NEW RUTHENIUM CATALYSTS FOR ASYMMETRIC HYDROGENATION

María Belén Díaz Valenzuela

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews

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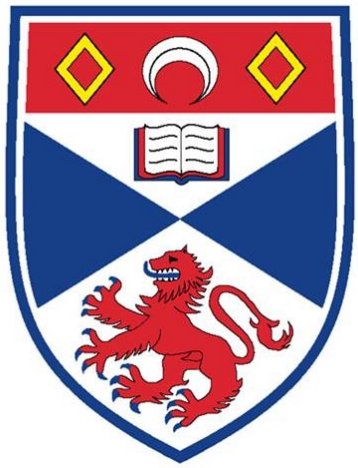

A thesis submitted for the degree of Ph.D. by

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St. Andrews November 2007

Declaration

I, María Belén Díaz Valenzuela, hereby certify that this thesis, which is approximately 28,700 words in length, has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree.

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I was admitted as a research student in October 2003 and as a candidate for the degree of Ph.D in October 2004; the higher study for which this is a record was carried out in the University of St Andrews between 2003 and 2006.

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In Memory Of

Ángel E. Barrera Saez

Life is not easy for any of us. But what of that?

We must have perseverance and above all confidence in ourselves.

We must believe that we are gifted for something

and that this thing must be attained.

Marie Curie

Acknowledgments

I would like to thank my supervisor Dr. Matt Clarke for giving me the opportunity to work in his laboratory. I am very thankful for his encouragement and invaluable advice. I would like to thank him as well as the friend that listen and cheer me up in difficult moments.

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I wish to express my gratitude to the School of Chemistry, University of St. Andrews for giving me the financial support to carry out my thesis project. Thanks to all people that have provided technical assistance during the course of this thesis.

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I would like to thank Alejandro. He has taught me that the best and most beautiful things in the world cannot be seen or even touched. They must be felt with the heart.

And finally, a mi familia, mis padres y hermano que con su amor y apoyo a lo largo de toda mi vida han hecho esto posible. ¡GRACIAS!

Abstract

A review on catalytic asymmetric hydrogenation of C=O double bonds is presented in the first chapter. Noyori's pioneering research on ruthenium complexes containing both phosphine and diamine ligands using ^{i}PrOH and ^{t}BuOK is described, this system gave impressive highly chemeo-selectivity for C=O bonds and extremely high enantioselectivity for a range of acetophenone derivatives. Numerous groups have been inspired by Noyori's catalyst of the type $RuCl_2$(chiraldiphosphine)(chiraldiamine), these systems often give excellent results for acetophenone. However, these catalysts have limitations, they are found to be either inactive or unselective for hydrogenation of tetralones, dialkylketones, bulky ketones, some heterocyclic ketones and imines prove difficult using this system.

In this project, we are searching for a new catalyst for asymmetric hydrogenation of ketones that solve the difficult challenges faced when using Noyori's [Ru(diphosphine)(diamine)Cl_2] catalysts system. Departing from Noyori's type catalyst in the second chapter is described our effort to synthesise new diamines derived from amino acids and the synthesis of [Ru(diamine)(diphosphine)Cl_2] complexes. These catalysts are tested in asymmetric hydrgenation of ketones. In the next two chapters the finding of a new tridentate P^N^NH_2 type ligand is reported and the novel ruthenium complex containing the tridentate ligand has been synthesised and characterised by X-ray crystallography and been found to be active in the hydrogenation of a range of C=O and C=N double bonds, including the enantioselective hydrogenation of normally unreactive bulky ketones with up to 93 % ee. The last chapter explains the transfer hydrogenation activity for this new catalyst, involving a novel method of transfer hydrogenation reaction under microwave irradiation.

Abbreviations

%	per cent
δ	chemical-shift, in parts per millions down-field of internal standard
$[\alpha]_D^{20}$	specific rotation at 20 ºC using the sodium D-line
Å	angström
AABPY	3-Amino-5-aminomethyl-Boc-pyrrolidine
Ac	acetyl ($CH_3C{=}O$)
acac	acetylacetonate
ala	alanina
Ar	aromatic
atm	atmosphere
bar	bar
BDPP	2,4-bis(diphenylphosphino)pentane (also SKEWPHOS)
BDPX	1,2-bis(diphenylphosphinomethyl)benzene
BHT	butylated hydroxy toluene (2,6-di-t-butyl-4-methylphenol)
BICP	2,2'-bis(diphenylphosphino)-1,1'-dicyclopentane
BINALH	lithium 2,2'-dihydroxy-1,1'-binaphthylethoxyaluminum hydride
BINAN	3,3'-N_2,N_2'-bis(6-pyridin-2-ylmethyl)-1,1'-binaphthyl-2,2'-diamine
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
BISBI	2,2'-bis((diphenylphosphino)methyl)-1,1'-biphenyl
Boc	*tertiary*-butyloxycarbonyl ($CO^tC_4H_9$)
br	broad (NMR)
Bu	butyl
c	concentration
cat	catalyst
CD	circular dichroism
ChiraPhos	2,3-Bis(diphenylphosphino)butane
CI	chemical Ionization (mass spec)
Cm	centimeter
Cod	cyclooctadiene
Cp	cyclopentadienyl

Cy	cymene
d	doublet (NMR)
d.e.	diastereomeric excess
DABCO	1,4-Diazabicyclo[2.2.2]octane
DAIPEN	2-1,1-Bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine
DAMDO	(2,3,5,6)-2,3-Dimethoxy-2,3-dimethyl-5,6-diaminomethyl-1,4-dioxane
DCM	dichloromethane
dd	doublet of doublets (NMR)
DIBAL	diisobutylaluminum Hydride
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPAMP	1,2-Bis(*ortho*-anisylphenylphosphino)ethane
DKR	dynamic kinetic resolution
dm	decimeter
DMAP	4-Dimethylaminopyridine
DMAPEN	2-dimethylamino-1-phenylethylamine
DM-DABN	3,3'-dimethyl-2,2'-diamino-1,1'-binaphthyl
DMF	dimethylformamide
DMO	dimethyl oxalate
DMSO	dimethyl Sulfoxide
DPBP	diphenylbutylpiperidine
DPEN	1,2-diphenylethylenediamine
Dppb	1,4-Bis(diphenylphosphino)butane
Dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
DPPN	1,8-bis(diphenylphosphino)naphthalene
d.r.	diastereoisomeric ratio
DuPhos	1,2-Bis(phospholano)benzene
e.e.	enantiomeric excess
e.g.	for example
EG	ethylene glycol
EI	electron Impact (MS)
eq.	equivalent
ES-	negative ion electrospray
ES+	positive ion electrospray

ESI	electrospray ionization
Et	ethyl
$Eu(hfc)_3$	tris-(3-heptafluorobutyryl-hydroxymethylene-(1*R*)-camphorato)-europium(III)
$Eu(thd)_3$	perfluoroalkyl camphorato chelates tris-(3-trifluoromethyl-hydroxymethylene-(1*R*)-camphorato)europium(III)
FAB	fast atom bombardment (MS)
FID	free induction decay (NMR)
FT	fourier transform
g	gram
GC	gas chromatography
GCMS	gas chromatography mass spectrometry
gly	glycine
h	hour
HexaPHEMP	4,4',5,5',6,6'-hexamethylbiphenyl
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrum
Hz	hertz
IPBAN	2,3-*O*-Isopropylidenebutane-1,4-diamine
Ipc_2BCl	bisisopinocampheylboranechloride
IPHAN	(*2*,3,4,5)-3,4-*O*-Isopropylidenehexane-2,5-diamine
^{i}Pr	isopropyl
IR	infrared
J	coupling constant (NMR)
KOH	potassium hydroxide
L	ligand
L-DOPA	3-(3,4-dihydroxyphenyl)-*L*-alanine
Lit	literature
m	medium (IR)
m	*metha*
M	moles per litre
m	multiplet (NMR)
m.p.	melting point
m/z	mass to charge ratio

M^+	molecular ion
Me	methyl
MeCN	acetonitrile
MG	methyl glycolate
mg	milligram
MHz	megahertz
min	minute
ml	millilitre
mm	millimetre
mmol	millimol
mol	mol
MOTPP	tris(4-methoxyphenyl)phosphine
MS	mass spectrum
MTBE	*tertiary*-Butyl methyl ether
n.d.	not determined
NMR	nuclear magnetic resonance
o	*ortho*
ºC	degree centigrade
OR	optical rotation
ORD	optical rotatory dispersion
p	*para*
Pd/C	palladium on activated carbon
PEG	polyethyleneglycol
PennPhos	1,2-bis-{2,5-disubstituted-7-phosphabicyclo[2.2.1]hept-7-yl)-benzenes
Ph	phenyl
PhanePhos	4,12-Bis(diphenylphosphino)-[2.2]-paracyclophane
P-Phos	2,2',6,6'-tetramethoxy-4,4'-bis(diphenylphosphino)-3,3'-bipyridine
ppm	parts per million
pro	proline
PTFE	polytetrafluoroethylene
Py	pyridine
q	quartet (NMR)
quin	quintet (NMR)

QUINAPHOS	1-(3,5-dioxa-4-phospha-cyclohepta[2,1-3,4]dinaphthalen-4-yl)-8-diphenylphosphanyl-1,2-dihydro-quinoline
r.t.	room temperature
Rf	retention Factor (chromatography)
s	singlet (NMR)
s	strong (IR)
S/C	substrate-catalyst ratio
SDP	spiro diphosphine
SKEWPHOS	2,4-bis-diphenylphosphino pentane (also BDPP)
solv	solvent
SYNPHOS	[(5,6),(5',6')-bis(ethylenedioxy)biphenyl-2,2'-diyl]bis(diphenylphosphine)
T	temperature
t	time
t	triplet (NMR)
TBDMS	*tert*-Butyldimethylsilyl
^{t}Bu	*tert*-butyl
Tf	triflate (CF_3SO_2)
TFA	trifluoroacetic acid
TFTPP	tris(4-trifluoromethylphenyl)phosphine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TOF	turn over frequency
TON	turn over number
Ts	tosyl (p-$CH_3C_6H_4SO_2$)
TS	transition state
UV	ultraviolet spectroscopy
w	weak (IR)
Xyl	xylyl
υ	wavenumbers (cm^{-1})

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CHAPTER I

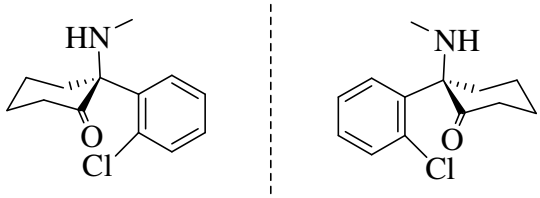
INTRODUCTION

Asymmetric Catalytic Hydrogenation of Ketones

1.1. Asymmetric catalysis

Asymmetric catalysis involves the conversion of an achiral or prochiral substrate to a chiral product with a preference for the formation of one optical isomer over the other by using a chiral catalyst to promote the transformation.

The demand for non racemic chiral compounds has increased a lot in the last years, especially due to the demands of the pharmaceutical industry for medicines, but also as agricultural chemicals, flavours, fragrances, and materials.[1] Many of the pharmaceutical compounds sold as medicines have to be single enantiomers. This is because in biological systems the (*R*) and (*S*) enantiomers can have very different effects, one of many examples is shown in Figure 1.1. This increased demand for chiral compounds has motivated intensive research to develop improved methods for the synthesis of optically pure compounds.[2]



(*S*) ketamine
anaesthetic

(*R*) ketamine
hallucinogen

Figure 1. 1. Each enantiomer has different properties.

Enantiomerically enriched compounds can come from natural sources '*the chiral pool*' and be further derivatised to give chemicals of commercial value, or by racemic synthesis followed by resolution of the two enantiomers. Both of these approaches have some disadvantages, in the first they require stoichiometric amounts of a suitable enantiopure

precursor and in the second approach the yields of the resolved enantiomers can only be up to 50 % for (*R*)- and (*S*)- respectively.[3]

In asymmetric catalysis each molecule of chiral catalyst is being continually regenerated and this can yield many molecules of chiral product, giving significant advantages over previous procedures.[2] Effective catalysts have been shown to come from natural sources (biocatalysts) or from synthetic methodology (chemocatalyst). Until recently, biocatalysts were superior and it is only in the last 20 years that asymmetric catalysis with synthetic catalysts achieved enantiomeric excesses close to 100 %.[3] Moreover, there are still very few catalytic reactions that achieve high ee under practical conditions suitable for industrial application.

Asymmetric catalysis has become one of the most powerful methods to produce single enantiomers, and now provides one of the most cost-effective and environmentally responsible methods for the production of a vast array of structurally diverse, enantiomerically pure compounds. Transition metal enantioselective catalysis is one of the most challenging and broadly investigated areas in modern organometallic chemistry.

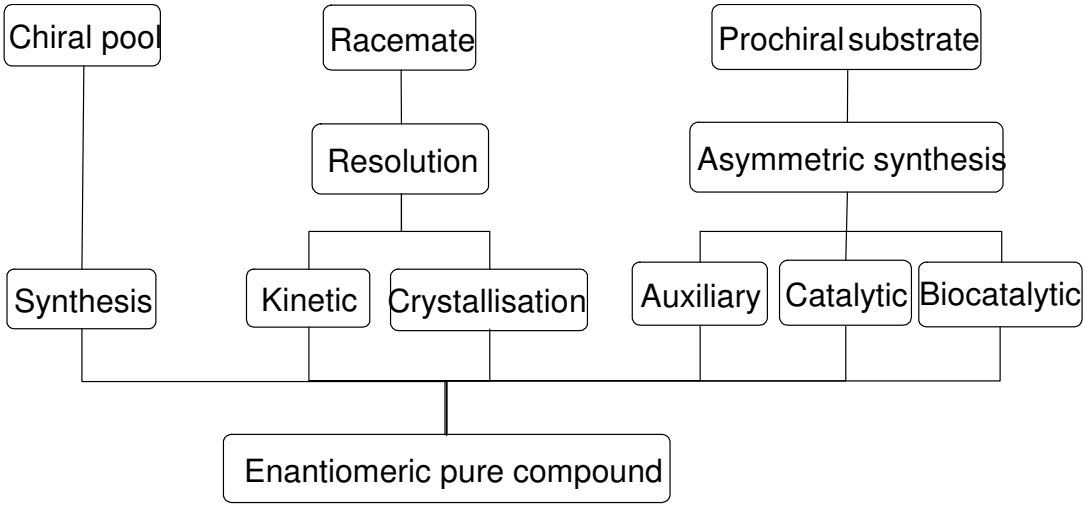


Figure 1. 2. Different approaches for enantiomeric pure compounds.

In 2001 the Nobel Prize in chemistry was awarded to W. S. Knowles,[4] R. Noyori[5] for their work on asymmetric hydrogenation and K. B. Sharpless[6] for his work on asymmetric catalytic oxidation.[7]

Asymmetric catalysis was dominated by oxidation and alkene hydrogenation in the early years but the scope of asymmetric catalysis has now grown to include a wide range of other reactions, greatly expanding the accessible methodologies for the generation of

enantiomerically enriched organic compounds. The generation of chiral carbon centres through C—C bond forming reactions: conjugate additions, aldol reactions, allylic alkylations, Diels–Alder reactions, cyclopropanation, and olefin-metathesis to name a few, are all examples of asymmetric catalysis that have grown over the last years. All these reactions can be applied in the synthesis of chiral natural products.

However, the most important challenges on this field are still to come, with much more research still remaining to be done so that a complete understanding of asymmetric catalysis can be achieved to the point where rational design of ligands can be undertaken. For many asymmetric catalytic reactions, high ee's have only been realised for a few simple model substrates under conditions that could not be viable in industry. In future years, it is expected that more and more asymmetric catalytic reactions will be developed to the extent that they can be considered practical. Asymmetric catalysis is therefore one of the most challenging and intensively researched areas in modern chemistry

1.2. Asymmetric Catalysis in Industry

Enantioselective catalysis is not just an academic model but can be a suitable tool for large-scale production of enantio-enriched intermediates. Technical-scale can be anything from a few kilograms of a chiral pharmaceutical compound to several thousand tons for a herbicide.[8]

The application of homogeneous enantioselective catalysis on industrial scale presents some problems.[3] Both, time and money are the most important factors in industrial synthesis, so when an asymmetric catalytic process wants to be applied in an industrial process two questions need to be answered; a) Can the costs for the over-all manufacturing process compete with alternative routes and b) can the catalytic step be developed in the given time frame. Many factors have to be taken into account before an industrial process can be accepted: enantioselectivity and chemoselectivity are critical factors for catalysis on an industrial scale, but equally important to this is the activity, as measured by the TON (turn over number) and TOF (turn over frequency). Many academic reactions only display TON of 20 or less. TON of >200 is acceptable at small scales, >10,000 is necessary at large scale. It is also important that the catalyst can be removed from the products and ideally recycled although this has been seldom achieved thus far. The other main issues are the cost of the reagents, development time, catalyst stability, handling problems, yield, poisoning, toxicity,

safety and whether special equipment is required complete the list. Process chemists have an important role in the application of catalytic processes to industrial scale.

Despite all the problems presented for industry when catalysis is involved, homogeneous asymmetric catalysis can be an applicable process for industry and in recent years the industrial application of enantioselective homogeneous catalysis has made slow but significant progress. Even if many processes has been proven to be suitable for application in industrial manufacture only, few are implemented as production processes operating on a regular basis, sometimes due to other non chemistry problems, eg. failure of a drug in phase III trials, licensing or sourcing issues. Some existing applications within industry that have a broad scope are hydrogenation of enamines, itaconates and β-functionalised C=O bonds. One of the reasons for the huge importance of hydrogenation is that chiral alkanes, acids, amines, amides and alcohols can all be prepared from the readily available alkenes and ketones using cheap hydrogen gas. It has been estimated that homogeneous diphosphine complexes of Ru, Rh and sometimes Ir are the most versatile for industrial asymmetric hydrogenation.

1.2.1. The Monsanto L-DOPA process

The first example of application of asymmetric catalytic hydrogenation in industry is the Monsanto L-DOPA process.[8] The development of catalysts for asymmetric hydrogenation of prochiral olefins began by replacing the triphenylphosphine ligand of the Wilkinson catalyst with a chiral ligand.[1] First, Knowles and co-workers replaced the triphenylphosphine by a chiral monophosphine where the phosphorus atom was the steoreogenic centre, however, low enantioselectivities were obtained. Later on Kagan and co-workers demonstrated that a chiral phosphorus atom was not necessary if a chiral bidentate ligand was used, as for example the C_2-symmetric DIOP (diphosphine ligand), with the chirality in the carbon backbone. After this development, Knowles invented with a chelating diphosphine ligand, DIPAMP, where the chirality resided on the phosphorus atom. The Rh-DIPAMP catalyst was very successful giving a 96 % ee in the L-DOPA process, making the Monsanto company the first supplier of this drug for Parkinson's disease.

Due to the success of this homogeneous hydrogenation catalyst a new era in catalytic processes began. There are now several industrial processes for asymmetric alkene hydrogenation running at commercial scale. The asymmetric hydrogenation of ketones is a newer field but has already reached industrial production in the case of functionalised ketones

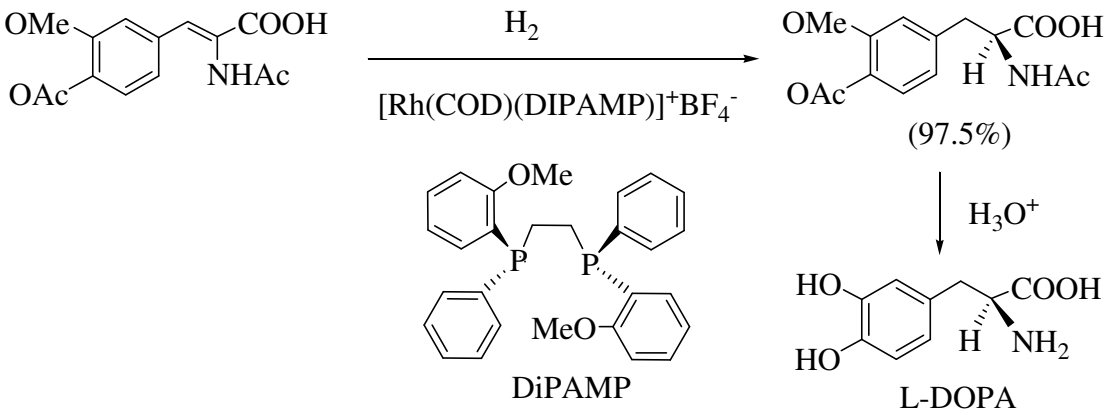


Figure 1. 3. The Monsanto L-DOPA synthesis

1.3. Ketone Hydrogenation

1.3.1. Hydrogenation of functionalised ketones

BINAP-Ru(II) complex catalysts have proved extremely efficient for the asymmetric hydrogenation of functionalized ketones[9, 10] which has resulted in the industrial production of synthetic intermediates of antibiotic carbapenems and antibacterial Levofloxacin. Rate improvement and stereochemical control are effectively accomplished by coordination of the functional group to the catalytic Ru (II) centre. BINAP-Ru (II) catalysts, though displaying a very wide scope, are unable to hydrogenate simple ketones that lack heteroatoms which anchor the substrate to the Ru metal.

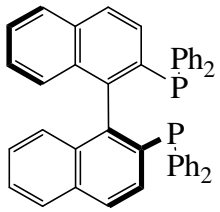
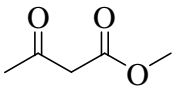
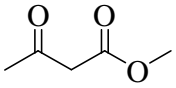
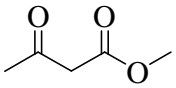
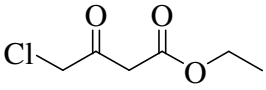
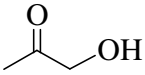
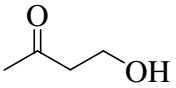
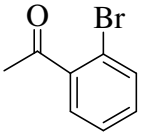


Figure 1. 4. (*S*)-BINAP

BINAP-Ru (II) complexes catalyze highly enantioselective hydrogenation of a wide variety of functionalised ketones including β-keto esters. In the BINAP-Ru (II) catalysed reaction, diverse polar functionalities facilitated hydrogenation of the neighbouring carbonyl group and allow the efficient enantioface differentiation. The halogen containing complexes of the type RuX_2(BINAP) can be used as catalysts with a wide range of functionalised ketones, giving excellent levels of enantioselectivity (Table 1. 1).[9, 10]

Table 1. 1[9, 10]

substrate	catalyst system	T / ºC	H_2 /atm	t / h	product	
					yield %	ee %
	$RuCl_2$[(*R*)-BINAP]	25	100	40	97	99 (*R*)
	$RuCl_2$[(*R*)-BINAP]	100	100	0.5	97	98 (*R*)
	$RuCl_2$[(*S*)-BINAP]	100	4	6	95	98 (*S*)
	$RuCl_2$[(*S*)-BINAP]	100	4	6	97	93 (*R*)
	$RuCl_2$[(*R*)-BINAP]	30	100	40	97	91 (*R*)
	$RuCl_2$[(*R*)-BINAP]	30	100	40	96	98 (*R*)
	$RuCl_2$[(*S*)-BINAP]	100	100	3	83	96 (*S*)

1.3.2. Hydrogenation of unfunctionalised ketones.

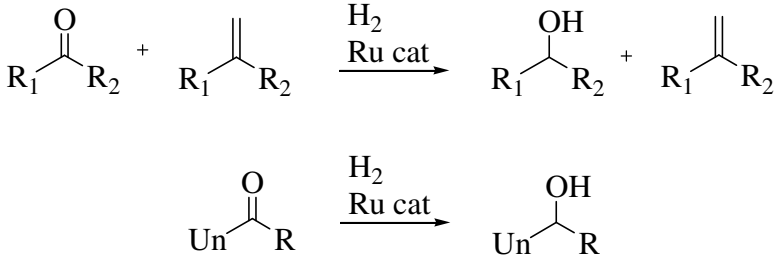
In the 1990s the development of new systems capable of catalysing homogeneous asymmetric hydrogenation of prochiral ketones was highly desirable because the majority of the existing homogeneous and heterogeneous catalysts hydrogenated unsaturated carbon-carbon bonds preferentially over a carbonyl moiety and the excellent results achieved with $Ru(BINAP)X_2$ catalysts were limited to functionalised ketones.[11]

In spite of the extensive studies, only a few metal catalysts were known to exhibit reasonable activity in hydrogenation of unfunctionalised simple ketones. Asymmetric hydrogenation of simple achiral ketones was even more difficult. The lack of reactivity of diphosphine-Ru (II) complex with simple ketones is due to the absence of coordinating heteroatom near the carbonyl group.[12]

Homogeneous hydrogenation of unfunctionalised ketones became a reality after Noyori report of ruthenium complexes containing both phosphine and diamine ligands in 1995.[13] Noyori contemplated, that using protic neutral ligands, like N-H, could improve the activity and selectivity of the BINAP-Ru (II) catalyst in asymmetric hydrogenation of ketones

by forming a hydrogen bond with the C=O moiety. The rationale behind this was a metal-ligand bifunctional catalyst that was capable of binding the substrate on a specific face by hydrogen bonds.

This catalytic system uses both hydrogen gas and alcohol solvent such as ^{i}PrOH, with the aid of Ru (II) complexes and a base co-catalyst, i.e., KOH. In their search for a reactive catalyst system, they used a solution in ^{i}PrOH containing $[RuCl_2\{P(C_6H_5)_3\}_3]$ and KOH (ketone:Ru:base.5000:1:20). Noyori and coworkers discovered that the addition of ethylenediamine enormously accelerated the hydrogenation giving a TOF of 6700. Subsequently they found that the preformed *trans*-$[RuCl_2(phosphine)_2(1,2\text{-diamine})]$ complexes serve as stable precatalysts and effect the even more rapid and productive hydrogenation of functionalised and unfunctionalised ketones. These systems were very active, chemoselective, enantioselective and diastereoselective in asymmetric catalytic hydrogenation.



R = H, alkyl, aryl
Un = olefin- or acetylene- containing group

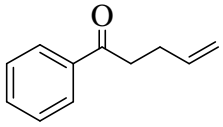
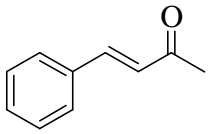
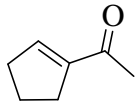
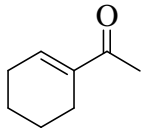
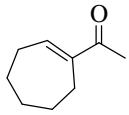
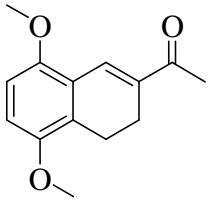
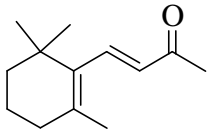
Figure 1. 5

$RuCl_2[P(C_6H_5)_3]_3$ is an excellent catalyst for olefin hydrogenation but very poor for carbonyl hydrogenation when there is no diamine present. A competition experiment using a mixture of heptanal and 1-octene with the Ru (II) complex under a H_2 atmosphere revealed that the terminal olefin was saturated 250 times faster than the aldehyde. However, when $NH_2(CH_2)_2NH_2$ and KOH (1 and 2 equiv with respect to Ru, respectively) were present under, the otherwise, identical conditions heptanal was hydrogenated 1500 times faster than 1-octene. This hydrogenation is very general and practical. A wide variety of conjugated and unconjugated enal or enone substrates were shown to be selectively converted to the corresponding unsaturated alcohols, often in near quantitative yield. The excellent C=O *versus* C=C selectivity is significant and comparable to that obtained by the stoichiometric $NaBH_4$ reduction.

1.3.3. Noyori's [$RuCl_2$(Diphosphine)(Diamine)] catalyst system

Replacing PPh_3 and $NH_2(CH_2)_2NH_2$ with the auxially chiral ligand BINAP, and a chiral diamine such as those shown in Figure 1. 6 allows extremely efficient asymmetric hydrogenation of unfunctionalised and unsaturated ketones. Table 1.2 lists some examples of the asymmetric hydrogenation attained with this catalytic system.[12] The extent of the enantioselection is dependent on the structures of the ketonic substrates and chiral ligands, while the chemoselectivity and chemical yield are consistently high. The hydrogenation of the enone (1-(5,8-dimethoxy-3,4-dihydro-naphthalen-2-yl)-ethanone), entry 6, catalyzed by a $RuC1_2$[(R)-BINAP](DMF)/(*R*)-DAIPEN/KOH system gave the unsaturated (*S*) alcohol in 94 % ee. This is a key intermediate for the synthesis of anthracyclin antibiotics.

Table 1. 2. Enantioselective Hydrogenation of unsaturated ketones by a $RuCl_2$(BINAP)(DMF)n/diamine/KOH system[12]

entry	enone	diphosphine/diamine	H_2 / atm	t / h	yield %	ee %
1		(*S*)-BINAP/(*S*)-DAIPEN	8	3	97	90 (*R*)
2		(*S*)-BINAP/(*S*)-DAIPEN	8	1	98	70 (*R*)
3		(*S*)-BINAP/(*S*)-DAIPEN	4	5	100	91 (*R*)
4		(*S*)-BINAP/(*S*)-DAIPEN	8	5	91	98 (*R*)
5		(*S*)-BINAP/(*S*)-DAIPEN	4	2	95	81
6		(*R*)-BINAP/(*R*)-DAIPEN	8	1.5	100	94(*S*)
7		(*R*)-BINAP/(*R,R*)-DPEN	8	20	95	92 (*S*)

Reactions conducted at 28 ºC using 0.4-1.3 M solution of substrate in ^{i}PrOH. Substrate/$RuCl_2(BINAP)(DMF)_n$/diamine /KOH ratio 500:1:1:2

Although the previous Ru-catalyst was very efficient, it was not universally applicable. To further improve on Noyori's preliminary results, a wide range of chiral ruthenium catalysts were prepared by different combinations of chiral diphosphine and diamine ligands (Figure 1. 6).

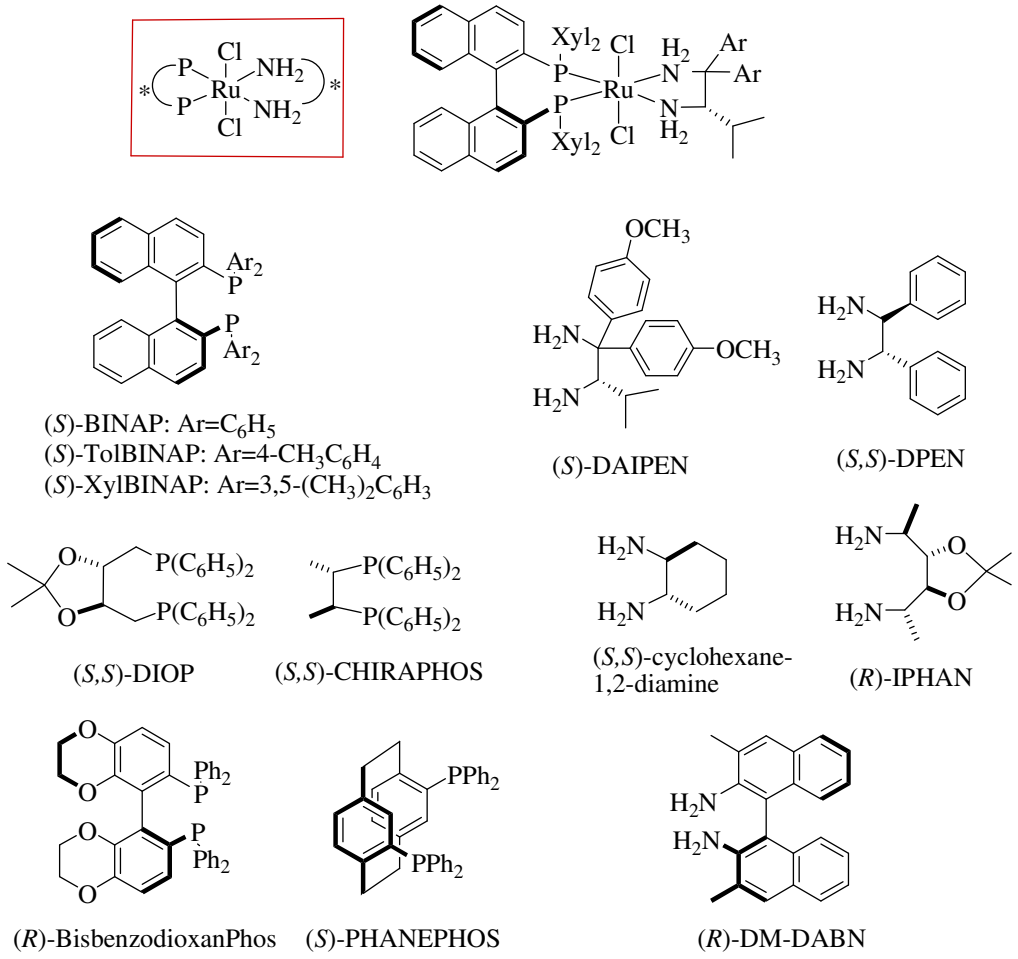


Figure 1. 6. Diphosphines and diamines ligands for Noyori's catalyst system.

Aromatic ketones can be hydrogenated enantioselectively by the BINAP-Ru(II)-diamine-inorganic base catalyst system, where the diamines act as the most effective chiral controllers, Table 1. 3 lists some representative examples. The extent of the enantioselectivity appears to be delicately influenced by the structures of the diamine auxiliaries as well as the substituents in the substrates and not by the hydrogen pressure.[5]

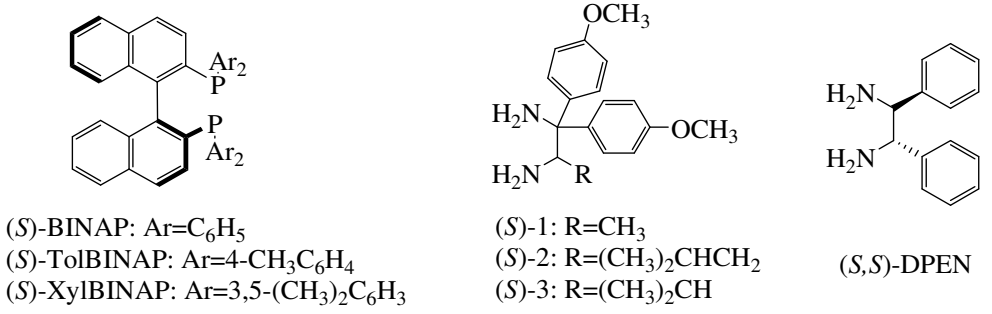
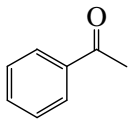
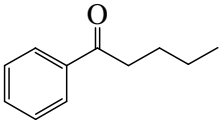
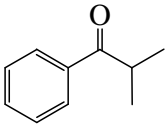
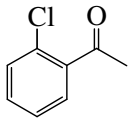
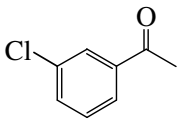
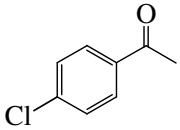


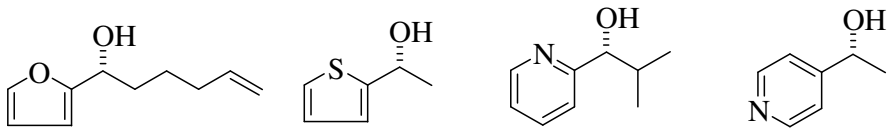
Figure 1. 7

Table 1. 3

ketone	phosphine/diamine	H_2 / atm	t / h	yield %	ee %
	(*S*)-BINAP/(*S*)-3	4	3	>99	87 (*R*)
	(*S*)-XylBINAP/(*S*)-3	4	3	>99	99 (*R*)
	(*S*)-TolBINAP/(*S*)-3	4	3	>99	91 (*R*)
	(*S*)-BINAP/(*S*)-1	4	3	>99	90 (*R*)
	(*S*)-TolBINAP/(*S*)-3	8	6	>99	95 (*R*)
	(*S*)-TolBINAP/(*S*)-DPEN	50	3	>99	94 (*R*)
	(*S*)-TolBINAP/(*S*)-3	8	1	96	90 (*R*)
	(*S*)-TolBINAP/(*S*)-3	8	16	>99	94 (*R*)

Reactions carried out at 28 ºC with S/C ratio up to 100 000

Hetereoaromatic ketones can be hydrogenated as well using this system. Heteroaromatic alcohols are obtained with very high ee in the presence of *trans*-[$RuCl_2${(*S*)-XylBINAP}{(*S*)-DAIPEN}], ^{t}BuOK, ^{i}PrOH, 8 atm H_2, and 25 – 30 ºC (Figure 1. 8). However, some heteroaromatic substrates required the presence of borate to obtain good selectively and some other substrates have not been reduced.

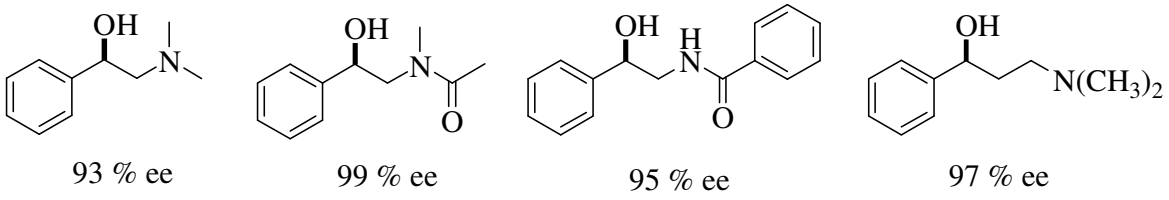


97 % ee 99 % ee 94 % ee 99.8 % ee

Figure 1. 8. Asymmetric hydrogenation with [$RuCl_2$(*S*)-XylBINAP/(*S,S*)-DAIPEN]

Difficult substrates for this system were found to be cyclopropyl ketones and dialkyl ketones. Hydrogenation of cyclohexyl methyl ketone catalysed by the (*R*)-XylBINAP/(*R*)-DAIPEN complex gave only an 85 % ee, 2-nonanone gave almost racemic material and 4-phenyl-2-butanone with (*S*)-XylBINAP/(*S,S*)-DPEN gave 51 % ee.

Amino ketones are very interesting substrates because the chiral amino alcohols obtained are often pharmaceutical intermediates. This Noyori's system proves to be efficient for the hydrogenation of these substrates.



93 % ee 99 % ee 95 % ee 97 % ee

Figure 1. 9. Asymmetric hydrogenation with [$RuCl_2$(*S*)-XylBINAP/(*S*,*S*)-DAIPEN]

1.4. Mechanism

Complexes of the type [RuX_2(diphosphine)] are catalysts for hydrogenation of functionalised ketones. The mechanism involves a monohydride route with an inner-sphere transfer of hydride to the carbonyl of the ketone. See Figure 1.10 and Figure 1.11.[14]

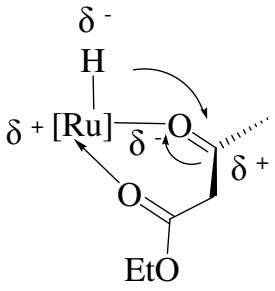


Figure 1. 10. Inner-sphere hydride transfer

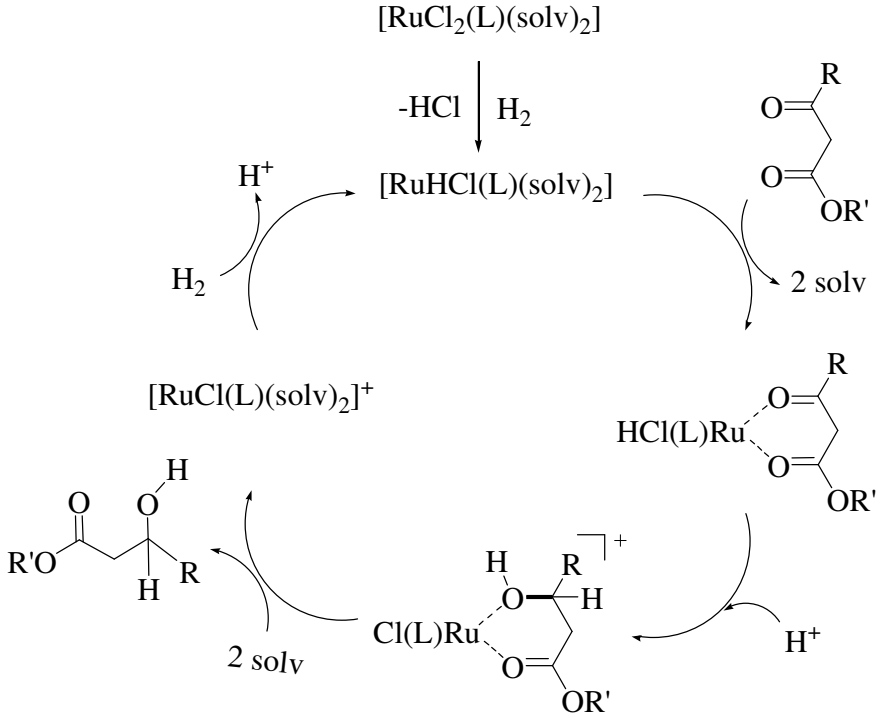


Figure 1. 11. Conventional mechanism for asymmetric hydrogenation with Ru(II).

Noyori's complexes containing diamines hydrogenate unfunctionalised ketones. These catalysts follow a different mechanism to simple $Ru(BINAP)X_2$ catalysts (Figure 1.11). In this case an outer-sphere transfer of the hydride to the carbonyl by an N-H group mechanism is described (**TS_1**, Figure 1. 12). In this hydrogenation mechanism both, ruthenium and amine are involved. The reason for the massively enhanced reactivity relative to simple Ru-phosphine catalysts is proposed to be the unique way in which the substrate hydrogen bonds to the N-H functionality in the diamine ligand.

The proposed mechanism of the reaction by Noyori is shown in Figure 1. 12. $RuCl_2(PR_3)_2\{NH_2(CH_2)_2NH_2\}$ (**1**) is converted into $RuHX(PR_3)_2\{NH_2(CH_2)_2NH_2\}$ (**2**; X=H or OR) in the presence of a base and a hydride source (H_2 and a trace of ^{i}PrOH). The major role of the strong base (2 equivalents relative to Ru) is to neutralize HCl formed by the loss of the 2 Cl^- ion in this process. The catalytic cycle involves two ground-state components, **2** and **3**, which are linked by transition state **TS_1**. The NH proton in **2** plays a key role in hydrogen delivery to ketones, while the amide nitrogen in **3** cleaves H_2 . The high turnover effectiveness depend on the functions of the complexes **2** and **3**, in which the metal centres and the ligands directly cooperate in bond-breaking and -forming reactions.[5]

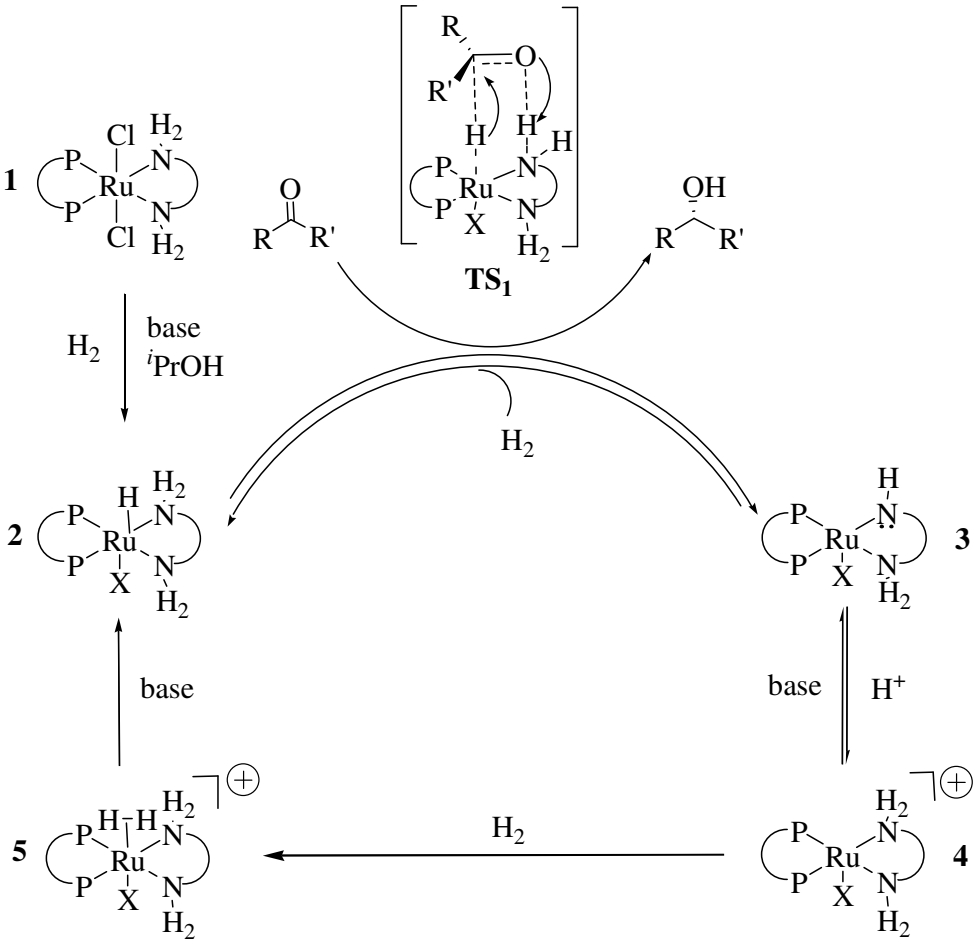


Figure 1. 12. Mechanism of Noyori's hydrogenation with [Ru(diamine)(diphosphine)X_2]

Recent mechanistic studies by Bergens[15] and Morris[16] suggest that a *trans*-dihydride complex and an amine amido complex are the active catalysts in the main cycle. The dihydride forms a six-membered Ru-H···C-O···H-N ring with the aryl ketone in the transition state, while simultaneous outer-sphere hydride and proton transfer gives the alcohol and an amine amido complex with a distorted trigonal bipyramidal geometry about Ru (II). Addition of dihydrogen to the ruthenium-amido bond *via* an unstable dihydrogen complex regenerates the *trans*-dihydride. The lack of *cis*- coordination sites to the hydride means that C=C bond cannot be hydrogenated by an inner-sphere mechanism, and so these catalysts are selective for the hydrogenation of polar bonds (C=O, C=N) over C=C bonds.

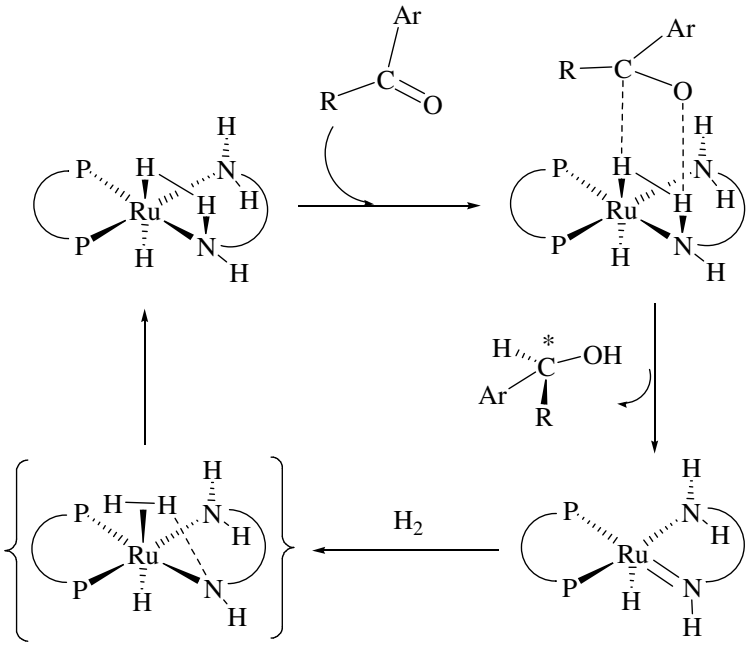


Figure 1. 13. Proposed mechanism with the *trans*-dihydride and hydridoamido.

The use of a diamine without α-hydrogens allows the isolation of well-defined *trans*-dihydrides (Figure 1. 14) and hydridoamido complexes so that mechanistic details of the hydrogenation of ketones catalyzed by Noyori's [$RuCl_2$(diamine)(phosphine)] complexes were examined.[17] The structure of chiral dihydrides is important because this determines the enantioselectivity of the hydrogenation of prochiral ketones.

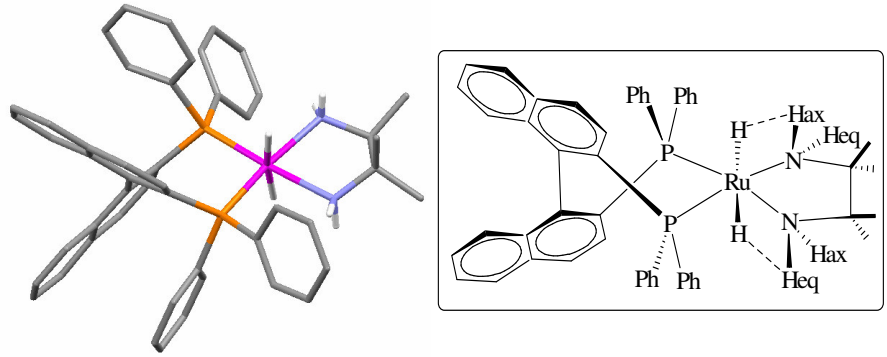


Figure 1. 14. Isolated intermediate by Morris[17]

Noyori has explained the origin of enantioselection for simple ketones as being according to the "metal-ligand bifunctional mechanism" (Figure 1. 12).[18] The absolute configuration of the alcohol is determined at the stage of **2 → 3.** Both possible diastereomeric transition states (TS_{Si} and TS_{Re}) utilise the H_{ax} proton for the formation of the ring due to the smaller H-Ru-N-H_{ax} dihedral angle. The (*R*) alcohol is selectively formed because the TS_{Re} that gives the (*S*) alcohol suffers a high repulsion between the phosphorous substituents (Tol or Xyl) and the phenyl ring of acetophenone.[19] This explanation is consistent with the result that the use of bulkier XylBINAP achieves higher optical yield.

