ASYMMETRIC TRANSFER HYDROGENATION USING A RHODIUM(I)

IN SITU SYSTEM CONTAINING CHIRAL SULPHOXIDE LIGANDS

By

KENNETH SHAWN MACFARLANE

B.Sc., University of British Columbia, 1986

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE STUDIES

DEPARTMENT OF CHEMISTRY

We accept this thesis as conforming

to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA

November 1989

© Kenneth Shawn MacFarlane, 1989

In presenting this thesis in partial fulfilment of the requirements for an advanced degree at the University of British Columbia, I agree that the Library shall make it freely available for reference and study. I further agree that permission for extensive copying of this thesis for scholarly purposes may be granted by the head of my department or by his or her representatives. It is understood that copying or publication of this thesis for financial gain shall not be allowed without my written permission.
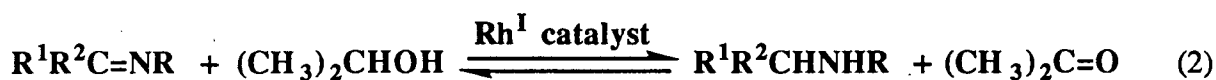
Department of ___CHEMISTRY___

The University of British Columbia
Vancouver, Canada

Date ___Dec 8 / 89___

ABSTRACT

This thesis describes the results from *in situ* catalytic rhodium(I) systems with acylated methionine sulphoxide ligands for the transfer hydrogenation of aryl alkyl ketones (eq. 1) and imines (eq. 2) from 2-propanol. All the chiral ligands studied are easily prepared derivatives of the amino acid methionine and include: *N*-acetyl-(*S*)-methionine-(*R,S*)-sulphoxide [(*S*)-AMSO], *N*-acetyl-(*R*)-methionine-(*R,S*)-sulphoxide [(*R*)-AMSO], and *N*-benzoyl-(*S*)-methionine-(*R,S*)-sulphoxide [(*S*)-BMSO].

$$R^1R^2C=O \ + \ (CH_3)_2CHOH \ \underset{}{\overset{Rh^I \ catalyst}{\rightleftharpoons}} \ R^1R^2CHOH \ + \ (CH_3)_2C=O \qquad (1)$$

$$R^1R^2C=NR \ + \ (CH_3)_2CHOH \ \underset{}{\overset{Rh^I \ catalyst}{\rightleftharpoons}} \ R^1R^2CHNHR \ + \ (CH_3)_2C=O \qquad (2)$$

The catalytic results for the transfer hydrogenation of acetophenone by (*S*)-AMSO with [RhCl(1,5-hexadiene)]$_2$ as the rhodium(I) precursor are, conversion = 26% and e.e. = 30% of the (*R*)-(+)-1-phenylethanol. The analogous system with (*R*)-AMSO as the chiral ligand gave approximately the same chemical and optical yields. However, when the ligand is (*R*)-AMSO, the (*S*)-(–)-alcohol is produced in excess, as opposed to the *R* enantiomer. A system with [RhCl(1,5-cyclooctadiene)]$_2$ added as the catalyst precursor gave, with either (*S*)- or (*R*)-AMSO as the chiral ligand, similar results for the optical yield (31-32%), but gave a somewhat larger chemical yield (34-36%) of 1-phenylethanol. With propiophenone as the substrate, the [RhCl(1,5-hexadiene)]$_2$ / (*S*)-AMSO system gave a 21% yield of 1-phenyl-1-propanol with 35% e.e. of the (*R*)-(+)-alcohol. (*S*)-BMSO was less successful as a ligand under the catalytic conditions used in these studies, giving both low chemical and optical yields with [RhCl(1,5-hexadiene)]$_2$ (10% and 13%, respectively). Use of this ligand with

[RhCl(1,5-cyclooctadiene)]$_2$ gave more reasonable chemical yields (29%), but no enantiomeric excess was observed in the product. All the catalytic reactions required the addition of KOH as a cocatalyst for the successful transfer of hydrogen from 2-propanol. The reverse reaction, where 1-phenylethanol acts as the hydrogen donor, and acetone as the hydrogen acceptor (or substrate), was also shown to be catalysed by these rhodium(I)-AMSO *in situ* systems. The chemical yield of acetophenone produced by transfer of hydrogen from racemic 1-phenylethanol to acetone was 15%. However, no e.e. was observed in the remaining 1-phenylethanol, showing it was not enantioselectively dehydrogenated.

This *in situ* rhodium-(*S*)-AMSO system also catalysed the transfer hydrogenation of the imine *N*-benzylideneaniline to *N*-phenylbenzylamine in 80% yield. However, two prochiral imines *N*-(1-methylbenzylidene)benzylamine and *N*-(1-methoxy-2-propylidene)2,6-dimethyl-aniline were not reduced under similar catalytic conditions; KOH was also added as a cocatalyst in these systems.

Several attempts at preparing coordination compounds of the ligands AMSO and BMSO proved unsuccessful. Further preparations of coordination compounds were not pursued in favour of concentrating on the more successful transfer hydrogenation studies involving these chiral ligands.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

The following list of abbreviations, most of which are commonly used in the chemical literature, will be employed in this thesis:

A	hydrogen acceptor
Ac	acetyl, CH_3CO-
Ar	argon
atm	atmosphere; 1 atm = 760 mm Hg
BDios	$(2R,3R)$-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(benzylsulphinyl)butane
(S,S)-BDPP	$(2S,4S)$-bis(diphenylphosphino)pentane; also called Skewphos
Benzphos	1-benzyl-1,2-bis(diphenylphosphino)ethane
Binap	(S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
bipy	2,2'-bipyridine
BMPP	(R)-(+)-benzylmethylphenylphosphine
BPPFA	1,1'-bis(diphenylphosphino)-2'-(1-N,N-α-dimethylaminoethyl)ferrocene
BPPM	$(2S,4S)$-N-(t-butoxycarbonyl)-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine
br	broad
Bz	benzoyl, C_6H_5CO-
c	concentration (in g/100 mL)
cat.	catalyst
cat.*	chiral catalyst
CD	circular dichroism
chel	chelating ligand

Chiraphos	(2*S*,3*S*)-bis(diphenylphosphino)butane
cod	1,5-cyclooctadiene
coe	cyclooctene
conv.	conversion
Cycphos	1-cyclohexyl-1,2-bis(diphenylphosphino)ethane
D	a hydrogen donor
D	configuration relative to D-glyceraldehyde
d	doublet (NMR)
d	dextrorotatory
DDios	(2*R*,3*R*)-2,3-dihydroxy-1,4-bis(methylsulphinyl)butane
dec.	decomposition point
Diop	(2*R*,3*R*) or (2*S*,3*S*)-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
Dios	(2*R*,3*R*)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(methylsulphinyl)butane
DiPAMP	1,2-bis(*ortho*-anisylphenylphosphino)ethane
DMSO-*d*$_6$	hexadeuterodimethylsulphoxide
dppb	1,4-bis(diphenylphosphino)butane
dt	doublet of triplets
EAC	ethyl-(*Z*)-α-acetamidocinnamate
e.e.	enantiomeric excess
FID	flame-ionisation detector
Fig.	Figure
GC	gas chromatography
hd	1,5-hexadiene
h	hour(s)
Hz	Hertz, cycles per second
IR	infra-red

J	coupling constant, in Hz
L	ligand
L	configuration relative to L-glyceraldehyde
l	path length (1.0 dm, optical rotation)
l	levorotatory
L-Dopa	3-(3,4-dihydroxyphenyl)-L-alanine
m	multiplet
$[M]_D^T$	molar rotation, $[M]_D^T = [\alpha]_D^T$ x molecular weight ÷ 100
MAC	methyl-(Z)-α-acetamidocinnamate
Me	methyl, CH_3
4,7-Me_2phen	4,7-dimethyl-1,10-phenanthroline
min	minute(s)
mmol	millimole(s)
mol	mole(s)
M.P.	melting point
nbd	2,5-norbornadiene
NMR	nuclear magnetic resonance
o.y.	optical yield
^{31}P	phosphorus nuclear magnetic resonance
P-P*	chiral chelating ditertiary phosphine
Ph	phenyl, C_6H_5
phen	1,10-phenanthroline
PPBI	2-pyridinal-1,2-diphenylethylimine
PPEI	2-pyridinal-1-phenylethylimine
ppm	parts per million
PR_3	tertiary phosphine
Prophos	1,2-bis(diphenylphosphino)propane

py	pyridine
(*R*)-	absolute configuration (latin: *rectus* ; right)
(*R*)-AMSO	*N*-acetyl-(*R*)-methionine-(*R*,*S*)-sulphoxide
(*R*)-METO	(*R*)-methionine-(*R*,*S*)-sulphoxide
R.T.	room temperature
Rx.	reaction
S	solvent or substrate
(*S*)-	absolute configuration (latin: *sinister* ; left)
s	singlet (NMR), strong (IR)
(*S*)-AMSO	*N*-acetyl-(*S*)-methionine-(*R*,*S*)-sulphoxide
(*S*)-BMSO	*N*-benzoyl-(*S*)-methionine-(*R*,*S*)-sulphoxide
(*S*)-METO	(*S*)-methionine-(*R*,*S*)-sulphoxide
T	temperature
t	triplet
TCD	thermal-conductivity detector
TMS	tetramethylsilane
α	observed rotation
$[\alpha]_D^T$	specific or absolute rotation (measured at the sodium D line) at temperature T
δ	chemical shift (in ppm downfield from TMS) or bend (IR)
ν	frequency (cm^{-1})
η	descriptor for hapticity
μ	descriptor for bridging
*	chiral centre

ACKNOWLEDGEMENTS

CHAPTER 1

INTRODUCTION

1.1 General Introduction

The use of soluble transition metal complexes to catalyse organic transformations has received much attention over the past three decades. These homogeneous systems have found increasing use in both academic laboratories and chemical industry to catalyse organic reactions.[1] The widespread interest in such systems is evidenced by the many books and textbooks (e.g. references 1-5) that have been published on the subject of homogeneous catalysis in the last ten years.

Many organic reactions have been found to be catalysed by transition metal complexes in solution, a few examples of which are: hydrogenation, hydrosilylation, hydroformylation, hydrocyanation, epoxidation, oxidation of olefins to aldehydes and ketones, and carbonylation of alcohols.[3] Interest in the use of homogeneous catalytic systems has arisen because they are generally found to exhibit higher selectivity[1, 6] and higher activity[5] compared to heterogeneous systems.

It is widely stated that, while homogeneous systems generally have higher activity and selectivity than their heterogeneous counterparts, the difficulty in separating the catalyst from both the reactants and products is a major disadvantage.[2, 6] Other problems noted with the use of homogeneous catalysts are their lower thermal stability as well as their sensitivity to oxygen and moisture.[6] However, the ability to follow homogeneous catalysed reactions, by conventional spectroscopic and other kinetic methods, provides the opportunity to understand these systems mechanistically.[7] Another advantage in homogeneous catalysis is the ease with which the catalytic properties of the system can be modified by simply changing the ligands.[7]

Efforts in the past two decades have been made in search of catalysts which incorporate the best properties of both homogeneous and heterogeneous systems.[6] These so-called heterogenised homogeneous catalysts typically consist of a metal complex bound to insoluble supports such as silica or crosslinked polystyrene.[4, 6] These supported metal complexes have the advantage of retaining the high reactivity and selectivity of the homogeneous system, while combining this with the ease of separation from the product(s) of a heterogeneous catalyst.[6]

Economic problems of separating the usually expensive transition metal complexes from the products of a catalytic reaction have limited the number of large scale industrial processes, which are currently catalysed by homogeneous catalysts, to approximately two dozen.[1] Some of the industrial processes currently using homogeneous catalysts are: the oxo process, the Wacker process, methanol carbonylation, and hydrocyanation of olefins.[3]

Another industrial application of homogeneous catalysts is the use of asymmetric hydrogenation of a prochiral olefin to produce the optically active drug L-Dopa, which is used in the treatment of Parkinson's disease.[7] The catalyst system used for this asymmetric transformation is a rhodium(I) catalyst with a chiral diphosphine ligand (eq. 1.1).[8]

$$1)\ [Rh(\overset{*}{P}R_3)_2(S)_2]^+ \qquad H_2,\ S = MeOH \qquad 2)\ H_3O^+ \qquad (1.1)$$
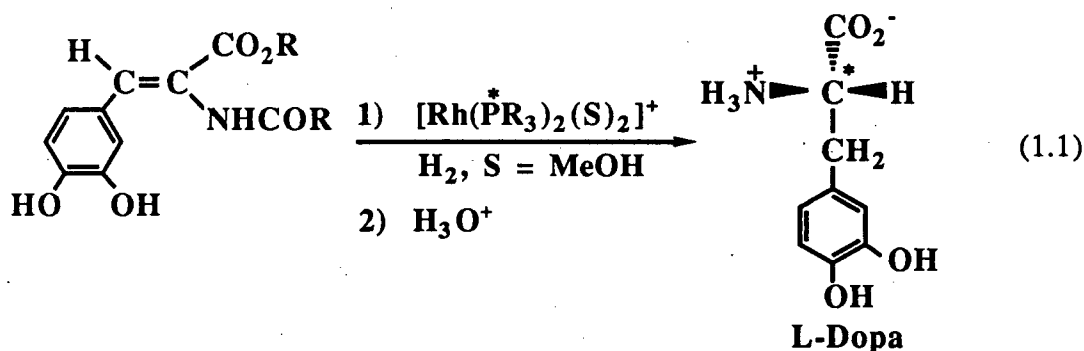
Also, the sweetener Aspartame, a methyl ester of a dipeptide consisting of L-phenylalanine and L-aspartic acid, relies on homogeneous chiral catalysts for the production

of the two amino acid precursors.[8] The asymmetry of these compounds plays an important role in determining their properties; for example, it was found that none of the other three diastereomers of Aspartame are sweet.[9]

1.2 Homogeneous Hydrogenation

Although reports of homogeneous hydrogenation date back as far as 1938 when Calvin reduced quinone using a copper acetate system, it is not until more recently that homogeneous hydrogenation began to be more thoroughly investigated.[7] An increase in the intensity of research in homogeneous hydrogenation came as a direct result of the discovery by Wilkinson's group in 1965 of the highly active $RhCl(PPh_3)_3$ system for the hydrogenation of olefins.[10, 11]

The literature in the area of homogeneous hydrogenation has become vast since the discovery of Wilkinson's catalyst. A number of comprehensive reviews,[12-15] specialised texts,[16] chapters in books,[4, 5, 7, 17] and whole books[18, 19] are available on this subject.

In the past, most of the interest in homogeneous hydrogenation has been directed toward the reduction of carbon-carbon double bonds. However, interest in reducing carbon-oxygen and carbon-nitrogen double bonds has increased in the last few years.[8] The concentration of research in the area of reducing olefins has occurred for probably two reasons: 1) carbon-carbon double bonds are more easily reduced than carbon-oxygen double bonds;[20] and 2) availability of substrates and interest in the use of the corresponding products.

1.2.1 Asymmetric Homogeneous Hydrogenation

Most of the work in asymmetric or enantioselective catalysis has been done in the area of hydrogenation.[8] This is probably a result of the fact that the vast majority of optically active compounds have a hydrogen atom at the asymmetric carbon atom.[21] A large number of the successful chiral catalysts consist of a transition metal complex containing a chiral phosphine ligand. A measure of the success of these systems is given by the optical yield (o.y.) or

enantiomeric excess (e.e.). Equations 1.2 and 1.3 show how the optical yield and enantiomeric excess are calculated. Usually the value for the optical yield and enantiomeric excess are taken to be equal.[22]

$$\text{o.y.(\%)} = \frac{\text{observed specific rotation } [\alpha]_D}{\text{specific rotation of pure enantiomer } [\alpha]_D} \times 100 \qquad (1.2)$$

$$\text{e.e.(\%)} = \frac{|\ [R] - [S]\ |}{[R] + [S]} \times 100 \qquad (1.3)$$

Over the past fifteen years there has been an enormous amount of work in the field of asymmetric homogeneous hydrogenation with numerous comprehensive reviews appearing in the literature.[8, 15, 21, 23-26]

The first chiral phosphine ligands were chiral at the phosphorus atom (e.g. PMePrPh). However, only poor optical inductions were observed with these systems.[8] The next significant development in the synthesis of new chiral phosphines came with the preparation by Kagan's group of the diphosphine Diop (Fig. 1.1).[8, 27, 28] This phosphine, while containing the centre of chirality on a carbon atom in the ligand backbone, gave high optical yields with prochiral olefins. Also, the starting material for the synthesis of Diop is tartaric acid and therefore the chirality on carbon arises from natural sources, making the ligand relatively cheap to prepare.[8]

The high enantioselectivities that were observed for Rh complexes of Diop provided the impetus for the development of new diphosphine ligands which contained their chirality on carbon. Some of the most notable diphosphines developed are: DiPAMP (chiral on P), which is used in Monsanto's synthesis of L-Dopa;[29] Prophos, prepared from lactic acid; Chiraphos, which has two asymmetric centres in its backbone; BPPM, a derivative of the amino acid proline; and BPPFA, a ferrocene derivative (Fig. 1.1).[8] The catalysts or "precatalysts" are generally prepared by two methods: either (1) *in situ*, by adding one equivalent of the chelating

4

ditertiary phosphine ligand per mol of Rh; or (2) by addition of a solid complex of the type [Rh(diphosphine)(diene)]$^+$BF$_4^-$, which already contains the chiral ligand.
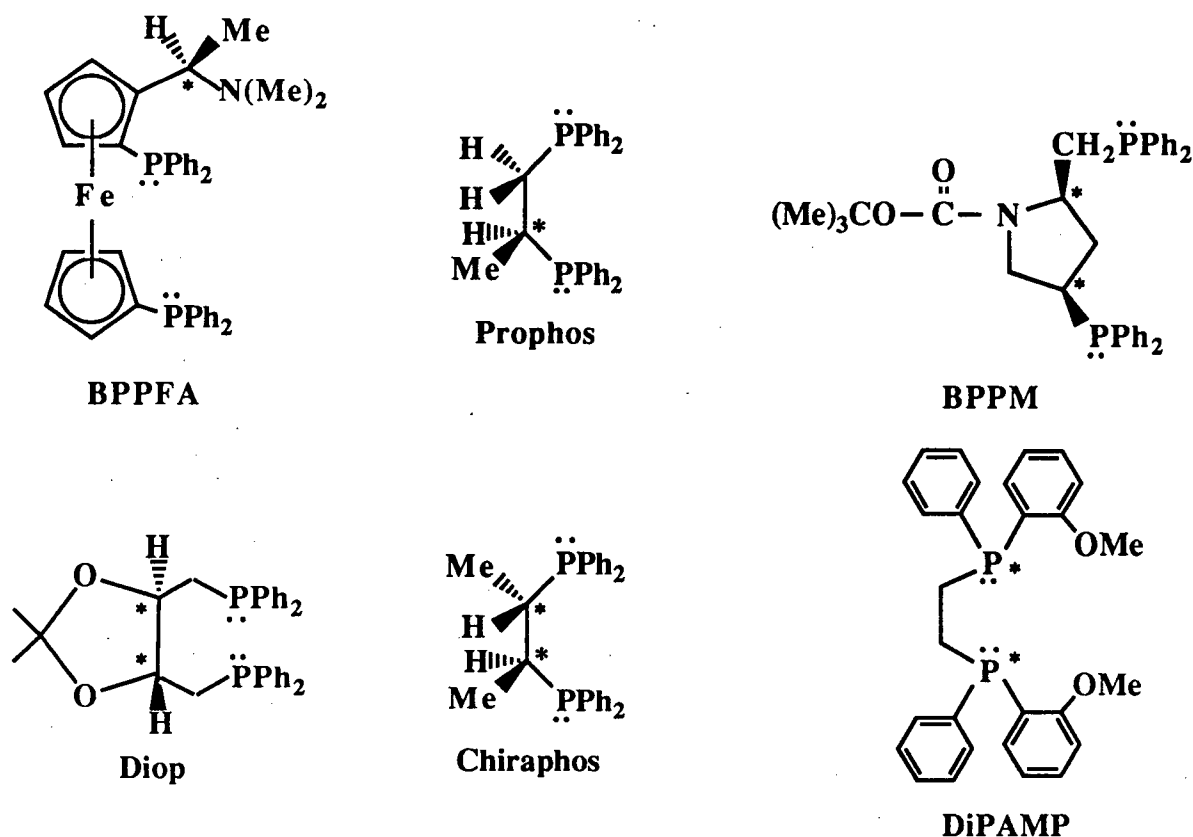
Figure 1.1 Selected chiral diphosphines used in asymmetric hydrogenation (based on ref. 7); the symbol * represents a chiral centre.

Monophosphines generally seem to give lower optical yields than diphosphine ligands, and it should be pointed out that the rigidity of the chelate ring formed with diphosphines seems to play a key role in obtaining high enantiomeric excess.[8] Ligands that form rigid five-membered chelate rings seem to be generally more efficient than those which form more flexible six- or seven-membered chelates.[25] This is thought to be manifested through a rigid chiral array of phenyl rings in the five-membered chelates which allows a degree of discrimination of the prochiral olefinic faces in the binding step.[25]

The prochiral substrates that have been reduced with the highest enantiomeric excesses to date are functionalised olefins that are believed to bind in a bidentate fashion. Therefore, it has been suggested that these substrates impose some rigidity on the system thereby increasing the optical yield of the product. For example, some enamide substrates have been hydrogenated with up to 100% e.e.[7] The formation of a bidentate olefinic complex in the transition state is thought to increase the optical yield.[24]

A probable mechanism for asymmetric hydrogenation has been suggested by Halpern et al., and is illustrated in Fig 1.2.[7] A combination of kinetic, X-ray, and NMR techniques were used to elucidate the pathway. It shows, in contrast to what was previously believed, that the major enantiomer obtained corresponds to the minor diastereomer of the catalyst-substrate adduct present in solution.[30, 31]

In Fig. 1.2, when R = Me, the substrate is methyl-(Z)-α-acetamidocinnamate (MAC), and when R = Et, the substrate is ethyl-(Z)-α-acetamidocinnamate (EAC). The structure of the major diastereomer of [Rh(S,S-Chiraphos)(EAC)]$^+$ ClO$_4^-$ was determined by X-ray crystal studies. Also, only one diastereomer could be identified in solution by ^{31}P NMR. It was originally thought that the diastereomeric ratio of the substrate-catalyst (A'/A") adduct determined the enantioselectivity of the reduction. However, studies by Halpern's group have revealed that it was the relative reactivity of the diastereomers with H$_2$ that leads to the observed optical yield.[30, 31] Thus the major species A' reacted with dihydrogen much more slowly than the minor species A". The S-enantiomer is produced in 95% e.e. due to k_2" being approximately 580 times greater than k_2' for the related [Rh(R,R-DiPAMP)]$^+$ system with MAC as the olefin. The above pathway also accounts for the observed decrease in optical yield with increasing H$_2$ pressure. If the H$_2$ pressure is increased, the increasing rate of both pathways causes the depletion of species A", the minor diastereomer, faster than the equilibrium between A' and A" can be re-established. This leads to increased amounts of the R-isomer and therefore decreased optical yields.
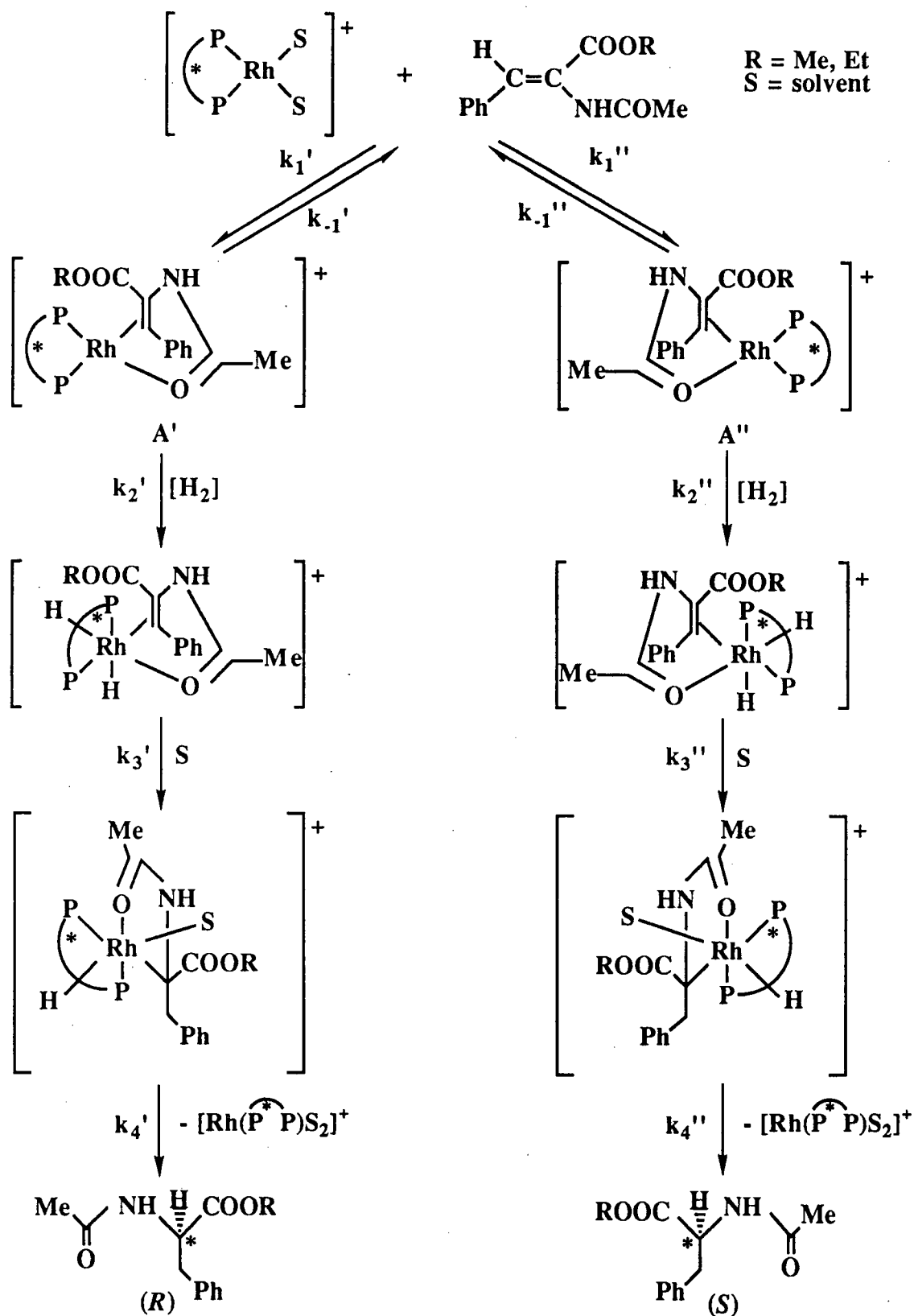
Figure 1.2 A possible mechanism for the chiral diphosphine rhodium-catalysed asymmetric hydrogenation of prochiral olefins.

Most of the catalytic systems to date have used Rh as the metal and phosphines, usually diphosphines, as the ligands. There has been interest in developing chiral ligands other than phosphines, due to the fact that phosphines are expensive because of their multistep syntheses and resolution. Other chiral ligands that have been employed in asymmetric catalysis are amides, amines, Schiff bases, carboxylates, and sulphoxides.[13] Generally, the optical yields obtained with these ligand systems are much lower than with phosphine ligands. For example, attempts at using optically active amino acids ligands with $Co(CN)_5^{3-}$ gave negligible optical yields for olefinic acid substrates.[13] Several of the chiral sulphoxides are shown in Fig. 1.3.
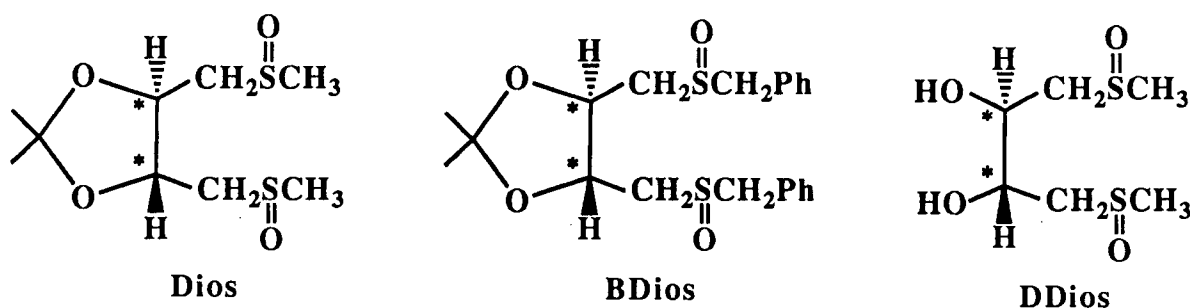
Figure 1.3 Chiral sulphoxides.

The above chiral sulphoxides, in terms of the number of carbon atoms between ligand binding sites, are all analogues of the diphosphine, Diop. An example of a typical result achieved when using sulphoxide ligands is with the complex $[RuCl_2(Dios)(DDios)]$ which gave 25% e.e. in the hydrogenation of the substrate itaconic acid.[13]

Another chiral diphosphine that is of interest in asymmetric hydrogenation is Binap (Fig. 1.4), which contains its chirality not on carbon or phosphorus atoms, as in the phosphines of Fig. 1.1, but as planar or axial chirality. Ruthenium-Binap systems have been reported to give high optical yields in the hydrogenation of dehydroamino acids as well as itaconic and related dicarboxylic acids.[32] Significantly, Ru-Binap catalysed homogeneous hydrogenations of carbonyl groups have recently been found to exhibit enantiomeric excesses between 95 and 100% for a variety of functionalised carbonyl substrates (eg. β-keto carboxylic

esters). High conversions are achieved with these systems in addition to the high optical yields observed.[33]
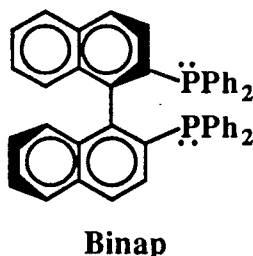
Binap

Figure 1.4 The chiral diphosphine Binap.

1.2.2 Homogeneous Hydrogenation of Ketones

As mentioned in section 1.2, most of the literature for homogeneous hydrogenation deals with the reduction of olefins, notably dehydroamino acids. Relatively few reports appear in the literature for the hydrogenation of aldehydes, ketones, esters, nitriles, imines, anhydrides, and nitro compounds.[7] Of the above mentioned substrates, probably the most widely studied are those containing carbonyl groups. Reviews on the homogeneous hydrogenation of carbonyl groups have appeared recently in the literature.[17, 20, 34]

As briefly mentioned in section 1.2, carbonyl groups are less easily reduced than carbon-carbon multiple bonds. Carbonyl groups have a lower affinity for a metal centre than olefins. There are few examples of complexes between H_2-activating metals and organic carbonyl compounds.[34] Finally, the product alcohols, produced by hydrogenation of the carbonyl, have a similar coordinating power as that of the parent ketone or aldehyde and therefore competitively inhibit further reduction. Alkanes, produced by reduction of the corresponding alkenes, have a coordinating ability which is negligible when compared to that of the olefin.[20]

Of the carbonyl containing compounds, aldehydes are the most easily reduced followed by ketones and finally esters.[20] However, the lifetime of the catalyst for the homogeneous

9

hydrogenation of aldehydes is often short due to irreversible poisoning by decarbonylation.[17] Ester reduction is usually more effectively carried out by the use of stoichiometric hydride reagents such as $LiAlH_4$ and $NaBH_4$,[20] although one effective system, an anionic ruthenium phosphine complex, has been developed which catalyses the hydrogenation of esters under mild conditions (90°C, 10 atm H_2).[35-37]

Functionalised ketones, such as aryl diketones and α-dicarbonyl compounds, are more difficult to reduce than simple aliphatic ketones using hydride reducing agents. However, the reverse is true for H_2-hydrogenation where the additional unsaturated groups assist in coordination to the metal.[17]

Metals of groups 8 and 9 have been found to be the most effective homogeneous catalysts for the hydrogenation of ketones to secondary alcohols. Most of the complexes which are effective for the reduction of ketones contain phosphines, as seen for the reduction of olefins.

The reduction of simple ketones (eg. acetone, acetophenone, etc.) with molecular hydrogen was observed by Schrock and Osborn[38] in 1970 using a cationic rhodium complex of the type $[RhH_2(PR_3)_2S_2]^+$ under mild conditions (S=solvent).[20] It was noted that the rate of this reaction could be dramatically increased by the addition of 1% water. However, these systems were still characterised by low total turnovers (20-40) and relatively slow rates. It was found later that by using more basic phosphines, like $PPhEt_2$ or PBu_3, at 60-80°C and ~ 7 atm H_2, catalyst turnovers of 1000 or more could be obtained (eq. 1.4).[39]

$$R^1 - \overset{\overset{\displaystyle O}{\|}}{C} - R^2 \ + \ H_2 \ \xrightarrow[1\% \ H_2O]{[Rh(diene)P_2] \ X} \ R^1 - \overset{\overset{\displaystyle OH}{|}}{C}H - R^2 \quad (1.4)$$

$$P = PAr_x R_{3-x}$$
$$X = PCl_6, \ BF_4, \ ClO_4$$
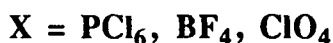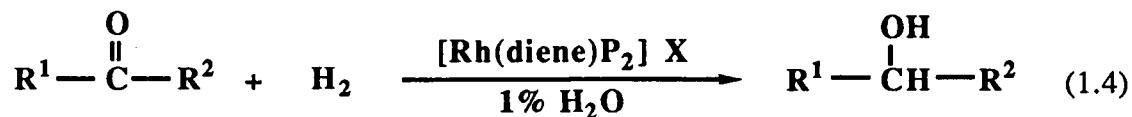
Schrock and Osborn proposed a mechanism (Fig. 1.5) for the hydrogenation of ketones.[38] The mechanism involves the replacement of a solvent molecule with the ketone substrate followed by a 1,3-hydride migration from a *cis* position on the metal to the carbon of the carbonyl group. This is followed by a water-promoted second proton transfer step. Finally, the catalyst is regenerated by dissociation of the product alcohol and addition of dihydrogen.

$$P = PAr_xR_{3-x}$$
$$S = solvent$$
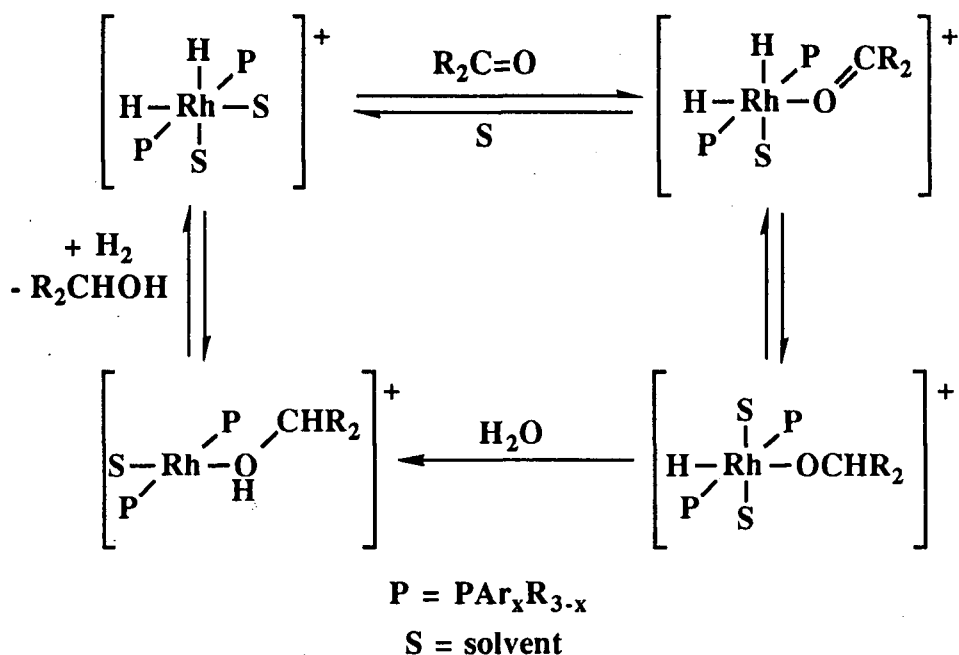
Figure 1.5 Proposed mechanism for ketone hydrogenation.

The role of water in the second proton transfer step is thought to occur as illustrated in Fig. 1.6.
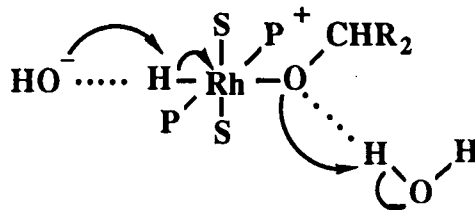
Figure 1.6 The role of H_2O in the second proton transfer step.

