpha]_D^{27}$ = -21.3, (*c* 0.38, CH_2Cl_2), lit[35] $[\alpha]_D^{25}$ = -25, (*c* 0. 53, CH_2Cl_2); ν_{max}(neat) 3255, 3056, 2935, 2857, 1595, 1578, 1499, 1320, 1157, 1088, 809, 705 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.64-8.62 (1H, m, PyH), 7.79 (1H, t, *J* 2.4, PyH), 7.76 (1H, t, *J* 2.4, PyH), 7.67 (1H, td, *J* 2.4, 10.0 PyH), 7.24-7.17 (4H, m, ArH), 3.90 (1H, d, *J* 20.8, CH_aH$_b$), 3.78 (1H, d, *J* 20.8, CH$_a$$H_b$), 2.74-2.66 (1H, m, CH), 2.39 (3H, s, CH_3), 2.27-2.24 (1H, m, CH), 2.23-2.18 (1H, m, CH_2-hexyl), 2.07-2.02 (1H, m, CH_2-hexyl), 1.67-1.60 (2H, m, CH_2-hexyl), 1.26-0.98 (4H, m, 2 x CH_2-hexyl); δ_C (100 MHz,$CDCl_3$) 159.76 (C), 148.71 (CH), 142.94 (C), 137.41 (C), 136.71 (CH), 129.43 (2 x CH), 127.14 (2 x CH), 122.09 (CH), 122.03 (CH), 60.01 (CH), 57.54 (CH), 50.93 (CH_2), 33.48 (CH_2), 32.34 (CH_2), 24.64 (CH_2), 24.33 (CH_2) 21.46 (CH_3). *m/z* (ESI) 360.1 $[M+H]^+$. HRMS found (ESI) 360.1740 ($C_{19}H_{25}N_3O_3S$ $[M+H]^+$ requires 360.1740, error = 0.0 ppm).

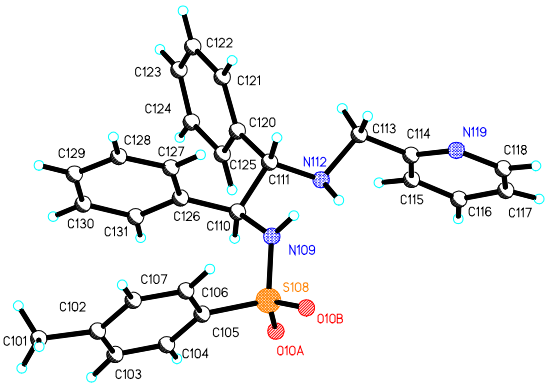
Synthesis of (*R,R*)-*N*-{1,2-diphenyl-2-[(pyridin-2-ylmethylene)-amino]-ethyl}-4-methyl-benzenesulfonamide (230):



This compound is known but not fully characterized.[149] To a stirred solution of (1*R*,2*R*-TsDPEN) (0.5 g, 1.36 mmol) in DCM (20 cm^3) were added at r.t. 2-pyridincaboxaldehyde (0.21 g, 1.36 mmol) in DCM (10 cm^3). The mixture was stirred o/n at r.t. Anhydrous $MgSO_4$ was added, the solution filtered and solvent removed at reduced pressure to obtain (*R*,*R*)-*N*-{1,2-diphenyl-2-[(pyridin-2-ylmethylene)-amino]-ethyl}-4-methyl-benzenesulfonamide **230** as a white solid compound (0.51 g, 1.10 mmol, 81%). Mp 130-133 °C; $[\alpha]_D^{27}$ = + 56.13, (*c* 0.0.5, $CHCl_3$); ν_{max}(neat) 3027, 1734, 1590, 1348, 1162, 1090, 996, 750, and 663 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.60 (1H, d, *J* 6.0, PyH), 8.01 (1H, d, *J* 10.4, PyH), 7.83 (1H, td, *J* 2.4, 7.6, PyH), 7.62 (2H, d, *J* 11.2, ArH), 7.32-7.28 (1H, m, PyH), 7.24-7.16 (10H, m, ArH), 6.98 (2H, dd, *J* 2.2, 7.2, ArH), 5.94 (1H, s, N=CH), 4.65 (1H, d, *J* 8.8, CH), 4.32 (1H, d, *J* 8.8, CH), 2.42 (3H, s, CH_3); δ_C (100MHz,$CDCl_3$) 158.58 (C), 148.99 (CH), 143.72 (C), 139.59 (C), 138.99 (C), 136.85 (CH), 134.09 (C), 129.49 (2 x CH), 128.37 (2 x CH), 128.21 (2 x CH), 127.93 (2 x CH), 127.55 (CH), 127.46 (CH), 127.21 (2 x CH), 126.88 (2 x CH), 123.69 (CH), 123.29 (CH), 78.72 (CH), 71.72 (CH), 69.69 (CH), 21.68 (CH_3). *m/z* (ESI) 456.1 $[M+H]^+$. HRMS found (ESI) 456.1741 ($C_{27}H_{26}N_3O_2S$ $[M+H]^+$ requires 456.1740, error = 0.9 ppm).

Synthesis of (*S*,*S*)-*N*-{1,2-Diphenyl-2-[(pyridin-2-ylmethyl)-amino]-ethyl}-4-methyl-benzenesulfonamide (231):

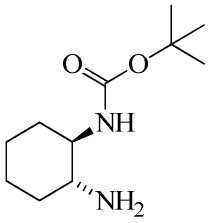




This compound is novel. (*R*,*R*)-*N*-{1,2-diphenyl-2-[(pyridin-2-ylmethylene)-amino]-ethyl}-4-methyl-benzenesulfonamide **230** (0.50 g, 1.1 mmol) was dissolved in MeOH (20 cm^3) and $NaBH_4$ (0.13 g, 3.3 mmol) was added portionwise and the reaction allowed to stir until all the imine has been consumed. The solvent was evaporated and the residue taken up in diethyl ether (15 cm^3) and sat. $NaHCO_3$ (15 cm^3). The organic layer was separated and the aqueous layer extracted with diethyl ether (2 x 15 cm^3). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in *vacuo* to afford the crude product, which was purified by silica gel column chromatography using (EtOAc:hexane 20:80) to give (*R*,*R*)-*N*-{1,2-diphenyl-2-[(pyridin-2-ylmethyl)-amino]-ethyl}-4-methyl-benzenesulfonamide **231** as a white solid compound (0.32 g, 0.68 mmol, 62%). Mp 108-110 °C; $[\alpha]_D^{25}$ = -38.75, (*c* 0.4, $CHCl_3$); ν_{max}(neat) 3029, 1593, 1453, 1325, 1155, 1091, 915, 844, 752 and 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.54 (1H, d, *J* 4.8, PyH), 7.59 (1H, td, *J* 1.2, 7.6, PyH), 7.42 (2H, d, *J* 8.0, PyH), 7.17-7.09 (5H, m, ArH), 7.03-6.95 (7H, m, ArH), 6.92-6.89 (2H, m, ArH), 4.35 (1H, d, *J* 8.0, *CH*Ph), 3.76 (1H, d, *J* 14.8, C*H*$_a$H$_b$), 3.72 (1H, d, *J* 8.0, *CH*Ph), 3.61 (1H, d, *J* 14.8, CH$_a$*H*$_b$), 2.31 (3H, s, CH_3); δ_C (100MHz,$CDCl_3$) 159.04 (C), 148.87 (CH), 142.75 (C), 138.88 (C), 138.46 (C), 137.18 (C), 136.61 (CH), 129.02 (2 x CH), 128.15 (2 x CH), 127.73 (2 x CH),