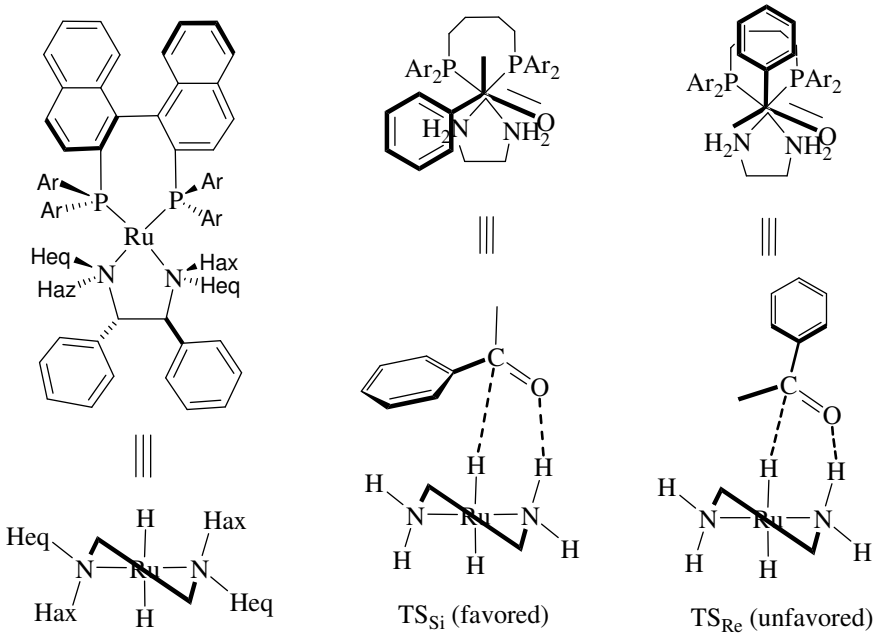


Figure 1. 15. Schematic explanation of the origin of enantioselectivity for simple ketones

1.5. Noyori inspired catalysts: new diphosphines and diamines.

The importance of asymmetric hydrogenation of ketones has led to a huge amount of research in this area especially throughout the last years. As seen before, Noyori's discovery of the highly effective Ru (II) catalytic system was a breakthrough in the field. From that moment even more intense research has been carried out, chemists are facing the task of designing a wide range of catalysts, these range from the Noyori inspired catalyst analogues to completely different systems with the aim of finding the best catalytic process for asymmetric hydrogenation of ketonic products without the constraints that were observed for the Noyori system.

It is useful to review here some of the most efficient developed systems up to early 2007. Some analogues of Noyori's catalyst have shown relevant improvements in hydrogenation of ketones, more importantly catalysts that differ from Noyori's system in

molecular design achieve the goals in asymmetric hydrogenation of ketones from a new perspective.

1.5.1. Base-Free hydrogenation

The development of a robust (pre)catalyst that promotes the enantioselective reaction under base-free conditions was desirable. Noyori designed a new type of chiral Ru complex that met this demand.[20] The asymmetric hydrogenation using a newly devised RuH(η^1-BH_4)(BINAP)(1,2-diamine) Figure 1. 16 complex proceeded without any base, with a high substrate/catalyst molar ratio (S/C), up to 100000, and with a 3-4 M substrate concentration in ^{i}PrOH.

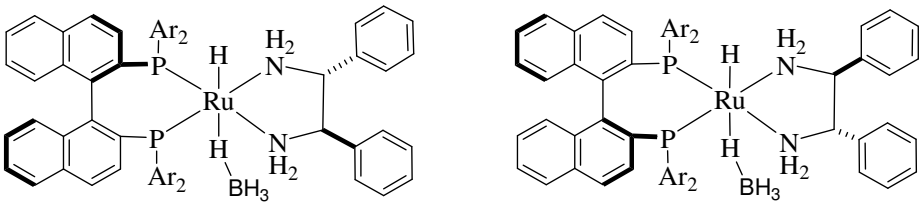
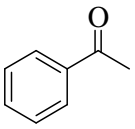
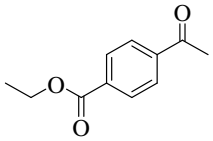
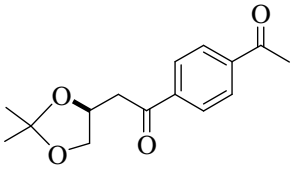
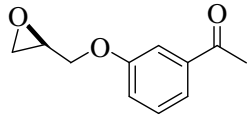
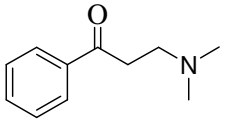
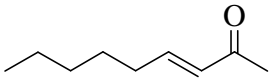


Figure 1. 16. Noyori's RuH(η^1-BH_4)(BINAP)(DPEN) catalysts

Table 1. 4[a]

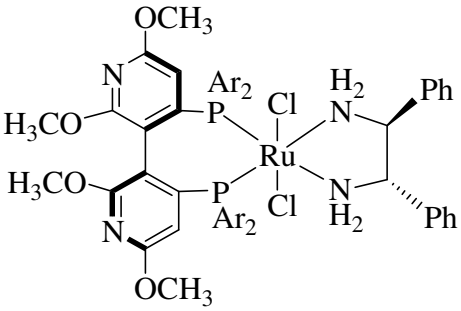
ketone	Ru cat	S/C	t / h	yield %	ee %
	(*R,RR*)[b]	100000	6[c]	99.9	82 (*S*)
	(*S,SS*)[b]	100000	7[d]	100	99 (*R*)
	(*S,SS*)	2000	12[e]	99.9	97 (*R*)
	(*S,SS*)	4000	12	99.9	99 (*R*)
	(*S,SS*)	4000	15	100	99 (*R*)
	(*S,SS*)	2000	16	100	97 (*R*)
	(*S,SS*)	2000	14	99	99 (*R*)
	(*S,SS*)	4000	12	100	97 (*R*)
	(*S,SS*)	4000	16	95	99 (*R*)

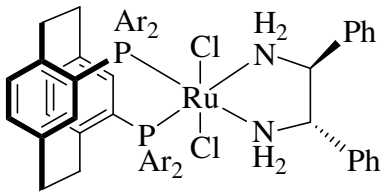
[a] Unless otherwise stated, reactions were conducted at 8 atm of H_2 at 23-25 °C using a 1.0-2.0 M ketone solution in ^{i}PrOH [b] Reaction using 102 g of substrate in 100 ml of ^{i}PrOH (3.4 M) [c] Reaction temperature was increased to 38 °C by the heat of reaction [d]At 45 °C [e] At 1 atm of H_2

This method demonstrated the excellent performance in hydrogenation of some base-sensitive ketones.[20] This base-free procedure using the new chiral Ru (II) complexes substantially expands the scope of asymmetric hydrogenation of ketones. In the presence of a base, these complexes are more reactive than the standard $RuCl_2$ complexes.

1.5.2. New diphosphines

$[RuCl_2(XylBINAP)(DAIPEN)]$ has been the best system for asymmetric hydrogenation of simple ketones. Many new diphosphine ligands have been reported, although few approach the utility of Noyori's catalyst. In 2000 Burk et al,[21] reported PhanePhos and Chan[22, 23] in 2002 developed a new class of chiral dipyridylphosphine ligands (Figure 1. 17). $Ru(PhanePhos)(DPEN)Cl_2$ and $Ru(PPhos)(DPEN)Cl_2$ gave equivalent results to the $Ru(BINAP)(DAIPEN)Cl_2$ system for asymmetric hydrogenation of ketones. These diphosphines in combination with Ru (II) and DPEN have a broad substrate scope, high catalytic activity and high level of absolute stereocontrol.





(*R*)-P-Phos, Ar = C_6H_5 (S)-PhanePhos, Ar=Ph
(*R*)-Tol-P-Phos, Ar = 4-$CH_3C_6H_4$ (S)-Xyl Phanephos, Ar= 3,5-$(CH_3)_2C_6H_3$
(*R*)-Xyl-P-Phos

Figure 1. 17

A wide variety of aromatic ketones can be hydrogenated quantitatively with excellent enantioselectivities (up to > 99.9 %) using these ligands in combination with DPEN and ^{t}BuOK in ^{i}PrOH solution with a substrate-to-catalyst ratio (S/C) up to 100000 under hydrogen pressure.

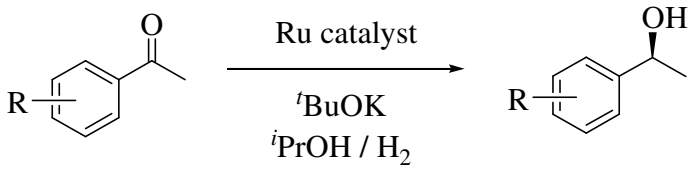


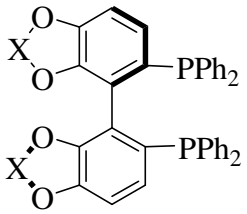
Figure 1. 18

Table 1. 5[a]

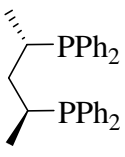
R-	Ru catalyst	conversion %	ee %
H-	(*R*)-Xyl-P-Phos / (*R,R*)-DPEN[b]	100	98.5 (*S*)
H-	(*S*)-PhanePhos / (*S,S*)-DPEN	100	98 (*S*)
H-	(*R*)-PhanePhos / (*S,S*)-DPEN	100	99 (*R*)
-*o*-CH_3	(*R*)-Xyl-P-Phos / (*R,R*)-DPEN[b]	100	98 (*S*)
-*o*-OCH_3	(*R*)-Xyl-P-Phos / (*R,R*)-DPEN[b]	99.6	94 (*S*)
-*o*-Br	(*R*)-P-Phos / (*R,R*)-DPEN[b]	90.7	>99.9 (*S*)
-*o*-Br	(*R*)-Tol-P-Phos / (*R,R*)-DPEN[b]	100	>99.9 (*S*)
-*o*-Br	(*R*)-Xyl-P-Phos / (*R,R*)-DPEN[b]	100	>99.9 (*S*)
-*o*-CH_3	(*S*)-XylPhanePhos / (*R,R*)-DPEN	100	97 (*R*)
-*o*-OCH_3	(*S*)-XylPhanePhos / (*R,R*)-DPEN[c]	100	94 (*R*)
-*o*-Br	(*S*)-XylPhanePhos / (*R,R*)-DPEN	100	99 (*R*)

[a] Reactions were performed with 1-2.5 M solutions of ketone in ^{i}PrOH at S/C 3000/1 unless otherwise noted, with added ^{t}BuOK base/Ru = 50/1 at 18-28 °C and 5.5-8.0 atm hydrogen pressure. Reactions were allowed to proceed for 0.5-2 h, giving complete conversion, unless otherwise noted [b] 20 atm of H_2 and 24h reaction time [c] Reaction time was 2.5 h at S/C = 500

Genêt (SKEWPHOS or SYNPHOS)[1, 24-26] or Lin (4,4'substituted-XylBINAP ligand)[27] have reported very effective catalyst systems for highly enantioselective hydrogenation of a diverse range of simple aromatic ketones. These catalysts combine desirable features, such a fast rate of reaction, broad substrate scope, excellent enantioselectivity (up to 99 % ee) and high substrate-to-catalyst ratio making the catalyst system of high practical interest.



(*S*)-SYNPHOS, X = C_2H_4
(*S*)-DIFLUORPHOS, X = CF_2



(*S*)-SKEWPHOS

Figure 1. 19. Genêt diphosphines ligands

A family of adjustable precatalysts Ru(4,4'-BINAP)(chiraldiamine)Cl_2 were synthesized and used for highly enantioselective hydrogenation of aromatic ketones.[28] The

bulky substituents at the 4,4'-positions of BINAP effectively create a suitable chiral pocket during the transition state, thus providing a new mechanism for improving chirality transfer. By taking advantage of bulky 4,4'-substituents on the BINAP moiety, excellent ee's were obtained without resorting to the bis(xylyl)phosphino groups.

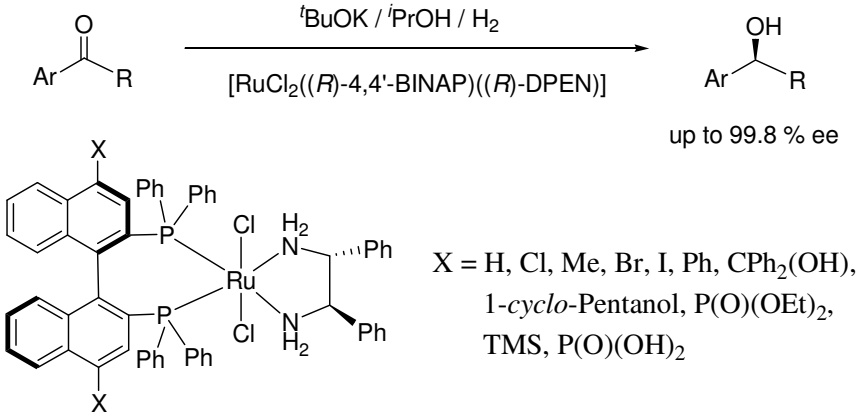


Figure 1. 20

Henschke et al [29-32] synthesised HexaPHEMP (Figure 1. 21), a novel biaryl diphosphine ligand. Ru (II) complex of type [Ru(HexaPHEMP)(DPEN)Cl_2] were found to have enhanced activity and enantioselectivity over [Ru(BINAP)(DPEN)Cl_2] in asymmetric hydrogenation of ketones.

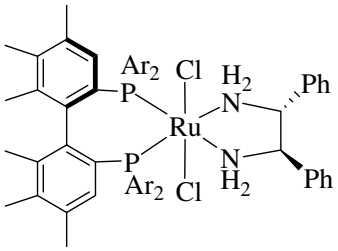


Figure 1. 21. HexaPHEMP (Ar = Ph or Xyl)

Chiral spiranes, a class of *C*2-symmetric molecules, which possess axial chirality can be used as ligands in catalytic asymmetric hydrogenation.[33] The high rigidity of the spiro cyclic framework should decrease the flexibility of the ligands and their related complexes, and consequently benefit asymmetric induction in the catalysis.

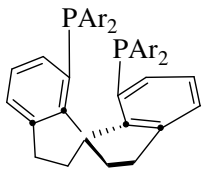


Figure 1. 22. (*S*)-SDP

The Ru (II) complexes of spiro diphosphine (SDP) ligands were very effective catalysts in the asymmetric hydrogenation of simple ketones. Among the SDP ligands, (*S*)-

Xyl-SDP (Figure 1. 23), having 3,5-dimethyl groups on the *P*-phenyl rings, was found to induce the highest amount of enantiselectivity. For instance, the catalyst {[(*S*)-Xyl-SDP]Ru[(*R,R*)-DPEN]Cl_2} provided 1-phenylethanol in 98 % ee and 100 000 turnover number in the hydrogenation of acetophenone. A variety of ketones, including aromatic, heteroaromatic, and α,β-unsaturated ketones, can be hydrogenated by {[(*S*)-Xyl-SDP]Ru[(*R,R*)-DPEN]Cl_2} catalyst in excellent enantioselectivities and high turnover numbers.[34] This catalyst is therefore comparable to Ru(XylBINAP)(DAIPEN)Cl_2.

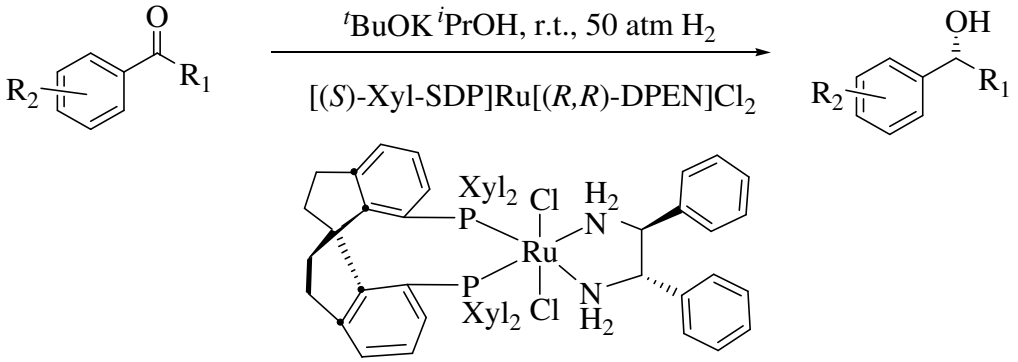


Figure 1. 23

Table 1. 6[a]

R_1	R_2	ee %	R_1	R_2	ee %
$-CH_3$	-H	99	$-CH_3$	-*p*-Me	98
$-CH_3$	-*o*-Cl	98	$-CH_3$	-*p*-Cl	99
$-CH_3$	-*o*-Br	99.2	$-CH_3$	-*p*-Br	99
$-CH_3$	-*m*-Br	99.2	$-CH_3$	-Ph	99.2
$-CH_3$	-*m*-CF_3	99	$-CH_2CH_3$	-H	99.5
$-CH_3$	-*m*-CH_3	99.2	$-CH_2Ph$	-H	98

[a] Reactions were conducted at 20-25 °C under 50 atm of H_2 pressure using a 2.0-2.5 M solution in ^{i}PrOH containing the catalyst (S/C = 5000) and ^{t}BuOK (S/B = 70). Full conversion for all the substrates

Kinetic resolution is the achievement of partial or complete resolution by diferent rates of reaction of the enantiomers in a racemate with a chiral agent. Therefore, kinetic resolution only gives yield up to 50 %. If racemisation can occur simultaneously with kinetic resolution, then theoretically 100 % of the racemic mixture can be converted to one enantiomer. This process is known as dynamic kinetic resolution (DKR). The first reported example of DKR by hydrogenation was Noyori in 1989 with the Ru-BINAP hydrogenation catalyst. β-ketoester, which readly isomerizes via an enol intermediate is reduced with the Ru-BINAP catalyst to give one of the four diastereoisomers in high de (99:1 syn:anti) and ee (98 %, 2*S*, 3*R*). The catalyst not only differentiates between the enantiotopic faces of the ketones, it can also discriminate between enantiomers at the α position.[35]

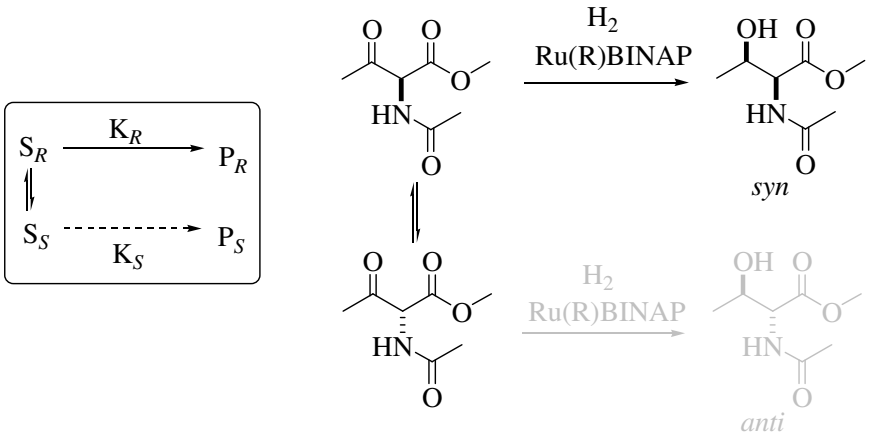


Figure 1. 24. Dynamic Kinetic Resolution

The $RuCl_2$[(*S*)-Xyl-SDP][(*R*,*R*)-DPEN] complex was also a highly efficient catalyst for the hydrogenation of 2-arylcyclohexanones *via* DKR.[36]

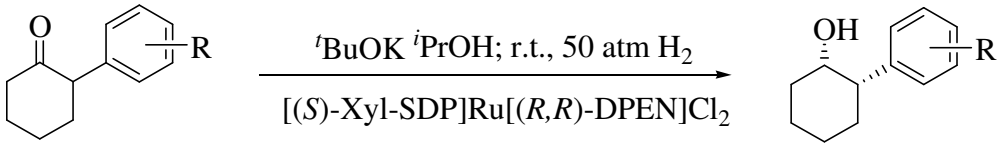


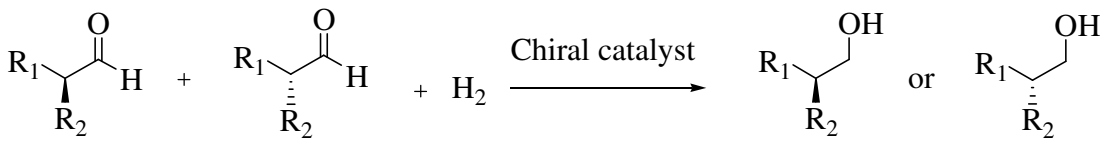
Figure 1. 25

Table 1. 7[a]

R-	cis/trans	ee %	R-	cis/trans	ee %
H-	>99:1	99	-*p*-CF_3	100:0	98
-*p*-Me	>99:1	99.5	-*m*-CH_3	>99:1	98
-*p*-OMe[b]	100:0	97	-*m*-OCH_3	100:0	92
-*p*-Cl	>99:1	99	-*o*-CH_3	>99:1	89

[a] Reactions were performed at 20-25 °C under 50 atm of H_2 using a 0.8 M solution of 2-arylcyclohexanone in ^{i}PrOH containing the cat (S/C = 2000) and ^{t}BuOK (S/B = 10). All conversions were > 99 % as judged by GC [b] A mixed solvent of ^{i}PrOH/toluene (5:1) was used to dissolve the substrate.

No stereogenic centre is generated in the hydrogenation of α-branched aldehydes which makes the enantiocontrol of the reaction extremely difficult. If a catalyst can selectively hydrogenate one of two enantiomers of the racemic aldehyde and the remaining enantiomer can be rapidly racemised under the same reaction conditions, then ultimately two enantiomers of aldehyde will be fully converted to primary alcohol enantioselectively. The asymmetric hydrogenation of racemic aldehydes *via* DKR is also possible (Figure 1. 26.)



chiral primary alcohol

Figure 1. 26

The complexes [$RuCl_2$(SDPs)(diamine)] were found to be competent catalysts for the asymmetric hydrogenation of racemic α-branched aldehydes *via* DKR, which provided a practical access to chiral primary alcohols in high enantiomeric excess (up to 96% ee) and in high yields.[37]

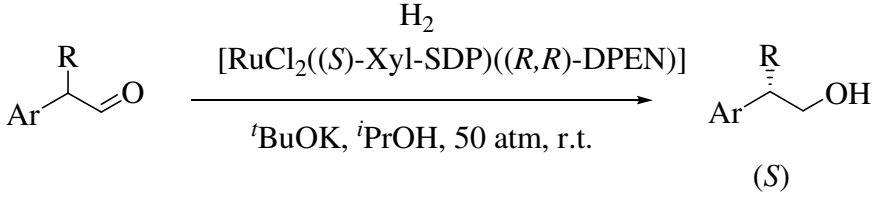


Figure 1. 27

Table 1. 8

R	Ar	ee	R	Ar	ee
Me	C_6H_5	78 (*S*)	^{i}Pr	3-$MeOC_6H_4$	93 (*S*)
^{i}Pr	C_6H_5	96 (*S*)	^{i}Pr	4-MeC_6H_4	93 (*S*)
^{c}Pent	C_6H_5	92 (*S*)	^{i}Pr	4-$MeOC_6H_4$	94 (*S*)
^{c}Hex	C_6H_5	92 (*S*)	^{i}Pr	4-ClC_6H_4	90 (*S*)
^{i}Pr	2-MeC_6H_4	95 (*S*)	^{i}Pr	2-Naphthyl	89 (*S*)
^{i}Pr	2-ClC_6H_4	93 (*S*)	^{c}Hex	4-MeC_6H_4	92 (*S*)
^{i}Pr	3-MeC_6H_4	89 (*S*)	^{c}Hex	4-$MeOC_6H_4$	94 (*S*)

Reaction conditions: (S/C = 1000) 0.2 mmol/ml, ^{t}BuOK, 0.04 mmol/ml, ^{i}PrOH, room temperature (25 to 30 °C), 50 atm of H_2, 8 h, 100 % conversion.

This Ru (II) catalyzed asymmetric hydrogenation of racemic α-arylaldehydes *via* DKR provided a highly efficient and economical method for the synthesis of chiral primary alcohols. The method shows great potential for wide application in the synthesis of optically active pharmaceuticals and natural products.

Another interesting ligand is QUINAPHOS that in combination with DPEN achieves very high conversions and enantioselectivities in Ru (II) catalytic hydrogenation of ketones.[38]

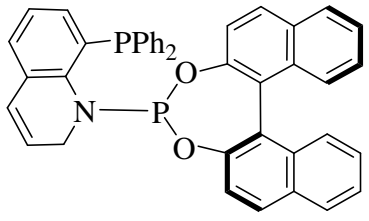


Figure 1. 28. (*R,S*)-QUINAPHOS

There is another movement to prepare novel phosphine ligand with a large backbone in order to improve the enantioselectivity. Phosphine ligands with different steric and electronic properties were synthesized by Li and their catalytic behaviours in the asymmetric

hydrogenations of aromatic ketones were investigated.[39] The size and electronic properties of phosphines affected, however, only the catalytic activity, and had no obvious effects on the enantioselectivity.

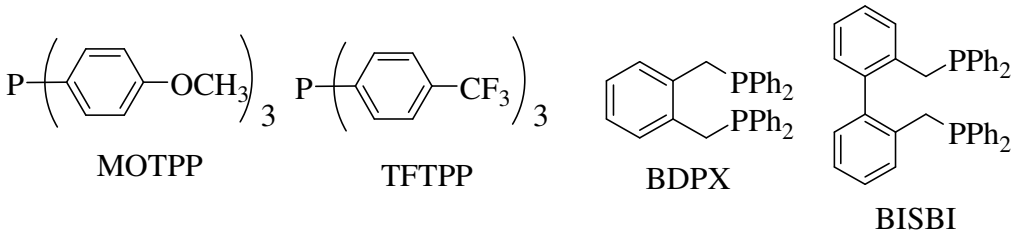


Figure 1. 29. Li phosphine ligands.

Mikami reported a achiral benzophenone-based complex, DPBP (2,2'-bis(diphenylphosphino)benzophenone, Figure 1. 30) as the diphosphine ligand, that affords high enantioselectivity in catalytic asymmetric ketone hydrogenation (up to 99 % ee, >99 % yield), even higher than the enantiopure BINAP. The benzophenone skeleton adopts a chiral propeller conformation in the Ru complex due to the presence of DPEN.[40]

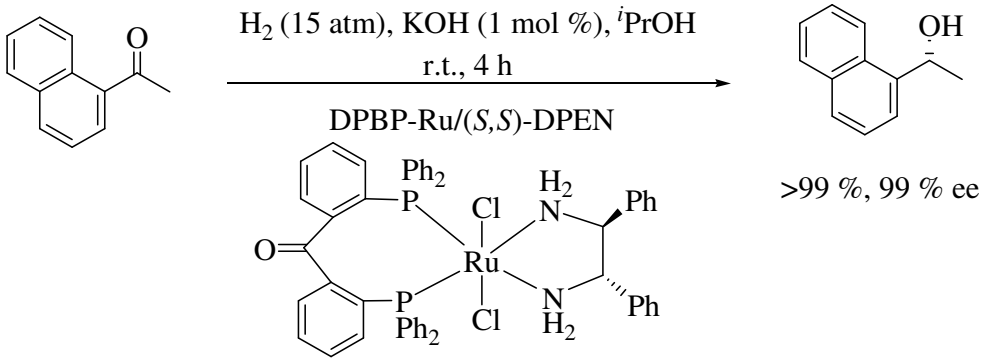


Figure 1. 30

1.5.3. New diamines

An increasingly large selection of chiral diphosphine ligands have been available to researchers for many years. Most of the new diphosphine that have found success were based on a biaryl backbone and used, in most of the cases, in combination with DPEN and DAIPEN. While there has been an over abundance of new diphosphine ligands developed for the Ru catalysts, surprisingly, there has been much less research focused on the development of new diamine partner ligands. However, when the diamine component is altered, a significant difference in catalytic activity is observed.

1.5.3.1. Changing the Nature of the Diamine Ligand

While our work was on going, Noyori published a new catalyst system that is effective for asymmetric reduction of bulky ketones. Noyori replaced one amino group with a pyridine in his catalytic system achieving a very successful catalyst for asymmetric hydrogenation of *tert*-alkyl ketones with excellent activity and enantioselectivity.[41] When our project was initiated such hydrogenations were not possible.

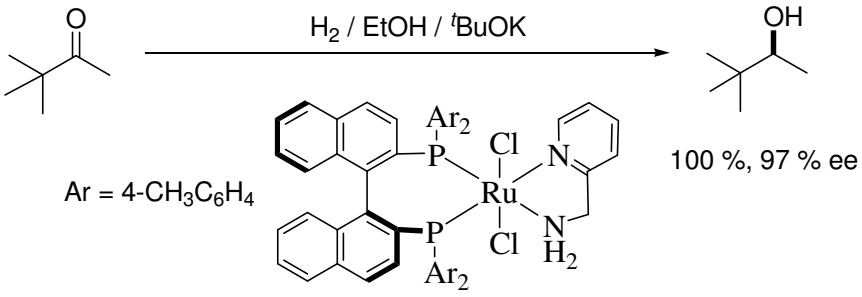


Figure 1. 31

This was the first example of the successful asymmetric hydrogenation of *tert*-alkyl ketones. Notably, the achiral aminopyridine does not result in an erosion of enantiomeric excess, and the stereochemical result is due to the chirality of the diphosphine ligand. No efficient homogeneous catalyst exists for enantioselective hydrogenation of aryl glyoxal dialkylacetals to the chiral α-hydroxy acetals. $RuCl_2$[(*R*)-XylBINAP][(*R*)-DAIPEN] catalytic system gives very low enantioselectivities for these substrates.

This difficult problem has very recently been solved by the use of 2-dimethylamino-1-phenylethylamine (DMAPEN), an *N*,*N*-dimethylethylenediamine ligand, instead of conventional ethylenediamine ligands with no *N*-substituent.[42] The new $RuCl_2$(TolBINAP)(DMAPEN)/^{t}BuOK catalyst system promotes hydrogenation of α-keto acetals with a high substrate-to catalyst (S/C) ratio to give the chiral α-hydroxy acetals in up to 98 % ee. In addition, hydrogenation of racemic α-heterosubstituted ketones affords the β-substituted alcohols with excellent enantio- and diastereoselectivity *via* DKR.

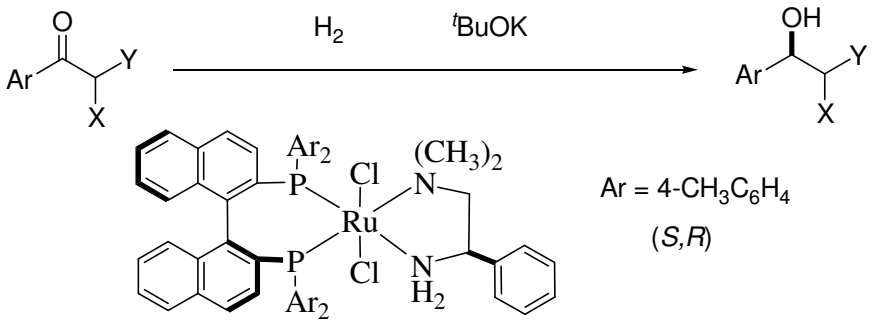


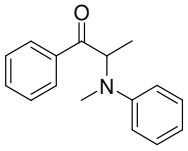
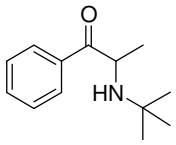
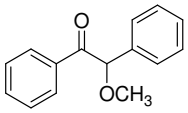
Figure 1. 32

Table 1. 9

Ar	X=Y	t / h	S/C	yield %	ee %
C_6H_5	$-OC_2H_5$	18	2000	95	96 (*R*)
C_6H_5	$-O(CH_2)_3O-$	24	1000	97	93 (*R*)
2-$CH_3C_6H_4$	$-OC_2H_5$	18	1000	96	92 (*R*)
4-$CH_3C_6H_4$	$-OC_2H_5$	4	1000	95	96 (*R*)
4-$CH_3OC_6H_4$	$-OC_2H_5$	5	1000	96	98 (*R*)
4-ClC_6H_4	$-OC_2H_5$	4	1000	95	92 (*R*)
2-naphthyl	$-OC_2H_5$	24	1000	91	97 (*R*)
C_6H_5	$-CH_3$	10	2000	94	95 (*S*)
4-FC_6H_5	$-(CH_2)_2NBoc(CH_2)_2-$	7	400	98	>99 (*S*)

Unless otherwise stated, reactions were conducted at 25-30 °C, 8 atm pressure H_2, using a 0.3-1.4 M ketone solution in ^{i}PrOH containing the cat and ^{t}BuOK. Conversion was >95% in all cases.

Table 1. 10

ketone	S/C	yield %	*syn : anti*	ee %
	500	90	>99:1	98 (1*R*, 2*R*)
	1000	92	96:4	99 (1*R*, 2*R*)
	1000	95	3:97	98 (1*R*, 2*S*)

Reaction carried out at 8 atm of H_2, 9 h and 30ºC. Ketone/Ru/Base of 500/1/45 and a 0.4 M solution of the substrate in ^{i}PrOH

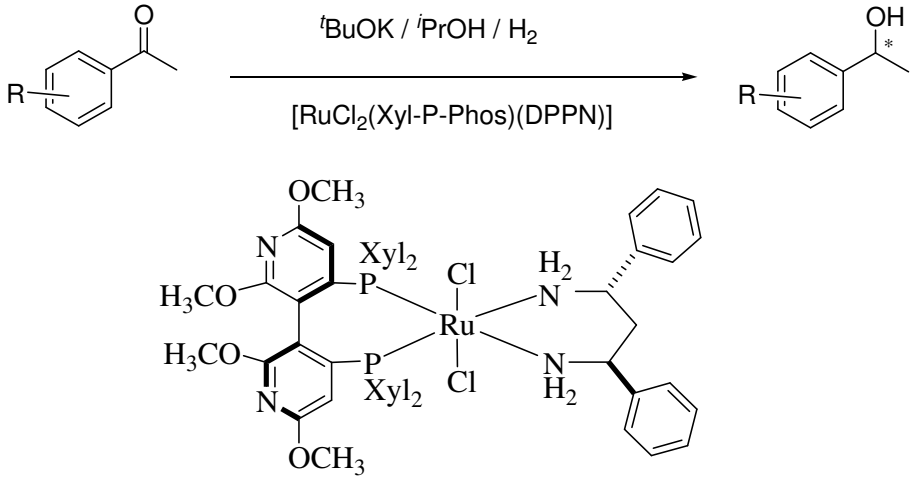
Hydrogenation of racemic α-amidopropiophenones *via* DKR selectively gives the *syn*-α-amido alcohols in excellent ee by precise control of two contiguous stereocenters. The [Ru(TolBINAP)(DMAPEN)] catalyst provides a general procedure for asymmetric hydrogenation of aromatic ketones with α-branched carbon moieties.

1.5.3.2. 1,3- and 1,4-diamines

By introduction of 1,3- and 1,4-diamine, the catalytic activity can be significantly altered such that new classes of ketones could be considered for [$RuCl_2$(diphosphine)(diamine)] asymmetric hydrogenation. This concept of changing the ring

size of the chelate between the diamine and metal centre would alter the orientation of the NH group, thus potentially changing the hydrogen bond interaction with the ketone, which is believed to occur in the catalytic cycle.

The introduction of the chiral 1,3-DPPN diamine[43] in combination with Xyl-P-Phos produces a ruthenium catalyst with a broad applicability towards the hydrogenation of substituted acetophenones.



Xyl = 3,5-$(CH_3)_2C_6H_3$

Figure 1. 33

Table 1. 11

ketone	cat	S/C	ee %	ketone	cat	S/C	ee %
H	(*R,SS*)	1000	95 (*S*)	*p*-OMe	(*S,RR*)	2500	97 (*R*)
H	(*S,SS*)	1000	69 (*R*)	*m*-Me	(*S,RR*)	2500	96 (*R*)
H	(*S,RR*)	2500	95 (*R*)	*o*-Me	(*R,SS*)	1000	86 (*S*)
H	(*S,RR*)	10000	95 (*R*)	*o*-OMe	(*R,SS*)	1000	84 (*S*)
p-F	(*S,RR*)	2500	95 (*R*)	3,5-CF_3	(*S,RR*)	1000	95 (*R*)

Reaction conditions: 2–5 mmol substrate; 25 ºC, 10 bar H_2. Reaction times 2–24 h to obtain 100 % conversion.

The data collected shows that the properties largely mirror the analogous 1,2-DPEN catalyst systems and that the structural modification associated with the presence of the six membered chelate ring instead of the five membered chelate ring, did not improve the catalytic system. The rates and enantioselectivities obtained using this catalyst are high and make this a practically useful process for the preparation of chiral alcohols.

The 1,3-diamine, DPPN, displayed a reactivity and selectivity similar to those of the 1,2-diamines except in the case of pinacolone reduction where vastly improved activities and selectivities were observed. The DPPN ligand can now be considered as a viable alternative to

the 1,2-systems, expanding the catalyst toolbox. The diphosphine (*S*,*S*)-Xyl-Skewphos in combination with the chiral 1,3-diamine (*R*,*R*)-DPPN in the asymmetric hydrogenation of propiophenone gives 92 % ee in high yield.

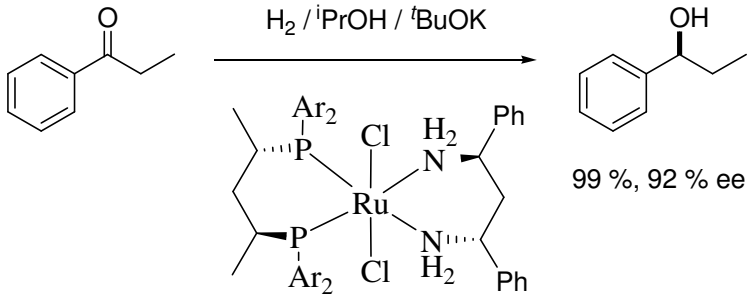


Figure 1. 34. Hydrogenation using [$RuCl_2$((*S*,*S*)-Xyl-Skewphos)((*R*,*R*)-DPPN)]

Noyori has exploited the combination of 1,4-diamines derived from tartaric acid (IPBAN) and mannitol (IPHAN) with BINAP to facilitate the Ru (II) catalyzed asymmetric hydrogenation of tetralones with excellent activity and selectivity.[44] 1,4-Diamine ligands form a seven-membered chelates with the metal center. This is analogous to other phosphine ligands that, upon coordination, also exist as seven membered chelates. Thus, the application of 1,4-diamine ligands has expanded the scope of the catalytic system to the, until now, less successful class of cyclic ketones; [$RuCl_2$(BINAP)(IPBAN)] hydrogenated tetralones with a 99 % ee.

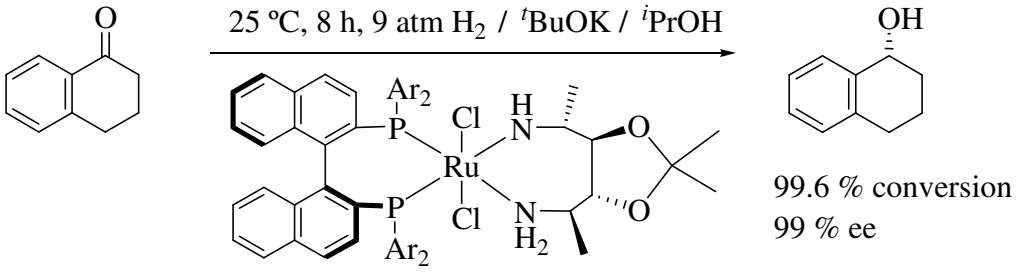


Figure 1. 35

Hems et al combined the Ru metal centre with 1,4-diamines and P-Phos and BINAP as the phosphines "partner ligand" for application in asymmetric catalytic hydrogenation.[45] They modified the diamine IPBAN to the 1,4-diamine DAMDO and synthesised the diamine 1,4-AABPY (Figure 1. 36).

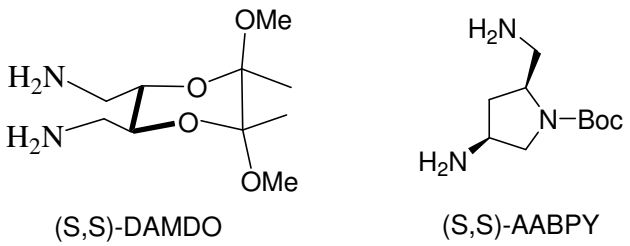


Figure 1. 36

These diamines were shown to be applicable towards a broad range of substrates in asymmetric hydrogenation of ketones. When $RuCl_2$(TolBINAP)(DAMDO) was tested in the asymmetric hydrogenation of tetralone. It was observed that the hydrogenation started rapidly but then appeared to stop. This suggests that the active Ru hydride species decomposed under the reaction conditions. The mode of decomposition is still unknown.

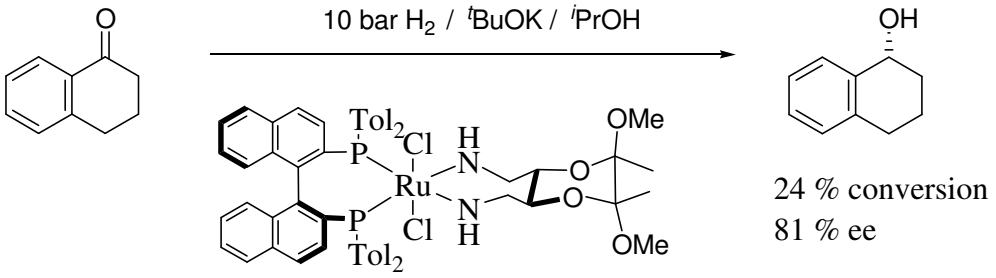


Figure 1. 37

1.5.4. Other Ru(diphosphine)(diamine)Cl_2 systems.

Deng recently developed a series of dendrite Ru(BINAP)(diamine) catalysts for asymmetric hydrogenation of a variety of simple aryl ketones with good catalytic activity, high enantioselectivity, and facile catalyst recycling.[46] An increase of enantioselectivities was obtained by using the dendritic catalysts compared with Noyori catalysts for a range of substrates. A remarkable effect on catalytic activity and enantioselectivity is observed which is explained by the variation in the structure of the ligand. Dendrimers are more advantageous compounds in catalysis because they exhibit catalytic activity in homogeneous catalysis but are in general easy to separate after use. This feature is attractive for economical and environmental reasons.

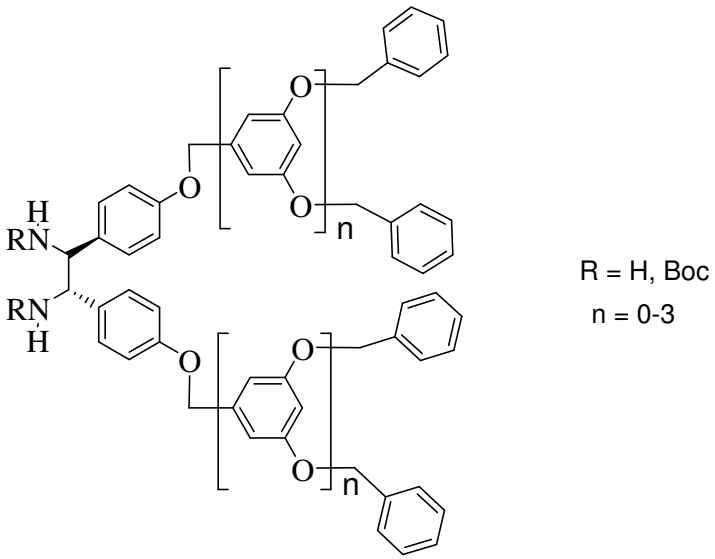
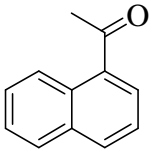
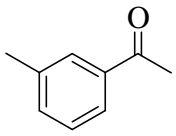


Figure 1. 38. Dendritic diamine

Table 1. 12

substrate	ligand	conversion %	ee %
	R=H, n=0	>99	96 (*R*)
	R=H, n=1	>99	94 (*R*)
	R=H, n=2	>99	95 (*R*)
	R=H, n=0	>99	94 (*R*)

Reaction conditions: 28 °C by using 0.6 mmol of ketones in 4 ml of solvents for 20 h; S:BINAP:Ru:dendritic diamine: ^{t}BuOK = 500:1.1:1:1:6 (molar ratio); H_2 pressure = 40 atm.

Polymer-supported and heterogenized ligands of Noyori catalysts have been reported for the asymmetric hydrogenation of ketones.[47-50] It is demonstrated that the use of soluble dendrimer-based catalysts might combine the advantages of homogeneous and heterogeneous catalysis.

Another way to use this catalytic asymmetric hydrogenation system is using ionic liquids. Chan reported polyethylene glycol (PEG) to be an inexpensive, non-toxic and recyclable reaction medium for Ru catalyzed asymmetric hydrogenation of β-keto esters and simple aromatic ketones.[51] In all cases, high catalytic activities and enantioselectivities were achieved, which are comparable to those obtained in conventional organic solvent systems. The Ru catalysts were prepared with commercially available chiral diphosphine ligands and could be readily recycled by simple extraction, as in the case of ionic liquids, and reused up to nine times without obvious erosion of catalytic activity and enantioselectivity. PEGs prove to be effective new reaction media with attractive alternatives to room temperature ionic liquids.

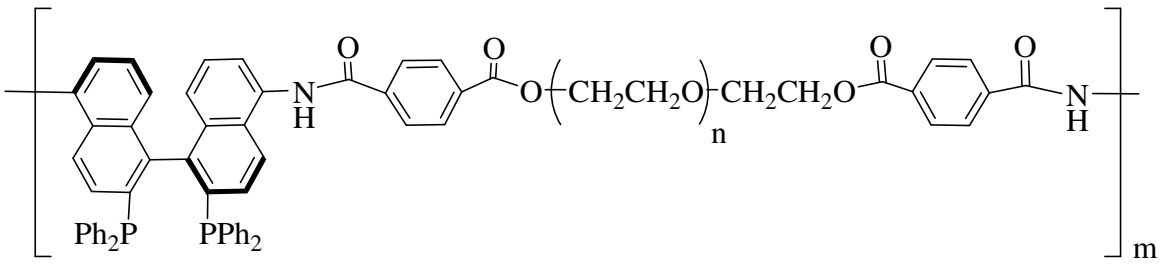


Figure 1. 39. PEG-supported (*R*)-BINAP

1.6. Catalysts that are not of the type Ru(diphosphine)(diamine)Cl_2

Recently much effort has been devoted towards the development of new catalytic systems, which are structurally different from the Noyori type methodology. Many of the catalyst described here have been reported during the course of this body of work, which is

testament to both the importance of asymmetric ketone hydrogenation, and the interest in ruthenium catalysts.

Ding reported Ru(II) complexes comprising of cheap achiral monodentate phosphine ligands used in combination with an enantiopure 1,2-diamine (DPEN) for enantioselective catalytic hydrogenation of ketones affording a variety of optically active secondary alcohols in high yields and enantioselectivities.[52] The steric impact of achiral monophosphine ligands in Ru complexes was found to be a critical factor for the high enantioselectivity of the reaction. This finding throws some light on a long-standing challenge, i.e., the high cost of chiral diphosphine ligands, associated with an industrial application of the asymmetric hydrogenation of ketones. Cheaper achiral monophosphines could be utilised for some hydrogenations. Anyway, it should be noted that complicated achiral ligands can still be quite costly.

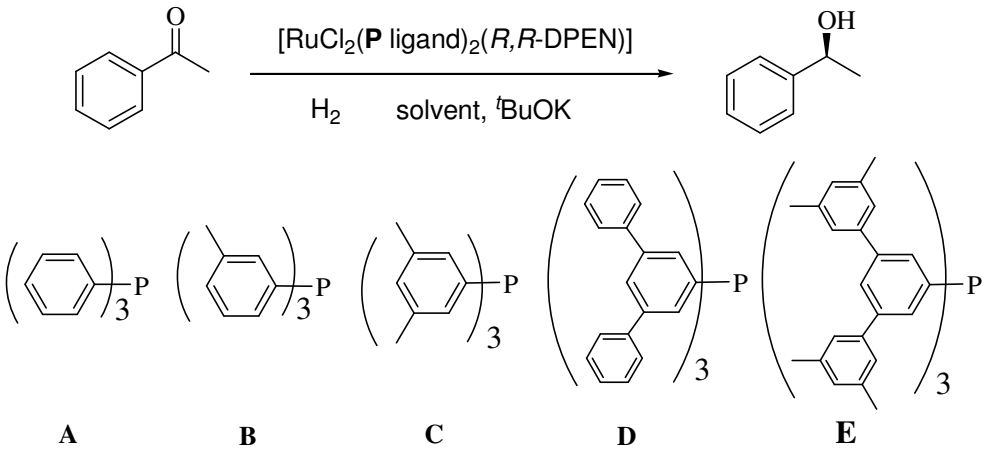


Figure 1. 40. Ding monodentates phosphines

Table 1. 13

ligand	solvent	conversion %	ee %
A	^{i}PrOH	>99	76.7 (*S*)
B	^{i}PrOH	96	77.4 (*S*)
C	^{i}PrOH	>99	87.0 (*S*)
D	^{i}PrOH	>99	88.8 (*S*)
E	^{i}PrOH	>99	89.0 (*S*)
E	MeOH	98	62.8 (*S*)
E	EtOH	>99	90.0 (*S*)
E	^{n}PrOH	>99	95.5 (*S*)
E	^{n}BuOH	>99	94.9 (*S*)
E	^{n}Pentanol	>99	94.7 (*S*)

[a]All the reactions were carried out at 25 ºC under 21 bar pressure of H_2 at a Substrate/Catalyst/Base ratio of 1000/1/20 for 10 h

Although the enantioselectivity of the reactions using the present catalyst system have not yet been optimized the results gained from this work should stimulate further research for development of practical catalysts for the enantioselective hydrogenation of ketones using simple and cheap achiral monodentate phosphine ligands. This is particularly important for industrial applications of asymmetric catalysis that are currently hindered due to the expense of chiral diphosphine ligands.

