Chiral nitrogen ligands in asymmetric catalysts

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Submitted by Christelle Moreau

for the degree of PhD

of the University of Bath

2000

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Abstract

In this thesis is described our studies on the synthesis of novel enantiopure nitrogen ligands and their applications in asymmetric reactions.

The first chapter contains a review on nitrogen containing ligands in metal-catalysed addition to C=O bonds, illustrated by mechanisms and how they can transfer their chirality to prochiral substrate. Asymmetric hydrogenation, transfer hydrogenation, hydrosilylation, aldol, ene, hetero Diels-Alder reactions, hydroboration and dialkylzinc additions will be discussed.

The second chapter will discuss our investigations on the synthesis of enantiopure nitrogen ligands using some recent chemistry developed by Hartwig and Buchwald, namely the palladium-catalysed amination of aryl halides.

In chapter three we will describe the screening of ligand libraries in the asymmetric hydrosilylation of ketones using parallel screening techniques. The optimisation of the results by screening of both ketones and solvents, as well as the optimisation of the ligands will be also developed. Catalysts studies and mechanistic considerations will also be discussed.

Finally in chapter four, we will see how these ligands libraries were used in the development of a rhodium mediated coupling of aryl boronic acids and aldehydes.

Key words: Nitrogen ligands, enantioselective reactions, palladium, hydrosilylation, ruthenium, parallel screening, rhodium

Abbreviations

Ac	Acetyl
Acac	2,4-Pentenedione
Ala	Alanine
Aib	2-Aminoisobutyric acid
(R)-AMIMPHOS	*N*-[2-(Diphenylphosphino)benzyl]-(R)-1-phenylethanamine
(R,R)-BDPP	(2R,4R)-(+)-*Bis*(diphenylphosphino)pentane
(R)-BINAP	(R)-(+)-2,2'-*Bis*(diphenylphosphino)-1,1'-binaphthyl
Box	Bis-oxazoline
(R,R)-CHIRAPHOS	(2R,3R)-*Bis*(diphenylphosphino)butane
Cod	1,4-Cyclooctadiene
Cps	Dicyclohexylphosphinoserine
Cy	Cyclohexane
Cystphos	(2-Dimethylamino)-1-(diphenylphosphino)-3-(methylthio) propane
Dba	Dibenzylideneacetone
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
(R,R)-DIOP	(4R,5R)-(-)-*O*-Isopropylidene-2,3-dihydroxy-1,4-*bis* (diphenylphosphino)butane
DME	Dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
(S,S)-DPEN	(S,S)-Diphenylethylene diamine
DPEphos	2,2'-*Bis*(diphenylphosphino)diphenylether

dppf	1,1'-*Bis*(diphenylphosphino)ferrocene
dppp	1,3-*Bis*(diphenylphosphino)propane
e.e.	Enantiomeric excess
Et	Ethyl
Hfc	Heptafluoropropylhydroxymethylene
GC	Gas chromatography
HPLC	High Performance Liquid Chromatography
H	Hour
IR	Infra red
IPA	Isopropyl alcohol
i-Pr	Isopropyl
J	Coupling constant
(R)-JOSIPHOS	(R)-(-)-1-[(S)-2-(Diphenylphosphino)ferrocenyl]-ethyldicyclohexylphosphine
L-men	L-Menthyl
Me	Methyl
MOP	2-Diphenylphosphino-2'-methoxy-1,1'-binaphthyl
m.p	Melting point
o-An	*Ortho* anisyl
NMR	Nuclear Magnetic Resonance
(R,R)-NORPHOS	(2R,3R)-(-)-2,3-*Bis*(diphenylphosphino)-bicyclo[2.2.1]-hept-5-ene
Ph	Phenyl
Phe	Phenylalanine
PMHS	Polymethylhydrosiloxane

Rac-PPFA	(R)-*N,N*-Dimethyl-1-[(S)-2-(diphenylphosphino)ferrocenylethyl amine
PPM	(2S,4S)-4-Diphenylphosphino-2-diphenylphosphinomethyl pyrrolidine
Pps	Diphenylphosphinoserine
(R)-PROPHOS	(R)-(+)-1,2-*Bis*(diphenylphosphino)propane
PYMOX	(S)-(-)-4-Alkyl-2-(2-pyridinyl)-2-oxazoline
PYTHIA	2-(2-Pyridinyl)-4-carbethoxy-1,3-thiazolidine
(R)-QUINAP	(R)-(+)-1-(2-Diphenylphosphino-1-naphthyl)isoquinoline
r.t.	Room temperature
TADDOL	(R,R) or (S,S)-α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanol
t-Bu	*Tert*-butyl
Tf	Trifluoromethylsulfonate
THF	Tetrahydrofuran
TMEDA	*N, N, N', N'*-Tetramethylethylenediamine
TEA	Triethylamine
Tol	Tolyl
(R)-tol-BINAP	(R)-(+)-2,2'-*Bis*(di-p-tolyl-phosphino)-1,1'-binaphthyl
Tlc	Thin layer chromatography
Ts	Tosyl

Contents

Nitrogen-containing ligands for asymmetric homogeneous metal-catalysed additions to C=O bonds

This review is intended to introduce the use of enantiopure nitrogen-containing ligands in catalytic additions to C=O bonds and thus illustrates the mechanisms by which they can transfer their own chirality to prochiral substrates. It is not our intention to provide a thorough description of this subject but instead briefly discuss a small number of synthetically useful reactions and some of the most recent developments which have taken place. Many excellent reviews of the use of amine ligands can be found elsewhere,[1-3] here we choose to discuss first the nature of each reaction, then the generally accepted mechanism and finally give a description of some of the most successful ligands for these processes and their evolution.

Three categories of reactions will be discussed; the first one involves the transition metal catalysed addition to C=O bonds in which a chiral ligand is bound to a metal centre (such as Ru, Ir, Rh, *etc*) to form optically active complexes which can transfer their chirality in a catalytic manner. Such complexes are used in asymmetric hydrogenation, transfer hydrogenation and hydrosilylation of ketones. More emphasis will be placed on the asymmetric hydrosilylation of ketones since much of our work has focused on this reaction. The second category is a Lewis acid catalysed addition to C=O bonds in which a chiral ligand is bound to a metal (such as Cu, Sn, Zn, *etc*). The resulting Lewis acid complex will activate the carbonyl group to which a nucleophile can add. Thus Lewis acid has the potential to catalyse carbon-carbon formation such as aldol, hetero Diels-Alder and carbonyl ene reactions. The third category includes asymmetric borane reduction and dialkylzinc addition to aldehydes, these reactions do not strictly belong to either of the first two categories, and serve to show a different mode of action of enantiopure N-containing ligands.

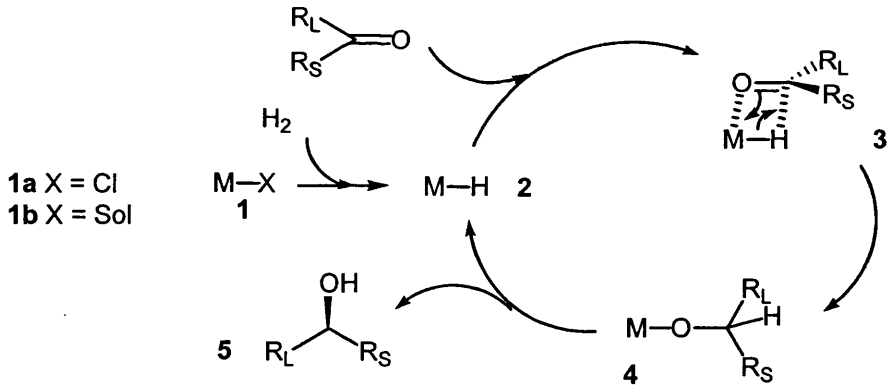
Transition metal catalysed reactions

Asymmetric hydrogenation

Recently the scope and selectivity of the homogeneous asymmetric hydrogenation reaction has greatly extended.[4] This research, principally carried out by Noyori and co-workers has yielded a methodology which is now beginning to rival the stoichiometric hydroboration chemistry previously used for such reductions and represents one of the most useful synthetic approaches to optically active compounds.

One possible mechanism is outlined in scheme **1** and involves firstly the formation of the metal hydride hydrogenation catalyst **2** formed from the chloride and hydrogen. The coordination of the ketone can then occur *via* **3** to give the alkoxide intermediate **4** which can then reductively generate the optically active alcohol product **5**.

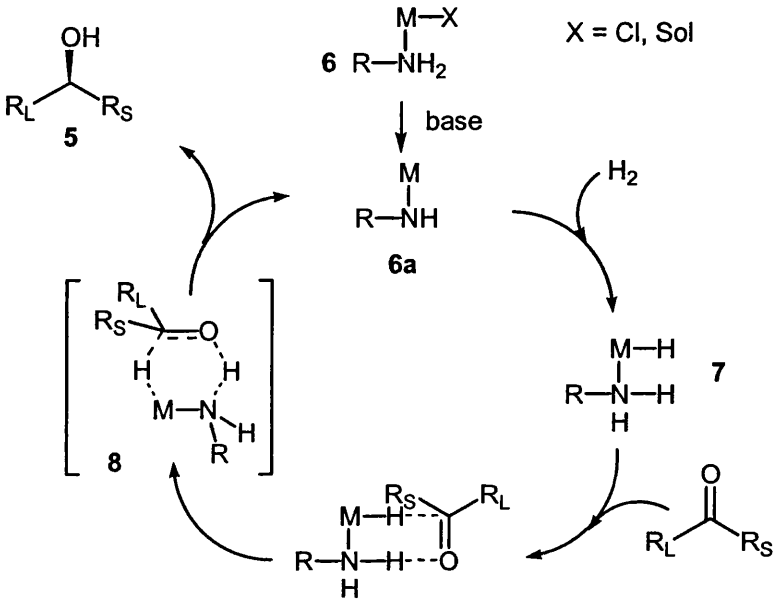
Scheme 1:



Very few examples of rhodium and iridium catalysed asymmetric hydrogenation of simple ketones have been reported.[5-6] It is only recently that Noyori reported a new efficient ruthenium catalyst, previously ruthenium dichloride *bis*-phosphines had proved to be catalytically inactive in the hydrogenation of simple ketones. Catalytic activity was found to be conferred by the addition of chiral diamines to the ruthenium *bis*-phosphine complex.[7] Noyori thus proposed a new mechanism for the hydrogenation of ketones in which he claimed that the ketone does not bind the ruthenium centre at any time.[8] In this mechanism complex **6** is reacted with a base to form the intermediate **6a** which is then

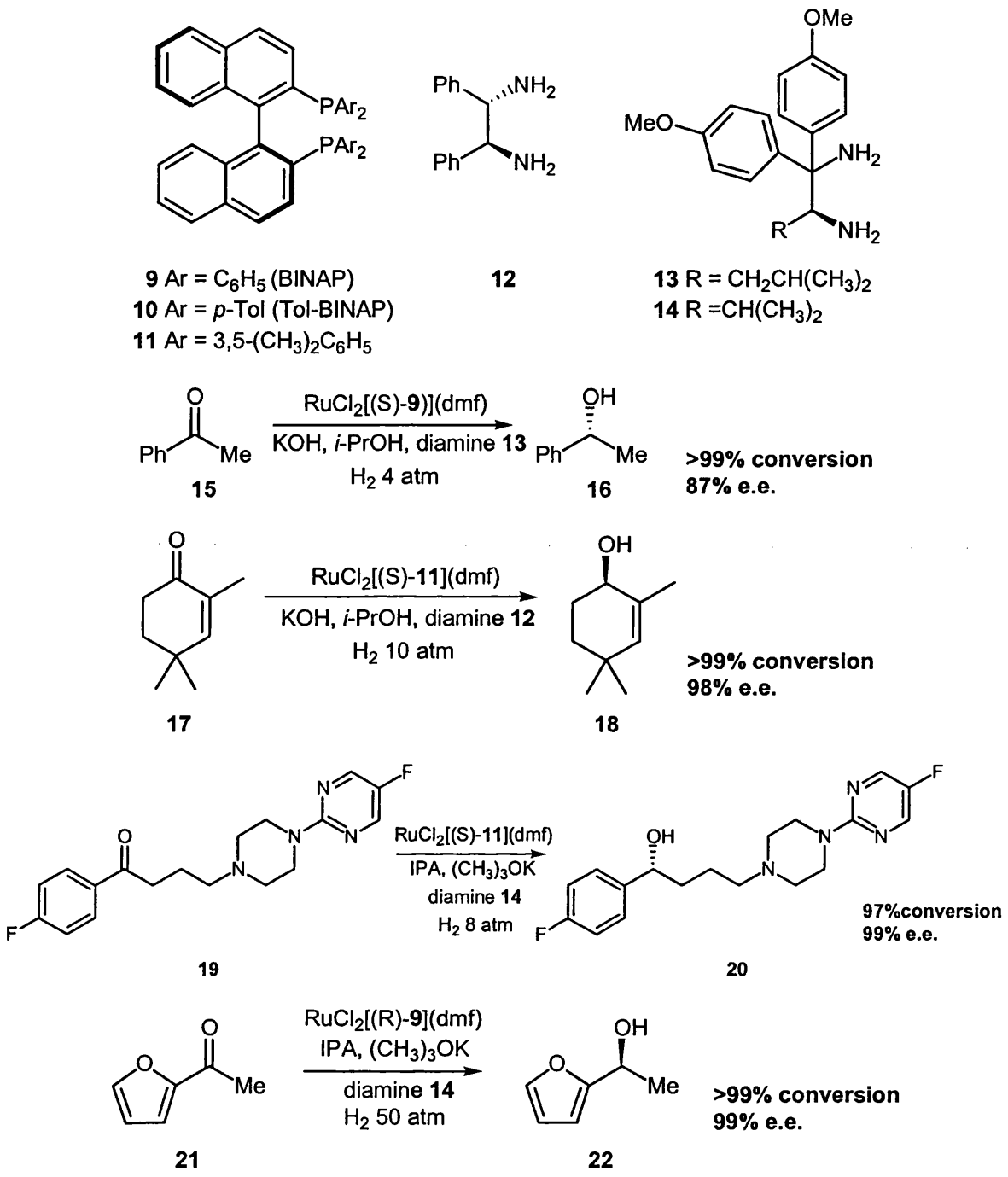
hydrogenated to complex **7**. The carbonyl oxygen can then interact with the acidic NH proton of **7** to form a six-membered cyclic transition state **8** in which the hydride delivery can take place (Scheme **2**).

Scheme 2:



Noyori's ruthenium complexes containing *bis*-phosphines (**9-11**) and chiral diamines (**12-14**) proved to be very efficient catalysts for the reduction of various simple ketones such as acetophenone **15** to phenethyl alcohol **16**, in excellent optical purity (99% e.e., scheme **3**). Although these reactions were carried out under reaction conditions close to those of transfer hydrogenation (both IPA and KOH are present), Noyori claimed that molecular hydrogen was the actual reductant. Under the same conditions, α,β-unsaturated ketones,[9-10] amino ketones[11] and hetero amino ketones[12] could also be reduced to yield high e.e. products; 2,4,4-trimethyl-2-cyclohexenone **17**, the functionalised γ-amino ketone **19** and the hetero amino ketone **21** could be converted in to their products **18**, **20** and **22** respectively with e.e.'s > 98%. These catalysts also provide turnover numbers of up to two millions making them suitable for large scale manufacturing processes. In the case of the hetero amino ketone, a substrate/catalyst ratio as high as 40000 could be used and still afford the desired alcohol in 99% e.e. (Scheme **3**).

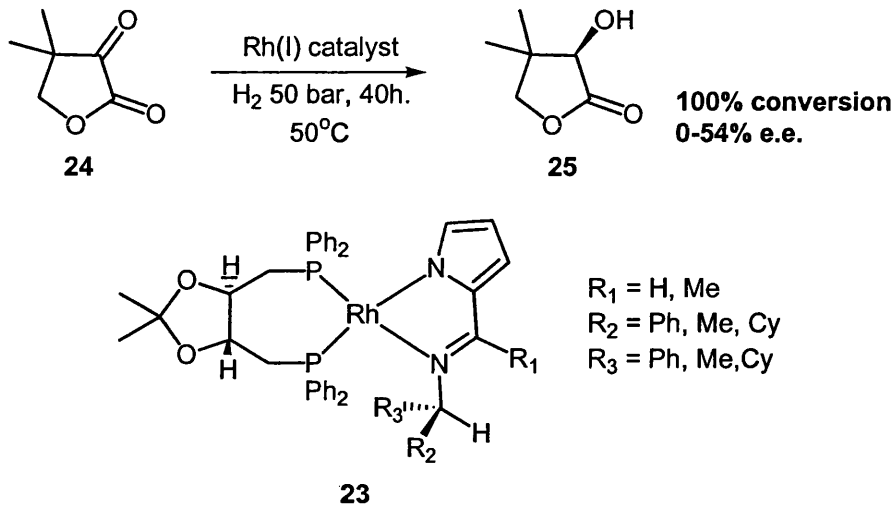
Scheme 3:



A similar rhodium catalyst **23**, containing (R,R)-DIOP and a pyrrole Schiff base ligand was used in the asymmetric hydrogenation of ketopantolactone **24**.[13] Stereoselectivities of 0 to 54% for (R)-pantolactone **25** were achieved using related catalysts made from (R,R)-DIOP in combination with both isomers of the amines (Scheme **4**). It is assumed that during catalysis the pyrroleimines are bound in a monodentate fashion through the pyrrole

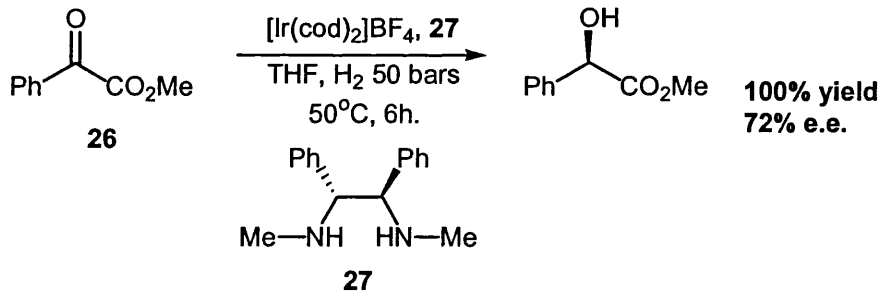
nitrogen atom thus leaving the asymmetric centre of the imine ligand relatively far from the catalytic site.

Scheme 4:



Asymmetric molecular hydrogenation of phenylglyoxylate methyl ester **26** was successfully achieved in the presence of a sub-stoichiometric amount of cationic rhodium and iridium species containing C_2-symmetric diamines. The best result of 72% e.e. was obtained with an iridium complex of ligand **27** (Scheme **5**).[14]

Scheme 5:



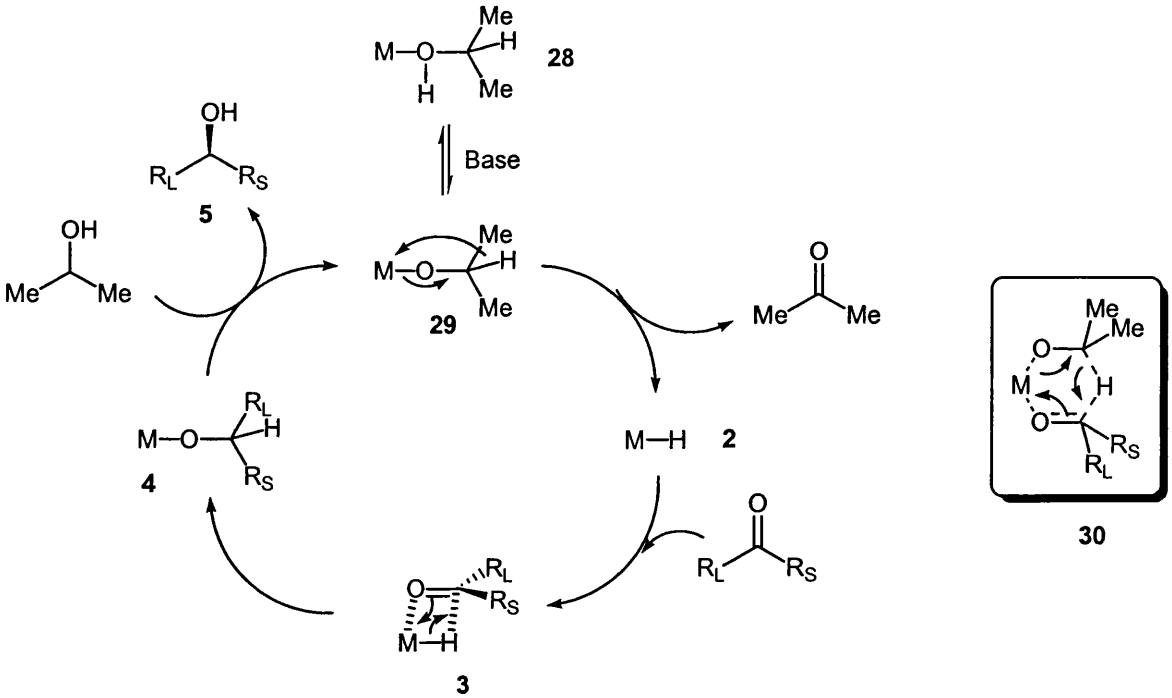
Asymmetric transfer hydrogenation

Catalytic transfer hydrogenation using either isopropanol (IPA) or a mixture of formic acid- triethylamine as a source of hydrogen is an especially useful method for the catalytic enantioselective reduction of C=O bonds.[15-19] Isopropanol is a good hydrogen source for the reaction with many favourable properties; it is easy to handle, stable, non-toxic,

inexpensive and dissolves many organic compounds. The transfer hydrogenation with IPA is however reversible, since both 2-propanol and the reaction product are both secondary alcohols which can be transformed to the corresponding ketone with loss of H_2 under the reaction conditions. Performing the reaction with formic acid as the hydride source results in an irreversible reaction.

The asymmetric transfer hydrogenation has been believed to proceed *via* the mechanism outlined in scheme **6**. The mechanism begins with a deprotonation of the coordinated alcohol **28**, followed by hydride abstraction from the resulting alkoxide **29** and elimination of acetone to form the metal hydride **2**. The insertion of the ketone into the M-H bond gives the alkoxide **4**. A final ligand exchange between **4** and IPA releases the optically pure alcohol **5**. This pathway involves a metal hydride intermediate although the possibility of a direct hydride delivery (such as the Meervein-Pondorf-Verley reduction) *via* **30** could not be eliminated.

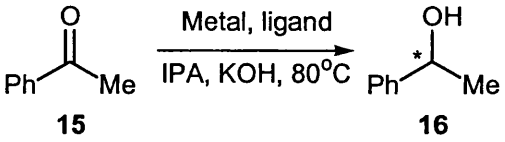
Scheme 6:



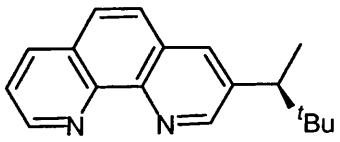
This traditional mechanism had been reported for transfer hydrogenation catalysed by transition metal complexes which in most cases possess tertiary phosphines or sp^2-

hybridized amine ligands such as the chiral phenanthroline **31**,[20] tetrahydro*bis*(oxazole) **32**,[21] or the tridentate N,P,N ligand **33**[22] (Scheme 7). These ligands have been employed in the asymmetric transfer hydrogenation of acetophenone **15** in combination with rhodium, iridium and ruthenium respectively to yield 2-phenylethanol **16** in moderate to good yield and selectivities.

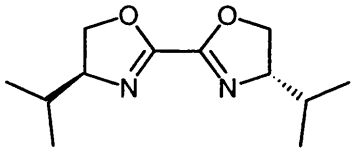
Scheme 7:



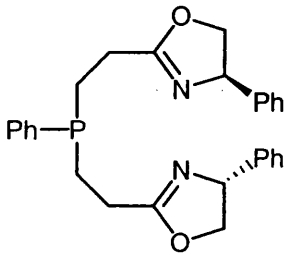
15 **16**



31 89% conversion
63% e.e. (S)



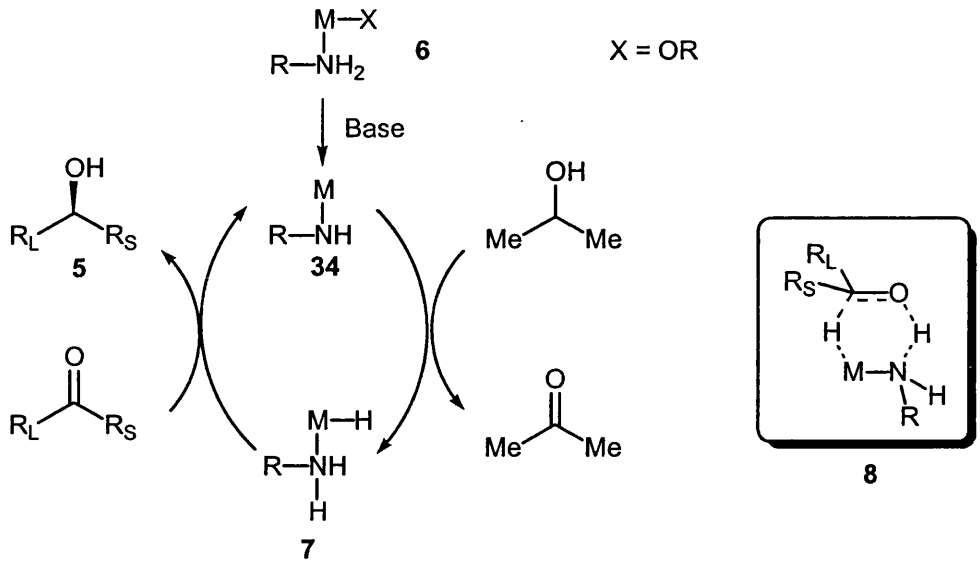
32 89% conversion
58% e.e. (R)



33 72% conversion
79% e.e. (R)

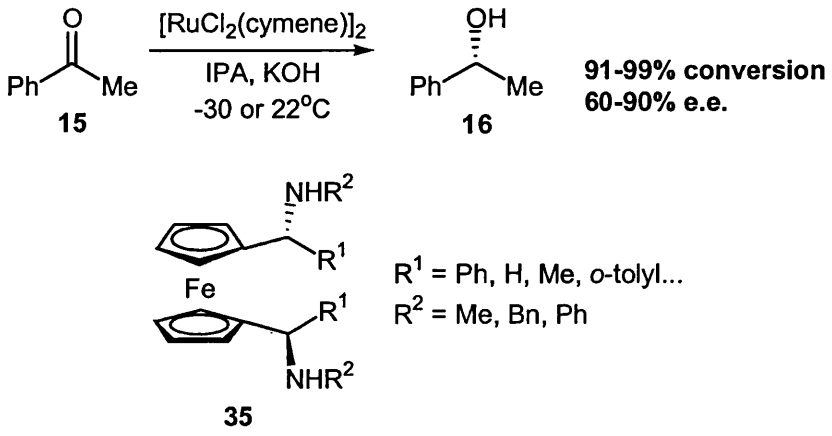
The classical mechanism did not explain an observation reported by Noyori, who claimed that the presence of an NH or NH_2 function in the ligands was crucial for high reactivity and enantioselectivity.[17] He proposed that hydrogen bonding between the oxygen atom in the ketone substrate and the NH function help to stabilize the transition state **8** in which the stereochemistry is important. A new catalytic cycle was thus proposed which is similar to the one proposed for the asymmetric hydrogenation (scheme **8**). In this mechanism the base abstracts a proton from the metal alkoxide **6** to form to the metal amide catalyst **34** upon elimination of the alcohol. The hydroxyl proton from IPA interacts with the basic N-atom of **34** while the ketone substrate interacts with the acidic NH proton of **7**. Therefore the ketone never coordinates directly to the metal centre and the hydride transfer occurs *via* a pericyclic transition state **8**.

Scheme 8:



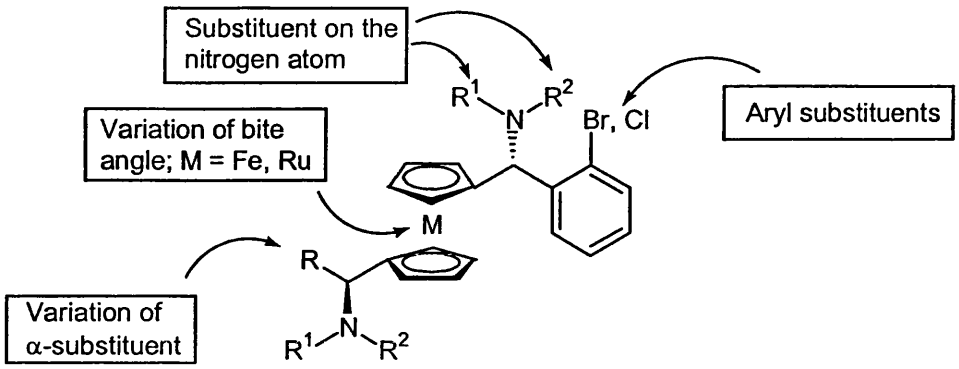
A good example of the use of bidentate N-N ligands is found in Knochel's report on C_2-symmetric diaminoferrocenyl derivatives as highly efficient ligands for the ruthenium-catalysed hydride transfer hydrogenation of ketones. A combination of ligand **35** with $[RuCl_2(cymene)]_2$ efficiently reduced acetophenone **15** in more than 90% conversion and up to 90% e.e. (Scheme **9**).[23]

Scheme 9:

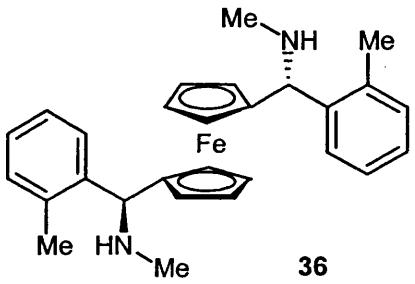


Knochel and co-workers went on to optimise the structure of ligand **35** for this reaction, variations of the metallocene core (which varies the bite angle of the ligand), the substituent on the nitrogen atom and the α-substituent were explored (Scheme **10**).

Scheme 10:

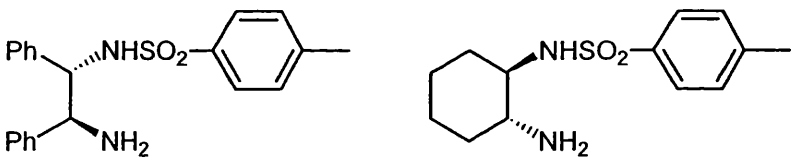


Ligand **36** was found to be the best optimised ligand which yielded 2-phenylethanol **16** in 97% conversion and 80% e.e. when used in combination with $[RuCl_2(cymene)]_2$.[24]



36

The most selective ligand reported to date for the transfer hydrogenation reaction was described by Noyori; ruthenium complex of the *N*-monosulfonated-1,2-DPEN ligand **37** gave 97% e.e. in the reduction of acetophenone **15** with IPA as the hydride.[25] Knochel reported the similar *N*-monosulfonated-1,2-diaminocyclohexane ligand **38** afforded 2-phenylethanol in 94% e.e. under the same conditions.[23]

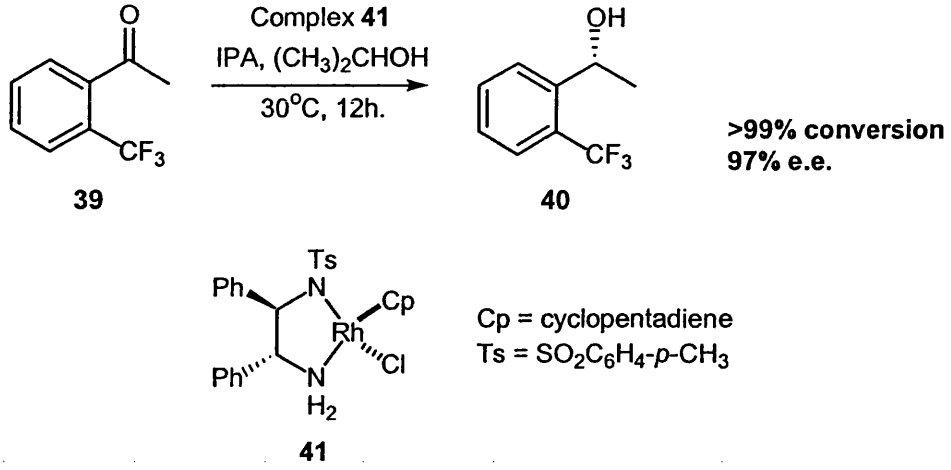


37 **38**

Recently, Noyori's group reported the synthesis of new iridium and rhodium complexes containing ligands **37** and **38**. These isolable complexes proved to efficiently catalyse the asymmetric hydrogen transfer of simple aromatic ketones in 2-propanol with ^{t}BuOK as a base.[26] The reaction of *p*-trifluoromethylacetophenone **39** in IPA containing the rhodium

complex **41** and ^{t}BuOK at 30°C for 12 hours afforded the desired alcohol **40** in 97% e.e. and 99% conversion (Scheme **11**).

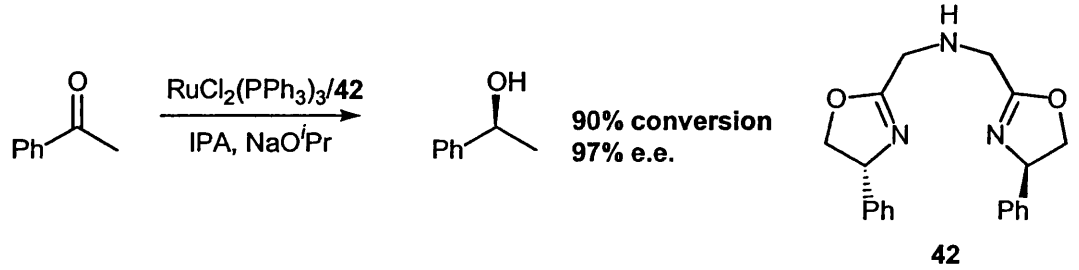
Scheme 11:



39 **40** **41**

Recently Zhang and co-workers have reported that the new chiral ligand ambox **42**, designed to incorporate an NH centre after Noyori's report, was effective in the hydride transfer reduction of acetophenone, yielding the desired alcohol in more than 90% conversion and 97% e.e. using $RuCl_2(PPh_3)_3$ as a metal precursor.[27] (Scheme **12**)

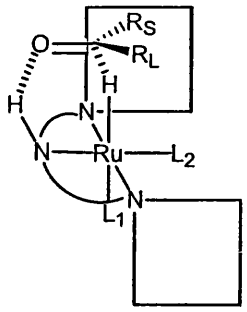
Scheme 12:



42

A possible cyclic transition state is shown in the case of the ambox ligand in scheme **13**. The mechanism would seem to involve a concerted transfer of both a proton and hydride as proposed by Noyori.

Scheme 13:

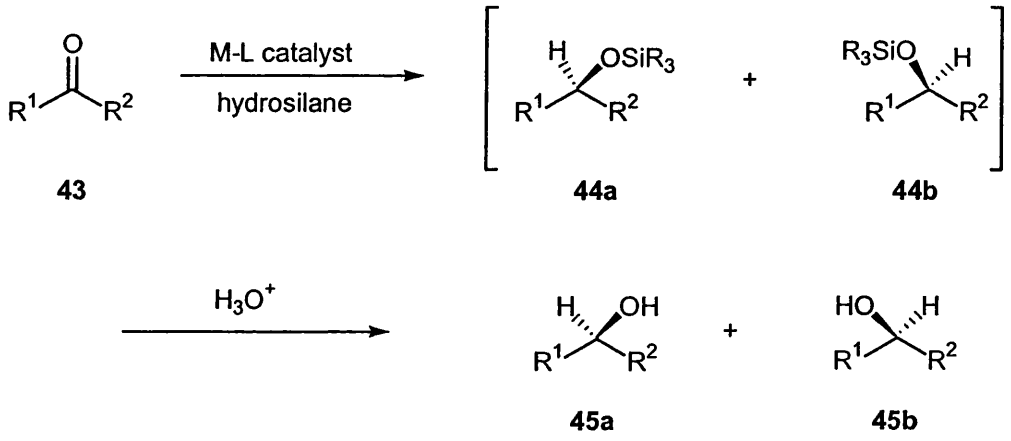


R_S = small group
R_L = large group
L_1, L_2 = ligand

Asymmetric hydrosilylation

The asymmetric catalytic reduction of ketones with certain organohydrosilanes and transition-metal catalysts is named hydrosilylation and has been recognised as an effective route to generate optically active secondary alcohols. In the asymmetric hydrosilylation of ketones (**43**), silyl ethers (**44a** and **44b**) are formed, which can be hydrolysed under mild acidic conditions in the reaction work-up to give the corresponding alcohols (**45a** and **45b**) (Scheme **14**).[28]

Scheme 14:



43 **44a** **44b**

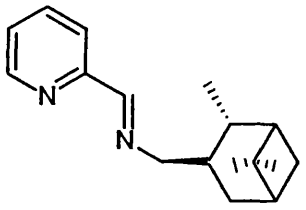
45a **45b**

Since the Wilkinson catalyst [$RhCl(PPh_3)_3$] was first found to catalyse the hydrosilylation of ketones in the early 1970's, the first attempts to develop asymmetric variants of the reaction involved rhodium catalysts bearing optically active phosphines.

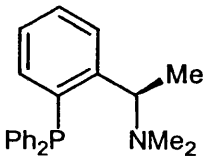
The asymmetric hydrosilylation of ketones using catalysts derived from optically active nitrogen ligands was first investigated in the early 1980's. A series of chiral pyridine based

ligands (prepared from pyridine-2-carboxaldehyde and optically active alkyl amine) were developed and evolved to give increased asymmetric inductions over a number of years.[29-30] Among them, the iminopyridine **46** was reported to give 79% e.e. for the hydrosilylation of acetophenone **15**. These ligands were found to be superior to the enantiopure phosphine ligands (50-52% e.e. had been achieved with Amphos **47** and Aminphos **48**) in the rhodium-catalysed hydrosilylation of ketones (Scheme **15**).[31] It was thus realised that enantiopure amine ligands were more promising ligands for the asymmetric hydrosilylation reaction. Over the past twenty years, the design of new ligands applicable to a wide range of substrates has brought the reaction to prominence as a successful, reliable means of accessing optically active alcohols in a catalytic manner.

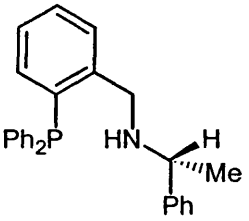
Scheme 15:



46 Iminopyridine



47 (R)-(+)-AMPHOS

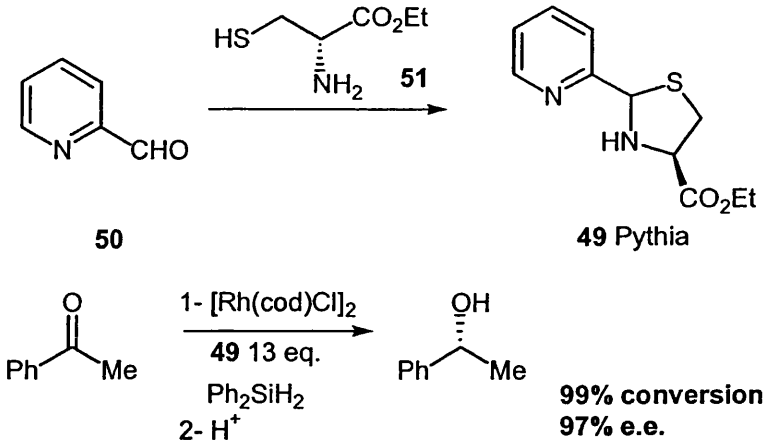


48 (R)-(+)-AMINPHOS

Chiral rhodium catalysts

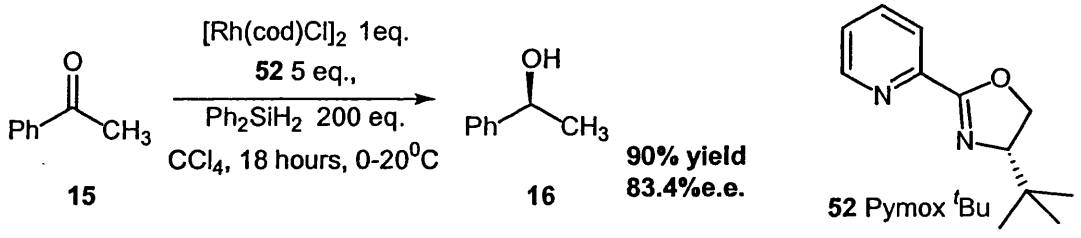
In the mid 1980's, a new ligand system, the enantiopure pyridine thiazolidine Pythia **49**, prepared from 2-pyridinecarboxaldehyde **50** and L-cysteine ethyl ester **51** was reported. Reduction of acetophenone performed with this ligand gave 97% e.e. when a 13-fold excess of ligand to the rhodium atom was used in the absence of solvent[32-33] (Scheme **16**). In this system, diphenylsilane was found to be more efficient than (1-naphthyl)phenylsilane. The studies showed that an increase from 3 to 13-fold ligand excess was beneficial for high enantiomeric excess.

Scheme 16:



In the late 1980s, chiral rhodium-oxazolinyl pyridine complexes (Rh-Pymox) were introduced as catalysts for the asymmetric hydrosilylation reaction. The pyridine oxazolines ligands are easily available from either a promoted Lewis acid condensation between 2-cyanopyridine and the appropriate enantiopure amino alcohol or by formation of the amide from the pyridine-2-carbonyl chloride, followed by cyclodehydration to produce the oxazoline.[34-37] The rhodium complexes of these ligands were prepared by refluxing with $RhCl_3.3H_2O$ in ethanol. The optimal result for this series was obtained with Pymox-*t*-Bu **52**:[34-35] 1-phenylethanol **16** was produced in 83.4% e.e. and 90% yield from acetophenone **15** (Scheme **17**). It was reported that the optical purity of product depended on the rhodium/ligand, rhodium/substrate and substrate/silane ratio as well as the solvent used for the reaction. Reactions in CCl_4 resulted in better chemical yields and optical purities though the precise reason for this remains unclear.[34]

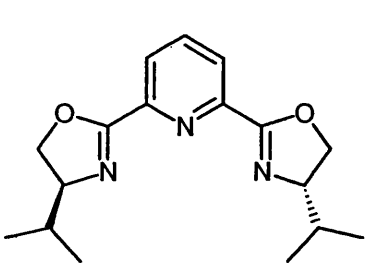
Scheme 17:



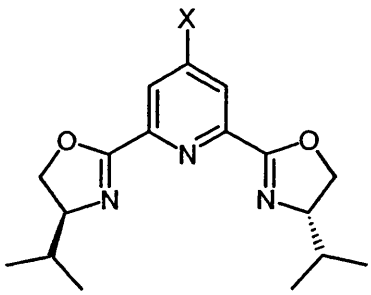
Since C_2-symmetric enantiopure phosphines (such as (R)-DIOP and (R)-BINAP) had been a great success in asymmetric catalysis, the same concept was tested with chiral nitrogen

ligands. A new optically active tridentate pyridine *bis*-oxazoline (Pybox) **53** was thus designed to explore whether such ligands could provide improved selectivities (Scheme 18). Pybox was synthesized from pyridine-2,6-dicarboxylic acid **54** and an optically active amino alcohol *via* an amido chloride intermediate. Treatment of Pybox with $RhCl_3.(H_2O)_3$ in ethanol at 80°C for 3 hours afforded the rhodium-Pybox complex as an air-stable solid.

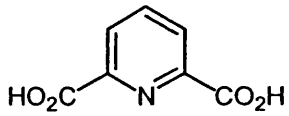
Scheme 18:



53a *i*-Pr Pybox



53b X=CO_2Me
53c X=NMe_2



54

i, ii, iii, iv

(S,S)-*i*-Pr-Pybox

53a

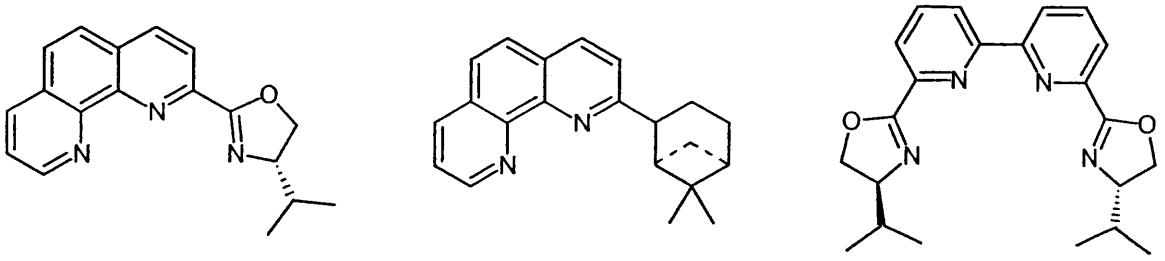
Reagents and conditions: i) $SOCl_2$, reflux, 10h; ii) (S)-Valinol, Et_3N, r.t., 1 day iii) $SOCl_2$, reflux, 3h; iv) NaOH, MeOH-H_2O, r.t., 3 days;

Preliminary experiments showed this complex failed to catalyse the hydrosilylation reaction, however when $AgBF_4$ was added to the reaction, the reduction yielded the desired product in 94% e.e. in THF in combination with diphenylsilane.[35,38]The addition of the silver salt gives a catalytically active cationic species which thus can react with the silane smoothly. Studies were carried out to determine what electronic effect a substituent at the *para* position of the pyridine skeleton would have.[39] It was found that the rhodium complex having an electron withdrawing group CO_2Me, catalysed the reduction of acetophenone with diphenylsilane to give the highest e.e.: 96% at -5°C for 4 hours, whilst the catalyst with an electron donating group, NMe_2 on the ligand proceeded at 20°C over

16 hours to give a 90% e.e., thus demonstrating the electronic effects of remote substituent are a factor in the reaction.

Optically active phenanthrolines have also been investigated in the rhodium-catalysed asymmetric hydrosilylation of acetophenone. The bidentate pinane functionalised phenanthroline derivative **56** was found to give a very good enantioselectivity (Scheme **19**): 75.6% for acetophenone, and is superior to the potentially tridentate phenanthroline-oxazoline **55** (10.8% e.e.).[40] The tetradentate *bis*(oxazolinyl)-bipyridine **57** complexed with $RhCl_3$ gave phenethylalcohol in 90% e.e.[41]

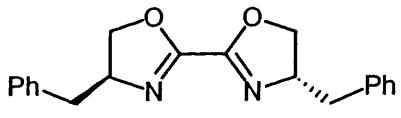
Scheme 19:



55 **56** **57**

Since enantiopure oxazolines have been successfully used in asymmetric synthesis and the C_2 symmetric Pybox being efficient in the asymmetric hydrosilylation reaction, the concept of C_2-symmetry has been applied to the oxazoline unit to generate alternative *bis*-oxazolines such as **58** and were examined in the asymmetric hydrosilylation of ketones.[42] A maximum e.e. of 84% in phenethylalcohol was achieved with the benzyl derivative using a 10-fold excess of ligand to metal, in carbon tetrachloride at room temperature (Scheme **20**).

Scheme 20:

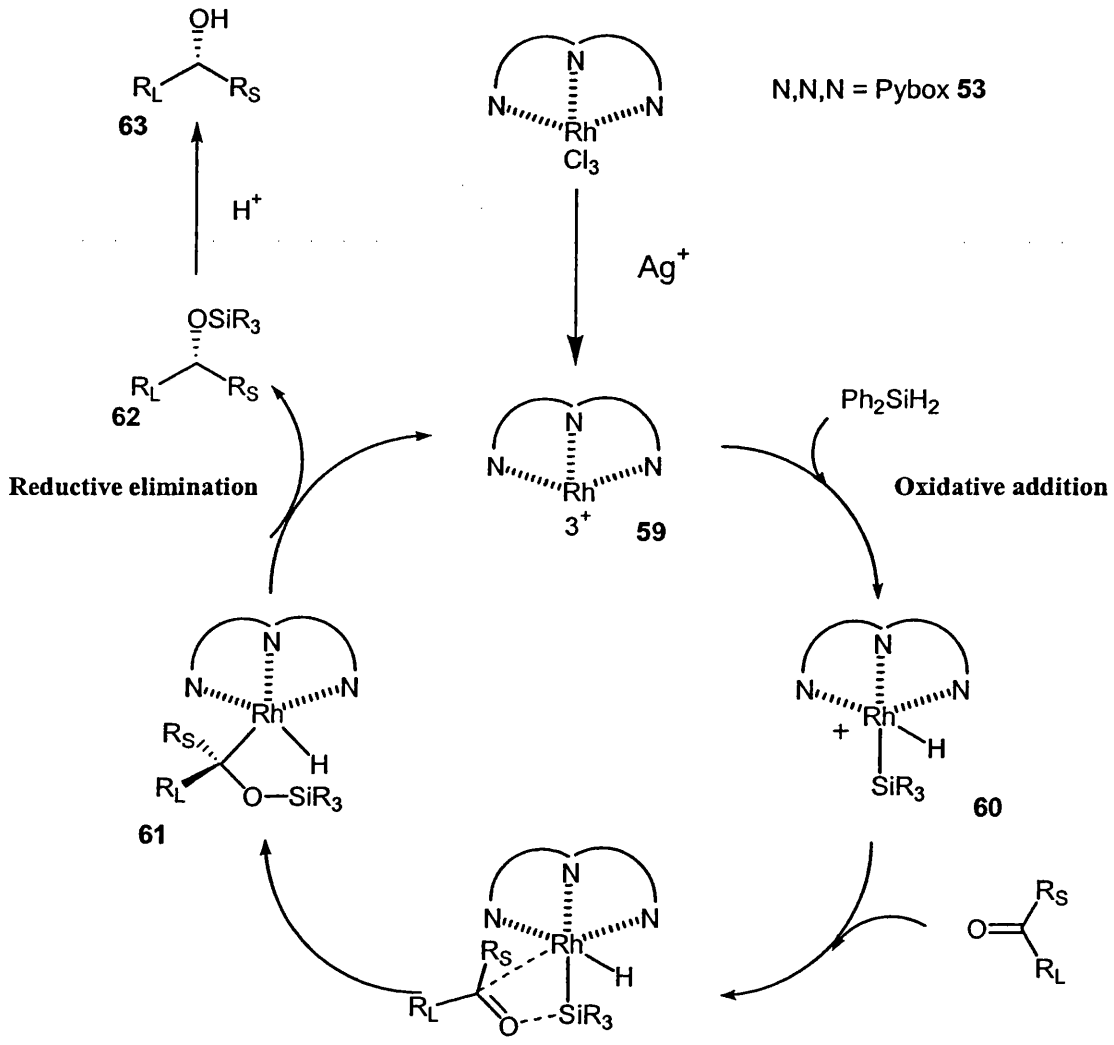


58

The reaction mechanism can be drawn as outined in scheme **21**: the silver salt forms the cationic complex **59** which allows an oxidative addition of the silane to the rhodium to take

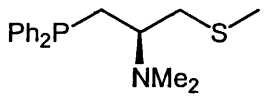
place to form the intermediate **60**. This step is followed by coordination and insertion of the ketone into the rhodium-silicon bond to form a diastereomeric silylalkyl-rhodium intermediate **61**. A reductive elimination of the alkoxysilane then forms the silyl ether **62** and regenerates the cationic rhodium complex **59**. Finally, an acidic work up affords the optically active alcohol **63**.

Scheme 21:



Some ligands containing both nitrogen and phosphorus atoms have already been examined (*e.g.* Amphos or Aminphos) but they afforded only moderate enantioselectivities. In the mid 90's, a new series of P-N ligands were designed which gave further improvements in selectivity. Cystphos **64** reduced acetophenone **15** in 64% e.e. and 99% conversion in the

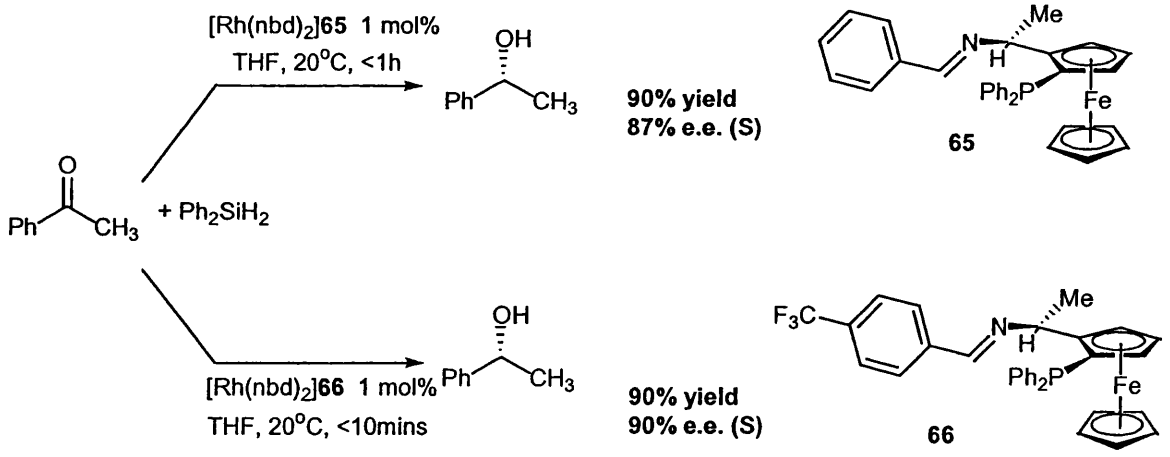
presence of $[Rh(cod)Cl]_2$ (L/M = 2.2: 1) in THF at 0°C for 24 hours giving the same kind of results than those obtained with Amphos or Aminphos.[45]



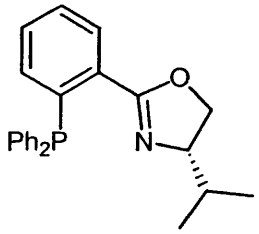
64

Further improvement was obtained with chiral ferrocenyl phosphine-imine ligands such as **65** and **66** which can be prepared by condensation of (S)-1-[(R)-2-diphenylphosphinoferrocenyl]ethylamine with aromatic aldehydes in benzene at room temperature.[44] These ligands were found to be very effective for the hydrosilylation of acetophenone, with 1 mol% of catalyst giving 90% yield and 87% e.e. in just one hour. A slightly higher enantioselectivity was observed in the reaction with ligand **66** derived from the aldehyde bearing an electron withdrawing group on the phenyl ring (Scheme **22**).

Scheme 22:



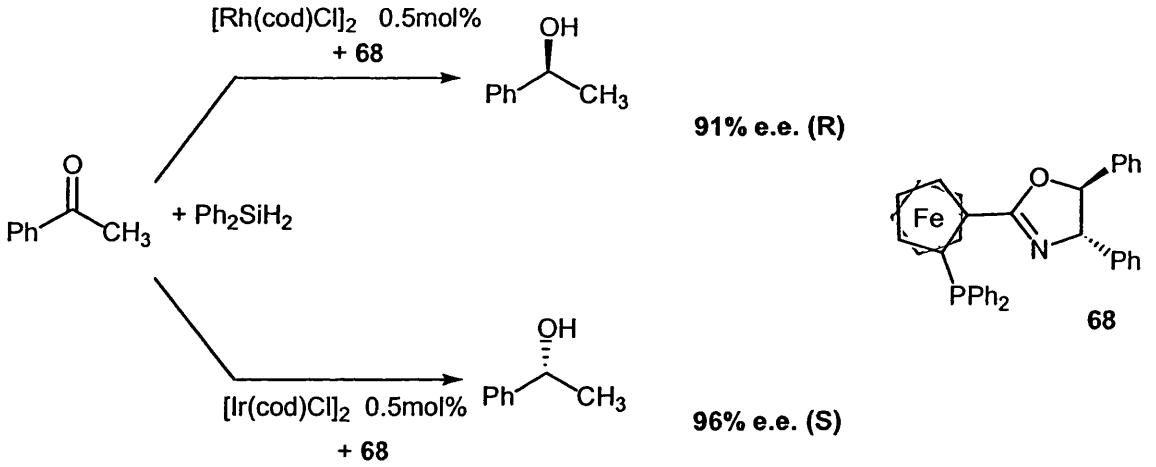
The phosphine-oxazoline **67** initially developed as a powerful ligand in asymmetric allylic substitution reaction,[45-47] has been applied in asymmetric hydrosilylation of ketones as an *in situ* catalyst with $[Rh(cod)Cl]_2$. Acetophenone **15** can be converted in 82% e.e. with diphenylsilane using the valinol derived ligand at -78°C in THF.[48-49] In this system, naphthylphenylsilane gave slightly higher e.e.'s up to 86% (R). However with 1-tetralone and 1-acetonaphthone e.e.'s of only 59% and 61% were obtained.



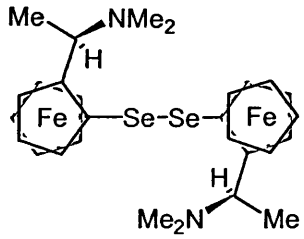
67

Similar results have been obtained with chiral oxazolinyl-ferrocene phosphine ligand **68**.[50] Acetophenone was reduced in 91% e.e. (R), using 0.5 mol% $[Rh(cod)Cl]_2$/**68** in ether at room temperature. Uemura has obtained intriging results with this ligand in that whilst the rhodium-catalyzed reaction of acetophenone provides mainly (R) alcohol, the corresponding reaction with iridium catalyst provided the (S) alcohol as product (Scheme **23**).

Scheme 23:



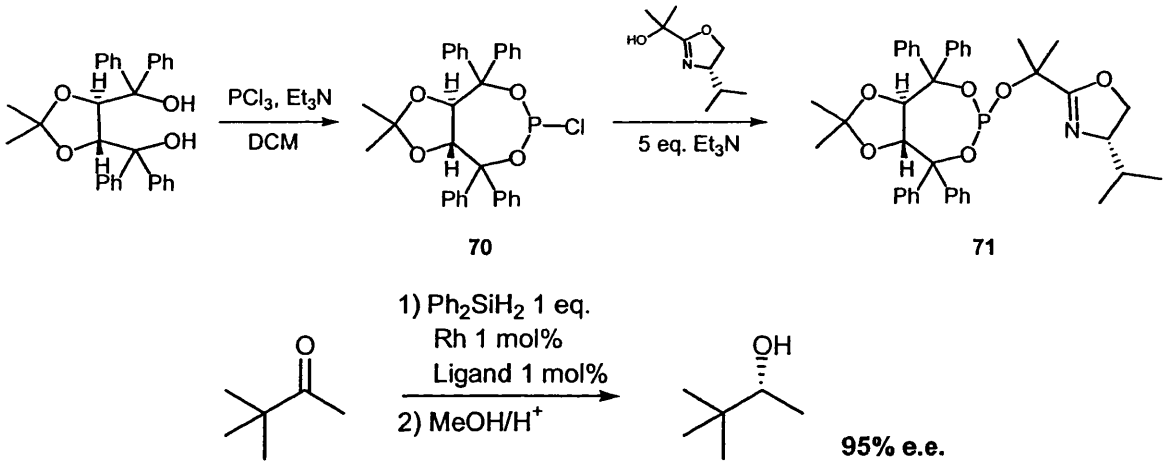
The unique chalcogenide bridged *bis*-ferrocenylamine **69** was developed for asymmetric hydrosilylation and gave a promising e.e. of 85% for acetophenone and 88% for $PhCOCH_2Cl$.[51] It was postulated that the ferrocenylamine binds to a single rhodium atom in a tetradentate mode.



69

A new type of phosphorus/nitrogen ligand, capable of forming six-membered ring metal chelates **71** has been designed and prepared from (R,R)-TADDOL **70** and a oxazolinyl alcohol. The rhodium complex of this ligand was tested in the asymmetric hydrosilylation of alkyl and aryl ketones with diphenylsilane to achieve a 95% e.e. for *t*-butylmethyl ketone (Scheme **24**).[52]

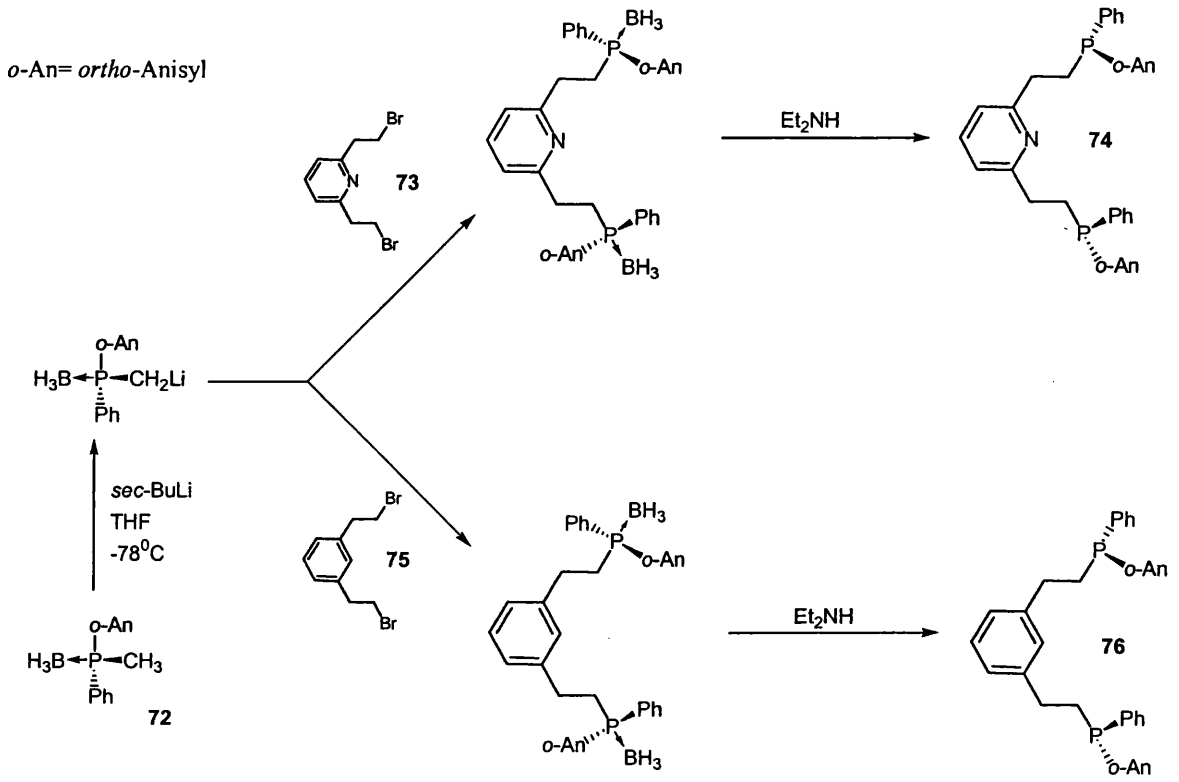
Scheme 24:



Chiral ruthenium catalyst

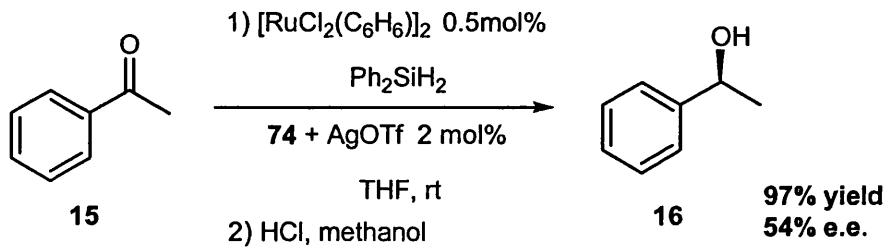
The first ruthenium-catalysed asymmetric hydrosilylation of simple ketones has been reported in 1997 by Zhang and co-workers.[53] They developed the synthesis of new tridentate and bidentate ligands, such as **74** and **76** respectively, which differ only by switching the central pyridine ring with benzene. The ligands were thus prepared from 2,6-*bis*(bromomethyl)pyridine **73** and 2,6-bis(bromomethyl)benzene **75** respectively and the optically active phosphine **72** (Scheme **25**).

Scheme 25:



Asymmetric hydrosilylation of acetophenone **15** catalysed by $[RuCl_2(C_6H_6)]_2$ with chiral tridentate ligand **74** proceeds with low selectivity (2% e.e.). The addition of AgOTf increased the enantioselectivity up to 54% (Scheme **26**). This increase is due to the removal of coordinated chlorides by Ag^+ salt which, in turn, generates vacant coordination sites for the binding of the ketone and activation of the Si-H bond.

Scheme 26:



An investigation of the enantioselectivity of the reaction by varying the amount of chiral ligand indicate that only 2 equivalents of ligand per ruthenium is sufficient to achieve maximum selectivity. A range of solvents were screened, carbon tetrachloride which is known to give high enantioselectivities in rhodium-catalysed asymmetric hydrosilylation,

was not a good solvent in this case as no reaction occured. The best results were achieved in THF (up to 54% e.e.). A range of ketones were screened under the optimised conditions improving the enantioselectivity up to 66% in excellent yield.

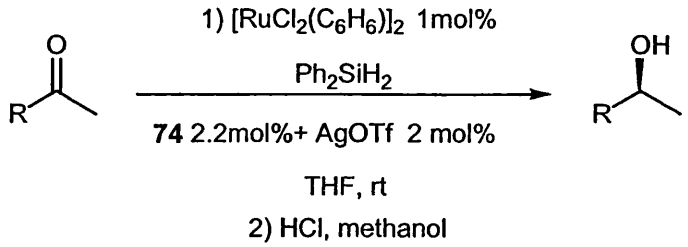
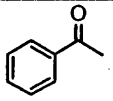
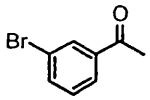
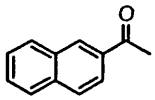


Table 1:

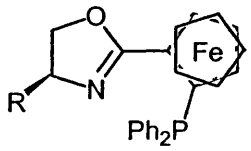
Ketone	Time (hour)	Yield (%)	e.e. (%)
	24	97	54
	72	93	62
	24	98	66

The role played by the tridentate ligand **74** was investigated further. The reactions were compared using several other chiral ligands such as (R)-BINAP and (S,S)-*i*-Pr Pybox (Table 2). The lack of selectivity using the bidentate ligand **76** implies that the pyridine is essential for achieving high selectivity. Chiral P-N ligands seemed to be the key for the enhancement of both activity and selectivity in the ruthenium-catalysed hydrosilylation of ketones.