127.66 (2 x CH), 127.49 (2 x CH), 127.37 (CH), 127.06 (CH), 127.01 (2 x CH), 122.11 (CH), 121.96 (CH), 67.40 (CH), 63.25 (CH), 51.70 (CH_2), 21.35 (CH_3). *m/z* (ESI) 458.1 $[M+H]^+$. HRMS found (ESI) 458.1896 ($C_{27}H_{28}N_3O_2S$ $[M+H]^+$ requires 458.1897, error = 0.3 ppm).

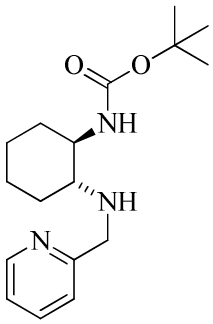
Synthesis of (*R*,*R*)-(2-Amino-cyclohexyl)-carbamic acid *tert*-butyl ester (236):



This compound is known but not fully characterised.[157] A solution of 3.0 cm^3 of HCl in MeOH (3M) was stirred at 0 °C for 15 min. Then, to this solution, was carefully added (*R*,*R*)-1,2-diaminocyclohexane (0.5 g, 4.36 mmol) at 0 °C. The mixture was stirred for 15 min at r.t. before adding water (1.0 cm^3) and stirring for another 0.5 h. To the solution, $(Boc)_2O$ (0.95 g, 8.76 mmol) in 4.0 cm^3 of MeOH was added at r.t. for 10 min, and the resultant solution was stirred for 1 h. The mixture was concentrated in *vacuo*. Unreacted diamine was removed by diethyl ether (30 cm^3 x 2). The residue was dissolved in DCM (20 cm^3), treated with 2 N NaOH solution (15 cm^3). The product in the organic layer was washed with of brine (20 cm^3) dried over anhydrous $MgSO_4$, and concentrated in *vacuo* to yield a mono-Boc product **236** as a white solid, (0.68 g, 3.18 mmol, 72%). Mp 109-112 °C; $[\alpha]_D^{25}$ = -1.2, (*c* 0.1, $CHCl_3$); ν_{max}(neat) 2929, 1691, 1545, 1317, 1240, 1040, 1016, 965, 850 and 759 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.46 (1H, br s, NH), 3.14-3.12 (1H, m, CH), 2.32 (1H, td, *J* 5.6, 10.1, CH), 2.04-1.98 (2H, m, CH_2), 1.72-1.69 (2H, m, CH_2), 1.45 (9H, s, t-*butyl*), 1.37 (2H, br s, NH_2), 1.29-1.07 (4H, m, 2 x CH_2); δ_C (100 MHz,$CDCl_3$) 156.49

(C=O), 57.69 (C), 55.63 (CH), 55.01, (CH), 35.20 (CH_2), 32.86 (CH_2), 28.36 (3 x CH_3), 25.15 (CH_2), 25.04 (CH_2). *m/z* (ESI) 215.2 $[M+H]^+$. HRMS found (ESI) 215.1751 ($C_{11}H_{23}N_2O_2$ $[M+H]^+$ requires 215.1754, error= 1.6 ppm).

Synthesis of (*R,R*)-{2-[(pyridin-2-ylmethyl)-amino]-cyclohexyl}-carbamic acid *tert*-butyl ester (238):



This compound is novel. To a solution of (*R,R*)-(2-amino-cyclohexyl)-carbamic acid *tert*-butyl ester **236** (0.6 g, 2.81 mmol) in DCM (20 cm^3) was added at r.t. (0.42 cm^3, 2.81 mmol) of 2-pyridine carboxaldehyde in DCM (10 cm^3). The mixture was stirred at r.t. o/n, anhydrous $MgSO_4$ was added, the solution filtered and the solvent removed to leave the imine intermediate (0.71 g, 2.30 mmol, 80%), which is used directly in the next step, (0.70 g, 2.3 mmol) of the imine was placed in round bottom flask and dissolved in MeOH (30 cm^3), then $NaBH_4$ (0.26 g, 6.9 mmol) was added slowly and the mixture stirred o/n. The solvent was removed, then the residue dissolved in DCM (20 cm^3), washed with water (15 x 3 cm^3) and solvent removed to give a crude product, which was purified by silica gel column chromatography using (EtOAc:EtOH 90:10) to give (*R,R*)-{2-[(pyridin-2-ylmethyl)-amino]-cyclohexyl}-carbamic acid *tert*-butyl ester **238** as a yellow oil compound (0.63 g, 2.01mmol, 77%); $[\alpha]_D^{26}$ = -16.12, (*c* 0.22, $CHCl_3$); ν_{max}(neat) 2927, 1686, 1522, 1389, 1253, 1167, 1012, 848 and 753 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.55 (1H, d, *J* 4.4, PyH), 7.63

(1H, td, *J* 1.6, 7.6, PyH), 7.31 (1H, d, *J* 8.0, PyH), 7.17-7.14 (1H, m, PyH), 5.34 (1H, br s, NH), 4.04 (1H, d, *J* 15.2, CH_aH$_b$), 3.88 (1H, d, *J* 15.1, CH$_a$$H_b$), 3.33-3.31 (1H, m, C*H*(NH)Boc), 2.30-2.25 (2H, m, CH_2), 2.18-2.15 (1H, m, C*H*(NH)CH_2-Pyr), 2.11-2.08 (1H, m, NH), 1.72-1.64 (2H, m, CH_2), 1.46 (9H, s, *t*-butyl), 1.30-1.07 (4H, m, CH_2); δ_C (100 MHz,$CDCl_3$) 160.41 (C=O), 156.05 (C), 148.97 (CH), 136.42 (CH), 122.26 (CH), 121.82 (CH), 66.52 (C), 60.63 (CH), 54.57 (CH), 51.94 (CH_2), 33.07 (CH_2), 31.87 (CH_2), 28.41 (3 x CH_3), 24.70 (CH_2), 24.61 (CH_2). *m/z* (ESI) 306.2 $[M+H]^+$. HRMS found (ESI) 306.2172 ($C_{17}H_{28}N_3O_2$ $[M+H]^+$ requires 306.2176, error = 1.2 ppm).