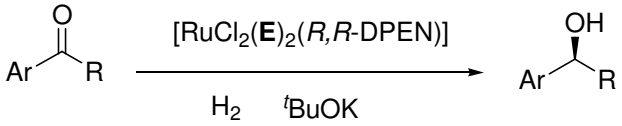


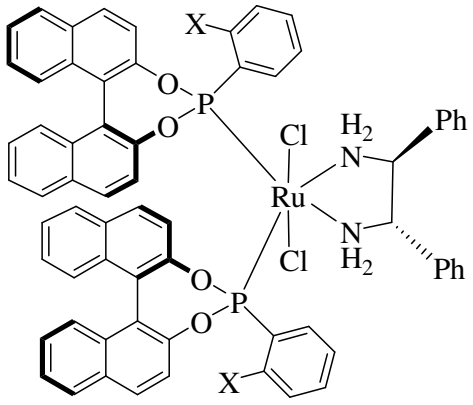
Figure 1. 41

Table 1. 14

Ar	R	ee %	Ar	R	ee %
Ph	Me	95.5 (*S*)	2'-$CF_3C_6H_4$	Me	96.5 (*S*)
2'-MeC_6H_4	Me	95.1 (*S*)	1-naphthyl	Me	94.7 (*S*)
2'-BrC_6H_4	Me	96.1 (*S*)	2-thienyl	Me	95.9 (*S*)
2'-ClC_6H_4	Me	96.3 (*S*)	Ph	Et	96.3 (*S*)
3'-ClC_6H_4	Me	95.3 (*S*)	Ph	$Me_2NCH_2CH_2$	96.7 (*S*)
2'-FC_6H_4	Me	95.1 (*S*)	Ph	Me	95.1 (*S*)

All of the reactions were carried out at 25 ºC under 20 bar pressure of H_2 for 10 h at a substrate/catalyst/^{t}BuOK ratio of 1000/1/20 for 10 h. The conversion of the substrates was determined to be >99 %

Wills *et al* synthesised a series of Ru (II) complexes containing BINOL based monodonor phosphorus ligands and applied them to the asymmetric hydrogenation of ketones with ee's up to 99 %.[53, 54] The best ligands were those which contain aromatic groups with either a methoxide or bromide in the *ortho* position.



X = H, Ph, OMe, Br, Me

Figure 1. 42. Wills Ru (II) complex containing mono phosphorus ligands

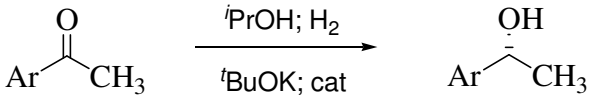


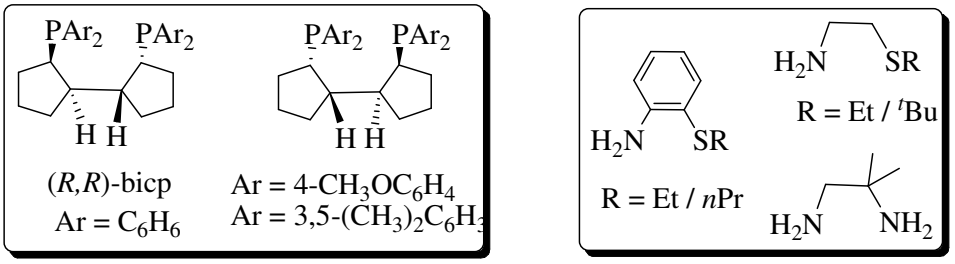
Figure 1. 43

Table 1. 15

cat / X	Ar-	T / ºC	t / h	S/C	P / bar	conversion %	ee %
H	Ph	22	10	1000	10	7	37 (*R*)
Ph	Ph	22	10	1000	10	5	35 (*R*)
OMe[a]	Ph	22	10	1000	10	100	88 (*R*)
Me	Ph	22	10	1000	10	0	n.a.
Br[b]	Ph-	22	10	1000	10	99	84 (*R*)
Br	Ph-	0	4	2000	50	95	93 (*R*)
Br	1'-naphthyl	22	10	2000	10	93	94 (*R*)
Br	1'-naphthyl	0	8	2000	50	92	99 (*R*)
Br	*o*-BrC_6H_4	22	10	2000	10	100	91 (*R*)
Br	*o*-BrC_6H_4	0	8	2000	50	93	99 (*R*)

[a] Reaction time: 40 h. [b] Reaction time: 15 h.

Genov and coworkers reported the preparation of new phosphine ligands in the bicp family.[55] $[RuCl_2\{(R,R)\text{-bicp}\}(dmf)_n]$ was used in combination with inexpensive achiral 2-(alkylthio)amine or 1,2-diamine and an alkoxide as the base. This system catalysed the hydrogenation of various aryl alkyl ketones to give enantioselectivities similar to those achieved with chiral 1,2-diamines. They show that the choice of solvent is essential to achieve high ee and conversion and consequently optimised the reaction conditions accomplishing ee's of up to 99 % in EtOH for a broad range of aromatic ketones. The Genov catalyst system is of great practical potential because of the low cost and availability of the achiral auxiliary amine ligand used even if this is tempered by a diphosphine that requires a multistep synthesis (Figure 1. 44).



Chiral diphosphane ligands in the bicp family | Achiral amino ligands

Figure 1. 44

Complexes prepared *in situ* from $RuCl_2(PPh_3)_3$ and chiral phosphine-oxazoline ligands are effective catalysts for the hydrogenation of various aryl ketones with ee's up to 99 % and substrate to catalyst ratios of 10,000 – 50,000.[56] This is such a useful method that a pilot process has been developed for the hydrogenation of 3,5-bistrifluoromethyl acetophenone. The best results with this catalytic system are shown in Table 1. 16

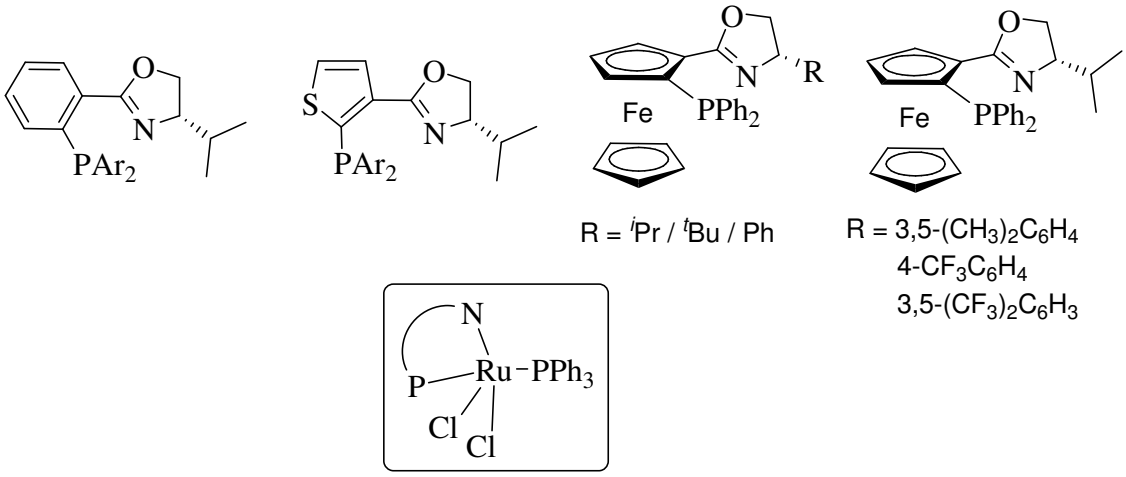


Figure 1. 45. Chiral phosphine oxazoline ligands

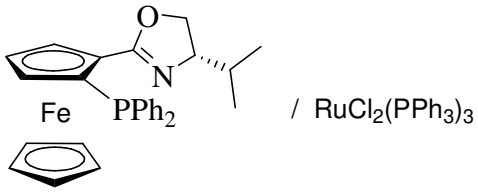
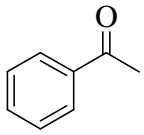
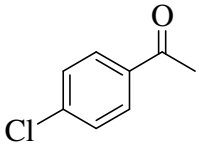
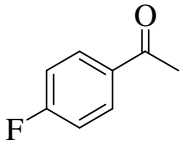
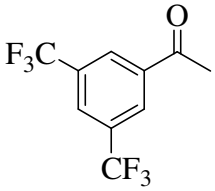


Figure 1. 46

Table 1. 16

substrate	P / bar	S/C	t / h	TOF	conversion %	ee %
	80	50000	78	635	99	99
	20	20000	1	184000	92	96.2
	20	500	1	500	100	97.4
	20	10000	2.3	4500	100	96

In situ catalyst; 100 mmol substrate; 9 – 12 ml toluene; 1 ml 1 M aq NaOH; 25 ºC

In contrast to the catalyst system described by Noyori or analogous systems, the Ru-(phosphine-oxazoline) complexes do not contain an N-H group. This means that the mechanistic pathway of these catalysts must be different as there is no H-Ru-N-H moiety for the coordination of the C=O bond. Mechanistic studies are still awaited on this recent development.

A series of ruthenium complexes with the chiral P-N ligand (1*R*,2*R*)-$PPh_2CHPhCHMeNH_2$ has been synthesised by Morris.[57] These have been shown to be precatalysts for the efficient asymmetric hydrogenation of simple ketones (Figure 1. 47).

The complexes *trans*-$RuHClL_2$ and *trans*-RuHCl-(BINAP)L are precatalysts to active ketone hydrogenation catalysts. The enantioselectivity in the asymmetric hydrogenation of acetophenone was higher in the latter complexes containing the BINAP ligand.

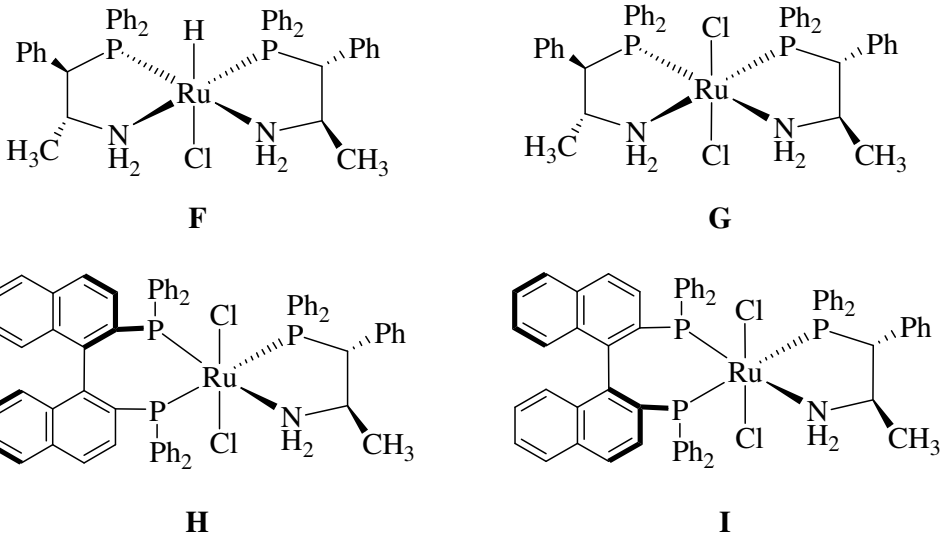


Figure 1. 47. P^N ligands by Morris

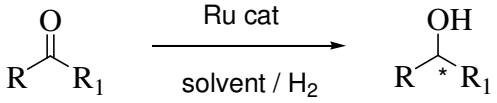


Figure 1. 48

Table 1. 17[a]

ketone		catalyst	P / bar	T / ºC	t / h	conversion %	ee %
R	R_1						
Ph	CH_3	**F**[b]	2	5	2	>99	47 (*R*)
Ph	CH_3	**G**[b]	2	5	4	>99	51 (*R*)
Ph	CH_3	**H**	2	5	4	97	61 (*S*)
Ph	CH_3	**I**	2	0	3	95	72 (*S*)
Me	^{t}Bu	**F**	7	20	4	>99	40 (*S*)

[a] Reaction conditions: under H_2, the ketone, base, and 2-propanol were mixed first to give a total volume of 4 mL and stirred for 5 min; then the complex (5x10-3 mmol) was added. The molar ratio of substrate to base to catalyst was 2000:30:1. [b] The molar ratio of substrate to base to catalyst was 5000:50:1

Morris *et al* prepared the new complexes $RuHCl(PPh_2CH_2CHRNH_2)_2$ and $RuHCl(PPh_2CH_2CHRNH_2)((R)\text{-BINAP})$.[58] These were used as catalyst precursors in the presence of a base for the hydrogenation of various ketones and imines. Acetophenone was hydrogenated with low ee (up to 40 %) when catalyzed by the enantiomerically pure complexes. These complexes are especially active in the hydrogenation of sterically congested and electronically deactivated ketones and imines and are selective for the hydrogenation of C=O bonds over C=C bonds. The S/C loading of up to 5000 can be used but the ee values are quite low in the asymmetric hydrogenation of ketones using these ligands (Figure 1. 49).

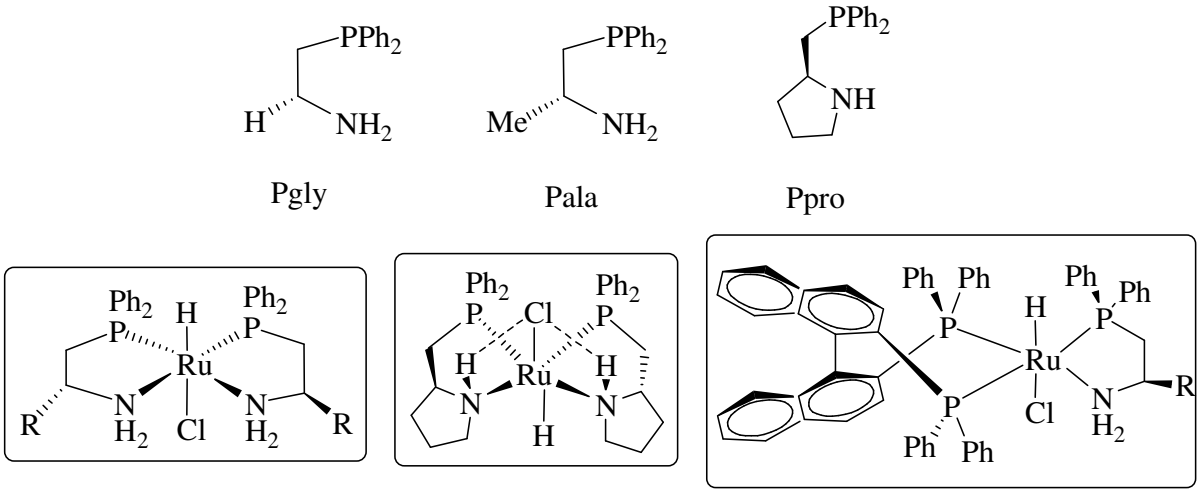
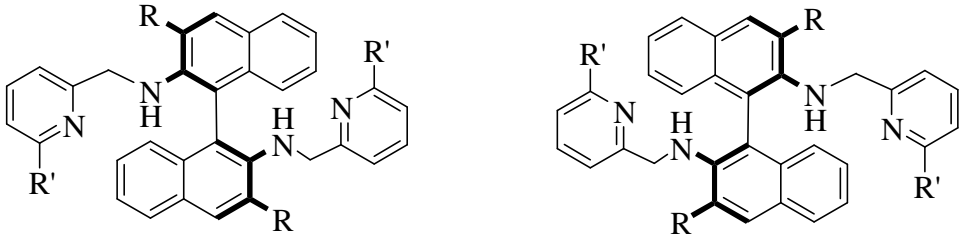


Figure 1. 49

Asymmetric hydrogenation using non-phosphine-based Ru complexes is still in the developmental stage but Kitamura[59] reported a very interesting catalytic system consisting of a new class of Goodwin-Lions-type combined ligand R-BINAN-R'-Py and a π-allyl Ru precursor, which can hydrogenate aromatic ketones with high enantioselectivity (Figure 1. 50).



(*R*)-R-BINAN-R'-Py (*S*)-R-BINAN-R'-Py

a) R = C_6H_5; R' = H
b) R = R' = H
c) R = H; R'= CH_3

Figure 1. 50. BINAN ligand

Interestingly this system is able to catalyse the reaction in the absence of base. Although the efficiency does not exceed that of the original BINAP-Ru-diamine complexes, the present results could significantly expand the range of possibilities in catalyst design.

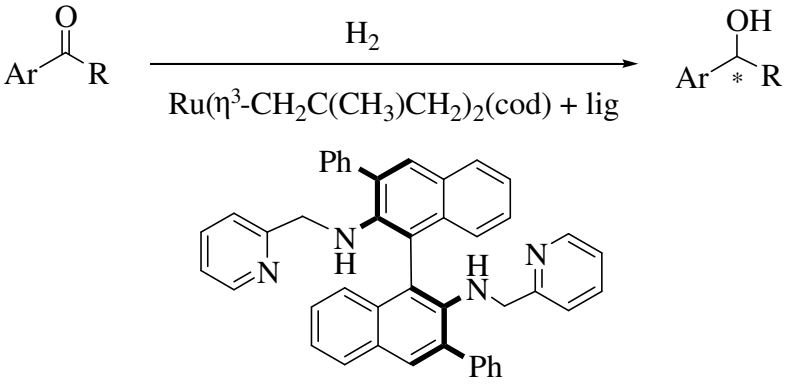


Figure 1. 51

Table 1. 18

ketone		yield %	ee %
Ar	R		
C_6H_5	CH_3	>99	94 (*R*)
4- $CH_3OC_6H_4$	CH_3	>99	98 (*R*)
4- $CH_3C_6H_4$	CH_3	>99	96 (*R*)
4-$CF_3C_6H_4$	CH_3	>99	80 (*R*)
2-naphthyl	CH_3	>99	95 (*R*)
C_6H_5	CH_2CH_3	>99	98 (*R*)
C_6H_5	$(CH_2)_7CH_3$	>99	94 (*R*)
C_6H_5	$CH(CH_3)_2$	>99	98 (*R*)
C_6H_5	C_6H_{11}	>99	97 (*R*)
C_6H_5	$C(CH_3)_3$	>99	86 (*R*)
C_6H_4-2-$(CH_2)_4$		>99	94 (*R*)
C_6H_4-2-$(CH_{2)3}$		>99	99 (*R*)
C_6H_4-2-$(CH_2)_2$ *b*		>99	93 (*R*)

a Reaction conditions: scale, 5.0 mmol; H_2, 50 atm; solvent, ^{i}PrOH; base, ^{t}BuOK, T, 25 °C; t, 12-18 h. *b* no base.

1. 7. Other metals

Ru (II) catalyst systems are the catalysts par excellence for ketone hydrogenation. However very interesting papers on Cu (I), Ir (I), and Rh (I) catalysed asymmetric ketone hydrogenation have appeared.[60-63] These "other-metals" ketone hydrogenation catalysts have not been developed further probably due to the extreme activity of the Ru catalysts.

The direct hydrogenation of isobutyrophenone has been reported using an Ir-BINAP catalyst under relatively harsh conditions by Takaya in 1994.[60]

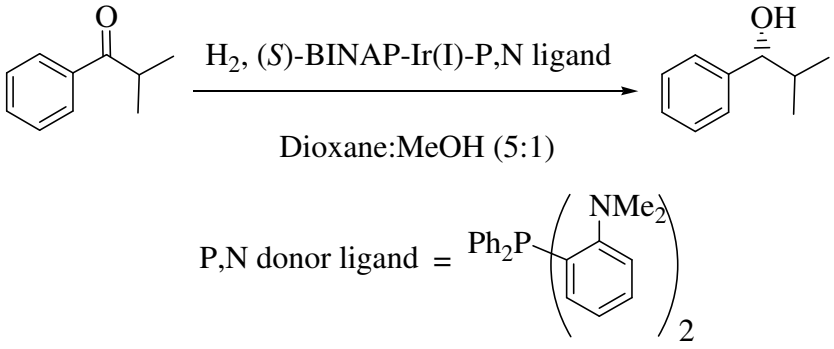


Figure 1. 52.Takaya's hydrogenation

Table 1. 19. Takaya's results for hydrogenation of isobutyrophenone at 54 atm H_2

T / ºC	t / h	conversion %	yield %	ee %
90	160	85	78	84 (*S*)
120	61	66	64	80 (*S*)

New conformationally rigid diphosphines ligands, i.e., PennPhos, were synthesised by Zhang in 1998,[61] for the asymmetric hydrogenation of ketones. Rh complexes of this ligand have notable additive effects with high enantioselectivities for both alkyl aryl and alkyl methyl ketones.

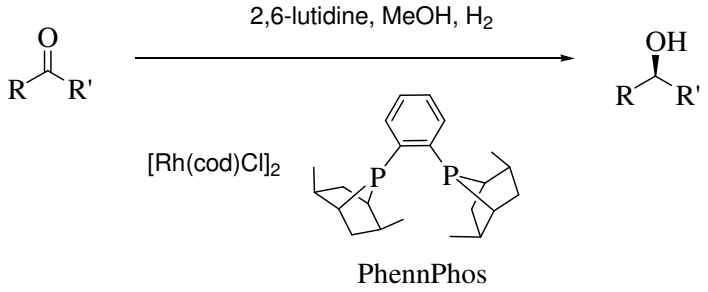


Figure 1. 53

Table 1. 20[a]

R	R'	t / h	yield %	ee %
Ph	CH_3	24	97	95 (*S*)
4- CH_3Ph	CH_3	53	94	95 (*S*)
4-OCH_3Ph	CH_3	48	83	94 (*S*)
Ph	CH_2CH_3	88	95	93 (*S*)
Ph	$CH(CH_3)_2$	94	20	72 (*S*)
$Ph(CH_2)_2$	CH_3	56	99	73 (*S*)
$CH_3(CH_2)_3$	CH_3	48	96	75 (*S*)
$(CH_3)_2CHCH_2$	CH_3	75	66	85 (*S*)
$(CH_3)_2CH$	CH_3	94	99	84 (*S*)
$C6H_{12}$	CH_3	106	90	92 (*S*)
$(CH_3)_3C$	CH_3	96	51	94 (*S*)

[a] Reaction conditions: r. t., 30 atm of H_2 , 0.5 mmol of substrate, 0.8 eq lutidine, substrate:$[Rh(cod)Cl]_2$:L = 1:0.005:0.01. Long reaction time was used to achieve the maxium conversion; for many substrates the reaction may be complete within a much shorter time.

A novel asymmetric hydrogenation protocol using a copper catalyst has recently been reported by Shimizu *et al*[62] The Cu (I) complex in the presence of nonracemic BDPP hydrogenates aryl ketones with moderate to high enantioselectivity.

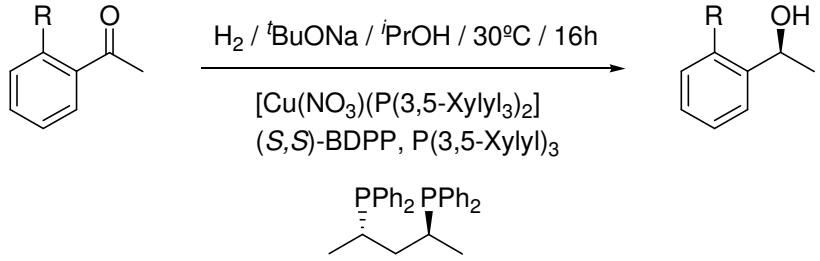


Figure 1. 54

Table 1. 21

R	conversion %	ee %
Me	99	86 (*S*)
OMe	>99	91 (*S*)
CF_3 [b, c]	95	90 (*S*)
Br[b]	98	81 (*S*)

All reactions were carried out with [$Cu(NO_3)(P(3,5\text{-xylyl})_3)_2$] (S/C = 500), (*S*,*S*)-BDPP (1 equiv to Cu), $P(3,5\text{-xylyl})_3$ (6 equiv to Cu), and ^{t}BuONa (10 equiv to Cu) under an initial hydrogen pressure of 5.0 mPa. b ^{t}BuONa (30 equiv to Cu) was used. *c* S/C = 400.

Copper catalysts have shown exceptional enantioselectivity in asymmetric reductions and it is known that copper is a useful catalyst for heterogeneous hydrogenation. A novel copper based system that hydrogenates aryl ketones with high catalytic activity has been reported. Although, the activity and enantioselectivity of the Cu catalysts is still modest relative to Noyori's Ru system. Cu catalysis may, in time, offer a more economical and effective protocol.

Peruzzini reported iridium complexes of planar-chiral ferrocenyl phosphine-thioether ligands capable of catalysing asymmetric hydrogenation of simple ketones with very high activity and enantioselectivities (up to > 99 %) together with full conversion.[63]

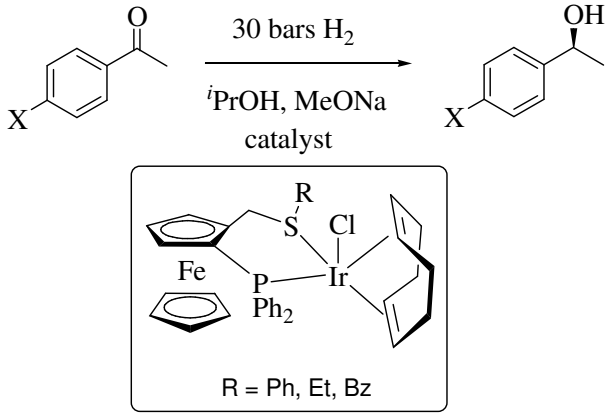


Figure 1. 55

Table 1. 22

catalyst	substrate	conversion %	ee %
R = Et	X = H	>99	78 (*S*)
R = Bz	X = H	99	87 (*S*)
R = Et	X = Me	86	93 (*S*)
R = Bz	X = Me	84	93 (*S*)
R = Et	X = F	>99	>99 (*S*)
R = Bz	X = F	96	>99 (*S*)

Reaction conditions: catalyst, 6.4×10^{-3} mmol; NaOMe, 3.2×10^{-2} mmol; substrate, 3.2 mmol (1/5/500) at 10 ºC.

The iridium complexes with planar chiral P,S ligands are effective catalysts for the asymmetric hydrogenation of various alkyl aryl ketones with high activities and ee's. These activities and enantioselectivities, reported by Peruzzini, are the best reported so far for the iridium-catalyzed hydrogenation of ketones.

1.8. Project aims

Reduction of C=O and C=N double bonds using molecular hydrogen is a very important process in industrial organic synthesis.[64] Noyori's pioneering research on ruthenium complexes containing both phosphine and diamine ligands using ^{i}PrOH and ^{t}BuOK gave impressively high chemo-selectivity for C=O bonds and extremely high enantioselectivity for a range of acetophenone derivatives.[5] Numerous groups have been inspired by Noyori's catalyst of the type $RuCl_2$(chiral diphosphine)(chiraldiamine), these systems often give excellent results for acetophenones as it has been described in the literature.

Using Noyori's catalytic system, aromatic unsaturated ketones can be reduced with excellent productivity and enantioselectivity. However, aliphatic ketones are reduced, but only with moderate or poor selectivity. Some heteroaromatic ketones can be problematic (no reduction or requiring $B(OR)_3$ additives). Very bulky ketones are not readily reduced with Ru catalysts, and Ru catalysed imine hydrogenation is in its infancy. Although, while our research was conducted, some quite exciting preliminary results have been reported and described in this chapter, many further studies are needed. In addition to more general problems, it is likely that some specific target molecules will need new catalysts.

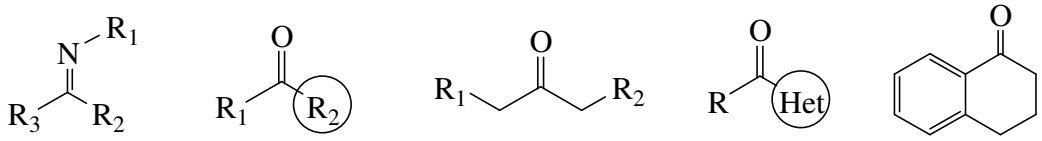
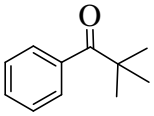
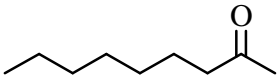
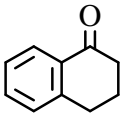
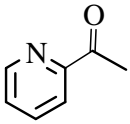
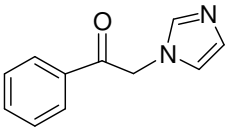


Figure 1. 56

Table 1. 23[5]

substrate	catalyst	yield %	ee %
	[$RuCl_2$((*S*)BINAP)((*S,S*)DPEN)]	6	61
	[$RuCl_2$((*R*)XylBINAP)((*R,R*)DAIPEN)]	100	1
	[$RuCl_2$((*R*)XylBINAP)((*S,S*)DPEN)]	81	82 (*S*)
	[$RuCl_2$((*S*)XylBINAP)((*S,S*)DAIPEN)]	0	n.a.
	[$RuCl_2$((*S*)XylBINAP)((*S,S*)DAIPEN)]	0	n.a.

First we focused on the synthesis of new diamines for use in Noyori's system, but with not so promising results (described in chapter 2) we decided to synthesise a new type of catalyst. The research presented here focussed on solving some of the difficult challenges faced when using a Noyori type system by studying catalysts based on a new design template. Given the absence of data on hydrogenation catalysis using tridentate ligands, ruthenium complexes of tridentate P^N^NH_2 type ligands seemed worthy of investigation. This is described in more detail in chapter **3**, where a tridentate Ru (II) complex has been synthesised and investigated.

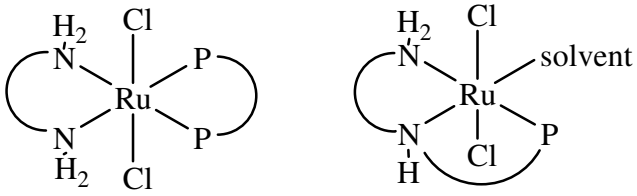


Figure 1. 57

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CHAPTER II

New chiral diamines for Ru catalysed hydrogenation of ketones

2.1. Introduction

The most impressive catalysts for hydrogenation of unfunctionalised ketones are Noyori's [$RuCl_2$(diphosphine)(diamine)] complexes. In ^{i}PrOH/^{t}BuOK, these complexes generate catalysts that are capable of reducing ketones with very high enantioselectivities. Most of the chiral diphosphines are used in conjunction with chiral 1,2-diamines, DPEN or DAIPEN. We were interested in exploring the effect of different *C*1 symmetric diamines on this catalyst system, and in particular, focus was directed towards expanding the scope of asymmetric catalysis of substrates that have proved especially challenging.

Given that rational design of asymmetric catalysts is only really possible once some catalytic results and the catalyst structure are known, our initial strategy was simply to employ chiral diamine ligands that were modular in nature. Thus, a small collection of precursors could be transformed into a ligand library rapidly by a facile, high yielding reaction between the precursor and a generic component.[1] Using the library, it should be possible to optimise catalytic activity and enantioselectivity in relatively rapid time.

One appealing route towards the family of diamine ligands was to convert the readily available *N*-Boc amino acids into *C*1 symmetric chiral diamines by an amide coupling with a range of primary amines, followed by deprotection and amide reduction using $LiAlH_4$. This type of synthesis should give ligands of type **3**.

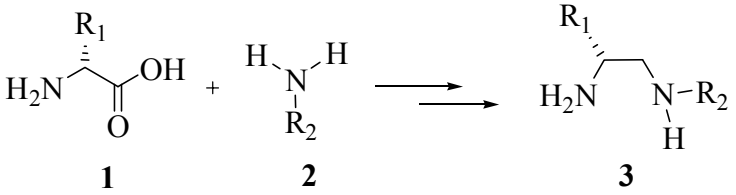


Figure 2. 1

Coupling of amino acids with primary amines was selected since there are many available, and the generated primary and secondary amines are generally stronger ligands than tertiary trialkyl amines.

We envisaged that the secondary amine end would not participate in the unique bifunctional mechanism to any great extent. The effect of this is that the incoming substrate will encounter a broadly similar environment to that observed with [$RuCl_2$(P^P)(DPEN)] catalysts, but enable a wide range of R^1 and R^2 groups to be investigated.

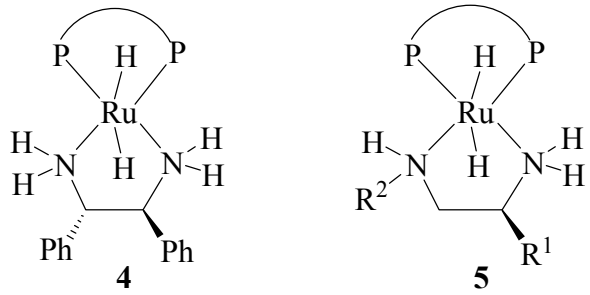


Figure 2. 2

2.2. Synthesis of the chiral diamine

Using *L*-valine as the test amino acid we synthesised the chiral diamine. By reaction of Boc protected *L*-valine (**1a**) and (*R*)-(+)-α-methylbenzylamine (**2a**) in presence of isobutyl chloroformate and *N*-methylmorpholine the *N*-Boc-α-amino amide **6** was obtained in a very good yield of 95 %.

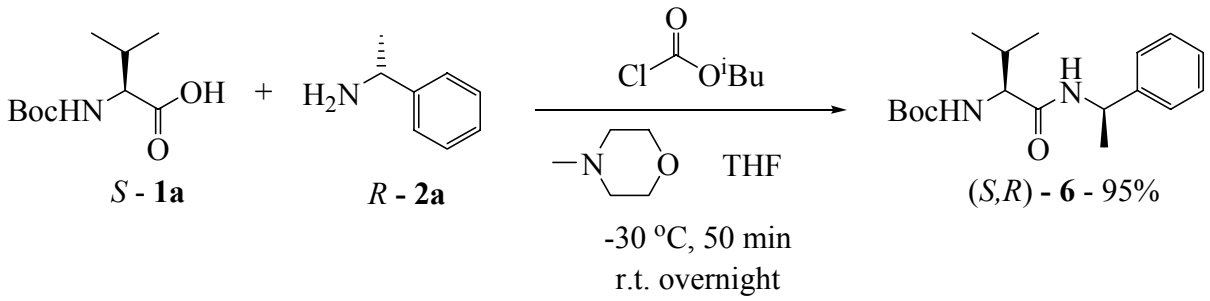


Figure 2. 3

Boc protected diamine **6** was used in the subsequent step without further purification. Amide **6** was treated with trifluoracetic acid to give (*S,R*)-1,2-diamine **7** in 99 % yield.

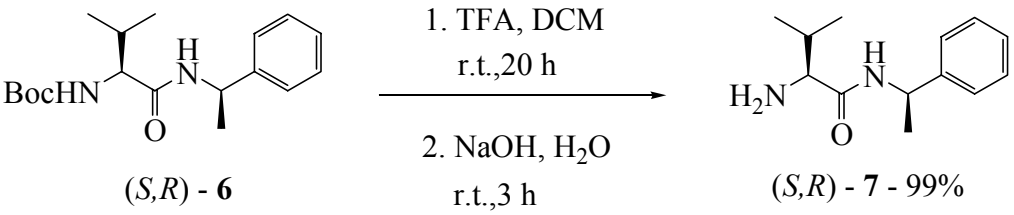


Figure 2. 4

(*S,R*)-3-Methyl-*N*-(1-phenyl-ethyl)-butane-1,2-diamine **3a** was obtained by refluxing **7** in THF with $LiAlH_4$ under N_2. Initially, racemisation occured giving both diastereoisomers but these were separable by column chromatography in 40 % combined yield. Further attempts to improve the synthesis showed that the racemisation could be avoided by using a reduced reaction time. After two days at 85 ºC no racemisation occured and only (*S,R*) diastereoisomer was obtained in an improved 71 % yield.

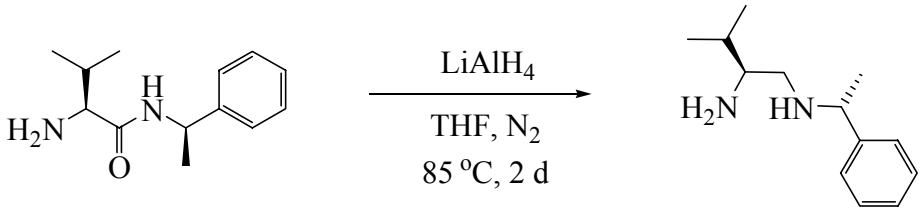


Figure 2. 5

Initial attempts to apply this type of synthesis with NBoc phenylalanine were not successful. This suggests that this methodology is, therefore, not generally applicable for the synthesis of ligand libraries, since all reaction steps are required to be facile, whereas the $LiAlH_4$ reduction did not meet this criterion.

2.3. Synthesis of catalysts

2.3.1. Synthesis of [$RuCl_2$(Diphosphine)(Diamine)] complexes

Initially the synthesis of these complexes was attempted using the traditional literature procedure. By refluxing $Ru(cod)Cl_2$ in DMF for 30 min in the presence of the chiral diphosphine and then 15 min with the diamine to obtain the desired complexes. This method has the inconvenience of DMF which has a boiling point of 153 ºC and it is difficult to remove from the reaction mixture. Additionally, for ligand **3a**, this procedure generated several side species which are not easily removed from the reaction mixture.

We therefore investigated the synthesis of the [$RuCl_2$(diphosphine)(diamines)] complexes using microwave irradiation, Figure 2. 6.

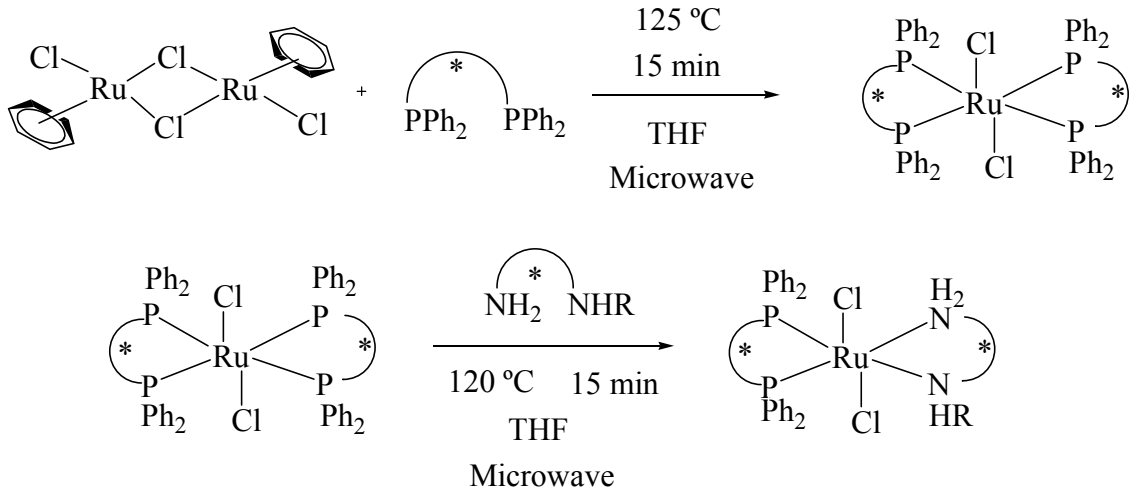


Figure 2. 6

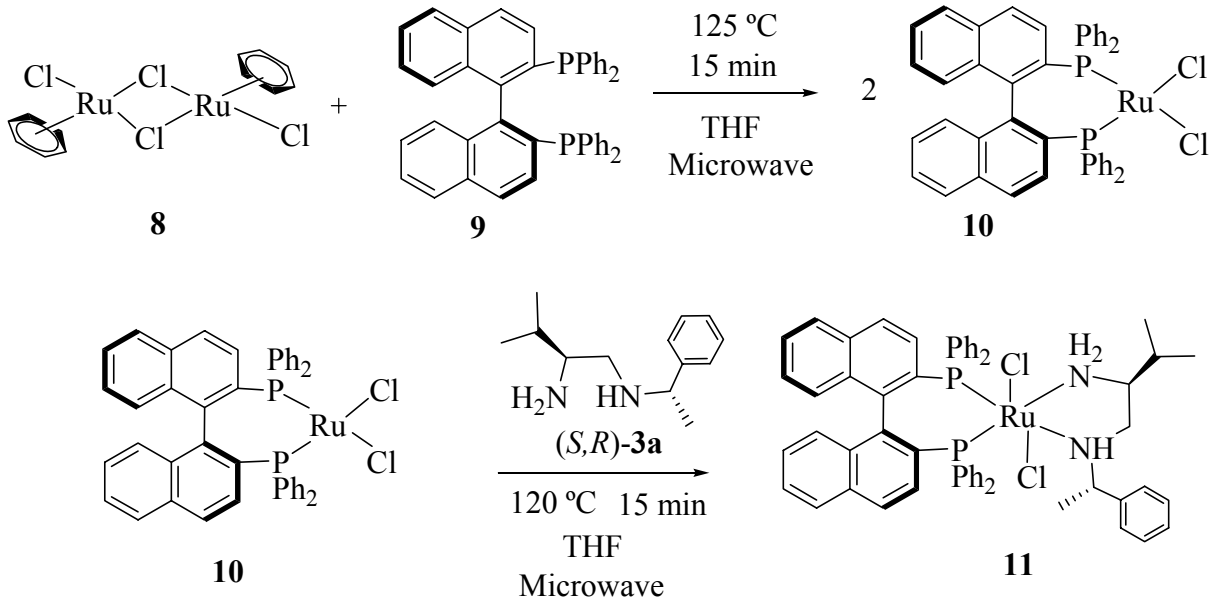
2.3.2. Microwave

Conventional reactions are carried out by conductive heating, ie, with an external heating source. This method is an inefficient method, since it has to take into account the thermal conductivity of the various materials that must be penetrated, and results in the temperature of the reaction vessel being higher than that of the reaction mixture.

On the other hand, microwave irradiation is considered more efficient as it produces internal heating by direct interaction of the microwave energy with the molecules that are present in the reaction mixture: vessels used in the microwave are commonly made out of microwave-transparent materials (borosilicate glass, quartz or teflon), which means that only the reaction mixture is heated, therefore there is almost no dispersion of heat.[2]

This direct microwave heating seems to be one of the main reasons why microwave assisted reactions have often shown good results: indeed, in many cases reaction times have been reduced from hours to minutes. There is often reduced side products and higher yields for many microwave reactions. In addition, since the microwave synthesis makes use of pressure vessels, it is possible to heat solvents above their boiling points, also known as the superheating effect. Microwave heating has been used for many reactions and is now quite routine, although prior to this report, there were not many examples where microwave heating improves the synthesis of transition metal phosphine complexes.[3]

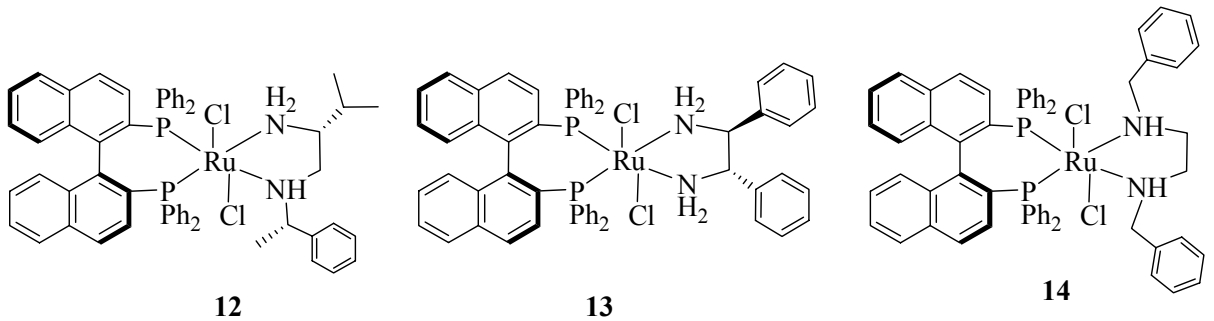
By reacting $[Ru(C_6H_6)Cl_2]_2$ with (*S*)-BINAP at 125 ºC for 15 min in THF under microwave irradiation [Ru((*S*)-BINAP)Cl_2] forms cleanly. The 1,2-diamine, (*S,R*)-**3a**, was added then and heated at 120 ºC affording complex **11** in improved yields when compared with traditional thermal methods. In the ^{31}P NMR the observation of two doublets at δ 49 and 38 ppm (J = 36.5 MHz) showed formation of the complex, there was a second signal at -14 ppm that corresponded to the free BINAP. The BINAP impurity was easily removed by column chromatography on silica gel isolating the complex **11** in pure form.



8 9 10 10 11

Figure 2. 7

The same procedure was used to synthesise diastereoisomer **12** from (*R,R*)-**3a**, and the complex of nonchiral *N,N*'-dibenzyl-ethylenediamine. Noyori's [$RuCl_2$((*S*)BINAP) ((*S,S*)DPEN)] was also prepared by this method as a control. The Ru complexes **12, 13** and **14** were obtained essentially in pure form using this procedure, as determined by ^{31}P NMR, and were used directly in catalysis, as has been the case in the literature.[4] The synthesis of all these complexes demonstrates the advantages of the new procedure using microwave heating. The complexes were obtained in a quick, easy and clean way.



12 13 14

Figure 2. 8

2.4. Hydrogenations

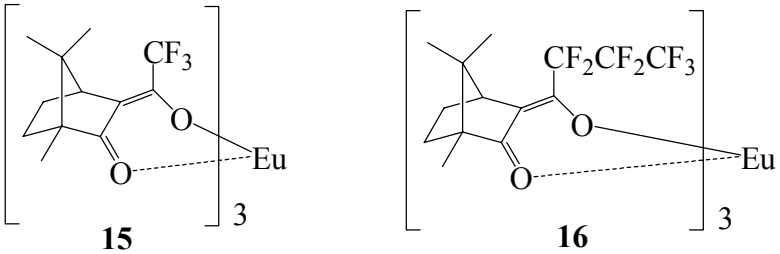
Catalysts **11-14** were tested in asymmetric hydrogenation of ketones and imines. It was necessary to decide which technique to use to determine the enantiomeric excess of our products.

2.4.1. General Methods for the determination of enantiomeric excess

A range of well-known methods exist for determining enantiomeric excess in asymmetric synthesis.[5, 6]

Some techniques involve the use of NMR spectroscopy normally by the intervention of a chiral reagent to convert a mixture of enantiomers into the corresponding mixture of diastereomers.[7] There are three types of chiral reagents, enantiomerically pure derivatising reagents[8, 9] in achiral solvents, chiral lanthanide shift reagents[10] and chiral solvating agents.[11, 12] Other ways to determine the enantiomeric excess are to use chromatography techniques, eg. GC (gas chromatography) and HPLC (high pressure liquid chromatography), which uses chiral stationary phases.[13] Methods such as optical rotation (OR), optical rotatory dispersion [14] and circular dichroism (CD) can also be used to determine the enantiomeric excess due to the physical property of the chiral molecules to rotate the plane of plane-polarised light, but only if authenticated values for the pure enantiomers exist.

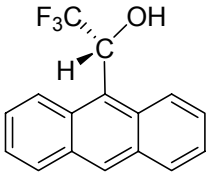
Chiral lanthanide shift reagents form diastereomeric association complexes with the enantiomers in solution, giving a shift in some resonances in the NMR spectrum. The most common reagents are the [Eu(thd)$_3$] (perfluoroalkyl camphorato chelates tris-(3-trifluoromethyl-hydroxymethylene-(1*R*)-camphorato)europium(III)) (**15**) and [Eu(hfc)$_3$] (tris-(3-heptafluorobutyryl-hydroxymethylene-(1*R*)-camphorato)-europium (III)) (**16**). They can be used with chiral alcohols, aldehydes, ketones, and esters. The ee is calculated by integration of the peaks corresponding to the diastereomeric complexes in the NMR.[15]



15 **16**

Figure 2. 9. Chiral lanthanide shift reagents [Eu(thd)$_3$] (15) and [Eu(hfc)$_3$] (16)[15]

The use of chiral solvating agents in NMR to resolve the enantiomeric excess has been studied.[11] This method is based on the stereochemical interaction between the homochiral solvating agent and the chiral compound and therefore the formation of diastereomeric solvation complexes with the enantiomers. The enantiomeric excess can be determined on the basis of such interactions.



17

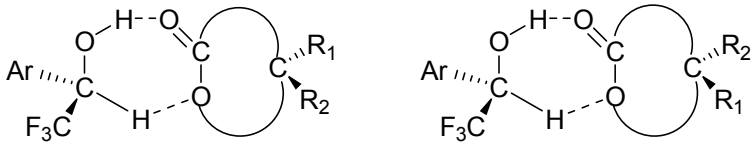


Figure 2. 10. Example of the interaction between the chiral solvating agent (2,2,2-trifluoro-1-(9-anthryl)ethanol) (17) and γ-lactone enantiomers[11]

Chromatographic methods to determined the enantiomeric excess are chiral HPLC and GC. Both methods use a chiral stationary phase which contains an auxiliary resolving agent of high enantiomeric purity. The comparison of relative peak areas provides the measurement of the enantiomeric excess. Chiral gas chromatography (GC) on capillary columns is an important tool for determining the optical purity of chiral compounds and its advantages are high resolution, precision and reproducibility. It is based on the separation of volatile substances, therefore only volatile compounds are suitable for this technique, and due to the high temperatures needed the studied compound needs to be thermally stable.