11

Deprotonation at the Rh centre could be carried out by a hydroxyl group or water, with the protonation of the alkoxy group occurring simultaneously or in a subsequent step.[38] Of note is the incorporation of deuterium at the α-carbon, when D_2 is used to reduce acetone, but no incorporation at the β-carbon. The lack of incorporation at the β-carbon rules out participation of the enol form in the catalytic cycle.

In situ catalysts of the type [Rh(diene)Cl]$_2$/PR$_3$ are most successful for the hydrogenation of ketones when basic unhindered phosphines are used. Other homogeneous systems successful at hydrogenating simple ketones are ruthenium phosphine systems at relatively high temperatures (150°C) and high pressures (68 atm) of dihydrogen. The hydrogenation of acetone catalysed by RuHCl(CO)(PPh$_3$)$_3$ resulted in high turnover numbers (~ 200 h^{-1}) and high conversions (95%).[40] An increase in rate was observed for these systems with the addition of water as previously seen by Schrock and Osborn.

Of interest is the inability of Wilkinson's complex, RhCl(PPh$_3$)$_3$, which is very active for the hydrogenation of olefins, to reduce ketones.[20] However, if small quantities of the base Et$_3$N are added, the system becomes active for the hydrogenation of ketones.[41]

Rhodium and iridium complexes containing nitrogen-coordinating ligands such as 1,10-phenanthroline (phen), 2,2'-bipyridine (bipy), and substituted phenanthrolines (Fig. 1.7) are examples of systems employing non-phosphine ligands for the hydrogenation of ketones.[42] The development of these nitrogen-containing ligand systems may become important as phosphines can sometimes undergo P-C oxidative addition or cleavage during catalytic hydrogenation.[43]

2,2'-bipyridine   1,10-phenanthroline
(bipy)   (phen)
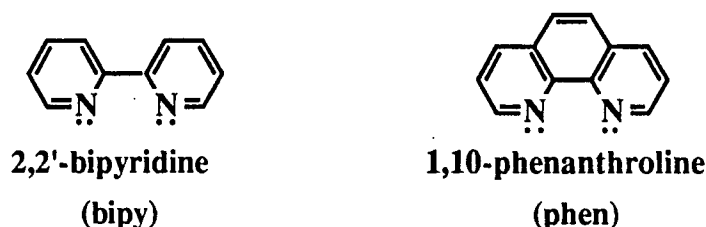
Figure 1.7 Chelating nitrogen donors.

12

The rhodium (I) complex, $[Rh(bipy)_2]^+$, in alkaline methanol solution under mild conditions (30°C, 1 atm H_2) hydrogenates 2-methylcyclohexanone stereoselectively (95%) to *cis*-2-methylcyclohexanol. The thermodynamically less stable alcohol is produced in higher yield. The above rhodium species, which can be prepared *in situ* by reducing $[Rh(bipy)_2Cl_2]Cl \cdot 2H_2O$, also catalyses the hydrogenation of a variety of simple ketones (eg. acetone, acetophenone, and propiophenone) with high rates.[42]

For the transfer of hydrogen from 2-propanol (or other hydrogen donors) to ketones, complexes of rhodium and iridium containing the nitrogenous ligands, bipy and phen, are also found to be very active and selective catalysts.[44-49] The activity of the catalytic systems containing these chelating nitrogen donor ligands is considerably higher than systems using monodentate phosphines. Transfer hydrogenation will be discussed in section 1.3.

1.2.3 Asymmetric Homogeneous Hydrogenation of Ketones

The hydrogenation of prochiral ketones (eq. 1.5) to give optically active alcohols is not as well understood and developed as the asymmetric reduction of olefins.[50] Methods of synthesising chiral alcohols are of interest because of their use in the preparation of pharmaceuticals.[51]

$$\underset{R^1}{\overset{O}{\underset{\diagup}{\overset{\|}{C}}}}\underset{R^2}{\diagdown} + H_2 \xrightarrow{cat.^*} R^1 - \overset{OH}{\underset{\underset{H}{\big\uparrow}}{\overset{|}{C^*}}} - R^2 \qquad (1.5)$$
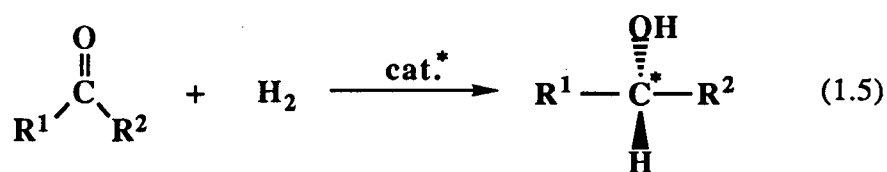
Asymmetric hydrogenations by heterogeneous systems generally have not given encouraging results. For example, reduction of methyl acetoacetate over a Raney nickel catalyst modified with tartaric acid gives 3-hydroxybutanoate with a maximum e.e. of 55% but with only 10% chemical yield.[26] However, a similar modified heterogeneous system has been reported to catalyse the reduction of acetylacetone to 2,4-pentanediol with high optical yields.[52, 53]

13

Homogeneous enantioselective hydrogenations of ketones were first performed with Schrock and Osborn type complexes $[RhH_2P_2S_2]^+$, where S is the solvent and P_2 is a chiral phosphine such as BMPP or Diop.[17, 34, 50] Low optical yields (8%) were obtained using these catalysts under mild conditions (30°C, 1 atm H_2) with acetophenone as the substrate.[54] Also, the rate of hydrogenation was slow.

Many chiral phosphine systems have been investigated for the direct H_2-hydrogenation of ketones. However, only a few of the chiral phosphines studied show good activity for the reduction of the carbonyl group. Unsuccessful attempts have been made to correlate the structure of the chiral phosphine with both optical selectivity and activity.[34] Interestingly, chiral bidentate phosphines which form five-membered chelate rings (e.g. Prophos) exhibit very low activity for the reduction of ketones.

As mentioned briefly in section 1.2.1, very high enantiomeric excess (e.e. ~ 100%) for a range of functionalised ketones has been achieved using Ru-chiral phosphine systems.[33] However, good results for simple, non-chelating ketones have not been achieved. It has been suggested that higher optical yields are observed for the functionalised ketones because the chelating effect of these substrates substantially enhances the rigidity of the substrate-bound catalytic intermediate (Fig. 1.8).[25, 51]
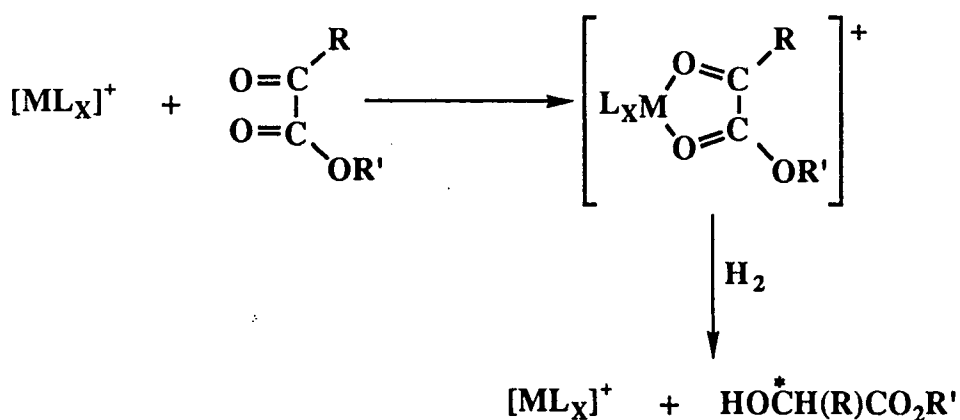
Figure 1.8 Chelating ability of functionalised substrates.

14

Simple ketones, on the other hand, do not have this chelating ability and therefore are less likely to give good optical yields. It has also been noted that higher enantioselectivity is generally observed with aryl alkyl ketones as opposed to dialkyl ketones. The best enantioselectivity for simple ketones has been achieved using an *in situ* catalyst generated from $[Rh(nbd)Cl]_2$ and (+)-Diop for the hydrogenation of acetophenone (eq. 1.6). The enantiomeric excess was reported as 51% under catalytic conditions of 50°C and 70 atm H_2, but upon addition of the base Et_3N, a dramatic increase in the e.e. was seen to 80%. Aliphatic ketones were hydrogenated with both low rates and optical yields with this catalytic system.[55]

$$
\underset{\substack{Me \diagup \diagdown Ph}}{\overset{\overset{\textstyle O}{\|}}{C}} + H_2 \xrightarrow[\substack{NEt_3,\ \text{benzene} \\ 50°C,\ 70\ atm}]{1/2\ [Rh(nbd)Cl]_2,\ (+)\text{-Diop}} Me-\overset{\overset{\textstyle OH}{\underset{\ast}{|}}}{\underset{\underset{\textstyle H}{|}}{C}}-Ph \qquad (1.6)
$$
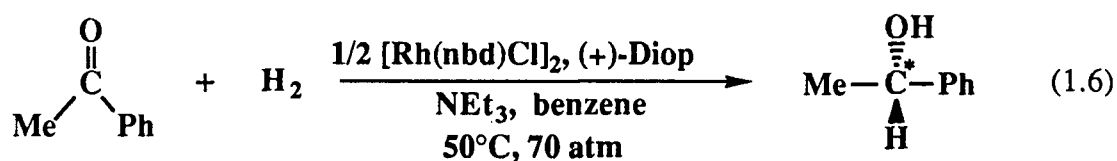
The high optical yields obtained when using aromatic ketones as the substrates suggest that an interaction between the phenyl ring of the substrate and those on the phosphine Diop may be responsible for the enantiotopic face discriminating complexation of the carbonyl to the metal.[55]

Chan and Landis recently studied the above *in situ* catalytic system in more detail and suggested a role for the promoter Et_3N.[51] The triethylamine is thought to assist in deprotonation of a rhodium dihydride species to form the active, anionic, catalytic species (Fig. 1.9). The triethylammonium cation generated is then thought to protonate the ketone thereby assisting in binding to the metal. Finally, the chiral alcohol is produced by reductive elimination.

The anionic nature of this rhodium system is thought to be important in the binding of the substrate. Unlike Schrock and Osborn type cationic complexes, which are thought to bind the ketone through the electron rich oxygen atom (Fig. 1.5), the above anionic complexes are believed to coordinate the substrate by the carbon atom. Binding through the carbon atom is

believed to increase enantioselectivity in the reduction because of the closer proximity of the resultant chiral centre to the chiral phosphine ligand.[51]

$$1/2 \ [Rh(Diop)Cl]_2 \ \xrightleftharpoons[-H_2]{H_2} \ RhH_2(Diop)Cl$$

$$+ H^+ \ \big\updownarrow \ + :NEt_3$$

$$[RhH(Diop)Cl]^- \ + \ Et_3NH^+$$

$$\begin{array}{c} R \\ \diagdown \\ C=O \\ \diagup \\ R' \end{array}$$

:NEt$_3$

$$\begin{array}{c} R \\ | \\ HO-C-RhH(Diop)Cl \\ | \\ R' \end{array} \longrightarrow [Rh(Diop)Cl] \ + \ HO\overset{*}{C}HRR'$$

Figure 1.9 The role of the base, Et$_3$N.

An interesting asymmetric reduction, that gives high optical yields, is a stoichiometric system which uses bovine serum albumin as the chiral template and achiral NaBH$_4$ as the source of hydride.[56] With propiophenone as the substrate, an optical yield of 78% was achieved. Other very effective enantioselective reductions of prochiral ketones and imines have been achieved stoichiometrically using chiral hydride reagents.[50]

An alternative, indirect route to chiral secondary alcohols is by hydrosilylation of prochiral ketones in the presence of suitable chiral transition metal catalysts followed by hydrolysis. Optical yields of up to 85% have been achieved with rhodium chiral phosphine systems.[34]

1.2.4 Hydrogenation of Imines

Very few papers have been published in the area of hydrogenation of carbon-nitrogen double bonds.[34] Complexes of the type $[Rh(diene)P_2]^+X^-$,[54] $RhCl(PPh_3)_3$, and *in situ* generated $([Rh(diene)Cl]_2 + PR_3)$ species are all active catalysts for the reduction of imines.[34] Hydrogen transfer reactions have also been used to reduce Schiff bases in the presence of $RhCl(PPh_3)_3$, $RhCl(CO)(PPh_3)_2$, and $RuCl_2(PPh_3)_2$ complexes, with 2-propanol as the hydrogen donor. It has been noted that KOH and minor amounts of water promote the hydrogenation of $PhCH=NPh$ with $RhCl(PPh_3)_3$ as the catalyst.[34]

Optical yields obtained, until recently,[57] were much lower than those reported for the hydrogenation of ketones and olefins. One of the first reports[54] of asymmetric hydrogenation of prochiral imines involved the use of a Rh-Diop complex under mild conditions (eq. 1.7). Optical yields of 22% were achieved with this system in 2-propanol. Interestingly, this complex was shown to catalyse the asymmetric hydrogenation of C=C, C=O, and C=N.[54]

$$\underset{Me}{\overset{Ph}{>}}C=NCH_2Ph \quad \xrightarrow[\text{30°C, 1 atm } H_2]{[Rh(nbd)(Diop)]^+ClO_4^-} \quad Ph-\overset{\overset{Me}{\vdots}}{\underset{H}{\overset{*}{C}}}-\overset{CH_2Ph}{\underset{H}{N\colon}} \qquad (1.7)$$
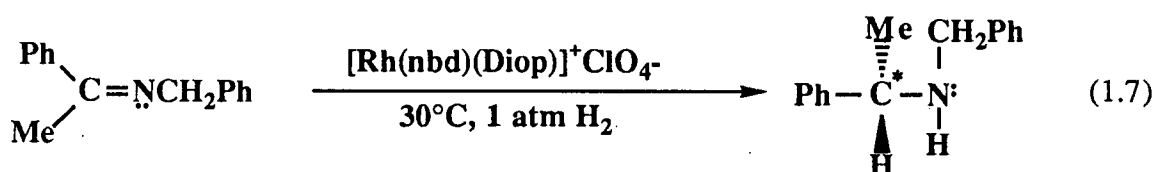
The highest e.e. obtained to date involves an *in situ* system generated from $[Rh(nbd)Cl]_2$ and (R)-$(+)$-Cycphos (Fig. 1.10) for the hydrogenation of an imine similar to that shown in eq. 1.7.[57]
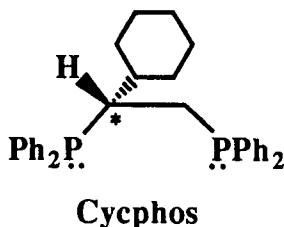
Cycphos

Figure 1.10 Structure of the chiral diphosphine, Cycphos.

Optical yields of 91% were obtained at low temperatures and high H_2 pressures (70 atm) with the addition of iodide for the hydrogenation of the substrate shown in Figure 1.11. In the absence of iodide only 71% e.e. was achieved.[57] Vastag et al.[58] have also reported increased optical yields upon the addition of halide, with iodide having the greatest effect out of Cl−, Br−, and I−.

$$MeO-\langle\bigcirc\rangle - \underset{Me}{C}=NCH_2Ph$$
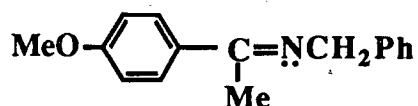
Figure 1.11 Imine substrate structure.

Some of the chiral amines that have been produced in greater than 70% e.e. are herbicides,[57] in which one enantiomer is found to be far more potent than the other enantiomer. The isolation of the more active enantiomer with high e.e. would allow for the use of smaller doses of these compounds.

The mechanism for the hydrogenation of imines is thought to be very similar to that of ketone hydrogenation because of the sensitivity of both systems to the ionic or *in situ* nature of the catalyst.[58] Different activity and optical yields are obtained depending on whether the catalyst is generated *in situ* or is ionic. Enamides (i.e. functionalised olefins) are believed to be hydrogenated by a different pathway. The difference in the two pathways is thought to exist because the enamides function as bidentate ligands, while simple ketones and imines function as monodentate ligands in the catalytic intermediate. In the case of ketones and imines, the remaining coordination site may be occupied by either added halide or solvent. This may result in a change in stereochemistry around the metal centre and therefore the enantioselectivity of the system may change.[58]

1.3 Transfer Hydrogenation

Direct hydrogenation by addition of molecular hydrogen is rarely the method of choice for the reduction of carbonyl compounds. Much better methods are boron- or aluminum-hydride reduction, via hydrosilylation, or transfer hydrogenation.[17] The best catalytic activity for the reduction of ketones is obtained by hydrogen transfer reactions.[20] Catalytic hydrogen transfer from an organic molecule (D) to a variety of organic acceptors (A) (eq. 1.8) has been reviewed in the literature.[13, 59, 60]

$$DH_2 + A \xrightleftharpoons{\text{cat.}} D + AH_2 \qquad (1.8)$$

Some of the organic donors which have been used as a source of hydrogen include alcohols, glycols, aldehydes, amides, acids, ethers, cyclic amines, and alkylbenzenes; alcohols are the most commonly used donors.[13] In fact, for the reduction of aldehydes and ketones, primary and secondary alcohols are almost always the donors of choice.[61] Secondary alcohols are more reactive than primary, but the latter are more selective.[17] 2-Propanol is used most commonly as the hydrogen source because it is inexpensive and its oxidised product acetone is easily distilled from the reaction mixture. Removing the dehydrogenated product is essential in driving the hydrogen transfer reaction towards completion. Benzyl alcohol is another good choice for a hydrogen donor, as dehydrogenation produces a conjugated product, which is therefore a driving force for hydrogen transfer.

The catalysts used for these hydrogen transfer reactions are complexes of the transition metals cobalt, iridium, rhodium, and ruthenium.[61] Hydrogen transfer has a number of advantages when compared with direct hydrogenation: (1) the reaction can be performed under mild conditions (usually at 1 atm and at the boiling point of the solvent), (2) the reaction avoids the use of relatively expensive H_2 and elaborate high pressure vessels, and (3) unusual selectivities are often observed.

Reversibility of the transfer hydrogenation reaction from a secondary alcohol can result in low conversions for ketone reduction because of the production of a further secondary alcohol, which can also act as a hydrogen donor for the concomitantly produced ketone (eq. 1.9).[34] The extent of reaction is, therefore, determined by thermodynamic parameters. Distillation of the resulting dehydrogenated product, R^3COR^4, from the reaction mixture is essential to shift the equilibrium to the right.

$$
\underset{R^1}{\overset{O}{\underset{}{\overset{\|}{C}}}}\!\!\diagdown_{R^2} \; + \; R^3\!-\!\underset{}{\overset{OH}{\underset{|}{C}H}}\!-\!R^4 \;\underset{}{\overset{catalyst}{\rightleftharpoons}}\; R^1\!-\!\underset{}{\overset{OH}{\underset{|}{C}H}}\!-\!R^2 \; + \; \underset{R^3}{\overset{O}{\overset{\|}{C}}}\!\!\diagdown_{R^4} \qquad (1.9)
$$
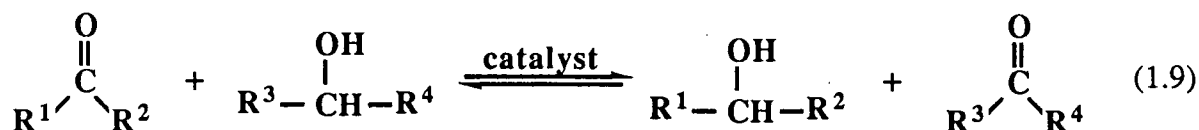
Two pathways have been suggested for the catalysed transfer of hydrogen from the donor to the acceptor. The first mechanism suggested is the unsaturate route (Fig. 1.12), which involves initial coordination of the substrate followed by coordination of the alcohol donor.[14] The formation of an alkoxide is followed by hydrogen transfer from the β-hydrogen of the alkoxide to the coordinated substrate. In the final step, protonolysis generates the product and regenerates the catalyst.

$$
M \; + \; substrate(S) \; \rightleftharpoons \; M(S) \; \xrightarrow[-H^+]{R^1R^2CH(OH)} \; \underset{OCHR^1R^2}{\overset{M(S)}{|}}
$$

$$
\underset{R^1}{\overset{O}{\underset{}{\overset{\|}{C}}}}\!\!\diagdown_{R^2} \; + \; SH_2 \; + \; M \; \xleftarrow{\;\;H^+\;\;} \; \underset{O=CR^1R^2}{\overset{M\!-\!SH}{|}}
$$
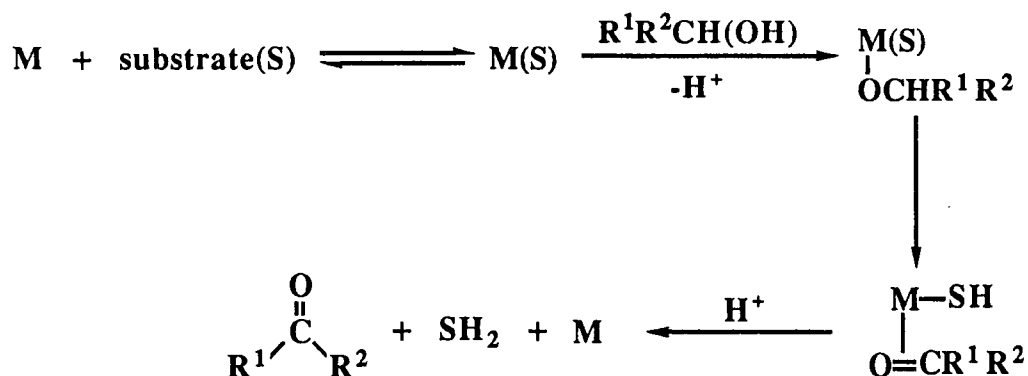
Figure 1.12 Catalytic hydrogen transfer: the unsaturate route.

The other mechanism that has been suggested is equivalent to the hydride route (Fig. 1.13), one suggested pathway when molecular hydrogen is used as the source of hydrogen.[14] This pathway involves initial reaction with the alcohol donor to form a metal hydrido alkoxide species. Then β-hydride transfer and coordination of the substrate generates a dihydride species which can either undergo transfer of both hydrides to the coordinated substrate to generate the product in a single step or by initial transfer of a single hydride followed by protonolysis.

$$MHClP_nL \xrightarrow[\text{-HCl}]{R^1R^2CHOH} MHP_n(OCHR^1R^2)L$$

$$MHClP_nL \xleftarrow{HCl} MP_nL$$

$$MP_nL \xleftarrow[\text{-SH}_2]{} MH_2P_n(S)L$$

$$MHP_n(OCHR^1R^2)L \xrightarrow{\text{substrate}(S)} MH_2P_n(S)L$$

$$R^1\!-\!\overset{\overset{O}{\|}}{C}\!-\!R^2$$

$$MH_2P_n(S)L \xrightarrow{} MHP_n(SH)L$$

$$MHClP_nL \xleftarrow[\text{HCl}]{\text{-SH}_2} MHP_n(SH)L$$
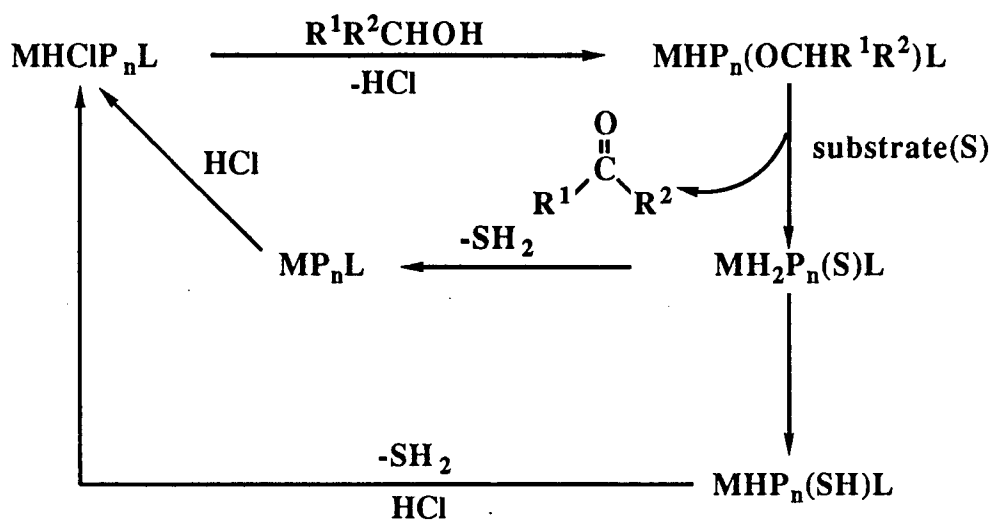
Figure 1.13 Catalytic hydrogen transfer: the hydride route.

Although the individual steps in either pathway are poorly understood, the β-hydrogen transfer step is generally thought to be rate determining. In general, hydrogen transfer reactions are quite difficult to investigate mechanistically due to the large numbers of species in solution.[17]

Hydrogen transfer reactions are usually carried out at the boiling point of the solvent with added base (usually KOH or NEt3). The role of the base is not well understood. Some, ^{31}P NMR studies on Rh-phosphine systems indicate that higher nuclearity complexes (di- and trinuclear) may be formed upon addition of base.[62] Although the base cocatalysts accelerate

the transition metal-catalysed hydrogen transfer, it should be noted that the base itself is capable of catalysing the hydrogen transfer by a different mechanism.[63] However, the solely base catalysed (transition metal free) system is generally much slower than the transition metal complex-base cocatalyst system and therefore does not compete effectively.[62] The order of addition of the substrate and the base cocatalyst seems to play an important role in the activity of a given system.[64, 65] However, no general order of addition has been substantiated, as some systems require prior addition of the base while others require the addition of the substrate initially.

Some excellent stereoselectivities can be obtained using hydrogen transfer systems to catalyse the reduction of ketones. For example, 98% selectivity to the *trans* isomer of 4-*t*-butylcyclohexanol can be achieved by hydrogen transfer from 2-propanol to the corresponding cyclic ketone with a H_2IrCl_6/(MeO)$_3$P *in situ* catalytic system.[17]

Ligands other than those containing phosphorus have also been used with metal complexes to catalyse transfer hydrogenations. Catalysts of the type [Ir(chel)(cod)]Cl, where chel = bipy, phen, or substituted phen, are very active for the transfer of hydrogen to cyclic ketones from 2-propanol. Turnovers of 126 cycles/min were achieved with [Ir(phen)(cod)]Cl as the catalyst and cyclohexanone as the substrate.[44] Stereoselectivity has also been observed for similar rhodium complexes with nitrogen donors as the ligands. Selective formation (80%) of the axial isomer of 4-*t*-butylcyclohexanol has been catalysed by [Rh(4,7-Me$_2$phen)$_2$Cl$_2$]Cl. The hydrogen donor is 2-propanol, although (*S*)-butan-2-ol is found to be just as effective. The system requires the addition of a base cocatalyst, KOH, and the presence of water should be restricted to less than 0.1% by volume for greatest activity.[49]

Unusual regioselectivity is observed in the catalytic reduction of α,β-unsaturated aldehydes under mild conditions using the complex $HIrCl_2(Me_2SO)_3$. An unsaturated alcohol is generated by selective hydrogen transfer from 2-propanol to the carbonyl group of the substrate (eq. 1.10).[66]

$$RCH{=}CHCHO \xrightarrow[\text{(CH}_3)_2\text{CH(OH)}]{\text{HIrCl}_2(\text{Me}_2\text{SO})_3} RCH{=}CHCH_2OH \quad (1.10)$$

$$R = C_6H_5, CH_3$$
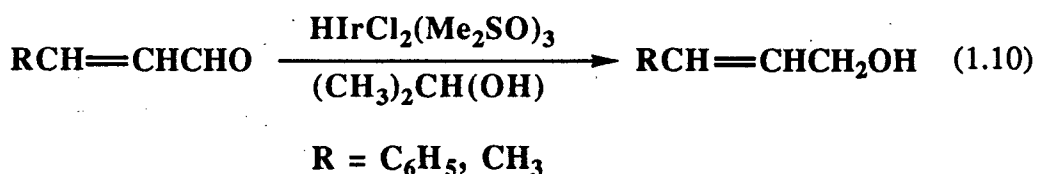
Interestingly, in the reduction of α,β-unsaturated ketones, the olefinic bond is hydrogenated preferentially using the same catalytic system.[66] Related complexes containing tertiary phosphine ligands catalyse the hydrogenation of the olefinic bond as opposed to the carbonyl group in α,β-unsaturated aldehydes. To date, few catalytic systems have been developed for the selective hydrogenation of α,β-unsaturated ketones to unsaturated alcohols, the opposite regioselectivity being far more common.[20]

1.3.1 Asymmetric Transfer Hydrogenation

Two types of asymmetric reactions are possible with transfer hydrogenation. The first (a method of kinetic resolution) is called enantiomer discrimination[17], and involves the enantioselective dehydrogenation of a racemic mixture of an alcohol (e.g. 1-phenylethanol) with one enantiomer reacting faster than the other. The presence of an unsaturated hydrogen acceptor is found to increase the enantioselection. One chiral catalyst for this reaction is RhCl((+)-neomenthyl-diphenylphosphine)$_3$ prepared *in situ* from [RhCl(CH$_2$=CH$_2$)$_2$]$_2$ and the chiral phosphine.[67] However, optical yields of the remaining enantiomer are low. The second type of enantioselective hydrogen transfer, termed enantioface discrimination,[17] involves the formation of a new chiral centre by selective addition of hydrogen to one face of the prochiral substrate. Therefore, the new chiral centre is generated in the hydrogen acceptor. The hydrogen donor may be chiral, achiral or a racemic mixture.

Only moderate optical yields have been obtained for the asymmetric transfer hydrogenation of simple ketones (aryl alkyl ketones). An e.e. of 33% is obtained in the reduction of propiophenone by hydrogen transfer from 2-propanol if the reaction is catalysed by an (+)-[Ir(cod)(PPEI)]$^+$ClO$_4^-$ species, where PPEI is a chiral Schiff base (Fig. 1.14).[68]
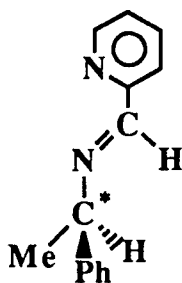
Figure 1.14 The chiral Schiff base, PPEI.

The activity of this hydrogen transfer system is greater than that of rhodium and ruthenium phosphine derivatives which have been used for the reduction of ketones. Similar Ir(I) complexes with chiral Schiff bases have achieved optical yields up to 50% (100% conversion) for the reduction of *t*-butyl phenyl ketone and benzyl phenyl ketone.[48] Also of note is the use of chiral carboxylate ligands[69] (*R*- or *S*-mandelic acids) with Ir complexes generated *in situ* to reduce acetophenone asymmetrically. Optical yields (12%) of 1-phenylethanol were low but are of interest because the chiral ligand is naturally occurring and is therefore inexpensive and readily available.

1.4 The Aim of this Work

As mentioned in section 1.2.1, chiral phosphines often require multistep syntheses and resolution or, if available commercially, are expensive, sometimes being even more costly than the platinum metal complexes that they are used with.[50] There has been interest in developing non-phosphine chiral ligands for use in asymmetric catalysis. Especially attractive are ligands which can be derived from naturally occurring centres of chirality. Naturally occurring chiral ligands or their easily prepared derivatives have the advantage of being readily available and are therefore inexpensive.

Sulphoxide ligands have been studied as an alternative to phosphine ligands in this laboratory in the past.[70-72] Some of the chiral sulphoxide ligands (Fig. 1.3) are analogues of successful chiral phosphines. The basis of the current study resulted from some preliminary

studies, reported in a communication,[71] on an *in situ* catalytic system consisting of a chiral sulphoxide ligand and a rhodium(I) precursor for the asymmetric transfer hydrogenation of ketones. The chiral sulphoxide, AMSO (*N*-acetyl-(*S*)-methionine-(*R,S*)-sulphoxide), used in this study is an easily prepared derivative of the amino acid methionine.

Asymmetric transfer hydrogenation studies on the reduction of some aryl alkyl ketones catalysed by the *in situ* rhodium-sulphoxide system are described in Chapter 3. The *in situ* system consists of a rhodium(I) dimer (either [RhCl(hd)]$_2$ or [RhCl(cod)]$_2$), the chiral sulphoxide AMSO, and base added as a cocatalyst. 2-Propanol acts as the source of hydrogen in these systems. Also, the activity and enantioselectivity of a new sulphoxide derivative, BMSO (*N*-benzoyl-(*S*)-methionine-(*R,S*)-sulphoxide), is described.

Preliminary results for the transfer hydrogenation of imines by this *in situ* catalytic system are presented in Chapter 4. Attempts at preparing coordination compounds containing these sulphoxide ligands are described in Chapter 2 along with related hydrogenation studies. Both of the sulphoxide ligands used, AMSO and BMSO, are racemic at sulphur (*R,S*) but are of a single configuration at carbon. Therefore, both sulphoxide ligands are actually used as mixtures of two diastereomers {either (*S,S*) and (*S,R*) or (*R,S*) and (*R,R*), where the first configuration listed refers to the asymmetric carbon and the second to the sulphoxide}. The separation of the diastereomers of the precursor METO, (*S*)-methionine-(*R,S*)-sulphoxide, by fractional crystallisation through the picrates is also described in Chapter 2. Of interest, but not yet studied, is the effect on the optical yield when only one diastereomer is used as the ligand, as opposed to using a mixture of the two diastereomers.

CHAPTER 2

EXPERIMENTAL PROCEDURES

2.1 Materials

2.1.1 Solvents

Spectral or analytical grade solvents were obtained from MCB, BDH, Aldrich, Eastman, Fisher or Mallinckrodt Chemical Co. Benzene, hexanes and toluene were refluxed with, and distilled from, sodium metal/benzophenone under an atmosphere of N_2. Methanol, ethanol, dichloromethane and acetone were distilled after refluxing with the appropriate drying reagents (Mg/I_2 for methanol and ethanol, P_2O_5 for dichloromethane and anhydrous $CaSO_4$ for acetone). 2-Propanol was refluxed with, and distilled from, CaO and was stored over molecular sieves (Aldrich: Type 5Å, 4-8 mesh) under an atmosphere of Ar. Anhydrous diethyl ether and pentane were used without further purification. All solvents were deoxygenated prior to use.

The deuterated solvents (D_2O, $CDCl_3$, DMSO-d_6, methanol-d_4, and 2-propanol-d_8), used in NMR spectroscopy, were obtained from Merck Frosst Canada Inc. and Aldrich Chemical Co. All of the solvents were used as received, with the exception of $CDCl_3$ which was dried over activated molecular sieves (Fisher: Type 4Å, 4-8 mesh) and stored under argon.

2.1.2 Gases

Purified argon (H.P.), nitrogen (U.S.P.) and hydrogen (U.S.P.) were obtained from Union Carbide Canada Ltd. All gases, except hydrogen, were used without further purification. Hydrogen was passed through an Engelhard Deoxo catalytic purifier to remove traces of oxygen.

2.1.3 Other Materials

2.1.3.1 Starting Materials

The dienes, 1,5-cyclooctadiene and 1,5-hexadiene (Aldrich) were used as supplied, without further purification, for synthetic purposes. L-Methionine ($\equiv$ (S)-methionine), D-methionine ($\equiv$ (R)-methionine) and N-acetyl-dl-methionine (Sigma and Aldrich) were used as supplied, as were the amines, n-hexylamine and amylamine (Aldrich). Benzoyl chloride (Eastman) and isopropyl isocyanate (Aldrich) were also used without further purification. Acetic anhydride (MCB) was freshly distilled under nitrogen before use in synthesis. Benzylamine was purified by stirring with KOH under argon, followed by distillation. The aryl alkyl ketones, acetophenone and propiophenone, which were used in synthesis as well as for substrates, were purified by vacuum distillation after having been stirred with anhydrous $CaSO_4$. Pure (R)-(+)-1-phenylethanol (Aldrich) was used without further purification. N-benzylideneaniline was synthesised by a previous worker in this laboratory and was used without further purification, as the M.P. and ^1H NMR spectrum agreed with the literature values. The corresponding amine, N-phenylbenzylamine (Aldrich) was used without further purification. An imine, $(C_6H_3(CH_3)_2)N=C(CH_3)(CH_2OCH_3)$, (Ciba-Geigy), formed as a condensation product of 1-methoxyacetone and 2,6-dimethylaniline, was used as supplied. Picric acid (2,4,6-trinitrophenol) was prepared by a standard method, and used as isolated.[73]

2.1.3.2 Preparation of N-(1-methylbenzylidene)benzylamine, $C_6H_5\text{-}C(CH_3)=NCH_2Ph$

The imine, N-(1-methylbenzylidene)benzylamine, was prepared by the condensation of acetophenone and benzylamine in a Dean-Stark apparatus. Acetophenone (10 mL, 86 mmol) was added to benzene (50 mL) under argon, followed by the addition of a catalytic amount of para-toluenesulfonic acid. Finally, benzylamine (9.3 mL, 86 mmol) was syringed into the reaction flask. The resulting mixture was refluxed until a stoichiometric amount of water (1.6 mL, 86 mmol) was measured in the graduated portion of the Dean-Stark apparatus. The

benzene was pumped off, and the resulting yellow oil was refrigerated under Ar overnight to yield a solid. Recrystallisation from dry ethanol yielded a highly crystalline white solid. Yield: 13.1 g (73%). M.P. 43.5-44°C; literature 43-44°C.[74] ^{1}H NMR (CDCl$_3$): δ (ppm) 2.37 (3H, s, CH$_3$C(Ph)=), 4.75 (2H, s, -CH$_2$Ph), 7.32-7.93 (10H, m, phenyl protons).