3.7. General procedure for asymmetric transfer hydrogenation of ketones:

A mixture of catalyst (2 mol%) and $Ru_3(CO)_{12}$ (0.67 mol%) in IPA (10 cm^3) was stirred at 80 °C under an inert atmosphere in schlenk tube for 30 min. To this solution, ketone (1 mmol) was added and the resulting mixture was stirred at 80 °C for 48 h. The reaction mixture was filtered through a short column of silica using (EtOAc:hexane 1:1), a small amount of the filtrate was dilluted in EtOAc and then injected on the GC to determine the conversion and enantiomeric excess.

Racemic:

The ketone (1mmol) was dissolved in MeOH (5cm^3) in schlenk tube, then $NaBH_4$ (3 mmol) was added slowly and the mixture was stirred at r.t. for o/n. The solvent was removed and the mixture was dissolved in DCM (10 cm^3), washed with water (10 cm^3), filtered and solvent removed. a small amount of the residue was dilluted in EtOAc and then injected on the GC to determine the conversion.

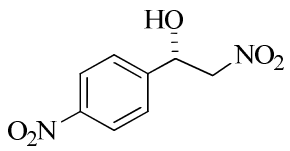
3.8. Reduction of ketones using tethered ruthenium diamine chiral complexes[171]

A solution of tethered ruthenium diamine chiral ligands (0.0150 mmol) in FA:TEA (5:2) azeotropic (1.5 cm^3) was stirred in a flame dried schlenk tube at 28 °C for 30 min. Substrate (3 mmol) in DCM (1.5 cm^3) was added. The reaction mixture was stirred at 28 °C and monitored by TLC. After the starting materials was consumed, the reaction mixture was diluted by DCM (20 cm^3) and washed by sat. $NaHCO_3$ solution (3 x 15 cm^3). The organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography.

3.9. General procedure for the addition of nitro methane to aldehydes.[172]

Under an argon atmosphere, the ligand (0.025 mmol, 10 mmol%) and CuBr (0.025 mmol, 10 mmol%) were suspended in anhydrous methanol (1.0 cm^3). After stirring for 1 h at r.t., nitro methane (10 mmol) and the aldehyde (1.0 mmol) were added and the reaction was stirred for a specific amount of time at r.t. The volatile components were then removed under reduced pressure, and the crude product was purified by flash column chromatography on silica gel (EtOAc:Hexane 20-30 %) to give the pure product. Conversions were determined by NMR and enantiomeric access were determined by HPLC analysis on a chiral OD-H column. The absolute configurations of the products were assigned by comparison to literature values.

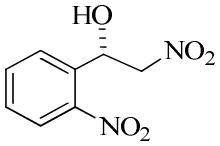
(*S*)-1-(4-Nitrophenyl)-2-nitroethanol



This compound has been reported and fully characterised.[173] Colourless oil. lit.[173] $[\alpha]_D^{25}$ = +30.5 (c 1.3, CH_2Cl_2) 88% ee; δ_H (400 MHz, $CDCl_3$) 8.28−8.25 (2H, m, ArH), 7.66−7.61 (2H, m, ArH), 5.63−5.59 (1H, m, CH), 4.64−4.57 (2H, m, CH_2),

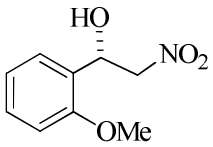
3.24 (1H, brs, OH); δ_C (100 MHz, $CDCl_3$) 148.17, 145.06, 126.92 (2C), 124.16 (2C), 80.60 (CH_2), 69.94 (CH). Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (n-hexane:IPA 80:20, 1.0 cm^3/min, 254 nm); *R* isomer 11.1 minutes, *S* isomer 13.4 minutes.

(*S*)-1-(2-Nitrophenyl)-2-nitroethanol



This compound has been reported and fully characterised.[173] Brown solid, Mp 80−81 ^oC. lit.[173] $[\alpha]_D^{25}$= −169.4 (c 0.22, CH_2Cl_2) 87% ee; δ_H (400 MHz, $CDCl_3$) 8.08 (1H, dd, *J* 8.4, 1.4, ArH), 7.96 (1H, dd, *J* 7.8, 2.4, ArH), 7.80−7.72 (1H, m, ArH), 7.60−7.52 (1H, m, ArH), 6.09−6.03 (1H, m, CH), 4.88 (1H, dd, *J* 13.8, 2.4, CH_aH_b), 4.56 (1H, dd, *J* 13.8, 9.2, CH_aH_b), 3.14 (1H, d, *J* 4.0, OH); δ_C (100 MHz, $CDCl_3$) 147.10, 145.06, 126.92 (2C), 124.16 (2C), 80.60 (CH_2), 69.94 (CH). Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (n-hexane:IPA 85:15, 1.0 cm^3/min, 254 nm); *R* isomer 9.4 minutes, *S* isomer 10.2 minutes.

(*S*)-1-(2-Methoxyphenyl)-2-nitroethanol



This compound has been reported and fully characterised.[173] Yellow oil, lit.[173] $[\alpha]_D^{25}$ = +35.6 (c 1.06, CH_2Cl_2) 72% ee; δ_H (400 MHz, $CDCl_3$) 7.42 (1H, d, *J* 7.7, ArH), 7.34−7.29 (1H, m, ArH), 6.98 (1H, t, *J* 7.2, ArH), 6.88 (1H, d, *J* 8.0, ArH), 5.62−5.58 (1H, m, CH), 4.85 (1H, d, *J* 8.1, OH), 4.64−4.51 (2H, m, CH_2), 3.86 (3H, s, OCH_3); δ_C (100 MHz, $CDCl_3$) 156.04, 129.81, 127.19, 126.10, 121.14, 110.59, 79.91 (CH_2), 67.78 (CH), 55.44 (CH_3). Enantiomeric excess was determined by

HPLC with a Chiralcel IB column (n-hexane:IPA 90:10, 0.50 cm^3/min, 210 nm); *R* isomer 17.4 minutes, *S* isomer 18.7 minutes.

3.10. Iron-catalysed hydrosilylation reaction of acetophenone.[174]

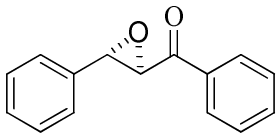
Acetophenone (1.0 mmol), ligand (0.03 mmol), $Fe(OAc)_2$ (0.02 mmol) were placed in a flask under nitrogen atmosphere, THF (3.0 cm^3) was added, and the mixture was stirred for 1 h at 65 °C, then $(EtO)_3SiH$ (2.0 mmol) was added and the mixture was stirred for 24 h at 65 °C. TBAF (THF solution, 1M, 1.0 cm^3). KF (112 mg), MeOH (1.0 cm^3) and H_2O (1.0 cm^3) were adde at 0 °C. The mixture were extracted with EtOAc (5 x 2.0 cm^3) and washed with H_2O (5.0 cm^3) and brine (5.0 cm^3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc:hexane 30:70) to give 1-phenylethanol. Conversion and enantiomeric excess were determined by GC.