Between 2004 and 2005 when the work described in parts of this thesis was carried out we did not have HPLC facilities. So, consequently, we determined the enantiomeric excess by NMR techniques. These experiments are also briefly described here. In each case, racemic samples of the alcohols were obtained in essentially quantitative yields by $NaBH_4$ reduction and then investigated using various techniques to determine the best one for each individual substrate.

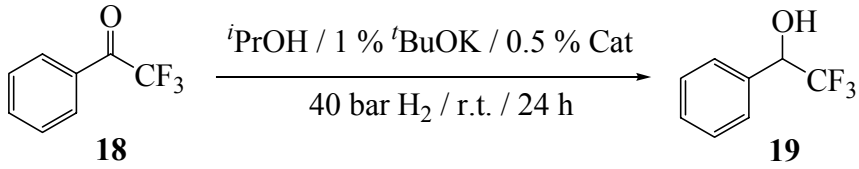
2.4.2 Hydrogenation of ketones

Some fluorinated simple aromatic ketones where chosen to test these catalysts in hydrogenation.

2.4.2.1. Trifluoroacetophenone

Hydrogenation of trifluoroacetophenone with catalyst **11** and **12**, containing as ligands the diastereoisomers of our diamine **3a** shows good activity. For this substrate full conversion was always achieved. Unfortunally, only a 33 % ee was obtained in the best of the cases when using catalyst **11.** Enantioselectivity drops to 18 % when using the diastereoisomer **12**. The catalysts were compared with Noyori's [$RuCl_2$((*S*)-BINAP)((*S,S*)-DPEN)] (**13**) which gave a 68 % ee, more than double than when using catalyst **11**. These experiments demonstrated that diastereoisomer **11** was a better combination of the two chiral ligands, and **11** was from that point used in further hydrogenations.

There could be many reasons why catalysts **11** and **12** are poorly selective in asymmetric ketone hydrogenation. However, it occurred to us that if ketones were being reduced at both primary and secondary NH sites of the ligand, then this may be the cause of the low selectivity. To investigate this, catalyst **14** derived from achiral secondary amine was tested. The *N,N*-dibenzylated diamine catalyst showed poor activity, but did promote some reduction in the hydrogenation of trifluoroacetophenone. Thus it is possible that ketone reduction can occur at both primary and secondary ends of the chiral diamine ligand, and therefore reduce the selectivity.



18 **19**

Figure 2. 11

Table 2. 1

catalyst	conversion[b] %	ee[c] %
11	>99	33
12	>99	18
13	>99	68
14	10	n.d.

[a] Reactions were conducted using a 0.33 M ketone solution in ^{i}PrOH containing 0.5 % of catalyst **10** and 1% of ^{t}BuOK, for 24h. [b] By ^{19}F and ^{1}H NMR [c] Determined by ^{19}F NMR with (*R*)-(+)-α-Methylbenzylamine.

Resolution of the alcohol was carried out using (*R*)-(+)-α-Methylbenzylamine. In Figure 2. 12 we can see the split of the ^{19}F NMR peak.

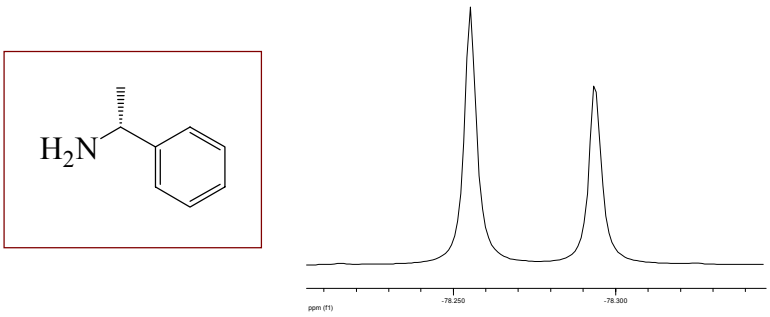


Figure 2. 12

2.4.2.2. p-Fluoroacetophenone

p-Fluoroacetophenone has been hydrogenated at 40 bar of hydrogen and room temperature for 24 h. ^{i}PrOH was used as solvent, in the presence of ^{t}BuOK as base. The hydrogenation was done in the presence of 0.5 % of catalyst.

Catalyst **11** gives a 60 % conversion to the desired alcohol in a 27 % ee. Catalyst **13** (Noyori's [$RuCl_2$((*S*)-BINAP)(*S,S*)-DPEN)]) was used to hydrogenated this substrate. Full conversion with 82 % ee was achieved under modified reaction conditions to Noyori's for the hydrogenation of this substrate with catalyst **13**. Noyori obtains a 73 % ee[16] which is less than we get under the conditions of 40 bar H_2 at r.t. for 24 h. Noyori gains the best result for this substrate with [$RuCl_2$((S)XylBINAP)((S,S)DPEN)]. Comparing catalyst **11** with catalyst **13,** it is obvious that our catalyst is less active and enantioselective than Noyori's catalyst.

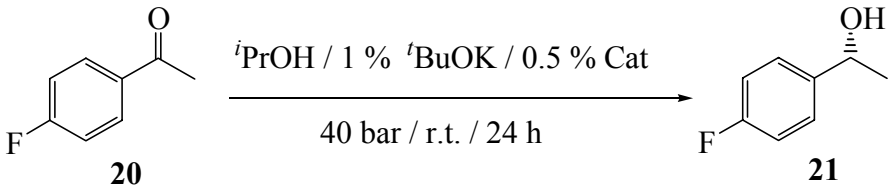


Figure 2. 13

Table 2. 2[a]

catalyst	conversion[b] %	ee[c] %
11	60	27 (*R*)
13	>99	82 (*R*)

[a] Reactions were conducted using a 0.33 M ketone solution in ^{i}PrOH containing 0.5 % of catalyst and 1 % of ^{t}BuOK, for 24 h at r.t.. [b] By ^{19}F and ^{1}H NMR [c] Determined by ^{19}F NMR with [Eu(hfc)$_3$]

Resolution of the alcohol can be done with [Eu(hfc)$_3$] by integration of the ^{19}F-NMR. In the figure below (Figure 2.15) can be seen the ^{19}F-NMR of the alcohol before (left) and

after addition of the europium reagent (middle) in the racemic sample and the ^{19}F-NMR of the resolved alcohol for the sample of 82 % ee (right).

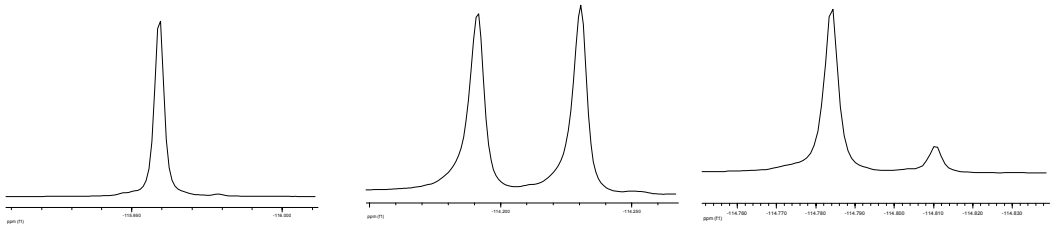


Figure 2. 14

2.4.2.3. 9-anthryl trifluoromethyl ketone

A very interesting substrate for asymmetric hydrogenation is 9-anthryl trifluoromethyl ketone, because the enantiomerically pure alcohol 2,2,2-trifluoro-1-(9-anthryl) ethanol is an important chiral solvating agent and chiral auxiliary.[17] Due to the relatively high cost of this reagent and the necessity of using typically 3 mol eq excess in NMR studies, it is of interest to find an alternative and economical route to this compound by asymmetric hydrogenation.

Unfortunately, catalyst **11** does not give more than a 26 % conversion and the ee is only 34 %. Noyori's DPEN-BINAP catalyst led us to a 56 % conversion and 82 % ee. Again catalyst **13** is much more enantioselective than our diamine **3a** system.

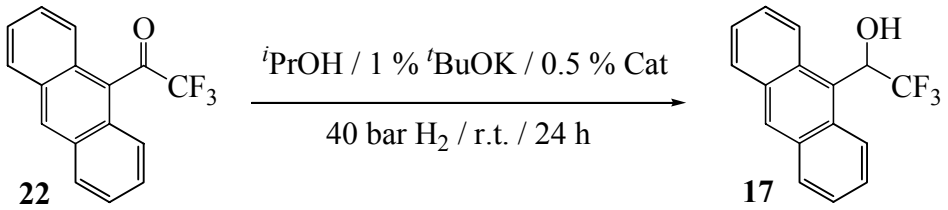


Figure 2. 15

Table 2. 3[a]

catalyst	conversion[b] %	ee[c] %
11	26	34
13	56	82

[a] Reactions were conducted using a 0.33 M ketone solution in ^{i}PrOH containing 0.5 % of catalyst and 1 % of ^{t}BuOK, for 24h at r.t. and 40 bar H_2. [b] By ^{19}F and ^{1}H NMR [c] Determined by ^{19}F NMR with (*R*)-(+)-α-Methylbenzylamine

Enantioselective excess determination of the alcohol was carried out by ^{19}F NMR in the presence of (*R*)-(+)-α-Methylbenzylamine as well. In Figure 2. 16 the ^{19}F NMR spectrum of the resolved racemic sample.

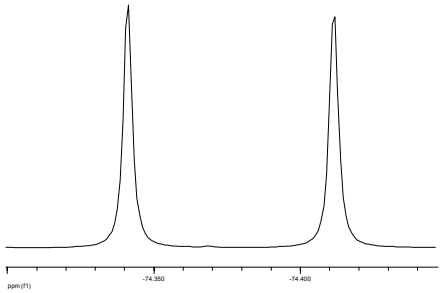
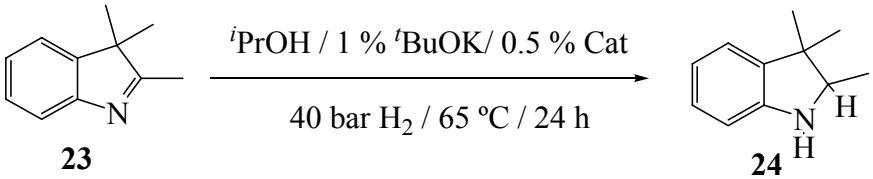


Figure 2. 16

2.4.3. Hydrogenation of imines

Enanantiomerically pure imines are highly important building blocks for biologically active molecules and the discovery of new and efficient methods for their preparation is a matter of interest. Catalytic asymmetric hydrogenation of imines offers a cheap and industrially viable process. Noyori's [$RuCl_2$(diphosphine)(diamine)] are generally very poor catalysts for asymmetric hydrogenation of imines. Only a limited number of diphosphines and diamines were tested in this reaction giving moderate selectivities.[18] Cobley *et al*. reported the [$RuCl_2$(Duphos)(DPEN)] catalyst giving reasonable activity (up to 94 % conversion) and enantioselectivity (up to 85 % ee) for asymmetric hydrogenation of some imines. Diphosphine/diamine combinations that were good for ketone hydrogenation were poor for imine hydrogenation and *vice versa*.[19]

2,3,3-Trimethylindoline was chosen to test our catalyst. The substrate was hydrogenated with 0.5 % of the catalyst at 40 bar of H_2, 65 ºC and 24 h with ^{i}PrOH as solvent and ^{t}BuOK as base. With catalyst **11** 25 % yield of the amine was obtained, in 18 % ee. With Noyori's catalyst **13** no product at all is observed. This catalyst is not good for this reaction even if it shows some activity.



23 **24**

Figure 2. 17

Table 2. 4[a]

catalyst	yield [b] %	ee [c] %
11	25	18
13	0	n.a.

[a] Reactions were conducted using a 0.33 M imine solution in ^{i}PrOH containing 0.5 % of catalyst and 1 % of ^{t}BuOK, for 24h, 65 ºC and 40 bar H_2. [b] isolated by filtration through a short pad of silica gel [c] determined by ^{1}H NMR with 2,2,2-Trifluoro-1-(9-anthryl)-ethanol

The e.e. of the amine can be determined by integration of ^{1}H NMR spectrum of the amine in the presence of enantiomeric pure samples either of the fluorinated alcohols (17 or 19) obtained before.

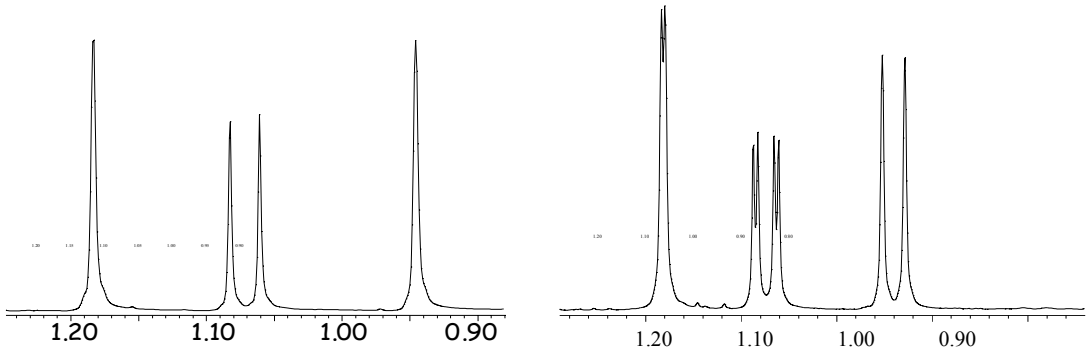


Figure 2. 18. Using 2,2,2-Trifluoro-1-(9-anthryl)-ethanol

2.5. Conclusions

A synthesis of a primary amine-secondary amine ligand ((*S,R*)-**3a** and (*R,R*)-**3a**) has been developed. Although racemisation of the amino acid chiral centre is sometimes observed, the diastereoisomers can be separated and racemisation can be avoided under optimised conditions

A series of [$RuCl_2$(diphosphine)(diamine)] were synthesised in a very effective way using the microwave. Unfortunately these catalysts do not appear to be especially effective in enantioselective Ru catalysed hydrogenation of ketones and imines.

Given that the first member of our proposed library was so ineffective, and that the amino acid derived ligands were not extremely easy to make, we felt that other approaches towards asymmetric ketone hydrogenation would hold more promise.

2.6. References

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CHAPTER III

Synthesis and reactivity of a ruthenium complex of a chiral tridentate ligand

3.1. Introduction

The selective reduction of carbonyl compounds to alcohols and imines to amines are very important processes in industrial and academic organic synthesis.[1-3] When the project started, there were no ruthenium catalysts available that were effective for hydrogenation of tetralones, dialkylketones, bulky ketones, some heterocyclic ketones and imines as described in chapter **1**. It was our desire to provide a solution and in this endeavour we designed, synthesised and tested a novel Ru-based tridentate catalyst for use in the hydrogenation of a range of substrates.

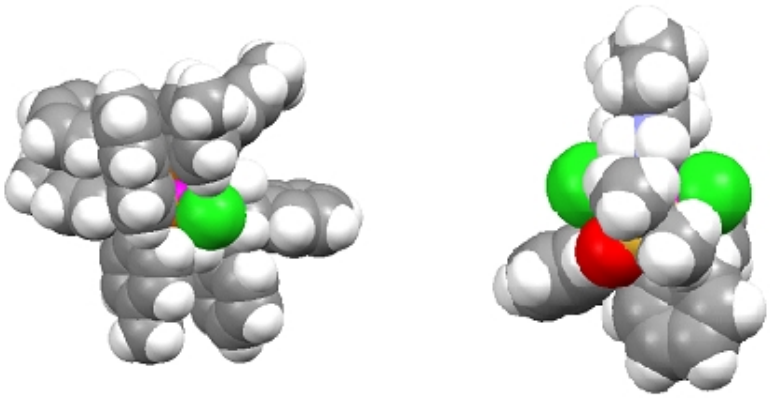
3.2. Ligand design

We initiated the project with the general impression that a departure from the [Ru(diphosphine)(diamine)Cl_2] blueprint would be required. There are some structural requirements that must be fulfilled before a catalyst system can be effectively applied towards asymmetric hydrogenation of ketones. First, Noyori's results suggest that a phosphorus ligand, NH functionality and Ru(II) are required for a ketone hydrogenation catalyst. Obviously, for asymmetric catalytic hydrogenation a readily available source of chirality is also necessary. Our catalyst design was influenced by Elseviers impressive ester hydrogenation catalyst [$Ru(acac)_3$ / triphosphine],[4] and our interest in applying phosphine-amine ligands in catalysis. Phosphine-amine ligands have provided some interesting niche applications in catalysis, and given the absence of data on hydrogenation catalysis using tridentate ligands, ruthenium complexes of tridentate P^N^NH_2 type ligands seemed worthy of investigation.

25 **26**

Figure 3. 1. Two bidentate ligands versus one tridentate ligand.

It was hoped that a tridentate P^N^NH_2 type ligand could form octahedral ruthenium complexes containing a potentially vacant co-ordination site and a more open environment, thus increasing substrate scope in hydrogenation. Another topical aspect that interested us was the use of only one ligand to play the roles carried out by both diphosphine and diamine ligands in Noyori catalysts.[5] The hydride ligands would most likely be located where the chloride ligands are shown in Figure 3. 1. It is clear that these positions are more accessible for bulky ketones in the case of the complex containing the tridentate ligand. See Figure 3. 2.



A **B**

Figure 3. 2. Comparation of space filling models of A) Noyori's catalyst [Ru(TolBINAP)(DPEN)Cl_2] and B) Ru Catalyst of one tridentate ligand, 33.

3.3. Synthesis of the tridentate ligand

The most attractive tridentate ligands would come from cheap starting materials in a minimal number of steps. Ligand **30** in Figure 3. 3 fulfilled these criteria and had been reported in the literature as an intermediate in the synthesis of a tetradentate phosphine applied in transfer hydrogenation.[6, 7] However, despite containing all the required functionalities for a ligand for transition metals, **30** has not been used for this purpose.

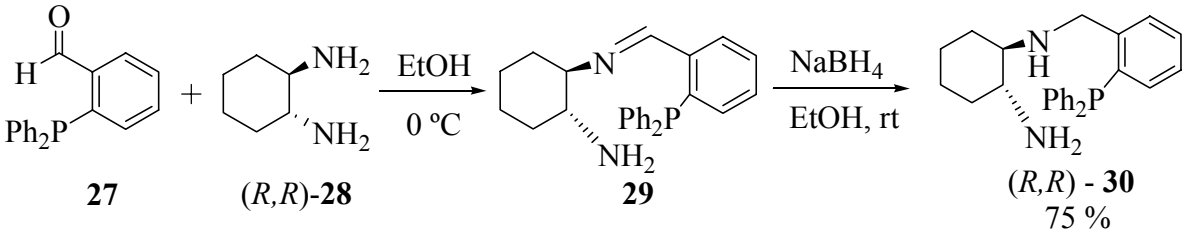


Figure 3. 3. Synthesis of the tridentate ligand 30.

The selective monofunctionalisation of (1*R*,2*R*)-diaminocyclohexane (**28**) was achieved by slow addition of 2-(diphenylphosphino)benzaldehyde (**27**). The course of the reaction was monitored by NMR: the imine proton of the mono and difunctionalised products can be clearly distinguished [imine signal monofunctionalised δ = 8.74 ppm (1H, d, C*H*), difunctionalised δ = 8.62 ppm (2H, d, C*H*)]. The monofunctionalised imine **29** was used directly without further purification and converted to the corresponding amine **30** by reduction using sodium borohydride. Purification of the product (**30**) was carried out by precipitation as the hydrochloride salt.

Imine **29** is also interesting and could act as a tridentate ligand using the reasons described earlier. In order to prepare pure **29** the procedure was slighted modified, and diamine **28** was added in 1:1 ratio to phosphine **27**. NMR analysis revealed that this imine was essentially 100 % pure and could therefore be used directly.

Using this synthetic procedure there are many possibilities for the synthesis of novel tridentate ligands, by using different phosphines or diamines. Since we had compound **3a** to hand, it was decided to investigated if the NH_2 group was required in the tridentate ligand for effective catalytic hydrogenation. We briefly investigated the use of (S,R)-**3a** as a diamine component for a tridentate ligand like (**30**). Unfortunately, during all the attempts to make this ligand, a large quantity of phosphine oxide and other minor side products were observed, even when work up and purification were carried out under Argon.

Due to much more promising results subsequently obtained using catalyst (**30**), this strategy was called to a halt.

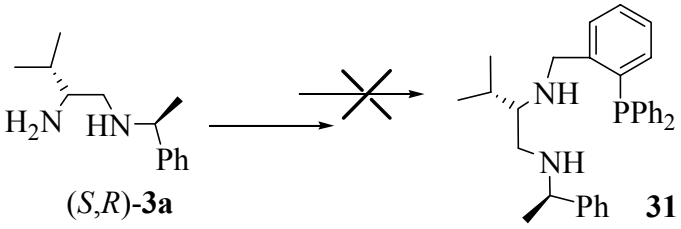
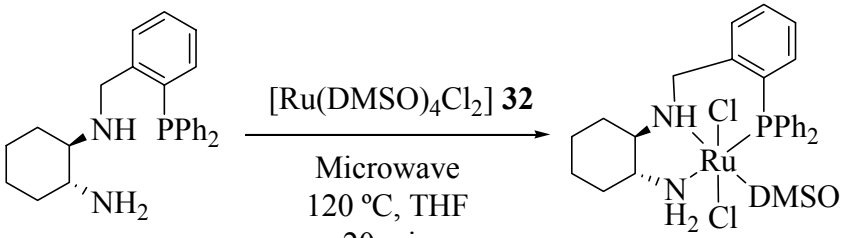


Figure 3. 4

3.4. Synthesis and characterisation of the ruthenium catalyst.

Ru(P^P)(N^N) complexes are known to be formed when the ligands are heated in the presence of a Ru starting material such as $[RuCl_2(benzene)]_2$, $[RuCl_2(COD)]_2$ or $[RuCl_2(DMSO)_4]$. The first attempt to make the Ru complex of the tridentate ligand (*R*,*R*)-**30** was with $[Ru(DMSO)_4Cl_2]$ in toluene at 105 ºC. This reaction gave several Ru species by ^{31}P NMR that could be separated by chromatography. The separated Ru species were screened for activity in catalytic hydrogenation reactions. However, only one of these species (^{31}P NMR +43 ppm) showed any catalytic activity. The inactive Ru species were not characterised further.

We developed a novel and optimised procedure for preparing the catalytically active species. Heating $[Ru(DMSO)_4Cl_2]$ and (*R*,*R*)-**30** in THF at 120 ºC in the microwave, gave a quantitative yield of the desired ruthenium complex (^{31}P NMR +43ppm) in sufficient purity (~90-95%) for the applications in catalytic hydrogenation. Many microwave reactions give higher purity than conventional heating methods and in this case, higher temperatures may well promote the coordination and minimise the oxidation of the phosphine by DMSO. When different starting ruthenium complexes were employed, the desired species was not present in significant amounts, for example $[Ru(COD)Cl_2]_2$ gave many different Ru-P species. In the case of $[Ru(C_6H_6)Cl_2]_2$ no reaction was observed at all.



Ligand 30 **Complex 33**

Figure 3. 4. Synthesis of the complex 10.

Ligand **29** was complexed in the same way by reacting with $[Ru(DMSO)_4Cl_2]$ under microwave irradiation giving a ruthenium complex with a single signal in the ^{31}P NMR at δ +52ppm.

3.4.1. X-Ray structure

It was not possible to unambiguously determine the structure of this complex spectroscopically, but eventually we obtained a crop of high quality crystals (MeCN, slow

evaporation) which were analysed by X-ray diffraction. The crystal structure of the complex is shown in Figure 3.5.

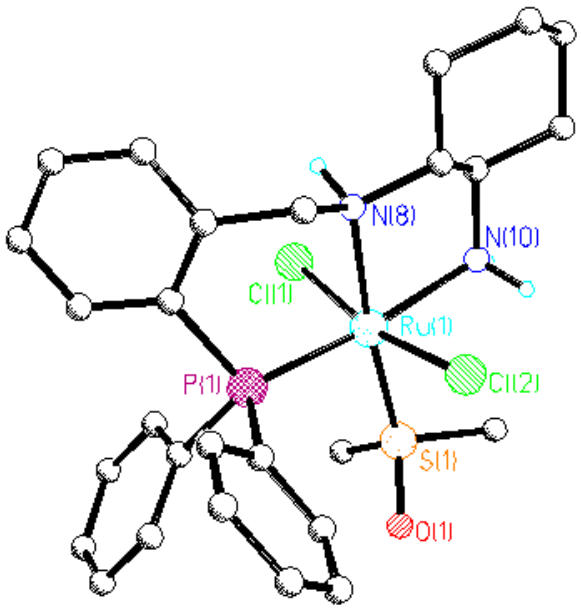


Figure 3. 5. X-ray structure of Complex 33. Two MeCN molecules and all hydrogen atoms are omitted for clarity. Selected bond lengths and angles: Ru-P(1) 2.2912(13) Å, Ru-N(8) 2.160(4) Å, Ru-N(10) 2.155(4) Å, N(10)-Ru(1)-P(1) 171.14(10)°, N(8)-Ru(1)-P(1) 91.67(10)°.

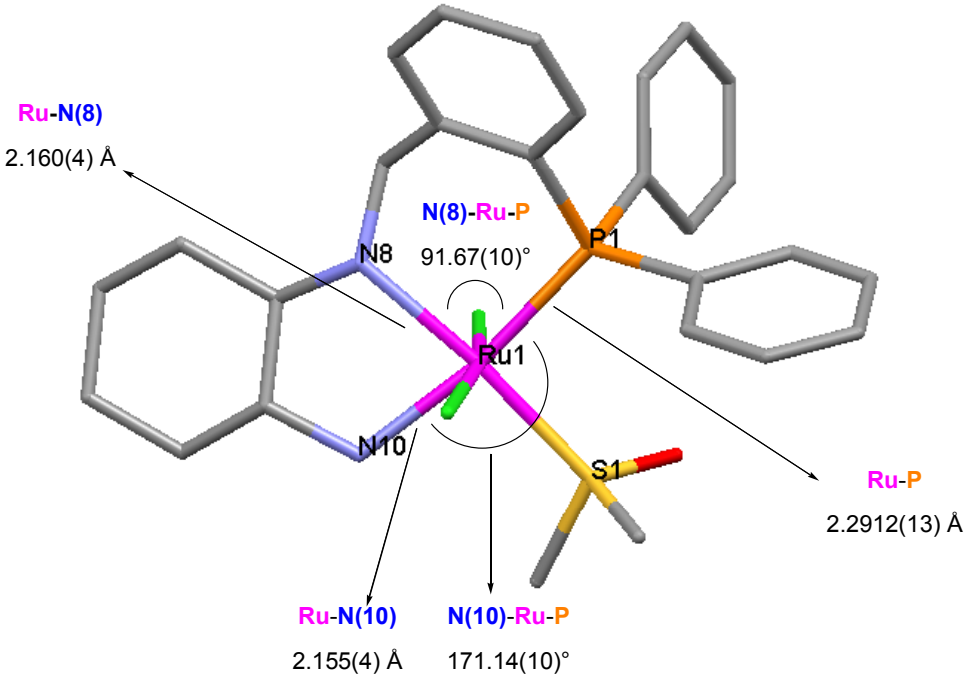


Figure 3. 6. Bond lengths and angles for complex 33.

Complex **33** is an octahedral Ru (II) complex in which ligand **30** acts as a tridentate neutral ligand. The secondary amine moiety is chiral at nitrogen in the free ligand, and as expected chirality is conserved during the complexation**.** The chiral nitrogen centre is configurationally unstable in the free ligand, whereas on complexation a single configuration was observed in the solid state. In the ^{1}H NMR a single NH resonance was observed, which is

consistent with, but does not prove, that this single configuration was retained in solution. A sulfur bonded of the DMSO ligand occupies the site *trans* to the secondary amine. Ru-P (2.2912 Å) and Ru-N (2.160 Å) bond lengths are similar to those found in [Ru (diphosphine)(diamine)Cl_2] complexes.[8] With the structurally characterised pre-catalyst in hand, we investigated its potential in the hydrogenation of a range of substrate classes.

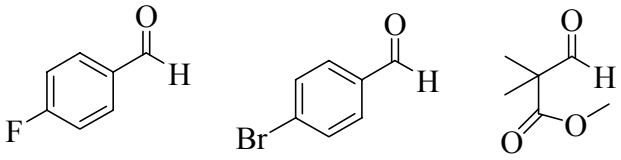
3.5. Catalytic applications

3.5.1. Aldehyde hydrogenation

α,β-Unsaturated aldehydes are known to be valuable intermediates in the field of fragrance and flavour chemistry, and very often the multistep synthesis to new products involves the selective reduction of the carbonyl function. Hydrogenation of C=C double bonds is readily achieved under mild conditions with high selectivity.[9, 10] Whereas the catalytic reduction of the aldehyde group is more challenging. Most of the popular selective reducing agents are metal hydrides and mainly those containing boron and aluminium.[11, 12] Catalytic hydrogenation is by far the most attractive way to carry out the reduction with respect to economical and industrial process considerations. Hydrogenation of aldehydes is not an especially difficult process, but some catalysts cause decarbonylation and when an aldehyde substrate has a C=C bond functionality present the majority of catalysts hydrogenate C=C in preference to C=O bonds.[13-16]

Complex **33** catalyses the reduction of *p*-fluorobenzaldehyde **34** quantitatively at 30 ^{o}C. The hydrogenation of the less reactive bulky aldehyde **36**, also proceeds at 30 ^{o}C but in reduced yield, quantitative yields are only achieved at 100 ^{o}C. In the case of the hydrogenation of the *p*-bromobenzaldehyde **35**, full conversion is achieved at 50 ºC. In all cases, there was no evidence for the competing decarbonylation reaction.

Due to the quantitative nature of these (and many other reductions reported in this thesis), the pure alcohols are readily isolated by removal of solvent and very simple column chromatography (single spot with $R_f > 0.1$).



34 **35** **36**

Figure 3. 7

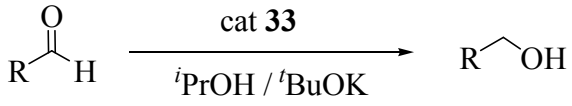


Figure 3. 8

Table 3. 1[a]

substrate	catalyst %	H_2 bar	T / ºC	conversion[b] %	yield[c] %
34	0.5	40	30	>99[d]	>99
35	0.5	50	50	>99	>99
35	0.1	50	50	>99	>99
36	0.5	50	100	>99	>99

[a] Reactions were conducted using a 0.33 M aldehyde solution in ^{i}PrOH containing catalyst **33** and ^{t}BuOK (2eq respect to the catalyst), overnight. [b] Conversions calculated by ^{1}H NMR analysis of the crude reaction mixture. [c] Pure alcohol isolated by filtration through a short pad of silica. [d] By ^{19}F NMR

These initial experiments used 0.5 % of catalyst **33**. To further investigate the catalytic activity, the catalyst loading was examined using substrates **34** and **35**.

Using 0.1 % catalyst, substrate **35** reacted fully (TON 1000) in the presence of 0.2 % of ^{t}BuOK as base and ^{i}PrOH as solvent, at 50 ºC and 50 bar of H_2 overnight. Full conversion of substrate **34** was not achieved if less than 0.5 % of catalyst was used (Table 3. 1), demonstrating that the catalyst **33** is less active for this substrate. It is not clear how the *para-halo* substituents affect the hydrogenation reaction. However, it is clear that the new catalyst belongs to quite a rare class that can reduce aldehydes cleanly and selectively under mild conditions. It should be noted that inert conditions and direct drive stirring are required to get high TOF's in Noyori catalysis. However all our reductions were set up in air (although used dry and degassed ^{i}PrOH) and stirred magnetically (at the same speed throughout).

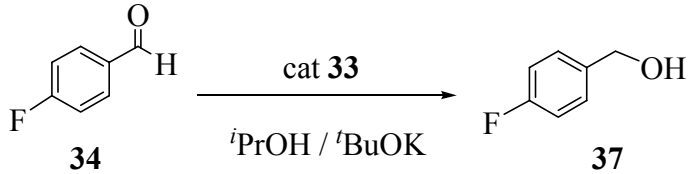


Figure 3. 9

Table 3. 1[a]

cat %	H_2 bar	T / ºC	conversion[b] %
0.5	40	30	>99
0.1	50	50	44
0.05	40	30	31
0.01	50	75	0

[a] Reactions were conducted using a 0.33 M aldehyde solution in ^{i}PrOH containing catalyst **33** and ^{t}BuOK (2eq respect to the catalyst), overnight. [b] Conversions calculated by ^{19}F NMR analysis of the crude reaction mixture.

The methyl ester **36**[17] was hydrogenated at 50 bar H_2 and 40 ºC in ^{i}PrOH and ^{t}BuOK (2 mol %) for 24 h but it was difficult to isolate the product and calculate the exact conversion due to the high volatility of the product. The reaction was therefore carried out at 50 bar H_2 and 100 ºC using deuterated methanol as solvent to allow for NMR analysis of the crude reaction mixture. The desired product was obtained in quantitative amounts.

Due to the conversion under mild conditions of substrates **18-20** this demonstrates the catalytic activity of catalyst **33.** To demonstrate the chemoselectivity a 1:1:1 mixture of an alkene (2-phenylpropene (**40**)), an aldehyde (*p*-fluorobenzaldehyde (**34**)) and an imine (N-(phenylmethylene)-benzenamine (**41**)) was prepared. In the reaction at 50 ºC with 20 bar H_2 for 20 h the aldehyde was hydrogenated to the alcohol with 100 % conversion, leaving unreacted the imine and alkene substrates (Figure 3. 10), this shows that catalyst **33** is chemoselective for C=O double bonds under mild conditions.

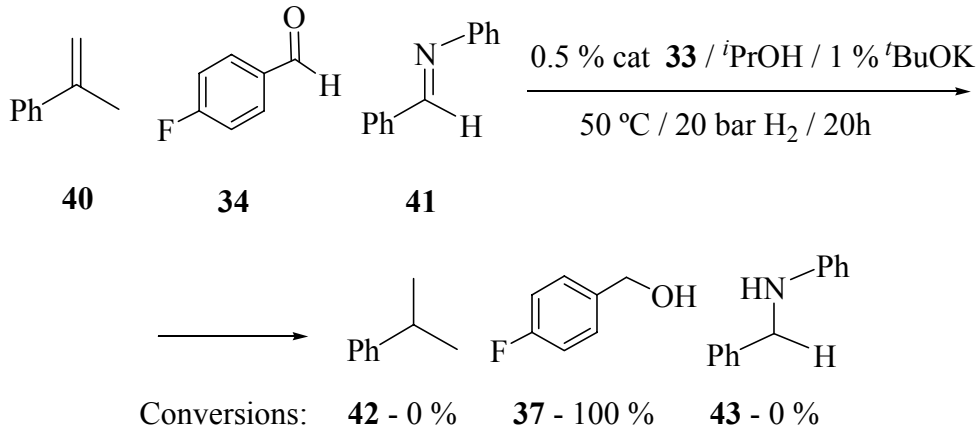


Figure 3. 10

Cinnamaldehyde, **44** is a particularly challenging substrate for hydrogenation. Initial experiments revealed that while the C=O bond is preferentially reduced, the reaction was sluggish, and sometimes accompanied by minor amounts of C=C hydrogenation products.

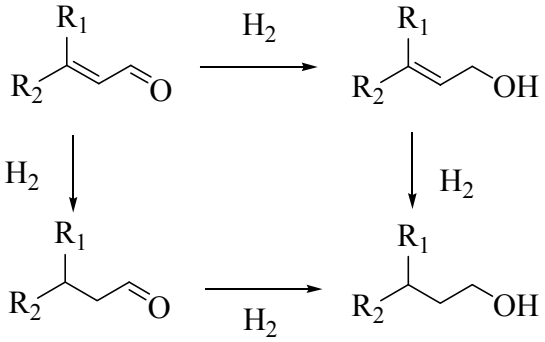


Figure 3. 11

^{1}H NMR analysis of the crude products reveals significant amounts of the fully reduced product. In a reaction that went to 82 % conversion of starting materials, pure

cinnamyl alcohol **45** was isolated after column chromatography in only 48 % yield. In the hydrogenation of cinnamaldehyde under these unoptimised conditions, this catalyst preferentially reduces C=O bonds, but shows lower chemoselectivity than the Noyori system. Addition of 4-dimethylaminopyridine (DMAP)[18] as a cocatalyst suppressed C=C reduction completely, and increased catalytic activity (>87 % conversion to alcohol; 76 % isolated yield for pure alcohol). A stoichiometric reaction between complex **33** and DMAP in $CDCl_3$ did not give a new DMAP-co-ordinated complex, and thus, the origin of the DMAP effect remains unclear. In addition DMAP does not provide beneficial effects in the hydrogenation of ketones, as discussed in chapter **4**.

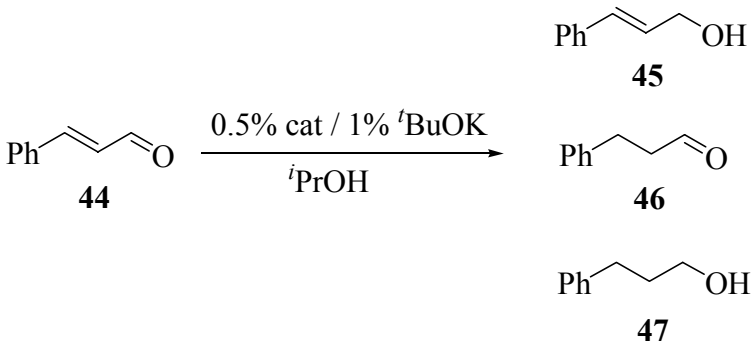


Figure 3. 12

Table 3. 2[a]

T / ºC	H_2 bar	additive	time / h	conversion %[b]		
				45	**46**	**47**
30	20	-	48	15	-	28
30	40	-	20	48	-	34
30	40	1.6% DMAP	20	87	-	2
50	10	-	24	13	10	6
50	no H_2	-	24	1	-	6

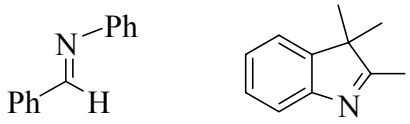
[a] Unless otherwise stated, reactions were conducted using a 0.33 M aldehyde solution in ^{i}PrOH containing 0.5 % catalyst **33** and 1% of ^{t}BuOK. [b] ^{1}H NMR analysis.

3.5.2. Imine hydrogenation

Chiral amines are considered important targets for synthetic chemists, and attempts to prepare such compounds enantioselectively date back to the 40's. Many publications show the use of Pd, Ru, Rh, Ir, and Ti complexes for imine hydrogenation in combination with some chiral auxiliaries (with the aim of transfering chirality from the auxiliary to the reactant).[19-21] Only few substrate types were studied, the enantioselectivities were low and could not always be reproduced. The first reports on homogeneous Ru and Rh catalysts appeared in 1975, but useful enantioselectivities were only reported in 1984 by Marko and coworkers.[20] Remarkable

progress has been made during the 1990's and today several very selective catalysts are available for the hydrogenation of different types of C=N functions, with the first industrial process being announced in 1996.[22] Despite the significant progress, the enantioselective hydrogenation of prochiral C=N groups, to obtain the corresponding chiral amines, still represents a major challenge.

In contrast to the wide scope of Ru based catalysts for the hydrogenation of alkenes and ketones, the hydrogenation of imines is not readily achieved by ruthenium catalysts. In 2003, Cobley and Hensche found that Ru(BINAP)(DPEN)Cl_2 has low activity in this reaction, a surprising improvement was found when [Ru(Duphos)((*S,S*)-DPEN)Cl_2], which is inactive for ketone hydrogenation, was employed.[23]



41 **23**

Figure 3. 13

In an initial screen, aldimine **41** and prochiral bulky ketimine **23** were hydrogenated quantitatively under similar conditions to those used by Cobley and Hensche.[23] The e.e. of the chiral amine **23** was 37 %, which although poor, is high enough to suggest potential for further research. If hydrogen was not present, there was no transfer hydrogenation from ^{i}PrOH to the imine, as was expected based on literature precedent.[23]

Table 3. 3[a]

substrate	H_2 bar	T / ºC	conversion[b] %	ee[d] %
41	40	65	>99 (99)	n.a.
23	50	65	>99 (98)	37*
23	0	65	0	n.a.

[a] Reactions were conducted using a 0.33 M imine solution in ^{i}PrOH containing 0.5 % of catalyst **33** and 1% of ^{t}BuOK, for 18h. [b] By 1H NMR [c] isolated by filtration through a short pad of silica [d] determined by ^{1}H NMR with 2,2,2-Trifluoro-1-(9-anthryl)-ethanol

3.5.3. Ester and Anhydride Hydrogenation

The hydrogenation of esters and anhydrides using molecular hydrogen is a difficult challenge. These substrates are more normally reduced using $LiAlH_4$, however, this produces waste salts. Molecular hydrogen has attracted considerable industrial attention, since it is cheap, clean, and does not generate any solid waste. Some heterogeneous catalysts are only

successfully used under severe conditions (200-250 ºC at 150-200 bar) which limits their application. Homogeneous ruthenium catalysed hydrogenations have been under development in several companies.[4, 24]

3.5.3.1. Anhydrides

In 1975, Lyons reported that $[Ru(PPh_3)_3Cl_2]$ catalyzes the reduction of phthalic anhydrides (**48**) to the lactone phthalide (**49**)[25] (Figure 3. 14). The *o*-phthalic acid is presumably formed by hydrolysis of the anhydride by water formed during lactonization. Neither acid nor lactone were further hydrogenated to any significant amount using this catalytic system under these conditions.

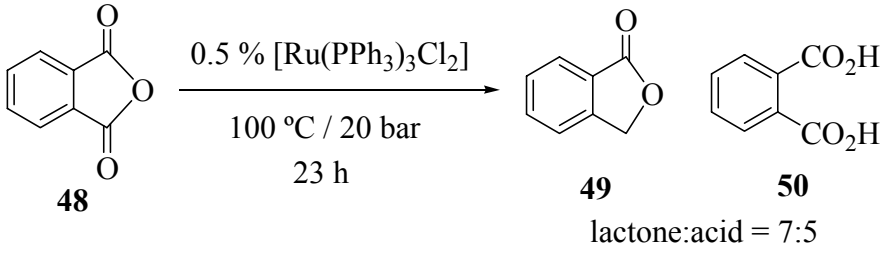


Figure 3. 14

Mitsubishi have reported several processes based on Ru-catalyzed hydrogenation of anhydrides and acids. Succinic anhydride can be converted into mixtures of 1,4-butanediol and γ-butyrolactone using $[Ru(acac)_3$/trioctylphosphine] and an activator (often a phosphonic acid).[26] Relatively high temperatures (~200 ºC) are required for this reaction. The lactone can be prepared selectively under the appropriate reaction conditions, and a process has been developed for isolating the products and recycling the ruthenium catalyst.

It is not clear which properties in the catalyst are essential for the hydrogenation of anhydrides, but it has been shown that Ru complexes hydrogenate them. We hypothesised that catalyst **33** could be a good catalyst for hydrogenation of anhydrides and tested it in hydrogenation of phthalic anhydride **48**.

Using 0.5 % of catalyst **33** for the reduction of the anhydride in ^{i}PrOH and ^{t}BuOK shows conversion of the starting material into lactone and diol (by ^{1}H NMR and GCMS). Using the same catalyst in MeOD as solvent and $LiHBEt_3$ as base, the crude reaction was directly analysed by ^{1}H NMR. The lactone and diol were observed as the only new products. Conversion was calculated by ^{1}H NMR with respect to 1,3-dimethyl naphthalene as the

internal standard. Anhydrides have rarely been successfully hydrogenated, so it was encouraging that **48** was reduced to a mixture of lactone **49** and diol **51** using catalyst **33**.

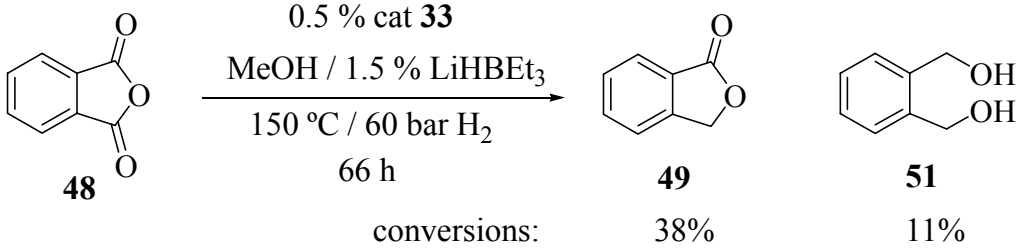
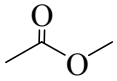
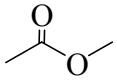
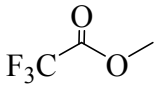
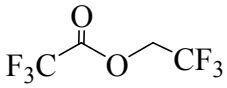
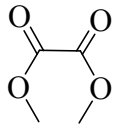


Figure 3. 15

3.5.3.2. Ester

The first example of a clean hydrogenation of an ester to an alcohol was reported by Grey *et al*.[27] Using what was formulated as a potassium hydrido (phosphine) ruthenate complex $K_2[Ru_2(Ph_3P)_3(Ph_2P)H_4]_2$ they were able to hydrogenated a range of esters, shown in Table 3. 4.

Table 3. 4.[a] Ester hydrogenation as reported by Grey[27]

cubstrate	ester conversion %
	22
	5[b]
	88
	100[c]
	70

[a] Reaction conditions unless otherwise stated: toluene (3 ml); ester (5.7 mmol); 90 ºC, 20 h; catalyst (0.017 mmol); H_2 (6.2 bar) [b] THF [c] 4h

The results suggest a pronounced electronic effect on ester hydrogenation. Esters containing electron-withdrawing groups adjacent to the carboxycarbonyl should be activated for reaction with the hydridometalates and might thus be easier to hydrogenate than methyl acetate.

There are many improvements that could be made in the hydrogenation of esters, since up to the late 1990's only the highly activated substrate could be hydrogenated. For example, dimethyl oxalate (DMO) can be partially hydrogenated to MG after 144 h at 180 ºC under a

high pressure of hydrogen by Matteoli.[28] Hydrogenation of dimethyl oxalate in the presence of $Ru(CO)_2(CH_3CO\text{-}O)_2(PBu_3)_2$ gives methyl glycolate (MG) and subsequently ethylene glycol (EG). The formation of the glycol is favoured by hydroxylated solvents.

Elsevier and coworkers[29] studied DMO hydrogenation using a broader range of catalysts, and under milder conditions. They showed that tetra- and tri-dentate phosphines, when used in combination with $[Ru(acac)_3]$, are very promising precatalysts for this class of reaction. This catalyst system was the most active one known when this work was carried out.

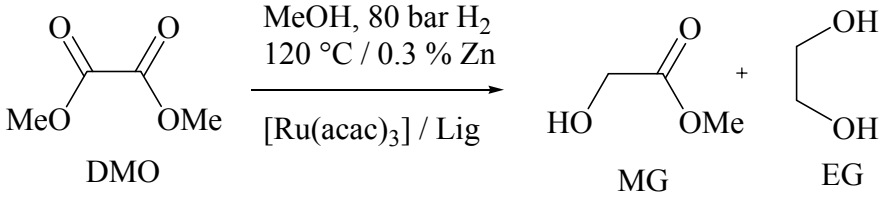


Figure 3. 16

Table 3. 5 Hydrogenation of dimethyl oxalate according to Elsevier[a]

Ligand	L:Ru ratio	Conv. %	MG %	EG %	TON
dppe	3.0	18	11	0	6
PPh_3	5.9	73	36	0	18
$PhP(C_2H_4PPh_2)_2$	1.7	76	67	0	38
$MeC(CH_2PPh_2)_3$	1.4	100	1	95	160
$(CH_2P(Ph)C_2H_4PPh_2)_2$	1.0	91	85	0	36

[a] Conditions: $Ru(acac)_3$, 120 °C, 80 bar H_2, 16 h, MeOH (12 ml), 0.3 % Zn as additive.

The Table 3. 5 show the improved activity of the multidentate ligand, especially the selective formation of EG using the Triphos ligand.

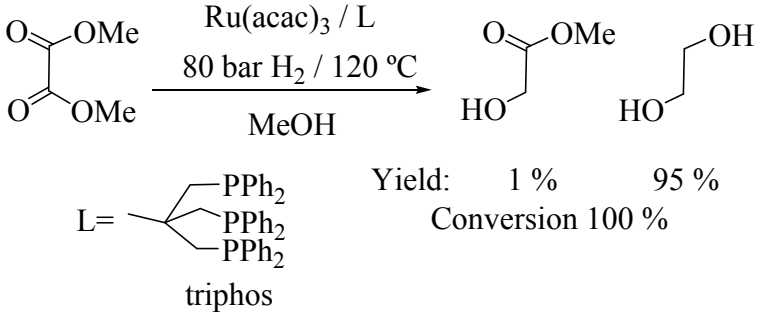
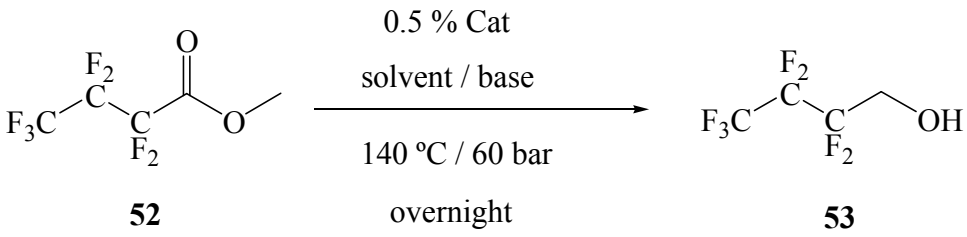


Figure 3. 17

Catalyst **33** was compared with $[Ru(PPh_3)_3Cl_2]$ in reduction of methyl-heptafluorobutanoate **52**, with either $LiBEt_3H$ (1.5 %) or ^tBuOK (1 %) used as catalytic additives to generate Ru-H species (Figure 3. 18). In both cases the catalyst reduces this ester to 1*H*,1*H*-heptafluorobutan-1-ol **53** with no other products detectable after 20 hours. $[Ru(PPh_3)_3Cl_2]$ was not effective under these conditions.