2.1.3.3 Preparation of 1-phenyl-1-propanol

A 3 M solution of NaOH was prepared by dissolving NaOH pellets (2.4 g, 60 mmol) in ethanol (20 mL). This solution was combined with a solution of NaBH$_4$ (1.9 g, 50 mmol) in ethanol (25 mL). The reaction was cooled in an ice bath, a solution of propiophenone (14 mL, 105 mmol) in ethanol (25 mL) introduced to the reaction flask through an addition funnel, and the mixture stirred for 15 minutes. Some HCl was then added in small portions until the reaction mixture was acidic. The solution was extracted with dichloromethane in a separatory funnel and then dried over anhydrous magnesium sulphate. The low boiling solvents were removed by rotary evaporation, leaving the colourless liquid product, 1-phenyl-1-propanol. Yield: ~ 11 mL (75%). ^{1}H NMR (CDCl$_3$): δ (ppm) 0.92 (3H, t, CH$_3$CH$_2$-), 1.80 (2H, m, CH$_3$CH$_2$-), 1.98 (1H, br, -OH), 4.60 (1H, t, -CH$_2$CH), 7.22-7.40 (5H, m, phenyl protons), consistent with literature data.[75]

2.1.4 Ligand Synthesis
2.1.4.1 Preparation of (S)-methionine-(R,S)-sulphoxide, (S)-METO[76, 77]

(S)-Methionine (30 g, 0.2 mol) was dissolved in a mixture of 12 M HCl (12 mL), water (150 mL) and methanol (250 mL). The mixture was cooled while 30% H$_2$O$_2$ (27 mL, 0.24 mol) was added. The solution was allowed to stand at room temperature for 3 hours after the solution had been brought to a total volume of 500 mL by the addition of distilled water. Amylamine (27 mL, 0.23 mol) and methanol (250 mL) were then added to quench the reaction. Acetone (2.4 L) was added to this solution to precipitate a white solid, which was collected in a Büchner funnel and washed with acetone. The solid was then redissolved in water (0.6 L),

filtered and reprecipitated with more acetone (2.0 L). The filtrate was tested with silver nitrate to be sure that all the chloride had been removed from the sulphoxide. Yield: 27.5 g (83%). Calculated for $C_5H_{11}O_3NS$: C 36.36, H 6.71, N 8.48%; found: C 36.12, H 6.82, N 8.43%. M.P. 240-244°C (dec.); literature 226-228°C (dec.). ^{1}H NMR (D$_2$O): δ (ppm) 2.25 (2H, overlapping dt, -SCH$_2$CH$_2$CH-), 2.69 (3H, s, CH$_3$S(O)-), 2.97 (2H, m, -SCH$_2$CH$_2$-), 3.83 (1H, t, J=6.3 Hz, -CH$_2$CH) (Fig. 2.1). IR (KBr): ν(S=O) 1022 cm^{-1} (s). Optical rotation $[α]_D^{25}$ (c=2, H$_2$O buffered at pH 7): +19°, $[M]_D^{25}$ (c=2, H$_2$O buffered at pH 7): +31°; literature $[M]_D^{25}$ (c=2, H$_2$O buffered at pH 7): +32-33°. The optical rotation depends on the ratio of the two diastereomers present and the pH at which the rotation is measured.[76] This applies to all the syntheses described in this sections 2.1.4.1 - 2.1.4.5; in each case described there is approximately 50% of each diastereomer present. The physical and spectroscopic data for this compound agree with those found in the literature.[76, 77]

2.1.4.2 Preparation of (R)-methionine-(R,S)-sulphoxide, (R)-METO

This compound was prepared from (R)-methionine (14.9 g, 0.1 mol) by exactly the same procedure as used for (S)-METO but on half the scale (section 2.1.4.1). Yield: 15.2 g (92%). Calculated for $C_5H_{11}O_3NS$: C 36.36, H 6.71, N 8.48%; found: C 36.23, H 6.65, N 8.40%. M.P. 240-244°C (dec.). ^{1}H NMR (D$_2$O): δ (ppm) 2.25 (2H, overlapping dt, -SCH$_2$CH$_2$CH-), 2.69 (3H, s, CH$_3$S(O)-), 2.97 (2H, m, -SCH$_2$CH$_2$-), 3.83 (1H, t, J=6.3 Hz, -CH$_2$CH). IR (KBr): ν(S=O) 1026 cm^{-1} (s). Optical rotation $[α]_D^{25}$ (c=2, H$_2$O buffered at pH 7): −17°, $[M]_D^{25}$ (c=2, H$_2$O buffered at pH 7): −27°.

2.1.4.3 Preparation of N-acetyl-(S)-methionine-(R,S)-sulphoxide, (S)-AMSO[71]

(S)-Methionine-(R,S)-sulphoxide (7.6 g, 0.046 mol) was dissolved in glacial acetic acid (20 mL, 0.35 mol) under argon in a Schlenk tube. Acetic anhydride (5.1 g, 0.05 mol) was then added to the resulting solution. The reaction mixture was stirred at 10-15°C for

approximately 6 hours. The solution was then pumped on to give a colourless, viscous material, which was dissolved in absolute ethanol, filtered, and diethyl ether added to the filtrate to precipitate a white solid. This was recrystallised from absolute ethanol (~15-20 mL) until a constant value was obtained for the optical rotation. Usually just two crystallisations were required. Yield: 5.8 g (61%). Calculated for $C_7H_{13}O_4NS$: C 40.57, H 6.32, N 6.76%; found: C 40.65, H 6.53, N 6.63%. M.P. 123-127°C; literature 120-129°C. ^{1}H NMR (various solvents) (Table 2.1 and Fig. 2.2). IR (KBr, cm^{-1}): ν(S=O) 1024 (s), δ(N-H) 1572 (s), ν(C=O, amide) 1615 (s), ν(C=O) 1724 (s). Optical rotation $[\alpha]_D^{20}$ (c=5, H_2O buffered at pH 7): +25°, $[M]_D^{20}$ (c=5, H_2O buffered at pH 7): +55°; literature $[\alpha]_D^{20}$ (c=5, H_2O): +26°. The physical and spectroscopic data for this compound agree with those found in the literature.[71]

Table 2.1 300 MHz ^{1}H NMR Chemical Shifts of (S)-AMSO (Fig. 2.2) in Different Solvents.

Solvent	δ (ppm)			
	D_2O	CDCl$_3$*	DMSO-d_6	2-propanol-d_8
H_a (1H, br s)	----	----	12.75	----
H_b (1H, d)	----	----	8.26	----
H_c (1H, m)	4.47	4.64	4.28	4.55
H_d (2H, m)	2.90	3.02	2.71	2.89
H_e (3H, s)	2.66	2.69, 2.72	2.53	2.63
H_f (2H, m)	2.20	2.44	2.07	2.21
H_g (3H, s)	1.99	2.06, 2.07	1.89	2.00

* Some protons within the two diastereomers are resolved in this solvent.
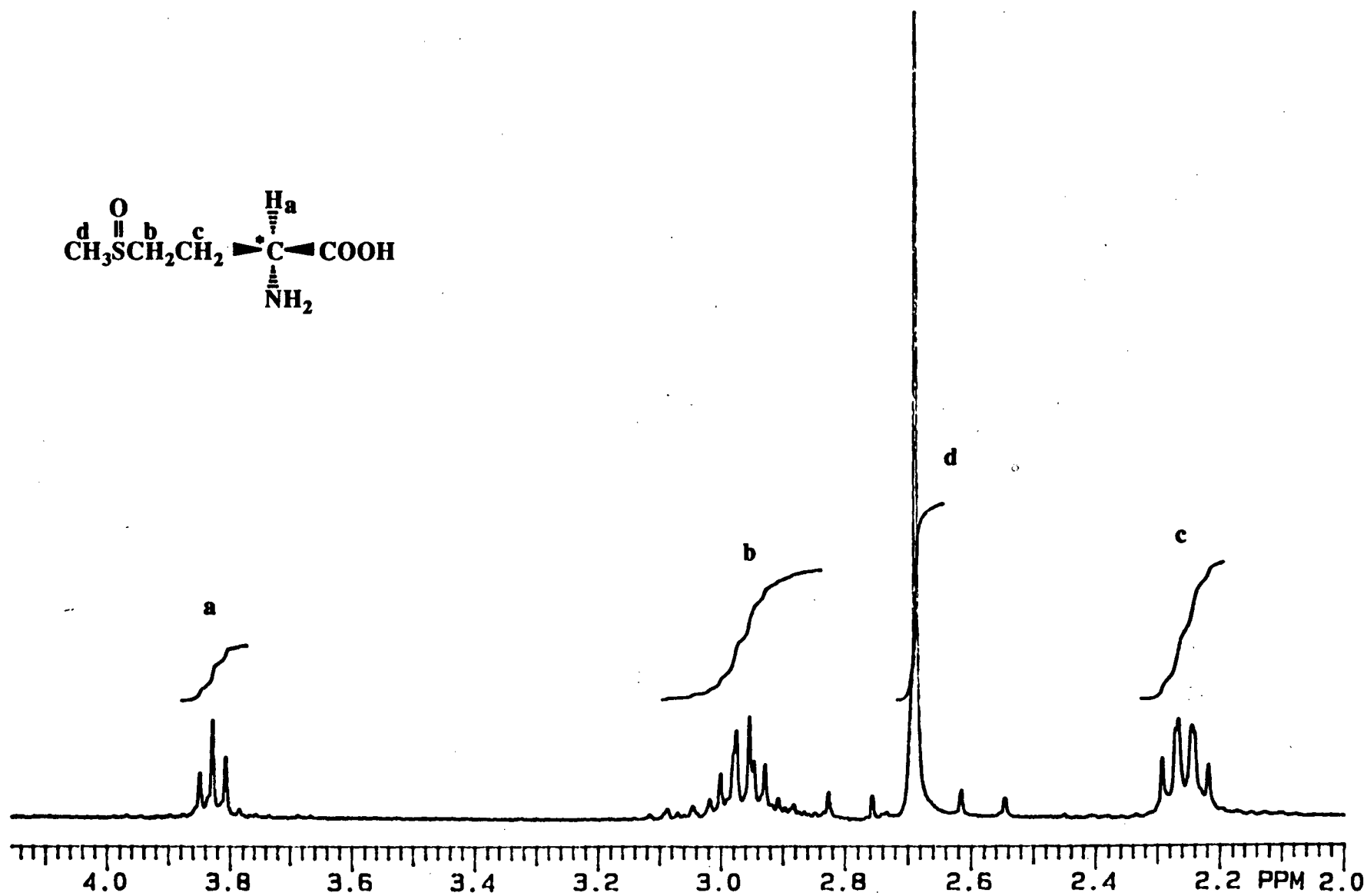
Figure 2.1   300 MHz ^{1}H NMR spectrum of (S)-methionine-(R,S)-sulphoxide in D$_2$O.
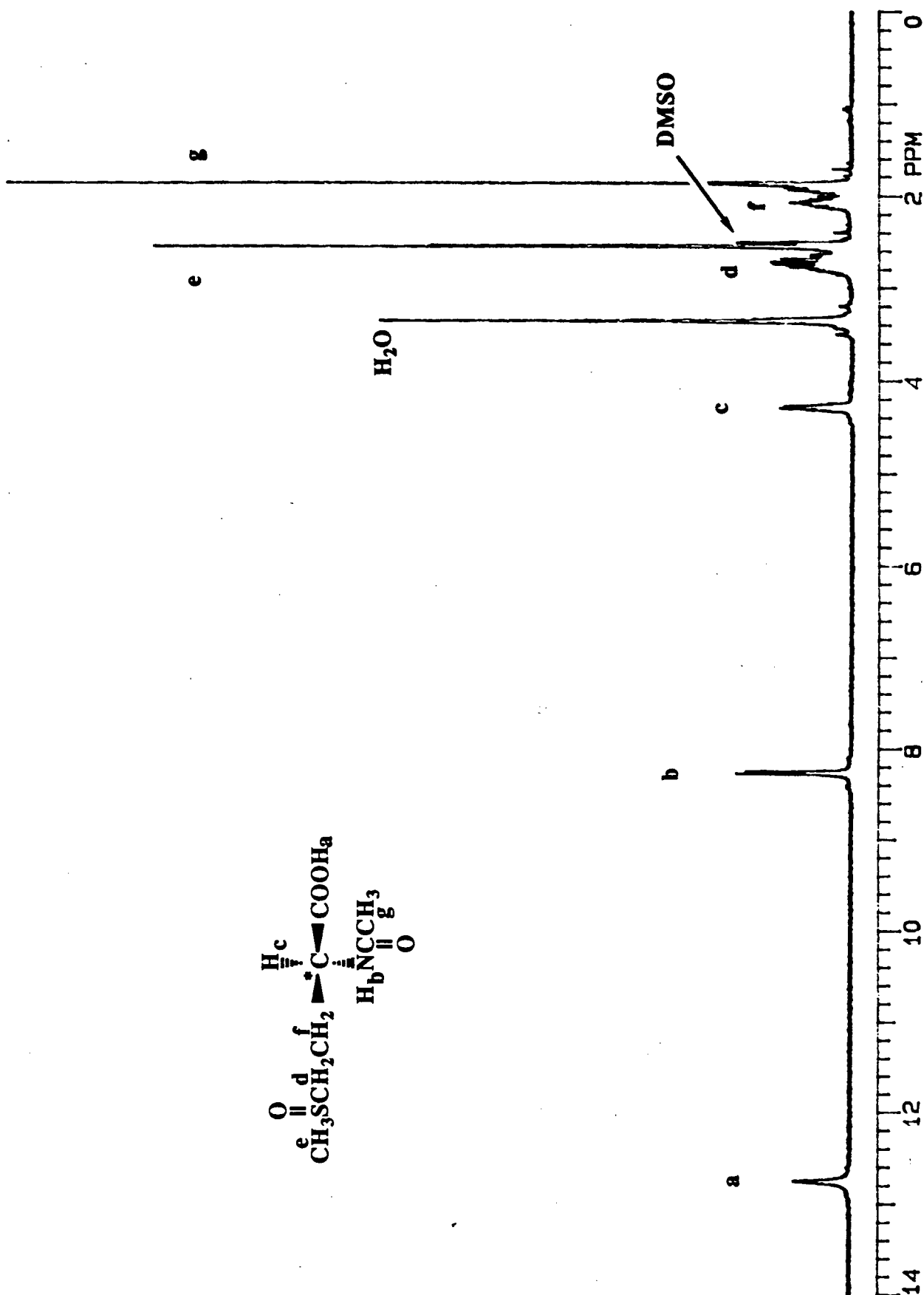
Figure 2.2 300 MHz ^{1}H NMR spectrum of *N*-acetyl-(*S*)-methionine-(*R*,*S*)-sulphoxide in DMSO-d_6.

$$CH_3SCH_2CH_2 \blacktriangleright \overset{H_c}{\underset{*}{C}} \blacktriangleleft COOH_a$$

2.1.4.4 Preparation of *N*-acetyl-(*R*)-methionine-(*R,S*)-sulphoxide, (*R*)-AMSO

This compound was prepared from (*R*)-METO (3.9 g, 0.024 mol) by exactly the same procedure as for (*S*)-AMSO, but on half the scale (section 2.1.4.3). Yield: 2.7 g (55%). Calculated for $C_7H_{13}O_4NS$: C 40.57, H 6.32, N 6.76%; found: C 40.67, H 6.45, N 6.65%. M.P. 126-129°C. ^1H NMR (D_2O): δ (ppm) 1.97 (3H, s, -HNC(O)C̲H̲3), 2.21 (2H, m, -SCH₂C̲H̲2CH-), 2.67 (3H, s, C̲H̲3S(O)-), 2.91 (2H, m, -SC̲H̲2CH₂-), 4.48 (1H, m, -CH₂C̲H̲). IR (KBr, cm⁻¹): ν(S=O) 1028 (s), δ(N-H) 1575 (s), ν(C=O, amide) 1615 (s), ν(C=O) 1727 (s). Optical rotation $[\alpha]_D^{20}$ (c=5, H_2O buffered at pH 7): −28°, $[M]_D^{20}$ (c=5, H_2O buffered at pH 7): −57°. Although both (*S*)- and (*R*)-AMSO are actually mixtures of diastereomers (racemic at sulphur), only the chirality at carbon will be referred to throughout this thesis for ease of discussion.

2.1.4.5 Preparation of *N*-benzoyl-(*S*)-methionine-(*R,S*)-sulphoxide, (*S*)-BMSO

(*S*)-BMSO was prepared using the Schotten-Baumann method of benzoylation.[73] (*S*)-Methionine-(*R,S*)-sulphoxide (5.0 g, 0.030 mol) was dissolved in a 10% NaOH solution (45 mL, 0.13 mol). A small excess of benzoyl chloride (3.8 mL, 0.033 mol) was added and the solution stirred for ~15 min at room temperature; a initial white suspension changed to a clear solution. A white solid (crude (*S*)-BMSO, 5.6 g) was precipitated by addition of an excess of 3M HCl (~30 mL). However, it was necessary to recrystallise the crude product from methanol to remove traces of benzoyl chloride and benzoic acid. (*S*)-BMSO was isolated as white crystals. Yield: 4.3 g (53%). Calculated for $C_{12}H_{15}O_4NS$: C 53.52, H 5.61, N 5.20%; found: C 53.23, H 5.62, N 5.09%. M.P. 194-195°C. ^1H NMR (DMSO-d_6): δ (ppm) 2.20 (2H, m, -SCH₂C̲H̲2CH-), 2.53 (3H, s, C̲H̲3S(O)-), 2.83 (2H, m, -SC̲H̲2CH₂-), 4.51 (1H, m, -CH₂C̲H̲), 7.50 (3H, m, -HNC(O)P̲h̲ (*m*- and *p*-protons)), 7.89 (2H, d, J=6.8 Hz, -HNC(O)P̲h̲ (*o*-protons)), 8.75 (1H, d, J=8.0 Hz, -H̲N̲) (Fig. 2.3). IR (KBr, cm⁻¹): ν(S=O) 993 (s), δ(N-H) 1522 (s), ν(C=O, amide) 1657 (s), ν(C=O) 1721 (s). Optical rotation $[\alpha]_D^{25}$ (c=1, DMSO): −50°.
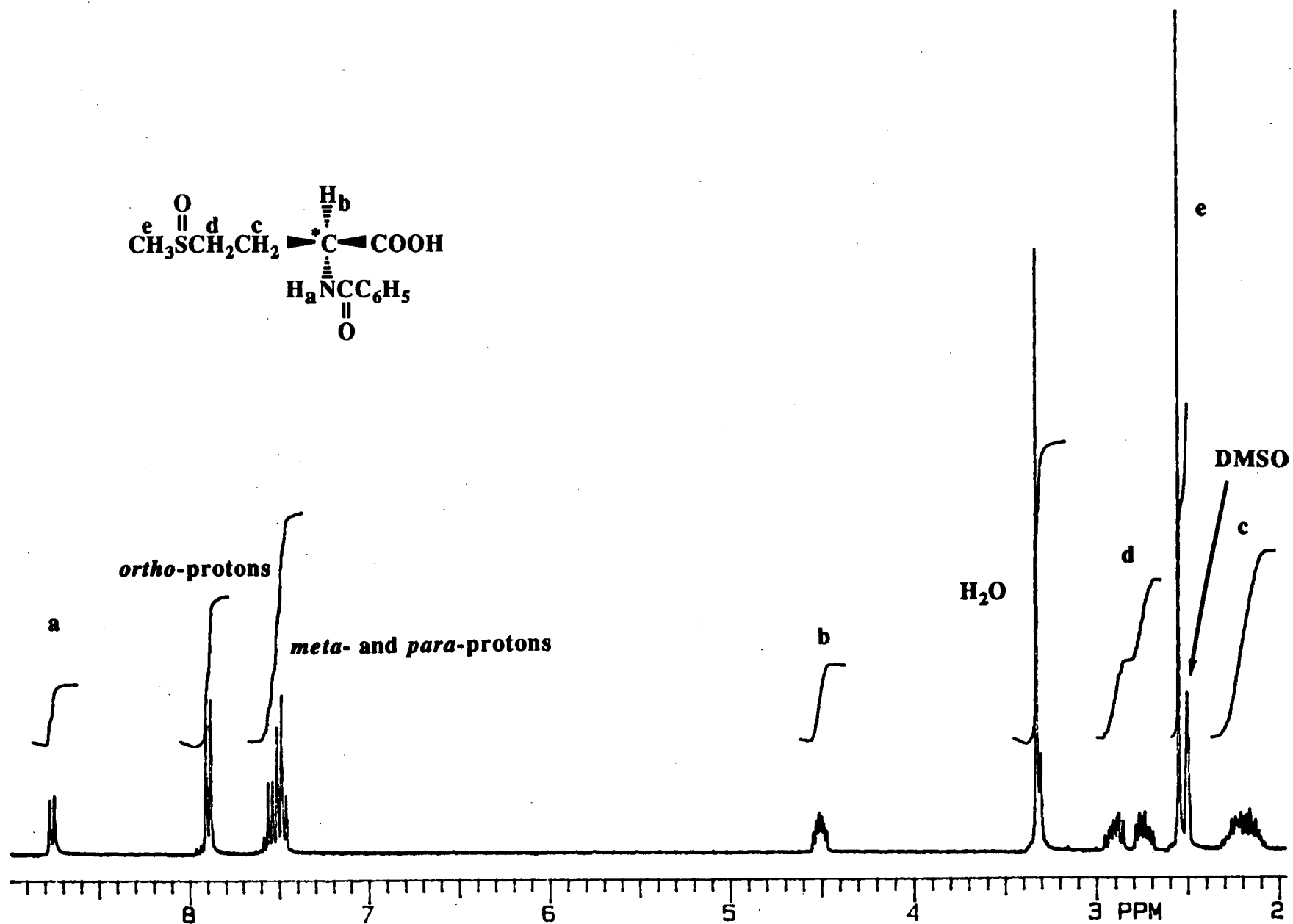
Figure 2.3 300 MHz ^{1}H NMR spectrum of N-benzoyl-(S)-methionine-(R,S)-sulphoxide in DMSO-d_6.

2.1.5 Separation of the Diastereomers of (S)-methionine-(R,S)-sulphoxide

Separation of the diastereomers of (S)-methionine-(R,S)-sulphoxide was achieved through fractional crystallisation of the picrates.[76, 77] The procedure described by Greenstein and Winitz was used to separate the two diastereomers.[76] A solution of picric acid (3.42 g, 0.0149 mol) in methanol (90 mL) was added slowly and dropwise to a solution of (S)-methionine-(R,S)-sulphoxide (2.35 g, 0.0142 mol) in H_2O (10 mL). The yellow precipitate was largely the picrate of (S)-methionine-d-sulphoxide. After the solution was allowed to stand at room temperature for ~20 hours, the yellow precipitate was collected on a Büchner funnel and washed with H_2O. The filtrate was saved for isolation of the other diastereomer. The precipitate was then suspended in H_2O (30 mL) and heated at 70-75°C for 10 min and then allowed to stand for ~23 hours at room temperature; the precipitate was isolated and this procedure repeated twice more. The yellow picrate was finally collected on a filter, weighed (1.36 g), and was decomposed in H_2O (20 mL) by the addition of a 10% excess of amylamine (0.44 mL). The free (S)-methionine-d-sulphoxide was precipitated by addition of acetone (~200 mL). The white solid obtained was collected by filtration and washed with acetone. Yield: 0.14 g (12%). M.P. 240-246°C (dec.); literature 240-245°C (dec.).[77] Optical rotation $[\alpha]_D^{25}$ (c=1.6, H_2O buffered at pH 7): +97°, $[M]_D^{25}$ (c=1.6, H_2O buffered at pH 7): +160°; literature $[\alpha]_D^{25}$ (0.1 M aqueous solution): +99°, $[M]_D^{25}$ (0.1 M aqueous solution): +163.5°.[77] The rotation agrees with the literature value, therefore this diastereomer has been isolated from the mixture of the two diastereomers.

The original filtrate containing the picrate of (S)-methionine-l-sulphoxide was evaporated to dryness on the rotary evaporator. The residue was taken up in H_2O (150 mL) and filtered to remove any remaining solid. The filtrate was, once again, evaporated to dryness. The residue was refluxed in absolute methanol (40 mL) and gravity filtered hot to remove some insoluble material. The filtrate was allowed to stand at room temperature for ~20 hours to crystallise the picrate of (S)-methionine-l-sulphoxide. The yellow picrate was collected on a Büchner funnel and washed with cold methanol. The picrate (0.86 g) was

decomposed in H2O (100 mL) by addition of a 10% excess of amylamine (0.33 mL). The free

(S)-methionine-l-sulphoxide was obtained by addition of acetone (500 mL). The white

precipitate was collected by filtration and washed with acetone. Yield: 0.17 g (14%).

M.P. 244-247°C (dec.); literature 238-239°C (dec.).[77] Optical rotation $[\alpha]_D^{25}$ (c=0.9, H2O

buffered at pH 7): +76°, $[M]_D^{25}$ (c=0.9, H2O buffered at pH 7): +125°; literature $[\alpha]_D^{26}$

(0.05 M aqueous solution): −71.6°, $[M]_D^{26}$ (0.05 M aqueous solution): −118.4°.[77] The

experimental rotation indicates that this diastereomer has not been isolated from the mixture,

and in fact probably contains more of the other diastereomer (S)-methionine-d-sulphoxide.

The yields of (S)-methionine-l-sulphoxide and (S)-methionine-d-sulphoxide are slightly

lower than those reported.[76] This fractional crystallisation needs to be performed on a larger

scale so that enough material can be isolated to allow for subsequent conversion into one

diastereomer of (S)-AMSO. Because of the low yields of the two diastereomers isolated, the

acetylation of either diastereomer of (S)-METO was not attempted.

2.1.6 Rhodium Compounds

The rhodium was obtained, on a loan from Johnson Matthey Ltd., as RhCl3·3H2O

(containing 39% Rh). All synthetic reactions were carried out in deoxygenated solvents under

an atmosphere of argon, employing Schlenk techniques.

2.1.6.1 Di-μ-chloro-bis(η^4-1,5-cyclooctadiene)dirhodium(I), [RhCl(C8H12)]2[78, 79]

Rhodium(III) trichloride trihydrate, RhCl3·3H2O (2.6 g, 9.9 mmol), was dissolved in

distilled water (4.5 mL), which had been previously degassed. This was followed by the

addition of ethanol (25.0 mL), and 1,5-cyclooctadiene (3.25 mL, 26 mmol) to the resulting

solution, which was refluxed with stirring for 18 hours. During this time, the product

precipitated as a yellow-orange solid, which was collected by vacuum filtration on a sintered

glass filter, dried under vacuum and stored under argon in the dark. Yield: 2.28 g (93%).

Calculated for $Rh_2Cl_2C_{16}H_{24}$: C 38.97, H 4.91, Cl 14.38%; found: C 38.99, H 4.84, Cl 14.08%. M.P. ~ 236°C (dec.); literature 220-254°C (dec.). ^1H NMR ($CDCl_3$): δ (ppm) 1.82 (4H, br, allylic protons), 2.58 (4H, br, allylic protons), 4.27 (4H , br, vinylic protons). IR (KBr): Characteristic strong bands appear in the IR spectrum at 816, 961, and 994 cm^{-1}; literature 819, 964 and, 998 cm^{-1} (Nujol mull). The physical and spectroscopic data for this dimer agree with those reported in the literature.[78, 79]

2.1.6.2 Di-μ-chloro-bis(η^4-1,5-hexadiene)dirhodium(I), [RhCl(C$_6$H$_{10}$)]$_2$[78]

Rhodium(III) trichloride trihydrate, $RhCl_3 \cdot 3H_2O$ (1.9 g, 7.4 mmol), was dissolved in distilled water (4.5 mL). To this red-purple solution, ethanol (25.0 mL) was added, followed by the addition of 1,5-hexadiene (2.6 mL, 22 mmol) by a syringe. This mixture was stirred under argon at room temperature for 24 hours. The resulting orange precipitate was collected by vacuum filtration on a Schlenk filter and dried in vacuo. The solid, once dry, was orange-brown in colour. Yield: 1.24 g (76%). Calculated for $Rh_2Cl_2C_{12}H_{20}$: C 32.68, H 4.57, Cl 16.08%; found: C 32.34, H 4.42, Cl 15.73%. M.P. 115-118°C; literature 116-118°C. ^1H NMR ($CDCl_3$): δ (ppm) 1.56 (2H, br m, H$_b$), 2.42 (4H, br m, methylene protons), 3.41 (2H, br m, H$_a$), 4.61 (2H, m, H$_c$); see Fig. 2.4 for assignment. IR (KBr): Characteristic strong bands appear in the IR spectrum at 850, 961, 1108, and 1436 cm^{-1}; literature 850, 963, 1106, and 1436 cm^{-1} (KBr pellet). The physical and spectroscopic data agree with those found in the literature.[78, 80]
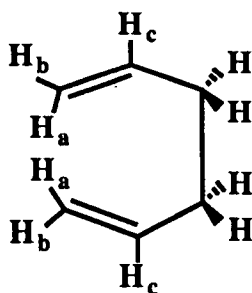
Figure 2.4 1,5-Hexadiene ligand.

2.2 Instrumentation

Infrared spectra were recorded on a Nicolet 5DX FT-IR spectrometer as either Nujol mulls between CsI plates or as KBr pellets.

[1]H nuclear magnetic resonance spectra were recorded on either a Bruker WP-80, a Bruker WP-270, or a Varian XL-300 spectrometer, with tetramethylsilane (TMS) at $\delta=0.0$ ppm as the standard. All samples containing ruthenium or rhodium species were sealed under argon, while all other samples were prepared in air.

Optical rotation measurements were determined on a Perkin-Elmer 141 Polarimeter using a glass optical cell with a path length of 10.000 cm (1.0000 dm) and a 1.0 mL capacity.

Measurements of pH were performed using a Corning Model 12 pH meter with a standard glass pH combination electrode (Fisher).

Gas chromatographic analyses were performed on a temperature programmable Hewlett Packard 5890A instrument equipped with either a 6' x 0.125" O.D. stainless steel-10% Carbowax 20M on Chromosorb W 80/100 (packed column) or a 15-m HP1 (crosslinked methyl silicone gum, capillary column, 0.2-mm x 0.33-μm film thickness). A chiral column, 25-m x 0.25-mm I.D. Chirasil-Val III (Alltech), was used to separate the enantiomers of chiral alcohols. Both thermal-conductivity (TCD) and flame-ionisation (FID) detectors were used to detect the products. Helium was used as the carrier gas in all analyses (rate of flow ~ 40 mL/min).

Melting points were recorded using a Fisher Johns type melting point apparatus and were uncorrected.

Elemental analyses were performed by Mr. Peter Borda of this department.

2.3 Measurement of the pK_a of *N*-acetyl-(*S*)-methionine-(*R*,*S*)-sulphoxide

The pK_a of (*S*)-AMSO was determined by titrations with 0.1 N NaOH. A 0.10 M solution of (*S*)-AMSO (5.0 mL) was diluted in a solution of the inert electrolyte KNO_3 (0.1 M), which had been previously prepared using degassed and distilled water. The NaOH

solution was also prepared using degassed and distilled water. Sodium hydroxide was added via a buret to the stirred (S)-AMSO solution and the pH was monitored with a pH-meter equipped with a combination glass electrode. The pH-meter had been previously standardised with buffer solutions of pH 4.0 and 7.0. The experiment was repeated twice (Appendix A1) and from a plot of pH versus volume of NaOH (Fig. 2.5), the pK_a of the ligand (S)-AMSO was determined from the half equivalence point. The pK_a determined for the carboxylic acid proton was 3.30 ± 0.05. The endpoint corresponded exactly to one equivalent of proton from the ligand as expected.
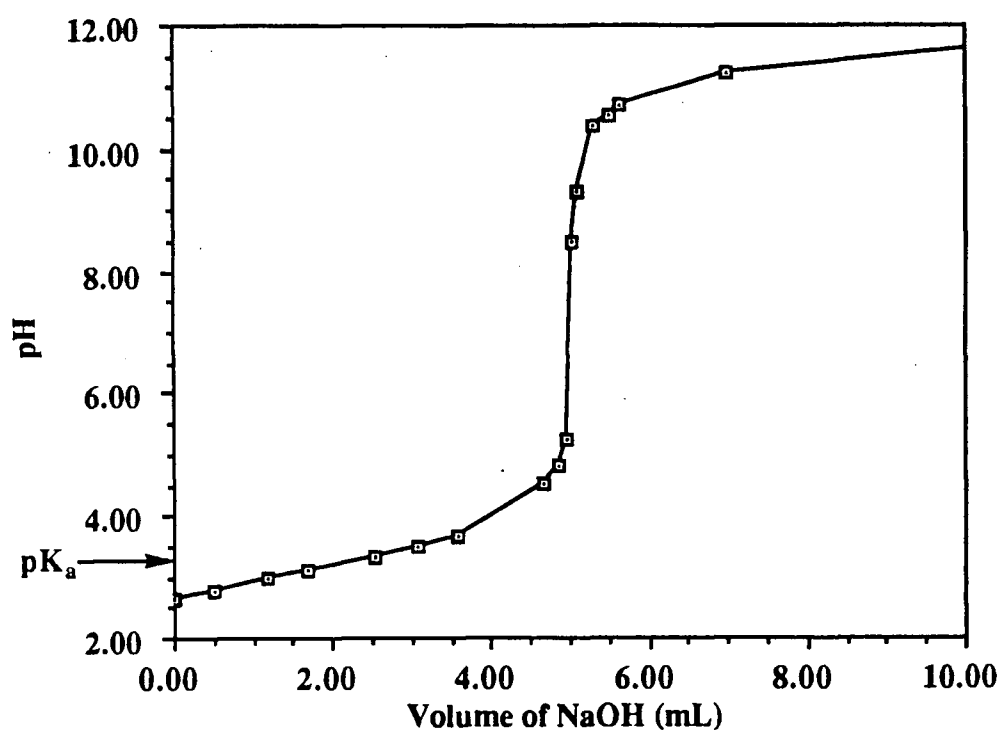
Figure 2.5 Titration curve of N-acetyl-(S)-methionine-(R,S)-sulphoxide.

2.4 Typical Catalytic Transfer Hydrogenation Experiments

2.4.1 Method 1 (Argon Stream Over Solution)

In a 50 mL three-neck round bottom flask, equipped with a reflux condenser, an Ar inlet and a septum, a Rh^I dimer (either $[RhCl(hd)]_2$ or $[RhCl(cod)]_2$) was dissolved, along with a chiral ligand {(S)-AMSO or (R)-AMSO}, in 2-propanol (10 mL). Typically, 5×10^{-5}

moles of Rh and 5-10x10^{-5} moles of sulphoxide ligand were used. This mixture was refluxed for approximately 15 minutes before the substrate, acetophenone (~ 1 mL), was added with a syringe, followed immediately by the addition of a KOH solution by syringe (1-2 mL of a solution prepared by dissolving 1.25-2.50x10^{-3} moles of KOH in 10 mL of 2-propanol). The pale yellow solution turned cloudy after the addition of acetophenone and, within five minutes of the addition of the KOH solution, the mixture had turned dark brown. The reaction was heated at reflux for 8-20 hours under a stream of argon. During the reaction, a brown-black solid precipitated out of the solution. The reaction mixture was transferred with a syringe to a Kugelrohr type apparatus (Fig.2.6) under a stream of argon.
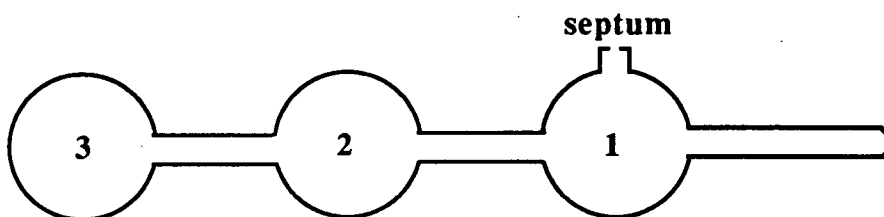
Figure 2.6 Kugelrohr type apparatus.