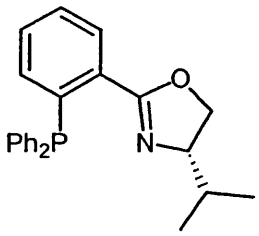
Table 2:

ligand	Time (h)	Yield (%)	e.e. (%)
74	24	97	54
(R)-BINAP	24	95	5
76	21	43	0
(S.S)-Pybox	72	16	0

Following this first report of the ruthenium-catalysed asymmetric hydrosilylation of ketones, a second group reported their results of fairly efficient ruthenium-catalysed asymmetric hydrosilylation of ketones.[54] Their new catalysts were prepared from $RuCl_2(PPh_3)_3$ and chiral bidentate P-N ligands **67** and **77.**



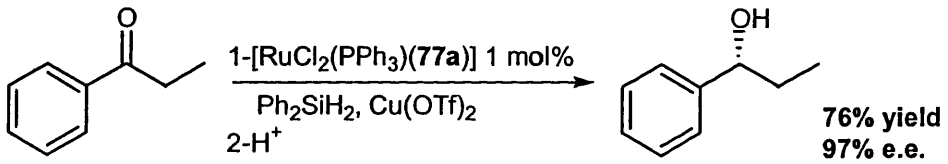
77a R=Ph
77b R=*i*-Pr
77c R=*t*-Bu



67

These new ruthenium complexes were tested as catalysts for the asymmetric hydrosilylation of acetophenone. The best result was achieved using [$RuCl_2(PPh_3)$(**77a**)] (1 mol%) and AgOTf or $Cu(OTf)_2$ as an additive to give excellent 95% e.e. and reasonable 59% conversion. The ruthenium complex having the phosphine oxazoline **67** showed lower catalytic activity than that having the (oxazolinylferrocenyl)phosphine **77b** (34 and 42% yield respectively). The asymmetric hydrosilylation of several other simple ketones with diphenylsilane proceeded with high enantioselectivity in the presence of the same catalyst, the best result being obtained with propiophenone **78** as substrate to give high yield and selectivity (76% yield, 97% e.e., scheme **27**).

Scheme 27:



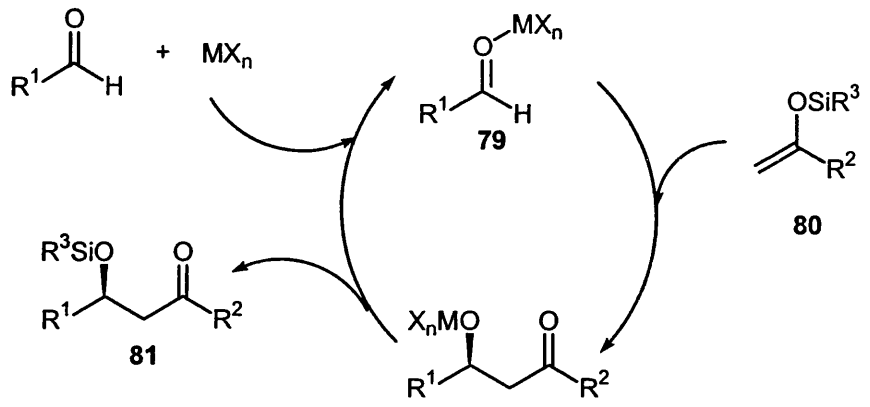
78

Lewis acid catalysed addition to C=O bonds

I-Asymmetric aldol reaction

The aldol reaction is a simple addition of an enolate to a carbonyl acceptor and is one of the most powerful methods of forming carbon-carbon bonds.[55] The general mechanism of the Mukaiyama aldol reaction proceeds by the coordination of the carbonyl oxygen to the Lewis acid MX_n to afford an activated electrophilic species **79**. (Coordination of C=O bond to Lewis acid leads to the enhancement of the electrophilicity of the carbonyl towards nucleophilic addition by the otherwise unreactive silane). Nucleophilic addition of the enol silane **80** leads to the C-C bond formation and generation of the aldol adduct **81**.

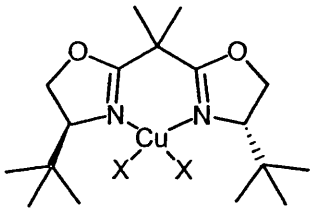
Scheme 28:



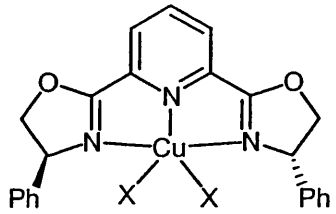
A successful catalyst must coordinate strongly enough with the oxygen atom of the carbonyl group to form a tight transition state for effective transfer of chirality, whilst not coordinating the product too strongly to suppress catalytic turnover. A number of systems have been developed using a range of metal/ligand combinations to catalyse this reaction.

The use of Cu(II) complexes as Lewis acid for the asymmetric Mukaiyama aldol reaction has been extensively studied by Evans and co-workers.[56-58] The catalysts **82** and **83** were generated upon treatment with CuX_2 (X = OTf or SbF_6) with the corresponding oxazoline ligands. These catalysts proved to be very efficient for the addition of ketene silyl acetal **85** to substrates such as α-benzyloxyaldehydes[59] **84** or pyruvate esters[60] **86** (Scheme **29**).

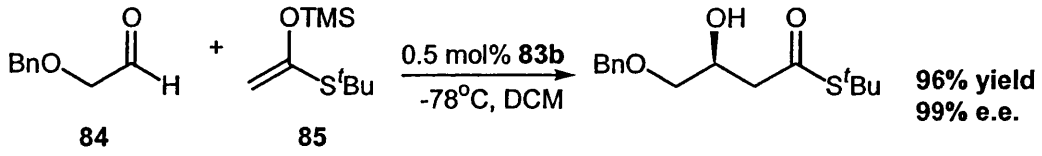
Scheme 29:



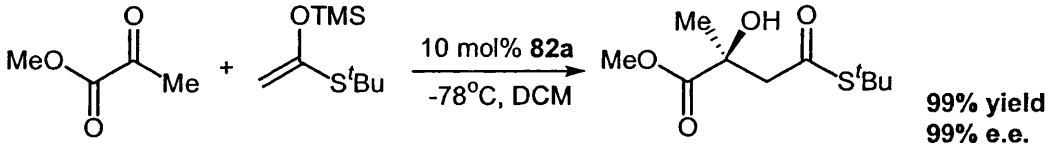
82a X = OTf
82b X = SbF_6



83a X = OTf
83b X = SbF_6



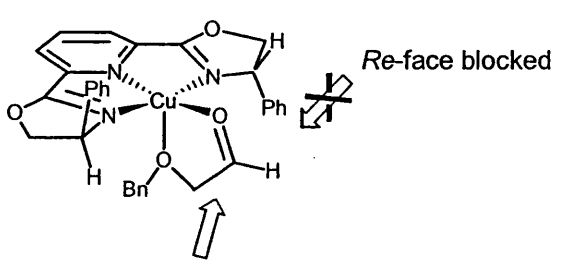
84 **85**

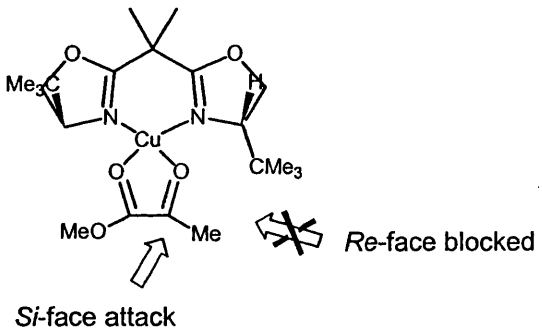


86 **85**

The sense of the induction was explained by invoking a square-pyramidal intermediate in the case of the Cu(II)-Pybox catalyst **83** and a square planar for the Cu(II)-box catalyst **82**. The nucleophilic attack takes place on the *Si* face as the *Re* face of coordinated ketone is shielded by the bulky phenyl or *tert*-butyl substituent on the ligand (Scheme **30**).

Scheme 30:



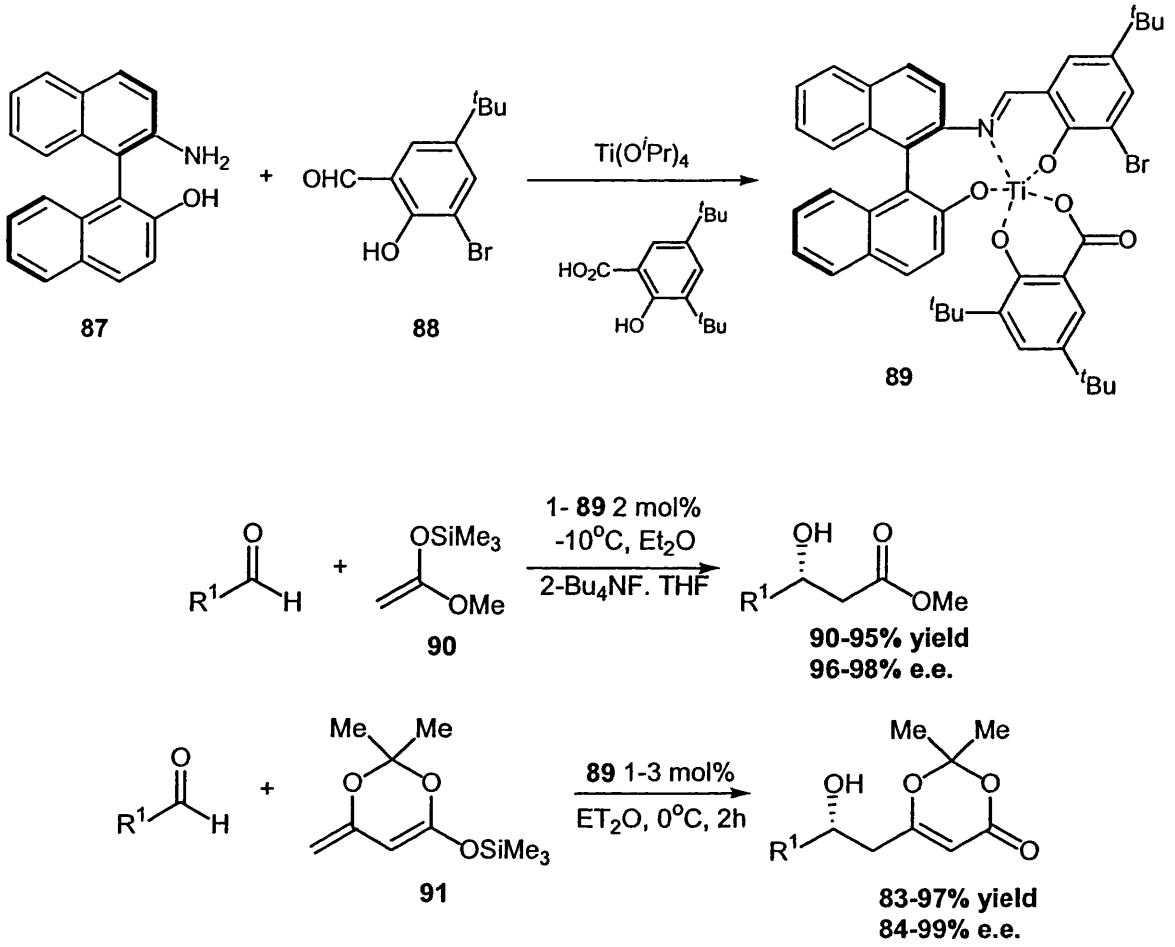


These observations suggest the important role of the substrate binding to the Lewis centre in producing a complex possessing a five-membered ring chelate that leads to aldehyde face differentiation. Evans recently published articles summarizing the scope and

mechanisms of the aldol addition of enolsilanes to α-benzyloxyaldehydes[61] and pyruvate esters[62] using these Cu(II)-box complexes.

The asymmetric catalytic Mukaiyama aldol reaction has also been reported with complexes derived from Ti(IV) leading to high level of enantioselectivity. Carreira[63] reported a series of studies towards the development of a series of tridentate ligands such as **89**, derived from aminohydroxybinaphthalene **87** and the salicylaldehyde moiety **88**. He speculated that better control over catalyst structure would be available with a ligand able to coordinate through more than two heteroatoms. Excellent enantioinductions have been observed for both the reaction of aliphatic and aromatic aldehydes with enol silanes[63] **90** and dienol silanes[64] **91** (Scheme **31**).

Scheme 31:

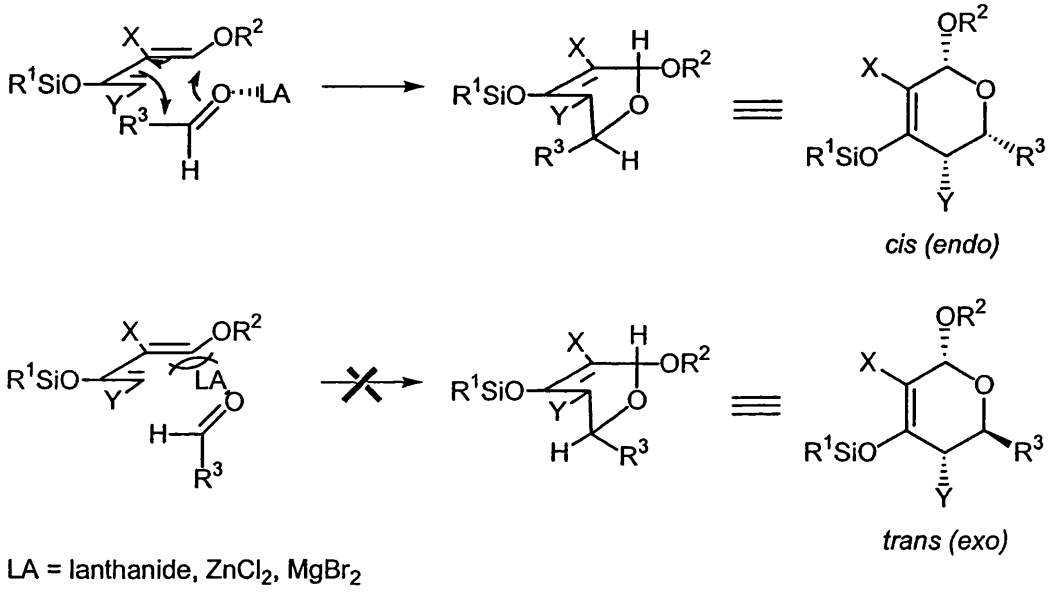


Cycloaddition reactions: Hetero Diels-Alder reactions

The hetero Diels-Alder reaction is a very powerful method for the formation of C-X bonds (with X = C, O, N).[65] This cycloaddition process can allow the formation of heterocycles in enantiomerically pure form when appropriate catalysts are used. A large number of metals, ligands and dienophiles have been studied. Until recently, the majority of successful catalysts contained chelating oxygen ligands, examples of the ligand used are BINOL,[66] TADDOL derivatives[67] and Yamamoto's CAB reagent.[68] Recent studies have focused on optically active nitrogen-containing ligands.

The Lewis acid catalysts increase the reactivity of the dienophile by complexing to the lone electron pair of the aldehyde *anti* to the R^3 group, forcing the R^3 group into an *endo* position in the transition state. In the case of lanthanide catalysts (such as $Eu(fod)_3$), the large steric bulk of lanthanide causes the increase in *cis* selectivity (Scheme **32**).

Scheme 32:

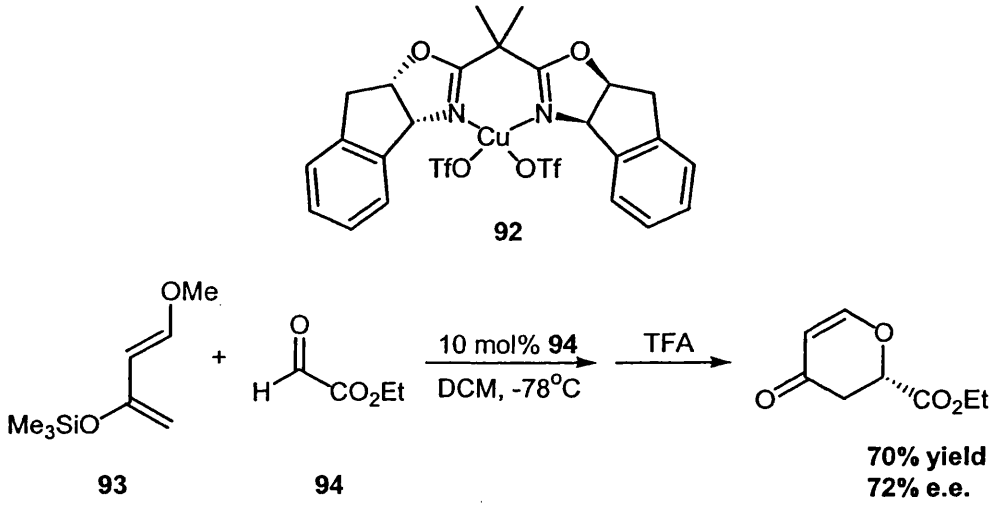


With the achievement of high stereochemical control resulting from nearly exclusive *endo* cycloadducts in the Lewis acid-catalysed hetero Diels-Alder reactions, the logical

progression was to research chiral Lewis acid catalysts. To date the best results have been obtained with *bis*-oxazoline copper complexes.

Ghosh and co-workers reported that the Cu(II)-*bis*oxazolines **92** catalysed the reaction of Danishefsky's diene **93** and ethyl glyoxylate **94**, afforded after treatment with trifluoroacetic acid the enantioenriched hetero Diels-Alder product in good yield (Scheme **33**).[69-70]

Scheme 33:



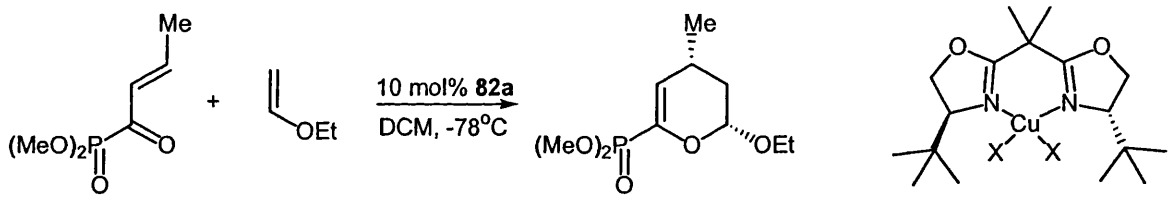
92

93 **94**

70% yield
72% e.e.

After having reported numerous examples of Cu(II)-*bis*oxazolines complexes that catalyse Diels-Alder reactions, Evans and co-workers reported that α,β-unsaturated acyl phosphonates **95** undergo enantioselective hetero Diels-Alder with enol ether **96**, allowing a selective method for the formation of dihydropyrans (Scheme **34**).[71-73]

Scheme 34:



95 **96**

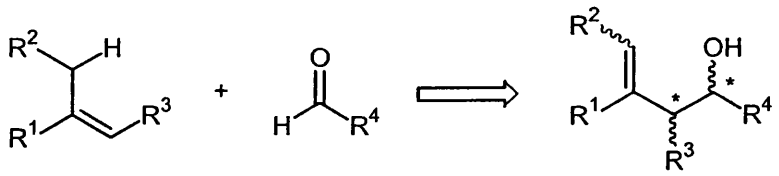
***endo/exo* = 99/1**
99% e.e. (*endo*)

82a X = OTf

Carbonyl ene reactions

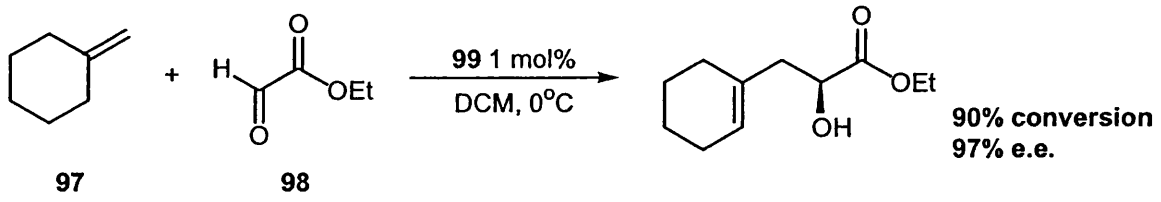
The carbonyl ene reaction is an important carbon-carbon bond forming process, which converts readily available olefins, *via* activation of an allylic C-H bond and allylic transposition of the C=C bond into more functionalized products (Scheme **35**).[73]

Scheme 35:

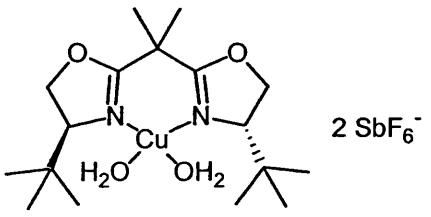


Most studies on the asymmetric ene reaction have employed aluminium or titanium species in combination with BINOL derivatives.[74-76] However very recently Evans has reported the development of a very efficient Cu(II)-box complex **99** for the reaction of 1,1'-disubstituted olefin **97** with ethyl glyoxylate **98**.[77]

Scheme 36:



97 **98**



99

Miscellaneous examples of diamine mediated asymmetric additions to C=O bonds

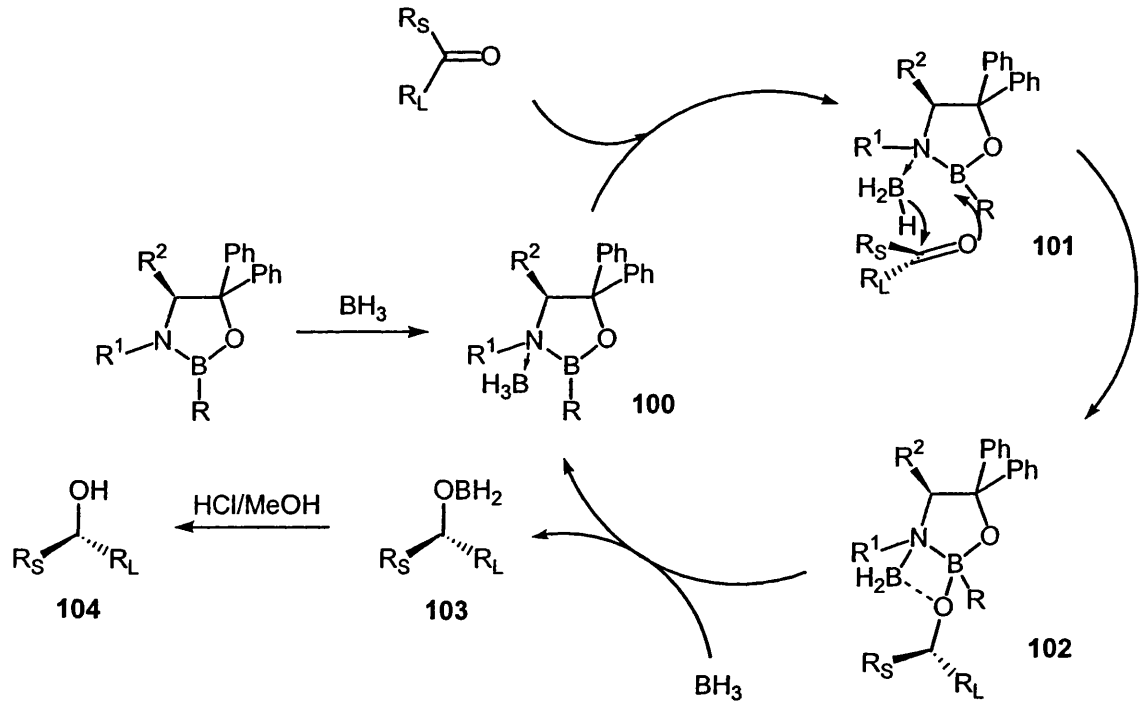
Asymmetric hydroboration

The introduction of metal hydride reagents such as lithium aluminium hydride and sodium borohydride for the reduction of carbonyl groups had a great impact in synthetic organic chemistry. A natural progression of the research which gave rise to these metal hydride

reagents was their extension to the development of chiral reagents which could selectively transfer hydride to give enantiopure alcohols. The oxazaborolidines have been developed into effective reagents for the selective reduction of C=O bond. Recently variants of this reaction which display catalytic transfer of chirality have been developed.[78-79]

The general mechanism developed for the reduction of ketones with oxazaborolidines catalysts is outlined in scheme **37**. The reaction may occur by the following sequence; a) coordination of BH_3 to the nitrogen atom activating BH_3 as the hydride donor and increasing the Lewis acidity of the boron of the oxazaborolidine. b) coordination of the ketone to the boron of the oxazaborolidine. c) hydride transfer from the coordinated borane to the carbonyl *via* a six-membered transition state to form **102** d) addition of BH_3 to regenerate **100** and the borinate **103** easily hydrolyze into the corresponding alcohol **104**.

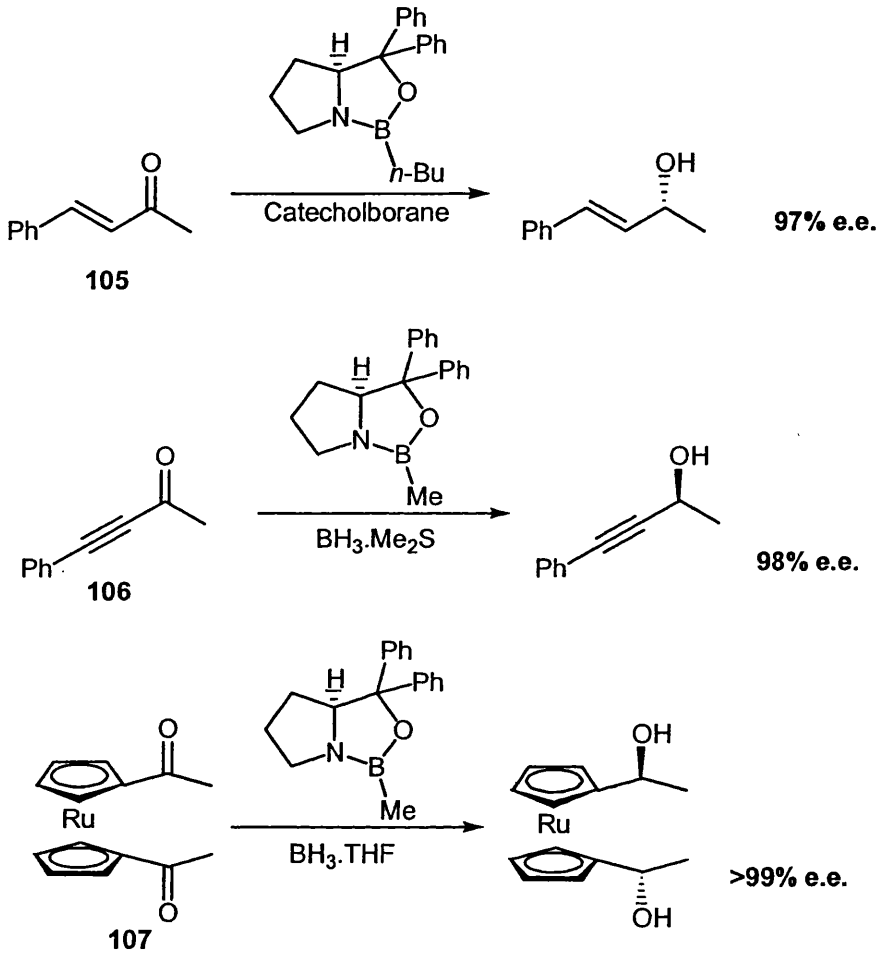
Scheme 37:



Oxazaborolidines are unique in that they contain a Lewis acidic and a Lewis basic centre next to each other, and are able to activate both the carbonyl functionality of the substrate and the borane.

Oxazaborolidines synthesized from chiral amino alcohols and borane were first reported by Itsuno in 1981[80] and optimised by Corey[79-81] with the development of new oxazoborolidines. This work also broadened the scope of the reaction to include reductions of α,β-enones **105**, α,β-ynones **106** and ketones in ligands of metal complexes **107**, among others (Scheme **38**).

Scheme 38:

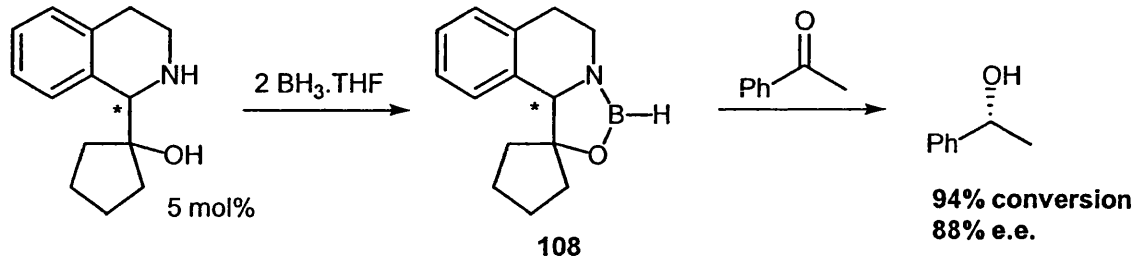


Numerous examples of asymmetric reductions with oxazaborolidines have since been published in the literature leading to their acceptance as perhaps the most successful chiral borane reagents.

Further examples have been reported recently by Martens and co-workers and Xie and co-workers among others. In order to limit the number of possible conformations of the intermediates, newly designed cyclic rigid amino alcohols were tested in the reduction of

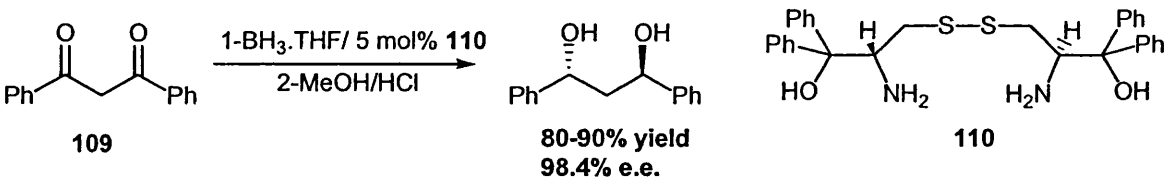
acetophenone. An *in situ* oxazaborolidine was used for the the β-amino acid **108**. This system reduced acetophenone to give phenethyl alcohol in 88% e.e.(Scheme **39**).[82]

Scheme 39:



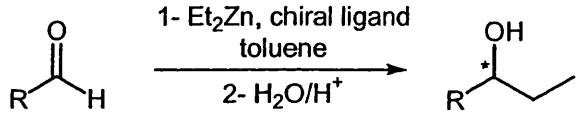
The C_2-symmetric ligand **110**, derived from the amino acid L-cysteine proved to be very successful in the reduction of prochiral aromatic ketones or diketones with BH_3.THF. It was suggested that cooperation between the two catalytic centres of **110** occurred during the reduction of diketones **109** (Scheme **40**).[83]

Scheme 40:



Nucleophilic addition of dialkylzinc reagents to aldehydes

The addition of dialkylzinc to aldehydes in the presence of a sub-stoichiometric amount of chiral ligand is a very efficient system for the formation of carbon-carbon bonds leading to the synthesis of secondary alcohols.[84]

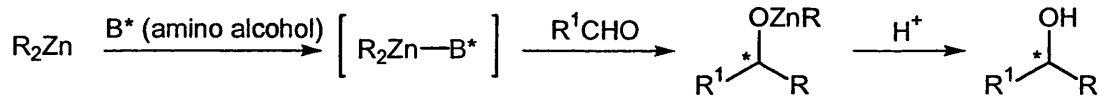


There are two possible mechanisms; the first mechanism is promoted by a Lewis base such as β-amino alcohols, here the dialkylzinc reagents is activated by the Lewis base to give a more nucleophilic reagent; thus the dialkylzinc can react with aldehydes to give optically pure alcohol product. The second mechanism is promoted by a Lewis acid which can

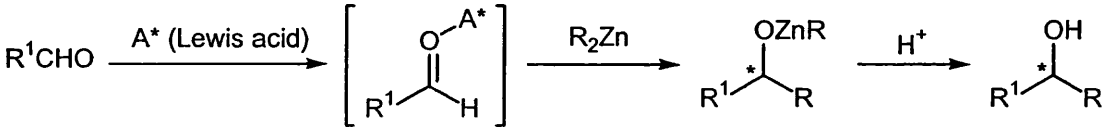
enhance the electrophilicity of the aldehyde by coordination on the oxygen atom, which thus facilitate the reaction with the dialkylzinc reagents (Scheme **41**). Only a brief dicussion of the reaction is given here as we do not wish to focus on reactions employing stoichiometric amount of metal reagents.

Scheme 41:

Lewis base promoted catalysis

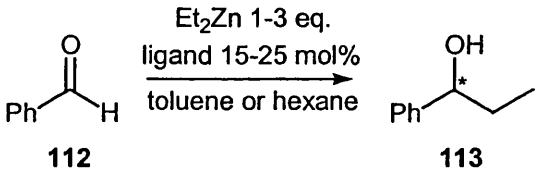


Lewis acid promoted catalysis

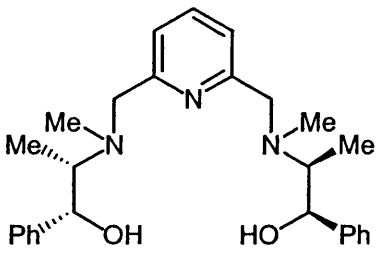


β-Amino alcohols have proved to be very efficient Lewis base catalysts for the reaction leading to very high levels of enantioselectivity, especially for the transformation of aromatic aldehydes.[85-88] Several N,N-ligands were recently used in the addition of diethylzinc addition to benzaldehyde **112** affording the desired secondary alcohol **113** in good yields and selectivities (Scheme **42**).[89-91]

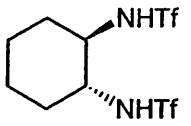
Scheme 42:



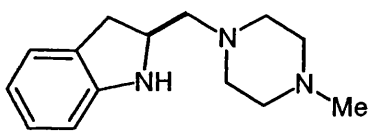
112 **113**



114
82% yield, 90% e.e. (R)



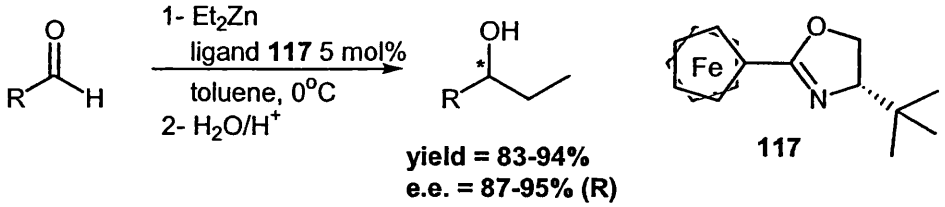
115
98% yield, 95% e.e. (S)



116
85% yield, 95% e.e. (R)

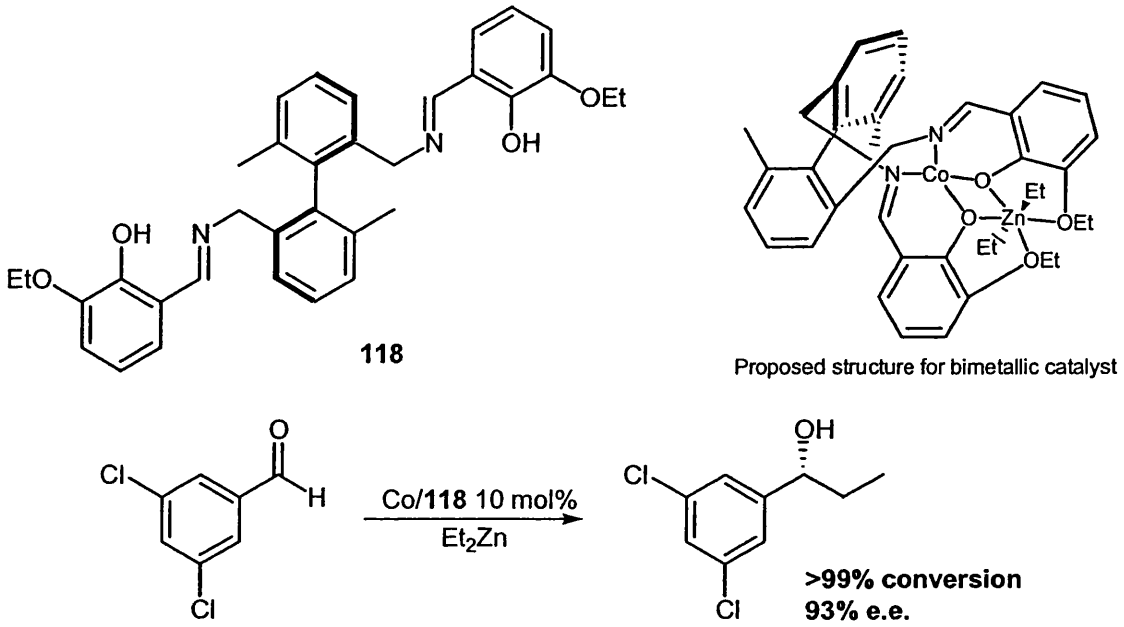
Other ligands such as the ferrocenyl oxazoline **117**, have been developed to perform the addition of diethylzinc on benzaldehyde. Bolm reported the ferrocenyl oxazoline **117** promoted high yielding, selective diethylzinc additions to both aromatic and aliphatic aldehydes (Scheme **43**).[92]

Scheme 43:



More recently, Ripert reported the efficiency of the salen ligand **118** in the enantioselective addition of diethylzinc to aldehydes.[93] Evidence was obtained for a bimetallic catalyst with Co^{II} in the central salen-type O-N-N-O core of the ligand, and the second metal, Zn^{II}, is coordinated to the two alkoxy substituents of the salicaldehyde of the ligand, as well as the two oxygen atom of the central core of the salen ligand. Therefore the reaction of the aldehyde took place in a chiral pocket (Scheme **44**).

Scheme 44:



Conclusion

Although this review is not comprehensive and only a small number af asymmetric reactions have been discussed, it becomes evident by looking in the literature that N-containing ligands are prevalent in many areas of asymmetric reactions. We have shown how chiral amine ligands can be used to create chiral templates for a range of asymmetric transformations. In the rest of this thesis we will discuss our attempts to extend some of these chemistries by accessing new ligands by development of new palladium-catalysed coupling methodology (chapter two), generation of targeted ligand librairies and their screening by high throughput and traditional methods (chapter three), ligand optimisation and finally the generation of a boronic acid/aldehyde coupling reaction previously carried out only with rhodium-phosphine complexes (chapter four).

Palladium-catalysed amination of aryl halides and triflates

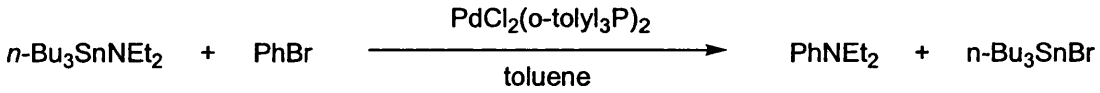
The amination of aryl systems continues to be an active area of research due to the importance of aromatic amines in nature and in modern organic synthesis. In this review a particular attention is given to the recently developed palladium-catalysed amination of aryl halides and triflates.[94-98]

Carbon-nitrogen bond formation

History and the use of aminostannanes

The first palladium-catalysed aryl C-N coupling reaction was reported by Migita and co-workers in 1983.[99] Their investigation into the use of organotin compounds in organic chemistry led to the development of a novel procedure for the amination of aryl halides using palladium catalysts and *N,N*-diethylaminostannanes (Scheme **45**).

Scheme 45:

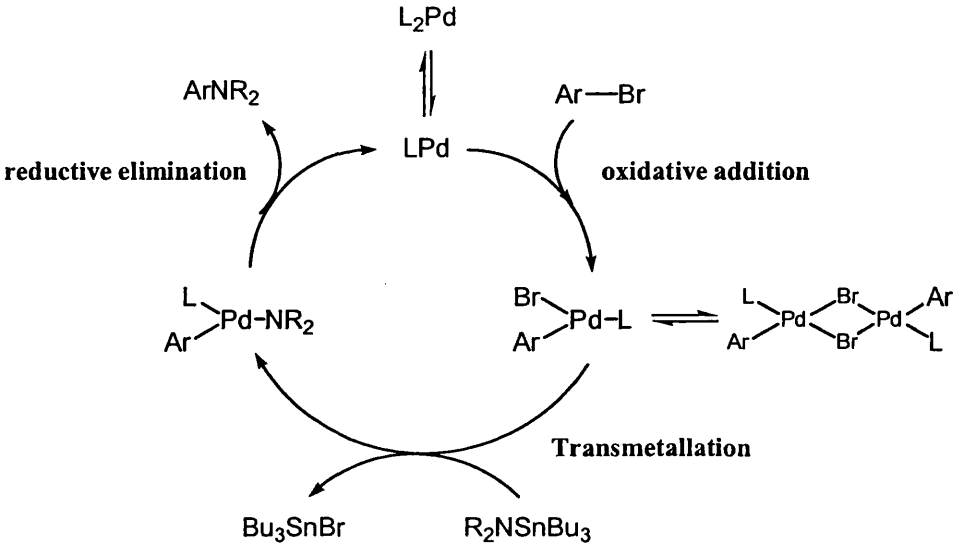


The reaction was found to work best with $PdCl_2(o\text{-tolyl}_3P)_2$ as catalyst but was limited to aryl bromide substrates, aryl chlorides and iodides did not give any product. The reaction was a breakthrough in that a Stille type coupling was possible with aminostannane nucleophile thus giving rise to a catalytic C-N bond forming reaction. The reaction was however very limited in substrates scope and thus provided little material benefit over known amination methods.

Ten years later, Hartwig[100] investigated the mechanism of the reaction and concluded that the reaction was likely to proceed as Migita had predicted. A representative reaction scheme for the palladium-catalysed formation of carbon-nitrogen bonds is shown in

scheme **46**. The reaction mechanism is believed to involve firstly the oxidative addition of the aryl bromide to the Pd^0 species. An intermediate Pd^{II} species is thus formed, to which the aminostannane adds to form the aryl palladium amide intermediate which thus undergoes reductive elimination to afford the aryl amine and regenerate the Pd^0 catalyst.

Scheme 46:



At the same time, independent studies by Buchwald's group[101] greatly extended the utility of this approach by increasing the variety of amines that could be used. This was accomplished by first transaminating the tributylaminostannane with higher boiling amines and then using the resulting aminostannane in the palladium-catalysed amination (Scheme **47**). This approach greatly increased the generality of Migita's reaction and meant that a wider range of aryl amines could now be synthesized.

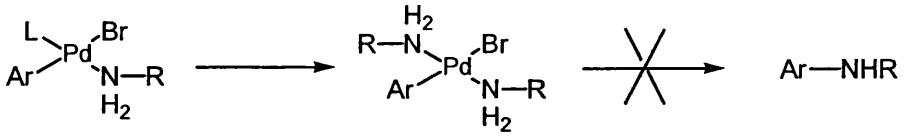
Scheme 47:

The use of aminostannanes of course presents its own problem. The aminostannanes are highly unstable making them difficult to work with and are also rather toxic, thus making them unattractive intermediates for the synthesis of pharmaceutical products. Clearly the development of the reaction to do away with the use of aminostannane altogether was highly desirable, this goal was later accomplished independently by Hartwig and Buchwald.

Limitations of palladium catalysed amination chemistry

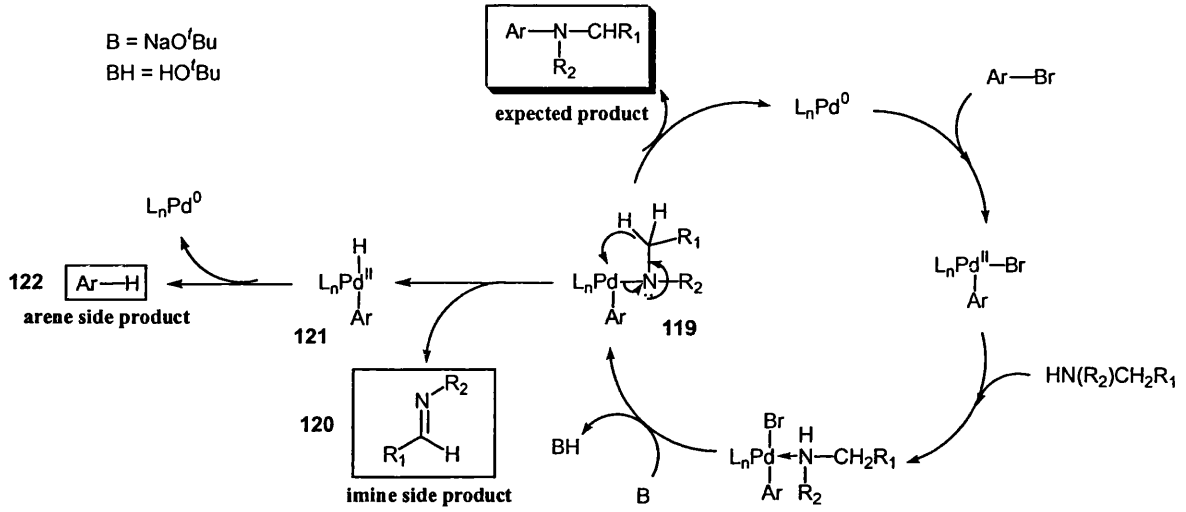
This early chemistry involving P(*o*-tolyl)$_3$ as a ligand presented some limitations: *sec*-amines, aryl iodides, halopyridines and aryl triflates were all poor substrates. Many reactions were slow and required high catalyst loadings. Also low yields of coupling product were observed between primary amines and aryl bromides which may result from the formation of a catalytically inactive palladium *bis*-amine complex (Scheme **48**).[102-103]

Scheme 48:

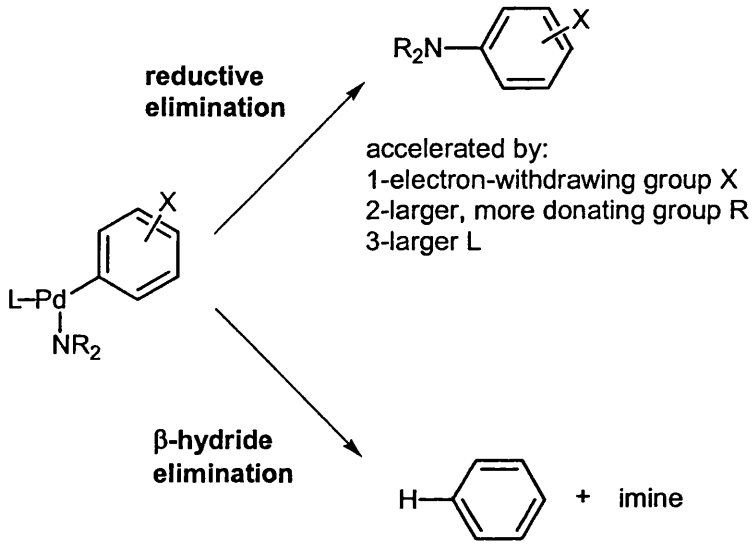


The reaction mechanism most likely proceeds *via* an oxidative addition, insertion of the amine and a reductive elimination sequence as outline in scheme **49**. The intermediate **119** can, however undergo a β-hydride elimination to give the imine side product **120** and a "ArPd^{II}-H" species **121** which can eliminate to give the arene **122**, a second side product, and regenerate palladium catalyst.

Scheme 49:



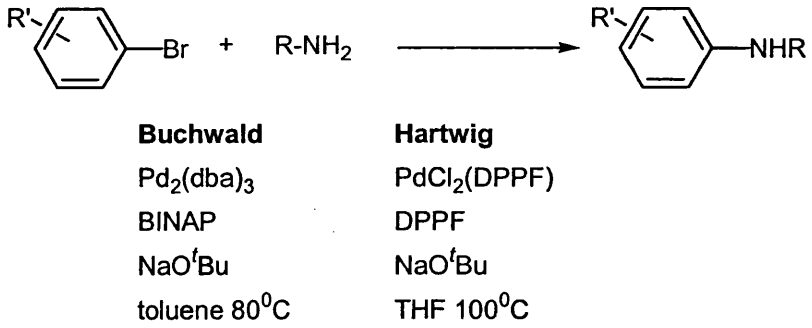
The amount of side product was found to be dependent on the steric and electronic properties of the aryl bromide, the amine and the phosphine. It was reported that larger, electron rich amines, and aryl bromide having electron withdrawing substituent produced small quantities of side product (*ie* the reductive elimination is favoured over β-hydride elimination with these groups).[104-105] Further details on the mechanistic pathway and the factors effecting this are given on pages 45 and 46.



General protocol for simple systems

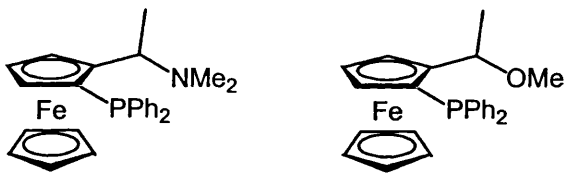
The use of bidentate phosphine ligands proved key to further improvements, Buchwald found that high yields were obtained by reacting aryl bromides with primary amines in the presence of $Pd_2(dba)_3$ and BINAP,[103] whilst Hartwig found that $PdCl_2$(DPPF) and DPPF worked well (Scheme **50**).[106]

Scheme 50:



Although a general protocol was developed for the palladium-catalysed coupling of primary and secondary cyclic amines with aryl bromide, the arylation of secondary acyclic amines remained problematic. Buchwald discovered that *rac*-PPFA **123** and *rac*-PPF-OMe **124** were highly effective ligands for the aryl amination reaction of acyclic secondary amines (Scheme **51**, table **3**).[107]

Scheme 51:



rac-PPFA **123** *rac*-PPF-OMe **124**

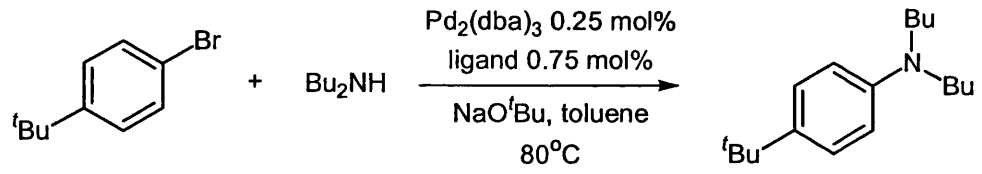


Table 3:

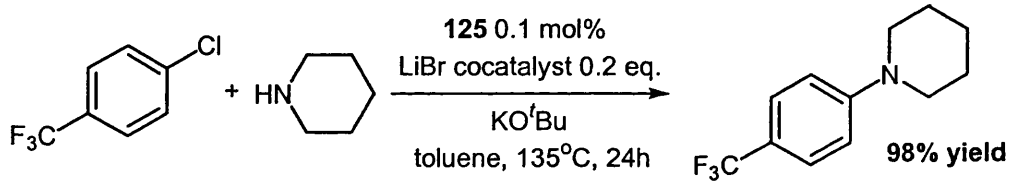
Ligand	Time (h)	GC yield (%)
BINAP	48	8
123	24	92
124	5	97

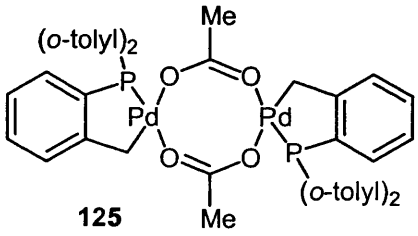
An X-ray crystal structure revealed that *rac*-PPF-OMe **124** was acting as a bidentate ligand through the phosphorus and the oxygen atom. This tetracoordinated palladium-complex which favours the reductive elimination pathway leading to the desired product (tricoordinated complexes were more subject to β-hydride elimination). It was also possible to carry out the reaction with a weaker base like caesium carbonate in place of NaO^{t}Bu. These new reaction conditions were sufficiently mild to tolerate the presence of enolizable ketones, nitro groups or methyl and ethyl esters, which are incompatible with reaction conditions employing NaO^{t}Bu.[108]

Amination of aryl chloride

The first palladium-catalysed amination of aryl chlorides was reported by Beller and co-workers.[109] The key for the success of this C-N formation was the use of potassium *tert*-butoxide as base (Scheme **52**).

Scheme 52:



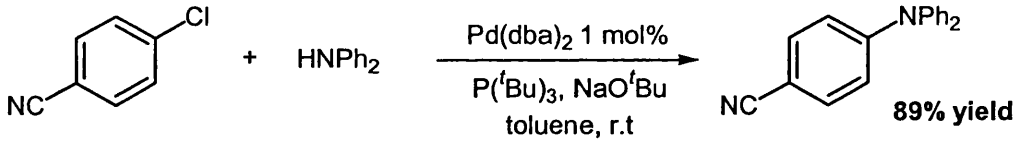


125

The mechanism would involve firstly the reduction of the palladacycle. The resulting Pd(0)-complex might undergo a reductive elimination with aryl chloride or could be involve in an aryne type mechanism (a low percentage of *meta*-regioisomer was observed which could be explained by an aryne intermediate).

Since then the work has been extanded by both Hartwig and Buchwald. The reaction of activated aryl chlorides with secondary amines proceeds remarkably well at room temperature in the presence of Pd(0) and the commercially available tri-*tert*-butylphosphine (Scheme **53**).[110-111]

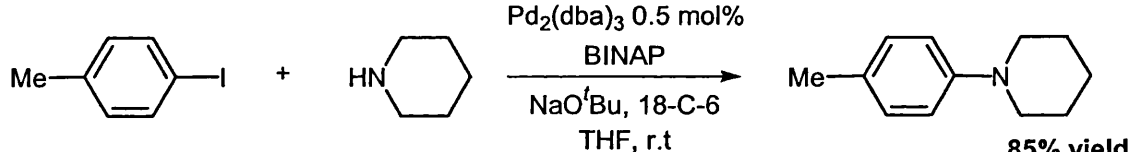
Scheme 53:



Amination of aryl iodide

Further improvements were reported by Buchwald who developed a general procedure for the palladium-catalysed intermolecular amination of aryl iodides which proceeds at room temperature.[112] For example, the reaction of *p*-iodotoluene **126** with piperidine **127** in the presence of stoichiometric amount of base, 18-crown-6 and a sub-stoichiometric amount of $Pd_2(dba)_3$/BINAP proceeds to completion in six hours at room temperature (Scheme **54**).

Scheme 54:



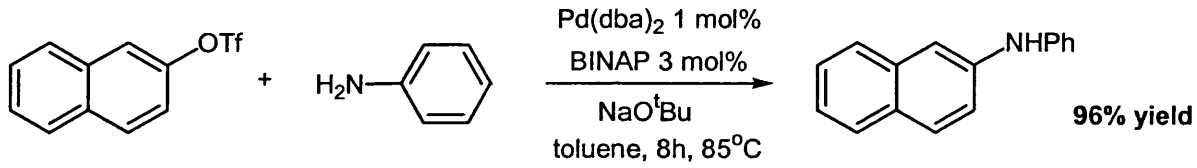
126 **127**

The role of the 18-crown-6 in this reaction is to increase the solvation of Na^+ ion, thus releasing the potential basicity of NaO^tBu.

Amination of aryl triflates

Aminations of aryl triflates also have a significant synthetic value due to the simple conversion of readily available phenols to aryl triflates. Hartwig's group reported that a combination of $Pd(dba)_2$ and DPPF or BINAP led to the amination of aryl triflates.[113] For example, the reaction of 2-naphthyl triflate **128** with aniline **129** afforded the coupling product **130** in 96% yield in the presence of $Pd(dba)_2$ and BINAP (Scheme **55**).

Scheme 55:

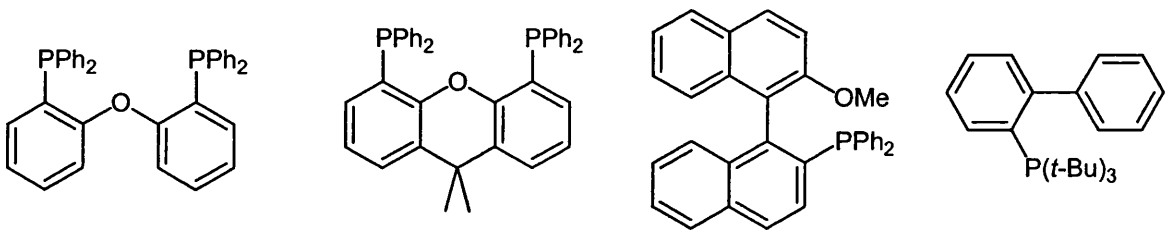


128 **129** **130**

New ligands for palladium catalysed amination reactions

A wide range of new chelating *bis*-phosphines have been designed and synthesized over the past few years which have greatly improved the palladium-catalysed amination of aryl halides and triflates (Scheme **56**).

Scheme 56:

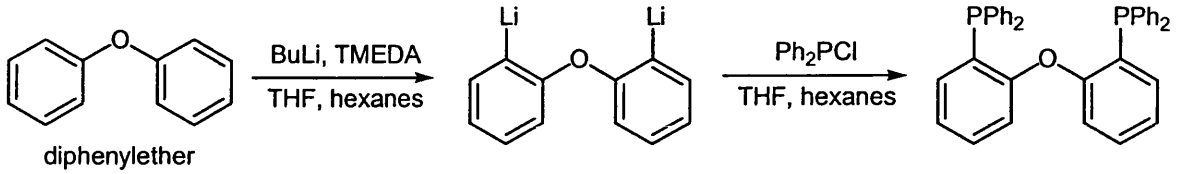


DPEphos **131** XANTphos **132** MOP **133** **134**

Ligands **131** and **132**[114-115] were prepared by deprotonation of the corresponding backbones with BuLi and TMEDA. The dilithiated parent ethers were reacted with

chlorodiphenylphosphine and then washed to remove excess lithium salts and the butyldiphenylphosphine byproduct to yield the desired *bis*-phosphine **131** (Scheme **57**).

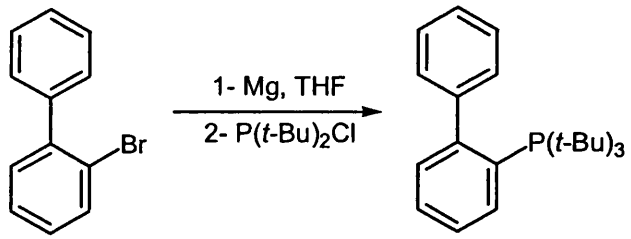
Scheme 57:



diphenylether
135 **136** **131**

Ligand **134** was used in the catalytic amination of aryl chlorides at room temperature [111]. It was simply prepared in one step from commercially available 2-bromobiphenyl **137** and di-*tert*-butylchlorophosphine (Scheme **58**).[116]

Scheme 58:



137 **134**

Conclusion

The reaction has progressed greatly from Migita's initial work with pioneering work from both Hartwig's and Buchwald's group developing a series of highly efficient catalysts systems, for the palladium-catalysed amination of aryl halides and triflates. This chemistry has been lately extended to other substrates to form aryl ethers and aryl sulfides and has now become a useful tool in the arsenal of the organic chemist. Further improvements will doubtless be made and the reaction is bound to become prominent in future synthesis.

The palladium amination reaction developed by Hartwig and Buchwald seemed to provide a rapid route to a variety of interesting compounds. We were especially attracted by the potential to rapidly generate novel ligands for enantioselective catalysis.

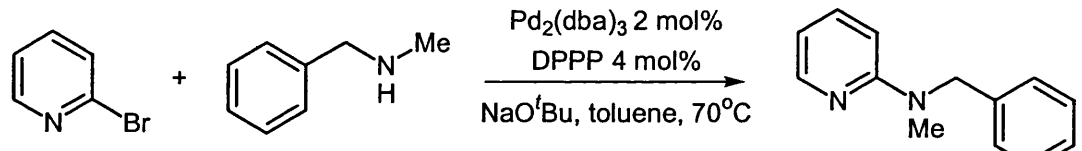
Synthesis of enantiomerically pure amino-pyridine ligands

Literature precedent

Synthesis of aminopyridines

Aminopyridines are important in various fields of chemistry. Their derivatives can be used as dyes or stimulants to the central nervous system. Buchwald found that by employing chelating *bis*-phosphine ligands, bromopyridines could be efficiently converted to their amino derivatives.[117] They have noted that *bis*-phosphines inhibit side reactions such as β-hydride elimination and a formation of inactive *bis*-amine complexes. They found that the same system could be used for the coupling of bromopyridine because the chelating *bis*-phosphine does not undergo a ligand exchange with the pyridine and consequently the formation of a *bis*-amine complex is prevented. BINAP and also the less expensive DPPP proved to be very effective ligands for the reaction. For example, the coupling of 2-bromopyridine **138** with *N*-benzylmethylamine **138** in the presence of $Pd_2(dba)_3$ and DPPP in toluene at 70°C yielded the desired aminopyridine **140** in 86% yield (Scheme **59**).

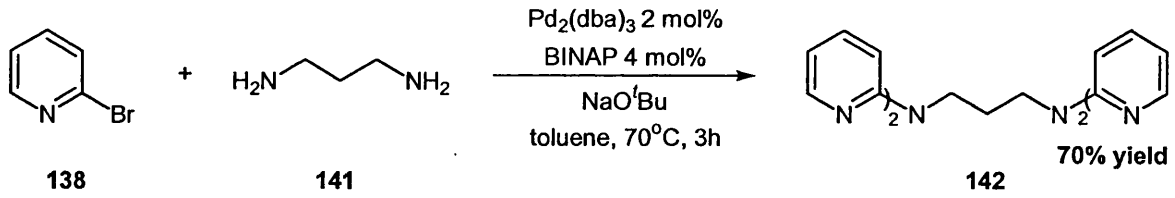
Scheme 59:



138 **139** NaO^{t}Bu, toluene, 70°C **140**

The same strategy was also very effective for diarylated diamines. Upon treatment with an excess of 2-bromopyridine **138** (4 equivalents), 1,3-propyldiamine **141** gave the tetraarylated diamine **142** (Scheme **60**).

Scheme 60:

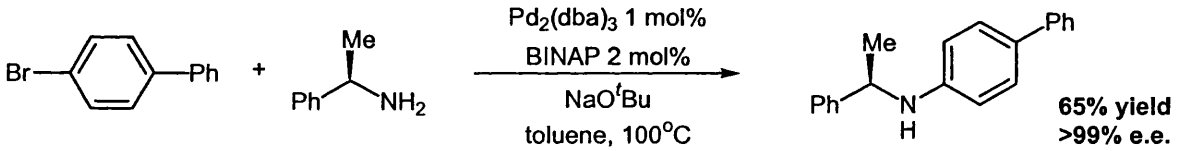


138 **141** **142**

Enantiomerically pure *N*-arylamines

A logical extension of the work was to prepare optically active *N*-arylamines by the cross-coupling reaction. It was found that L_nPd/*bis*phosphine are required to obtain enantiomerically pure products in intermolecular coupling reactions of optically active amine with aryl halides. The choice of ligand was crucial to avoid erosion of the enantioselectivity. The use of BINAP as a ligand preserved the optical purity (Scheme **61**).[118] The use of P(*o*-tolyl)$_3$ afforded the product in a range of enantiomeric purity, indeed racemic mixtures were obtainable under some conditions.

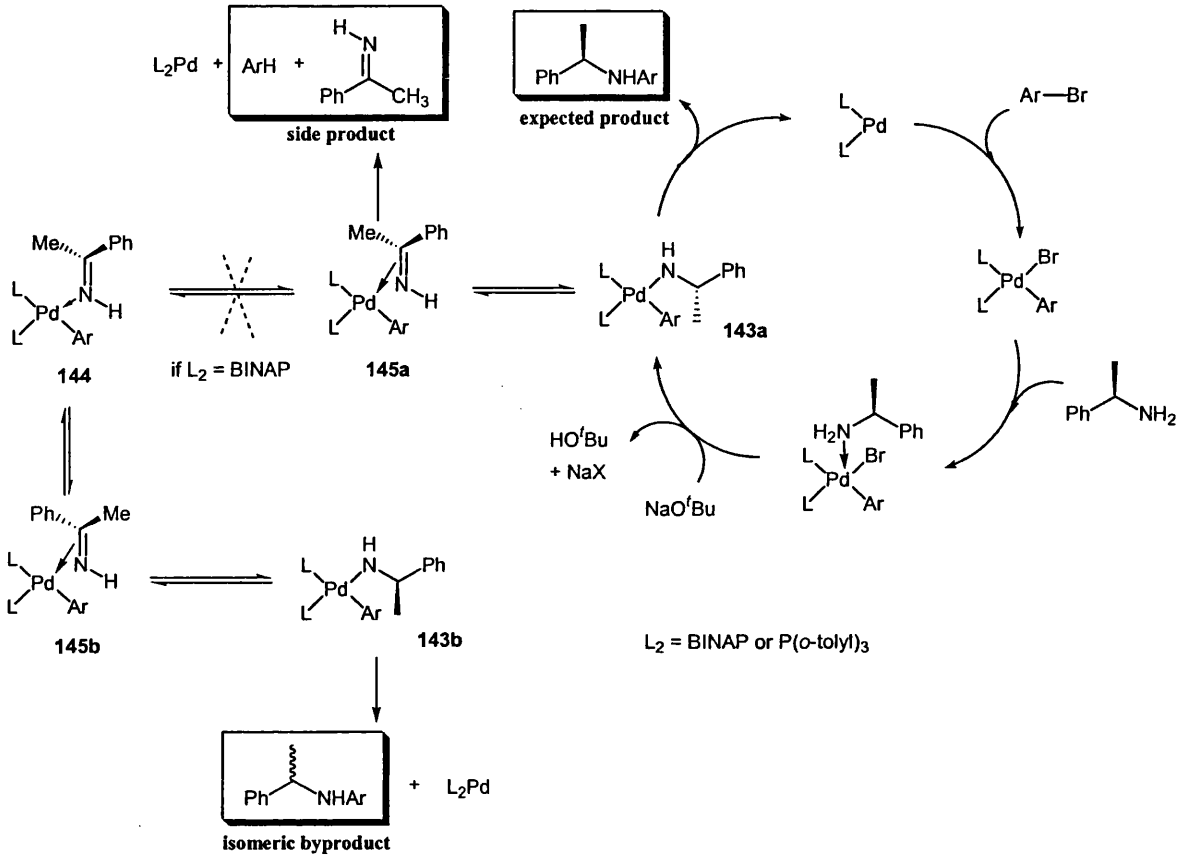
Scheme 61:



The catalytic cycle proceeds *via* an oxidative addition, then complexation of the amine followed by deprotonation (to give the amide) and finally a reductive elimination. As we previously noted (p.37), for amines having an hydrogen in the α-position, a β-hydride elimination can occur leading to the formation of an imine and a dehalogenated arene as common side products. At this stage, **145a** is in equilibrium with **145b** *via* a σ-coordinated imine intermediate **144**: *e.g.* either face of the prochiral imine can be bound to the metal center due to this equilibrium. A migration of the π-coordinated imine into the palladium-hydride bond of **145a** and **145b** forms enantiomeric Pd(II)-amido complex **143a** and **143b** respectively. Reductive elimination of **143a** and **143b** then produces a single isomer, though the presence of both imines gives rise to a mixture of both isomers in the bulk reaction. When BINAP is used as a ligand, the competing side reactions is shut down. It

might be that the π-bound imine **145a** is unable to equilibrate with **145b** for steric reasons: as a disfavoured rotation of the methyl group around the bulky diphenylphosphino group of BINAP would be required (Scheme **62**).