52 **53**

Figure 3. 18

Table 1. 1[a]

catalyst	solvent	base	conversion[b] %
Ru(P^N^N)Cl_2 (**33**)	^{i}PrOH	1 % ^{t}BuOK	>99
Ru(P^N^N)Cl_2 (**33**)	CD_3OD	1.5 % $LiHBEt_3$	>99
$Ru(PPh_3)_3Cl_2$	CD_3OD	1.5 % $LiHBEt_3$	47

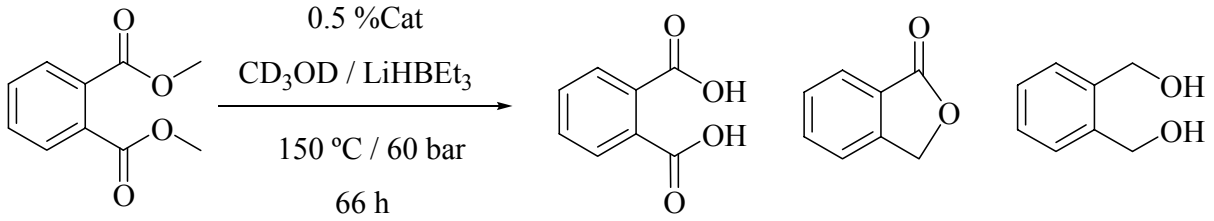
Reaction conditions: 3 ml of solvent containing 1 mmol of substrate, 0.5 % of catalyst and the respective amount of base. 140 ºC at 60 bar of H_2 overnight. [b] Conversion calculated directly from the ^{19}F and ^{1}H NMR spectrums.

The hydrogenation of substrate **54** show 33 % of the corresponding alcohol when the hydrogenation conditions were 160 ºC, 60 bar H_2, in CD_3OD and $LiHBEt_3$ for 70 h using 1 % catalyst **33**. When hydrogenating the non activated ester **55** under the same conditions no alcohol was observed.

54 **55**

Figure 3. 19

The hydrogenation of ester **58** (carried out for 66 h at 150 bar of H_2 in methanol-d^4 as solvent using 0.5 % catalyst and 1.5 % $LiHBEt_3$ base) gave a mixture of 34 % lactone **49** and 54 % diol **51**. The remaining mass balance is ester **58** and the corresponding acid **50**. The results obtained suggest that using the additives explored to date, catalyst **33** is less active than the Elsevier system, but more active than prior ester hydrogenation catalysts such as $Ru(PPh_3)_3Cl_2$.



58 8% **50** 34% **49** 54% **51**

Figure 3. 20

After these experiments were completed Milstein and coworkers reported another P^N^N ligand based Ru catalyst that seems to be the most active catalyst yet reported.[30] It is likely that in the future, new heterotridentate ligands will further improve homogeneous Ru catalysed ester hydrogenation.

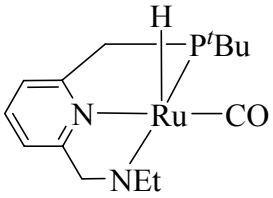
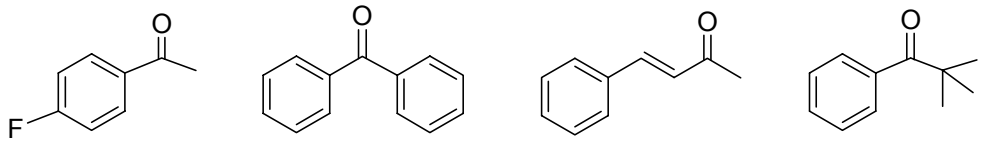


Figure 3. 21. Milstein Ru catalyst.

3.5.4. Ketone hydrogenation

One of the initial aims of this research was to hydrogenate unreactive ketones using the new catalysts, ideally with some asymmetric induction. Thus, the enantiopure variant of complex **33** was used for the hydrogenation of a range of ketones.

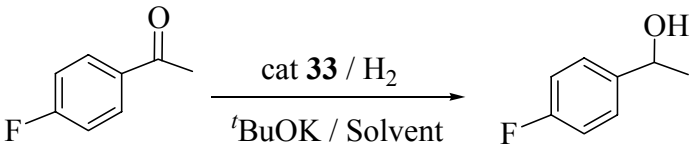


20 **59** **61** **65**

Figure 3. 22

4-Fluoroacetophenone (**20**) was tested with the previously described hydrogenation protocol to give quantitative yields.

All of the hydrogenation experiments were set up under non-inert conditions in simple steel autoclaves with magnetic stirring. For these reasons, we have not fully optimized turnover frequencies, since direct drive stirring and inert conditions are known to maximize TOF's for homogeneous hydrogenation. However, 4-fluoroacetophenone **20** could be cleanly hydrogenated to alcohol with a S/C ratio of 10000 (30 ^{o}C, 40 bar, ^{i}PrOH, 1 % ^{t}BuOK, < 20 hours). This hydrogenation proceeded equally well in ethanol or ^{i}PrOH.



20

Figure 3. 23

Table 3. 6[a]

% cat	solvent	T / ºC	H_2 bar	conversion[b] / %
0.5	^{i}PrOH	r.t.	40	67
0.5	^{i}PrOH	30	40	>99
0.5	^{i}PrOH	50	50	>99
0.1	^{i}PrOH	50	50	>99
0.01	^{i}PrOH	50	50	>99
0.01	EtOH	50	50	>99
0.01	^{i}PrOH	50	—	0

[a] Reactions were conducted using a 0.33 M ketone solution containing catalyst **33** and ^{t}BuOK (2eq) for 18h under a pressure of H_2. [b] Conversions calculated by ^{19}F and ^{1}H NMR analysis.

Catalyst loading for substrate **59** was studied giving full conversion when just 0.05 % of catalyst was used (2000 TON).

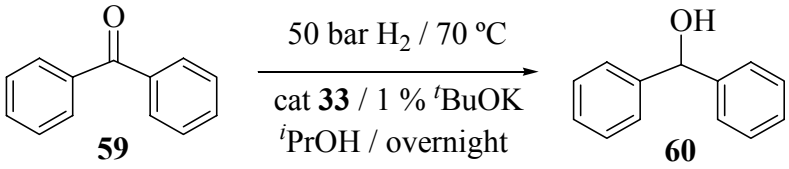


Figure 3. 24

Table 3. 7[a]

% cat	S/C	TON	conversion[b] / %
0.5%	200	200	>99
0.05%	2000	2000	>99
0.01%	10000	2300	23

[a] Reactions were conducted using a 0.33 M ketone solution containing catalyst **33** and ^{t}BuOK (2eq) overnight under a pressure of 50 bar H_2, at 70ºC. [b] Conversions calculated by ^{1}H NMR.

It was desirable to know the selectivity of catalyst **33** for C=O double bonds in ketones as well as aldehydes. When the hydrogenation of substrate **61** was carried out at 4 bar of H_2 a 35 % conversion was obtained and only the desired alcohol was observed by NMR, no hydrogenation of the C=C double bond was detected. Increasing the presure to 40 bar of H_2 full conversion occured to give a mixture of the three different products containing only a 22 % of the desired alcohol. Catalyst **33** does belong to a rare class of catalyst that hydrogenates C=O in preference to C=C bonds, but **33** is less chemoselective than Noyori catalysts. However, there are many unexplored derivatives of catalyst **33** that may have improved chemoselectivity.

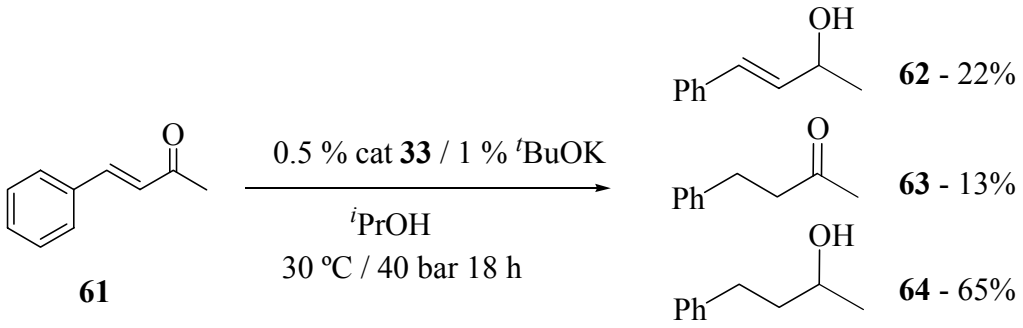


Figure 3. 25

Noyori and coworkers reported that 1,1',1''-trimethylacetophenone **65** gave only a 6 % yield when hydrogenated using [Ru(BINAP)(DPEN)Cl_2]. When our work was carried out, there were no effective ruthenium catalysts for asymmetric hydrogenation of this or related substrates, therefore it was investigated as a challenging bulky ketone substrate with the new catalyst **33**. It was pleasing to discover that the hydrogenation proceeds smoothly at 50 ºC to give the alcohol in quantitative yield.

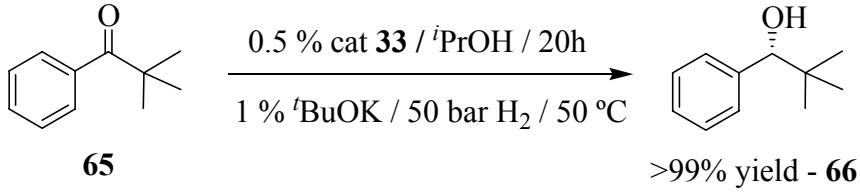


Figure 3. 26

As a result of this encouraging reactivity a more extensive study on asymmetric hydrogenation of relative unreactive ketones was carried out. This is discussed in Chapter **4**.

3.6. Conclusions

In conclusion, the new ruthenium complex reported here shows good activity for hydrogenation of an extraordinary broad range of substrates. These include the hydrogenation of ketones that are not hydrogenated with [Ru(BINAP)(DPEN)Cl_2] catalyst. It was felt that the clean reduction of bulky ketones using catalyst **33** was especially promising and in Chapter **4** a thorough examination of the enantioselective reduction of challenging ketones is discussed.

3.7. References

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CHAPTER IV

Enantioselective Hydrogenation of ketones

4.1. Introduction

The challenges and some of the recent developments in asymmetric hydrogenation of unfunctionalised ketones have been reviewed in chapter **1**. Noyori's pioneering work from 1995 onwards has inspired many groups to research this reaction. When this study was initiated, there were no good solutions for pressure hydrogenation of bulky ketones and we considered the reactivity discussed in chapter **3** a very promising lead. In particular we observed complete reduction of 1,1',1''-trimethylacetophenone using catalyst **33**. In this chapter we have thoroughly investigated the potential of catalyst **33** in the asymmetric hydrogenation of a range of ketones.

4.2. Asymmetric Hydrogenation of acetophenone derivatives

4.2.1. *p*-Fluoroacetophenone

In Chapter **3** was described the hydrogenation with catalyst **33** of the substrate **20**, *p*-fluoroacetophenone. Excellent yields were observed even using a S/C of 10000. Although in all the attempts to obtain a high level of enantiomeric excess (ee) only a 9 % was achieved. Using Noyori's catalysts, ketone **20** is readily reduced in high ee.[1]

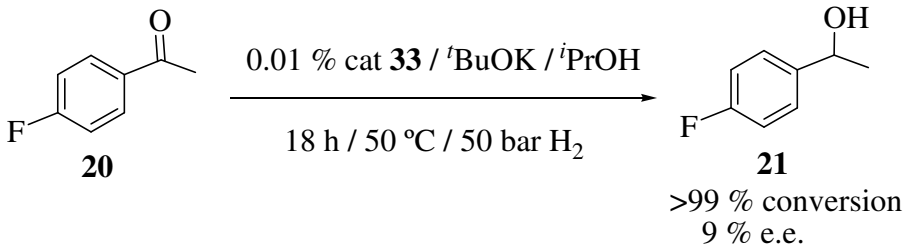


Figure 4. 1

4.2.2 Isobutyrophenone

When catalyst **33** was designed the plan was to apply it in hydrogenation of bulky ketones. It was desired to prove if pronounced steric bulk within the ketone substrates leads to significant enantioselectivity. Isobutyrophenone (**67**) is a moderately bulky ketone and was therefore investigated. Racemic alcohol was first prepared by $NaBH_4$ reduction in order to develop an HPLC method for ee determination. Substrate **67** was hydrogenated, using 0.5 % of cat **33**, 1 % of base (^{t}BuOK), ^{i}PrOH as solvent at 50 ºC and 50 bar of H_2 for 24 h. The reaction gives a 99 % conversion to the chiral alcohol. The product was analysed by HPLC to find a 48 % ee of the (*S*) enantiomer, the configuration being determined by comparison of optical rotation values with the literature.

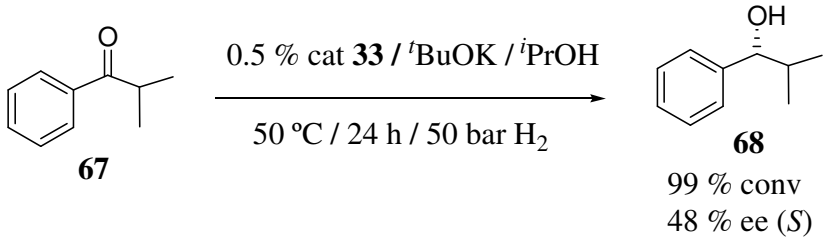


Figure 4. 2

In chapter **3** DMAP was found to have a desirable effect on the hydrogenation of cinnamaldehyde. Ketone **67** was therefore hydrogenated in the presence of several amines (Table 4.2) to see the influence of additives in the reaction. The conditions were the same in all cases, 0.5 % catalyst in ^{i}PrOH with ^{t}BuOK as base for 24 h, 50 bar of H_2 and 50 ºC, adding 1.6 % of amine.

Table 4. 1[a]

additive	conversion[b] %	e.e.[c] %
-----	99	48 (*S*)[d]
Pyridine	97	43 (*S*)
DMAP	38	52 (*S*)
DABCO	60	37 (*S*)
α-Methylbenzylamine	40	33 (*S*)

[a] Reactions were conducted using a 0.33 M ketone solution in ^{i}PrOH containing 0.5 % catalyst **33** and 1 % ^{t}BuOK at 50 ºC, 50 bar H_2 for 24h. 1.6 % of the amine as additive was added. [b] Conversions calculated by ^{1}H NMR of the crude reaction mixture. [c] Determined by HPLC [d] Determined by comparation of the optical rotation value with the literature

As observed from the results in Table 4. 1, these amines do not give a substantial increase of activity or enantioselectivity as additives for the hydrogenation of ketone **67**. Due to this, the studies on this direction were stopped.

In order to optimise the reaction, a brief study varying the catalyst loading was carried out. Using 0.1 % mol of catalyst **33**, no conversion was observed at 50 ºC. Increasing

temperature to 70 ºC led to full conversion but enantioselectivity dropped to 17 % ee of the (*S*) enantiomer. As expected, if the reaction was carried out with 0.1 % catalyst but without using any base, no conversion occurred. The base is required to form the active catalyst species. Afterwards 1 % and 2 % of base were used (10 eq and 20 eq respect to the catalyst) to see if the base could have any positive effect on the activity of the catalyst, but unfortunately this didn't improve the reaction conversion. The optimal amount of base is 2 eq with respect to the catalyst and more than 50 ºC disturbs the enantioselectivity. Noyori has commented that the very high TON and TOF reported by his group are only possible using careful inert atmosphere conditions and direct drive stirring. We did not use such autoclaves in our experiments, so the optimum TOF and TON is still not clear.

Table 4. 2[a]

cat **33** %	base %	T / ºC	conversion[b] %	e.e.[c] %
0.5	1	50	99	48
0.1	0.2	50	0	n.d.
0.1	0.2	70	99	17
0.1	-	50	0	n.d.
0.1	1	50	3	n.d.
0.1	2	50	5	n.d.

[a] Reactions were conducted using a 0.33 M ketone solution in ^{i}PrOH containing catalyst **33** and ^{t}BuOK with 50 bar H_2 for 24h. [b] Conversions calculated by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by HPLC

4.2.3. 1,1',1''-trimethylacetophenone

When this research started, a challenging substrate was 1,1',1''-trimethyl acetophenone **65** because Noyori's catalyst [Ru(BINAP)(DPEN)Cl_2] gave only a 6 % yield when hydrogenated under their standard reaction conditions.

The reduction initially was carried out overnight (20 h), using 1 mmol substrate, 1 mol % catalyst **33**, 2 mol % ^{t}BuOK. Conversion was calculated by NMR, and HPLC and isolated yields for pure products by flash silica gel column chromatography. The enantiomeric excess of the product was determined using HPLC, showing an encouraging 74 %, and absolute configuration determined to be (*S*) by comparison of optical rotation values with the literature.[2]

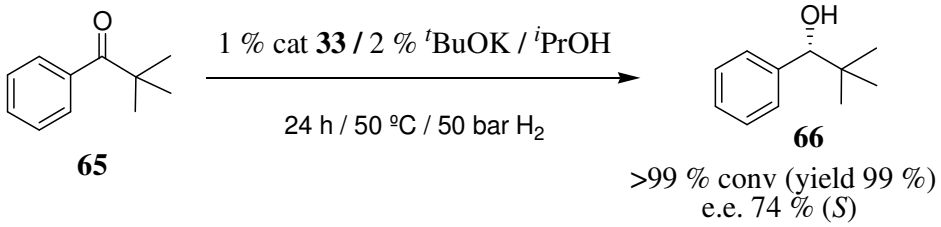


Figure 4. 3

Given that this catalyst is the first member of what could be a diverse series of catalysts to achieve this level of enantioselectivity for a difficult substrate is very promising. While this work was in progress, Noyori and co-workers reported the first effective ruthenium catalysed hydrogenation of tertiary alkyl ketones.[3] It was shown that a new type of catalyst was required comprising a ruthenium complex of an unsymmetrical planar NH_2 / pyridine hybrid ligand in combination with the ubiquitous BINAP ligand (Figure 4. 4), and also by the use of ethanol rather than ^{i}PrOH as solvent.

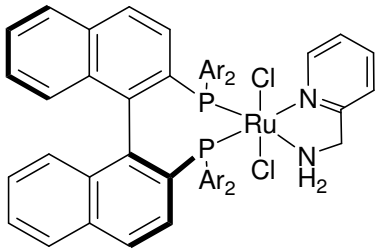


Figure 4. 4

When replacing the solvent ^{i}PrOH for EtOH in hydrogenation of substrate **65** with catalyst **33** a decrease in enantioselectivity is observed. Quantitative conversion is obtained but the ee is 53 % of the (*S*) enantiomer.

Both, EtOH and ^{i}PrOH systems were tried in hydrogenation of substrate **65** using 0.01 % of catalyst **33**, but very low conversions were achieved. This shows that the catalyst is not as active for this substrate relative to *p*-fluoroacetophenone. The reaction was carried out under different conditions; a resume of the results can be seen in Table 4.3.

Table 4. 3[a]

substrate	solvent	cat **33** %	conversion[b] %	e.e.[c] %
1mmol	3ml ^{i}PrOH	1	>99	74 (*S*)
1mmol	3ml EtOH	1	>99	53 (*S*)
0.5mmol.	1ml ^{i}PrOH / 1ml Acetone	1	>99	75 (*S*)
1mmol	0.5ml ^{i}PrOH / 2ml THF	0.5	>99	51 (*S*)
1mmol	30ml ^{i}PrOH	1	>99	74 (*S*)
5mmol[d]	3ml ^{i}PrOH	1	>99	74 (*S*)
1mmol[e]	3ml ^{i}PrOH	0.5	>99	77 (*S*)
1mmol[e]	3ml ^{i}PrOH	0.1	>99	56 (*S*)

[a] Unless otherwise stated, *r*eactions were conducted with catalyst **33** and ^{t}BuOK at 50 bar H_2 and 50 ºC for 24h. [b] Conversions calculated by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by HPLC [d] 6 h; [e] 70 ºC

From these results we can conclude that the concentration does not affect the conversion or e.e. of the reaction. With respect to catalyst loading a 1000 TON was achieve but the e.e. decreased to 56 %. ^{i}PrOH is the optimal solvent for the reaction. When the

temperature was increased to 70 ºC catalyst can be reduced to 0.5 % maintaining the high level of e.e., 77 %.

When transfer hydrogenation was carried out in ^{i}PrOH the same level of enantioselectivity to that observed in hydrogenation was obtained.

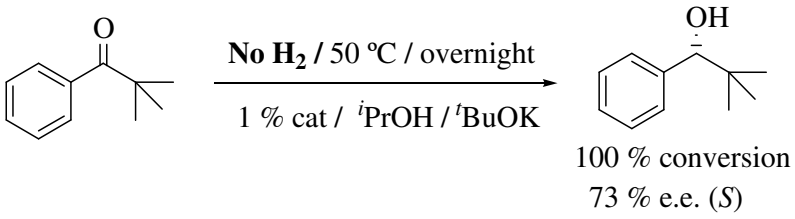


Figure 4. 5. Transfer hydrogenation

Ketones can sometimes be reduced using ^{i}PrOH as hydrogen donor, but it is highly unusual for catalysts to be effective for both hydrogenation and transfer hydrogenation.[4] The results of these experiments are very interesting due to the fact that they show that catalyst **33** is giving the same results (full conversion and same level of ee) in hydrogenation and transfer hydrogenation.[5] In industry, hydrogenation is prefered versus transfer hydrogenation because they do not want to use high amounts of solvent. But in the research laboratory, transfer hydrogenation is more convenient because no pressure vessels are required. For us, it was important to prove which mechanism is the dominant in our catalytic system.

The first experiment to prove the dominant mechanism of the reaction was the hydrogenation in ^{i}PrOD-d_8. By NMR was observed that 19 % of the deuterium label was incorporated by hydride transfer. Thus, approximately 19 % of the hydride comes from the solvent by transfer hydrogenation. The rest, 81 % by integration of the C***H***-OH proton, is assumed hydrogenation product. This result shows that hydrogenation is really happening and it is the dominant reaction.

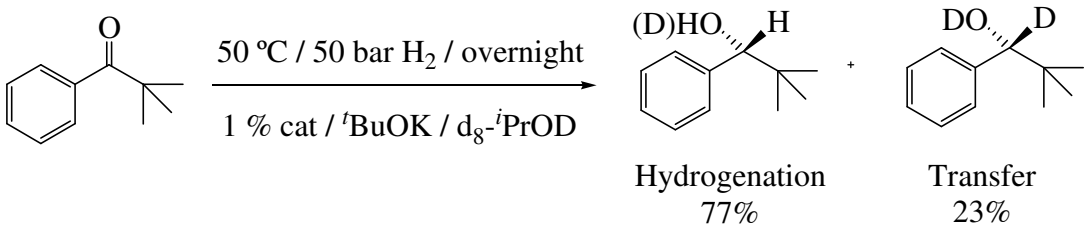
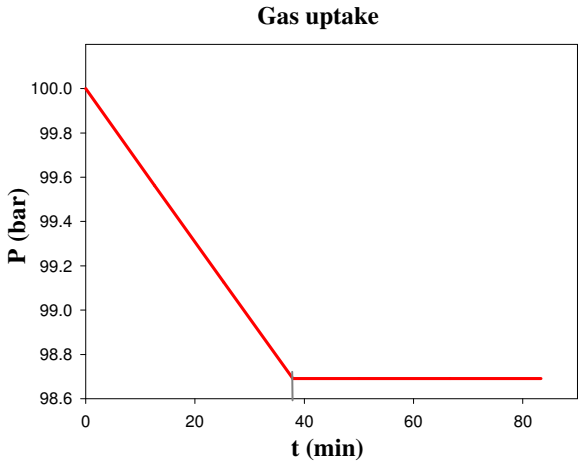


Figure 4. 6

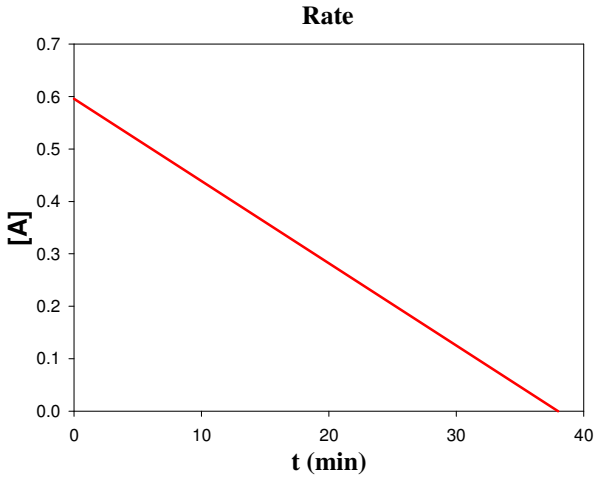
To have further proof of this, some kinetic studies were done. Prof. David Cole-Hamilton, at the University of St Andrews, generously allowed us to use his equipment consisting of an autoclave of constant pressure fed by a pressure chamber containing a known

amount of pressure of H_2 connected to a computer that measures the gas uptake. In this way is possible to follow the rate of gas uptake.



Graph 4. 1

When the reaction started the chamber contained 100 bar of H_2 and it was observed that the reaction was complete after 38 minutes with consumption of H_2. This experiment shows as well that the hydrogenation is occurring because H_2 is being consumed. Furthermore, when transfer hydrogenation was set up under identical conditions without hydrogen, only a 21 % conversion was observed after 38 min. This provides good agreement with the deuterium labelling experiment. The rate of reaction is a constant. The reaction is of *zero* order in substrate because the rate of reaction is independent of the concentration of substrate.



Graph 4. 2

$$y = -0.0003x + 0.596$$

$$-\frac{d[A]}{dt} = k$$

$$k = 3\text{x}10^{-4}$$

In chapter **5** asymmetric transfer hydrogenation will be discussed more in detail.

4.2.4. 2,2-dimethyl-1-phenyl-butan-1-one

An even bulkier ketone, substrate **69**, was chosen to be tested in hydrogenation with catalyst **33**. The racemic sample of the alcohol was prepared by $NaBH_4$ reduction and used to develop an analytical (HPLC) method for ee determination.

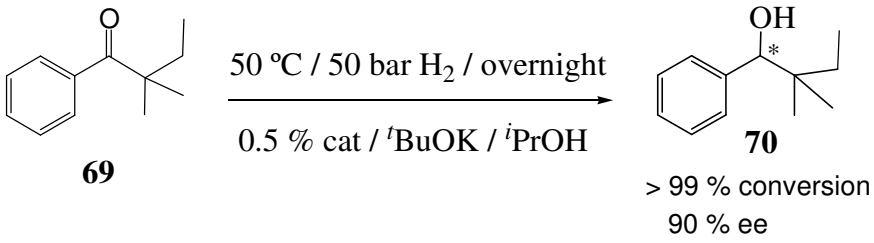


Figure 4. 7

No example has been found in the literature of the hydrogenation of this substrate or any others that are bulkier than **65**. Hydrogenation of substrate **69** with 0.5 % of catalyst **33** gives full conversion and 90 % ee under 50 bar of H_2 and 50 ºC using ^{i}PrOH and ^{t}BuOK. The absolute configuration is likely to be also (*S*) given that the same sign of optical rotation is observed. This even bulkier ketone is smoothly hydrogenated with even higher selectivity which is in agreement with the initial theory that catalyst **33** will proceed better with bulky ketones. It is observed for substrates **65**, **67** and **69** that the selectivity increases with the size of the subsistent.

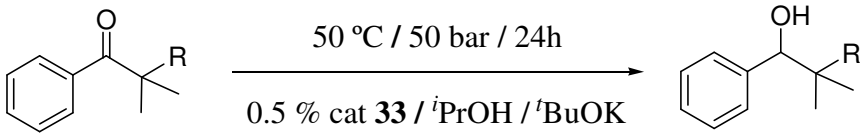
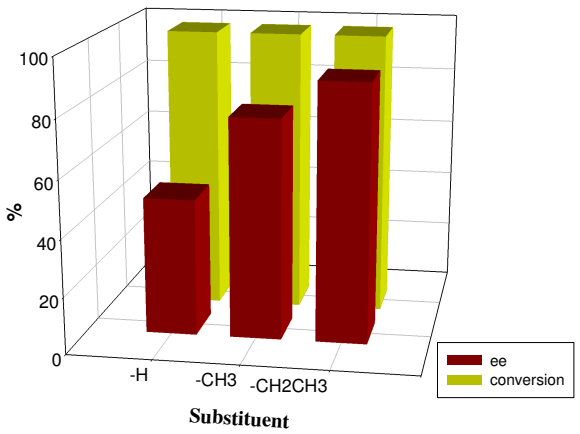


Figure 4. 8

Table 4. 4

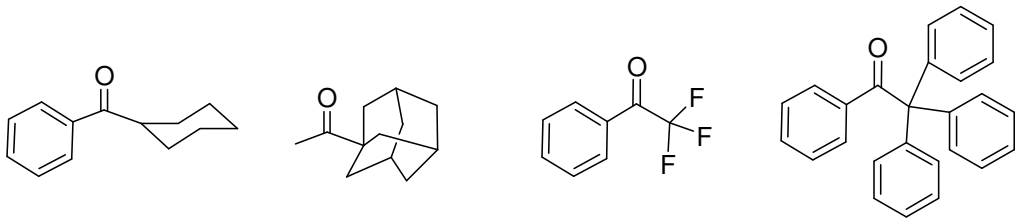
-R	conversion %	ee %
-H	>99	48 (*S*)
$-CH_3$	>99	77 (*S*)
$-CH_2CH_3$	>99	90



Graph 4. 3

4.3. Asymmetric hydrogenation of other bulky ketones

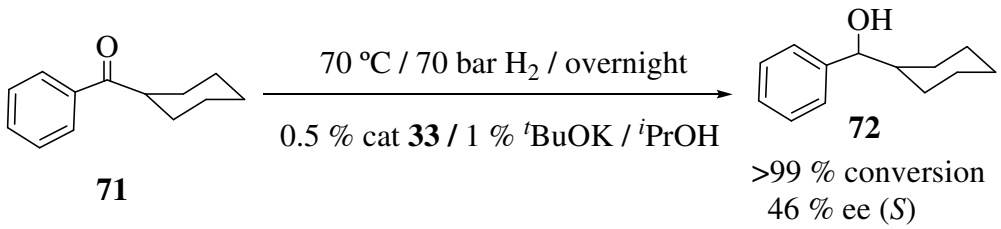
Other ketones were study in asymmetric hydrogenation with catalyst **33**.



71 **73** **18** **75**

Figure 4. 9

When catalyst **33** was used for hydrogenation of cyclohexyl-phenyl ketone, substrate **71**, at 70 ºC and 70 bar of H_2, full conversion was obtained and 46 % ee of the *S* enantiomer (determined by HPLC and optical rotation respectively). The catalytic conditions for this substrate were not optimized.



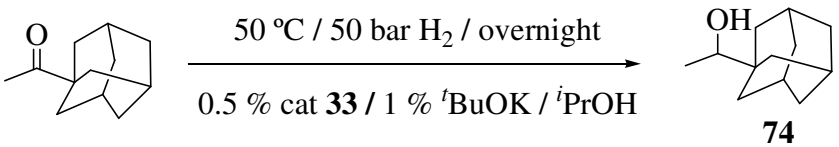
71

72
>99 % conversion
46 % ee (*S*)

Figure 4. 10

Cyclohexyl-phenyl ketone, **71**, which is less bulky than **65** and **69** can actually be hydrogenated using Noyori's [$RuCl_2$(TolBINAP)(Daipen)] system which gives a 98 % yield and 92 % ee of the *R* enantiomer using just 10 bar of H_2 and room temperature.[6]

1-Adamantylmethylketone, substrate **73,** gives full conversion under the standard conditions with catalyst **33** but basically racemic material (determined by ^{1}H NMR in the presence of Eu(hfc)$_3$) even with the large difference in steric bulk between the substituents.



73

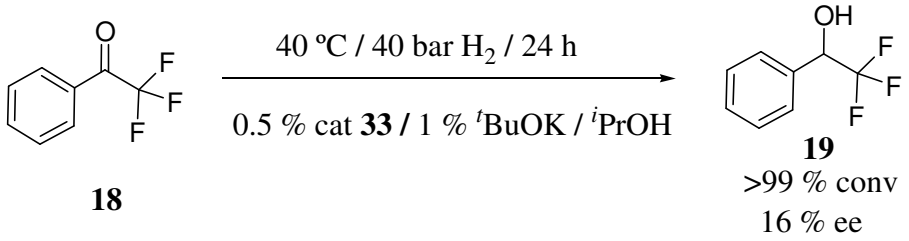
74
>99 % conversion
3 % ee

Figure 4. 11

In the case of substrate **75** hydrogenation with catalyst **33** didn't work at all after many attempts. This substrate is excessively hindered. When the racemic reaction was attempted as usual with $NaBH_4$ or $LiAlH_4$ there was no conversion. Only by

hydrogenation with Pd/C was 39 % conversion to the racemic product achieved after 3 days at 40 ºC. It was assumed that substrate **75** is too bulky to access the free site in the catalyst.

Asymmetric hydrogenation of 2,2,2-trifluoroacetophenone, substrate **18** is one of the less challenging (less bulky) ketones since it can be reduced with [$RuCl_2$\{(*S*)-XylBINAP\}\{(*S*)-Daipen\}] in 96 % e.e. Catalyst **33** hydrogenated substrate **18** with full conversion but only 16 % e.e.

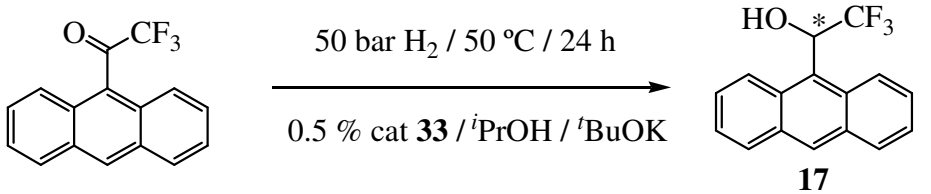


18

19
>99 % conv
16 % ee

Figure 4. 12

Hydrogenation of substrate **22** with catalyst **33** was tried several times under different conditions, the best result was obtained at 50 ºC and 50 bar H_2 giving 63 % conversion and 43 % e.e. Enantioselectivity was calculated by ^{19}F-NMR using the chiral amine (*R*)-(+)-*α*-methylbenzylamine.



22

17
63 % conversion
43 % ee

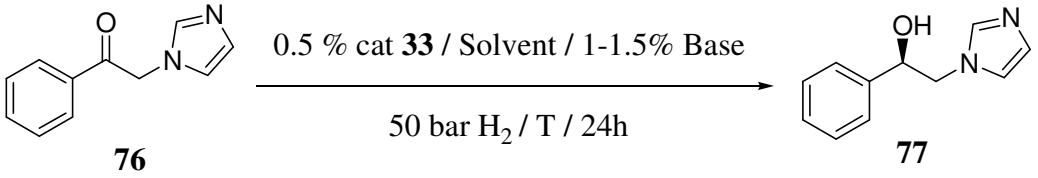
Figure 4. 13

4.4. Heteroaromatic ketones

Hydrogenation of heterocyclic ketones is important because the chiral alcohol products are useful as building blocks of biologically active compounds and chiral ligands. Asymmetric hydrogenation of heteroaromatic ketones is less explored and is sometimes problematic since the heterocycles coordinate to the catalyst in place of the ketone moiety.

Asymmetric reduction of 2-imidazol-1-yl-1-phenyl-ethanone, **76,** has been studied for an industrial synthesis of a pharmaceutical intermediate, and unfortunately found to be

resistant to hydrogenation using Noyori type catalysts.[7] However, when this substrate was subjected to hydrogenation catalysed by **33** at 50 ºC quantitative yields of alcohol of 61 % ee are obtained under optimised conditions, using ^{i}PrOH as solvent and ^{t}BuOK as base. A change of solvent or base does not result in higher ee.



76 **77**

Figure 4. 14

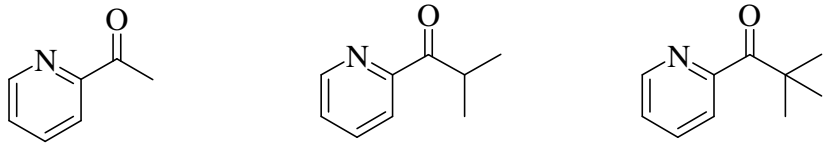
Table 4. 5[a]

solvent	base	T / ºC	conversion[b] %	ee[c] %
Hexafluoropropanol	$LiHBEt_3$	50	0	-
Hexafluoropropanol	^{t}BuOK	50	0	-
MeOH	$LiHBEt_3$	50	100	58 (*R*)
MeOH	^{t}BuOK	50	92	60 (*R*)
^{i}PrOH	^{t}BuOK	50	100	61 (*R*)
^{i}PrOH	^{t}BuOK	25	0	-

[a] Reactions were conducted in a 0.33 M substrate solution containing 0.5 % of catalyst **33** and base at 50 bar H_2 for 24h. [b] Conversions calculated by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by HPLC

For this substrate the absolute configuration of the major enantiomer was found to be *R*, in contrast to reduction with catalyst **33** of substrates **65**, **67**, **69** and **71**. However, in this case the opposite configuration can be explained because of the change in the Cahn-Ingold-Prelog priority for substrate **76**. It is likely that the ketone orientates itself in the same particular way as the bulky ketones during the transition state. However, the hetereoaromatic ring could still have an effect on the coordination of the substrate with the ruthenium complex.

A series of heteroaromatic ketones, substrates **78**, **80** and **82,** has been studied under hydrogenation conditions with catalyst **10.** In this way we will be able to see the effect of the bulky substrates.



78 **80** **82**

Figure 4. 15

Substrates **78** and **80** have been hydrogenated by Noyori with the ubiquitous [$RuCl_2$\{(S)-XylBINAP\}\{(S)-DAIPEN)] obtaining a 96 % and 94 % ee respectively, but require the addition of $B(OH)_3$ as an additive to prevent inhibition of the catalyst[1]. Substrate **78** is commercially available, so it was used directly for the hydrogenation reaction. Substrates **80** and **82** were synthesised by Mary Gunn during a summer project in the Clarke group in 2006. She carried out the synthesis and the hydrogenation of these two substrates. The results from hydrogenation experiments are shown in Table 4.7.

Substrate **82** is a combination of both steric bulk and a possibly problematic 2-pyridine substituent. This potentially awkward substrate has not been studied.

An increase in the enantioselectivity of the hydrogenation is observed with the bulkier ketone. For the heteroaromatic ketone with the methyl substituent an 18 % ee is obtained whereas for the one with the ^{t}Butyl substituent the ee is 61 %.

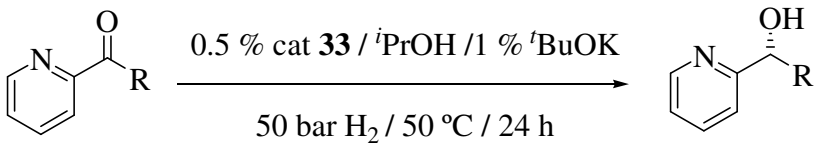
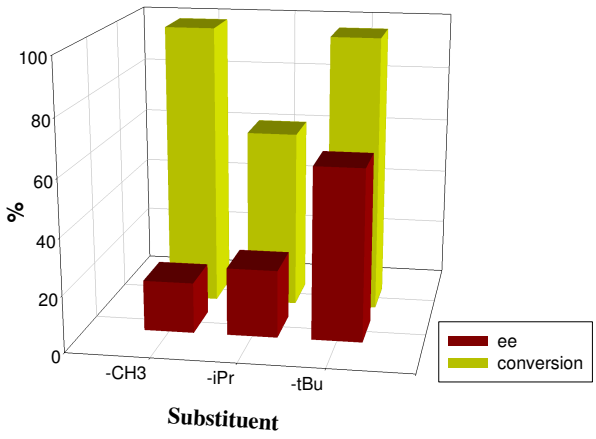


Figure 4. 16

Table 4. 6

R	conversion %	e.e. %
Me (**78**)	100	18 (*R*)
^{i}Propyl (**80**)	63	24
^{t}Butyl (**82**)	98	61



Graph 4. 4

4.5. Asymmetric hydrogenation of diketones

Several diketones were synthesised by adapting a literature procedure.[8] Substrate **84** was synthesised from terephthaloyl chloride reacting with $CuBr{\cdot}SMe_2$ and ^{t}BuLi in pentane affording the desired *p*-Dipivaloyl-benzol in a 61 % yield.

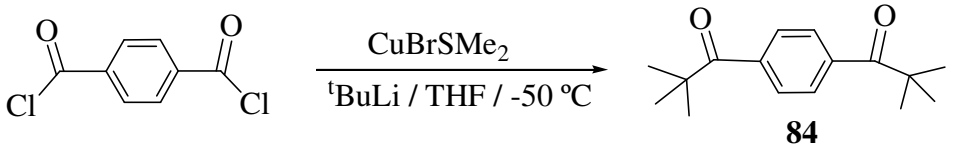


Figure 4. 17

Substrate **86** was synthesised by the same procedure starting from 2,6-pyridinecarbonyl dichloride and obtaining the 2,6-bis(2',2'-dimethylpropionyl)pyridine in a 67 % yield.

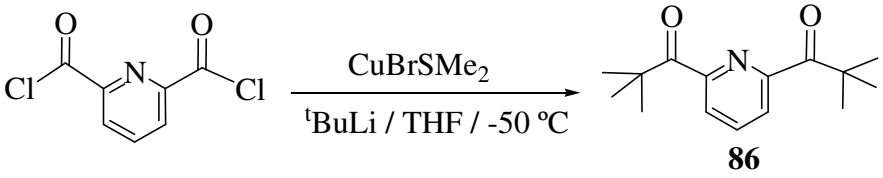


Figure 4. 18

Substrate **88,** *o*-Dipivaloyl-benzol, was synthesised in a 57 % yield from phthaloyl dichloride.

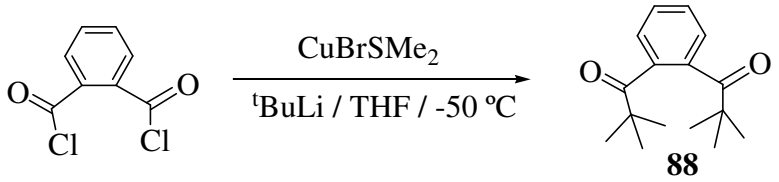


Figure 4. 19

The Horeau effect is sometimes applicable to increase enantioselectivity (Figure 4. 20). Hydrogenation of acetophenone derivatives with an (*S*)-TolBINAP/(*S*)-DAIPEN combined system gives the *R* alcohols normally with less than 90 % ee and >99 % yield. However, reaction of 1,4-diacetylbenzene afforded enantiomerically pure *R,R* diol (>99 % ee) in 85 % yield at the expense of the minor *R,S* diastereoisomer formed in the second hydrogenation.

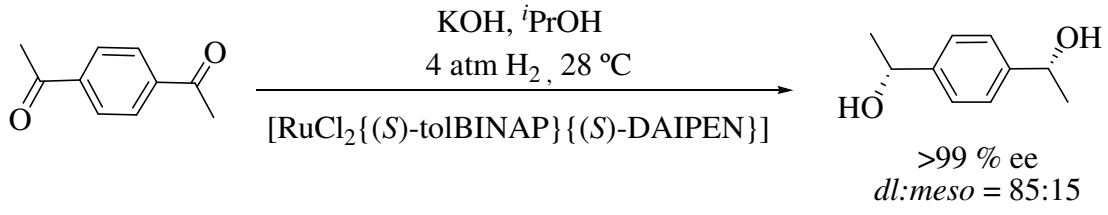


Figure 4. 20 Noyori's hydrogenation of 1,4.diacetylbenzene

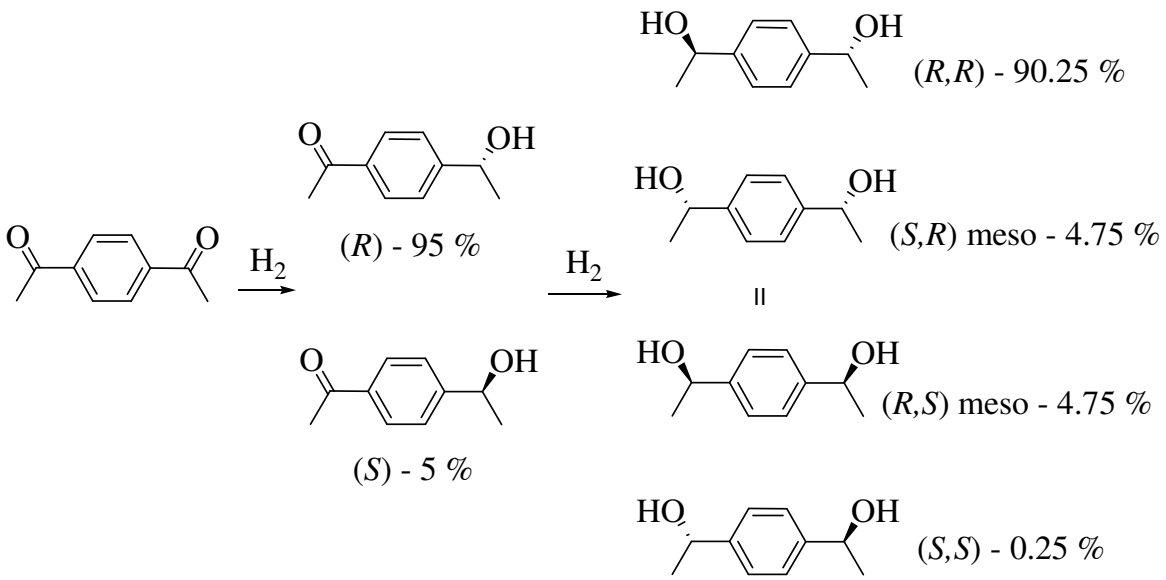
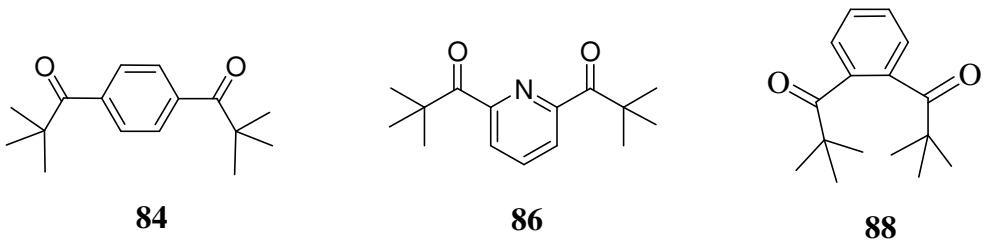


Figure 4. 21. Example of the Horeau effect.

Diketones were reduced using $NaBH_4$ and an HPLC analytical method was developed for ee determination.

Substrates **84**, **86** and **88** were hydrogenated with 0.5 % of catalyst **33** at 50 ºC, 50 bar for 24 h, with ^{i}PrOH as solvent and in the presence of ^{t}BuOK as base.



84 **86** **88**

Figure 4. 22

Substrate **84** was hydrogenated under these conditions giving full conversion and 94 % ee by HPLC. Substrate **86** gives only a 23 % conversion under the same conditions, so the hydrogenation was tried at 100 ºC and in this case 70 % conversion was achieved with an enantiomeric excess of the (*S,S*) of 71 %. Substrate **88** gives a full conversion with 93 % ee. The diastereoisomeric ratio for all the cases shows that the *meso* compound forms in less amount, as would be expected, and shows that the ee has been amplified due to the formation of minor amounts of the *meso* isomer.

Table 4. 7[a]

substrate	conversion[b] %	yield %	d.r.[c] (*S,R*)+(*R,S*):*meso*	ee[d] %
84	>99	98	83:17	94
86	23	-	n.d.	n.d.
86[e]	70	62	76:24	71 (*S,S*)
88	>99	95	84:16	93

[a] Unless otherwise stated: Reactions were conducted in a 0.33 M of ketone in ^{i}PrOH containing 0.5 % of catalyst **33** and ^{t}BuOK at 50 bar H_2 and 50 ºC for 24h. [b] *C*alculated by ^{1}H NMR analysis [c] These diastereoisomeric ratios are estimated values based on uncorrected HPLC data assuming equal absorbance for both diastereomers. Values are in agreement with those determined by ^{1}H NMR integration [d] Determined by HPLC [e] 100ºC

4.6. Conclusions

These result for all the ketone hydrogenations show that this new catalyst has different and complementary activity and selectivity to the [Ru(diphosphine)(diamine)Cl_2] systems. Ruthenium complex **33** containing a tridentate ligand proved to be more active and enantioselective for some bulky ketones and hetereoaromatic ketones than the Noyori's catalysts, suggesting considerable promise for this new system. The broad applicability of catalyst **33** should lead to future work consisting of exploring new substrates and modifying the structure of the catalyst to achieve new goals.