The mixture was frozen in bulb 3 by immersing that bulb in a Dewar of liquid nitrogen. The Kugelrohr apparatus was then removed from the liquid N$_2$, and the 2-propanol pumped off under vacuum until the third bulb had returned to room temperature. At this point, all of the solvent had been removed. The mixture of substrate and product were then isolated from the solid by bulb-to-bulb distillation in the Kugelrohr apparatus. This was achieved by freezing the solution again in bulb 3 and then pumping, while the second and third bulb of the apparatus was heated in a small oven at ~ 100°C. The first bulb was cooled with liquid nitrogen in order to collect the product-substrate mixture. The resulting mixture was injected into the gas chromatograph to determine the conversion of acetophenone to 1-phenylethanol (section 2.5.1). Finally, the optical purity of the product was determined either by: (1) measuring the rotation of the solution using a polarimeter (section 2.5.2); or (2) injection of a derivative of the product onto a chiral column (section 2.5.3).

2.4.2 Method 2 (Sealed Under Argon)

To a ~ 60 mL thick-walled Schlenk tube equipped with a Kontes valve was added a Rh^I dimer (either [RhCl(hd)]$_2$ or [RhCl(cod)]$_2$) and a chiral ligand ((S)-AMSO or (R)-AMSO). Typically, 5×10^{-5} moles of Rh and $5\text{-}10 \times 10^{-5}$ moles of sulphoxide ligand were used. The Schlenk tube was evacuated before 2-propanol (10 mL) was added under argon to dissolve the two solids. The resulting mixture was heated at 80°C in an oil-bath for approximately 15 minutes. The substrate, acetophenone (~ 1 mL), followed immediately by a KOH solution (1-2 mL of a solution prepared by dissolving $1.25\text{-}2.50 \times 10^{-3}$ moles of KOH in 10 mL of 2-propanol), were then added via syringes. As in method 1, the pale yellow solution turned cloudy after the addition of acetophenone and soon after the addition of the KOH solution, the mixture had turned dark brown. The reaction mixture was heated for between 8-20 hours; a brown-black solid again precipitated out of the solution. After the heating was complete, the reaction mixture was transferred with a syringe to a Kugelrohr type apparatus under a stream of argon. The work-up and analyses of the products were the same as outlined in section 2.4.1.

2.5 Analysis of the Hydrogenation Products

2.5.1 Gas Chromatographic Analysis

The extent of transfer hydrogenation was determined by gas chromatographic analysis of the product mixture using a Carbowax 20M packed column (alcohols) or an HP1 capillary column (amines). Amines were injected as a solution in 2-propanol. Analyses were performed isothermally at 160°C with an injector temperature of 300°C and a detector temperature of 325°C. Alcohols were injected as solutions in either 2-propanol or hexanes (10 µL of product mixture in ~1 mL of solvent). Analyses of the alcohol product mixtures were performed isothermally at 150°C with injector and detector temperatures of 250°C. The conversion of substrate to product was always taken as an average value obtained from 3-4 injections of each diluted substrate-product solution.

The concentration of the alcohol present in the substrate-product mixture obtained from the transfer hydrogenation experiments was determined by injection of the mixture (undiluted) on the Carbowax 20M column. The retention times and response factors under the above conditions for the substrate (acetophenone), the corresponding hydrogenated product (1-phenylethanol), and any remaining 2-propanol are shown in Table 2.2. The retention times of the alcohols were determined by injection of authentic samples of the racemic alcohols.

Table 2.2 Retention Times and Response Factors.

Compound	Retention time (min)	Response factor
2-propanol	0.7	1.0
acetophenone	5.8	4.0
1-phenylethanol	9.6	4.0

The concentration of the product alcohol was determined from the areas obtained from the GC integrator and by division of the appropriate response factor. Determination of the concentration was necessary for calculation of the specific rotation from the observed rotation (eq. 2.1).

2.5.2 Optical Rotation Measurements

Optical rotations were measured on mixtures of the chiral products and substrates (e.g. 1-phenylethanol and acetophenone). The rotations were corrected for the presence of substrate using calibration curves, knowing the amount of substrate present from GC analysis. The observed rotation, α, once corrected was used to calculate the specific rotation $[\alpha]_D^T$ in eq. 2.1, where c = concentration (or density for a neat liquid) in g/mL, l = path length in dm, and T = temperature. The e.e. can be calculated from the specific rotation of the product mixture and knowledge of the specific rotation of a pure enantiomer (eq. 1.2).

$$[\alpha]_D{}^T = \frac{\alpha}{c \cdot l} \qquad (2.1)$$

2.5.3 Separation of Enantiomers of Chiral Products using a Chiral Column

In order to separate effectively the enantiomers of chiral alcohols it was first necessary to prepare a derivative of the alcohol.[81] Enantiomer separation of alcohols was achieved using isopropyl urethane derivatives (eq. 2.2). The isopropyl urethane derivative was prepared by dissolving the product alcohol mixture (1-20 µL, depending on the conversion of the substrate to the product) in dichloromethane (200 µL) followed by addition of isopropyl isocyanate (~100 µL, ≤100 fold excess). The mixture was heated in a screw-capped vial at 100°C for 20 min.

$$(2.2)$$
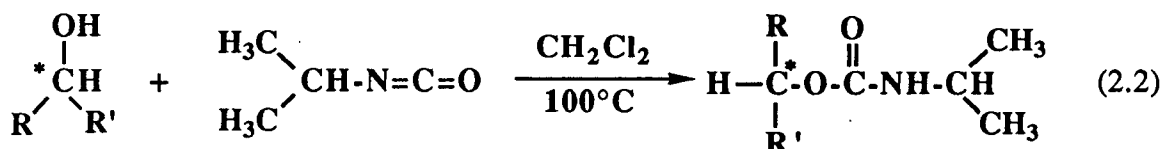
The solvent and excess isopropyl isocyanate were removed with a stream of nitrogen, and the urethane derivatives were dissolved in diethyl ether (~0.5 mL) for injection onto the chiral column, Chirasil-Val III. Gas chromatographic analysis was performed isothermally at 145°C with an injector temperature of 250°C and a detector temperature of 300°C (Fig. 2.7). Enantiomer separation can also be achieved for chiral amines using this isocyanate method.[82] The e.e. was taken as the average of 3-4 injections. No racemisation was observed when this procedure was performed on pure enantiomers, in keeping with previous reports.[51] This method of e.e. determination was checked by injection of derivatives of known enantiomeric composition. A linear correlation was observed (Table 2.3).
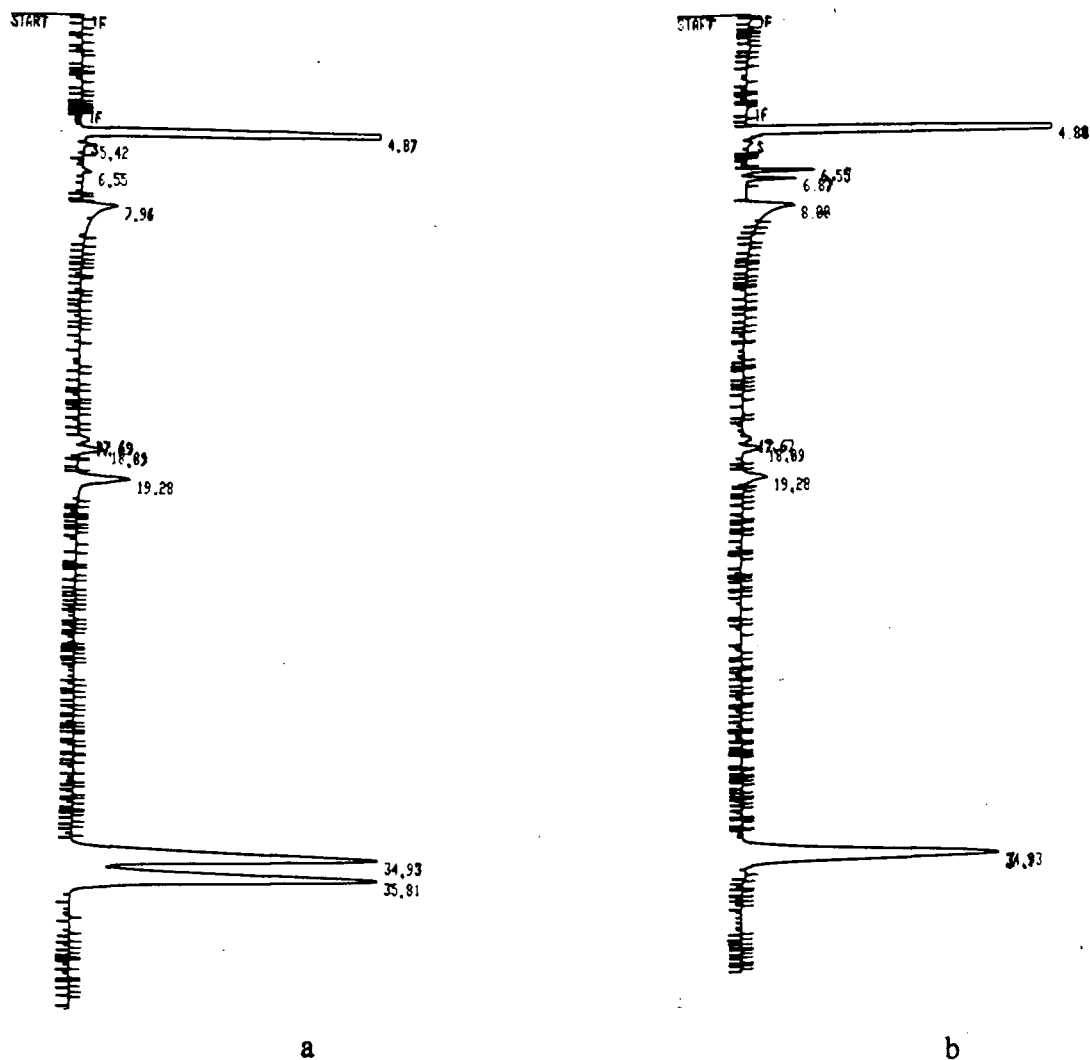
Retention times of derivatives (GC, diagram a).

Retention times (min)	Component
4.87	Solvent (diethyl ether)
5.42, 6.55	isopropyl isocyanate impurities
7.96	unreacted alcohol
17.69, 18.89, 19.28	isopropyl isocyanate impurities
34.93	(R)-(+)-derivative
35.81	(S)-(−)-derivative

Figure 2.7 Gas chromatograms of urethane derivatives separated on the chiral Chirasil-Val III column: (a) derivative of racemic 1-phenylethanol; (b) derivative of (R)-(+)-1-phenylethanol.

Table 2.3 Response of Gas Chromatograph Integrator for Varying Enantiomeric Compositions.

Composition (% of (R)-(+)-alcohol)[†]	e.e.(%) (determined from GC integrator)
pure (R)-(+)-alcohol	100
77.6	74.8
58.5	57.0
48.6	48.4
28.0	26.9
racemic alcohol	0

† Known mixtures of racemic and enantiomerically pure 1-phenylethanol were prepared; for example, the 48.6% (R)-(+)-alcohol sample was prepared by mixing 3 µL of each (R)-(+)- and racemic-1-phenylethanol (0.00278 g and 0.00294 g, respectively). Use of eq. 1.3 gives an e.e. of 48.6%.

Note: The error of 2.8% seen for the 77.6% pure (R)-(+)-alcohol is larger than the actual error for this method of e.e. analysis. This is due to the difficulty in weighing such small amounts of alcohol. The error for this method of e.e. determination is ~1%, as determined by repeating the preparation of a derivative from one particular transfer hydrogenation experiment.

2.5.4 Separation of Diastereomeric Derivatives of Chiral Alcohols by Conventional Gas Chromatography

Separation of chiral alcohols by conventional gas chromatography (non-chiral) was attempted by preparation of diastereomeric derivatives.[83] The derivatives were prepared by reaction of the chiral alcohol with acetyl (S)-lactyl chloride reagent (kindly provided by Dr. K. N. Slessor at Simon Fraser University). The acetyl (S)-lactyl chloride reagent was prepared from (S)-(+)-lactic acid (Sigma) as shown in Fig. 2.8.

To the product alcohol (10 µg) was added a pyridine solution (15 µL of a solution of 50 µL C_5H_5N in 1 mL of diethyl ether), followed by a solution of acetyl-(S)-lactyl chloride (40 µL of a solution of 100 mg acetyl-(S)-lactyl chloride in 4 mL of CH_2Cl_2); Fig. 2.9 summarises the relevant chemistry. The reactant mixture was sealed in an ampoule prepared

from a disposable pipet and left overnight at room temperature. Then the ampoule was opened and the solution diluted with hexanes (50 μL) followed by washing with H_2O (50 μL). The aqueous phase was removed and the organic phase washed with an aqueous 5% solution of $NaHCO_3$ (3 x 50 μL) followed by an additional H_2O wash (50 μL). The organic layer was diluted with hexanes (100 μL) for injection onto the HP1 column.
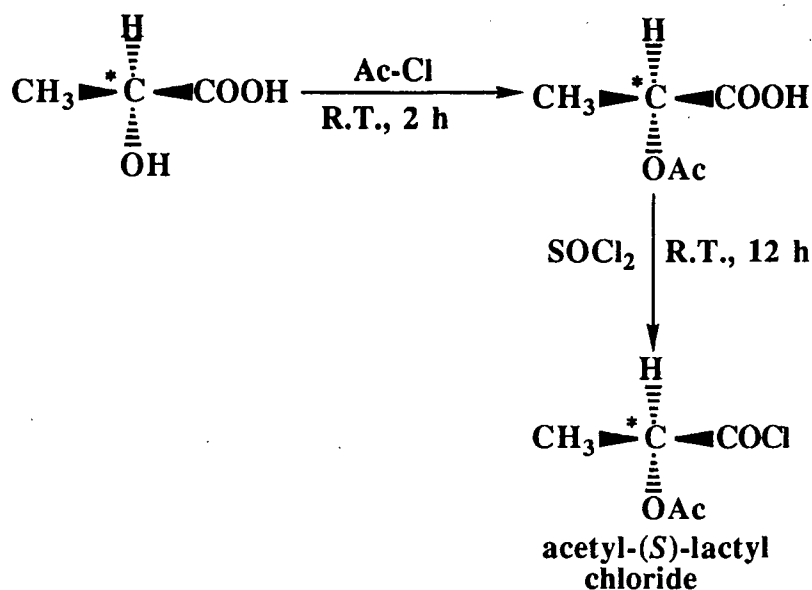
Figure 2.8 Synthesis of acetyl-(S)-lactyl chloride reagent.

The above separation was attempted using racemic 1-phenylethanol, but the chiral alcohol derivatives were not resolved by GC under the column conditions used (T = 160°C, isothermal, injector and detector temperatures: 250°C). However, it is believed that separation could be achieved using this method if the correct GC conditions were found. This method was only attempted briefly and discontinued in favour of separation on the chiral column (section 2.5.3). The method outlined in section 2.5.3 has the advantage over the method described here in that the derivative, necessary for separation, is easily prepared in 20 min from a commercially available inexpensive reagent. The required diastereomeric derivatives (Fig. 2.9) take more than 12 hours to prepare, and also the reagent used to synthesise the

derivatives must be prepared from more expensive chiral starting materials. On the more positive side, this method avoids the use of an expensive chiral column.
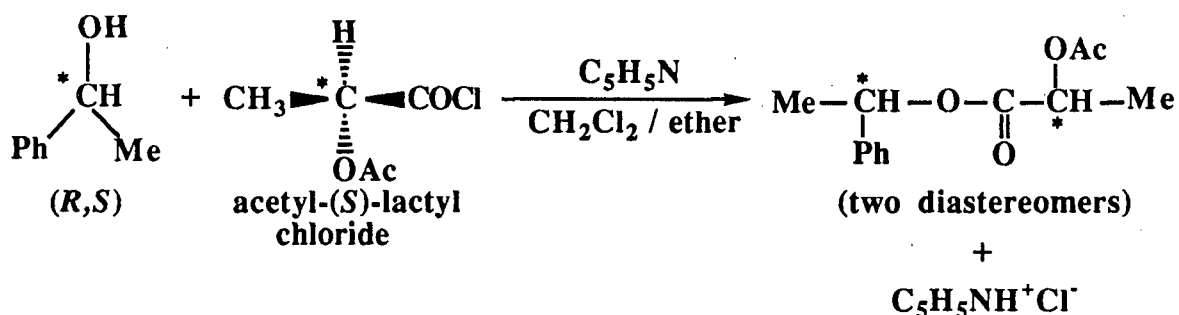
Figure 2.9 Preparation of diastereomeric derivatives for separation by GC.

2.5.5 Chiral Shift Reagents

The enantiomeric composition of the transfer hydrogenation product alcohol was examined also by ^{1}H NMR with the use of a chiral shift reagent. The analysis was attempted with racemic 1-phenylethanol in CDCl$_3$ with the tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III) derivative (Aldrich) (Fig. 2.10).
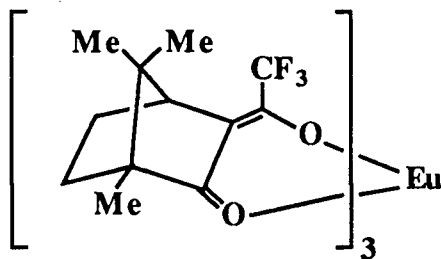
Figure 2.10 Europium(III) chiral shift reagent.

The α-proton of 1-phenylethanol was observed while the decoupler was set on the methyl resonance. A small separation for the enantiomeric α-proton resonances was observed in CDCl$_3$ ($\Delta\delta$(CH) ~ 0.05 ppm) (Fig. 2.11). Of note, larger enantiomeric resolutions ($\Delta\delta$(CH) ~ 0.2 ppm) of 1-phenylethanol have been reported in CS$_2$ using a slightly different

europium shift reagent [Eu(facam)₃].[55, 71] Baseline separation of the two peaks was not achieved in CDCl₃, so this method of determining the enantiomeric excess was less favoured than using separation on the chiral column (section 2.5.3). Although some degree of separation is achieved, this method suffers from two disadvantages: (1) the error in the integration is relatively large (when compared to the error in GC integration), and (2) the chiral shift reagents are expensive and quite large amounts are necessary (e.g. [chiral shift reagent]: [$CH_3CH(OH)C_6H_5$] ~ 0.2).[55]
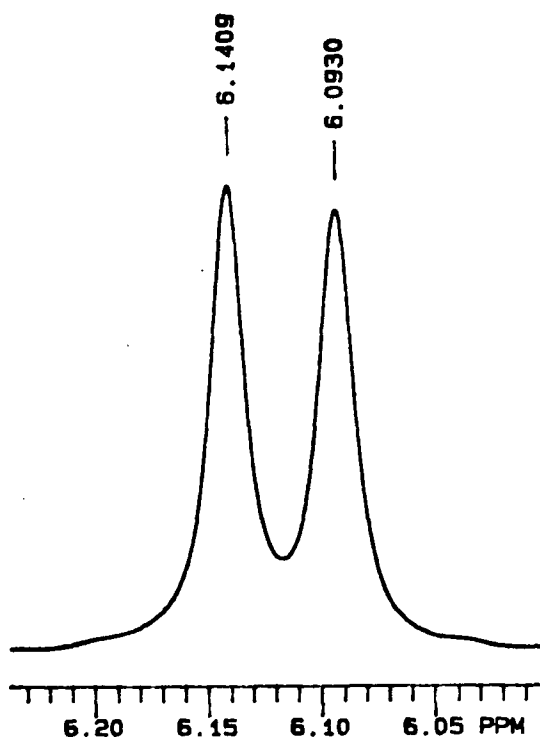
Figure 2.11 300 MHz ^{1}H NMR spectrum (CDCl₃) of α-proton resonances of racemic 1-phenylethanol in the presence of a chiral shift reagent.

2.6 Attempts at Preparing Coordination Compounds of AMSO and BMSO

2.6.1 Ruthenium Compounds

The ruthenium was obtained, on a loan from Johnson Matthey Ltd., as $RuCl_3 \cdot xH_2O$ (containing 42.49% Ru). All synthetic reactions were carried out in deoxygenated solvents under an atmosphere of argon, employing Schlenk techniques.

2.6.2 Coordination Compound of Ruthenium and (S)-AMSO

$RuCl_3 \cdot xH_2O$ (0.21 g, 0.90 mmol) and (S)-AMSO (0.85 g, 4.1 mmol) were dissolved in degassed ethanol (25 mL). The resulting brownish solution was refluxed under argon for 3 hours. The solution was reduced in volume by pumping off the solvent and diethyl ether was added to precipitate the product. A yellow solid began to precipitate but quickly became a brown oil on the bottom of the Schlenk tube. The solvent was removed at the pump leaving the brown oil. A number of different solvent mixtures were used without success in an attempt to isolate a solid. Finally, all the solvent was removed leaving an orange-brown material which could be ground into a powder. This orange-brown solid proved difficult to characterise by ^{1}H NMR and IR. A transfer hydrogenation experiment (substrate: acetophenone) with this orange-brown compound or mixture of compounds as the catalyst was unsuccessful. Therefore, this material was not studied any further in favour of studies of transfer hydrogenation experiments involving *in situ* rhodium systems.

2.6.3 Coordination Compound of Ruthenium and (S)-BMSO

$RuCl_3 \cdot xH_2O$ (0.27 g, 1.1 mmol) and (S)-BMSO (0.54 g, 2.0 mmol) were dissolved in degassed ethanol (~ 10 mL). The resulting dark orange-brown solution was refluxed for 4.5 hours under argon. The volume of the now light orange-brown solution was reduced to ~3-4 mL and diethyl ether was added to precipitate the product. Some yellow solid began to precipitate from the solution but quickly became a brown oil. This was accompanied by a change in the solution colour to a cloudy light brown. The solvent was pumped off leaving a

brown solid clump which was ground into a powder. The brown solid was difficult to characterise by ^{1}H NMR and IR. Indeed, TLC on neutral alumina with a solvent mixture of methanol and dichloromethane (1 : 19) showed more than one species to be present.

2.6.4 Other Coordination Compounds

Other attempts at preparing coordination compounds of (*S*)-AMSO and the metals Co and Ni proved unsuccessful or at least gave compounds which were impossible to characterise. Both experiments involved starting with $MCl_2 \cdot 6H_2O$, where M = Co or Ni. The preparation of the Co compound seemed the most promising as a bright blue solid was isolated. Unfortunately, this material was extremely hygroscopic (in air turns to oil) and seemed to be paramagnetic (NMR peaks are broad).

CHAPTER 3

CATALYTIC ASYMMETRIC TRANSFER HYDROGENATION OF ARYL ALKYL KETONES BY *IN SITU* RHODIUM-SULPHOXIDE SYSTEMS

3.1 General Introduction

The asymmetric hydrogenation of aryl alkyl ketones has been most effectively carried out under H_2 with catalytic systems that use phosphines as the ligands. For example, acetophenone has been asymmetrically hydrogenated with approximately 80% e.e. using rhodium-chiral phosphine catalytic systems (Table 3.1).

Table 3.1 Asymmetric Hydrogenation of Acetophenone.

Catalyst	H_2 pressure(atm)	Rx. time(h)	T(°C)	Conv.(%)	e.e.(%)
(i) [Rh(nbd)((+)-Diop)Cl]	7	96	22	51	78[a]
(ii) [Rh(nbd)Cl]$_2$ + (+)-Diop	70	6	50	64	80[b]
(iii) [Rh(nbd)Cl]$_2$ + (S,S)-BDPP	70	24	50	72	82[c]

(i)   Ref. 51; added (–)-(CH$_3$)$_2$NCH$_2$CH(OH)CH$_3$ as a promoter.
(ii) Ref. 55; added Et$_3$N in the ratio Et$_3$N : Rh = 2.
(iii) Ref. 84.

(a) determined by GC using a chiral column.
(b) determined by NMR using a chiral shift reagent.
(c) determined by conventional optical rotation measurements.

The above hydrogenations use expensive chiral phosphines as the ligands and require the use of hydrogen gas at high pressures. Hydrogen transfer reactions avoid the use of hydrogen and therefore can be performed in standard glassware. The substrate acetophenone

has been asymmetrically reduced using hydrogen transfer systems with up to 63% optical yield (Table 3.2).

Table 3.2 Asymmetric Transfer Hydrogenation of Acetophenone from 2-Propanol.

Catalyst	Rx. time(h)	T(°C)	Conv.(%)	e.e.(%)
(i) [Ir(PPBI)(cod)]ClO$_4$	1	83	93	42[a]
(ii) [Rh$_3$(Chiraphos)$_3$(OMe)$_2$]$^+$	3	83	30	25[a]
(iii) [RhCl(hd)]$_2$ + (S)-AMSO	10	83	45	63[a,b]

(i)   Ref. 48; added KOH.
(ii) Ref. 62; added KOH.
(iii) Ref. 71; added KOH (eq. 3.1).

(a) determined by conventional optical rotation measurements.
(b) determined by NMR using a chiral shift reagent.

The present work involves further studies of the *in situ* catalytic system (iii) shown in Table 3.2. This catalytic system involves the inexpensive and easily prepared chiral ligand AMSO. The chiral ligand AMSO is bifunctional containing both sulphoxide and carboxylate donors, and therefore has the ability to act as a chelate. There are examples of systems which use chiral sulphoxides with ruthenium[13, 72] and rhodium complexes,[13, 70, 72] and examples of chiral carboxylates with iridium,[69] ruthenium,[13, 85] or rhodium complexes,[50, 86] but no previous examples are known of ligands which contain both functionalities. AMSO is an interesting ligand because of the many possible modes of binding. The sulphoxide moiety can bind through S or O while the carboxylate group has several possible modes of binding.

The initial studies[71] performed in this laboratory on this system focused primarily on optimising the ratio of Rh : AMSO : KOH. Also investigated was the effect of changing the base cocatalyst (NaOMe, KOBu^t, LiOH, and NEt$_3$) and the effect on the optical yield when the diene in the rhodium precursor was changed (eq. 3.1).[71] KOH was found to be the base cocatalyst which provided the optimum performance for this system in terms of e.e., at least

when acetophenone was the substrate. With the exception of NEt$_3$, a commonly used cocatalyst, which gave no conversion of acetophenone, the chemical yield of 1-phenylethanol obtained with the bases listed above was similar to that obtained when KOH was the added base.[71, 87]

$$\underset{\underset{Ph}{}\overset{O}{\underset{\backslash}{\overset{\parallel}{C}}}\overset{}{\underset{CH_3}{}}} \quad + \quad \underset{CH_3}{\overset{OH}{\underset{\diagup}{\overset{\mid}{CH}}}}\overset{}{\underset{CH_3}{\diagdown}} \quad \underset{KOH;\ 83°C}{\overset{[RhCl(diene)]_2 + (S)\text{-}AMSO}{\rightleftharpoons}} \quad \overset{OH}{\underset{CH_3}{\overset{\mid}{\underset{\diagup}{*CH}}}}\overset{}{\underset{Ph}{\diagdown}} \quad + \quad \underset{CH_3}{\overset{O}{\underset{\diagup}{\overset{\parallel}{C}}}}\overset{}{\underset{CH_3}{\diagdown}} \quad (3.1)$$
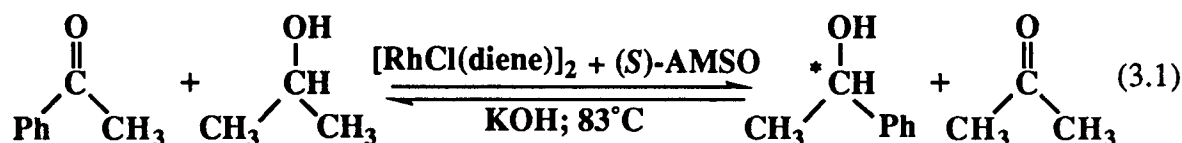
It was observed that somewhat higher optical yields of 1-phenylethanol were obtained when the diene was 1,5-hexadiene compared with 1,5-cyclooctadiene. If the coordinated olefin was either the diene, 2,5-norbornadiene, or two cyclooctenes, the optical yield was less than 10%. While if the corresponding iridium(I) precursors, [IrCl(cod)]$_2$ or [IrCl(hd)]$_2$, were used, higher conversions but negligible optical yields were observed.[71] It was also found that dialkyl ketones were not effectively reduced by this system under conditions which were optimum for hydrogenation of aryl alkyl ketones. Similar observations have been made by other workers using Rh-phosphine systems.[34]

The present studies focused on examining the catalytic transfer of hydrogen to acetophenone in greater detail than the initial studies.[71] The role of the chiral ligand was examined by substituting (R)-AMSO (opposite configuration at carbon) for (S)-AMSO. The previous work on this system showed that when (S)-AMSO was the ligand, the enantiomer produced in excess was (R)-(+)-1-phenylethanol. Therefore, the use of (R)-AMSO would be expected to produce (S)-(–)-1-phenylethanol in excess. Also investigated was the effect on the system, in terms of both chemical and optical yield, on changing the reaction conditions (e.g. temperature, concentration, and varying ratios of ligand to metal). A new ligand (S)-BMSO was also examined for catalytic activity.

3.2 Replacement of (S)-AMSO by (R)-AMSO or (S)-BMSO

Chemical and optical yields for the transfer hydrogenation of acetophenone by the (S)-AMSO system were reported to be as high as 45% and 63%, respectively.[71] However, significantly lower values for both the chemical and optical yields were achieved in the current study under the same conditions (Table 3.3). The nature of the discrepancy is not known but a possible explanation for the lower optical yield is the method of analysis. The analytical methods available for determination of e.e. are discussed in section 3.14.

Table 3.3 Comparison of Transfer Hydrogenation Results for Acetophenone when (S)- and (R)-AMSO and (S)-BMSO are the Chiral Ligands.

Rh dimer, [RhCl(diene)]$_2$	Ligand, L	Conversion(%)	e.e.(%)[†]	Configuration[‡]	Reference
(i)	hd	(S)-AMSO	45	63[a]	(R)-(+)	71
(ii)	hd	(S)-AMSO	20-26	21-44[a]	(R)-(+)	present work
(iii)	hd	(S)-AMSO	26	30[b]	(R)-(+)	present work
(iv)	hd	(R)-AMSO	25	36[b]	(S)-(−)	present work
(v)	cod	(S)-AMSO	49	36[a]	(R)-(+)	87
(vi)	cod	(S)-AMSO	36	32[b]	(R)-(+)	present work
(vii)	cod	(R)-AMSO	34	31[b]	(S)-(−)	present work
(viii)	cod	(S)-BMSO	29	0[b]	------	present work
(ix)	hd	(S)-BMSO	10	13[b]	(S)-(−)	present work

Conditions: [Rh monomer] ~ 5.0x10^{-3} M in 2-propanol (10.0 mL); T = 83°C, sealed under Ar (section 2.4.2), except for those performed by other workers which were done with Ar bubbling; Reaction time: 8-10 hours; Ratio Rh : L : KOH : acetophenone ~ 1 : 2 : 5 : 175. All entries with the exception of (ii) are the results from single experiments; entry (ii) shows the range over which the results, from three experiments performed under similar conditions, varied.

†   (a) determined by optical rotation measurements or with NMR chiral shift reagents (or both).
      (b) determined by injection of an urethane derivative of the alcohol on a chiral column.

‡   Configuration of the enantiomer of 1-phenylethanol that was obtained in excess.

To allow for easier comparison of the enantiomeric excess, one method of chiral analysis, namely chiral GC will be used throughout the remainder of this thesis unless stated otherwise. For the results shown in Table 3.3 which were obtained by previous workers in this laboratory, the concentrations of Rh quoted refer to the concentration of Rh monomer. The concentrations given throughout this work are initial Rh monomer concentrations (i.e. the concentration of Rh monomer before the addition of acetophenone or KOH solution).

As expected substitution of the chiral ligand (S)-AMSO with (R)-AMSO produced the opposite enantiomer of 1-phenylethanol in excess (Table 3.3). (S)-AMSO gave (R)-(+)-1-phenylethanol in excess while (R)-AMSO gave the (S)-(−)-1-phenylethanol in excess. It is interesting to note that use of (S)-BMSO in place of (S)-AMSO, ligands which have the same configuration at carbon, gives the opposite configuration of the product alcohol, (S)-(−)-1-phenylethanol, in excess. Use of (S)-BMSO as the ligand with [RhCl(hd)]$_2$ as the Rh precursor gives significantly lower chemical and optical yield of 1-phenylethanol than if (S)-AMSO was used as the chiral ligand. Surprisingly, when [RhCl(cod)]$_2$ was the Rh precursor and (S)-BMSO was the ligand, no e.e. was observed. However the conversion of acetophenone to the corresponding alcohol was only slightly less than when (S)-AMSO was the chiral ligand.

The catalytic results obtained throughout the course of this thesis varied somewhat from trial to trial in both chemical and optical yields. Therefore, in order to ensure that accurate comparisons were made on the behaviour of the system under different conditions, experimental reactions were usually run side-by-side in the same oil bath. One experiment was used as the control, run under what had been determined to be the "optimum" conditions, while one or more other experiments had one reaction parameter varied to examine the effect on the system. Comparisons could be easily made between the control and the other experiments regardless if the control gave results which were lower or higher in chemical and optical yield than were obtained on average.

3.3 Blanks

The role of the chiral ligand AMSO in the catalytic asymmetric transfer of hydrogen was investigated by eliminating various reaction components (e.g. KOH, Rh, etc.) and examining the effect on the system. In other words, blanks were performed to determine the necessity of all the reaction components in this *in situ* system for the effective reduction of acetophenone. The importance of the ligand AMSO requirement of containing both a sulphoxide and a carboxylate group was analysed for by comparing the catalytic activity of the system with that of systems in which the precursors of AMSO, METO and *N*-acetyl-*dl*-methionine, were substituted as the ligand.

3.3.1 Use of (S)-METO as the Ligand

The use of (S)-METO as the ligand gave very slow reaction rates. Under the same conditions as outlined in Table 3.3, when ligand L was (S)-METO, the conversion of acetophenone to 1-phenylethanol was only 8% after 20.5 hours. The initial yellow colour of the solution did not change when the acetophenone and KOH solution were added. When AMSO was used as the ligand, the solution very quickly became dark in colour after the addition of KOH. Also, the solution colour at the end of the heating period was a much lighter brown than that observed for the AMSO system. The optical yield (as determined by optical rotation measurements) was very low, only 1.4% of the (R)-(+) enantiomer (see Table 3.4).

Table 3.4 Effect of Substituting (S)-METO for (S)-AMSO on the
Catalytic Transfer Hydrogenation of Acetophenone.

	Catalyst	Concentration(M)	Rx. time(h)	Conversion(%)	e.e.(%)[†]
(i)	[RhCl(hd)]₂/(S)-METO	4.75x10⁻³	20.75	7	1.6 (R)-(+)
(ii)	[RhCl(hd)]₂/(S)-METO	5.63x10⁻³	20.5	8	1.4 (R)-(+)

Conditions: [Rh monomer] ~5x10⁻³ M in 2-propanol (10 mL); sealed under Ar (section 2.4.2); T = 83°C; Ratio Rh : L : KOH : acetophenone ~ 1 : 2 : 5 : 175.

† determined by optical rotation measurement.

Acetylation of methionine sulphoxide seems to play an important role in the generation of an active catalytic species. It has been suggested that the acetylation probably prevents binding through the amine-N and thereby promotes the interaction of the sulphoxide group with the metal.[71] The use of METO, which contains the free amine functionality, probably ties up the rhodium in a catalytically inactive form through strong binding of the amine functionality to the Rh centre. Therefore, a previously vacant site on the metal would now be unavailable for the coordination of the substrate and 2-propanol, and lead to the dramatic decrease in conversion compared to that observed when AMSO is the ligand.

3.3.2 Use of *N*-Acetyl-*dl*-methionine as the Ligand

To examine the necessity of oxidising methionine at sulphur in the AMSO ligand, another ligand *N*-acetyl-*dl*-methionine, a precursor to AMSO was examined for catalytic activity for the reduction of acetophenone. Conditions similar to those shown in Table 3.3 were used with racemic *N*-acetyl-*dl*-methionine replacing (*S*)-AMSO as the ligand. The initial yellow solution turned brown-black soon after the addition of acetophenone and KOH, as was the case when AMSO was the ligand. Table 3.5 compares the conversion of acetophenone to 1-phenylethanol using the two ligands.

Table 3.5 Effect of Substituting *N*-Acetyl-*dl*-methionine for (*S*)-AMSO on the Catalytic Transfer Hydrogenation of Acetophenone.

Catalyst	Concentration(M)	Rx. time(h)	Conversion(%)
(i) [RhCl(cod)]$_2$/*N*-acetyl-*dl*-methionine	5.58×10^{-3}	21	23
(ii) [RhCl(cod)]$_2$/(*S*)-AMSO	4.75×10^{-3}	9	36

Conditions: [Rh monomer] ~5×10^{-3} M in 2-propanol (10 mL); entry (ii) sealed under Ar (section 2.4.2), entry (i) Ar bubbling (section 2.4.1); T = 83°C; Ratio Rh : L : KOH : acetophenone ~ 1 : 2 : 5 : 175.