3.11. Iron-catalyzed asymmetric epoxidation reaction of aromatic alkene[175]

A solution of $Fe(OTf)_2$ (0.025 M solution in CH_3CN (0.31 cm^3, 7.8 μmol) was added to ligand (10 mg, 15.6 μmol) under nitrogen atmosphere at r.t. After rinsed with additional CH_3CN (0.31 cm^3), the reaction mixture was stirred at r.t. for 3h. To the reaction of iron complex was added a solution of corresponding enone in CH_3CN (0.156 mmol) and the mixture was cooled in ice bath. To the reaction was rapidly added CH_3CO_3H (32 wt% solution in CH_3CO_2H, 0.05 cm^3, 0.234 mmol). After being stirred in ice bath for 30 min., the reaction was quenched by adding a mixture of 10% aq. NaS_2O_3 (2.0 cm^3) and aq. $NaHCO_3$ (2.0 cm^3), and diluted with EtOAc (5.0 cm^3). The organic layer was separated and washed with brine (5.0 cm^3), dried over $MgSO_4$ and concentrated at reduced pressure. The residue was purified by silica

gel column chromatography (EtOAc:Hexane 15-20 %) to affered the corresponding epoxide. Conversions were determined by NMR and enantiomeric access were determined by HPLC analysis on a chiral OD-H column.

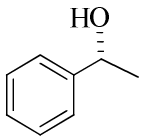
(2*R*,3*S*)-*trans*-Epoxy-3-phenyl-1-phenylpropan-1-one.



This compound has been reported and fully characterised.[176] Colorless crystals; lit.[176] $[\alpha]_D^{23} = -183.6$ (c 1.00, $CHCl_3$) 69% ee (2*R*,3*S*); δ_H (400 MHz, $CDCl_3$) 8.02-7.99 (2H, m, ArH), 7.62-7.36 (8H, m, ArH), 4.29 (1H, d, *J* 2.0, CH), 4.08 (1H, d, *J* 2.0, CH)); δ_C (100 MHz, $CDCl_3$) 171.91, 135.51, 134.07, 133.80, 130.33, 130.23, 129.12, 128.93 (2C), 128.83, 128.52, 128.41, 125.85, 61.07 (CH), 59.46 (CH). Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (n-hexane:IPA 90:10, 1.0 cm^3/min, 254 nm); *R* isomer 15.86 minutes, *S* isomer 17. minutes.

3.12. Analysis of reduction products.

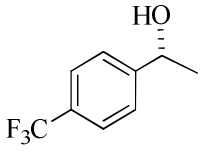
1-Phenylethanol.



This compound has been reported and fully characterised.[177] Colourless oil. $[\alpha]_D^{22}$ +47.6 (c 0.2, $CHCl_3$) 94% ee (*R*), lit.[177] $[\alpha]_D^{23}$ +36.4 (c 2.4, $CHCl_3$) 76% ee (*R*); δ_H (300 MHz, $CDCl_3$) 7.42-7.28 (5H, m, ArH), 4.83 (1H, q, *J* 6.4, *CH*OH), 3.57 (1H, br s, OH), 1.49 (3H, d, *J* 6.4, CH_3); δ_C (75 MHz,$CDCl_3$) 146.1 (C), 128.4 (2 x CH), 127.3 (CH), 125.6 (2 x CH), 70.1 (CH), 25.2 (CH_3). Enantiomeric excess and

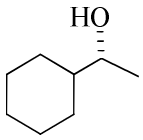
conversion determined by chiral GC; (Chrompak cyclodextrin 50m x 0.25 mm x 0.25 μm column, T = 115 °C, P = 15 psi, retention times 9.4 (acetophenone), *R* isomer 14.56 minutes, *S* isomer 15.76 minutes.

1-(4-(trifluoromethyl)phenyl)ethanol.



This compound has been reported and fully characterised.[178] Colourless oil. $[\alpha]_D^{26}$ +17.9 (c 0.5, $CHCl_3$) 94% ee (*R*) , lit.[178] $[\alpha]_D^{23}$ -31.5 (c 5.49, $CHCl_3$) 90% ee (*R*); δ_H (400 MHz, $CDCl_3$) 7.59 (2H, d, *J* 8.2, 2 x ArH), 7.45 (2H, d, *J* 8.2, 2 x ArH), 4.92 (1H, q, *J* 6.5, *CH*OH),), 2.40 (1H, br s, *OH*), 1.48 (3H, d, *J* 6.5, CH*CH*$_3$); δ_C (100.6 MHz,$CDCl_3$) 149.7 (C), 129.8 (C), 125.7 (2 x CH), 125.4 (CF_3), 69.8 (CH), 69.8 (CH), 25.3 (CH_3). Enantiomeric excess and conversion determined by chiral GC; (Chrompak cyclodextrin 50m x 0.25 mm x 0.25 μm column, T = 130°C, P = 15 psi, retention times 6.87 (trifluoromethylacetophenone), *R* isomer 13.46 minutes, *S* isomer 14.78 minutes.

1-Cyclohexylethanol.

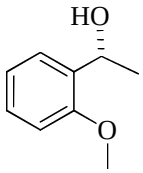


This compound has been reported and fully characterised.[179] Colourless oil. 19% ee (S), lit.[179] $[\alpha]_D^{21}$ +3.51 (c 3.1, $CHCl_3$) 95% ee (S); δ_H (400 MHz, $CDCl_3$) 3.54-3.51 (1H, m, *CH*OH), 2.09 (1H, br s, OH), 1.88-1.63 (5H, m, cyclohexyl), 1.14 (3H, d, *J* 6.3, CH_3), 1.31-0.91 (5H, m, cyclohexyl); δ_C (100.6 MHz,$CDCl_3$) 72.1(CH), 45.1

(CH), 28.7 (CH_2), 28.5 (CH_2), 26.6 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 20.3 (CH_3). Conversion determined by GC analysis: Chrompak cyclodextrin-β-236M-19 50 m x 0.5 mm x 0.25 μm, T = 82 °C, P= 15 psi H_2, det = FID 220 °C, retention times ketone 26.70 min., alcohol 50.25, 51.95 minutes. Enantiomeric excess and conversion determined by GC for the acetate derivative: analysis: Chrompak cyclodextrin-β-236M-19 50 m x 0.5 mm x 0.25 μm, T = 115 °C, P= 15 psi H_2, det = FID 220 °C, retention times *R* isomer 12.51 minutes, *S* isomer 13.58 minutes.