4.7. References

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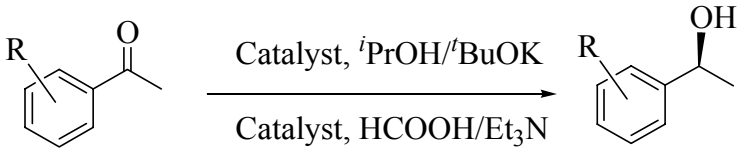
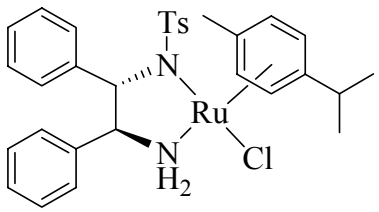
CHAPTER V

Transfer Hydrogenation

5.1. Introduction

In transfer hydrogenation, the metal hydride responsible for the reduction of the ketone in the catalytic cycle is regenerated *in situ* from organic molecules acting as hydrogen donors. In the 1990s Noyori and Ikariya developed catalysts suitable for this type of catalysis. The catalysts consist of a (sulfonyl-diamine)RuCl(arene) general type (Figure 5. 1), and hydrogen donors such as ^{i}PrOH or formic acid are typically used.[1-4]





[RuCl(Ts-DPEN)(*p*-cymene)]

Figure 5. 1

In the catalytic cycle for transfer hydrogenation, the hydrogen donor generates a ruthenium hydride species. This species stereoselectively transfers the hydride to the substrate *via* a 'bifunctional' mechanism related to the one that operates for hydrogenation.[5]

Transfer hydrogenation with isopropanol and a base is a reversible reaction that can affect negatively the yield and enantioselectivity. The transfer hydrogenation with formic acid and triethylamine is irreversible.[6]

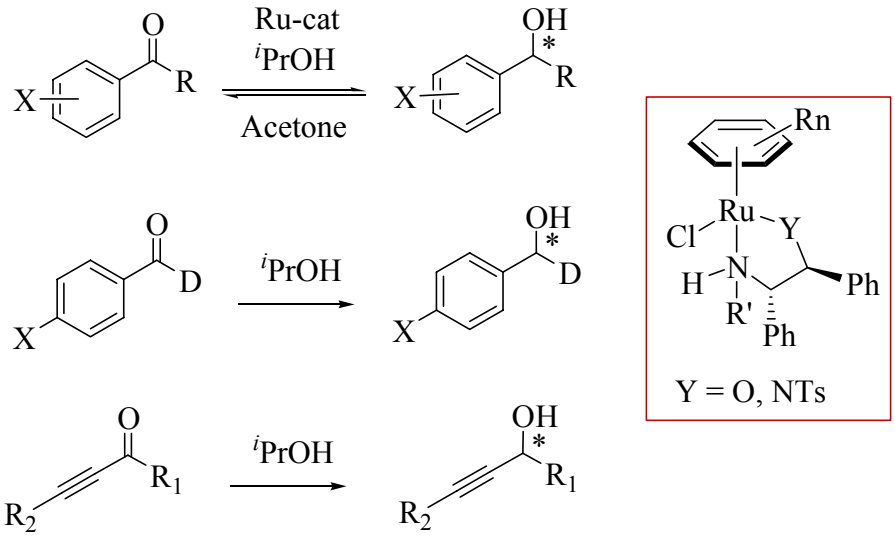


Figure 5. 2

This catalytic system can be modified in the same way as the system for hydrogenation, so by changing the arene ligand,[1-4] the diamine or the sulfonyl substituent, it is possible to control the activity and selectivity to adapt to a specific substrate.

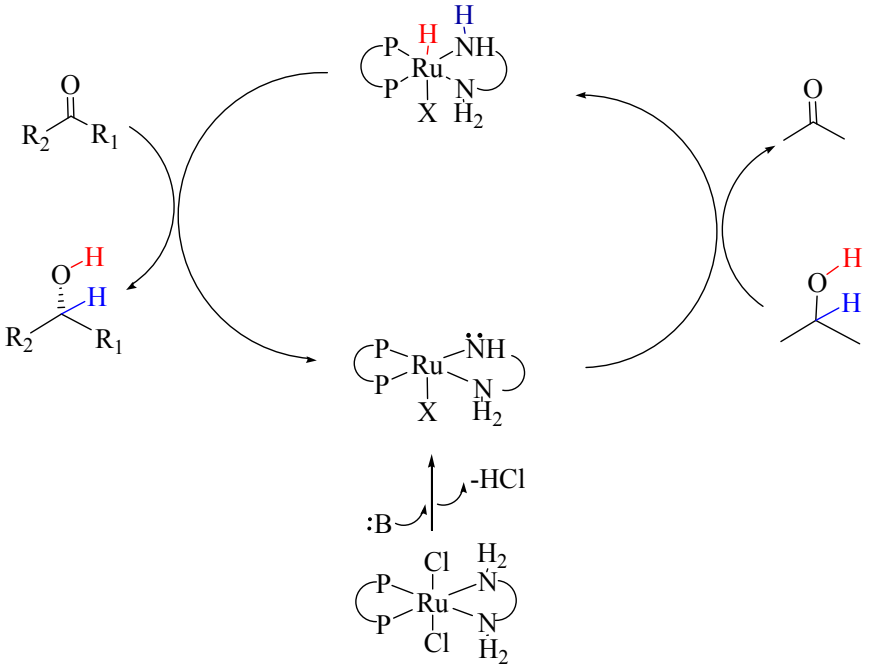


Figure 5. 3. Proposed mechanism for catalytic transfer hydrogenation of ketones

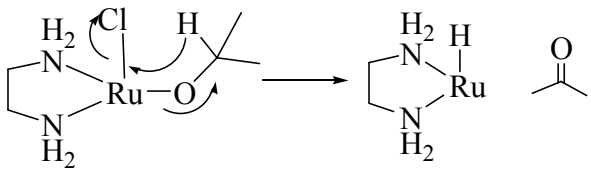


Figure 5. 4. Formation of the hydride

This catalyst system has a broad substrate scope. Catalytic transfer hydrogenation of acetophenone gives excellent results. Transfer hydrogenation of aryl substituted ketones or aryl alkyl ketones gives the corresponding alcohols in excellent yields (99 %) and enantioselectivities (up to 97 %).

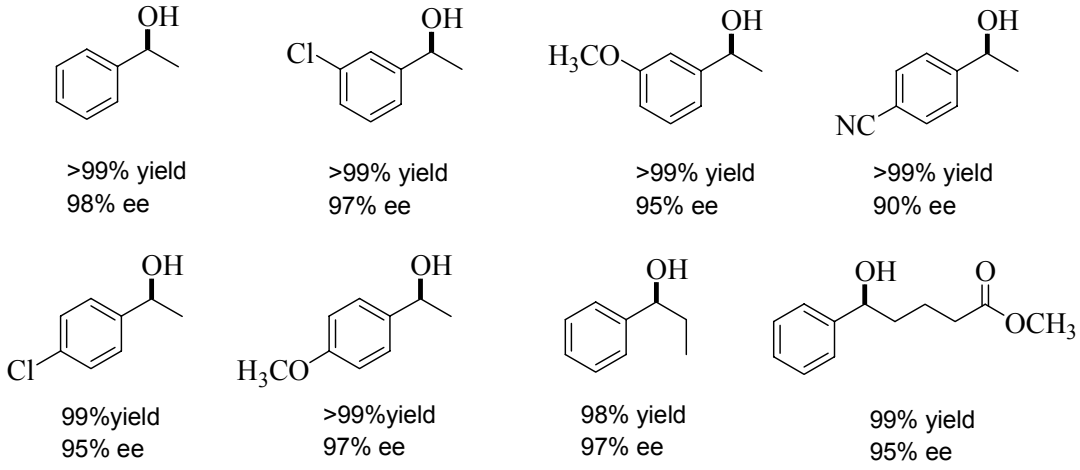


Figure 5. 5. Conditions: (*S,S*)-Ru cat, HCO_2H, Et_3N, 28ºC, 14-90h

Many catalysts reported for the enantioselective transfer hydrogenation of ketones with different ligands, feature various combinations of nitrogen, oxygen, phosphorus, sulphur and even arsenic as the donor atoms, and different metals as well (Rh, Ir or Ru). There are some good reviews in the literature, from Wills[7] or Gladiali[8] for example, summarising the different catalysts used in asymmetric transfer hydrogenation of ketones.

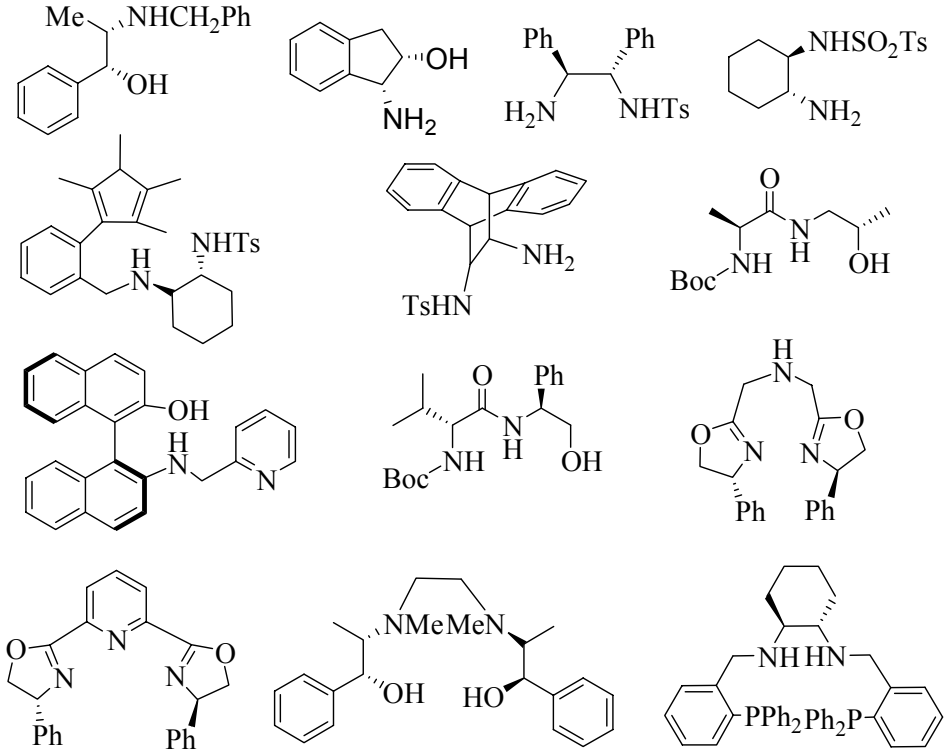


Figure 5. 6

The most effective in catalyst performance (activity and enantioselectivity) and substrate scope, are 1,2-amino alcohols and monotosylated diamine (Figure 5. 7). Half-sandwich π-complexes, such as Ru–arene and Rh– or Ir–cyclopentadienyl complexes, are the most proper metal fragment to be associated to 1,2-amino alcohols and to monotosylated diamine ligands. Noyori's complex seems to be the catalyst with the broadest scope as it provides significant ee's with a large variety of substrates.

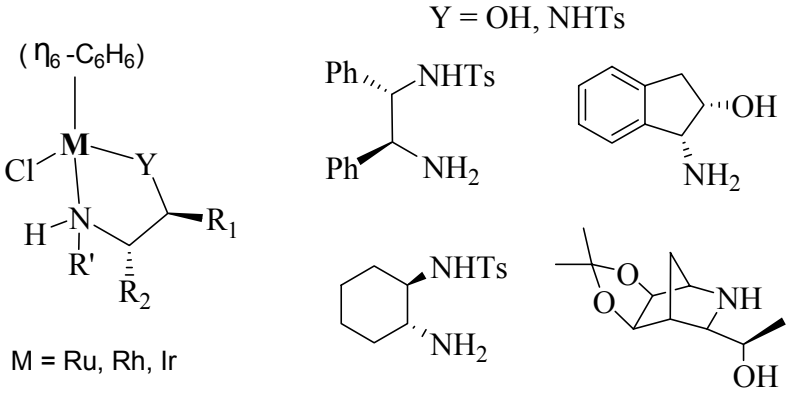


Figure 5. 7. Best catalysts for asymmetric transfer hydrogenation of ketones

5.2. Transfer hydrogenation with catalyst 33

Transfer hydrogenation is a promising method for the production of secondary alcohols. Some advantages to asymmetric hydrogenation are for example that no hazardous hydrogen needs to be use.[7] The main problem found is the unfavourable thermodynamics associated with the transfer hydrogenation of ketones using alcohols, especially ^{i}PrOH, as hydrogen source,[9] lower catalytic activities and far greater solvent use.

Using catalyst **33** in transfer hydrogenation reduction for substrate **65**, under identical reaction conditions to pressure hydrogenation experiments (50 ºC, 50 bar H_2, ^{i}PrOH, ^{t}BuOK), the (*S*)-alcohol was produced with the same yield and e.e. It has been reported by Morris that some hydrogenation catalysts can also promote transfer hydrogenation, but in these examples, low enantioselectivity was observed in the latter process.[10] It appears that this catalytic system can catalyse both hydrogenation and transfer hydrogenation with similar enantioselectivity.

Experiments carried out with substrate **65** are in Table 5. 1. In entry 2 it is observed that the transfer hydrogenation in EtOH does not work, or in the case of entry 5, a mixture of solvents was used: 0.5ml of ^{i}PrOH and 2ml of THF, the conversion decreases to 30%. Obviously ^{i}PrOH is the solvent of choise.

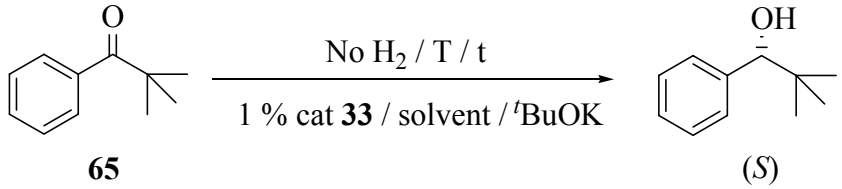


Figure 5. 8

Table 5. 1[a]

entry	T / ºC	t / h	solvent	conversion[b] %	ee[c] %
1	50	18	^{i}PrOH	82	73
2	50	24	EtOH	9	n.d.
3	50	24	^{i}PrOH	>99	71
4	50	6	^{i}PrOH	8	n.d.
5	50	24	^{i}PrOH/THF	30	70
6	70	0.63[d]	^{i}PrOH	19	61
7	70	24	^{i}PrOH	>99	60
8[e]	50	24	^{i}PrOH	>99	72

[a] Unless otherwise stated, reactions were conducted using a 1 mmol ketone solution containing 1 % of catalyst **33** and ^{t}BuOK [b] By ^{1}H NMR analysis [c] HPLC analysis. [d] 38 min [e] using 0.5% of the catalyst

At 70 ºC the enantiomeric excess decrease to 60 %, and after 38 minutes only a 19 % conversion was observed. The same reaction under pressure hydrogenation promotes full conversion for this substrate under identical conditions in 38 minutes. Transfer hydrogenation is the slower reaction. Entry 8 was carried out with 0.5 % of catalyst and 1 % of base. Decreasing the catalyst amount to half still gives the same conversion and enantioselectivity.

Substrate 46 gives 89 % conversion after 24 h under transfer hydrogenation conditions at 50 ºC with catalyst **33,** 90 % ee is maintained.

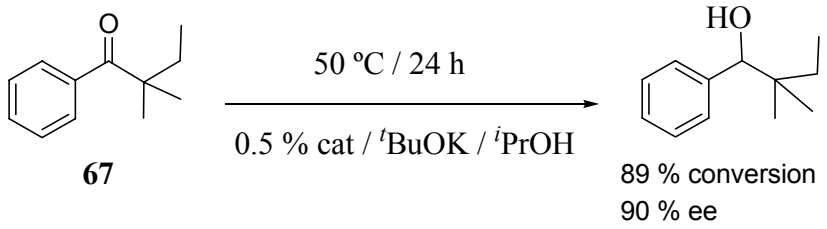


Figure 5. 9

Substrates **84** and **88** in transfer hydrogenation with catalyst **33** at 50 ºC and 24 h gives lower conversion than when hydrogenated under H_2 pressure but retains the same enantioselectivity, 93 %.

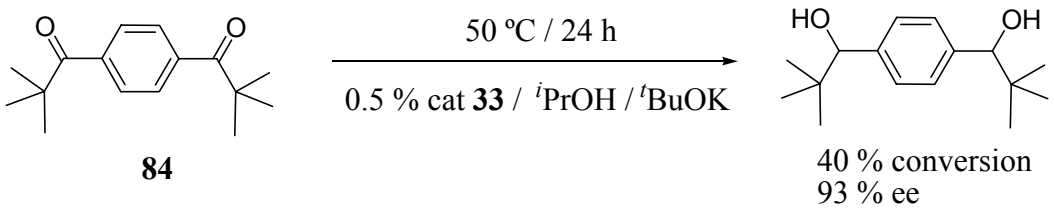


Figure 5. 10

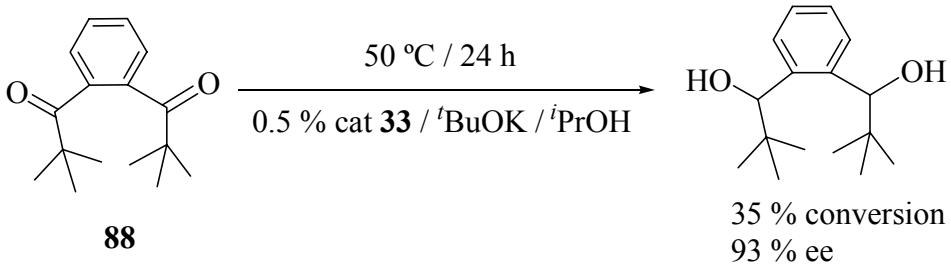


Figure 5. 11

Transfer hydrogenation was tried with substrate **67** under the "standard conditions" giving full conversion and 72 % ee. In this case the transfer hydrogenation does not keep the same level of ee, instead ee increases by around 20 %.

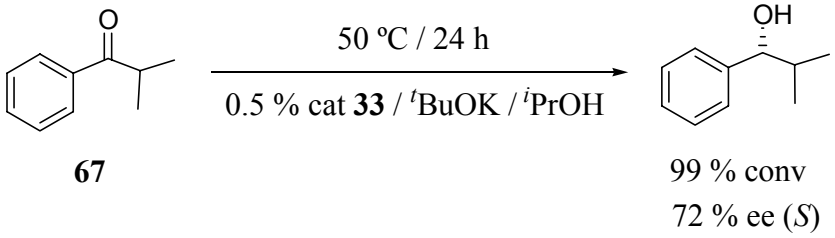


Figure 5. 12

Transfer hydrogenation with catalyst **33** is a much slower reaction than pressure hydrogenation. Therefore, transfer hydrogenation reduction with catalyst **33** maintains the same level of enantioselectivity as the pressure hydrogenation reaction.

5.3. Transfer hydrogenation using microwave heating.

In asymmetric catalysis, apart from the selectivity, the turnover frequency and convenience are also importance factors. Some of the most efficient catalysts for transfer hydrogenation are anyway slow. For these reasons was decided to employ microwave irradiation in hydrogen transfer process. Only one publication was found where they do transfer hydrogenation in microwaves. Moberg always found lower ee's using microwave than with standard transfer hydrogenation conditions,[11] even if very fast and efficient conversions were generally achieved.

The investigation started with substrate **65**. In order to optimise the conditions for the catalytic process, the reaction time and the temperature were varied. All optimization reactions were done using ^{i}PrOH as solvent, 1 mol % of the catalyst and 2 mol % of ^{t}BuOK as base. All reactions were performed under N_2.

Earlier in this chapter evidence was provided that the reaction time for completition of the hydrogenation of substrate **65** was 38 minutes. But when a transfer hydrogenation reaction under the same conditions was carried out, after 38 minutes at 70 ºC only 20 % conversion was observed. It was desired to get full conversion, keeping the enantioselectivity high for this substrate in less reaction time under the transfer hydrogenation conditions. For that reason microwave transfer hydrogenation looks a good choice. We started carrying out the reaction in the microwave for 38 minutes at 70 ºC (see Table 5. 2). Under these conditions a 50 % conversion was achieved and a 75 % enantioselectivity. The conversion is more than double compared with the transfer without microwave irradiation and the ee stays the same. This result proved that microwave heating can advantegeously affect the transfer hydrogenation reduction. At 60 ºC the enantioselectivity stay the same but the conversion is only 21%. We increased the temperature by 10 ºC every time. At 80 ºC, conversion is 98 % with a 76 % ee. Full conversion was achieved at 90 ºC (38 min) staying in the level of 77 % ee.

Table 5. 2[a]

T / ºC	conversion[b] %	ee[d] %
60	21	76 (*S*)
70	50	75 (*S*)
80	98	76 (*S*)
90	>99	77 (*S*)
100	>99	68 (*S*)
140	>99	50 (*S*)

[a] Conditions of transfer hydrogenation in the microwave: 38 min, 1 % cat **33**, 2 % ^{t}BuOK, 3 ml ^{i}PrOH, 1 mmol of substrate **65** [b] By ^{1}H NMR [c] By HPLC

Higher temperatures were tried with the thought of decreasing the reaction time. If, at higher temperatures, the ee does not drop off, the time could be decrease and the TOF will increased, which is the aim. But when the reaction was carried out at 100 ºC or 140 ºC the enantioselectivity decreased to 68 % and 50 % ee respectively. In all cases enantiomer (*S*) was obtained. We conclude that the optimised temperature for this substrate is 90 ºC.

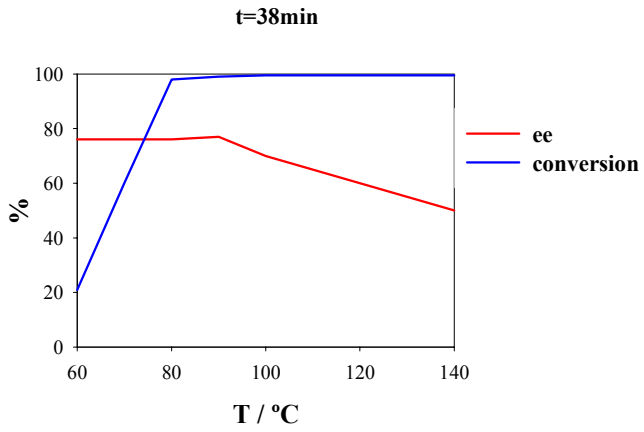


Figure 5. 13

With the optimised temperature at 90 ºC the next step will be to try to reduce the reaction time. Again, using substrate **65**, in the same concentration and catalyst loading at 90 ºC, the conversions were recorded reducing the reaction time.

Table 5. 3[a]

t / min	conversion[b] %	ee[c] %
38	>99	77 (*S*)
20	98	77 (*S*)
15	90	76 (*S*)
10	82	77 (*S*)

[a] Conditions of transfer hydrogenation in the microwave: 90 ºC, 1 % cat **33**, 2 % ^{t}BuOK, 3 ml ^{i}PrOH, 1 mmol of substrate **65** [b] By ^{1}H NMR [c] By HPLC

From the results we can see that the shorter efficient time is 20 minutes. If the time is decreased more, full conversion is not obtained. It is interesting that the enantioselectivity is conserved so well in the microwave if the conditions are carefully controlled.

The optimum conditions for substrate **65** in transfer hydrogenation in the microwave are 90 ºC and 20 min. It was desired to apply the same conditions for other substrates. One thing we wanted to observe is if all substrates keep the same level of enantioselectivity as in pressure hydrogenation or substrate **65** is an exception. For that substrates **69** and **84** were chosen due to the fact that are the ones giving higher ee in pressure hydrogenation. Both of them were carried out under the same condition as substrate **65**, 1 mol % cat **33**, 2 % ^{t}BuOK, 3ml of ^{i}PrOH and 1 mmol of substrate, using of course the optimised 90 ºC and 20 minutes as microwave reaction conditions.

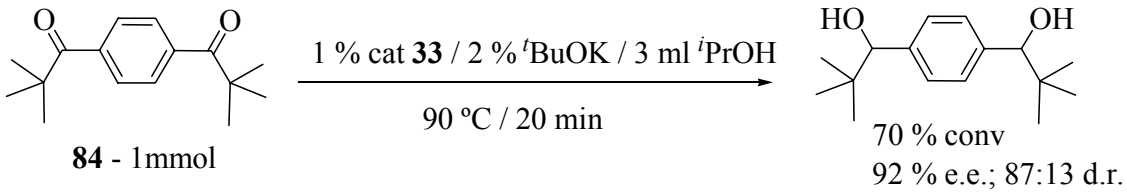


Figure 5. 14

It was observed that the enantioselectivity is still as high as before, and the conversion compared with the transfer hydrogenation using conventional heating is very much better. It will still be necessary to find the optimum conditions for this substrate: leaving a few more minutes or increasing the temperature will give the full conversion. Applying the same conditions to substrate **69,** 87 % conversion is obtained with 91 % ee. As expected the ee does not change either for this substrate. Just as for substrate **84** these conditions, 90 ºC and 20 minutes, are not optimised conditions. Consequently, this result could be improved varying the reaction conditions.

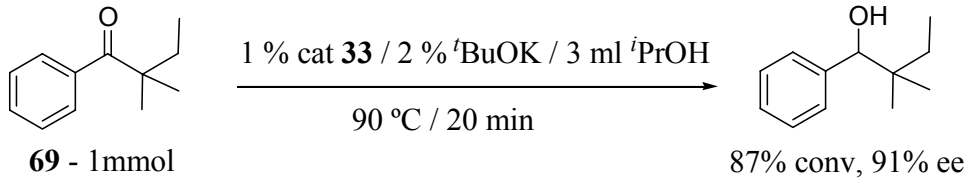


Figure 5. 15

5.4. Conclusions

It has been shown that catalyst **33** has the great potential of giving similar enantioselectivities for pressure hydrogenation and transfer hydrogenation. In our desire to improve the low speed reaction of transfer hydrogenations, microwave irradiation was applied to carry out the transfer hydrogenation reactions. Fast and efficient transfer hydrogenation of different substrates with ruthenium catalyst **33** in ^{i}PrOH was achieved using microwave irradiation. The enantioselectivity remained the same as that observed under standard conditions when the conditions were optimised.

5.5 Future work

The development of catalyst **33**, and its broad and talented applicability in hydrogenation of ketones motivates future work. The synthesis of new ruthenium catalysts containing tridentate ligands of the type P^N^N is of interest. Using diferent diamines a family of new catalysts can be developed. At has been seen in asymmetric catalytic hydrogenation the variation of a substituent in the catalyst can lead to new properties for the catalyst. In this way, the new catalysts could direct greater enantioselectivity and activity for some of the substrates studied here as well as for other challenging substrates.

5.6. References

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CHAPTER VI

Experimental

6.1. GENERAL

All chemicals were obtained from commercial sources and used as received. Dry, degassed solvents were used for reactions that were carried out under an N_2 atmosphere unless otherwise indicated. Normal grade solvents were used for chromatography and work-up procedures under aerobic conditions. Solvents were removed by rotary evaporation on a Heidolph labrota 4000. Flash column chromatography (eluents given in brackets) was performed using Davisil silica gel Fluorochem 60 Å, particle size 35-70 micron. Thin-layer chromatography (TLC) was performed on pre-coated Aldrich TLC plates (POLYGRAM SIL G/UV_{254}). All microwave syntheses were carried out in a Biotage Initiator Microwave reactor using 5ml heavy-walled vials equipped with an air tight septum. Melting points were determined with a Gallenkamp melting point apparatus Nº 889339 and are uncorrected. ^{1}H NMR, ^{13}C NMR, ^{31}P NMR and ^{19}F NMR spectra were recorded on Bruker Avance 300 instruments (^{1}H 300.1 MHz, ^{13}C 75.5 MHz, ^{31}P 121.4 MHz and ^{19}F 282 MHz). Chemical shifts are reported in ppm from tetramethyl silane (TMS) with the solvent resonance as the internal standard. Chemical shift values for ^{31}P spectra are reported downfield of phosphoric acid, and chemical shifts values for ^{19}F spectra are relative to $CFCl_3$. Proton resonance multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad) or a combination of them. When appropriate, coupling constants (*J*) are quoted in Hz and are reported to the nearest 0.1Hz. All spectra were recorded at room temperature and the solvent for a particular spectrum is given in parentheses. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 Spectrum GX FT-IR system. Compounds were analysed using disposable PTFE IR card with an aperture diameter of 15mm obtained from Aldrich. When disposable IR cards were not available, liquids were analysed as film and solids were analysed as KBr disks. Absorptions maxima are reported in wavenumbers (cm^{-1}). The characteristic absorption is reported as strong (s), medium (m) or weak (w). Mass spectra were recorder on Water Micromass GCT (Time of flight) fitted with lockspray for accurate mass (ESI) or GCT (CI) instruments. Only major peaks are reported and intensities are quoted as percentages of

the base peaks. Optical rotations were measured on an Optical Activity Ltd AA-1000 digital polarimeter using a 5ml cell with a 1 m path length at room temperature using the sodium D-line, and a suitable solvent that is reported along with the concentration (c:g/100ml). Microanalysis for carbon, hydrogen and nitrogen were performed using a EA 1110 CHNS CE instruments elemental analyser at the University the St Andrews. X-Ray crystallography data were recorded at the University of St Andrews by Alex Slawin in a Bruker SMART CCD Diffractometer. HPLC analysis has been determined using a Varian Prostar operated by Galaxie workstation PC software.

The following compounds were prepared by exactly following literature procedures, (1*R*,2*R*)-*N*-(2-Diphenylphosphanylbenzyl)cyclohexane-1,2-diamine (**30**)[1], $Ru(DMSO)_4Cl_2$ (**32**)[2], 1-[4-(2,2-dimethyl-propionyl)-phenyl]-2,2-dimethyl-propan-1-one (**84**)[3], and N-benzylideneaniline (**41**)[5].

6.2. GENERAL PROCEDURES.

6.2.1. GENERAL PROCEDURES FOR HYDROGENATION.

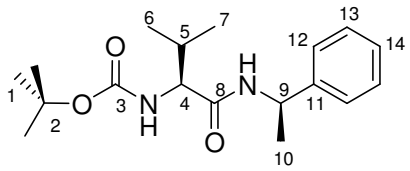
A glass-lined stainless steel autoclave equipped with a magnetic stirring bead was charged with the catalytic solution, prepared before in a dried and degassed Schlenk tube, containing the catalyst (0.5 mol%, 3.2 mg) dissolved in 3ml of dry ^{i}PrOH. The substrate was added (1.0 mmol) and ^{t}BuOK (1 mol%, 0.01 ml of 1 M solution in ^{t}BuOH) was added prior to sealing the autoclave. The autoclave was flushed three times with hydrogen and finally charged with hydrogen to the specific reaction pressure. The reactions were stirred at the same speed for the desired times at the required temperature using a stainless steel heating jacket connected to a thermocouple and heater. After the desired time passed, the autoclave was opened and the solvent removed. The conversion of the reaction was calculated by NMR. The products were isolated in pure form by column chromatography and characterised by comparison of NMR, IR, MS, HPLC/GCMS, optical rotation and where appropriate melting point data with authentic samples. The enantiomeric excess was calculated by HPLC or using a chiral shift reagent as indicated. Racemic authentic samples of all the products from ketone and imine hydrogenation were first prepared by $NaBH_4$ or $LiAlH_4$ reduction. HPLC retention times and NMR data from hydrogenation experiments matched the authentic samples exactly.

6.2.2. GENERAL PROCEDURE OF REDUCTION USING $NaBH_4$.

To a solution of the substrate (1 eq) in EtOH was added powdered $NaBH_4$ (3 eq) portionwise. The reaction mixture was stir overnight. The reaction was monitored by TLC and quenched with HCl (10 %) The organic phase was washed with DCM and water several times. The solvent were removed in the rotavaporator and the product isolated.

6.3. SYNTHESIS OF THE DIAMINE 3a

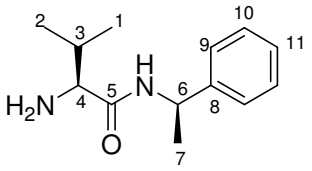
Synthesis of (*S,R*)-6 (Prepared by modification of a procedure in the literature[6])



To a cold solution (–15 ºC) of *N*-Boc-*L*-valine (2.25 g, 10.38 mmol) and *N*-methylmorpholine (1.14 ml, 10.38 mmol) in dry THF (30 ml), isobutyl chloroformate (1.36 ml, 10.38 mmol) in THF (5 ml) was added dropwise over a period of 30 min. After stirring for another 20 min, (*R*)-(+)-α-methylbenzylamine (1.34 ml, 10.38 mmol) was added in one portion. Then, the reaction mixture was allowed to warm to room temperature and stirred overnight. After evaporation of the solvent *in vacuo*, the residue was diluted with EtOAc and the organic phase was washed with 10 % Na_2CO_3, 0.1 M HCl, brine and dried over anhydrous Na_2SO_4. Removal of the solvent *in vacuo* gave crude *N*-Boc-α-amino amide **6** as a white solid (3.17 g, 95 %), which was used in the subsequent step without further purification.

^{1}H-NMR (300MHz, $CDCl_3$) δ 0.84 (d, *J* 6.3Hz, 3H, C^7*H*$_3$), 0.90 (d, *J* 6.7Hz, 3H, C^6*H*$_3$), 1.36 (s, 9H, C^1*H*$_3$), 1.42 (d, *J* 6.9Hz, 3H, C^{10}*H*$_3$), 2.03-2.14 (m, 1H, C^5*H*), 3.77 (dd, *J* 6.5Hz, 1H, C^9*H*), 4.92 (br d, *J* 6.5Hz, 1H, N*H*), 5.04 (q, *J* 6.8Hz, *J* 7.2Hz, 1H, C^4*H*), 6.10 (br d, *J* 7.2Hz, 1H, N*H*), 7.15-7.28 (m, 5H, ArC*H*). ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 18.3 (*C*^{10}H$_3$), 19.7(*C*^{6}H$_3$), 22.3(*C*^{7}H$_3$), 28.7 (*C*^{1}H$_3$), 30.9 (*C*^{5}H), 49.2 (*C*^{9}H), 60.6 (*C*^{4}H), 80.3 (*C*^{2}(CH$_3$)$_3$), 126.4 (Ar*C*H), 127.7 (Ar*C*H), 129.1 (Ar*C*H), 143.3 (Ar*C*), 156.3 (*C*^{3}=O), 171.0 (*C*^{8}=O). MS (ES+) m/z: 345.23 (5%), 344.22 ([M+Na]$^+$, 100).

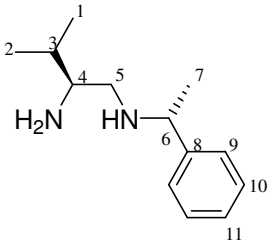
Synthesis of (*S*,*R*)-7



N-Boc-α-amino amide **6** (3.17 g, 10 mmol) was treated with trifluoracetic acid (6.15 ml, 80 mmol) in DCM (20 ml) at room temperature for 19 h. The reaction mixture was made basic with NaOH 1 M (35 ml) and stirred for 3 h. The organic phase was separated and the aqueous solution was extracted with EtOAc (4 x 10 ml). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give (*S*,*R*)-1,2-diamine **7** as a pale yellow oil (2.41g, 99 %).

^{1}H-NMR (300MHz, $CDCl_3$) δ 0.67 (d, *J* 6.9 Hz, 3H, C^1*H*$_3$), 0.88 (d, *J* 6.9 Hz, 3H, C^2*H*$_3$), 1.34 (br s, 2H, N*H*$_2$), 1.41 (d, *J* 6.9 Hz, 3H, C^7*H*$_3$), 2.22 (m, 1H, C^3*H*), 3.15 (d, *J* 3.8 Hz, 1H, C^4*H*), 5.05 (m, 1H, C^6*H*), 7.13-7.28 (m, 5H, ArC*H*), 7.55 (br d, *J* 6.9 Hz, 1H, N*H*). ^{13}C-NMR (75.5MHz, $CDCl_3$) 16.4 (*C*^{1}H$_3$), 20.1 (*C*^{2}H$_3$), 22.4 (*C*^{7}H$_3$), 31.2 (*C*^{3}H), 48.6 (*C*^{4}H), 60.4 (*C*^{6}H), 126.5 (Ar*C*H), 127.5 (Ar*C*H), 128.9 (Ar*C*H), 144.0 (Ar*C*), 173.6 (*C*=O).

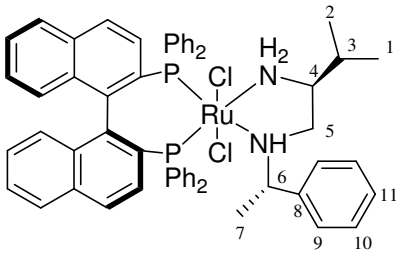
Synthesis of (*S*,*R*)-3a



(*S*,*R*)-α-amino amide **7** (1.7 g, 7.7 mmol) was dissolved in dry THF (60 ml) in a round bottom flask equipped with a reflux condenser. $LiAlH_4$ (1 M in THF) (1.7 g, 45mmol) was added under a nitrogen atmosphere at rt and the mixture was refluxed (80 ºC) for 2 days and then was allowed to warm to room temperature. The excess of $LiALH_4$ was decomposed with H_2O under ice-bath cooling. The sticky precipitated formed was filtered off and washed with DCM. The combined organic layers were washed with 1M NaOH, brine and dried over anhydrous K_2CO_3, filtered and concentrated under vacuo to give a pale yellow oil (1.53 g) containing (*S*,*R*)-**3a**. The diamine was purified by chromatography on a SiO_2 column using EtOAc/MeOH (10:1) as eluent to give compound (S,*R*)-**3a** as a colourless oil (1.12 g, 71%).

$[\alpha]_D^{20}$ +20.0 (*c* 1, $CHCl_3$); IR (ν_{max}, KBr) 3294 (w), 2956 (m), 2885 (m), 1559 (m), 1491 (w), 1450 (s) and 1368 cm^{-1} (m); ^{1}H-NMR (300MHz, $CDCl_3$) δ 0.76 (d, *J* 6.8 Hz, 3H, C^1H_3), 0.79 (d, *J* 6.8 Hz, 3H, C^2H_3), 1.30 (d, *J* 6.6 Hz, 3H, C^7H_3), 1.40-1.51 (m, 1H, C^3H), 1.67 (br s, 3H, NH_2NH), 2.06-2.15 (m, 1H, C^5H_2), 2.46-2.57 (m, 2H, $C^5H_2C^4H$), 3.70 (q, *J* 6.6 Hz, 1H, C^6H), 7.13-7.29 (m, 5H, ArC*H*). ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 18.4 (C^1H_3), 19.7 (C^2H_3), 25.0 (C^7H_3), 32.8 (C^3H), 52.0 (C^5H_2), 57.2 (C^4H), 58.7 (C^6H), 127.0 (Ar*C*H), 127.2 (Ar*C*H), 128.8 (Ar*C*H), 146.0 (Ar*C*). MS (ESI) m/z: 207.19 (MH^+, 100%), 190.17 (7), 105.08 (4); Found (HRMS ESI) 207.1865 (MH^+), $C_{13}H_{23}N_2$ requires 207.1861.

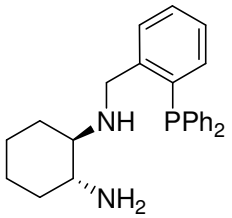
6.4. Preparation of complex 11



$[Ru(C_6H_6)Cl_2]_2$ (15 mg, 0.03 mmol) was added to a solution of (*S*,*S*)-BINAP (37mg, 0.06 mmol) in dry and degassed THF (2 ml) prepared in a microwave tube. The reaction was heated in the microwave for 15 min at 125 ºC. Then a solution of diamine (*S,R*)-**3a** (12 mg, 0.06 mmol) in THF (2 ml) was added to the reaction mixture into the microwave tube and heated in the microwave for 15 min at 120 ºC. The solvent was removed under vacuum to give a brown oil (30 mg) containing the complex **11**. The complex was purified by chromatography on a SiO_2 column using Et_2O/Petrol (4:6) as eluent. Compound **11** was obtained pure as a brown solid (20 mg, 66 %).

M.p. 122ºC; $[\alpha]^{20}_D$ (*c* 0.02, $CHCl_3$) -400; ^{1}H-NMR (300MHz, $CDCl_3$) δ 0.38 (d, *J* 6.7Hz, 3H, C^1H_3), 0.39 (d, *J* 6.7Hz, 3H, C^2H_3), 1.25 (d, *J* 7.3Hz, 3H, C^7H_3), 1.93 (d, *J* 11.7Hz, 2H, NH_2), 2.16 (d, J 6.7Hz, 1H, CH), 2.33 (d, *J* 7.9Hz, 1H, NH), 2.80 (q, *J* 11.9Hz, 1H, C^6H), 2.95 (m, 1H, C^4H), 3.54 (d, *J* 10.3Hz, 2H, C^5H_2), 7.0-8.4 (m, 37H, ArC*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 14.4 (CH_3), 18.7 (CH_3), 28.4 (*C*H), 28.7 (CH_2), 55.8 (*C*H), 56.1 (*C*H), 123-135 (37Ar*C*H, 9Ar*C*); ^{31}P-NMR (121.4 MHz, $CDCl_3$) δ 38.65 (d, *J* 36.6), 49.68 (d, *J* 36.6) ; MS (ES+) m/z: 965.16 (M-Cl, 100%).

6.5. Preparation of P^N^N Ligand 30[1]

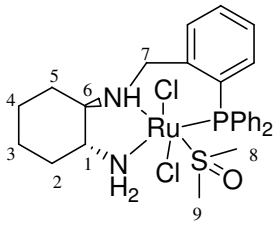


A solution of 2-dphenylphosphanylbenzaldehyde (195 mg, 0.67 mmol) in absolute ethanol (19 ml) at 45 ºC was added over a period of 5 h to a solution of (*1R*,*2R*)-cyclohexane-1,2-diamine (250 mg, 2.19 mmol) in absolute ethanol (39 ml) at 0ºC. ^{1}H NMR showed the formation of an imine (8.74 ppm) and disappearance of the carbonyl (10.44 ppm) by conversion. Sodium borohydride (106 mg, 2.81 mmol) was added and the reaction solution stirred for another 12 hours at room temperature. ^{1}H NMR reaction control showed complete reduction of the imine. The reaction was quenched by adding acetone (1 x 7.8 ml) and the solvent was removed under reduced pressure. The residue was dissolved by stirring with saturated ammonium hydrochloride solution (7.8 ml) and dichloromethane (7.8 ml). After extraction of the aqueous phase with dichloromethane (2 x 3.9 ml), the combined organic phases were washed with water (7.8 ml) and 10% hydrochloric acid (7.8 ml) was added. The product, a colourless precipitate (hydrochloride salt), was filtered off and dried under vacuum; yield: 302 g (98 %).

The hydrochloride salt was dissolved in a saturated sodium hydrogen carbonate solution (1 x 7.8 ml) and extracted with dichloromethane (3 x 4.7 ml). The combined organic phases were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and dried under vacuum to give the desired product as an oil (261 mg , 43 % overall yield).

^{1}H-NMR (300MHz, $CDCl_3$) δ 0.7-0.9 (m, 1H, C*H*$_2$), 0.9-1.2 (m, 3H, C*H*$_2$), 1.5-1.6 (m, 5H, C*H*$_2$, N*H*$_2$, N*H*), 1.7-1.8 (m, 1H, C*H*$_2$), 1.9-2.0 (m, 2H, NC*H*, C*H*$_2$), 2.1-2.2 (m, 1H, NC*H*), 3.83 (d, *J* 13Hz, 1H, C*H*$_2$NH), 4.02 (d, *J* 13Hz, 1H, C*H*$_2$NH), 6.7-6.8 (m, 1H, ArC*H*), 7.0-7.1 (m, 1H, ArC*H*), 7.1-7.3 (m, 11H, ArC*H*), 7.4-7.5 (m, 1H, ArC*H*); ^{31}P-NMR (121.4 MHz , $CDCl_3$) δ -14.81.

6.6. Preparation of complex 33

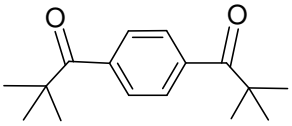


$[RuCl_2(DMSO)_4]$ (28.6 mg, $5.92x10^{-2}$ mmol) was added to a solution of (1*R*,2*R*)-*N*-(2-dphenylphosphanylbenzyl)cyclohexane-1,2-diamine (23 mg, $5.92x10^{-2}$ mmol) in dry THF prepared in a microwave tube. The reaction was heated in the microwave for 15min at 120 ºC. The solvent was removed under vacuum and the product was obtained as a brown solid in quantitative yield and >95 % purity. Recrystallisation by slow evaporation of MeCN gave crystals of the bis acetonitrile adduct (24.5 mg, 0.038 mmol, 65 % yield) suitable for X-Ray determination. The complex can also be purified by chromatography and isolated as a brown powder. Crystals, powder and crude material gave similar results in hydrogenation experiments.

M.p. 170 ºC; $[\alpha]^{20}_D$ +60 (*c* 0.5, $CHCl_3$); IR (ν_{max}, KBr) 3432(w), 3282(s), 3214(s), 3136(s), 3053(s), 2929(w), 2856(s), 1648(s), 1587(s), 1483(s), 1434(w), 1092 (w, R_2S=O), 1047(w) and 1018(w) cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$) δ 0.9-1.5 (m, 4H, C^3H_2-C^4H_2), 1.55 (br s, 2H, NH_2), 1.6-1.8 (m, 2H, C^2H_2-C^5H_2), 2.95 (s, 6H, $2CH_3$), 2.0-2.2 (m, 1H, C^2H_2-C^5H_2), 2.5-2.7 (m, 1H, C^2H_2-C^5H_2), 3.0-3.2 (m, 1H, C^1H), 3.2-3.3 (m, 1H, C^6H), 3.6-3.9 (m, 1H, N*H*), 3.9-4.4 (m, 2H, C^7H_2), 7.1-7.6 (m, 14H, ArC*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 23.4 (C^4H_2, cyclohexane), 23.8 (C^4H_2, cyclohexane), 29.5 (C^2H_2, cyclohexane), 35.1 (C^5H_2, cyclohexane), 44.2 (C^8H_3, DMSO), 45.8 (C^9H_3, DMSO), 51.5 (C^7H_2, $^3J_{C\text{-}P}$=7.7Hz), 56.1 (C^1H-NH_2), 62.7 (C^6H-NH), 126-135 (12Ar*C*H, 4Ar*C*); ^{31}P-NMR (121.4 MHz, $CDCl_3$) δ 43.56; MS (ES+) m/z: 644 (M-Cl+MeCN, 100%), 603 (58); HRMS found (ES+) 644.1205 (Me-Cl+MeCN) ($C_{29}H_{38}N_3OPS^{35}ClRu$) requires 644.1212; Found: C, 49.3%; H, 5.5%; N, 6.7%. $C_{27}H_{35}Cl_2N_2OPRuS$ + 1 DMSO + 2 CH_3CN requires: C, 49.6%; H, 5.9%; N, 7.0%.

6.7. Preparation of substrates for hydrogenation reactions.

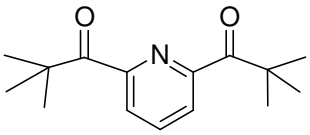
1-[4-(2,2-dimethyl-propionyl)-phenyl]-2,2-dimethyl-propan-1-one, 84[3]



To a suspension of 2.26g of $CuBr{\cdot}SMe_2$ (11 mmol) in 50 ml of THF was added 6.45 ml of a 1.7 M solution of *tert*-butyllithium (11 mmol) in pentane at -50 ºC. After stirring for 30 min, a solution of 1.01 g of terephthaloyl chloride (5 mmol) in 40 ml of THF was added slowly via cannula. After an additional 4 h, the reaction mixture was allowed to warm to room temperature and then quenched with 25 ml of a saturated solution of ammonium chloride. The organic layer was separated, and the aqueous layer was back-extracted with diethyl ether (3x8 ml). The combined organic layers were washed with brine and water, dried over sodium sulfate, and concentrated under vacum. Flash column silica gel chromatography (1:4, diethyl ether:hexanes) afforded 0.75 g of *p*-dipivaloyl benzol (3 mmol, 61 % yield) as a white solid.

M.p. 83 ºC (m.p.[3] 83-84 ºC); IR (ν_{max}, KBr) 3379 (w), 2963 (s), 2360 (w), 1772 (s), 1700 (m) and 1465 (m) cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$) δ 1.25 (s, 18H, 6xCH_3), 7.59 (s, 4H, Ar*CH*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 27.8 (*C*H_3), 44.3 (*C*$(CH_3)_3$), 127.4 (Ar*C*H), 140.5 (Ar*C*), 208.8 (*C*=O); MS (ES+) m/z:269.16 ($[M+Na]^+$, 100%), 301.20 ($[M+Na+MeOH]^+$, 30).

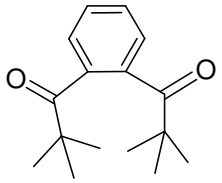
2,6-bis(2',2'-dimethylpropionyl)pyridine, 86



To a suspension of 2.26 g of $CuBr{\cdot}SMe_2$ (11 mmol) in 50 ml of THF was added 6.45 ml of a 1.7 M solution of tert-butyllithium (11 mmol) in pentane at -50 ºC. After stirring 30 min, a solution of 1.02 g of 2,6-pyridinecarbonyl dichloride chloride (5 mmol) in 40 ml of THF was introduced slowly via cannula. After an additional 4 h the reaction mixture was allowed to warm to room temperature and then quenched with 25 ml of a saturated solution of ammonium chloride. The organic layer was separated, and the aqueous layer was back-extracted with diethyl ether (3x8 ml). The combined organic layers were washed with brine and water, dried over anhydrous sodium sulfate, and concentrated under vacum. Flash column silica gel chromatography (1:4, diethyl ether:hexanes) afforded 0.83 g of 2,6-bis(2',2'-dimethylpropionyl)pyridine (3.36 mmol, 67% yield) as a yellow oil.