Although the two reactions were not run side-by-side and were run for different reaction times, a comparison of the results is still useful. The use of *N*-acetyl-*dl*-methionine as

the ligand gives a lower conversion than when (S)-AMSO is used as the ligand; however, N-acetyl-dl-methionine gives a surprisingly high conversion when compared with the value obtained with (S)-METO as the ligand (Table 3.4). The necessity of oxidising methionine at sulphur remains somewhat in question because a significant conversion was observed with the thioether derivative acting as a ligand. A chiral derivative, N-acetyl-(S)-methionine, should be prepared and examined for catalytic activity as a ligand to determine the necessity of a sulphoxide moiety (as in AMSO). The e.e. obtained could then be compared with the value obtained when (S)-AMSO was used as the chiral ligand. The current experiment suggests that further blanks need to be done to ensure that the sulphoxide functionality is essential to the transfer hydrogenation in terms of obtaining optimum chemical and optical yields.

3.3.3 Does (S)-AMSO Racemise Under Catalytic Conditions?

To ensure that (S)-AMSO was neither racemised or decarboxylated during the catalytic experiment, the fate of the ligand was investigated under conditions similar to that of the transfer hydrogenation experiments. Initially the optical rotation of (S)-AMSO (0.05 g, 0.024 mmol) in 2-propanol (10 mL) was determined ($[\alpha]_D^T = +43.6°$) and then the solution was heated at 83°C for 18 hours and the optical rotation measured again ($[\alpha]_D^T = +41.0°$). Then acetophenone (1 mL) was added and heating resumed for another 165 hours. The optical rotation was determined to be $[\alpha]_D^T = +43.3°$ after corrections had been made for the change in concentration due to the addition of acetophenone. Changes in the composition of the solution (i.e. presence of acetophenone) were not corrected for and were shown to have a small effect on the value of the rotation. The small changes observed in the rotation of the solution were due to changes in the temperature at which the rotation was measured (the cell was not thermostated) and to the difference in composition of the solution (acetophenone added). Since only small changes were observed in the optical rotation, it was determined that the ligand was neither racemised or decarboxylated under the above conditions, which were similar in terms of temperature, solvent, and substrate to the catalytic transfer hydrogenation conditions.

Injection of this solution onto a Carbowax 20M column at the end of the last heating period showed only acetophenone and 2-propanol to be present. Also, a ^{1}H NMR of the solution showed all the (S)-AMSO signals. Therefore, the above experiment shows that the chiral ligand (S)-AMSO does not catalyse the reduction of acetophenone in the absence of transition metal species and base cocatalyst or added KOH alone. Thermal decarboxylation of aliphatic α-amino acids and N-mono-methyl amino acids is known to give the corresponding amine in the presence of ketones. Both leucine and N-methylleucine are decarboxylated in acetophenone.[88] It has been suggested that a Schiff base is formed between the ketone and the amino acid, and that the Schiff base is more readily decarboxylated to the corresponding amine (still in the form of the Schiff base).[88] However, (S)-AMSO must not have been decarboxylated as both the optical rotation and ^{1}H NMR spectrum of the ligand remained unchanged after heating in the presence of acetophenone. The acetylation of the amine functionality in the ligand AMSO must prevent formation of the Schiff base and consequently, no decarboxylation takes place.

3.3.4 KOH-Catalysed Reaction

Although bases are frequently added as cocatalysts or promoters in hydrogenation experiments (especially hydrogen transfer reactions), it has rarely been mentioned that the base itself is capable of catalysing the transfer hydrogenation. Sasson and Blum briefly mentioned that the base catalysed hydrogen transfer had a much slower reaction rate than the transition metal-base catalysed system.[63] To ensure that the base-catalysed transfer hydrogenation of acetophenone was in fact slow compared to the transition metal-base catalysed system under investigation, an experiment was performed under similar conditions to those of the Rh-sulphoxide-KOH catalysed system.

The same concentration of KOH in 2-propanol that was used in the Rh-AMSO catalytic experiments was used in this experiment. Initially, 2-propanol (10 mL) was heated at 83°C in a sealed Schlenk tube under Ar for a few minutes and then the acetophenone (1 mL) was

introduced with a syringe followed immediately by addition of the KOH solution (2 mL of a solution prepared by dissolving 1.25×10^{-3} moles of KOH in 10 mL of 2-propanol). The original colourless solution turned yellow in colour following the addition of KOH, and had become orange-brown after 22.5 hours of heating. Following work-up of the solution by distillation, injection of the substrate-product mixture into the GC revealed 17% conversion of acetophenone to 1-phenylethanol. Small amounts of condensation products were also detected as side-products. The condensation products were eluted on the Carbowax column at retention times of 22.8 and 25.3 minutes. The integration of the two condensation products was less than 1% of the total integration for the product-substrate mixture. The identities of the condensation products were not established but they are presumably β–hydroxyketones or the α,β-unsaturated ketone, 1,3-diphenyl-2-buten-1-one. Two molecules of acetophenone in the presence of base are known to condense to give this α,β-unsaturated product.[89]

Analysis of another experiment in which heating at 83°C was limited to 7.5 hours gave only 7% conversion. No condensation products were detected in this experiment. Therefore, comparison of conversion values with those of the transition metal-base catalysed system (Table 3.3 and Fig. 3.3) reveals that the solely base catalysed transfer of hydrogen is much slower than the transition metal catalysed system. These results are consistent with those reported by Sasson and Blum for a ruthenium system.[63]

Originally, the transfer hydrogenation experiments were not followed by GC because direct injection onto the column of solutions containing either metal species or in this case KOH was not recommended. Injection of solutions containing metal species was avoided because of the possibility of either catalysing reactions on the column or damaging the stationary phase. Therefore, all of the early experiments that were performed involved allowing a reaction to run for a certain period of time and then, following distillation from the metal species or KOH (or both), the product mixture was analysed by GC. However, it was decided that if a plug of glass wool was placed at the injector end of the column and an old Carbowax column was used, direct sampling and injection of the catalytic experiments could be performed. Therefore,

a graph of conversion vs. time was plotted (Fig. 3.1) and proved more useful than the previously described single conversion-single time experiments for comparing extent of reaction at various selected reaction times. The sampling experiment was performed at 83°C under Ar in a Schlenk flask equipped with a septum for sample withdrawal. The KOH solution (2.8 mL of a solution prepared by dissolving 9.0×10^{-4} moles of KOH in 10 mL of 2-propanol) was added immediately after the acetophenone (1 mL) was added to 2-propanol (10 mL). Samples (~0.1-0.2 mL) were withdrawn with a syringe and put in a vial which was kept on ice until the gas chromatographic analysis was complete.
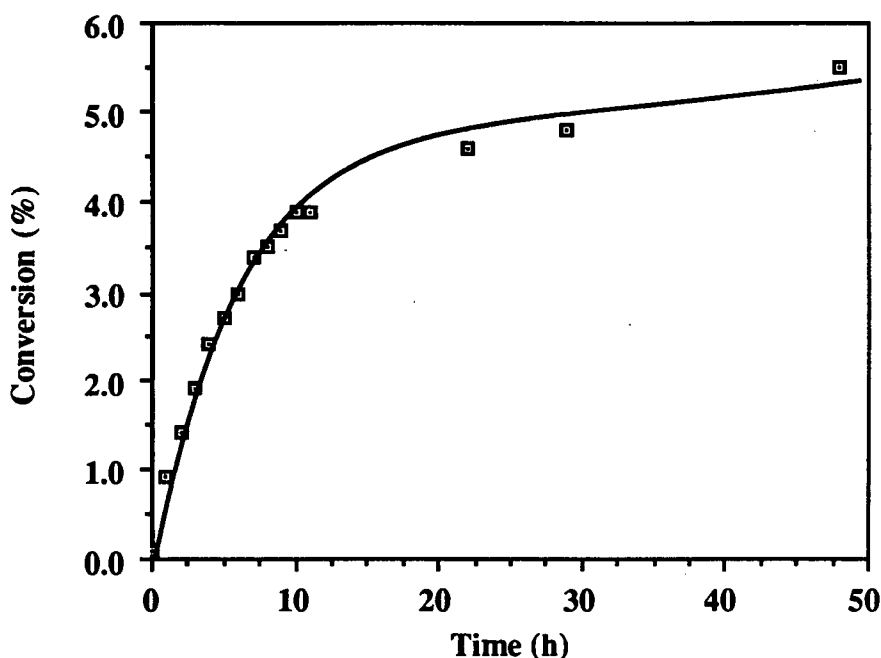
Figure 3.1 Graph of conversion vs. time for the KOH-catalysed transfer hydrogenation of acetophenone.

Although the values obtained for the conversion from the two single experiments do not agree well with the above plot, both Fig. 3.1 and the individual measurements show that the base-catalysed reaction is significantly slower than the transition metal-base catalysed system.

An individual measurement performed by another worker in this laboratory[90] suggests that the values obtained for the conversion from the two "individual" experiments are more

representative of the actual rate than the values obtained from the sampling reaction. This other experiment was performed under similar conditions (83°C, under Ar) and after 48 hours gave a conversion of ~30%. The above plot shows only 5.5% conversion after 48 hours. Further data should be obtained in order to offer an explanation for the differences in the results, although a difference in KOH concentration might be the reason. The KOH, being hygroscopic, is both difficult to weigh and difficult to dissolve in 2-propanol. Another possibility was that the individual experiments were misleadingly high in the conversion value because of the reaction proceeding further during the distillation (oven was heated to ~100°C; section 2.4). However, this possibility was ruled out by the direct injection of a sample into the GC after 48 hours of heating and then immediate distillation of the same solution followed by another injection. The two values for the conversion (5.5% before distillation, 5.6% after distillation) were identical, thus ruling out any detectable reaction during the distillation procedure.

3.3.5 Reaction in Absence of Added KOH

No conversion of acetophenone to 1-phenylethanol was observed if KOH was not added to the *in situ* catalytic transfer hydrogenation system. In this experiment, the rhodium concentration was the same as that during the asymmetric transfer hydrogenation (5.0×10^{-3} M, monomer concentration) and the ratio of (*S*)-AMSO to Rh was 2 : 1 (Table 3.3). During the course of the reaction, Rh metal plated out on the walls of the Schlenk tube. The reaction was heated for 21 hours at 83°C under argon. The necessity of added base for the reduction had been reported previously, when it was shown that if the ratio of KOH : Rh was < 3 : 1 that metal formation was observed.[71] The role of the added base is poorly understood, although the generation of polynuclear systems with bridging alkoxides has been suggested.[62] In this literature work, complexes of the type [Rh(diene)(P-P)]+PF$_6$−, where P-P is Chiraphos or Prophos, were added as the catalyst precursor for the base-promoted transfer hydrogenation of acetophenone from 2-propanol. An optical yield of 13% was observed for these systems. The

use of ^{31}P NMR and CD spectroscopy suggested the formation of trimeric species of the type [Rh$_3$(P-P)$_3$(O-^{i}Pr)$_2$]$^+$ and other polynuclear species during the catalytic cycle.[62] This trimeric species was suggested by analogy of this system with the known species [Rh$_3$(diphos)$_3$(μ_3-OMe)$_2$]$^+$, which was isolated from a basic methanol solution of [Rh(nbd)(diphos)]$^+$.[91] Complexes of the type [Rh$_3$(P-P)$_3$(μ_3-OMe)$_2$]$^+$ were synthesised and used as catalysts with KOH added as a cocatalyst for the transfer hydrogenation of acetophenone (entry (ii), Table 3.2).[62] Also suggested for the role of the base in similar systems which use rhodium diene dimers as catalyst precursors is the possible removal of Cl$^-$ from the coordination sphere and its replacement by OH$^-$ to generate rhodium hydroxo complexes.[34, 71]

The order of addition of the substrate and the base is also important. In the present work, the substrate must be added first and then the base, otherwise Rh metal begins to precipitate until the substrate is added. Other workers have also reported that the mixing order of reactants and catalyst has an influence on the initial rate of the reaction.[64, 65]

3.3.6 Reaction in Absence of Added Sulphoxide

In the absence of (S)-AMSO , with only [RhCl(hd)]$_2$ and KOH present, a conversion of ~82% of acetophenone to 1-phenylethanol was observed after the reaction mixture had been heated at 83°C for ~22 hours in 10 mL of 2-propanol (Table 3.6). The initial pale yellow solution turned brown within five minutes of the addition of KOH. During the course of the reaction, a brown-black solid precipitated as was observed when AMSO was present.

Table 3.6 Catalytic Transfer Hydrogenation of Acetophenone in the Absence of AMSO.

	Catalyst	Concentration(M)	Rx. time(h)	Conversion(%)	e.e.(%)
(i)	[RhCl(hd)]$_2$	6.12x10^{-3}	21	83	----
(ii)	[RhCl(hd)]$_2$	5.39x10^{-3}	22.5	81	----

Conditions: [Rh monomer] ~5x10^{-3} M in 2-propanol (10 mL); sealed under Ar (section 2.4.2); T = 83°C; Ratio Rh : AMSO : KOH : acetophenone ~ 1 : 0 : 5 : 175.

The measured e.e. for the above two catalytic reactions was 0%, as expected in the absence of a chiral ligand. It is interesting to note that Joshi in this laboratory has seen similar conversions for ruthenium-phosphine systems;[90] he performed a transfer hydrogenation experiment with [RuCl$_2$(dppb)]$_2$ added as the catalyst precursor. The ruthenium dimer was dissolved in 2-propanol (5 mL) to give a monomeric Ru concentration of 5.40×10^{-3} M. KOH was added to this solution (as a solid; 0.0030 g, 5.4×10^{-5} moles) followed immediately by the addition of acetophenone (1 mL) to give a ratio of Ru : KOH : acetophenone of approximately 1 : 2 : 350. The reaction was heated in a sealed Schlenk tube under Ar at 83°C for 1 hour. As the reaction proceeded, the initial orange colour of the solution turned red. The conversion of acetophenone to 1-phenylethanol was ~82%, which is similar to that seen for the rhodium system studied.

These catalytic results indicate that the equilibrium concentrations of acetone, acetophenone, 2-propanol, and 1-phenylethanol have probably been reached, or at least the system is very near equilibrium. Calculation of the equilibrium constant (K) for reaction 3.1 (p. 53) with the rhodium system (assuming that 82% conversion corresponds to the equilibrium mixture) gives K=0.27 at 83°C while the ruthenium system gives a value of K=0.51 at 83°C. Although the values are somewhat different, using the equilibrium constant obtained from the ruthenium system (K=0.51) for the rhodium system and performing a back calculation using the starting concentrations of 2-propanol and acetophenone yields an equilibrium mixture which corresponds to 90% conversion of acetophenone. This conversion is not much larger than the 82% actually found for the rhodium system. Therefore, the catalytic transfer hydrogenation reaction is most probably either at equilibrium or approaching equilibrium. To confirm this, the non-asymmetric catalytic reaction should be monitored by GC, as were the solely base-catalysed reaction (Fig. 3.1) and the Rh-sulphoxide-KOH-catalysed reaction (Fig. 3.3). The equilibrium may be reached in a shorter or longer reaction time than the 21-22.5 hours indicated in Table 3.6. It would be useful to know the rate of this

non-enantioselective pathway so it could be effectively compared with the rate of the base-catalysed and Rh-AMSO-KOH-catalysed systems.

3.4 Test for Homogeneity of the Catalytic Transfer Hydrogenation

Several methods of testing for the homogeneity of catalytic systems have been suggested:[7] (1) the use of elemental mercury, which poisons heterogeneous catalysts by blocking the pores of high-surface-area solids or by forming amalgams with metals;[92] (2) the employment of cross-linked polymers as substrates, which heterogeneous catalysts are ineffective in hydrogenating;[93] or (3) the use of polymeric catalyst poisons such as polythiols which have no effect on heterogeneous catalysts but retard homogeneous catalysts.[93] Although rhodium has not been observed to form amalgams with mercury, it does have some solubility in the liquid metal.[92] Even though solution or amalgam formation may not be possible for rhodium systems, the test is still considered feasible, because Hg may adsorb on the metal surface thereby preventing possible heterogeneously catalysed reactions.[92] Crabtree and Anton found that the addition of Hg completely inhibited a reaction catalysed by colloidal Rh but had no effect on a homogeneous Rh system.[94] The presence of a brown-black solid in the reaction mixture during the course of the transfer hydrogenation reaction hinted at the possibility of the reaction being heterogeneously catalysed (section 2.4). Therefore, the homogeneity of this Rh-sulphoxide catalytic system was investigated by the addition of a drop of mercury to a catalytic reaction.

A reaction containing a drop of Hg was run concurrently under the same conditions as a reaction with no added Hg. Table 3.7 outlines the results obtained for both catalytic experiments.

Conversions of 39% of acetophenone to 1-phenylethanol in the absence of Hg and 42% in the presence of Hg indicate that the addition of Hg has no effect on the reduction. The results show that the catalytic transfer hydrogenation is truly homogeneous as the presence of Hg had no effect on either the e.e. or conversion. If the reaction were heterogeneously catalysed, the

conversion of acetophenone to 1-phenylethanol would be expected to be negligible in the presence of mercury, although the presence of the base KOH would probably catalyse the reaction to some degree (section 3.3.4). The slightly higher conversion of acetophenone in the catalytic reaction with added Hg is probably due to the higher concentration of Rh in that reaction mixture. Difficulty in introducing exactly 11 mg of the Rh dimer into the reaction vessel accounts for the slight difference in concentration. Although this method of testing indicates that the reaction is homogeneously catalysed, it would be wise to employ a further method of distinguishing between heterogeneous and homogeneous systems (e.g. inhibition of the homogeneous pathway by poisoning with polythiols). A second method of testing is advisable because of the small number of reports on the added Hg technique and its unknown limit of applicability. A physical method such as light scattering could also prove useful in detecting the presence of colloidal metal, but does not provide information about the catalytic activity of any colloidal species observed.

Table 3.7 Test for Homogeneity of the Catalytic Transfer Hydrogenation of Acetophenone.

	Catalyst	Concentration(M)	Rx. time(h)	Hg	Conversion(%)	e.e.(%)[†]
(i)	[RhCl(hd)]₂/(S)-AMSO	5.25×10^{-3}	20	Not added	39	38 (R)-(+)
(ii)	[RhCl(hd)]₂/(S)-AMSO	6.90×10^{-3}	20	Added	42	36 (R)-(+)

Conditions: [Rh monomer] ~5×10^{-3} M in 2-propanol (10 mL); sealed under Ar (section 2.4.2); T = 83°C; Ratio Rh : AMSO : KOH : acetophenone ~ 1 : 2 : 5 : 175.

† determined by injection of a urethane derivative of the product alcohol on a chiral column.

3.5 Effect of Using Method 1 or 2 on Transfer Hydrogenation (section 2.4)

The asymmetric transfer hydrogenation experiments were initially performed in three-neck round bottom flasks equipped with a reflux condenser with argon bubbling (Method 1, section 2.4.1), following the method used by other workers.[71, 87] Some reduction in volume of the solution (~ 1-2 mL) during the course of the reaction was difficult to avoid using this

method. However, the lowest boiling compound in the mixture would be expected to be evaporated first. The lowest boiling component of these catalytic mixtures is acetone, the dehydrogenated product of 2-propanol. Removal of acetone from these reaction mixtures is favourable because the equilibrium would then be shifted to the right in favour of the product 1-phenylethanol (see eq. 3.1). The majority of the transfer hydrogenation experiments performed in this work were done using a different experimental method. Method 2 (section 2.4.2) was a system closed under argon in a thick-walled Schlenk tube. Side-by-side reactions were run early on in this work in which one experiment was performed using each of the experimental methods 1 and 2. The effect of these different methods on the asymmetric transfer hydrogenation is shown in Table 3.8.

Table 3.8 Effect of Using Method 1 or 2 on the Asymmetric
Transfer Hydrogenation of Acetophenone.

Catalyst	Concentration(M)	Rx. time(h)	Method	Conversion(%)	e.e.(%)[†]
(i) [RhCl(hd)]$_2$/(S)-AMSO	4.41×10^{-3}	20.5	1	17	19 (R)-(+)
(ii) [RhCl(hd)]$_2$/(S)-AMSO	5.55×10^{-3}	20.5	2	54	30 (R)-(+)

Conditions: [Rh monomer] ~5×10^{-3} M in 2-propanol (10 mL); T = 83°C; Ratio Rh : AMSO : KOH : acetophenone ~ 1 : 2 : 5 : 175.

† determined by injection of a urethane derivative of the product alcohol on a chiral column.

The system sealed under argon showed a surprisingly large conversion and, compared to the system with argon bubbling, had gone more toward equilibrium. The result obtained for entry (ii) does in fact show too large a conversion value when compared with subsequent experiments which were performed in a similar manner. The conversion after 20.5 hours was usually found to be approximately 35-40% as opposed to the 54% observed (see Fig. 3.3 later). However, the results in Table 3.8 still show that a larger conversion and e.e. are obtained with a system closed under argon than a system with argon bubbling. That method 2 was more effective for transfer hydrogenation was unexpected, because a reduction in volume,

as observed when method 1 was used, should remove acetone and shift the equilibrium to the right (eq. 3.1). This phenomenon is difficult to explain and remains unclear. However, the results are reproducible and agree with the results found when acetone was actually added to the catalytic reactions (section 3.9). It is possible that the majority of the acetone is actually in the gas phase in the sealed reactions (head space ~ 50 mL) as the experiment is run above the boiling point of acetone. Therefore, the acetone concentration would remain low in solution and reduce the rate of the back reaction. The majority of the experiments throughout this work were performed using method 2 as it was both easier to handle and seemed to give better results.

3.6 Time Dependence

The rate of transfer hydrogenation of acetophenone was originally examined by the concurrent running of three experiments in which the systems were heated in the same oil-bath at 83°C for certain periods and then immediately distilled. One experiment was stopped at each of 1, 2, and 4 hours. Also, included on the graph (Fig. 3.2) were experiments run for 8 and 9 hours, although these trials were performed at a different time. The conversion of acetophenone to 1-phenylethanol was determined, after distillation from the metal species, by GC as was the enantiomeric excess. Each experiment provided a single point for a graph of conversion vs. time (Fig. 3.2). The experiments were performed with Rh monomer concentrations of ~5x10^{-3} M in 2-propanol (10 mL). (S)-AMSO was used as the ligand with the following ratio of starting materials: Rh : AMSO : KOH : acetophenone ~ 1 : 2 : 5 : 175.

The data points at 8 and 9 hours agree well with the data collected at 1, 2, and 4 hours, despite the possibility of slightly different reaction conditions. It is difficult to find a trend in the e.e., although a small increase in e.e. may be observed with increasing reaction time. After 1 hour the e.e. was 24.8%; 2 hours, 25.6%; 4 hours, 27.7%; 8 hours, 26.9%; and 9 hours, 30.1%, as measured by chiral GC. Little change in the e.e. during the course of the reaction should be observed, unless the active chiral catalyst loses its activity and a non-chiral species

(e.g. KOH) begins to slowly catalyse the reaction. In the present work which has KOH present, the e.e. should remain relatively constant, perhaps increasing slightly, with time until a maximum is reached and then, if contributions from the KOH-catalysed reaction become significant, slowly decrease with reaction time. It has been suggested that with rhodium-chiral phosphine catalytic systems, little change occurs in the optical purity of the product with time.[39]
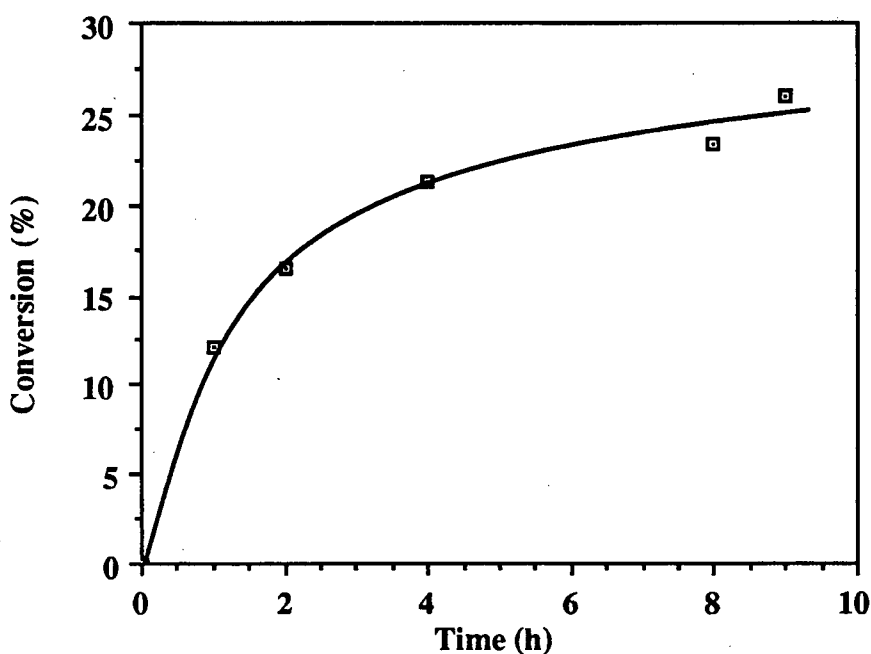
Figure 3.2 Graph of conversion vs. time for the Rh-sulphoxide-KOH-catalysed transfer hydrogenation of acetophenone (single experiments, run using method 2).

Originally, the transfer hydrogenation experiments were followed by the above method because the direct injection of metal species onto the GC columns was not recommended. Therefore, individual runs had to be performed and the liquid phase distilled from the metal species before gas chromatographic analysis was performed to determine the extent of reaction. However, it was decided that special precautions (section 3.3.4) could be taken to allow for the direct monitoring of a single catalytic reaction. The transfer hydrogenation reaction that was monitored contained as the catalyst precursor [RhCl(hd)]$_2$ and (R)-AMSO. The Rh monomer

concentration used was 4.81×10^{-3} M and the ratio of Rh : (R)-AMSO : KOH : acetophenone = 1 : 2 : 5 : 175. The experiment was performed under Ar at 83°C in a Schlenk flask equipped with a septum which allowed for easy sample withdrawal. Samples (~0.1-0.2 mL) were withdrawn with a syringe and placed in vials which were kept on ice until gas chromatographic analysis was performed.
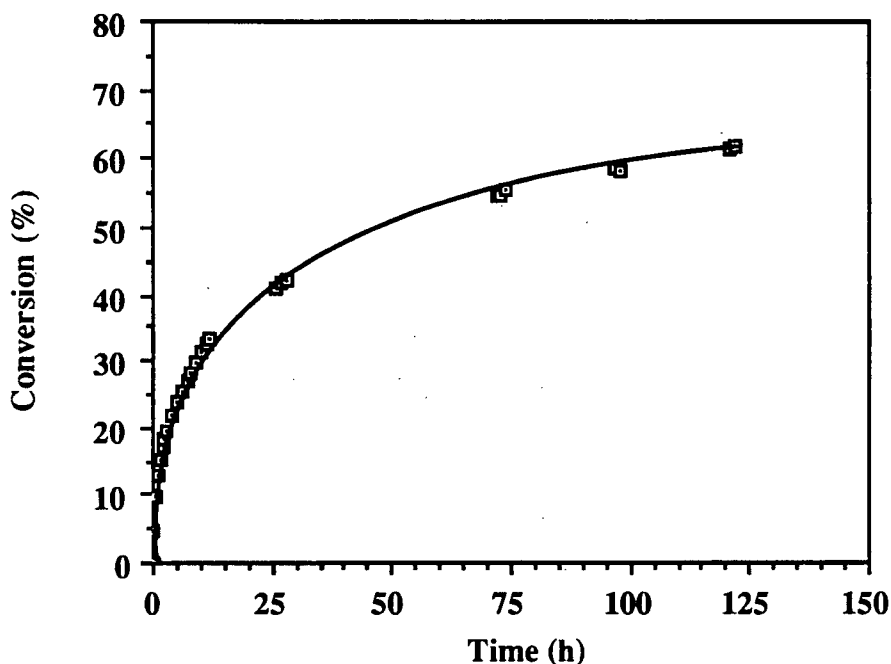
Figure 3.3 Graph of conversion vs. time for the Rh-sulphoxide-KOH-catalysed transfer hydrogenation of acetophenone (samples withdrawn periodically, run using method 2).

The graph of conversion of acetophenone vs. time obtained by the second method, where samples were withdrawn periodically (Fig. 3.3), agrees very well with the graph obtained by running concurrent reactions (Fig. 3.2). In fact, the data points collected from the two methods at 1, 2, and 4 hours agree within 0.7% conversion units (see Tables A3 and A4 in the appendix). The values obtained for the conversion at 8 and 9 hours from the first method are about 4-5% units lower in conversion than the data obtained from the sampled catalytic reaction. However, both graphs show the rate at which the reaction is approaching

equilibrium. The results from section 3.3.6, in which the catalysis was performed in the absence of any added ligand, indicate that the equilibrium lies at about 90% conversion of acetophenone. Therefore, in the presence of the ligand AMSO, the rate at which the system is approaching equilibrium is slower than in the absence of ligand. In fact, Fig. 3.3 shows that in the presence of AMSO that only ~62% conversion is reached after 122 hours of heating and the system is still far from equilibrium. The total turnover number for acetophenone was 109 after 122 hours. The reaction slowed dramatically after about the first four hours. Average turnover numbers decreased from 1.71 cycles per min in the first five minutes to 0.16 cycles per min over the first four hours. Over the entire 22 hours of reaction, the turnover number was a very low 0.02 cycles per min. Clearly the reaction has become extremely slow, and it is estimated that if the reaction continued at the current rate (0.02 cycles/min), it would take at least 40 more hours to reach equilibrium (assuming that equilibrium lies at approximately 90% conversion of acetophenone).

The reaction liquid was distilled off the brown-black residue after 122 hours and injected into the GC as a solution in hexanes (section 2.5.1) to observe if any change in the conversion was observed after the distillation procedure. Before the distillation, direct injection gave a value of 62% conversion while after distillation a conversion of 67% was measured. It is possible that the oven temperature of 100°C shifts the equilibrium slightly toward the products. The brown-black residue left at the end of the reaction was examined for catalytic activity by re-dissolving the residue in 2-propanol (5 mL) and adding more acetophenone (0.5 mL). Heating was resumed and samples taken periodically. However, the catalyst was inactive unlike findings in other experiments (section 3.12) which showed some activity upon re-use. Sampling out of the reaction as many as 26 times while monitoring the reaction probably caused the septum to fail. The septum was probably unable to re-seal properly after numerous punctures and therefore this could allow air into the reaction vessel. Air oxidation of catalysts has been reported previously to stop reactions of this type; such exposure of reaction solutions to air is often enough to quench the reaction, thus allowing for analysis.[48, 49, 68]

The enantiomeric excess could not be monitored in the same manner (by sampling) as the conversion because the chiral column is expensive and damage to the column could not be risked by the injection of metal-containing solutions. The e.e. of the asymmetric transfer hydrogenation followed above was analysed for, after distillation from the metal species, by chiral GC at the end of the 122 hours. The e.e. of 1-phenylethanol was found to be 21% of the (S)-(−) alcohol, which is consistent with (R)-AMSO being used as the ligand.

3.7 Temperature Dependence

The effect of varying the temperature on the asymmetric transfer hydrogenation of acetophenone was examined by running sets of side-by-side reactions at four different temperatures. Previously, it has been reported that the rate of transfer hydrogenation of prochiral ketones with ruthenium-chiral phosphine systems increases, while the e.e. of these systems decreases, with increasing temperatures.[95] It has also been reported that for the direct H_2 hydrogenation of olefins using a Ru-chiral phosphine system, the e.e. decreased dramatically from 97 to 19% on raising the reaction temperature from 30 to 70°C.[96, 97] The optical purity of the product alcohols generated from the direct hydrogenation of prochiral ketones was also seen to decrease on raising the temperature in some systems catalysed by rhodium-chiral phosphines.[39] The opposite has been predicted from the mechanism for asymmetric hydrogenation proposed by Halpern et al. (Fig. 1.2), namely that decreasing the reaction temperature should decrease the optical yield;[7, 30] in this case with a rhodium-chiral phosphine system the e.e. increased from 0 to 60% on increasing the temperature from 0 to 100°C for the reduction of some amino acid precursors.[98, 99] In fact, the inversion of the configuration of these products has been observed, in some cases, on increasing the temperature (i.e. (R) at 0°C and (S) at higher temperatures or vice versa).[98, 99] Halpern's proposed mechanism (section 1.2.1) predicts that decreasing the temperature will reduce the rate of interconversion of the diastereomeric adducts as this has a higher activation enthalpy than the subsequent reactions with H_2. The interconversion of the diastereomeric adducts

determines the e.e. of the reaction and, therefore, a reduction in this interconversion leads to a reduction in the e.e.[30] This phenomenon has been observed in the rhodium-chiral phosphine systems discussed above. The effect of varying the temperature on the enantioselectivity of the products was found to be far less pronounced in the presence of added triethylamine for the above rhodium-phosphine systems.[98, 99]

Table 3.9 Effect on Conversion and e.e. of Varying the Temperature for the Catalytic Transfer Hydrogenation of Acetophenone.

Catalyst	Concentration(M)	Rx. time(h)	T(°C)	Conversion(%)	e.e.(%)[†]
(i) [RhCl(hd)]$_2$/(S)-AMSO	5.01x10^{-3}	76.5	R.T. (~20)	2	----
(ii)[RhCl(hd)]$_2$/(S)-AMSO	5.05x10^{-3}	8	50	4	23 (R)-(+)
(iii)[RhCl(hd)]$_2$/(S)-AMSO	5.31x10^{-3}	8	83	23	27 (R)-(+)
(iv)[RhCl(hd)]$_2$/(S)-AMSO	5.12x10^{-3}	8.5	83	25	31 (R)-(+)
(v)[RhCl(hd)]$_2$/(S)-AMSO	5.29x10^{-3}	8.5	120	40	23 (R)-(+)

Conditions: [Rh monomer] ~5x10^{-3} M in 2-propanol (10 mL); sealed under Ar (section 2.4.2) with the exception of entry (i) which was performed with Ar bubbling (section 2.4.1); Ratio Rh : AMSO : KOH : acetophenone ~ 1 : 2 : 5 : 175.

† determined by injection of a urethane derivative of the product alcohol on a chiral column.

Entries (iv) and (v) in Table 3.9 show that the present Rh-AMSO transfer hydrogenation reaction increases in rate and shows a slight decrease in optical yield upon increasing the temperature from 83 to 120°C. Comparison of all the entries in Table 3.9 is somewhat difficult because the experiments were performed for different reaction times. It is more useful to compare the pairs of reactions shown in the table which were run side-by-side. The experiment performed at room temperature was left running for a longer period because the solution was orange in colour instead of the characteristic brown-black colour of the reactions run at higher temperatures. The low conversion observed for this reaction suggests that the active catalytic species is brown-black. No attempt was made to measure the e.e. of the reaction run at room temperature as the conversion was too low. Comparison of entries (ii)

and (iii) shows a marked increase in rate on changing the reaction temperature from 50 to 83°C. The optical yield shows a slight increase with increasing temperature for these two runs, which is opposite to the trend observed for entries (iv) and (v). Further complicating any conclusions on the effect of raising the temperature on the enantioselectivity of the reaction is that the e.e. was observed to increase slightly with increasing conversion (section 3.6). Therefore, Table 3.9 shows that the rate of the transfer hydrogenation increases with increasing temperature and that the effect on the e.e. is not very pronounced. In fact, the enantioselectivity of the reaction was actually found to increase slightly over the temperature range 20-83°C, and then decrease at 120°C.

3.8 Variation of Rhodium Concentration and Ratio of Starting Materials

The effect on the transfer hydrogenation of changing the catalyst precursor concentration and the ratio of ligand to metal was examined by performing sets of reactions and comparing both the chemical and optical yields obtained. As the system is quite sensitive to changes in conditions, comparisons are best made within the pairs of reactions. External comparisons (i.e. between one pair of experiments run at one time and another set run at a different time) should be avoided where possible, although careful external comparisons may establish some trends in rates of reaction and enantioselectivity. Previously, it was observed that if the ratio of ligand to Rh was increased from 1 : 1 to 2 : 1, both the chemical and optical yields approximately doubled (entries (viii) and (ix), Table 3.10).[71] The catalyst precursor monomer concentration used previously had been fixed at 5×10^{-3} M [71, 87] and, therefore, the reaction was run at a few different concentrations of Rh and the influence on the system examined (Table 3.10). Also, the ratio of ligand to transition metal species was again varied and the efficiency of the system observed (Table 3.10).