Preparation of the acetate derivative: The reduction product (10 mg) was dissolved in of DCM (1 cm^3). To this was then added acetic anhydride (0.02 cm^3) and DMAP (3 crystals). The reaction was stirred overnight and then volatiles were removed by rotary evaporation. A small amount of the residue was dilluted in EtOAc and then injected on the GC.

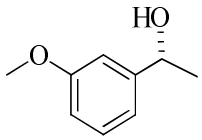
1-(2-Methoxyphenyl)ethanol.



This compound has been reported and fully characterised.[180] Colourless oil. $[\alpha]_D^{24}$ +24.8 (c 2.0, $CHCl_3$) 90% ee (*R*), lit[180] $[\alpha]_D^{22}$ +32.3 (c 2.0, $CHCl_3$) 94% ee (*R*); δ_H (400 MHz, $CDCl_3$) 7.33 (1H, dd, *J* 7.5, 1.7, ArH), 7.21 (1H, dt, *J* 7.8, 7.8, 1.7, ArH), 6.93 (1H, dd, *J* 8.2, 7.5, ArH), 6.84 (1H, d *J* 8.2, ArH), 5.07 (1H, dd, *J* 6.5 , 5.3, *CH*OH), 3.80 (3H, s, O*CH*$_3$), 2.95 (1H, br s, OH), 1.46 (3H, d, *J* 6.5, CH*CH*$_3$); δ_C (100.6 MHz,$CDCl_3$) 156.5, 133.7, 128.2, 126.1, 120.8, 110.4, 66.2 (CH), 55.3 (CH_3), 23.0 (CH_3). Enantiomeric excess and conversion determined by chiral GC; (Chrompak cyclodextrin 50m x 0.25 mm x 0.25 μm column, T = 130 °C, P = 15 psi,

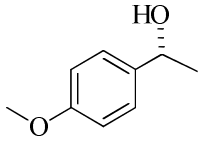
retention times 17.90 (2′-methoxyacetophenone), *S* isomer 23.71 minutes, *R* isomer 24.77 minutes.

1-(3-Methoxyphenyl)ethanol



This compound has been reported and fully characterised.[181] Colourless oil. $[\alpha]_D^{22}$ +38.1 (c 1.0, $CHCl_3$) 96% ee (*R*), Lit[181] $[\alpha]_D^{22}$ +31.8 (c 1.1, $CHCl_3$) 94% ee (*R*); δ_H (400 MHz, $CDCl_3$) 7.23 (1H, dd, *J* 8.0, 8.1, ArH), 6.91-6.90 (2H, m, ArH), 6.78 (1H, dd, *J* 8.1, 2.5, ArH), 4.80 (1H, q, *J* 6.5 , *CH*OH), 3.77 (3H, s, O*CH*$_3$), 2.57 (1H, br s, OH),1.44 (3H, d, *J* 6.5, CH*CH*$_3$); δ_C (100.6 MHz,$CDCl_3$) 159.7, 147.7, 129.5, 117.8, 112.8, 111.0, 70.3 (CH), 55.2 (CH_3), 25.1 (CH_3). Enantiomeric excess and conversion determined by chiral GC; (Chrompak cyclodextrin 50m x 0.25 mm x 0.25 μm column, T = 130 °C, P = 15 psi, retention times 18.67 (3′-methoxyacetophenone), *R* isomer 29.74 minutes, *S* isomer 31.62 minutes.

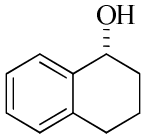
(*R*)-1-(4-methoxyphenyl)ethanol.



This compound has been reported and fully characterised.[182] Colourless oil. $[\alpha]_D^{22}$ +51.76 (c 1.2, $CHCl_3$) 93% ee (*R*), lit.[182] $\alpha]_D^{24}$ +33.8 (c 0.54, $CHCl_3$) 67% ee (*R*); δ_H (300 MHz, $CDCl_3$) 7.26 (2H, d, *J* 8.4, ArH), 6.87-6.84 (2H, m, ArH), 4.81 (1H, q, *J* 6.6, *CH*(OH)CH_3), 3.77 (3H, s, *CH*$_3$O-), 2.15 (1H, br s, O*H*), 1.46 (3H, d, *J* 6.6, CH*CH*$_3$); δ_C (100.6 MHz,$CDCl_3$) 158.78, 138.09, 129.11, 128.86, 127.16, 126.56,

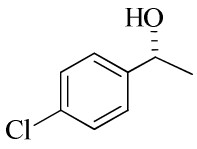
69.72 (CH), 55.15 (CH_3), 24.99 (CH_3). Enantiomeric excess and conversion determined by chiral GC; (Chrompak cyclodextrin 50 m x 0.25 mm x 0.25 μm column, oven 120 °C, inj.: split 220 °C, 100 Pa H_2) retention times 41.1(4′-methoxyacetophenone), *R* isomer 46.56 minutes, *S* isomer 49.45 minutes.

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



This compound has been reported and fully characterised.[183] White solid. Mp 46-49 °C, $[\alpha]_D^{24}$ -4.9 (c 0.75, $CHCl_3$) 95% ee, lit[183] -15.0 (c -0.57, $CHCl_3$) 53% ee; δ_H (300 MHz, $CDCl_3$) 7.48-7.36 (1H, m, ArH), 7.26-7.18 (2H, m, ArH), 7.16-7.08 (1H, m, ArH), 4.78 (1H, t, *J* 4.5, -*CH*(OH)CH_2-), 2.91-2.67 *(*2H, m, -OH and –*CH*H-), 2.10-1.72 (5H, m, 3 x –C*H*H- and 2 x -CH*H*-); δ_C (100.6 MHz,$CDCl_3$) 138.71, 136.95, 128.81, 128.56, 127.35, 125.98, 67.99 (CH), 32.11 (CH_2), 29.28 (CH_2), 18.72 (CH_2). Enantiomeric excess and conversion determined by chiral GC; (Chrompak cyclodextrin 50 m x 0.25 mm x 0.25 μm column, oven 120 °C, inj.: split 220 °C, 100 Pa H_2) retention times 41.25 (α-tetralone), *R* isomer 57.65 minutes, *S* isomer 55.97 minutes.

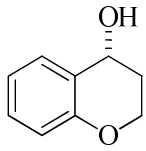
(*R*)-1-(4-chlorophenyl)ethanol.