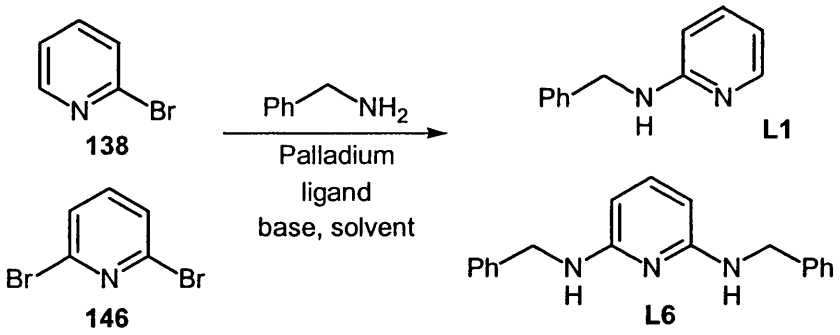
Scheme 62:



Our approach to the synthesis of enantiomerically pure aminopyridines

Since we wanted to investigate chiral nitrogen-containing ligands in enantioselective reactions, our goal was to synthesize optically pure bidentate or tridentate ligands. Building on work previously done in the group, we first looked at the possibility of using the palladium-catalysed amination approach to produce small libraries of ligands. The aryl bromides used for this purpose were 2-bromopyridine **138** and 2,6-dibromopyridine **146**. In order to find optimum reaction conditions, we initially started using the inexpensive achiral amine benzylamine (Scheme **63**).

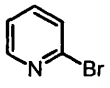
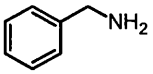
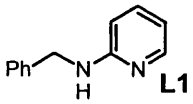
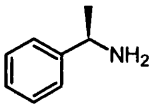
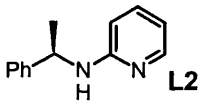
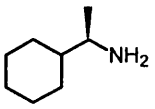
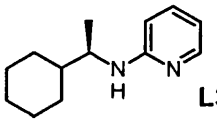
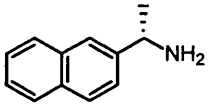
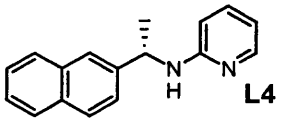
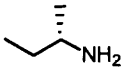
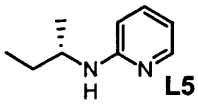
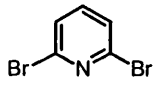
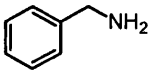
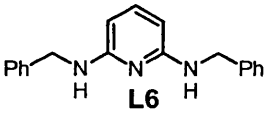
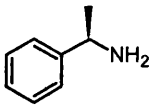
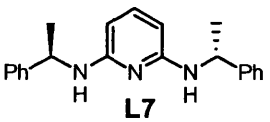
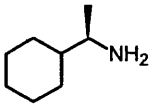
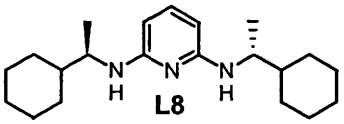
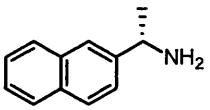
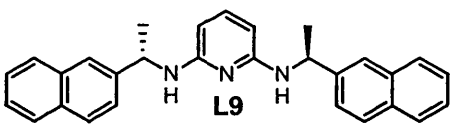
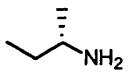
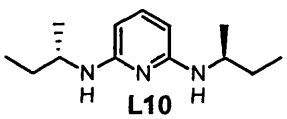
Scheme 63:



Each reaction was carried out in a pressure tube sealed with a teflon screw top under a nitrogen atmosphere. $Pd(dba)_2$, ligand (DPPF or BINAP), base (Cs_2CO_3 or NaO^tBu), benzylamine and aryl bromide were mixed in dry solvent (THF or toluene; the use of degassed solvent was found to be unnecessary) and heated to 80°C for four hours. TLC analysis (using DCM/MeOH 9:1 as the eluent) was used to monitor product formation. Insignificant differences in yield were observed with DPPF or BINAP as ligand, and thus we chose to use DPPF due to its lower cost. Toluene/sodium *tert*-butoxide was prefered to THF/caesium carbonate as the solvent base combination. We found the reaction led to the formation of a complex mixture of products when caesium carbonate was used as the base. Amination reactions using the combination of 5 mol% $Pd(dba)_2$, 11 mol% of DPPF, NaO^tBu and dry toluene proved efficient affording good to excellent yield of the desired product with little evidence of reduction of the aryl bromide. The reactions between simple primary amines and aryl bromides resulted clean reactions: TLC analysis showed a small trace of amine (used in excess) and the product. Thus a facile purification was carried out using a short column chromatography with neat dichloromethane as the eluent. Four hours was usually sufficient to provide a decent yield of product, although by leaving the reaction overnight all the starting aryl bromide was consummed. All of the reactions were carried out on less than one mmol scale (50 mgs of aryl bromide). The reaction proved difficult to scale up; a significant amount of side products were formed in bigger reactions. Following these encouraging results, we proceeded to prepare a range of ligands using

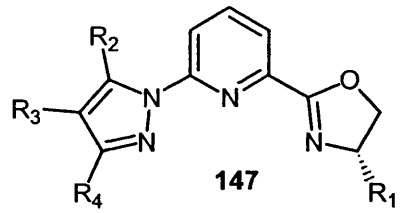
enantiopure primary amines. Gratifyingly these ligands were synthesized without loss of enantiopurity. This was verified by chiral HPLC (by comparing the retention time with the racemic product) using a Chiralcel OD column, with 10% IPA/hexane mobile phase, and a flow rate of 0.5 mL/min (Table 4).

Table 4:

Aryl halides	Amines	Product	Yield (%)	e.e.
		 **L1**	60	-
		 **L2**	91	>99
		 **L3**	88	>99
		 **L4**	69	>99
		 **L5**	77	>99
		 **L6**	72	-
		 **L7**	60	>99
		 **L8**	58	>99
		 **L9**	97	>99
		 **L10**	74	>99

This library of ligands (**L1-L10**) was then screened in the asymmetric hydrosilylation of acetophenone using parallel screening techniques. The results of this work are discussed in chapter three.

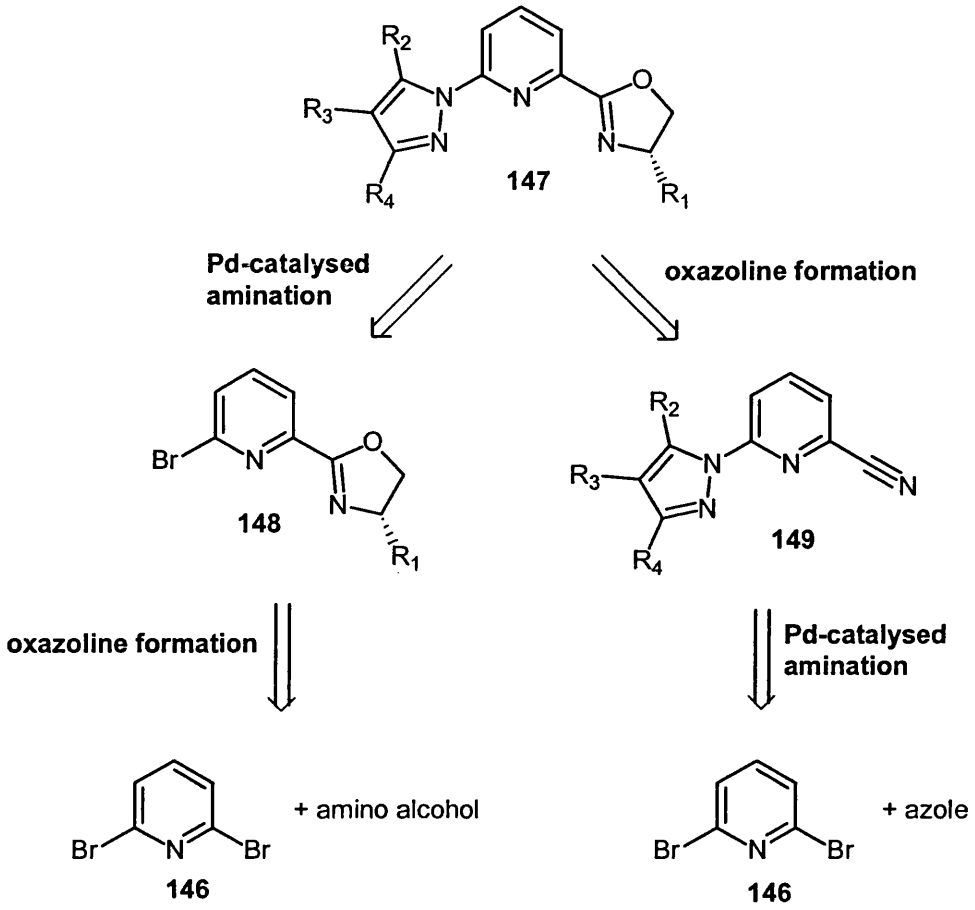
After the preparation of this library, we focused on the generation of other ligand libraries and their screening and optimisation on the asymmetric hydrosilylation of ketones (see Chapter three). We did, however, decide to return to this chemistry to investigate some novel, more synthetically demanding, ligands for screening. These ligands were designed on the basis of the requirements we found necessary for successful catalysis of the hydrosilylation reaction. An outline of this work is given below with primary target ligands being tricyclic systems such as **147**.



147

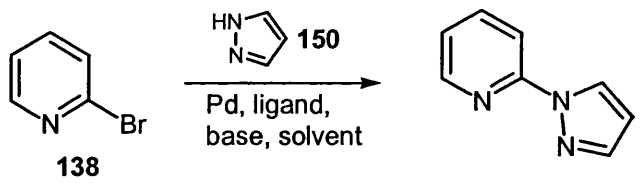
We anticipated that the synthesis of this ligand would be possible starting from the commercially available 2,6-dibromopyridine **146**. Then we have two options: we could ideally prepare the pyridine oxazoline **148** on a large scale and then, incorporating the azole with the palladium cross-coupling reaction could be carried out. However, this second step might present a few problems: the oxazoline might not be stable enough under these conditions (strong base such as sodium *tert*-butoxide and high temperature) and therefore at risk of racemisation. Alternatively the palladium-catalysed amination reaction could be carried out first with the construction of the oxazoline completing the synthesis. That way, the difficult chemistry can be done first and the chiral centre can be introduced in the final step only (Scheme **64**).

Scheme 64:



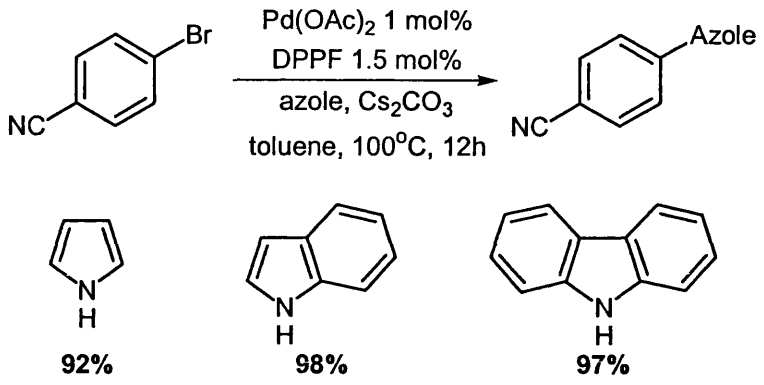
Firstly, we investigated the palladium-catalysed amination reaction on a model system, starting from 2-bromopyridine **138** and pyrazole **150** (Scheme **65**).

Scheme 65:



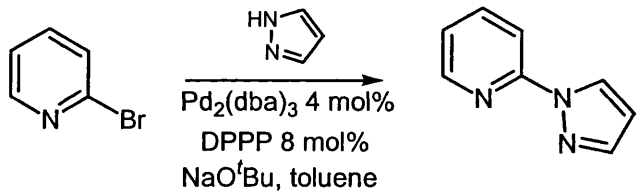
Looking back in to the literature, we found that Buchwald reported the coupling of bromopyridine and primary or secondary amine using the combination $Pd_2(dba)_3$/DPPP as a catalyst.[117] Buchwald has stated that BINAP was a generally more effective ligand for the reaction. Hartwig later reported that the $Pd(OAc)_2$/DPPF was an efficient catalyst for the coupling of aryl bromides with azoles[119] (Scheme **66**).

Scheme 66:



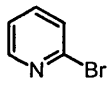
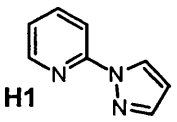
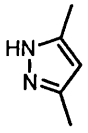
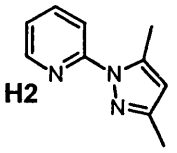
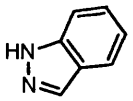
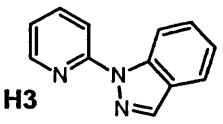
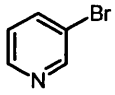
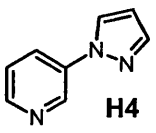
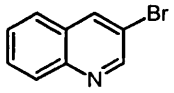
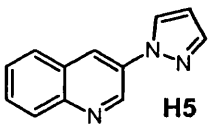
We decided to screen a range of conditions for this coupling; when BINAP, DPPF and DPEphos were used in combination with either $Pd_2(dba)_3$ or $Pd(OAc)_2$, the reaction seemed partially successful but gave rise to many side products from which it proved impossible to isolate the desired product. We found out that the combination of $Pd(dba)_2$ (4 mol%) and DPPP (8 mol%) acted as an efficient catalyst with NaO^tBu as base and toluene as solvent (Scheme **67**). Cleaner reactions and higher yields were thus obtained with column chromatography delivering pure products. The reaction was also successful in THF. However these coupling of azoles and bromopyridine proved to be much harder than the first couplings using primary amines. The purification proved to be more difficult than previously due to the higher amount of by products and therefore yields are much lower.

Scheme 67:



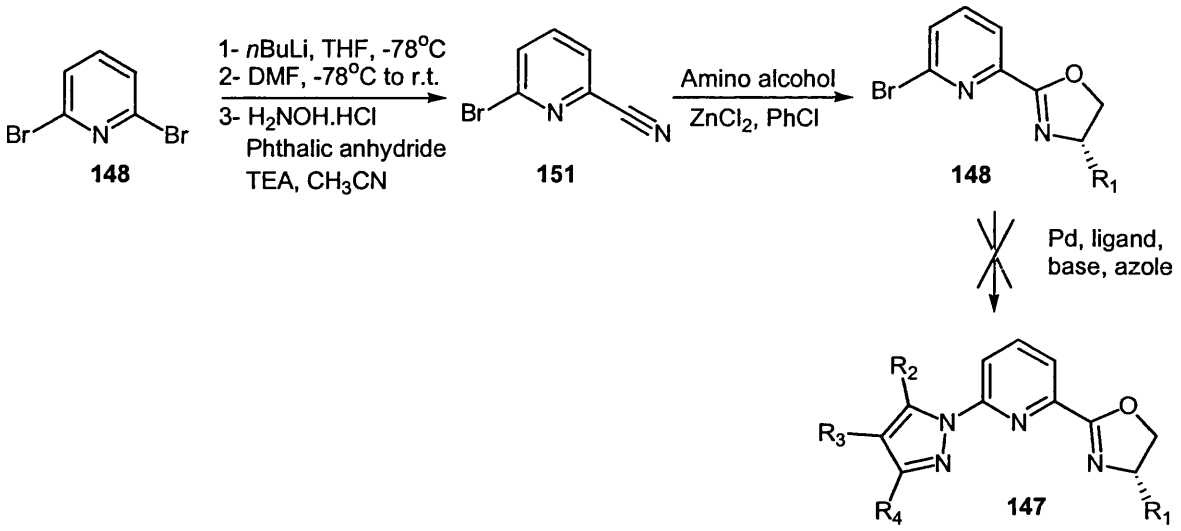
A selection of products were generated using these conditions and different halides. (Table 5).

Table 5:

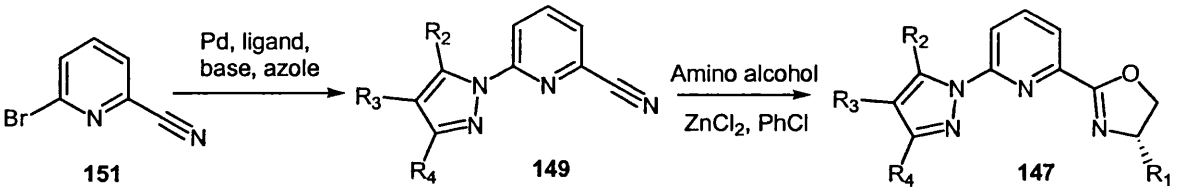
Aryl bromide	Azole	Product	Yield (%)
		 **H1**	55
		 **H2**	62
		 **H3**	53
		 **H4**	56
		 **H5**	60

Since the coupling between the bromopyridine and azoles was successful, we continued to apply this method to the synthesis of ligand **147**. We thought the first retrosynthetic approach was quite attractive due to the fact that we could prepare the oxazoline on a large scale and then do the palladium cross-coupling. The first two steps of this synthesis involved very simple chemistry; starting from the 2,6-dibromopyridine the aldehyde was first formed and converted to the corresponding nitrile **151**, *via* the oxime in good overall yield (*ca.* 70%). The next step however proved to be disappointing, with the desired oxazoline **148** being obtained in only 40% yield after many attempts. The concluding step however proved the most troublesome, despite numerous attempts we have been unable to carry out a successful coupling of the azole and brominated pyridine: it seemed that the oxazoline was unstable under these reaction conditions and high temperature (Scheme **68**).

Scheme 68:



We tried the other synthetic route which involved first the palladium-catalysed amination chemistry and then elaboration of the oxazoline to complete the synthesis.



Using the bromo-nitrile **151** as the substrate for the amination reaction proved to be problematic. It appeared that the nitrile changed either the electronic environment of the pyridine group or the stability of intermediates in the cycle to such an extend that our previously developed coupling conditions were no longer successful. A simple change of $Pd(dba)_2$ for $Pd(OAc)_2$, in combination with DPPP allowed us to access product **149** in moderate yield (42%). The synthesis of the oxazoline also proved to be difficult. The use of different Lewis acids, in particular cadmium acetate and zinc chloride failed to yield the oxazoline. The major obstacle for further exploration of this route proved to be the palladium chemistry, for some unknown reason, the reaction could not be scaled up, with 100 mgs of starting bromide being the maximum amount we could use. Use of more starting material led to excessive by-product formation and inefficient reactions.

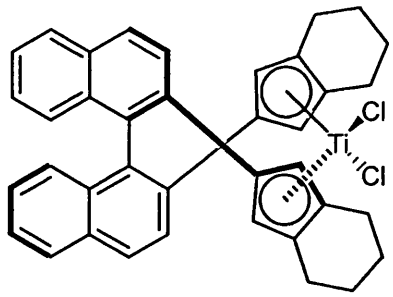
With the time becoming more pressing, we decide to focus on screening the libraries of ligands we had already prepared and the synthesis of these ligands was abandoned, although it would have been interesting to see if we could synthesize the ligand **147** without the use of palladium. A group of researchers have subsequently found that the coupling of an aryl bromide with an azole can be carried out quite efficiently by employing sodium hydride and 15-Crown-5 in DMF. It is possible that the use of these conditions may overcome the difficulties we have encountered in our attempted synthesis as could the use of alternate approaches to the oxazoline ring system.

Catalytic asymmetric hydrosilylation reactions

A detailed review on asymmetric hydrosilylation of ketones catalysed by rhodium and ruthenium complexes is contained in chapter one. Here we wish to discuss the recently developed titanium catalysed hydrosilylation of ketones as well as the hydrosilylation of other unsaturated functional groups by a range of metal.

Hydrosilylation of C=O with chiral titanium catalysts

As well as rhodium-catalysed hydrosilylation, asymmetric titanium-catalysed hydrosilylations have also been reported. The first attempt at asymmetric hydrosilylation of ketones by titanium-silane catalysts were published independently by two groups in 1994. Halterman's group reported that the binaphthyl catalyst derivative **152** exhibited a catalytic activity in THF for the reduction of several ketones with triethylsilane at -78°C to room temperature and resulted in high yield with e.e.'s of 40% and 32% for 2-acetonaphthone and acetophenone respectively.[120]

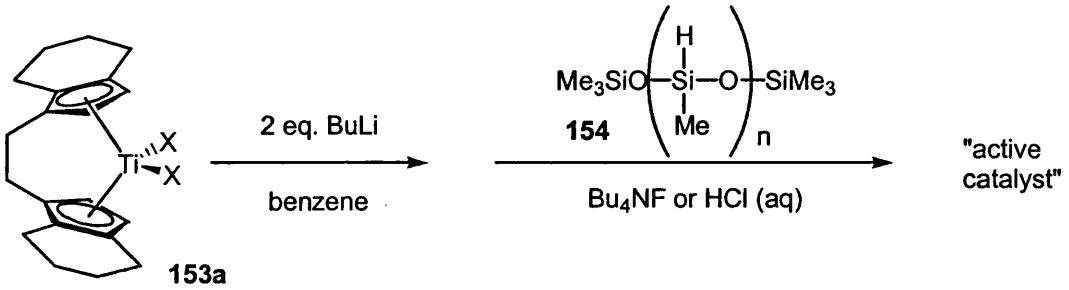


152

Buchwald's group reported that the hydrosilylation of ketones using the enantiopure (tetrahydroindenyl)titanium (IV)-binaphthdiolate catalyst **153a** in combination with the inexpensive polymethylhydrosilane **154** appeared to be the most general reagents.[121] Reactions were run by activation of the titanocene catalyst with 2 equivalents of butyllithium, followed by the addition of polymethylhydrosilane **154**, then ketone and finally work up with fluoride or acid to remove the silyl groups. The reactions were

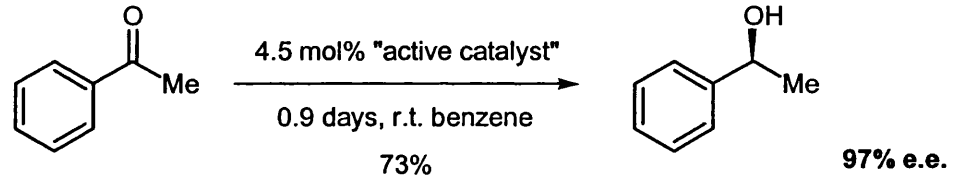
suggested to take place *via* a titanium (III) hydride although there is uncertainty over the details of the mechanism. Acetophenone **15** and tetralone **155** were reduced with good enantioselectivity following this procedure[122] (Scheme **69**). At this stage high catalyst loading (4.5-10 mol%) was required to achieve complete conversion of substrate to product.

Scheme 69:

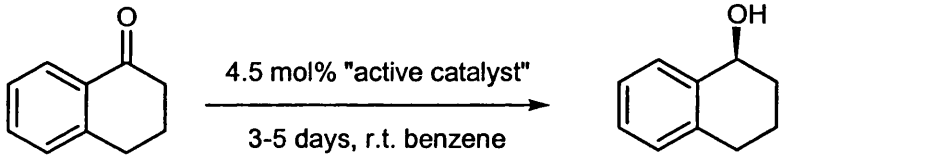


153a

X,X = 1,1'-binaphth-2,2'-diolate



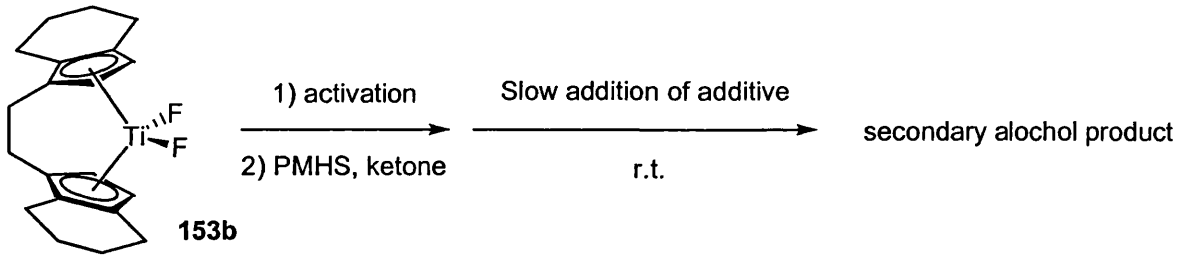
15 **97% e.e.**

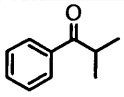
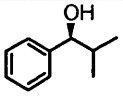
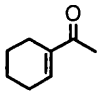


155 **91% e.e.**

These results were improved by the introduction of a nucleophilic catalyst to convert the titanium intermediate into a more reactive complex. Addition of MeOH resulted in a great enhancement of the reaction rate, compared to that previously reported, allowing the reduction of the catalyst loading greatly to 0.5-2 mol% (Table 6).[123]

Table 6:



Ketone	Alcohol	Catalyst	Additive	Time	Yield (%)	e.e. (%)
		4.5 mol% (I)	None	4.5 days	79	92
		1 mol% (II)	3-7 eq. MeOH	8h	86	99
		4.5 mol% (I)	None	1 day	72	90
		2 mol% (II)	3-7 eq. MeOH	5h	87	96

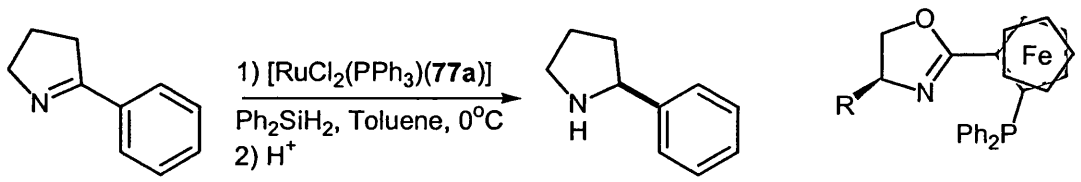
Recent developments

Asymmetric hydrosilylation of imines

Although there has been little research done into the hydrosilylation of functionality other than carbonyls, the work which has been published provides some exceptionally good examples of enantioselective catalysis.

In the course of their studies concerning the use of ruthenium complexes, derived from ligands **77**, as catalysts for the hydrosilylation of ketones, Uemura and co-workers further demonstrated that these complexes also catalysed the enantioselective hydrosilylation of imines.[54] Yields of 60% with 88% e.e. were achieved using the imine **156** with diphenylsilane using a catalytic amount of ruthenium complex in toluene at 0°C for 48 hours (Scheme **70**).

Scheme 70:

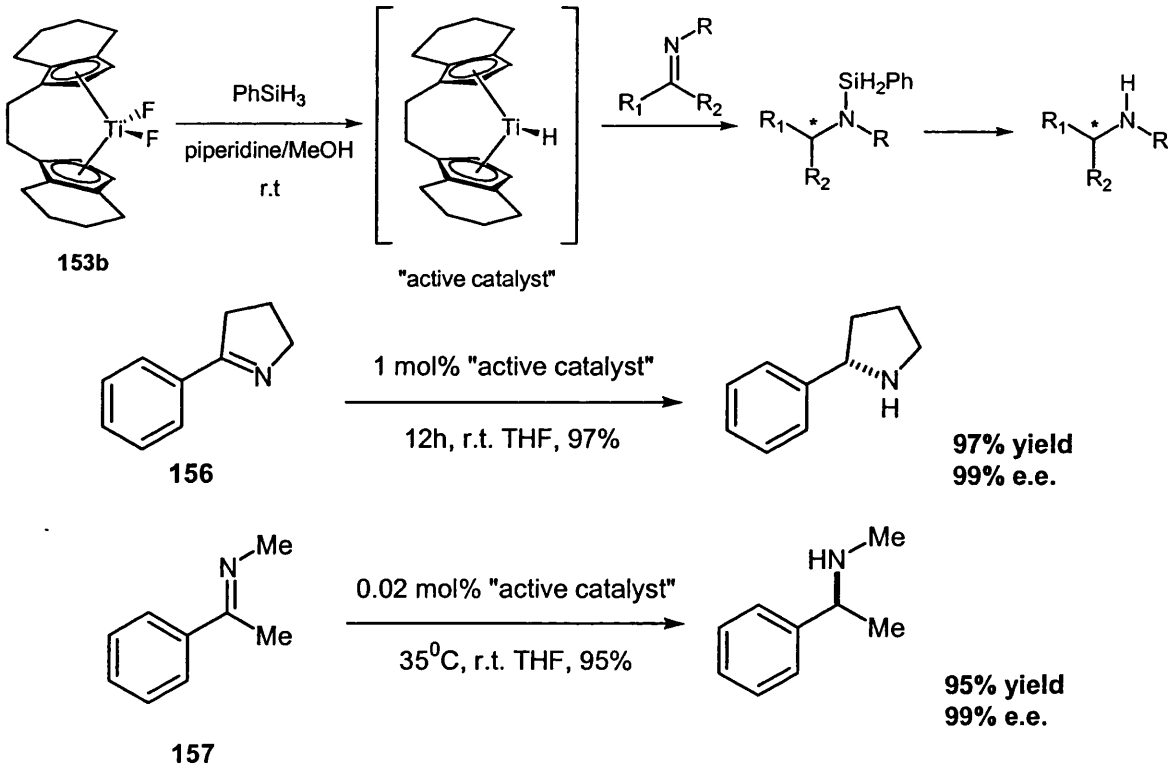


156 **60% yield** **88% e.e.** **77a** R=Ph **77b** R=*i*-Pr **77c** R=*t*-Bu

This is, to date, the best ruthenium complex applicable to asymmetric catalytic hydrosilylation of ketones and imines.

Buchwald's group has reported a superb example of an asymmetric reaction using the difluorotitanocene catalyst **153**. Using catalyst loading as low as 0.02 mol%, the catalyst gives very high e.e.'s for the hydrosilylation of a wide range of imine substrates, including cyclic **156** and acyclic imines **157**[124] (Scheme **71**).

Scheme 71:

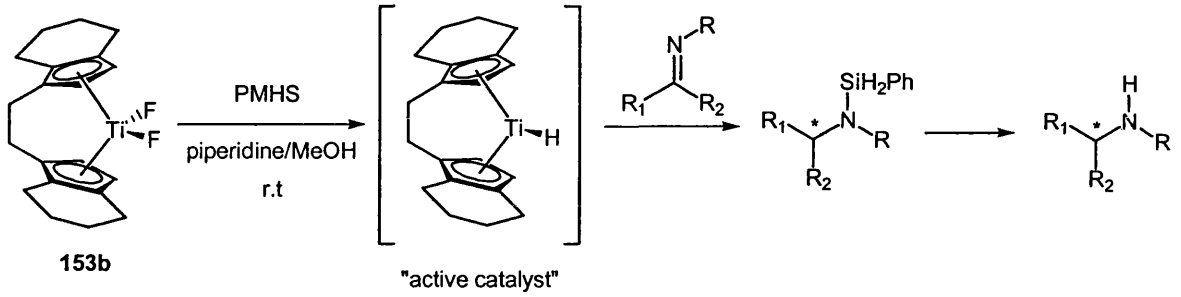


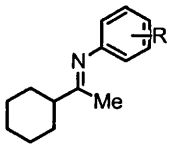
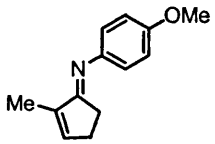
153b "active catalyst" **156** **97% yield** **99% e.e.** **157** **95% yield** **99% e.e.**

Buchwald also reported that a variety of *N*-arylimines derived from non-aromatic ketones were reduced with high enantioselectivity employing complex **153** as the precatalyst with

polymethylhydrosiloxane (PMHS) as the stoichiometric reducing agent (instead of phenylsilane) in combination with an amine additive (isobutylamine, table 7).[125]

Table 7:

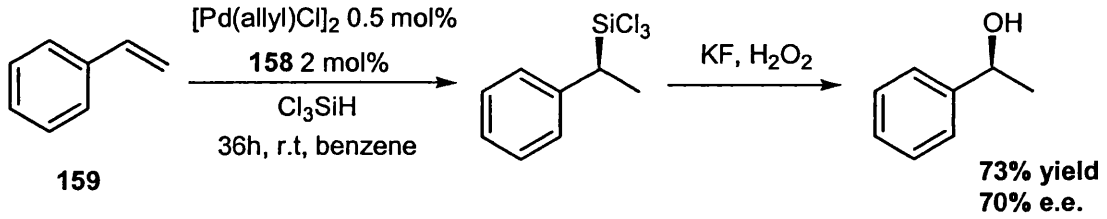


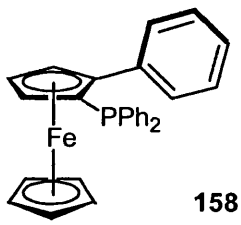
Imine	Yield (%)	e.e. (%)
		
R = *p*-OMe	79	99
R = H	63	99
	90	98

Asymmetric hydrosilylation of styrene

Johannsen's group have synthesized a new family of monophosphine ferrocene ligands **158** in just two steps from optically pure ferrocenyl sulfoxide and the first preliminary studies employing these ligands in asymmetric hydrosilylation of styrene **159** have given encouraging results: 73% yield and 70% e.e. (Scheme **72**).[126]

Scheme 72:



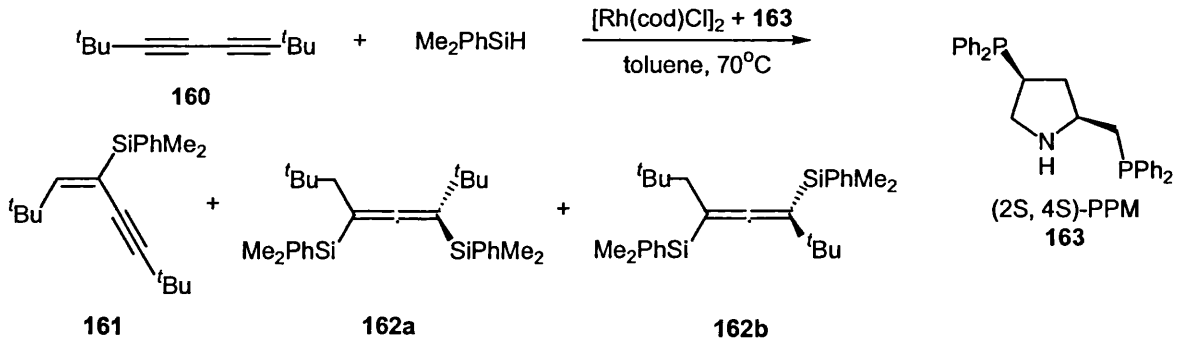


158

Asymmetric hydrosilylation of butadiynes

Recently a rhodium-catalysed synthesis of chiral allenes *via* asymmetric hydrosilylation of butadiyne **160** has been reported.[127] A chiral Rh-phosphine catalyst has proved to be the best catalyst to date for this reaction. The best results of 27% yield and 22% e.e. have been obtained using 1 mol% of $[Rh(cod)Cl]_2$ and 2 mol% of chiral bidentate phosphine PPM **163** in toluene at 70°C for 24 hours.

Scheme 73:

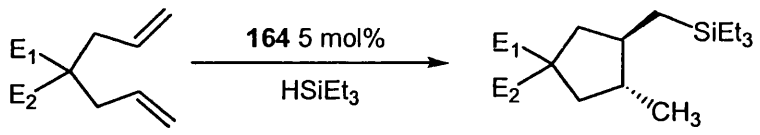


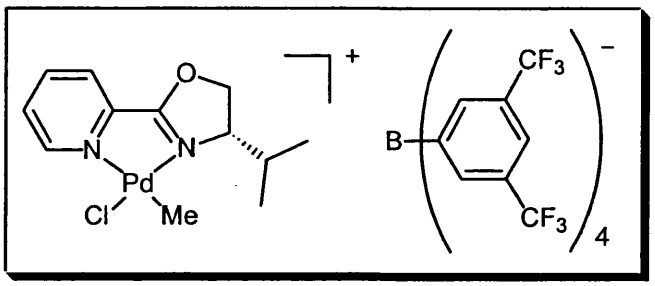
Asymmetric cyclisation/hydrosilylation of 1,6-dienes

All the reactions referenced so far involved the addition of an H-Si bond across a C=X (X = O or N). In contrast, highly enantioselective catalytic protocols which form C-C bonds are less common; Catalytic carbocyclisation remains a significant challenge in organic synthesis. One recent approach which shows good potential is the cyclisation/hydrosilylation of dienes which is emerging as a potential route toward the synthesis of functionalised carbocycles.

Widenhoefer's group reported the first examples of a asymmetric cyclisation/hydrosilylation of 1,6 and 1,7-dienes employing palladium-catalysed protocols to achieve very good results (Scheme **74**, table 8).[128]

Scheme 74:





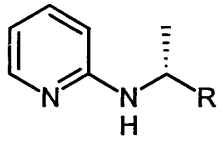
Precatalyst **164**

Table 8:

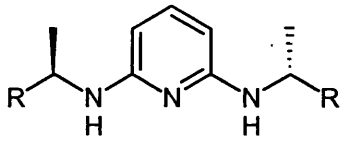
Diene	T (°C)	Yield (%)	e.e .(%)
$E_1 = E_2 = CO_2CMe_3$	-40	79	90
$E_1 = CO_2Me$	-18	84	89
$E_2 = Ph$			
$E_1 = E_2 = CH_2OCOCMe_3$	-18	89	91

The asymmetric hydrosilylation of ketones have now reached very high level of enantioselectivity with either rhodium or the recently developed titanium catalysts. Other functionalitites such as imines proved to be more difficult to reduce although some excellent results are emerging in the literature with titanium catalysts.

At the start of our studies, we extended some work done in the group on the palladium-catalysed amination of aryl bromides, chemistry developed mainly by Hartwig and Buchwald. We have prepared a first series of optically pure (bidentate and tridentate) nitrogen ligands employing this chemistry (see chapter two).



L1-L5



L6-L10

R = Phenyl, cyclohexyl, naphthyl, ethyl

Preliminary reactions employing these ligands have been carried out on the asymmetric hydrosilylation reaction of acetophenone. Parallel screening techniques were used to accelerate this process.

Combinatorial approaches to catalysis

The major application of combinatorial chemistry remains the search for biologically active molecules. It has recently been recognized that such methods might be effective to speed up the identification of compounds with any attractive properties.[129] Combinatorial and related approaches have indeed been utilized in investigations in asymmetric catalysis. There are two extreme approaches to the task of preparing and testing chemicals libraries. The classical one is *via* a sequential method, a single compound is designed, synthesized and tested, in a one-at-a-time fashion. In contrast, a high-throughput strategy generates and tests simultaneously considerably larger numbers of compounds, potentially reducing the entire search cycle to one or two iterations.

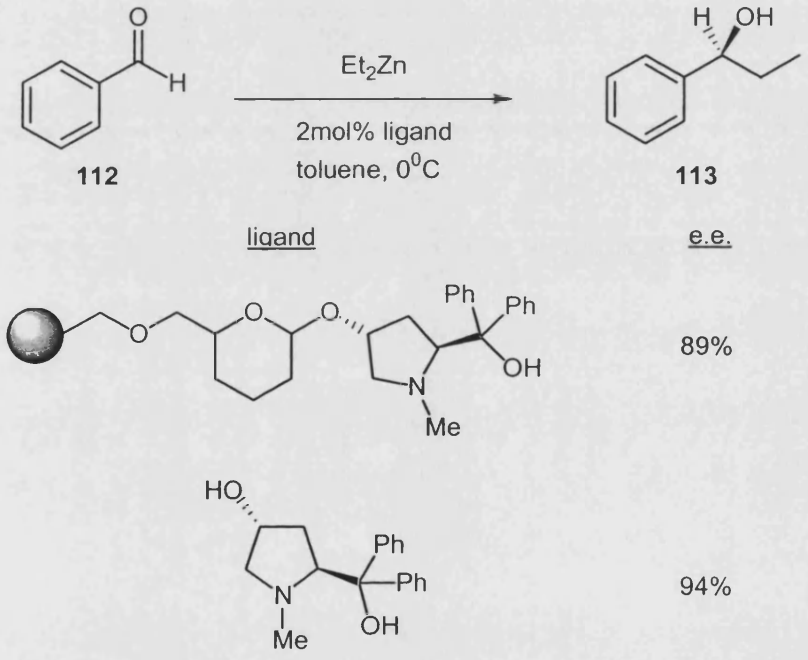
Combinatorial chemistry brings together rational design and high-throughput evaluation. It is particularly well-suited to the optimisation of novel and previously unexamined reactions for which little mechanistic data is available. The first attempts to use principles

of combinatorial chemistry and high-throughput strategies to identify effective organometallic chiral catalyst are detailed below.

Asymmetric aldehyde alkylation

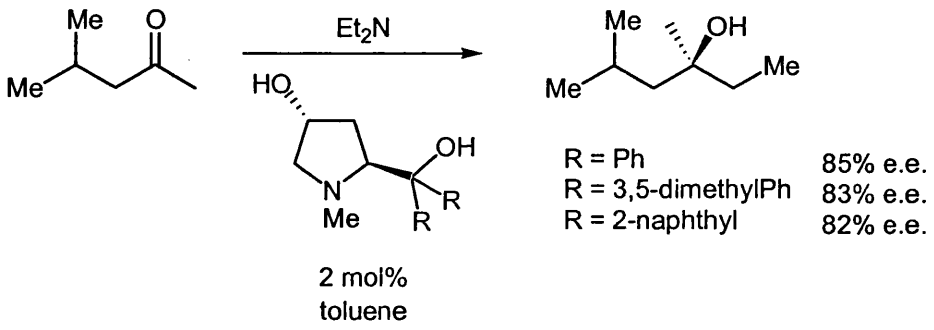
In 1995, Ellman used a combinatorial approach for the diethylzinc addition to aldehydes.[130] Thirteen ligands were synthesized on a solid support from 4-hydroxyproline, attached on a Merrifield resin through its 4-hydroxy substituent. The ligands were initially screened still attached to the support and proved to give slightly lower enantioselectivity than the free ligand themselves (89% *vs* 94% e.e., scheme **75**).

Scheme 75:



Screening was then carried out with the ligands free from the resin. It is important to note that little or no purification of the ligands was required to maintain excellent enantioselectivity. Representative examples are given in scheme **76**. These examples demonstrate that solid phase combinatorial strategies may be useful for the development of asymmetric catalysts.

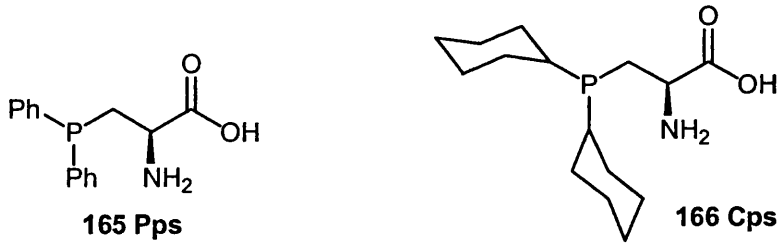
Scheme 76:



Asymmetric hydrogenation

As with many other metal catalysed asymmetric reactions, it is often difficult to predict which phosphine ligand or metal centre will lead to the most efficient and selective hydrogenation. Gilbertson's group set out to prepare a 63 member library of chiral phosphines, built within an helical peptide scaffold.[131] Three amino acids were placed on each end of the peptide, with the peptide sequence fixed as Ac-Ala-Aib-Ala-{ }-Ala-Aib-Ala-NH_2. Two phosphines, **165** and **166**, were inserted between the two peptides at spacing (i, i+1) and (i, i+4). These phosphines were hoped to bring a chiral environment bear upon the transition metal and thus catalyse selective reactions (Scheme **77**).

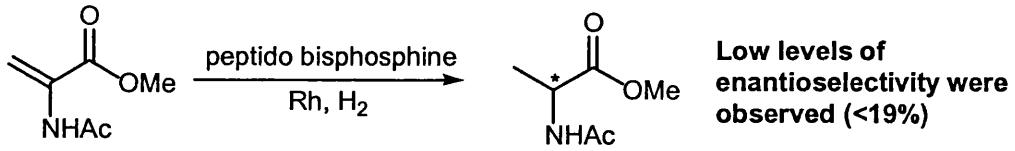
Scheme 77:



e.g. (i, i+1) Phe-Ala-Ala-**Pps**-**Pps**
(i, i+4) **Cps**-Ala-Ala-Aib-**Pps**

Rhodium was complexed to each member of the phosphine library while they were still attached to the solid phase support. Each member of the library was then screened for its ability to catalyse the asymmetric hydrogenation of enamide **167** to α-amino ester **168** (Scheme **78**).

Scheme 78:



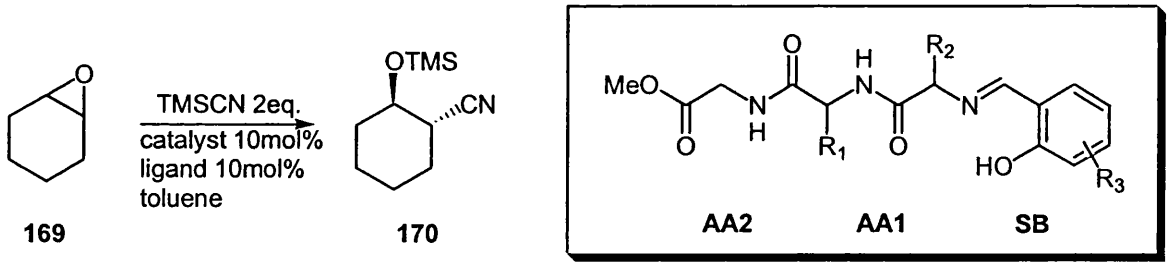
167 **168**

Although low levels of enantioselectivity were observed (<19% e.e.), this study demonstrated that a combinatorial protocol can efficiently provide the chemist with a wealth of data in a short period of time.

Catalytic enantioselective addition of TMSCN to *meso* epoxides

In 1996, Hoveyda's group designed a library of peptide-ligands composed of three subunits: Schiff base (SB), amino acid 1 (AA1) and amino acid 2 (AA2), which were screened in the enantioselective addition of TMSCN to epoxides such as **169** (Scheme 79).[132]

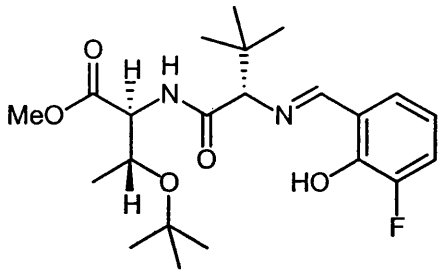
Scheme 79:



169 **170**

These ligands offered some attractive features since chiral amino acids are readily available in the non-racemic form and peptides can be efficiently prepared establishing solid phase protocols. Each of the 3 subunits were successively optimized. To determine the best candidate for amino acid 1 (AA1), ten ligands were prepared on solid support (the other two variables being kept constant), cleaved, and screened in a parallel fashion as catalysts for the enantioselective formation of **170**. *Tert*-Leucine was found to be optimal at this position. Then AA2 was varied in the analagous manner before final optimisation of

the Schiff base terminus. Thus dipeptide Schiff base **171** was identified as an effective ligand for the Ti-catalysed addition of TMSCN, indeed, **170** has been obtained in 86% e.e.



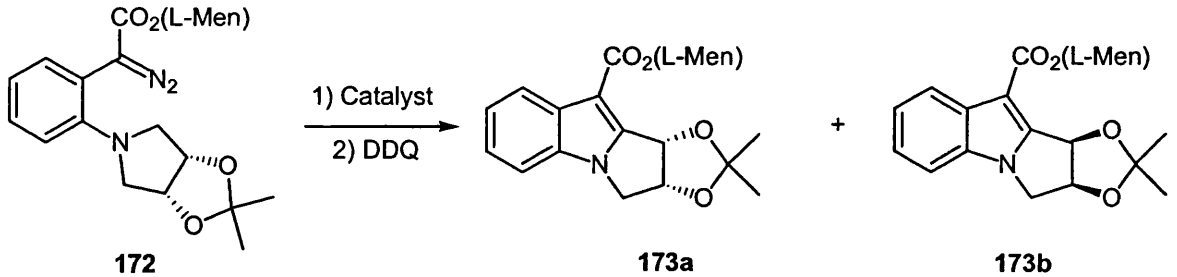
86% e.e.
80% conversion

171

Catalytic asymmetric carbene insertion

Diazo compounds with suitable oriented substituents can undergo cyclization by metal-promoted reactions that presumably involve insertion of metallocarbenes into C-H bonds. Most of the known reactions of this type involve rhodium complexes though in some cases, optically active copper catalysts have been reported to be superior for the reaction (Scheme **80**).

Scheme 80:



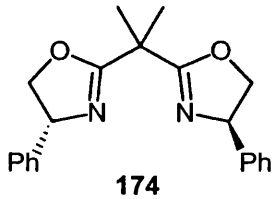
172 **173a** **173b**

In 1996, Burgess's group studied the above reaction using high-throughput catalyst screening to improve the results. Ninety six potential systems were examined for the reaction.[133] Three different bis-oxazoline ligands, a salen type ligand and sparteine were used in combination with seven different metal salts (although not for each ligand) and four different solvents.

A simple apparatus was used for this purpose consisting of an aluminium block having the same base size as a 96-well microtiter plate, with 34 holes to hold 1.1 mL polypropylene

microtubes as reaction vessels. A U-shaped channel was drilled in the block parallel with 3 sides to facilitate cooling of the block *via* circulation of cooling fluid from a cryostat.

To use this apparatus, metal salts and other insoluble solid components were weighed into appropriate wells, all manipulations being done in a glove box. Standard solutions of the soluble ligands, reagents and additives were prepared, and aliquots were pipetted into the wells as appropriated. The reaction vessels were capped, then the plate was placed on a commercial horizontal shaker for a 96-well microtiter plate. The solvents were allowed to evaporate and the contents of each well were passed through a short column of silica eluted with hexane/EtOAc (3: 2) for a crude purification. Naphthalene was added to serve as an internal standard prior to analysis carried out on an HPLC equiped with an autosampler. The most effective catalyst was found to be a Cu^{I}.bis-oxazoline ligand complex **174** which was optimized to give a 3.9:1 diastereomeric ratio and a 47% yield in THF at 10°C.



174

• Cu(OTf)

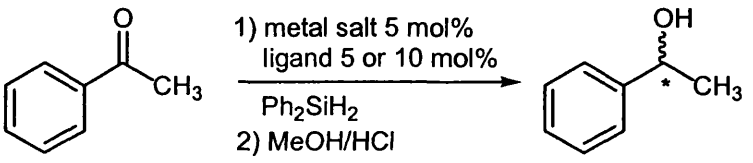
Optimum ligand/ metal combinations afforded 3.9:1 diastereoselectivity in THF at 10°C

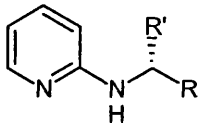
Screening of the first ligand series

We adopted the strategy pioneered by Burgess which involves performing the transformations in parallel in a 96-well microtiter plate and following the reactions by automated GC. These facilities were only available on a sporadic basis by the generous support of Johnson Matthey Plc. Four bidentate ligands (three chiral **L2-L5** and one racemic **L1**) and four tridentate ligands (three chiral **L7-L9** and one racemic **L6**), synthesized as described in chapter two, were combined with three metal complexes: $RuCl_2(dmso)_4$, $[RuCl(cymene)]_2$ and $[Ir(cod)Cl]_2$. The first screening was carried out in air. Standard solutions of ligands, metal and other reagents were prepared in THF beforehand. The three metal precursors were placed in twelve vials respectively, then the eight different

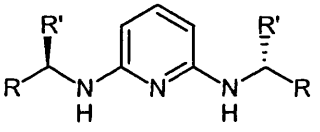
ligands (bidentate ligands were added in quantities of one and two equivalents) were added to each of the three different metals in their respective vials. Acetophenone and diphenylsilane were then added to each of the 48 vials. The plate was then sealed and left overnight at room temperature, after which time a 1:1 mixture of methanol/HCl was added. These reaction mixtures were then transferred in to GC vials and analysed by automated GC to obtain conversions (Scheme **81**, table 9, graph 1). High yielding reactions were then analysed for enantioselectivity by chiral GC.

Scheme 81:





L1 R = Ph, R' = H
L2 R = Ph, R' = Me
L3 R = C_6H_{11}, R' = Me
L5 R = C_2H_5, R' = Me



L6 R = Ph, R' = H
L7 R = Ph, R' = Me
L8 R = C_6H_{11}, R' = Me
L9 R =naphthyl, R' = Me

Table 9: conversion (%) of acetophenone to 2-phenylethanol in air.

Ligands	$RuCl_2(dmso)_4$	$[RuCl(cymene)]_2$	$[Ir(cod)Cl]_2$
L1 1 eq.	7	0	**41**
L2 1 eq.	3	2	32
L3 1 eq.	13	0	19
L5 1 eq.	14	0	29
L1 2 eq.	3	0	**52**
L2 2 eq.	9	3	29
L3 2 eq.	10	0	16
L5 2 eq.	10	2	23
L6 1 eq.	21	0	43
L7 1 eq.	**28**	0	24
L8 1 eq.	**29**	0	32
L9 1 eq.	0	0	15

These few results were quite encouraging, in that moderate conversions (up to 52%) were obtained with the iridium precursor. Although $RuCl_2(dmso)_4$ was less efficient than

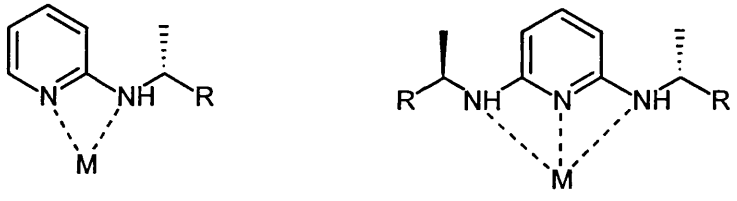
$[Ir(cod)Cl]_2$, we could still achieve up to 29% conversion using the chiral tridentate ligand **L8**. However, the $[RuCl(cymene)]_2$ showed no activity at all. The use of two equivalents of the bidentate ligands did not improve the conversions. Tridentate ligands seemed to give better yields, especially with ruthenium as a metal centre. This process was then repeated in an argon box but with only $RuCl_2(dmso)_4$ and $[Ir(cod)Cl]_2$. (table 10, graph 2). The conversions increased significantly: yields obtained with $RuCl_2(dmso)_4$ equalled those obtained with $[Ir(cod)Cl]_2$ as a precursor.

Table 10: conversion (%) of acetophenone in 2-phenylethanol under argon atmosphere.

Ligands	$RuCl_2(dmso)_4$	$[Ir(cod)Cl]_2$.
L2 1 eq.	32	38
L3 1 eq.	30	27
L5 1 eq.	33	36
L7 1 eq.	32	28
L8 1 eq.	32	29
L10 1 eq.	16	28

We managed to achieve moderate levels of conversion which was quite encouraging for a first screening, however, no enantioselectivity was observed which is easily rationalised and should, perhaps, have been anticipated (Scheme **82**).

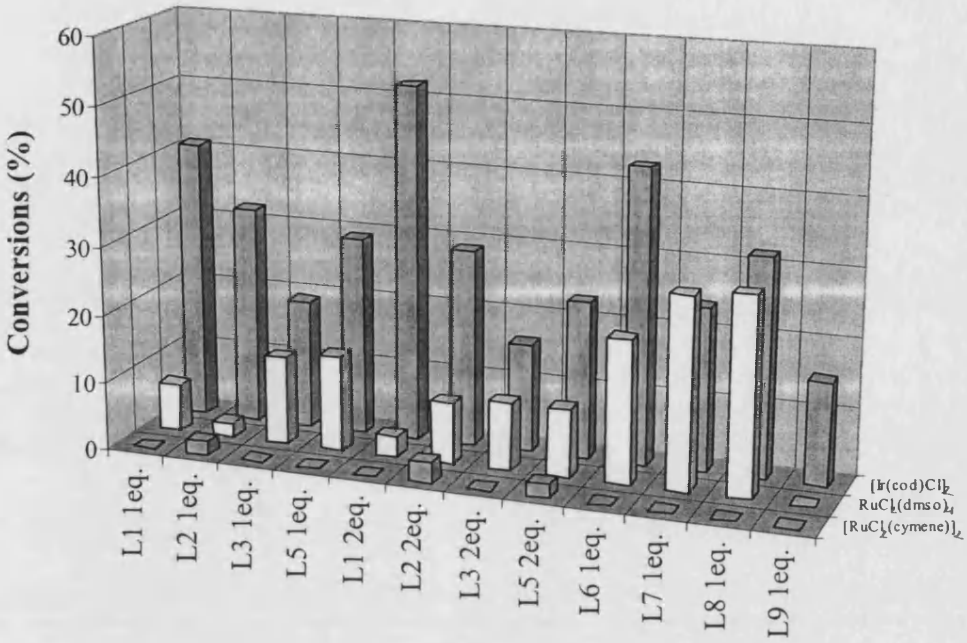
Scheme 82:



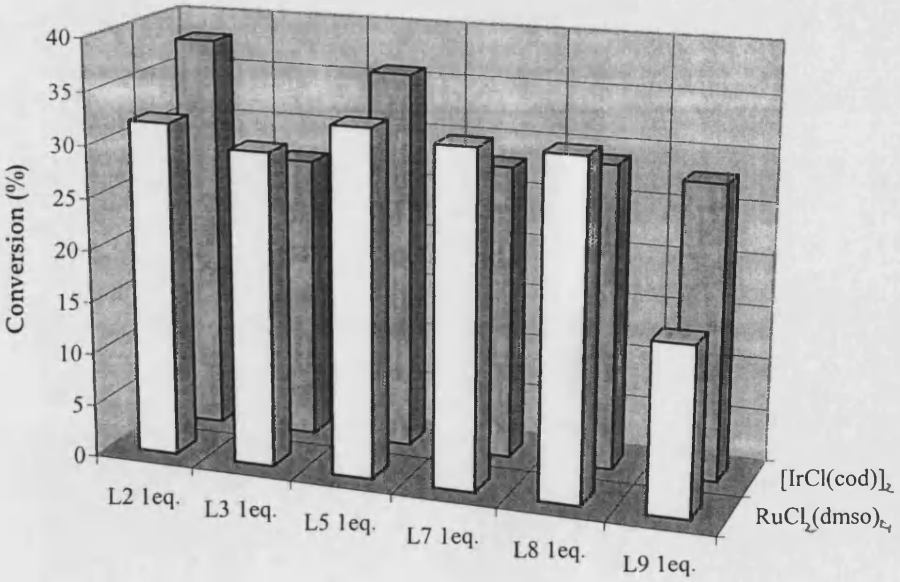
In the case of bidentate ligand, a strained four-membered ring would have to be formed between the metal and the two chelating nitrogen atoms in order to express the chirality of the ligand efficiently in the reaction. Although the formation of a four-membered ring is possible, it is clearly thermodynamically disfavoured and thus, although our ability to rapidly synthesize these ligands had encouraged us to make and screen them, the chances of this approch were limited. Likewise in the tridentate ligand, the metal cannot be bound

to all three nitrogen atom and share the requirement for strained four membered chelate rings to be formed from these flat ligands for effective, selective catalysis.

Graph 1: Asymmetric hydrosilylation of acetophenone in air



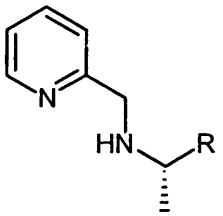
Graph 2: Asymmetric hydrosilylation of acetophenone under argon



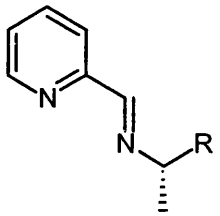
New libraries of nitrogen ligands

The formation of both 5 and 6-membered chelates are thermodynamically much more favourable and thus we synthesized new libraries **A1-A6** and **I1-I6** (Scheme **83**).

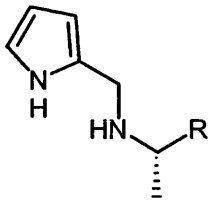
Scheme 83:



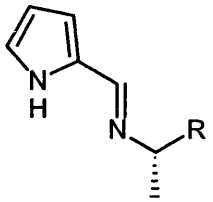
A1-(S) R = phenyl
A2-(S) R = cyclohexyl
A3-(S) R = naphthyl



I1-(S) R = phenyl
I2-(S) R = cyclohexyl
I3-(S) R = naphthyl



A4-(S) R = phenyl
A5-(S) R = cyclohexyl
A6-(S) R = naphthyl

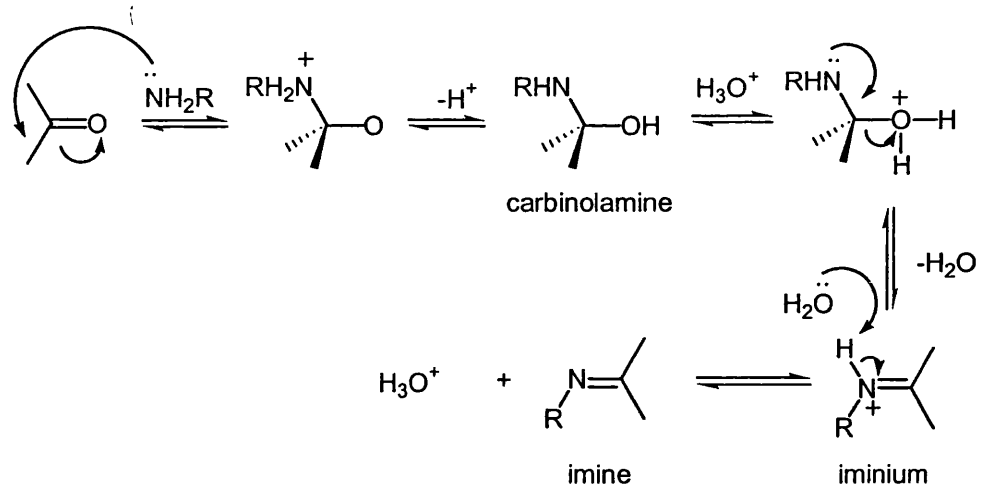


I4-(S) R = phenyl
I5-(S) R = cyclohexyl
I6-(S) R = naphthyl

The chiral imine ligands (**I1-I6**) were simply prepared by mixing under an inert atmosphere, pyridine-2-carboxaldehyde or pyrrole-2-carboxaldehyde with the corresponding chiral primary amine in dry methanol and 4A molecular sieves. After stirring for 4 hours at room temperature, the product was identified by infra red with a band at 1645 cm^{-1} for the imine bond (CH=N) whilst ^1H NMR showed a characteristic singlet at 8.5 ppm for the imine proton. The imines were obtained in quantitative manner after filtration of the molecular sieves and evaporation of solvent.

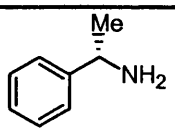
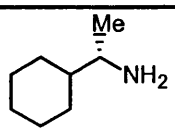
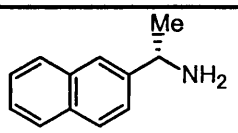
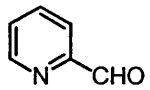
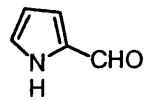
The mechanism of the imine formation is shown in scheme **84**. Firstly, a nucleophilic attack of the lone pair on the nitrogen of the amine on the carbonyl group occurs. A proton is then transfered from the nitrogen to the oxygen. The acid catalyst protonates the hydroxyl group. The lone pair on the nitrogen expels water giving an iminium ion. Finally loss of H^+ from nitrogen then gives the desired imine. All steps in this overall reaction are equilibrium processes.

Scheme 84:



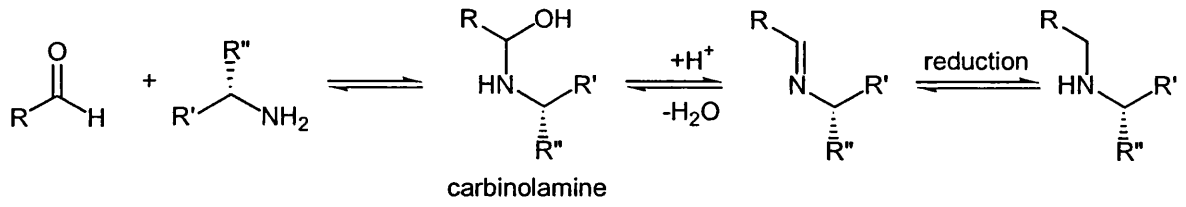
The chiral amine ligands (**A1-A6**) were prepared by mixing pyridine-2-carboxaldehyde or pyrrole-2-carboxaldehyde with the corresponding chiral primary amine in the presence of sodium triacetoxyborohydride as a reducing reagent in dry THF or DCE. After stirring at room temperature under a nitrogen atmosphere, TLC showed product formation. This reductive amination protocol has been chosen due to the mild, non toxic reducing reagent used.

Table 11: Yields (%) of amine (S)

			
	71	69	23
	75	69	60

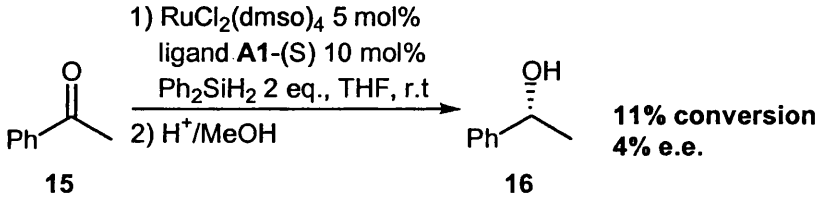
The reaction involves the initial formation of the intermediate carbinolamine which dehydrates to form an imine. Under the reaction conditions, which are usually weakly acidic to neutral, the imine is protonated to form an iminium ion. The iminium is then reduce to produce the desired amine (scheme **85**).

Scheme 85:



We first examined the asymmetric hydrosilylation of acetophenone **15** by a combination of **A1**-(S) and $RuCl_2(dmso)_4$ as a metal catalyst. The catalytic activity was found to be very low (11% conversion, <4% e.e., scheme **86**).

Scheme 86:



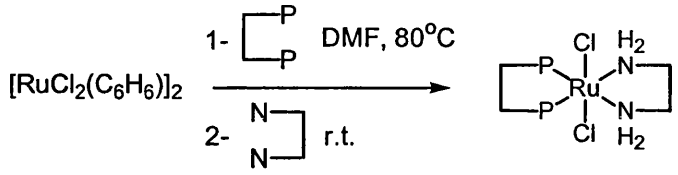
The results were slightly improved using ligand **I1**-(S) in combination with $RuCl_2(dmso)_4$ with 12% conversion and 15% e.e. (S). However this ligand gave 57.3% e.e. and 95% conversion when $[Rh(cod)Cl]_2$ was substituted for ruthenium (a 13 fold excess of ligand to the rhodium was used).[29] Although the results obtained with rhodium are reasonable, they are known in the literature and wishing to explore novel, ruthenium catalysed hydrosilylation, we moved on to further catalyst systems.