IR (ν_{max}, KBr) 3355 (w), 2958 (s), 2871 (m), 2360 (w), 1684 (s) and 1481 (s) cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$) δ 1.34 (s, 18H, C*H*$_3$), 7.85 (br s, 3H, ArC*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 26.2 (*C*H$_3$), 42.7 (*C*(CH$_3$)$_3$), 125.0 (Ar*C*H), 136.8 (Ar*C*H), 152.4 (Ar*C*), 205.0 (*C*=O); MS (ES+) m/z: 270.03 ([M+Na], 100%)

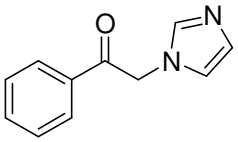
1-[2-(2,2-dimethyl-propionyl)-phenyl]-2,2-dimethyl-propan-1-one, 88



To a suspension of 2.26 g of CuBr·SMe$_2$ (11 mmol) in 50 ml of THF was added 6.45 ml of a 1.7 M solution of *tert*-butyllithium (11 mmol) in pentane at -50 ºC. After stirring 30 min, a solution of 1.01 g of phthaloyl dichloride (5 mmol) in 40 ml of THF was introduced slowly via cannula. After an additional 4 h the reaction mixture was allowed to warm to room temperature and then quenched with 25 ml of a saturated solution of ammonium chloride. The organic layer was separated, and the aqueous layer was back-extracted with diethyl ether (3x8 ml). The combined organic layers were washed with brine and water, dried over anhydrous sodium sulfate, and concentrated under vacuum. Flash silica gel column chromatography (1:4, diethyl ether:hexanes) afforded 0.70 g of *o*-Dipivaloyl-benzol (2.8 mmol, 57 %) as a white oil.

^{1}H-NMR (300MHz, $CDCl_3$) δ 1.21 (s, 18H, C*H*$_3$), 7.3-7.5 (m, 4H, ArC*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 28.3 (*C*H$_3$), 44.5 (*C*(CH$_3$)$_3$), 126.9 (Ar*C*H), 129.1 (Ar*C*H), 140.7 (Ar*C*), 212.2 (*C*=O).

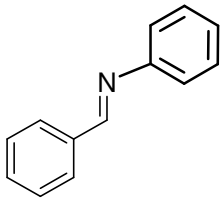
2-imidazol-1-yl-1-phenyl-ethanone, 76 (Prepared by modification of a literature procedure[7]).



A round-bottoned flask was charged with imidazole (2.9 g, 42 mmol) and 35 ml DCM. To the solution was slowly added α-bromoacetophenone (3.98 g, 20 mmol). The yellow solution was stirred 3 h at room temperature. The reaction was quenched with water. The organic phase washed with brine and form a white solid that it is remove by filtration. The solvent was removed under vacuum and the residue was dissolve in EtOAc and filtrate again. Removing the solvent for the last time under vacuum the product was obtained as a brownish solid (1.84 g, 50 % yield).

M.p.: 117 ºC; IR (ν_{max}, KBr) 2967 (w), 2920 (w), 1696 (m), 1505 (m), 1459 (s), 1344 (w), 1230 (m), 1074 (m), 1038 (w), 988 (w) and 762 (w) cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$) δ 5.37 (s, 2H, C*H*$_2$), 6.90-7.93 (m, 8H, ArC*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 52.9 (CH2), 120.7 (Ar*C*H), 128.2 (Ar*C*H), 129.3 (Ar*C*H), 134.6 (Ar*C*H), 138.5 (Ar*C*H), 192.4 (C=O); MS (ES+) m/z: 187.15 ($[M+H]^+$, 100%), 209.15 ($[M+Na]^+$, 69%)

N-benzylideneaniline, 41[5]

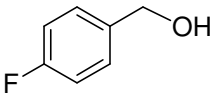


A solution of benzaldehyde (1 ml, 9.8 mmol) and aniline (0.9 ml, 9.8 mmol) in DCM (30 ml) containing $MgSO_4$ was stirred for 12 h at room temperature. The crude of the reaction was purified by column silica gel chromatography (4:6, Et_2O:Petrol) and the pure imine was obtained as a white solid (1.4 g, 80 % yield).

IR: 1628 (s, C=N), 1585 (s, C=C), 1180 (m, C-N) cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$) δ 7.13 -7.19 (m, 3H, ArC*H*), 7.29-7.36 (m, 2H, ArC*H*), 7.39-7.44 (m, 3H, ArC*H*), 7.82-7.86 (m, 2H, ArC*H*), 8.40 (s, 1H, N=C*H*); ^{13}C NMR (75.5MHz, $CDCl_3$) δ 121.2 (Ar*C*H), 126.3 (Ar*C*H), 129.4 (Ar*C*H), 129.6 (Ar*C*H), 129.7 (Ar*C*H), 131.8 (Ar*C*H), 136.5 (Ar*C*), 152.4 (Ar*C*), 160.8 (N=*C*H); MS (ES+) m/z: 182 ($[M+H]^+$, 45 %).

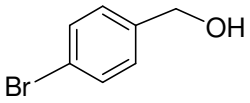
6.8. Spectroscopy data for aldehyde hydrogenation products:

4-fluoro-benzyl alcohol, 37



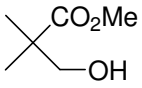
^{1}H-NMR (300MHz, $CDCl_3$) δ 3.30 (br s, 1H, O*H*), 4.40 (s, 2H, C*H*$_2$), 6.87 (dd, *J* 8.8Hz, *J* 8.8Hz, 2H, ArC*H*), 7.12 (dd, *J* 8.8Hz, *J* 5.4Hz, 2H, ArC*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 64.2 (*C*H$_2$), 115.2 (d, *J* 21.6 Hz, Ar*C*H), 128.7 (d, *J* 7.7 Hz, ArCH), 136.6 (d, *J* 2.8 Hz, Ar*C*), 162.2 (d, *J* 245.5 Hz, Ar*C*); (^{19}F-NMR {^{1}H} (282MHz, $CDCl_3$) of aldehyde -102.7) ^{19}F-NMR {^{1}H} (282MHz, $CDCl_3$) -115.6; MS (ES+) m/z: 149.06 ($[M+Na]^+$, 43%), 127.05 ($[M+H]^+$, 25), 126.05 (100).

4-bromo-benzyl alcohol, 38



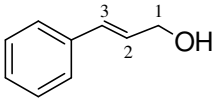
IR (ν_{max}, IR card) 3250 (m), 2856 (w), 1652 (w), 1486 (m), 1069 (m), 1009 (s), 913 (s) and 743 (s) cm^{-1} ; ^{1}H-NMR (300MHz, $CDCl_3$) δ 2.70 (br s, 1H, O*H*), 4.46 (s, 2H, CH_2), 7.07 (d, *J* 8.4Hz, 2H, ArC*H*), 7.34 (d, *J* 8.4Hz, 2H, ArC*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 64.5 (*C*H_2), 121.5 (Ar*C*H), 128.5 (Ar*C*H), 131.5 (Ar*C*), 139.5 (Ar*C*); MS (ES+) m/z: 188.97 (10%), 187.97 (50), 186.97 (10), 185.97 (100).

3-hydroxy-2,2-dimethyl-propionic acid methyl ester, 39



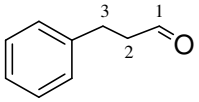
IR (ν_{max}, $CDCl_3$) 3460 (w), 2980 (m), 2930 (m) and 1700 (w) cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$) δ 1.05 (s, 6H, C(CH_3)$_2$), 3.25 (s, 3H, OCH_3), 3.44 (s, 2H, CH_2), 4.77 (br s, 1H, O*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 22.4 (C(*C*H_3)$_2$), 45.8 (*C*(CH$_3$)$_2$), 50.0 (O*C*H$_3$), 70.2 (*C*H_2), 178.9 (*C*=O); MS (ES+) m/z 155.02 ([M+Na]$^+$, 100%).

Cinnamyl alcohol, 45



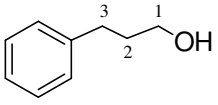
IR (ν_{max}, $CDCl_3$) 3350 (br s), 3090 (m), 3058 (m), 3030 (w), 2870 (m), 1658 (s), 1590 (m), 1494 (m), 1425 (m), 1295 (m) and 1205 (w) cm^{-1} ; ^{1}H-NMR (300MHz, $CDCl_3$) δ 2.10 (br s, 1H, O*H*), 4.20 (dd, *J* 1.4Hz, *J* 5.6Hz, 2H, C$^1H_2$), 6.25 (dt, *J* 5.6Hz, *J* 15.9Hz, 1H, C^2H), 6.50 (d, *J* 15.9Hz, 1H, C^3H), 7.1-7.3 (m, 5H, ArC*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 63.6 (*C*^{1}H$_2$OH), 126.5 (Ar*C*H), 127.7 (*C*^{2}H), 128.6 (*C*^{3}H), 128.6 (Ar*C*H), 131.0 (Ar*C*H), 136.7 (Ar*C*); MS (EI) m/z 168.99 ([M+Cl], 8%), 134.07 ([M], 40).

Benzenepropanal, 46



^{1}H-NMR (300MHz, $CDCl_3$) δ 2.82 (t, *J* 7.5Hz, 2H, C$^3H_2$), 2.99 (t, *J* 7.5Hz, 2H, C$^2H_2$), 7.2-7.3 (m, 5H, ArC*H*), 9.86 (s, 1H, C^1H)

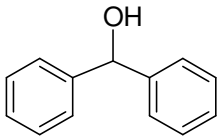
Benzenepropanol, 47



^{1}H-NMR (300MHz, $CDCl_3$) δ 1.8-1.9 (m, 3H, C$^1H_2$, O*H*), 2.72 (t, *J* 7.5Hz, 2H, C$^3H_2$), 3.68 (t, *J* 7.5Hz, 2H, C$^2H_2$), 7.2-7.4 (m, 5H, ArC*H*)

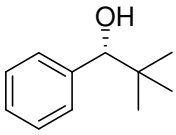
6.9. Selected data for ketone hydrogenation products.

Diphenylmethanol, 60



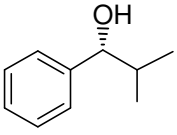
M.p: 69 ºC (m.p.[8] 68ºC); IR: 3400 (OH), 3048, 1590, 1490 cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$) δ 3.17 (O*H*), 5.56 (C*H*), 7.1-7.2 (Ar*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 76.2 (C*H*), 126.1 (ArC*H*), 127.6 (ArC*H*), 128.4 (ArC*H*), 143.0 (Ar*C*); MS (EI) m/z 184 (M^+, 30 %), 183 (12), 105 (100).

2,2-dimethyl-1-phenyl-propan-1-ol, 66



M.p. 45 ºC (m.p.[9] 45ºC); $[\alpha]_D^{20}$ -19.3 (*c* 0.3, acetone); (lit[2] (*S,* 100 %ee) $[\alpha]_D^{25}$ -30.3 (*c* 0.36, acetone)); IR (ν_{max}, $CDCl_3$) 3432 (br s), 2954 (s), 1623 (w), 1452 (m), 1363 (m), 1047 (m) and 1006 (m) cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$) δ 0.83 (s, 9H, CH_3), 1.97 (br s, 1H, O*H*), 4.28 (s, 1H, C*H*-OH), 7.19 (m, 5H, ArC*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 26.0 (*C*H_3), 35.6 (*C*$(CH_3)_3$), 82.4 (*C*HOH), 127.3 (Ar*C*H), 127.6 (Ar*C*H), 127.6 (Ar*C*H), 142.2 (Ar*C*); MS (ES+) m/z 187.10 ($(M+Na)^+$, 100%). Enantioselectivity determined by HPLC. ChiralPak OD-H, 1ml/min, 99.5:0.5 Hexane:2-Propanol. Retention times: 10.5 min (*S*, major enantiomer) and 13.6 min (*R*, minor enantiomer). The ee could also be measured by ^{1}H-NMR integration in the presence of Europium (II) tris (3-[Heptafluoropropyl-hydroxylmethylene]-d-camphorato) shift reagent.

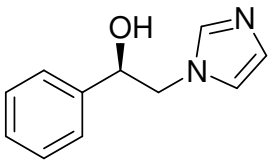
2-methyl-1-phenyl-propan-1-ol, 68



$[\alpha]_D^{25}$ -28.6 (*c* 0.16, acetone); (lit[10] (*S,* 25% ee) $[\alpha]_D^{22}$ -12.08 (*c* 8.8, Et_2O)); IR (ν_{max}, $CDCl_3$) 3380 (br s), 2890 (w), 1600 (m) and 1490 (s) cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$) δ 0.67 (d, 3H, *J* 6.8Hz, CH_3), 0.87 (d, *J* 6.8Hz, 3H, CH_3), 1.82 (octet, *J* 6.8Hz, 1H, C*H*), 2.23

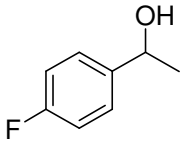
(br s, 1H, O*H*), 4.18 (d, *J* 6.8Hz 1H, C*H*-OH), 7.11-7.24 (m, 5H, ArC*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 18.8 (*C*H_3), 19.4 (*C*H_3), 35.6 (*C*H(CH_3)$_2$), 80.4 (*C*HOH), 127.1 (Ar*C*H), 127.8 (Ar*C*H), 128.6 (Ar*C*H), 144.1 (Ar*C*); MS (CI+) m/z 133.11 ((M-OH)$^+$, 100%). Enantioselectivity determined by HPLC. ChiralPak OD-H, 0.5 ml/min, 90:10 Hexane:2-Propanol. Retention times: 10.8min (*S*, major enantiomer) and 11.8 min (*R*, minor enantiomer).

2-imidazol-1-yl-1-phenyl-ethanol, 77



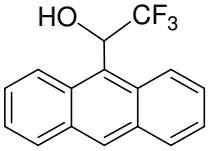
M.p. 150 ºC (m.p[11]. 145.0-145.5ºC); $[\alpha]^{20}_D$ -37.5 (*c* 1x10^{-3}, chloroform), (lit[11] (*R*, 99%) $[\alpha]_D^{25}$ –47.6 (*c*: 1x10^{-2}, ethanol)); IR (ν_{max}, KBr) 3120 (br s), 1600 (s), 1465 (m) cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$) δ 2.18 (br s, 1H, O*H*), 4.02-4.08 (m, 2H, CH_2), 4.84-4.90 (dd, *J* 4.2Hz , *J* 7.4Hz, 1H, C*H*), 6.82 (br s, 1H, ArC*H*), 6.70 (br s, 1H, ArC*H*), 7.20 (s, 1H, ArC*H*), 7.21-7.39 (m, 5H, ArC*H*);^{13}C-NMR (75.5MHz, $CDCl_3$) δ 54.7 (*C*H_2), 73.5 (*C*HOH), 125.8 (Ar*C*), 128.3 (Ar*C*H), 128.6 (Ar*C*H), 128.8 (Ar*C*H), 140.8 (Ar*C*); MS (EI+) m/z: 188.10 ((M+H)$^+$, 5%). Enantioselectivity determined by HPLC. ChiralPak OD-H, 0.5ml/min, 90:10 Hexane:2-Propanol. Retention times: 42min (*S*, minor enantiomer) and 52min (*R*, major enantiomer).

1-(4-fluorophenyl)-ethanol, 21



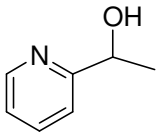
IR (ν_{max}, KBr) 3214 (br s), 2920 (w), 1555 (w), 1207 (s) and 1150 (s) cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$) δ 1.36 (d, *J* 6.4Hz, 3H, CH_3), 2.27 (s, 1H, O*H*), 4.75 (q, *J* 6.4Hz 1H, C*H*), 6.92 (t, *J* 8.6Hz, *J* 8.6Hz, 2H, ArC*H*), 7.22 (q, *J* 8.6Hz, *J* 5.4Hz 2H, ArC*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 25.2 (*C*H_3), 69.5 (*C*H), 115.1 (d, *J* 21.0Hz, Ar*C*H), 127.1 (d, *J* 7.7 Hz ArCH), 141.6 (d, *J* 3.3Hz ArC), 162.0 (d, *J* 244.9 Hz, Ar*C*F); (^{19}F-NMR {^{1}H} (282MHz, $CDCl_3$) of ketone -106) ^{19}F-NMR {^{1}H} (282MHz, $CDCl_3$) -115.9; MS (EI-) m/z: 138.99 ((M-H)$^-$, 100%). Enantioselectivity determined by ^{19}F-NMR integration in the presence of Europium (II) tris (3-[Heptafluoropropyl-hydroxylmethylene]-d-camphorato) shift reagent.

1-(9-anthryl)-2,2,2-trifluoroethanol, 17



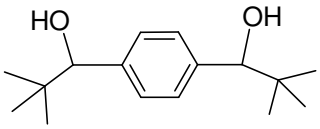
M.p. 140ºC (m.p.[12] 140-142ºC); IR (ν_{max}, KBr) 3400 (m), 2961 (w), 2359 (w), 1675 (m), 1652 (m), 1493 (m), 1448, (m), 1373 (w, C-F), 1333 (w, C-F), 1285 (w, C-F) and 913 (s) cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$) δ 2.89 (br s, 1H, O*H*), 6.57 (q, *J* 7.9Hz, 1H, C*H*), 7.3-8.8 (m, 9H, ArC*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 69.9-70.4 (q, *C*H-CF_3), 123.6 (Ar*C*), 124.9-134.2 (Ar*C*H); ^{19}F-NMR {^{1}H} (282MHz, $CDCl_3$) -74.5; MS (EI-) m/z: 274.94 ($[M]^-$). Enantioselectivity determined by ^{19}F-NMR using (*R*)-(+)-α-methylbenzylamine as chiral solvating agent.

1-pyridin-2-yl-ethanol, 79



$[\alpha]^{20}_D$ -9.8 (*c* 1x10^{-3}, chloroform), (lit[13] (*R*, 98%) $[\alpha]_D^{25}$ –58.3 (*c*: 0.5, ethanol)); IR (ν_{max}, KBr) 3371 (m), 2970 (w), 2933 (w), 1700 (m), 1590 (m), 1435 (m) and 1080 (m) cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$) δ 1.42 (d, *J* 6.5Hz, 3H, CH_3), 4.52 (br s, 1H, O*H*), 4.81 (q, *J* 6.5Hz, 1H, C*H*OH), 7.1-8.4 (m, 4H, ArC*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 22.7 (*C*H_3), 69.0 (*C*HOH), 118.7 (Ar*C*H), 121.0 (Ar*C*H), 136.2 (Ar*C*H), 146.5 (Ar*C*H), 163.7 (Ar*C*); MS (ES+) m/z: 146.05 ($[M+Na]^+$, 100%). Enantioselectivity determined by HPLC. ChiralPak OD-H, 0.5ml/min, 90:10 Hexane:2-Propanol. Retention times: 8.8min (*R*, major enantiomer) and 9.8min (*S*, minor enantiomer).

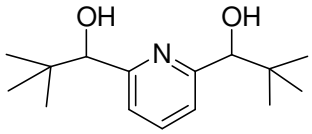
1,4-bis(2,2-dimethylpropan-1-ol)benzene, 85



M.p. 129ºC; $[\alpha]^{18}_D$ +8.3 (*c* 0.4, $CHCl_3$); IR (ν_{max}, disposable card) 3411 (m, OH), 2952 (m), 1363 (w), 1046 (w), 1005 (w); ^{1}H-NMR (300MHz, $CDCl_3$) δ 1.85 (s, 18H, 6xCH_3), 4.33 (s, 2H, 2xC*H*-OH) 7.18 (s, 4H, ArC*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 25.9 (*C*H_3), 35.7 (*C*$(CH_3)_3$), 82.2 (*C*HOH) 126.8 (Ar*C*H), 141.2 (Ar*C*); MS (ES+) m/z: 252.20 (2%), 251.20 (20), 250.19 (100). Enantioselectivity determined by HPLC. ChiralPak AD, 0.5ml/min, 90:10

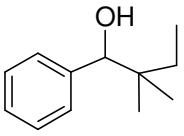
Hexane:2-Propanol. Retention times: 8.8min (+, major enantiomer), 9.9min (-, minor enantiomer) and 16min (*meso*).

2,6-bis(1'-hydroxy-2',2'-dimethylpropyl)pyridine, 87



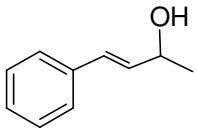
M.p: 87ºC, (m.p[14] 88ºC); $[\alpha]^{18}_{D}$ -26.3 (*c* 0.4, $CHCl_3$) (lit[14] ((*S*-*S*), 100%ee) $[\alpha]_D^{25}$ -40.5 (*c* 1, EtOH));; IR (ν_{max}, disposable IR card) 3403 (s), 2953 (s), 2904 (m), 2867 (m), 2360 (w) 1576 (m), 1456 (m), 1362 (m), 1093 (w), 1056 (s) and 1014 (s) cm^{-1}; First diastereomer ^{1}H-NMR (300MHz, $CDCl_3$) δ 0.84 (s, 18H, C*H*$_3$), 3.88 (br s, 2H, O*H*), 4.28 (s, 2H, C*H*), 7.0-7.5 (m, 3H, ArC*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 24.98 (*C*H$_3$), 35.46 (*C*(CH$_3$)$_3$), 79.45 (*C*H), 120.55 (Ar*C*H), 134.31(Ar*C*H), 157.53 (Ar*C*); Second diastereomer ^{1}H-NMR (300MHz, $CDCl_3$) δ 0.84 (s, 18H, C*H*$_3$), 3.88 (br s, 2H, O*H*), 4.30 (s, 2H, rac-C*H*), 7.0-7.5 (m, 3H, ArC*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 24.9 (*C*H$_3$), 35.3 (*C*(CH$_3$)$_3$), 79.7 (*C*H), 120.4 (Ar*C*H), 134.5 (Ar*C*H), 157.7 (Ar*C*); MS (ES+) m/z: 253.20 (5%), 252.19 (36), 251.19 (100). Enantioselectivity determined by HPLC. ChiralPak AD, 0.5ml/min, 90:10 Hexane:2-Propanol. Retention times: 10.5min ((*S*,*S*) major enantiomer), 11.7min ((*R*,*R*), minor enantiomer) and 21min (*meso*).

2,2-dimethyl-1-phenyl-butan-1-ol, 70



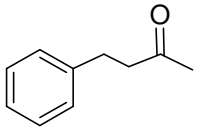
$[\alpha]^{19}_{D}$ -25.6 (*c* 0.3, $CHCl_3$); IR (ν_{max}, disposable IR card): 3460 (w), 3086 (m), 3063 (m), 3029 (m), 2964 (s), 2879 (m), 1494 (w), 1453 (m), 1419 (m), 1384 (s), 1347 (s), 1082 (w), 1062 (w), 1024 (s); ^{1}H-NMR (300MHz, $CDCl_3$) δ 0.73 (s, 3H, C*H*$_3$), 0.81 (t, *J* 7.5Hz, 6H, C*H*$_3$), 1.1-1.4 (m, 2H, C*H*$_2$), 1.31 (br s, 1H, O*H*), 4.39 (s, 1H, C*H*OH), 7.1-7.3 (m, 5H, ArC*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 8.3 (*C*H$_3$), 22.2 (*C*H$_3$), 22.3 (*C*H$_3$), 31.0 (*C*H$_2$), 38.1 (*C*(CH$_3$)$_2$), 81.0 (*C*HOH), 127.2 (Ar*C*H), 127.5 (Ar*C*H), 127.8 (Ar*C*H), 142.2 (Ar*C*); MS (ES+) m/z 201.11 ($[M+Na]^+$, 100%). Enantioselectivity determined by HPLC. ChiralPak AD, 0.5ml/min, 99:1 Hexane:2-Propanol. Retention times: 26min ((-) major enantiomer) and 28min ((+), minor enantiomer).

4-Phenyl-but-3-en-2-ol, 62



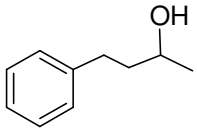
M.p: 36ºC, (m.p[15] 36-38ºC), IR: 3460 (m), 3028 (s), 2973 (s), 2872 (m), 1958 (w), 1660 (w), 1578 (w), 1480 (m), 1205 (w), 1180 (w); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.24 (d, *J* 6.3 Hz, 3H, C*H*$_3$), 1.46 (bs, 1H, O*H*), 4.36 (dq, *J* 6.3 Hz, 1.1 Hz, 1H, C*H*), 6.13 (dd, *J* 15.9 Hz, 6.3 Hz, 1H, C*H*=CH), 6.44 (dd, *J* 15.9 Hz, 0.8 Hz, 1H, CH=C*H*), 7.26-7.10 (m, 5H, ArC*H*); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 23.4, 68.9, 126.4, 127.6, 128.4, 128.6, 129.4, 133.5; MS m/z: 148.09 (10%), 130 (19), 105 (100).

4-phenyl-butan-2-one, 63



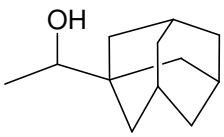
^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.15 (s, 3H, C*H*$_3$), 2.75-2.78 (m, 2H, C*H*$_2$), 2.87-2.90 (m, 2H, C*H*$_2$), 7.2-7.3 (m, 5H, ArC*H*);

4-phnenyl-butan-2-ol, 64



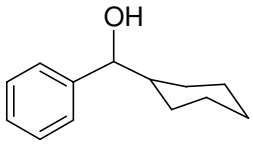
^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.23 (d, *J* 7.2 Hz, 3H, C*H*$_3$), 1.48 (bs, 1H, O*H*), 1.7-1.8 (m, 2H, C*H*$_2$), 2.6-2.8 (m, 2H, C*H*$_2$), 3.7-3.8 (m, 1H, C*H*), 7.2-7.3 (m, 5H, ArC*H*); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 23.8, 32.7, 41.2, 67.9, 126.0, 128.6, 143

1-Adamantanylethan-1-ol, 74



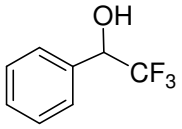
^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.02 (d, *J* 6.4 Hz, 3H, C*H*$_3$), 1.3-1.9 (m, 16H, C*H*$_2$, C*H*, O*H*), 3.21 (q, *J* 6.4 Hz, 1H, C*H*OH); MS (ES+ formic acid added) m/z: 163.14 ([M-OH]$^{+}$ 100%).

Cyclohexyl-phenyl-methanol, 72



M.p: 50ºC, (m.p[16] 49-50ºC); $[\alpha]^{19}_D$ -19.50 (*c* 0.2, $CHCl_3$) (lit[17] $[\alpha]^{22}_D$ +28.27 (*c* 3, C_6H_6, *R*); IR (ν_{max}, disposable IR card) 3384 (s), 3062 (w), 3028 (w), 2922 (s), 2851 (s), 1492 (w), 1450 (m) and 1015 (m) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.8-1.9 (m, 11H, C*H*$_2$+C*H*) , 1.91 (s, 1H, O*H*), 4.34 (d, *J* 7.5Hz, 1H, C*H*-OH), 7.2-7.3 (m, 5H, ArC*H*); ^{13}C-NMR (75 MHz, $CDCl_3$, ppm): δ 24.0 (C*H*$_2$), 26.0 (C*H*$_2$), 26.3 (C*H*$_2$),, 28.6 (C*H*$_2$), 29.2 (C*H*$_2$), 45.0 (*C*H), 79.2 (*C*H), 126.7 (Ar*C*H), (Ar*C*H), 127.4 (Ar*C*H), 128.0 (Ar*C*H), 147.3 (Ar*C*); MS m/e: 191.14 ($[M+1]^+$, 14%), 190.14 ($[M]^+$, 100). Enantioselectivity determined by HPLC. ChiralPak AD, 0.5ml/min, 98:2 Hexane:2-Propanol. Retention times: 23.5min ((*S*) major enantiomer) and 26.5min ((*R*), minor enantiomer).

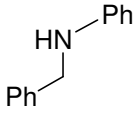
2,2,2-trifluoro-1-phenylethanol, 19



^{1}H-NMR (300MHz, $CDCl_3$) δ 4.06 (s, 1H, O*H*), 4.75 (q, *J* 5.17Hz, 1H, C*H*), 7.2-7.3 (m, 5H, ArC*H*); (^{19}F-NMR {^{1}H} (282MHz, $CDCl_3$) of ketone -72.01) ^{19}F-NMR {^{1}H} (282MHz, $CDCl_3$) -78.61. Enantioselectivity determined by ^{19}F-NMR integration in the presence of chiral phenyl ethyl amine shift reagent.

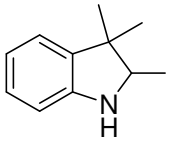
6.10. Selected data from imine hydrogenation products

N-phenylbenzylamine, 43



IR (ν_{max}, KBr) 3418 (s, NH), 3025 (w), 1601 (s), 1505 (s, C=O), 1452 (w, C=C), 1429 (w), 1323 (w, C-N), 1215 (w) and 1154 (s) cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$) δ 4.13 (br t, *J* 5.6Hz, 1H, N*H*), 4.45 (d, *J* 5.6Hz, 2H, C*H*$_2$), 6.78 (d, *J* 7.7Hz, 2H, ArC*H*), 6.89 (t, *J* 7.3Hz, 1H, ArC*H*), 7.34 (dd, *J* 7.7Hz, *J* 7.3Hz, 2H, ArC*H*), 7.4-7.6 (m, 5H, ArC*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 48.43 (*C*H$_2$), 113.02 (Ar*C*H), 117.71 (Ar*C*H), 127.39 (Ar*C*H), 127.67 (Ar*C*H), 128.81 (Ar*C*H), 129.45 (Ar*C*H), 139.65 (Ar*C*), 148.34 (Ar*C*); MS (ES+) m/z: 184.11 ($(M+H)^+$, 100%).

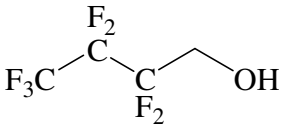
2,3,3-Trimethyl-indolin, 24



IR (ν_{max}, KBr) 3386 (w), 2959 (w), 1606 (s), 1455 (w), 1209 (s) and 1153 (s) cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$) δ 0.95 (s, 3H, C*H*$_3$), 1.08 (d, *J* 6.6Hz , 3H, CHC*H*$_3$), 1.19 (s, 3H, C*H*$_3$), 3.4 (q, *J* 6.6Hz, 1H, C*H*), 3.68 (s, NH), 6.52 (d, *J* 7.5Hz, 1H, ArC*H*), 6.65 (t, *J* 7.5Hz 1H, ArC*H*) , 6.93 (t, *J* 7.5Hz, 1H, ArC*H*), 7.41 (d, *J* 7.5Hz, ArC*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 15.47 ($CHCH_3$), 22.81 (C(*C*H$_3$)$_2$), 26.24 (C(*C*H$_3$)$_2$), 43.42 (*C*(CH$_3$)$_2$), 65.21 (*C*H), 109.89 (Ar*C*H), 118.89 (Ar*C*H), 122.29 (Ar*C*H), 127.21 (Ar*C*H), 139.17 (Ar*C*), 149.40 (Ar*C*); MS (ES+) m/z: 162.12 $(M+1)^+$ (100%), 160.10 (12); MS (ES+) m/z: 162.12 ($(M+H)^+$, 100%). Enantioselectivity determined by ^{1}H-NMR integration in the presence of (R)-2,2,2-trifluoro-1,1-(9-anthryl)-ethanol chiral solvating agent. The optical rotation of this product has never been assigned to the absolute configuration.

6.11. Selected data for ester and anhydride hydrogenation products

2,2,3,3,4,4,4-heptafluoro-1-butanol, 53

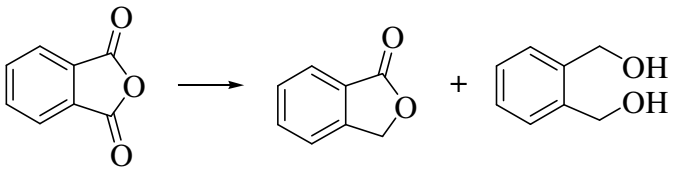


Due to the volatility of the hydrogenated products, this reaction was run in deuterated methanol with yields and purity assessed on the reaction mixture using ^{19}F, ^{1}H and ^{13}C NMR and GCMS.

^{1}H-NMR (300MHz, $CDCl_3$) δ 3.9 (t, 2H, C*H*$_2$); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 60.92 (t, *C*H$_2$, *J* 26Hz), 111.18 (t, *C*F$_2$, *J* 34.8Hz), 117.73 (t, *C*F$_3$, *J* 33.7Hz), 121.53 (t, *C*F$_2$, *J* 33.7Hz); (^{19}F-NMR {^{1}H} (282MHz, $CDCl_3$) of ester -129.39, -121.60, -83.31) ^{19}F-NMR {^{1}H} (282MHz, CDCl3) -131.33, -126.34, -84.86; MS[18] m/z 199.56 (M) (16 %) Deuterium exchange from CD_3OD solvent, 198.56 $(M-1)^-$ (16), 168.47 (100)

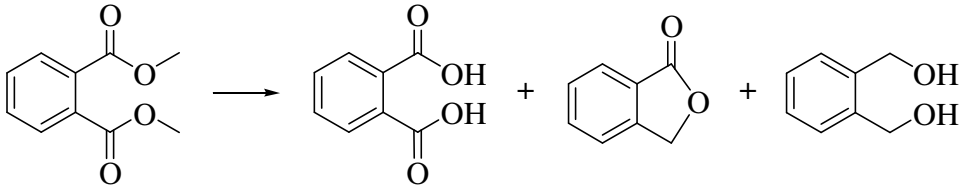
.

Hydrogenation of phthalic anhydride, 48



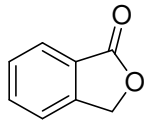
Conversions determined by ^{1}H-NMR comparing with 1,3-dimethyl naphtalene as internal standard. On one of the hydrogenation experiments, phthalide and 1,2-benzendimethanol were isolated, by column chromatography in 10 % and 27 % yield respectively.

Hydrogenation of phthalic acid dimethyl ester, 58



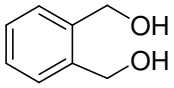
Conversion determined by integration in the ^{1}H-NMR of the methylene protons of the products and methyl esters protons of the starting material (^{1}H-NMR of **58** 3.90 (s, 6H, C*H*$_3$), 7.5-7.8 (m, 4H, ArC*H*).

Phthalide, 49



^{1}H-NMR (300MHz, $CDCl_3$) δ 5.35 (s, 2H, C*H*$_2$), 7.5-8.95 (m, 4H, ArC*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 70.07 (*C*H$_2$), 122.05 (Ar*C*H), 126.21 (Ar*C*H), 129.46 (Ar*C*H), 134.35 (Ar*C*H), 147.12 (Ar*C*), 171.20 (*C*=O); MS (ES+) m/z 135.09 $(M+1)^+$ (25%), 134.08 (40), 106.08 (75), 105.07 (100).

1,2-benzenedimethanol, 51



^{1}H-NMR (300MHz, $CDCl_3$) δ 4.58 (s, 4H, C*H*$_2$), 5.01 (s, 1H, O*H*), 7.1-7.4 (ArC*H*); ^{13}C-NMR (75.5MHz, $CDCl_3$) δ 64.75 (*C*H$_2$), 129.04 (Ar*C*H), 130.16 (Ar*C*H)140.10 (Ar*C*).

6.12. References

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APPENDIX I

Synthesis of a P^N ligand for Ir catalysed enantioselective imine hydrogenation

1. Introduction. Asymmetric imine hydrogenation

One of the most direct and efficient methods to prepare chiral amines is using asymmetric imine hydrogenation. A number of efficient asymmetric catalysts for reduction of alkenes and ketones are unfortunately ineffective for the hydrogenation of imine functional groups. Currently, only a few efficient chiral catalytic systems are available for hydrogenation of some imines. The Ir complex $\{Ir(COD)(Py)PCy_3\}^+$ (Figure AI.1) was reported by Crabtree as a highly active achiral catalyst for hydrogenation of tri- and tetra- substituted olefins.[1]

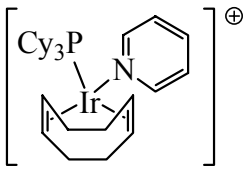


Figure AI.1. Crabtree's catalyst

An obvious extension to Crabtree's catalyst is to prepare enantiomerically pure analogues that combine the high reactivity with enantioselectivity. The development of efficient chiral P^N ligands for Ir-catalyzed asymmetric hydrogenation was neglected until ligand in Figure AI.2 was applied by Pfaltz and co-workers for Ir-catalyzed hydrogenation of trisubstituted olefins.[2]

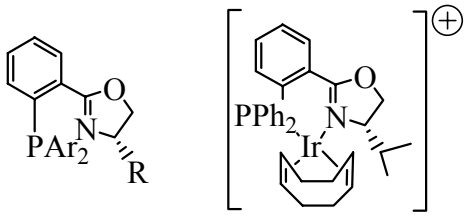


Figure AI.2. P^N ligand and the Ir catalyst used by Pfaltz.

Since, Ir catalyst tend to be better for hydrogenation of highly substituted species, the Pfaltz analogue of Crabtree's catalyst was tested in imine hydrogenation (Figure AI.3) and found to be a good asymmetric catalyst for some acyclic imines. Other imine substrates gave

disappointing selectivity. These research concluded that the search for other chiral P^N ligand systems is highly pertinent. Hydrogenation of imines has remained a difficult challenge.

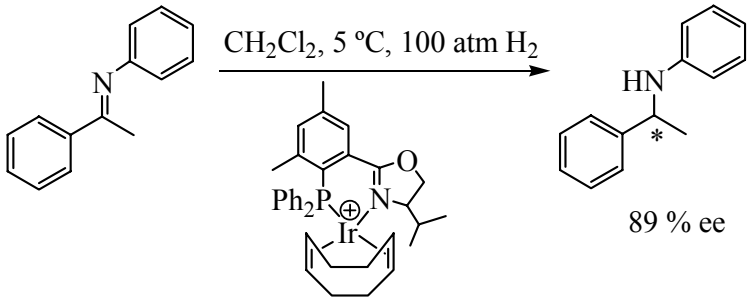


Figure AI.3

The Ir catalyst developed by Pfaltz suggests a bright future for chiral ligand containing P and N donor atoms in asymmetric imine hydrogenation. We wished to develop new chiral phosphines that possess an auxiliary nitrogen donor.

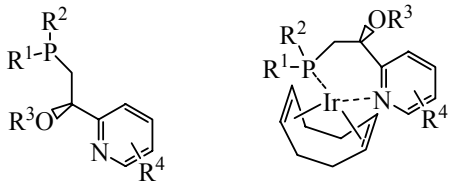
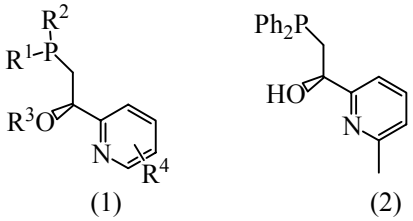


Figure AI.4

3. Results and discussion

3.1. Synthesis of the P^N ligand

Our first target ligands have the general structure (1) shown in Figure AI.5. The first ligand to be studied is shown on the right (2).



(1) (2)

Figure AI.5. General structure (1) and a P^N ligand (2)

The methyl phosphine borane (4) was synthesized directly from diphenylmethylphosphine (3) and borane·THF. Compound (4) was metalated with *sec*-BuLi in THF at -78ºC. The carbanion generated could then react with various electrophiles.[3] The reaction with 6-methyl-2-pyridinecarboxaldehyde (6) (Figure AI.6) gives, after column chromatography, the new phosphine borane (7), in an unoptimised yield of 50 % for the 2 steps.

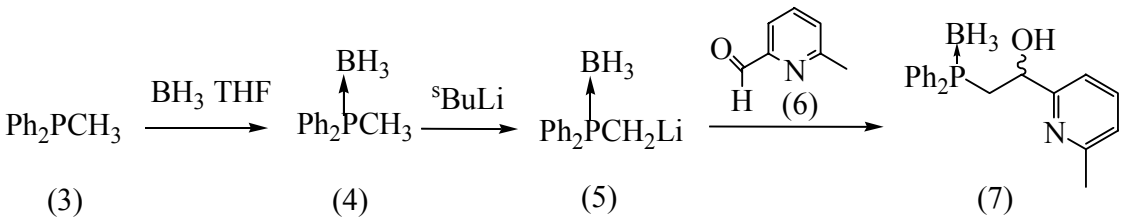


Figure AI.6. Synthesis of alcohol containing phosphine

3.2. Deprotection

The boronato group can be removed on treatment with a large excess of an amine such as diazabicyclooctane 1,4-[2,2,2] (DABCO) (Figure AI.7). This reaction is easily monitored using ^{31}P spectroscopy [(7), δ_P = 14.02 ppm; (2), δ_P = -21.70 ppm].

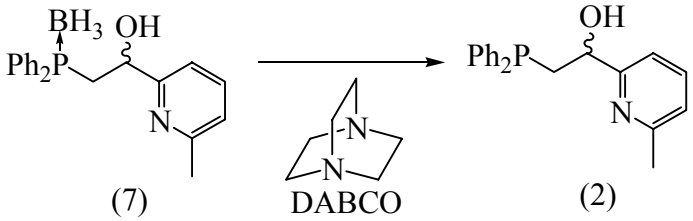


Figure AI.7. Deprotection of phosphine borane

3.3. Resolution

3.3.1. We next considered how to make ligand (2) in enantiomerically pure form. A method to determine the ee of the ligand was required. The resolution of (2) was tried using optically active Pd (II) complex. Commercially available chiral palladium dimers have been used for both determining ee of chiral phosphines and for their resolution.[4] The reaction of ligand (2) with palladium dimer in dichloromethane gave three main products by ^{31}P NMR spectrum (δ_P = 28.4, 30.5, 32.6). Electrospray mass spectroscopy gave a good agreement for the expected mass and isotope pattern for the complex. This suggests, along with literature precedent, that the peaks correspond to the diastereoisomers and positional isomers possible for complexes of type (8). However, the two diastereomers could not be separated in our first attempts.

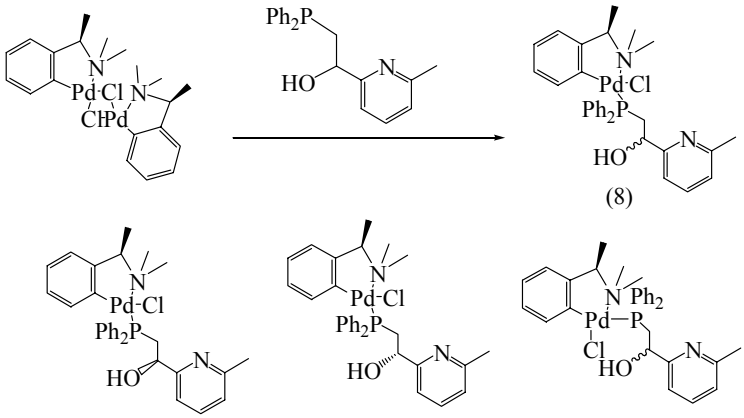


Figure AI.8. Reaction of Ligand (2) with (+) Di-µ-chlorobis{2-(1-(dimethylamino)ethyl)phenyl-C,N}

3.3.2. An empirically derived correlation of configuration and NMR chemical shifts for diastereomeric mandelate, Mosher's esters has been reported.[5] The correlations involve the relative chemical shifts of the proton resonances from the groups attached to the carbonyl carbon of the diastereomeric esters. We hope that this should be applicable for determining ee of our ligand (Figure AI.9). The reaction of the phosphine borane (7) with Mosher's acid chloride (using pyridine as base) was complicated by deboronation, as indicated by the formation of sharp singlets up field of (7) in the ^{31}P NMR spectra and accompanying sharp singlets in the phosphine oxide region. Examination of the ^{19}F, ^{1}H and ^{31}P NMR spectra does show that the major products are probably Mosher's esters of the free phosphine and its oxide as does the presence of an IR band at 1750 cm^{-1}. Although the diastereoisomers of the major product do show individual resonances in the ^{31}P NMR spectra, the air and moisture sensitivity of the deboronated product, along with the presence of side reactions led us to abandon this approach.

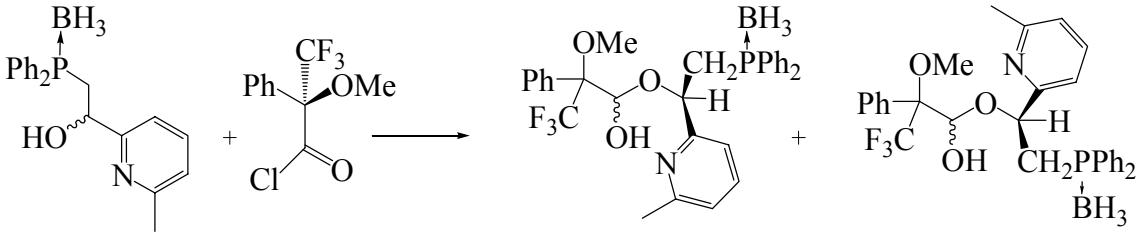


Figure AI.9

3.3.3. Since the NMR spectrum of the Pd complex (8) was complicated by the presence of other isomers, and the Moshers ester was impure, we thought to try to determine the ee of the phosphine containing alcohol using a lanthanide shift reagent. For this we use the $[Eu(hfc)_3]$.[6] It reversibly forms adducts with alcohols that can permit us to determine ee. The proton NMR resonances began to overlap at the point at which the two enantiomers could be observed. However, a ^{13}C NMR spectrum did show the presence of each enantiomer.

3.4. Ketone synthesis

Although other possibilities for resolution exist, it was decided to try to reprepare the alcohol containing phosphine (7) in an enantioselective manner. It seemed that the most straight forward method to do this would be to prepare the ketone derivative, and reduce this in an enantioselective manner. We needed to utilise a mild oxidising agent that would not affect other parts of the molecule.

The selective and efficient oxidation of the secondary alcohol to a ketone is possible by periodinane.[7] The reaction avoids some of the difficulties encountered in using other

methods for the oxidation of alcohols such as long reaction times, difficult workup procedures, or the need to use a large excess of the oxidising agent. It was pleasing to find that alcohol (7) could be cleanly converted into ketone (9) in 70 % isolated yield. This compound was also fully characterised using spectroscopy.

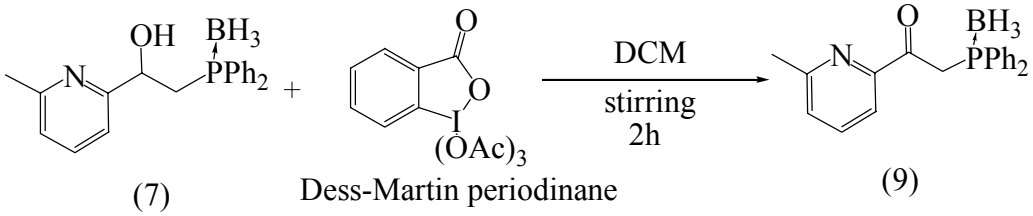


Figure AI.10. Oxidation by Dess-Martin periodinane

3.5. Ketone reduction

3.5.1. Now that we had the ketone, we wanted to reduce it enantioselectively to produce the chiral ligand in enantiomericaly form. The resolution was attempted using a chiral derivative of Lithium Aluminium Hydride, (S)-BINAL-H.[8] However, inspection of ^{31}P NMR and IR spectra reveal that there is no reaction (Figure AI.11).

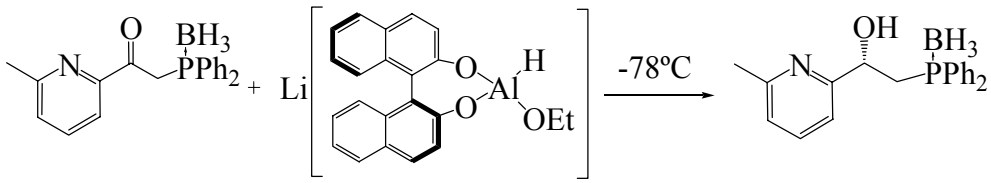


Figure AI.11

3.5.2. Another procedure that produces enantiomerically enriched alcohols from ketones involves the stereoselective Ru(BINAP) catalyst formed by the combination of $[Ru(C_6H_6)Cl_2]_2$ and (S)-BINAP in DMF. We saw that this reaction gives several products and at this stage it is not clear if some of this is our product. However, this preliminary result suggests that this method may prove troublesome for reduction of our ketone.

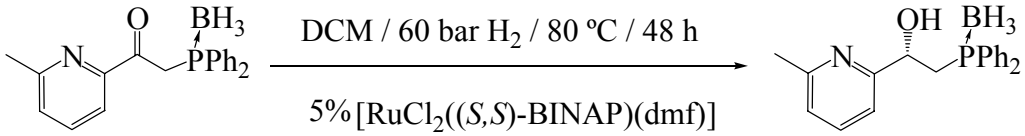


Figure AI.11

3.6. Some bad news...

There were still many other strategies to pursue regarding synthesis of this ligand in enantiomerically pure form. However, a paper published in early 2004 in Angewandte Chemie came to our attention during the progress of our research in May 2004.[9] Andreas Pfaltz research group, whose work on chiral analogues of Crabtree's catalyst inspired this

project had also been investigating the general ligand structure described in the previous pages. They found that ketone (9) (identical to our ketone yet without the 6 methyl group) could be reduced selectively by the chiral borane reducing agent, Ipc_2BCl to give an alcohol that was protected by a silicon protecting group and used as a ligand for Ir catalysed hydrogenation of highly substituted alkenes. The catalysts formed are very efficient, giving high reactivity and ee's up to 87 %. Although no results for imine hydrogenation were reported, if was felt that different new ligand structures based on amine containing phosphines should be pursued in St. Andrews. Consequently this aspect of my research was set aside.