This compound has been reported and fully characterised.[184] Colourless oil. $[\alpha]_D^{24}$ + 47.5 (c 0.5, Et_2O), 92% ee (*R*), lit.[184] $[\alpha]_D^{26}$ +52.6 (c 0.56, Et_2O) 95% ee (*R*); δ_H

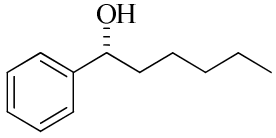
(400 MHz, $CDCl_3$) 7.29 (2H, dd, *J* 3.0, 6.5, ArH), 7.28-7.20 (2H, m, ArH), 4.85 (1H, q, *J* 6.5, -*CH*(OH)CH_3), 2.11 (1H, br s, -*OH*), 1.50 (3H, d, *J* 6.5, *CH_3*) ; δ_C (100.6 MHz,$CDCl_3$) 144.28, 133.04, 228.22, 127.51, 127.10, 126.82, 69.70 (CH), 25.26 (CH_3). Enantiomeric excess and conversion determined by chiral GC; (Chrompak cyclodextrin 50m x 0.25 mm x 0.25 μm column, oven 115 °C, inj.: split 220 °C, 100 Pa H_2) retention times 24.44 (4′-chloroacetophenone), *R* isomer 53.47 minutes, *S* isomer 61.28 minutes.

(*R*)-3,4-Dihydro-2H-chromen-4-ol.



This compound has been reported and fully characterised.[184] White solid. Mp 74-78 °C. $[\alpha]_D^{25}$ + 68.25 (*c* 0.2, $CHCl_3$) > 99% ee (*R*), lit.[184] $[\alpha]_D^{31}$ +61.0 (*c* 0.045, $CHCl_3$) 99% ee (*R*); δ_H (400 MHz, $CDCl_3$) 7.27-7.24 (1H, m Ar-*H*), 7.20-7.15 (1H, m Ar-*H*), 6.90-6.87 (1 H, m, Ar-*H*), 6.82-6.79 (1 H, m, Ar-*H*), 4.69-4.66 (1 H, m, *CH*(OH)CH_2-), 4.24-4.18 (2 H, m, -*CH_2*O-), 2.46 (1H, s, -OH), 2.09-1.91 (2H, m, -*CH_2*-); δ_C (100.6 MHz,$CDCl_3$) 154.57, 129.76, 129.68, 124.34, 120.58, 117.04, 63.16 (CH), 61.97 (CH_2), 30.84 (CH_2). Enantiomeric excess and conversion determined by chiral GC; (Chrompak cyclodextrin 50m x 0.25 mm x 0.25 μm column, T = 115 ^oC, P = 15 psi, G = H_2, retention times 24.54 (4-chromanone), *R* isomer 42.52 minutes, *S* isomer 41.87 minutes.

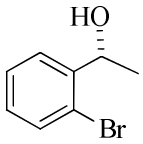
(*R*)-1-phenylhexan-1-ol.



This compound has been reported and fully characterised.[185] Colourless oil. $[\alpha]_D^{26}$ – 28.6 (*c* 1.0, $CHCl_3$) 91% ee (*R*), lit[185] $[\alpha]^{24}{}_D$ = -30.60 (*c* = 1.09, $CHCl_3$) 93% ee (*R*) ; δ_H (400 MHz, $CDCl_3$) 7.33-7.05 (5H, m, ArH), 4.47 (1H, t, *J* 8.7, CH), 2.38 (1H, s, OH), 1.76-1.44 (2H, m, CH_2), 1.41-1.03 (6H, m, 3 x CH_2), 0.77 (3H, t, *J* 6.6, CH_3); δ_C (100.6 MHz,$CDCl_3$) 145.02, 129.01, 128.43, 128.07, 127.46, 126.55, 74.69 (CH), 39.10 (CH_2), 31.78 (CH_2), 25.53 (CH_2), 22.6 1 (CH_2), 14.08 (CH_3).

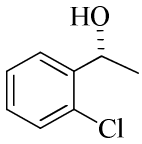
Enantiomeric excess and conversion were determined by chiral GC; (Chrompak cyclodextrin 50m x 0.25 mm x 0.25 μm column,, T = 140 ^oC, P = 15 psi, G = H_2, retention times 23.20 (hexanophenone), *R* isomer 31.97 minutes, *S* isomer 31.52 minutes.

1-(2-Bromophenyl) ethanol.



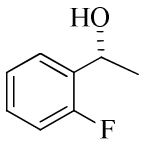
This compound has been reported and fully characterised.[186] $[\alpha]_D^{33}$ +62.9 (*c* 0.42 in $CHCl_3$) 86.2% ee (*R*), lit[187] $[\alpha]_D^{25}$ +54.1 (*c* 1.18 in $CHCl_3$) 99% ee (*R*); δ_H (300 MHz, $CDCl_3$) 7.58 (1 H, dd, *J* 7.9, 1.4, ArH), 7.50 (1 H, dd, *J* 7.9, 1.4, ArH), 7.36-7.31 (1 H, m, ArH), 7.14-7.09 (1 H, m, ArH), 5.22 (1 H, dq, *J* 6.4, 3.2, CH), 2.20 (1 H, d, *J* 3.2, OH), 1.47 (3 H, d, *J* 6.4, CH_3); δ_C (75 MHz, $CDCl_3$) 144.61 (C), 132.54, 128.65, 127.77, 126.62, 121.60, 69.05 (CH), 23.53 (CH_3). Conversion and enantiomeric excess were determined by chiral G.C; (Chrompak β-Cyclodextrin 50 m x 0.25 mm x 0.25 μm column, oven 145 °C, inj.: split 220 °C, det.: FID 220 °C, 100 Pa H_2) retention times 11.5 (2'-bromoacetophenone), *R* isomer 20.36 minutes, *S* isomer 24.31 minutes.

1-(2-Chlorophenyl) ethanol.



This compound has been reported and fully characterised.[186] $[\alpha]_D^{26}$ +48.9 (*c* 0.37 in $CHCl_3$) 87.9% ee (*R*), lit.[186] $[\alpha]_D^{33}$ +44.5 (*c* 0.70 in $CHCl_3$) 70% ee (*R*); δ_H (300 MHz, $CDCl_3$) 7.59 (1 H, dd, *J* 7.7, 1.8, ArH), 7.34-7.26 (2 H, m, ArH), 7.20 (1 H, dt, *J* 7.7, 1.8, ArH), 5.29 (1 H, dq, *J* 6.4, 3.5, CH), 2.07 (1 H, d, *J* 3.5, OH), 1.49 (3 H, d, *J* 6.4, CH_3); δ_C (75 MHz, $CDCl_3$) 143.02,131.52, 129.30, 128.30, 127.13, 126.35, 66.83 (CH), 23.43 (CH_3). Conversion and enantiomeric excess were determined by chiral G.C; (Chrompak β-Cyclodextrin 50 m x 0.25 mm x 0.25 μm column, oven 150 °C, inj.: split 220 °C, det.: FID 220 °C, 100 Pa H_2) retention times 6.8 (2′-chloroacetophenone), *R* isomer 10.5 minutes, *S* isomer 11.6 minutes.