Literature background

During the course of our work, a paper appeared from Noyori on complexes formed with the use of ruthenium, a diphosphine and a chiral diamine as a successful catalyst for the asymmetric hydrogenation of ketones.[9-11] Noyori used $[RuCl_2(C_6H_6)]_2$ as a precursor and prepared a series of catalysts by the sequential addition of 2.1 equivalents of the diphosphine to the metal and reflux for 15 minutes in DMF, and then 2.1 equivalents of the chiral diamine and the mixture was stirred for three hours. These isolated ruthenium

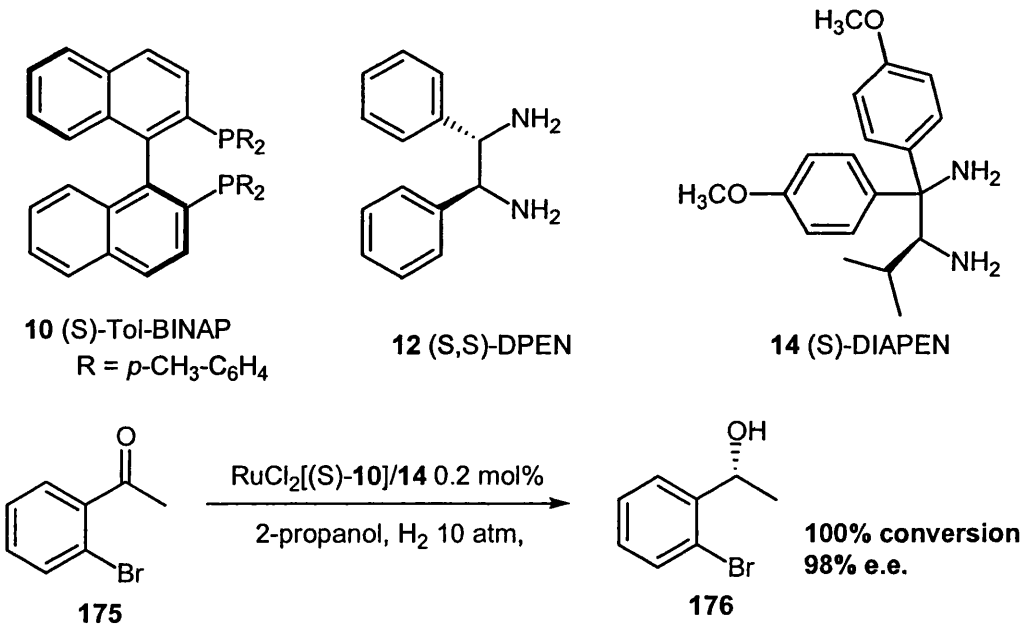
complexes were air and moisture stable and could be stored in an ordinary vial for long periods (Scheme **87**).

Scheme 87:



These ruthenium complexes have proved to be very efficient in the asymmetric hydrogenation of ketones. Excellent results have been achieved using the ruthenium catalyst made with (S)-Tol-BINAP **10** and (S)-DIAPEN **14**. A range of aromatic ketones have been have been reduced in excellent yield and enantioselectivity. *o*-Bromoacetophenone **174** has been reduced in quantitative yield and excellent 98% e.e. in to the corresponding 2-bromophenylethyl alcohol **175** (Scheme **89**).

Scheme 89:



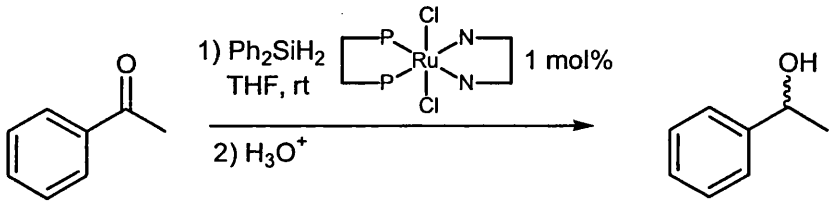
Since Zhang and co-workers had reported P-N ligands were superior to P-P ligands in the ruthenium-catalysed hydrosilylation of ketones,[53] we believed "Noyori's system" would be

a well-suited candidate for this reaction and offered us the opportunity to produce an optimised catalyst by use of parallel screening of both diphosphines and chiral diamines.

Mixed ligand ruthenium complexes: screening and optimisation

We chose to start with (R)-Tol-BINAP **10**-(R) as a chiral *bis*-phosphine and keep it constant during screening whilst we varied the (S)-enantiomer of the chiral *bis*-amines. It is important to note that all these reactions were carried out in a one-at-a-time fashion as we did not have access to the parallel screening facilities at this time (Scheme **90**).[134]

Scheme 90:



It is also important to note that neither *bis*-phosphine nor bidentate nitrogen ligand in combination with ruthenium were effective on their own, giving at best low yields of racemic product. Only a combination of ruthenium, P-P and N-N gave rise to effective, selective reactions.

The ruthenium catalyst was first prepared *in situ* by the sequential treatment of $[RuCl_2(C_6H_6)]_2$ with (R)-Tol-BINAP and then the chiral amine in THF. Acetophenone was then added, followed by diphenylsilane at 0°C. The reaction was then stirred at room temperature for 18 hours after which time any product was hydrolyzed to afford the alcohol by addition of methanol and 1M HCl. The mixture was then submitted to NMR (to obtain conversion) and chiral HPLC (to obtain e.e.) using an OD column with 98:2 hexane/IPA as the eluent at 1mL/min. Enantiomers are well resolved and appear at 14.6 min (R) and 18.5 min (S) respectively (table 12, graphs 3 and 4).

The first point to note was that the Noyori's system using (S,S)-DPEN **12** was completely inactive under the screening conditions. The most significant hits featured the pyridine based ligand, drawn for our library which gave several very high conversions. The highest enantioselectivity of 63% (R) was observed with **A2**-(S). The cyclohexyl substituent was significantly superior to the planar naphthyl and phenyl substituted ligands in the same ligand set, this trend was also observed in the case of pyrrole ligand **A5**-(S) which afforded the product alcohol with 52% e.e. (R). The complexes containing the (R)-enantiomer of tol-BINAP predominantly gave (R)-enantiomer product.

It was not surprising to note that the relative stereochemistry of the two ligands had a significant effect on reaction enantioselectivity. For example, the diastereomeric combinations (R)-Tol-BINAP/**A2**-(S) and (R)-Tol-BINAP/**A2**-(R) gave 63% and 0% e.e. respectively. This indicates the likelihood of matched/mismatched ligand pairs.

This results prompted us to synthesize the (R)-series of diamines ligands and screen them also using (S)-Tol-BINAP to investigate complementary stereochemical effects. These ligands were prepared using the same experimental procedure as described previously; yields for the ligands **A1**-(R)-**A6**-(R) are given in table 13, the imine ligands **I1**-(R)-**I6**-(R) being obtained in quantitative yields.

Table 13: Yields (%) of amine (R)

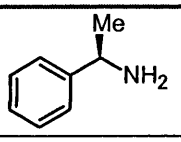
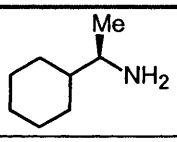
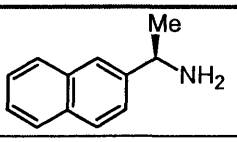
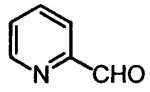
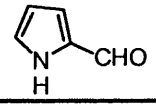
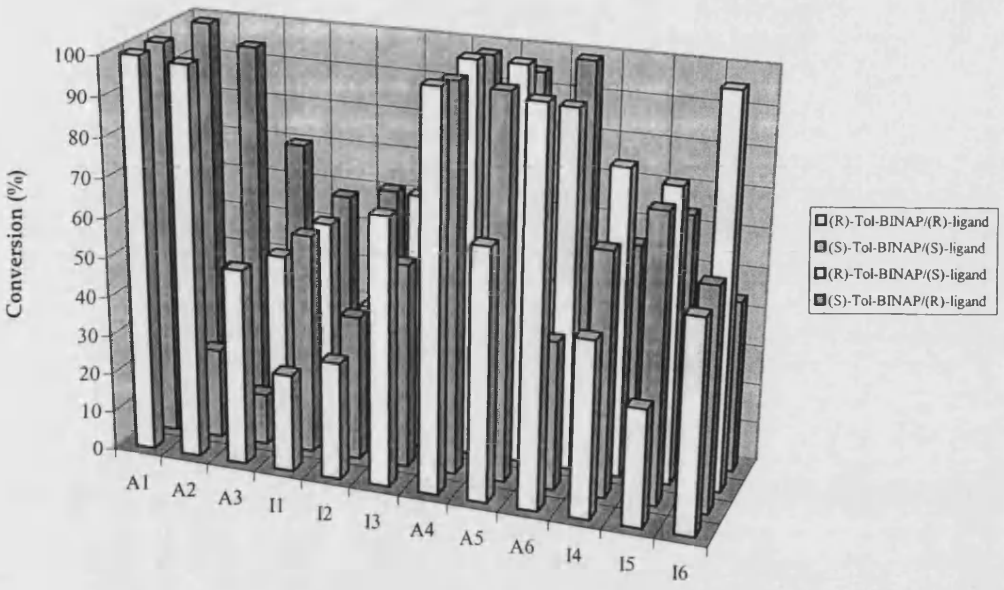
			
	75	71	42
	81	67	65

Table 12: Conversion (e.e.) of acetophenone to 2-phenylethanol using "Noyori's system"

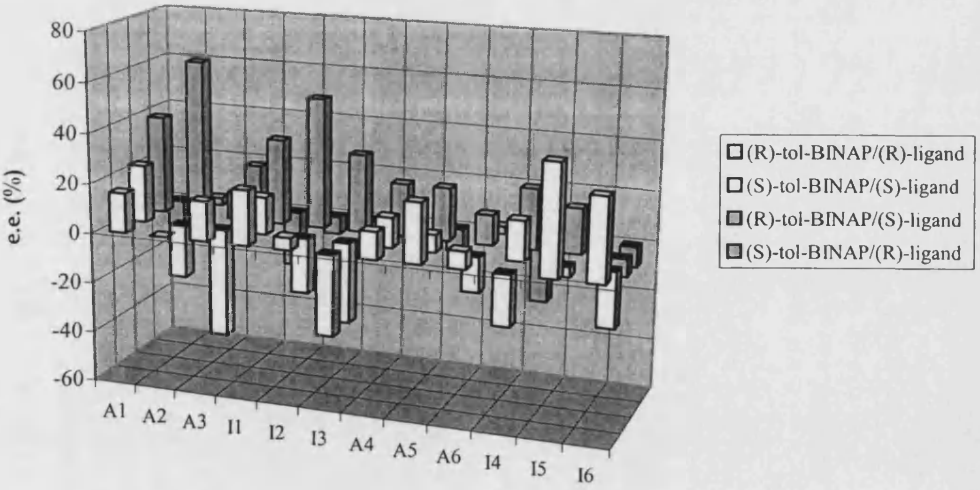
Entry	Ligands	(R)-Tol-BINAP	(S)-Tol-BINAP
1	**A1** (R)	100 (16)	99 (10,S)
	(S)	61 (39)	100 (23)
2	**A2** (R)	**99 (0)**	94 (3)
	(S)	**40 (63)**	23 (21,S)
3	**A3** (R)	50 (16)	70 (18)
	(S)	45 (11)	13 (43,S)
4	**I1** (R)	25 (22)	58 (22,S)
	(S)	55 (34)	56 (15)
5	**I2** (R)	30 (5)	61 (7,S)
	(S)	**35 (52)**	37 (22,S)
6	**I3** (R)	68 (32,S)	55 (12,S)
	(S)	65 (31)	52 (32,S)
7	**A4** (R)	100 (11,S)	98 (14,S)
	(S)	100 (21)	98 (12)
8	**A5** (R)	64 (24)	95 (9,S)
	(S)	100 (21)	97 (7)
9	**A6** (R)	99 (7)	99 (3)
	(S)	91 (12)	38 (14,S)
10	**I4** (R)	45 (20,S)	55 (26,S)
	(S)	78 (24)	62 (16)
11	**I5** (R)	30 (44)	64 (11)
	(S)	75 (18)	73 (4,S)
12	**I6** (R)	54 (33)	44 (8,S)
	(S)	99 (7,S)	57 (22,S)

It is also important to note that the complexes formed from (R)-Tol-BINAP/(R)-ligands as well as (S)-Tol-BINAP/(S)-ligands are enantiomeric, therefore these complexes should give the same enantioselectivities in 2-phenylethanol which was indeed observed in entries 1, 6 and 7. Variations from this rule may be explained by the fact that the reactions were carried out at different times and therefore under slightly different reaction conditions. In these small scales, experiments errors due to mass measurements could also be significant.

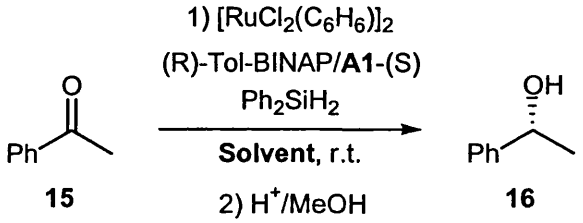
Graph 3:



Graph 4:



The best system ((R)-Tol-BINAP/**A2**-(S)) was then tested in a range of solvents. All the solvents were dried before use either over sodium (THF, toluene), calcium hydride (DME), phosphorus pentoxide (acetonitrile) or simply passed through a column of basic alumina (CCl_4).



15 **16**

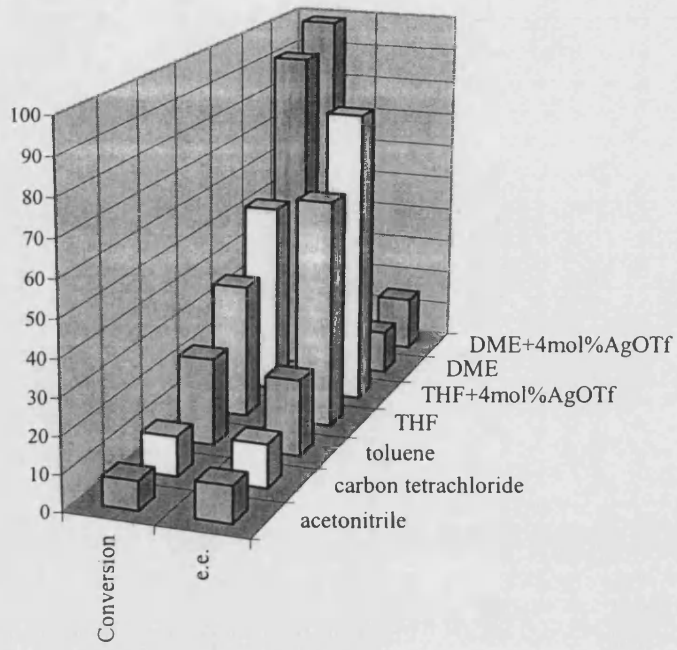
Changing solvent had a detrimental effect on both conversion and enantioselectivity (table 14, graph 5). The ideal solvent should be easily coordinated to (or removed from) the metal centre, stabilizing reactive intermediates as required. We noticed slight solubility problems using acetonitrile and carbon tetrachloride which was reflected by poor conversions (entry 1 and 2). Polar, coordinating solvents proceed to be more effective solvents for the reaction. Excellent conversions could be achieved in DME (92%, entry 6), a rarely used solvent for the hydrosilylation of ketones, however the enantioselectivity remained very low with this solvent.

Table 14: Effect of reaction solvent on conversion and selectivity

Entry	Solvent	Conversion (%)	e.e. (%)*
1	Acetonitrile	8	10
2	Carbon tetrachloride	11	12 (S)
3	Toluene	24	21
4	THF	37	63
5	**THF + 4 mol% Ag(OTf)**	**53**	**82**
6	DME	92	12
7	**DME + 4 mol% Ag(OTf)**	**>99**	**15**

*(R)-enantiomer obtained unless otherwise stated

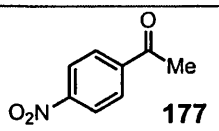
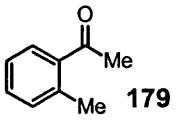
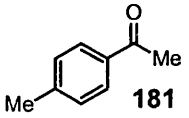
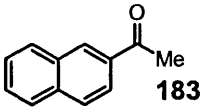
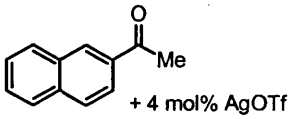
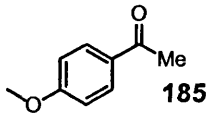
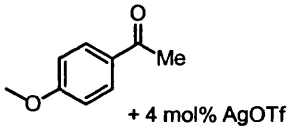
Graph 5: Effect of reaction solvent on conversion and selectivity



It is known that the addition of copper or silver ions improved the conversions by making the complex more active as a cationic species. Thus 4 mol% of AgOTf was added to the reaction mixture. We immediately noticed an increase of both conversion and e.e. (entry 5 and 7) in THF or DME. Although the reaction was complete in DME, the solvent of choice for the reaction remained THF since 53% conversion and up to 82% e.e. could be achieved (99% conversion and 15% e.e. for DME). This is consistent with the observations reported previously for both ruthenium and rhodium-catalysed hydrosilylation and is due to the generation of coordination sites for binding the ketones and activating the Si-H bond.

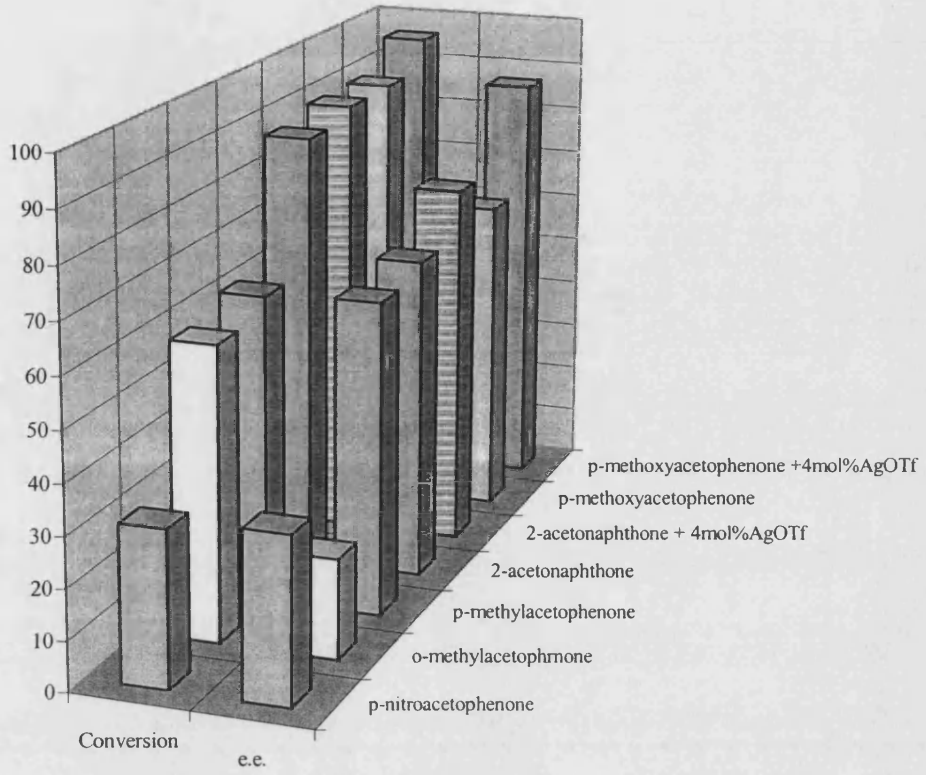
The optimised system proved to be effective for the hydrosilylation of a range of different ketones (Table 15, graph 6)

Table 15: Effect of ketone structure on conversion and selectivity

Entry	Ketones	Conversion (%)	e.e. (%)*
1	 **177**	31	33
2	 **179**	59	20
3	 **181**	62	63
4	 **183**	88	65
5	 + 4 mol% AgOTf	**90**	**74**
6	 **185**	90	65
7	 + 4 mol% AgOTf	**96**	**69**

*(R)-enantiomer obtained unless otherwise stated

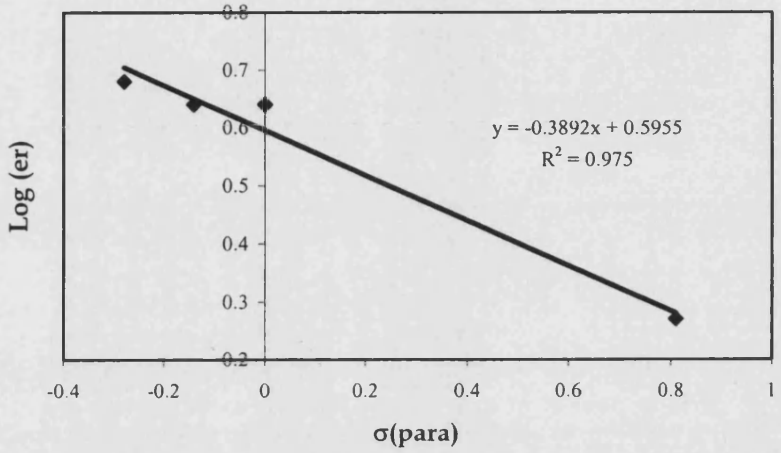
Graph 6: Effect of ketone structures on conversion and selectivity



Introduction of an electron withdrawing *p*-nitro goup greatly reduced the asymmetric induction and gave a lower yield of alcohol and slower reaction. However, the enantiomeric excess and the rate of reduction increased with the addition of electron donating *p*-methyl and *p*-methoxy groups. Again the addition of silver triflate in the case of the *p*-methoxyacetophenone increased the conversion further to 96% and the e.e. to 69% (entry 7). Good results could also be obtained with 2-acetonaphthone as the substrate, a 90% conversion and 74% e.e. could be achieved in the presence of AgOTf (entry 5). In general, electron donating substituents (OMe, Me) gave better results than electron withdrawing substituents. This could be formalised by a plot of Log(enantiomeric ratio) for the reduction of substituted acetophenone (X = NO_2, H, Me, MeO) catalysed by the optimised system versus σ_p where σ_p represents a constant characteristic of the substituent X[120,135,136]. The plot suggests a correlation between the electronic effects of various electron-withdrawing and electron-donating substituents (Figure 1). The negative value of

the slope indicates the electron withdrawing group reduces the reactivity of aryl ketones towards hydrosilylation.

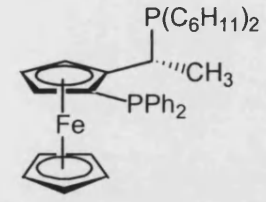
Figure 1: Log(enantiomeric ratio) of 4-XPhCH(OH)Me produced using the optimised system vs σ_p



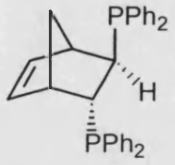
Screening of phosphines and reaction optimisation

The influence of phosphine ligands in the reaction was then investigated, a series of the five best chiral nitrogen ligands [**A1**-(S), **A2**-(S), **A3**-(S), **A5**-(S) and **I5**-(R)] were selected and screened in a parallel manner with eight chiral phosphines (Scheme **91**).

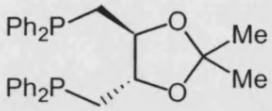
Scheme 91:



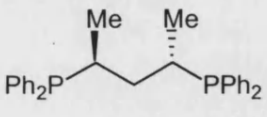
(R)-JOSIPHOS **187**



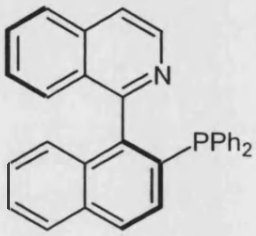
(R,R)-NORPHOS **188**



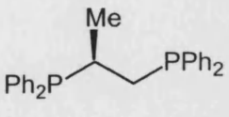
(R)-DIOP **189**



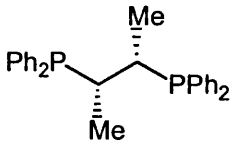
(R,R)-BDPP **190**



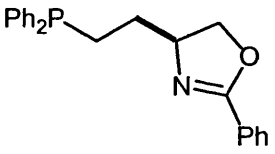
(R)-QUINAP **191**



(R)-PROPHOS **192**



(R,R)-CHIRAPHOS **193**



BURGESS **194**

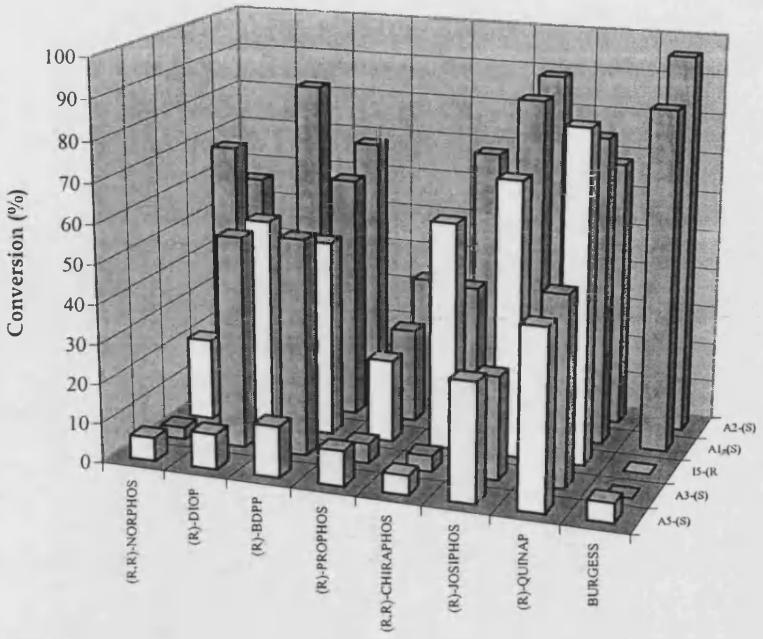
For these experiments, we were able to use the parallel screening technique (involving performing multiple reactions in parallel and analysis by automated GC) to accelerate the process. A 96-well microtiter plate was used in an argon fitted glove box for this purpose. The ruthenium precursor $[RuCl_2(C_6H_6)]_2$ was weighed in to each of the 45 vials. Each of the eight chiral phosphines were added in five wells (a solution of the phosphines being prepared in THF beforehand). The wells were then capped and put in an oven at 60-62°C for 15 mins. Each of the five chiral bidentate nitrogen ligands were pipetted into eight wells each containing different phosphine. The mixtures were then shaken for 3 hours after which time acetophenone and diphenylsilane were added to each of the 40wells. The plate was then capped and left in the argon box for 18 hours. After hydrolysis (using methanolic HCl), the reaction mixture were then submitted to GC (Table 16, graph 7).

Table 16: hydrosilylation of acetophenone to 2-phenylethanol*

	A1-(S)	**A2**-(S)	**A3**-(S)	**A5**-(S)	**I5**-(R)
(R)-PROPHOS	24	33	5	9	21
(R,R)-CHIRAPHOS	37	68 (30,S)	4	5	58 (9, S)
(R)-BDPP	62 (13, S)	68 (13, S)	55 (14, S)	13	50
(R)-DIOP	40	82	54	9	54
(R)-JOSIPHOS	**86**	**89**	26	30	**69**
(R)-NORPHOS	68	56	3	6	23
(R)-QUINAP	78 (8, R)	69	48 (8, R)	45 (9, R)	83
BURGESS	**86**	**95**	0	5	1

*reactions gave racemic product unless otherwise stated; enantioselectivities were only determined for reactions with yields>50%.

Graph 7:



This screen showed that the initially chosen phosphine, (R)-Tol-BINAP, was the best for the transformation: good conversions were obtained with (R)-DIOP, (R)-JOSIPHOS and (R)-QUINAP, however the selectivities remained disappointing (<30% ee). The maximum conversion was obtained with **A2**-(S) and (R,R)-CHIRAPHOS. The catalytic activity seemed slower when (R)-prophos (a *bis*-phophine having a small bite angle, <90°) was used, whereas the reaction was more successful using (R)-Josiphos which has a larger bite angle.[137,138] If we inspect these *bis*-phosphines according to their "natural" bite angle, Prophos has the smallest, followed by Chiraphos and BDPP (≈ 90°), then DIOP (97°) or JOSIPHOS (96°), and Norphos (123°). The conversion of acetophenone to 2-phenylethanol seemed to follow this trend in the case of ligands **A1**-(S), **A2**-(S) and **I5**-(R) (the other two giving poor results), the smaller the bite angle, the slower the reaction. It seemed that after reaching an "ideal" bite angle (Josiphos), the catalytic activity decreased again probably due to larger bite angle such as Norphos. Chiral monophosphines proved to be also very efficient for the reaction; up to 80% and 95% conversion could be obtained

with the combination Quinap/**A1**-(S) and Burgess/**A2**-(S) respectively. A further screening with a range of solvents (table 17) in conjunction with this phosphines also proved to be fruitless.

Table 17: solvent effect on yields

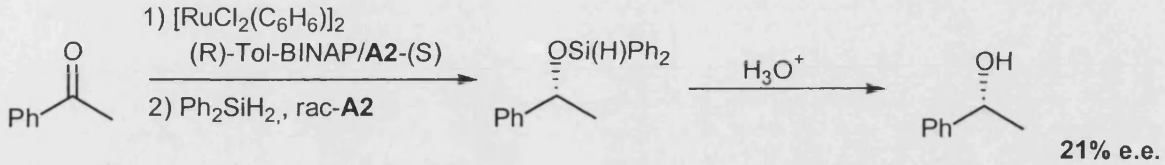
	DCM	**Ether**	**DMF**	***p*-xylene**	**1,4-dioxane**
DIOP/**A2**-(S)	**64**	0	0	2	3
BURGESS/**A2**-(S)	**95**	0	0	0	2
JOSIPHOS/**A1**-(S)	**96**	1	0	0	0
JOSIPHOS/**A2**-(S)	**99**	2	0	3	1

Excellent conversions could be achieved in dichloromethane, whereas no reaction occurred in solvents such as ether, xylene, dimethylformamide or dioxane mainly because of solubility problems with the ruthenium precursor and phosphine.

Catalyst studies

In order to gain further insight into the reaction and the factors affecting the selectivity, some further experiments were carried out. We have carried out some studies on our ruthenium pre-catalyst which suggests that one of the ruthenium-nitrogen bond is labile. To explore the integrity of the Ru-N bonds of the catalyst, we added an equivalent of the racemic form of the ligand **A2**-(S) after the pre-catalyst was made in our normal *in situ* manner, to see if a ligand exchange reaction was possible. We observed a decrease in the enantioselectivity of the product alcohol from 40% to 21 % upon addition of the racemic ligand, thus providing evidence for a ligand exchange during the course of the reaction (Scheme **92**). This observation suggests at least partial lability of the Ru-N bond in our active catalyst. Similar observations have been reported by Nishiyama for the Rh-Pybox complex in the asymmetric hydrosilylation of ketones.[38]

Scheme 92:



21% e.e.

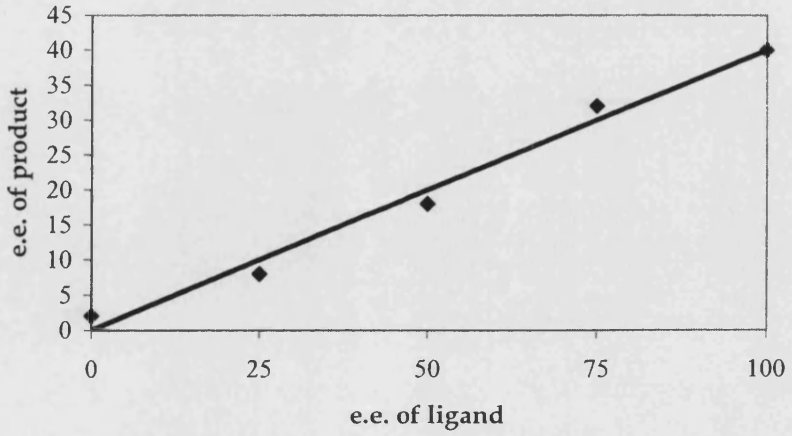
A second series of reactions was performed to test whether the e.e. of product is a function of the e.e. of the diamine, thus the ligand was introduced into the reaction with a range of optical purities. Results obtained from these experiments are shown in table 18.

Table 18:

e.e. of ligand	0	25	50	75	100
e.e. of product	2	8	18	32	40

These studies showed a linear relationship between the e.e. of product alcohol and the e.e. of ligand which strongly suggests that the nitrogen ligand is present in the catalytic active species and furthermore that only one equivalent of amine is present in the catalytically active species (Figure 2).

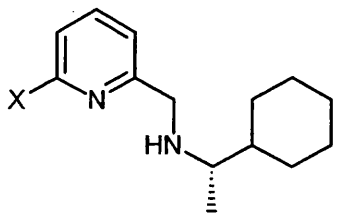
Figure 2: e.e. of product alcohol *vs* e.e. of ligand



Substituent effects on the pyridine ring

In an attempt to further improve the enantioselectivity of the ruthenium-catalysed hydrosilylation of acetophenone with our catalysts, we sought to fine tune the electronic properties of the diamine ligand **A2**-(S) by adding various substituents to the pyridine ring. Replacement of the hydrogen at the 6-position was first attempted (bromo, methyl, methoxy *etc.* were introduced) due the ready availability of 2,6-dibromopyridine **146** as a starting material (of course modification at this position would also express a steric effect but representative trends were expected) (Scheme **93**).

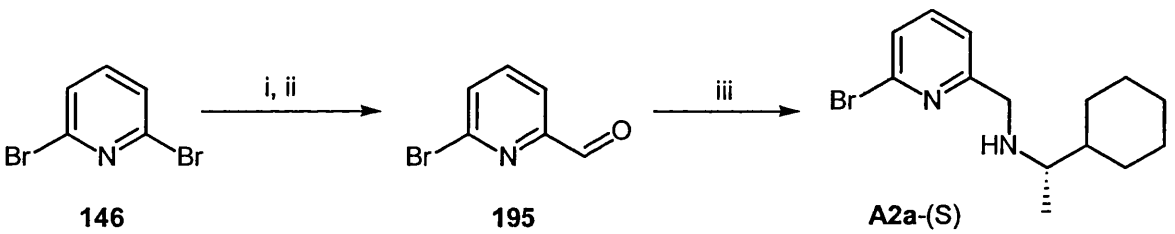
Scheme 93:



A2-(S)

A series of 6-substituted pyridine amine **A2**-(S) were synthesized from the commercially available 2,6-dibromopyridine **146**. Formylation using one equivalent of *n*BuLi in THF followed by quench with DMF (80%), was followed by reductive amination to afford the 6-bromo derivative **A2a**-(S) in 73% overall yield as illustrated in scheme **94**.

Scheme 94:



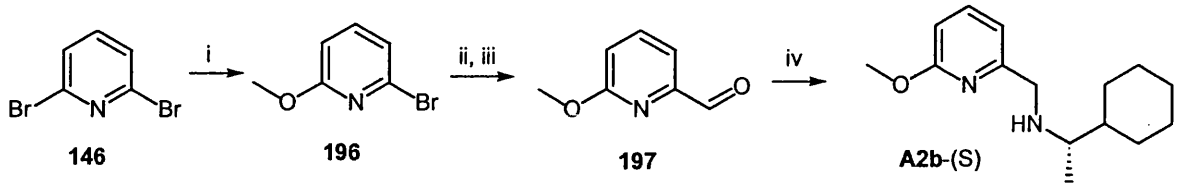
146 **195** **A2a**-(S)

Reagents and conditions: i) BuLi, THF, -78°C ii) DMF iii) (S)-cyclohexylethylamine, $NaBH(OAc)_3$, THF

The corresponding 6-methoxy substituted ligand **A2b**-(S) was obtained from the same starting material. An aromatic nucleophilic substitution of bromine with methoxide was

carried out with sodium in methanol (66%); the synthesis could then be concluded by the formylation/reductive amination sequence used previously (50%, scheme **95**).

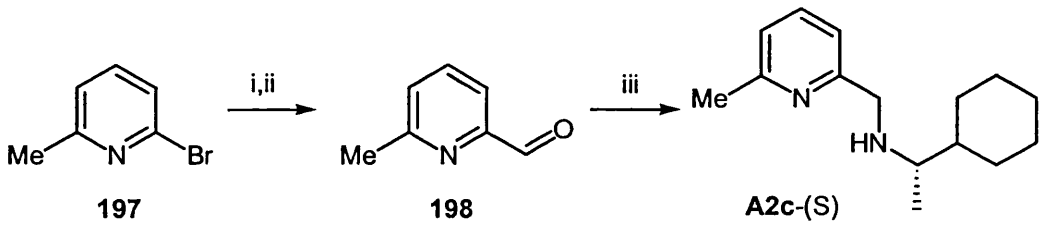
Scheme 95:



Reagents and conditions: i) NaOMe, MeOH, reflux ii) BuLi, THF, -78°C; iii) DMF iv) (S)-cyclohexylethylamine, $NaBH(OAc)_3$, THF

The 6-methyl derivative **A2c**-(S) was obtained from the commercially available 2-bromo-6-methylpyridine in a similar manner, the desired product being obtained in 86% overall yield as outlined in scheme **96**.

Scheme 96:



Reagents and conditions: i) BuLi, THF, -78°C; ii) DMF iii) (S)-cyclohexylethylamine, $NaBH(OAc)_3$, THF

We examined the ruthenium-catalysed hydrosilylation of acetophenone **15** with diphenylsilane in the presence of these 6-substituted ligands. Pleasingly we achieved an increased level of enantioselectivity by adding an electron donating group at the six-position (71 % e.e. with the 6-methoxy group **A2b**-(S)) albeit at the expense of reduced conversion (21%). A further improvement in e.e. was realised by the addition of AgOTf, thus an 86% e.e. was obtained though the conversion remained disappointing at 29%. The addition of the electron withdrawing substituent, **A2a**-(S), had the inverse effect, an excellent conversion being obtained at the expense of the e.e. (21 % e.e. and 81 %

conversion). The intermediate 6-methyl group **A2c**-(S), a moderate electron donating group, gave a 60 % e.e. and 48 % conversion (table 19).

Table 19:

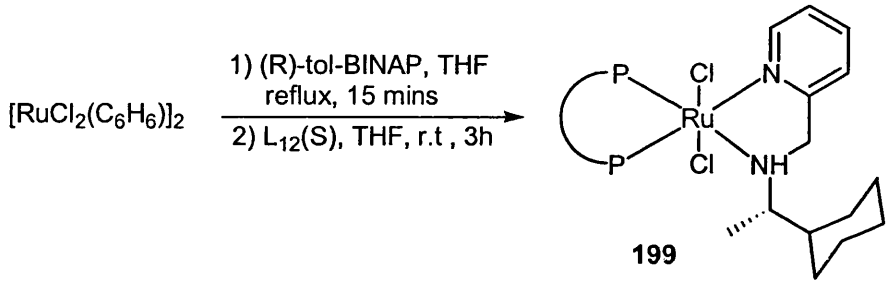
	X = H	H + AgOTf	X = Br	X = Me	X = OMe	OMe + AgOTf
Conversion (%)	40	53	81	48	21	29
e.e. (%)	63	82	31	60	71	86

The dramatic effects of these simple ligand modifications may be attributed to several factors. The change in electron donating ability of the pyridine nitrogen would be expected to change the ruthenium-nitrogen bond length in the active species and should thus change the active site geometry to some extent (the limited steric effect of the 6-substituent on pyridine may equally become more pronounced). The electronic density on the ruthenium centre and its ability to co-ordinate substrate will also change with the electron donating ability of the pyridine ligand.

Ruthenium complex and mechanistic studies

Chiral ruthenium complex **199** was prepared by reaction of $[RuCl_2(C_6H_6)]_2$ with two equivalents of (R)-Tol-BINAP in THF followed by the addition of two equivalents of optically pure amine at room temperature for 3 hours (scheme **97**). This route generated the complex as a light brown powder, whose ^{31}P NMR exhibited a pair of doublets at δ 37.1 and δ 29.5 with $J_{P\text{-}P}$= 63.2 Hz indicating that both phosphines are bound to the metal centre and but are non-equivalent.

Scheme 97:



199

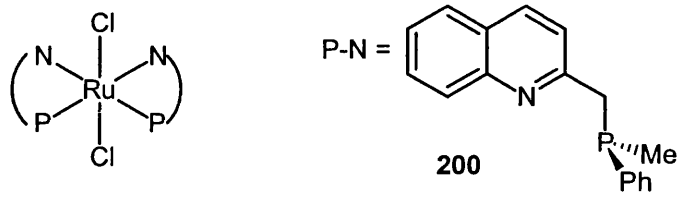
Many attempts to get an X-ray crystal structure were made. The complex was slowly recrystallized by diffusion in DCM/ether to give after two weeks some bright red crystals. These crystals proved to be too sensitive to be solved using the facilities at Bath, and thus we tried to have them resolved on a fast diffractometer by Dr Jon Steed of King's College London. Unfortunately the efforts proved to be in vain and we were left to draw conclusions on the structure of these complexes from the available spectral data and the behaviour of the catalyst in its reactions.

Since the metal centre is somewhat crowded, we thought that one of the ligand-metal bonds might break during the catalytic cycle. We were pretty confident that the *bis*-phosphine stayed attached to the metal. Phosphorus atoms possess accessible d-orbitals (in contrast to nitrogen) which can accept electron density from the ruthenium by d→π back bonding interactions. The Ru-P bond is thus less labile than the Ru-N bond.

This similar bond dissociations have been observed and reported several times in the literature. Studies by Mathieu and co-workers[139] (using X-ray structure determination and variable temperature NMR experiments) on ruthenium complexes containing optically active P,N ligands (Scheme **98**) showed that the two chlorine are *trans* to each other and due to steric crowding one of the two ligands is more weakly bound to the ruthenium. The

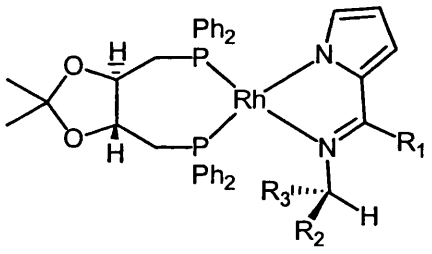
NMR experiments have shown that a dissociation of one of the Ru-N bond occurred in solution at room temperature.

Scheme 98:



200

Brunner also reported the synthesis of chiral rhodium complexes **23** containing (R,R)-DIOP as a *bis*-phosphine and a pyrrole Schiff base as a diamine, which are similar to Noyori's catalysts.[13] Brunner explained the low levels of enantioselectivities obtained in asymmetric hydrogenation of ketopantalactone, by a dissociation of the Rh-N bond of the imine which thus distance the chiral subtituents from the metal centre.



23

Although we have no real evidence of this in our system, we assume that one of the Ru-N bonds can dissociate as suggested by our previous studies (see II-6), but we cannot determine which bond is the most labile.

A general mechanism for the hydrosilylation of ketone is outlined in scheme **99**. In this scheme we will treat both nitrogen atoms as equivalent to facilitate an easier understanding of the scheme. Ru complex **199** is first formed *in situ*, which upon addition of silver triflate is transformed into the cationic complex **201**, a 16 electrons species which can undergo oxidative addition with diphenylsilane to generate the ruthenium-hydride intermediate **203**.

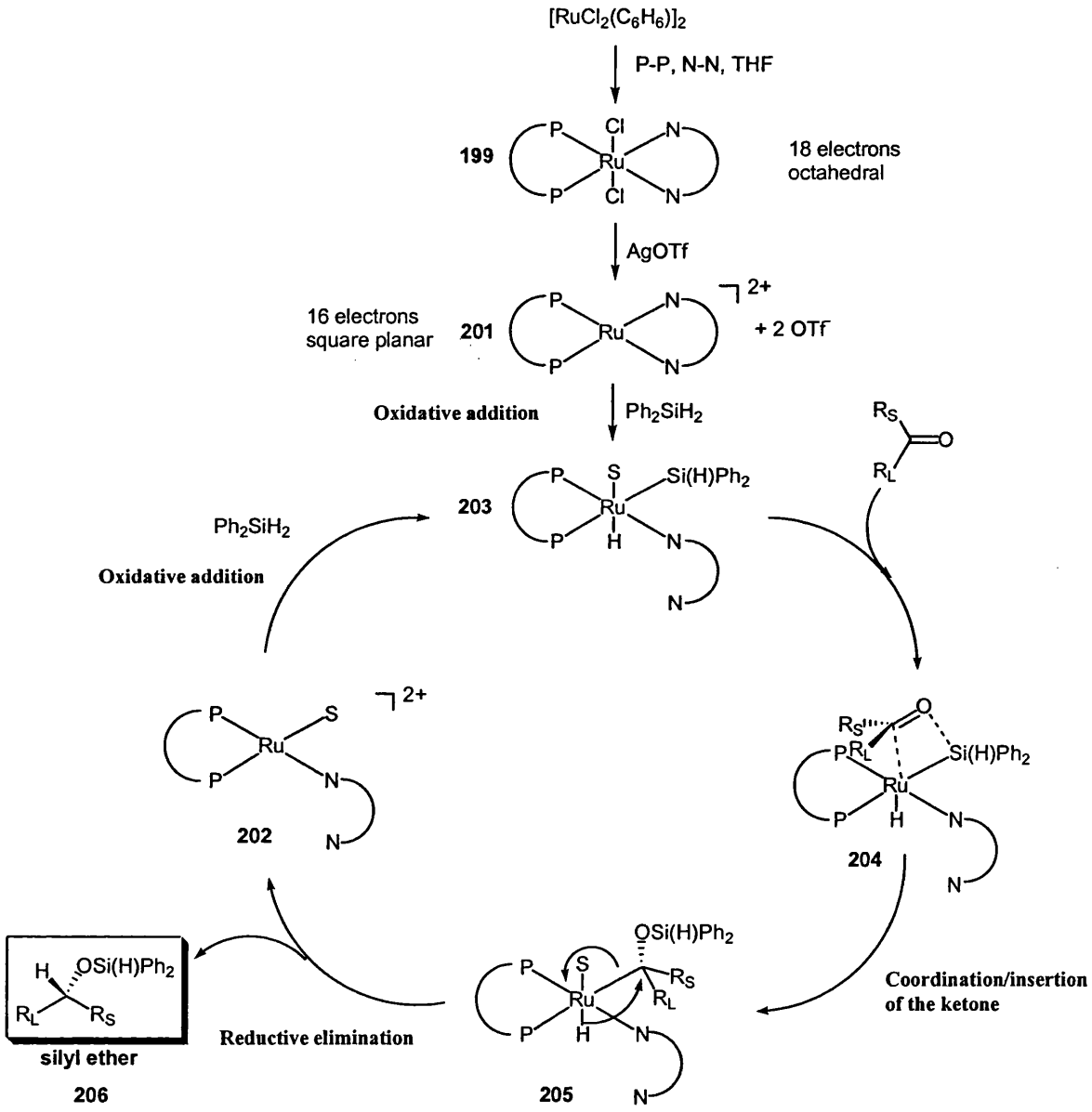
It seemed likely that the dissociation of the Ru-N occurs at this stage. The ketone can then be coordinated and insert into the Ru-Si bond to afford **205**. Finally, a reductive elimination occurs *via* hydride transfer to generate the chiral silyl ether **206** and solvated intermediate **202** which can undergo oxidative addition with the silane and thus start a new catalytic cycle.

The step determining the enantioselectivity in this process is the coordination /insertion of the ketone into the ruthenium-silicon bond. Therefore we tried to understand how the chirality of the diamine ligand would effect the enantioselectivity of the hydrosilylation reaction. Two pathways seemed possible:

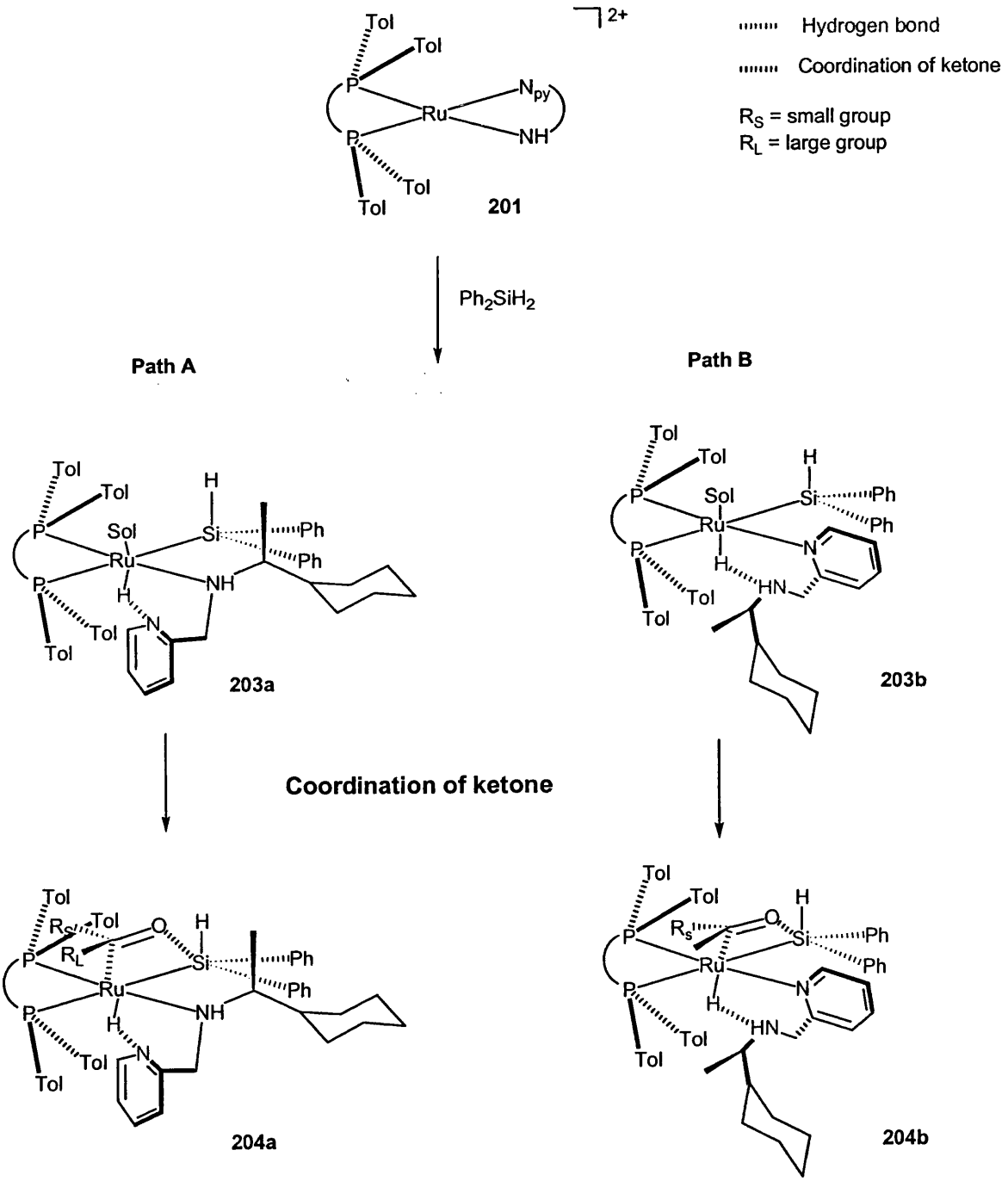
Path A) If the ruthenium-pyridine bond dissociates during the oxidative addition, then the ligand can rotate around its ruthenium-amine bond until the nitrogen from the pyridine and the ruthenium hydride form an hydrogen bond (intermediate **203a** in scheme **100**). This afford a stabilised transition state with some conformational rigidity. Thus the chiral centre on the diamine ligand may prevent the two bulky phenyl groups from the silane from rotating around the ruthenium-silicon bond and thus force them to face downwards. The ketone can then coordinate to the ruthenium and silicon atoms (**204a**) in such a manner that the steric interactions between the ketone and the tol-BINAP are minimised. This step could then be followed by an insertion of the ketone into the ruthenium-silicon bond (generating a chiral intermediate), followed by a rapid reductive elimination to afford the optically pure silyl ether.

Path B) The second possibility would involve the dissociation of the ruthenium-NH bond and as in path A, the NH and the ruthenium-hydride can form an hydrogen bond (intermediate **204b**) forcing the chiral centre of the diamine to be far from the metal centre which would result in poor enantioselectivity.

Scheme 99:

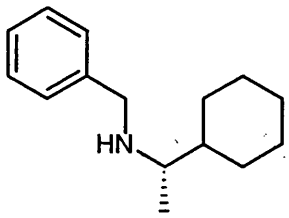

[RuCl2(C6H6)]2
P-P, N-N, THF
199
18 electrons
octahedral
AgOTf
16 electrons
square planar
201
2+
+ 2 OTf
Oxidative addition
Ph2SiH2
203
Si(H)Ph2
Ph2SiH2
Oxidative addition
202
2+
204
Coordination/insertion
of the ketone
205
OSi(H)Ph2
Reductive elimination
silyl ether
206

Scheme 100:

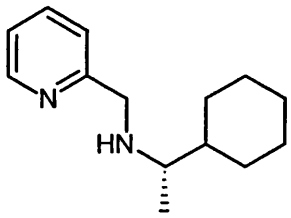

Hydrogen bond
Coordination of ketone
R_S = small group
R_L = large group
2+
Tol
Tol
P
Ru
N_{py}
NH
Tol
Tol
201
Ph_2SiH_2
Path A
Path B
Sol
H
Si
Ph
Ph
N
HN
203a
203b
Coordination of ketone
O
R_S
R_L
204a
204b

Such metal hydride hydrogen bonds have be extensively studied by Crabtree among others,[140] it should be noted that both mechanisms may act simultaneously and that the observed selectivity reflects the proportion of each substrate converted by each pathway. There is a real possibility that such bonding could be present in our transition state. To test whether the presence of the pyridine nitrogen is required ligand **207** was prepared and introduced into the reaction (Scheme **101**).

Scheme 101:



207



A2-(S)

This ligand was easily prepared by reductive amination of benzaldehyde and the corresponding optically pure amine. The resulting hydrosilylation of acetophenone with this ligand showed very low catalytic activity (<20% conversion, 0% e.e.), thus suggesting that the second coordinating amine is needed for the reaction which may support our suggestion of an hydrogen bond between the ruthenium hydride and the pyridine.

Conclusion

Chiral mixed-ligand ruthenium complexes have been studied in the asymmetric hydrosilylation of ketones. A range of enantiopure diamines have been synthesized for this purpose and screened in the reaction in combination with a range of commercially available chiral phosphines. Parallel screening techniques have been used to accelerate the process. The best results of 63% e.e. have been obtained with (R)-Tol-BINAP and the pyridine amine **A2**-(S). This initial result was improved further by optimisation of the reaction solvents and ketone subtrates; electron rich ketones such as *p*-methoxyacetophenone were found to be optimal whilst coordinating solvents such as THF

were found to give good selectivities and conversions. The substituent on the six-position of the pyridine ring of the ligand was also found to be important for selectivity. Through our work we found that e.e.'s of 86% could be obtained with the *bis*-phosphine/diamine complexes of ruthenium we developed.

Studies have also been carried out on the catalyst itself; we have evidence that only one equivalent of the enantiopure pyridine amine ligand is contained in to the catalytic active species and one of our experiments strongly suggested that a dissociation of one of the ruthenium-nitrogen bond occurs.

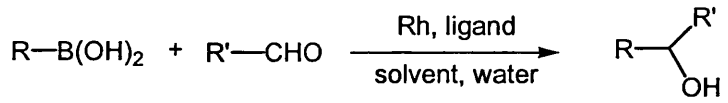
From our mechanistic studies we have proposed two plausable mechanistic pathways for the reaction. Both pathways involve an hydrogen bond between the ligand and the metal hydride and it seems that such an interaction could be the key for the stabilisation of the transition state during the step where the enantioselectivity is expressed.

Future work could focus on attempts to optimise the interactions we believe are important in determining the selectivity of the reaction. An example of this would be further modification of the ligand to give better hydrogen-bond interactions and thus higher selectivities.

Rhodium-catalysed addition of arylboronic acids to aldehydes

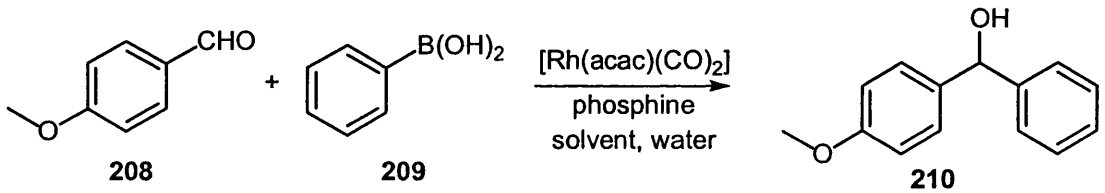
Transmetallation between main group metal reagent (lithium, magnesium) and transition metal compounds is of great importance since it can allow the direct access to carbon-carbon bond forming reactions. Miyaura and co-workers have developed a transmetallation between boron and rhodium in the 1,4-addition of boronic acid to esters[141] and enones.[142] Recently they have extended this work with aldehydes as the electrophilic component and showed that 1,2 addition reactions of boronic acid and aldehydes can be catalysed by certain rhodium complexes (Scheme **102**).

Scheme 102:



In their first communication, Miyaura and co-workers reported the use of rhodium-phosphine complexes in aqueous phase for the addition of aryl organoboronic acid to aldehydes.[143] [Rh(acac)$(CO)_2$] was used as the catalyst precursor and when employed in combination with *bis*phosphines having a large bite angle (such as DPPF, DPPP or DIOP), it was found that effective addition of phenyl boronic acid **209** to 4-methoxybenzaldehyde **208** took place (72-99% yield). In contrast, complexes derived from monophosphines (such as PPh_3 or $AsPh_3$) were found to be totally ineffective catalysts. They also noted that in the absence of water, the reaction was very slow (Scheme **103**, table 20).

Scheme 103:



208 **209** **210**

Table 20: effect of phosphine and solvent on the addition of phenyl boronic acid to 4-methoxybenzaldehyde

Ligand	Solvent	Yield
PPh_3	DME/H_2O	0
$AsPh_3$	DME/H_2O	<1
DPPP	DME/H_2O	82
DPPF	DME/H_2O	99
DPPF	dioxane/H_2O	72
DIOP	DME/H_2O	66

A reinvestigation of these results revealed that the catalyst is highly dependent on basicity[144] of the phosphine ligand.[112] For example, they reported that the reaction was accelerated by bulky and donating trialkylphosphines such as tri(isopropyl)phosphine **212** and tri(*tert*-butyl)phosphine **213** when one equivalent of phosphine to rhodium was used. This new correlation indicated that monophosphines were now successful in the reaction (Table 21).[145]

Table 21: effect of phosphine ligand on reaction yield[a]

Phosphine	Yield (%)
PMe_3 **211**	48
P(*i*-Pr)$_3$ **212**	86
P(*t*-Bu)$_3$ **213**	99[b]

[a] Addition of benzene boronic acid to 4-methoxybenzaldehyde in DME/water at 80°C for 16 hours.

[b] Yield at 50°C.

They noticed that the reaction is highly sensitive to electronic effect of substituents on both aldehydes and boronic acids. The results showed that the reaction was facilitated in the presence of an electron-withdrawing group on the aldehyde and an electron-donating group on the boronic acid which would imply a nucleophilic attack of the aryl group on the coordinated carbonyl group. Addition to aliphatic aldehydes such as

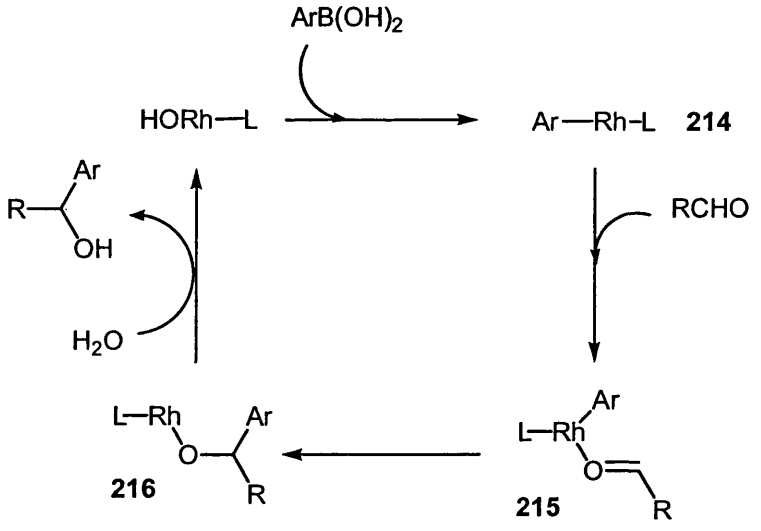
cyclohexanecarboxaldehyde or hexanal were very slow due to their poor electrophilicity (Table 22).

Table 22: addition of aryl boronic acid to aldehydes

Aryl boronic acid	Aldehyde	Yield (%)
$PhB(OH)_2$	$4\text{-}MeCOC_6H_4CHO$	93
$4\text{-}MeC_6H_4B(OH)_2$	$4\text{-}NCC_6H_4CHO$	99
$2.4.6\text{-}Me_3C_6H_2B(OH)_2$	$4\text{-}MeOC_6H_4CHO$	31
$PhB(OH)_2$	1-Naphthaldehyde	91
$PhB(OH)_2$	Hexanal	69
$PhB(OH)_2$	Cyclohexylcarboxaldehyde	45

The proposed catalytic cycle is thought to involve firstly a transmetallation between the boronic acid and the rhodium(I) complex to afford a Ar-Rh(I) species **214**. An insertion of the C=O bond into the Rh-C bond, and finally, hydrolysis of the O-Rh(I) bond with water can then occur to complete the overall 1,2-addition process (Scheme **103**).

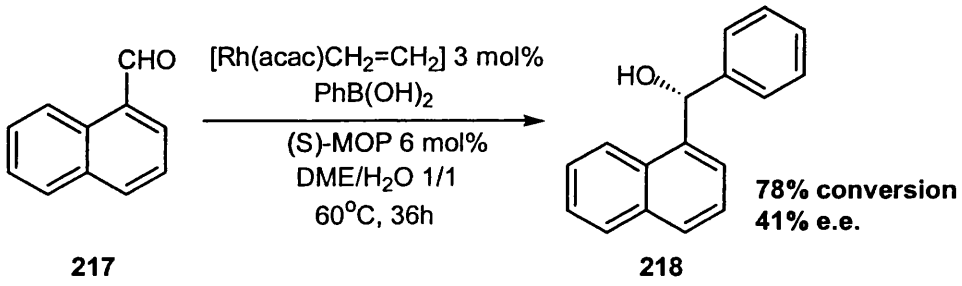
Scheme 103:



Two opposing factors in the catalyst were found to be necessary to reach good catalytic activity. The ligand has to be donating enough to enhance the nucleophilicity on the rhodium metal to facilitate the transmetallation, yet the metal centre must retain sufficient Lewis acidity to be able to coordinate the carbonyl of the aldehyde.

A first asymmetric version of this protocol was elaborated using the monodentate chiral ligand (S)-MOP. The addition of phenyl boronic acid **209** to 1-naphthaldehyde **217** in DME/water at 60°C for 36 hours yielded the desired product **218** in 78% conversion and 41% e.e. (Scheme **104**).

Scheme 104:



217 **218**

Introduction

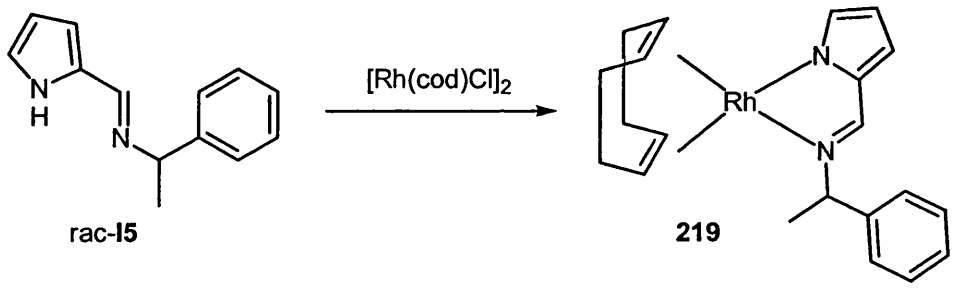
Since the addition of organoboronic acid to aldehydes had been successfully catalysed by rhodium-phosphine complexes, we wondered if the reaction would work using similar nitrogen-Rh complexes and if so could we produce a more enantioselective catalyst for the reaction. Since rhodium-amine complexes were found to be relatively easy enough to synthesize, we initially prepared racemic rhodium-diamines complexes with a view to investigate chiral variants of the hits we obtained. For this purpose, we thought about employing the libraries of nitrogen ligands previously synthesized for investigations on the asymmetric hydrosilylation of ketones (chapter three).

Addition of boronic acids to aldehydes

Preliminary studies

We synthesized complex **219** using $[Rh(cod)Cl]_2$ as a precursor and the racemic pyrrole ligand **I5**. The ligand was firstly deprotonated with sodium hydride, and added to a solution of $[Rh(cod)Cl]_2$ in THF. After stirring for 1 hour, the solvent was removed to yield the rhodium complex **219** as a yellow powder (Scheme **105**).

Scheme 105:



rac-**I5** **219**

This complex was then tested in the addition of boronic acids to aldehydes, initially using Miyaura's conditions; the reaction was thus stirred at 80°C for 16 hours in a 1:1 mixture of DME and water as solvent (Table 23).

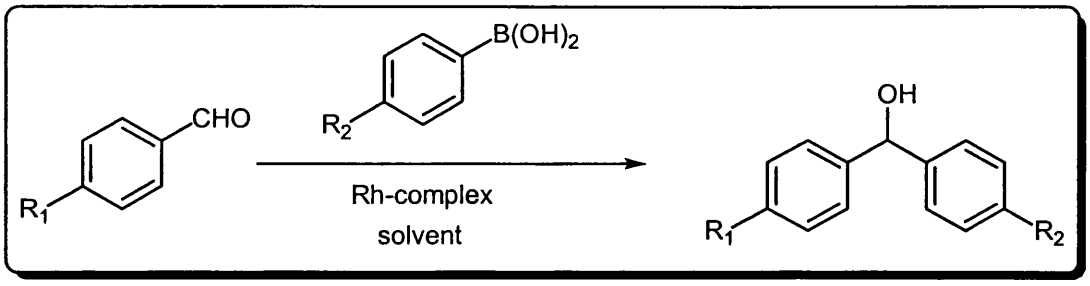


Table 23:

Entry	R_1	R_2	Rh-complex[a]	solvent	T (°C)	Time (hour)	Yield (%)[b]
1	H	H	**219**	DME	80	16	47
2	H	H	**219**	DME/H_2O	80	16	32
3	H	H	**219**	Dioxane	80	16	34
4	H	H	**219**	Dioxane/H_2O	80	16	27
5	H	H	**219**	DME	rt	84	38
6	H	H	**219**	DME	40	84	54
7	H	H	**219**	DME/H_2O	rt	84	0
8	H	H	**219** (10mol%)	DME	80	16	66
9	H	H	**219** (7.5mol%)	DME	80	16	54
10	CH_3	H	**219**	DME	80	16	10
11	CH_3O	H	**219**	DME	80	16	5
12	H	OCH_3	**219**	DME	80	16	27

[a]5 mol% of Rh-1 used unless otherwise stated. [b] Isolated yield of product after column chromatography (5:1 hexane/EtOAc as the eluent).