Entries (i) and (ii) show that neither the rate of reaction nor the enantioselectivity of the reduction is significantly effected on doubling the concentration of Rh monomer from $\sim 5 \times 10^{-3}$ M to 1.0×10^{-2} M, when the ligand to metal ratio is 1 : 1. However, runs (vi) and

74

Catalyst	Concentration(M)	Rh : AMSO	Rx. time(h)	Conversion(%)	e.e.(%)[†]
(i) [RhCl(hd)]$_2$/(R)-AMSO	4.56x10^{-3}	1 : 1	8.5	23	19 (S)-(–)[a]
(ii)[RhCl(hd)]$_2$/(R)-AMSO	10.6x10^{-3}	1 : 1	8.5	22	20 (S)-(–)[a]
(iii)[RhCl(hd)]$_2$/(R)-AMSO	5.03x10^{-3}	1 : 2	9	25	36 (S)-(–)[a]
(iv)[RhCl(hd)]$_2$/(S)-AMSO	1.79x10^{-3}	1 : 2	8	16	27 (R)-(+)[b]
(v)[RhCl(hd)]$_2$/(S)-AMSO	5.31x10^{-3}	1 : 2	8	23	27 (R)-(+)[b]
(vi)[RhCl(hd)]$_2$/(S)-AMSO	2.98x10^{-3}	1 : 2	11	21	24 (R)-(+)[b]
(vii)[RhCl(hd)]$_2$/(S)-AMSO	5.75x10^{-3}	1 : 2	11	30	33 (R)-(+)[b]
(viii)[RhCl(hd)]$_2$/(S)-AMSO	5x10^{-3}	1 : 1	11	22	38 (R)-(+)[a]
(ix)[RhCl(hd)]$_2$/(S)-AMSO	5x10^{-3}	1 : 2	10	45	63 (R)-(+)[a]

Conditions: Rh concentration in Table 3.10 refers to monomer in 2-propanol (10 mL) except entry (iv) which was in 30 mL of 2-propanol; T = 83°C; entries (iii)-(vii) were sealed under Ar; entries (i), (ii), (viii), and (ix) were performed with Ar bubbling; Ratio Rh : KOH : acetophenone ~ 1 : 5 : 175; entries (i)-(vii) are from the present work; entries (viii) and (ix) are from references 71 and 87.

†   (a) determined by optical rotation measurements or with NMR chiral shift reagents
(or both).
(b) determined by injection of an urethane derivative of the alcohol on a chiral column.

(vii) show that when the ratio of AMSO to Rh is 2 : 1 increasing the concentration of the catalyst precursor from ~ 3x10^{-3} M to 6x10^{-3} M causes a substantial increase in both the rate and the enantioselectivity of the reduction of acetophenone. Dilution of the Rh concentration from ~ 5x10^{-3} M to 2x10^{-3} M by the addition of more solvent (entries (iv) and (v)) resulted in a decrease in reaction rate as expected. However, the value obtained for the e.e. remained unchanged, which is unlike the decrease in e.e. that was observed for entry (vi), which had less catalyst precursor added to the same amount of solvent to generate the change in concentration (as opposed to dilution as was used in run (iv)). Therefore, an increase in the Rh

concentration causes an increase in the rate of reaction, but a trend in the e.e. could not be established, although there seems to be some dependence on the catalyst precursor concentration.

As mentioned above, the effect of changing the Rh to AMSO ratios had been examined before (runs (viii) and (ix)), with both the optical and chemical yields showing an approximate doubling on changing the ratio from 1 : 1 to 1 : 2.[71, 87] Runs (i) and (iii) also show an approximate doubling in the value obtained for the e.e., but the chemical yield was not seen to change on increasing the ratio of ligand to metal. Therefore, a ratio of 2 moles of AMSO to 1 mole of Rh provides an "optimum" catalytic system in terms of the asymmetric induction achieved; however, the rate of reduction of the substrate does not seem to be affected by changing the ratio from 1 to 2 (at least in the two relevant experiments carried out in the present work). It has been reported that if the ratio is increased to 3 moles of ligand per mole of rhodium or greater, that Rh metal is produced and the reaction does not proceed.[87]

3.9 Effect of Added Acetone and Added H_2O

As mentioned in section 3.5, the presence of acetone should shift the equilibrium (eq. 3.1) in favour of the reactants, acetophenone and 2-propanol. However, it was observed that a sealed reaction (method 2) gave a larger chemical yield of 1-phenylethanol than did a reaction that used argon bubbling (method 1). The methods of work-up outlined in section 2.4 were such that the reaction product acetone could not be detected, as it was pumped off with the 2-propanol. Therefore, a slightly modified work-up was performed in order to check for acetone. The modified method omitted the removal of 2-propanol at the pump and instead collected the whole liquid phase by distillation from bulb 3 to bulb 1 of the Kugelrohr apparatus. The isolated solution was injected neat into the gas chromatograph, and acetone was detected under GC conditions slightly different than those outlined in section 2.5.1. Gas chromatographic analyses were run isothermally at 45°C with injector and detector temperatures of 250°C (Fig. 3.4). The carrier gas flow was the same as in the previous analyses.

76
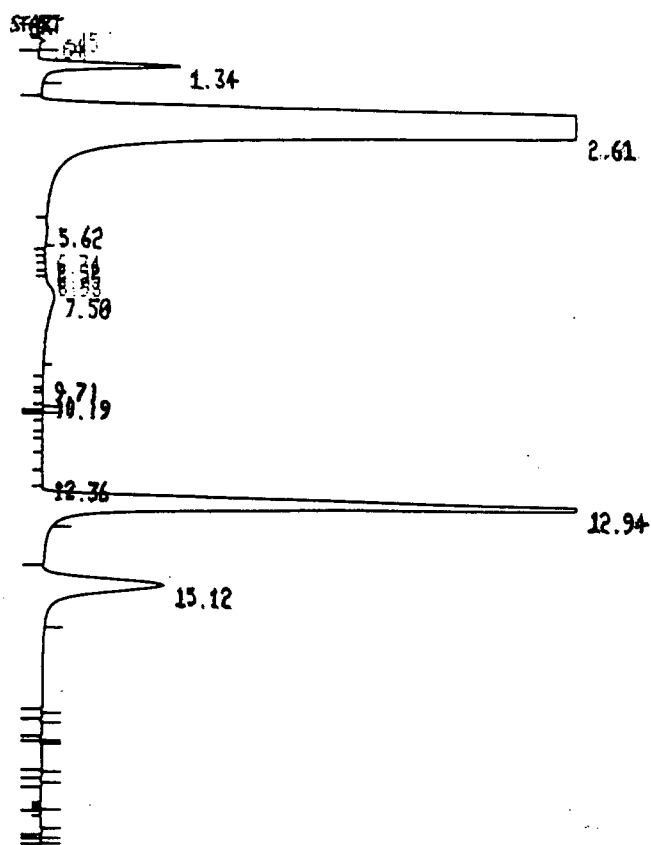
Compound	Retention time (min)	Approximate Response factor
acetone	1.34	1.0
2-propanol	2.61	1.6
acetophenone	12.94	6.3
1-phenylethanol	15.12	6.3

Figure 3.4 Gas chromatogram of the product mixture obtained from the transfer hydrogenation of acetophenone.

The integration of the peaks on the gas chromatogram revealed (as expected) that approximately the same number of moles of acetone and 1-phenylethanol were produced in the transfer hydrogenation reaction. The response factors shown above are approximate as only

the relative responses of acetone and 2-propanol were determined under these conditions. Acetophenone and 1-phenylethanol response factors were estimated under these conditions by comparing the response of 2-propanol under both conditions and making appropriate adjustments. Although the response factors are not that accurate, the ratio of moles of products, acetone and 1-phenylethanol, is near unity (1.5 : 1).

Acetone was added to a catalytic transfer hydrogenation reaction to examine the effect on the rate and the optical yield. These experiments were performed as described in section 2.4.2, except that acetone (2.0 mL, 2.72×10^{-2} moles) was added to the reaction mixture before the substrate and KOH were introduced to the Schlenk tube. The acetone was distilled and degassed and then pipetted under argon into the reaction vessel. The reaction mixture, as usual, turned dark brown from the original pale yellow colour shortly after the addition of KOH. A reaction with added acetone was run concurrently with a control reaction which had no added acetone. The results are shown in Table 3.11 along with another reaction that had acetone added to it but was not run side-by-side with a control. An experiment that was run for approximately the same reaction time is included in Table 3.11 to allow for easy comparison.

Table 3.11 Effect of Adding Acetone to a Catalytic Transfer Hydrogenation Reaction.

Catalyst	Concentration(M)	Rx. time(h)	Acetone	Conversion(%)	e.e.(%)[†]
(i) [RhCl(hd)]$_2$/(S)-AMSO	5.31×10^{-3}	8	Not Added	23	27 (R)-(+)
(ii)[RhCl(hd)]$_2$/(S)-AMSO	5.27×10^{-3}	8	Added	31	21 (R)-(+)
(iii)[RhCl(hd)]$_2$/(S)-AMSO	5.25×10^{-3}	20	Not Added	39	38 (R)-(+)
(iv)[RhCl(hd)]$_2$/(S)-AMSO	4.97×10^{-3}	22.5	Added	49	20 (R)-(+)

Conditions: [Rh monomer] ~ 5×10^{-3} M in 2-propanol (10 mL); sealed under Ar (section 2.4.2); T = 83°C; Ratio Rh : AMSO : KOH : acetophenone ~ 1 : 2 : 5 : 175; entries (i) and (ii) were run side-by-side; reactions (iii) and (iv) were not run side-by-side and, in fact, were run for slightly different reaction times, but nonetheless seemed useful to compare.

† determined by injection of an urethane derivative of the alcohol on a chiral column.

Reactions that had acetone added (runs (ii) and (iv)) showed an increase in the rate of reduction of acetophenone. This result was unexpected, as an increase in the concentration of acetone should increase the rate of the back reaction (eq. 3.1) and shift the equilibrium towards the left as written. This result remains difficult to explain (see section 3.5), but nonetheless is reproducible. The enantiomeric excess obtained from the two experiments with added acetone was lower than in the absence of acetone. The decrease in optical yield observed in the presence of acetone is also reproducible. The origin of this phenomenon is not known, although an increase in the rate of the back reaction, as expected for the addition of acetone, would be expected to decrease the optical yield because the reverse reaction is known to proceed non-enantioselectively (section 3.11). Small amounts of condensation products were detected as side-products in the reactions with added acetone. These compounds were eluted from the Carbowax column at approximately the same retention times as were the species seen for the base-catalysed transfer hydrogenation described in section 3.3.4 (22.5 and 25.2 minutes). The integration of these two peaks was less than 2% of the total integration for the product-substrate mixture. No condensation products were observed in the absence of added acetone and in the presence of the usual Rh-AMSO catalyst. Increased amounts of these condensation products in the presence of added acetone suggests that these side-products may be produced by the condensation of acetone. Acetone and its aldol product 4-hydroxy-4-methyl-2-pentanone (diacetone alcohol) are known to be in rapid equilibrium in the presence of base catalysts, the amount of aldol product in the equilibrium being only a few percent.[100] Similar high-boiling condensation products, predominantly diacetone alcohol, have been observed for the direct H_2-hydrogenation of acetone catalysed by ruthenium systems in basic media.[40]

It has been reported in the literature that the addition of H_2O increases the rate of H_2-hydrogenation of ketones catalysed by cationic Rh-phosphine complexes; Schrock and Osborn found that the initial rate of reduction of ketones is markedly enhanced (30 times) by adding 1% water.[34, 38] However, Solodar et al. using related systems found that although the rate of

was achieved at 0.1% added water.[39] Increases above these levels of added water showed both a reduction in rate and in the optical yield attained. However, with systems employing neutral rhodium complexes as the catalyst for the direct hydrogenation of ketones, as opposed to the cationic complexes used in the above systems, the addition of small amounts of water did not affect the rate of reduction, although the extent of asymmetric induction was lowered.[40] Systems using ruthenium-phosphine catalysts for the hydrogenation of ketones also show increased rates with the addition of H_2O, but the rate of reduction now increased with up to 10% added water.[40] However, the addition of more than 5% H_2O resulted in decreased selectivity for the reduction of acetone to isopropanol and condensation products were produced as side-products.[40] The rate of hydrogen transfer has also been reported to be influenced by the addition of water. Maximum rates for the transfer hydrogenation of ketones catalysed by rhodium(I) complexes with phenanthroline type ligands were achieved at approximately 0.1% added water.[49] Other rhodium(I) systems which use phosphines as the ligands are poisoned by moisture, and therefore the rate of transfer hydrogenation is slowed by the addition of water.[101]

In order to examine the effect of added water on the rate and asymmetric induction of the transfer hydrogenation under investigation in the current work, approximately 1% water by volume was added to a catalytic experiment, which was run concurrently with another reaction without added H_2O as a control. Some H_2O (0.1 mL) was added to a solution of [RhCl(hd)]$_2$ and (S)-AMSO in 2-propanol, followed by the addition of acetophenone and KOH solution as described in section 2.4.2. The effect of added water on the chemical and optical yield for the transfer hydrogenation of acetophenone is small as shown in Table 3.12.

The e.e. values are not significantly different in the presence or absence of added H_2O (see note accompanying Table 2.3 for the error limits of this method of chiral analysis). The rate of transfer hydrogenation, if affected at all by the addition of water, may slightly decrease in the presence of water as indicated by the somewhat lower conversion value in Table 3.12. In any case, the effect of added H_2O is minimal on the performance of this transfer

hydrogenation system. In fact, H_2O may be present in trace amounts in all the catalytic reactions as water is difficult to exclude because KOH is very hydroscopic. Efforts were made to minimise the amount of water introduced into a catalytic reaction by first grinding the KOH pellet into a powder and then pumping on this in a Schlenk tube. The powder was then dissolved in 2-propanol and transferred by syringe to the reaction vessel under argon. Also, two catalytic reactions were performed in which one had KOH added as a solid and the other had KOH added as a solution in 2-propanol. The method of addition had no influence on the chemical or optical yield of the 1-phenylethanol product.

Table 3.12 Effect of Adding H_2O to a Catalytic Transfer Hydrogenation Reaction.

Catalyst	Concentration(M)	Rx. time(h)	H_2O	Conversion(%)	e.e.(%)[†]
(i) [RhCl(hd)]$_2$/(S)-AMSO	4.52×10^{-3}	9	Not Added	22	22 (R)-(+)
(ii) [RhCl(hd)]$_2$/(S)-AMSO	5.49×10^{-3}	9	Added	19	24 (R)-(+)

Conditions: [Rh monomer] $\sim 5 \times 10^{-3}$ M in 2-propanol (10 mL); sealed under Ar (section 2.4.2); T = 83°C; Ratio Rh : AMSO : KOH : acetophenone $\sim$ 1 : 2 : 5 : 175.

† determined by injection of an urethane derivative of the alcohol on a chiral column.

3.10 Effect of Added H_2

The effect of adding dihydrogen to the transfer hydrogenation experiment was examined by performing side-by-side reactions. It was thought that perhaps the presence of H_2 might allow for a larger degree of conversion of the substrate to product. This hypothesis was investigated by running two experiments, one under an atmosphere of H_2 and the other as a control under Ar. The results obtained from the two experiments are shown in Table 3.13.

Comparison of the conversion values shows that the reaction with no added H_2 gave a larger chemical yield of the alcohol. A possible explanation, though highly speculative, is that rhodium hydride species are formed when H_2 is added. These rhodium hydride species could be catalytically inactive for transfer hydrogenation and therefore tie up the rhodium as a species

which does not take part in the catalysis. This would explain the lower conversion obtained in the presence of hydrogen. The optical yield values obtained for the above two experiments are low when compared with the results shown in Table 3.3. The method used for the determination of the e.e. is probably largely responsible for the differences between the above results and those of Table 3.3 (section 3.14). Also, low ratios of ligand to metal (1.5 : 1, as opposed to the required 2 : 1) were inadvertently used in these reactions, which has been previously shown to lower the e.e.[87] However, the above two reactions were run side-by-side so it is only necessary to compare the two results. Therefore, the addition of dihydrogen has no effect on the enantiomeric excess of 1-phenylethanol.

Table 3.13 Effect of Added H_2 on the Catalytic Transfer Hydrogenation of Acetophenone.

Catalyst	Concentration(M)	Rx. time(h)	H_2	Conversion(%)	e.e.(%)[†]
(i) [RhCl(hd)]$_2$/(S)-AMSO	5.61×10^{-3}	20.5	Not added	33	13 (R)-(+)
(ii)[RhCl(hd)]$_2$/(S)-AMSO	5.06×10^{-3}	20.5	1 atm	23	12 (R)-(+)

Conditions: [Rh monomer] ~5×10^{-3} M in 2-propanol (10 mL); sealed under Ar (section 2.4.2); T = 83°C; Ratio Rh : AMSO : KOH : acetophenone ~ 1 : 1.5 : 5 : 175.

†   determined by optical rotation measurement.

3.11 The Reverse Reaction

The reverse reaction, or transfer of hydrogen from 1-phenylethanol to acetone, was performed to determine if it was also catalysed by this Rh-sulphoxide-KOH system (eq. 3.2). The experiment was performed in a sealed Schlenk tube in the same manner as the forward reaction. The rhodium dimer [RhCl(hd)]$_2$ (6.63×10^{-5} mol of monomer) and (S)-AMSO (9.98×10^{-5} mol) were dissolved in acetone (10 mL) under argon. The resulting yellow solution was heated for 15 minutes and then dl-1-phenylethanol (1.0 mL) was added followed immediately by the addition of KOH solid (3.6×10^{-4} mol). KOH was added as a solid rather than as a solution (the base was added in 2-propanol solution for studies on the forward

reaction) because KOH is not very soluble in acetone. The solution turned a cloudy orange-brown colour after the addition of KOH. The reaction mixture was heated for 9 hours, the acetone was pumped off under vacuum and the remaining dl-1-phenylethanol and product acetophenone were distilled off the orange residue.

$$\underset{dl}{\underset{CH_3 \nearrow \ \diagdown Ph}{\overset{\overset{OH}{|}}{\overset{*}{CH}}}} \ + \ \underset{CH_3 \diagup \ \diagdown CH_3}{\overset{\overset{O}{\parallel}}{C}} \ \underset{\xrightarrow{\hspace{1.5cm} KOH; \ 83°C \hspace{1.5cm}}}{\overset{[RhCl(diene)]_2 \ + \ (S)\text{-}AMSO}{\rightleftharpoons}} \ \underset{Ph \diagup \ \diagdown CH_3}{\overset{\overset{O}{\parallel}}{C}} \ + \ \underset{CH_3 \diagup \ \diagdown CH_3}{\overset{\overset{OH}{|}}{CH}} \quad (3.2)$$
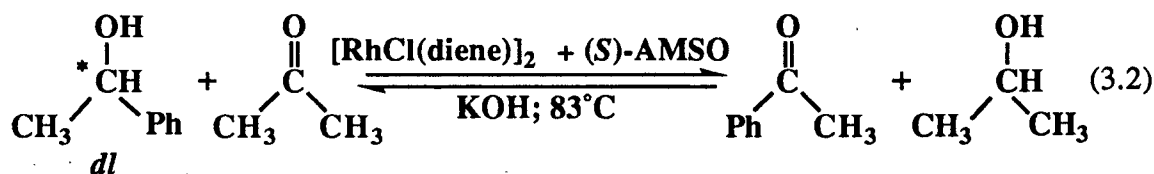
The conversion of dl-1-phenylethanol to acetophenone was 15% as determined by GC. Unlike the forward reaction (ie. transfer of hydrogen from 2-propanol to acetophenone), the reverse reaction did not give an excess of one enantiomer of 1-phenylethanol. The reaction did not proceed with enantiomer discrimination, both enantiomers were dehydrogenated at the same rate, and therefore the e.e. was 0%.

Using either of the K values shown in section 3.3.6 for the forward reaction (K = 0.27 or 0.51) and taking the inverse of these values gives the equilibrium constant for equation 3.2 as written (K = 3.7 and 2.0, respectively). Back calculation from these values and the initial concentration of starting materials reveals that the equilibrium should lie between 96 and 99% conversion of 1-phenylethanol to acetophenone. As only 15% conversion was achieved after 9 hours of reaction, the system is still far from equilibrium.

3.12 Catalytic Activity of the Residue Left at the End of the Reaction

Two experiments were performed in which the brown-black residue, left after the work-up of an original catalytic transfer hydrogenation, was re-used. The distillation of the substrate-product mixture from the residue was performed under inert atmosphere to avoid

possible air oxidation of the active catalytic species. The residue, once isolated from the original solution, was re-dissolved in 2-propanol (10 mL) and new substrate added (1 mL). Heating was continued at 83°C for ~24 hours. The solution was distilled from the metal species and analysed by GC. The catalytic activity of both the original reaction and the re-used catalytic reaction are shown in Table 3.14.

Table 3.14 Comparison of Catalytic Activity When the Catalysts is Re-used.

Experiment	Catalyst	Use	Rx. time(h)	Conversion(%)	e.e.(%)
1	[RhCl(hd)]$_2$/(S)-AMSO	1st	9	22	22 (R)-(+)
1	[RhCl(hd)]$_2$/(S)-AMSO	2nd	24	18	10 (R)-(+)
2	[RhCl(hd)]$_2$/(S)-AMSO	1st	9	26	30 (R)-(+)
2	[RhCl(hd)]$_2$/(S)-AMSO	2nd	26	24	27 (R)-(+)

The results in Table 3.14 show that the residue, left after work-up of an original catalytic reaction, is still active as a catalyst for the transfer of hydrogen to acetophenone. Although the reduction of acetophenone now seems to be somewhat slower (see conversion vs. time graph in Figs. 3.2 and 3.3), experiment 2 suggests that the enantioselectivity of the hydrogenation is not affected. However, experiment 1 suggests that the enantioselectivity of the reaction decreases when the catalyst is re-used. No conclusion other than that the catalyst remains active can be drawn from the above results. More catalytic experiments should be performed with the residue to determine its relative activity for conversion and e.e.

The brown-black residue left at the end of the transfer hydrogenation experiments is soluble in both H_2O and acetone. A UV-visible spectrum recorded on this residue dissolved in H_2O over the range of 200-900 nm proved uninformative. A ^1H NMR spectrum of the brown-black residue in D_2O was also recorded (Fig. 3.5); the region of the spectrum shown shows the ligand (S)-AMSO resonances along with a spectrum for the free ligand. Three of the five ligand resonances in the residue are shifted upfield by up to ~0.2 ppm from those of the free

ligand (the peaks labelled c, d, and f in Fig. 3.5). Although this change in chemical shift for the ligand protons indicates that the ligand is coordinated to rhodium, it provides little information on the nature of this metal species.

Other workers in this laboratory have noted decomposition of the catalyst precursor to metal and/or reduction of the chiral sulphoxide ligand to the thioether during attempted catalytic hydrogenations (both H_2 and hydrogen transfer hydrogenations) of prochiral ketones and olefins.[50, 70] These systems involve rhodium- and iridium-sulphoxide species which are either added as a specific complex or generated *in situ* for the catalytic reaction.[70] However, in the present studies, none of the ^{1}H NMR spectra recorded for any of the residues left at the end of the transfer hydrogenation reactions showed proton resonances which corresponded to the peaks seen for the reduced product of (S)-AMSO, N-acetyl-(S)-methionine. Therefore, reduction of the ligand AMSO to the corresponding thioether does not occur during these catalytic reactions.

3.13 ^{1}H NMR Studies on Catalytic Transfer Hydrogenation

A catalytic transfer hydrogenation of acetophenone was performed in a screw-capped NMR tube equipped with a septum; starting material ratios were similar to those used in the other catalytic experiments performed (see Table 3.3 for ratios). Some [RhCl(hd)]$_2$ (5.9 mg, 2.7×10^{-5} moles of monomer) and (S)-AMSO (12.3 mg, 5.9×10^{-5} moles) were dissolved in 2-propanol-d_8 (~ 1.5 mL) under argon and a ^{1}H spectrum recorded. This solution was then heated at 83°C for 30 minutes and another spectrum recorded. The substrate acetophenone (10 μL, 8.6×10^{-5} moles) was then added to the NMR tube with a syringe followed immediately by the addition of KOH as a solid (7.5 mg, 1.3×10^{-4} moles). Heating was resumed for another hour at which time another spectrum was recorded. A brown-black residue precipitated shortly after the addition of the substrate and the base, as was seen in the other transfer hydrogenation experiments (section 2.4). Finally, the reaction was left at 83°C for a further 8 hours and a final spectrum was recorded. The ratio of Rh : AMSO : KOH :
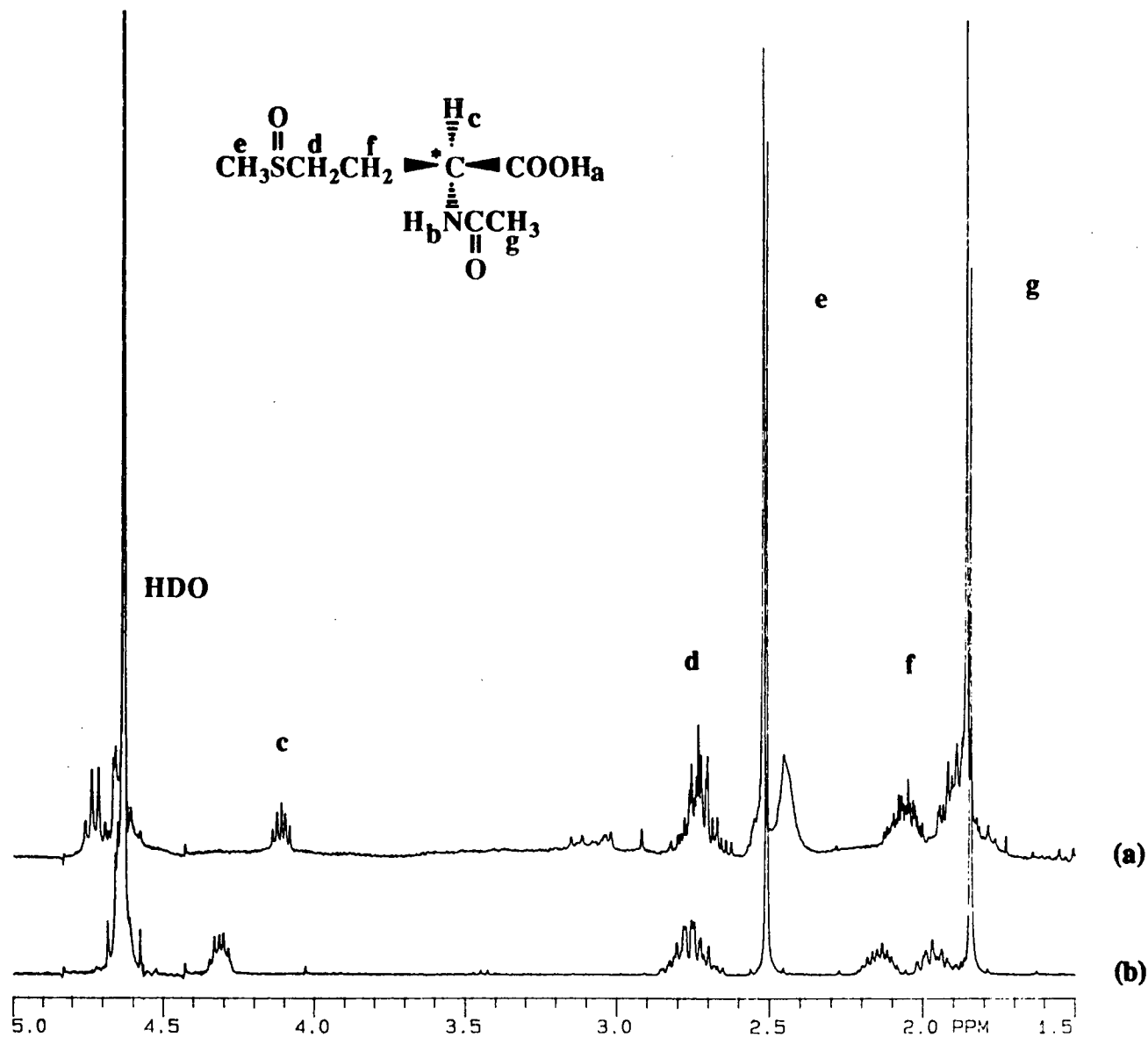
Figure 3.5 300 MHz ^{1}H NMR spectrum of the brown-black residue left at the completion of a transfer hydrogenation reaction of acetophenone from 2-propanol catalysed by [RhCl(hd)]$_2$-(S)-AMSO-KOH. Spectrum (a): residue in D$_2$O; spectrum (b): free ligand in D$_2$O.

substrate was 1 : 2 : 5 : 3, which was the same ratio of catalytic species used in most of the transfer hydrogenation experiments. The amount of acetophenone added had to be reduced from that normally used in order to avoid completely obscuring any signals due to any rhodium species and the ligand AMSO. The NMR studies were originally undertaken in the hope that signals due to catalytic rhodium intermediates would be observed, and thereby provide some information on the steps involved in the catalysis and the binding of the chiral ligand AMSO to the metal. Unfortunately, the only peaks that could be assigned were those of acetophenone and the corresponding hydrogenated product 1-phenylethanol. It was impossible to observe the shift in the ^{1}H resonances for AMSO that were observed for the catalytic residue (section 3.12); because of to the large number of species in solution with protons which resonate in this region of the spectrum (between 1 and 4.5 ppm). Therefore, ^{1}H NMR spectra proved useful only in following the conversion of substrate to product (Fig.3.6).

The conversion of acetophenone to 1-phenylethanol after 1 hour of heating at 83°C was ~23% as determined by integration of the peaks in the phenyl region due to each species (see spectrum (a), Fig. 3.6). After 9 hours of reaction time, the integration of the phenyl region of the spectrum gave ~75% conversion of the substrate to the product alcohol (see spectrum (b), Fig. 3.6). The phenyl region was most easily used for determination of the conversion as no other resonances appeared in this area and the protons from each compound were distinct (no overlap). The phenyl protons of 1-phenylethanol resonate between 7.2-7.5 ppm while those of acetophenone resonate between 7.5-8.1 ppm. The conversion value obtained in this experiment (75%) is much larger than that observed after 9 hours for a regular catalytic experiment (30%, see Fig. 3.3.and Table A4). This is not surprising as the ratio of Rh : substrate is much larger (1 : 3) than the ratio normally used (1 : 175).
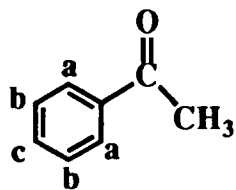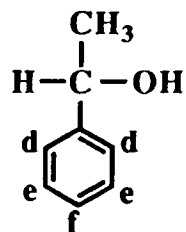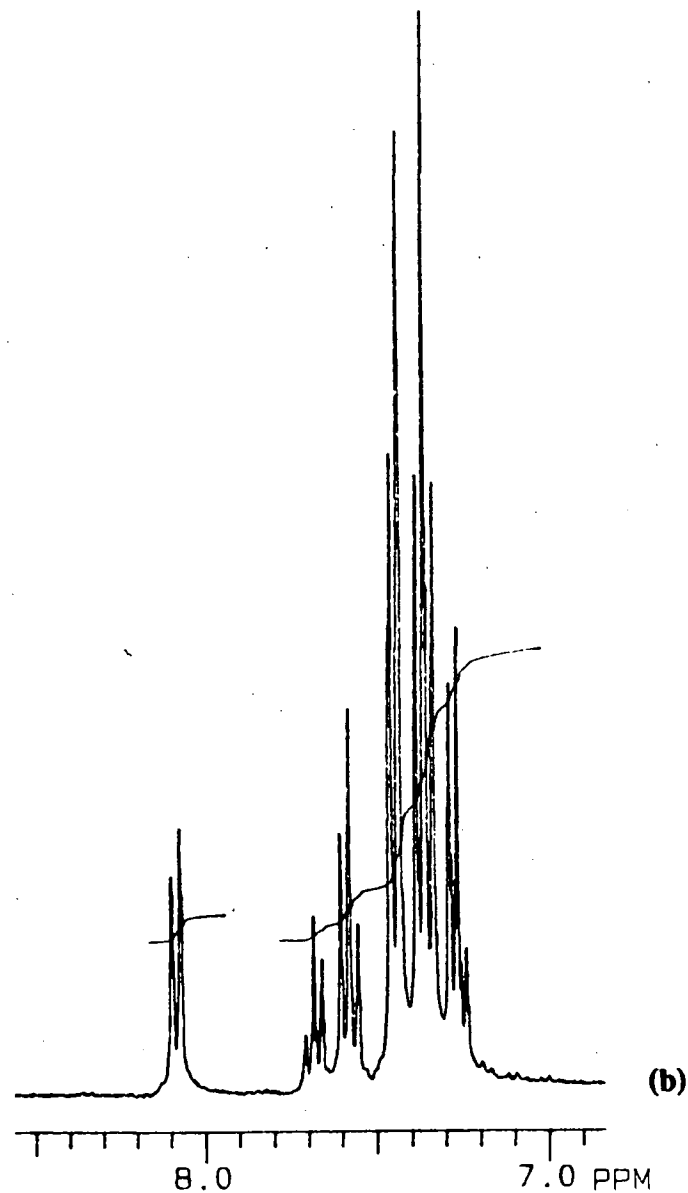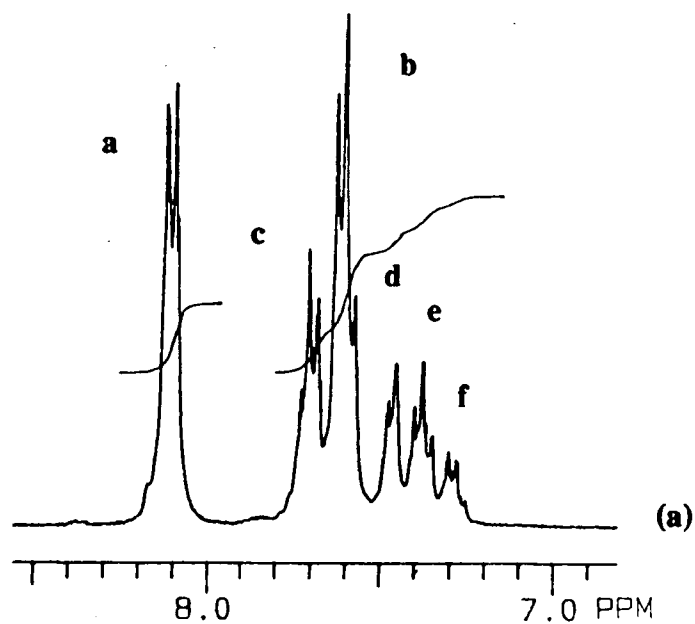
Figure 3.6 300 MHz ^{1}H NMR spectrum of the Rh-AMSO catalysed transfer hydrogenation of acetophenone performed in 2-propanol-d_8. Spectrum (a): phenyl region after 1 hour of heating; spectrum (b): after 9 hours.

3.14 Comparison of the Analytical Methods Available for Determination of Enantiomeric Excess

In the literature to date, most of the enantiomeric excess determinations (or optical yield measurements) have been made by measurement of the rotation of the reaction product and comparison of this value with the reported optical rotation for a pure enantiomer. Little mention of the experimental procedure for measuring these rotations is given in the papers. In fact, in some papers the value used for the optical rotation of the pure enantiomer is not given. In the case of 1-phenylethanol at least seven different values for the optical rotation have been reported for one enantiomer or the other in different solvents and at different temperatures (Table 3.15).

Table 3.15 Literature Values for the Absolute Rotation of Pure 1-Phenylethanol.

Enantiomer	Absolute Rotation[†]	Concentration (g/100 mL)[‡]	T (°C)	Reference
(R)-(+)-1-phenylethanol	+39.5°	neat	22	102
(R)-(+)-1-phenylethanol	+42.9°	neat	19	103
(R)-(+)-1-phenylethanol	+42.9°	neat	20	104
(R)-(+)-1-phenylethanol	+52.5°	CH_2Cl_2, c=2.27	22	105
(S)-(–)-1-phenylethanol	–41.3°	neat	23	102
(S)-(–)-1-phenylethanol	–43.2°	neat	20	106
(S)-(–)-1-phenylethanol	–43.6°	neat	17	107
(S)-(–)-1-phenylethanol	–45.5°	MeOH, c=5	20	103

† measured at the sodium D line, 589 nm.
‡ density of 1-phenylethanol at 20°C is 1.0129 g/mL.[103]

Most of the reports that appear in the literature for the asymmetric hydrogenation of acetophenone use –43.5° for the value of the absolute rotation of (S)-(–)-1-phenylethanol but often incorrectly cite reference 104 as the source of this value. Pickard and Kenyon[104] were

actually unable to prepare the (S)-(–)-alcohol in this paper, but did report the absolute rotation for the (R)-(+)-alcohol, $[\alpha]_D^{20} = +42.9°$. A value of –43.2° close to the –43.5° used by some authors does however appear in a later paper by Houssa and Kenyon.[106] Incorrect temperatures at which the optical rotation measurements of the pure enantiomers were performed are also often quoted. However, for 1-phenylethanol, the absolute rotation does not actually change that much with temperature (Table A5). More significant changes in optical rotation values have been observed for other chiral compounds on changing the temperature.[108] Therefore, care should be taken to both thermostat the optical cell and measure the rotation at a temperature where the absolute rotation of the pure enantiomer has been reported. It is also important to report the concentration of the solution used to determine the rotation. In the past, in at least one case, workers have re-evaluated their own determinations of e.e. and have found significant differences from their originally reported values.[108] Originally, optical yields as high as 95% were reported for the asymmetric hydroformylation of styrene with a chiral phosphine-platinum system, however re-evaluation of this result gave an e.e. of 73%.[108] The rotation measurements were initially performed at both a different temperature and concentration than the reported value for the absolute rotation of the hydroformylation product, (S)-2-phenylpropanal. It was found that in some cases, $[\alpha]_D$ can be remarkably different in dilute solutions and at different temperatures. The re-evaluated optical yields were confirmed by ^{1}H NMR using chiral shift reagents.[108]

Other workers have also noted the limitations of the more traditional optical rotation measurements. Chan and Landis[51] found, on repeating some asymmetric hydrogenation experiments performed by other researchers,[55] that they could not reproduce the 82% e.e. of 1-phenylethanol reported and obtained an e.e. of only approximately 60%. Chan and Landis found that if optical rotation methods (section 2.5.2) were used to determine the optical yield, the e.e. appeared to be somewhat higher (5-15%) than when chiral GC methods (section 2.5.3) were used to analyse the hydrogenation products.[51] Chiral GC analysis was found to be more convenient and reliable by these workers.