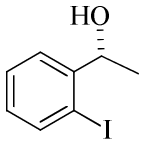
1-(2-Fluorophenyl) ethanol.



This compound has been reported and fully characterised.[188] $[\alpha]_D^{28}$ +37.9 (*c* 0.45 in MeOH) 83.7% ee (*R*), lit.[187] $[\alpha]_D^{18}$ +44.5 (*c* 0.77 in MeOH) 54% ee (*R*); δ_H (300 MHz, $CDCl_3$) 7.48 (1 H, dt, *J* 7.7, 1.8, ArH), 7.28-7.20 (1 H, m, ArH), 7.14 (1 H, dt, *J* 7.7, 1.3, ArH), 7.04-6.98 (1 H, m, ArH), 5.23-5.15 (1 H, m, CH), 2.06 (1 H, d, *J* 4.2, OH), 1.51 (3 H, d, *J* 6.6, CH_3); δ_C (75 MHz, $CDCl_3$) 159.62, 132.61, 128.65, 126.56, 124.22, 64.35 CH), 23.92 (CH_3); δ_F (300 MHz, $CDCl_3$) -120.07 (s). Conversion and enantiomeric excess were determined by chiral G.C; (Chrompak β-

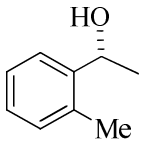
Cyclodextrin 50 m x 0.25 mm x 0.25 μm column, oven 120 °C, inj.: split 220 °C, det.: FID 220 °C, 100 Pa H_2) retention times 6.4 (2′-fluoroacetophenone) *R* isomer 12.5 minutes, *S* isomer 13.5 minutes.

(S)-(-)-1-(2′–Iodophenyl) ethanol



This compound has been reported and fully characterised.[189] lit.[189] $[\alpha]_D^{24}$ +37.7 (*c* 0.93, $CHCl_3$) 97% ee (*S*); δ_H (300 MHz, $CDCl_3$) 7.78 (1 H, dd, *J* 7.7, 1.1, ArH), 7.54 (1 H, dd, *J* 7.7, 1.7, ArH), 7.36 (1 H, t, *J* 7.7, ArH), 6.95 (1 H, dt, *J* 7.7, 1.7, ArH), 5.04 (1 H, qd, *J* 6.4, 3.2, CH), 2.28 (1 H, d, *J* 3.2, OH), 1.43 (3 H, d, *J* 6.4, CH_3); δ_C (75 MHz, $CDCl_3$) 147.42 (C), 139.25 (CH), 129.10 (CH), 128.68 (CH), 126.28 (CH), 97.17 (C), 73.65 (CH), 23.70 (CH_3). Conversion and enantiomeric excess were determined by chiral G.C; (Chrompak β-Cyclodextrin 50 m x 0.25 mm x 0.25 μm column, oven 160 °C, inj.: split 220 °C, det.: FID 220 °C, 100 Pa H_2) retention times 12.4 (2'-iodoacetophenone), *R* isomer 18.3 minutes, *S* isomer 21.5 minutes.

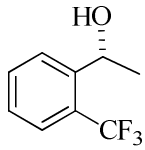
1-(2-Methylphenyl) ethanol.



This compound has been reported and fully characterised.[190] $[\alpha]_D^{30}$ +56.9 (*c* 0.41 in EtOH) 93.8% e.e. (*R*), lit.[187] $[\alpha]_D^{20}$ +60.6 (*c* 0.71 in EtOH) 95% e.e. (*R*); δ_H (300 MHz, $CDCl_3$) 7.47 (1 H, dd, *J* 7.4, 1.5, ArH), 7.24-7.08 (3 H, m, ArH), 5.06 (1 H, dq, *J* 6.4, 3.3, CH), 2.31 (3 H, s, (Ar-*CH*$_3$) 2.14 (1 H, d, *J* 3.3, OH), 1.42 (3 H, d, *J*

6.4, CH_3); δ_C (75 MHz, $CDCl_3$) 143.79, 134.09, 130.25, 127.03, 126.26, 124.41, 66.64 (CH), 23.82 (CH_3), 18.82 (CH_3). Conversion and enantiomeric excess were determined by chiral G.C; (Chrompak β-Cyclodextrin 50 m x 0.25 mm x 0.25 μm column, oven 125 °C, inj.: split 220 °C, det.: FID 220 °C, 100 Pa H_2) retention times 8.9 (2′-methylacetophenone) *R* isomer 18.1 minutes, *S* isomer 21.2 minutes.

1-(2-Trifluoromethylphenyl) ethanol.



This compound has been reported and fully characterised.[191] δ_H (300 MHz, $CDCl_3$) 7.79 (1 H, d, *J* 7.9, ArH), 7.60-7.54 (2 H, m, ArH), 7.34 (1 H, t, *J* 7.6, ArH), 5.33-5.26 (1 H, m, CH), 2.40 (1 H, d, *J* 3.0, OH), 1.44 (3 H, d, *J* 6.40, CH_3); δ_C (75 MHz, $CDCl_3$) 145.02 (*C*-CF_3), 132.33 (CH), 127.27 (CH), 127.07 (CH), 126.59 (C), 125.27 (q, J^{CF} 6.0, CH), 124.36 (q, J^{CF} 273.9, CF_3), 65.61 (CH), 25.35 (CH_3); δ_F (300 MHz, $CDCl_3$) -58.95 (s). Conversion and enantiomeric excess were determined by chiral G.C; (Chrompak β-Cyclodextrin 50 m x 0.25 mm x 0.25 μm column, oven 120 °C, inj.: split 220 °C, det.: FID 220 °C, 100 Pa H_2) retention times 7.6 (2′-trifluoromethylacetophenone), *R* isomer 13.0 minutes, *S* isomer 13.8 minutes.