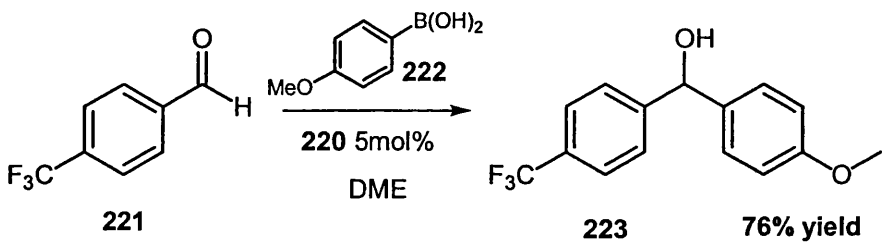
We were pleased to find that this complex successfully catalysed the coupling of phenyl boronic acid and benzaldehyde. However, we rapidly noticed that Miyaura's conditions, which used the 1:1 DME/water as solvent were not as good as the use of neat DME for our complex (32 and 47% yield respectively, entry 1 and 2).The same effect was observed when using dioxane instead of DME as a solvent (entry 3 and 4). At room temperature, no reaction occurred in the presence of water, (entry 7) whilst in neat DME successful coupling, albeit relatively slow and low yielding, did occur (38% in 84 hours, entry 5). An

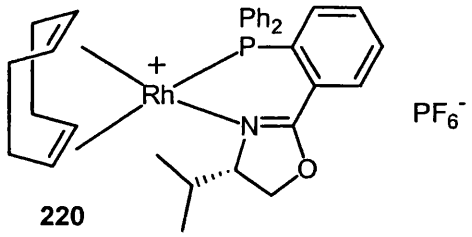
increase of catalyst loading up to 10 mol% using DME at 80°C increased the yield further to 66% (entry 8 and 9). The reaction was very slow when electron rich aldehydes were used (entry 10 and 11), an observation which parallels that seen by Miyaura. However, we were delighted to see that the reaction had proved to be viable with a nitrogen-containing ligand. We thus sought to extend these first results to the development of a better catalyst capable of improving the yield of the arylation reaction ideally in combination with high level of enantioselectivity.

Catalyst development[146]

We decided to use a chiral phosphine-oxazoline ligand in the reaction and thus synthesized **220**. The rhodium-complex was prepared from $[Rh(cod)Cl]_2$ by stirring in an aqueous solution of NH_4PF_6 and then adding phosphine-oxazoline to yield the desired complex **220** as air-stable, deep red crystals. Our observations were consistent with Miyaura's paper which suggested that the reaction was facilitated by electron-rich boronic acids and electron-deficient aldehydes. Thus the optimum combination proved to be the reaction of 4-(trifluoromethyl)benzaldehyde **221** with 4-methoxyphenyl boronic acid **222** in the presence of 5 mol% of **220**; a 76% isolated yield of desired alcohol **223** was obtained (Scheme **106**).

Scheme 106:

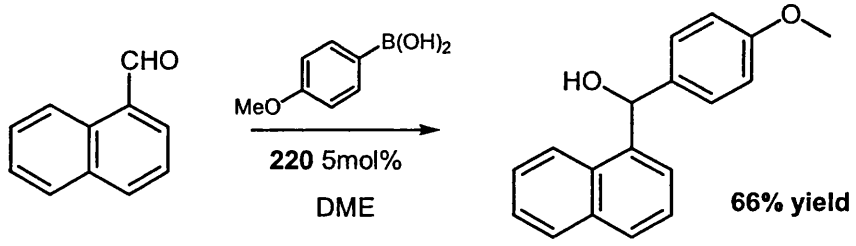




220

However, it proved difficult to get a good resolution of the product on the chiral HPLC, a fact which can be attributed to the small steric and electronic difference between the trifluoromethyl and methoxy groups. We thus determined the enantioselectivity by NMR using [Eu(hfc)$_3$] as chiral shift reagent and found that the product was racemic. In order to facilitate reaction analysis, we changed the first choice substrates to 1-naphthaldehyde **224** and 4-methoxybenzene boronic acid **222**. A 66% yield of the desired alcohol **225** was obtained in the presence of 5 mol% of **220** at 80°C in DME (Scheme 107).

Scheme 107:



224 **225**

The product proved to be racemic. Chiral HPLC was suitable for determination of the e.e. for this particular example as a very good resolution of enantiomers was obtained using a Chiralcel OD column, a 20% IPA/hexane as the mobile phase and a flow rate of 1mL/min. The retention time for the enantiomeric alcohols were 9.7 and 20.9 mins respectively. Although the product obtained at 80°C was racemic, we could obtain a small e.e. just by decreasing the temperature to 40°C, and further reduction to room temperature increased the e.e. albeit at the expense of chemical yield (15% e.e.; table 24).

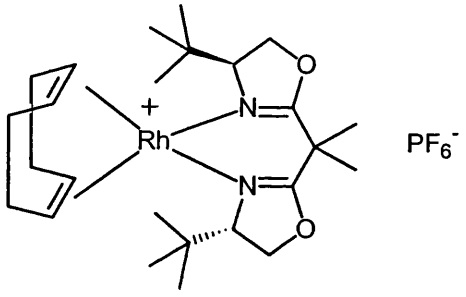
Table 24: effect of temperature of conversion and enantioselectivity

Entry	Solvent	T (°C)	Time (h)	Yield (%)	e.e. (%)
1	DME	80	16	66	0
2	DME	40	16	52	4
3	DME	rt	48	42	15

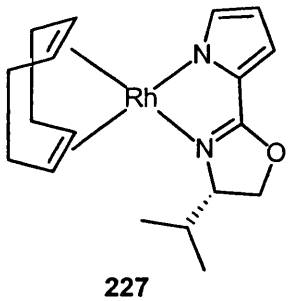
A kinetic study of the reaction was done using HPLC to follow the course of the reaction (the conversions given by HPLC were compared to those obtained by ^{1}H NMR and were found to be accurate to ± 6%). We noticed during a study carried out at 80°C the catalyst showed good initial activity (60% yield after 30 mins) but after two hours, no more product formation occured The reaction was slower at 40°C with a maximum yield of 61% obtained after 24 hours (table 25, graph 8).

Since low levels of enantioselectivity were observed using **220** as a catalyst, we then decided to see if we could obtain more active selective catalyst with N,N ligands. Rhodium-complexes were prepared as before from the appropriate *bis*oxazoline and pyrrole oxazoline ligands (Scheme 108). We managed to obtain crystals of suitable quality to allow an absolute determination of the structure of rhodium complex **226a** by X-ray diffraction (Figure **3**).

Scheme 108:

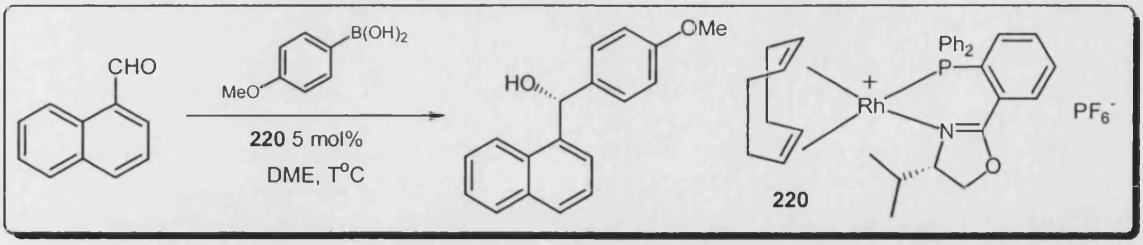


226a



227

Table 25:



Time (hour)	0	0.3	0.4	0.6	0.9	1.4	2	2.3	3
80°C	0	46	57	62			63	65	
40°C	0		11		15	17			29
r.t.	0								

3.3	4.7	6	9	14	18	24	33	38	42	48
64	65	65				65	66			66
		36	47			61		61		
				23	26	31		36	39	41

Graph 8:

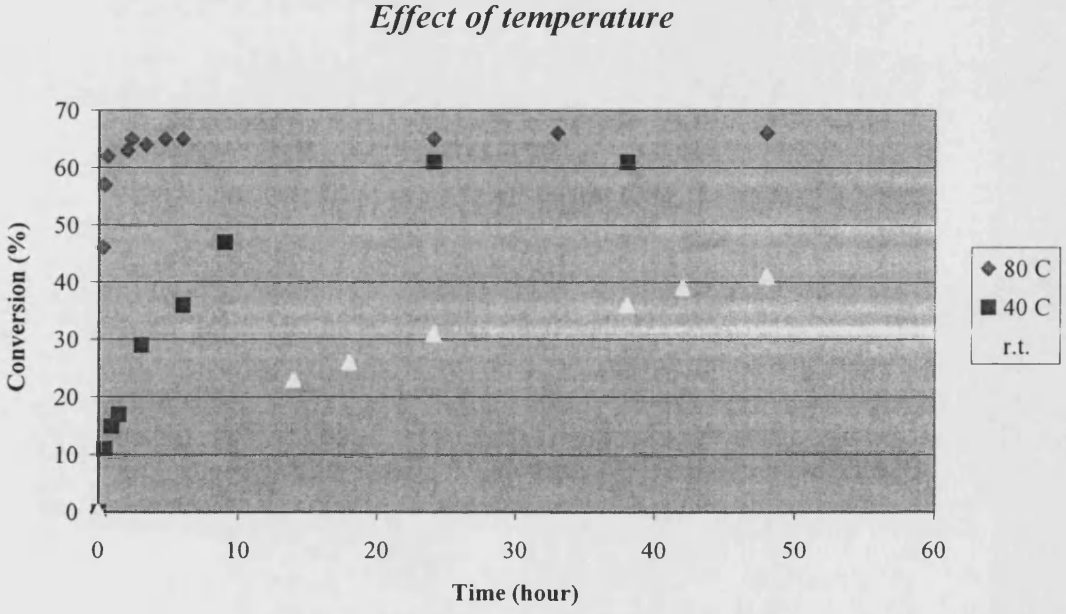
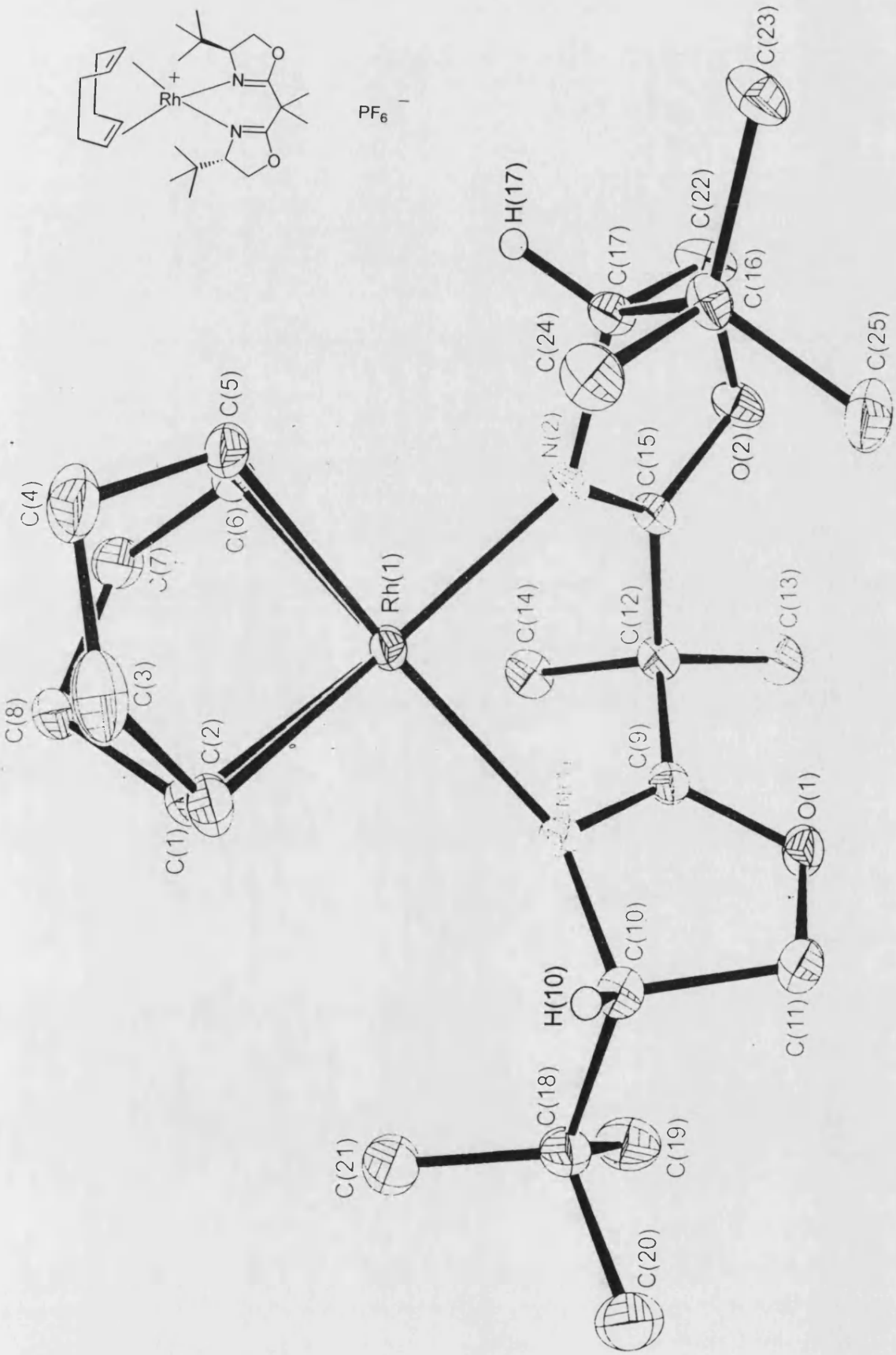


Figure 3: Crystal structure of **226a**

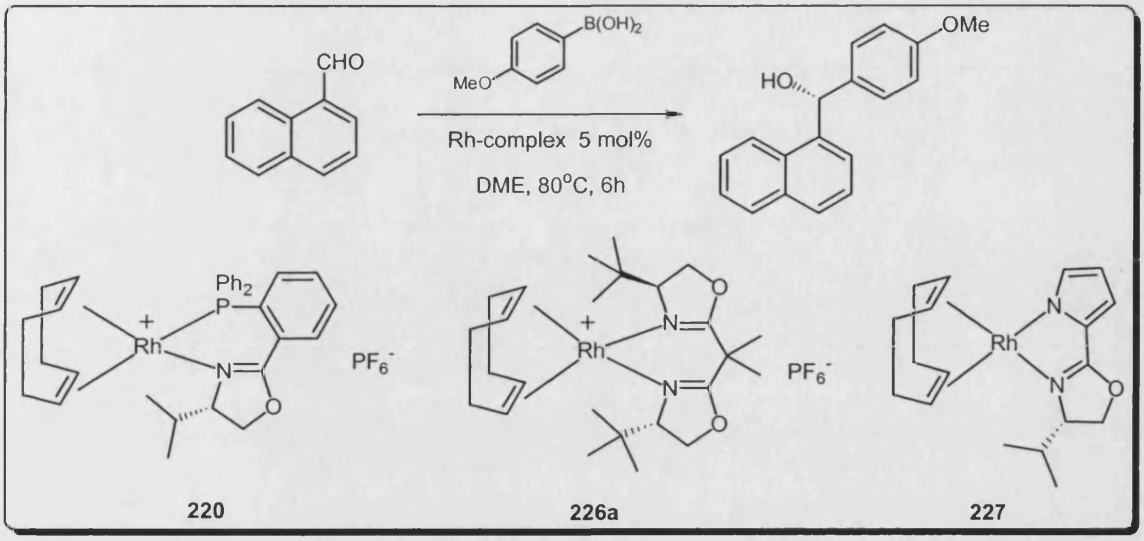


Our previous experiments had shown that at 80°C the coupling proceeded rapidly (about two hours). Studies of the reaction catalysed by complexes **226a** and **227** were monitored by HPLC (table 26, graph 9). Our experiments showed that complex **226a** was a better catalyst (75% conversion after 2 hours) than **220** and **227**. It seemed that C_2-symmetric nitrogen ligands may be the key to better results. Although very good conversions could be obtained with **226a**, the enantioselectivity remained very poor (<10%) which was somewhat disappointing.

Influence of catalyst loading

Using the Rh-BOX **226a** complex, we decided to work on optimisation of the reaction catalyst loading. Three reactions were carried out at different catalyst loadings: 1, 0.5 and 0.1 mol%; using 1-naphthaldehyde **224** and 4-methoxybenzene boronic acid **222**, reactions were stopped after two hours (table 27, graph 10). The use of 0.1 mol% of catalyst resulted in a lower reaction yield, just 43% conversion after 2 hours. However little difference was observed between the reactions using 0.5 and 1mol%: both reactions were equally fast affording approximately 70% of product alcohol after 2 hours. The reaction was initially faster using 5 mol% of catalyst, but after two hours a similar chemical yield of 77% was obtained. Thus 0.5 mol% of **226a** was used for subsequent reactions.

Table 26:



Time (hour)	0	0.25	0.33	0.5	0.58	0.75	0.92	1	1.33
220	0		46		57		62		
226a	0	64		67		72		74	
227	0	28			30	33			41

1.5	2	2.17	2.33	3	3.25	4	4.66	5.5	6
63			65		64		65		63
	75					74			78
		45		44				45	

Graph 9:

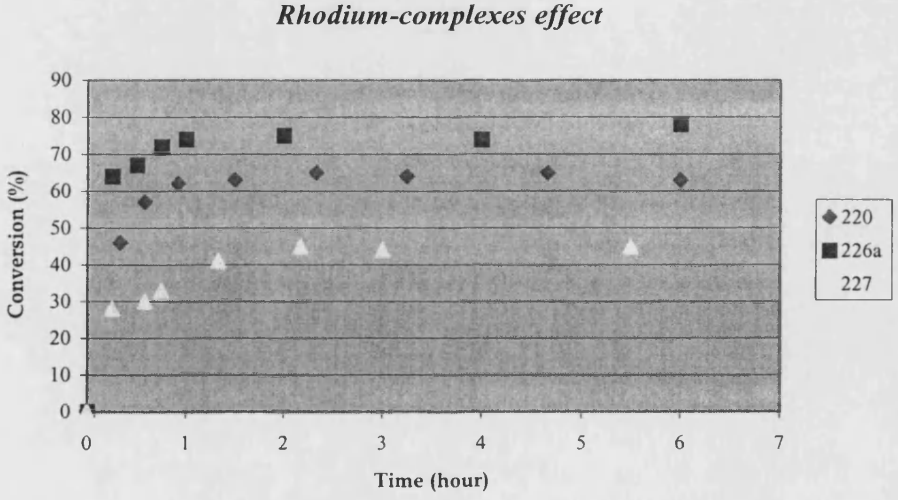
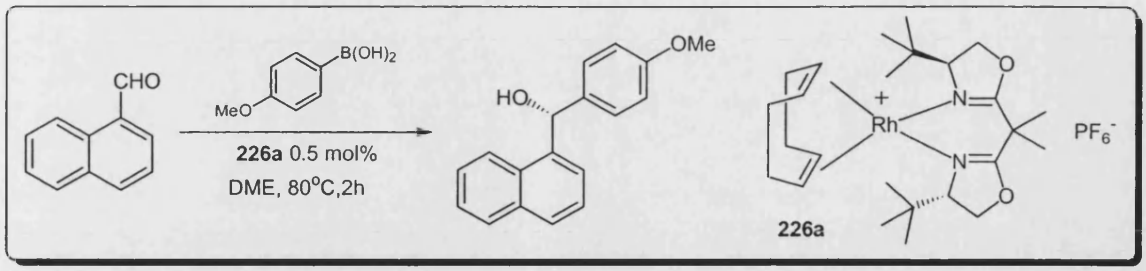


Table 27:

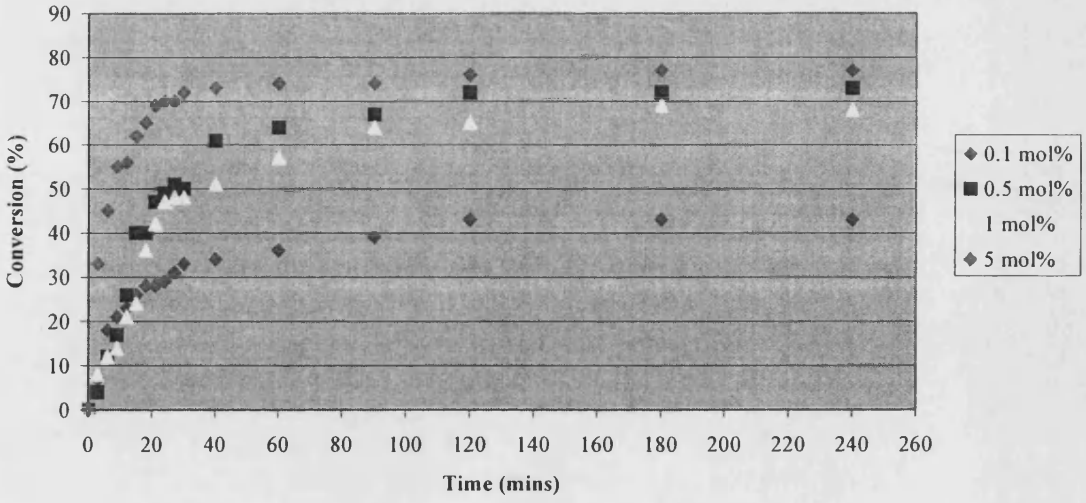


Time (mins)	0	3	6	9	12	15	18	21
0.1 mol%	0	7	18	21	23	26	28	28
0.5 mol%	0	4	12	17	26	40	40	47
1 mol%	0	8	12	14	21	24	36	42
5 mol%	0	33	45	55	56	62	65	69

24	27	30	40	60	90	120	180	240
29	31	33	34	36	39	43	43	43
49	51	50	61	64	67	72	72	73
47	48	48	51	57	64	65	69	68
70	70	72	73	74	74	76	76	77

Graph 10:

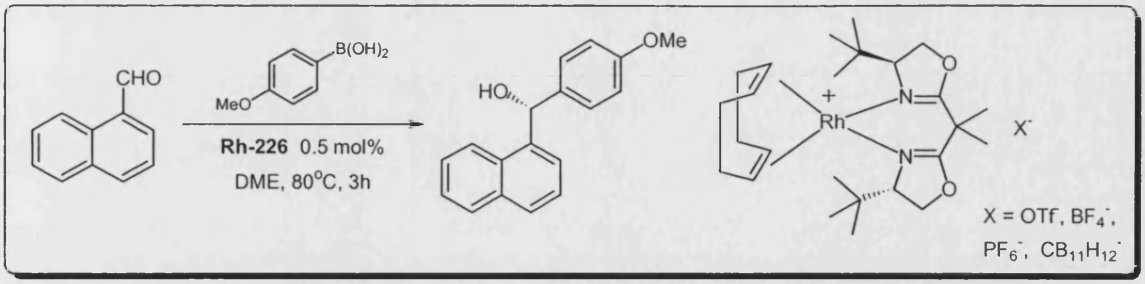
Effect of catalyst loading



Counterion effect

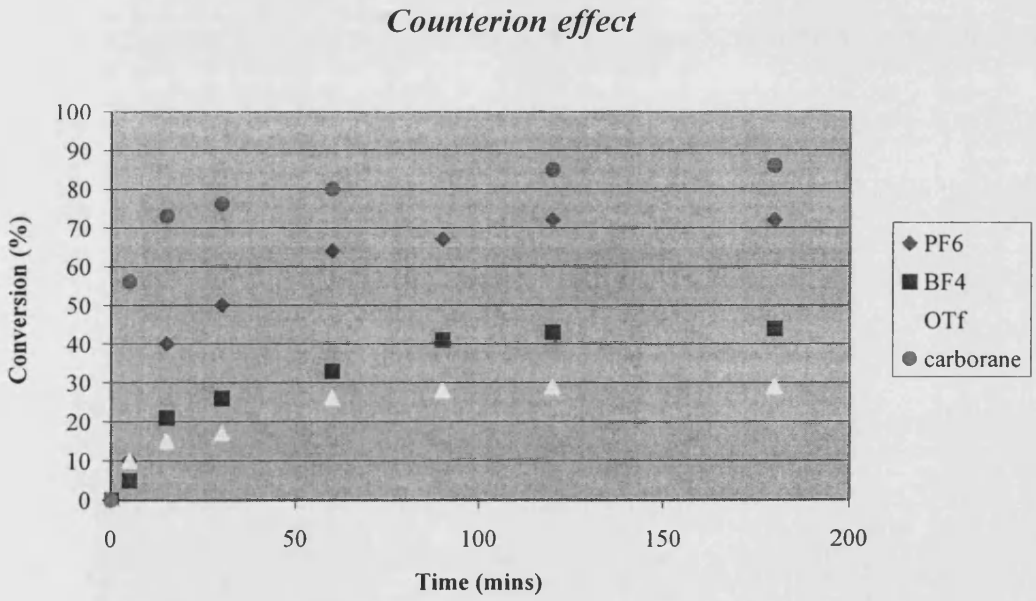
Although often overlooked, it is well-documented that many catalytic processes involving charged organometallic complexes are dependent on the nature of counterion. We anticipated that in Rh-BOX complex **226a**, the counterion would influence the Lewis acidity of the metal centre. To test this theory we prepared complexes with varying counterions (OTf^- **226b**, BF_4^- **226c**, PF_6^- **226a**) and compared their catalytic activity for the coupling of 1-naphthaldehyde and 4-methoxybenzene boronic acid at 80°C in DME using 0.5 mol% of catalyst (table 28, graph 11). The counterion was observed to have a dramatic effect on the rate of the reaction. The observed trend appeared to reflect the increasing Lewis acidity of the metal centre with weaker coordinating anions; larger weaker coordinationg counterion gave higher yield. To comfirm this trend, we wanted to try another weaker counterion and were fortunate enough to obtain an analogous complex with carborane ($CB_{11}H_{12}^-$, **226d**) as a counterion from Dr Andy Weller of Bath University. As we had anticipated the use of this complex with its extremely weakly coordinating counterion gave our best results, a conversion of 56% was observed after just 5 minutes and within 15 minutes the conversion has risen 70%. However, even at low temperatures the enantioselectivity remained very low (<10% e.e.).

Table 28:



Time (mins)	0	5	15	30	60	90	120	180
OTf	0	10	15	17	26	28	29	29
BF_4^-	0	5	21	26	33	41	43	44
PF_6^-	0	10	40	50	64	67	72	72
$CB_{11}H_{12}^-$	0	56	73	76	80	-	85	86

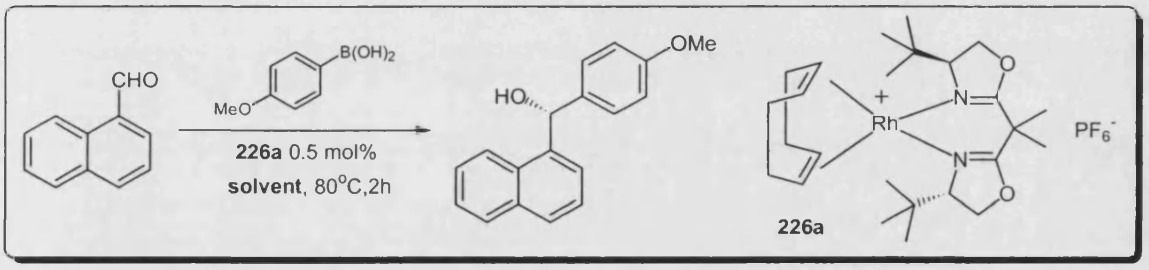
Graph 11:



Solvent effects

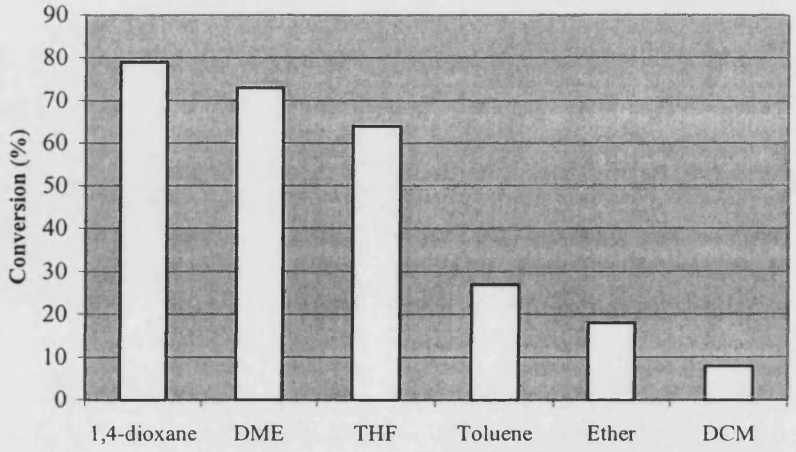
The reaction proved to be less efficient in non-coordinating solvents such as dichloromethane (8%) and toluene (18%). The conversion obtained in ether was also very low (27%) which can be partially attributed to low solubility of the Rh-complex and the boronic acid. THF proved to be a good solvent although slightly less efficient than DME or dioxane. The use of 1,4-dioxane resulted in comparable conversion (79%) to product after two hours (table 29, graph 12). However it was still disappointing to note the lack of enantioselectivity.

Table 29: solvent effect on conversion of aldehyde



Solvent	1,4-dioxane	DME	THF	Toluene	Ether	DCM
Conversion (%)	79	73	64	27	18	8

Graph 12:



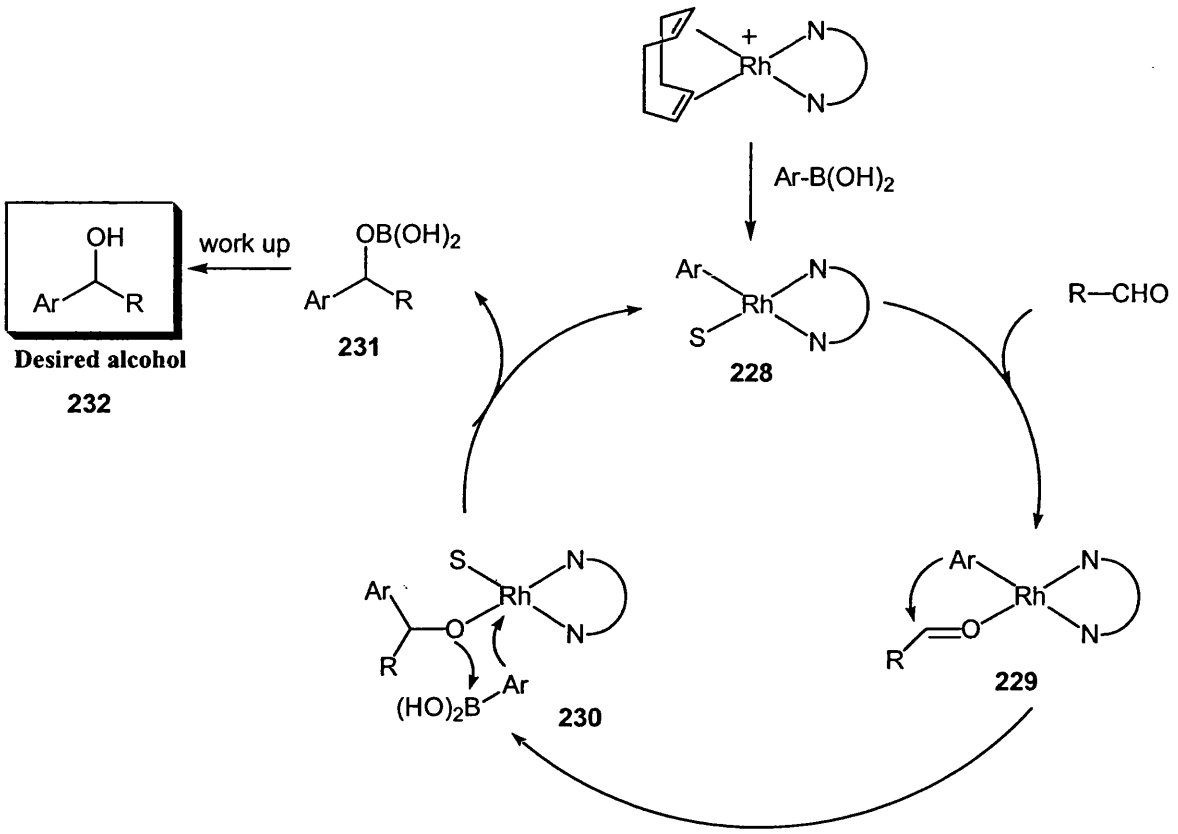
Effect of water

At this stage, we still can not explain why the reaction shuts down after about two hours without going to completion. A possible explanation would be because of the lack of water. Even by taking precaution to keep everything dry (DME which was distilled over CaH_2) we could not exclude the possibility that water may be present in the reaction. Thus, at the beginning of the reaction the water from the solvent might be consumed until no more remains, this could explain why the reaction stopped after a couple of hours. Three more reactions were thus carried out in the presence of 0.5, 1 and 2 equivalents of water to the boronic acid. The addition of two equivalents of water resulted in the complete loss of activity, whilst reactions with 0.5 and one equivalent of water severely reduced the activity of the catalyst.

Mechanistic studies

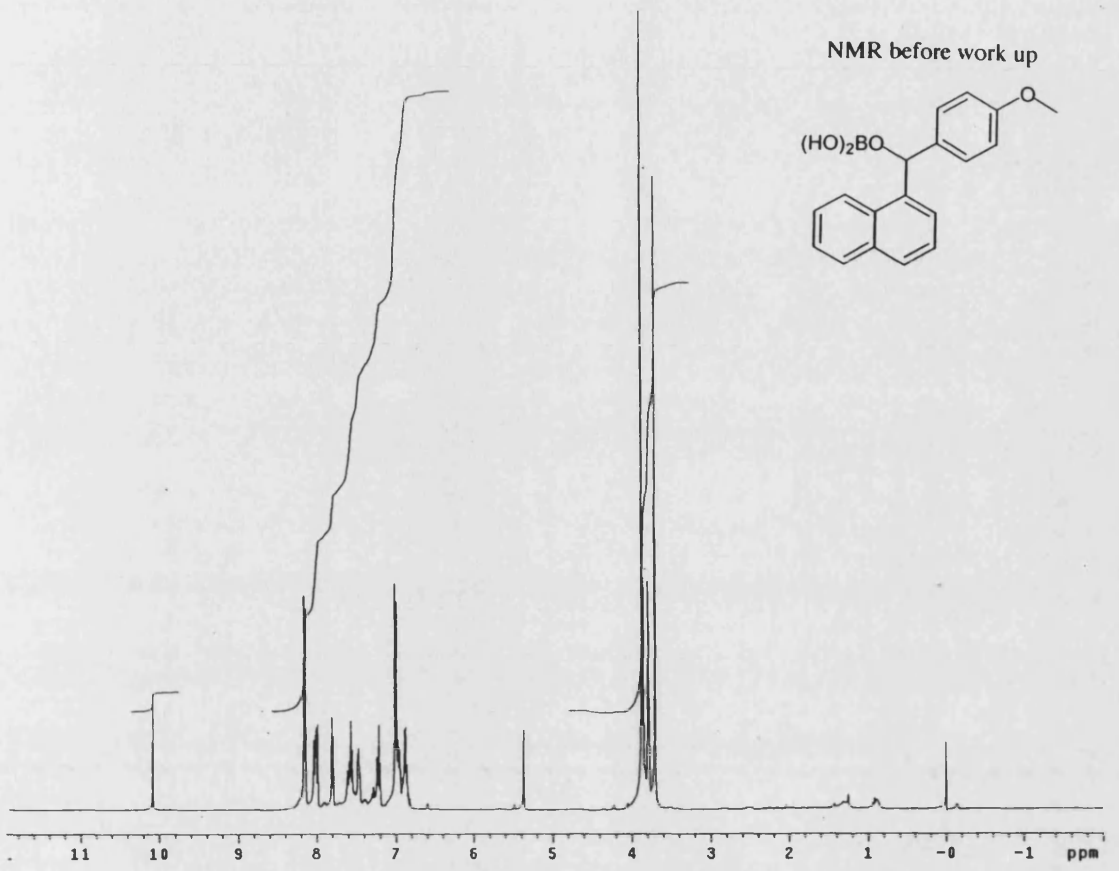
The proposed mechanism outlined in scheme **109** involves the transmetallation between the boronic acid and the Rh(cod)diamine$^+$ (although this step has not been studied) to give an Ar-Rh$^+$ **228** species. This is then followed by the insertion of the aldehyde into the Ar-Rh bond to form the intermediate **229**. The final step in the cycle yields the boronic ester **231** which can be hydrolyzed during work up to afford the desired alcohol **232**. This last step differed from that Miyaura proposed. Since Miyaura carried out the reaction in an aqueous solvent, the final step of their catalytic cycle involved the hydrolysis of the O-Rh bond with water.

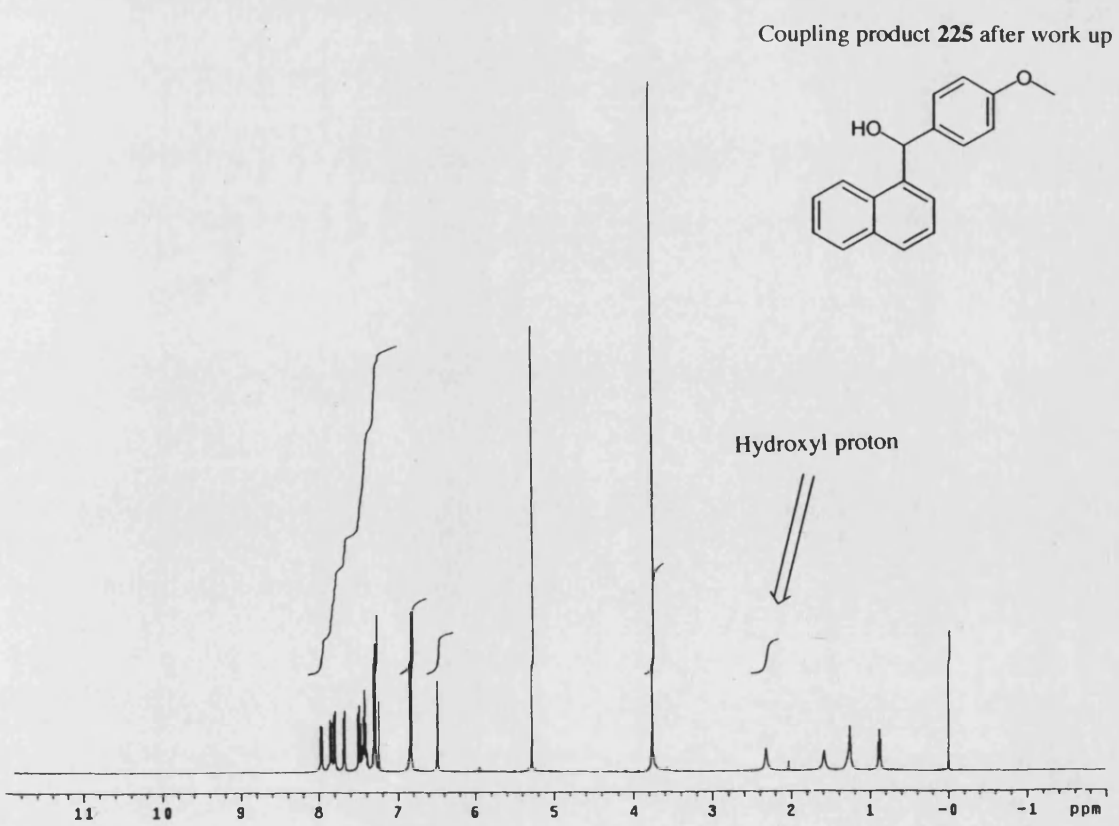
Scheme 109:



We have evidence that the hydrolysis occurs during work up. A ^{1}H NMR before work up showed no sign of an hydroxyl proton at 2.3 ppm (figure **4**).

Figure 4: NMR's of coupling product obtained before (a) and after (b) work up.

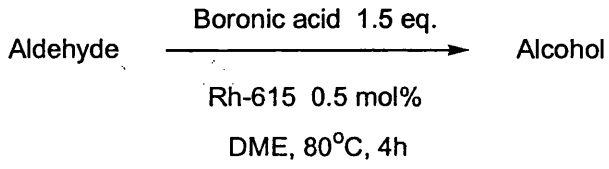


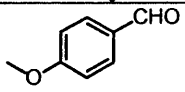
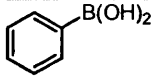
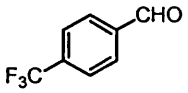
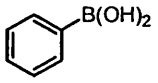
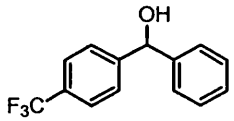
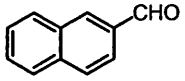
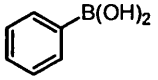
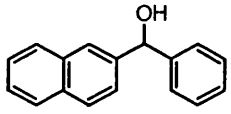
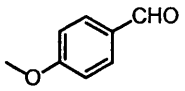
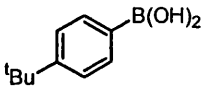
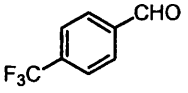
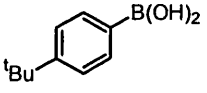
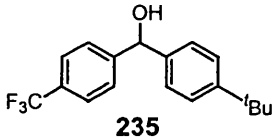
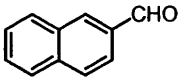
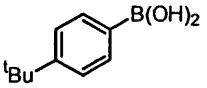
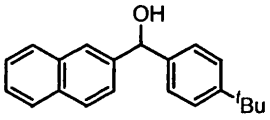
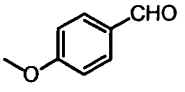
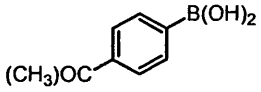


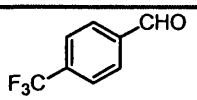
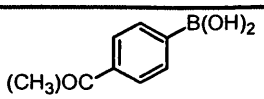
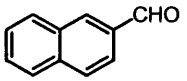
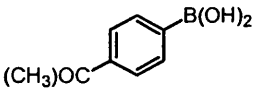
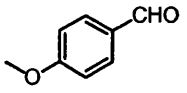
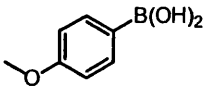
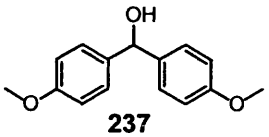
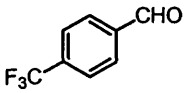
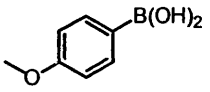
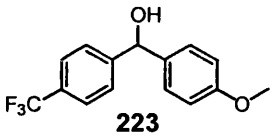
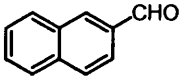
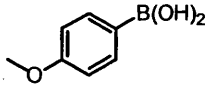
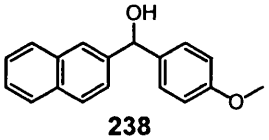
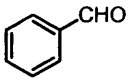
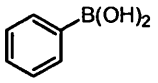
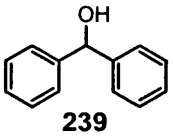
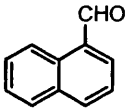
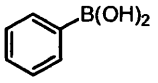
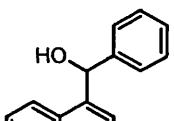
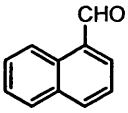
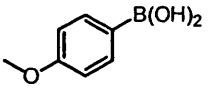
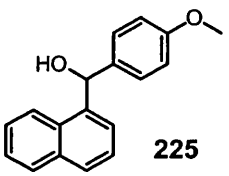
Scope of the reaction

The scope of the reaction was examined under our optimised conditions (0.5 mol% of **226a** in DME at 80°C for 2 hours). The optimum was obtained as before, with an electron-rich boronic acid and electron-deficient aldehyde (table 30, entries 5, 11, 12 and 15). The use of the electron-deficient *p*-acetylbenzene boronic acid resulted in the lack of activity (entries 7, 8 and 9) which can be attributed to an electronic deactivation due to the acyl group or the co-ordination of the carbonyl group to the metal centre.

Table 30:



Entry	Aldehyde	Boronic acid	Product	Yield (%)
1			none	0
2			 **233**	64
3			 **234**	53
4			none	0
5			 **235**	72
6			 **236**	59
7			none	0

8			none	0
9			none	0
10			 **237**	49
11			 **223**	86
12			 **238**	74
13			 **239**	52
14			 **218**	50
15			 **225**	72

Conclusion

We have developed a novel coupling reaction between aryl boronic acids and aldehydes using rhodium-diamine complexes. Through our experiments we have discovered that [Rh-box]$^{+}$Cb^{-} was a particularly good catalyst for this reaction with very good conversions being obtained in a rapid manner. The choice of counterion and solvent was found to be crucial for good conversions. However, to date, only low levels of enantioselectivity have been obtained (<15% e.e.).

Future developments of this work should focus on the further development of this reaction to improve yield and selectivity. Due to the early stage at which our knowledge of this reaction lies we do not yet know how the ligand conveys chiral information to give enantioselectivity in the reaction. It would thus be interesting, given the lack of knowledge on this reaction, to design experiments or analytical methods to give us further information on the nature of the active catalyst and the course of the reaction. A focussed screening of diverse ligand libraries in a parallel manner (ferrocene and salen based ligands would be likely to be candidates) could then be used to speed development and optimisation of the reaction. Mechanistic knowledge would also enable rational design of new ligands for use in this process. Given this knowledge we could determine the full scope of suitable substrates and ideally realise a catalytic approach to a range of secondary alcohols and related compounds (additions to imines for example would lead to amine products).

Experimentals

General considerations

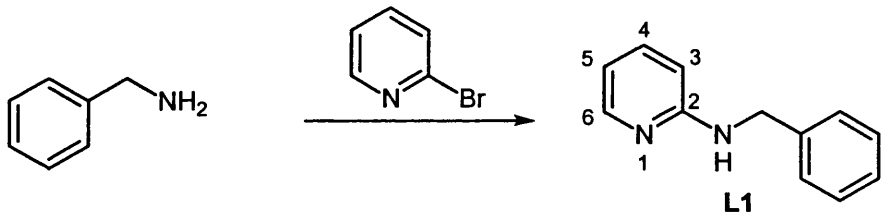
^{1}H and ^{13}C NMR spectra were recorded on either JEOL 270 EX or JEOL 400 EX spectrometers at 270 MHz and 400 MHz for ^{1}H respectively. The following abbreviations are used throughout; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, br s = broad singlet *etc.*. *J* values are quoted in Hertz. The abbreviations δ_H and δ_C denote ^{1}H and ^{13}C NMR respectively. Chemical shifts (δ_H and δ_C) are reported in parts per million (ppm) from tetramethylsilane (or chloroform) and are corrected to 0.00 (TMS) and 7.27 ($CHCl_3$) ppm for ^{1}H NMR and 77.00 ($CHCl_3$) for ^{13}C NMR. Unless stated deuteriochloroform was used as solvent for NMR measurements. Infra red spectra were recorded in the range of 4000cm-1 -600cm-1 on a Perkin Elmer FT 1000 spectrometer with internal calibration. Mass spectra were carried out by the University of Bath Mass Spectroscopy Service. High Performance Liquid Chromatography (HPLC) was performed on a SP thermoSeparation products spectra SERIES system using chiral columns such as Chiralcel OD columns obtained from Fisher Scientific suppliers. Analytical tlc's were performed on MERCK precoated silica gel plates. Visualisation was accomplished by UV light followed by staining with either phosphomolybdic acid, vanillin or ninhydrin followed by heating.

Solvents and reagents were purified according to procedures outlined in "Purification of Laboratory Chemicals" by D.D Perrin and W.L.F Armarengo. All reactions using air or/and moisture sensitive reagents were performed in oven or flame dried apparatus under a nitrogen atmosphere. Petrol refers to light petroleum, b.p. 40-60°C; ether refers to diethyl ether. Butyl lithium refers to *n*-butyl lithium, in all cases this was the commerciallly available solution in hexane (1.6M).

General procedure for the synthesis of the monodentate amino-pyridine ligands

In a pressure tube under nitrogen atmosphere was added $Pd(dba)_2$ (0.05 eq.), dppf (0.11 eq.) and sodium *tert*-butoxide (1.6 eq.). To this mixture was added the amine (1.4 eq.) and the 2-bromopyridine (1eq.) in dry toluene (2-3 mL). The tube was then sealed with a teflon screw top before heating to 80-90°C and stirring for 4 hours after which time tlc analysis (SiO_2 plate, eluent 9:1 DCM/CH_3OH) indicated product formation. The solvent was removed by evaporation and the crude product was then purified by a short column chromatography using dichloromethane as eluent.

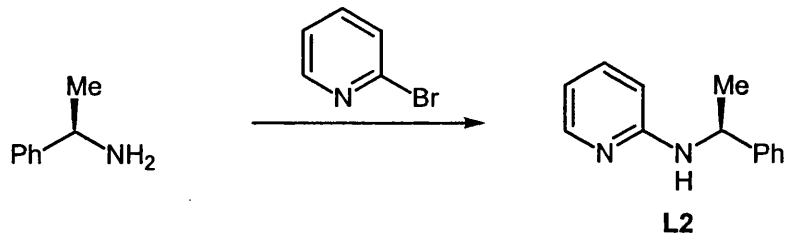
***N*-Benzyl-*N*-(2-pyridinyl)amine L1**



L1

2-Bromopyridine (18mg, 0.114 mmol) and benzylamine (17mg, 0.16 mmol) were reacted under the general protocol to give the desired product **L1** as a yellow oil (13mg, 60% yield) which showed δ_H 8.10 (1H, m, CH_6), 7.15-7.48 (6H, m, ArH), 6.58 (1H, ddd, CH_5, $J_{5,4}$ 8.4, $J_{5,6}$ 5.0 and $J_{5,3}$ 0.9), 6.37 (1H, app.d, CH_3, $J_{3,4}$ 8.4), 4.98 (1H, br, NH) and 4.51 (2H, d, J 5.9, CH_2); δ_C 158.9 (C), 148.5 (CH), 139.4 (C), 137.8, 129.1, 128.9, 127.7, 113.5, 107.1 (all CH) and 46.6 (CH_2); m/z (FAB^+) 185 (100%, M^++H) [found M^++H 185.10715. $C_{12}H_{12}N_2$ requires M^++H 185.10787]; ν_{max}/cm $^{-1}$ 2923 (s), 1998 (s), 1526 (m), 1456 (m) and 769 (w).

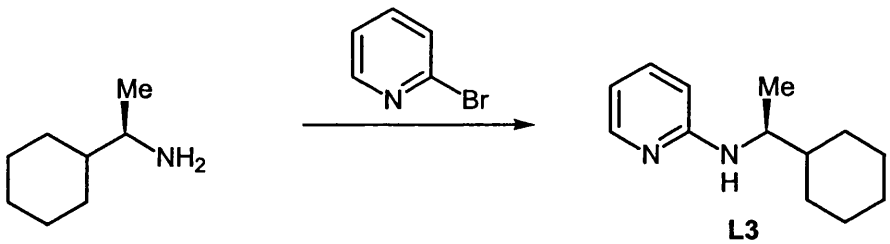
N-[(1*R*)-1-Phenylethyl]-*N*-(2-pyridinyl)amine L2



L2

2-Bromopyridine (50mg, 0.314 mmol) and (S)-α-methylbenzylamine (53mg, 0.439 mmol) were reacted under the standard protocol to give the desired product **L2** as a pale yellow oil (57mg, 91% yield) which showed δ_H 8.06 (1H, dd, CH_6, $J_{6,4}$ 1 and $J_{6,5}$ 4.9), 7.21-7.39 (6H, m, Ar-H), 6.54 (1H, ddd, CH_5, $J_{5,4}$ 8.4, $J_{5,6}$ 4.9 and $J_{5,3}$ 0.9), 6.19 (1H, app.d, CH_3, $J_{3,4}$ 8.4), 4.71 (1H, q, *J* 6.6, CH-Me) and 1.54 (3H, d, *J* 6.6); δ_C 165.1 (C), 145 (CH), 141.7 (C), 134.7, 128.5, 127.3, 125.9, 120.1, 106.9 (all CH), 53.2 (CH-Me) and 24.13 (CH_3); m/z (FAB^+) 199 (100%, M^++H) 183 (15) [found M^++H 199.12374. $C_{13}H_{14}N_2$ requires M^++*H* 199.12352]; ν_{max}/cm^{-1} 3025 (m), 2972 (m), 2927 (m), 2869 (m), 1600 (s), 1484 (s), 1445 (s) and 769 (m); Anal. Calcd. for $C_{13}H_{14}N_2$: C, 78.8; H, 7.12; N, 14.13. Found: C, 78.9; H, 7.13; N, 13.5. $[\alpha_D]^{20}$ = -28.3 (c 0.6, $CHCl_3$). HPLC was performed using Chiralcel OD column, 90:10 hexane/IPA, λ = 254 nm, 0.5 mL/min, R_t (R)-**L2** = 9.9 mins.

N-[(1*R*)-1-Cyclohexylethyl]-2-pyridinamine L3

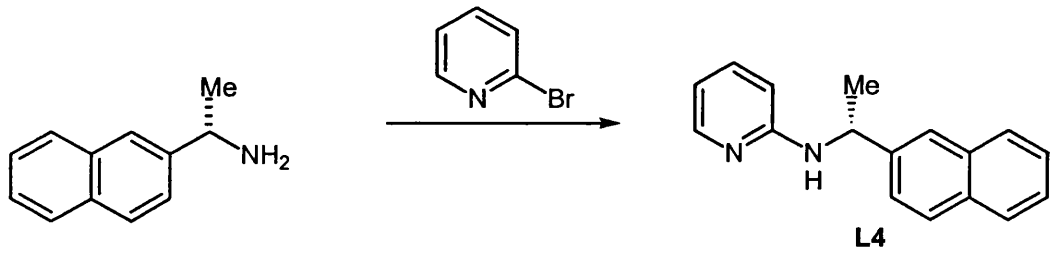


L3

2-Bromopyridine (40mg, 0.246 mmol) and (R)-cyclohexylethylamine (44mg, 0.345 mmol) were reacted under the standard protocol to give the desired product **L3** as a yellow oil (44mg, 88% yield) which showed δ_H 8.04 (1H, dd, CH_6, $J_{6,4}$ 0.9 and $J_{6,5}$ 4.9), 7.37 (1H, app.dt, CH_4, $J_{4,5} = J_{4,3}$ 8.4 and $J_{4,6}$ 1), 6.49 (1H, ddd, CH_5, $J_{5,4}$ 8.4, $J_{5,6}$ 4.9 and $J_{5,3}$ 0.9), 6.33

(1H, app d, CH_3, $J_{3,4}$ 8.4), 4.42 (1H, br, NH), 3.61 (1H, m, *J* 6.4, C*H*-Me), 0.96-1.88 (11H, m, CH_2 and CH) and 1.16 (3H, d, *J* 6.4, CH_3); δ_C 158.5 (C), 148.2, 137.3, 112.1, 106.4 (all CH), 51.5 (*C*H-Me), 43.3 (CH), 29.4, 28.7, 26.5, 26.3, 26.2 (all CH_2) and 17.7 (CH_3); m/z (FAB^+) 205 (100%, M^++H) 121 (40), 95 (15) [found M^++H 205.17125. $C_{13}H_{20}N_2$ requires M^++*H* 205.17047]; ν_{max}/cm $^{-1}$ 3050 (m), 2926 (m), 2852 (m), 1600 (s), 1498 (s), 1447 (s) and 738 (m); Anal. Calcd. for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87 N, 13.71. Found: C, 76.3; H, 9.84; N, 13.0. $[\alpha_D]^{20}$ = -18.4 (c 0.38, $CHCl_3$). HPLC was performed using Chiralcel OD column, 90:10 hexane/IPA, λ = 254 nm, 0.5 mL/min, R_t (R)-**L3** = 11.9 mins.

N-[(1*S*)-1-(2-Naphthyl)ethyl]-*N*-(2-pyridinyl)amine L4

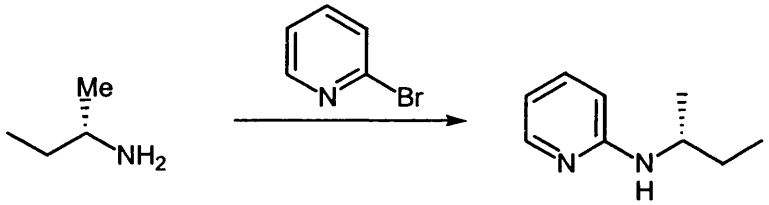


L4

2-Bromopyridine (24mg, 0.150 mmol) and (S)-naphthylethylamine (36mg, 0.21 mmol) were reacted under the general protocol to give the desired product **L4** as a pale yellow solid (26mg, 68.9% yield) which showed δ_H 8.10 (1H, dd, CH_6, $J_{6,4}$ 0.9 and $J_{6,5}$ 5), 7.30-7.90 (9H, m, Ar-H), 6.06 (1H, app.d, CH_3, $J_{3,4}$ 8.4), 5.52 (1H, q, *J* 6.4, :CH-Me), 5.08 (1H, br, NH) and 1.69 (3H, d, *J* 6.4, CH_3); δ_C 157.8 (C), 148.3 (CH), 139.6 (C), 137.4 (CH), 134.1 (C), 130.8 (C), 129.1, 127.7, 126.2, 125.8, 125.5, 122.7. 122.2, 113.1, 106.7 (all CH), 48.1 (CH-Me) and 23.1 (CH_3); m/z (FAB^+) 249 (100%, M^++H) 155 (45), 95 (20); [found M^++H 249.13942. $C_{17}H_{16}N_2$ requires M^++*H* 249.13917]; ν_{max}/cm $^{-1}$ 3053 (m), 2985 (m), 1600 (s), 1506 (m), 1445 (m) and 740 (m); Anal. Calcd. for $C_{17}H_{16}N_2$: C, 82.23; H, 6.49; N, 11.28. Found: C, 81.4; H, 6.51; N, 11.05. $[\alpha_D]^{20}$ = 185.2 (c 0.405, $CHCl_3$). HPLC

was performed using Chiralcel OD column, 90:10 hexane/IPA, λ = 254 nm, 0.5 mL/min, R_t (S)-**L4** = 18.9 mins.

_N_-[(1_S_)-1-Methylpropyl]-_N_-(2-pyridinyl)amine L5



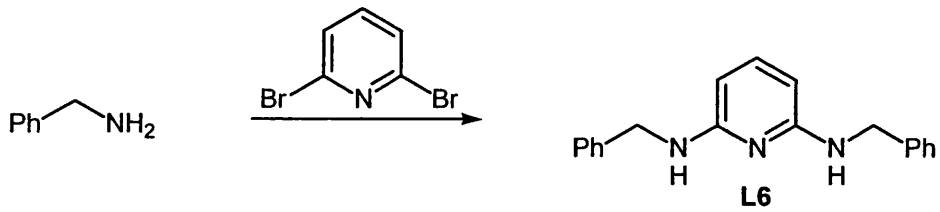
L5

2-Bromopyridine (30mg, 0.190 mmol) and (S)-*sec*-butylamine (19mg. 0.266 mmol) were reacted under the general protocol to give the desired product **L5** as a white solid (22mg, 77% yield) which showed δ_H 8.05 (1H, m, Ar-H), 7.44 (1H, app.dt, CH_4, $J_{4,5} = J_{4,3}$ 8.4 and $J_{4,6}$ 0.9), 6.53 (1H, ddd, CH_5, $J_{5,4}$ 8.4, $J_{5,6}$ 4.9 and $J_{5,3}$ 0.9), 6.37 (1H, app.d, CH_3, $J_{3,4}$ 8.4), 4.37 (1H, br, NH), 3.67 (1H, m, CH-Me), 1.54 (2H, m, CH_2), 1.19 (3H, d, J 6.4, CH_3) and 1.09 (3H, t, J 7.4, CH_3); δ_C 158.4 (C), 148.2, 137.4, 112.3, 106.6 (all CH), 48.5 (*C*H-Me), 29.8 (CH_2), 20.3 and 10.3 (both CH_3); m/z (FAB^+) 151 (100%, M^++H) 95 (35); [found M^++H 151.12332. $C_9H_{14}N_2$ requires M^++H 151.12352]; ν_{max}/cm $^{-1}$ 2923 (s), 2854 (s), 1600 (s), 1460 (m) and 767 (m); $[\alpha_D]^{20}$ = +48.3 (c 0.145, $CHCl_3$).

General procedure for the synthesis of the tridentate amino-pyridine ligands

In a pressure tube under a nitrogen atmosphere was added $Pd(dba)_2$ (0.05 eq.), dppf (0.11 eq.), and sodium *tert*-butoxide (1.8 eq.). To this mixture was added the amine (2.2 eq.) and 2,6 dibromopyridine (1 eq.) in dry toluene (2-3 mL). The tube was then sealed with a teflon screw top and heated to 80-90°C. After 4 hours of stirring tlc analysis (SiO_2 plate, eluent 9:1 DCM/CH_3OH) indicated product formation. The solvent was then removed by evaporation and the crude product was purified by column chromatography using dichloromethane as eluent.

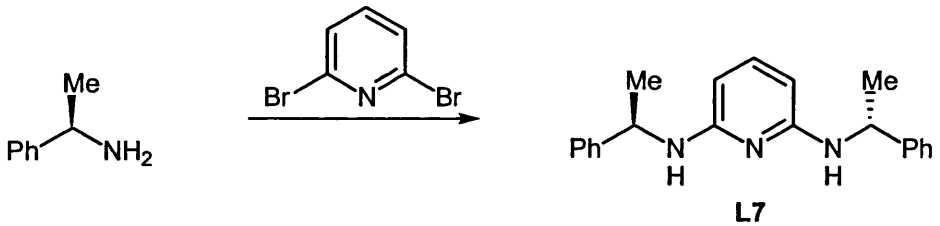
_N_-Benzyl-_N_-[6-(benzylamino)-2-pyridinyl]amine L6



L6

2,6-Dibromopyridine (19mg, 0.081 mmol) and benzylamine (19mg, 0.18 mmol) were reacted under the standard protocol to give the desired product **L6** as a clear oil (15mg, 62% yield) which showed δ_H 7.06-7.47 (10H, m, Ar-H), 5.72 (2H, d, *J* 7.8, CH_3 and CH_5), 5.28 (1H, t, CH_4, *J* 7.9), 4.62 (2H, br, NH) and 4.41 (4H, d, *J* 5.4, 2 x CH_2); δ_C 157.9, 139.7 (both C), 139.1, 128.7 , 127.4, 127, 95.2 (all CH) and 46.3 (CH_2); m/z (FAB^+) 290 (100%, M^++H) [found M^++H 290.16485. $C_{19}H_{19}N_3$ requires M^++*H* 290.16572]; ν_{max}/cm^{-1} 3054 (m), 2985 (m), 1596 (s), 1495 (m), 1451 (m) and 740 (m).

_N_-[(1_R_)-1-Phenylethyl]-_N_-(6-{[(1_R_)-1-phenylethyl]amino}-2-pyridinyl)amine L7

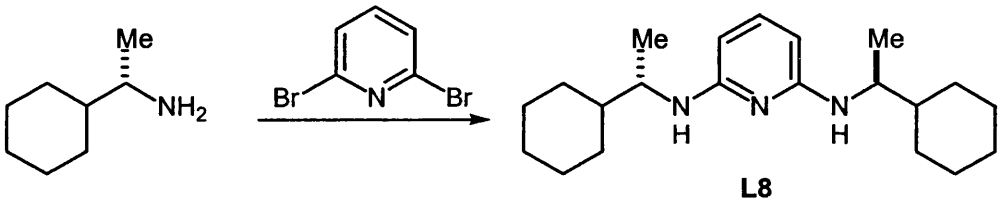


L7

2,6-Dibromopyridine (18mg, 0.075 mmol) and (R)-α-methylbenzylamine (19mg, 0.158 mmol) were reacted under the standard protocol to give the desired product **L7** as a pale yellow oil (14mg, 60% yield) which showed δ_H 7.18-7.37 (10H, m, ArH), 7.02 (1H, t, *J* 7.9, CH_4), 5.49 (2H, d, *J* 7.9, CH_3 and CH_5), 4.62 (2H, q, *J* 6.4, 2 x CH-Me) and 1.46 (6H, d, *J* 6.41, 2 x CH_3); δ_C 157.5 (C), 139.3 (C), 128.7, 127.2, 126.1, 125.8, 95.7 (all CH), 52.1 (CH-Me) and 24.7 (CH_3); m/z (FAB^+) 318 (100%, M^++H) [found M^++H 318.19748. $C_{21}H_{23}N_2$ requires M^++*H* 318.19702]; ν_{max}/cm^{-1} 3052 (m), 2980 (m), 2927 (m), 1591 (s),

1467. (m) and 738(m); Anal. Calcd. for $C_{21}H_{23}N_2$ C, 79.46; H, 7.30; N, 13.24. Found: C, 79.2; H, 7.29; N, 12.8. $[\alpha_D]^{20}$ = -63.1 (c 0.32, $CHCl_3$).

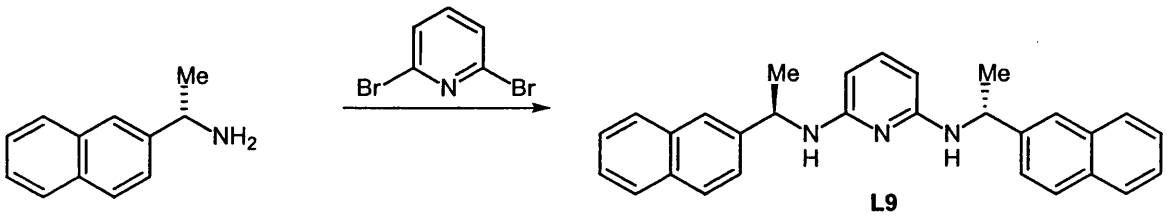
_N_-[(1_R_)-1-Cyclohexylethyl]-_N_-(6-{[(1_R_)-1-cyclohexylethyl]amino}-2-pyridinyl)amine L8



L8

2,6-Dibromopyridine (18mg, 0.075 mmol) and (R)-cyclohexylethylamine (20mg, 0.158 mmol) were reacted under the standard protocol to give the desired product **L8** as a yellow oil (14mg, 57.6% yield) which showed δ_H 7.19 (1H, t, *J* 7.8, CH_4), 5.62 (2H, d, *J* 7.8, CH_3 and CH_5), 4.15 (2H, br, NH), 3.45 (2H, m, *J* 6.4, CH-Me), 1.37-1.84 (8H, m, CH_2), 1.33 (2H, m, 2 x CH), 1.04-1.25 (12H, m, 6 x CH_2) and 1.09 (6H, d, *J* 6.35, 2 x CH_3); δ_C 157.9 (C), 139.0, 94.6 (both CH), 51.6 (CH-Me), 43.3 (CH), 29.7, 28.6, 28.4, 26.3, 25.9 (all CH_2) and 17.7 (CH_3); m/z (FAB^+) 330 (75%, M^++H) 246 (20) [found M^++H 330.28966. $C_{21}H_{35}N_3$ requires M^++H 330.29092]; ν_{max}/cm $^{-1}$ 2925 (s), 2851 (s), 1589 (s), 1450 (s) and 789 (m); $[\alpha_D]^{20}$ = +17.8 (c 0.225, $CHCl_3$).