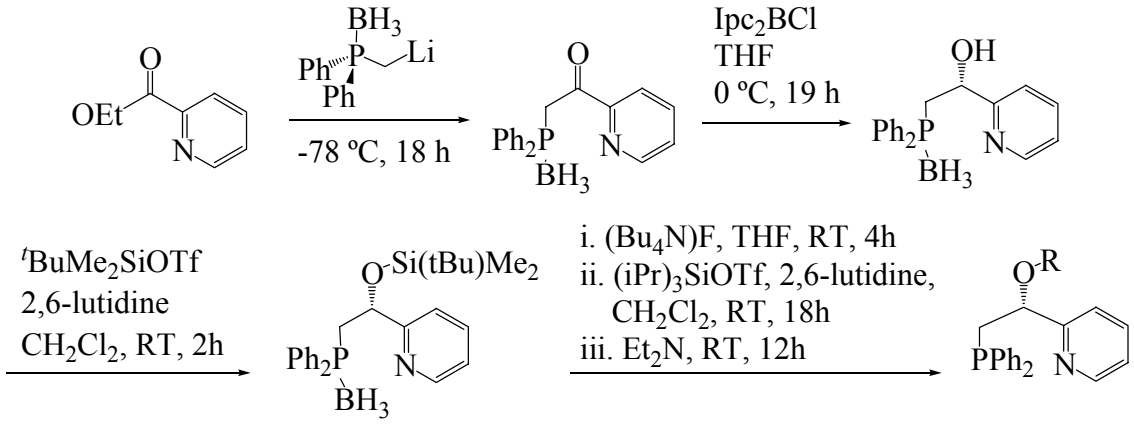


Figure AI.12

4. Conclusions

The aim was the development of new chiral phosphine ligands that might be efficient for metal-catalysed imine hydrogenation to obtain chiral amines. Phosphine borane lithiation chemistry can be use to prepare a novel phosphine containing alcohol and pyridine groups. The racemic phosphine alcohol ligand developed was tested in imine hydrogenation but it didn't work efficiently in our first attempts. It should also be noted that chiral P^N ligands have found important applications in other asymmetric reactions. NMR methods to determine enantiomeric excess of the phosphine were used.

5. Experimental

Synthesis of Diphenylmethylphosphine-borane[3] (4)

This compound was prepared by a modification of the literature procedure. A solution of methyldiphenylphoshine (0.957 g, 4.78 mmol) in dry THF was cooled to 0 ºC under nitrogen. To this solution, borane-THF complex (6.4 ml of 1M solution, 1.3 eq) was added. After stirring at 0 ºC for one day, the solvent was removed in vacuum. The residual powder was passed through a short column of silica gel eluting with a solution diethyl ether/petroleum

ether 40/60. The product was left in the fridge for some hours to give a white solid (0.8 g, 78 % yield). ^{31}P NMR (121.4 MHz, $CDCl_3$) δ_P 11.27; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.5-1.1 (3H, BH_3), 1.69 (3H, d, $^2J_{H-P}$ 10.21Hz, CH_3), 7.23 – 7.56 (10H, m, Ar-H).

Synthesis of compound (7)

A solution of diphenylmethylphosphine-borane (0.64 g, 2.9 mmol) in dry THF (6 ml) was cooled to -78 ºC under N_2, and *sec*-butyllithium (3.57 ml of 1.3 M solution in cyclohexane/hexane 92/8, 1.6eq) was added to the solution. After keeping the temperature for 2 h and stirring the generated carbanion was added to a solution of 6-methyl-2-pyridinecarboxaldehyde (0.36 g, 2.9 mmol) in dry THF and stirred overnight. A work up in CH_2Cl_2 and NH_4Cl solution, followed by removal of solvent from the dried ($MgSO_4$) organic fraction and a column on silica gel (diethyl ether/petroleum ether 60:40) to obtain the product in a purified form (0.54 g, 55.5 %). ^{31}P NMR (121.4 MHz, $CDCl_3$) δ_P 14.02; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.80-1.20 (3H, BH_3) 2.40 (3H, s, CH_3), 2.72 (2H, m, CH_2), 4.04 (1H, s, OH), 5.05 (1H, td, $^3J_{H-H}$=9.21Hz, $^3J_{H-H}$=3.6Hz, CH), 6.88 - 7.07 (3H, dd, Py-H), 7.34 – 7.64 (10H, m, Ar-H); ^{13}C (75.45MHz, $CDCl_3$) δ_C 24.00 (CH_3), 34.25 (CH_2), 67.60 (CH), 116.52-136.09 (Arx2, Py); IR ν_{max}/cm^{-1} ν_{CN}= 1593; ν_{OH}=3250; MS [ES-] 334.2 (M-H).

Synthesis of (2)

(5.45 g, 30 eq) of DABCO (1,4-Diazabicyclo (2,2,2) octane) are added to a solution of (0.54 g, 1.6 mmol) of (7) in THF. The mixture was heating at 50 ºC for 8 h under N_2 and stirring. The product was passed down a column of silica gel (ether acetate/petroleum ether 95:5) to obtain the product in a purified form (0.29 g, 56.4 %). The ligand is sensitive to air. ^{31}P NMR (121.4 MHz, $CDCl_3$) δ_P -21.70; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.10 (2H, s, CH_2), 2.45 (3H, m, CH_3), 4.36 (1H, s, CH) 4.74 (1H, s, OH), 6.90-7.44 (13H, m, Py-H and Ar-H). MS [EI+] 321 (M).

Synthesis of (8)

(+) Di-μ-chlorobis {2-(dimethylamino)ethyl]phenyl-C,N} dipalladium[4] (132 mg, 0.227 mmol) are added to a solution of (2) (146 mg, 0.455 mmol). ^{31}P NMR (121.4 MHz, $CDCl_3$) δ_P 28.2 ppm, 30.5 ppm, 36.4 ppm, 36.8 ppm (4 isomers); MS [EI+] 575.1 (M-Cl). Good agreement with expected isotope pattern.

Synthesis of (9)[6]

A solution of (7) (0.5 g, 1.5 mmol) in 5 ml DCM was added to a solution of Dess-Martin periodinane (0.70 g, 1.65 mmol) in 6.7 ml DCM with stirring. After 40min the

homogenous reaction mixture was diluted with 50 ml of ether, and the resulting suspension of iodinane was added to 20 ml of 1.3 M NaOH to hydrolyze it to the water-soluble 2-iodosobenzoate. After the mixture was stirring for 20min, the ether layer was extracted with 20 ml of 1.3 M NaOH and with 25 ml of water. The ether was removed under vacuum. The residual powder was passed through a column of silica gel eluting with a solution diethyl ether/petroleum ether 60/40 to obtain the product in a purified form (0.35 g, 70 %). ^{31}P NMR (121.4 MHz, $CDCl_3$) δ_P 17.89; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.41 (3H, s, CH_3) 4.30 – 4.34 (2H, d, CH_2) 7.14 - 7.07 (1H, d, Py) 7.50 – 7.55 (1H, t, Py) 7.61- 7.64 (1H, d, Py) 7.28 – 7.71 (10H, m, Ar-H); ^{13}C (75.45MHz, $CDCl_3$) δ_C 20.9 (CH_3), 39 (CH_2), 158.16 (C=O), 128-137 (Ar); IR ν_{max}/cm^{-1} $\nu_{C=O}$=1693, $\nu_{C=N}$=1450; MS [ES+] 334.2 (M^+).

Resolution of (7) using Mosher's esters[5]

Dry pyridine (0.9ml, 900mg), α-methoxy-α-trifluoromethylphenylacetate (105mg, 0.08ml, 0.42mmol), DCM (0.9ml) and the alcohol (7) (0.1g, 0.3mmol) was added to a round bottom flask in this order. The reaction was stirred at room temperature overnight. The reaction mixture was worked up with a saturated solution of Na_2SO_4 in water and DCM as quick as possible to avoid the oxidation. The solvent was removed in the rotary evaporator to give the crude product. IR ν_{max}/cm^{-1} $\nu_{C=O(Ester)}$=1745.9. ^{31}P NMR show that the borane group has been removed and both diastereomers of the phosphine are accompanied by both diastereomers of the phosphine borane.

Resolution of (7) using [Eu(hfc)$_3$][5]

Tris (3- [Heptafluoropropyl- hydroxylmethylene]-d- camphorate) Europium (II) (32.2mg, 0.027mmol) are added to a solution of (7) (5mg, 0.015mmol) in an NMR tube. All the peaks in the proton and carbon NMR shared paramagnetic shifts. ^{13}C NMR of (7) (75.45MHz, $CDCl_3$) one of the aryl carbons in (7) shows 2 singlets δ_C = 122.536, 117.866; ^{13}C NMR of (7)+Eu complex (75.45MHz, $CDCl_3$) shows both of these split into 2 peaks δ_C=120.23-120.10 (d), 116-115.85 (d).

Reduction of the ketones (9) to (2) using BINAL-H[8]

To a solution of BINAL-H (0.225g, 0.72 mmol) in THF it was added the ketone (9) (80mg, 0.24mmol). The mixture was cooled to -78 ºC under N_2 and leave overnight under stirring. An extraction was necessary. After the solvent was remove under vacuum. The reaction didn't work.

Ketone reduction using $RuCl_2$(BINAP)

A solution of [Ru(BINAP)Cl_2(solvent)] (6 ml, 0.078 mmol) and (9) (50 mg, 0.156 mmol) in 10 ml of DCM was placed in the autoclave and leave for 48 h under 60 bar of H_2 at 80 ºC.

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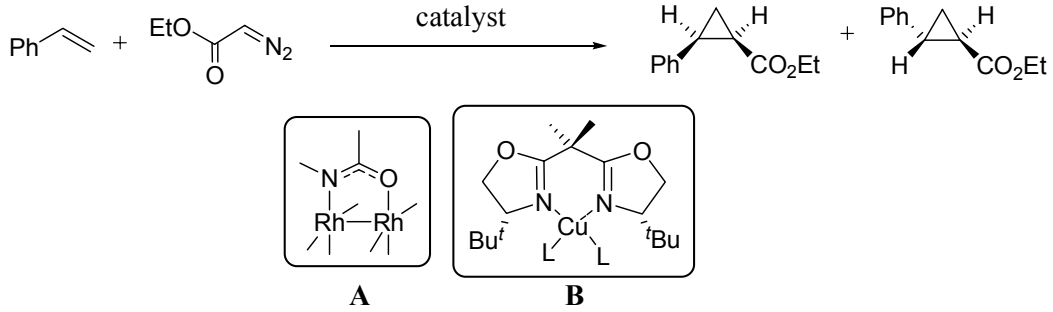
APENDIX II

Cyclopropanation

1. Introduction

We briefly examined the potencial of complex **33** in styrene cyclopropanation althought with modest results.

The cyclopropane moety is common in the synthesis of complex molecules and in medicinal chemistry due to a unique combination of reactivity and structural properties[1-3]. These properties have made the preparation of cyclopropanes an attractive target for new methodology development. Despite the many processes for the synthesis of functionalized cyclopropanes, there are surprisingly few general catalytic enantioselective methods.[4] The most commonly employed transition metals are rhodium and copper. Among the di-rhodium(II) catalysts studied, the highest levels of stereocontrol are observed with di-rhodium(II) carboxamidates (Figure AII. 1), 36 % de.[5] When compared to the levels of stereocontrol achieved with copper catalysis (50 % de), rhodium-mediated intermolecular cyclopropanation reactions are inferior. As with dirhodium(II) complexes, copper(I) and copper(II) catalysts are very versatile reagents due to the number of different complexes that can be formed. Excellent levels of stereoselectivity have been achieved using a copper metal-bis(oxazoline) complex protocol.



A **B**

Figure AII. 1

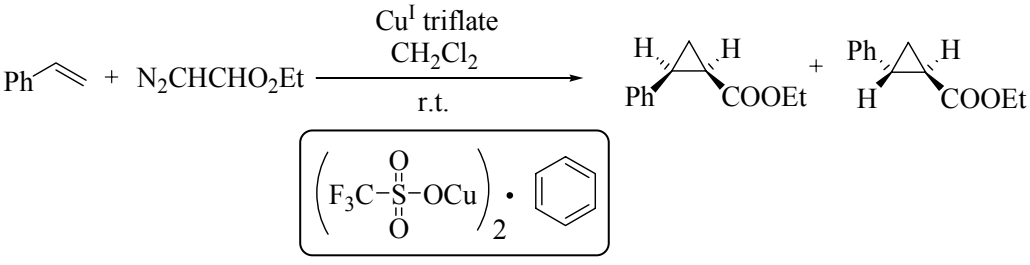
Table AII. 1[5]

R	catalyst	yield / %	ratio (cis:trans)	de %
Et	$RuCl_2(PPh)_3$	80	44:56	12
Et	**A**	73	32:68	36

Et	$CuCl(P(OPh)_3)$	85	28:72	44
Et	**B**	80	25:75	50
^{t}Bu	**B**	73	20:80	60
BHT	**B**	85	6:94	88

2. Results

The cyclopropanation reaction with Cu(I) triflate was carried out affording the expected 44 % dr.



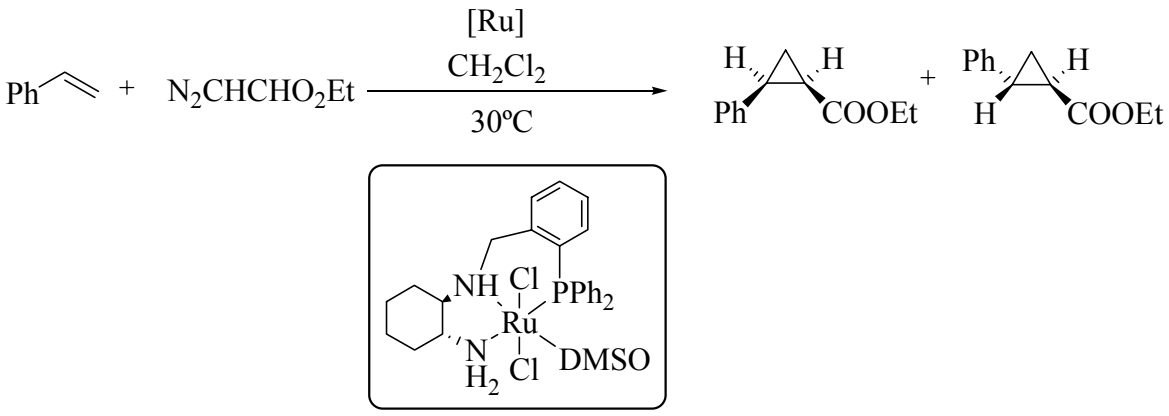
C

Figure AII. 2

Table AII. 2

Diastereoisomers	Conversion by ^{1}H NMR	Isolated Yield	ee
Trans	72%	71%	0%
Cis	28%	23%	0%

The ruthenium catalyst **33** under the same reaction condition as the copper catalyst gives a similar diatereoisomeric ratio (2.6:1). As high levels of enantioselectivity were not observed, studies in this reaction were abandoned.



33

Figure AII. 3

Table AII. 3

Diastereoisomers	Conversion by ^{1}H NMR	Isolated Yield	ee
Trans	73%	27%	3%
Cis	27%	4%	7%

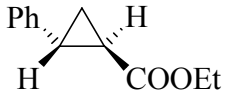
3. Experimental

3.1 General procedure for cyclopropanation

A 25 ml Schlenk flask containing a small magnetic stir bar was subject in to three pump-purge cycles to remove any air in hose and replace it with nitrogen. The metal complex was added, (copper (I) triflate (0.015 mmol, 0.75 eq, 7.6 mg) or metal complex **33** (0.015 mmol, 0.75 eq, 9.6 mg)). 1.5 ml of anhydrous methylene chloride were injected into the flask through the septum once the flask was completely under nitrogen. After 25min, the olefin was added (styrene, 8.7 mmol, 435 eq) via syringe. The reaction mixture was allowed to react for another 30 minutes. In the meantime, in a separate 10ml round bottom flask that has been purged with nitrogen a solution of the diazo compound was prepared by adding 1.5 ml of methylene chloride to ethyldiazoacetate (0.86 mmol, 0.09 ml, 46 eq). The diazo solution was added to the Schlenk flask over a period of 16h and them the mixture was stirred overnight. The Schlenk was open once the reaction has been completed. A pipette was plugged with cotton and two centimetres of neutral alumina to form a column and the reaction mixture was passed through the column. The flask was rinsed several times with methylene chloride and the washings run through the column. The resulting solution was rotavaporated and once the solvent has been removed a sample was prepared for the HPLC analysis. The reaction products were purified by column chromatography using silica gel and Hexane:EtOAc (15:1) as eluent.

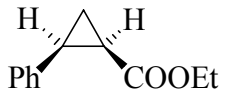
3.2. Selected data from cyclopropnantion products

(1*S*)-*trans*-2-phenyl-cyclopropanecarboxylic acid ethyl ester



^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.18 (t, *J* 7.2Hz, 3H, C*H*$_3$), 1.50 (m, 1H, C*H*), 1.80 (m, 1H, C*H*), 2.42 (m, 1H, C*H*), 4.07 (q, *J* 7.2Hz, 2H, C*H*$_2$), 6.9-7.2 (m, 5H, ArCH).

(1*S*)-*cis*-2-phenyl-cyclopropanecarboxylic acid ethyl ester



^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.88 (t, *J* 7.1Hz, 3H, C*H*$_3$), 1.23 (m, 1H, C*H*), 1.62 (m, 1H, C*H*), 2.00 (m, 1H, C*H*), 2.48 (q, *J* 8.8Hz, 2H, C*H*$_2$), 3.78 (q, *J* 7.2Hz, 2H, C*H*$_2$), 7.1-7.2 (m, 5H, ArC*H*).

4. References

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X-Ray Crystallographic data for [RuCl$_2$(P^N^N)DMSO], 33

Figure AIII.1. ORTEP diagram of Ru(II)-complex **33** showing the atom-labelling scheme.

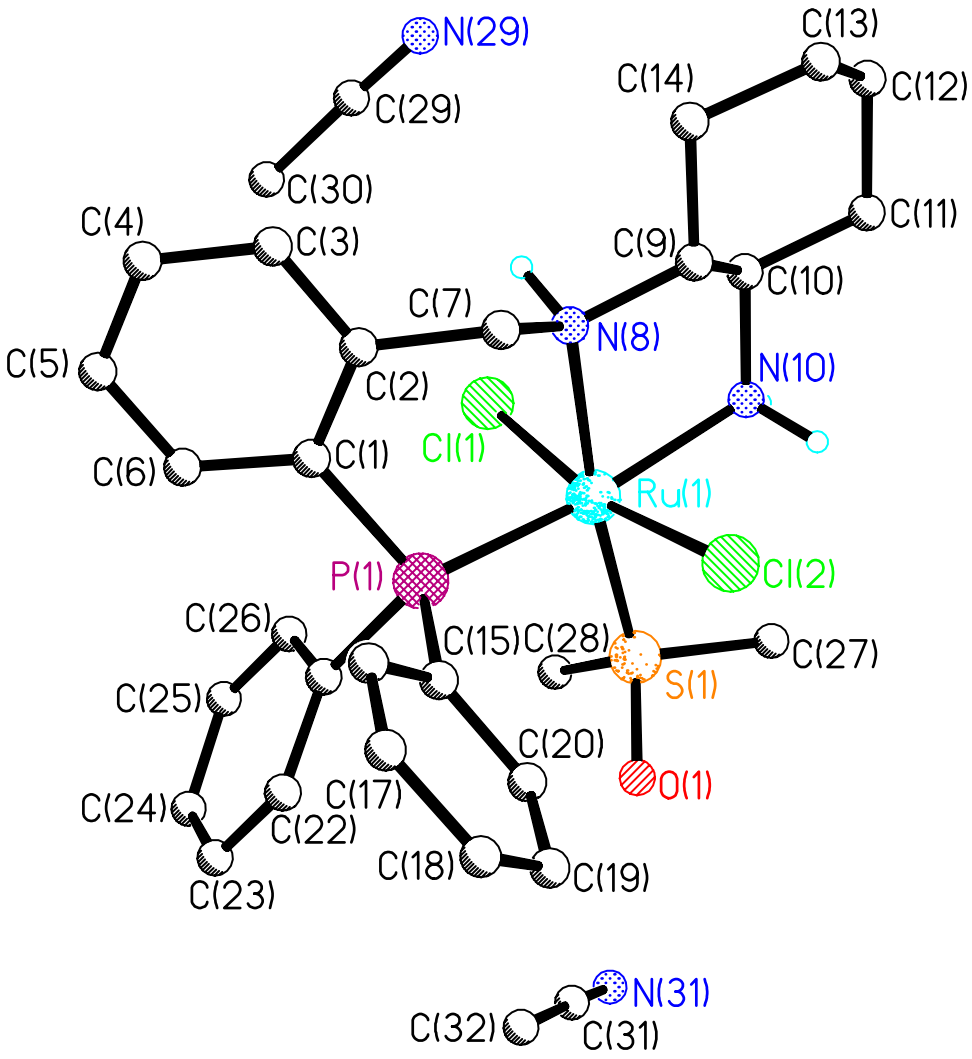

Table AIII.1. Crystal data and structure refinement for Ru (II) complex 33.

Empirical formula	$C_{31}H_{41}Cl_2N_4OPRuS$	
Formula weight	720.68	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 9.6872(13) Å	□= 90°.
	b = 14.333(2) Å	□= 90°.
	c = 24.351(4) Å	□ = 90°.
Volume	3381.0(9) $Å^3$	
Z	4	
Density (calculated)	1.416 Mg/m^3	
Absorption coefficient	0.761 mm^{-1}	
F(000)	1488	
Crystal size	0.0300 x 0.0300 x 0.1000 mm^3	
Theta range for data collection	2.26 to 25.32°.	
Index ranges	-9<=h<=11, -10<=k<=17, -29<=l<=29	
Reflections collected	20813	
Independent reflections	5997 [R(int) = 0.0472]	
Completeness to theta = 25.32°	98.6 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.8093	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5997 / 3 / 386	
Goodness-of-fit on F^2	1.133	
Final R indices [I>2sigma(I)]	R1 = 0.0420, wR2 = 0.0683	
R indices (all data)	R1 = 0.0531, wR2 = 0.0735	
Absolute structure parameter	-0.01(3)	
Largest diff. peak and hole	0.880 and -0.470 $e.Å^{-3}$	

Table AIII.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for complex 33. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Ru(1)	8824(1)	1835(1)	813(1)	13(1)
Cl(1)	6334(1)	1774(1)	824(1)	17(1)
Cl(2)	11249(1)	2203(1)	772(1)	17(1)
P(1)	9071(1)	885(1)	1564(1)	16(1)
C(1)	8283(4)	1420(3)	2174(2)	18(1)
C(2)	8430(4)	2391(3)	2255(2)	17(1)
C(3)	7791(4)	2806(4)	2712(2)	24(1)
C(4)	7070(4)	2268(4)	3089(2)	27(1)
C(5)	6938(5)	1319(4)	3021(2)	33(1)
C(6)	7528(5)	902(3)	2561(2)	24(1)
C(7)	9263(4)	3003(3)	1865(2)	21(1)
N(8)	8609(3)	3055(3)	1327(2)	16(1)
C(9)	9011(4)	3896(3)	994(2)	17(1)
C(10)	8272(4)	3820(3)	449(2)	17(1)
N(10)	8624(4)	2905(2)	196(2)	12(1)
C(11)	8565(5)	4626(3)	63(2)	23(1)
C(12)	8269(5)	5563(4)	341(2)	29(1)
C(13)	9025(4)	5640(3)	891(2)	28(1)
C(14)	8665(5)	4835(3)	1273(2)	26(1)
C(15)	10853(4)	660(3)	1797(2)	16(1)
C(16)	11307(4)	811(3)	2325(2)	19(1)
C(17)	12657(4)	618(3)	2475(2)	21(1)
C(18)	13579(4)	272(3)	2084(2)	23(1)
C(19)	13135(4)	123(3)	1556(2)	25(1)
C(20)	11785(4)	300(3)	1408(2)	20(1)
C(21)	8317(4)	-295(3)	1572(2)	18(1)
C(22)	9070(5)	-1088(3)	1713(2)	25(1)
C(23)	8473(4)	-1967(4)	1705(2)	29(1)
C(24)	7104(5)	-2071(3)	1559(2)	28(1)
C(25)	6334(5)	-1293(3)	1436(2)	31(1)
C(26)	6937(4)	-419(4)	1443(2)	28(1)
O(1)	10248(3)	20(2)	267(1)	28(1)
S(1)	9079(1)	680(1)	207(1)	17(1)
C(27)	9219(5)	1132(4)	-471(2)	26(1)
C(28)	7615(5)	-33(4)	91(3)	44(2)
N(29)	5133(5)	4248(4)	1775(2)	43(1)
C(29)	4681(5)	3530(4)	1845(2)	29(1)
C(30)	4152(5)	2587(4)	1934(2)	40(2)
N(31)	9483(5)	-2179(4)	-546(3)	58(2)
C(31)	10058(6)	-2153(4)	-142(3)	40(2)
C(32)	10820(6)	-2140(4)	370(2)	43(2)

Table AIII.3. Bond lengths [Å] and angles [°] for complex 33.

Ru(1)-N(10)	2.155(4)	C(15)-C(16)	1.376(6)
Ru(1)-N(8)	2.160(4)	C(15)-C(20)	1.407(6)
Ru(1)-S(1)	2.2326(12)	C(16)-C(17)	1.386(6)
Ru(1)-P(1)	2.2912(13)	C(16)-H(16A)	0.9500
Ru(1)-Cl(2)	2.4096(10)	C(17)-C(18)	1.397(6)
Ru(1)-Cl(1)	2.4137(9)	C(17)-H(17A)	0.9500
P(1)-C(1)	1.838(5)	C(18)-C(19)	1.371(7)
P(1)-C(21)	1.843(5)	C(18)-H(18A)	0.9500
P(1)-C(15)	1.846(4)	C(19)-C(20)	1.381(6)
C(1)-C(6)	1.406(6)	C(19)-H(19A)	0.9500
C(1)-C(2)	1.413(6)	C(20)-H(20A)	0.9500
C(2)-C(3)	1.404(6)	C(21)-C(26)	1.386(6)
C(2)-C(7)	1.525(6)	C(21)-C(22)	1.393(6)
C(3)-C(4)	1.387(7)	C(22)-C(23)	1.386(6)
C(3)-H(3A)	0.9500	C(22)-H(22A)	0.9500
C(4)-C(5)	1.376(7)	C(23)-C(24)	1.381(6)
C(4)-H(4A)	0.9500	C(23)-H(23A)	0.9500
C(5)-C(6)	1.391(7)	C(24)-C(25)	1.375(6)
C(5)-H(5A)	0.9500	C(24)-H(24A)	0.9500
C(6)-H(6A)	0.9500	C(25)-C(26)	1.382(6)
C(7)-N(8)	1.456(6)	C(25)-H(25A)	0.9500
C(7)-H(7A)	0.9900	C(26)-H(26A)	0.9500
C(7)-H(7B)	0.9900	O(1)-S(1)	1.483(3)
N(8)-C(9)	1.505(5)	S(1)-C(28)	1.771(5)
N(8)-H(8N)	0.9799(11)	S(1)-C(27)	1.778(5)
C(9)-C(10)	1.511(6)	C(27)-H(27A)	0.9800
C(9)-C(14)	1.545(6)	C(27)-H(27B)	0.9800
C(9)-H(9A)	1.0000	C(27)-H(27C)	0.9800
C(10)-N(10)	1.488(6)	C(28)-H(28A)	0.9800
C(10)-C(11)	1.516(6)	C(28)-H(28B)	0.9800
C(10)-H(10A)	1.0000	C(28)-H(28C)	0.9800
N(10)-H(10B)	0.9800(11)	N(29)-C(29)	1.131(6)
N(10)-H(10C)	0.9800(11)	C(29)-C(30)	1.461(7)
C(11)-C(12)	1.531(6)	C(30)-H(30A)	0.9801
C(11)-H(11A)	0.9900	C(30)-H(30B)	0.9801
C(11)-H(11B)	0.9900	C(30)-H(30C)	0.9801
C(12)-C(13)	1.530(7)	N(31)-C(31)	1.130(8)
C(12)-H(12A)	0.9900	C(31)-C(32)	1.449(8)
C(12)-H(12B)	0.9900	C(32)-H(32A)	0.9800
C(13)-C(14)	1.522(6)	C(32)-H(32B)	0.9800
C(13)-H(13A)	0.9900	C(32)-H(32C)	0.9800
C(13)-H(13B)	0.9900	N(10)-Ru(1)-N(8)	79.62(13)
C(14)-H(14A)	0.9900	N(10)-Ru(1)-S(1)	94.37(10)
C(14)-H(14B)	0.9900	N(8)-Ru(1)-S(1)	173.85(11)

N(10)-Ru(1)-P(1)	171.14(10)	C(9)-N(8)-H(8N)	102(3)
N(8)-Ru(1)-P(1)	91.67(10)	Ru(1)-N(8)-H(8N)	113(3)
S(1)-Ru(1)-P(1)	94.30(5)	N(8)-C(9)-C(10)	107.0(3)
N(10)-Ru(1)-Cl(2)	84.42(10)	N(8)-C(9)-C(14)	113.9(3)
N(8)-Ru(1)-Cl(2)	86.64(9)	C(10)-C(9)-C(14)	110.2(4)
S(1)-Ru(1)-Cl(2)	91.53(4)	N(8)-C(9)-H(9A)	108.5
P(1)-Ru(1)-Cl(2)	93.54(4)	C(10)-C(9)-H(9A)	108.5
N(10)-Ru(1)-Cl(1)	86.77(10)	C(14)-C(9)-H(9A)	108.5
N(8)-Ru(1)-Cl(1)	85.82(9)	N(10)-C(10)-C(9)	108.5(3)
S(1)-Ru(1)-Cl(1)	95.18(4)	N(10)-C(10)-C(11)	111.9(4)
P(1)-Ru(1)-Cl(1)	94.24(4)	C(9)-C(10)-C(11)	113.6(4)
Cl(2)-Ru(1)-Cl(1)	169.31(4)	N(10)-C(10)-H(10A)	107.5
C(1)-P(1)-C(21)	102.1(2)	C(9)-C(10)-H(10A)	107.5
C(1)-P(1)-C(15)	102.3(2)	C(11)-C(10)-H(10A)	107.5
C(21)-P(1)-C(15)	101.9(2)	C(10)-N(10)-Ru(1)	111.0(3)
C(1)-P(1)-Ru(1)	110.69(15)	C(10)-N(10)-H(10B)	112(3)
C(21)-P(1)-Ru(1)	120.88(16)	Ru(1)-N(10)-H(10B)	106(3)
C(15)-P(1)-Ru(1)	116.57(14)	C(10)-N(10)-H(10C)	110(3)
C(6)-C(1)-C(2)	118.6(5)	Ru(1)-N(10)-H(10C)	118(3)
C(6)-C(1)-P(1)	122.5(4)	H(10B)-N(10)-H(10C)	100(4)
C(2)-C(1)-P(1)	118.9(4)	C(10)-C(11)-C(12)	111.1(4)
C(3)-C(2)-C(1)	118.9(5)	C(10)-C(11)-H(11A)	109.4
C(3)-C(2)-C(7)	119.0(4)	C(12)-C(11)-H(11A)	109.4
C(1)-C(2)-C(7)	122.1(4)	C(10)-C(11)-H(11B)	109.4
C(4)-C(3)-C(2)	120.7(5)	C(12)-C(11)-H(11B)	109.4
C(4)-C(3)-H(3A)	119.6	H(11A)-C(11)-H(11B)	108.0
C(2)-C(3)-H(3A)	119.6	C(13)-C(12)-C(11)	111.1(4)
C(5)-C(4)-C(3)	121.1(5)	C(13)-C(12)-H(12A)	109.4
C(5)-C(4)-H(4A)	119.5	C(11)-C(12)-H(12A)	109.4
C(3)-C(4)-H(4A)	119.5	C(13)-C(12)-H(12B)	109.4
C(4)-C(5)-C(6)	118.9(5)	C(11)-C(12)-H(12B)	109.4
C(4)-C(5)-H(5A)	120.5	H(12A)-C(12)-H(12B)	108.0
C(6)-C(5)-H(5A)	120.6	C(14)-C(13)-C(12)	111.7(4)
C(5)-C(6)-C(1)	121.7(5)	C(14)-C(13)-H(13A)	109.3
C(5)-C(6)-H(6A)	119.1	C(12)-C(13)-H(13A)	109.3
C(1)-C(6)-H(6A)	119.1	C(14)-C(13)-H(13B)	109.3
N(8)-C(7)-C(2)	111.1(3)	C(12)-C(13)-H(13B)	109.3
N(8)-C(7)-H(7A)	109.4	H(13A)-C(13)-H(13B)	107.9
C(2)-C(7)-H(7A)	109.4	C(13)-C(14)-C(9)	110.0(4)
N(8)-C(7)-H(7B)	109.4	C(13)-C(14)-H(14A)	109.7
C(2)-C(7)-H(7B)	109.4	C(9)-C(14)-H(14A)	109.7
H(7A)-C(7)-H(7B)	108.0	C(13)-C(14)-H(14B)	109.7
C(7)-N(8)-C(9)	114.4(3)	C(9)-C(14)-H(14B)	109.6
C(7)-N(8)-Ru(1)	115.9(3)	H(14A)-C(14)-H(14B)	108.2
C(9)-N(8)-Ru(1)	108.1(2)	C(16)-C(15)-C(20)	118.9(4)
C(7)-N(8)-H(8N)	103(3)	C(16)-C(15)-P(1)	124.0(3)

C(20)-C(15)-P(1)	117.1(3)	C(21)-C(26)-H(26A)	119.1
C(15)-C(16)-C(17)	121.1(4)	O(1)-S(1)-C(28)	105.0(2)
C(15)-C(16)-H(16A)	119.5	O(1)-S(1)-C(27)	105.4(2)
C(17)-C(16)-H(16A)	119.5	C(28)-S(1)-C(27)	97.1(3)
C(16)-C(17)-C(18)	119.6(4)	O(1)-S(1)-Ru(1)	119.56(14)
C(16)-C(17)-H(17A)	120.2	C(28)-S(1)-Ru(1)	116.40(18)
C(18)-C(17)-H(17A)	120.2	C(27)-S(1)-Ru(1)	110.63(17)
C(19)-C(18)-C(17)	119.6(4)	S(1)-C(27)-H(27A)	109.5
C(19)-C(18)-H(18A)	120.2	S(1)-C(27)-H(27B)	109.5
C(17)-C(18)-H(18A)	120.2	H(27A)-C(27)-H(27B)	109.5
C(18)-C(19)-C(20)	120.9(5)	S(1)-C(27)-H(27C)	109.5
C(18)-C(19)-H(19A)	119.5	H(27A)-C(27)-H(27C)	109.5
C(20)-C(19)-H(19A)	119.5	H(27B)-C(27)-H(27C)	109.5
C(19)-C(20)-C(15)	119.9(5)	S(1)-C(28)-H(28A)	109.5
C(19)-C(20)-H(20A)	120.1	S(1)-C(28)-H(28B)	109.5
C(15)-C(20)-H(20A)	120.1	H(28A)-C(28)-H(28B)	109.5
C(26)-C(21)-C(22)	117.2(4)	S(1)-C(28)-H(28C)	109.5
C(26)-C(21)-P(1)	119.8(4)	H(28A)-C(28)-H(28C)	109.5
C(22)-C(21)-P(1)	123.0(3)	H(28B)-C(28)-H(28C)	109.5
C(23)-C(22)-C(21)	121.3(4)	N(29)-C(29)-C(30)	177.8(6)
C(23)-C(22)-H(22A)	119.4	C(29)-C(30)-H(30A)	109.5
C(21)-C(22)-H(22A)	119.4	C(29)-C(30)-H(30B)	109.5
C(24)-C(23)-C(22)	120.2(4)	H(30A)-C(30)-H(30B)	109.5
C(24)-C(23)-H(23A)	119.9	C(29)-C(30)-H(30C)	109.5
C(22)-C(23)-H(23A)	119.9	H(30A)-C(30)-H(30C)	109.5
C(25)-C(24)-C(23)	119.3(5)	H(30B)-C(30)-H(30C)	109.5
C(25)-C(24)-H(24A)	120.4	N(31)-C(31)-C(32)	178.4(7)
C(23)-C(24)-H(24A)	120.4	C(31)-C(32)-H(32A)	109.5
C(24)-C(25)-C(26)	120.2(4)	C(31)-C(32)-H(32B)	109.5
C(24)-C(25)-H(25A)	119.9	H(32A)-C(32)-H(32B)	109.5
C(26)-C(25)-H(25A)	119.9	C(31)-C(32)-H(32C)	109.5
C(25)-C(26)-C(21)	121.8(5)	H(32A)-C(32)-H(32C)	109.5
C(25)-C(26)-H(26A)	119.1	H(32B)-C(32)-H(32C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table AIII.4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for complex 33. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11}+... +2\ h\ k\ a^*b^*\ U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Ru(1)	12(1)	13(1)	15(1)	0(1)	1(1)	0(1)
Cl(1)	12(1)	18(1)	19(1)	2(1)	0(1)	-1(1)
Cl(2)	13(1)	20(1)	19(1)	0(1)	1(1)	0(1)
P(1)	15(1)	15(1)	17(1)	4(1)	2(1)	2(1)
C(1)	15(2)	24(3)	15(3)	6(2)	-3(2)	4(2)

C(2)	16(2)	20(3)	16(3)	0(2)	-5(2)	2(2)
C(3)	22(3)	29(3)	22(3)	-3(2)	-2(2)	6(2)
C(4)	23(3)	41(4)	17(3)	-1(3)	5(2)	5(2)
C(5)	30(3)	41(4)	28(4)	9(3)	7(2)	2(2)
C(6)	29(3)	17(3)	26(3)	2(2)	8(2)	3(2)
C(7)	27(2)	12(3)	24(3)	1(2)	1(2)	-3(2)
N(8)	19(2)	12(2)	17(2)	-2(2)	3(2)	2(2)
C(9)	17(2)	11(3)	24(3)	2(2)	2(2)	0(2)
C(10)	11(2)	20(3)	19(3)	5(2)	2(2)	3(2)
N(10)	11(2)	14(2)	12(2)	0(2)	-1(2)	-1(2)
C(11)	21(3)	20(3)	29(3)	4(2)	0(2)	1(2)
C(12)	29(3)	23(3)	35(4)	-2(3)	-1(2)	0(2)
C(13)	34(3)	13(3)	37(3)	-6(2)	12(3)	-3(2)
C(14)	28(3)	22(3)	28(3)	-8(2)	2(2)	-1(2)
C(15)	16(2)	15(3)	17(3)	8(2)	0(2)	0(2)
C(16)	16(2)	19(3)	22(3)	7(2)	4(2)	0(2)
C(17)	21(2)	25(3)	18(3)	6(2)	-3(2)	-4(2)
C(18)	16(2)	29(3)	24(3)	7(2)	-2(2)	1(2)
C(19)	18(2)	25(3)	30(3)	3(3)	7(2)	7(2)
C(20)	19(2)	21(3)	20(3)	8(2)	-5(2)	4(2)
C(21)	18(2)	17(3)	19(3)	1(2)	6(2)	2(2)
C(22)	24(3)	21(3)	30(3)	5(2)	0(2)	6(2)
C(23)	32(3)	17(3)	36(3)	2(2)	0(2)	7(2)
C(24)	28(3)	16(3)	40(4)	2(2)	8(2)	-2(2)
C(25)	16(3)	22(3)	56(4)	6(3)	4(2)	-4(2)
C(26)	15(2)	24(3)	44(4)	11(3)	6(2)	2(2)
O(1)	34(2)	23(2)	27(2)	-4(2)	-7(2)	14(2)
S(1)	16(1)	18(1)	18(1)	-2(1)	1(1)	0(1)
C(27)	37(3)	24(3)	16(3)	-6(2)	-2(2)	3(2)
C(28)	32(3)	42(4)	59(4)	-33(3)	21(3)	-20(3)
N(29)	60(3)	45(4)	23(3)	-5(3)	-15(2)	-17(3)
C(29)	31(3)	38(4)	17(3)	-8(3)	-3(2)	-7(3)
C(30)	49(4)	34(4)	37(4)	2(3)	14(3)	-4(3)
N(31)	66(4)	52(4)	56(4)	-20(3)	5(3)	-14(3)
C(31)	37(3)	34(4)	47(4)	-14(3)	12(3)	-5(2)
C(32)	54(4)	23(3)	53(4)	3(3)	5(3)	-4(2)

Table AIII.5. Hydrogen coordinates (x10^4) and isotropic displacement parameters (Å^{2}x10^3) for catalyst 33.

	x	y	z	U(eq)
H(3A)	7852	3461	2763	29
H(4A)	6662	2559	3399	32
H(5A)	6451	954	3283	40

H(6A)	7418	249	2508	29
H(7A)	9346	3639	2020	25
H(7B)	10205	2743	1825	25
H(8N)	7644(17)	3190(40)	1420(20)	56(16)
H(9A)	10029	3871	925	21
H(10A)	7258	3819	526	20
H(10B)	9520(30)	2920(30)	7(18)	40(16)
H(10C)	8020(40)	2790(30)	-117(12)	45(17)
H(11A)	7984	4564	-269	28
H(11B)	9544	4604	-52	28
H(12A)	8568	6076	97	35
H(12B)	7263	5626	402	35
H(13A)	10033	5644	825	34
H(13B)	8774	6237	1070	34
H(14A)	7669	4856	1364	31
H(14B)	9194	4894	1619	31
H(16A)	10684	1051	2591	23
H(17A)	12955	721	2842	25
H(18A)	14508	141	2182	27
H(19A)	13766	-105	1289	29
H(20A)	11485	180	1043	24
H(22A)	10010	-1025	1817	30
H(23A)	9007	-2499	1800	34
H(24A)	6699	-2674	1544	34
H(25A)	5384	-1357	1346	38
H(26A)	6389	111	1356	33
H(27A)	9953	1601	-483	39
H(27B)	8341	1419	-577	39
H(27C)	9439	624	-725	39
H(28A)	7821	-486	-199	66
H(28B)	6834	357	-21	66
H(28C)	7380	-366	430	66
H(30A)	4900	2135	1882	60
H(30B)	3412	2459	1670	60
H(30C)	3790	2535	2308	60
H(32A)	10347	-2533	641	65
H(32B)	10873	-1499	508	65
H(32C)	11754	-2380	308	65

Table AIII.6. Torsion angles [°] for catalyst 33

N(10)-Ru(1)-P(1)-C(1)	34.0(7)
N(8)-Ru(1)-P(1)-C(1)	23.66(18)
S(1)-Ru(1)-P(1)-C(1)	-157.80(16)

Cl(2)-Ru(1)-P(1)-C(1)	110.40(16)
Cl(1)-Ru(1)-P(1)-C(1)	-62.27(16)
N(10)-Ru(1)-P(1)-C(21)	153.1(6)
N(8)-Ru(1)-P(1)-C(21)	142.80(19)
S(1)-Ru(1)-P(1)-C(21)	-38.66(16)
Cl(2)-Ru(1)-P(1)-C(21)	-130.46(16)
Cl(1)-Ru(1)-P(1)-C(21)	56.87(17)
N(10)-Ru(1)-P(1)-C(15)	-82.3(7)
N(8)-Ru(1)-P(1)-C(15)	-92.60(19)
S(1)-Ru(1)-P(1)-C(15)	85.94(17)
Cl(2)-Ru(1)-P(1)-C(15)	-5.86(17)
Cl(1)-Ru(1)-P(1)-C(15)	-178.53(17)
C(21)-P(1)-C(1)-C(6)	10.1(4)
C(15)-P(1)-C(1)-C(6)	-95.1(4)
Ru(1)-P(1)-C(1)-C(6)	140.1(3)
C(21)-P(1)-C(1)-C(2)	-169.3(3)
C(15)-P(1)-C(1)-C(2)	85.5(4)
Ru(1)-P(1)-C(1)-C(2)	-39.3(4)
C(6)-C(1)-C(2)-C(3)	-1.5(6)
P(1)-C(1)-C(2)-C(3)	177.9(3)
C(6)-C(1)-C(2)-C(7)	178.3(4)
P(1)-C(1)-C(2)-C(7)	-2.3(6)
C(1)-C(2)-C(3)-C(4)	2.4(6)
C(7)-C(2)-C(3)-C(4)	-177.4(4)
C(2)-C(3)-C(4)-C(5)	-1.4(7)
C(3)-C(4)-C(5)-C(6)	-0.7(8)
C(4)-C(5)-C(6)-C(1)	1.6(8)
C(2)-C(1)-C(6)-C(5)	-0.5(7)
P(1)-C(1)-C(6)-C(5)	-179.9(4)
C(3)-C(2)-C(7)-N(8)	-113.4(4)
C(1)-C(2)-C(7)-N(8)	66.9(5)
C(2)-C(7)-N(8)-C(9)	157.6(3)
C(2)-C(7)-N(8)-Ru(1)	-75.5(4)
N(10)-Ru(1)-N(8)-C(7)	-152.0(3)
S(1)-Ru(1)-N(8)-C(7)	-139.8(8)
P(1)-Ru(1)-N(8)-C(7)	26.4(3)
Cl(2)-Ru(1)-N(8)-C(7)	-67.0(3)
Cl(1)-Ru(1)-N(8)-C(7)	120.6(3)
N(10)-Ru(1)-N(8)-C(9)	-22.1(2)
S(1)-Ru(1)-N(8)-C(9)	-9.9(10)
P(1)-Ru(1)-N(8)-C(9)	156.3(2)
Cl(2)-Ru(1)-N(8)-C(9)	62.9(2)
Cl(1)-Ru(1)-N(8)-C(9)	-109.5(2)
C(7)-N(8)-C(9)-C(10)	178.4(3)
Ru(1)-N(8)-C(9)-C(10)	47.7(3)
C(7)-N(8)-C(9)-C(14)	-59.5(5)

Ru(1)-N(8)-C(9)-C(14)	169.7(3)
N(8)-C(9)-C(10)-N(10)	-55.3(4)
C(14)-C(9)-C(10)-N(10)	-179.6(3)
N(8)-C(9)-C(10)-C(11)	179.6(3)
C(14)-C(9)-C(10)-C(11)	55.3(5)
C(9)-C(10)-N(10)-Ru(1)	35.9(4)
C(11)-C(10)-N(10)-Ru(1)	161.9(3)
N(8)-Ru(1)-N(10)-C(10)	-7.5(2)
S(1)-Ru(1)-N(10)-C(10)	173.8(2)
P(1)-Ru(1)-N(10)-C(10)	-18.0(8)
Cl(2)-Ru(1)-N(10)-C(10)	-95.1(2)
Cl(1)-Ru(1)-N(10)-C(10)	78.8(2)
N(10)-C(10)-C(11)-C(12)	-177.0(3)
C(9)-C(10)-C(11)-C(12)	-53.7(5)
C(10)-C(11)-C(12)-C(13)	52.7(5)
C(11)-C(12)-C(13)-C(14)	-55.9(5)
C(12)-C(13)-C(14)-C(9)	57.4(5)
N(8)-C(9)-C(14)-C(13)	-176.4(3)
C(10)-C(9)-C(14)-C(13)	-56.1(5)
C(1)-P(1)-C(15)-C(16)	5.0(4)
C(21)-P(1)-C(15)-C(16)	-100.3(4)
Ru(1)-P(1)-C(15)-C(16)	125.9(3)
C(1)-P(1)-C(15)-C(20)	-175.8(4)
C(21)-P(1)-C(15)-C(20)	78.8(4)
Ru(1)-P(1)-C(15)-C(20)	-54.9(4)
C(20)-C(15)-C(16)-C(17)	0.2(7)
P(1)-C(15)-C(16)-C(17)	179.4(3)
C(15)-C(16)-C(17)-C(18)	0.5(7)
C(16)-C(17)-C(18)-C(19)	-0.3(7)
C(17)-C(18)-C(19)-C(20)	-0.7(7)
C(18)-C(19)-C(20)-C(15)	1.5(7)
C(16)-C(15)-C(20)-C(19)	-1.3(7)
P(1)-C(15)-C(20)-C(19)	179.5(4)
C(1)-P(1)-C(21)-C(26)	71.6(4)
C(15)-P(1)-C(21)-C(26)	177.1(4)
Ru(1)-P(1)-C(21)-C(26)	-51.7(4)
C(1)-P(1)-C(21)-C(22)	-107.3(4)
C(15)-P(1)-C(21)-C(22)	-1.8(5)
Ru(1)-P(1)-C(21)-C(22)	129.4(4)
C(26)-C(21)-C(22)-C(23)	2.2(7)
P(1)-C(21)-C(22)-C(23)	-178.8(4)
C(21)-C(22)-C(23)-C(24)	-0.5(7)
C(22)-C(23)-C(24)-C(25)	-1.6(8)
C(23)-C(24)-C(25)-C(26)	1.9(8)
C(24)-C(25)-C(26)-C(21)	-0.1(8)
C(22)-C(21)-C(26)-C(25)	-2.0(8)

P(1)-C(21)-C(26)-C(25)	179.0(4)
N(10)-Ru(1)-S(1)-O(1)	129.63(19)
N(8)-Ru(1)-S(1)-O(1)	117.7(9)
P(1)-Ru(1)-S(1)-O(1)	-48.56(17)
Cl(2)-Ru(1)-S(1)-O(1)	45.11(17)
Cl(1)-Ru(1)-S(1)-O(1)	-143.23(17)
N(10)-Ru(1)-S(1)-C(28)	-102.5(3)
N(8)-Ru(1)-S(1)-C(28)	-114.5(9)
P(1)-Ru(1)-S(1)-C(28)	79.3(3)
Cl(2)-Ru(1)-S(1)-C(28)	172.9(2)
Cl(1)-Ru(1)-S(1)-C(28)	-15.4(3)
N(10)-Ru(1)-S(1)-C(27)	6.99(19)
N(8)-Ru(1)-S(1)-C(27)	-5.0(9)
P(1)-Ru(1)-S(1)-C(27)	-171.20(17)
Cl(2)-Ru(1)-S(1)-C(27)	-77.53(16)
Cl(1)-Ru(1)-S(1)-C(27)	94.13(16)

Symmetry transformations used to generate equivalent atoms:

Table AIII.7. Hydrogen bonds for 33 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(8)-H(8N)...Cl(1)	0.9799(11)	2.80(5)	3.119(4)	100(3)
N(10)-H(10B)...Cl(1)#1	0.9800(11)	2.717(19)	3.644(4)	158(4)
N(10)-H(10C)...Cl(2)#2	0.9800(11)	2.339(12)	3.299(4)	166(4)

Symmetry transformations used to generate equivalent atoms:
#1 x+1/2,-y+1/2,-z #2 x-1/2,-y+1/2,-z