Originally, the optical yields obtained in the present work for the Rh-AMSO catalysed transfer hydrogenation of acetophenone were determined by measuring the rotation of the substrate-product mixture and dividing this value by a literature value for the absolute rotation of a pure enantiomer (section 2.5.2). However, difficulty in obtaining consistent and reproducible results suggested that more care should be taken in correcting for the concentration of the solution and thermostatting the optical cell. Calibration curves were prepared by measuring the variation of the observed rotation (α) of pure (R)-(+)-1-phenylethanol (purchased from Aldrich) with temperature and concentration. A plot of the observed rotation (α) vs. temperature gave a straight line (graph A6 in the appendix). The effect of temperature on the optical rotation was not very pronounced, the observed rotation changing by only about 1° over the ~30°C temperature range investigated. Absolute rotations ($[\alpha]_D^T$) were calculated by dividing the observed rotation (α) by the density of (R)-(+)-1-phenylethanol (see equation 2.1) at the appropriate temperature (Table A5). The density of (R)-(+)-1-phenylethanol has been reported at seven different temperatures;[103, 104] therefore a plot of density vs. temperature, which is linear with a negative slope, allows for the correct value of the density at any given temperature to be found. A plot of the absolute rotation ($[\alpha]_D^T$) of the (R)-(+)-alcohol vs. temperature also gave a straight line. Over the approximately 30°C temperature range investigated, the absolute rotation was observed to change very little (~0.06°).

Another calibration curve was prepared to examine the effect of changing the concentration (i.e. the degree of conversion of substrate to product, as the rotation was measured on the substrate-product mixture) on the observed rotation of the pure enantiomer at a temperature of 25°C. Only a small amount of the pure enantiomer was available (1 g), therefore the rotation of the pure enantiomer was initially measured and then 0.900 mL of the pure enantiomer was added with a microburet to a vial containing acetophenone (0.100 mL), which had previously been added with a 100 μL syringe, and the rotation of this mixture measured. The rotations of more dilute mixtures were measured by successively diluting the

solution by mixing 0.850 mL of the previous solution with 0.200 mL of acetophenone. The concentration of the (R)-(+)-alcohol in these solutions was calculated using the known densities of 1-phenylethanol and acetophenone, and by assuming that the total volume of the solution was the sum of the volumes of the pure enantiomer and acetophenone. These solutions were also injected neat onto a Carbowax column and both the concentration and "conversion" calculated. The absolute rotation was calculated from both values for the concentration (the calculated value and the value obtained from GC) and the observed rotation measured (Table A7). A plot of observed rotation vs. % of (R)-(+)-1-phenylethanol proved most useful for calibrating the hydrogenation results (Graph A8). The data for the above plot were best fit by a slight curve, as observed for other chiral compounds.[108] Absolute rotation (values calculated from the calculated concentrations) vs. %-(R)-(+)-1-phenylethanol was less useful as a calibration curve, as the data were best fit by a curve which increased from a value of ~43.4° at 100% of the alcohol to a maximum at ~48.8° for 25% of the pure enantiomer and then decreased on further dilution. The absolute rotation values calculated from the concentration obtained by GC were less reliable than the values obtained by using the concentrations obtained by calculation from the amounts of acetophenone and (R)-(+)-1-phenylethanol added. The concentrations obtained from GC were in fairly good agreement with the values obtained by calculation from the amount added, with the exception of a few data points (see Table A7 in the appendix). Fairly significant errors in the concentrations of the more dilute solutions are likely because of the nature of the sample preparations (successive dilutions); the integration of the peaks in the GC is also likely to be less accurate with the injection of undiluted solutions (fairly broad peaks). In any case, the e.e is best calculated by comparing the observed rotation for a hydrogenation product mixture with the observed rotation of the pure enantiomer at the appropriate % of (R)-(+)-1-phenylethanol. Comparison of the observed rotations as opposed to the absolute rotations allows for the e.e. to be calculated without having to use the concentration of the solutions (although it is necessary to know the %-(R)-(+)-1-phenylethanol for use of the calibration curve) and thus eliminates any

error introduced from division of the observed rotation by the concentration when calculating the absolute rotation (eq. 2.1).

If the chemical yield of the hydrogenation product is much less than 100% and if the e.e. is to be calculated by optical rotation measurements, then either a calibration curve should be constructed or preparative gas chromatography should be performed to isolate the product, in order to ensure that the e.e. value obtained is representative of the actual enantioselectivity of the reaction. If preparative gas chromatography is used to isolate the product alcohol from any unreacted substrate, then the optical rotation measured (absolute rotation) can be compared directly with a literature value of a pure enantiomer to find the optical yield.[109] This method eliminates any concentration effects which might give a misleading value for the e.e. In the literature, workers often report that in the calculation of the e.e. they have corrected for the presence of unreacted material; however rarely do any details for this procedure appear.[48, 62] In at least one case, workers have reported that the e.e. values were corrected by using a plot of the optical activity of the alcohol-ketone mixture against the alcohol concentration (this was for the reduction of propiophenone).[68]

Valentine and Scott suggest that optical rotation measurements should not be used to evaluate the enantiomeric excess because these measurements are very sensitive to experimental conditions and affected by unsuspected impurities.[26] They suggest that attempts to remove impurities may lead to enantiomeric fractionation and therefore give a misleading result.[26] It is suggested by these workers that a direct method which does not rely on optical rotation measurements should be used to determine the optical yield. Alternative direct methods include: (1) reaction with a second pure chiral substance to generate diastereomers which can be analysed by NMR or separated by GC or HPLC;[26] or (2) preparation of a derivative for injection on a chiral column. These methods are advantageous in that they are generally not sensitive to impurities and also may be used to analyse chiral products that have not previously been prepared in an enantiomerically pure form (i.e. the absolute rotation of the pure enantiomer need not be known). Several workers have analysed chiral alcohols, which were

produced through asymmetric reduction of the corresponding ketones, by preparation of MPTA ester derivatives ((+)-α-methoxy-α-(trifluoromethyl)phenylacetates).[33, 109] These diastereomeric esters were then analysed by ^{1}H NMR, GC, or HPLC.

In the present work, chiral GC (section 2.5.3) gave more reproducible results for the e.e. and was more convenient to use than the more traditional optical rotation measurements. Optical rotation measurements require ~ 1 mL of sample to analyse for the e.e., as the optical cell volume is 1 mL, while the chiral GC method only requires 1-20 μL of sample (depending on the conversion of prochiral ketone to alcohol) for the same analysis. Table 3.16 shows the values obtained for some selected transfer hydrogenation experiments by using both optical rotation and chiral GC methods to determine the enantiomeric excess. Two values are shown for the optical yield as determined by polarimetry, one being determined by use of a literature value of a pure enantiomer (absolute rotation) and the other being determined by use of the calibration curve A8 (observed rotation).

The values for the e.e. shown in Table 3.16 illustrate the importance of calibrating the measured rotations for concentration effects on the value of the rotation for the pure enantiomer. The optical yields determined by comparing the absolute rotation of the sample with a literature absolute rotation were significantly different, in most instances, from the e.e. found by either chiral GC or upon calibration of the rotations. The enantiomeric excesses determined by the calibration method, with the exception of entries (i), (ii), and (vi), were usually somewhat higher (2-15%) than the values obtained by chiral gas chromatography. This is in agreement with the results found by Chan and Landis.[51] The results obtained from chiral GC are more reliable and reproducible than the values found by optical rotation methods. A repeat of the chiral analysis for entries (i) and (ii) by GC gave results of 23.6 and 28.0% e.e., respectively. Both of these values agree within 1% e.e. of the original measurements, as mentioned in Table 2.3.

Table 3.16 Enantiomeric Excess Values of 1-Phenylethanol Obtained by Different Methods of Analysis.

Conversion (%)		Observed Rotation (α) (°)[a]	e.e. (%)		
			literature value[b]	calibration curve[c]	chiral GC[d]
(i)	4	+0.171	45.6	30.5	22.9
(ii)	16	+0.740	11.2	23.2	27.2
(iii)	17	+1.204	22.7	19.1	18.8
(iv)	17	+0.687	28.3	26.2	25.6
(v)	20	+3.547	43.8	35.8	33.2
(vi)	49	+1.225	8.8	14.8	19.5
(vii)	54	+6.345	41.1	34.2	30.3

(a) measured at 25°C, the temperature at which the calibration curve had been constructed (Graph A8 and Table A7).

(b) the literature value used was $[\alpha]_D = 43.5°$, that most often used in the literature (despite not appearing in Table 3.15).

(c) the measured observed rotation (α) of the hydrogenation mixture was compared with the observed rotation of the pure (R)-(+)-alcohol at the appropriate %-(R)-(+)-1-phenylethanol, which was determined by injection of the sample undiluted into the GC (Graph A8).

(d) determined by injection of an urethane derivative of the alcohol on a chiral column (see section 2.5.3).

3.15 Asymmetric Transfer Hydrogenation of Propiophenone

Another aryl alkyl ketone which was reduced catalytically by this rhodium-sulphoxide system was propiophenone. Propiophenone was hydrogenated by transfer of hydrogen from 2-propanol under the same catalytic conditions that were used to reduce acetophenone. The ratio of Rh : (S)-AMSO : KOH : propiophenone was 1 : 2 : 5 : 160 and the starting concentration of Rh monomer was 5.48×10^{-3} M. The reaction was performed in a sealed Schlenk tube under Ar (section 2.4.2) and heated at 83°C for 8.5 hours. The original pale yellow solution turned brown-black five minutes after the addition of the substrate and the

KOH solution. During the reaction, a brown-black solid precipitated as when acetophenone was the substrate used. The retention times of the product and substrate are shown in Table 3.17 using the same GC conditions used for acetophenone hydrogenation (section 2.5.1). The retention time of 1-phenyl-1-propanol was determined by injection of the racemic alcohol which was prepared by sodium borohydride reduction of propiophenone (section 2.1.3.3).

Table 3.17 Retention Times and Response Factors.

Compound	Retention time (min)	Response factor
2-propanol	0.7	1.0
propiophenone	7.5	4.1
1-phenyl-1-propanol	12.4	4.1

The conversion of propiophenone to 1-phenyl-1-propanol (Table 3.18) was identical with the value obtained in a preliminary study.[71] However, the value obtained for the e.e. was significantly lower than that reported previously (Table 3.18).[71] Again, as in the case of the 1-phenylethanol product obtained from acetophenone reduction (Table 3.3), the nature of the discrepancy is not known but at least part of the difference in the values obtained can be accounted for by the different methods of chiral analysis used (see section 3.14).

Table 3.18 Transfer Hydrogenation Results for Propiophenone.

Rh dimer, [RhCl(diene)]2	Ligand, L	Conversion(%)	e.e.(%)[†]	Configuration[‡]	Reference
(i)	hd	(S)-AMSO	21	71[a]	(R)-(+)	71
(ii)	hd	(S)-AMSO	21	35[b]	(R)-(+)	present work

† (a) determined by optical rotation measurements.
  (b) determined by injection of an urethane derivative of the alcohol on a chiral column.

‡ Configuration of the enantiomer of 1-phenyl-1-propanol that was obtained in excess.

The retention times for the urethane derivatives of 1-phenyl-1-propanol are shown in Fig. 3.7 using approximately the same GC conditions that were used for 1-phenylethanol (section 2.5.3). The same oven, detector, and injector temperatures were used, but the carrier gas flows may have changed slightly, which would account for the change in retention time of the solvent when compared with Fig. 2.7.

The (R)-(+)-urethane derivative (relative to the (S)-(–)-urethane derivative) was eluted from the chiral column first. This was somewhat expected as the urethane derivative of (R)-(+)-1-phenylethanol was eluted before the (S)-(–)-derivative; and because the manufacturers of the chiral column have reported that d amino acid derivatives (N-pentafluoropropyl or isopropyl ester derivatives) elute before the l enantiomeric derivatives. Both acetophenone and propiophenone were enantioselectively hydrogenated to the (R)-(+)-alcohol when (S)-AMSO was used as the chiral ligand. The optical rotation of the isolated product-substrate mixture was measured to ensure that it was in fact the (R)-(+)-alcohol that was obtained in excess. A positive value for the observed rotation confirmed that the (R)-(+)-alcohol was eluted first.

3.16 Discussion

Although both the chemical and optical yields of the alcohols produced by the rhodium-AMSO catalysed transfer hydrogenation of acetophenone or propiophenone are low to moderate, at least some promise is shown for the asymmetric reduction of ketonic substrates by this route. Aryl alkyl ketones have been most effectively hydrogenated with systems which use chiral phosphines as ligands and high pressures of H_2 (Table 3.1, p. 51). Probably the most effective system to date for the hydrogenation of ketones is a ruthenium-Binap catalyst; however, this system requires that the substrates are functionalised.[33] This Binap system was found to be very effective for the hydrogenation of ortho-substituted acetophenone (92% e.e. for o-bromoacetophenone in 97% yield) but unsuccessful for m-, p-, or unsubstituted acetophenones (< 1% chemical yield).[33] Table 3.2 (p. 52) shows that for the transfer

97
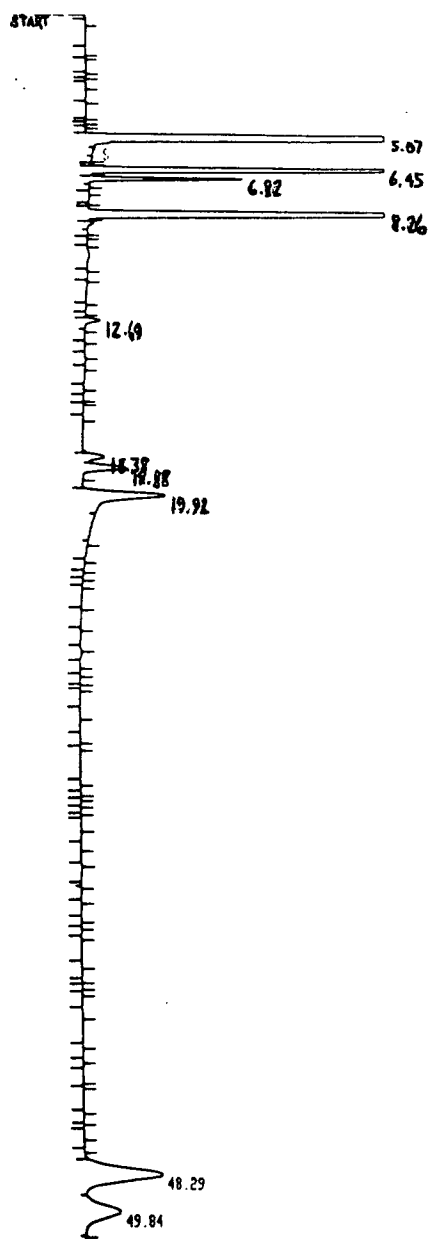
Retention times of urethane derivatives.

Retention times (min)	Component	Area (%)
5.07	Solvent (diethyl ether)	----
6.45, 6.82	isopropyl isocyanate impurities	----
8.26	propiophenone	----
12.69	unreacted 1-phenyl-1-propanol	----
18.38, 18.80, 19.92	isopropyl isocyanate impurities	----
48.29	(R)-(+)-derivative	0.228
49.84	(S)-(+)-derivative	0.110

Figure 3.7 Gas chromatogram of the urethane derivatives of 1-phenyl-1-propanol separated on the chiral Chirasil-Val III column (Table 3.18, entry (ii)).

hydrogenation of acetophenone, the present system is approximately as effective in terms of the optical yield obtained as any other transfer hydrogenation system studied to date. Perhaps the use of *ortho*-substituted aryl alkyl ketones would increase both the chemical and optical yields obtained by the rhodium-AMSO system, as observed for the Binap catalyst mentioned above.

These *in situ* rhodium-AMSO and BMSO catalytic systems remain quite difficult to study, as are most of the *in situ* generated systems and especially those used to catalyse hydrogen transfer reactions. Hydrogen transfer systems are difficult to examine spectroscopically because of the large number of species added to the solution. Systems involving phosphines are somewhat easier to examine as these ligands provide a "handle" in the ^{31}P NMR. In the present system, however, NMR is less informative as all the species added to the catalytic reaction show peaks in the ^1H spectrum. A ^1H NMR spectrum of the residue left at the end of the catalytic reaction, although not providing any clues about the nature of the structure, at least indicates that the ligand AMSO is coordinated to rhodium (Fig. 3.5). This information coupled with the fact that somewhat different chemical and optical yields are observed with different rhodium precursors (hd or cod dimers, Table 3.3), suggests both AMSO and the diene are coordinated in species involved in the catalytic cycle. Also, the preparation by previous workers in this laboratory[70] of complexes of the type [RhCl(coe)(R$_2$SO)]$_2$ (where R = [CH$_2$]$_2$ or Ph) that contain *S*-bonded sulphoxides indicate that displacement of the coordinated diene by AMSO from the rhodium(I) precursors is unlikely.

^1H NMR studies and the blank reactions that were performed indicate that the chiral ligand AMSO remains intact during the catalytic reactions. No reduction of the sulphoxide, decarboxylation, or hydrolysis of the acetyl group are observed during the course of the reaction or are apparent in the residue left at the end of the reaction (sections 3.3.3, 3.12, and 3.13). Other blanks (sections 3.3.1 and 3.3.2) indicate that both the sulphoxide and carboxylate functionalities are important for the catalysis to occur effectively. Although the results obtained in section 3.3.2, where *N*-acetyl-*dl*-methionine was used as the ligand, do not

provide conclusive evidence for the necessity of the sulphoxide group, other workers have reported that amino acid complexes of the type [Rh(cod)(NH$_2$CH(R)CO$_2$)] are poor hydrogenation catalysts.[110] This suggests that the sulphoxide group in the ligand AMSO is important for an effective transfer hydrogenation catalyst to be generated. The chelating ability of AMSO through the sulphoxide and carboxylate groups is almost certainly utilised in the catalytic cycle, although there is no indication from these studies as to whether the ligand is *S*- or *O*-bonded at the S=O moiety. The use of other techniques (UV-vis or solution IR) to elucidate further information about the system is difficult as a brown-black solid precipitates during the catalysis (section 2.4).

Although the new ligand BMSO was found to be inferior to AMSO for the transfer hydrogenation of acetophenone (Table 3.3), it may be more effective for the asymmetric reduction of other substrates. On the other hand, the bulkiness of the benzoyl group may limit the utility of BMSO as a chiral ligand in asymmetric hydrogenation reactions. Similar optical yields were observed for both the product alcohols obtained by transfer hydrogenation of the ketonic substrates acetophenone and propiophenone by the rhodium-AMSO system. The role of the added base has not been established, although possible functions have been suggested and are outlined in section 3.3.5. Nonetheless, the added base cocatalyst is found to be essential for the transfer of hydrogen from 2-propanol to proceed.

Although further testing to confirm the homogeneity of this AMSO system is suggested, the catalytic reaction is thought to occur in solution as the addition of elemental mercury has no effect on the system (section 3.4). Also, the fact that a significant e.e. is observed for these reactions suggests that the system is homogeneously catalysed, as few heterogeneous systems have been found which give significant optical yields (with the exception of the few systems mentioned in section 1.2.3).

The activity of the catalyst is retained in the brown-black residue left after distillation of the liquid phase. This residue after addition of more hydrogen donor and substrate was found to catalyse the reaction, at least to some degree (section 3.12). The rate of the rhodium-AMSO

catalysed transfer hydrogenation decreases quite dramatically after the first four hours of reaction, and becoming extremely slow after 12 hours (Fig. 3.3). The reverse reaction, with 1-phenylethanol acting as the hydrogen donor, is also catalysed by this rhodium-AMSO system (section 3.11). However, the reverse reaction did not take place with enantioselective dehydrogenation of racemic 1-phenylethanol, no e.e. being observed in the remaining alcohol.

CHAPTER 4

CATALYTIC TRANSFER HYDROGENATION OF IMINES BY *IN SITU*
RHODIUM-SULPHOXIDE SYSTEMS

4.1 General Introduction

The catalytic reduction of carbon-nitrogen double bonds by transition metal systems has
been less well studied than the hydrogenation of carbon-carbon and carbon-oxygen double
bonds.[111] As with the hydrogenation of ketones, imines have been most effectively
hydrogenated with rhodium-phosphine systems under H_2. The imines which have been most
often used as substrates in catalytic hydrogenation experiments are
N-(1-methylbenzylidene)benzylamine (the condensation product of acetophenone and
benzylamine) and N-benzylideneaniline (the condensation product of benzaldehyde and
aniline), although other imines have also been reduced to the corresponding secondary amines
by these systems.[57, 111] Very few reports on the catalytic asymmetric hydrogenation of
prochiral imines have appeared in the literature to date. However, some optical yields as high
as 91% have recently been reported (see section 1.2.4).[57] Some of the catalytic systems used,
and the results observed for these systems for the hydrogenation of the above two imine
substrates, are shown in Table 4.1.

The systems which give the best results for the asymmetric hydrogenation of the
prochiral imine N-(1-methylbenzylidene)benzylamine generally require long reaction times,
high H_2 pressures, or both (Table 4.1). Very few systems, other than rhodium-phosphine
systems, have been used to hydrogenate imines, although one *in situ* iridium(I)-Diop system is
known to hydrogenate imines enantioselectively with up to 75% e.e.[112] The only other
systems known by this author for the catalytic hydrogenation of imines use metal carbonyl

compounds (Cr, Fe, Mo, and W) under H_2, CO, or both.[111] An example of one such system is the reduction of N-benzylideneaniline catalysed by $Fe(CO)_5$, with an added base cocatalyst (NaOH or NEt_3).[113] However, this system is somewhat different from the rhodium-phosphine hydrogenation catalysts, as the source of hydrogen is not H_2 gas, but rather water gas shift components, CO (100 atm) with added H_2O.[113]

Table 4.1 Catalytic Hydrogenation of Selected Imines.

Catalyst	Imine[a]	$P(H_2$, atm)	Time(h)	T(°C)	Conv.(%)	e.e.(%)
(i) $[Rh(PPh_3)_2(nbd)]^+PF_6^-$	A	1	6	25	>99	---
(ii) $RhCl(PPh_3)_3$	A	1	21	25	>99	---
(iii) $[Rh(nbd)Cl]_2$ + PPh_3	A	30	6	50	99	---
(iv) $[Rh(nbd)Cl]_2$ + PPh_3	B	70	6	50	92	---
(v) $[Rh(nbd)Cl]_2$ + (+)-Diop	B	70	9	50	82	3.3
(vi) $[Rh(nbd)(Diop)]^+ClO_4^-$	B	1	24	30	67-80	22
(vii) $[Rh(nbd)Cl]_2$ + (+)-Benzphos	B	69	96-120	25	98	72
(viii) $[Rh(nbd)Cl]_2$ + (S,S)-BDPP	B	70	6	20	96	73
(ix) $[Rh(nbd)Cl]_2$ + (+)-Cycphos	B	68	90	20	>99	79

(a)   The imines used as substrates are: A = N-benzylideneaniline,
       B = N-(1-methylbenzylidene)benzylamine

(i) and (ii)	Ref. 111.
(iii) and (v)	Ref. 114.
(iii)	Ref. 115.
(vi)	Ref. 54.
(vii)	Ref. 58; (R)-(+)-Benzphos = $Ph_2PCH(CH_2Ph)CH_2PPh_2$.
(viii)	Ref. 84.
(ix)	Ref. 57; added KI as cocatalyst, (R)-(+)-Cycphos = $Ph_2PCH(C_6H_{11})CH_2PPh_2$.

Other catalytic routes used to produce amines from imines involve the indirect method of hydrosilylation followed by hydrolysis. Asymmetric hydrosilylation of prochiral imines has

produced some chiral amines in reasonably good optical yield.[34] For example, hydrosilylation of PhMeC=NCH$_2$Ph with Ph$_2$SiH$_2$ at low temperatures (2°C), using a rhodium-(+)-Diop catalyst, followed by hydrolysis, gave the chiral amine (*S*)-*N*-benzyl-α-phenylethylamine in 97% yield and 65% e.e.[116]

Transfer hydrogenation of imines has only been reported for a few systems. *N*-Benzylideneaniline has been hydrogenated to the corresponding amine in 85% yield by transfer of hydrogen from 2-propanol. This system uses RhCl(PPh$_3$)$_3$ as the catalyst, with added sodium carbonate as a cocatalyst.[117] Also examined as possible catalysts for the transfer hydrogenation of imines were RuCl$_2$(PPh$_3$)$_4$, OsHCl(CO)(PPh$_3$)$_3$, and RhCl(CO)(PPh$_3$)$_2$, all in the presence of added sodium carbonate. All of these systems reduced the imine to some degree, but all were inferior to Wilkinson's catalyst.[117] It was suggested that the active species in this system was actually a hydride RhH(PPh$_3$)$_{3 \text{ or } 4}$, and that the function of the base was to remove hydrogen chloride from RhCl(PPh$_3$)$_3$ to generate the hydrido-metal complex. Thus, RhH(PPh$_3$)$_4$ was prepared and found to be the most active catalyst studied for the transfer hydrogenation of imines.[117] Another system reported for the transfer hydrogenation of imines is unique in that the ligands employed in these catalytic systems are monodentate amines, as opposed to the usually used phosphines;[118] Rh(py)$_3$Cl$_3$ with added NaOMe was used to transfer hydrogen from 2-propanol to *N*-benzylideneaniline (conversion 52% after 3 h).[118]

The present work for some preliminary studies on the transfer hydrogenation of some selected imines involves using the same *in situ* rhodium-AMSO system that was used in chapter 3 for the transfer hydrogenation of aryl alkyl ketones. As of yet, there has been no system reported for the asymmetric transfer hydrogenation of prochiral imines. The current work involves transfer hydrogenation experiments using the substrates *N*-benzylideneaniline and the two prochiral imines, *N*-(1-methylbenzylidene)benzylamine and *N*-(1-methoxy-2-propylidene)2,6-dimethylaniline.

4.2 Catalytic Transfer Hydrogenation of *N*-Benzylideneaniline, $C_6H_5CH=NC_6H_5$

The transfer hydrogenation of *N*-benzylideneaniline from 2-propanol (eq. 4.1) was performed by a method similar to that used for the transfer of hydrogen to aryl alkyl ketones (section 2.4.2). Rhodium dimer [RhCl(hd)]$_2$ (13.0 mg, or 5.91×10^{-5} mol of monomer), (*S*)-AMSO (24.5 mg, 1.18×10^{-4} mol), and *N*-benzylideneaniline (0.20 g, 1.1×10^{-3} mol) were put in a Schlenk tube equipped with a Kontes valve, and the tube evacuated. 2-Propanol (10 mL) was introduced under a stream of argon and the three species dissolved to give a yellow solution. This yellow solution was heated in an oil-bath at 83°C for about 15 minutes at which time KOH (2.5×10^{-4} mol, added as 1.6 mL of a solution prepared by dissolving 1.56×10^{-3} mol of KOH in 10 mL of 2-propanol) was syringed into the solution under Ar. The ratio of Rh : (*S*)-AMSO : KOH : imine was approximately 1 : 2 : 5 : 20. It should be noted that for the transfer hydrogenation of ketones (chapter 3), the substrate was added immediately before the KOH; however, in this case, because the substrate is a solid, it was easier to add the substrate before the solvent was introduced to the Schlenk tube. Therefore, the substrate was added 15 minutes before the base was introduced into the solution.

$$\text{(4.1)}$$
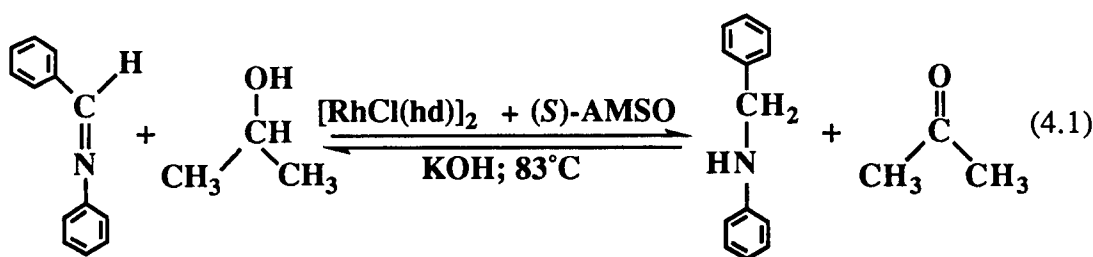
Within five minutes of the addition of KOH, the solution had become dark brown. As in the case of acetophenone reduction by this system, a brown-black solid precipitated during the reaction. The brown-black residue left after distillation of the liquid phase from the mixture was found to be soluble in H_2O. Heating was discontinued after 20 hours and the solution was isolated from the metal species by distillation with a Kugelrohr apparatus by the same

method used in section 2.4.1 for the work-up of the product-substrate mixture from the transfer hydrogenation of acetophenone.

The product-substrate mixture isolated was a colourless solution. The product amine (*N*-phenylbenzylamine) is an almost colourless solid when isolated in its pure form. However, isolation of the solid was not attempted; instead, a ^{1}H NMR spectrum of the product-substrate mixture was run in CDCl$_3$ to determine the degree of conversion of the imine to the amine. Also, a solution of the product-substrate mixture in 2-propanol was injected into the GC for analysis of the sample composition.

A ^{1}H NMR spectrum of the substrate-product mixture (Fig. 4.1) revealed 79% conversion of the imine to the amine, as calculated by comparison of the integration of the peaks assigned to 3 protons for each of the amine product (g and i) and imine substrate (a and b). Only these peaks were used in determining the conversion, as the majority of the remaining peaks appeared between 7-7.5 ppm in the phenyl region. This region of the spectrum had many peaks from both compounds (the solvent residue also appeared in this region at 7.25 ppm), and therefore assignments in this region was difficult.

Injection of the product-substrate mixture, which was diluted in 2-propanol, on a HP1 column gave a reasonably good separation of the substrate imine and product amine (Fig. 4.2). Integration of the peaks corresponding to the amine and the imine (more exactly, aniline formed from the imine, see below) gave a conversion of 80.2%. The retention times of the peaks corresponding to the imine and the amine were determined by prior injection of authentic samples of each. The response factor of the amine to imine was taken as 1.

The peak at 9.22-9.34 minutes, which was originally thought to be due to *N*-benzylideneaniline, was actually found to correspond to aniline. Hydrolysis of the imine on the column (or possibly pyrolysis due to the high injector temperature of 300°C) gave benzaldehyde and aniline. This hydrolysis was confirmed by comparing the retention times of the peaks observed when *N*-benzylideneaniline was injected with those of the peaks observed when benzaldehyde and aniline were injected (see Fig. 4.2 for retention times). Therefore,

$$\text{conversion} = \frac{33.1}{33.1+5.7+3.0} = 79.2\%$$
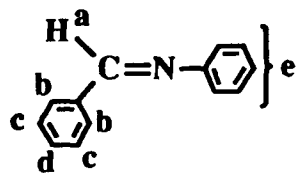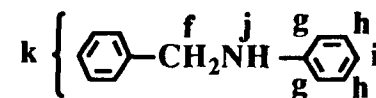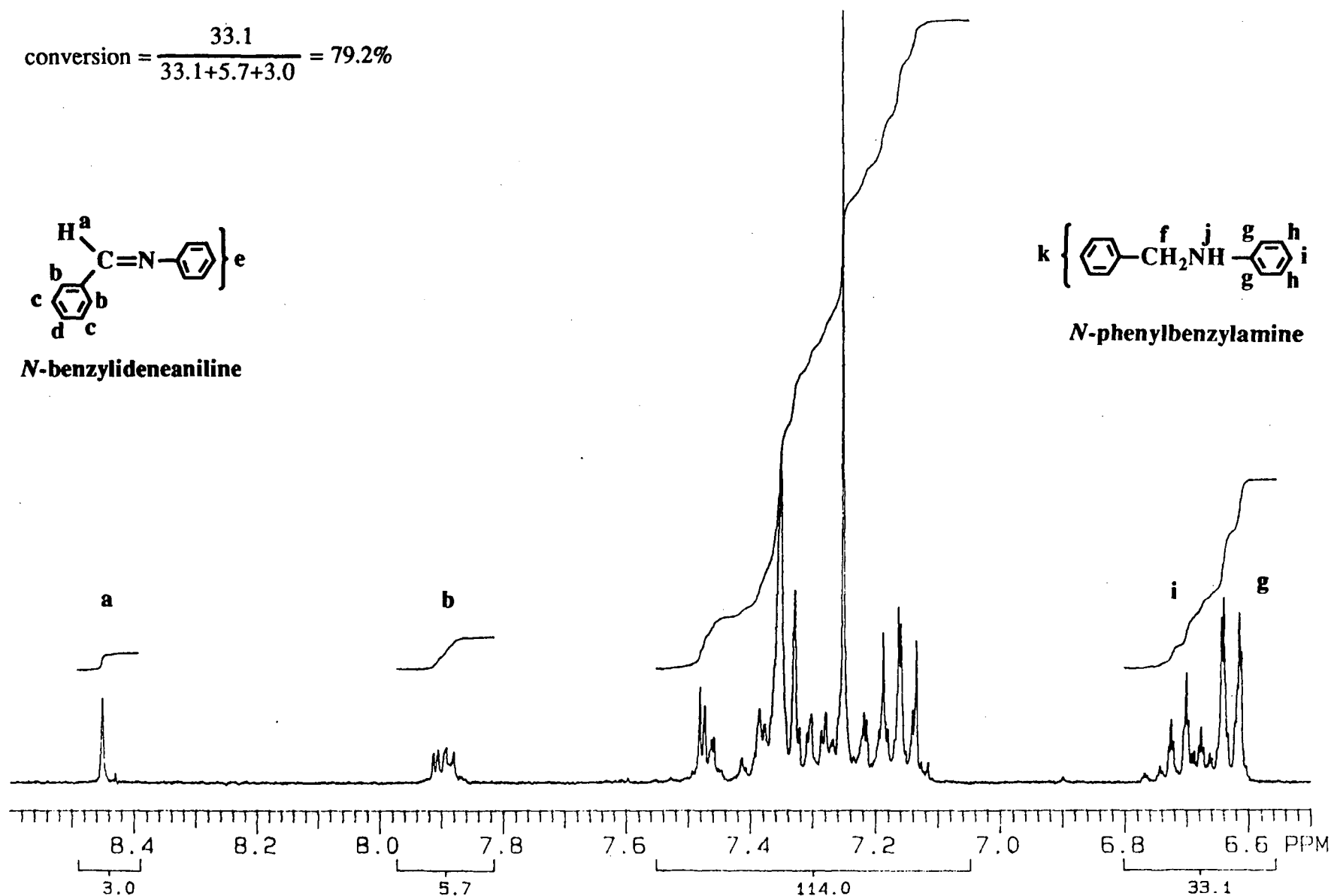
Figure 4.1 300 MHz ^{1}H NMR spectrum of the substrate-product mixture isolated from the transfer hydrogenation of N-benzylideneaniline from 2-propanol, as catalysed by Rh-AMSO.