_N_-[(1_R_)-1-(2-Naphthyl)ethyl]-_N_-(6-{[(1_R_)-1-(2-naphthyl)ethyl]amino}-2-pyridinyl)amine L9

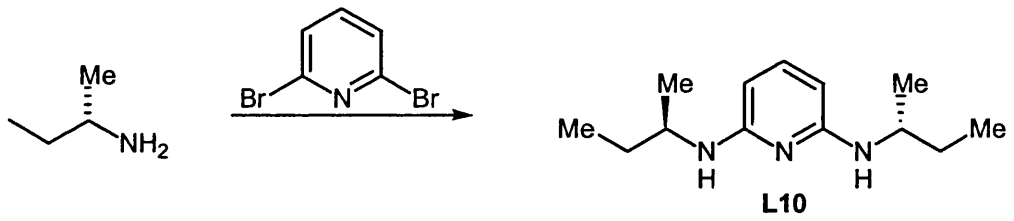


L9

2,6-Dibromopyridine (47mg, 0.198 mmol) and (R)-naphthylethylamine (74mg, 0.435 mmol) were reacted under the standard protocol to give the desired product **L9** as a yellow

oil (85mg, 97% yield) which showed δ_H 7.37-8.15 (14H, m, Ar-H), 6.90 (1H, t, *J* 7.8, CH_4), 5.47 (2H, q, *J* 6.4, CH-Me), 5.41 (2H, d, *J* 7.8, CH_3 and CH_5), 4.82 (2H, br s, NH) and 1.57 (6H, d, *J* 6.4, 2 x Me); δ_C 157.3 (C), 141.2 (C), 140.1 (CH), 134.8 (C), 131.9 (C), 129.9, 128.3, 126.9, 126.7, 126.3, 123.7, 123.1, 96.4 (all CH), 48.7 (CH-Me) and 23.87 (CH_3); m/z (FAB^+) 418 (100%, M^++H) 277 (60) [found M^++H 418.22746. $C_{29}H_{27}N_3$ requires M^++H 418.22832]; ν_{max}/cm $^{-1}$ 3054 (m), 2986 (m), 1598 (s), 1422 (m) and 740 (m); $[\alpha_D]^{20}$ = +133.3 (c 0.075, $CHCl_3$).

N-[(1S)-1-Methylpropyl]-N-(6-{[(1S)-1-methylpropyl]amino}-2-pyridinyl)amine L10



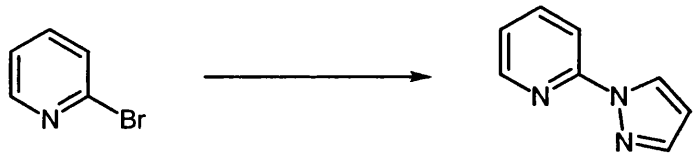
L10

2,6-dibromopyridine (29mg, 0.121 mmol) and (S)-*sec*-butylamine (19mg, 0.266 mmol) were reacted under the standard protocol to give the desired product **L10** as a pale yellow oil (20mg, 74.4% yield) which showed δ_H 7.18 (1H, t, *J* 7.9, CH_4), 5.65 (2H, d, *J* 7.8, CH_3 and CH_5), 4.22 (2H, br s, NH), 3.53 (2H, m, 2 x CH-Me), 1.41-1.62 (4H, m, 2 xCH_2), 1.15 (6H, d, *J* =6.4, 2 x Me) and 0.92 (6H, t, *J* 7.3, 2 x Me); δ_C 151.8 (C), 139 (CH), 94.1 (CH), 48.5 (CH-Me), 29.8 (CH_2), 20.3 and 10.4 (both CH_3); m/z (FAB^+) 222 (100%, M^++H) 192 (30), 110 (15) [found M^++H 222.19624. $C_{13}H_{23}N_3$ requires M^++H 222.19702]; ν_{max}/cm $^{-1}$ 3054 (m), 2985 (m), 1591 (s) and 747 (m); $[\alpha_D]^{20}$ = +66.7 (c 0.03, $CHCl_3$).

General procedure for the synthesis of aminopyridines

The appropriate bromopyridine (1 eq.) and azole or indazole (1.2 eq.) were combined with $Pd_2(dba)_3$ (4 mol%), dppp (8 mol%), NaO^tBu (1.4 eq.), and toluene (0.11 M with 2-bromopyridine, 3 mL) in an oven-dried pressure tube under a nitrogen atmosphere. After stirring for 5 minutes the reaction tube was sealed then heated to 70°C overnight. The reaction mixture was then allowed to cool to room temperature, taken up in diethyl ether (6 mL), washed 3 times with brine (6 mL), dried over $MgSO_4$, and evaporated to give the crude product. Purification by flash chromatography (95:5 DCM/ methanol) afforded the analytically pure product.

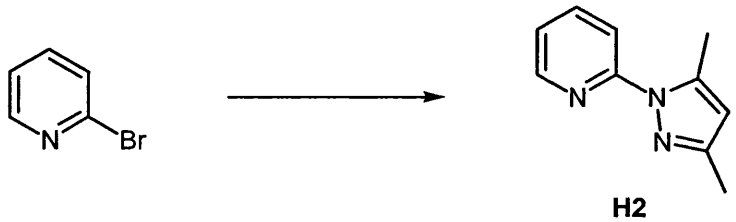
2-(1*H*-Pyrazol-1-yl)pyridine H1



H1

2-Bromopyridine (50mg, 0.32 mmol) and pyrazole (26mg, 0.38 mmol) were reacted under the general protocol to give a white solid **H1** (26mg, 55% yield) m.p.30-32°C which showed δ_H 8.57 (1H, app. d, *J* 3.8, CH), 8.42 (1H, d, *J* 7.8, CH), 7.99 (1H, d, *J* 8.3, CH), 7.81 (1H, dt, *J* 1.8 and *J* 7.9, CH), 7.74 (1H, s, CH), 7.21 (1H, m, CH) and 6.47 (1H, m, CH); δ_C 173.1 (C), 148, 142.1, 138.7, 128.7, 121.4, 112.4 and 107.8 (all CH); m/z (EI^+) 146 (85%, M^++H) [found M^++H 146.07214. $C_8H_7N_3$ requires M^++*H* 146.07181]; ν_{max}/cm $^{-1}$ 2931 (m), 1590 (s), 1578 (m), 1472 (m), 1430 (m) and 1362 (w).

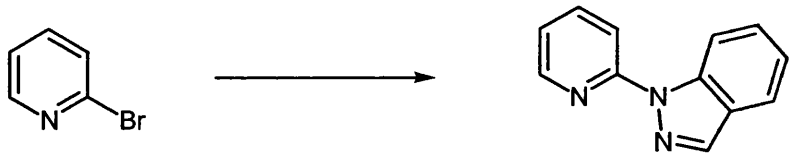
2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)pyridine H2



H2

2-Bromopyridine (50mg, 0.32 mmol) and 2,5-dimethylpyrazole (37mg, 0.38 mmol) were reacted under the general protocol to give a clear oil **H2** (34mg, 62% yield) which showed δ_H 8.40 (1H, m, CH_6), 7.73-7.84 (2H, m, CH_4 and CH_5), 7.12-7.17 (1H, m, CH_3), 5.99 (1H, s, CH_7), 2.30 (3H, s, CH_3) and 2.01 (3H, s, CH_3); δ_C 149.2 (C), 147.5 (CH_6), 142.2 (C), 138.2 (CH_4), 120.7 (CH), 115.9 (CH), 109 (CH), 60.0 (C), 14.4 and 13.6 (both CH_3); m/z (FAB^+) 174 (40%, M^++H) [found M^++H 174.10379. $C_{10}H_{11}N_3$ requires M^++H 174.10311]; ν_{max}/cm $^{-1}$ 2931 (m), 1590 (s), 1578 (m), 1472 (m), 1430 (m) and 1362 (w).

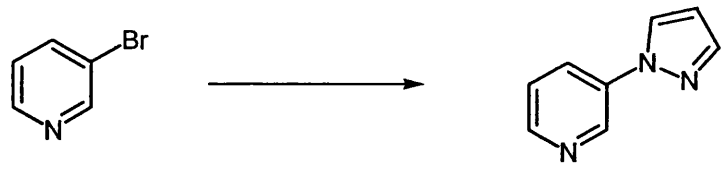
1-(2-Pyridinyl)-1*H*-indazole H3



H3

2-Bromopyridine (50mg, 0.32 mmol) and indazole (45mg, 0.38 mmol) were reacted under the general protocol to give a pale yellow solid **H3** (33mg, 53% yield) which showed δ_H 8.69 (1H, s, CH), 8.40 (1H, d, *J* 7.9, CH), 8.11 (1H, s, CH), 7.74-7.84 (2H, m CH) and 7.13-7.49 (4H, m, CH); δ_C 156.2 (C), 149.3 (CH), 140.3 (C), 137.2, 134.8, 130.8, 128.9, 126.9, 123.9 (all CH), 122.1 (C), 121.4 and 110.1 (CH); m/z (FAB^+) 196 (100%, M^++H) [found M^++H 196.08796. $C_{12}H_9N_3$ requires M^++H 196.08746]; ν_{max}/cm $^{-1}$ 2931 (m), 1590 (s), 1578 (m), 1472 (m), 1430 (m) and 1362 (w).

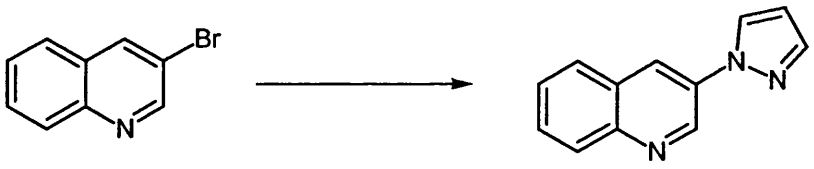
3-Pyrazol-1-yl-pyridine H4



H4

3-Bromopyridine (50mg, 0.32 mmol) and pyrazole (26mg, 0.38 mmol) were reacted under the general protocol to give a colourless oil **H4** (29mg, 56% yield) which showed δ_H 8.69 (1H, app. d, *J* 3.9, CH_6), 8.52 (1H, s, CH_2), 7.91 (1H, m, CH_4), 7.74 (1H, m, CH_5), 7.69 (1H, s, CH), 7.21-7.26 (1H, m CH) and 6.49 (1H, m, CH); δ_C 148.3 (CH_6), 139.8 (CH_2), 137.2 (C), 125.3 (CH_4), 123.1 (CH_6), 131.5, 130.6 and 108.2 (all $CH_{pyrazole}$); m/z (FAB^+) 161 (100%, M^++H) [found M^++H 161.09245. $C_8H_7N_3$ requires M^++*H* 161.09530].

3-pyrazol-1-yl-quinoline H5



H5

3-Bromoquinoline (50mg, 0.24 mmol) and pyrazole (27mg, 0.29 mmol) were reacted under the general protocol to give a yellow oil **H5** (28mg, 60% yield) which showed δ_H 8.86 (1H, s, CH), 7.95 (1H, m, CH), 7.69-7.86 (4H, m, ArH), 7.63 (1H, m, CH), 7.26-7.31 (1H, m, CH) and 6.75 (1H, m, CH); δ_C 148.6 (C), 141.3, 131.5, 130.5 (all CH), 129.1, 128.6 (both C), 128.4, 127.2, 126.3, 125.2, 124.6 and 105.2 (all CH); (m/z (FAB^+) 196 (100%, M^++H) [found M^++H 196.08635. $C_{12}H_9N_3$ requires M^++*H* 196.08747].

2,2'-*Bis*(Diphenylphosphino)diphenylether: DPEphos 131

131

A room temperature solution of diphenylether (1.0g, 5.87 mmol) in dry THF (8 mL) was added dropwise to a stirred mixture of butyl lithium (5.2 mL, 2.5M in hexane, 13 mmol) and TMEDA (1.96 mL, 13 mmol). The reaction mixture was stirred for 16 hours before introducing chlorodiphenylphosphine (2.86g, 13 mmol) in hexane (2 mL) in a dropwise manner (the reaction flask was cooled in a water bath during the addition) causing a white precipitate to form. The mixture was stirred for a further 16 hours, before adding DCM (8 mL) and water (8 mL), the resulting mixture was vigorously stirred. The aqueous layer was then removed, the organic phase was dried over Na_2SO_4 and the solvent was evaporated to afford a sticky solid which was purified by column chromatography (eluent petrol/ether 95: 5) to give a pale yellow solid **131** m.p 175-176°C which showed δ_H 7.18-7.40 (11H, m, ArH), 6.95 (1H, m, CH), 6.80 (1H, m, CH), 6.67 (1H, m, CH); δ_C 159.4 (C-O), 136.8 (C-P), 134.2, 133.9, 130.3, 129.2, 128.6, 128.4, 123.8 and 118.2 (all CH); m/z 539 (100 %, M^++H) [found M^++H 539.16862. $C_{36}H_{28}OP_2$ requires M^++H 539.16936]; Data identical to those in the literature.[114]

6-Bromo-2-pyridinecarbaldehyde 195

146 **195**

To a stirred solution of 2,6-dibromopyridine (2g, 8.45 mmol) in THF (6 mL) maintained at -78°C was added a solution of n-butyl lithium (5.3 mL of a 1.6 M solution in hexanes, 8.45 mmol). After a further 0.5 hour, dimethylformamide (1.35 mL, 17.5 mmol) in THF (5 mL)

was added. The solution was maintained at -78 C for a further hour before bringing to room temperature and quenching with brine (3 mL). The organic layer was separated and the aqueous layer extracted with ether (3 x 40 mL). The combined organic extracts were washed with water (40 mL) and brine (40 mL) then dried and evaporated. Final purification was achieved by chromatography (20% ethyl acetate/ petrol) to give the desired aldehyde **195** (1.2g, 80% yield) as a yellow solid. m.p. 80-81°C which showed δ_H 9.52 (1H, s, C*H*O) and 7.23-7.46 (3H, m, CH); δ_C 191.5 (C=O), 153.6 (C), 142.5 (C-Br), 139.3, 132.6 and 120.3 (all CH); m/z (EI^+) 186 (100%, M^++H) [found M^++H 186.94511. C_6H_4NOBr requires M^++H 186.95541]; Anal. Calcd. for C_6H_4NOBr: C, 38.74; H, 2.17; N, 7.53. Found: C, 38.5; H, 2.17; N, 7.43.

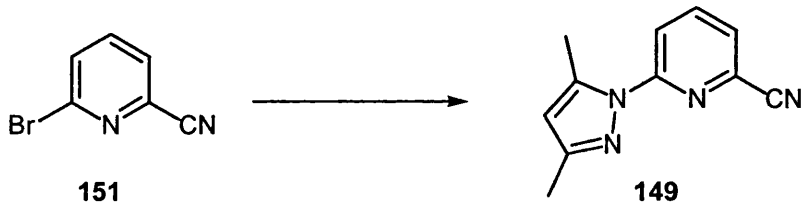
6-Bromo-2-pyridine carbonitrile 151[147]

195 **151**

To a cold solution of hydroxylamine hydrochloride (0.2g, 2.9 mmol) in dry acetonitrile (45 mL), was added triethylamine (2.97 mmol, 0.4 mL) and 6-bromopyridine-2-carbaldehyde (0.5g, 2.7 mmol). The resulting mixture was stirred for 0.5h before addition of phthalic anhydride (0.4g, 2.7 mmol) and then heated to reflux for 8 hours. The solution was then concentrated under reduced pressure, and the resulting residue was extracted by stirring with cold DCM (3 x 30 mL) and then filtering. The combined filtrates were washed with 5% aqueous ammonia to remove any residual phthalic acid, dried over $MgSO_4$ and then evaporated under reduced pressure to afford the crude product. Further purification was achieved by flash chromatography (20% ethyl acetate/ petrol) followed by recrystallization from toluene to afford the desired product **151** (2.5g, 93% yield) as a white solid. m.p 162-164°C which showed δ_H (d_4-methanol) 7.71 (1H, t, *J* 7.7, CH), 7.59 (1H, t, *J* 7.7, CH) and

7.45 (1H, d, *J* 7.7, CH); δ_C 155.3 (CN), 149.1 (C), 144.1 (C-Br), 140.9, 129.5 and 120.6 (all CH); ν_{max}/cm^{-1} 2932 (m), 2856 (m), 2230 (m), 1488 (m), 1438 (m), 1230 (s) and 680 (s). Attempts to obtain mass spectral data (EI and FAB) proved unsuccessful.

6-(3,5-Dimethyl-pyrazol-1-yl)-pyridine-2-carbonitrile 149



151 **149**

6-Bromo-2-pyridine carbonitrile (40mg, 0.22 mmol), 3,5-dimethylpyrazole (25mg, 0.26 mmol), $Pd(OAc)_2$ (0.009 mmol, 4 mol%), dppp (7.2 mg, 0.017 mmol, 8 mol%), NaO^{t}Bu (30mg, 0.31 mmol), and toluene (0.11 M with 6-bromo-2-pyridine carbonitrile, 2 mL) were added to an oven-dried pressure tube under a nitrogen atmosphere after stirring for 5 minutes the tube was sealed and heated to 70°C overnight. The reaction mixture was then allowed to cool to room temperature, taken up in diethyl ether (6 mL), washed 3 times with brine (6 mL), dried over $MgSO_4$, and condensed *in vacuo* to give the crude product. Purification by flash chromatography (8:2 petrol/EtOAc) afforded the pure product **149** (23mg, 42% yield) as a pale yellow solid which showed δ_H 8.17 (1H, dd, *J* 1.1 and 7.4, ArH), 7.73 (1H, dd, *J* 7.4 and 7.4, CH_4), 7.63 (1H, dd, *J* 1.1 and 7.4, ArH), 5.82 (1H, s, CH_{azole}), 2.26 (6H, s, 2 x CH_3); δ_C 165.2 (CN), 150.5, 140.6, 139.9 (All C), 139.6, 131.1 (both CH), 127.3 (C), 121.5 (CH), 121.1 (C), 104.1 (CH) and 12.2 (CH_3); m/z (FAB^+) 199 (100%, M^++H) [found M^++H 199.09534. $C_{11}H_{10}N_4$ requires M^++H 199.09837]; ν_{max}/cm^{-1} 2931 (m), 2230 (m), 1590 (s), 1578 (m), 1472 (m), 1430 (m), 1362 (w).

Asymmetric hydrosilylation of ketones

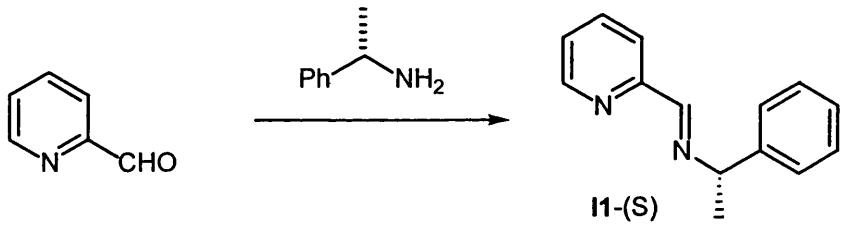
Parallel screening reactions: Hydrosilylation of acetophenone in air

A 96-well microtiter plate was used for this purpose. A 20 mmolar solution of the three metal precursors were placed in twelve vials respectively, then the eight different ligands (bidentate ligands were added in quantities of one and two equivalents) were added to each of the three different metal complexes in their respective vials. Acetophenone (0.1 mmol, 1.2 mL) and diphenylsilane (0.13 mmol, 2.4 mL) in THF (20 mL) were then added to each of the 48 vials. The plate was then sealed and left overnight at room temperature, after which time a 1:1 mixture of methanol/HCl was added. These reaction mixtures were then transferred in to GC vials before automated GC analysis was used to obtain conversions. Yields for these reactions are given in tabular form in chapter 3.

Parallel screening reactions: hydrosilylation of acetophenone under argon

The procedure used for the parallel screening in air (detailed above) was carried out in an argon filled glove box. After hydrolysis the samples were removed from the glove box for automated GC analysis. Yields for these reactions are given in tabular form in chapter 3.

***N*-[(1S)-1-Phenylethyl]-*N*-[pyridin-2-ylmethylene]amine I1-(S)**

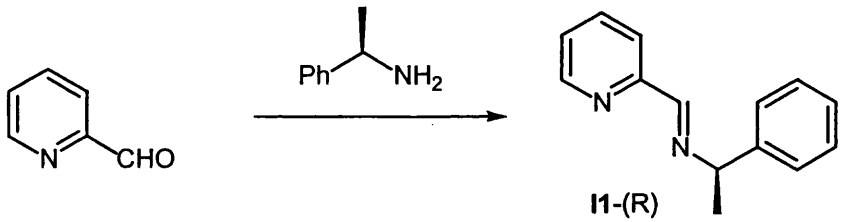


I1-(S)

In a round bottomed flask under a nitrogen atmosphere was mixed (S)-methylbenzylamine (0.58g, 0.67 mL) and pyridine-2-carboxaldehyde (0.51g, 0.5 mL) in dry methanol over 4Å molecular sieves. The reaction mixture was stirred at room temperature for 4 hours after which time infra red spectra showed the presence of the desired imine (1645 cm^{-1}). The

mixture was stirred for a few more hours until the reaction was complete. The reaction mixture was then filtered and the residue washed with methanol. The filtrate was evaporated under reduced pressure to give a yellow oil **I1**-(S) (1.09g, 100% yield) which showed δ_H 8.61 (1H, dd, $J_{6,5}$ 4.9 and $J_{6,4}$ 0.9, CH_6), 8.46 (1H, s, C*H*=N), 8.07 (1H, app d, $J_{5,4}$ 7.7, CH_5), 7.68 (1H, app dt, $J_{4,3} = J_{4,5}$ 7.7 and $J_{4,6}$ 1.8, CH_4), 7.21-7.36 (6H, m, ArH), 4.64 (1H, q, *J* 6.8, CH-Me) and 1.61 (3H, d, *J* 6.8, Me); δ_C 160.3 (CH=N), 154.6 (C), 149.2(CH), 144.3 (C), 136.4, 128.4, 127.2, 126.9, 124.6, 121.4 (all CH), 69.5 (CH-Me) and 24.44 (CH_3); m/z (FAB^+) 211.(100%, M^++H) [found M^++H 211.12364. $C_{14}H_{14}N_2$ requires M^++*H* 211.12351], 105 (35); ν_{max}/cm^{-1} 2972 (m), 2927 (m), 2861 (m), 1645 (s), 1586 (m), 1464 (m), 764 (m) and 699 (m); $[\alpha_D]^{20}$= +38.5 (c 1.5, $CHCl_3$). Data identical to those in the literature.[148]

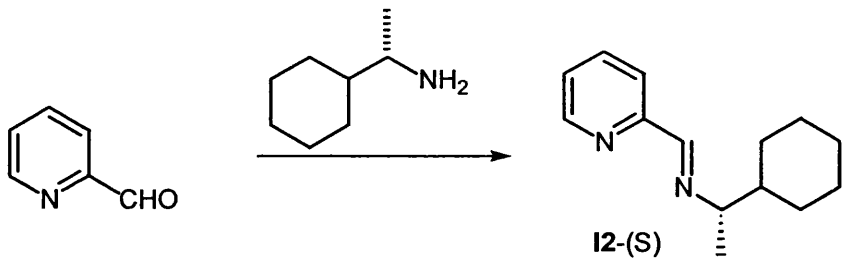
***N*-[(1R)-1-Phenylethyl]-*N*-[pyridin-2-ylmethylene]amine I1-(R)**



I1-(R)

Pyridine-2-carboxaldehyde (56mg, 0.524 mmol) and (R)-α-methylbenzylamine (63mg, 0.524 mmol) were reacted under the general procedure to give a pale yellow oil **I1**-(R) (110 mg, 100% yield) which showed δ_H 8.61 (1H, dd, $J_{6,5}$ 4.9 and $J_{6,4}$ 0.9, CH_6), 8.46 (1H, s, CH=N), 8.07 (1H, app d, $J_{5,4}$ 7.7, CH_5), 7.68 (1H, app dt, $J_{4,3} = J_{4,5}$ 7.7 and $J_{4,6}$ 1.8, CH_4), 7.21-7.36 (6H, m, ArH), 4.64 (1H, q, *J* 6.8, CH-Me) and 1.61 (3H, d, *J* 6.8, Me); $[\alpha_D]^{20}$ = -62.2 (c 1.3, Ethanol). Spectral data matches the enantiomeric product **I1**-(S).

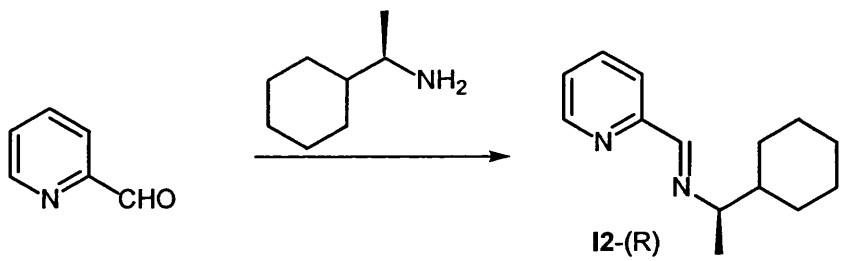
_N_-[(1S)-1-Cyclohexylethyl]-_N_-[pyridin-2-ylmethylene]amine I2-(S)



I2-(S)

In a round bottomed flask under nitrogen was added (S)-cyclohexylethylamine (0.66g, 0.78 mL) and pyridine 2-carboxaldehyde (0.56g, 0.5 mL) in methanol (3 mL) over 4Å molecular sieves. The mixture was stirred for 4 hours after which time infra red spectrum showed the presence of the desired imine (1647 cm^{-1}). The mixture was stirred for a few more hours until completion of the reaction, then filtered and the residue washed with methanol. The filtrate was evaporated *in vacuo* to give a yellow oil **I2**-(S) (1.13g, 100% yield) which showed δ_H 8.63 (1H, dd, $J_{6,5}$ 4.9 and $J_{6,4}$ 0.9, CH_6), 8.31 (1H, s, C*H*=N), 8.01 (1H, m, CH_4), 7.71 (1H, m, CH_5), 7.29 (1H, m, CH_3), 3.11 (1H, m, *J* 6.4, C*H*-Me), 0.85-1.92 (11H, m) and 1.22 (3H, d, *J* 6.4, CH_3); δ_C 159.6 (CH=N), 154.8 (C), 149.2, 136.3, 124.3, 121.2 (all CH), 71.6 (CH-Me), 43.5 (CH), 29.8, 29.6, 26.4, 26.3, 26.1 (all CH_2) and 19.7 (CH_3); m/z (FAB$^+$) 217 (100%, M^++H) [found M^++H 217.17079. $C_{14}H_{20}N_2$ requires M^++*H* 217.17046]; ν_{max}/cm $^{-1}$ 2927 (m), 2852 (m), 1647 (s), 1470 (m), 1459 (m), 1376 (m), 776 (m); $[\alpha_D]^{20}$ = +29.6 (c 5.8, acetone). Data identical to those in the literature.[30]

_N_-[(1R)-1-Cyclohexylethyl]-_N_-[pyridin-2-ylmethylene]amine I2-(R)



I2-(R)

Pyridine-2-carboxaldehyde (56mg, 0.524 mmol) and (R)-cyclohexylethylamine (66mg, 0.524 mmol) were reacted under the general procedure to give a yellow oil **I2**-(R) (113mg,

100% yield) which showed δ_H 8.63 (1H, dd, $J_{6,5}$ 4.9 and $J_{6,4}$ 0.9, CH_6), 8.31 (1H, s, CH=N), 8.01 (1H, m, CH_4), 7.71 (1H, m, CH_5), 7.29 (1H, m, CH_3), 3.11 (1H, m, *J* 6.4, CH-Me), .0.85-1.92 (11H, m) and 1.22 (3H, d, *J* 6.4, CH_3); m/z (FAB^+) 217 (100%, M^++H) [found M^++H 217.17047. $C_{14}H_{20}N_2$ requires M^++*H* 217.17046]; $[\alpha_D]^{20}$ = -2.0 (c 1, $CHCl_3$); Data identical to those in the literature.[30]

General procedure for hydrosilylation of acetophenone under nitrogen at room temperature

In a round bottomed flask under a nitrogen atmosphere was added the ligand (0.5 eq.) and $RuCl_2(dmso)_4$ (5 mol%) in dry THF (2 mL). The mixture was stirred at room temperature for 10 min. after which time acetophenone (1 eq.) and then diphenylsilane (2.2 eq.) were added. The reaction mixture was stirred under nitrogen for 24 hours. A solution of methanol (1 mL) and 1N hydrochloric acid (1 mL) was then added to hydrolyse the silyl ether product and after 15 minutes stirring the reaction mixture was extracted with ether (3 x 10 mL). The organic extracts were washed with brine over Na_2SO_4. The crude products were then analysed by ^1H NMR. Yields and enantioselectivities for these reactions are given in tabular form in chapter 3.

General procedure for the hydrosilylation of acetophenone under nitrogen at 0°C

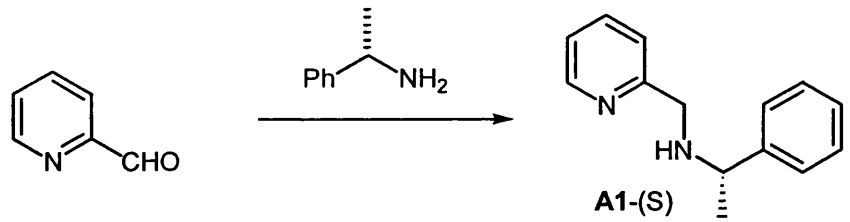
In a round bottomed flask under nitrogen was added the ligand (0.5 eq) and $RuCl_2(dmso)_4$ (0.05 eq.) in dry THF (2 mL). The mixture was stirred at room temperature for 10 minutes and then treated with acetophenone (1 eq.). The mixture was then cooled to 0°C and diphenylsilane (2.2 eq.) was added dropwise. The temperature was then allowed to come to room temperature over the next 24 hours, after which time the solution was cooled to 0°C before addition of methanol (1 mL). The mixture was then poured onto a an ice cold solution of hydrochloric acid 1N (3 mL), stirred at 0°C for 1 hour and then extracted with

ether (3 x 10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The crude product was then analysed to ^1H NMR. Yields and enantioselectivities for these reactions are given in tabular form in chapter 3.

General procedure for reductive amination of aldehydes[149]

In a round bottomed flask under a nitrogen atmosphere were mixed the appropriate amine (1eq.) and aldehyde (1eq.) in dry THF (3 mL) before treatment with sodium triacetoxyborohydride (1.4eq., 300 mg). The mixture was stirred at room temperature for 6 hours before quenching with aqueous saturated $NaHCO_3$ (2 mL). The reaction mixture was then was extracted with EtOAc (3 x 5mL), the organic extracts dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The crude product was analysed to ^1H NMR. Yields for these reactions are given in tabular form in chapter 3.

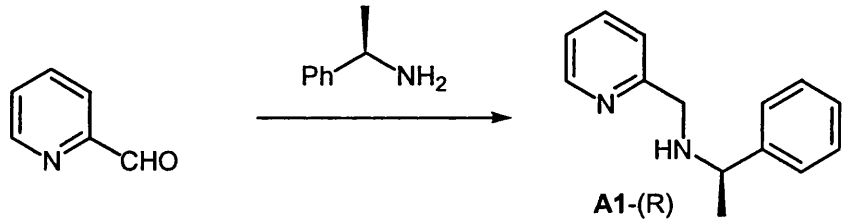
***N*-[(1*S*)-1-Phenylethyl]-*N*-[pyridin-2-ylmethyl]amine A1-(S)**



Pyridine-2-carboxaldehyde (94mg, 0.883 mmol) and (S)-α-methylbenzylamine (107mg, 0.883 mmol) were reacted under the general procedure to give a clear oil **A1**-(S) (133mg, 71% yield) which showed δ_H 8.56 (1H, m, CH_6), 7.60 (1H, app dt, $J_{4,6}$ 1.8 and $J_{4,5}$ =$J_{4,3}$ 7.7, CH_4), 7.12-7.38 (7H, m, ArH), 3.84 (1H, q, *J* 6.6, CH-Me), 3.75 (2H, s, CH_2), 1.99 (1H, br, NH), 1.41 (3H, d, *J* 6.6, CH_3); δ_C 159.6 (C), 149.3, 145.2 (C), 136.4, 128.5, 127.0, 126.8, 122.5, 121.9 (all CH), 57.9 (CH), 52.9 (CH_2) and 24.4 (CH_3); m/z (FAB^+) 213 (100%, M^++H) [found M^++H 213.13985. $C_{14}H_{16}N_2$ requires M^++*H* 213.13916]; ν_{max}/cm^{-1}

3061 (m), 3025 (m), 2967 (m), 2926 (m), 1591 (s), 1473 (s), 1450 (s), 1433 (s) and 761 (m); $[\alpha_D]^{20}$= -46.9 (c 13.1, acetone). Data identical to those in the literature.[30]

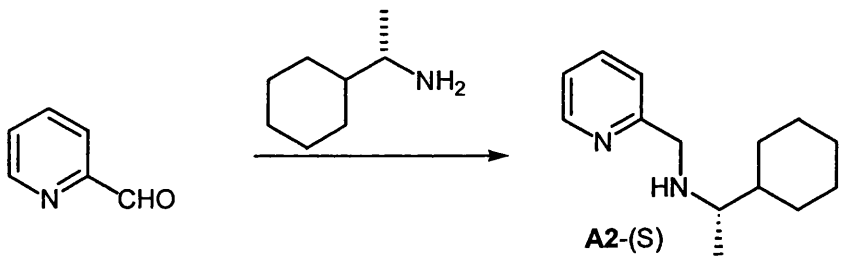
_N_-[(1_R_)-1-Phenylethyl]-_N_-(pyridin-2-ylmethyl]amine A1-(R)



A1-(R)

Pyridine-2-carboxaldehyde (106mg, 0.994 mmol) and (R)-α-methylbenzylamine (120mg, 0.994 mmol) were reacted under the general procedure to give a pale yellow oil **A1**-(R) (158mg, 75% yield) which showed δ_H 8.56 (1H, m, CH_6), 7.60 (1H, ddd, $J_{4,3}$ 7.7, $J_{4,5}$ 7.7 and $J_{4,6}$ 1.8, CH_4), 7.12-7.38 (7H, m, Ar-H), 3.84 (1H, q, J 6.6, CH-Me), 3.75 (2H, s, CH_2), 1.99 (1H, br, NH) and 1.41 (3H, d, J 6.6, CH_3); m/z (FAB$^+$) 213 (100%, M^++H) [found M^++H 213.13990. $C_{14}H_{16}N_2$ requires M^++H 213.13916]; $[\alpha_D]^{20}$= -12.0 (c 13.1, $CHCl_3$). Spectral data matches the enantiomeric product **A1**-(S).

_N_-[(1_S_)-1-Cyclohexylethyl]-_N_-(pyridin-2-ylmethyl]amine A2-(S)

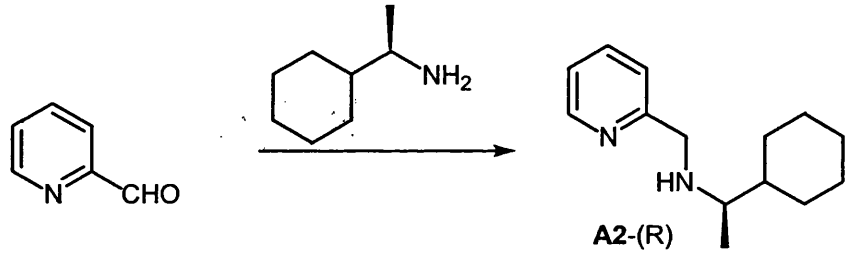


A2-(S)

Pyridine-2-carboxaldehyde (85mg, 0.798 mmol) and (S)-cyclohexylethylamine (101.mg, 0.798 mmol) were reacted under the general procedure to give a yellow oil **A2**-(S) (120mg, 69% yield) which showed δ_H 8.49 (1H, dd, $J_{6,5}$ 4.7 and $J_{6,4}$ 0.8, CH_6), 7.62 (1H, ddd, $J_{4,5}$ 7.7, $J_{4,3}$ 7.7 and $J_{4,6}$ 0.8, CH_4), 7.35 (1H, app d, $J_{5,4}$ 7.7, CH_5), 7.14 (1H, m, CH_3), 3.86 (1H, d, J 14 .1, CH_aH$_b$NH), 3.72 (1H, d, CH_bH$_a$NH), 2.57 (1H, q, J 6.6, CH-Me), 1.82 (1H,

br, NH), 1.03-1.16 (11H, m, CH_2 and CH) and 1.06 (3H ,d, *J* 6.6, Me); δ_C 207.4 (C), 160.9, 136.5, 122.7, 121.7 (all CH), 59.6 (CH-Me), 5206 (CH_2-N), 41.5 (CH_{cy}), 31.1, 30.9, 30.7, 26.6, 26.4 (all CH_2) and 16.6 (CH_3); m/z (FAB^+) 219 (80%, M^++H) [found M^++H 219.18595. $C_{14}H_{22}N_2$ requires M^++*H* 219.18612]; ν_{max}/cm^{-1} 2924 (s), 2852 (s), 1591 (s), 1449 (m), 1433 (m), 1373 (m) and 755 (m); $[\alpha_D]^{20}$ = +22 (c 1, $CHCl_3$).

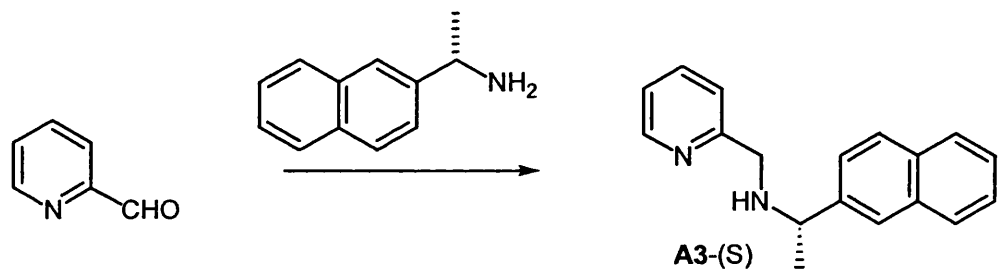
N-[(1*R*)-1-Cyclohexylethyl]-*N*-[pyridin-2-ylmethyl]amine A2-(R)



A2-(R)

Pyridine-2-carboxaldehyde (90mg, 0.846 mmol) and (R)-cyclohexylethylamine (107mg, 0.846 mmol) were reacted under the general procedure to give a yellow oil **A2**-(R) (130mg, 71% yield) which showed δ_H 8.49 (1H, dd, $J_{6,4}$ 0.9 and $J_{6,5}$ 4.7, CH_6), 7.62 (1H, ddd, $J_{4,5}$ 7.7, $J_{4,3}$ 7.7 and $J_{4,6}$ 0.9, , CH_4), 7.35 (1H, app.d, $J_{5,4}$ 7.7, CH_5), 7.14 (1H, m, CH_3), 3.88 (2H, s, *J* 14 .1, CH_2-NH), 2.56 (1H, q, *J* 6.6, CH-Me), 1.81 (1H, br, NH), 1.03-1.16 (11H, m, CH_2 and CH), 1.06 (3H ,d, *J* 6.6, :CH_3); m/z (FAB^+) 219 (100%, M^++H) [found M^++H 219.18696. $C_{14}H_{22}N_2$ requires M^++*H* 219.18612]; $[\alpha_D]^{20}$ = -44.3 (c 2.1, $CHCl_3$).

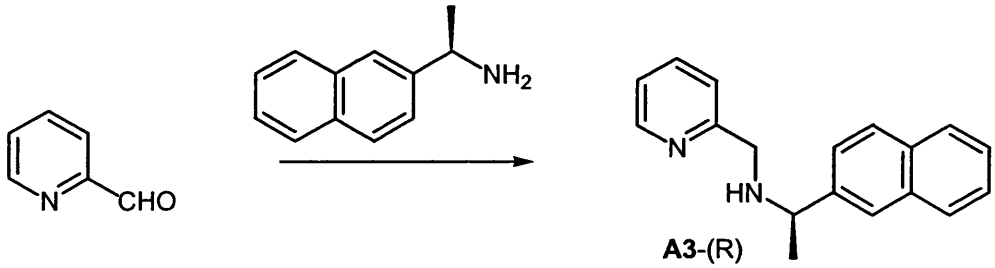
N-[(1*S*)-1-(2-Naphthyl)ethyl]-*N*-[pyridin-2-ylmethyl]amine A3-(S)



A3-(S)

Pyridine-2-carboxaldehyde (45mg, 0.418 mmol) and (S)-naphthylethylamine (71mg, 0.418 mmol) were reacted under the general procedure to give a pale orange oil **A3**-(S) (58mg, 53% yield) which showed δ_H 8.56 (1H, m, CH_6), 8.14-8.16 (1H, m Ar-H), 7.85-7.89 (1H, m Ar-H), 7.74-7.81 (2H, m, Ar-H), 7.59 (1H, ddd, $J_{4,5}$ 7.7, $J_{4,3}$ 7.7 and $J_{4,6}$ 1.8, CH_4), 7.41-7.52 (3H, m, ArH), 7.13-7.21 (2H, m, ArH), 4.76 (1H, q, *J* 6.6, CH-Me), 3.78 (2H, s, CH_2-NH), 1.82 (1H, br, NH), 1.55 (3H ,d, *J* 6.6, Me); δ_C 160.4 (C), 148.6 (CH), 140.4 (C), 136.1 (CH), 133.9 (C), 131.4 (C), 128.9, 127.7, 125.8, 125.3, 125.0, 124.8, 123.5, 121.9, 121.7 (all CH), 57.3 (CH_2), 53.3 (CH-Me) and 23.8 (CH_3); m/z (FAB$^+$) 263 (45%, M^++H) [found M^++H 263.15518. $C_{18}H_{18}N_2$ requires M^++*H* 263.15481]; ν_{max}/cm $^{-1}$ 3048 (m), 2969 (m), 2924 (m), 1589 (s), 1473 (s), 1433 (s) and 779 (s).

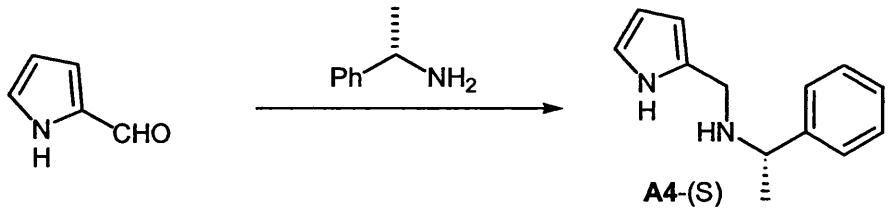
***N*-[(1*R*)-1-(2-Naphthyl)ethyl]-*N*-[pyridin-2-ylmethyl]amine A3-(R)**



A3-(R)

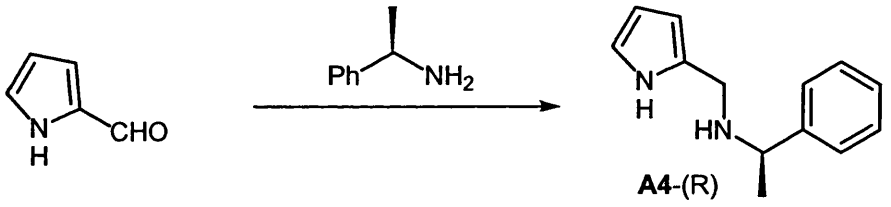
Pyridine-2-carboxaldehyde (65mg, 0.605 mmol) and (R)-naphthylethylamine (103mg, 0.605 mmol) were reacted under the general procedure to give a pale orange oil **A3**-(R) (67mg, 42% yield) which showed δ_H 8.56 (1H, m, CH_6), 8.12-8.14 (1H, m Ar-H), 7.83-7.87 (1H, m ArH), 7.72-7.79 (2H, m, ArH), 7.57 (1H, ddd, $J_{4,5}$ 7.7, $J_{4,3}$ 7.7 and $J_{4,6}$ 1.8, CH_4), 7.39-7.50 (3H, m, ArH), 7.12-7.22 (2H, m, ArH), 4.76 (1H, q, *J* 6.6, CHMe), 3.78 (2H, s, CH_2-NH), 1.82 (1H, br, NH,) and 1.55 (3H ,d, *J* 6.6, Me); m/z (FAB$^+$) 263 (45%, M^++H) [found M^++H 263.15550. $C_{18}H_{18}N_2$ requires M^++*H* 263.15481]. Spectral data matches the enantiomeric product **A3**-(S).

_N_-[(1_S_)-1-Phenylethyl]-_N_-[1_H_-pyrrol-2-ylmethyl]amine A4-(S)



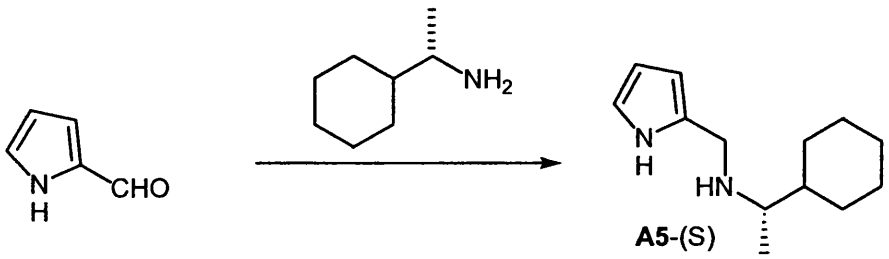
Pyrrole-2-carboxaldehyde (94mg, 0.995 mmol) and (S)-α-methylbenzylamine (120mg, 0.995 mmol) were reacted under the general procedure to give yellow oil **A4**-(S) (149mg, 75% yield) which showed δ_H 7.23-7.37 (5H, m, ArH), 6.71 (1H, m, CH), 6.10 (1H, dd, *J* 2.7 and *J* 5.7, CH), 5.96 (1H, br s, CH), 3.77 (1H, q, *J* 6.6, CH-Me), 3.62 (2H, s, CH_2NH), 2.12 (2H, br s, NH) and 1.36 (3H, d, *J* 6.6Hz, CH_3); δ_C 150.2 (CH), 144.7 (C), 130.2 (C), 128.6, 125.7, 117.2, 108.0, 106.1 (All CH), 57.5 (CH-Me), 44.2 (CH_2), 23.9 (CH_3); m/z (FAB^+) 201 (80%, M^++H) [found M^++H 201.13940. $C_{13}H_{16}N_2$ requires M^++*H* 201.13916]; ν_{max}/cm^{-1} 2971 (m), 2931 (m), 2860 (m), 1493 (s), 1451 (s), 1373 (m), 762 (m); $[\alpha_D]^{20}$ = -60.9 (c 12.2, acetone).

_N_-[(1_R_)-1-Phenylethyl]-_N_-[1_H_-pyrrol-2-ylmethyl]amine A4-(R)



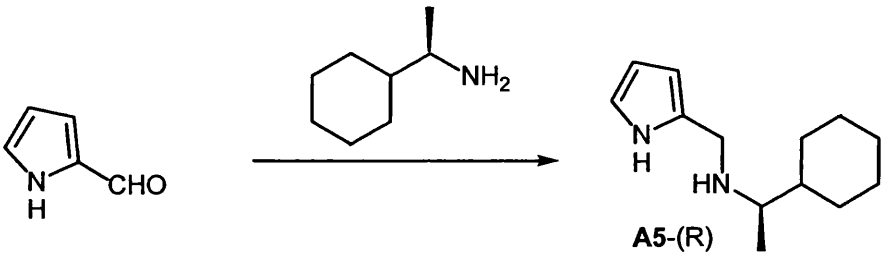
Pyrrole-2-carboxaldehyde (109mg, 1.146 mmol) and (R)-α-methylbenzylamine (139mg, 1.146 mmol) were reacted under the general procedure to give pale yellow oil **A4**-(R) (186mg, 81% yield) which showed δ_H 7.22-7.37 (5H, m, Ar-H), 6.71 (1H, m, CH_a), 6.11 (1H, dd, CH, *J* 2.7 and *J* 5.7), 5.96 (1H, br s, CH), 3.77 (1H, q, *J* 6.6, CH-Me), 3.62 (2H, s, CH_2NH), 2.12 (2H, br, NH), 1.36 (3H, d, *J* 6.6Hz, CH_3); m/z (FAB^+) 201 (80%, M^++H) [found M^++H 210.13961. $C_{13}H_{16}N_2$ requires M^++*H* 201.13916]; $[\alpha_D]^{20}$ = -78.3 (c 0.115, $CHCl_3$). Spectral data matches the enantiomeric product **A4**-(S).

_N_-[(1_S_)-1-Cyclohexylethyl]-_N_-[1_H_-pyrrol-2-ylmethyl]amine A5-(S)



Pyrrole-2-carboxaldehyde (75mg 0.785 mmol) and (S)-cyclohexylethylamine (100mg, 0.785 mmol) were reacted under the general procedure to give a yellow oil **A5**-(S) (111mg, 69% yield) which showed δ_H 6.73 (1H, m, CH), 6.11 (1H, dd, *J* 5.7 and *J* 2.7, CH), 6.01 (1H, br s, CH), 3.86 (1H, d, *J* 14 .1, C*H*$_a$H$_b$NH), 3.74 (1H, d, C*H*$_b$H$_a$NH), 2.51 (1H, m, *J* 6.6, CH-Me), 0.87-1.72 (11H, m, CH_2 and CH_{cy}) and 1.01 (3H ,d , *J* 6.6, Me); δ_C 148.3 (C), 117.1, 107.8, 106.0 (all CH), 57.2 (CH-Me), 44.0 (*C*H_2-NH), 42.7 (CH), 29.7, 27.9, 26.6, 26.5, 26.3 (all CH_2) and 16.2 (CH_3); m/z (FAB$^+$) 207 (55%, M^++H) [found M^++H 207.18671. $C_{13}H_{22}N_2$ requires M^++*H* 207.1861; ν_{max}/cm $^{-1}$ 2925 (m), 2851 (m), 1636 (s), 1558 (w), 1448 (m), 1427 (m) and 733 (m).

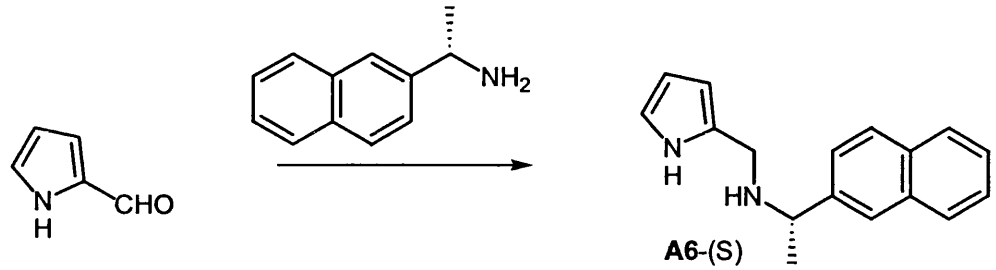
_N_-[(1_R_)-1-Cyclohexylethyl]-_N_-[1_H_-pyrrol-2-ylmethyl]amine A5-(R)



Pyrrole-2-carboxaldehyde (71mg, 0.748 mmol) and (R)-cyclohexylethylamine (95mg, 0.748 mmol) were reacted under the general procedure to give a yellow oil **A5**-(R) (103mg, 67% yield) which showed δ_H 6.73 (1H, m, CH), 6.09 (1H, dd, *J* 5.7 and *J* 2.7, CH), 6.01 (1H, br s, CH), 3.81 (1H, d, *J* 14 .1, C*H*$_a$H$_b$NH), 3.77 (1H, d, C*H*$_b$H$_a$NH), 2.52 (1H, m, *J* 6.6, CH-Me), 0.87-1.72 (11H, m) and 1.01 (3H, d, *J* 6.6, CH_3); m/z (FAB$^+$) 207

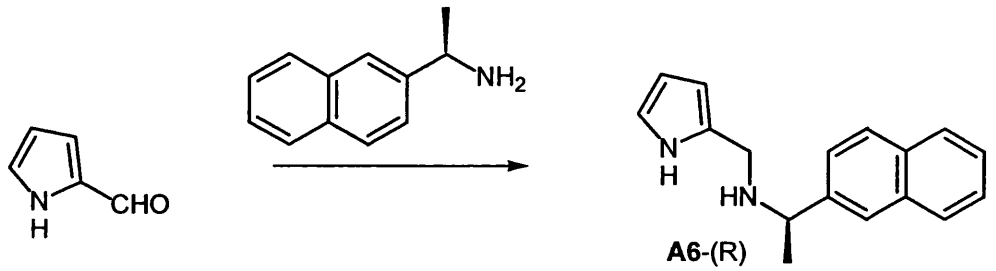
(70%, M^++H) [found M^++H 207.18626. $C_{13}H_{22}N_2$ requires M^++H 207.18612]; $[\alpha_D]^{20}$ = -37.5 (c 0.08, $CHCl_3$). Spectral data matches the enantiomeric product **A5**-(S).

***N*-[(1*S*)-1-(2-Naphthyl)ethyl]-*N*-[1*H*-pyrrol-2-ylmethyl]amine A6-(S)**



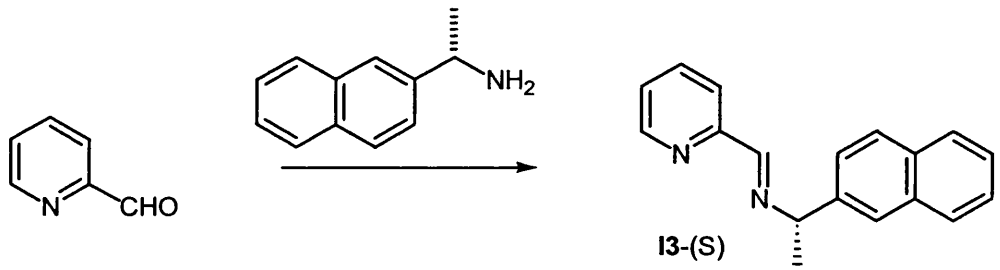
Pyrrole-2-carboxaldehyde (50mg, 0.525 mmol) and (S)-naphthylethylamine (90mg, 0.525 mmol) were reacted under the general procedure to give a pale yellow oil **A6**-(S) (79mg, 60% yield) which showed δ_H 8.09-8.12 (1H, m, ArH), 7.86-7.89 (1H, m, ArH), 7.74-7.78 (1H, m, ArH), 7.64-7.66 (1H, m, ArH), 7.46-7.53 (3H, m, ArH), 6.73 (1H, m, CH), 6.11 (1H, dd, *J* 2.7 and *J* 5.7, CH), 5.97 (1H, br s, CH), 4.69 (1H, q, *J* 6.6 , C*H*-Me), 4.39 (2H, s, CH_2), 2.15 (1H, br, NH) and 1.52 (3H ,d, *J* 6.6, CH_3); δ_C 140.4 (C), 134 (C), 131.3 (C), 130.2 (C), 127.5, 126.0, 125.9, 125.7, 125.5, 122.9, 122.6, 117.1, 108.1, 106.2 (All CH), 52.7 (*C*H-Me), 44.3 (CH_2) and 23.2 (CH_3); m/z (FAB^+) 251 (85%, M^++H) [found M^++H 251.15538. $C_{17}H_{18}N_2$ requires M^++H 251.15481]; ν_{max}/cm $^{-1}$ 3051 (m), 2970 (m), 1595 (m), 1437 (m) and 778 (s); $[\alpha_D]^{20}$= +318.7 (c 0.16, $CHCl_3$).

***N*-[(1*R*)-1-(2-Naphthyl)ethyl]-*N*-[1*H*-pyrrol-2-ylmethyl]amine A6-(R)**



Pyrrole-2-carboxaldehyde (58mg, 0.611 mmol) and (S)-naphthylethylamine (104mg, 0.611 mmol) were reacted under the general procedure to give a pale yellow oil **A6**-(R) (99mg, 65% yield) which showed δ_H 8.09-8.12 (1H, m, Ar-H), 7.86-7.89 (1H, m, Ar-H), 7.74-7.78 (1H, m, Ar-H), 7.64-7.66 (2H, m, Ar-H), 7.46-7.53 (3H, m, ArH), 6.73 (1H, m, CH), 6.11 (1H, dd, *J* 2.7 and *J* 5.7, CH), 5.97 (1H, br s, CH), 4.69 (1H, q, *J* 6.6, CH-Me), 4.39 (2H, s, CH_2), 2.15 (1H, br, NH) and 1.52 (3H, d, *J* 6.6, CH_3); m/z (FAB^+) 251 (85%, M^++H) [found M^++H 251.15475. $C_{17}H_{18}N_2$ requires M^++*H* 251.15481]. Spectral data matches the enantiomeric product **A6**-(S).

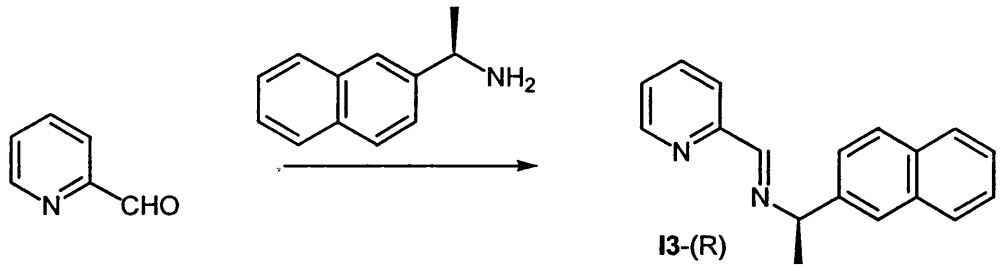
***N*-[(1*S*)-1-(2-Naphthyl)ethyl]-*N*-[pyridin-2-ylmethylene]amine I3-(S)**



I3-(S)

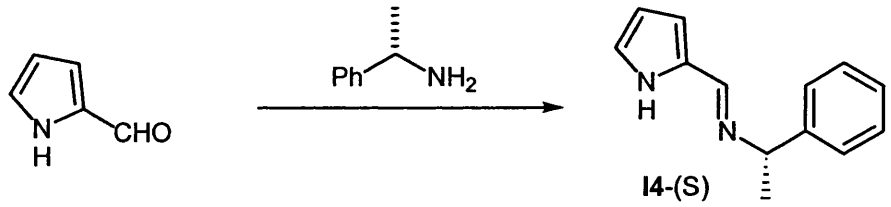
Pyridine-2-carboxaldehyde (50mg, 0.467 mmol) and (S)-naphthylethylamine (80mg, 0.467 mmol) were reacted under the general procedure to give a pale yellow oil **I3**-(S) (120mg, 100% yield) which showed δ_H 8.65 (1H, m, CH_6), 8.51 (1H, s, CH=N), 8.23 (1H, d, *J* 7.4, CH), 8.11-8.16 (1H, m, ArH),7.85-7.89 (1H, m, ArH), 7.72-7.79 (3H, m, ArH), 7.45-7.56 (3H, m, ArH), 7.31 (1H, ddd, *J* 7.3, *J* 4.8 and *J* 1.4, ArH), 5.47 (1H, q, *J* 6.6, CH-Me) and 1.76 (3H, d, *J* 6.6, Me); δ_C 160.7 (CH), 154.8 (C), 149.3(CH), 140.3 (C), 136.6 (CH), 134 (C), 130.7 (C), 128.9, 127.5, 125.9. 125.4, 124.8, 124.1, 123.5, 122.7, 121.4 (All CH), 65.2 (*C*H-Me) and 24.1 (CH_3); m/z (FAB^+) 261 (75%, M^++H) [found M^++H 261.13966. $C_{18}H_{16}N_2$ requires M^++*H* 261.13916]; ν_{max}/cm^{-1} 3053 (m), 2972 (m), 2926 (m), 2863 (m), 1646 (s), 1467 (m), 1436 (m) and 778 (m); $[\alpha_D]^{20}$ = +156 (c 0.5, $CHCl_3$).

_N_-[(1_R_)-1-(2-Naphthyl)ethyl]-_N_-[pyridin-2-ylmethylene]amine I3-(R)



Pyridine-2-carboxaldehyde (55mg, 0.514 mmol) and (S)-naphthylethylamine (88mg, 0.514 mmol) were reacted under the general procedure to give a pale yellow oil **I3**-(R) (142 mg, 100% yield) which showed δ_H 8.65 (1H, m, CH_6), 8.51 (1H, s, CH=N), 8.23 (1H, d, *J* 7.4, ArH), 8.11-8.16 (1H, m, ArH), 7.85-7.89 (1H, m, ArH), 7.72-7.79 (3H, m, ArH), 7.45-7.56 (3H, m, ArH), 7.31 (1H, ddd, *J* 7.4, *J* 4.8 and *J* 1.3, ArH), 5.47 (1H, q, *J* 6.6, CH-Me) and 1.76 (3H, d, *J* 6.6, CH_3); m/z (FAB^+) 261 (75%, M^++H) [found M^++H 261.13879. $C_{18}H_{16}N_2$ requires M^++H 261.13916]; $[\alpha_D]^{20}$ = -170.16 (c 1.81, $CHCl_3$). Spectral data matches the enantiomeric product **I3**-(S).

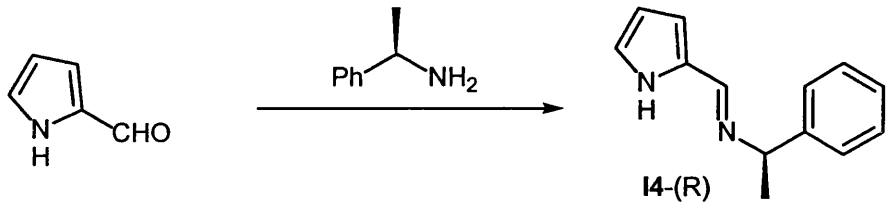
_N_-[(1_S_)-1-Phenylethyl]-_N_-[1_H_-pyrrol-2-ylmethylene]amine I4-(S)



Pyrrole-2-carboxaldehyde (63mg, 0.663 mmol) and (S)-α-methylbenzylamine (80.mg, 0.663 mmol) were reacted under the general procedure to give a pale yellow oil **I4**-(S) (142mg, 100% yield) which showed δ_H 8.11 (1H, s, CH=N), 7.20-7.34 (5H, m, Ar-H), 6.84 (1H, m, CH), 6.48 (1H, dd, *J* 5.8 and *J* 2.7, CH), 6.20 (1H, m, CH), 4.44 (1H, q, *J* 6.6, CH-Me), 3.35 (1H, br, NH), 1.55 (3H, d, *J* 6.6, CH_3); δ_C 150.7 (CH), 144.7 (C), 129.7 (C), 128.4, 126.9, 126.5, 125.6, 122.3, 115.2, 109.6 (all CH), 66.7 (CH=N), 51.2 (CHMe) and 24.1 (CH_3); m/z (FAB^+) 199 (100%, M^++H) [found M^++H 199.12345. $C_{13}H_{14}N_2$ requires

M^++*H* 199.12351]; ν_{max}/cm $^{-1}$ 2969 (m), 2927 (m), 2858 (m), 1634 (s), 1492 (s), 1450 (s), 1421 (s) and 763 (m); $[\alpha_D]^{20}$ = +178 (c 17, acetone).

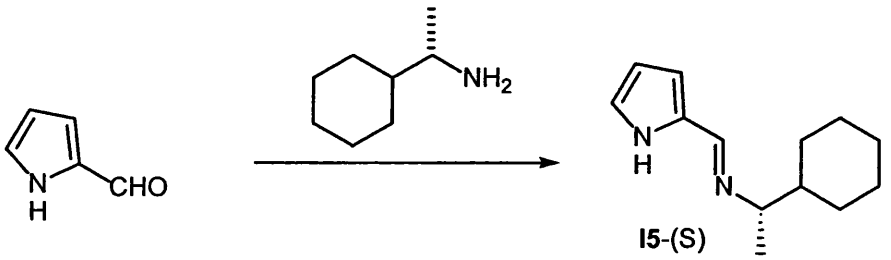
N-[(1*R*)-1-Phenylethyl]-*N*-[1*H*-pyrrol-2-ylmethylene]amine I4-(R)



I4-(R)

Pyrrole-2-carboxaldehyde (66mg, 0.695 mmol) and (R)-α-methylbenzylamine (84mg, 0.695 mmol) were reacted under the general procedure to give a pale yellow oil **I4**-(R) (149mg, 100% yield) which showed δ_H 8.11 (1H, s, CH=N), 7.20-7.34 (5H, m, Ar-H), 6.84 (1H, m, CH), 6.48 (1H, m, CH), 6.20 (1H, m, CH), 4.44 (1H, m, *J* 6.6, CH-Me), 3.35 (1H, br, NH) and 1.55 (3H, d, *J* 6.6, CH_3); m/z (FAB$^+$) 199 (100%, M^++H) [found M^++H 199.12367. $C_{13}H_{14}N_2$ requires M^++*H* 199.12351]; $[\alpha_D]^{20}$ = -139.5 (c 0.43, $CHCl_3$). Spectral data matches the enantiomeric product **I4**-(S).