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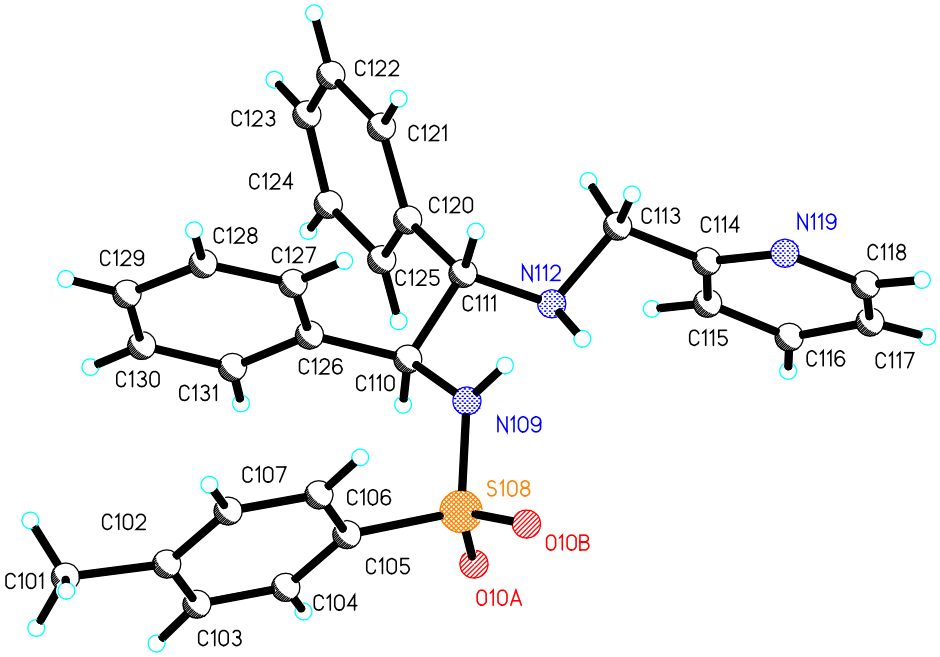
5. Appendix

(*S*,*S*)-*N*-{1,2-Diphenyl-2-[(pyridin-2-ylmethyl)-amino]-ethyl}-4-methyl-benzenesulfonamide (231)



Solid state structure of one of the crystallographically independent but chemically identical molecules in the asymmetric unit of **231**. The minor disordered component of the methyl pyridyl ring has been removed for clarity.

Experimental data for **231.**

There are two molecules in the asymmetric unit, eight in the unit cell. Due to the rather high values of the thermal parameters of the pyridyl nitrogen in the methylpyridyl group (C114-C119) a model was developed where the nitrogen was disordered over the two ortho positions of the ring and refined to an occupancy of 7:3 C115-N119 : N115-C119.

The atoms involved in this disorder (C115, N115, N119, C119) were refined isotropically.

The methyl pyridyl group was disordered over two positions (C221-C219 and C11A-C19A)

in the other molecule. The occupancy was originally allowed to refine but then fixed at 60:40 once it settled down. AFIX 66 restraints were used to constrain these rings to a hexagon.

The hydrogens on the amine N112 and N212 were located in a difference map and allowed to refined with a DFIX restraint and given thermal parameters equal to1.5 times that of the equivalent isotropic displacement parameter of the atom to which they are attached. No

hydrogen was located for the minor component amine N12A but this was added to the formula so as to calculate the correct density etc.

Many SIMU restraint were used to give the thermal parameters of the disordered components reasonable values. There were 6004 Friedel pairs giving a Flack parameter of 0.003(9) and a Hooft y parameter of 0.03(15) (Olex2).

This means you can be reasonably confident in the assignment of the stereochemistry

(But you started from a know stereochemistry anyway). Some of the NHs of the sulphonamide and amine form H bond contacts tabulated below.

Specified hydrogen bonds (with esds except fixed and riding H)

D-H	H...A	D...A	<(DHA)	
0.86	2.22	2.928(4)	139.5	N109-H109...O20A_$1
0.86	2.10	2.957(4)	173.5	N209-H209...O10B_$2
0.89(2)	2.31(12)	2.817(12)	115(10)	N212_a-H212_a...N219

Symmetry operators used to generate equivalent atoms in the above contacts were

$1 -1+X,+Y,+Z

$2 1+X,+Y,+Z

There is pi stacking interaction described by the atoms used to define the mean planes, the angle between mean planes and the closest atomic contactC102 C103 C104 C105 C106 C107 to C126 C127 C128 C129 C130 C131 is 19.50 (0.18) degreeswith the closest atomic contact C105 - C126 3.3048 (0.0050) Angstroms.

Crystal Data

C27 H27 N3 O2 S, M = 457.58, Orthorhombic, space group P2(1)2(1)2(1)

a = 11.9961(2), b = 18.3565(3), c = 22.6663(3) A , alpha = 90 deg., beta = 90 deg., gamma = 90 deg., U = 4991.26(13) A^3 (by least squares refinement on 14229 reflection positions), T =293(2)K, lambda = 0.71073 A, Z = 8, D(cal) = 1.218 Mg/m^3, F(000) = 1936. mu(MoK-alpha) = 0.158 mm^-1. Crystal character:colourless block. Crystal dimensions 0.45 x 0.45 x 0.45 mm.

Data Collection and Processing.

Oxford Diffraction Gemini four-circle system with Ruby CCD area detector.

The crystal was held at 293(2) K with the Oxford Cryosystem Cryostream Cobra.

Maximum theta was 30.64 deg. The hkl ranges were -16/ 17, -25/ 26, -28/ 32. 50473 reflections measured, 14062 unique [R(int) = 0.0271]. Absorption correction by Semi-empirical from equivalents; minimum and maximum transmission factors: 0.96; 1.00. no crystal decay

Structure Analysis and Refinement. Systematic absences indicated space group P2(1)2(1)2(1) and shown to be correct by successful refinement. The structure was solved by direct methods using SHELXS (Sheldrick, 1990) (TREF) with additional light atoms found by Fourier methods. Hydrogen atoms were added at calculated positions and refined using a riding model with freely rotating methyl groups. Anisotropic displacement

parameters were used for all non-H atoms; H-atoms were given isotropic displacement parameters equal to 1.2 (or 1.5 for methyl hydrogen atoms) times the equivalent isotropic displacement parameter of the atom to which the H-atom is attached (see above)The absolute structure of the individual crystal chosen was checked by refinement of a delta-f" multiplier. Absolute structure parameter x = 0.03(9). The weighting scheme was calc w=1/[\s^2^(Fo^2^)+(0.1272P)^2^+1.6970P] where P=(Fo^2^+2Fc^2^)/3. Goodness-of-fit on F^2 was 1.053, R1[for 10183 reflections with I>2sigma(I)] = 0.0846, wR2 = 0.2438.

Data / restraints / parameters 14062/ 92/ 602. Largest difference Fourier peak and hole 0.894 and -0.336 e.A^-3 . Refinement used SHELXL 97 (Sheldrick, 1997). Additional material available from the Cambridge Crystallographic Data Centre comprises H-atom coordinates, thermal parameters and the remaining bond lengths and angles.

The Oxford Diffraction Gemini XRD system was obtained through the Science City Advanced Materials project: Creating and Characterising Next Generation Advanced Materials, with support from Advantage West Midlands (AWM) and part funded by the European Regional Development Fund (ERDF)

References

For relevant information for the SHELXTL suite of programmes used to solve, refine and produce the files for this structure, please refer to "A Short History of Shelx, G. M. Sheldrick, Acta Cryst. 2008, A64, 112-122"

Use Mercury (Free from CCDC at www.ccdc.cam.ac.uk/products/mercury) to view the structure.