START

2.99
3.38

4.28

9.22
9.34
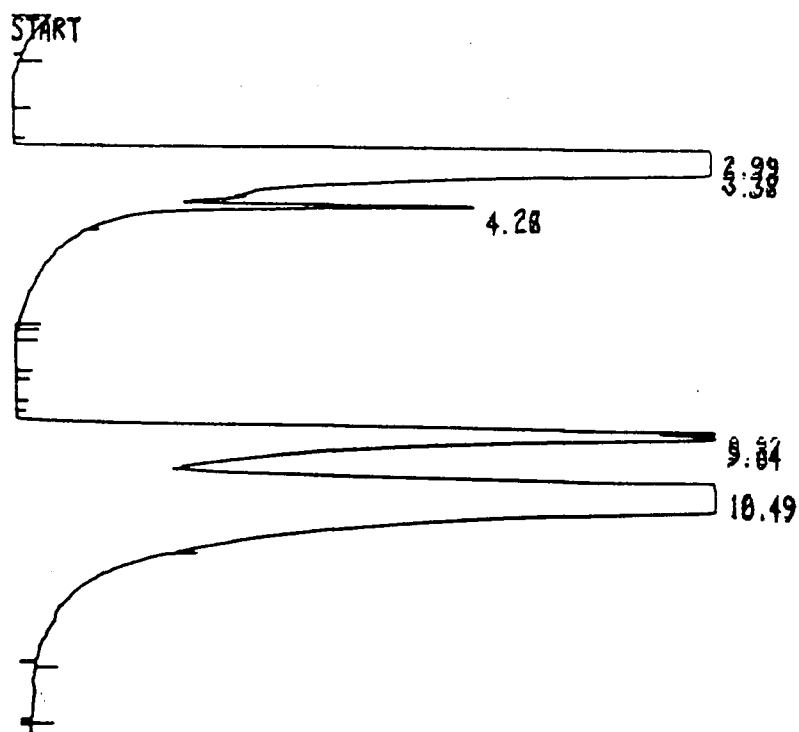
10.49

Compound	Retention time (min)
2-propanol	2.99-3.38
benzaldehyde	2.99-3.38
aniline	9.22-9.34
N-phenylbenzylamine	10.49

Figure 4.2 Gas chromatogram of the product-substrate mixture obtained from the transfer hydrogenation of N-benzylideneaniline.

both GC and ^{1}H NMR revealed that this Rh-AMSO system catalysed the transfer hydrogenation of N-benzylideneaniline to the corresponding amine in 80% yield under the present conditions.

4.3 Catalytic Transfer Hydrogenation of *N*-(1-Methylbenzylidene)benzylamine, C$_6$H$_5$-C(CH$_3$)=NCH$_2$Ph

The prochiral imine *N*-(1-methylbenzylidene)benzylamine was examined as a substrate for transfer hydrogenation from 2-propanol under conditions similar to those used for the successful reduction of *N*-benzylideneaniline (section 4.2). Rhodium dimer [RhCl(hd)]$_2$ (12.2 mg, or 5.55×10^{-5} mol of monomer) and (*S*)-AMSO (20.1 mg, 9.72×10^{-5} mol) were dissolved in 2-propanol (10 mL). The imine *N*-(1-methyl-benzylidene)benzylamine (1.0 g, 4.8×10^{-3} mol) was then added, followed immediately by the addition of KOH (2.5×10^{-4} mol, added as 1.6 mL of a solution prepared by dissolving 1.60×10^{-3} mol of KOH in 10 mL of 2-propanol). This yellow solution was heated under argon at 83°C for 8.5 hours. The ratio of Rh : (*S*)-AMSO : KOH : imine was approximately 1 : 2 : 5 : 90. At the end of the heating period, the mixture was an orangish-brown colour. The solvent 2-propanol was removed from the mixture at the pump in a Kugelrohr apparatus, leaving the product-substrate mixture and any metal species which may have been present. This residue was dissolved in CDCl$_3$ and a ^{1}H NMR spectrum recorded. The spectrum of this mixture revealed that there was no conversion of the imine to the amine. The catalytic transfer hydrogenation of this particular imine substrate, at least under the present conditions, was unsuccessful with this system.

4.4 Catalytic Transfer Hydrogenation of *N*-(1-Methoxy-2-propylidene)-2,6-dimethylaniline

Another prochiral imine *N*-(1-methoxy-2-propylidene)2,6-dimethylaniline (Fig. 4.3) was also examined as a hydrogen acceptor for the Rh-AMSO catalytic transfer of hydrogen from 2-propanol. Interest has been expressed in asymmetrically hydrogenating this particular imine, as the corresponding amine is a precursor to an important herbicide.[57] One enantiomer of this herbicide is more potent then the other, and therefore it is advantageous to prepare selectively one enantiomer of the chiral amine.
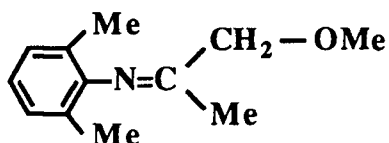
Figure 4.3 *N*-(1-Methoxy-2-propylidene)2,6-dimethylaniline.

Rhodium dimer [RhCl(hd)]$_2$ (21.3 mg, 9.68x10^{-5} mol of monomer) and (*S*)-AMSO (21.4 mg, 1.03x10^{-4} mol) were dissolved in 2-propanol (10 mL). Then *N*-(1-methoxy-2-propylidene)2,6-dimethylaniline (1.0 ml, ~5x10^{-3} mol assuming that the density is 1 g/mL) was added, followed immediately by the addition of KOH (2.50x10^{-4} mol, added as 1.4 mL of a solution prepared by dissolving 1.84x10^{-3} mol of KOH in 10 mL of 2-propanol). After the addition of the substrate and base, the solution immediately turned dark brown. The ratio of Rh : AMSO : KOH : imine was approximately 1 : 1 : 2.5 : 52. The solution was heated at 83°C under Ar for 9 hours. Then 2-propanol was removed at the pump and the product-substrate mixture isolated from the brown residue by bulb-to-bulb distillation.

Injection of a 2-propanol solution of the isolated mixture onto a HP1 column showed less than 1% conversion of the imine to the corresponding amine. No other catalytic conditions (i.e. other ratios of catalyst precursors) were examined for activity in the transfer hydrogenation of this substrate.

4.5 Discussion

The above preliminary experiments show some promise for the transfer hydrogenation of imines, at least for some particular substrates, by the *in situ* rhodium-sulphoxide system. Although neither of the prochiral imines was successfully hydrogenated by this system, the reduction of *N*-benzylideneaniline shows that at least some substrates containing C=N can be hydrogenated by transfer from 2-propanol. The structure of the imine plays an important role in determining whether or not the transfer of hydrogen will take place. It has previously been shown that the rate of H$_2$-hydrogenation decreases with increased steric crowding around the

C=N bond.[111] Also, for some transfer hydrogenation systems, workers have reported that the rate of reduction is enhanced by electron-withdrawing groups in the aromatic rings.[34, 117] It is difficult to generalise about the effect of substrate structure on transfer hydrogenation by this system because of the small number of experiments performed. However, the imine with the simplest structure of the three examined as potential substrates was the only one successfully reduced by the present system.

CHAPTER 5

GENERAL CONCLUSIONS AND SOME RECOMMENDATIONS
FOR FUTURE WORK

5.1 General Conclusions

The transfer hydrogenation of aryl alkyl ketones and selected imines from 2-propanol is successfully accomplished by *in situ* catalytic systems prepared from: (1) [RhCl(diene)]$_2$ (where the diene is either 1,5-hexadiene or 1,5-cyclooctadiene); (2) (*S*)-AMSO, (*R*)-AMSO, or (*S*)-BMSO; and (3) KOH. Although both the chemical and optical yields of the alcohols produced by these catalytic reactions are low to moderate (approximately 30-35% depending on the exact conditions) and no prochiral imines have been reduced by this system to date, the nature of the ligand makes this an attractive system for asymmetric hydrogenation. The facts that other successful systems use expensive chiral phosphines and often require the use of high H$_2$ pressures make this system all the more appealing. Still, the optical and chemical yields of the product alcohols must be improved for this system to be of practical utility in the synthesis of chiral compounds. The chemistry of these *in situ* systems is still relatively poorly understood due to the number of species in solution.

The results obtained for the transfer hydrogenation of acetophenone when (*S*)-AMSO was the ligand were: (1) conversion = 26% and e.e. = 30% of the (*R*)-(+)-alcohol when [RhCl(hd)]$_2$ was the Rh^I precursor; and (2) conversion = 36% and e.e. = 32% when [RhCl(cod)]$_2$ was used. When (*R*)-AMSO was used as the ligand, approximately the same conversion and e.e. was observed, except that the alcohol obtained in excess was the other enantiomer (see Table 3.3). Use of (*S*)-BMSO as the chiral ligand gave 29% conversion with [RhCl(cod)]$_2$ and 0% e.e.; while with [RhCl(hd)]$_2$, 10% conversion and 13% e.e. of the

(*S*)-(–)-alcohol was obtained. It is interesting to note that (*S*)-AMSO and (*S*)-BMSO gave excesses of different enantiomers of the alcohol under the same conditions, even though the ligands both exhibit the same configuration at carbon. The transfer hydrogenation of propiophenone, where (*S*)-AMSO and [RhCl(hd)]$_2$ were the catalytic precursors, gave a chemical yield of 21% and an e.e. of 35% of the (*R*)-(+)-alcohol.

N-Phenylbenzylamine was obtained in 80% chemical yield by transfer of hydrogen from 2-propanol to the corresponding imine, as catalysed by (*S*)-AMSO-[RhCl(hd)]$_2$. Two other imines, *N*-(1-methylbenzylidene)benzylamine and *N*-(1-methoxy-2-propylidene)2,6-dimethylaniline, were not reduced by this catalytic system under conditions similar to those used for the transfer hydrogenation of *N*-benzylideneaniline.

The reverse reaction to acetophenone hydrogenation using 2-propanol, where 1-phenylethanol is now the hydrogen donor and acetone the substrate, was also catalysed by the rhodium-AMSO system. Acetophenone was produced by transfer of hydrogen from racemic 1-phenylethanol to acetone in 15% chemical yield. However, the dehydrogenation of 1-phenylethanol did not take place enantioselectively (i.e. by a kinetic resolution process); there was no e.e. in the remaining 1-phenylethanol.

Optical rotation measurements were found to be fairly unreliable as an analytical technique for the evaluation of enantiomeric excess, reproducibility was a problem (section 3.14). Preparation of isopropyl urethane derivatives and separation of these enantiomeric derivatives on a chiral column provide a much more convenient and reliable method for the determination of enantiomeric excess. However, the optical rotation should still be measured qualitatively to determine which alcohol (*R* or *S*) is the one obtained in excess, as chiral GC does not provide this information unless a known pure enantiomer is available.

The coordination compounds of AMSO and BMSO remain difficult to isolate, although no attempts were made to prepare coordination compounds of rhodium (section 2.6). Isolation of a coordination compound of either of these ligands would be useful in that it would provide

some insight into which of the possible binding modes of AMSO is utilised in the catalytic cycle.

5.2 Recommendations for Future Work

Isolation of one of the diastereomers of (S)-AMSO (either N-acetyl-(S)-methionine-(R)-sulphoxide or N-acetyl-(S)-methionine-(S)-sulphoxide), and its subsequent use as a chiral ligand for the transfer hydrogenation of prochiral ketones, would be interesting in that a diastereomer ligand system might give increased optical yields of the product alcohol over the present system (see section 2.1.5). Certainly the results obtained by these rhodium-sulphoxide systems for the asymmetric transfer of hydrogen from 2-propanol can be improved by a combination of : (1) adjusting the catalytic conditions; (2) slight modifications of the ligand; and/or (3) finding the correct substrate-catalyst combination, as substrate structure is known to effect the e.e. of the reaction. However, until the chemistry of this system (i.e. the role of the base) and the nature of the catalytic species are better understood, the catalytic experiments will continue to be largely a trial and error process. Therefore, isolation of some AMSO or BMSO coordination compounds, although difficult, would prove invaluable in providing some insight into the role of the ligand in the catalytic cycle. Unfortunately, these ligands do not have the luxury, as phosphines do, of a good NMR "handle" for analysis of possible coordination compounds, and therefore product analysis of any preparations will have to rely heavily on $v(S=O)$ and $v(C=O)$ shifts in the IR spectrum for the coordinated ligand unless single crystals can be obtained and analysed by x-ray diffraction. Also, of interest is the use of *ortho*-substituted acetophenones as substrates in the rhodium-AMSO catalysed transfer hydrogenation. These substrates have produced exceptionally high enantiomeric excesses with ruthenium-Binap systems under high H_2 pressures.

REFERENCES

1. G. W. Parshall, Homogeneous Catalysis, Wiley Interscience, New York, 1980.

2. A. Nakamura and M. Tsutsui, Principles and Applications of Homogeneous Catalysis, Wiley Interscience, New York, 1980.

3. J. R. Jennings, Selected Developments in Catalysis, Blackwell Scientific Publications, Oxford, Vol. 12, 1985.

4. R. S. Dickson, Homogeneous Catalysis with Compounds of Rhodium and Iridium, D. Reidel Publishing Co., Dordrecht, 1985.

5. C. Masters, Homogeneous Transition-metal Catalysis-a gentle art, Chapman and Hall, London, 1981.

6. F. R. Hartley, Supported Metal Complexes, Catalysis by Metal Complexes Ser. (R. Ugo and B. R. James, eds.), D. Reidel Publishing Co., Dordrecht, 1985, Chapter 1.

7. J. P. Collman, L. S. Hegedus, J. R. Norton, and R. G. Finke, Principles and Applications of Organotransition Metal Chemistry, University Science Books, Mill Valley, Calif., 1987, Chapter 10.

8. H. Brunner, J. Organomet. Chem., 300, 39 (1986).

9. M. Hatada, J. Jancarik, B. Graves, and S. H. Kim, J. Am. Chem. Soc., 107, 4279 (1985).

10. K. E. Koenig, in Catalysis of Organic Reactions (J. R. Kosak, ed.), Marcel Dekker, New York, 1984, Chapter 3.

11. J. F. Young, J. A. Osborn, F. H. Jardine, and G. Wilkinson, J.Chem. Soc., Chem. Commun., 131 (1965).

12. J. M. Brown, Angew. Chem., Int. Ed. Engl., 26, 190 (1987).

13. B. R. James, Adv. Organomet. Chem., 17, 319 (1979).

14. B. R. James, in Comprehensive Organometallic Chemistry (G. Wilkinson, ed.), Pergamon, Oxford, Vol. 8, 1982, Chapter 51.

15. P. Pino and G. Consiglio, in Fundamental Research in Homogeneous Catalysis (M. Tsutsui, ed.), Plenum, New York, Vol. 3, 1979, p. 519.

16. M. Freifelder, Practical Catalytic Hydrogenation, Wiley Interscience, New York, 1971.

17. P. Chaloner, Handbook of Coordination Catalysis in Organic Chemistry, Butterworths, Toronto, 1986, Chapter 2.

18. B. R. James, Homogeneous Hydrogenation, Wiley, New York, 1973.

19. P. N. Rylander, Catalytic Hydrogenation in Organic Syntheses, Academic Press, New York, 1979.

20. G. Mestroni, A. Camus, and G. Zassinovich, in Aspects of Homogeneous Catalysis (R. Ugo, ed.), Reidel, Dordrecht, Vol. 4, 1981, p. 71.

21. H. Brunner, Synthesis, 645 (1988).

22. P. Pino and G. Consiglio, in Fundamental Research in Homogeneous Catalysis (M. Tsutsui and R. Ugo, eds.), Plenum, New York, Vol. 1, 1977, p. 147.

23. W. S. Knowles, Acc. Chem. Res., 16, 106 (1983).

24. V. Caplar, G. Comisso, and V. Sunjic, Synthesis, 85 (1981).

25. B. Bosnich and M. D. Fryzuk, in Topics in Inorganic and Organometallic Stereochemistry (G. Geoffrey, ed.), Wiley, New York, 1981, p. 119.

26. D. Valentine and J. W. Scott, Synthesis, 329 (1978).

27. T. P. Dang and H. B. Kagan, J. Chem. Soc., Chem. Commun., 481 (1971).

28. H. B. Kagan and T. P. Dang, J. Am. Chem. Soc., 94, 6429 (1972).

29. B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, and D. J. Weinkauff, J. Am. Chem. Soc., 99, 5946 (1977).

30. J. Halpern, Science, 217, 401 (1982).

31. A. S. C. Chan, J. J. Pluth, and J. Halpern, J. Am. Chem. Soc., 102, 5952 (1980).

32. H. Kawano, Y. Ishii, T. Ikariya, M. Saburi, S. Yoshikawa, Y. Uchida, and H. Kumobayashi, Tetrahedron Lett., 28, 1905 (1987).

33. M. Kitamura, T. Ohkuma, S. Inoúe, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya, and R. Noyori, J. Am. Chem. Soc., 110, 629 (1988).

34. B. Heil, L. Markó, and S. Tórös, in Homogeneous Catalysis with Metal Phosphine Complexes (L. H. Pignolet, ed.), Plenum Press, New York, 1983, p. 317.

35. G. P. Pez, R. A. Grey, and J. Corsi, J. Am. Chem. Soc., 103, 7528 (1981).

36. R. A. Grey, G. P. Pez, and A. Wallo, J. Am. Chem. Soc., 103, 7536 (1981).

37. G. P. Pez and R. A. Grey, in Fundamental Research in Homogeneous Catalysis (M. Graziani and M. Giongo, eds.), Plenum, New York, Vol. 4, 1982, p. 97.

38. R. R. Schrock and J. A. Osborn, J. Chem. Soc., Chem. Commun., 567 (1970).

39. J. Solodar, Chemtech, 421 (1975).

40. R. A. Sánchez-Delgado and O. L. De Ochoa, J. Organomet. Chem., 202, 427 (1980).

41. B. Heil, S. Törös, J. Bakos, and L. Markó, J. Organomet. Chem., 175, 229 (1979).

42. G. Mestroni, R. Spogliarich, A. Camus, F. Martinelli, and G. Zassinovich, J. Organomet. Chem., 157, 345 (1978).

43. P. E. Garrou, Chem. Rev., 85, 171 (1985).

44. A. Camus, G. Mestroni, and G. Zassinovich, J. Mol. Catal., 6, 231 (1979).

45. G. Zassinovich, G. Mestroni, and A. Camus, J. Organometal. Chem., 168, C37 (1979).

46. G. Mestroni, G. Zassinovich, A. Camus, and F. Martinelli, J. Organomet. Chem., 198, 87 (1980).

47. A. Camus, G. Mestroni, and G. Zassinovich, J. Organomet. Chem., 184, C10 (1980).

48. G. Zassinovich and G. Mestroni, J. Mol. Catal., 42, 81 (1987).

49. G. Mestroni, G. Zassinovich, E. Alessio, and M. Tornatore, J. Mol. Catal., 49, 175 (1989).

50. B. R. James, A. Joshi, P. Kvintovics, R. H. Morris, and I. S. Thorburn, in Catalysis of Organic Reactions (D. W. Blackburn, ed.), Marcel Dekker, New York, 1989, Chapter 2.

51. A. S. C. Chan and C. R. Landis, J. Mol. Catal., 49, 165 (1989).

52. K. Ito, T. Harada, A. Tai, and Y. Izumi, Chem. Lett., 1049 (1979).

53. J. Bakos, I. Tóth, and L. Markó, J. Org. Chem., 46, 5427 (1981).

54. A. Levi, G. Modena, and G. Scorrano, J. Chem. Soc., Chem. Commun., 6 (1975).

55. S. Törös, B. Heil, L. Kollár, and L. Markó, J. Organomet. Chem., 197, 85 (1980).

56. T. Sugimoto, Y. Matsumura, S. Tanimoto, and M. Okano, J. Chem. Soc., Chem. Commun., 926 (1978).

57. G. Kang, W. R. Cullen, M. D. Fryzuk, B. R. James, and J. P. Kutney, J. Chem. Soc., Chem. Commun., 1466 (1988).

58. S. Vastag, J. Bakos, S. Törös, N. E. Takach, R. B. King, B. Heil, and L. Markó, J. Mol. Catal., 22, 283 (1984).

59. G. Brieger and T. J. Nestrick, Chem. Rev., 74, 567 (1974).

60. I. S. Kolomnikov, V. P. Kukolev, and M. E. Volpin, <u>Russ. Chem. Rev. (Engl. Transl.)</u>, <u>43</u>, 399 (1974).

61. H. Imai, T. Nishiguchi, and K. Fukuzumi, <u>J. Org. Chem.</u>, <u>41</u>, 665 (1976).

62. R. Spogliarich, J. Kaspar, and M. Graziani, <u>J. Catal.</u>, <u>94</u>, 292 (1985).

63. Y. Sasson and J. Blum, <u>J. Org. Chem.</u>, <u>40</u>, 1887 (1975).

64. D. Beaupére, L. Nadjo, R. Uzan, and P. Bauer, <u>J. Mol. Catal.</u>, <u>14</u>, 129 (1982).

65. D. Beaupére, L. Nadjo, R. Uzan, and P. Bauer, <u>J. Mol. Catal.</u>, <u>20</u>, 185 (1983).

66. B. R. James and R. H. Morris, <u>J. Chem. Soc., Chem. Commun.</u>, 929 (1978).

67. K. Ohkubo, T. Ohgushi, and K. Yoshinaga, <u>Chem. Lett.</u>, 775 (1976).

68. G. Zassinovich, C. D. Bianco, and G. Mestroni, <u>J. Organomet. Chem.</u>, <u>222</u>, 323 (1981).

69. B. Heil, P. Kvintovics, L. Tarszabo, and B. R. James, <u>J. Mol. Catal.</u>, <u>33</u>, 71 (1985).

70. R. H. Morris, Ph. D. Dissertation, University of British Columbia, Vancouver, B.C. (1978).

71. P. Kvintovics, B. R. James, and B. Heil, <u>J. Chem. Soc., Chem. Commun.</u>, 1810 (1986).

72. B. R. James, R. S. McMillan, R. H. Morris, and D. K. W. Wang, <u>Adv. Chem. Series</u>, <u>167</u>, 122 (1978).

73. F. G. Mann and B. C. Saunders, <u>Practical Organic Chemistry</u>, Longman Group Ltd., London, 1960.

74. A. Hantzsch and E. v. Hornbostel, <u>Chem. Ber.</u>, <u>30</u>, 3006 (1897).

75. Spectrum from <u>The Sadtler Handbook of Proton NMR Spectra</u> (W. S. Simons, ed.), Sadtler Research Laboratories, Inc., Philadelphia, 1978, p.768.

76. J. P. Greenstein and M. Winitz, <u>Chemistry of the Amino Acids</u>, Vol. 3, John Wiley and Sons, New York, 1961, p. 2146.

77. T. F. Lavine, <u>J. Biol. Chem.</u>, <u>169</u>, 477 (1947).

78. G. Giordano and R. H. Crabtree, <u>Inorg. Synth.</u>, <u>19</u>, 218 (1979).

79. J. Chatt and L. M. Venanzi, <u>J. Chem. Soc.</u>, 4735 (1957).

80. G. Winkhaus and H. Singer, <u>Chem. Ber.</u>, <u>99</u>, 3602 (1966).

81. W. A. König, W. Francke, and I. Benecke, <u>J. Chromatogr.</u>, <u>239</u>, 227 (1982).

82. W. A. König, I. Benecke, and S. Sievers, <u>J. Chromatogr.</u>, <u>238</u>, 427 (1982).

83. K. N. Slessor, G. G. S. King, D. R. Miller, M. L. Winston, and T. L. Cutforth, J. Chem. Ecol., 18, 1659 (1985).

84. J. Bakos, I. Tóth, B. Heil, and L. Markó, J. Organomet. Chem., 279, 23 (1985).

85. G. Sbrana, G. Braca, and E. Giannetti, J. Chem. Soc., Dalton Trans., 1847 (1976).

86. F. Pruchnik, B. R. James, and P. Kvintovics, Can. J. Chem., 64, 936 (1986).

87. P. Kvintovics and B. R. James, unpublished results.

88. G. Chatelus, Compt. Rend., 248, 690 (1959).

89. R. T. Morrison and R. N. Boyd, Organic Chemistry, 3rd edition, Allyn and Bacon Inc., Boston, 1974, p. 711.

90. A. M. Joshi, unpublished results.

91. J. Halpern, D. P. Riley, A. S. C. Chan, and J. J. Pluth, J. Am. Chem. Soc., 99, 8055 (1977).

92. G. M. Whitesides, M. Hackett, R. L. Brainard, Jean-Paul P. M. Lavalleye, A. F. Sowinski, A. N. Izumi, S. S. Moore, D. W. Brown, and E. M. Staudt, Organometallics, 4, 1819 (1985).

93. J. P. Collman, K. M. Kosydar, M. Bressan, W. Lamanna, and T. Garrett, J. Am. Chem. Soc., 106, 2569 (1984).

94. D. R. Anton and R. H. Crabtree, Organometallics, 2, 855 (1983).

95. M. Bianchi, U. Matteoli, G. Menchi, P. Frediani, S. Pratesi, F. Piacenti, and C. Botteghi, J. Organomet. Chem., 198, 73 (1980).

96. I. S. Thorburn, Ph. D. Dissertation, University of British Columbia, Vancouver, B.C. (1985).

97. B. R. James, A. Pacheco, S. J. Rettig, I. S. Thorburn, R. G. Ball, and J. A. Ibers, J. Mol. Catal., 41, 147 (1987).

98. I. Ojima, T. Kogure, and N. Yoda, J. Org. Chem., 45, 4728 (1980).

99. D. Sinou, Tetrahedron Lett., 22, 2987 (1981).

100. A. Streitwieser, Jr., and C. H. Heathcock, Introduction to Organic Chemistry, second edition, Macmillan Publishing Co., Inc., New York, 1981, p. 394.

101. R. Sariego, I. Carkovic, M. Martínez, and M. Valderrama, J. Mol. Catal., 35, 161 (1986).

102. Data from Aldrich Catalog Handbook of Fine Chemicals, Aldrich Chemical Co., Milwaukee, Wisconsin, 1988-1989, p. 1186.

103. Data from <u>CRC Handbook of Chemistry and Physics</u>, 64th edition, R. C. Weast, ed., CRC Press, Boca Raton, Florida, 1983-1984, p. C-446.

104. R. H. Pickard and J. Kenyon, <u>J. Chem. Soc.</u>, <u>99</u>, 45 (1911).

105. U. Nagai, T. Shishido, R. Chiba, and H. Mitsushashi, <u>Tetrahedron</u>, <u>21</u>, 1701 (1965).

106. A. J. H. Houssa and J. Kenyon, <u>J. Chem. Soc.</u>, 2260 (1930).

107. E. Downer and J. Kenyon, <u>J. Chem. Soc.</u>, 1156 (1939).

108. G. Consiglio, P. Pino, L. I. Flowers, and C. U. Pittman, Jr., <u>J. Chem. Soc., Chem. Commun.</u>, 612 (1983).

109. H. C. Brown, J. Chandrasekharan, and P. V. Ramachandran, <u>J. Am. Chem. Soc.</u>, <u>110</u>, 1539 (1988).

110. Z. Nagy-Magos, P. Kvintovics, and L. Markó, <u>Transition Met. Chem.</u>, <u>5</u>, 186 (1980).

111. C. J. Longley, T. J. Goodwin, and G. Wilkinson, <u>Polyhedron</u>, <u>5</u>, 1625 (1986).

112. H-U. Blaser, B. Pugin, and F. Spindler, <u>Sixth International Symposium on Homogeneous Catalysis</u>, Vancouver, Canada, 1988, Abstr. P-145.

113. M. A. Radhi, G. Pályi, and L. Markó, <u>J. Mol. Catal.</u>, <u>22</u>, 195 (1983).

114. S. Vastag, B. Heil, S. Törös, and L. Markó, <u>Transition Met. Chem.</u>, <u>2</u>, 58 (1977).

115. Z. Nagy-Magos, S. Vastag, B. Heil, and L. Markó, <u>Transition Met. Chem.</u>, <u>3</u>, 123 (1978).

116. H. B. Kagan, N. Langlois, and T. P. Dang, <u>J. Organomet. Chem.</u>, <u>90</u>, 353 (1975).

117. R. Grigg, T. R. B. Mitchell, and N. Tongenyai, <u>Synthesis</u>, 442 (1981).

118. P. Kvintovics and B. Heil, <u>J. Organomet. Chem.</u>, <u>361</u>, 117 (1989).

APPENDIX

Table A1 Data for Fig. 2.4 (Titration of (S)-AMSO with NaOH).

Run 1 (Figure 2.5)		Run 2	
Volume of NaOH(mL)	pH	Volume of NaOH(mL)	pH
0.00	2.65	0.00	2.62
0.52	2.79	2.55	3.31
1.18	2.98	2.70	3.33
1.70	3.09	2.84	3.40
2.53	3.32	3.05	3.48
3.08	3.48	3.15	3.51
3.59	3.65	3.26	3.53
4.65	4.52	3.37	3.59
4.85	4.80	3.51	3.65
4.95	5.25	3.79	3.79
5.05	8.51	3.89	3.82
5.10	9.31	4.05	3.92
5.32	10.38	4.25	4.09
5.50	10.55	4.34	4.18
5.65	10.72	4.44	4.27
7.00	11.22	4.59	4.45
10.10	11.60	4.63	4.62
15.00	11.80	4.73	4.92
20.00	11.90	4.85	5.97
25.00	12.00	4.90	8.65
		4.95	9.68
		5.02	10.00
		5.31	10.49
		5.61	10.75
		6.04	10.97
		7.54	11.31
		10.83	11.61
		16.56	11.81
		25.00	11.99

Table A2 Data for Fig. 3.1 (KOH-Catalysed Transfer Hydrogenation of Acetophenone).

Time (h)	Conversion (%)
0.0	0.0
0.08	0.1
1.0	0.9
2.0	1.4
3.0	1.9
4.0	2.4
5.0	2.7
6.0	3.0
7.0	3.4
8.0	3.5
9.0	3.7
10.0	3.9
11.0	3.9
22.0	4.6
29.0	4.8
48.0	5.5

Conditions: $[KOH] \sim 2.5 \times 10^{-2}$ M in 2-propanol (10 mL); sealed under Ar (section 2.4.2); T = 83°C; Ratio KOH : acetophenone $\sim$ 1 : 35.

Table A3 Data for Fig. 3.2 (Rh-AMSO-KOH-Catalysed Transfer Hydrogenation of Acetophenone; Single Experiments, Run Using Method 2).

Concentration of [RhCl(hd)]$_2$ monomer (M)	Time (h)	Conversion (%)
-------	0.0	0.0
5.03×10^{-3}	1.0	12.0
5.84×10^{-3}	2.0	16.6
5.07×10^{-3}	4.0	21.4
5.31×10^{-3}	8.0	23.4
5.40×10^{-3}	9.0	26.0

Conditions: [Rh monomer] $\sim 5 \times 10^{-3}$ M in 2-propanol (10 mL); sealed under Ar (section 2.4.2); T = 83°C; Ratio Rh : (S)-AMSO : KOH : acetophenone $\sim$ 1 : 2 : 5 : 175.

Table A4 Data for Fig. 3.3 (Rh-AMSO-KOH-Catalysed Transfer Hydrogenation of Acetophenone; Samples Withdrawn Periodically, Run Using Method 2).

Time (h)	Conversion (%)
0.0	0.0
0.08	4.8
0.5	9.8
1.0	12.7
1.5	15.3
2.0	17.1
2.5	18.4
3.0	19.6
4.0	21.9
5.0	23.7
6.0	25.5
7.0	26.9
8.0	28.2
9.0	29.8
10.0	31.2
11.0	32.2
12.0	33.3
26.0	41.1
27.0	41.8
28.0	42.1
72.0	54.5
73.0	54.6
74.0	55.3
97.0	58.4
98.0	58.0
121.0	61.3
122.0	61.5

Conditions: [RhCl(hd)]$_2$, [Rh monomer] = 4.81x10^{-3} M in 2-propanol (10 mL); sealed under Ar (section 2.4.2); T = 83°C; Ratio Rh : (*R*)-AMSO : KOH : acetophenone ~ 1 : 2 : 5 : 175.

**Table A5** Data for the Effect of Temperature on the Optical Rotation of Pure (*R*)-(+)-1-Phenylethanol.

Temperature (°C)[a]	Observed Rotation (°)[b] (α)	Density (g/mL)[c]	Absolute Rotation (°) $[\alpha]_D$
12.4	44.215	1.0196	43.366
14.3	44.158	1.0180	43.376
17.3	44.060	1.0156	43.383
17.8	44.040	1.0152	43.380
19.9	43.972	1.0135	43.386
22.1	43.895	1.0117	43.386
24.4	43.821	1.0099	43.393
25.0	43.798	1.0094	43.391
27.6	43.715	1.0073	43.399
29.2	43.661	1.0060	43.401
29.3	43.661	1.0059	43.404
31.8	43.579	1.0039	43.410
35.9	43.444	1.0006	43.419
39.4	43.324	0.9978	43.42
39.8	43.308	0.9974	43.42

(a) error in readings is ± 0.1°C.
(b) error from instrument is ± 0.2% of the reading, while the reproducibility is ± 0.002°; measured at the sodium D line.
(c) relative density.

Graph A6 Plot of Observed Rotation (α) of Pure (R)-(+)-1-Phenylethanol vs. Temperature.

$y = 44.629 - 3.3121e{-}2x \quad R^2 = 1.000$
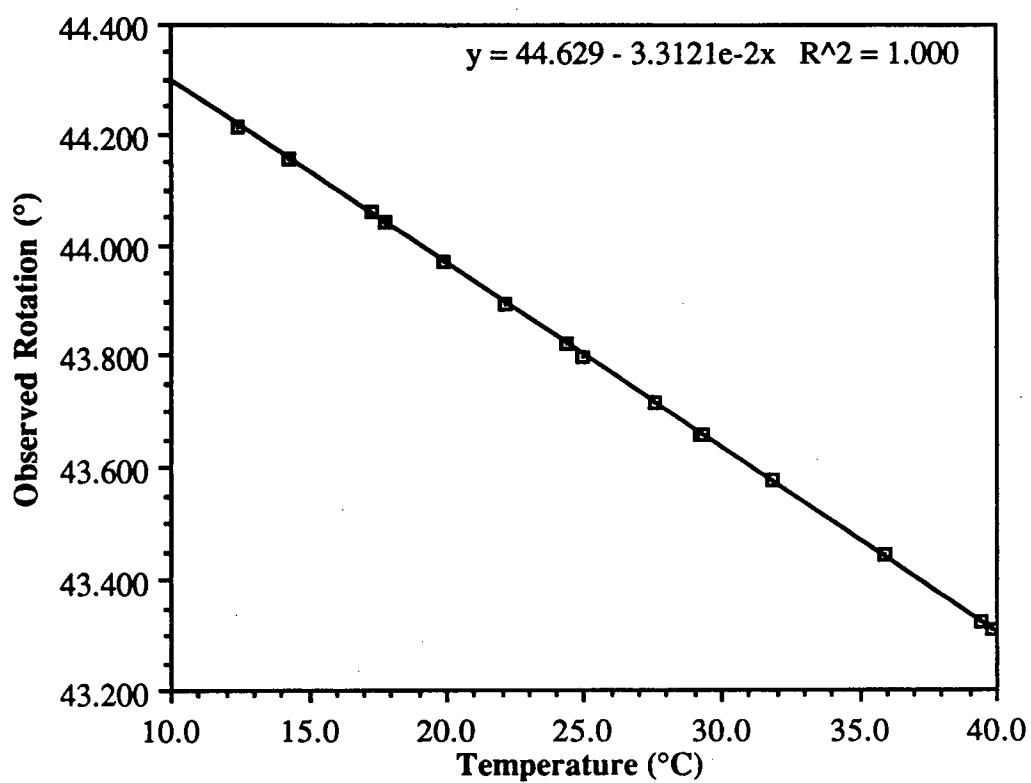
Table A7 Data for the Effect of Concentration on the Optical Rotation of (R)-(+)-1-Phenylethanol at 25°C.

Conc. (g/mL)[a]		Conversion (%)[b]	Observed Rotation (°)[c]	Absolute Rotation $[\alpha]_D^{25}$ (°)[a]	
(A)	(B)		(α)	(A)	(B)
pure	pure	100	43.798	43.4	43.4
0.908	0.877	86.85	40.301	44.4	46.0
0.609	0.584	56.95	28.656	47.1	49.1
0.493	0.472	46.70	23.545	47.8	49.9
0.399	0.353	35.01	19.220	48.2	54.5
0.322	0.319	31.59	15.675	48.7	49.1
0.261	0.220	21.76	12.729	48.8	57.9
0.211	0.214	19.77	10.223	48.5	47.8
0.163	0.171	16.84	7.827	48.0	45.9
0.119	0.095	9.31	5.623	47	59.1
0.086	0.086	8.53	4.006	47	47
0.070	0.057	7.17	3.008	43	53
0	0	0	0	0	0

(a) A - calculated from the amounts of acetophenone and 1-phenylethanol added; B - calculated from the integration of the peaks in the gas chromatograms of the mixtures.

(b) the conversion (or %-(R)-(+)-1-phenylethanol) was calculated from the integration of the peaks in the gas chromatograms of the mixtures.

(c) error from instrument is ± 0.2% of the reading, while the reproducibility is ± 0.002°; measured at the sodium D line.

Graph A8 Plot of Observed Rotation of (R)-(+)-1-Phenylethanol vs. % of (R)-(+)-1-Phenylethanol at a Temperature of 25°C.