N-[(1*S*)-1-Cyclohexylethyl]-*N*-[1*H*-pyrrol-2-ylmethylene]amine I5-(S)

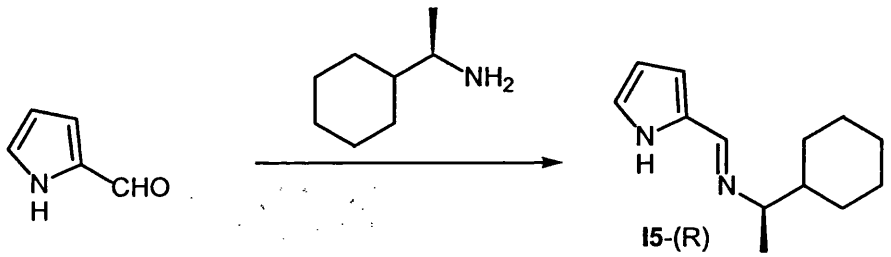


I5-(S)

Pyrrole-2-carboxaldehyde (65mg, 0.684 mmol) and (S)-cyclohexylethylamine (87mg, 0.684 mmol) were reacted under the general procedure to give a pale yellow oil **I5**-(S) (153mg, 100% yield) which showed δ_H 7.95 (1H, s, CH=N), 6.90 (1H, m, ArH), 6.49 (1H, ddd, *J* 1.5, *J* 3.6 and *J* 9, ArH), 6.45 (1H, m, ArH), 2.92 (1H, m, *J* 6.4, CH-Me), 0.81-1.81 (11H, m) and 1.17 (3H, d, *J* 6.4, CH_3); δ_C 129.9 (C), 121.7, 114.4, 109.4 (all CH), 71.2

(CH=N), 51.2 (CH-Me), 43.9 (CH), 29.9, 28.4, 26.7, 26.5, 26.3 (all CH_2) and 19.9 (CH_3); m/z (FAB$^+$) 205 (100 %, M$^+$+H) [found M$^+$+H 205.17082. $C_{13}H_{20}N_2$ requires M^++H 205.17046]; ν_{max}/cm $^{-1}$ 2924 (m), 2850 (m), 1636 (s), 1448 (s), 1421 (s) and 732 (m); $[\alpha_D]^{20}$ = +121 (c 1, toluene). Data identical to those in the literature.[13]

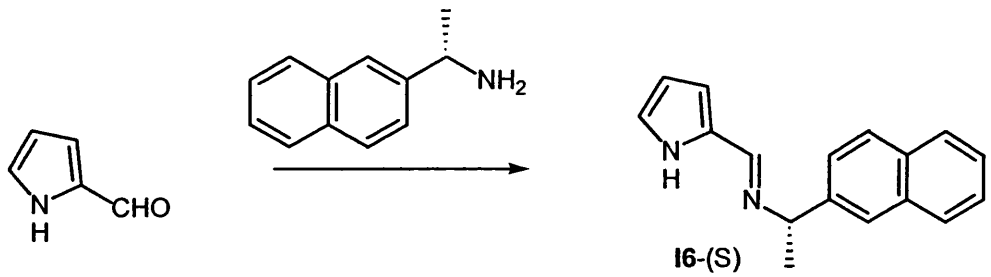
_N_-[(1*R*)-1-Cyclohexylethyl]-_N_-[1*H*-pyrrol-2-ylmethylene]amine I5-(R)



I5-(R)

Pyrrole-2-carboxaldehyde (65mg, 0.684 mmol) and (R)-cyclohexylethylamine (87mg, 0.684 mmol) were reacted under the general procedure to give a pale yellow oil **I5**-(R) (152mg, 100% yield) which showed δ_H 7.95 (1H, s, CH=N), 6.87 (1H, br s, ArH), 6.87 (1H, m, ArH), 6.45 (1H, m, ArH), 2.92 (1H, m, *J* 6.4, CH-Me), 0.81-1.81 (11H, m) and 1.17 (3H, d, *J* 6.4, CH_3); m/z (FAB$^+$) 205 (100 %, M$^+$+H) [found M$^+$+H 205.17118. $C_{13}H_{20}N_2$ requires M^++H 205.17046]; $[\alpha_D]^{20}$= -131 (c 1, toluene). Data identical to those in the literature.[13]

_N_-[(1*S*)-1-(2-Naphthyl)ethyl]-_N_-[1*H*-pyrrol-2-ylmethylene]amine I6-(S)

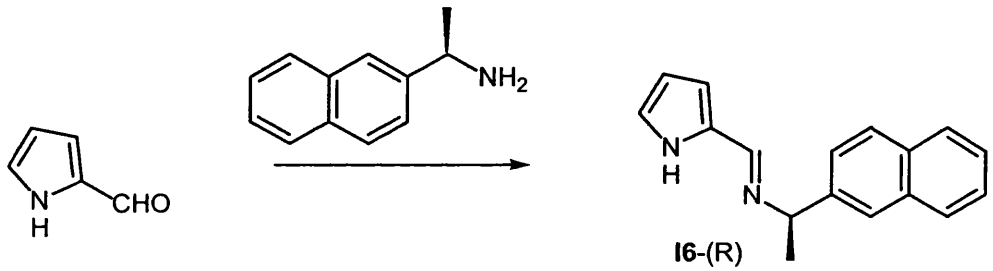


I6-(S)

Pyrrole-2-carboxaldehyde (60mg, 0.631 mmol) and (S)-naphthylethylamine (108mg, 0.631 mmol) were reacted under the general procedure to give a yellow oil **I6**-(S) (168mg, 100%

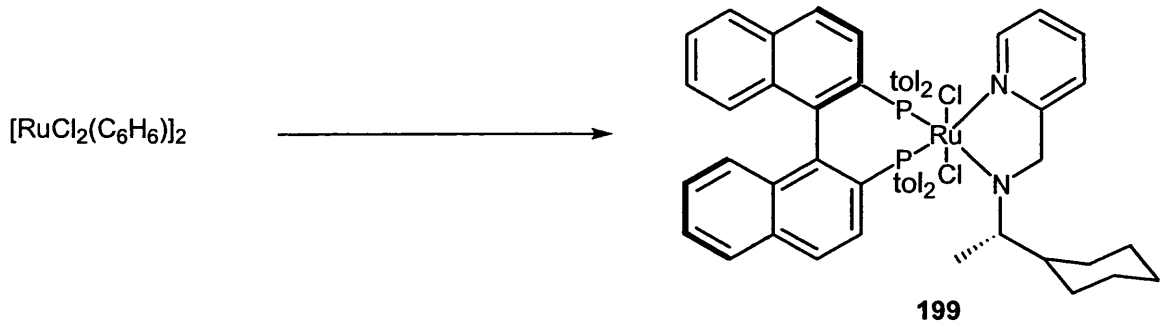
yield) which showed δ_H 8.17 (1H, s, CH=N), 8.02-8.08 (1H, m, Ar-H), 7.84-7.88 (1H, m Ar-H), 7.68-7.77 (2H, m, Ar-H), 7.44-7.54 (3H, m, ArH), 6.88 (1H, m, ArH), 6.45 (1H, dd, *J* 1.4 and *J* 3.6, ArH), 6.21 (1H, m, ArH), 5.30 (1H, q, *J* 6.6, CH-Me) and 1.70 (3H, d, *J* 6.6, CH_3); δ_C 150.7 (CH), 143.2, 140.8, 133.9, 130.7 (all C), 128.9, 127.6, 127.3, 126.3. 126.0, 125.6, 125.4, 114.8, 109.6 (all CH), 64 (CH=N), 46.2 (CH-Me) and 24.7 (CH_3); m/z (FAB^+) 249 (100%, M^++H) [found M^++H 249.13927. $C_{17}H_{16}N_2$ requires M^++H 249.13916]; ν_{max}/cm^{-1} 2969 (m), 2927 (m), 2863 (m), 1633 (s), 1446 (s), 1421 (s), 777 (m);

N-[(1*R*)-1-(2-Naphthyl)ethyl]-N-[1*H*-pyrrol-2-ylmethylene]amine I6-(R)



Pyrrole-2-carboxaldehyde (60mg, 0.631 mmol) and (R)- naphthylethylamine (108mg, 0.631 mmol) were reacted under the general procedure to give a yellow oil **I6**-(R) (168mg, 100% yield) which showed δ_H 8.17 (1H, s, CH=N), 8.02-8.08 (1H, m, ArH), 7.84-7.88 (1H, m ArH), 7.68-7.77 (2H, m, ArH), 7.44-7.54 (3H, m, ArH), 6.88 (1H, m, ArH), 6.45 (1H, dd, *J* 1.4 and *J* 3.6, ArH), 6.21 (1H, m, CH), 5.30 (1H, q, *J* 6.6, CH-Me) and 1.70 (3H, d, *J* 6.6, Me); m/z (FAB^+) 249 (95%, M^++H) [found M^++H 249.13932. $C_{17}H_{16}N_2$ requires M^++H 249.13916]; $[\alpha_D]^{20}$ = -118.5 (c 0.135, $CHCl_3$). Spectral data matches the enantiomeric product **I6**-(S).

[(R)-(+)-2,2'-*Bis*(di-*p*-tolyl-phosphino)-1,1'-binaphthyl][2*N*-[(1*S*)-1-Cyclohexylethyl]-*N*-(pyridin-2-ylmethyl)amine]{μ-dichloro}ruthenium 199



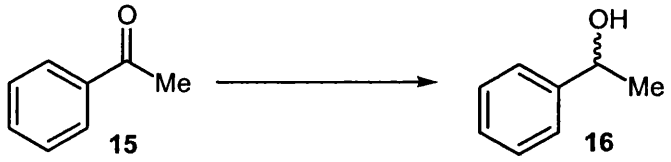
To a round bottom flask fitted with a condenser was added $[RuCl_2(C_6H_6)]_2$ (200 mg, 0.4 mmol) and (R)-tol-BINAP (577 mg, 0.85 mmol) in dry THF (20 mL) under a nitrogen atmosphere. The mixture was brought to reflux for 15 minutes then cooled down to room temperature, and treated with *N*-[(1*S*)-1-cyclohexylethyl]-*N*-(2-pyridinylmethyl)amine **A2**-(S) (0.85 mmol). After stirring at room temperature for a further 4 hours the solvent was evaporated *in vacuo*, the residue dissolved in DCM (10 mL) and solid residues were removed by filtration. The filtrate was concentrated to about 1 mL, and precipitated with ether (10 mL) to afford a light brown powder (704 mg. 66% yield). The supernatant was removed and the resulting solid was dried under reduced pressure to afford the desired complex **199** as a light brown powder in 66% conversion which showed δ_H 6.37-8.69 (44H, m, ArH), 3.88 (2H, s, CH_2NH), 2.74 (1H, m, NH), 2.51 (1H, m, CHMe), 1.12-1.35 (11H, m) and 1.14 (3H, d, Me); δ_P 37.1 (1P, d, *J* 63.2), 29.5 (1P, d, *J* 63.2), m/z (FAB^-) 1067 (45%, M^--H), 219 (32), 679 (9), 778 (22) [Found 1067.27457 $C_{62}H_{62}Cl_2N_2P_2Ru$ requires 1067.27304];

General procedure for hydrosilylation used to study the influence of ketone structure on reaction yield and selectivity

In a round bottomed flask under a nitrogen atmosphere was added $[RuCl_2(C_6H_6)]_2$ (1 mol%) and (R)-Tol-BINAP (2 mol%) in dry THF (2 ml). The mixture was refluxed for 15

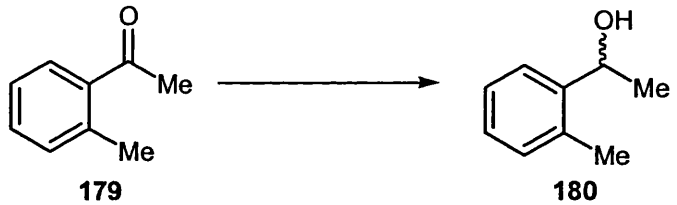
minutes after which time amine **A2**-(S) (5mg, 2 mol%) was added. The mixture was stirred at room temperature for 3 hours. The ketone (0.5 mmol) was then added followed by diphenylsilane (1 mmol, 2 eq.). The reaction mixture was stirred under nitrogen for 16 hours. A solution of methanol (1 mL) and 1N hydrochloric acid (1 mL) was then added to hydrolyse the silyl ether product and after 15 minutes stirring the reaction mixture was extracted with ether (3 x 10 mL). The organic extracts were washed with brine dried over Na_2SO_4 and evaporated. The crude products were then analysed by ^1H NMR. Yields and enantioselectivities for these reactions are given in tabular form in chapter 3.

1-Phenylethanol 16



Acetophenone **15** (0.5 mmol) was reacted under the general protocol (page 151) to afford the alcohol product **16** as a colourless oil (40% conversion, 63% e.e.) which showed δ_H 7.23-7.36 (5H, m, ArH), 4.87 (1H, q, *J* 6.4, CH-Me), 2.04 (1H, br s, OH) and 1.48 (3H, d, *J* 6.5, CH_3); ν_{max} /cm $^{-1}$ 3356 (s), 2973 (m), 2927 (m), 1600 (m) and 1451 (m). HPLC was performed using a Chiralcel OD, 98:2 hexane/IPA, λ = 254 nm, 1mL/min, R_t (R)-**16** = 14.2 mins and R_t (S)-**16** = 18.4 mins. Data identical to those found in the literature.[155]

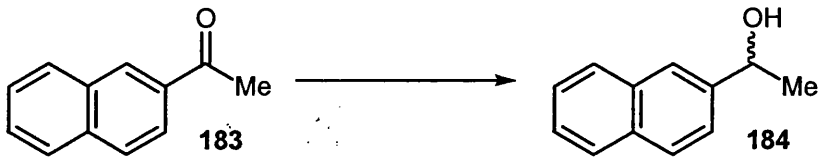
1-(2-Methylphenyl)ethanol 180



o-Methylacetophenone **179** (65 μL, 0.5 mmol) was reacted under the general protocol (page 151) to afford the alcohol product **180** as a colourless oil (59% conversion, 20% e.e.)

which showed δ_H 7.1-7.6 (4H, m, ArH), 5.13 (1H, q, *J* 6.4, CH-Me), 2.35 (3H, s, *o*-Me), 1.70 (1H, br s, OH) and 1.47 (3H, d, *J* 6.4, CH_3); ν_{max} /cm $^{-1}$ 3345 (s), 2971 (m), 2927 (m), 1488 (m) and 1460 (m). HPLC was performed using a Chiralcel OD, 98:2 hexane/IPA, λ = 254 nm, 1mL/min, R_t (R)-**180** = 14.7 mins and R_t (S)-**180** = 16.1 mins. Data identical to those found in the literature.[155]

1-(2-Naphthyl)ethanol 184



2-Acetonaphthone **183** (85mg, 0.5 mmol) was reacted under the general protocol (page 151) to afford the alcohol product **184** as a white solid (88% conversion, 65% e.e.) m.p. 69°C which showed δ_H 7.65-7.91 (4H, m, ArH), 7.32-7.54 (3H, m, Ar-H), 4.95 (1H, q, *J* 6.4, CH-Me), 2.43 (1H, br s, OH) and 1.23 (3H, d, *J* 6.4, Me); HPLC was performed using a Chiralcel OD, 98:2 hexane/IPA, λ = 254 nm, 1mL/min, R_t (R)-**184** = 19.2 mins and R_t (S)-**184** = 22.7 mins. Data identical to those found in the literature.[155]

1-(4-Methoxyphenyl)ethanol 186

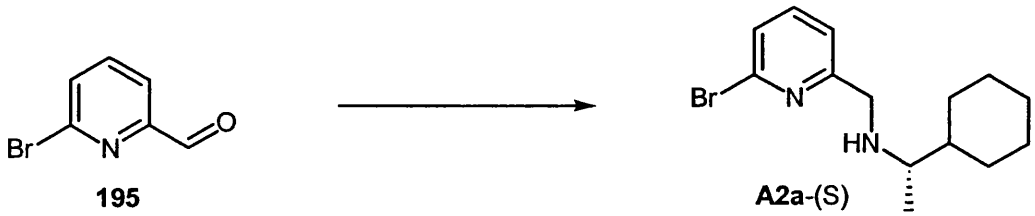
p-Methoxyacetophenone **185** (85mg, 0.5 mmol) was reacted under the general protocol (page 151) to afford the alcohol product **186** as a colorless oil (90% conversion, 65% e.e.) which showed δ_H 7.85-7.95 (2H, m, ArH), 7.25-7.35 (2H m, ArH), 4.85 (1H, q, *J* 6.5, CH-Me), 3.82 (3H, s, OMe), 1.93 (1H, br s, OH) and 1.50 (3H, d, *J* 6.5, CH_3); ν_{max}/cm $^{-1}$ 3356 (s), 2972 (m), 2924 (m), 1451 (m) and 1415 (m). HPLC was performed using a Chiralcel

OD, 98:2 hexane/IPA, λ = 254 nm, 1mL/min, R_t (R)-**186** = 20.3 mins and R_t (S)-**186** = 22.8 mins. Data identical to those found in the literature.[155]

Parallel screening of chiral phosphines in the hydrosilylation of acetophenone with "Noyori" type complexes

$[RuCl_2(C_6H_6)]_2$ (1μmol, 1 eq.) was weighed into in 45 vials, to screen against the eight chiral phosphines available the set of vials was divided into eight subsets of five vials. To each of these vials in the subsets was added the respective chiral phosphine (110 μL of a 10 mM solution in THF, 1.1 μmol, 1.1 eq.) under an argon atmosphere, each vial was then sealed with a screw cap and put in an oven at 60-62°C for 15 mins to allow the formation of the respective metal ligand complexes (a library of eight sets of phosphine metal complexes where each subset has five vials as its component was thus generated). The library of complexes was then cooled to room temperature and to each vial of the metal/phosphine library was added one of a range of five chiral diamines (110 μL, 1.1 μmol of a 10 mM solution in THF, 1.1 eq.) in the argon box (thus fourty individual complexes were generated in a parallel manner). Complex formation was allowed 2 hours after which time diphenylsilane (37 μL in each of the 45 vials, 200 eq.) and acetophenone (100 μL of a 1M solution in THF, 100 μmol, 100 eq.) were added to each individual vial. All the reactions were left in the argon box overnight (18 hours). To hydrolyse the reaction products, a mixture 1:1 methanol/1M HCl (200 μL) was added in each vial. These reactions were then transfered in to GC vials and analysed by GC using a Carbowax column. The results of this screening are given in tabular form in chapter 3.

_N_-[(1_S_)-1-cyclohexylethyl]-_N_-[6-Bromo-pyridin-2-ylmethyl]amine A2a-(S)



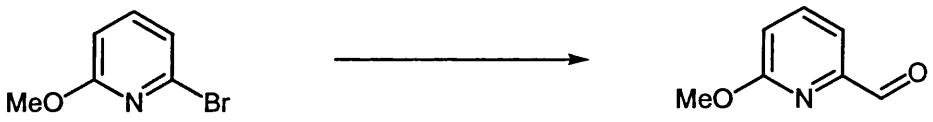
In a round bottom flask under nitrogen were added 6-bromopyridine-2-carbaldehyde **195** (30mg, 0.16 mmol) and (S)-cyclohexylethylamine (20mg, 0.16 mmol) in 2 mL of dry THF. Sodium triacetoxyborohydride (47.5 mg) was added and the mixture was stirred at room temperature until completion. The reaction mixture was then quenched by adding aqueous saturated $NaHCO_3$, the organic layer was extracted twice with EtOAc, dried over Na_2SO_4 and the solvent was evaporated *in vacuo* to give a brown oil which was purified by column chromatography (eluent DCM/MeOH 95:5) to afford a pale yellow oil **A2a**-(S) (44 mg. 92% yield) which showed δ_H 7.49 (1H, dd, *J* 7.8, CH_4), 7.33 (2H, app d, *J* 7.8, CH_3 and CH_5), 3.92 (2H, s, CH_2N), 2.44-2.50 (1H, m, CHN), 1.00-1.79 (11H, m) and 1.02 (3H, d, *J* 6.6, Me); δ_C 162.3 (CBr), 141.3 (CCH_2), 138.5, 125.9, 120.9 (all CH), 57.4 (CH-Me), 52.4 (CH_2N), 43.0 (CH_{cy}), 29.9, 28.1, 26.8, 26.7, 26.6 (all CH_2) and 16.8 (CH_3); m/z (FAB^+) 297 (100%, M^++H) [Found M^++H 297.09562. $C_{14}H_{21}N_2Br$ requires M^++*H* 297.11663]; $[\alpha_D]^{20}$ = +12.9 (c 3.1, $CHCl_3$).

2-Bromo-6-methoxypyridine 196

To a stirred solution of 2,6-dibromopyridine **146** (1g, 4.22 mmol) in dry methanol (5 mL) was added sodium methoxide (1.9 mL of a 25% w/v solution in MeOH, 7.2 mmol). The mixture was refluxed for 25 hours and poured into cold 5% $NaHCO_3$ (5mL). The mixture

was then extracted with ether (3 x 5 mL), washed with brine (5mL), dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography (eluent petrol/EtOAc 9:1) to afford a clear colourless oil **196** (525 mg. 66 %); δ_H 7.40 (1H, dd, *J* 8.2 and 8.2, ArH), 7.04 (1H, app d, *J* 8.2, CH), 6.67 (1H, app d, *J* 8.2, CH) and 3.92 (3H, s, Me); δ_C 163.5 (COMe), 140.1 (CH), 138.4 (CBr), 120.0 (CH), 109.2 (CH) and 54.0 (CH_3); m/z (EI^+) 188 (100%, M^++H) [Found M^++H 187.95277. C_6H_6ONBr requires M^++H 187.99110]. Data identical to those in the literature.[150]

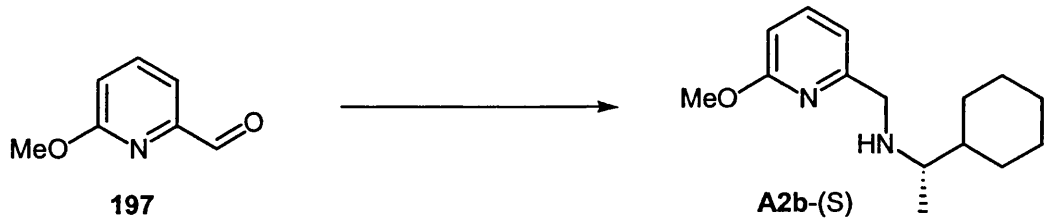
6-Methoxypyridine-2-carbaldehyde 197



196 **197**

To a stirred solution of 2-bromo-6-methoxypyridine **196** (2g, 8.45 mmol) in THF (6 mL) maintained at -78°C was added a solution of n-butyl lithium (5.3 mL of a 1.6 M solution in hexanes, 8.45 mmol) and after a further 0.5 hour, dimethylformamide (1.35 mL, 17.5 mmol) in THF (5 mL). The solution was maintained at -78 C for a further hour before bringing to room temperature and quenching with brine (3 mL). The organic layer was separated and the aqueous layer extracted with ether (3 x 40 mL). The combined organic extracts were washed with water (40 mL), brine (40 mL) then dried ($MgSO_4$) and evaporated. The crude product was then purified was by column chromatography (20% ethyl acetate/ petrol) to give the desired aldehyde **197** (1.2 g, 80 %) as a clear colourless oil which showed δ_H 9.96 (1H, s, C*H*O), 7.73 (1H, dd, *J* 7.4 and 7.4, ArH), 7.56 (1H, dd, *J* 7.4 and 1.1, ArH), 6.97 (1H, dd, *J* 7.4 and 1.1, ArH) and 4.03 (3H, s, CH_3); δ_C 192.8 (CHO), 164.2 (COMe), 150.0 (CBr), 138.9, 116.2, 115.4 (all CH) and 53.7 (CH_3); ν_{max}/cm^{-1} 2956 (m), 2923 (m), 2852 (m), 1720 (s), 1598 (m), 1578 (m), 1470 (s) and 1274 (m); Data identical to those in the literature.[150]

N-[(1S)-1-Cyclohexylethyl]-N-[(6-methoxy-pyridin-2-ylmethyl]amine A2b-(S)



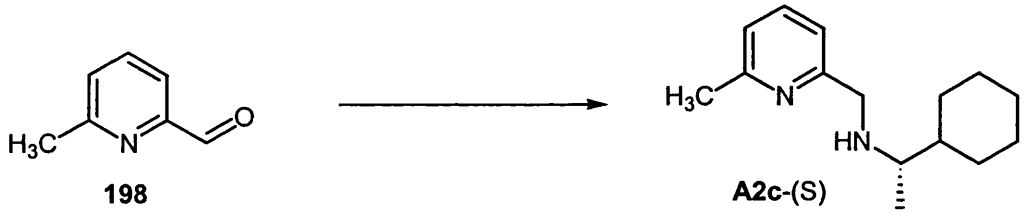
In a round bottom flask under nitrogen were added 6-methoxypyridine-2-carbaldehyde **197** (50mg, 0.37 mmol) and (S)-cyclohexylethylamine (47mg, 0.37 mmol) in 2 mL of dry THF. Sodium triacetoxyborohydride (110mg, 1.4 eq.) was added and the mixture was stirred at room temperature until no starting material was left. The reaction mixture was then quenched by adding aqueous saturated $NaHCO_3$ (5mL), the organic layer was extracted with EtOAc (2 x 10 mL), dried over Na_2SO_4 and evaporated to give a brown oil. The crude product was purified by column chromatography (eluent DCM/MeOH 95:5) to afford a pale yellow oil **A2b**-(S) (87mg, 95% yield) which showed δ_H 7.51 (1H, m, ArH), 6.82 (1H, m, ArH), 6.59 (1H, m, ArH), 3.92 (3H, s, OCH_3), 3.89 (2H, s, CH_2N), 2.66-2.52 (1H, m, CHN), 1.02-1.81 (11H, m) and 1.06 (3H, d, *J* 6.5, Me); δ_C 157.7 (COMe), 138.7 (*C*-CH_2), 116.3, 108.6, 98.4 (all CH), 57.2 (CH-N), 52.4 (CH_2-N), 51.8 (CH_3-O), 42.9 (CH_{cy}), 29.8, 28.2, 26.8, 26.7, 26.6 (all CH_2) and 16.6 (CH_3); m/z (FAB$^+$) 249.1 (100%, M^++H) [Found M^++H 249.19675. $C_{15}H_{24}N_2O$ requires M^++*H* 249.19669]; ν_{max}/cm $^{-1}$ 2924 (m), 2851 (m), 1578 (m), 1456 (m), 1413 (w), 1306 (m) and 1261 (m); $[\alpha_D]^{20}$ = +10 (c 8, $CHCl_3$).

6-Methyl-2-pyridine carbaldehyde 198

To a stirred solution of 2-bromo-6-methylpyridine (500mg, 2.89 mmol) in THF (3 mL) maintained at -78°C was added a solution of n-butyl lithium (1.8 mL of a 1.6 M solution in

hexanes, 2.89 mmol); after a further 0.5 hour dimethylformamide (0.67 mL, 8.67 mmol) was added. The solution was maintained at -78 C for a further hour before bringing to room temperature and quenching with brine (3 mL). The organic layer was separated and the aqueous layer extracted with ether (3 x10 mL) the combined organic extracts were washed with water (10 mL) and brine (10 mL) then dried and evaporated. The crude product was purified by column chromatography (20% ethyl acetate/petrol as eluent) to give the desired aldehyde **198** (314mg, 90% yield) as a clear colourless oil which showed δ_H 10.0 (1H, s, CHO), 7.74-7.79 (2H, m, CH), 7.39 (1H, dd, *J* 6.6 and *J* 2.3, ArH) and 2.67 (3H, s, CH_3); δ_C 193.4 (CHO), 159.0 (CMe), 152.1 (*C*CHO), 136.9, 127.5, 118.9 (all CH) and 24.3 (CH_3); m/z (EI^+) 122 (100%, M^++H) [Found M^++H 122.06011. C_7H_7NO requires $M^+ + H$ 122.06059]; ν_{max}/cm^{-1} 2924 (m), 2853 (m), 1713 (s). 1592 (m) and 1458 (m).

N-[(1*R*)-1-Cyclohexylethyl]-*N*-[6-methyl-pyridin-2-ylmethyl]amine A2c-(S)

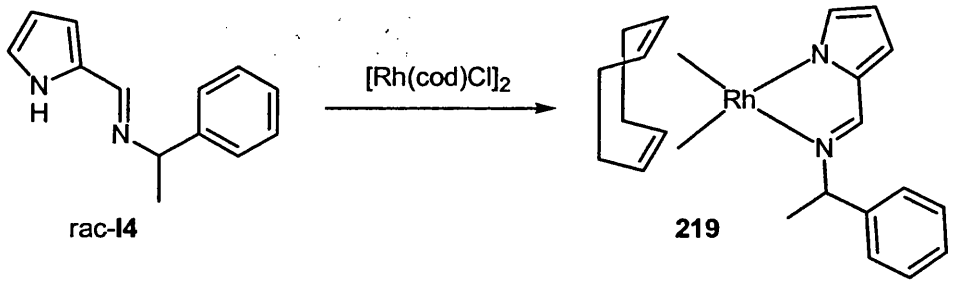


In a round bottom flask under nitrogen were added 6-methylpyridine-2-carbaldehyde (50mg, 0.41 mmol) and (S)-cyclohexylethylamine (52mg, 0.41 mmol) in 2 mL of dry THF. Sodium triacetoxyborohydride (122mg, 1.4 eq.) was added and the mixture was stirred at room temperature until completion. The reaction mixture was then quenched by adding aqueous saturated $NaHCO_3$, the organic layer was extracted twice with EtOAc, dried over Na_2SO_4 and evaporated to give a brown oil which was purified by column chromatography (eluent DCM/MeOH 95:5) to afford a pale yellow oil **A2c**-(S) (91mg, 95% yield) which showed δ_H 7.53 (1H, m, ArH), 7.13 (1H, m, ArH), 7.01 (1H, m, ArH), 3.82 (2H, s, CH_2N), 2.54 (3H, s, CH_3), 2.42-2.47 (1H, m, CH-Me) 1.03-1.73 (11H, m) and 1.06 (3H, d, CH_3);

δ_C 158.9, 157.6 (both C), 136.5, 121.2, 119.1 (all CH), 57.6 (CHN), 52.7 (CH_2N), 42.8 (CH_{cy}), 30.0, 28.1, 26.8, 26.7, 26.6 (all CH_2), 24.5 and 16.6 (both CH_3); m/z (FAB^+) 233.2 (100%, M^++H) [Found M^++H 233.20184. $C_{15}H_{24}N_2$ requires M^++H 233.20177]; ν_{max}/cm $^{-1}$ 3326 (w), 2922 (m), 2851 (m), 1592 (m), 1578 (m), 1450 (m), 1373 (w); $[\alpha_D]^{20}$ = +70.5 (c 0.7, $CHCl_3$).

Coupling of organoboronic acids and aldehydes

(η^4-1,5-Cyclooctadiene){2-*N*-[1-phenylethyl]pyrrolylcarbaldimine} rhodium(I) 219

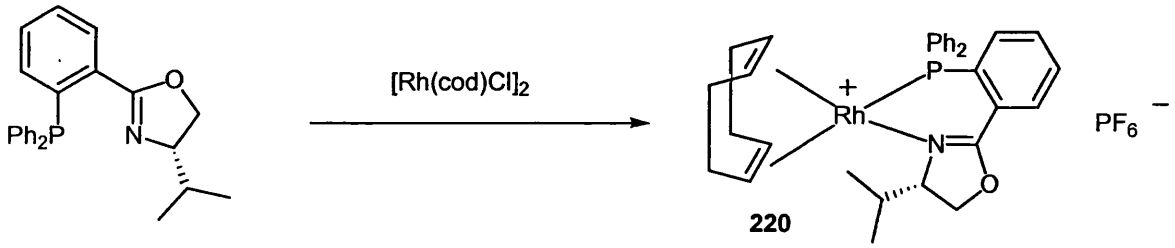


rac-**I4** **219**

A solution of (1-phenylethyl)-pyrrol-2-ylmethylene-amine rac-**I4** (24mg, 0.121 mmol) in dry ether (15 mL) was stirred with sodium hydride (15mg, 0.38 mmol) for 1 hour at room temperature before filtering *via* cannula. $[Rh(cod)Cl]_2$ (30mg, 0.061 mmol) was dissolved in dry THF (3 ml) and added to the deprotonated ligand solution.. A colour change from orange to bright yellow was observed. After stirring for half an hour, the solvent was removed and the residue was recrystallised from DCM/hexane to afford the complex **219** as a yellow powder (43mg, 87% yield) which showed δ_H 7.55 (1H, s, CH=N), 7.24-7.36 (5H, m, ArH), 6.56 (1H, s, ArH), 6.48 (1H, m, ArH), 6.10 (1H, dd, *J* 3.5 and *J* 1.9, ArH), 4.60-4.67 (1H, m, :CH_{cod}), 4.36 (1H, q, *J* 7.02, CH-Me), 4.20-4.23 (1H, m, :CH cod), 3.93-3.96 (1H, m, :CH_{cod}), 3.82 (1H, m, :CH_{cod}), 2.30-2.51 (4H, m, $CH_{2\ cod}$), 1.82-1.84 (4H, m, $CH_{2\ cod}$), 1.56 (3H, d, *J* 7.03, CH_3); δ_C 159.2 (CH=N), 144.7 (C), 142.9, 139.7 (CH), 129.7 (C) 128.4, 126.9, 126.7 (all CH phenyl) 122.3, 116.7, 115.2, 111.3, 109.7 (all CH), 51.2 (CH-Me), 31.4, 31.1, 30.4, 30.3 (all CH_2) and 22.2 (CH_3); ν_{max} /cm $^{-1}$ 2962 (m), 2918 (m),

2849 (m), 1576 (m), 1260 (w) and 798 (s); m/z (FAB^+) 408 (100%, M^++H) [Found M^++H 408.10611. $C_{21}H_{25}N_2Rh$ requires M^++H 408.10727).

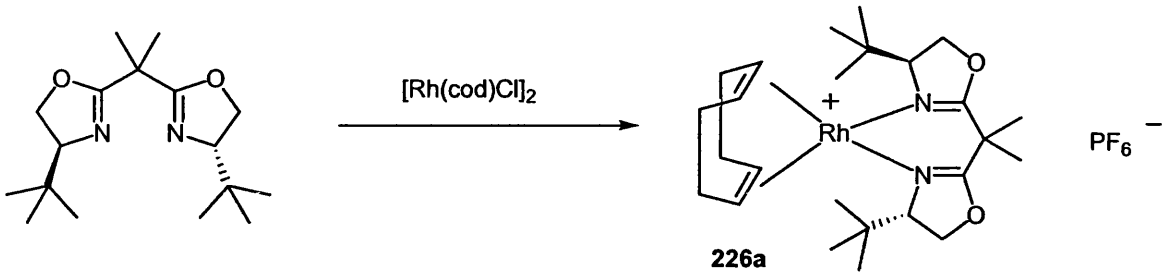
(+)-(η^4-1,5-Cyclooctadiene){(S)-2-(2-diphenylphosphinophenyl)-4-isopropyl-4,5-dihydro-oxazole} rhodium hexafluorophosphate 220



220

To a solution of $[Rh(cod)Cl]_2$ (20mg, 0.04 mmol) in dry DCM (1 mL) was added an aqueous solution of NH_4PF_6 (18mg, 0.11 mmol). The mixture was vigorously stirred for 30 mins and then treated with phosphineoxazoline (30mg, 0.08 mmol). The solution was then stirred for another 30 mins before separating the DCM layer, washing with water (3 x 1mL) and concentrating to about 1 mL with a flow of nitrogen. Deep red crystals were formed upon addition of *n*-hexane (2 mL). The red crystalline complex **220** was filtered, washed with hexane and air-dried (50 mg, 86% yield) which showed δ_H 8.19-8.22 (1H, m, CH_4), 7.05-7.74 (13H, m, ArH), 5.60-5.67 (1H, m, :CH_{cod}), 5.33-5.42 (1H, m, :CH_{cod}), 4.62 (1H, dd, *J* 9.5 and *J* 9.5, $CH_aH_{b\ ox}$), 4.35 (1H, dd, *J* 9.5 and *J* 3.4, $CH_aH_{b\ ox}$), 3.95-4.01 (1H, m, CHN_{ox}) 3.38-4.01 (2H, m, :CH_{cod}), 2.77-2.92 (2H, m, $CH_{2\ cod}$), 2.23-2.34 (2H, m, $CH_{2\ cod}$), 2.09-2.20 (2H, m, $CH_{2\ cod}$), 1.93-2.07 (2H, m, $CH_{2\ cod}$), 1.75-1.90 (1H, m, $CHMe_2$) and 0.88 (6H, d, *J* 7.0, 2 x CH_3); ν_{max}/cm^{-1} 2954 (m), 2918 (m), 2884 (m), 1607 (m), 1436 (s) and 839 (s); m/z (FAB^+) 584 (100%, M^++H) [found M^++H 584.15932. $C_{32}H_{36}NOPRh$ requires M^++H 584.15895]; Anal. Calcd. for $C_{32}H_{36}NOP_2F_6Rh$: C, 50.7; H, 4.93; N, 1.92. Found: C, 50.2; H, 5.04; N, 1.76.

(+)-(η^4-1,5-Cyclooctadiene){2,2-*bis*[2-{(4S)-4,5-dihydro-4-(*tert*-butyl)-oxazolyl}-propane} rhodium hexafluorophosphate 226a



226a

To a solution of $[Rh(cod)Cl]_2$ (20mg, 0.04 mmol) in dry DCM (1 mL) was added an aqueous solution of NH_4PF_6 (18mg, 0.11 mmol). The mixture was vigorously stirred for 30 mins before adding the bisoxazoline (24mg, 0.08 mmol). Stirring was continued for a further 30 mins before separating the DCM layer, washing with water (3 x 1 mL) and evaporating to about 1 mL under a flow of nitrogen. Precipitation was triggered by addition of *n*-hexane (2 mL), the precipitate was collected by filtration, washed with hexane and then air-dried to give the desired product **226a** as an orange crystalline complex (19mg, 92% yield) which showed δ_H 4.62 (2H, dd, *J* 9.7 and *J* 2.4, 2 x $CH_aH_{b\ ox}$), 4.31-4.49 (6H, m, 4 x :CH_{cod} and 2 x CHN_{ox}), 3.66 (2H, dd, *J* 9.7 and *J* 4.4, 2 x $CH_aH_{b\ ox}$), 2.56-2.73 (2H, m, CH_{2cod}), 2.28-2.42 (2H, m, CH_{2cod}), 2.08 (6H, s, 2 x Me), 1.95-2.10 (2H, m, CH_{2cod}), 1.68-1.83 (2H, m, CH_{2cod}), 0.89 (18H, s, 6 x Me); δ_C 178.2 (C=N), 82.8, 80.5 (:CH_{cod}), 73.1 (CH_2O), 72.5 (CHN), 40.8 (CMe_2), 34.3 (CMe_3), 31.3, 29.4 (both CH_{2cod}), 25.6 and 25.4 (both CH_3); δ_P –143.5 (1P, septet, PF_6, *J* 711); m/z (FAB^+) 505 (100%, M^++H) [found M^++H 505.22345. $C_{25}H_{42}N_2O_2Rh$ requires M^++*H* 505.23013]; Anal. Calcd. for $C_{25}H_{42}N_2O_2PF_6Rh$: C, 46.1; H, 6.45; N, 4.30. Found: C, 45.7; H, 6.66; N, 4.46.

X-ray structural determination of 226a

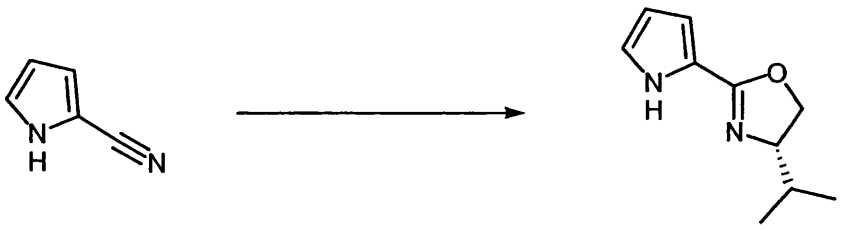
An orange crystal grown by slow diffusion of n-hexane into dichloromethane at 2-3°C was subjected to X-ray diffraction studies. Crystal data for $C_{25}H_{42}N_2O_2RhPF_6$ are as follows:

Mw = 650.49, orange crystal, 0.25 x 0.25 x 0.15 mm, orthorhombic, space group $P2_12_12_1$; *a* = 9.937, *b* = 14.793, *c* =19.32 A, $\alpha = \beta = \delta = 90°$, *V* = 2840.30(6) A^3, *Z* = 4, ρ_{cacld} = 1.521 mg/m^3, μ = 0.722 mm^{-1}, *T* = 170 K. All the hydrogen atoms were calculated from ideal geometries, fixed, and included in the calculation of the structural factor *R* = 0.0281, *Rw* = 0.0858.

1*H*-Pyrrole-2-carbonitrile

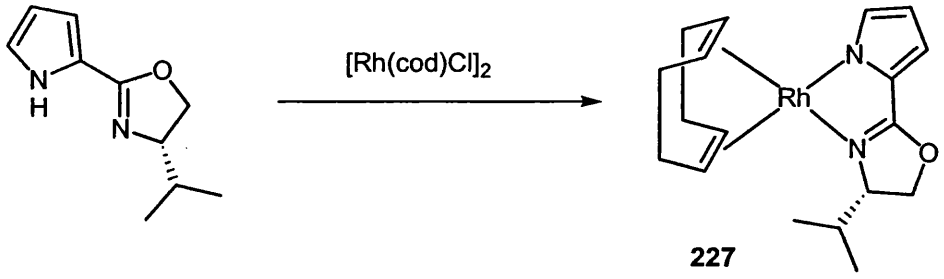
To a cold solution of hydroxylamine hydrochloride (0.8g, 11.5 mmol) in dry acetonitrile (60 mL) was added triethylamine (1.6 mL, 11.5 mmol) and pyrrole-2-carbaldehyde (1.0 g, 10.5 mmol) after 30 minutes stirring phthalic anhydride (1.6g, 10.6 mmol) was added in a portionwise manner under nitrogen. The resulting solution was heated under reflux for 8 hours before concentrating under reduced pressure. The resulting residue was extracted with cold DCM (3 x 40 mL), filtered and the combined filtrates washed with 5% aqueous ammonia to remove any residual phthalic acid. The separated organic layer was dried with $MgSO_4$ and then evaporated under reduced pressure to afford the crude product. The product was purified by flash chromatography (eluent 20% ethyl acetate/petrol) to give the desired product (0.92g, 95% yield) as colourless oil which showed δ_H 6.88-6.91 (1H, m, ArH), 6.81-6.84 (1H, m, ArH) and 6.18-6.21 (1H, s, ArH); δ_C 123.9, 120.0 (both CH), 114.7 (C), 109.6 (CH) and 99.7 (CN); m/z (EI^+) 92.1 (100 %, M^++H) [found M^++H 92.03772. $C_5H_4N_2$ requires M^++*H* 92.03745].

(4*R*)-4-Isopropyl-2-(1*H*-pyrrol-2-yl)-4,5-dihydro-1,3-oxazole



In a two-necked-round bottom flask, $ZnCl_2$ (0.82g, 6 mmol) was melted under high vacuum and cooled under nitrogen. After cooling to room temperature chlorobenzene (300 mL) was added followed by 1*H*-pyrrole-2-carbonitrile (1.11g, 12 mmol) and (L)-valinol (3.71g, 36 mmol). The mixture was heated under reflux for 24 hours before removal of the solvent under reduced pressure to give an oily residue which was dissolved in 20 mL of DCM. The solution was extracted with water (3 x 10mL) and the aqueous phase with DCM (20 mL). The combined organic phases were then dried over $MgSO_4$, the solvent evaporated and the crude product was purified flash chromatography (eluent 40% ethyl acetate/petrol) to afford a beige solid (1.72g. 81% yield) which showed δ_H 6.87 (1H, s, ArH), 6.71 (1H, m, ArH), 6.22 (1H, m, ArH), 4.36-4.40 (1H, m, C*H*N), 4.04-4.16 (2H, m, OCH_2), 1.75-1.83 (1H, m, CH-Me_2), 0.95 (3H, d, *J* 7.0, CH_3) and 0.89 (3H, d, *J* 7.0, CH_3); δ_C 171.7 (C=N), 122.0 (CH), 112.7 (CH), 109.7 (CH), 72.2 (CHN), 70.4 (CH_2), 33.4 (CH-Me_3), 19.1 and 18.6 (both CH_3); m/z (FAB^+) 179 (100 %, M^++H) [found M^++H 179.11900. $C_{10}H_{14}N_2O$ requires M^++*H* 179.11844]. Data identical to those in the literature.[13]

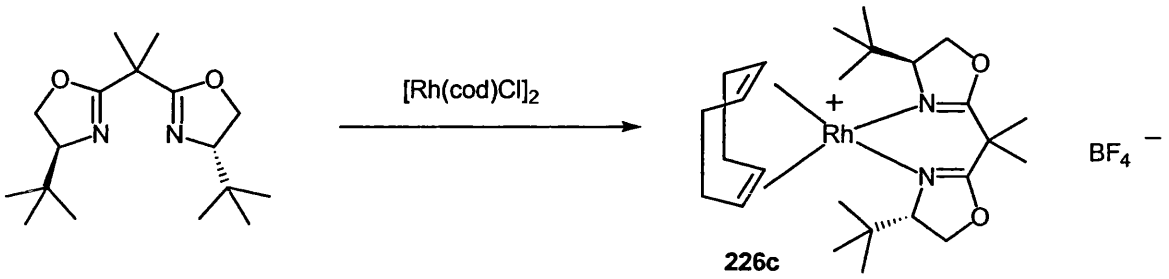
(+)-(η^4-1,5-Cyclooctadiene){2-[(4S)-4,5-dihydro-4-isopropyl]pyrrolyloxazol} rhodium(I) 227



227

A solution of the pyrroleoxazoline (11mg, 0.061 mmol) in dry diethylether (8 mL) was stirred with an excess of sodium hydride (8mg, 0.187 mmol) for 30 mins at room temperature and then filtered *via* canula. $[Rh(cod)Cl]_2$ (15mg, 0.03 mmol) was dissolved in dry THF (1.5 mL) and then added to the solution of deprotonated ligand. A colour change from orange to yellow was observed. After 30 mins stirring the solvents were evaporated, the residue dissolved in toluene and chromatographed on silica (DCM eluent) to afford the complex **227** as a yellow powder (32mg, 75% yield) which showed δ_H 6.57 (1H, s, ArH), 6.51 (1H, dd, *J* 3.5 and *J* 1.9, ArH), 6.11 (1H, m, ArH), 4.50-4.58 (2H, m, :CH_{cod}), 4.33-4.42 (2H, m, CH_aH_b $_{ox}$ and CH_{ox}), 4.26-4.32 (1H, m, :CH_{cod}), 4.12-4.18 (1H, m, :CH_{cod}), 3.86-3.93 (1H, m, CH_aH_b $_{ox}$), 1.54-2.64 (8H, m, CH_{2cod}), 1.77-1.86 (1H, m, $CHMe_2$), 0.86 (3H, d, *J* 4.7, CH_3) and 0.84 (6H, d, *J* 4.7, 2 x CH_3); ν_{max}/cm $^{-1}$ 2955 (m), 2920 (m), 2873 (m), 1596 (m), 1451 (s), 1411 (m), 1172 (m), 1033 (w) and 733 (s); m/z (FAB^+) 389 (85%, M^++H) [found M^++H 389.10895. $C_{18}H_{25}N_2ORh$ requires M^++*H* 389.11001].

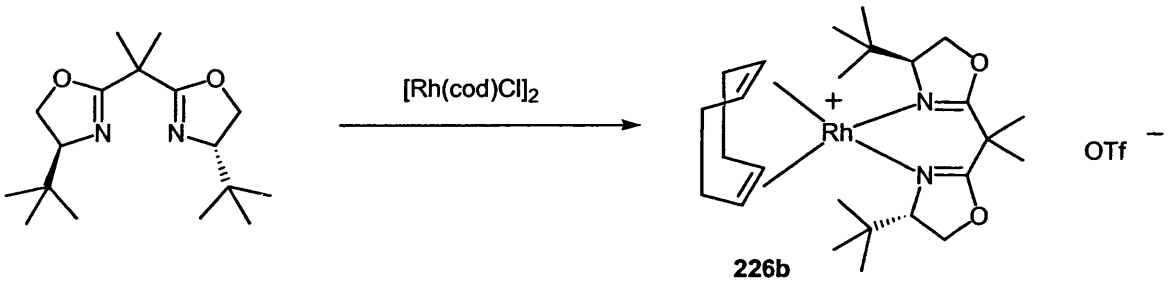
(+)-(η^4-1,5-Cyclooctadiene){2,2-*bis*[2-{(4S)-4,5-dihydro-4-(*tert*-butyl)-oxazolyl}-propane} rhodium tetrafluoroborate 226c



226c

To a solution of $[Rh(cod)Cl]_2$ (20mg, 0.04 mmol) in dry DCM (1 mL) was added an aqueous solution of NH_4BF_4 (16mg, 0.11 mmol). The mixture was vigorously stirred for 30 mins before adding the bisoxazoline (24mg, 0.08 mmol). Stirring was continued for a further 30 mins before separating the DCM layer, washing with water (3 x 1 mL) and evaporating to about 1 mL under a flow of nitrogen. Precipitation was triggered by addition of *n*-hexane (2 mL), the precipitate was collected by filtration, washed with hexane and then air-dried to give the desired product **226a** as a yellow powder (44mg, 81 % yield); δ_H 4.62 (2H, dd, *J* 9.7 and *J* 2.4, 2 x $CH_aH_{b\ ox}$), 4.29-4.45 (6H, m, 4 x :CH_{cod} and 2 x CHN_{ox}), 3.66 (2H, dd, *J* 9.7 and *J* 4.4, 2 x $CH_aH_{b\ ox}$), 2.53-2.69 (2H, m, $CH_{2\ cod}$), 2.25-2.40 (2H, m, $CH_{2\ cod}$), 2.08 (6H, s, 2 x CH_3), 1.93-1.99 (2H, m, $CH_{2\ cod}$), 1.65-1.79 (2H, m, $CH_{2\ cod}$) and 0.90 (18H, s, 6 x CH_3); δ_C 177.9 (C=N), 82.6, 80.5 (CH_{cod}), 72.1 (CH_2O), 72.4 (CHN), 40.8 (CMe_2), 34.2 (CMe_3), 30.9, 29.1 (both $CH_{2\ cod}$), 25.6 and 25.5 (CH_3); m/z (FAB^+) 505 (100%, M^++H) [found M^++H 505.22552. $C_{25}H_{42}N_2O_2BF4_6Rh$ requires M^++*H* 505.23013].

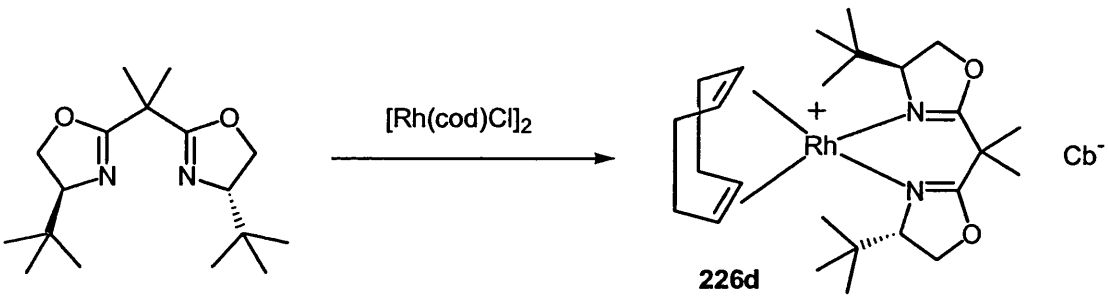
(+)-(η^4-1,5-Cyclooctadiene){2,2-*bis*[2-{(4S)-4,5-dihydro-4-(*tert*-butyl)-oxazolyl}-propane} rhodium triflate 226b



226b

Complex **226b** was synthesized by the procedure described for complex **226a**, using NH_4OTf (18mg, 0.11 mmol). The desired complex was obtained as a yellow powder (38mg, 84 % yield) which showed δ_H 4.62 (2H, dd, *J* 9.7 and 2.4, 2 x $CH_aH_{b\ ox}$), 4.27-4.41 (6H, m, 4 x :CH_{cod} and 2 x CHN_{ox}), 3.65 (2H, dd, *J* 9.7 and 4.4, 2 x $CH_aH_{b\ ox}$), 2.53-2.65 (2H, m, $CH_{2\ cod}$), 2.21-2.38 (2H, m, $CH_{2\ cod}$), 2.07 (6H, s, 2 x CH_3), 1.90-2.05 (2H, m, $CH_{2\ cod}$), 1.63-1.78 (2H, m, $CH_{2\ cod}$) and 0.90 (18H, s, 6 x CH_3); δ_C 177.4 (C=N), 82.2, 80.3 (both CH_{cod}), 72.4 (CH_2O), 72.2 (CHN), 40.5 (CMe_2), 34.3 (CMe_3), 30.7, 29.1 (both $CH_{2\ cod}$), 25.6 and 25.4 (both CH_3); m/z (FAB^+) 505 (100%, M^++H) [found M^++H 505.22921. $C_{32}H_{49}N_2O_5SRh$ requires M^++*H* 505.23013].

(+)-(η^4-1,5-Cyclooctadiene){2,2-*bis*[2-{(4S)-4,5-dihydro-4-(*tert*-butyl)-oxazolyl}-propane} rhodium carborane 226d



226d

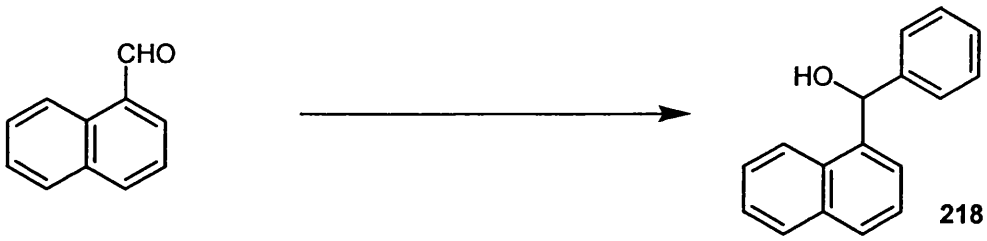
Complex **226d** was synthesized by Dr A.S. Weller. The desired complex was obtained as a yellow powder which showed δ_H 4.62 (2H, dd, *J* 9.7 and 2.4, 2 x $CH_aH_{b\ ox}$), 4.35-4.39 (6H, m, 4 x :CH_{cod} and 2 x CHN_{ox}), 3.65 (2H, dd, *J* 9.7 and 4.4, 2 x $CH_aH_{b\ ox}$), 2.58-2.63 (2H,

m, $CH_{2\ cod}$), 2.38-2.44 (2H, m, $CH_{2\ cod}$), 2.08 (6H, s, 2 x CH_3), 1.95-2.08 (2H, m, $CH_{2\ cod}$), 1.76-1.79 (2H, m, $CH_{2\ cod}$) and 0.90 (18H, s, 6 x CH_3); δ_C 180.2 (C=N), 83.9, 80.5 (both CH_{cod}), 73.8 (CH_2O), 72.9 (CHN), 41.8 (CMe_2), 34.6 (CMe_3), 31.3, 29.4 (both $CH_{2\ cod}$), 25.6 and 25.4 (both CH_3); δ_B -8.0, -14.2 and -17.1; m/z (FAB^+) 505 (100%, M^++H) [found M^++H 505.22952. $C_{25}H_{42}N_2O_2Rh$ requires M^++H 505.23013]; Anal. Calcd. for $C_{26}B_{11}H_{54}N_2O_2Rh$: C, 48.15; H, 8.39; N, 4.32. Found: C, 47.6; H, 8.23; N, 4.18.

Typical procedure for the coupling of organoboronic acidsto aldehydes

$[Rh(cod)N_2]PF_6$ (0.005 eq.) and the appropriate boronic acid (1.5 eq.) were weighed into a round bottomed flask equipped with a condenser and a magnetic stirrer bar. The flask was flushed with nitrogen and then charged with DME (1 mL) and the appropriate aldehyde (1 eq.). The reaction was then stirred at 80°C for 16 hours. The product was then extracted with ethyl acetate (5 mL), washed with water (5 mL), brine (5 mL), dried over $MgSO_4$ and evaporated. Purification of the product was accomplished by column chromatography using hexane/EtOAc (8:2) as the eluent.

Naphthalen-1-yl-phenyl-methanol 218



218

1-Naphthaldehyde (6mg, 0.038 mmol) and benzene boronic acid (7mg, 0.054 mmol) were reacted under the standard conditions to give the desired alcohol **218** as a white solid (5mg, 50 % yield) m.p. 86-87°C which showed δ_H 7.15-7.86 (12H, m, ArH), 6.62 (1H, s, ArCH) and 2.41 (1H, br s, OH); m/z (FAB^+) 235 (100%, M^++H); [Found M^++H 235.11196. $C_{17}H_{14}O$ requires M^++H 235.11229]. Data identical to those in the literature.[151]

(4-Methoxyphenyl)-(4-trifluoromethyl-phenyl)-methanol 223

223

4-Trifluoromethylbenzaldehyde (20mg, 0.113 mmol) and 4-methoxybenzene boronic acid (26mg, 0.169 mmol) were reacted under the standard conditions to give the desired alcohol **223** as a white solid (27mg,86 % yield) m.p 76-77°C which showed δ_H 7.58 (2H, d, *J* 8.2, ArH), 7.50 (2H, d, , *J* 8.2, ArH), 7.25-7.27 (2H, m, ArH), 6.88 (2H, d, *J* 8.6, CH), 5.85 (1H, s, ArCH), 3.79 (3H, s, OCH_3) and 2.23 (1H, br s, OH); δ_C 150.1, 147.5, 129.2 (All C), 128.3 (CH), 127.1 (C), 126.7, 125.5 (all CH), 120.6 (C), 114.3 (CH), 75.6 (CH-OH) and 55.6 (CH_3); δ_F -62.9; m/z (FAB^+) 283 (100%, M^++H) [Found M^++H 283.09419. $C_{15}H_{13}F_3O_2$ requires $M^+ + H$ 283.09459].

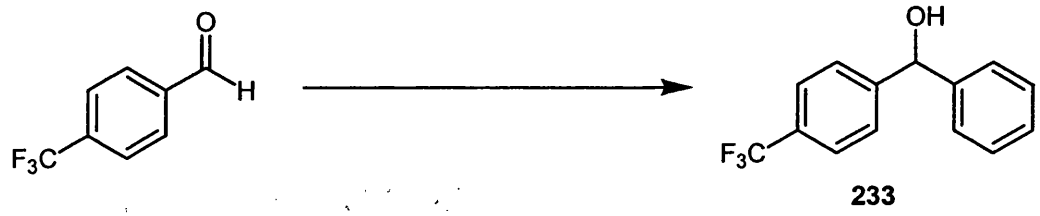
(4-Methoxy-phenyl)-naphthalen-1-yl-methanol 225

225

1-Naphthaldehyde (12mg, 0.079 mmol) and 4-methoxybenzene boronic acid (18mg, 0.118 mmol) were reacted under the standard conditions to give the desired alcohol **225** as a white solid (14mg, 72 % yield) m.p 88-89°C which showed δ_H 7.95-7.98 (1H, m, ArH), 7.79-7.86 (2H, m, ArH), 7.68 (1H, d, *J* 7.0, ArH), 7.40-7.51 (3H, m, ArH), 7.30 (2H, d, *J* 9.0, ArH), 6.83 (2H, d, *J* 9.0, ArH), 6.49 (1H, s, ArCH), 3.76 (3H, s, OCH_3) and 2.32 (1H, br s, OH); δ_C 159.2, 139.1, 135.6, 134.1, 130.7 (all C), 128.9, 128.6, 128.5, 126.2, 125.5, 124.9, 124.4, 124.2, 114.1 (all CH), 73.5 (CHOH) and 55.6 (CH_3); m/z (FAB^+) 265

(100%, M^++H) [Found M^++H 265.12211. $C_{18}H_{16}O_2$ requires M^++H 265.12286]; ν_{max}/cm^{-1} 3384 (m), 2925 (m), 2848 (w), 1609 (m), 1509 (m), 1174 (s) and 833 (m). HPLC was performed using Chiralcel OD column, 80:20 hexane/IPA , λ = 254 nm, 1 mL/min, R_t (R)-**225** = 9.7 mins and R_t (S)-**225** = 20.9 mins.

Phenyl(4-trifluoromethylphenyl)methanol 233



233

4-Trifluoromethylbenzaldehyde (7mg, 0.061 mmol) and benzene boronic acid (11mg, 0.091 mmol) were reacted under the standard conditions to give the desired alcohol **233** as a white solid (10mg, 64% yield) m.p 62-63°C which showed δ_H 7.59 (2H, d, *J* 8.2, ArH), 7.52 (2H, d, *J* 8.3, ArH), 7.26-7.37 (5H, m, ArH), 5.89 (1H, s, ArCH) and 2.37 (1H, br s, OH); δ_C 150.1, 147.5, 143.1 (All C), 128.7, 128.1, 126.6, 125.5, 125.4, 122.8 (all CH) and 75.7 (CHOH); m/z 253 (100%, M^++H) [Found M^++H 253.08312. $C_{14}H_{11}OF_3$ requires M^++H 253.08402]; ν_{max}/cm^{-1} 3300 (OH), 2930 (m), 2830 (m), 1600 (m) and 1450 (m). Data identical to those in the literature.[152]

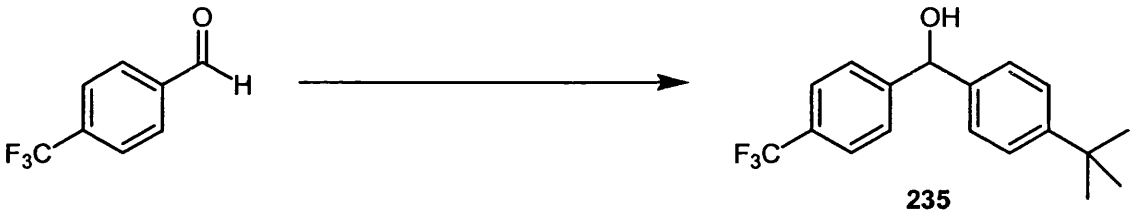
Naphthalen-2-yl-phenyl-methanol 234

234

2-Naphthaldehyde (9mg, 0.054 mmol) and benzene boronic acid (10mg, 0.081 mmol) were reacted under the standard conditions to give the desired alcohol **234** as a white solid (7mg, 53 % yield) m.p 87-88°C which showed δ_H 7.26-7.91 (12H, m, ArH), 6.02 (1H, S, ArCH)

and 2.37 (1H, br s, OH); m/z (FAB$^+$) 235 (100%, M$^+$+H) [Found M$^+$+H 235.11189. $C_{17}H_{14}O$ requires M^++H 235.11229]; ν_{max}/cm $^{-1}$ 3300 (m), 3021 (m), 1521 (m), 1475 (m), 1423 (m), 1101 (s) and 765 (m); Data identical to those in the literature.[151]

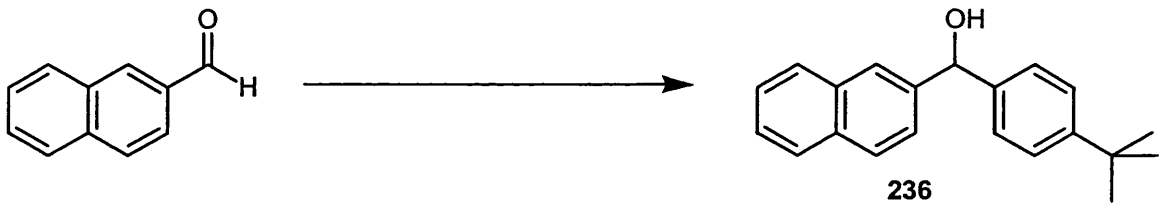
(4-*tert*-Butyl-phenyl)-(4-trifluoromethyl-phenyl)-methanol 235



235

4-Trifluoromethylbenzaldehyde (14mg, 0.079 mmol) and 4-*t*-butylbenzene boronic acid (21mg, 0.118 mmol) were reacted under the standard conditions to give the desired alcohol **235** as a white solid (18mg, 72 % yield) m.p 97-98°C which showed δ_H 7.59 (2H, d, *J* 8.4, ArH), 7.51 (2H, d, *J* 8.4, ArH), 7.36 (2H, d, *J* 8.4, ArH), 7.26 (2H, d, *J* 8.4, ArH), 5.85 (1H, s, ArCH), 2.30 (1H, br s, OH) and 1.30 (9H, s, ^{t}Bu); δ_C 164.6, 151.1, 147.6, 140.2, 126.6 (all C), 126.4, 125.7, 125.4, 125.3 (all CH), 75.6 (CH-OH), 31.2 (CH_3), 1C missing; m/z (FAB$^+$) 309 (100%, M$^+$+H) [Found M$^+$+H 309.09359. $C_{18}H_{19}F_3O$ requires M^++H 309.14662].

(4-*tert*-Butyl-phenyl)-naphthalen-2-yl-methanol 236



236

2-Naphthaldehyde (8mg, 0.053 mmol) and 4-*t*-butylbenzene boronic acid (14mg, 0.079 mmol) were reacted under the standard conditions to give the desired alcohol **236** as a white solid (9mg, 59 % yield) m.p. 104-105°C which showed δ_H 7.25-7.88 (11H, m, ArH), 5.99 (1H, s, ArCH), 2.30 (1H, br s, OH) and 1.31 (9H, s, ^{t}Bu); m/z (FAB$^+$) 291 (100%,

M^++H) [Found M^++H 291.17419. $C_{21}H_{22}O$ requires M^++H 291.17489]; ν_{max}/cm $^{-1}$ 3301 (m), 3028 (w), 1518 (m), 1475 (m), 1423 (m), 1131 (s) and 829 (m); Data identical to those in the literature.[153]

(4-Methoxy-phenyl)-naphthalen-2-yl-methanol 238

238

2-Naphthaldehyde (13mg, 0.084 mmol) and 4-methoxybenzene boronic acid (19mg, 0.126 mmol) were reacted under the standard conditions to give the desired alcohol **238** as a white solid (16mg, 74 % yield) m.p 72-73°C which showed δ_H 6.84-7.91 (11H, m, ArH), 5.98 (1H, s, ArCH), 3.80 (3H, s, OCH_3) and 2.46 (1H, br s, OH); m/z (FAB^+) 265 (100%, M^++H) [Found M^++H 265.12208. $C_{18}H_{16}O_2$ requires M^++H 265.12286]; ν_{max}/cm $^{-1}$ 3379 (m), 2914 (m), 2892 (w), 1519 (m), 1476 (m), 1423 (m), 1103 (s), 821 (m).

Diphenylmethanol 239

239

Benzaldehyde (5mg, 0.051 mmol) and benzene boronic acid (9mg, 0.076 mmol) were reacted under the standard procedure to give the desired alcohol **239** as a white solid (5mg, 52% yield) m.p 66-67°C which showed δ_H 7.28-7.39 (10H, m, Ar-H), 5.85 (1H, s, Ar-CH) and 2.21 (1H, br s, OH); δ_C 143.8 (C), 128.4, 127.5, 136.5 (all CH) and 76.2 (CH-OH); m/z (FAB^+) 185 (100%, M^++H). Data identical to those in the literature.[154]

References

1- Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.*, **2000**, 100, 2159.

2- Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed. Engl.*, **1998**, 37. 2581.

3- Togni, A.; Venanzi, L. M. *Angew. Chem. Int. Ed. Engl.*, **1994**, 33. 497.

4- For comprehensive reviews on asymmetric hydrogenation see Takaya, H.; Ohta, T.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; p1. Ohkuma, T.; Noyori, R. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, 1999, p 221.

5- Toros, S.; Heil, B.; Kollar, L.; Marko, L. *J. Organomet. Chem.*, **1980**, 197, 85.

6- Bakos, J.; Toth, I.; Heil, B.; Marko, L. *J. Organomet. Chem.*, **1985**, 279, 23.

7- Ohkuma, T.; Oaka, H.; Hashigushi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.*, **1995**, 117, 2675.

8- Noyori, R. *Abst. Am. Chem. Soc.*, **2000**, Aug. 20-24

9- Ohkuma, T.; Ikehira, H.; Ikariya, T.; Noyori, R. *Synlett*, **1997**, 467.

10- Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kozawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem. Int. Ed. Engl.* **1998**, 37, 1703.

11- Ohkuma, T.; Ishii, D.; Takeno, H.; Noyori, R. *J. Am. Chem. Soc.*, **2000**, 122, 6510.

12- Ohkuma, T.; Koizuma, M.; Yoshida, M.; Noyori, R. *Org. Lett.*, **2000**, 2, 1749.

13- Brunner, H.; Tracht, T. *Tetrahedron: Asymmetry*, **1998**, 9, 3773.

14- Tommasino, M. L.; Thomazeau, C.; Touchard, F.; Lemaire, M. *Tetrahedron: Asymmetry*, **1999**, 10, 1813.

15- For comprehensive reviews on asymmetric transfer hydrogenation see Ohkuma, T.; Noyori, R. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, 1999, p 227.

16- Palmer, M.; Wills, M. *Tetrahedron: Asymmetry*, **1999**, 10, 2045.

17- Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.*, **1997**, 30, 97.

18- Yamakawa, M.; Ito, H.; Noyori. *J. Am. Chem. Soc.*, **2000**, 122, 1466.

19- Alonso, D. A.; Brandt, P.; Nordin, S. J. M.; Anderson, P. G. *J. Am. Chem. Soc.*, **1999**, 121, 9580.

20- Khai, B. T.; Arcelli, A. *Tetrahedron Lett.*, **1996**, 37, 6599.

21- Muller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta.*, **1991**, 74, 232.

22- Jiang, Y.; Jiang. Q.; Zhu, G.; Zhang, X. *Tetrahedron Lett.*, **1997**, 38, 215.

23- Puntener, K.; Schwink, L.; Knochel, P. *Tetrahedron Lett.*, **1996**, 37, 8165.

24- Schwink, L.; Ireland, T.; Puntener, K.; Knochel, P. *Tetrahedron: Asymmetry*, **1998**, 9, 1143.

25- Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.*, **1995**, 117, 7562.

26- Murata, K.; Ikariya, T. *J. Org. Chem.*, **1999**, 64, 2186.

27- Jiang, Y.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.*, **1998**, 120, 3817.

28- For comprehensive reviews on asymmetric hydrosilylation of ketones see: Brunner, H; Nishiyama, H; Itoh, K. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; p303. Nishiyama, H. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, 1999, p 267.

29- Brunner, H; Riepl, G. *Angew. Chem. Int. Ed. Engl.*, **1982**, 21, 377.

30- Brunner, H; Reiter, B; Riepl, G. *Chem. Ber.*, **1984**, 117,1330.

31- Brunner, H; Rahman, AFM. *Chem. Ber.*, **1984**, 117, 710.

32- Brunner, H; Riepl, G; Weiltzer, H. *Angew. Chem. Int. Ed. Engl.*, **1983**, 22, 331.

33- Brunner, H; Becker, R; Riepl, G. *Organometallics*, **1984**, 3, 1354.

34- Brunner, H; Obermann, U. *Chem.Ber.*, **1989**, 122, 499.

35- Nishiyama, H; Sakaguchi, H; Nakamura, T; Horihata, M; Kondo, M; Itoh, K. *Organometallics*, **1989**, 8, 846.

36- Brunner, H; Brandl, P. *J. Organomet. Chem.*, **1990**, 390, C81.

37- Brunner, H; Brandl, P. *Tetrahedron: Asymmetry*, **1991**, 2, 919.

38- Nishiyama, H; Nakamura, T;; Kondo, M; Itoh, K. *Organometallics*, **1991**, 10, 500.

39- Nishiyama, H; Yamaguchi, S; Kondo, M; Itoh, K. *J. Org. Chem.*, **1992**, 57, 4306.

40- Gladialy, S; Pinna, L; Graf, E; Brunner, H. *Tetrahedron: Asymmetry*, **1990**, 1, 937.

41- Nishiyama, H; Yamaguchi, S; Park, SB; Itoh, K. *Tetrahedron: Asymmetry*, **1993**, 4, 143.

42- Hemlchen, G; Krotz, A; Ganz, KT; Hansen, D. *Synlett*, **1991**, 257.

43- Faller, JW; Chase, KJ. *Organometallics*, **1994**, 13, 989.

44- Hayashi, T; Hayashi, C; Uozumi, Y. *Tetrahedron: Asymmetry*, **1995**, 6, 2503.

45- Sprinz, J; Helmchen, G. *Tetrahedron Lett.* **1993**, 34, 1769;

46- Vonmatt, P; Pfaltz, A. *Angew. Chem. Int. Ed. Engl.*, **1993**, 32, 566;

47- Dawson, GJ; Frost, CG; Williams, JMJ, Coote, SJ. *Tetrahedron Lett.*, **1993**, 34, 3149.

48- Newman, LM; Williams, JMJ; McCague, R; Potter, GA. *Tetrahedron: Asymmetry*, **1996**, 7, 1597.

49- Langer, T; Jansen, J; Helmchem, G. *Tetrahedron: Asymmetry*, **1996**, 7, 1599.

50- Nishibayashi, Y; Segawa, K; Ohe, K; Uemura, S. *Organometallics*, **1995**, 14, 5486.

51- Nishibayashi, Y; Segawa, K; Singh, JD; Fukuzawa, S; Ohe, K; Uemura, S. *Organometallics*, **1996**, 15, 370.

52- Heldmann, DK; Seebach, D. *Helv. Chim. Acta.*, **1999**, 82, 1096.

53- Zhu, G; Terry, M; Zhang, X. *J. Organomet. Chem.*, **1997**, 547, 97.

54- Nishibayashi, Y; Takei, I; Fukuzawa, S; Uemura, S, Hidai, M. *Organometallics*, **1998**,17, 3420.

55- For reviews on asymmetric aldol reaction see: Carreira, E. M. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer:

Berlin, 1999, p 997 (vol. 3). Machajewski, T. D.; Wong, C. *Angew. Chem. Int. Ed. Engl.* **2000**, 39, 1353.

56- Evans, D. A.; Kozlowski, M. C.; Tedrow, J. S. *Tetrahedron Lett.*, **1996**, 37, 7481.

57- Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.*, **1996**, 118, 4322.

58- Johnson, J. S.; Evans, D.A. *Acc. Chem. Res.*, **2000**, 33, 325.

59- Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.*, **1996**, 118, 5814.

60- Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.*, **1997**, 119, 7893.

61- Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.*, **1999**, 121, 669.

62- Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.*, **1999**, 121, 686.

63- Singer, R. A.; Carreira, E. M. *Tetrahedron Lett.*, **1997**, 38, 927.

64- Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.*, **1994**, 116, 8837.

65- For reviews on hetero Diels-Alder reaction see: Ooi, T.; Maruoka, K. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, 1999, p 1237 (vol. 3). Jorgensen, K. A. *Angew. Chem. Int. Ed. Engl.*, **2000**, 39, 3559.

66- Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.*, **1988**, 110, 310. Maruoka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.*, **1988**, 110, 3588. Graven, A.; Johannsen, M.; Jorgensen, K. A. *J. Chem. Soc., Chem. Comm.*, **1996**, 2373. Hattori, K.; Yamamoto, H. *J. Org. Chem.*, **1992**, 57, 3264.

67- Wada, E.; Yasuoka, H.; Kanemasa, S. *Chem. Lett.*, **1994**, 1637.

68- Gao, Q.; Maruyama, T.; Mouri, M.; Yamamoto, H. *J. Org. Chem.*, **1992**, 57, 1951.

69- Ghosh, A. K.; Mathivanan, P.; Capiello, J.; Krishnan, K. *Tetrahedron: Asymmetry*, **1996**, 7, 2165.

70- Ghosh, A. K.; Mathivanan, P.; Capiello, J. *Tetrahedron Lett.*, **1997**, 38, 2427.

71- Evans, D. A.; Johnson, J. S.; Olhawa, E. J. *J. Am. Chem. Soc.*, **2000**, 122, 1635.

72- Evans, D. A.; Olhawa, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem. Int. Ed. Engl.*, **1998**, 37, 3372.

73- For reviews on ene reaction see: Mikami, K.; Terada, M. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, 1999, p 1143 (vol. 3).

74- Maruoka, K.; Hoshino, Y.; Shirasaka, T.; Yamamoto, H. *Tetrahedron Lett.*, **1988**, 29, 3967.

75- Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T. *Synlett*, **1992**, 255. Mikami, K.; Terada, Nakai, T. *J. Am. Chem. Soc.*, **1990**, 112, 3949. Terada, M.; Mikami, K. *J. Chem. Soc., Chem. Comm.*, **1995**, 2391.

76- Mikami, K.; Yajima, T.; Terada, M.; Suzuki, Y.; Kobayashi, I. *J. Chem. Soc., Chem. Comm.*, **1997**, 57. Mikami, K.; Yoshida, A.; Matsumoto, Y. Tetrahedron Lett., 1996, 37, 8515.

77- Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.*, **1998**, 120, 5824.

78- For reviews on hydroboration of carbonyl groups see: Itsuno, T. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, 1999, p 289 (vol. 1).

79- Corey, E. J.; Helai, C. J. *Angew. Chem. Int. Ed. Engl.* **1998**, 37, 1986.

80- Hirao, A.; Itsuno, T.; Nakahama, S.; Yamakazi, N. J. *J. Chem. Soc. Chem. Commun.*, **1981**, 315.

81- Bonnemann, H.; Braun, G. A. *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 1992.

82- Kossenjans, M.; Martens, J. *Tetrahedron: Asymmetry*, **1998**, 9, 1409. Reiners, I.; Martens, J. *Tetrahedron: Asymmetry*, **1997**, 8, 277.

83- Li, X.; Xie, R. *Tetrahedron: Asymmetry*, **1997**, 8, 2283.

84- For reviews on alkylation of carbonyl groups see: Soai, K.; Shibata, T. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, 1999, p 911 (vol. 2).Soai, K.; Niwa, S. *Chem. Rev.*, **1992**, 92, 833. Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed. Engl.*, **1991**, 30, 49.

85- Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.*, **1991**, 56, 4264.

86- Soai, K.; Ookawa, A.; Kaba, T.; ogawa, K. *J. Am. Chem. Soc.*, **1987**, 109, 7111.

87- Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.*, **1986**, 108, 6071.

88- Bolm, C.; Zehnder, M.; Bur, D. *Angew. Chem. Int. Ed. Engl.*, **1990**, 29, 205.

89- Bringmann, G.; Breuning, M. *Tetrahedron: Asymmetry*, **1998**, 9, 667.

90- Lutz, C.; Knochel, P. *J. Org. Chem.*, **1997**, 62, 7895. Berger, S.; Langer, F.; Lutz, C.; Knochel, P.; Mobley, T. A.; Reddy, C. K. *Angew. Chem. Int. Ed. Engl.*, **1997**, 36, 1496.

91- Asami, M.; Watanabe, H.; Honda, K.; Inoue, S. *Tetrahedron: Asymmetry*, **1998**, 9, 3461.

92- Bolm, C.; Fernandez, K. M.; Seger, A.; Raabe, G. *Synlett*, **1997**, 1051.

93- Keller, F.; Rippert, A. J. *Helv. Chim. Acta.*, **1999**, 82, 125.

94- Hartwig, J. F. *Synlett*, **1997**, 329.

95- Hartwig, J. F. *Angew. Chem. Int. Ed. Engl.* **1998**, 37, 2046.

96- Wolfe, J. P.; Wagaw, S.; Marcoux, J-F.; Buchwald, S.F. *Acc. Chem. Res.* **1998**, 31, 805.

97- Hartwig, J. F. *Acc. Chem. Res.* **1998**, 31, 852.

98- Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, 576,125.

99- Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927.

100- Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, 116, 5969.

101- Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, 116, 7901.

102- Widenhoefer, R. A.; Buchwald, S. L. *Organometallics*, **1996**, 15, 3534.

103- Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, 118, 7215.

104- Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 1348.

105- Hartwig, J. F.; Richards, S.; Baranano, D.; Paul, F. *J. Am. Chem. Soc.* **1996**, 118, 3626.

106- Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, 118, 7217.

107- Marcoux, J-F.; Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1997**, 62, 1568.

108- Wolfe, J. P,; Buchwald, S. L. *Tetrahedron Lett.* **1997**, 38, 6359.

109- Beller, M.; Riermeier, T. H.; Reisinger, C-P.; Herrmann, W. A. *Tetrahedron Lett.* **1997**, 38, 2073.

110- Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, 64, 5575.

111- Wolfe, J. P.; Buchwald, S. L. *Angew. Chem. Int. Ed. Engl.* **1999**, 38, 2413.

112- Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, 61, 6066.

113- Louie, J.; Driver, M. S.; Hamman, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, 62, 1268.

114- Kranenburg, M.; Van der Burgt, Y. E. M.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M. *Organometallics*, **1995**, 14, 3081.

115- Sadighi, J. P.; Harris, M. C.; Buchwald, S. L. *Tetrahedron Lett.* **1998**, 39, 5327.

116- Avanyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, 120, 4369.

117- Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, 61, 7240

118- Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, 119, 8451.

119- Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernandez-Rivas, C. *J. Am. Chem. Soc.* **1998**, 120, 827.

120- Halterman, R. L; Ramsey, T. M; Chen, Z. *J. Org. Chem.*, **1994**, 59, 2642.

121- Barr, K. J; Beck, S. C; Buchwald, S. L. *J. Org. Chem.*, **1994**, 59, 4323.

122- Carter, M. B; Schiott, B; Gutierrez, A; Buchwald, S. L. *J. Am. Chem. Soc.*, **1994**, 116, 11667.

123- Yun, J; Buchwald, S. L. *J. Am. Chem. Soc.*, **1999**, 121, 5640.

124- Verdaguer, X; Lange, U. E. W; Reding, M. T, Buchwald, S. L. *J. Am. Chem. Soc.*, **1996**, 118, 6784.

125- Hansen, M. C; Buchwald, S. L. *Org. Lett.*, **2000**, 2, 713.

126- Pedersen, H. L; Lohannsen. *J. Chem. Soc: Chem. Comm.*, **1999**, 2517.

127- Tillack, A; Michalik, D; Koy, C; Michalik, M. *Tetrahedron Lett.*, **1999**, 40, 6567.

128- Perch, N; Widenhoefer, R. A. *J. Am. Chem. Soc.*, **1999**, 121, 6960.

129- Borman, S. *Chem. Eng. News.*, **1996**, November 4, 37.

130- Liu, G.; Ellman, J. *J. Org. Chem.*, **1995**, 60, 7712.

131- Gilbertson, S.R.; Wang, X. *Tetrahedron Lett.*, **1996**, 37, 6475.

132- Cole, B.M.; Shimizu, K.D.; Krueger, C.A.; Harrity, J.P.A.; Snapper, M.L.; Hoveyda, A.H. *Angew. Chem. Int. Ed. Engl.*, **1996**, 35, 1668. A similar approach was used to identify Schiff base catalysts for asymmetric Strecker reactions. Sigman, M.S.; Jacobsen, E.N. *J. Am. Chem. Soc.*, **1998**, 120, 4901.

133- Burgess, K.; Lim, H-J.; Porte, A.M.; Sulikowski, G.A. *Angew. Chem. Int. Ed. Engl.*, **1996**, 35, 220.

134- Moreau, C.; Frost, C.G.; Murrer, B. *Tetrahedron Lett.*, **1999**, 40, 5617.

135- The σ_p values were found in *Advanced Organic Chemistry*, March, J.; Wiley: New York, 4th Ed, 280.

136- For other examples see Pioda, G.; Togni, A. *Tetrahedron: Asymmetry*, **1998**, 9, 3903. Doucet , H.; Fernandez, E.; Layzell, T. P.; Brown, J. M. *Chem. Eur. J.*, **1999**, 5, 1320.

137- For recent reviews on bite angle effects: Dierhes, P.; van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalt. Trans.*, **1999**, 1519.

138- van Leeuwen, P. W. N. M. J.; Reek, J. N. H.; Dierhes, P. *Chem. Rev.*, **2000**, 100, 2741.

139- Yang, H.; Lugan, N.; Mathieu, R. *C. R. Acad. Sci. Paris, t.2*, serie IIc, **1999**, 251.

140- Crabtree, R.H.; Eisenstein, O.; Sini, G.; Peris, E. *J. Organomet. Chem.*, **1998**, 567, 7.

141- Oi, S.; Moro, M.; Ono, S.; Inoue, Y. *Chem. Lett.*, **1998**, 83.

142- Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.*, **1998**, 120, 5579.

143- Sakai, M.; Ueda, M.; Miyaura, N. *Angew. Chem. Int. Ed. Engl.*, **1998**, 37, 3279.

144- Rahman, M.; Liu, H-Y.; Eriks, K.; Prock, A.; Giering, W. P. *Organometallics*, **1989**, 8, 1

145- Ueda, M.; Miyaura, N. *J. Org. Chem.*, **2000**, 65, 4450.

146- Frost, C. G.; Moreau, C.; Murrer, B.; Weller, A. S. *J. Organomet. Chem.*, in preparation.

147- Wang, E-C.; Lin, G-J.; *Tetrahedron Lett.*, **1998**, 39, 4047.

148- Merlic, C. A.; Adams, B. *J. Organomet. Chem.*, **1992**, 431, 313.

149- Abdel-Magrid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, 61, 3849.

150- Comins, D. L.; Killpack, M. O. *J. Org. Chem.*, **1990**, 55, 69.

151- Seebach, D.; Beck, A. K.; Roggo, S.; Wonnacott, A. *Chem. Ber.*, **1985**, 118, 3673.

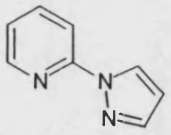
152- Stanchev, S.; Rakovska, R.; Berova, N.; Snatzke, G. *Tetrahedron: Asymmetry*, **1995**, 6, 183.

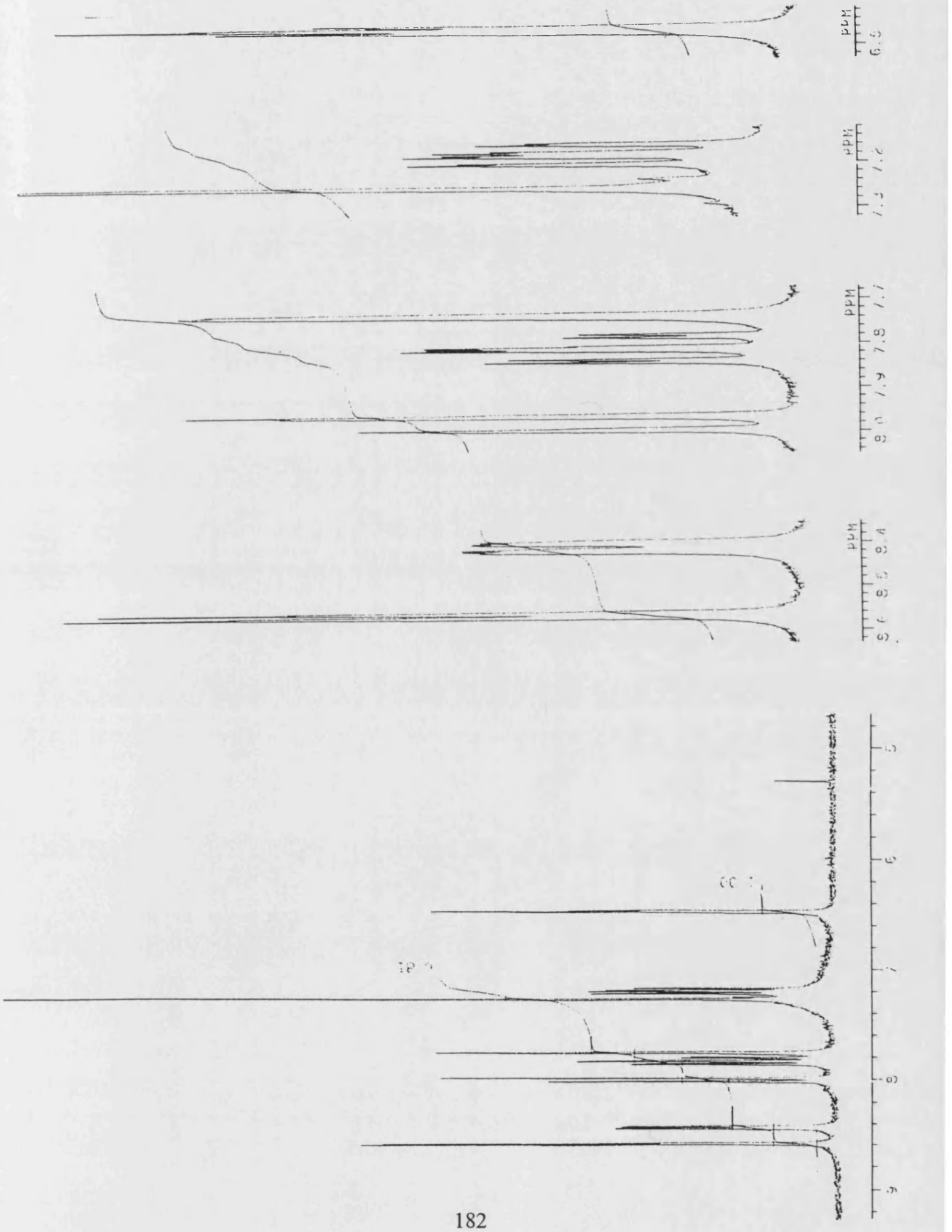
153- Weber, E.; Seichter, W.; Goldberg, I. *Chem. Ber.*, **1990**, 123, 811.

154- Guijaro, D.; Yus, M. *Tetrahedron*, **1994**, 50, 3446.

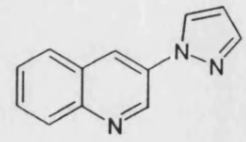
155- Carter, M. B.; Schiott, B.; Gutierrez, A.; Buchwald, S. L. *J. Am. Chem. Soc.*, **1994**, 116, 11667

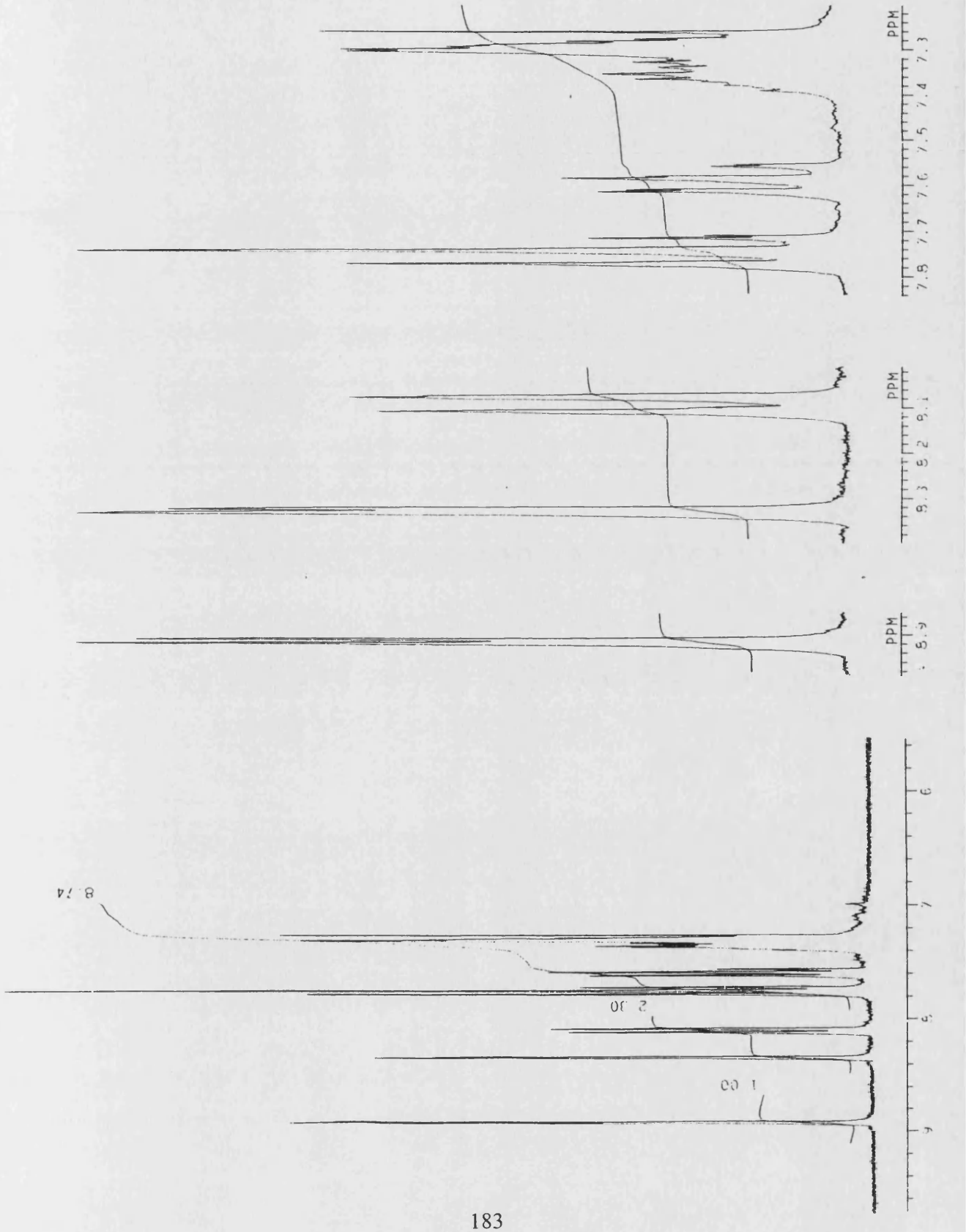
2-(1*H*-Pyrazol-1-yl)pyridine H1



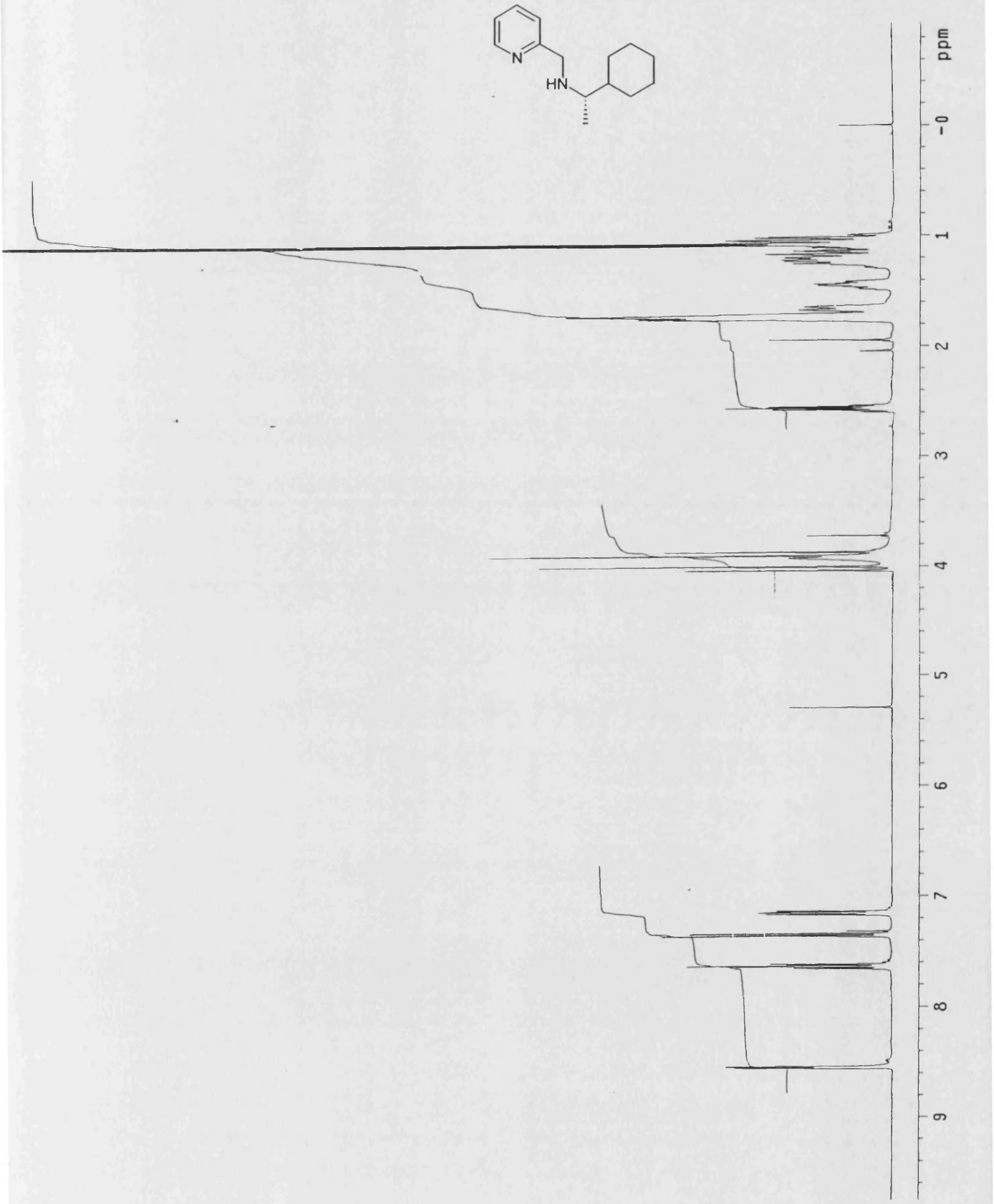


3-pyrazol-1-yl-quinoline H5





N-[(1S)-1-Cyclohexylethyl]-N-(2-pyridinyl methyl)amine A2-(S)



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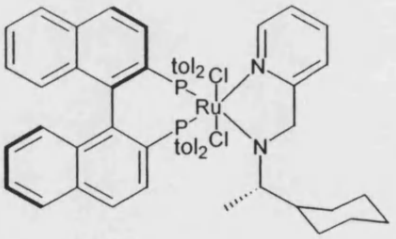

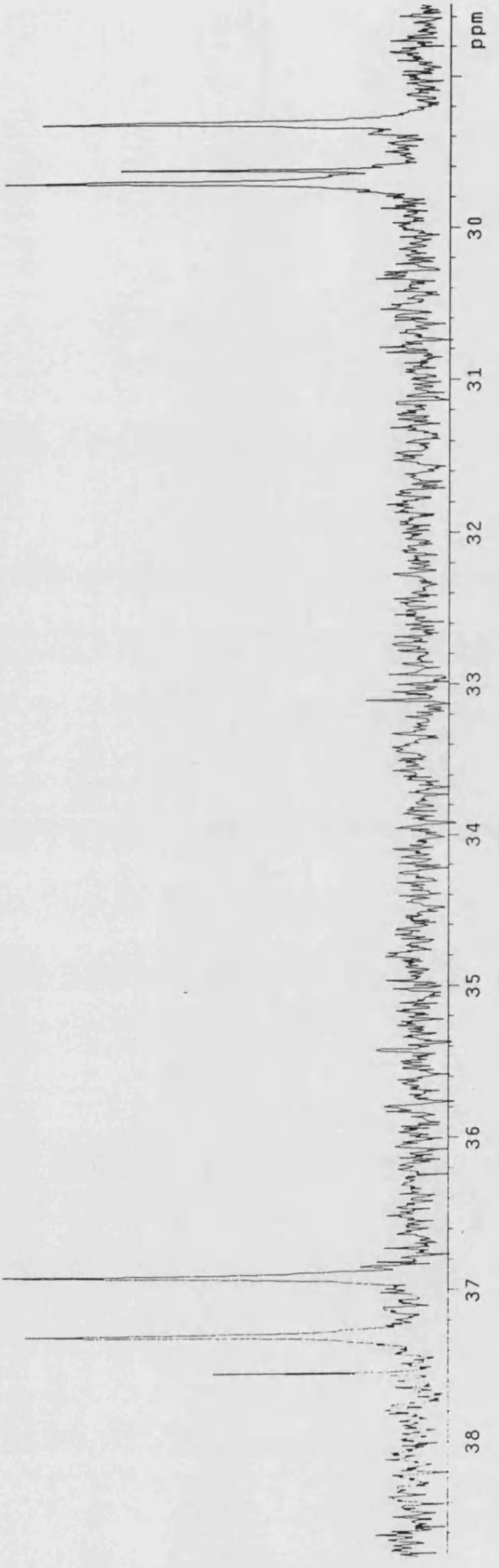

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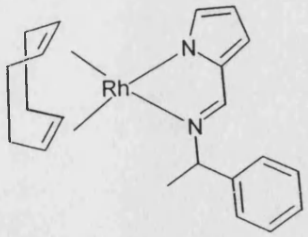

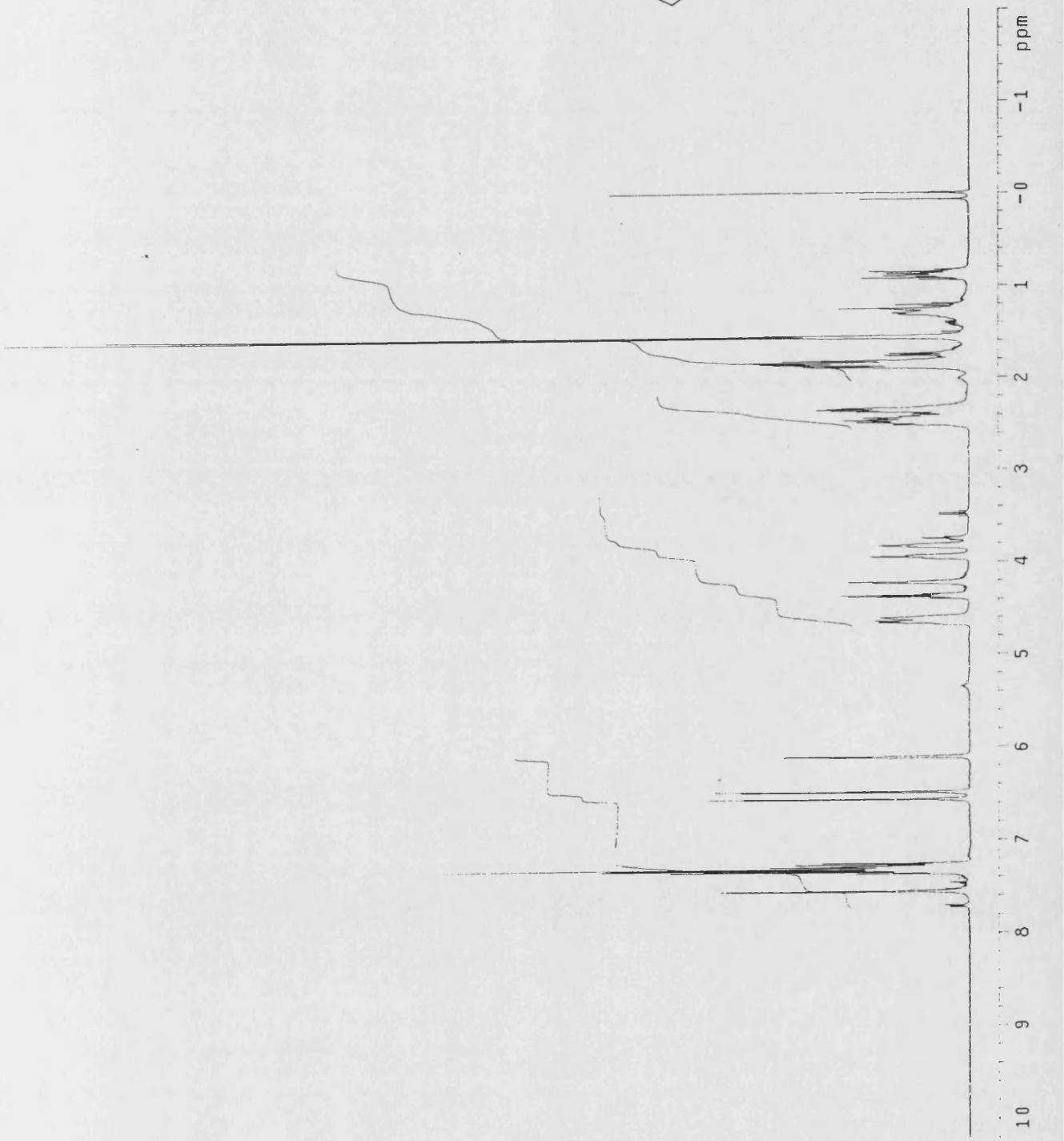

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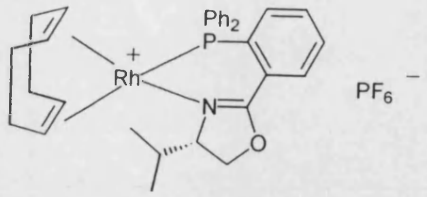

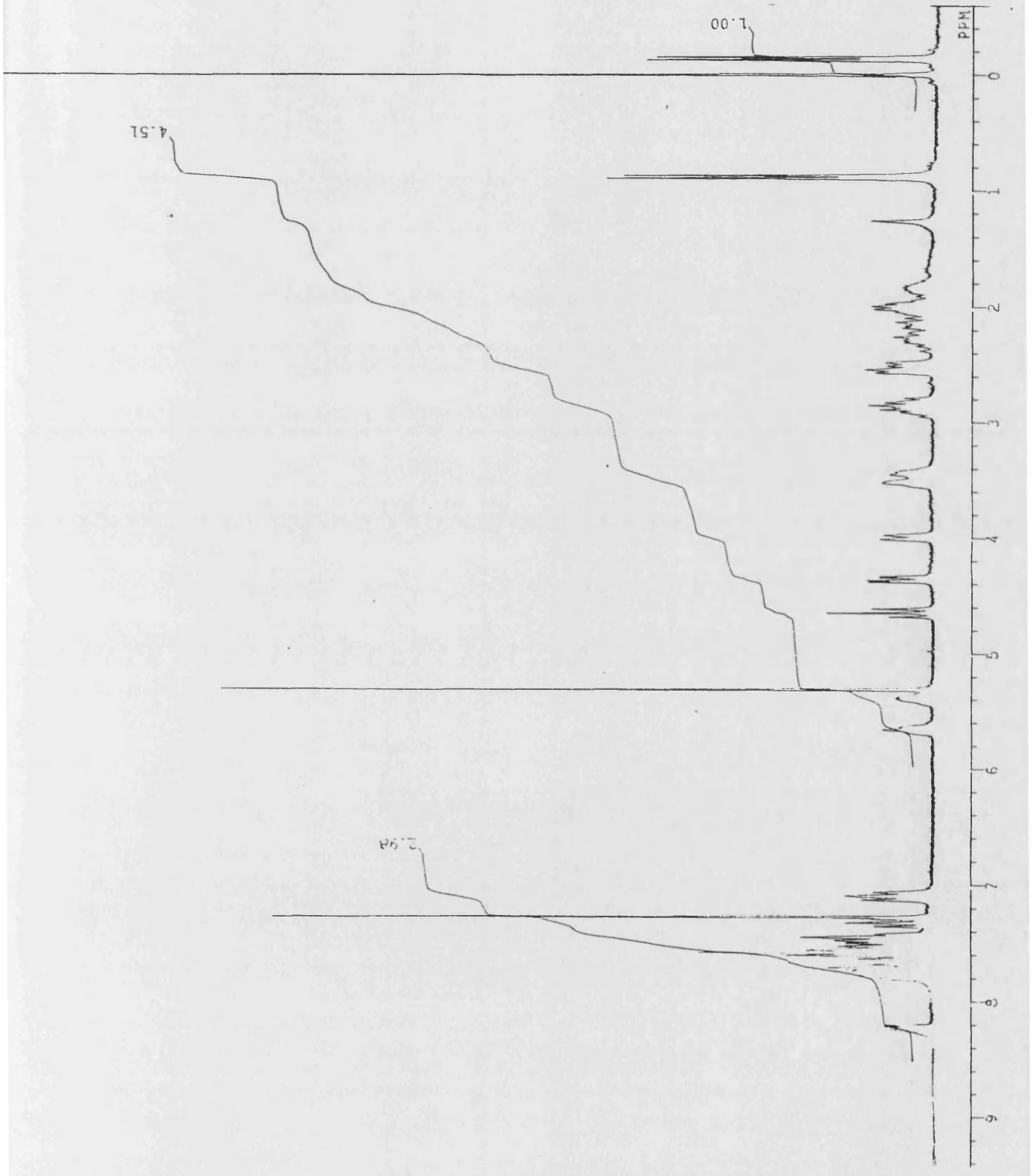

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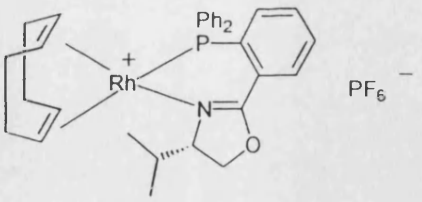

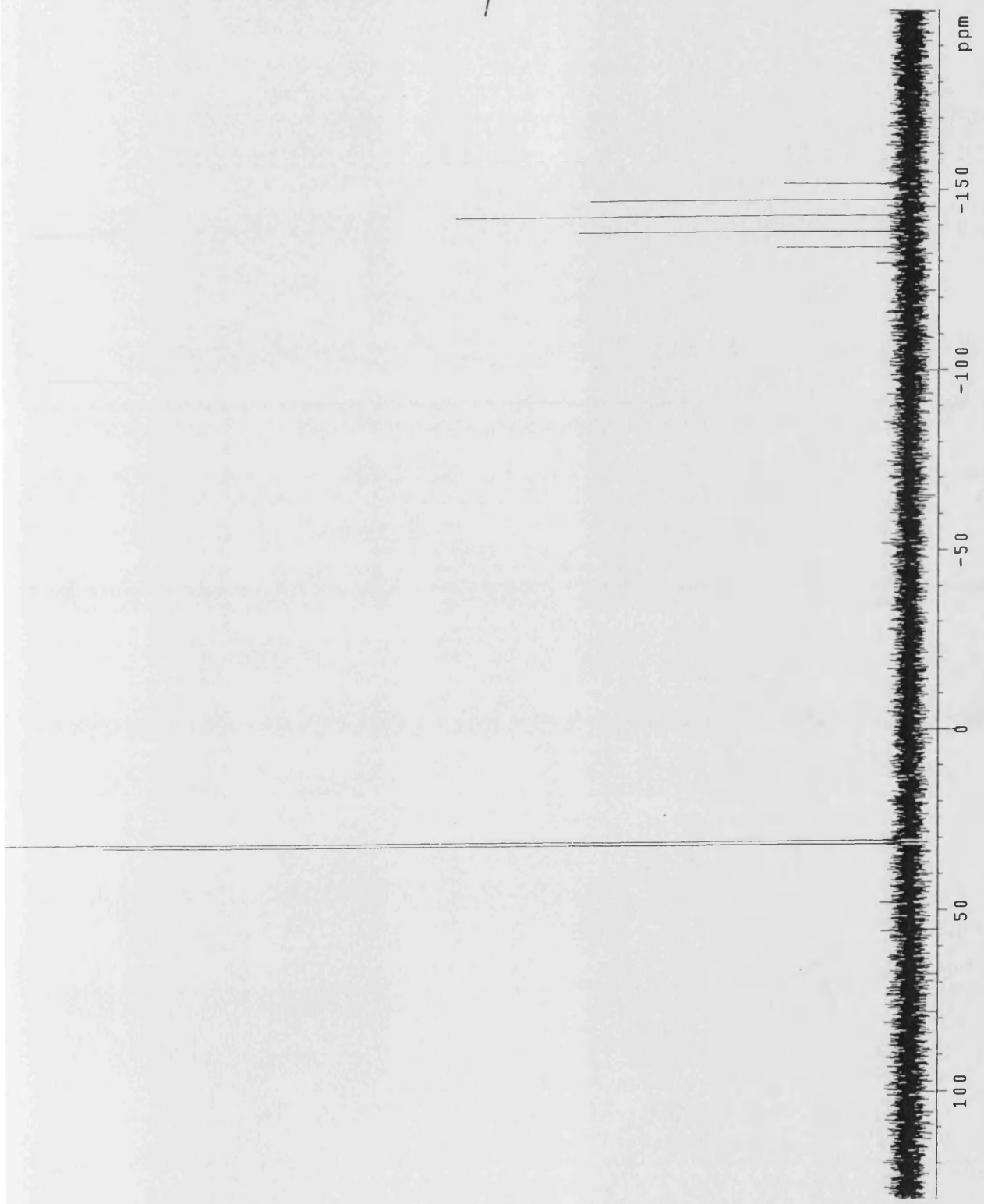

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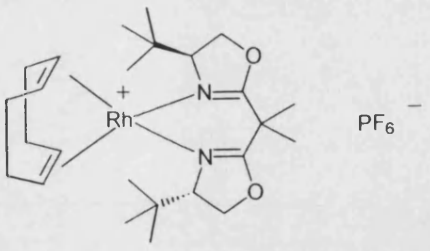

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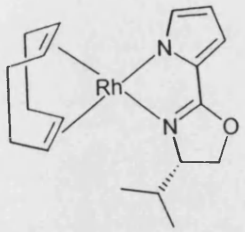

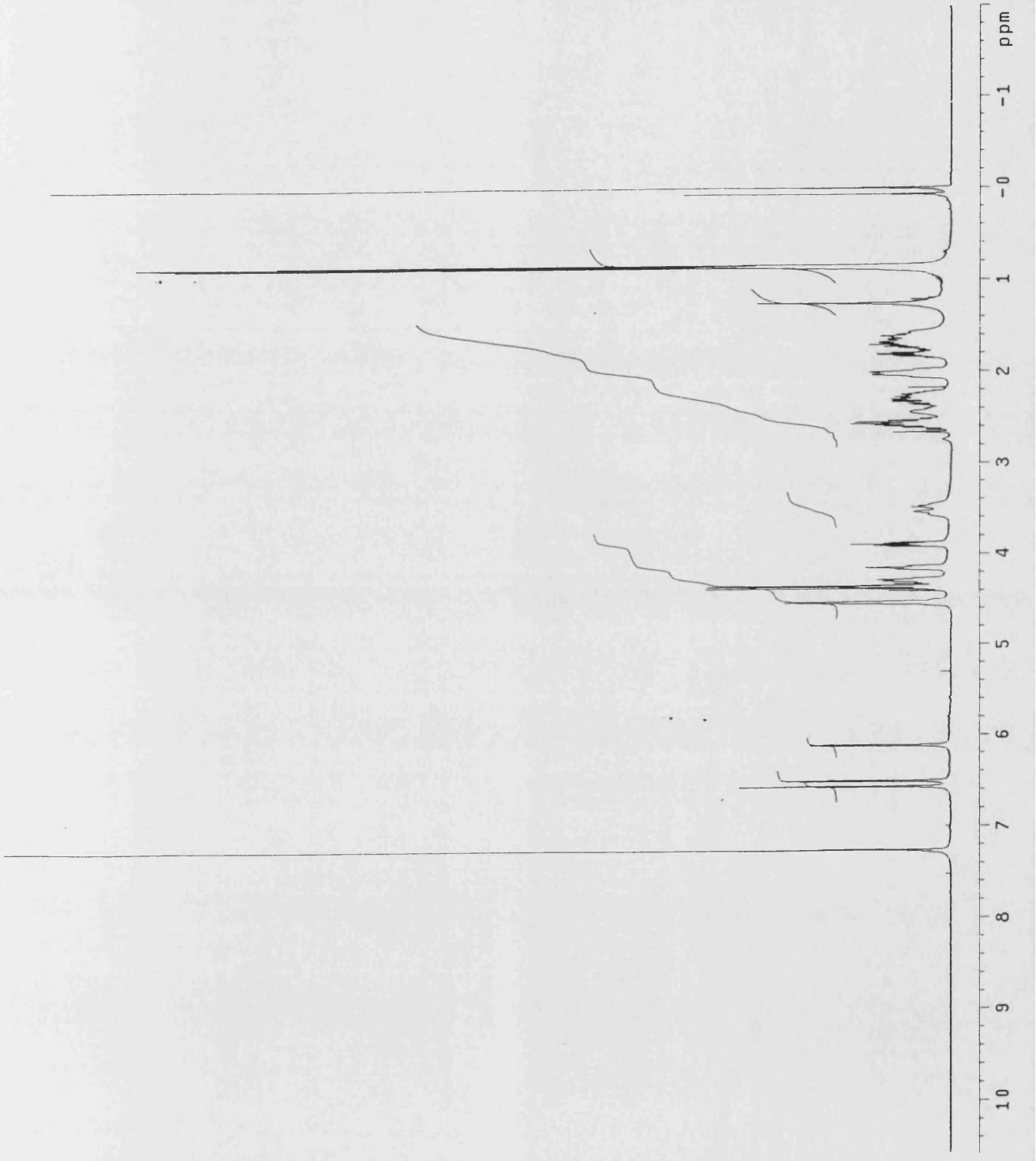

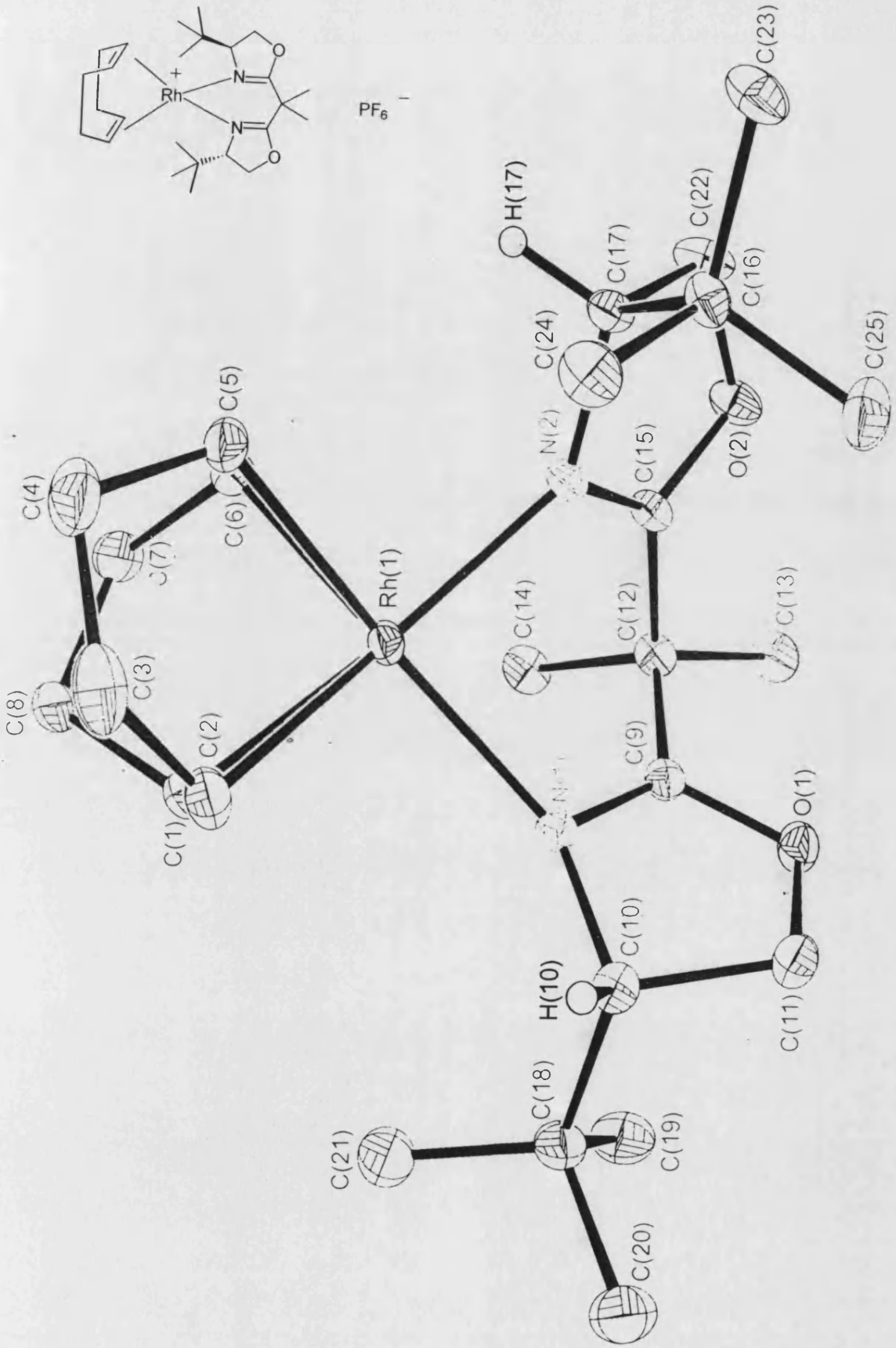
Rh
N
O
PF6 −
H(17)
C(23)
C(22)
C(17)
C(16)
C(24)
C(25)
C(5)
N(2)
O(2)
C(15)
C(4)
C(6)
C(7)
Rh(1)
C(14)
C(12)
C(13)
C(3)
C(8)
C(2)
C(9)
O(1)
C(1)
N(1)
C(10)
H(10)
C(11)
C(18)
C(21)
C(19)
C(20)

Table 1. Crystal data and structure refinement for 1.

Identification code	k00cgf1
Empirical formula	C25 H42 F6 N2 O2 P Rh
Formula weight	650.49
Temperature	170(2) K
Wavelength	0.71070 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 9.9370(1)Å α = 90°
	b = 14.7930(2)Å β = 90°
	c = 19.3220(2)Å γ = 90°
Volume	2840.30(6) $Å^3$
Z	4
Density (calculated)	1.521 Mg/m^3
Absorption coefficient	0.722 mm^{-1}
F(000)	1344
Crystal size	0.25 x 0.25 x 0.15 mm
Theta range for data collection	2.11 to 27.47 °.
Index ranges	-12<=h<=12; -19<=k<=19; -25<=l<=24
Reflections collected	56910
Independent reflections	6487 [R(int) = 0.0480]
Reflections observed (>2σ)	6273
Max. and min. transmission	0.8994 and 0.8401
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6487 / 4 / 359
Goodness-of-fit on F^2	0.685
Final R indices [I>2σ(I)]	R_1 = 0.0260 wR_2 = 0.0772
R indices (all data)	R_1 = 0.0281 wR_2 = 0.0858
Absolute structure parameter	-0.03(2)
Largest diff. peak and hole	0.871 and -0.533 $eÅ^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 1.U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
Rh(1)	2048(1)	1271(1)	1557(1)	22(1)
P(1)	5982(1)	431(1)	4647(1)	29(1)
F(1)	7158(2)	-243(1)	4869(1)	50(1)
F(2)	5925(3)	827(2)	5411(1)	59(1)
F(3)	4822(2)	1110(2)	4425(1)	58(1)
F(4)	6067(2)	24(1)	3879(1)	48(1)
F(5)	4887(3)	-307(2)	4850(2)	65(1)
F(6)	7096(2)	1173(1)	4445(1)	53(1)
N(1)	2529(2)	-177(1)	1447(1)	23(1)
N(2)	749(2)	857(1)	2368(1)	24(1)
O(1)	1948(2)	-1516(1)	1913(1)	30(1)
O(2)	390(2)	154(1)	3380(1)	33(1)
C(1)	3719(3)	1768(2)	963(1)	29(1)
C(2)	2606(3)	1653(2)	536(1)	33(1)
C(3)	1683(4)	2397(2)	285(2)	47(1)
C(4)	1305(4)	3058(2)	854(2)	48(1)
C(5)	1224(3)	2603(2)	1556(2)	35(1)
C(6)	2269(3)	2548(2)	2033(2)	33(1)
C(7)	3689(3)	2901(2)	1928(2)	38(1)
C(8)	4221(3)	2689(2)	1202(2)	35(1)
C(9)	2314(2)	-649(2)	1991(1)	24(1)
C(10)	2482(3)	-831(2)	847(1)	28(1)
C(11)	1699(3)	-1613(2)	1166(1)	31(1)
C(12)	2381(2)	-313(2)	2735(1)	26(1)
C(13)	2365(3)	-1095(2)	3259(2)	38(1)
C(14)	3641(3)	272(2)	2852(2)	35(1)
C(15)	1137(2)	270(2)	2813(1)	25(1)
C(16)	-667(3)	844(2)	3343(1)	35(1)
C(17)	-602(2)	1192(2)	2592(1)	25(1)
C(18)	3889(3)	-1130(2)	582(2)	36(1)
C(19)	4674(3)	-1668(3)	1130(2)	48(1)
C(20)	3636(4)	-1735(2)	-53(2)	49(1)
C(21)	4746(4)	-325(2)	362(3)	57(1)
C(22)	-1747(2)	843(2)	2120(1)	26(1)
C(23)	-3077(2)	1215(2)	2401(2)	36(1)
C(24)	-1568(3)	1193(2)	1375(1)	34(1)
C(25)	-1769(3)	-190(2)	2105(2)	39(1)

Table 3. Bond lengths [Å] and angles [°] for 1.

Rh(1)-C(6)	2.111(3)
Rh(1)-N(2)	2.119(2)
Rh(1)-C(2)	2.126(3)
Rh(1)-C(5)	2.133(3)
Rh(1)-C(1)	2.149(2)
Rh(1)-N(1)	2.206(2)
P(1)-F(3)	1.588(2)
P(1)-F(2)	1.589(2)
P(1)-F(5)	1.590(2)
P(1)-F(1)	1.595(2)
P(1)-F(4)	1.6042(19)
P(1)-F(6)	1.607(2)
N(1)-C(9)	1.279(3)
N(1)-C(10)	1.511(3)
N(2)-C(15)	1.282(3)
N(2)-C(17)	1.495(3)
O(1)-C(9)	1.343(3)
O(1)-C(11)	1.471(3)
O(2)-C(15)	1.335(3)
O(2)-C(16)	1.466(3)
C(1)-C(2)	1.390(4)
C(1)-C(8)	1.521(4)
C(2)-C(3)	1.513(5)
C(3)-C(4)	1.519(6)
C(4)-C(5)	1.515(5)
C(5)-C(6)	1.390(4)
C(6)-C(7)	1.518(4)
C(7)-C(8)	1.531(4)
C(9)-C(12)	1.522(4)
C(10)-C(11)	1.524(4)
C(10)-C(18)	1.554(4)
C(12)-C(15)	1.514(3)
C(12)-C(13)	1.537(3)
C(12)-C(14)	1.538(4)
C(16)-C(17)	1.541(4)
C(17)-C(22)	1.546(3)
C(18)-C(21)	1.525(4)
C(18)-C(19)	1.536(5)
C(18)-C(20)	1.540(4)
C(22)-C(25)	1.528(4)
C(22)-C(23)	1.532(3)
C(22)-C(24)	1.541(3)
C(6)-Rh(1)-N(2)	90.02(10)
C(6)-Rh(1)-C(2)	97.99(11)
N(2)-Rh(1)-C(2)	157.13(10)
C(6)-Rh(1)-C(5)	38.23(12)
N(2)-Rh(1)-C(5)	91.97(10)
C(2)-Rh(1)-C(5)	81.58(12)
C(6)-Rh(1)-C(1)	81.14(10)
N(2)-Rh(1)-C(1)	164.62(10)
C(2)-Rh(1)-C(1)	37.95(11)
C(5)-Rh(1)-C(1)	88.83(10)
C(6)-Rh(1)-N(1)	152.66(10)

N(2)-Rh(1)-N(1)	85.56(8)
C(2)-Rh(1)-N(1)	96.42(10)
C(5)-Rh(1)-N(1)	168.57(10)
C(1)-Rh(1)-N(1)	96.51(9)
F(3)-P(1)-F(2)	89.54(13)
F(3)-P(1)-F(5)	90.27(14)
F(2)-P(1)-F(5)	90.01(14)
F(3)-P(1)-F(1)	179.40(14)
F(2)-P(1)-F(1)	90.37(12)
F(5)-P(1)-F(1)	90.32(13)
F(3)-P(1)-F(4)	91.49(12)
F(2)-P(1)-F(4)	178.91(13)
F(5)-P(1)-F(4)	90.35(13)
F(1)-P(1)-F(4)	88.60(11)
F(3)-P(1)-F(6)	90.14(13)
F(2)-P(1)-F(6)	89.94(13)
F(5)-P(1)-F(6)	179.59(16)
F(1)-P(1)-F(6)	89.27(13)
F(4)-P(1)-F(6)	89.70(12)
C(9)-N(1)-C(10)	106.0(2)
C(9)-N(1)-Rh(1)	114.46(17)
C(10)-N(1)-Rh(1)	133.60(16)
C(15)-N(2)-C(17)	107.49(19)
C(15)-N(2)-Rh(1)	120.57(16)
C(17)-N(2)-Rh(1)	131.66(16)
C(9)-O(1)-C(11)	104.43(19)
C(15)-O(2)-C(16)	105.5(2)
C(2)-C(1)-C(8)	123.4(3)
C(2)-C(1)-Rh(1)	70.14(15)
C(8)-C(1)-Rh(1)	113.40(18)
C(1)-C(2)-C(3)	125.7(3)
C(1)-C(2)-Rh(1)	71.91(15)
C(3)-C(2)-Rh(1)	109.4(2)
C(2)-C(3)-C(4)	112.7(3)
C(5)-C(4)-C(3)	112.1(3)
C(6)-C(5)-C(4)	125.4(3)
C(6)-C(5)-Rh(1)	70.05(15)
C(4)-C(5)-Rh(1)	113.0(2)
C(5)-C(6)-C(7)	125.8(3)
C(5)-C(6)-Rh(1)	71.72(16)
C(7)-C(6)-Rh(1)	110.26(18)
C(6)-C(7)-C(8)	111.9(2)
C(1)-C(8)-C(7)	110.4(2)
N(1)-C(9)-O(1)	118.3(2)
N(1)-C(9)-C(12)	126.2(2)
O(1)-C(9)-C(12)	115.5(2)
N(1)-C(10)-C(11)	101.1(2)
N(1)-C(10)-C(18)	114.1(2)
C(11)-C(10)-C(18)	112.1(2)
O(1)-C(11)-C(10)	103.7(2)
C(15)-C(12)-C(9)	104.14(19)
C(15)-C(12)-C(13)	110.8(2)
C(9)-C(12)-C(13)	112.0(2)
C(15)-C(12)-C(14)	109.3(2)
C(9)-C(12)-C(14)	110.9(2)
C(13)-C(12)-C(14)	109.6(2)
N(2)-C(15)-O(2)	118.1(2)
N(2)-C(15)-C(12)	124.4(2)

O(2)-C(15)-C(12)	117.5(2)
O(2)-C(16)-C(17)	104.4(2)
N(2)-C(17)-C(16)	101.48(19)
N(2)-C(17)-C(22)	112.29(19)
C(16)-C(17)-C(22)	114.3(2)
C(21)-C(18)-C(19)	108.2(3)
C(21)-C(18)-C(20)	108.8(3)
C(19)-C(18)-C(20)	109.4(3)
C(21)-C(18)-C(10)	111.9(2)
C(19)-C(18)-C(10)	112.2(2)
C(20)-C(18)-C(10)	106.3(3)
C(25)-C(22)-C(23)	110.7(2)
C(25)-C(22)-C(24)	108.6(2)
C(23)-C(22)-C(24)	108.1(2)
C(25)-C(22)-C(17)	110.9(2)
C(23)-C(22)-C(17)	107.8(2)
C(24)-C(22)-C(17)	110.7(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for 1. The anisotropic displacement factor exponent takes the form: $-2\ gpi^2\ [\ h^2\ a^{*2}\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U$

Atom	U11	U22	U33	U23	U13	U12
Rh(1)	19(1)	21(1)	26(1)	2(1)	2(1)	-3(1)
P(1)	28(1)	31(1)	28(1)	2(1)	6(1)	3(1)
F(1)	52(1)	56(1)	41(1)	-3(1)	-7(1)	21(1)
F(2)	72(1)	69(1)	36(1)	-12(1)	16(1)	14(1)
F(3)	48(1)	50(1)	76(2)	5(1)	-8(1)	18(1)
F(4)	59(1)	54(1)	30(1)	-3(1)	-5(1)	2(1)
F(5)	54(1)	47(1)	94(2)	3(1)	32(1)	-13(1)
F(6)	50(1)	44(1)	66(1)	-11(1)	24(1)	-13(1)
N(1)	21(1)	24(1)	26(1)	1(1)	2(1)	0(1)
N(2)	18(1)	27(1)	27(1)	3(1)	4(1)	1(1)
O(1)	33(1)	24(1)	33(1)	5(1)	2(1)	-2(1)
O(2)	29(1)	47(1)	22(1)	6(1)	3(1)	6(1)
C(1)	25(1)	27(1)	34(1)	-1(1)	11(1)	-7(1)
C(2)	41(2)	32(1)	27(1)	3(1)	3(1)	-11(1)
C(3)	53(2)	48(2)	42(2)	22(1)	-8(2)	-11(2)
C(4)	42(2)	36(2)	66(2)	23(2)	2(2)	2(1)
C(5)	25(1)	23(1)	57(2)	7(1)	9(1)	0(1)
C(6)	36(2)	23(1)	39(1)	-5(1)	12(1)	-3(1)
C(7)	35(2)	32(1)	47(2)	-11(1)	5(1)	-11(1)
C(8)	29(1)	32(1)	45(2)	-3(1)	11(1)	-10(1)
C(9)	17(1)	23(1)	31(1)	4(1)	2(1)	3(1)
C(10)	28(1)	26(1)	29(1)	0(1)	0(1)	-1(1)
C(11)	34(1)	25(1)	33(1)	-2(1)	-2(1)	-3(1)
C(12)	22(1)	30(1)	26(1)	6(1)	-2(1)	3(1)
C(13)	40(1)	39(2)	34(1)	13(1)	-1(1)	8(1)
C(14)	25(1)	46(2)	33(1)	0(1)	-6(1)	-2(1)
C(15)	20(1)	32(1)	22(1)	0(1)	2(1)	-1(1)
C(16)	27(1)	54(2)	25(1)	-2(1)	4(1)	9(1)
C(17)	19(1)	29(1)	25(1)	-3(1)	3(1)	0(1)
C(18)	35(1)	31(1)	41(1)	-1(1)	12(1)	6(1)
C(19)	38(2)	52(2)	54(2)	-5(2)	7(1)	17(1)
C(20)	69(2)	39(2)	38(2)	-2(1)	11(2)	8(2)
C(21)	47(2)	42(2)	83(3)	-7(2)	34(2)	0(2)
C(22)	20(1)	29(1)	28(1)	3(1)	0(1)	-4(1)
C(23)	19(1)	51(2)	39(1)	7(1)	3(1)	2(1)
C(24)	34(1)	40(1)	27(1)	3(1)	-1(1)	0(1)
C(25)	36(2)	30(1)	52(2)	3(1)	-7(1)	-10(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x10^3) for 1.

Atom	x	y	z	U(eq)
H(1)	4370(20)	1324(16)	955(15)	20(7)
H(2)	2720(40)	1149(18)	275(18)	48(10)
H(3A)	853	2123	94	57
H(3B)	2133	2732	-94	57
H(4A)	1982	3548	873	57
H(4B)	423	3334	744	57
H(5)	380(20)	2570(20)	1674(19)	41(10)
H(6)	2030(40)	2440(20)	2486(11)	38(9)
H(7A)	4292	2624	2276	46
H(7B)	3698	3563	2000	46
H(8A)	3914	3160	875	42
H(8B)	5217	2692	1207	42
H(10)	1953	-562	458	33
H(11A)	726	-1563	1061	37
H(11B)	2035	-2202	994	37
H(13A)	1507	-1418	3225	57
H(13B)	2471	-853	3728	57
H(13C)	3106	-1511	3157	57
H(14A)	4449	-99	2787	52
H(14B)	3631	515	3323	52
H(14C)	3648	772	2519	52
H(16A)	-490	1340	3675	42
H(16B)	-1560	579	3444	42
H(17)	-604	1868	2592	29
H(19A)	5555	-1838	943	72
H(19B)	4170	-2214	1252	72
H(19C)	4799	-1293	1543	72
H(20A)	3192	-1381	-416	73
H(20B)	3060	-2244	79	73
H(20C)	4497	-1965	-228	73
H(21A)	5586	-542	155	86
H(21B)	4953	48	768	86
H(21C)	4251	37	22	86
H(23A)	-3224	987	2871	55
H(23B)	-3818	1020	2102	55
H(23C)	-3040	1877	2410	55
H(24A)	-1620	1854	1372	51
H(24B)	-2280	944	1080	51
H(24C)	-688	1002	1197	51
H(25A)	-921	-414	1910	59
H(25B)	-2522	-396	1817	59
H(25C)	-1878	-422	2577	59